Transition Metal and Oxidant Free Sustainable Syntheses of Heterocyclic Molecules

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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Dedicated to

My Teachers

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

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STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Transition Metal and Oxidant Free Sustainable Syntheses of Heterocyclic Molecules***" is the result of investigations carried out by me under the supervision of Prof. Subhas Chandra Pan, Department of Chemistry, Indian Institute of Technology Guwahati, India, for the award of the degree of Doctor of Philosophy.

In harmony with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Transition Metal and Oxidant Free Sustainable Syntheses of Heterocyclic Molecules***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Subas Chandra Sahoo (Roll No: 146122003) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati — Prof. Subhas Chandra Pan

September, 2019 — Supervisor

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I would like to appreciate all the peoples around me who have assisted and guided me directly and indirectly throughout my academic journey. Without their contributions this thesis would not have been a reality.

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Sincerely,

Subas Chandra Sahoo

CONTENTS

Abbreviation

Ar	Aryl group	h	Hours
AcOH	Acetic Acid	HPLC	High performance liquid chromatography
Bu	Butyl	HRMS	High Resolution Mass Spectrometry
CCDC	Cambridge Crystallographic Data Centre	Hz	Hertz
COSY	Correlation spectroscopy	Hex	Hexane
^{o}C	Degrees Celsius	*i*	Iso
CAN	ceric ammonium nitrate	i-PrOH	2-propapnol
CH_3CN	Acetonitrile	*J*	Coupling Constant
C_6H_6	Benzene	KBr	Potassium bromide
$CHCl_3$	Chloroform	m	Multiplet
$PhCh_3$	Toluene	*m*	*meta*
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene	*m*CPBA	*meta*-Chloroperoxybenzoic acid
DCE	1,2-Dichloroethane	Me	Methyl
DCM	Dichloromethane	mg	Miligram
DIPEA	*N*,*N*-Diisopropylethylamine	mL	Millilitre
DMAP	4-Dimethylaminopyridine	mmol	Milimole
DMF	*N*,*N*-Dimethylformamide	mp	Melting point
DMSO	Dimethylsulfoxide	MTBE	Methyl tertiary butyl ether
dr	Diastereomeric ratio	MS	Molecular sieves
DTBP	Di-*tert*-butyl peroxide	ppm	Parts per million
EA	Ethyl acetate	q	Quartet
ee	Enantiomeric excess	s	Singlet
equiv	Equivalent	t	triplet
ESI	Electrospray ionization	d	Doublet
Et	Ethyl	dd	Doublet of doublet

n	Normal	*t*	*tert*
NMR	Nuclear magnetic resonance	TC	Thiocarboxylate
NOESY	Nuclear Overhauser effect spectroscopy	TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program	TFA	Trifluoroacetic acid
o	*ortho*	TFAA	Trifluoroacetic anhydride
p	*para*	UV	Ultra violet
Ph	Phenyl	THF	Tetrahydrofuran
ppm	Parts per million	TMS	Tetramethylsilane
Pr	Propyl	TBHP	tert-Butyl hydroperoxide
PS	Proton sponge	TBAI	Tetra^{n}butylammonium iodide
PTSA	*para*-Toluenesulfonic acid	Ts	*p*-Toluenesulfonyl
$PhCF_3$	Trifluorotoluene	UV	Ultra violet
PPA	Polyphosphoric acid	XRD	X-ray diffraction
rt	Room temperature	δ	Chemical shift

General Remarks

The present investigations are carried out in Department of Chemistry, Indian Institute of Technology Guwahati, during the period from July-2014 to september-2019 as a Ph.D. student under the supervision of Prof. Subhas Chandra Pan.

Mostly, all reactions were carried under air using oven dried glassware and magnetic stirring. All solvents and reagents were used as received from Aldrich, Merck and Spectrochem without purification.

But reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Methanol and ethanol were freshly distilled from magnesium/iodine under argon. THF and diethylether (Et_2O) were freshly distilled from Sodium under argon. Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane ($ClCH_2CH_2Cl$) were freshly distilled from calcium hydride (CaH_2). Chloroform ($CHCl_3$) was distilled calcium chloride ($CaCl_2$) and store under argon. *N*, *N*-diisopropylethylamine (DIPEA) was distilled from CaH_2 and stored under argon. Commercial grade xylene, benzene, toluene and were distilled from calcium hydride (CaH_2) before use. Trifluorotoluene ($PhCF_3$) was used as received from Sigma Aldrich India. All other solvents and reagents were purified according to standard procedures.

^{1}H &^{13}C NMR spectroscopy: *Bruker DRX 400 MHz*, *Bruker DRX 500 MHz* and *Bruker DRX 600 MHz*. Chemical shifts, δ (in ppm), are reported relative to TMS (δ (1H) 0.0 ppm, δ (13C) 0.0 ppm) which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.23 ppm; CD_3OD, (^{1}H) 3.31 ppm, δ (^{13}C) 49.15 ppm) were used for calibration.

Column chromatography: Merck or Spectrochem silica gel 60-120, 230-400 mesh or neutral alumina (Merck or Fischer Scientific) under gravity. After purifications the solvent was usually removed in Büchi R-114V rotavapour.

MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

XRD: X-ray crystallographic data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo-Kα radiation (l =

0.71073 Å) at 296(2) K, with increasing w (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods using SHELXS-97 and refined with full matrix least squares on *F*2 using SHELXL-97.

HPLC: HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic materials.

TLC: Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm).

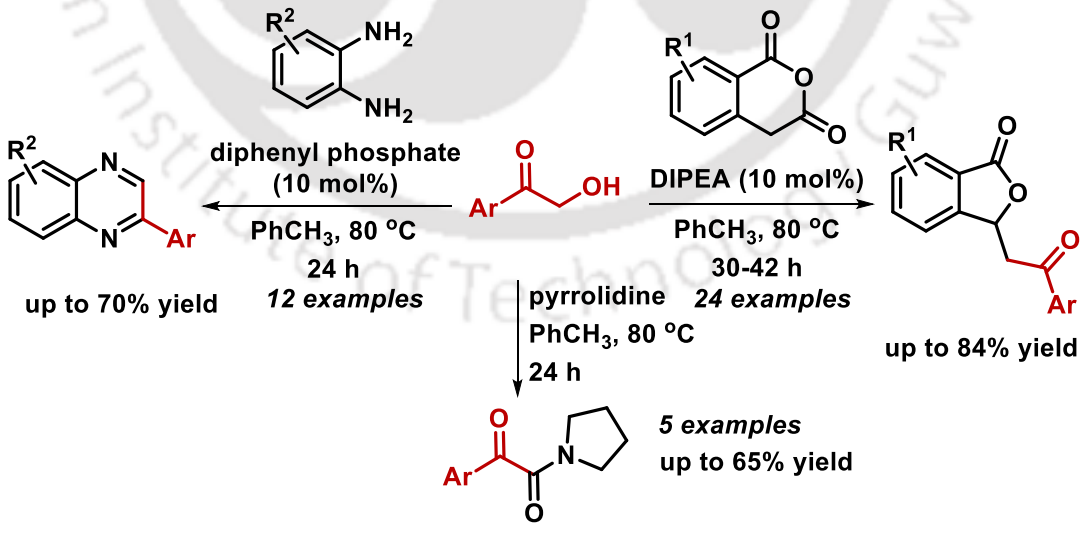
Melting Point: Melting points were measured using BüCHI melting point B-540 apparatus.

Abstract

The contents of the present thesis entitled as "***Transition Metal and Oxidant Free Sustainable Syntheses of Heterocyclic Molecules***" have been divided into five chapters based on the results achieved from the experimental works performed during the entire course of the PhD research programme.

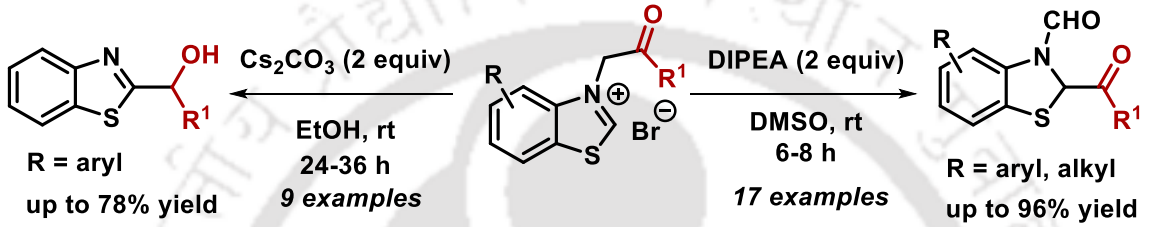
Chapter 1 contains a brief introduction and the literature review of heterocyclic molecules. Different strategies including non-asymmetric as well as asymmetric reactions for the synthesis of useful heterocyclic products were also discussed.

Chapter 2 highlights an efficient method for the facile synthesis of heterocycles *via* aerobic oxidation of 2-hydroxyacetophenones without any need of redox catalyst system. Catalytic amount of base has been added for synthesis of phthalides. Also catalytic amount of acid has been added for synthesis of quinoxalines which supports easy formation of imine bond. Base/acid has no role in the oxidation process. In addition, mechanistic studies have been performed to understand the plausible reaction pathway involved for the oxidation process which is discussed in this section in details. Different α-ketoamides and olefin are also synthesized under the reaction conditions with moderate to good yields.



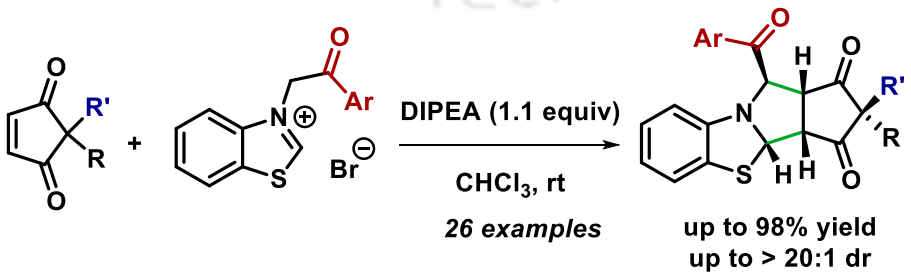
Scheme 1

Chapter 3 represents base mediated an unusual aerobic hydrolysis-cascade reaction for the first synthesis of *N*-formyl-2-benzoyl benzothiazolines and *N*-formyl disulfides from *N*-phenacylbenzothiazolium bromides. The reaction proceeds *via* aerobic formation of iminium ion intermediate. 2-Substituted benzothiazole with benzylic hydroxyl group was formed when DIPEA was replaced with cesium carbonate. Also synthetic applications such as cascade formation of *N*-substituted imidazoles and 2-benzoyl benzothiazole have been demonstrated under mild reaction conditions. Detailed mechanistic studies have been performed to understand the plausible reaction pathway.



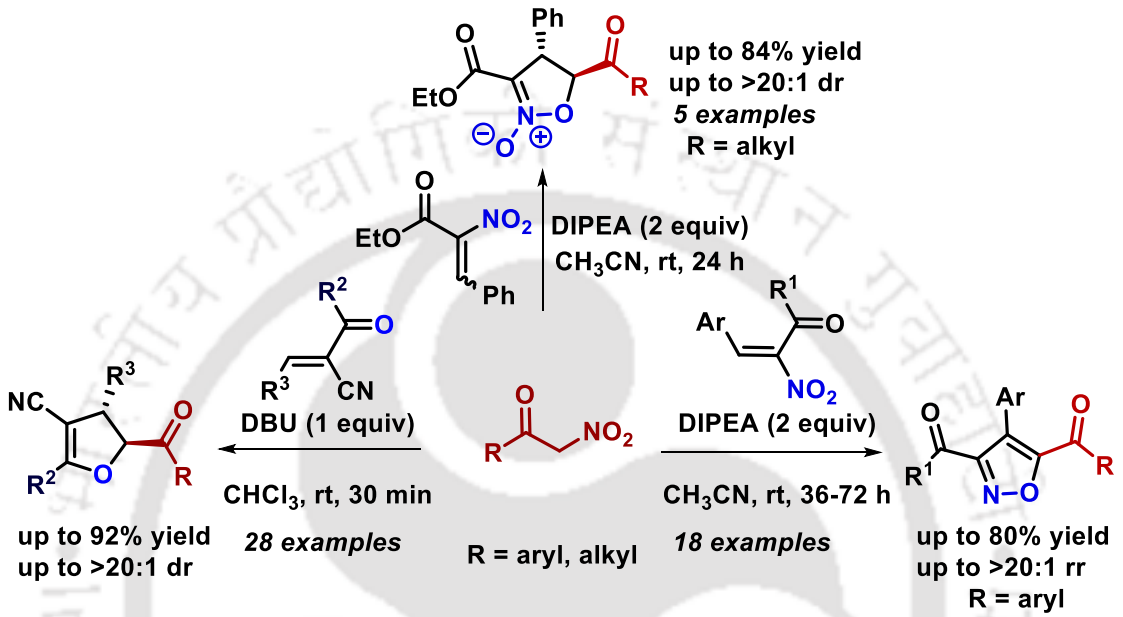
Scheme 2

Chapter 4 describes metal-free highly diastereoselctive [3+2] cycloaddition reaction between *N*-phenacylbenzothiazolium bromides and prochiral cyclopentene-1,3-diones which results a tetracyclic product with five stereogenic centres. Benzothiazolium *N*-phenacylide is the active 1,3-dipole intermediate generated *in situ* with the treatment of DIPEA with *N*-phenacylbenzothiazolium bromide. The short reaction time and mild reaction conditions are some of the salient features of this protocol. A few synthetic transformations of this method were also demonstrated which results interesting fused heterocyclic molecules. A catalytic asymmetric variant of this process is also studied preliminary using hydroquinine derived thiourea catalyst in combination with proton sponge.



Scheme 3

Chapter 5 demonstrates base mediated denitration reactions of nitroketones. Versatile nature of α-nitroketones triggered the construction of various heterocyclic molecules. We have able to synthesize isoxazoles in regioselective manner, isoxazoline *N*-oxides and dihydrofurans with excellent diastereomeric ratio and β,γ-unsaturated diesters. The scope of this reaction is quite broad for different heterocyclic moieties.



Scheme 4

Each of these chapters contain introduction, previous reported works, present result and discussion, experimental section, references, along with characterization data of products including few selective spectral data. Overall, this thesis demonstrates some new and efficient approaches for the synthesis of different heterocyclic moieties.

Chapter 1

General Introduction

1.1 Introduction

Most of the chemical compounds are classified on the basis of their structure, bonding patterns and number of atoms. When all the atoms in a molecule are carbon and are arranged in cyclic ring format, molecule is called **carbocyclic molecule**. When the cyclic compound contains only one type of element, compound is called **isocyclic compound**. **Heterocyclic molecules** are cyclic ring structures containing at least one **heteroatom**. Nitrogen, oxygen, and sulfur atoms are the common heteroatoms mostly found in heterocycles. Other heterocycles having heteroatoms like, boron, phosphorous, silicon, arsenic, antimony, selenium, tellurium etc. are also well known and have wide applications.[1]

A convenient classification of heterocycles can be done by considering ring size. Three- and four-membered rings are geometrically strained and thus susceptible to ring opening because of their small size. Such heterocycles are thus well-known reactive intermediates. Four-membered heterocyclic rings are less strained, and hence more stable than the three-membered rings and therefore, ring cleavage is less expected. Moreover, synthesis of four-membered heterocycles is more difficult than the three-membered heterocycles by direct intramolecular cyclization. Five- and six-membered rings are readily formed and are very stable. Maximum variety of heterocycles includes five- and six-membered rings. Their sizes also allow the development of aromatic character. Compared to five- and six-membered rings, the seven-membered ring skeleton is difficult to construct due to the unfavourable transannular interactions and entropic factors. Similarly, synthesis of eight or more membered heterocycles is more difficult because of their associated torsional, large-angle strain and the high activation energy needed for the ring closure.

Heterocyclic compounds can also be classified as aliphatic and aromatic heterocyclic compounds.

The history of heterocyclic chemistry started in the 1800s with the development of organic chemistry.[2] In this regard; some notable developments can be highlighted.

(i) Isolation of alloxan from uric acid by Brugnatelli in 1818

(ii) Production of furfural by treating starch with sulfuric acid by Dobereiner in 1832

(iii) Separation of pyrrole by dry distillation of bones by Runge in 1834

(iv) Synthesis of indigo dye by Friedlander in 1906

(v) Isolation of chlorophyll derivatives from crude oil and explanation of biological origin of petroleum by Treibs in 1936

(vi) Role of heterocyclic compounds (purines and pyrimidines) in the genetic code by Chargaff's rules in 1951

Heterocyclic compounds are extensively distributed in nature and play vital roles in the metabolism in living cells. Almost all compounds such as vitamins, hemoglobin, DNA, RNA, co-enzymes, essential amino acids and many other natural products contain heterocycles (Figure 1.1).[1] A large number of heterocyclic compounds are pharmacologically active such as nelfinavir, cathepsin-D inhibitor, ampicillin etc. (Figure 1.1).[3] Heterocyclic compounds include many synthetic dyes, the majority of drugs and most biomass (cellulose and related materials).

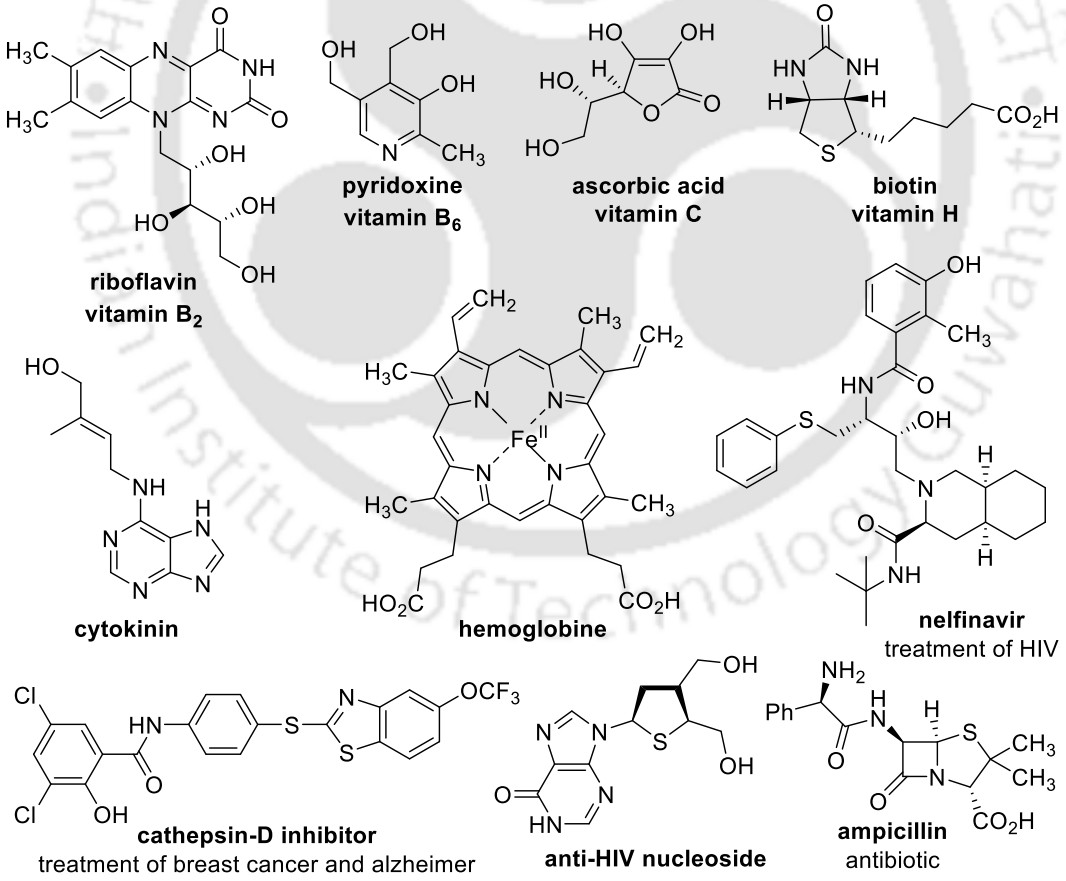


Figure 1.1: Some important heterocyclic molecules

1.2 Synthesis of heterocycles

Heterocycles are considered as the largest classical division of organic structures covering more than half of the known compounds.[4] The chemistry of heterocyclic compounds, dealing with preparation, properties and application, is very vast. Therefore, synthesis of heterocycles is still highly demanding.

Over the last decade, many new approaches have been applied for the synthesis of heterocyclic molecules. General methods for the synthesis of heterocycles can be classified into two parts.

A. Classical cycloaddition reactions
B. Oxidative cyclization reactions.

A. Classical cycloaddition reactions

Cycloadditions[5] are one of the fundamental reaction processes which have been utilized with great success for the construction of a variety of heterocyclic skeletons. Classical cycloaddition reactions have been reported by using diene-dienophiles chemistry. Some of the dienophiles posses pre-existing dipole system which can be activated by catalytic amount of simple acid/base or under heating; whereas some dienophiles require stoichiometric amount of base/acid to generate dipoles. Synthesis of heterocyclic molecules mainly follows some general strategies (Figure 1.2).

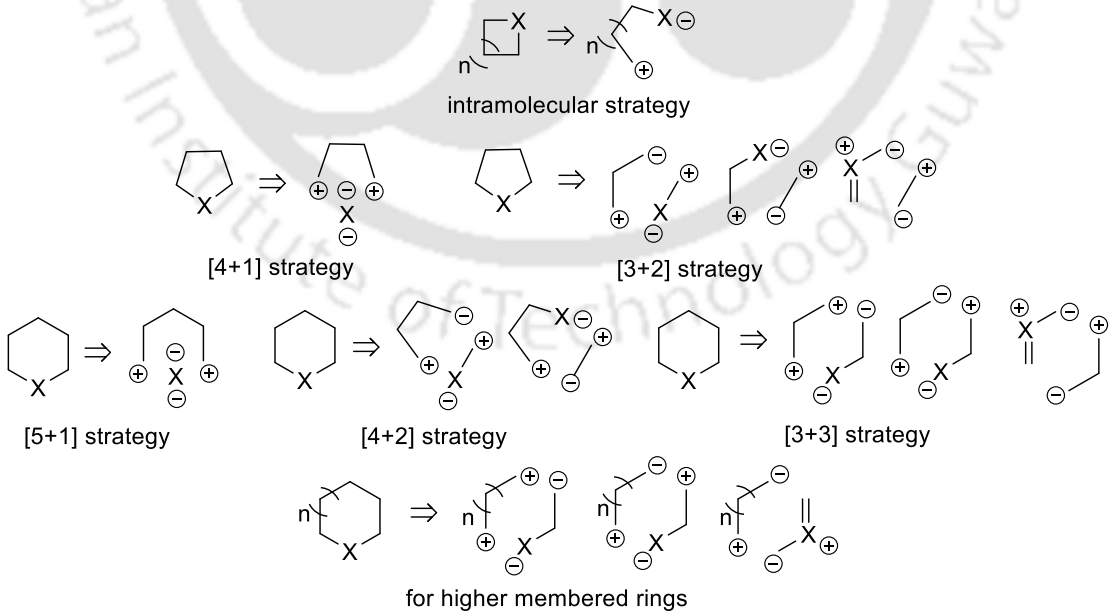
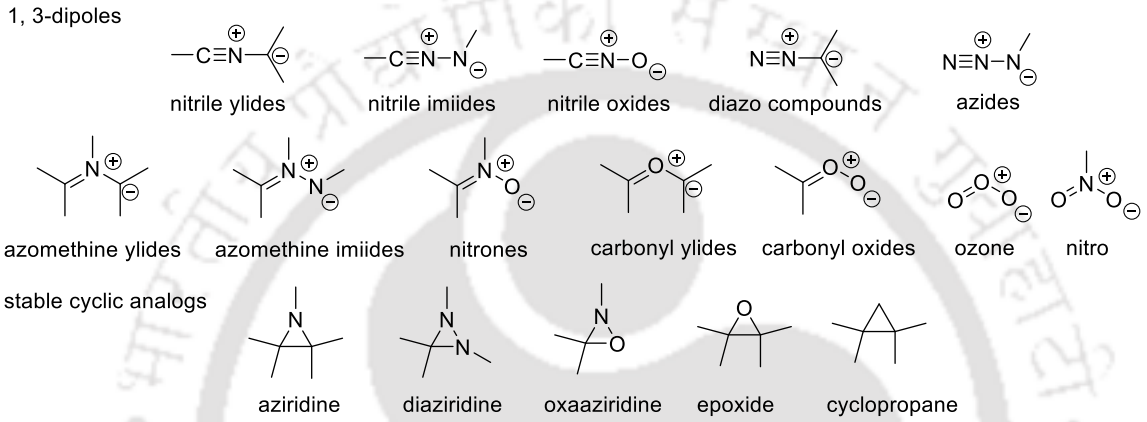


Figure 1.2: General classical strategies for the synthesis of heterocycles

Common strategies include [3+2][6] cycloaddition for five membered rings formation, [3+3][7] cycloaddition for six membered rings formation, [4+3][8] cycloaddition for seven membered rings formation. The construction of heterocycles by classical cycloaddition reactions involve 1,3-dipoles and dipolarophiles. Common examples of 1,3-dipoles are provided in Scheme 1.1. Some stable cyclic analogous are there which also serve as 1,3-dipoles under thermal/photochemical conditions or in the presence of a Lewis acid (Scheme 1.1).

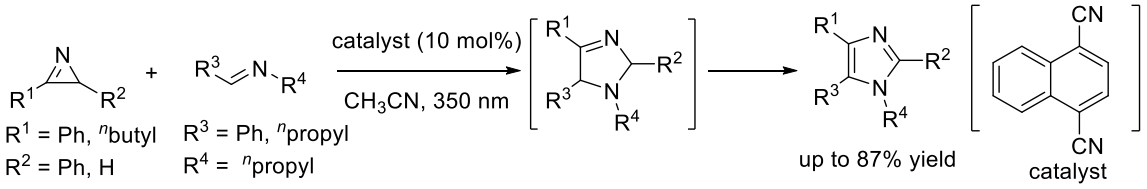


Scheme 1.1: Common examples of 1, 3-dipoles

Cycloaddition strategy covers enormous number of reactions. Herein, we have discussed some selective recent reactions.

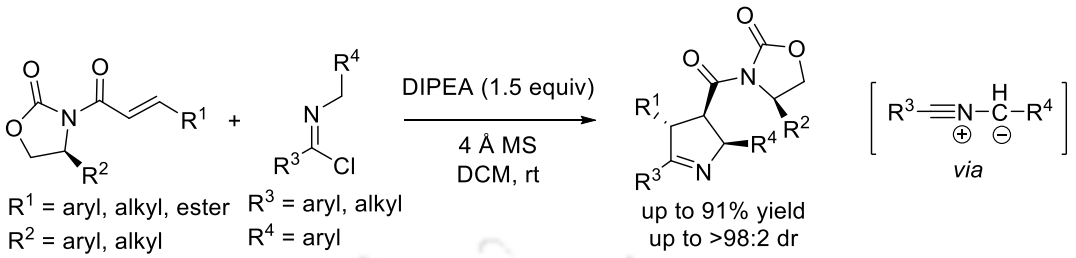
Nitrile ylides[9] can be obtained by dehydrochlorination of imidoyl chlorides. Photochemical ring opening of azirines and addition of electrophilic carbenes to nitriles also generate nitrile ylide.

Mattay group developed a new synthetic methodology for the synthesis of *N*-substituted imidazoles *via* [3+2] cycloaddition of azirine and imine using 1,4-naphthalene dicarbonitrile as photocatalyst (Scheme 1.2).[10] This reaction is also comfortable for olefins with electron withdrawing groups.



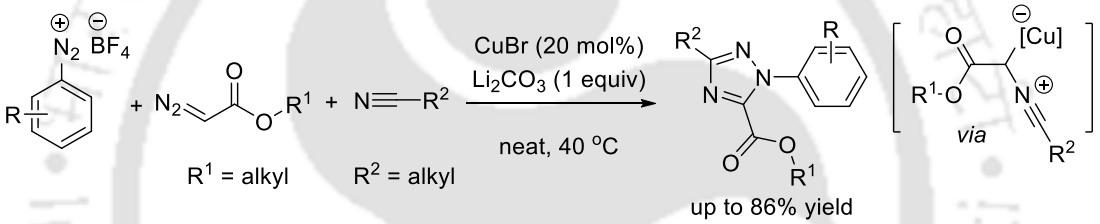
Scheme 1.2: Photo-catalyzed reaction of azirines and imines

Sibi *et al.* reported base mediated diastereoselective cycloadditions of nitrile ylides and chiral oxazolidinones (Scheme 1.3).[9b]



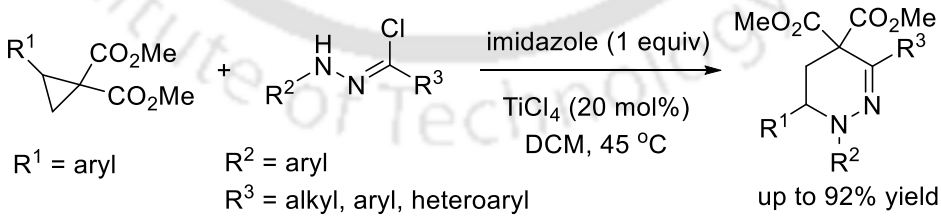
Scheme 1.3: Base mediated cycloadditions *via* nitrile ylides

Wan and co-workers disclosed a methodology for copper catalysed synthesis of fully substituted 1,2,4-triazoles from diazonium salts and nitriles *via* nitrile ylide intermediate (Scheme 1.4).[9f]



Scheme 1.4: Cupper bromide catalysed synthesis of 1,2,4-triazoles

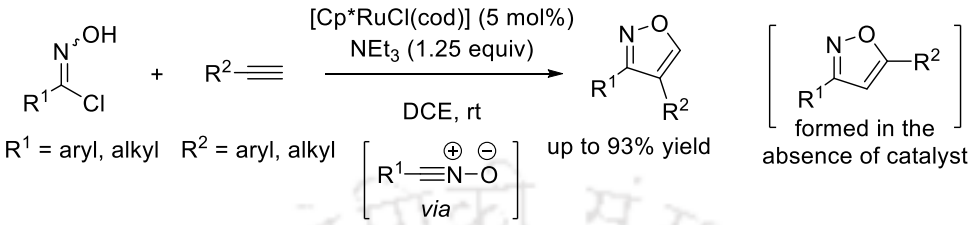
Werz group established [3+3] cycloaddition of nitrile imines and donor-accepter cyclopropanes to afford tetrahydropyridazines in the presence of titanium tetrachloride (Scheme 1.5).[11] The nitrile imine was generated *in situ* from hydrazonyl chloride and imidazole.



Scheme 1.5: Synthesis of tetrahydropyridazines *via* nitrile imine

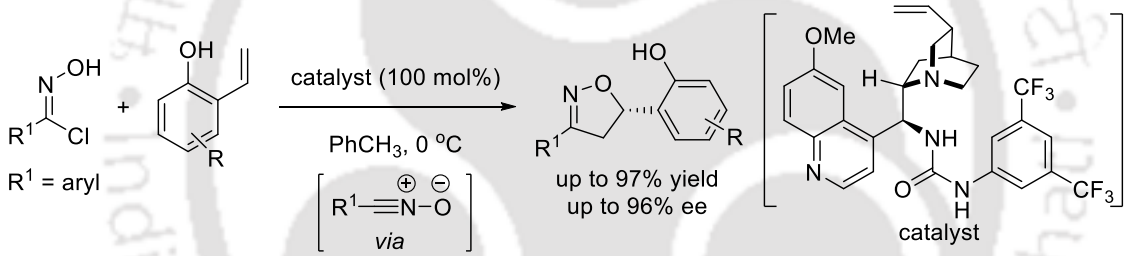
Nitrile oxides[12] can also be generated either by *in situ* treatment of *N*-hydroxybenzimidoyl chloride/*α*-nitroketones with mild bases and then immediately reacted with dipolarophiles or from the corresponding aldoximes by oxidation reactions.

Fokin and co-workers developed a regioselective synthesis of isoxazoles *via* 1,3-dipolar cycloaddition of nitrile oxides and alkynes using ruthenium catalyst. In the absence of catalyst, other regioisomer was formed (Scheme 1.6).[12g]



Scheme 1.6: Ruthenium catalysed regioselective synthesis of isoxazoles

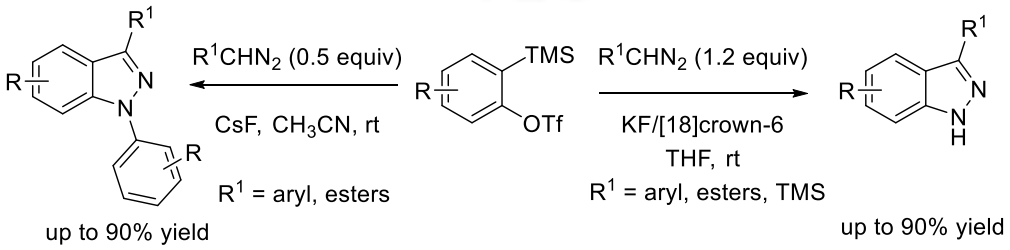
Suga *et al.* demonstrated cinchona-alkaloid based tertiary amine urea catalyzed first asymmetric 1,3-dipolar cycloaddition between nitrile oxides and *o*-hydroxystyrenes to access chiral isoxazoline derivatives (Scheme 1.7).[12h]



Scheme 1.7: Synthesis of chiral isoxazoline derivatives

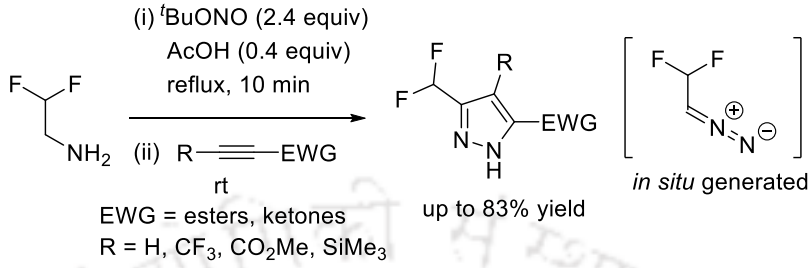
Diazomethanes[13] are highly reactive as well as toxic and explosive. They are mainly used for cycloaddition reaction, cyclopropanation, esterification etc.

Yamamoto group developed 1,3-dipolar cycloaddition of arynes with diazomethane derivatives for the synthesis of 1*H*-indazoles and 1-arylated indazoles (Scheme 1.8).[13e]



Scheme 1.8: Synthesis of 1*H*-indazoles and 1-arylated indazoles

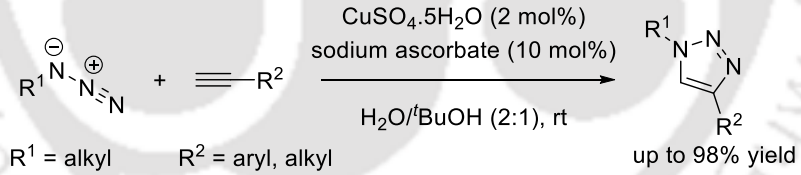
A novel synthetic approach for difluoromethyl-substituted pyrazoles was explored by Mykhailiuk *et al* (Scheme 1.9). CF_2HCHN_2 was synthesized *in situ* and subjected to [3+2] cycloaddition reaction with various alkynes.[13f]



Scheme 1.9: Synthesis of difluoromethyl-substituted pyrazoles *via* diazomethane

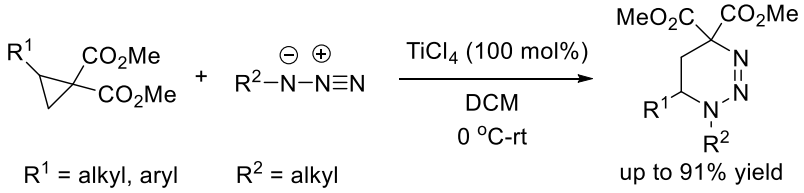
Organic azides[14] are frequently used in organic synthesis. The terminal nitrogen is mildly nucleophilic. Aryl azides can be prepared by displacement of the appropriate diazonium salt with sodium azide or trimethylsilyl azide. Synthesis of aryl azides is also possible by nucleophilic aromatic substitution of chlorides and diazotization of anilines and aromatic hydrazines.

Fokin group developed 1,3-dipolar cycloaddition reaction of azides and alkynes, providing 1,4-disubstituted 1,2,3-triazoles using copper(I) catalyst (Scheme 1.10). [14b]



Scheme 1.10: [3+2] Cycloaddition reaction of azides and alkynes

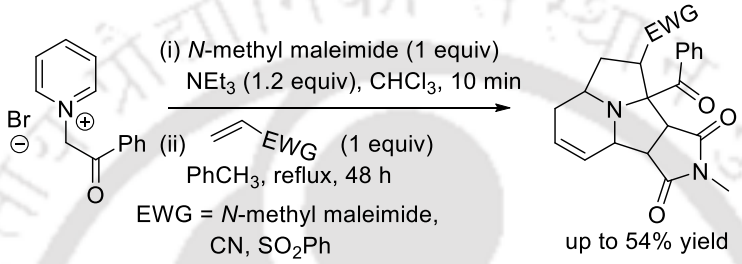
Xu *et al*. developed $TiCl_4$ promoted formal [3+3] cycloaddition reaction of azides and cyclopropane 1,1-diester for the synthesis of highly functionalized triazinines (Scheme 1.11).[14e]



Scheme 1.11: Synthesis of triazinines using azides

Azomethine ylides[15] can be synthesized *in situ* by treating *N*-alkyl imines with strong/mild bases and immediately reacted with dipolarophiles. Reactions of azomethine ylides are highly stereo- and regioselective, and have the potential to form four new contiguous stereocenters. Azomethine ylides thus have high utility in the formation of chiral ligands and in total synthesis. More information have been provided in chapter 4.

Kanemasa *et al.* disclosed cycloaddition reaction of pyridinium methylides with electron-deficient olefins in stepwise manner (Scheme 1.12).[15a]

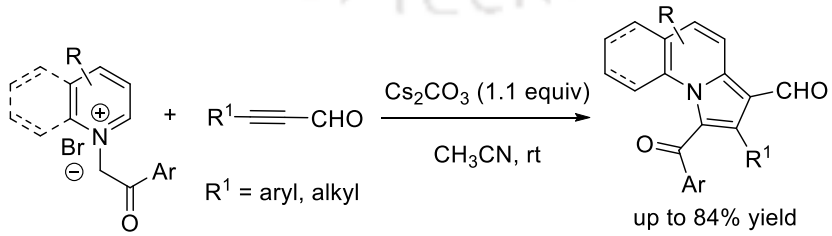


Scheme 1.12: Cycloaddition reaction of pyridinium methylides

Ryan and co-workers demonstrated a transformation of *N*-protected isatoic anhydrides into 1,3-benzodiazepin-5-ones using *in situ* formed azomethine ylide (Scheme 1.13).[15c]

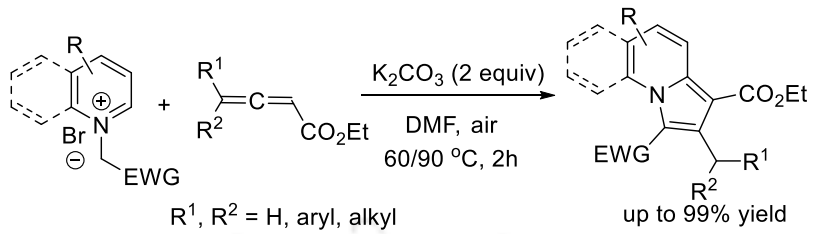
Scheme 1.13: Synthesis of 1,3-benzodiazepin-5-ones using azomethine ylide

Xing group published general and direct synthesis of indolizine-1-carbaldehydes *via* 1,3-dipolar cycloaddition of phenylpropiolaldehyde with pyridinium ylides (Scheme 1.14).[15d]



Scheme 1.14: [3+2] Cycloaddition reaction of azomethine ylides

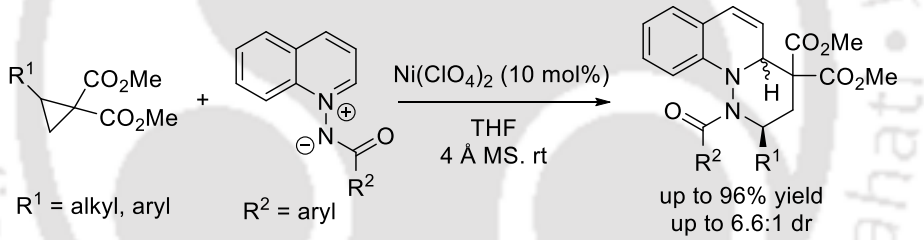
Recently, Bakshi *et al.* developed transition metal free synthesis of nitrogen containing heterocycles having a fully substituted *N*-fused pyrrole ring (Scheme 1.15).[15e]



Scheme 1.15: Synthesis of *N*-fused pyrrole ring

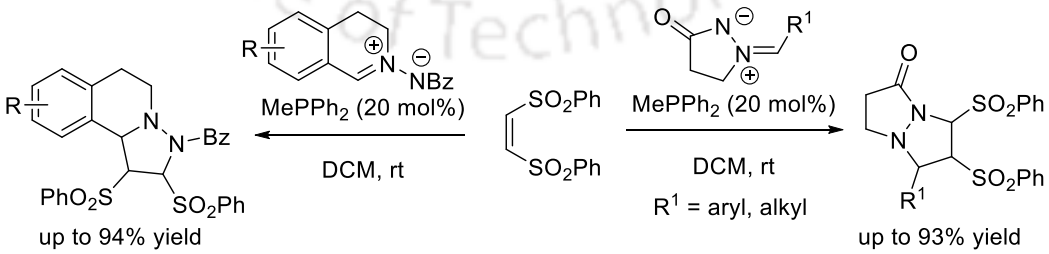
Azomethine imines[16] are relatively stable intermediates which can provide dinitrogen fused heterocycles. Some chiral reactions of azomethine imines are also known because of its stability.

Charette and co-workers disclosed a [3+3] cycloaddition reaction of aromatic azomethine imines with 1,1-cyclopropane diesters (Scheme 1.16).[16a]



Scheme 1.16: Nickel catalyzed [3+3] cycloaddition reaction of azomethine imines

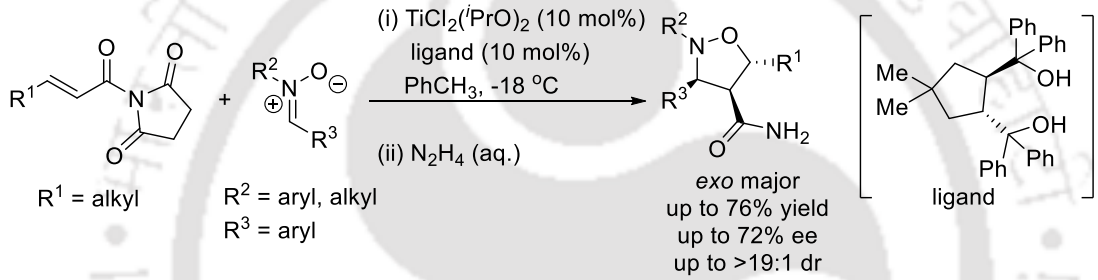
Li *et al.* established the synthesis of dinitrogen fused heterocycles by phosphine-catalyzed [3+2] cycloaddition of azomethine imines with electron deficient alkenes (Scheme 1.17).[16b]



Scheme 1.17: [3+2] Cycloaddition reaction of azomethine imines using phosphine based catalyst

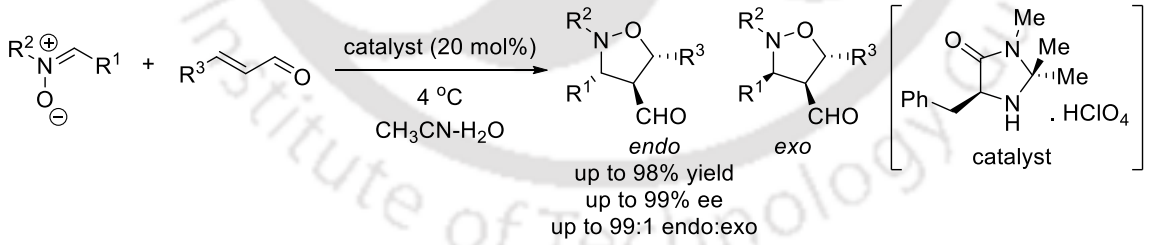
Nitrones[5, 17] can be prepared by condensation of *N*-monosubstituted hydroxylamine/-nitrobenzene and aldehydes/ketones in the presences of a Lewis acid or under heating conditions. Also it can be readily synthesized by oxidations of *N*,*N*-disubstituted hydroxyl amines, secondary amines, *N*-alkyl-*α*-amino acids and imines. Recently, synthesis of nitrones has also been demonstrated by electrolysis of benzyl alcohol and nitrobenzene.[18]

Jørgensen group disclosed 1,3-dipolar cycloaddition reactions of acyclic nitrones with *α*,*β*-unsaturated carbonyl compounds. In the presence of $TiCl_2(^iPrO)_2$ catalyst, *N*-crotonoyl succinimide reacts with nitrone to give the *exo*-product where as in the absence of a catalyst, the *endo*-isoxazolidine was obtained (Scheme 1.18).[17a]



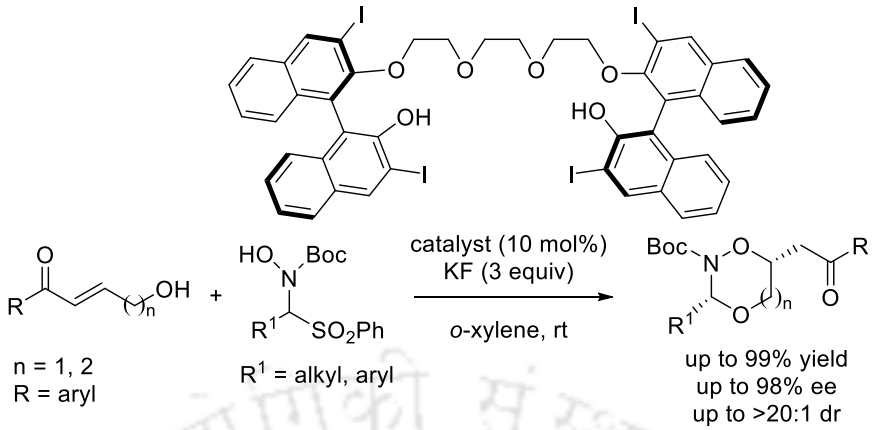
Scheme 1.18: [3+2] Cycloaddition reaction of nitrone

MacMillan and co-workers established the first enantioselective organocatalyzed 1,3-dipolar cycloaddition of nitrone and crotonaldehyde (Scheme 1.19).[17b]



Scheme 1.19: [3+2] Cycloaddition reaction with crotonaldehyde

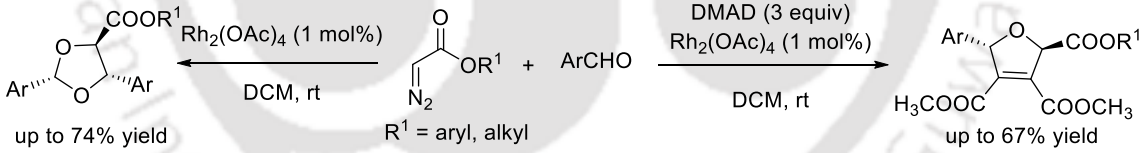
Song *et al*. developed asymmetric cycloaddition reaction between *N*-Boc-*N*-hydroxy amido sulfone (nitrone precursor) and *γ*,*δ*-hydroxyenones and synthesized highly enantio- and diastereo-enriched diaxazinane and dioxazepane heterocycles by using Song's chiral oligo ethylene glycol as a cation binding catalyst and KF as the base to activate the catalyst (Scheme 1.20).[17c]



Scheme 1.20: Asymmetric synthesis of diaxazinane and dioxazepane heterocycles

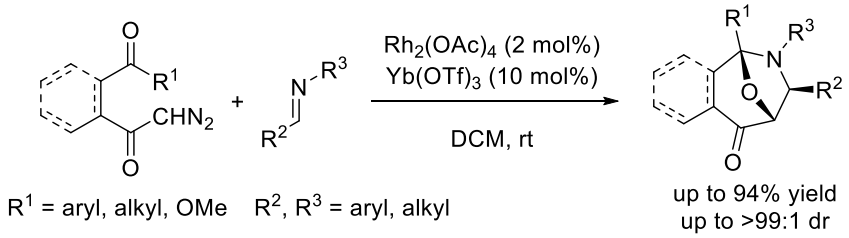
Carbonyl ylide[19] can be generated upon reaction of the carbenes (generated by metal catalysis of diazo compounds) with ketones/aldehydes, by photocatalysis, by intra-molecular hydrogen transfer of 5-hydroxy-4-pyrones or by acid catalysis of hydroxy-3-pyrones. [3+2] cycloaddition reactions containing carbonyl ylides have widely been employed to generate oxygen containing heterocyclic molecules.

Doyle group synthesized dioxolanes and dihydrofurans by rhodium(II)-catalyzed carbonyl ylide formation and reaction with aldehydes and dimethyl acetylene-dicarboxylate (Scheme 1.21). [19a]



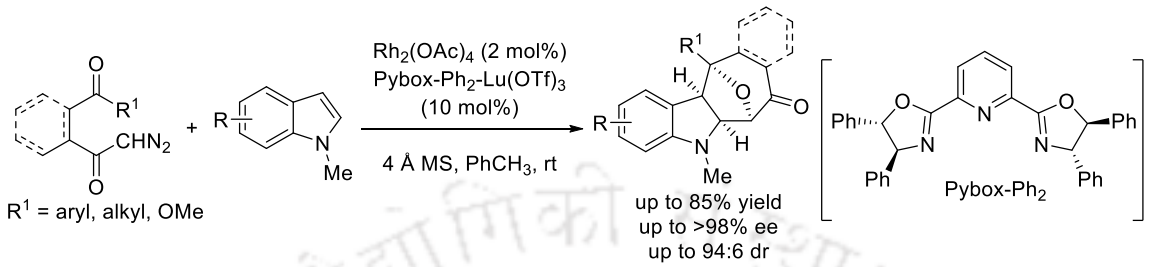
Scheme 1.21: Synthesis of dioxolanes and dihydrofurans from carbonyl ylide

Suga *et al*. established 1,3-dipolar cycloaddition reactions of carbonyl ylides with imines and also shown the effect of Lewis acid in the reaction (Scheme 1.22).[19b]



Scheme 1.22: Reaction of carbonyl ylide with imines

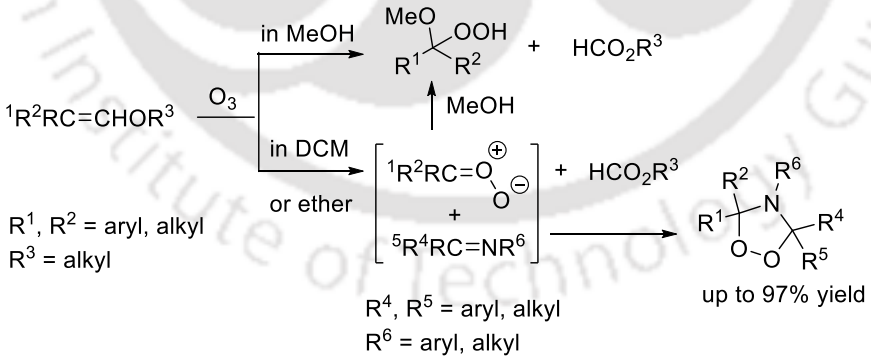
Suga *et al*. disclosed another 1,3-dipolar cycloaddition reactions between cyclic carbonyl ylides that were derived from diazodiketone or diazoketoester precursor and *N*-methylindoles in the presence of chiral Pybox ligand (Scheme 1.23).[19e]



Scheme 1.23: Asymmetric reaction of carbonyl ylides with *N*-methylindoles

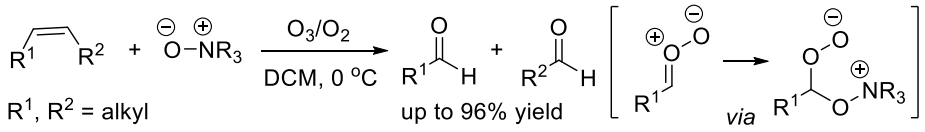
Ozonolysis[20] of alkenes to produce carbonyl compounds is a traditional and influential synthetic transformation. Carbonyl oxide is a reactive 1,3-dipolar species, derived from the ozonolysis of alkenes and may undergo [3+2] cycloaddition reaction with carbonyls, olefins and thioketones.

McCullough *et al.* reported [3+2] cycloadditions of carbonyl oxide (generated from ozonolysis of vinyl ethers) with imines and provided the corresponding 1,2,4-dioxazolidines. 1,2,4-Dioxazolidines undergo ring cleavage reactions on either treatment with base or upon thermolysis (Scheme 1.24).[20c]



Scheme 1.24: [3+2] Cycloadditions of carbonyl oxide with imines

Dussault group reported an excellent approach for the ozonolysis of alkenes in the presence of amine *N*-oxides and it resulted in the direct formation of aldehydes. The reaction also continued well in the presence of methanol (Scheme 1.25).[20d]

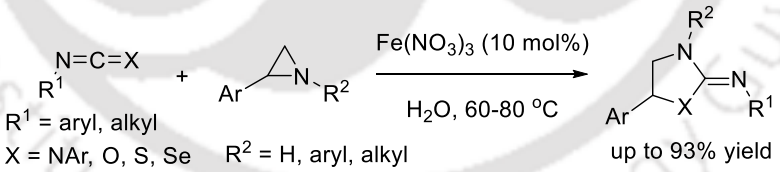


Scheme 1.25: Ozonolysis of alkenes in the presence of amine *N*-oxides

Nitro group has been considered as an important building block in organic synthesis because of its facile transformations into various functionalities as well as its electron-withdrawing effect.[21] Nitro group also acts as a leaving group under suitable reaction conditions. Nitro groups are rarely found in nature and are generally synthesized by nitration reactions using nitric acid. More detailed information of nitro compounds have been provided in chapter 5.

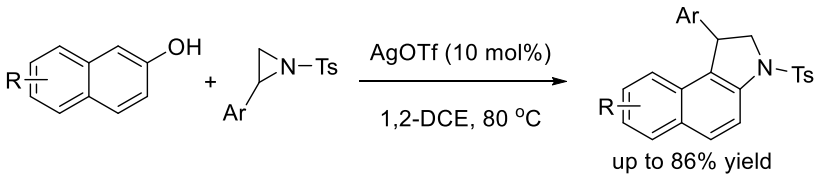
Aziridines,[22] diaziridines, oxa-aziridines, epoxides and cyclopropyls are the stable cyclic precursors which generate 1,3-dipoles in the presence of acid/Lewis acid catalyst.[23-28] Dioxiranes are comparatively less stable and are observed during ozonolysis. Sometimes dioxiranes are synthesized *in situ* and used for epoxidation reaction. Some selective examples have been described here.

[3+2] cycloaddition reaction of aziridines with heterocumulenes which provided five membered heterocycles in the presence of ferric salt in aqueous suspension was established by Punniyamurthy group (Scheme 1.26).[23a]



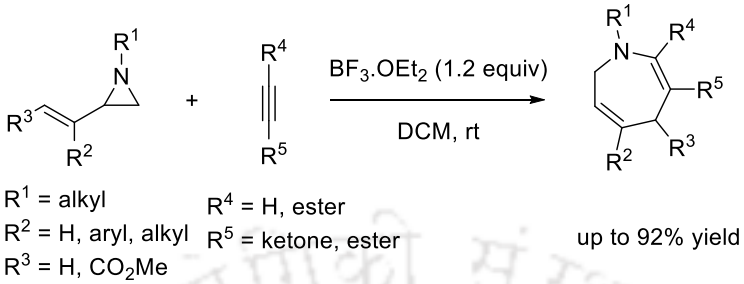
Scheme 1.26: [3+2] cycloaddition reaction of aziridines

Biju and co-workers reported the reaction of aziridines with 2-naphthols in the presence of AgOTf *via* formal [3+2] annulation (Scheme 1.27).[23c]



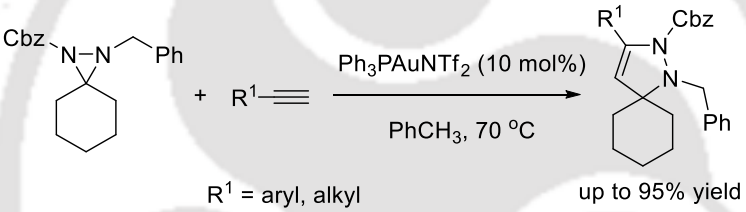
Scheme 1.27: Reaction of aziridines with 2-naphthols

Singh *et al.* reported a metal free *aza*-Claisen type ring expansion of vinyl aziridines achieving the synthesis of seven membered *N*-heterocycles (Scheme 1.28).[23d]



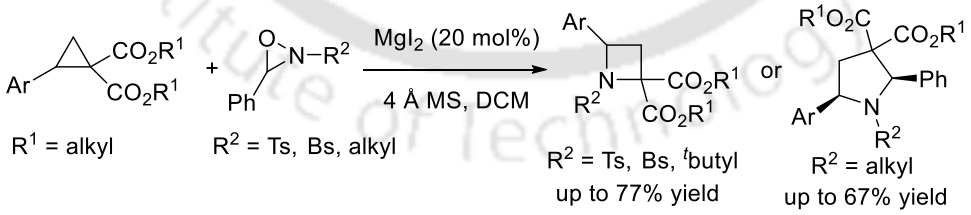
Scheme 1.28: $BF_3.OEt_2$ catalyzed synthesis of seven membered *N*-heterocycles

He and co-workers developed gold(I)-catalyzed synthesis of 3-pyrazolines *via* [3+2] cycloaddition of diaziridine and alkynes (Scheme 1.29).[24]



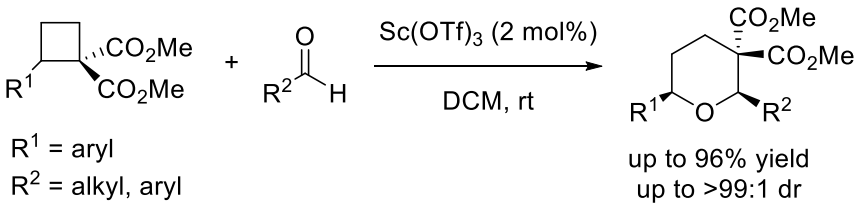
Scheme 1.29: Gold(I)-catalyzed synthesis of 3-pyrazolines

Banerjee group explored *N*-substituent controlled electrophilic *N*-transfer of oxaziridines with donor-acceptor cyclopropanes in the presence of magnesium iodide (Scheme 1.30).[25]



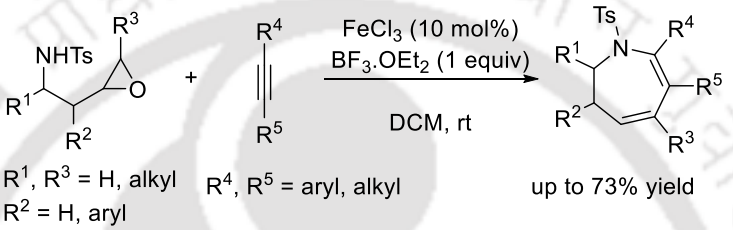
Scheme 1.30: *N*-substituent controlled reaction of oxaziridines

Johnson group synthesized tetrahydropyran derivatives by scandium(III)triflate catalyzed formal [4+2] cycloaddition reaction between donor-acceptor (DA) cyclobutanes and aldehydes (Scheme 1.31).[26]



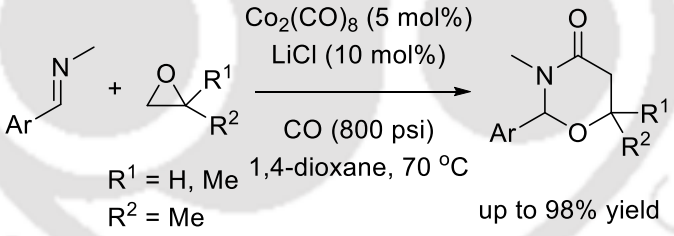
Scheme 1.31: Synthesis of tetrahydropyran *via* [4+2] cycloaddition reaction

Hu *et al.* reported a novel [5+2] cycloaddition reaction of 2-(2-aminoethyl)oxiranes with alkynes using $FeCl_3$ catalyst and $BF_3.OEt_2$ as co-catalysis (Scheme 1.32).[27b]



Scheme 1.32: $FeCl_3$ catalyzed [5+2] cycloaddition reaction

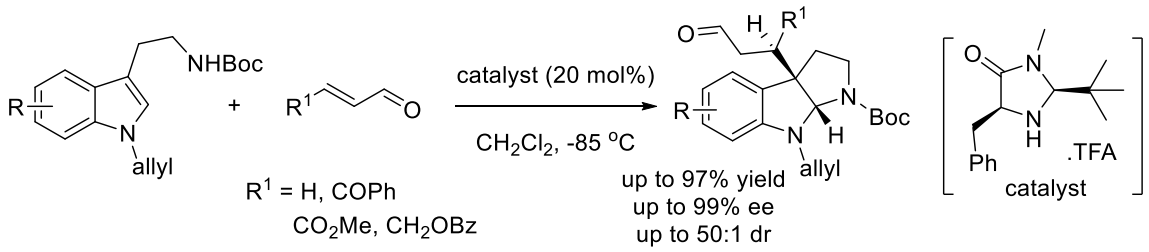
Jia and co-workers developed cobalt catalyzed cyclization of CO, imine and epoxide, and synthesized substituted 1,3-oxazinan-4-ones (Scheme 1.33).[28]



Scheme 1.33: Synthesis of substituted 1,3-oxazinan-4-ones

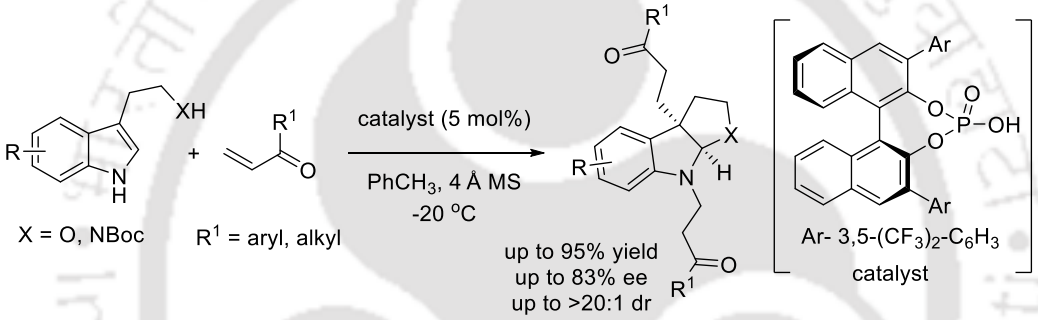
Classical cycloaddition reaction also includes organocatalysis[29] where chiral bases/acids were used as catalyst. Some selective examples have been given below.

MacMillan and co-workers reported enantioselective organocatalytic construction of pyrrolindolines by cascade addition-cyclization strategy and synthesized (-)-flustramine B (Scheme 1.34).[30] The addition–cyclization of tryptamines with *α,β*-unsaturated aldehydes in the presence of imidazolidinone catalyst provided pyrroloindoline adducts in high yield and excellent enantioselectivities.



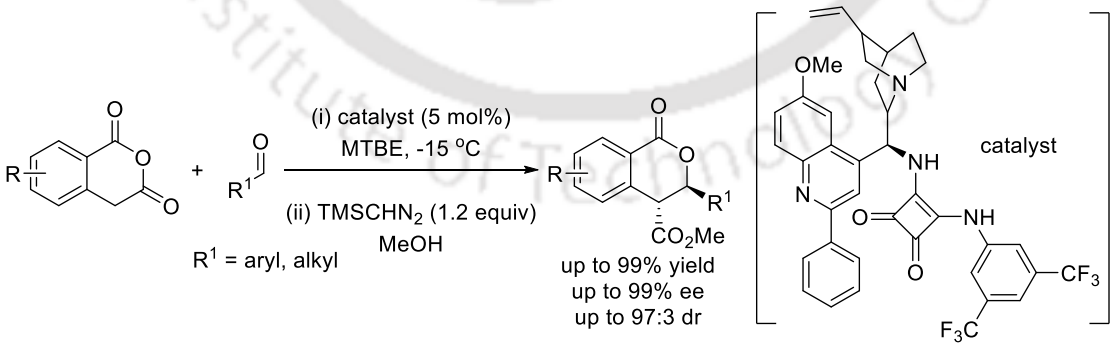
Scheme 1.34: Secondary amine catalysed cyclization reaction

You group developed an enantioselective construction of pyrroloindolines *via* chiral phosphoric acid catalyzed cascade Michael addition-cyclization of tryptamines (Scheme 1.35).[31] Enantio-enriched pyrroloindoline derivatives were obtained from readily available tryptamines and enones with good yields.



Scheme 1.35: Chiral phosphoric acid catalyzed cyclization reaction

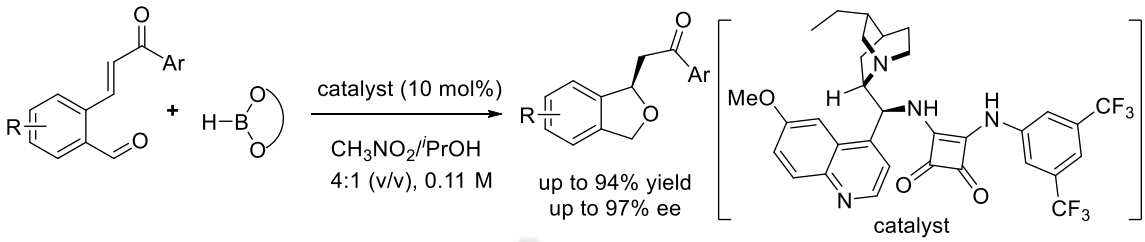
Cornaggia *et al*. established reaction of homophthalic anhydrides with a range of aromatic and aliphatic aldehydes in the presence of bifunctional organocatalyst under mild conditions to give dihydroisocumarins with excellent results (Scheme 1.36).[32]



Scheme 1.36: Bifunctional squaramide catalyzed cyclization reaction

Ghorai and co-workers reported a new strategy for the synthesis of 1-substituted 1,3-dihydroisobenzofurans *via* organocatalytic intramolecular *oxa*-Michael reaction of *o*-

alkoxyboronate. The corresponding alkoxyboronate intermediates have been readily prepared *in situ* from *o*-formyl chalcones and neutral borane (Scheme 1.37).[33]



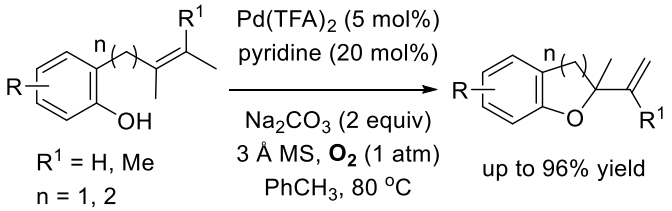
Scheme 1.37: Organocatalytic cyclization *via* alkoxyboronate intermediates

B. Oxidative cyclization reactions

Classically, a number of oxidation[34] catalysts have been described, but most of them involve toxic metals.[35] Recently, numerous oxidative cyclization reactions have been reported with oxidizing sources like TBHP, DTBP, oxone, DDQ, oxygen, molecular iodine, hypervalent iodine etc.[36] Recently, several aerobic oxidation reactions have also been reported in the presence/absence of metal catalyst.[37]

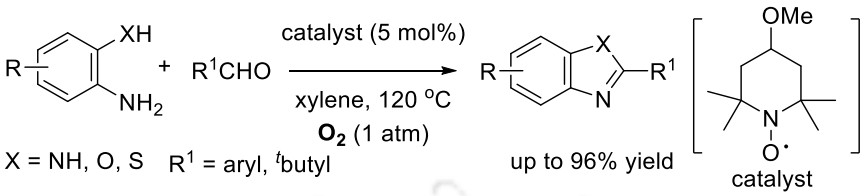
In classical cyclization reactions, C-H bonds were activated and subsequently undergo cyclization with strong or mild acids/bases depending upon the bond energy. But there are some more stable bonds (sp^2 C-H, sp^3 C-H) which require the presence of an oxidant for activation under heating conditions. Bond cleavage occurs after the particular amount of bond dissociation energy been supplied from the external source. Sometimes higher wavelength lights were used in the presence/absence of oxidant for bond cleavage at room temperature. This is the current fantacy for the synthesis of a range of heterocycles.

Stoltz group developed Pd-catalyzed oxidative cyclization reactions under aerobic conditions that proceeded with excellent yields (Scheme 1.38).[38] They also reported an asymmetric version of the reaction by using sparteine ligand and $Ca(OH)_2$.



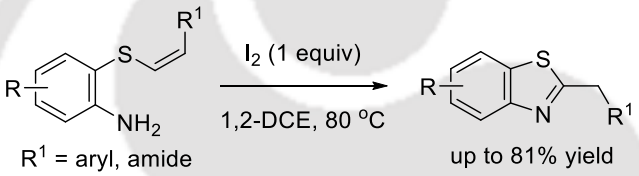
Scheme 1.38: Pd-catalyzed aerobic oxidative cyclization

Han group reported a methodology for the synthesis of 2-substituted benzoxazoles, benzothiazoles and benzimidazoles by an efficient aerobic oxidation reaction catalyzed by 4-methoxy-TEMPO (Scheme 1.39).[39]



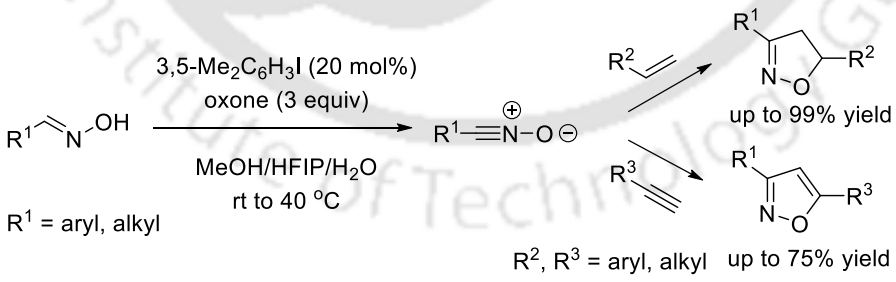
Scheme 1.39: Aerobic oxidation by using 4-methoxy-TEMPO

Tang and co-workers developed a protocol for the synthesis of 2-substituted benzothiazoles by a novel metal-free iodine-mediated intramolecular oxidative cyclization of 2-(styrylthio)anilines (Scheme 1.40).[40]



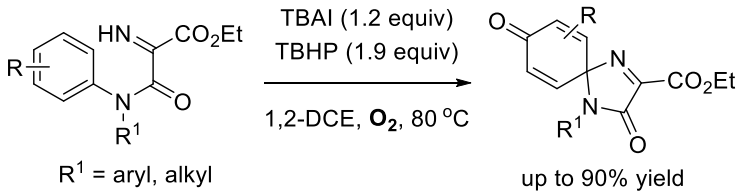
Scheme 1.40: I_2 mediated intramolecular oxidative cyclization

Yoshimura group demonstrated that *in situ* generated hypervalent iodine could oxidize aldoximes to nitrile oxides and generate isoxazolines/isoxazoles after reaction with alkenes/alkynes (Scheme 1.41).[41]



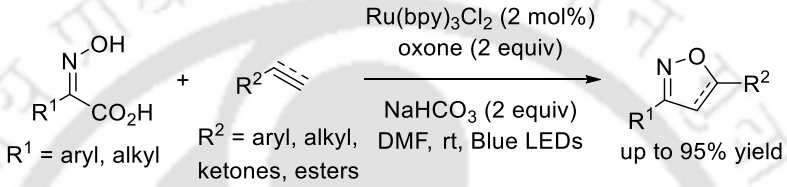
Scheme 1.41: Nitrile oxide generation from aldoximes by hypervalent iodine

Li *et al.* reported TBHP and TBAI mediated metal free radical cyclization of *α*-imino-*N*-arylamides *via α*-(arylaminocarbonyl)iminyl radical intermediate (Scheme 1.42).[42]



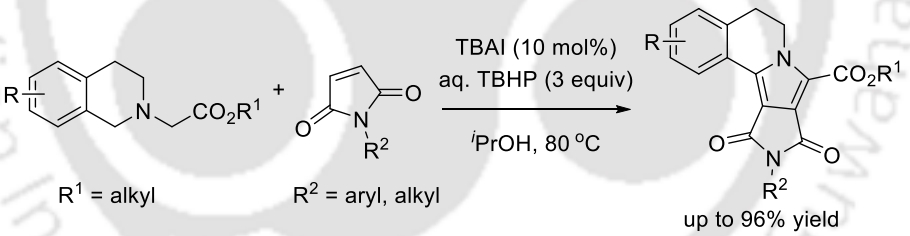
Scheme 1.42: TBHP/TBAI promoted free radical cyclization

Leonori group established a photoredox catalysed reaction for the synthesis of isoxazolines and isoxazoles *via* nitrile oxides, generated from oximes on visible-light irradiation (Scheme 1.43).[43]



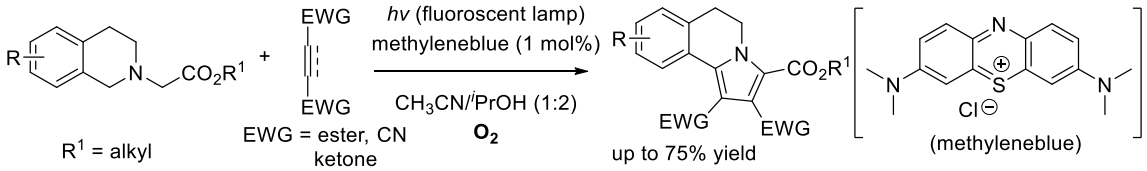
Scheme 1.43: Nitrile oxides generation by photoredox catalysis

Shankaraiah group demonstrated the synthesis of pyrrolo[2,1-*a*]isoquinolines and indolizino[8,7-*b*]indoles using TBHP/TBAI catalyst *via* [3+2] cycloaddition/oxidation/ aromatization sequence (Scheme 1.44).[44]



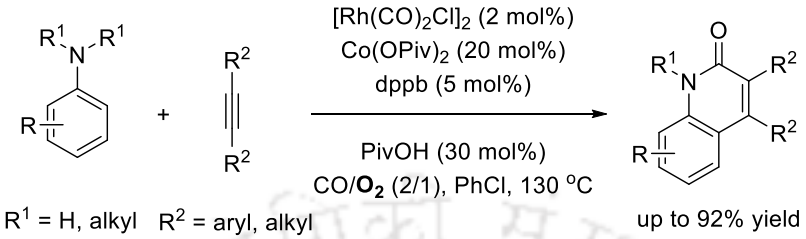
Scheme 1.44: TBHP/TBAI catalyzed [3+2] cycloaddition

Itoh and co-workers developed an efficient method for the synthesis of pyrrolo[2,1-*a*]isoquinoline derivatives using methylene blue catalyst with fluorescent light irradiation under oxygen atmosphere *via* [3+2] cycloaddition/oxidative aromatization reactions (Scheme 1.45).[45]



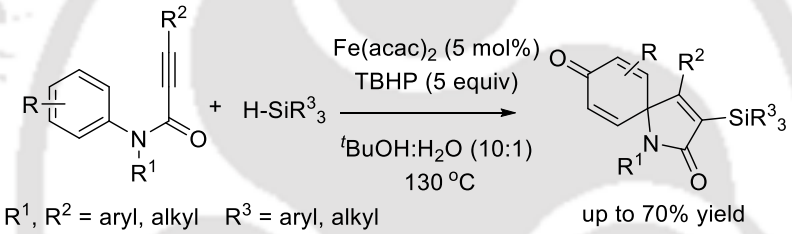
Scheme 1.45: Fluorescent light irradiated [3+2] cycloaddition reaction

Jiao group established rhodium-catalyzed aerobic oxidative C–H cyclization of anilines, alkynes and carbon monoxide for an efficient construction of *N*-heterocycles (Scheme 1.46).[46]



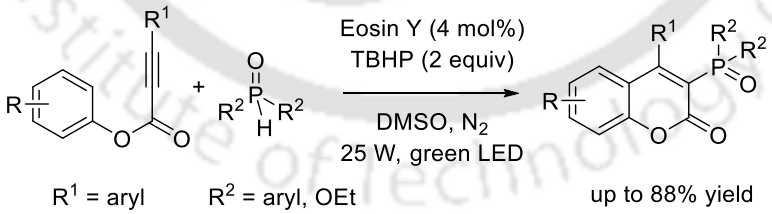
Scheme 1.46: Rhodium-catalyzed aerobic oxidative C–H cyclization

Iron catalyzed oxidative spirocyclization of *N*-arylpropiolamide derivatives with silanes using TBHP as an oxidant was developed by Wu *et al* (Scheme 1.47).[47]



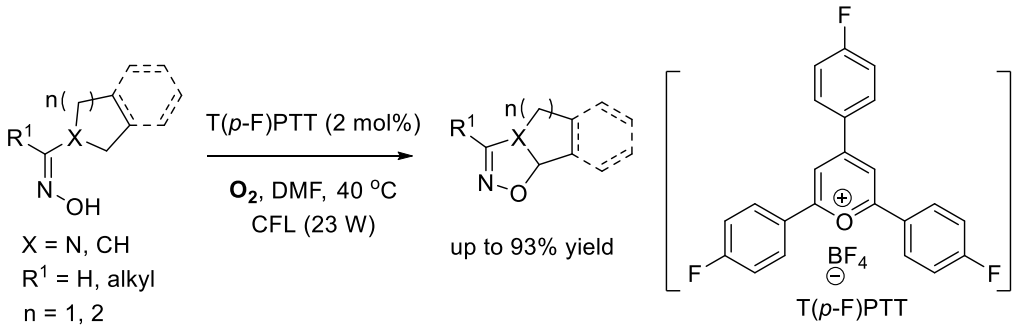
Scheme 1.47: Iron catalyzed oxidative spirocyclization

Xu group established metal free visible-light promoted synthesis of 3-phosphorylated coumarins (Scheme 1.48).[48]



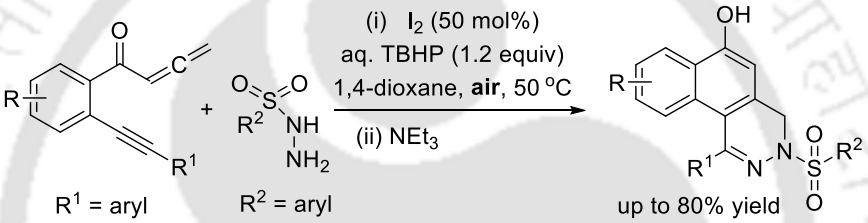
Scheme 1.48: Metal free synthesis of 3-phosphorylated coumarins

A synthesis of 1,2,4-oxadiazolines by organocatalytic oxidative cyclization of amidoximes using molecular oxygen as the green oxidant was reported by Cho group (Scheme 1.49).[49]



Scheme 1.49: Organocatalytic aerobic oxidative cyclization of amidoximes

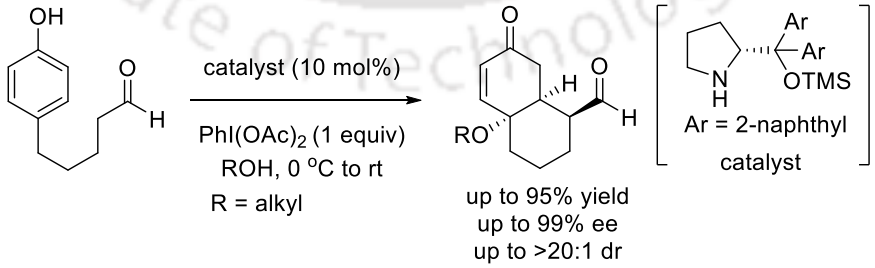
Jiang group developed I_2/TBHP mediated annulation cascade between yne-allenones and sulfonyl hydrazides and synthesized 3,4-dihydrobenzo[*f*]phthalazines *via* one-pot, two-step strategy under metal-free conditions (Scheme 1.50).[50]



Scheme 1.50: Metal-free synthesis of 3,4-dihydrobenzo[*f*]phthalazines

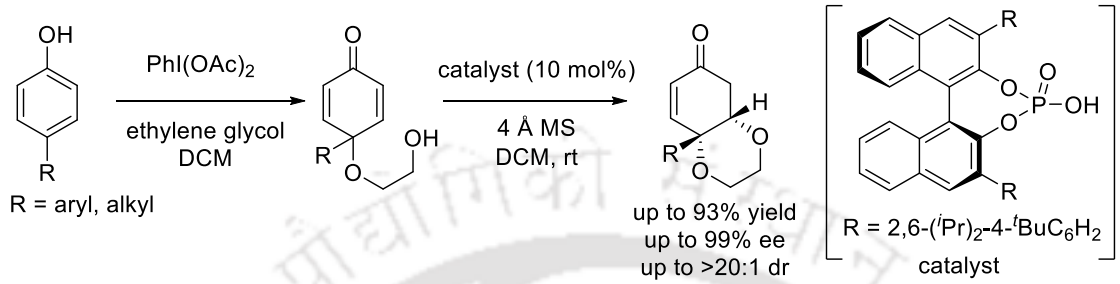
Oxidative cyclization reactions using chiral catalysts:

Gaunt and co-workers developed an enantioselective organocatalytic oxidative dearomatization for the synthesis of fused ring ethers (Scheme 1.51).[51] Under oxidizing conditions, the dearomatization of *ortho*, *para*-substituted phenols formed cyclohexadienones, which further converted to the product *via* amine catalyzed Michael addition reaction.



Scheme 1.51: Organocatalytic oxidative dearomatization reaction

You group reported desymmetrization of cyclohexadienones *via* Brønsted acid catalyzed enantioselective *oxa*-Michael reaction (Scheme 1.52).[52] Dearomatization process provided a facile construction of optically active cyclic and polycyclic compounds in one pot strategy.



Scheme 1.52: Desymmetrization reaction of cyclohexadienones

The literature survey revealed that hererocyclic compounds had been synthesized in various methodologies as well as utilized in different areas. Still continuous intrest has been focused on the synthesis of various heterocycles and their novel application towards the therapeutic uses such as antibacterial, antifungal, anti-inflammatory, muscle relaxants, anti-HIV activity, antimalarial, anticancer, insecticidal agents etc. Therefore, the exploration of a variety of methods with suitable reactants for the construction of new heterocyclic molecules is still required. Infact, 59% of US FDA-approved drugs cover at least one nitrogen containing heterocycles. Thus we became interested in the convenient syntheses of substituted heterocycles and in the following chapters, few new methodologies and syntheses of useful heterocycles have been described.

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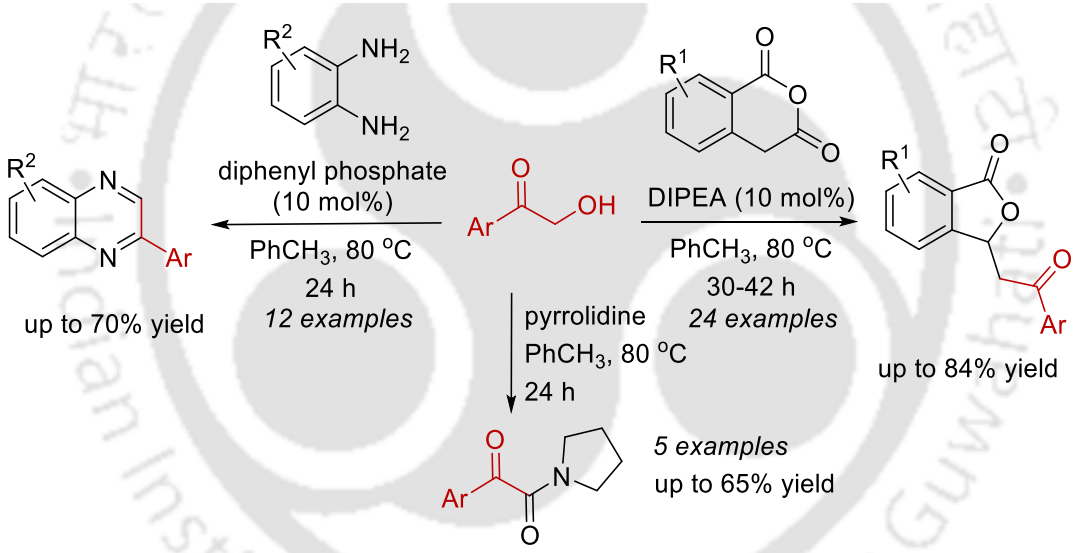
Chapter 2

Synthesis of Heterocycles via Aerobic Oxidation of 2-Hydroxyacetophenones



2.1 Introduction

The selective oxidation of alcohols to the corresponding carbonyl compounds is considered as one of the essential organic transformations and widely performed in laboratory as well as on industrial scale. Traditionally, stoichiometric amounts of toxic organic or inorganic reagents have been used for such transformations.[1] Many of these processes have demerits like high reagent cost, operational complexity and production of harmful by-products. During the last two decades, there has been a tremendous development in this field and consequently, the catalytic versions of the reaction using environment-friendly oxidants have been identified.[2]

The direct oxidation of alcohol compounds with molecular oxygen is rare due to the high energy barrier involved in the electron transfer from alcohol to oxygen and *vice versa*.[2] For molecular oxygen, which has a triplet ground state, this high-energy barrier is nature's way of protecting organic compounds from destructive oxidation.[3] Some oxidation reactions need stoichiometric amount of reagents such as dimethyl sulfoxide, lead acetates, chromium and manganese oxide. But aldehyde, on exposure to oxygen or air, gets slowly converted to the corresponding peracid, which further reacts with the aldehyde to form the normal acid.[4] In fact, all the alcohols have a different rate of oxidation depending upon their stability. Some catalytic aerial oxidation reactions using transition metals as reported by Stahl, Sigman, Stoltz, Bäckvall, Katsuki and Taylor are noteworthy.[5] Few metal-free aerial oxidative approaches have also been reported with *tert*-butyl hydroperoxide (TBHP), H_2O_2, DMSO, TEMPO etc. as oxidants.[6] We presumed that activated alcohols like α-hydroxyketones might be aerially converted to the corresponding aldehydes *i.e* 2-ketoaldehydes in small equilibrium quantities. If this *in situ* formed aldehyde could be trapped by other reagents or reacted with other compounds in catalytic condition, then this equilibrium could be shifted and overall high yield of the final product could be attained. We were particularly interested in the oxidation of 2-hydroxyacetophenones (**1**) as the resulting products 2-ketoaldehydes (**2**) are potentially valuable synthetic intermediates for the synthesis[5i] of crotonates, quinoxalines, dihydropyrazines, imidazoles,[7a] piperidines,[7b] furans,[7c] α-ketoimines, α-

ketoamides[8] and many other important class of compounds. Therefore, we planned to react the *in situ* formed 2-ketoaldehydes with reactive partners like homophthalic anhydride,[9] *o*-phenylenediamine, pyrrolidine and stabilized ylide which could provide phthalide,[10] quinoxaline,[11] α-ketoamide[8] and olefin[5j] respectively. These are important core motifs present in various biologically active natural products[10e, 12] (Figure 2.1).

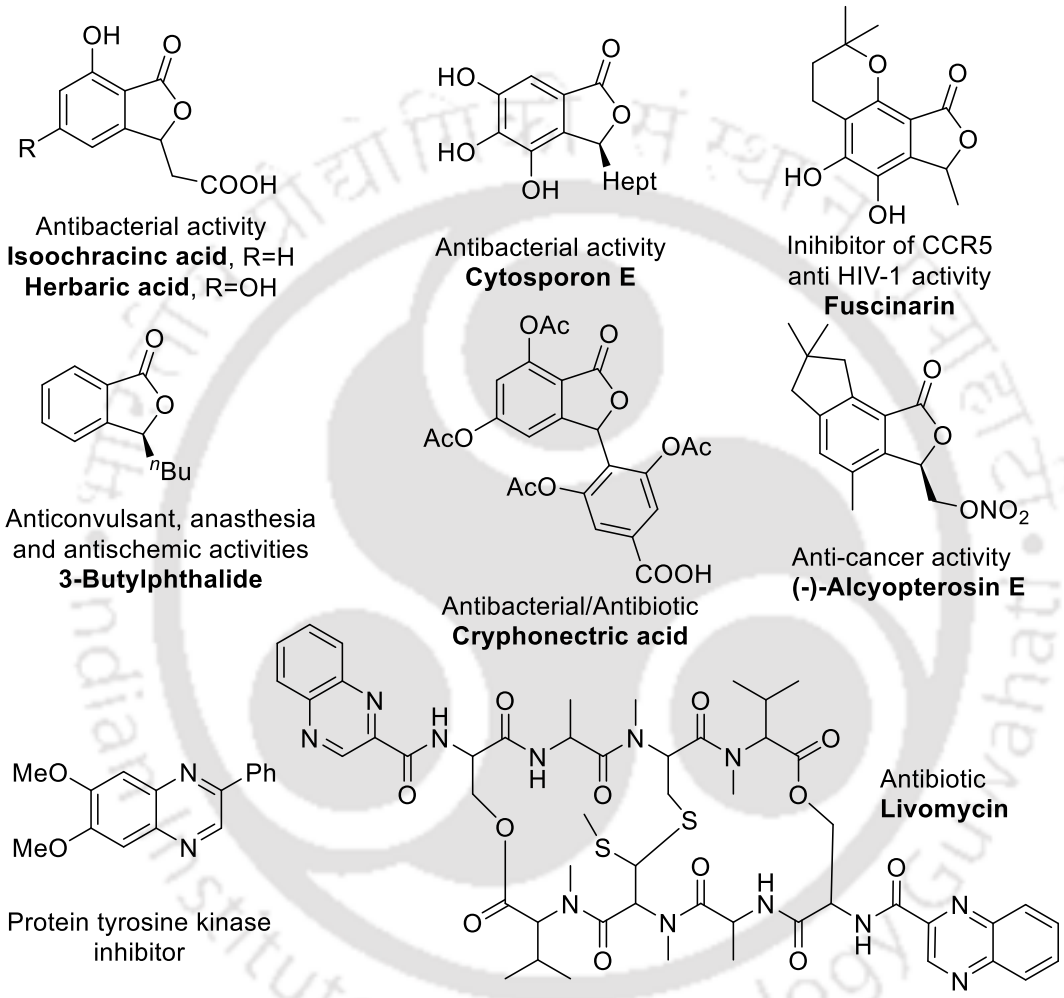


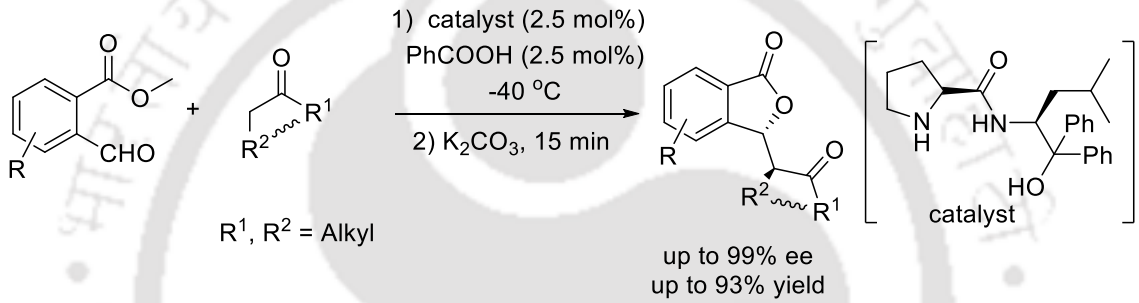
Figure 2.1: Some important biologically active natural products containing phthalide and quinoxaline as core structure

Owing to the impressive biological activities, enormous emphasis has been given on the efficient construction of phthalides, quinoxalines and α-ketoamides. Previous reports for the oxidation of alcohols and 2-hydroxyacetophenones have also been studied thoroughly for synthesis of those heterocycles.

2.2 Known methods towards synthesis of phthalide, quinoxalines and *α*-ketoamide

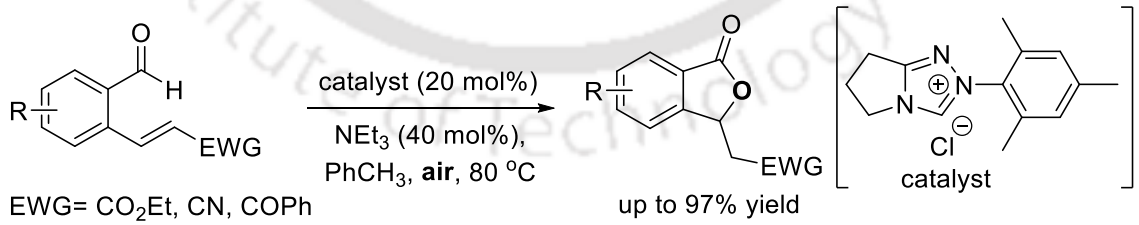
In the past decades, phthalides, quinoxalines and *α*-ketoamides have been used as an effective building block in organic synthesis, thus a large number of synthetic strategies have been developed for their preparation. Some of the representative examples have been shown in this section.

Zhang *et al*. accomplished organocatalytic enantioselective aldol-lactonization reaction by using chiral (L) prolinamide alcohol catalyst and synthesized high optically active 3-substituted phthalides under mild reaction conditions (Scheme 2.1).[10e]



Scheme 2.1: Synthesis of phthalide using chiral organocatalyst

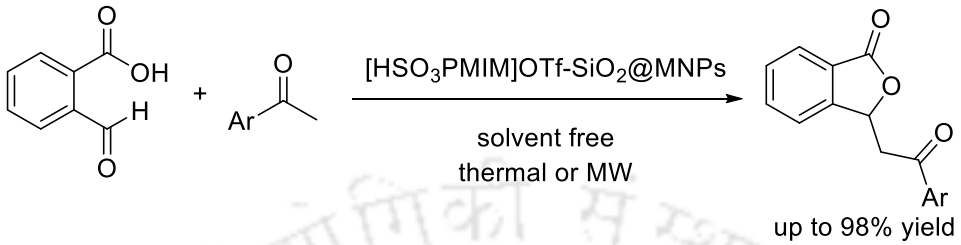
Youn group developed the synthesis of 3-substituted phthalides from 2-alkenyl-benzaldehydes by NHC-catalyzed domino oxidation/oxa-Michael addition reaction. This methodology provided a broad substrate scope and extensive functional group tolerance in economical, sustainable and eco-friendly route (Scheme 2.2).[10f]



Scheme 2.2: Synthesis of phthalide using NHC catalyst

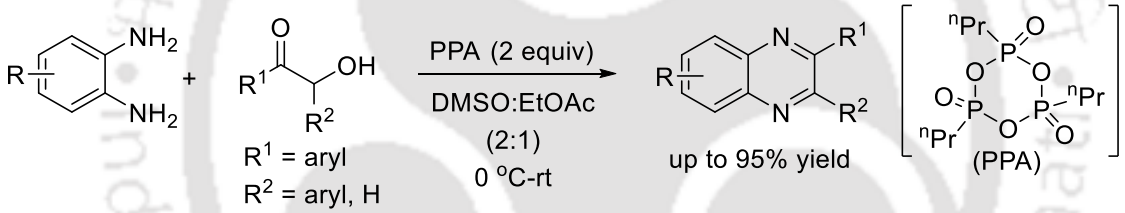
1-Methyl-3-(propyl-3-sulfonic acid) imidazolium triflate supported on magnetic nanoparticles ([HSO_3PMIM]OTf–SiO_2@MNPs) catalyzed reaction of 2-formylbenzoic acid and acetophenone for the preparation of isobenzofuran-1(3*H*)-one derivative, was

achieved by Khosropour and co-workers (Scheme 2.3).[10g] The catalyst could be easily separated by an external magnet and could be reused six times without significant loss of its activity under thermal conditions and MW irradiation.



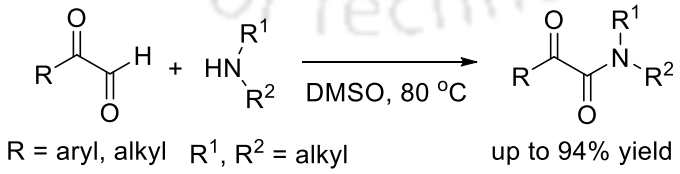
Scheme 2.3: Synthesis of phthalide catalyzed by [HSO_3PMIM]OTf–SiO_2@MNPs]

Rangappa group developed propylphosphonic anhydride–DMSO mediated oxidation–condensation reaction for the synthesis of functionalized quinoxalines with broad substrate scope and in high yield (Scheme 2.4).[11e]



Scheme 2.4: Synthesis of quinoxalines from α-hydroxy ketones

DMSO catalyzed metal-free oxidative amidation of 2-oxoaldehydes for the synthesis of α-ketoamide was illustrated by Ahmed and co-workers (Scheme 2.5).[8b] They have also reported the one-pot synthesis of α-ketoamides from acetophenones by utilizing iodine as oxidant.

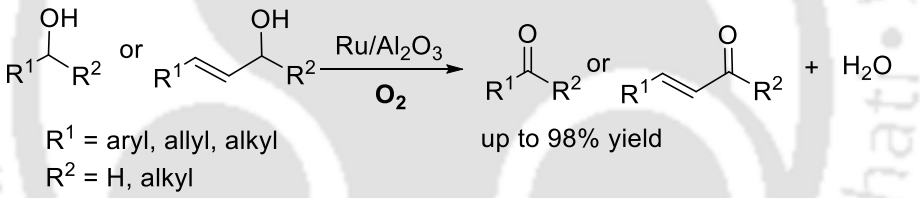


Scheme 2.5: Synthesis of α-ketoamide

2.3 Known methods for the oxidation of alcohols and 2-hydroxyacetophenones

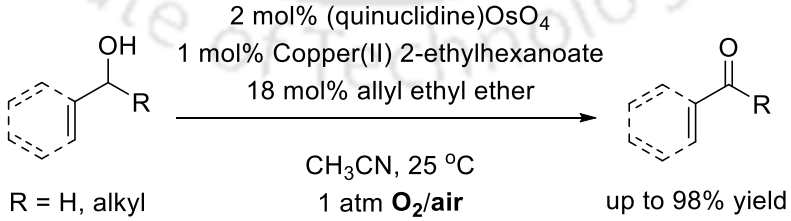
Oxidation reactions play an important role in organic synthesis and molecular oxygen is an ideal oxidant for both economic and ecological reasons. The use of molecular oxygen as a stoichiometric oxidant in combination with a catalytic amount of metal has exceptional practical advantages for applications in organic synthesis. In the past few years, metal-catalyzed oxidative kinetic resolution reactions provided excellent levels of enantioselectivity using ambient air/oxygen as the stoichiometric oxidant. However, catalytic oxidation of alcohols to carbonyl compounds has attracted much attention both in the laboratory and industrial synthetic chemistry.

In 2002, Mizuno and co-workers disclosed Ru/Al_2O_3 heterogeneous catalyzed oxidation of alcohols. Primary and secondary allylic alcohols afforded the corresponding enals or enones without intramolecular hydrogen transfer or geometrical isomerization of double bonds. (Scheme 2.6).[13a]



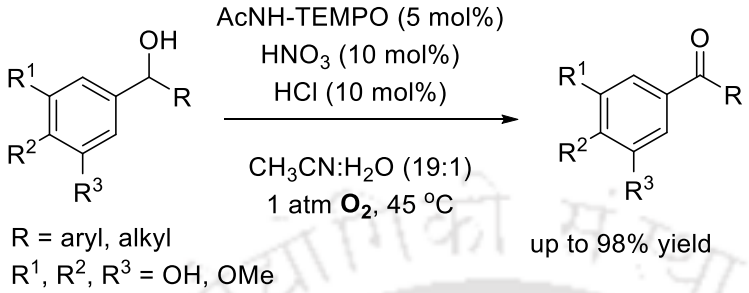
Scheme 2.6: Oxidation of alcohol using Ru/Al_2O_3

Aerobic oxidation of primary and secondary allyl and benzyl alcohols was described by Brown group using catalytic amount of copper salts and osmium tetroxide, activated with quinuclidine and prereduced with an alkene (allyl ethyl ether) (Scheme 2.7).[13b]



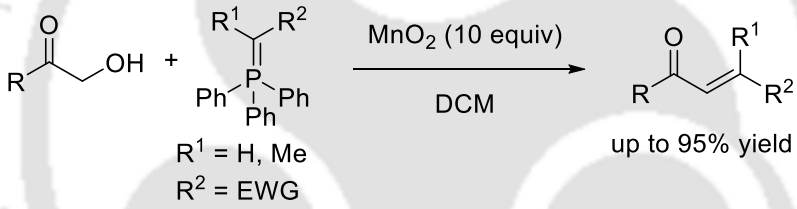
Scheme 2.7: Aerobic oxidation of alcohol

Stahl and co-workers disclosed an efficient organocatalytic method for chemoselective aerobic oxidation of 2° alcohols in the presence of unprotected 1° alcohols, which are prevalent in lignin model compounds. (Scheme 2.8).[6i]



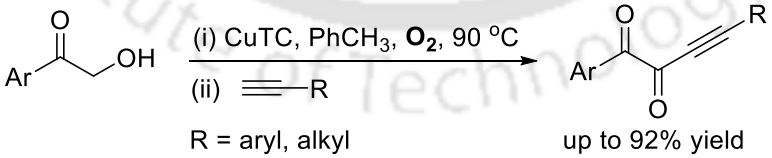
Scheme 2.8: Metal-free aerobic oxidation of lignin models

Taylor group explored the *in situ* oxidation–Wittig reaction of *α*-hydroxyketones using 10 equivalents of manganese dioxide as an oxidant. The highly stereoisomeric (*E* isomer) products were obtained with high yields (Scheme 2.9).[5i]



Scheme 2.9: *In situ* oxidation–Wittig reactions using *α*-hydroxyketones

Jiang group exploited an efficient copper-catalyzed one-pot synthesis of ynediones through the oxidative coupling of alkynes with *α*-hydroxy ketones. The distinct mechanism was proved by control experiments, *in situ* IR measurements and isotopic labelling experiments. (Scheme 2.10).[5f]



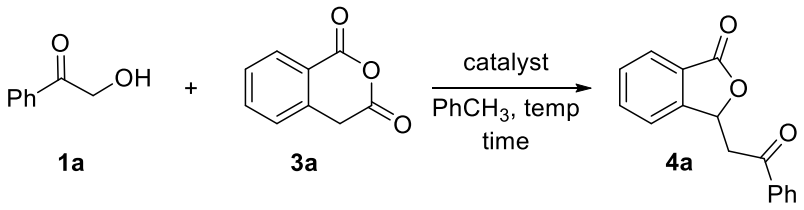
Scheme 2.10: Oxidative coupling of *α*-hydroxy ketone with terminal alkyne under O_2

2.4 Result and discussion

We realized that activated alcohols like *α*-hydroxyketones might be aerobically converted to the corresponding aldehydes i.e. 2-ketoaldehydes in small equilibrium quantities. If this *in situ* formed aldehyde could be domesticated by different reagents or reacted with another reactive partner in catalytic conditions, then this equilibrium could be shifted and overall high yield of the final product could be attained. To test the concept, initially, we heated 2-hydroxyacetophenone **1a** in toluene to 80 ^{o}C for 30 hours. Interestingly, we got some amount of benzaldehyde[14] (detected by TLC and GC) which could be formed by aerial oxidation of 2-hydroxyacetophenone to phenylglyoxal **2a** followed by decarboxylation.

Encouraged by this interesting outcome, we have planned to perform the reactions of 2-hydroxyacetophenone with other compounds under this condition. Initially, homophthalic anhydride was chosen as the reaction partner. Since homophthalic anhydride **3a** needed to be activated with base, we screened different bases for this reaction (Table 2.1). No reaction was observed with potassium carbonate but 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided 20% yield of the phthalide product **4a** (confirmed by X-ray crystallography). 1,4-Diazabicyclo[2.2.2]octane (DABCO) as catalyst provided an increased yield (40%) of the product (entry 3). Also, a similar yield was observed with 1,1,3,3 tetramethylguanidine (TMG) (entry 4). Slightly higher yields were obtained with 4-dimethylaminopyridine (DMAP) and diisobutylamine (entries 5-6). Interestingly, triethylamine was found to be a better catalyst providing 60% yield of the product (entry 7). Finally, DIPEA was found to be best catalyst to afford the maximum yield i.e. 70% of the product. The yield was unaffected but reaction rate was increased with more loading of the catalyst (entries 9-10). Surprisingly, yield of the product was decreased and that of the by-product (benzaldehyde) was increased when the reaction temperature was raised up to 100 ^{o}C (entry 11). To test the role of atmospheric oxygen, the reaction was tried under oxygen atmosphere by using oxygen balloon. Although the yield has not been improved, the reaction rate got increased (entry 12).

Table 2.1: Catalyst screening

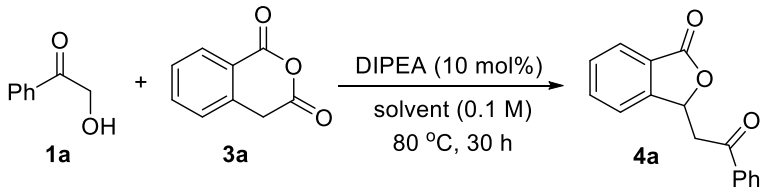


entry[a]	catalyst (mol%)	temperature	time (h)	yield (%)[b]
1	K_2CO_3 (10)	80 °C	30	0
2	DBU (10)	80 °C	30	20
3	DABCO (10)	80 °C	30	40
4	TMG (10)	80 °C	30	40
5	DMAP (10)	80 °C	30	50
6	$(^t Bu)_2NH$ (10)	80 °C	30	50
7	Et_3N (10)	80 °C	30	60
8	**DIPEA (10)**	**80 °C**	**30**	**70**
9	DIPEA (20)	80 °C	22	70
10	DIPEA (30)	80 °C	18	70
11	DIPEA (10)	100 °C	18	60
12[c]	DIPEA (10)	80 °C	18	70

[a] Reactions were carried out with 0.025 mmol of **1a** and 0.025 mmol of **3a** in 0.25 mL toluene. [b] Isolated yield after silica gel column chromatography. [c] Reaction under an oxygen atmosphere.

Then different solvents were screened in presence of DIPEA (Table 2.2). Only 20% of the product was observed with DCE solvent (entry 2). Other solvents such as CH_3CN, DMSO and DMF, provided only a trace amount of the desired product (entries 3-5). In ethanol, only 25% of the product was isolated. Many nonpolar solvents like benzene, chlorobenzene, mesitylene etc were tried to improve the yield of the reaction (entries 7-11). But toluene was found to be the best in comparison to others.

Table 2.2. Solvent Screening



entry[a]	solvent	yield (%)[b]
1	**$PhCH_3$**	**70**
2	DCE	20
3	CH_3CN	0
4	DMSO	0
5	DMF	<10
6	EtOH	25
7	C_6H_6	30
8	PhCl	30
9	$PhCF_3$	60
10	xylene	50
11	mesitylene	50

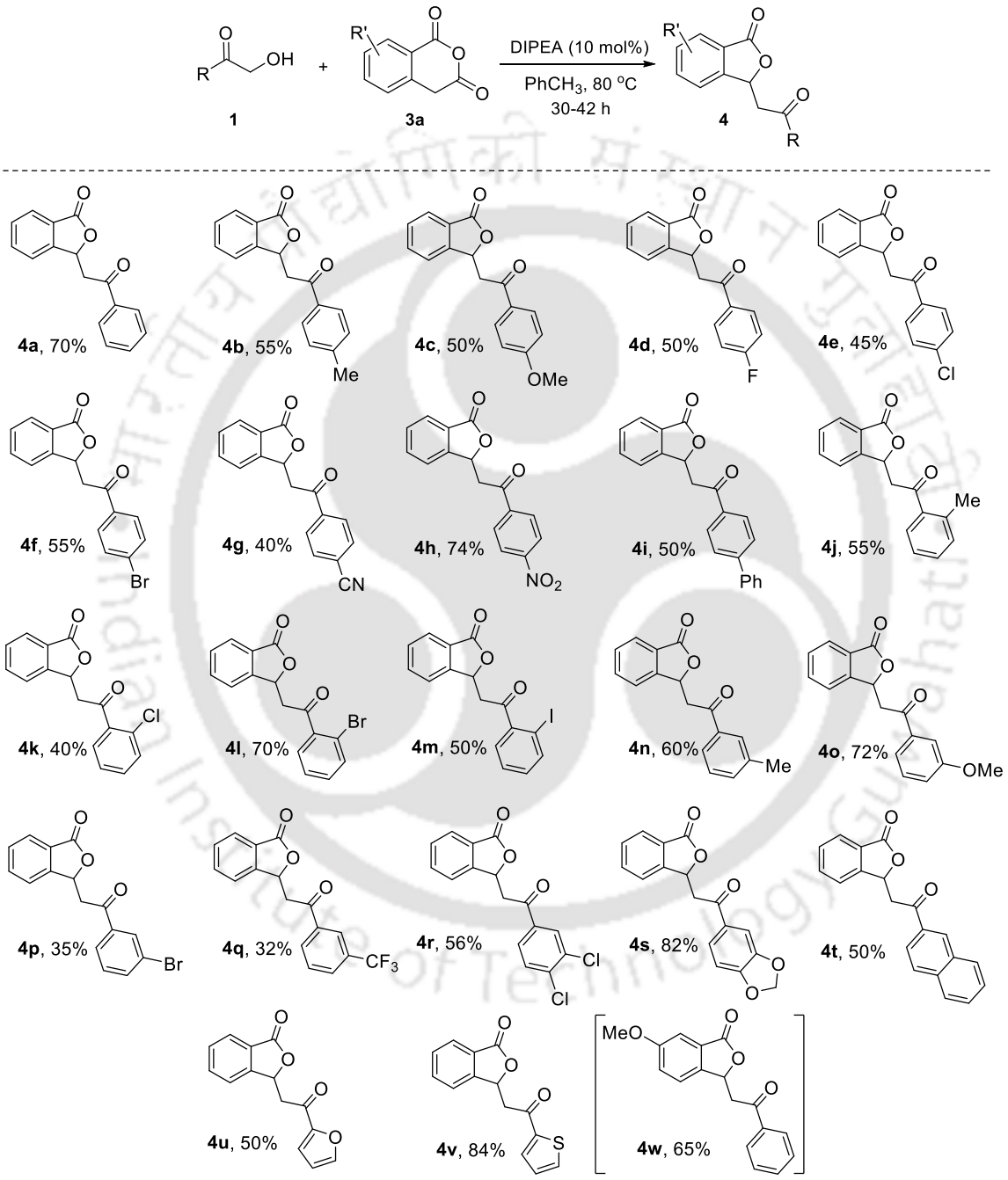
[a]Reactions were carried out with compound **1a** (0. 025 mmol) and **3a** (0.025 mmol) in 0.25 mL solvent. [b]Isolated yield after silica gel column chromatography.

2.5 Substrate scope of phthalides

After identifying the optimized conditions, the scope of the reaction was studied. Initially, a variety of 2-hydroxyacetophenones **1** was examined with homophthalic anhydride **3a** (Scheme 2.11). Pleasingly, different electron-withdrawing and electron-donating groups in the *ortho*, *meta*, and *para* positions of the aryl group were engaged in the reaction and moderate to good yields were achieved with most of the substrates. *p*-Tolyl and *p*-anisyl derivatives reacted well and provided the products **4b** and **4c** in good

yields i.e. 55% and 50% respectively. 4-Halo substituted hydroxyacetophenones also employed in the reaction and delivered the corresponding products in good yields. 4-Cyano containing product **4g** was isolated with a moderate yield.

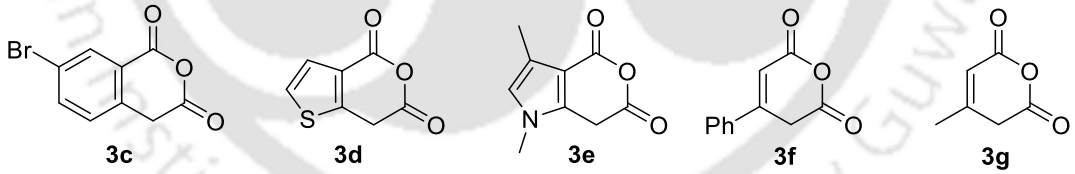
Scheme 2.11: Scope of phthalide with different 2-hydroxyacetophenones [a,b]



[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **3** in 1 mL toluene. [b] Isolated yield after silica gel column chromatography.

Also, a good yield of 74% was attained with hydroxyacetophenone **1h** having 4-nitro group. Incorporation of the biphenyl group did not change the outcome of the reaction. Delightfully, different *ortho*-tolyl and halo substituted hydroxyacetophenones were studied and here too, good yields were obtained. 2-Hydroxyketones containing *meta*-substituted aryl group, were also screened and the products **4n-q** were attained with acceptable yields. Interestingly, better yield (72%) was obtained for the compound **4o** with 3-methoxy substitution. Disubstituted hydroxyacetophenones such as **1r** and **1s** could also be employed and the products **4r-s** were isolated in acceptable yields. The reaction also worked well with hydroxyketone **1t** having 2-naphthyl group and delivered the product **4t** with 50% yield. Our reaction was also suitable for heteroaryl hydroxyketones. Gratifyingly the highest yield of 84% was obtained with 2-thieyl containing hydroxyketone **1v**. 2-Hydroxyacetone **1w** was also employed in the reaction, but no desired product was formed.

Then we focused on the employment of other substituted homophthalic anhydrides. 7-Methoxy substituted anhydride **3b** delivered the corresponding product **4w** in 65% yield. 7-Bromo substituted anhydride **3c** reacted slowly with **1a** but an inseparable mixture of product and **1a** was obtained. Unfortunately, other anhydrides (e.g. **3d-g**) did not deliver the desired products under the same reaction conditions (Scheme 2.12).

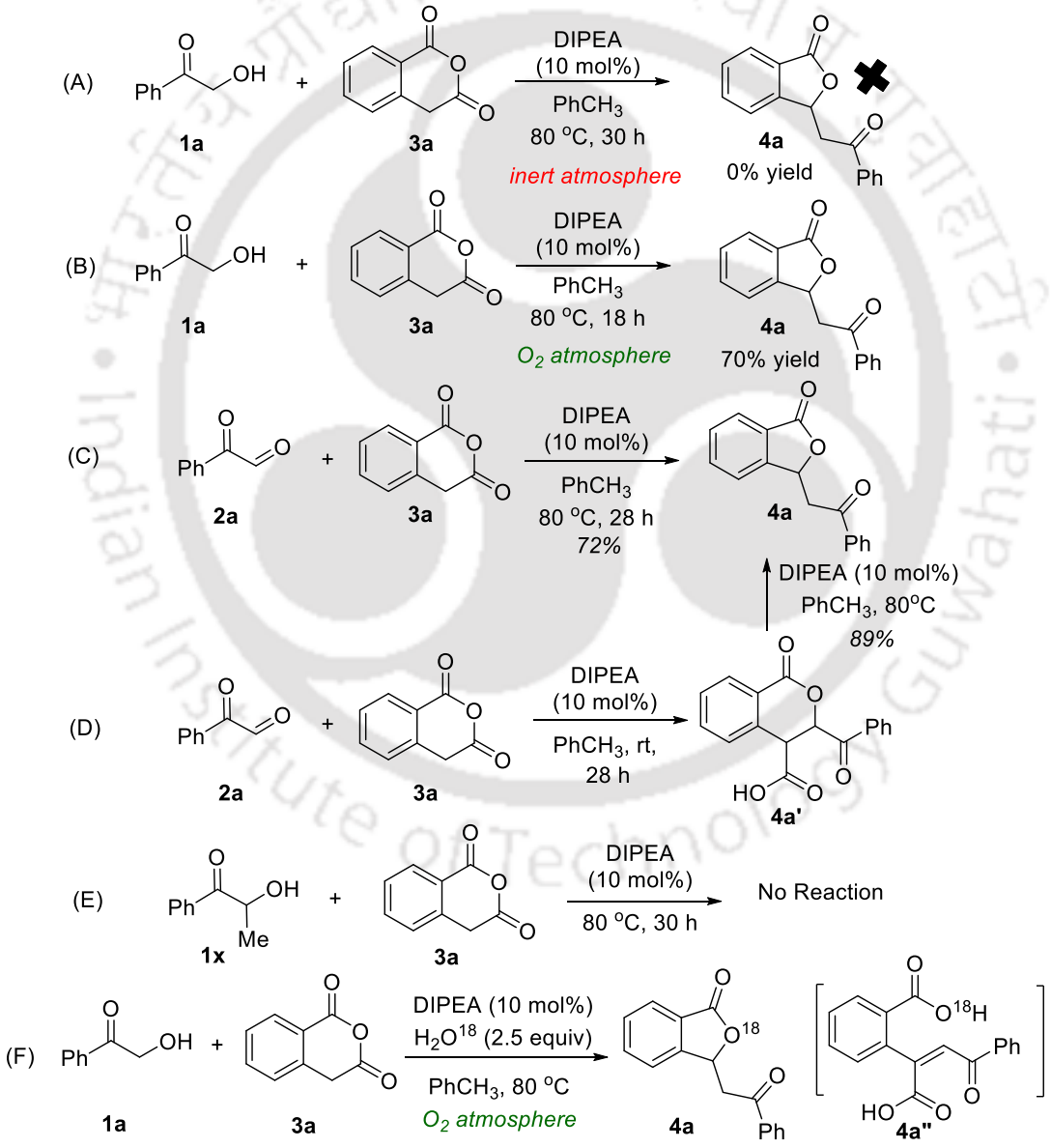


3c **3d** **3e** **3f** **3g**

Scheme 2.12: Unproductive anhydrides

Role of base and oxygen: To further investigate the aerial oxidation of 2-hydroxyacetophenone (**1a**), we performed a few controlled experiments (Scheme 2.13). When the reaction of 2-hydroxy-acetophenone (**1a**) and homophthalic anhydride (**3a**) was carried out in the inert atmosphere for 30 hours, no product was detected which indicated the importance of air for the reaction. To clarify the requirement of air environment, the same reaction between **1a** and **3a** in the presence of oxygen atmosphere was conducted. Interestingly, reaction rate got remarkably enhanced and 70% yield of **4a**

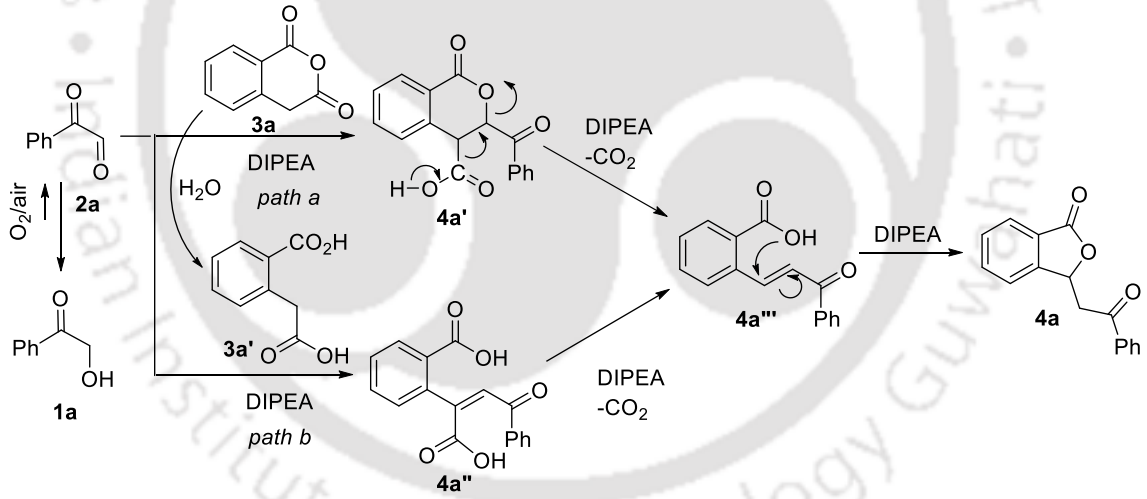
was observed in only 18 hours. Thus it proves that oxygen in air is the actual oxidant. To confirm that phenylglyoxal (**2a**) is the actual reactive intermediate, we carried out a reaction between **2a** and **3a** and product **4a** was formed in 72% yield. We synthesized intermediate **4a'** from **2a** and **3a** at room temperature[9] (observed in mass spectrometry) and proceed under standard reaction condition without purification. Interestingly, we obtained the desired product **4a**. Also, we observed that DIPEA does not participate in the oxidation process. Hydroxyl ketone **1x** (secondary alcohol) was also employed in the reaction with **3a** in presence of DIPEA catalyst; however no reaction occurred.



Scheme 2.13: Controlled experiments and Screening of **1x**, **2a**

Role of Moisture: To further check whether moisture in the air also plays a role in the phthalide (**3**) formation, a reaction in the presence of H_2O^{18} (2.5 equiv) was performed (Scheme 2.13f). Indeed, in the product **4a**, O^{18} incorporation was found that was confirmed by mass spectrometry. Thus the possibility for the formation of an intermediate **4a′′** was envisaged that could be generated *via* aldol condensation between homophthalic acid **3a′** (hydrolyzed form of homophthalic anhydride) and phenylglyoxal.

Based on the experiments, a plausible mechanism has been depicted in Scheme 2.14 for the formation of phthalides. It reveals that DIPEA catalyzes the reaction either between homophthalic anhydride (**3a**) and small equilibrium quantities of phenylglyoxal (**2a**) (*path a*) or between homophthalic acid (**3a′**) and phenylglyoxal **2a** (*path b*) that provides **4a′′′** on decarboxylation of corresponding intermediates **4a′** and **4a′′** respectively. Finally, DIPEA facilitates the conjugate addition of carboxylic acid functionality to enone moiety in **4a′′′** to afford phthalide **4a**.



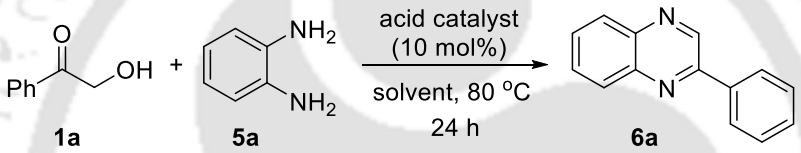
Scheme 2.14: Proposed mechanism for phthalide synthesis

Different alcohols like 2-nitroethanol **1y** and ethyl 2-hydroxyacetate **1z** were also examined for aerobic oxidation. Unfortunately, no fruitful result was observed.

Then we became curious about the direct synthesis of quinoxalines **6** by the reaction of 2-hydroxyacetophenone (**1a**) with *o*-phenylenediamine (**5a**). Bioactivity and uses of quinoxaline derivatives have been discussed earlier (Figure 2.1). The previous reports on quinoxalines synthesis include oxidative reaction of 2-hydroxyacetophenones

with *o*-phenylenediamine but either a metal catalyst in the presence of air or a stoichiometric oxidant such as MnO_2 had been used.[11] Based on our preceding discovery, we predicted that direct synthesis of quinoxaline might be possible by aerobic oxidation of 2-hydroxyacetophenone. For easy formation of imine, catalytic amount of acid could be added. Then we optimized the reaction with different acids and solvents (Table 2.3). Initially, different acids like benzoic acid, diphenyl phosphate and *p*-TSA were tested in the reaction (entries 1-3). Interestingly, diphenyl phosphate gave the best yield of 62% in toluene solvent. Various solvents were also screened in the reaction. Similar yields were obtained in DMSO and DMF (entries 4-5). But slightly lower yields were isolated in acetonitrile and chlorobenzene solvents (entries 6-7).

Table 2.3. Optimization table



1a 5a 6a

entry[a]	catalyst	solvent	yield (%)[b]
1	PhCOOH	$PhCH_3$	58
2	**diphenyl phosphate**	**$PhCH_3$**	**62**
3	*p*-TSA	$PhCH_3$	55
4	diphenyl phosphate	DMSO	58
5	diphenyl phosphate	DMF	60
6	diphenyl phosphate	CH_3CN	40
7	diphenyl phosphate	PhCl	42

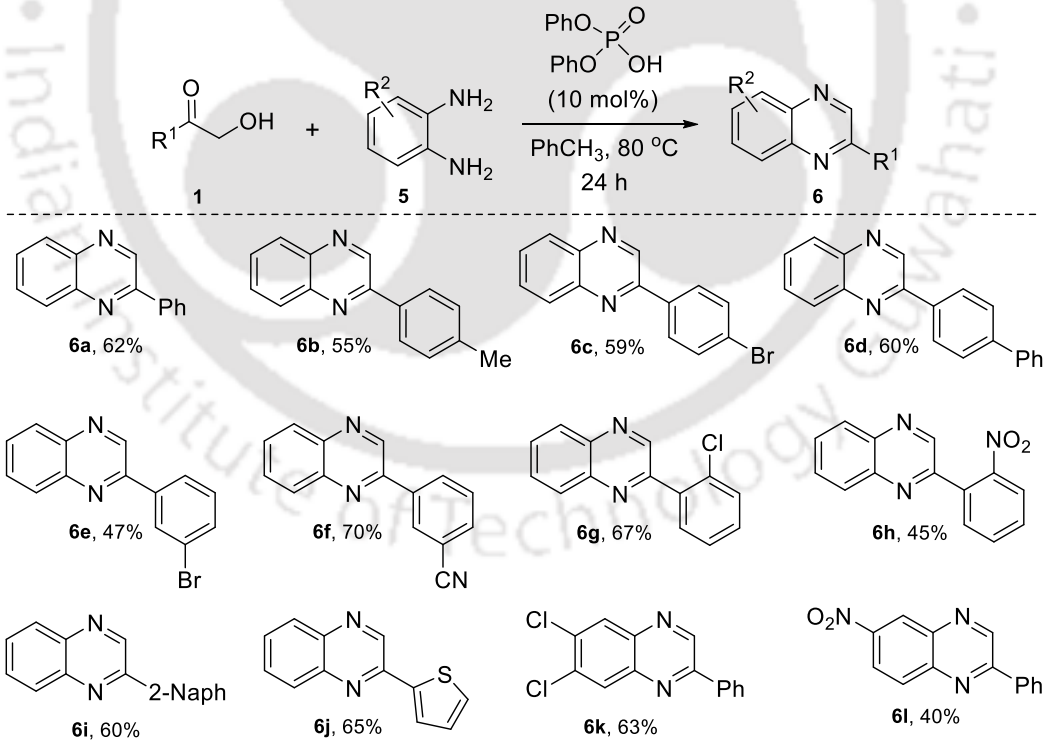
[a]Reactions were carried out with **1a** (0.05 mmol) and **5a** (0.05 mmol) in 0.5 mL solvent. [b]Isolated yield after silica gel column chromatography.

2.6 Substrate scope of quinoxalines

Next, we sought to enhance the generality of the reaction by incorporating a range of 2-hydroxyacetophenones and *o*-phenylenediamines (Scheme 2.15). Gratifyingly, different

substitutions at the *ortho*-, *meta*- and *para*- positions of the phenyl group of 2-hydroxyacetophenone were well tolerated. Different substituents in the *para* position were explored and it did not significantly affect the reaction and high yields were maintained. For example, 4-methyl, 4-bromo and 4-phenyl substituted hydroxyacetophenones provided the analogous yields of the products **6b** (55%), **6c** (59%) and **6d** (60%). Pleasingly, the highest yield of 70% was achieved for product **6f** having a 3-cyano substituent. *Ortho*-substitution of the aryl group was also tolerated and the products **6g** and **6h** were obtained with 67% and 45% yields respectively. Hydroxyketones **1t** containing a 2-naphthyl substituent provided the corresponding product **6i** in good yield. For heteroaromatic hydroxyketone **1u** having 2-furyl moiety, high yield (65%) of the product **6j** was obtained. Different *o*-phenylenediamines were also screened and good yields of the corresponding products **6k**-**l** were observed under the same reaction conditions.

Scheme 2.15: Scope of quinoxalines [a,b]

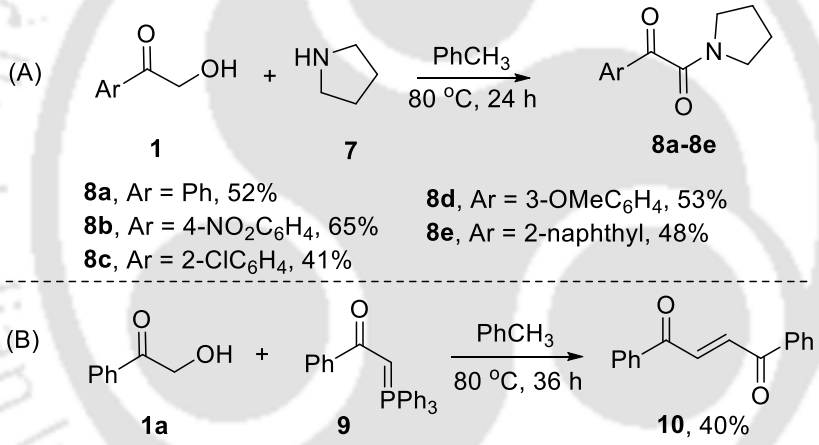


[a]Reactions were carried out with 0.2 mmol of **1** and 0.2 mmol of **5** in 2 mL toluene. [b]Isolated yield after silica gel column chromatography.

We further explored the possibility of uncatalyzed aerial oxidative reactions of 2-hydroxyacetophenones (Scheme 2.16). To our delight, when the reaction of 2-hydroxyacetophenone (**1a**) and pyrrolidine (**7**) was carried out at 80 ^{o}C in toluene, the desired α-ketoamide product **8a** was isolated in 52% yield. Inspired by this result, we further screened different *para*-, *ortho*-, and *meta*- substituted hydroxyacetophenones **1h**, **1k** and **1o** respectively and gratifyingly the corresponding products **8b-d** were obtained in acceptable yields. A naphthyl group was also well-tolerated and product **8e** was isolated in an acceptable yield.

To further domesticate the intermediate formed from aerobic oxidation of 2-hydroxyacetophenone, we performed a Wittig reaction with stabilized ylide **9**. Here also moderate yield (40%) of the product **10** was achieved (Scheme 2.16).

Scheme 2.16: Synthesis of α-ketoamides and Wittig Reaction [a,b]



[a]Reactions were carried out with 0.2 mmol of **1** and 0.2 mmol of **7**/**9** in 2 mL toluene. [b] Isolated yield after silica gel column chromatography.

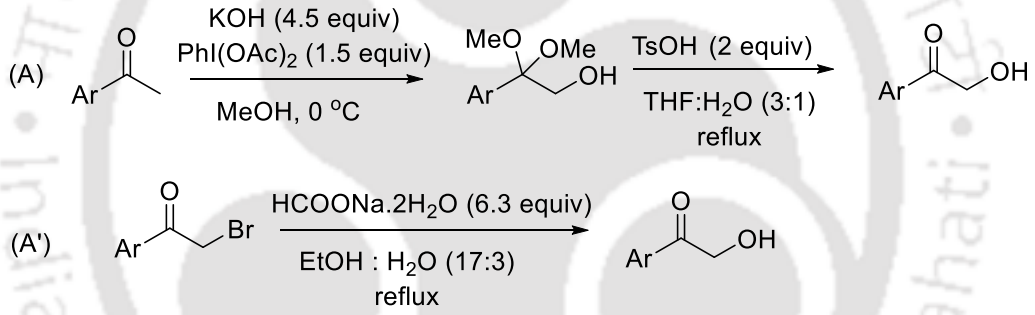
In summary, we have disclosed an unprecedented metal and external oxidant free aerobic oxidative reaction of 2-hydroxyacetophenones without any need of redox catalyst system. The *in situ* trapping concept was not exploited previously in the aerial oxidation reaction. The aerobic oxidative reactions of 2-hydroxyacetophenones allow synthesis of compounds such as phthalides, quinoxalines, α-ketoamides under reaction condition. To our knowledge, this is the first example of metal-free aerobic oxidation of 2-hydroxyacetophenones.

2.7 Experimental section

Starting materials like **1a**, **3a**, **5a**, **5b**, **5c** were purchased from Aldrich. Pyrrolidine and *N*,*N*-diisopropylethylamine (DIPEA) were purchased from Spectrochem. Anhydride derivatives (**3b-3g**) were prepared from the corresponding acids according to the previously reported procedure.[9]

A. General procedure for the synthesis of 2-hydroxyacetophenones

2-Hydroxyacetophenones **1c**, **1g, 1h, 1i, 1j, 1k, 1l, 1m, 1n, 1o, 1p, 1q, 1s, 1t, 1u, 1v** were prepared from the corresponding acetophenones according to the previously reported procedure **A**.[5f] 2-Hydroxyacetophenones **1b**, **1d, 1e, 1f, 1r** were prepared from the corresponding 2-bromo acetophenones according to the previously reported procedure **A′**.[5f]



Scheme 2.17: Synthesis of α-hydroxyketones

Procedure A: To a solution of KOH (9 mmol) in MeOH (6 mL) was added a suspension of substituted acetophenone (2 mmol) in MeOH (4 mL) at 0 ^{o}C. Then $PhI(OAc)_2$ (3 mmol) was added in four portions. After stirring for 3 hours at room temperature, the reaction was quenched by the addition of water. MeOH was removed under vacuum. The product was extracted with EtOAc (4 mL × 3), and the combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4. After removal of the solvent in vacuum, crude was obtained without further purification. Crude was dissolved in THF:H_2O (1.5 mL:0.5 mL) with the addition of *p*-TsOH.H_2O (4 mmol). The mixture was stirred at reflux for 4.5 hours. When the reaction was completed (monitored by TLC), the reaction was quenched with water and the product was extracted with EtOAc (4 mL × 3). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4.

After removal of the solvent *in vacuum* the residue was purified by column chromatography to give the corresponding 2-hydroxyacetophenone.

Procedure A′: A solution of substituted 1-bromoacetophenone (2 mmol) and sodium formate (12.5 mmol) in 2.5 mL 85% ethanol was stirred at reflux for 12 hours. Then ethanol was removed and diluted to dissolve the excess sodium formate and caused the product to precipitate. Then the product was isolated by filtration and recrystallized from 95% ethanol.

B. General procedure for the synthesis of 3-substituted phthalides (4a-4w)

In a 5 mL round bottom flask, compound **1** (0.1 mmol), **3** (0.1 mmol) and DIPEA (10 mol%) were taken in 1 mL toluene. Then the round bottom flask was sealed with a glass stopper and placed in a heating bath at 80 ^{o}C. After completion of the reaction, as monitored by TLC, the reaction mixture was allowed to cool at room temperature and diluted with EtOAc (3 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (7%-15% EtOAc/hexane) to afford 3-substituted phthalides **4**.

C. General procedure for the synthesis of Quinoxalines (6a-6l)

In a 5 mL round bottom flask, compound **1** (0.2 mmol), **5** (0.2 mmol) and diphenyl phosphate (10 mol%) were taken. Then 2 mL toluene was added to it. Then the round bottom flask was sealed with a glass stopper and placed in a heating bath at 80 ^{o}C for 24 hours. After completion of the reaction, as monitored by TLC, the reaction mixture was allowed to cool at room temperature and diluted with EtOAc (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (3%-7% EtOAc/hexane) to afford quinoxalines **6**.

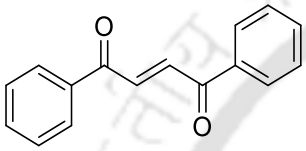
D. General procedure for the synthesis of *α*-Ketoamides (8a-8e)

In a 5 mL round bottom flask compound **1** (0.1 mmol) and pyrrolidine **(7)** (0.1 mmol) in 1 mL toluene were taken. Then the round bottom flask was sealed with a glass stopper and placed in a heating bath at 80 ^{o}C for 24 hours. After completion of the reaction, as monitored by TLC, the reaction mixture was allowed to cool at room temperature and diluted with EtOAc (3 mL). The organic layer was washed with water, brine and dried

(anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (20%-25% EtOAc/hexane) to afford *α*-ketoamides **8**.

E. General procedure for the synthesis of (*E*)-1,4-diphenylbut-2-ene-1,4-dione (10)

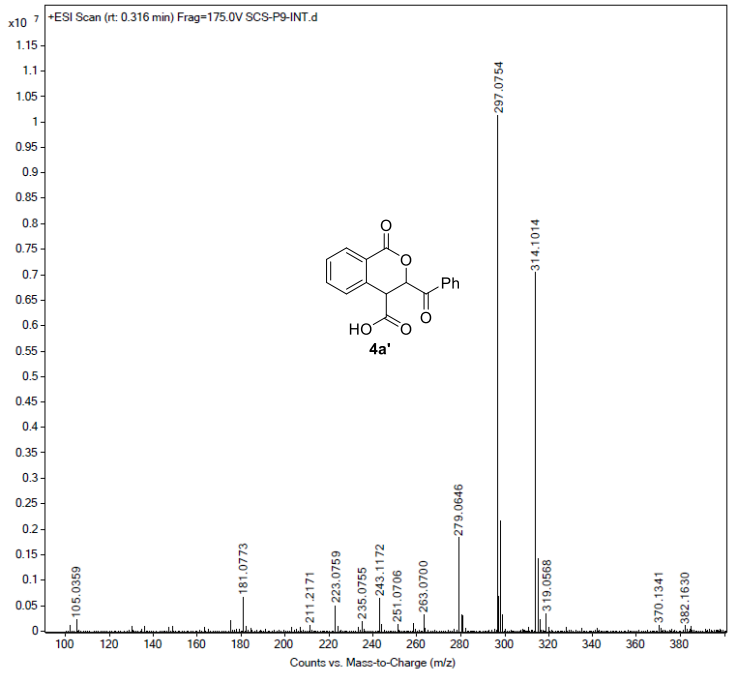
In a 5 mL round bottom flask compound **1a** (0.2 mmol) and **9** (0.2 mmol) in 2 mL toluene were taken. Then the round bottom flask was sealed with a glass stopper and placed in a heating bath at 80 ^oC for 36 hours. After completion of the reaction, as monitored by TLC, the reaction mixture was allowed to cool at room temperature and diluted with EtOAc (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (3% EtOAc/hexane) to afford 40% of olefin **10**. Yellow solid (yield 40%, 18.5mg); **^{1}H NMR (600 MHz, $CDCl_3$):**[5j] δ 8.07 (d, *J* = 7.4 Hz, 2H), 8.02 (s, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 190.1, 137.1, 135.4, 134.1, 129.1; **HRMS (ESI-TOF):** Calc for $C_{16}H_{13}O_2$ $[M+H]^+$ 237.0910; found: 237.0914.



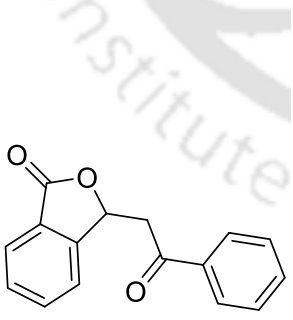
F. General procedure[9] for the synthesis of 3-benzoyl-1-oxoisochromane-4-carboxylic acid (4a′)

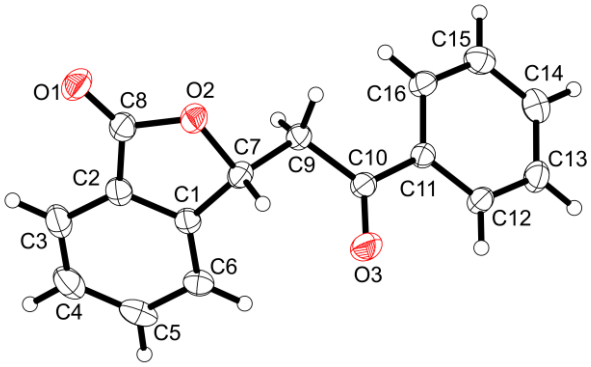
In a 5 mL round bottom flask, phenylglyoxal **2a** (0.2 mmol), homophthalic anhydride **3a** (0.2 mmol), 4 Å MS (200 mg) and DIPEA (0.02 mmol) were taken in 2 mL toluene. Then the reaction mixture was stirred for 28 hours at room temperature. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with DCM (10 mL) and sat. $NaHCO_3$ (pH~10). The mixture was stirred for 10 minutes. Then the aqueous layer was washed with DCM (3 times). 10% HCl was added to the aqueous layer carefully (pH~1) and extracted with DCM. Then the organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated *in vacuum*. Mass spectrometry of the crude sample was taken. HRMS of the product **4a′** was observed and move for the next reaction without purification. **HRMS (ESI-TOF):** Calc for $C_{17}H_{13}O_5$ $[M+H]^+$ 297.0757; found: 297.0754.

Sample Name	SAMPLE 31	**Position**	P1-C7	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	20	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	SCS-P9-INT.d
ACQ Method	ESI ALS 100-500.m	**Comment**		**Acquired Time**	24-Jul-19 4:44:11 PM (UTC+05:30)



G. Crystal structure of compound 4a





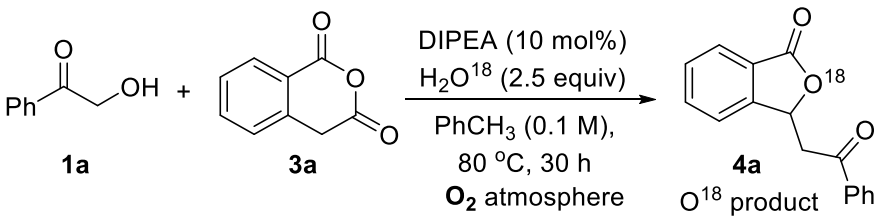
ORTEP crystal structure

Table 2.4: Crystal data and structure refinement for compound 4a

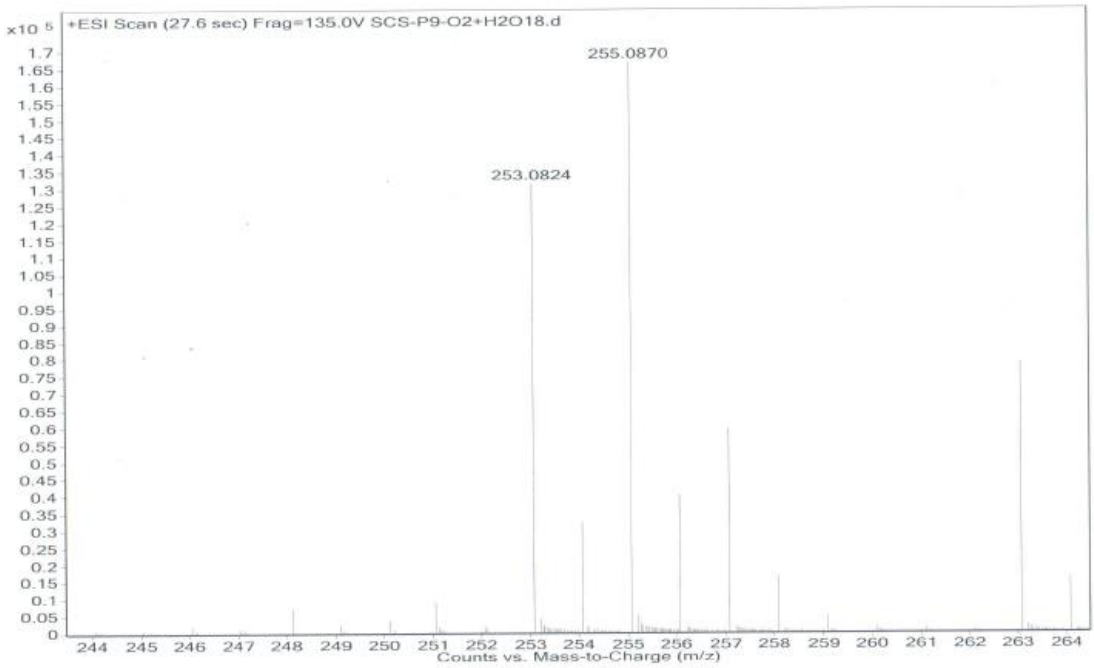
Empirical formula	$C_{16}H_{12}O_3$
Formula weight	251.25
CCDC Number	1518677
Crystal habit, colour	Block, White
Crystal size, mm^3	0.30×0.25×0.20
Temperature, T	293 (2)
Wavelength, λ (Å)	0.71073
Crystal system	orthorhombic
Space group	'P 21 21 21'
Unit cell dimensions	a = 5.1674(3) Å
	b = 11.2335(7) Å
	c = 21.3205(14) Å
	α = 90.00°, β = 90.00°, γ = 90.00°
Volume, V ($Å^3$)	1237.61(13)
Z	4
Calculated density, $Mg\cdot m^{-3}$	1.348
Absorption coefficient, μ (mm^{-1})	0.093
F(000)	524.0
θ range for data collection	3.39° to 24.980°
Limiting indices	$-5 \le h \le 6$, $-13 \le k \le 10$, $-23 \le l \le 25$
Reflection collected/unique	3266/1945 [R(int) = 0.0209]
Completeness to θ	99.8% (θ = 24.98°)
Max. and min. transmission	0.995/0.994
Refinement method	'SHELXL–97(Sheldrick, 1997)'
Data/restraints/parameters	1945/0/172
Goodness–of–fit on F^2	1.012
Final R indices [I>2sigma(I)]	$R1$ = 0.0470, $wR2$ = 0.1008
R indices (all data)	$R1$ = 0.0637, $wR2$ = 0.1132
Largest diff. peak and hole	0.135 and –0.156 $e\cdot Å^{-3}$

[a]GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined). [b]$R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0$, [c]$wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{½}$

H. Isotopic Labelling Experiment:



In a Schlenk tube, compound **1a** (0.1 mmol), **3a** (0.1 mmol), H_2O^{18} (0.25 mmol) and DIPEA (10 mol%) were taken in 1 mL dry toluene under oxygen atmosphere. Then the tube was sealed with a septum and placed in a heating bath at 80 °C in presence of an oxygen balloon. After completion of the reaction, as monitored by TLC, HRMS of the reaction mixture was taken. **HRMS (ESI-TOF):** Calc for $C_{16}H_{13}{}^{16}O_2{}^{18}O$ $[M+H]^+$ 255.0901; found: 255.0870.



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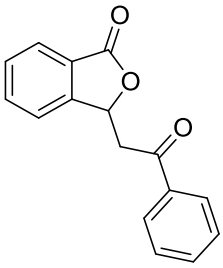
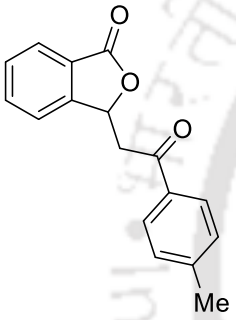
15. CCDC 1518677 contains the crystallographic data for **4a**. The data can be obtained from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

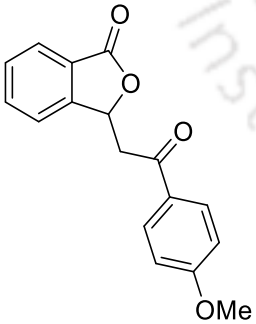
2.9 Characterization Data of Products



3-(2-oxo-2-phenylethyl)isobenzofuran-1(3H)-one (4a):[10h] Pale yellow solid (yield: 70%, 17.5 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.56 (dd, *J* = 18.3, 8.3 Hz, 2H), 7.49 (t, *J* = 7.9 Hz, 2H), 6.19 (t, *J* = 7.0 Hz, 1H), 3.79 (dd, *J* = 17.5, 6.2 Hz, 1H), 3.40 (dd, *J* = 17.6, 7.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.0, 170.2, 149.7, 136.1, 134.3, 133.9, 129.4, 128.8, 128.1, 125.8, 125.7, 122.8, 77.2, 43.7; **HRMS (ESI-TOF):** Calc for $C_{16}H_{13}O_3$ $[M+H]^+$ 253.0859; found: 253.0864.

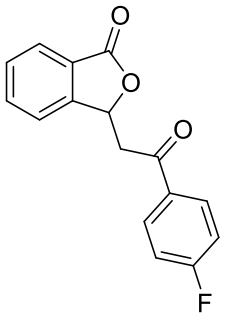


3-(2-oxo-2-(p-tolyl)ethyl)isobenzofuran-1(3H)-one (4b): Pale yellow solid (yield: 55%, 14.5 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.18 (t, *J* = 6.6 Hz, 1H), 3.76 (dd, *J* = 17.5, 5.7 Hz, 1H), 3.37 (dd, *J* = 17.5, 7.4 Hz, 1H), 2.42 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 195.9, 170.4, 150.1, 145.1, 134.5, 133.9, 129.7, 129.6, 128.5, 126.1, 125.9, 123.1, 77.5, 43.78, 21.92; **HRMS (ESI-TOF):** Calc for $C_{17}H_{15}O_3$ $[M+H]^+$ 267.1016; found: 267.1016.

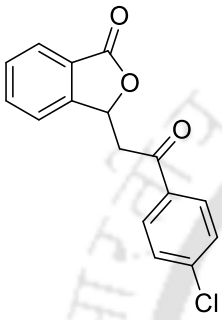


3-(2-(4-methoxyphenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4c): White solid (yield: 50%, 14.2 mg); R_f = 0.4 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.93 (d, *J* = 8.9 Hz, 2H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.19 – 6.15 (m, 1H), 3.87 (s, 3H), 3.73 (dd, *J* = 17.3, 5.7 Hz, 1H), 3.33 (dd, *J* = 17.3, 7.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.7, 170.4, 164.3, 150.1, 134.4, 130.7, 129.6, 129.5, 126.1, 125.9, 123.1, 114.2, 77.7, 55.8, 43.5; **HRMS (ESI-TOF):** Calc for $C_{17}H_{15}O_4$ $[M+H]^+$ 283.0965; found: 283.0968.

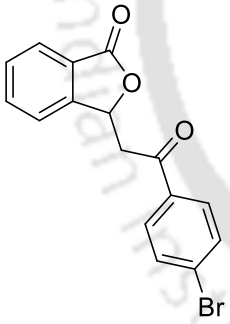
3-(2-(4-fluorophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4d): Yellow solid (yield: 50%, 13.5 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (dd,



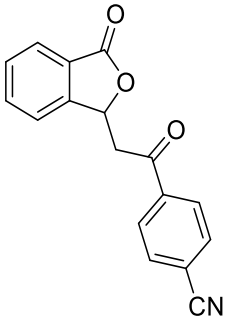
J = 8.8, 5.4 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.16 (t, *J* = 8.5 Hz, 2H), 6.16 (t, *J* = 6.5 Hz, 1H), 3.74 (dd, *J* = 17.5, 5.9 Hz, 1H), 3.37 (dd, *J* = 17.5, 7.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.6, 170.3, 167.2, 165.5, 149.8, 134.5, 132.8, 131.1, 131.1, 129.7, 126.1, 126.0, 122.9, 116.3, 116.2, 77.3, 43.8; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}FO_3$ $[M+H]^+$ 271.0765; found: 271.0768.



3-(2-(4-chlorophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4e): Yellow solid (yield: 45%, 12.8 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61 (t, *J* = 8.0 Hz, 3H), 7.37 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 5.86 (t, *J* = 6.5 Hz, 1H), 3.44 (dd, *J* = 17.6, 6.0 Hz, 1H), 3.08 (dd, *J* = 17.6, 7.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 195.0, 170.3, 149.7, 140.6, 134.7, 134.5, 129.8, 129.7, 129.4, 126.1, 126.0, 122.9, 77.2, 43.9; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}ClO_3$ $[M+H]^+$ 287.0469; found: 287.0470.



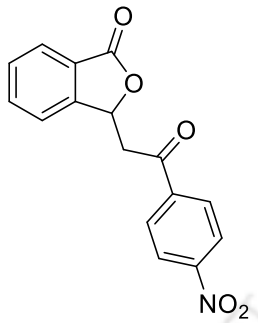
3-(2-(4-bromophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4f): Yellow solid (yield: 55%, 18.0 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.56 (t, *J* = 6.3 Hz, 2H), 6.16 (t, *J* = 6.5 Hz, 1H), 3.73 (dd, *J* = 17.6, 6.0 Hz, 1H), 3.36 (dd, *J* = 17.6, 7.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 195.2, 169.8, 149.7, 135.1, 134.5, 132.4, 129.8, 129.7, 129.4, 126.1, 126.0, 122.9, 77.1, 43.8; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}BrO_3$ $[M+H]^+$ 330.9964; found: 330.9961.



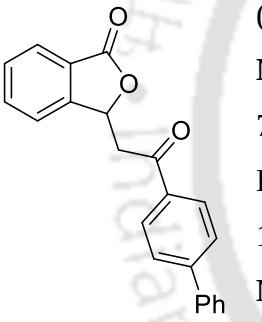
4-(2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)acetyl)benzonitrile (4g): Yellow solid (yield: 40%, 11.0 mg); R_f = 0.4 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.69 (t, *J* = 7.1 Hz, 1H), 7.57 (dd, *J* = 16.1, 7.7 Hz, 2H), 6.16 (t, *J* = 6.4 Hz, 1H), 3.75 (dd, *J* = 17.7, 6.2 Hz, 1H), 3.42 (dd, *J* = 17.7, 6.6 Hz, 1H); **^{13}C NMR (150**

MHz, $CDCl_3$): δ 195.0, 169.5, 149.4, 139.2, 134.6, 132.9, 129.9, 128.8, 126.2, 122.8, 117.8, 117.4, 76.9, 44.2; **HRMS (ESI-TOF):** Calc for $C_{17}H_{12}NO_3$ $[M+H]^+$ 278.0812; found: 278.0809.

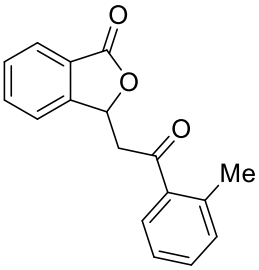
3-(2-(4-nitrophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4h): Yellow solid (yield: 74%, 21.9 mg); R_f = 0.3 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.34 (d, *J* = 8.6 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.57 (dd, *J* = 13.3, 7.4 Hz, 2H), 6.17 (t, *J* = 6.3 Hz, 1H), 3.78 (dd, *J* = 17.7, 6.3 Hz, 1H), 3.46 (dd, *J* = 17.7, 6.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.8, 169.9, 151.0, 149.3, 140.7, 134.6, 129.9, 129.4, 126.2, 126.1, 124.3, 122.7, 76.8, 44.4; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}NO_5$ $[M+H]^+$ 298.0710; found: 298.0703.

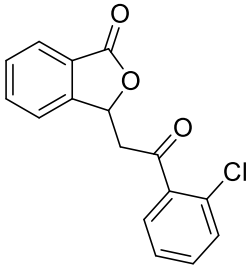


3-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)isobenzofuran-1(3H)-one (4i): Yellow solid (yield: 50%, 16.4 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.68 (dd, *J* = 16.0, 7.9 Hz, 3H), 7.64 – 7.54 (m, 4H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 6.23 – 6.18 (m, 1H), 3.81 (dd, *J* = 17.6, 5.8 Hz, 1H), 3.43 (dd, *J* = 17.6, 7.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.6, 170.2, 149.7, 146.5, 139.5, 134.8, 134.3, 129.4, 129.0, 128.8, 128.4, 127.4, 127.3, 125.9, 125.8, 122.8, 77.2, 43.7; **HRMS (ESI-TOF):** Calc for $C_{22}H_{17}O_3$ $[M+H]^+$ 329.1172; found: 329.1172.



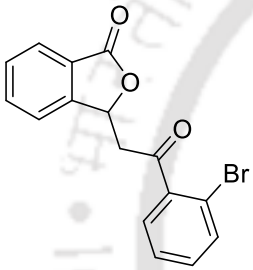
3-(2-oxo-2-(o-tolyl)ethyl)isobenzofuran-1(3H)-one (4j): Yellow solid (yield: 55%, 14.6 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.59 – 7.53 (m, 2H), 7.44 – 7.39 (m, 1H), 7.27 (dd, *J* = 13.3, 6.0 Hz, 3H), 6.17 (t, *J* = 6.5 Hz, 1H), 3.67 (dd, *J* = 17.5, 6.4 Hz, 1H), 3.37 (dd, *J* = 17.5, 6.7 Hz, 1H), 2.59 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$);** δ 199.4, 170.4, 149.9, 139.2, 136.6, 129.6, 129.2, 126.1, 126.0, 122.8, 77.6, 46.3, 21.9; **HRMS (ESI-TOF):** Calc for $C_{17}H_{15}O_3$ $[M+H]^+$ 267.1016; found: 267.1016.





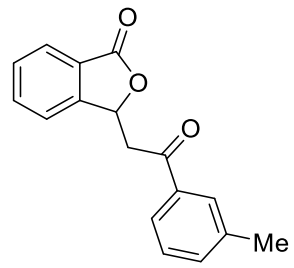
3-(2-(2-chlorophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4k): Yellow gummy solid (yield: 40%, 11.4 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.61 – 7.55 (m, 3H), 7.44 – 7.42 (m, 2H), 7.38 – 7.35 (m, 1H), 6.13 (t, *J* = 6.5 Hz, 1H), 3.68 (dd, *J* = 17.6, 6.8 Hz, 1H), 3.49 (dd, *J* = 17.6, 6.4 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.8, 170.2, 149.5, 138.2, 134.5, 132.9, 131.5, 131.0, 129.9, 129.7, 127.4, 126.1, 126.0, 122.7, 77.3, 48.0; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}ClO_3$ $[M+H]^+$ 287.0469; found: 287.0467.

3-(2-(2-bromophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4l): Yellow solid (yield: 70%, 23.0 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.63 – 7.54 (m, 3H), 7.49 (d, *J* = 9.3 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 6.12 (t, *J* = 6.5 Hz, 1H), 3.64 (dd, *J* = 17.6, 6.7 Hz, 1H), 3.47 (dd, *J* = 17.6, 6.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$);** δ 199.7, 170.2, 149.4, 140.3, 134.5, 134.2, 132.6, 129.7, 129.4, 127.9, 126.0, 122.7, 119.1, 77.0, 47.5; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}BrO_3$ $[M+H]^+$ 330.9964; found: 330.9965.



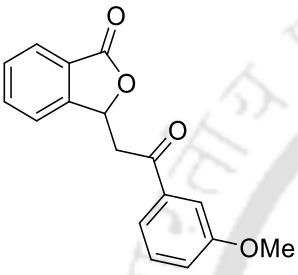
3-(2-(2-iodophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4m): Yellow oily liquid (yield: 50%, 18.8 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.94 (dd, *J* = 13.4, 7.8 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (dd, *J* = 17.6, 8.1 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.14 (t, *J* = 6.5 Hz, 1H), 3.65 (dd, *J* = 18.1, 6.7 Hz, 1H), 3.41 (dd, *J* = 17.7, 6.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 199.8, 169.9, 149.1, 142.5, 140.9, 134.2, 132.3, 129.4, 128.4, 128.2, 125.7, 122.6, 91.0, 77.0, 46.4; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}IO_3$ $[M+H]^+$ 378.9826; found: 378.9822.

3-(2-oxo-2-(m-tolyl)ethyl)isobenzofuran-1(3H)-one (4n): Yellow solid (yield: 60%, 15.9 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$);** δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.77 (s, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.58 – 7.53 (m,

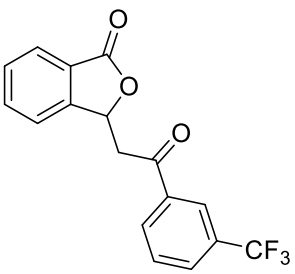


2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.20 – 6.15 (t, 1H), 3.77 (dd, *J* = 17.6, 5.7 Hz, 1H), 3.38 (dd, *J* = 17.6, 7.4 Hz, 1H), 2.41 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 196.5, 170.4, 150.0, 138.9, 136.4, 134.8, 134.5, 129.6, 128.9, 128.9, 126.1, 125.9, 125.6, 123.0, 77.5, 44.0, 21.5; **HRMS (ESI-TOF):** Calc for $C_{17}H_{15}O_3$ $[M+H]^+$ 267.1016; found: 267.1018.

3-(2-(3-methoxyphenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4o): Yellow solid (yield: 72%, 20.3 mg); R_f = 0.4 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.92 (d, *J* = 5.3 Hz, 1H), 7.66 (s, 1H), 7.59 – 7.52 (m, 2H), 7.50 (s, 2H), 7.38 (s, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.17 (s, 1H), 3.86 (s, 3H), 3.76 (d, *J* = 17.6 Hz, 1H), 3.39 (d, *J* = 17.6 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 196.1, 170.3, 160.2, 149.9, 137.7, 134.5, 130.0, 129.6, 126.1, 126.0, 123.0, 121.0, 120.6, 112.5, 77.4, 55.7, 44.0; **HRMS (ESI-TOF):** Calc for $C_{17}H_{15}O_4$ $[M+H]^+$ 283.0965; found: 283.0968.

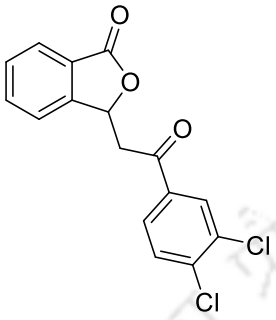


3-(2-(3-bromophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4p): Yellow solid (yield: 35%, 11.5 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.09 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 6.0 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 6.8 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.16 (t, *J* = 6.5 Hz, 1H), 3.73 (dd, *J* = 17.8, 6.0 Hz, 1H), 3.38 (dd, *J* = 17.8, 7.0 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ 194.7, 170.0, 149.4, 137.8, 136.7, 134.3, 131.2, 130.4, 129.5, 126.7, 125.8, 123.2, 122.7, 76.9, 43.8; **HRMS (ESI-TOF):** Calc for $C_{16}H_{12}BrO_3$ $[M+H]^+$ 330.9964; found: 330.9961.

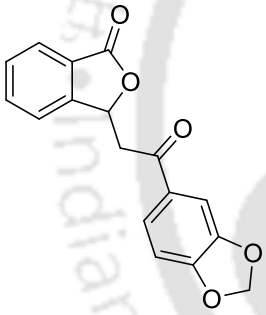


3-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)isobenzofuran-1(3H)-one (4q): Yellow solid (yield: 32%, 10.2 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 8.22 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.58 – 7.55 (m, 2H), 6.19 (t, *J* = 6.4 Hz, 1H), 3.79 (dd, *J* = 17.7, 6.0 Hz, 1H), 3.44 (dd, *J* =

17.7, 6.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.9, 170.1, 149.6, 136.9, 134.5, 131.5, 130.4, 129.8, 126.2, 126.1, 125.2, 122.8, 76.9, 44.0; **HRMS (ESI-TOF):** Calc for $C_{17}H_{12}F_3O_3$ $[M+H]^+$ 321.0733; found: 321.0738.

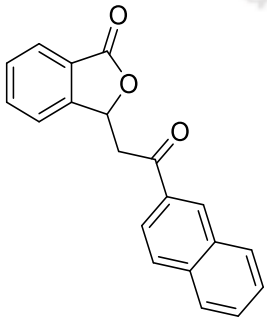


3-(2-(3,4-dichlorophenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (4r): Pale yellow solid (yield: 56%, 17.9 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.04 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 10.4 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.59 – 7.53 (m, 3H), 6.15 (t, *J* = 6.4 Hz, 1H), 3.71 (dd, *J* = 17.7, 6.1 Hz, 1H), 3.37 (dd, *J* = 17.7, 6.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.1, 170.1, 149.5, 138.8, 135.8, 134.6, 133.9, 131.2, 130.4, 129.8, 127.4, 126.1, 126.1, 122.8, 76.9, 43.9; **HRMS (ESI-TOF):** Calc for $C_{16}H_{11}Cl_2O_3$ $[M+H]^+$ 321.0080; found: 321.0077.



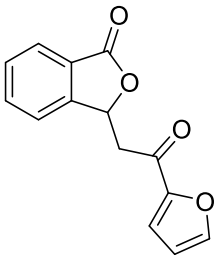
3-(2-(benzo[d][1,3]dioxol-5-yl)-2-oxoethyl)isobenzofuran-1(3H)-one (4s): Yellow solid (yield: 82%, 24.2 mg); R_f = 0.35 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.57 – 7.51 (m, 3H), 7.45 (s, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.16 (t, *J* = 6.5 Hz, 1H), 6.06 (s, 2H), 3.69 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.31 (dd, *J* = 17.4, 7.3 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.3, 170.5, 152.7, 150.1, 148.7, 134.5, 131.4, 129.7, 126.2, 126.0, 125.1, 123.1, 108.3, 108.1, 102.3, 77.7, 43.7; **HRMS (ESI-TOF):** Calc for $C_{17}H_{13}O_5$ $[M+H]^+$ 297.0757; found: 297.0755.

3-(2-(naphthalen-2-yl)-2-oxoethyl)isobenzofuran-1(3H)-one (4t): Yellow solid (yield: 50%, 15.0 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.45 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.93 (dd, *J* = 14.3, 7.4 Hz, 3H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.62 (dd, *J* = 12.2, 7.6 Hz, 2H), 7.56 (dd, *J* = 14.5, 7.2 Hz, 2H), 6.24 (t, *J* = 6.5 Hz, 1H), 3.92 (dd, *J* = 17.4, 5.8 Hz, 1H), 3.54 (dd, *J* = 17.5, 7.3 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 196.2, 170.4, 150.0, 136.1, 134.5, 133.7, 132.6, 130.5, 129.9,

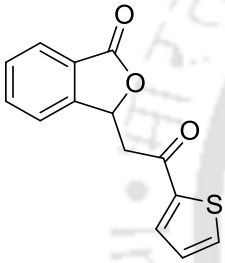


129.7, 129.2, 129.0, 128.0, 127.3, 126.1, 126.0, 123.7, 123.1, 77.5, 44.0; **HRMS (ESI-TOF):** Calc for $C_{20}H_{15}O_3$ $[M+H]^+$ 303.1016; found: 303.1006.

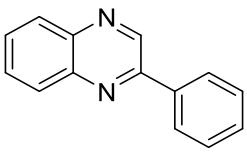
3-(2-(furan-2-yl)-2-oxoethyl)isobenzofuran-1(3H)-one (4u): Grey solid (yield: 50%, 12.0 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.61 (s, 1H), 7.55 (t, *J* = 8.4 Hz, 2H), 6.58 (dd, *J* = 3.5, 1.6 Hz, 1H), 6.12 (t, *J* = 6.7 Hz, 1H), 3.60 (dd, *J* = 17.1, 6.6 Hz, 1H), 3.27 (dd, *J* = 17.1, 6.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 184.9, 170.2, 152.4, 149.6, 147.3, 134.5, 129.7, 126.1, 126.0, 122.8, 118.4, 112.9, 77.0, 43.6; **HRMS (ESI-TOF):** Calc for $C_{14}H_{11}O_4$ $[M+H]^+$ 243.0652; found: 243.0655.



3-(2-oxo-2-(thiophen-2-yl)ethyl)isobenzofuran-1(3H)-one (4v): Pale yellow solid (yield: 84%, 21.6 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.70 (dt, *J* = 3.5, 1.0 Hz, 2H), 7.66 (d, *J* = 6.7 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.15 (dd, *J* = 4.8, 3.9 Hz, 1H), 6.13 (t, *J* = 6.6 Hz, 1H), 3.68 (dd, *J* = 17.0, 6.2 Hz, 1H), 3.34 (dd, *J* = 17.0, 7.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 188.6, 170.1, 149.4, 143.3, 134.9, 134.6, 132.9, 129.5, 128.4, 128.4, 125.8, 122.7, 77.0, 44.1; **HRMS (ESI-TOF):** Calc for $C_{14}H_{11}O_3S$ $[M+H]^+$ 259.0423; found: 259.0427.

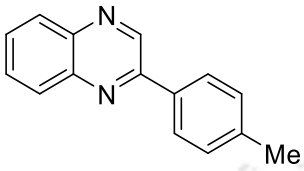


6-methoxy-3-(2-oxo-2-phenylethyl)isobenzofuran-1(3H)-one (4w): Pale yellow solid (yield: 65%, 18.3 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 8.8 Hz, 2H), 7.62 – 7.59 (m, 1H), 7.48 (dd, *J* = 7.5, 5.4 Hz, 3H), 7.34 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.14 – 6.09 (m, 1H), 3.87 (s, 3H), 3.77 (dd, *J* = 17.6, 5.6 Hz, 1H), 3.36 (dd, *J* = 17.6, 7.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.0, 171.4, 160.6, 141.9, 135.9, 133.6, 129.9, 128.6, 128.2, 123.6, 122.9, 107.3, 77. 0, 55.6, 43.6; **HRMS (ESI-TOF):** Calc for $C_{17}H_{15}O_4$ $[M+H]^+$ 283.0965; found: 283.0976.

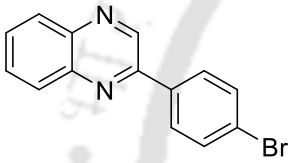


2-phenylquinoxaline (6a):[11f] White solid (yield 62%, 25.5 mg); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.33 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J*

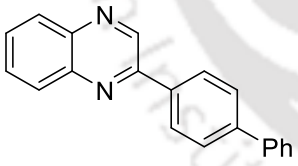
= 8.3 Hz, 1H), 7.78 (t, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 6.9 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 2H), 7.54 – 7.50 (m, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 152.1, 143.6, 142.5, 141.8, 136.99, 130.5, 130.4, 129.8, 129.7, 129.4, 129.3, 127.8; **HRMS (ESI-TOF):** Calc for $C_{14}H_{11}N_2$ $[M+H]^+$ 207.0917; found: 207.0922.



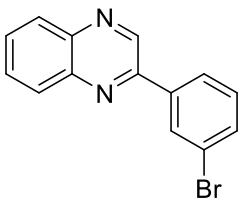
***2-(p-tolyl)quinoxaline (6b)**:* White solid (yield 55%, 24.2 mg); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.31 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 3H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 2H), 2.45 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 152.0, 143.5, 142.5, 141.6, 140.7, 134.2, 130.4, 130.1, 129.7, 129.5, 129.3, 127.6, 21.6; **HRMS (ESI-TOF):** Calc for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1073; found: 221.1076.



***2-(4-bromophenyl)quinoxaline (6c)**:* Yellow solid (yield 59%, 33.6 mg); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.27 (s, 1H), 8.11 (t, *J* = 8.6 Hz, 2H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.76 (dt, *J* = 15.1, 6.8 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 150.8, 143.0, 142.4, 141.9, 135.8, 132.5, 130.7, 130.0, 129.8, 129.4, 129.2, 125.2; **HRMS (ESI-TOF):** Calc for $C_{14}H_{10}BrN_2$ $[M+H]^+$ 285.0022; found: 285.0021.

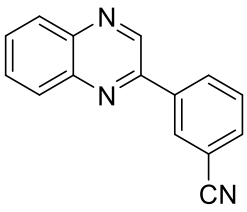


***2-([1,1'-biphenyl]-4-yl)quinoxaline (6d)**:* White solid (yield 60%, 33.7 mg); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.37 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 3H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 151.6, 143.5, 143.2, 142.6, 141.8, 140.4, 135.8, 130.5, 129.8, 129.7, 129.3, 129.1, 128.2, 128.1, 128.0, 127.4; **HRMS (ESI-TOF):** Calc for $C_{20}H_{15}N_2$ $[M+H]^+$ 283.123; found: 283.1225.

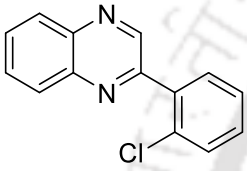


***2-(3-bromophenyl)quinoxaline (6e)**:* White solid (yield 47%, 26.7 mg); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.28 (s, 1H), 8.38 (s, 1H), 8.17 – 8.07 (m, 3H), 7.78 (dt, *J* = 14.9, 7.1 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H); **^{13}C**

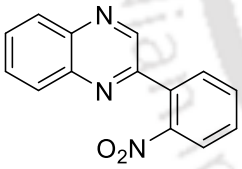
NMR (150 MHz, $CDCl_3$): δ 150.4, 143.1, 142.4, 142.0, 139.0, 133.3, 130.8, 130.7, 130.2, 129.9, 129.4, 126.2, 123.7; **HRMS (ESI-TOF):** Calc for $C_{14}H_{10}BrN_2$ $[M+H]^+$ 285.0022; found: 285.0023.



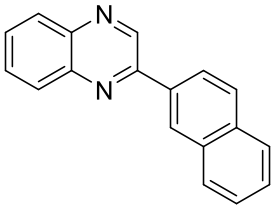
3-(quinoxalin-2-yl)benzonitrile (6f)*:* White solid (yield 70%, 32.2 mg); R_f = 0.35 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.31 (s, 1H), 8.53 (s, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.14 (t, *J* = 8.8 Hz, 2H), 7.84 – 7.77 (m, 3H), 7.67 (t, *J* = 7.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 149.4, 142.6, 142.3, 142.2, 138.1, 133.5, 131.6, 131.4, 131.0, 130.6, 130.2, 129.9, 129.4, 118.6, 113.8; **HRMS (ESI-TOF):** Calc for $C_{15}H_{10}N_3$ $[M+H]^+$ 232.0869; found: 232.0872.



2-(2-chlorophenyl)quinoxaline (6g)*:* Yellow solid (yield 67%, 32.1 mg); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.21 (s, 1H), 8.19 – 8.16 (m, 2H), 7.81 (dd, *J* = 6.1, 3.7 Hz, 2H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.47 – 7.44 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 152.6, 146.4, 142.5, 141.5, 136.7, 132.8, 132.2, 131.0, 130.5, 130.4, 129.8, 129.4, 127.7; **HRMS (ESI-TOF):** Calc for $C_{14}H_{10}ClN_2$ $[M+H]^+$ 241.0527; found: 241.0532.

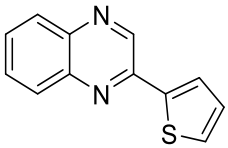


2-(2-nitrophenyl)quinoxaline (6h)*:* Yellow solid (yield 45%, 22.5 mg); R_f = 0.3 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.96 (s, 1H), 8.17 (d, *J* = 9.7 Hz, 1H), 8.11 (dd, *J* = 11.7, 5.4 Hz, 2H), 7.83 – 7.80 (m, 2H), 7.76 (dd, *J* = 18.8, 7.5 Hz, 2H), 7.67 (t, *J* = 7.7 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 151.3, 144.5, 142.0, 141.7, 133.5, 133.2, 132.1, 130.8, 130.6, 130.5, 129.8, 129.5, 125.2; **HRMS (ESI-TOF):** Calc for $C_{14}H_{10}N_3O_2$ $[M+H]^+$ 252.0768; found: 252.0771.

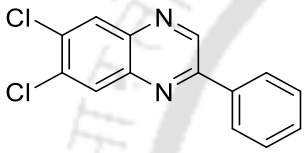


2-(naphthalen-2-yl)quinoxaline (6i)*:* White solid (yield 60%, 30.6 mg); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.48 (s, 1H), 8.65 (s, 1H), 8.36 (d, *J* = 7.1 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.02 (dd, *J* = 10.6, 6.1 Hz, 2H), 7.93 – 7.89 (m, 1H), 7.82 – 7.75 (m, 2H), 7.56

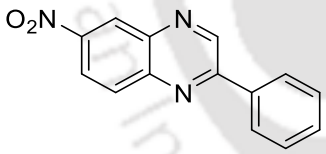
(dd, *J* = 5.3, 4.0 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 151.9, 143.7, 142.6, 141.8, 134.3, 134.3, 133.6, 130.6, 129.8, 129.8, 129.4, 129.3, 129.1, 128.0, 127.7, 127.5, 126.9, 124.7; **HRMS (ESI-TOF):** Calc for $C_{18}H_{13}N_2$ $[M+H]^+$ 257.1073; found: 257.1067.



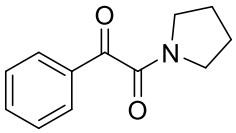
2-(thiophen-2-yl)quinoxaline (6j): White solid (yield 65%, 27.5 mg); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.23 (s, 1H), 8.06 (dd, *J* = 7.9, 5.2 Hz, 2H), 7.85 (d, *J* = 3.6 Hz, 1H), 7.75 – 7.71 (m, 1H), 7.68 (t, *J* = 7.1 Hz, 1H), 7.54 (d, *J* = 5.0 Hz, 1H), 7.19 (t, *J* = 5.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 147.6, 142.4, 142.3, 142.2, 141.5, 130.6, 130.0, 129.4, 129.3, 128.7, 127.2; **HRMS (ESI-TOF):** Calc for $C_{12}H_9N_2S$ $[M+H]^+$ 213.0481; found: 213.0485.



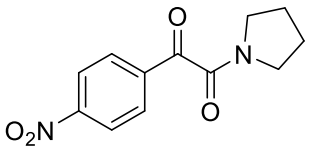
6,7-dichloro-2-phenylquinoxaline (6k): White solid (yield 63%, 34.4 mg); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.29 (s, 1H), 8.24 (d, *J* = 3.2 Hz, 1H), 8.21 (d, *J* = 2.8 Hz, 1H), 8.16 (s, 2H), 7.56 (q, *J* = 6.1 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 152.8, 144.4, 141.3, 140.4, 136.2, 135.1, 134.2, 131.0, 130.4, 130.0, 129.5, 127.8; **HRMS (ESI-TOF):** Calc for $C_{14}H_9Cl_2N_2$ $[M+H]^+$ 275.0137; found: 275.0142.



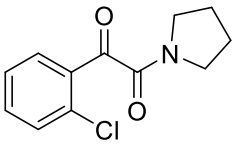
6-nitro-2-phenylquinoxaline (6l):[11g] Yellow solid (yield 40%, 20.0 mg); R_f = 0.35 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.50 (s, 1H), 9.04 (s, 1H), 8.56 (d, *J* = 9.1 Hz, 1H), 8.29 (d, *J* = 9.2 Hz, 1H), 8.27 (d, *J* = 9.4 Hz, 2H), 7.64 – 7.60 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 154.5, 147.6, 145.7, 145.1, 140.4, 135.7, 131.6, 131.4, 129.6, 128.2, 125.9, 124.0; **HRMS (ESI-TOF):** Calc for $C_{14}H_{10}N_3O_2$ $[M+H]^+$ 252.0768; found: 252.0765.



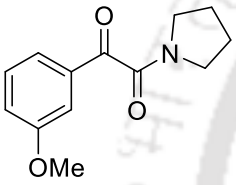
1-phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (8a):[8e] Yellow gummy solid (yield 52%, 10.5 mg); R_f = 0.5 (EtOAc/hexane 1:8); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 7.7 Hz, 2H), 7.65 – 7.62 (m, 1H), 7.53 – 7.48 (m, 2H), 3.68 – 3.64 (m, 2H), 3.45 – 3.42 (m, 2H), 2.00 – 1.91 (m, 4H); **HRMS (ESI-TOF):** Calc for $C_{12}H_{14}NO_2$ $[M+H]^+$ 204.1019; found: 204.1021.



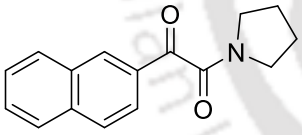
1-(4-nitrophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (8b):[8b] Yellow solid (yield 65%, 16.0 mg); R_f = 0.35 (EtOAc/hexane 1:8); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.34 (d, *J* = 8.6 Hz, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 3.67 (t, *J* = 6.7 Hz, 1H), 3.50 (t, *J* = 6.3 Hz, 1H), 1.99 (s, 2H); **HRMS (ESI-TOF):** Calc for $C_{12}H_{13}N_2O_4$ $[M+H]^+$ 249.0870; found: 249.0874.



1-(2-chlorophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (8c):[8e] Yellow oily liquid (yield 41%, 9.7 mg); R_f = 0.45 (EtOAc/hexane 1:8); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.83 (d, *J* = 6.2 Hz, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.44 – 7.38 (m, 2H), 3.60 (t, *J* = 6.8 Hz, 4H), 2.08 – 1.87 (m, 4H); **HRMS (ESI-TOF):** Calc for $C_{12}H_{13}ClNO_2$ $[M+H]^+$ 238.0629; found: 238.0632.

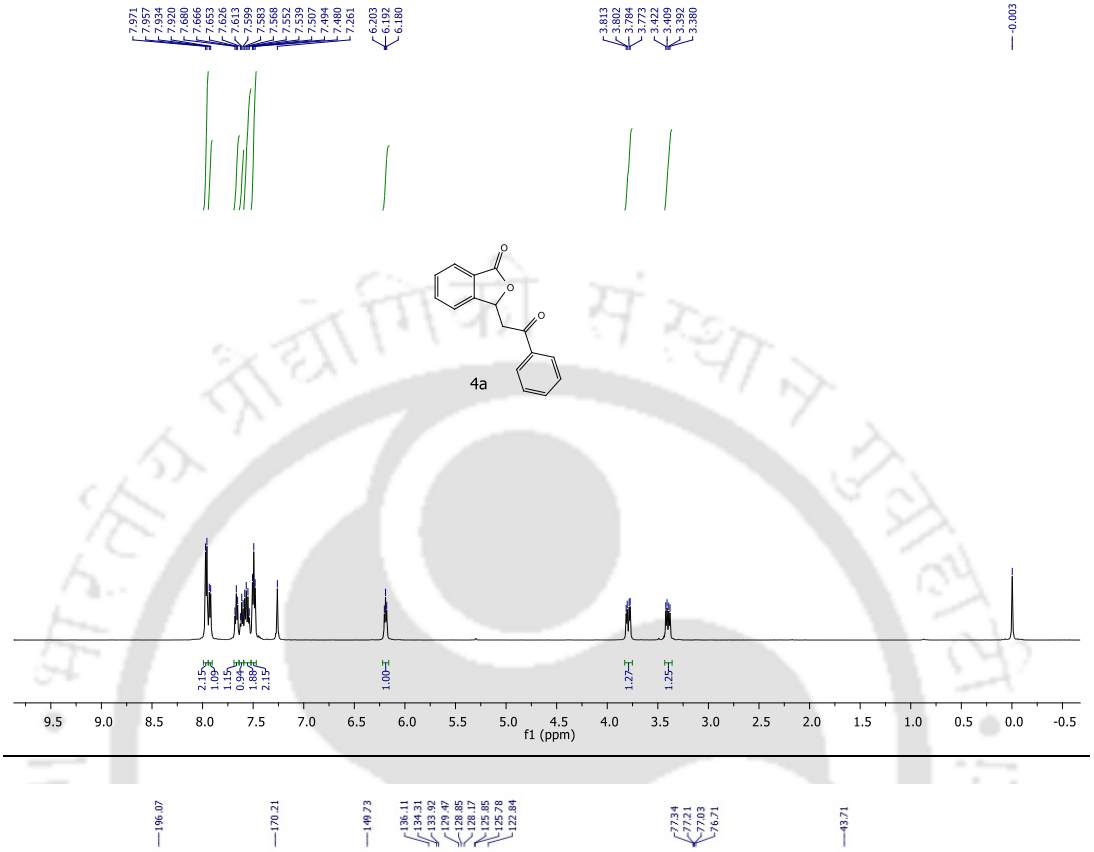


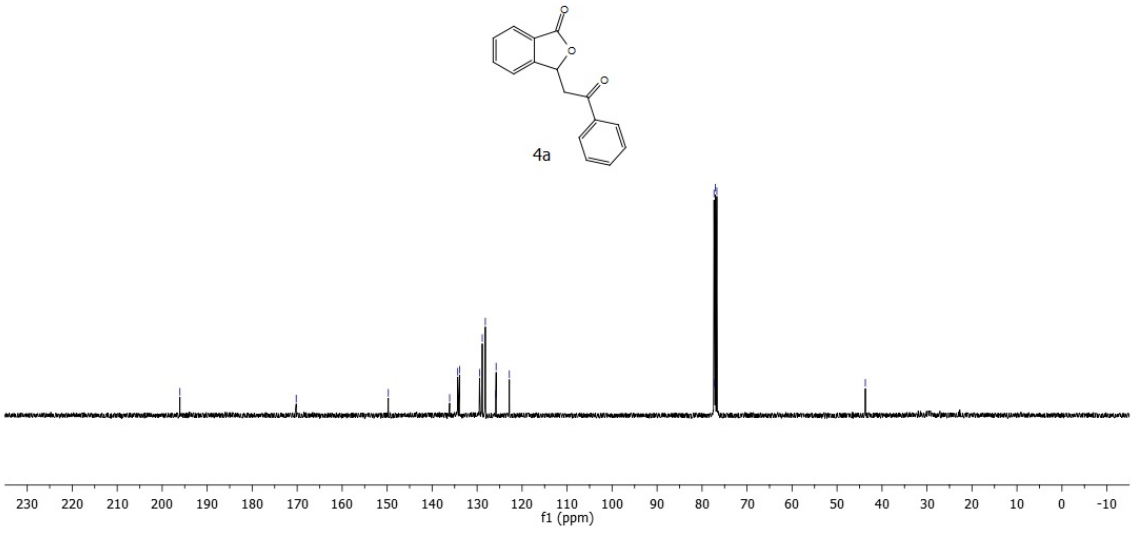
1-(3-methoxyphenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (8d):[8b] Yellow gummy solid (yield 53%, 12.3 mg); R_f = 0.35 (EtOAc/hexane 1:8); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.83 (d, *J* = 6.2 Hz, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.44 – 7.38 (m, 2H), 3.60 (t, *J* = 6.8 Hz, 4H), 2.08 – 1.87 (m, 4H); **HRMS (ESI-TOF):** Calc for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125; found: 234.1128.

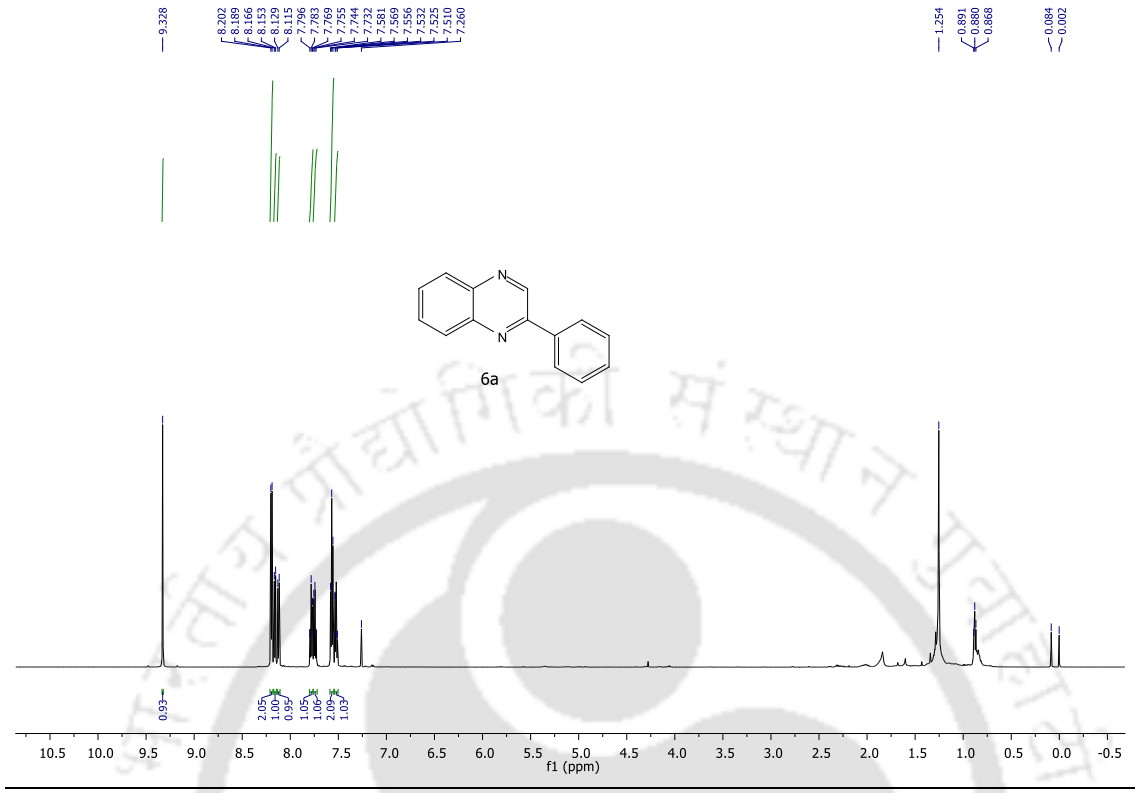


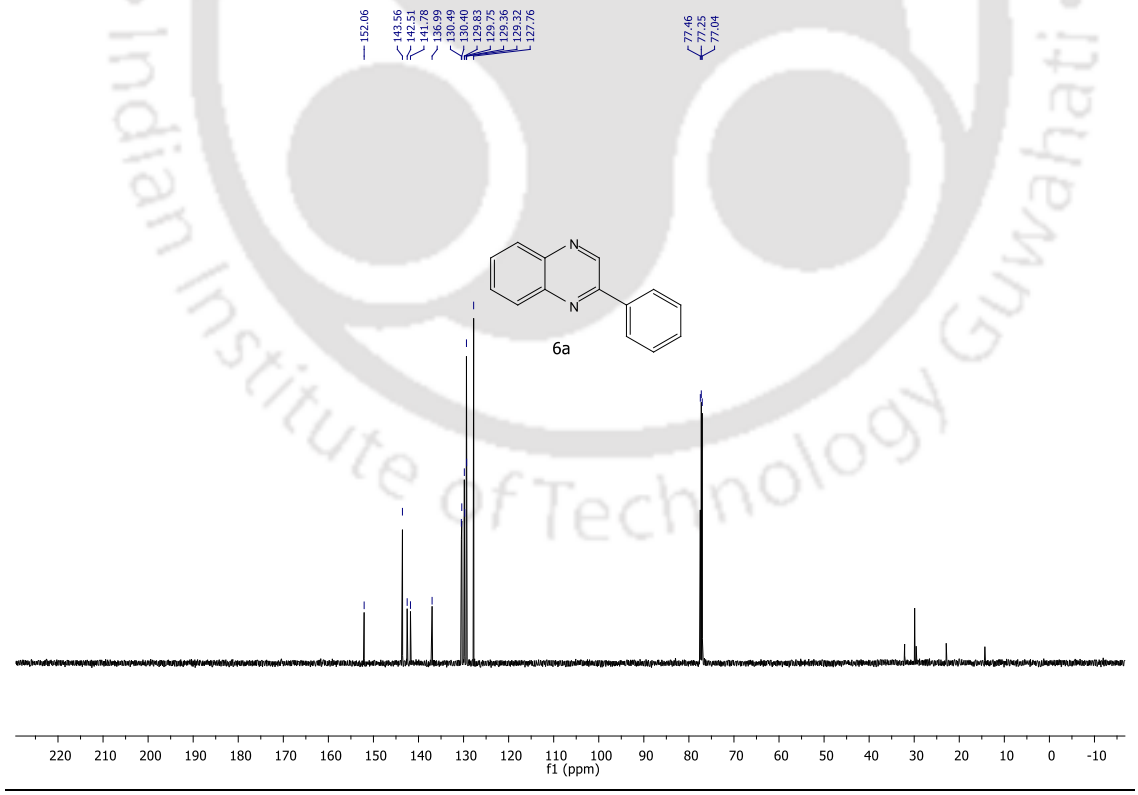
1-(naphthalen-2-yl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (8e):[8e] Yellow gummy solid (yield 48%, 12.0 mg); R_f = 0.5 (EtOAc/hexane 1:8); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.52 (s, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 3.72 (t, *J* = 6.8 Hz, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 2.02 – 1.93 (m, 4H); **HRMS (ESI-TOF):** Calc for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.1176; found: 254.1173.

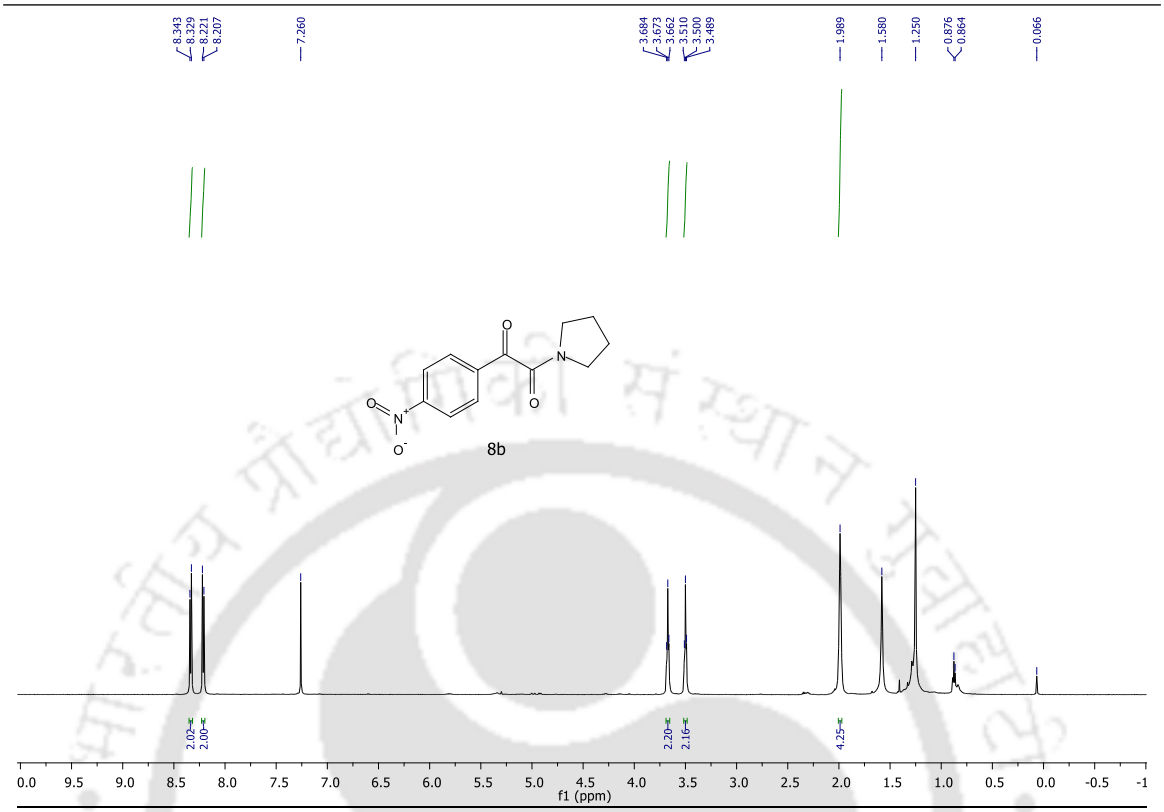
2.10 Selected spectra of products

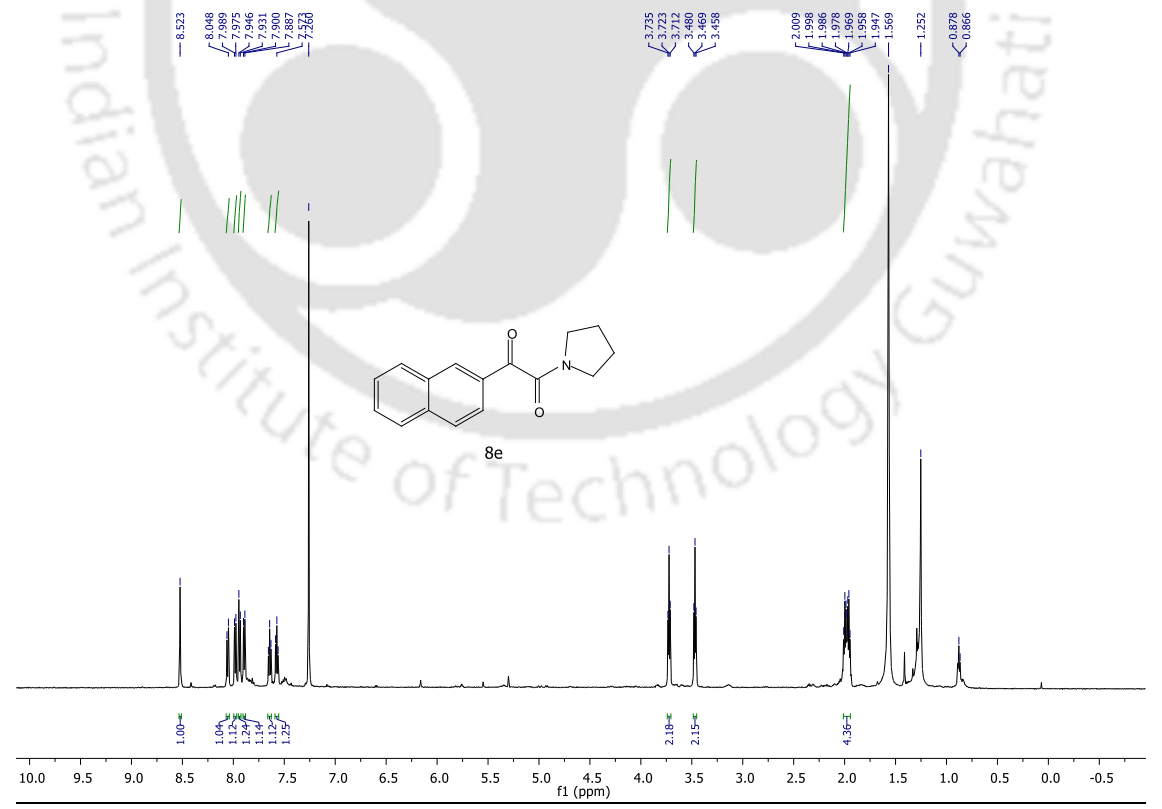


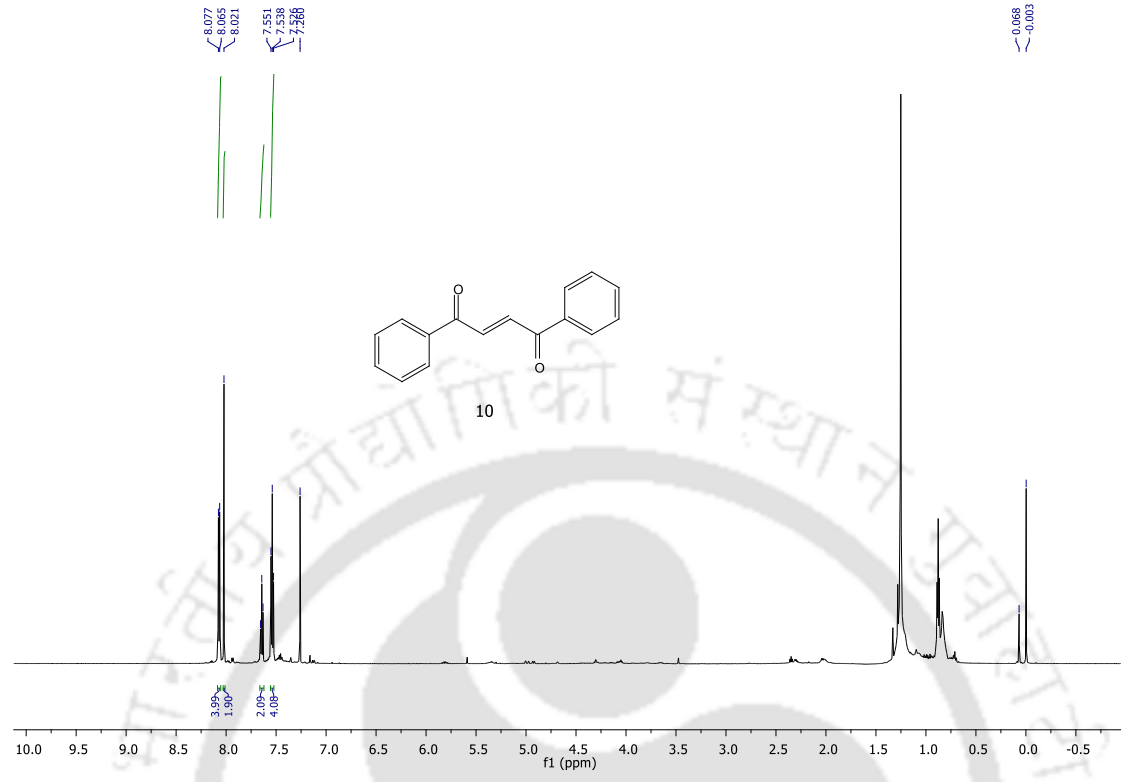


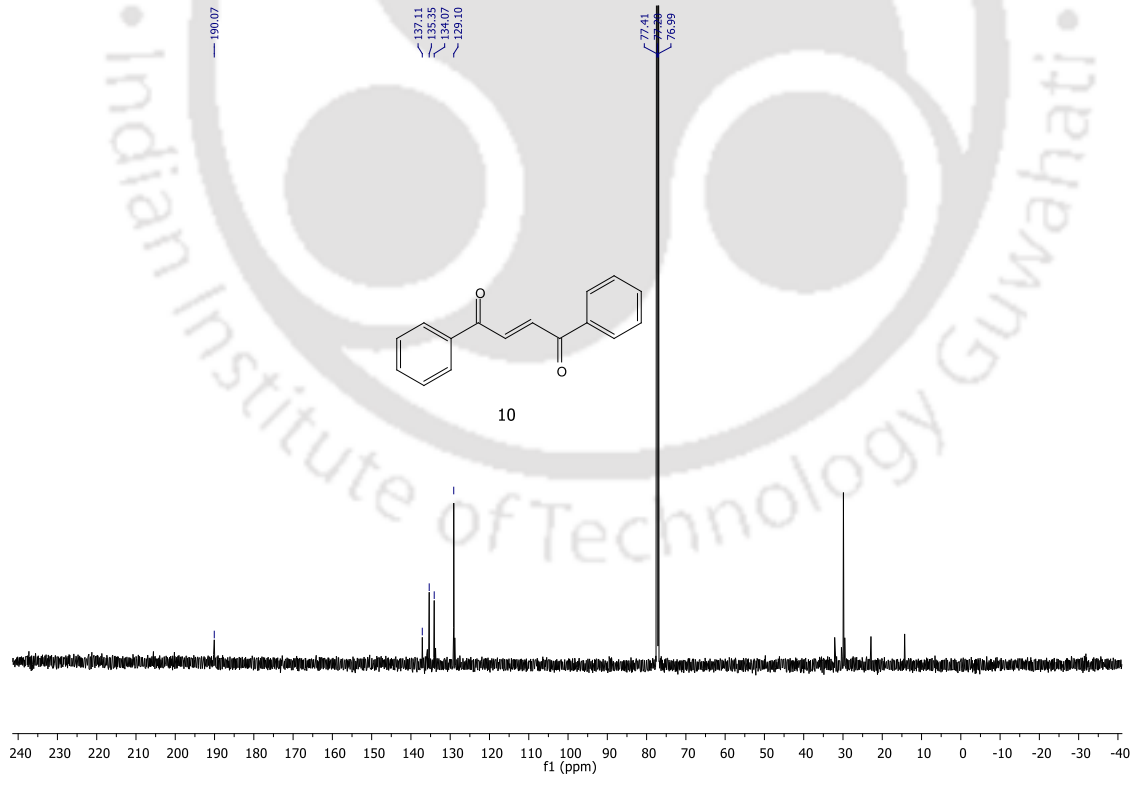






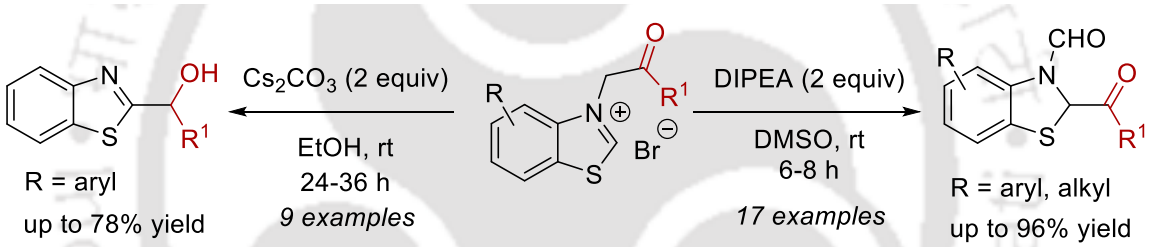






Chapter 3

Synthesis of N-Formyl-2-Benzoyl Benzothiazolines and 2-Substituted Benzothiazoles from N-Phenacylbenzothiazolium Bromides



3.1 Introduction

One of the current challenges in synthetic organic chemistry is to develop efficient, selective and metal-free oxidation of organic substrates that utilize dioxygen as the terminal oxidant.[1] The direct oxidative synthesis of heterocycles using molecular oxygen is rare. Benzothiazolines are important classes of heterocycles which display a wide range of biological and medicinal activities and are used as antiglutamates, antioxidants, anticonvulsants and also as efficient reducing agents[2] (Figure 3.1). Benzothiazole motifs are also present in a myriad of natural products and biologically active compounds.[3] In particular, 2-substituted benzothiazoles are utilized as antiparasitics, antituberculotics, antitumor agents, and calcium channel antagonists (Figure 3.1).[4]

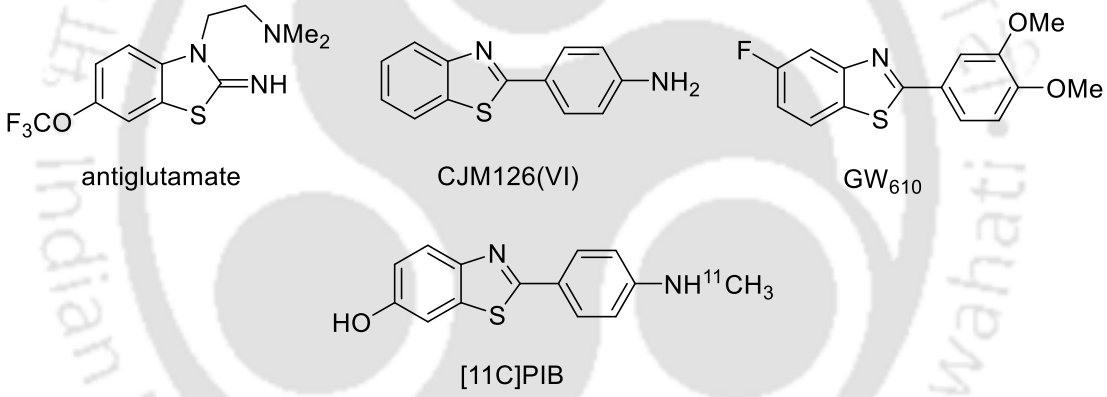


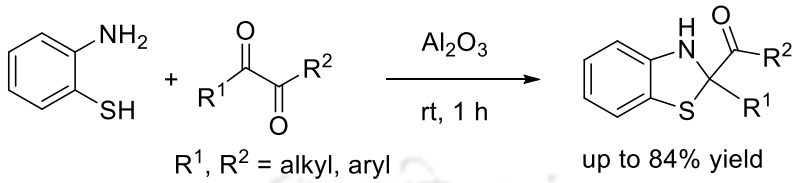
Figure 3.1: Representative bioactive benzothiazoline and benzothiazoles

Thus, the interest in the rapid construction of benzothiazolines[5] and 2-substituted benzothiazoles[6] has been observed over the years. However little attentions were given for the C2-substituted benzothiazoles with benzylic hydroxyl group.[7]

3.2 Reported strategies for 2-acyl heterocycles synthesis

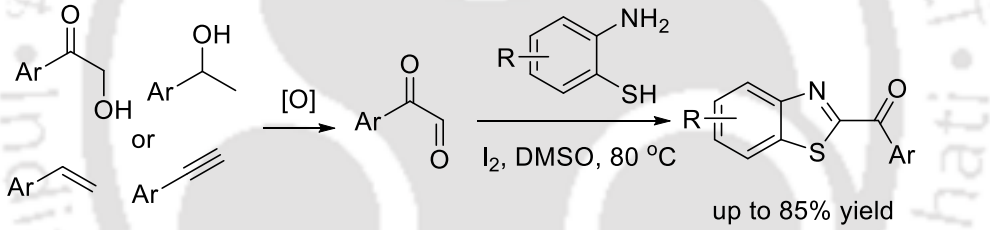
Over the past decades, quiet a number of synthetic methodologies have been reported in the literature for the effective synthesis of 2-acyl heterocycles. Some of the selective reported strategies have been shown in the following section.

Kodomari *et al*. accomplished a reaction of *o*-aminothiophenol and ketones in the presence of neutral alumina under solvent-free conditions to give 2,2-disubstituted benzothiazolines in high yields (Scheme 3.1).[5d]



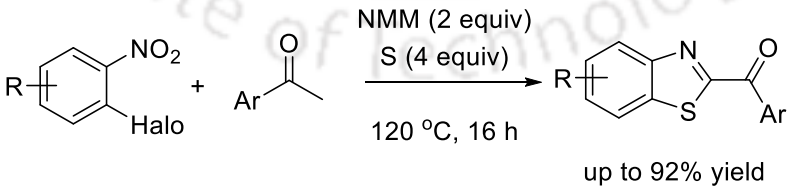
Scheme 3.1: Synthesis of 2,2-disubstituted benzothiazolines

Wu group developed a synthesis of 2-acylbenzothiazoles from *o*-aminothiophenol and arylethenes/arylacetylenes/2-hydroxyaromatic ketones/carbinols by one pot metal free oxidation/cyclization sequence (Scheme 3.2).[8a] The same group had also shown another synthetic route by I_2/KOH promoted direct ring-opening aroylation of benzothiazole.[8b]



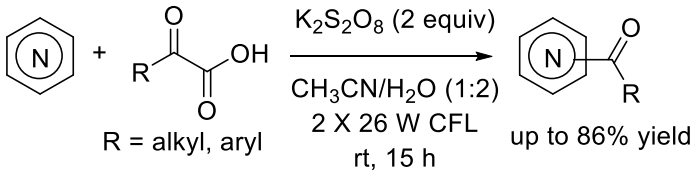
Scheme 3.2: Synthesis of 2-acylbenzothiazoles

A convenient redox condensation reaction between *o*-halonitrobenzenes, acetophenones, and sulphur catalyzed by *N*-methylmorpholine (NMM) has been reported by Nguyen *et al.* for the formation of 2-aroylbenzothiazoles (Scheme 3.3).[8c]



Scheme 3.3: Synthesis of 2-acylbenzothiazoles from *o*-halonitrobenzenes

Delord and co-workers demonstrated metal and photo-catalyst free visible light triggered C-H acylation of *N*-heterocycles (Scheme 3.4).[8d]

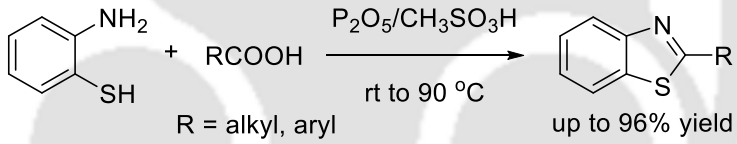


Scheme 3.4: Acylation of *N*-heterocycles using visible light

3.3 Selective methodologies for 2-substituted benzothiazoles synthesis

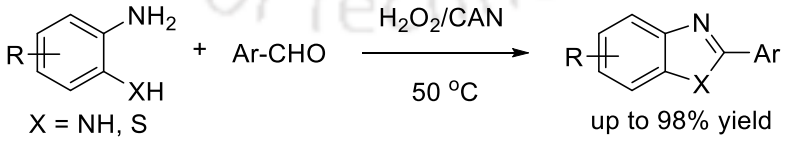
2-Substituted benzothiazoles have enormous usefulness in pharmaceuticals. Hence, a range of synthetic methodologies have been developed for their preparation.[6]

Boger *et al*. reported syntheses of 2-substituted benzothiazoles directly from 2-aminothiophenol and corresponding carboxylic acid by warming with P_2O_5/CH_3SO_3H (1/10, w/w) followed by aqueous basic workup. Aliphatic and aromatic carboxylic acids afforded the corresponding 2-substituted benzothiazoles. The reaction was not useful for *α,β*-unsaturated carboxylic acids (Scheme 3.5).[9a]



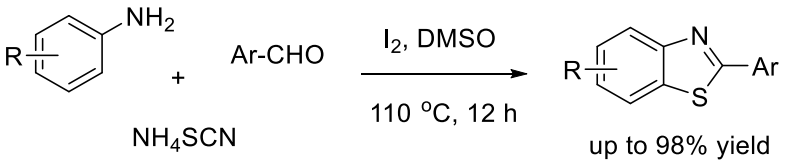
Scheme 3.5: P_2O_5 catalyzed syntheses of 2-substituted benzothiazoles

Barhami and co-workers developed a new convenient method for the syntheses of 2-substituted benzimidazole and benzothiazole with excellent yields using H_2O_2/CAN system from 1,2-phenylenediamines and 2-aminothiophenols respectively (Scheme 3.6).[9b]



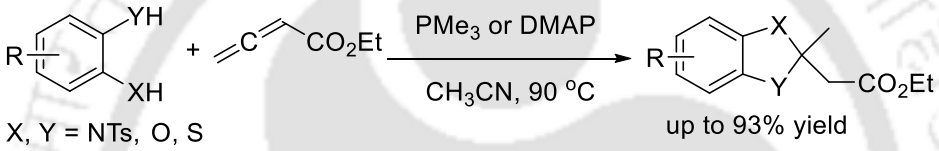
Scheme 3.6: Syntheses of 2-aryl benzimidazole and benzothiazole

Recently, I_2-mediated oxidative annulation reaction for synthesis of 2-arylbenzothiazoles from arylaldehydes, aromatic amines, and ammonium thiocyanate has been developed by Hajra and co-workers (Scheme 3.7).[6g]



Scheme 3.7: I_2-mediated oxidative synthesis of 2-arylbenzothiazoles

Kwon group developed phosphine initiated double-Michael reaction that enables the syntheses of C2-functionalized five-membered heterocyclic rings from dinucleophiles and allenes (Scheme 3.8).[5e]

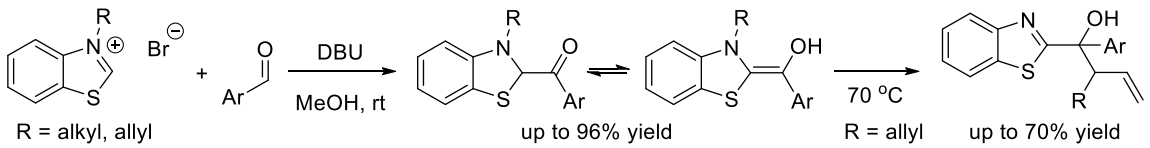


Scheme 3.8: Syntheses of 2,2-disubstituted heterocycles

3.4 Synthetic methodologies using thiazolium salt

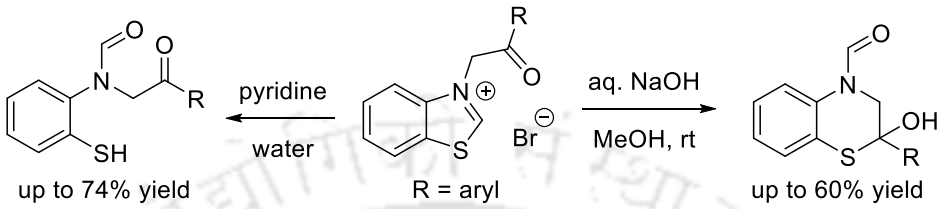
N-Phenacylbenzothiazolium bromides are useful heterocyclic ammonium salts and deliver highly reactive azo-methine ylides[10] in the presence of base. A range of cycloaddition reactions have been developed by treating this ylide with various olefinic dipolarophiles.[11] In the absence of suitable dipolarophiles, self-isomerized products were observed.[12]

Matthias *et al*. reported DBU catalyzed C2-benzoylation of azole from *N*-alkyl thiazolium salts in presence of weak base (Scheme 3.9). Upon heating *N*-allyl benzothiazoline derivative, the C2-alkyl benzothiazole product was formed as stable product *via* Claisen rearrangement.[13]



Scheme 3.9: DBU catalyzed C2-benzoylation of thiazole

Hydrolysis of *N*-phenacylbenzothiazolium bromide with strong bases like sodium hydroxide delivered hemiketalic 1,4-benzothiazines. But in the presence of pyridine/hot water conditions, ring opening occurred and *N*-formyl-*N*-phenacyl thiophenol product was observed (Scheme 3.10).[12]



Scheme 3.10: Self-isomerization of *N*-phenacylbenzothiazolium

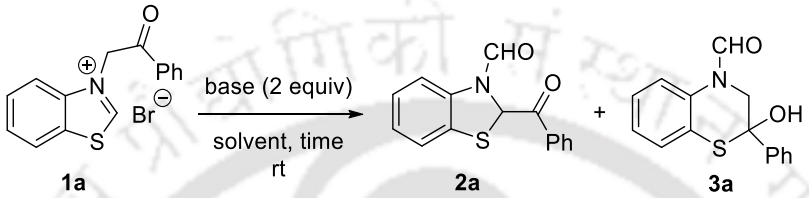
Though hemiketalic 1,4-benzothiazines products were synthesized for biological study, further derivatizations are not known in the literature.

3.5 Result and discussion

The investigation was started by stirring *N*-phenacylbenzothiazolium bromide **1a** with an excess amount of base in ethanol at room temperature (Table 3.1). When 2 equivalents of DABCO was treated (Table 3.1, entry 1), pleasingly *N*-formyl-2-benzoyl benzothiazoline **2a** was formed in 25% yield along with hemiketalic 1,4-benzothiazine **3a** (10%) in 24 hours. The structure of **2a** was confirmed by X-ray crystallography.[14] To improve the yield of the product, different bases were screened. The yield of **2a** got decreased with pyridine but a significant 78% yield was attained for **3a**. Thus it was expected that **3a** is an intermediate for the formation of **2a**. Piperidine provided almost equal amounts of **2a** and **3a** (entry 3). Interestingly, the yield of **2a** got improved with DBU. The reaction also worked with inorganic base such as sodium carbonate though moderate yield was detected (entry 5). Cs_2CO_3 was also employed in the reaction and surprisingly one different product (neither **2a** nor **3a**) was observed after 24 hours. When NaOH was used, **3a** was observed as the major product after 6 hours (entry 6) and it decomposed to a complex reaction mixture after long reaction time. Finally, DIPEA was found to be the best base to provide 80% yield of **2a** in 6 hours (entry 7). To further enhance the yield of the product **2a**, different solvents were checked. Similar yields were obtained in CH_3CN

and DMF (entries 8-9). Slightly lower yield (62%) was observed in $CHCl_3$ solvent. Finally, DMSO turned out to be the best solvent to deliver product **2a** in 90% yield (entry 11). When water was used as the solvent, hemiketalic 1,4-benzothiazine **3a** was formed in 90% yield along with trace amount of **2a** (entry 12). NaOH was also used in DMSO solvent and **3a** was again observed as the major product after 6 hours.

Table 3.1: Optimization of reaction condition



1a 2a 3a

entry[a]	base	solvent	time (h)	yield (%)[b] (2a)	yield (%)[b] (3a)
1	DABCO	EtOH	24	25	10
2	pyridine	EtOH	24	18	72
3	piperidine	EtOH	24	42	48
4	DBU	EtOH	24	68	15
5	Na_2CO_3	EtOH	36	57	0
6	NaOH	EtOH	6	15	70
7	DIPEA	EtOH	6	80	5
8	DIPEA	CH_3CN	6	80	15
9	DIPEA	DMF	6	82	10
10	DIPEA	$CHCl_3$	6	62	10
11	**DIPEA**	**DMSO**	**6**	**90**	**5**
12	**DIPEA**	**H_2O**	**6**	**5**	**90[c]**

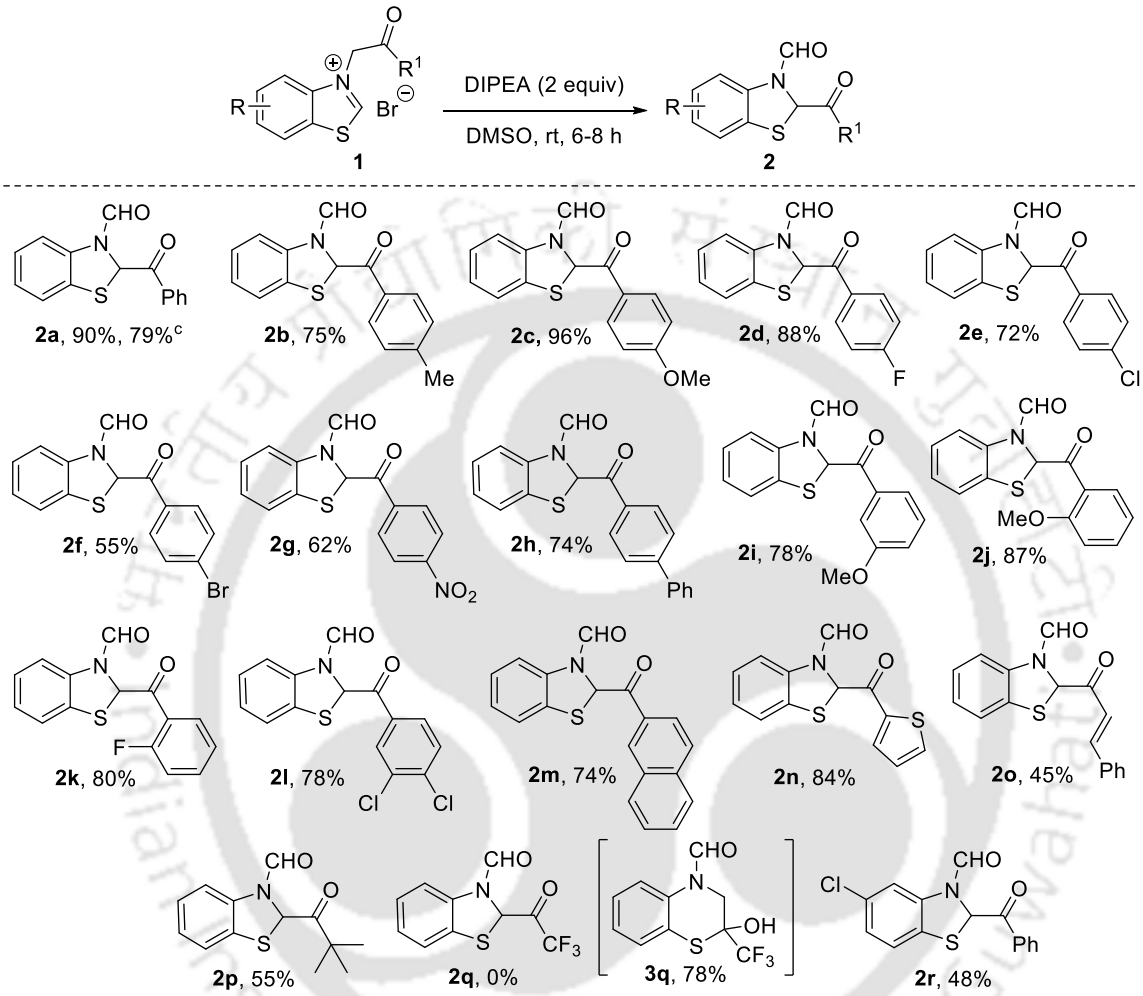
[a]Reaction conditions: 0.1 mmol of **1a** in 1 mL solvent using 2 equivalents of base. [b]Isolated yield after silica gel column chromatography. [c]product was filtered and washed with cold water.

3.6 Substrate scope of *N*-formyl-2-benzoyl benzothiazolines

After getting *N*-formyl-2-benzoyl benzothiazoline **2a** in decent yield, the scope and generality of the methodology was studied under the optimized conditions. At the beginning, the ketoaryl group in **1** was varied (Scheme 3.11). It turned out that a range of substitutions at the *ortho*-, *meta*-, and *para*- positions of the aryl group were tolerated. Initially, different *para*-substitutions were checked and good results were attained. For example, acceptable yield was achieved with benzothiazolium bromide **1b** having *para*-tolyl group. Gratifyingly, an excellent result was achieved with 4-anisyl group containing salt **1c** and the corresponding product **2c** was isolated in 96% yield. Then different 4-halo substitutions were investigated and the products **2d**-**2f** were obtained in varied yields. 4-Fluoro and 4-chlorophenacyl substituted salts **1d** and **1e** provided good yields 88% and 72% respectively while 4-bromophenacyl substituted salt **1f** afforded moderate yield of 55%. Benzothiazolium bromide **1g** having electron poor nitro group also participated in the reaction, and moderate yield was detected. Then biphenyl group containing salt **1h** was employed in the reaction, and product **2h** was isolated in 74% yield. The reaction was also smooth with *m*-methoxy substituted aryl group containing salt **1i**, and gratifyingly produced good yield. Then *ortho*-substituted aryl group containing salts **1j** and **1k** were screened, and the desired products **2j**-**2k** were obtained in 87% and 80% yields respectively. 3,4-Disubstituted salt was also well tolerated to delivered product **2l** in 78% yield. Benzothiazolium bromide **1m** having 2-napthyl group also took part in the reaction, and 74% yield for **2m** was detected. Then a reaction was carried out with 2-thienyl substituted salt **1n**, and gratifyingly product **2n** was obtained in 84% yield. Moreover, our methodology is also suitable for cinnamyl substituted benzothiazolium bromides **1o**, albeit slightly lower yield was observed for the corresponding product **2o**. Aliphatic substituted salts **1p** and **1q** having ^{t}butyl keto and CF_3 keto group were also prepared and engaged in the reaction. Product **2p** having ^{t}butyl keto group was isolated with 55% yield. But the corresponding hemiketalic 1,4-benzothiazine product **3q** was observed for CF_3 keto containing salt **1q**. When the reaction was carried out in 1 mmol scale, the yield slightly dropped for **2a**. Then we decided to vary aryl part of **1**. Thus, 5-choloro substituted *N*-phenacylbenzothiazolium bromide **1r** was prepared and engaged in

the reaction (Scheme 3.11). Gratifyingly, the reaction progressed well to provide **2r** in moderate yield.

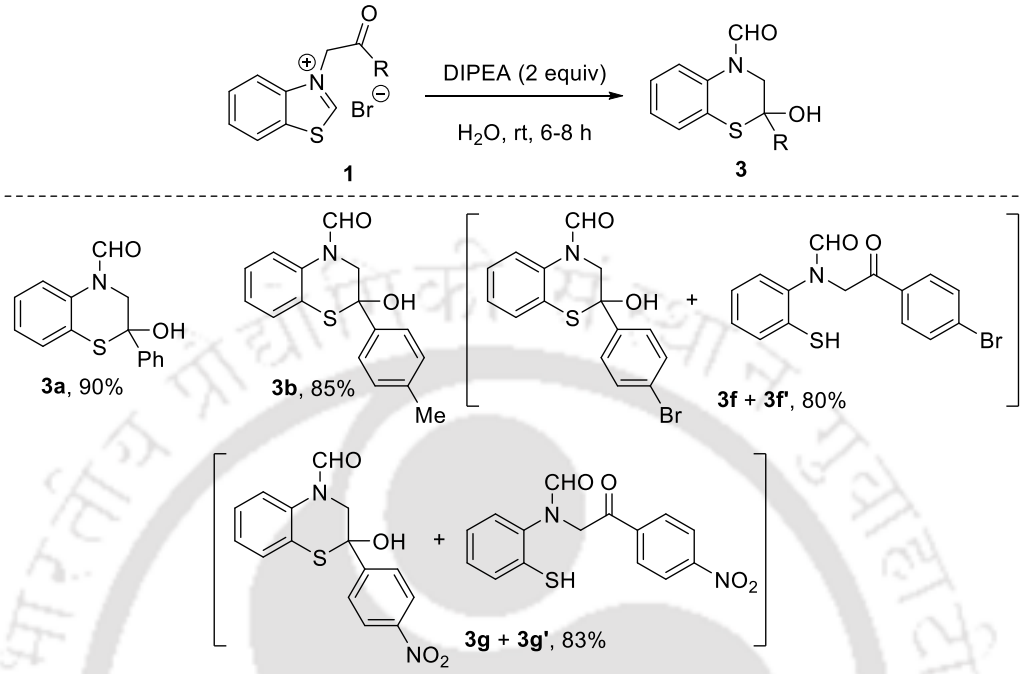
Scheme 3.11: Substrate scope of *N*-formyl-2-benzoyl benzothiazolines [a,b]



[a]Reactions were carried out with 0.2 mmol of **1** in 2 mL DMSO using 2 equivalents of DIPEA at rt for 6-8 hours. [b]Yields were determined after isolation from silica gel column chromatography. [c]Reaction was carried out with 1 mmol of **1a**.

Then we move for substrate scope of the hemiketalic 1,4-benzothiazine product **3**. Initially different electron donating and withdrawing substituents were incorporated at the *para* position (Scheme 3.12). Product **3b** having *para*-tolyl substituent was isolated with 85% yield. But a mixture of products was observed for electron-withdrawing 4-bromo and 4-nitro substrates **1f** and **1g** respectively.

Scheme 3.12: Substrate scope of hemiketalic 1,4-benzothiazine[a,b]



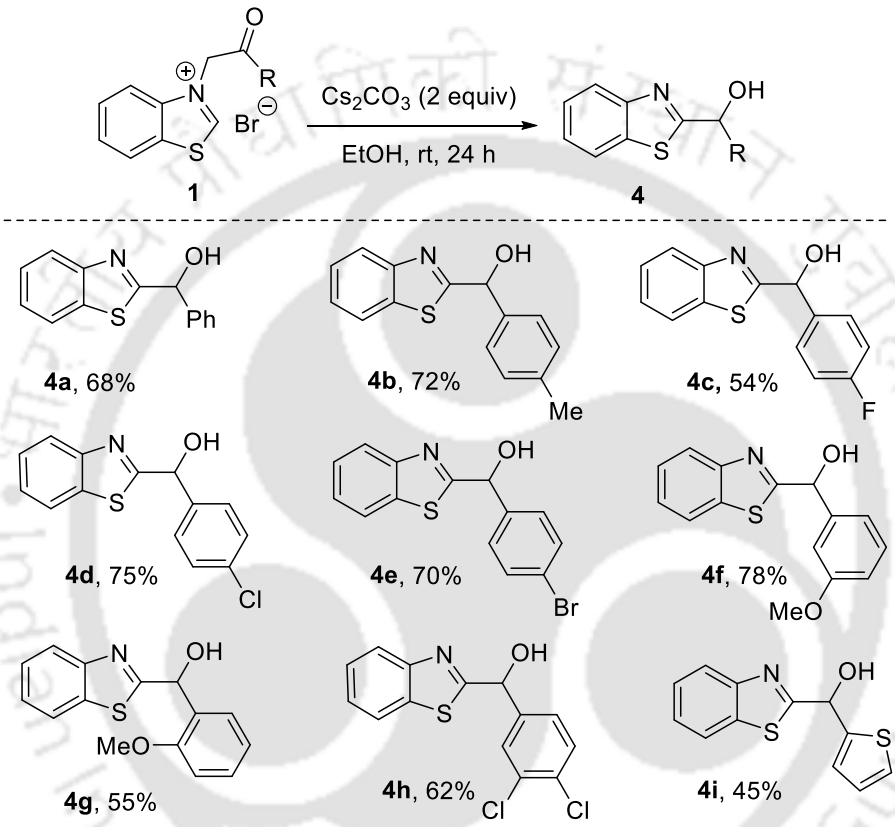
[a]Reactions were carried out with 0.2 mmol of **1** in 2 mL water using 2 equivalents of DIPEA at rt for 6-8 hours. [b]Products were filtered and washed with cold water

3.7 Substrate scope of 2-substituted benzothiazole

We observed a facile formation of 2-substituted benzothiazole **4a** (68% yield) after treatment of *N*-phenacylbenzothiazolium bromide **1a** with caesium carbonate in ethanol during optimization. Different solvents were also screened to improve the yield of **4a**, but still ethanol was the best solvent. Encouraged by this result, different keto group containing benzothiazolium bromides **1** were screened in this condition (Scheme 3.13). Initially, *p*-substituted aryl group containing salts **1** were employed in the reaction, and gratifyingly good results were observed. For example, product **4b** having tolyl group was isolated in 72% yield. Different 4-halo substitutions were also tolerated and the corresponding products **4c**-**4e** were obtained in acceptable yields. The reaction also took place with *meta*-anisyl group containing salt **1i**, and the desired product **4f** was attained in 78% yield. *Ortho*-anisyl group containing salt **1j** also participated in the reaction to deliver **4g** in moderate yield. Then 3,4-dicholosubstiuted salt **1l** was screened and good

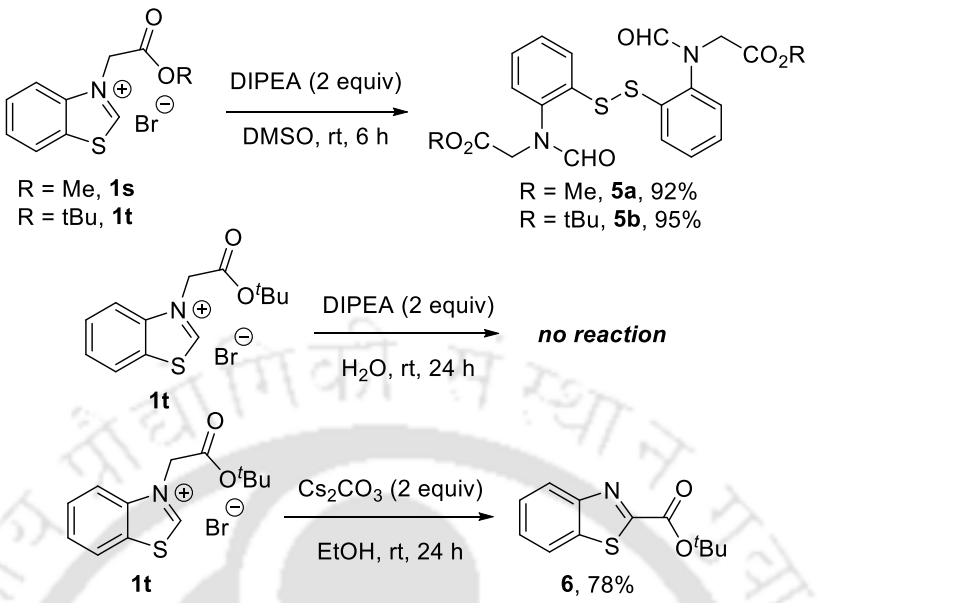
result was observed for product **4h**. Moreover, heteroaromatic thienyl keto group can also be incorporated in **1**, and the product **4i** was isolated in moderate yield. Interestingly, when ^{t}butyl keto group containing salt **1p** was employed, only formation of benzothiazoline **2p** was observed.

Scheme 3.13: Substrate scope of 2-substituted benzothiazole[a,b]



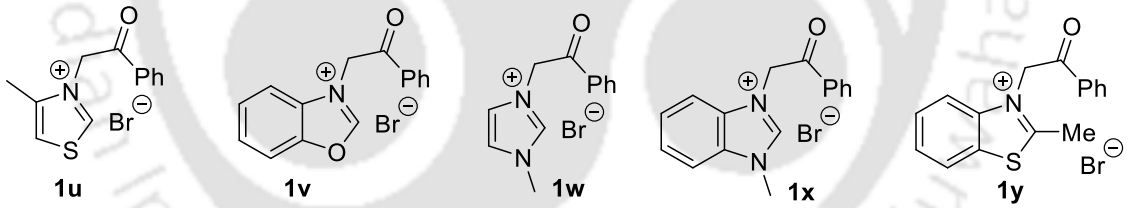
[a]Reactions were carried out with 0.2 mmol of **1** in 2 mL EtOH using 2 equivalents of cesium carbonate at rt for 24 hours. [b]Yields after silica gel column chromatography.

Then we observed formation of symmetrical disulfide **5a** after stirring methylester containing salt **1s** with DIPEA in DMSO (Scheme 3.14). Organic disulfides are important structural moieties found in various marine natural products,[15] pharmaceuticals,[16] materials,[17] and polymers.[18] The reaction was also checked with ^{t}butyl ester containing salt **1t**, and product **5b** was formed in 95% yield.[19] When ^{t}butyl ester containing salt **1t** was stirred with DIPEA in water no reaction occurred. But treatment of **1t** with Cs_2CO_3 in ethanol provided the 2-substituted benzothiazole **6**.



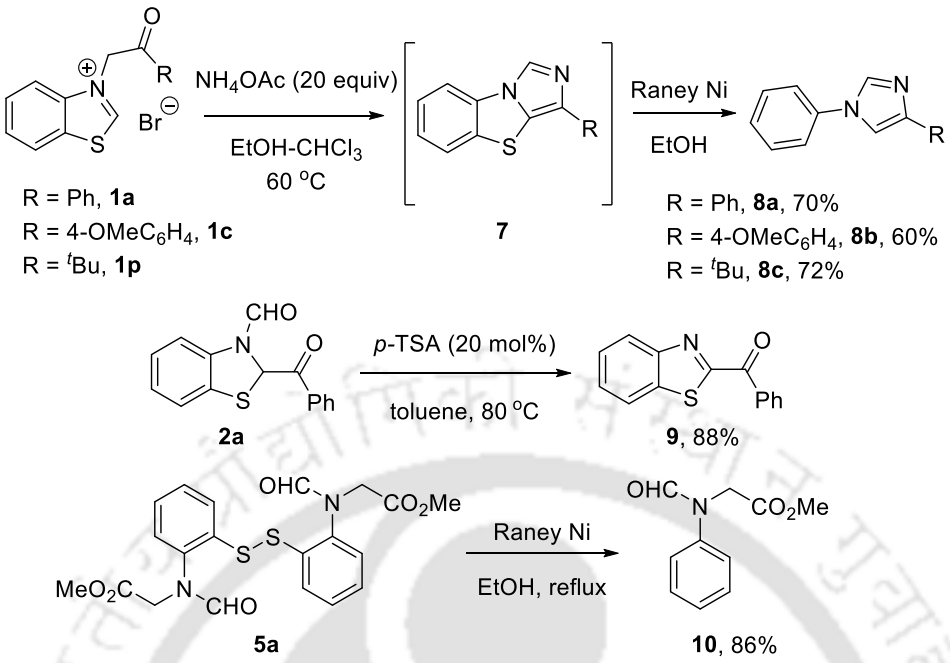
Scheme 3.14: Anomalous behaviour of ester containing salts

Then we focused on the employment of other *N*-phenacyl heterocyclic ammonium salts **1u-1y**. Unfortunately, the desired products (*N*-formyl heterocycles/2-substituted heterocycles) were not achieved under the same reaction conditions (Scheme 3.15).



Scheme 3.15: Unproductive salts

The synthetic utility of our method was established by performing few useful transformations (Scheme 3.16). Initially, a one-pot tandem reaction of **1a** was carried out with ammonium acetate to deliver **7a**, which was further treated with Raney Ni in dry ethanol to deliver 4-substituted *N*-phenylimidazole[20] **8a** in good overall yield. Similar yield was also observed when **2a** was treated under similar reaction conditions. Inspired by this outcome, other derivatives **8b** and **8c** were also prepared. Then acid treatment of **2a** resulted in the formation of 2-benzoyl benzothiazole **9** in high yield. Finally, disulfide **5a** was refluxed in dry ethanol with Raney Ni. Gratifyingly, desulfurization[11e] happened and the desired methyl *N*-formyl-*N*-phenylglycinate (**10**) was formed in 86% yield.



Scheme 3.16: Synthetic Transformations

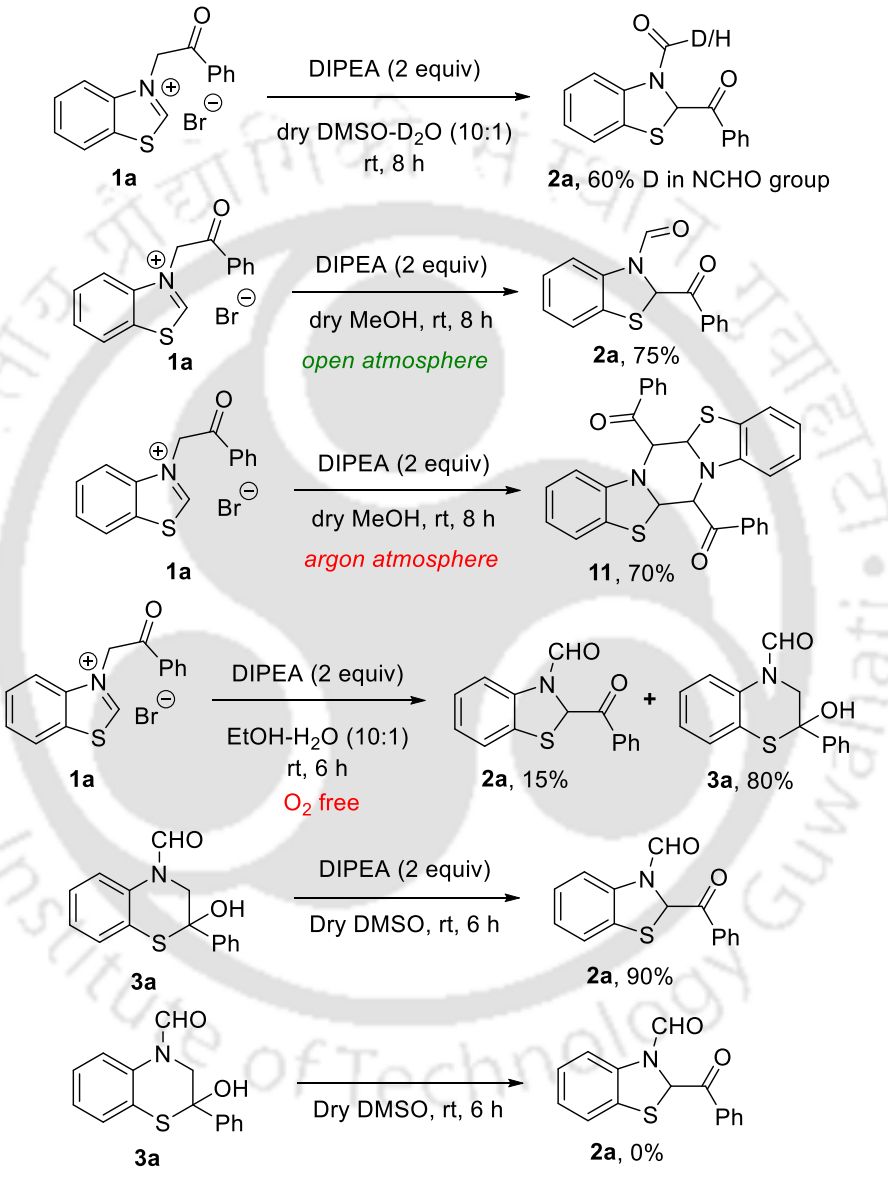
3.8 Plausible reaction mechanism

To understand the mechanism of the reaction, few reactions were carried out (Scheme 3.17). Some reactions have been performed in dry EtOH/MeOH to avoid oxidation by DMSO.

Role of H_2O: After treatment of **1a** with DIPEA in DMSO-D_2O mixture (10:1), product **2a** was formed with 60% D in the formamide functionality. Thus it dictates that formamide motif could be generated from hydrolysis of **1a** with the moisture present in the solvent. Reaction was also performed in absolute methanol under open atmosphere as well as under argon atmosphere. As a result, *N*-formyl-2-benzoyl benzothiazolines formation has been observed under open atmosphere because of hygroscopic nature of methanol. But formation of dimerized [3+3] cycloaddition product (5a,6,12a,13-tetrahydrobenzo[4,5]thiazolo[3,2-*a*]benzo[4,5]thiazolo[3,2-*d*]pyrazine-6,13-diyl)bis-(phenyl-methanone) **11** was observed under argon as checked in mass spectroscopy instead of *N*-formyl-2-benzoyl benzothiazolines. Inseparable mixture was isolated from column chromatography.

Role of O_2 and base: Also, oxygen/air free reaction was performed in ethanol-water mixture solvent (frizzed in liquid nitrogen). Here the major product was **3a**. Thus, it is

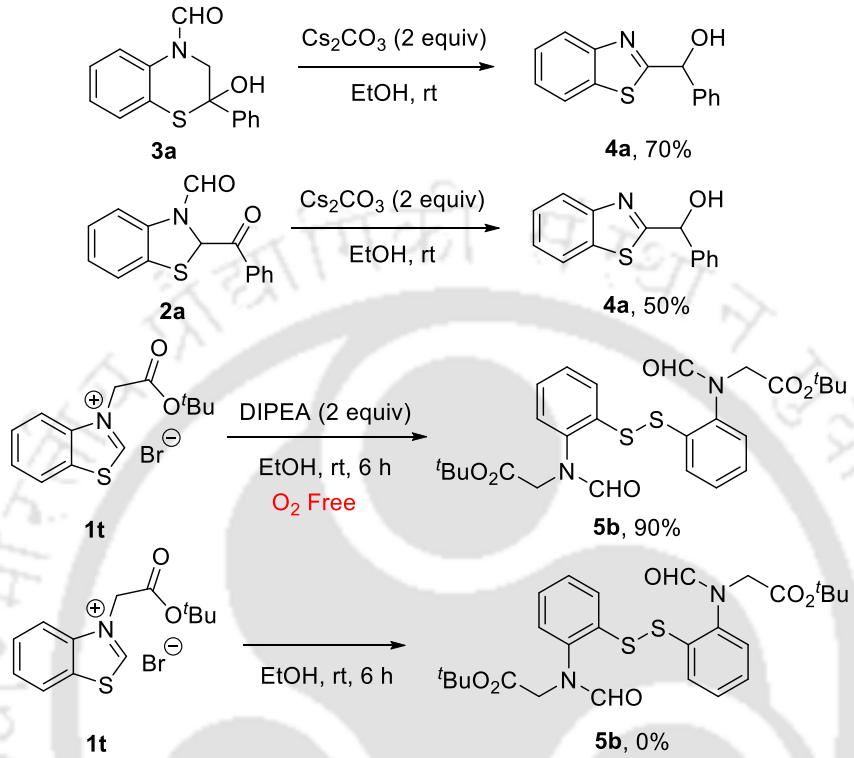
clear that oxygen is helping for an iminium ion formation which led to formation of **2a**. To support the observation **3a** as the key intermediate, reaction was performed by treating **3a** under the reaction conditions and gratifyingly product **2a** was observed. It has been observed that the base has a significant role in the reaction.



Scheme 3.17: Control Experiments for product **2a**

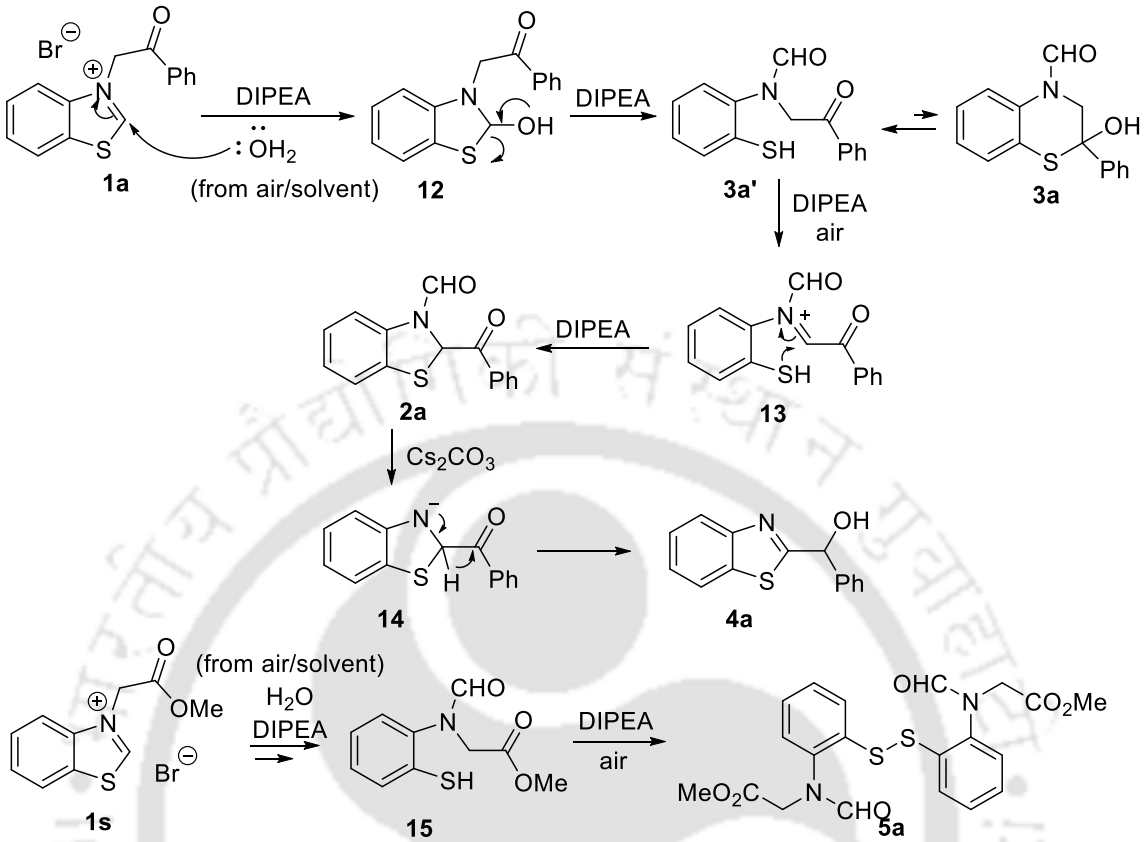
When **3a** was treated with cesium carbonate in ethanol, product **4a** was obtained in 70% yield. Also, reaction of **2a** with cesium carbonate delivered **4a** in 50% yield. Thus, it is expected that **4a** was formed from **2a** *via* intermediate **3a** (Scheme 3.18).

Also it has been observed that atmospheric oxygen has no significant role in the formation of disulfide compound **5b** but base has a vital role in the reaction (Scheme 3.18).



Scheme 3.18: Control Experiments for product **4a** and **5b**

Based on the observations from control experiments, a plausible mechanism has been shown in Scheme 3.19 for the formations of **2a**, **4a** and **5a**. It is expected that **12** will first form by hydrolysis, which under basic condition generates **3a'**. Then an unusual imine (**13**) formation takes place under air.[21] Finally, cyclization of **13** delivers **2a**. Also, **3a'** is in equilibrium with **3a**, and interestingly, in our condition, **3a'** predominates. On cesium carbonate treatment, **2a** is hydrolyzed to form **14**. Then 1,2-hydride shift along with aromatization takes place, and benzothiazole **4a** is formed. Similarly, **1s** is converted to **15**, which converted to disulphide **5a** in presence of base.



Scheme 3.19: Proposed mechanistic pathway

In summary, this report demonstrates an unusual aerobic hydrolysis-cascade reaction for the first synthesis of *N*-formyl-2-benzoyl benzothiazolines and green approaches for 2-substituted benzothiazoles and disulfides. The aerobic formation of iminium ion intermediates as well as disulfides and 1,2-hydride shift for aromatization are rare and will lead further investigations. Also, synthetic applications such as cascade formation of *N*-substituted imidazoles have been demonstrated. Given the high pharmaceutical importance of benzothiazoline and benzothiazoles, the newly synthesized products will be useful for the development of new drugs.

3.9 Experimental section

2-Bromoacetophenone and Cs_2CO_3 were purchased from aldrich. Pyrrolidine, DIPEA, DABCO and DBU were purchased from spectrochem. Benzothiazole was purchased from alfa aesar.

A. General procedure for the synthesis of *N*-Arylbenzothiazolium bromides

N-Arylbenzothiazolium bromides salts **1** were prepared by refluxing benzothiazole with corresponding phenacyl bromides in ethanol (1M) for 2 hours. Then the solid was filtered and washed using diethyl ether/DCM.

B. Synthesis of *N*-formyl-2-benzoyl benzothiazoline (2a-2q)

In a 5 mL round bottom flask, compound **1** (0.2 mmol) and DIPEA (0.4 mmol) were taken in 2 mL DMSO. Then the reaction mixture was stirred at room temperature for 6-8 hours. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with EtOAc (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (10%-20% EtOAc/hexane) to afford *N*-formyl-2-benzoyl benzothiazoline **2**.

C. Synthesis of hemiketalic 1,4-benzothiazine (3)

In a 5 mL round bottom flask, compound **1** (0.2 mmol) and DIPEA (0.4 mmol) were taken in 2 mL water. Then the reaction mixture was stirred at room temperature for 6-8 hours. The solid was filtered and washed repeatedly with water. Then the compound was dried under *vacuum* and kept in desiccator for 12 hours. Compound **3** was obtained.

D. General procedure for the synthesis of 2-Substituted Benzothiazoles (4a-4i)

In a 5 mL round bottom flask, compound **1** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) were taken in 2 mL ethanol. Then the reaction mixture was stirred at room temperature for 24-36 hours. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with EtOAc (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (10%-20% EtOAc/hexane) to afford 2-substituted benzothiazoles **4**.

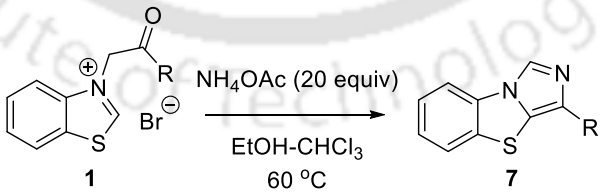
E. Synthesis of Symmetrical Disulfides (5)

In a 5 mL round bottom flask, compound **1s/1t** (0.2 mmol) and DIPEA (0.4 mmol) were taken in 2 mL DMSO. Then the reaction mixture was stirred at room temperature for 6 hours. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with EtOAc (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (40%-50% EtOAc/hexane) to afford desired products **5a/5b**.

F. Synthesis of tert-butyl benzo[*d*]thiazole-2-carboxylate (6)

In a 5 mL round bottom flask, compound **1t** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) were taken in 2 mL ethanol. Then the reaction mixture was stirred at room temperature for 24 hours. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with EtOAc (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated in *vacuum* and purified by silica gel column chromatography to afford tert-butyl benzo[*d*]thiazole-2-carboxylate **6** as colourless sticky liquid. Yield 78%, 36.5 mg; R_f = 0.5 (EtOAc/hexane 1:10); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.23 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 1.68 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 160.3, 159.7, 153.5, 136.9, 127.5, 127.1, 125.7, 122.2, 84.8, 28.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{12}H_{14}NO_2S$ 236.0740; found: 236.0744.

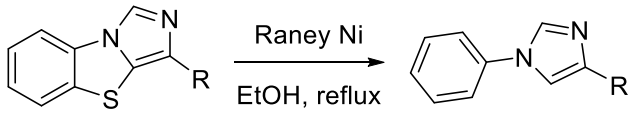
G. Synthesis of 4-substituted *N*-phenylimidazole (8a-8c)



Scheme 3.20: Synthesis of benzothiazole fused imidazoles

In a 5 mL round bottom flask, compound 1 (0.3 mmol) and NH_4OAc (6 mmol) were taken in 2 mL EtOH:$CHCl_3$ (3:1). Then the reaction mixture was stirred at 60 °C for 24 hours.[22] After completion of the reaction, as monitored by TLC, the reaction mixture was

diluted with DCM (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated in *vacuum* and purified by silica gel column chromatography (10%-20% EtOAc/hexane) to afford 3-substituted benzo[*d*]imidazo[5,1-b]thiazole **7**.



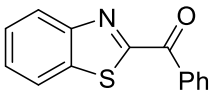
7 **8**

Scheme 3.21: Synthesis of 4-substituted *N*-phenylimidazole

Raney Nickel (600 mg) was taken in a 5 mL round bottom flask and washed repeatedly with dry ethanol. Then compound **7** was dissolved in 2 mL dry ethanol and added to it. The reaction mixture was set to reflux under argon atmosphere. After completion of the reaction, as monitored by TLC, the reaction mixture was filtered using DCM. The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated in *vacuum* and purified by silica gel column chromatography (10%-20% EtOAc/hexane) to afford 4-substituted *N*-phenylimidazole **8.**

H. Synthesis of 2-benzoyl benzothiazole (9)

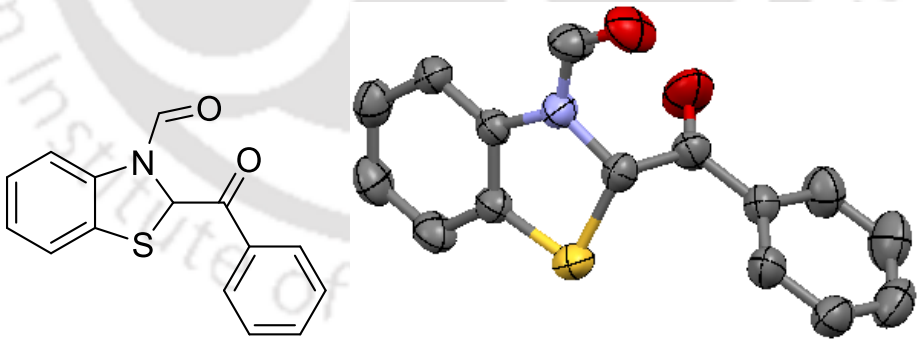
In a 5 mL round bottom flask, compound **2a** (0.2 mmol) and *p*-TSA (0.04 mmol) were taken in 2 mL toluene. Then the reaction mixture was stirred for 8 hours at 80 ^oC. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with EtOAc (5 mL). The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (4% EtOAc/hexane) to afford 2-benzoyl benzothiazole **9** (42 mg). R_f = 0.5 (EtOAc/hexane 1:30); mp 96-98 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.56 (d, *J* = 7.3 Hz, 2H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.61 – 7.54 (m, 4H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 185.6, 167.3, 154.1, 137.2, 135.1, 134.1, 131.5, 128.7, 127.8, 127.1, 125.9, 122.4; **HRMS (ESI-TOF) m/z:** $[M+Na]^+$ Calcd for $C_{14}H_9NNaOS$ 262.0297; found: 262.0315.



I. Synthesis of methyl *N*-formyl-*N*-phenylglycinate[23] (10)

Raney Nickel (400 mg) was taken in a 5 mL round bottom flask and washed repeatedly with dry ethanol. Then compound **5a** (0.1 mmol) was dissolved in 2 mL dry ethanol and added to it. The reaction mixture was set to reflux under argon atmosphere. After completion of the reaction, as monitored by TLC, the reaction mixture was filtered using DCM. The organic layer was washed with water, brine and dried (anhyd. Na_2SO_4). The solvents were concentrated *in vacuum* and purified by silica gel column chromatography (20% EtOAc/hexane) to afford *N*-formyl-*N*-phenylglycinate **10** (33 mg). R_f = 0.5 (EtOAc/hexane 1:5); colourless sticky liquid; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.49 (s, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 4.50 (s, 2H), 3.76 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 169.0, 162.6, 141.2, 130.0, 127.5, 124.1, 52.6, 47.5; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{10}H_{12}NO_3$ 194.0812; found: 194.0823.

J. <u>Single crystal X-ray diffraction data of compound 2a:</u>



ORTEP crystal structure

Table 3.2. Crystal data and structure refinement for compound 2a.

Empirical formula	C15 H11 N O2 S
Formula weight	280.71
CCDC Number	1921604
Crystal habit, colour	Block, Pale Yellow
Crystal size, mm^3	0.30×0.25×0.20
Temperature, T	293
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	'P21/c
Unit cell dimensions	a = 11.5827(8) Å
	b = 8.0597(3)Å
	c = 14.5854(9)Å
	α = 90.00°, β = 105.805°, γ = 90.00°
Volume, V ($Å^3$)	1310.12(14)
Z	4
Calculated density, $Mg·m^{-3}$	1.365
Absorption coefficient, μ (mm^{-1})	0.328
F(000)	560.0
θ range for data collection	2.52° to 28.7420°
Reflection collected/unique	2993/2161
Completeness to θ	99.86% (θ = 26.32°)
Max. and min. transmission	1.00000/0.86350
Refinement method	'SHELXL–2018/3'
Data/restraints/parameters	2993/0/172
Goodness–of–fit on F^2	0.905
Final R indices [I>2sigma(I)]	$R1$ = 0.0455, $wR2$ = 0.1142
R indices (all data)	$R1$ = 0.0690, $wR2$ = 0.1410

[a]GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined). [b]$R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0$, [c]$wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{½}$

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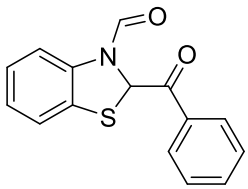
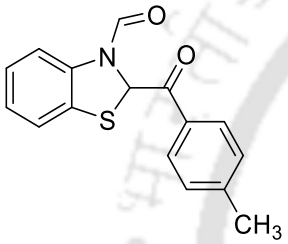
3.11 Characterization data of products

2-benzoylbenzo[d]thiazole-3(2H)-carbaldehyde (2a):



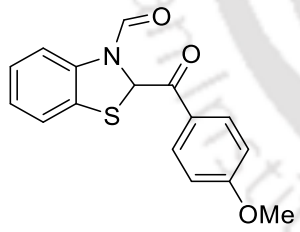
Pale yellow solid (yield: 90%, 48 mg); R_f = 0.5 (EtOAc/hexane 1:9); mp 132-134 ^oC; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.03 (s, 1H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.13 (m, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.03 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 188.2, 158.4, 137.5, 134.3, 132.9, 129.2, 129.0, 128.0, 126.6, 125.9, 123.5, 111.4, 62.4; **HRMS (ESI-TOF):** Calc for $C_{15}H_{12}NO_2S$ $[M+H]^+$ 270.0583; found: 270.0593.

2-(4-methylbenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2b):

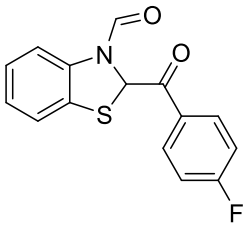


Pale yellow solid (yield: 75%, 42.4 mg); R_f = 0.5 (EtOAc/hexane 1:9); mp 172-174 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 9.03 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 3H), 7.18 – 7.12 (m, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 2.44 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 187.9, 158.5, 145.4, 137.4, 130.2, 129.9, 129.1, 128.0, 126.6, 125.8, 123.5, 111.4, 62.3, 22.0; **HRMS (ESI-TOF):** Calc for $C_{16}H_{14}NO_2S$ $[M+H]^+$ 284.0740; found: 284.0759.

2-(4-methoxybenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2c):



Yellow solid (yield: 96%, 57 mg); R_f = 0.4 (EtOAc/hexane 1:9); mp 184-186 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.02 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.16 – 7.12 (m, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.99 (s, 2H), 6.97 (s, 1H), 3.89 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 187.1, 164.5, 158.5, 131.3, 128.1, 126.5, 125.8, 125.4, 123.4, 114.4, 111.4, 62.1, 55.8; **HRMS (ESI-TOF):** $C_{16}H_{14}NO_3S$ $[M+H]^+$ 300.0689; found: 300.0705.

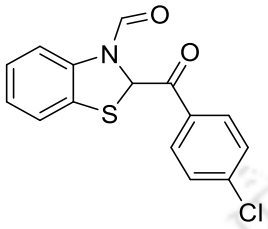


2-(4-fluorobenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2d):

Yellow solid (yield: 88%, 50 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 164-166 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.05 (s, 1H), 7.99 - 7.97 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.15 (m, 4H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ

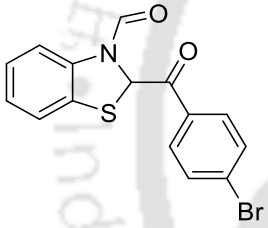
186.9, 166.2 (d, *J* = 105.3 Hz), 158.5, 137.3, 131.7 (d, *J* = 9.4 Hz), 129.2, 127.8, 126.7, 126.0, 123.6, 116.5 (d, *J* = 21.9 Hz), 111.5, 62.3; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -102.92; **HRMS (ESI-TOF):** $C_{15}H_{11}FNO_2S$ $[M+H]^+$ 288.0489; found: 288.0506.

2-(4-chlorobenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2e):



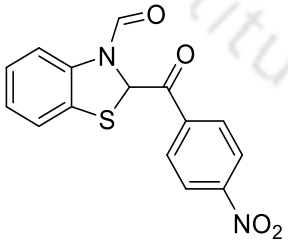
Yellow solid (yield: 72%, 43.5 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 188-190 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.01 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.97 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 187.1, 158.4, 140.9, 137.3, 131.2, 130.3, 129.6, 127.7, 126.8, 126.0, 123.6, 111.5, 62.3; **HRMS (ESI-TOF):** $C_{15}H_{11}{}^{35}ClNO_2S$ $[M+H]^+$ 304.0194; found: 304.0212.

2-(4-bromobenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2f):



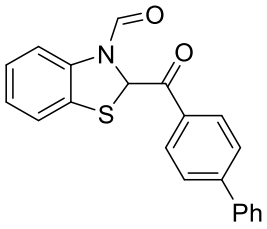
Yellow solid (yield: 55%, 38.0 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 190-192 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.02 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.96 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 187.3, 158.4, 137.2, 132.5, 131.6, 130.3, 129.6, 127.6, 126.7, 125.9, 123.5, 116.6, 111.4, 62.3; **HRMS (ESI-TOF):** $C_{15}H_{11}{}^{79}BrNO_2S$ $[M+H]^+$ 347.9688; found: 347.9721.

2-(4-nitrobenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2g):



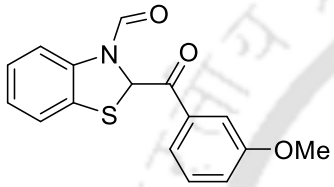
Yellow solid (yield: 62%, 39.0 mg); R_f = 0.3 (EtOAc/hexane 1:9); mp 180-182 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.31 (s, 1H), 8.26 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.35 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.4, 159.0, 153.1, 148.4, 143.6, 134.9, 128.5, 126.9, 126.2, 124.3, 123.9, 122.0, 73.7; **HRMS (ESI-TOF):** $C_{15}H_{11}N_2O_4S$ $[M+H]^+$ 315.0434; found: 315.0439.

2-([1,1'-biphenyl]-4-carbonyl)benzo[d]thiazole-3(2H)-carbaldehyde (2h):



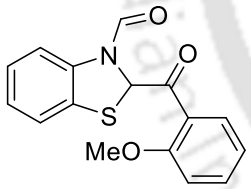
Yellow solid (yield: 74%, 51mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 152-154 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.05 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.19 -7.15 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.06 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 187.8, 158.5, 147.0, 139.8, 137.4, 129.6, 129.2, 128.7, 128.0, 127.8, 127.5, 126.7, 125.9, 123.5, 111.5, 62.4; **HRMS (ESI-TOF):** $C_{21}H_{16}NO_2S$ $[M+H]^+$ 346.0896; found: 346.0917.

2-(3-methoxybenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2i):



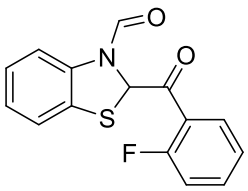
Yellow solid (yield: 78%, 46.5 mg); R_f = 0.4 (EtOAc/hexane 1:9); mp 105-107 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.03 (s, 1H), 7.49 – 7.44 (m, 2H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.12 (m, 3H), 7.07 (t, *J* = 7.1 Hz, 1H), 7.00 (s, 1H), 3.85 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 188.1, 160.3, 158.4, 137.5, 134.2, 130.1, 128.0, 126.6, 125.9, 123.5, 121.2, 120.9, 113.3, 111.4, 62.5, 55.7; **HRMS (ESI-TOF):** $C_{16}H_{14}NO_3S$ $[M+H]^+$ 300.0689; found: 300.0706.

2-(2-methoxybenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2j):



Yellow solid (yield: 87%, 52 mg); R_f = 0.4 (EtOAc/hexane 1:9); mp 154-156 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** 9.00 (s, 1H), 8.04 – 8.02 (m, 1H), 7.56 (t, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.14 – 7.06 (m, 3H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.98 (s, 1H), 4.00 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$);** δ 188.0, 159.4, 158.6, 138.3, 135.7, 132.7, 127.9, 126.2, 125.7, 123.4, 122.2, 121.7, 111.7, 111.2, 67.4, 56.0; **HRMS (ESI-TOF):** $C_{16}H_{14}NO_3S$ $[M+H]^+$ 300.0689; found: 300.0704.

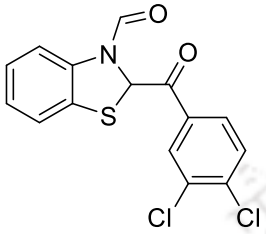
2-(2-fluorobenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2k):



Yellow solid (yield: 80%, 46 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 137-139 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.02 (s, 1H), 8.02 (t, *J* = 8.3 Hz, 1H), 7.63 -7.30 (m, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.22 – 7.19 (m, 1H), 7.18 – 7.13 (m, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 3.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 185.8, 185.7, 162.3 (d, *J* = 251.8 Hz), 161.4, 158.4, 137.7, 136.3 (d, *J* = 9.1 Hz), 132.3 (d, *J* = 2.5 Hz), 127.2, 126.6,

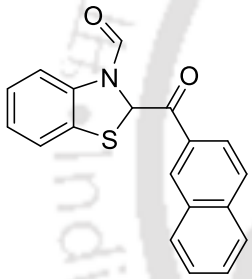
125.9, 125.4 (d, *J* = 3 Hz), 123.7, 120.9 (d, *J* = 12.6 Hz), 116.8 (d, *J* = 23.8 Hz), 111.3, 66.4, 66.3.; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -104.79; **HRMS (ESI-TOF):** $C_{15}H_{11}FNO_2S$ $[M+H]^+$ 288.0489; found: 288.0489.

2-(3,4-dichlorobenzoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2l):



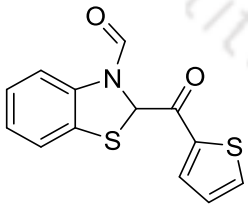
Yellow solid (yield: 78%, 52.5 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 165-167 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.94 (s, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.67 - 7.65 (m, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.86 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$);** δ 186.3, 158.4, 139.0, 137.2, 134.1, 132.7, 131.3, 130.9, 127.7, 127.5, 126.9, 126.1, 123.7, 111.5, 62.4; **HRMS (ESI-TOF):** $C_{15}H_{10}{}^{35}Cl_2NO_2S$ $[M+H]^+$ 337.9804; found: 337.9801.

2-(2-naphthoyl)benzo[d]thiazole-3(2H)-carbaldehyde (2m):



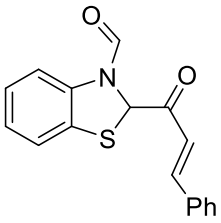
Yellow solid (yield: 74%, 47 mg); R_f = 0.5 (EtOAc/hexane 1:9); mp 154-156 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.07 (s, 1H), 8.44 (s, 1H), 8.00 – 7.94 (m, 3H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.19 – 7.13 (m, 2H), 7.08 (t, *J* = 7.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 188.2, 158.5, 137.4, 136.1, 132.6, 130.7, 130.2, 129.9, 129.3, 129.2, 128.1, 128.0, 127.4, 126.6, 125.9, 124.3, 123.5, 111.5, 62.5; **HRMS (ESI-TOF):** $C_{19}H_{14}NO_2S$ $[M+H]^+$ 320.0740; found: 320.0756.

2-(thiophene-2-carbonyl)benzo[d]thiazole-3(2H)-carbaldehyde (2n):



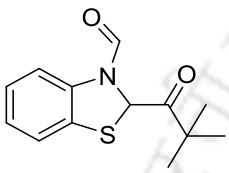
Red solid (yield: 84%, 46 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 128-130 °C; **^{1}H NMR (600 MHz, $CDCl_3$);** δ 9.04 (s, 1H), 7.79 – 7.76 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.20 – 7.15 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.88 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 182.3, 158.4, 139.0, 137.2, 135.5, 133.0, 128.7, 128.0, 126.6, 125.9, 123.4, 111.3, 63.1; **HRMS (ESI-TOF):** $C_{13}H_{10}NO_2S_2$ $[M+H]^+$ 276.0147; found: 276.0167.

2-cinnamoylbenzo[d]thiazole-3(2H)-carbaldehyde (2o):



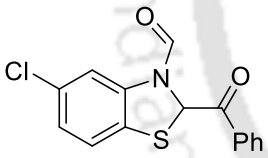
Yellow solid (yield: 45%, 26.5 mg); R_f = 0.55 (EtOAc/hexane 1:9); mp 160-162 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.02 (s, 1H), 7.77 (d, *J* = 15.9 Hz, 1H), 7.58 (d, *J* = 6.3 Hz, 2H), 7.45 – 7.41 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.21 - 7.17 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 15.9 Hz, 1H), 6.47 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 188.1, 158.6, 146.3, 137.3, 134.2, 131.3, 129.2, 128.9, 127.7, 126.6, 126.1, 123.7, 120.3, 111.4, 65.2; **HRMS (ESI-TOF):** $C_{17}H_{14}NO_2S$ $[M+H]^+$ 296.0740; found: 296.0752.

2-pivaloylbenzo[d]thiazole-3(2H)-carbaldehyde (2p):



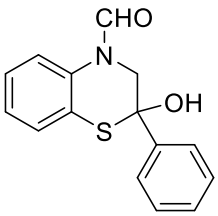
White solid (yield: 55%, 27.5 mg); R_f = 0.4 (EtOAc/hexane 1:9); mp 118-120 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.85 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.39 (s, 1H), 1.22 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 204.0, 157.8, 137.8, 127.6, 126.5, 125.6, 123.4, 110.8, 60.9, 42.8, 27.2; **HRMS (ESI-TOF):** $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.0896; found: 250.0912.

2-benzoyl-5-chlorobenzo[d]thiazole-3(2H)-carbaldehyde (2r):

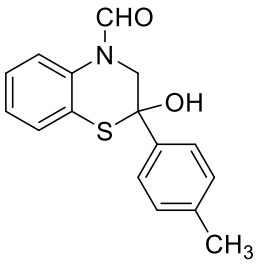


Pale yellow solid (yield: 48%, 29 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 150-152 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.30 (s, 1H), 7.04 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 187.9, 158.1, 138.6, 134.5, 132.6, 132.5, 129.3, 129.0, 126.5, 125.8, 124.1, 112.0, 63.1; **HRMS (ESI-TOF):** Calc for $C_{15}H_{11}{}^{35}ClNO_2S$ $[M+H]^+$ 304.0194; found: 304.0209.

2-hydroxy-2-phenyl-2,3-dihydro-4H-benzo[b][1,4]thiazine-4-carbaldehyde[12b, 12c] (3a):

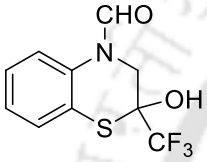


Yellow solid (yield 90%, 48.8 mg); R_f = 0.5 (EtOAc/hexane 1:5); mp 140-142 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.74 (s, 1H), 7.65 (d, *J* = 7.3 Hz, 2H), 7.37 (dd, *J* = 10.1, 4.9 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.17 – 7.08 (m, 4H), 4.86 (d, *J* = 13.4 Hz, 1H), 3.29 (d, *J* = 13.4 Hz, 1H), 3.15 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 162.6, 140.9, 134.0, 129.1, 128.9, 127.3, 126.3, 126.3, 125.9, 120.7, 83.2, 50.1; **HRMS (ESI-TOF) m/z:** $[M-OH]^+$ Calcd for $C_{15}H_{12}NOS$ 254.0634; found: 254.0659.



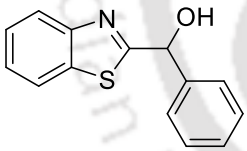
2-hydroxy-2-(p-tolyl)-2,3-dihydro-4H-benzo[b][1,4]thiazine-4-carbaldehyde (3b): Yellow solid (yield 85%, 48 mg); R_f = 0.5 (EtOAc/hexane 1:5); mp 145-147 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.79 (s, 1H), 7.59 (d, *J* = 8.2 Hz, 3H), 7.24 – 7.14 (m, 8H), 4.91 (d, *J* = 13.4 Hz, 1H), 3.34 (d, *J* = 13.4 Hz, 1H), 3.22 (s, 1H), 2.38 (s, 4H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 162.6, 139.0, 138.0, 134.0, 129.5, 128.4, 127.2, 126.6, 126.3, 126.1, 125.8, 120.7, 83.2, 50.1, 21.3; **HRMS (ESI-TOF) m/z:** $[M\text{-}OH]^+$ Calcd for $C_{16}H_{15}NOS$ 269.0874; found: 269.0876.

2-hydroxy-2-(trifluoromethyl)-2,3-dihydro-4H-benzo[b][1,4]thiazine-4-carbaldehyde

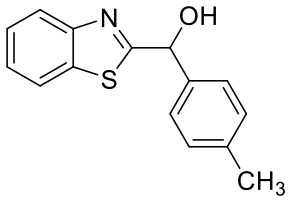


(3q): Red solid (yield 78%, 41mg); R_f = 0.5 (EtOAc/hexane 1:4); mp 125-127 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.63 (s, 1H), 7.26 – 7.22 (m, 2H), 7.20 – 7.12 (m, 2H), 4.79 (d, *J* = 13.5 Hz, 1H), 3.47 (d, *J* = 13.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 162.4, 134.5, 127.3, 127.1, 126.7, 124.4, 123.1 (q, $J_{C\text{-}F}$ = 310 Hz), 121.2, 83.0 (q, $J_{C\text{-}C\text{-}F}$ = 31 Hz), 43.8; **HRMS (ESI-TOF) m/z:** $[M\text{-}OH]^+$ Calcd for $C_{10}H_8F_3NOS$ 247.0279; found: 247.0290.

benzo[d]thiazol-2-yl(phenyl)methanol (4a):[7]



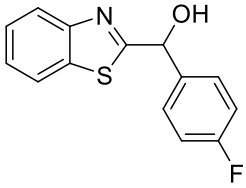
Pale yellow solid (yield 68%, 32.5 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 6.9 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.41 – 7.31 (m, 4H), 6.14 (s, 1H), 4.02 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 175.1, 152.8, 141.1, 135.5, 129.0, 128.9, 127.0, 126.3, 125.4, 123.3, 122.0, 74.6; **HRMS (ESI-TOF):** Calc for $C_{14}H_{12}NOS$ $[M+H]^+$ 242.0634; found: 242.0647.



benzo[d]thiazol-2-yl(p-tolyl)methanol (4b)*:*

Pale yellow (yield 72%, 38.8 mg); R_f = 0.5 (EtOAc/hexane 1:9); mp 120-123 ^oC; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.11 (s, 1H), 3.79 (s, 1H), 2.35 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 152.8, 138.8, 138.2,

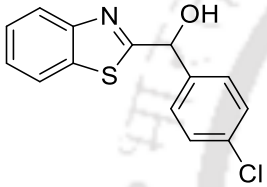
135.5, 129.7, 126.9, 126.3, 125.3, 123.3, 122.0, 74.54, 21.4; **HRMS (ESI-TOF):** Calc for $C_{15}H_{14}NOS$ $[M+H]^+$ 256.0791; found: 256.0812.



***benzo[d]thiazol-2-yl(4-fluorophenyl)methanol (4c)**:*

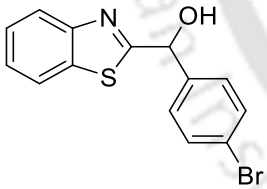
Yellow solid (yield 54%, 28 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 108-110 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.38 (t, *J* = 7.2 Hz, 1H), 6.13 (s, 1H), 3.93 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 174.8, 163.0 (d, *J* = 245.7 Hz), 152.8, 137.0, 135.5, 128.8 (d, *J* = 10 Hz), 126.5, 125.5, 123.3, 122.0, 115.9 (d, *J* = 10 Hz), 73.9; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -113.05; **HRMS (ESI-TOF):** Calc for $C_{14}H_{11}FNOS$ $[M+H]^+$ 260.0540; found: 260.0547.

***benzo[d]thiazol-2-yl(4-chlorophenyl)methanol (4d)**:*



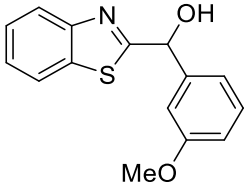
Yellow solid (yield 75%, 41 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 115-117 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 3H), 7.39 - 7.34 (m, 3H), 6.12 (s, 1H), 4.11 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 152.7, 139.5, 135.4, 134.7, 129.2, 128.3, 126.5, 125.5, 123.3, 122.0, 73.9; **HRMS (ESI-TOF):** Calc for $C_{14}H_{11}{}^{35}ClNOS$ $[M+H]^+$ 276.0244; found: 276.0249.

***benzo[d]thiazol-2-yl(4-bromophenyl)methanol (4e)**:*



Yellow solid (yield 70%, 44.5 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 115-117 ^oC; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.13 (s, 1H), 3.96 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.9, 143.5, 130.2, 130.1, 130.0, 128.5, 127.3, 126.8, 115.3, 114.2, 56.4; **HRMS (ESI-TOF):** Calc for $C_{14}H_{11}{}^{79}BrNOS$ $[M+H]^+$ 319.9739; found: 319.9755.

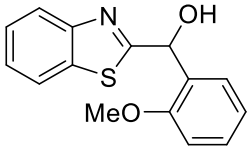
***benzo[d]thiazol-2-yl(3-methoxyphenyl)methanol (4f)**:*



Yellow solid (yield 78%, 42.2 mg); R_f = 0.4 (EtOAc/hexane 1:9); mp 130-132 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.09 (s, 1H), 6.88 – 6.86 (m, 1H), 6.11 (s, 1H), 3.88 (s, 1H), 3.80 (s, 3H); **^{13}C NMR (150**

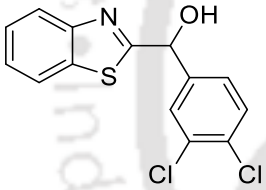
MHz, $CDCl_3$): δ 174.8, 160.2, 152.8, 142.7, 135.6, 130.1, 126.3, 125.4, 123.3, 122.0, 119.2, 114.6, 112.3, 74.6, 55.5; **HRMS (ESI-TOF):** Calc for $C_{15}H_{14}NO_2S$ $[M+H]^+$ 272.0740; found: 272.0742.

***benzo[d]thiazol-2-yl(2-methoxyphenyl)methanol (4g)**:*



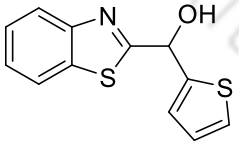
Yellow solid (yield 55%, 29.5 mg); R_f = 0.4 (EtOAc/hexane 1:9); mp 138-140 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.34 (dt, *J* = 15.6, 7.8 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.35 (d, *J* = 5.2 Hz, 1H), 4.19 (s, 1H), 3.87 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 175.0, 156.9, 152.8, 135.7, 130.0, 129.4, 128.4, 126.1, 125.1, 123.3, 121.9, 121.4, 111.2, 71.2, 55.7; **HRMS (ESI-TOF):** Calc for $C_{15}H_{14}NO_2S$ $[M+H]^+$ 272.0740; found: 272.0741.

***benzo[d]thiazol-2-yl(3,4-dichlorophenyl)methanol (4h)**:*



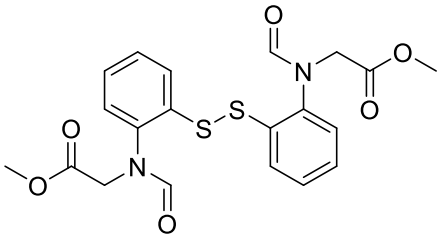
Yellow solid (yield 62%, 38 mg); R_f = 0.45 (EtOAc/hexane 1:9); mp 125-127 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.40 – 7.36 (m, 2H), 6.11 (s, 1H), 4.24 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 173.8, 141.1, 135.4, 133.2, 132.9, 131.0, 128.9, 126.6, 126.2, 125.7, 123.4, 122.1, 73.3; **HRMS (ESI-TOF):** Calc for $C_{14}H_{10}{}^{35}Cl_2NOS$ $[M+H]^+$ 309.9855; found: 309.9858.

***benzo[d]thiazol-2-yl(thiophen-2-yl)methanol (4i)**:*



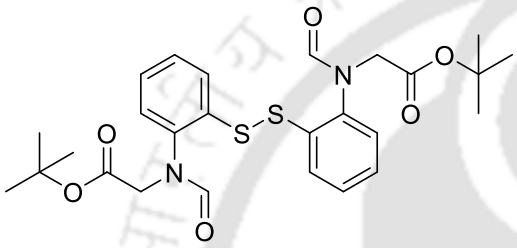
Yellow sticky solid (yield 45%, 22 mg); R_f = 0.45 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 5.0 Hz, 1H), 7.21 (d, *J* = 3.3 Hz, 1H), 7.04 - 7.03 (m, 1H), 6.44 (s, 1H), 3.82 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 173.7, 152.8, 144.4, 135.6, 129.3, 127.1, 126.7, 126.5, 126.3, 125.6, 123.5, 122.1, 111.0, 70.7; **HRMS (ESI-TOF):** Calc for $C_{12}H_{10}NOS_2$ $[M+H]^+$ 248.0198; found: 248.0204.

dimethyl 2,2'-((disulfanediylbis(2,1-phenylene))bis(formylazanediyl))diacetate (5a):



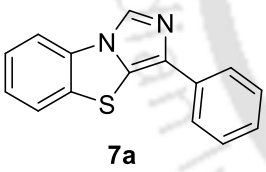
Colourless sticky liquid (yield 92%, 41 mg); R_f = 0.5 (EtOAc/hexane 1:3); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.16 (s, 2H), 7.58 – 7.55 (m, 2H), 7.50 – 7.46 (m, 2H), 7.37 – 7.34 (m, 4H), 4.39 (s, 4H), 3.74 (s, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 168.8, 163.1, 138.9, 134.9, 130.4, 130.1, 129.5, 129.2, 52.6, 47.5; **HRMS (ESI-TOF):** Calc for $C_{20}H_{21}N_2O_6S_2$ $[M+H]^+$ 449.0836; found: 449.0862.

di-tert-butyl 2,2'-((disulfanediylbis(2,1-phenylene))bis(formylazanediyl))diacetate (5b):



Colourless sticky liquid (yield 95%, 16.0 mg); R_f = 0.5 (EtOAc/hexane 1:2); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.16 (s, 2H), 7.56 (d, *J* = 6.6 Hz, 2H), 7.49 (d, *J* = 6.3 Hz, 2H), 7.35 (m, 4H), 4.27 (s, 4H), 1.46 (s, 18H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 167.3, 163.1, 139.1, 135.0, 130.4, 129.9, 129.2, 128.9, 82.6, 48.6, 28.2; **HRMS (ESI-TOF):** Calc for $C_{20}H_{21}N_2O_6S_2$ $[M+H]^+$ 533.1775; found: 533.1827.

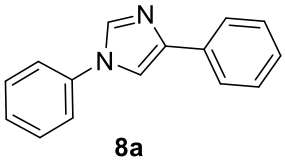
3-phenylbenzo[d]imidazo[5,1-b]thiazole (7a):



7a

As per condition D, **6a** was isolated as white solid (yield 78%, 58.5 mg); R_f = 0.5 (EtOAc/hexane 1:6); mp 148-150 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.39 (s, 1H), 7.80 – 7.75 (m, 3H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 3H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.28 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 133.4, 133.4, 131.3, 130.6, 129.0, 126.8, 126.5, 126.5, 126.1, 124.8, 124.7, 124.1, 113.1; **HRMS (ESI-TOF):** Calc for $C_{15}H_{11}N_2S$ $[M+H]^+$ 251.0637; found: 251.0652.

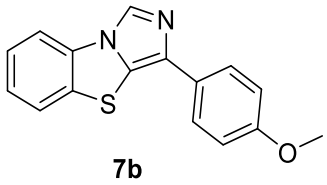
1,4-diphenyl-1H-imidazole (8a):[20]



8a

White solid (yield 90%, 46.2 mg); R_f = 0.5 (EtOAc/hexane 1:9); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.91 (s, 1H), 7.85 (d, *J* = 7.3 Hz, 2H), 7.57 (s, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.46 – 7.37 (m, 5H), 7.28 (t, *J* = 7.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.4, 137.4, 135.9, 133.9, 130.1, 128.9, 127.8, 127.3, 125.1, 121.5, 114.0; **HRMS (ESI-TOF):** Calc for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1073; found: 221.1082.

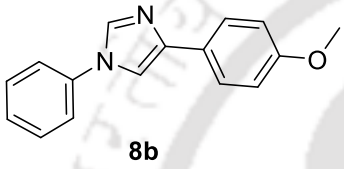
3-(4-methoxyphenyl)benzo[d]imidazo[5,1-b]thiazole (7b):



7b

White sticky solid (yield 75%, 63 mg); R_f = 0.4 (EtOAc/hexane 1:6); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.36 (s, 1H), 7.72 (t, *J* = 8.5 Hz, 3H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 159.1, 143.3, 137.5, 135.7, 130.1, 127.7, 126.8, 126.4, 121.5, 114.3, 112.9, 55.5; **HRMS (ESI-TOF):** Calc for $C_{16}H_{13}N_2OS$ $[M+H]^+$ 281.0743; found: 281.0751.

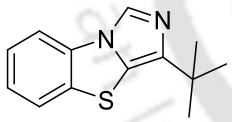
4-(4-methoxyphenyl)-1-phenyl-1H-imidazole (8b):



8b

Light yellow sticky solid (yield 80%, 45 mg); R_f = 0.4 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.89 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.52 – 7.48 (m, 3H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 159.1, 143.3, 137.5, 135.7, 130.1, 127.7, 126.8, 126.4, 121.5, 114.3, 112.9, 55.5; **HRMS (ESI-TOF):** Calc for $C_{16}H_{15}N_2O$ $[M+H]^+$ 251.1179; found: 251.1182.

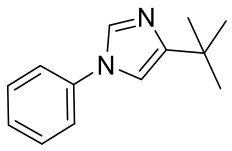
3-(tert-butyl)benzo[d]imidazo[5,1-b]thiazole (7c):



7c

White sticky solid (yield 80%, 55 mg); R_f = 0.4 (EtOAc/hexane 1:6); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.26 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 1.41 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 140.1, 133.9, 131.5, 126.0, 125.6, 125.5, 124.3, 121.4, 112.8, 32.1, 30.1; **HRMS (ESI-TOF):** Calc for $C_{13}H_{15}N_2S$ $[M+H]^+$ 231.0950; found: 231.0954.

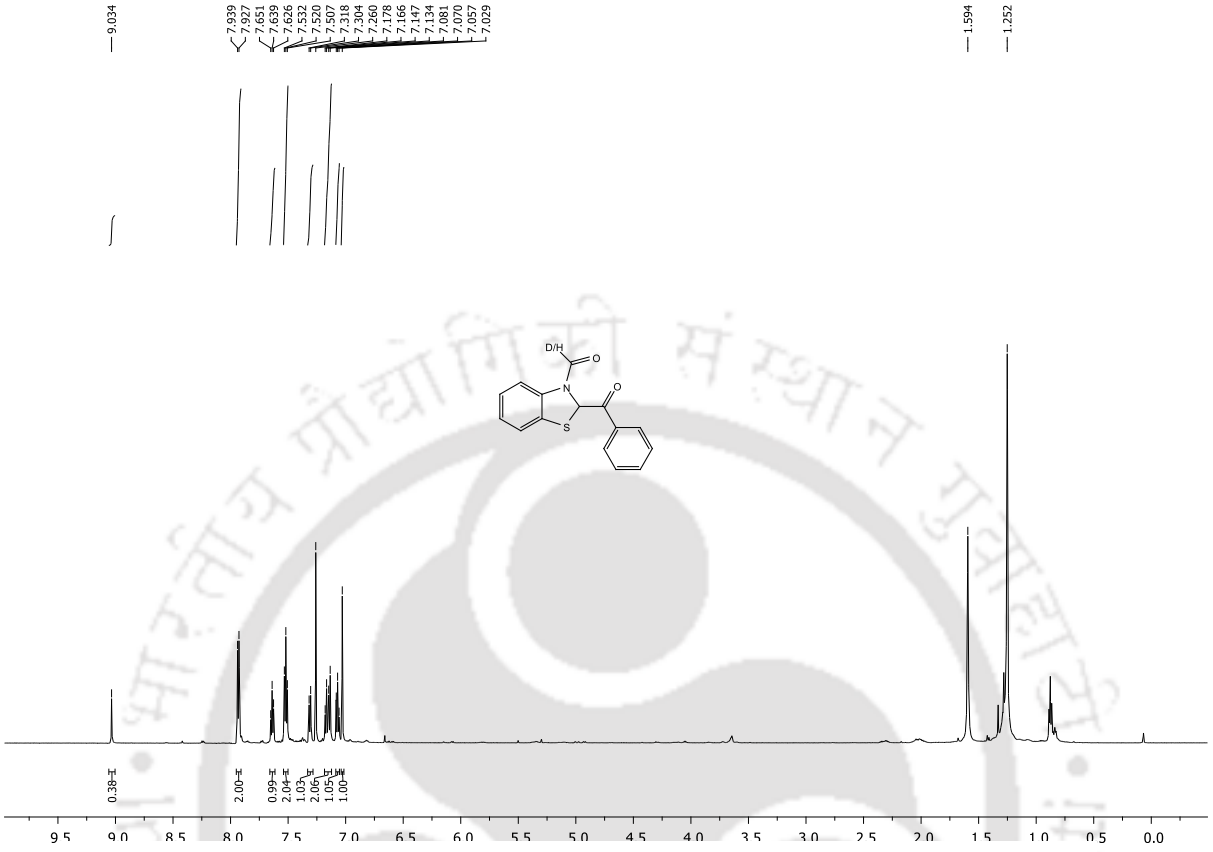
4-(tert-butyl)-1-phenyl-1H-imidazole (8c):



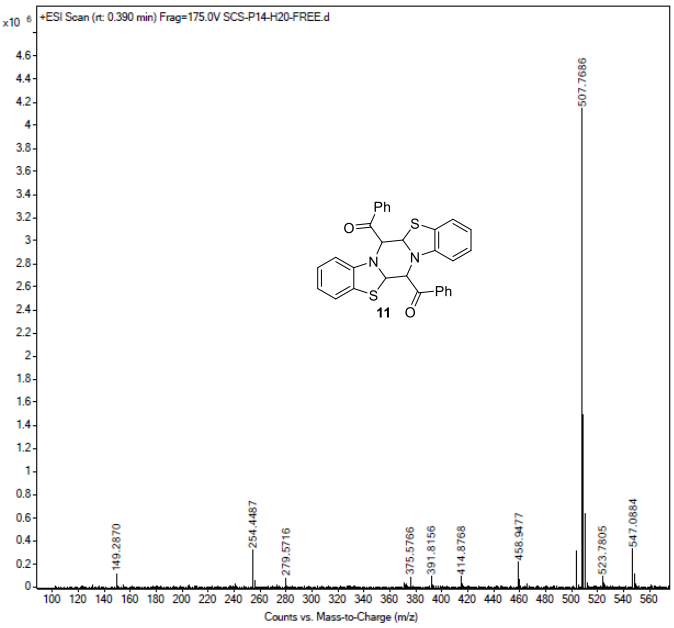
8c

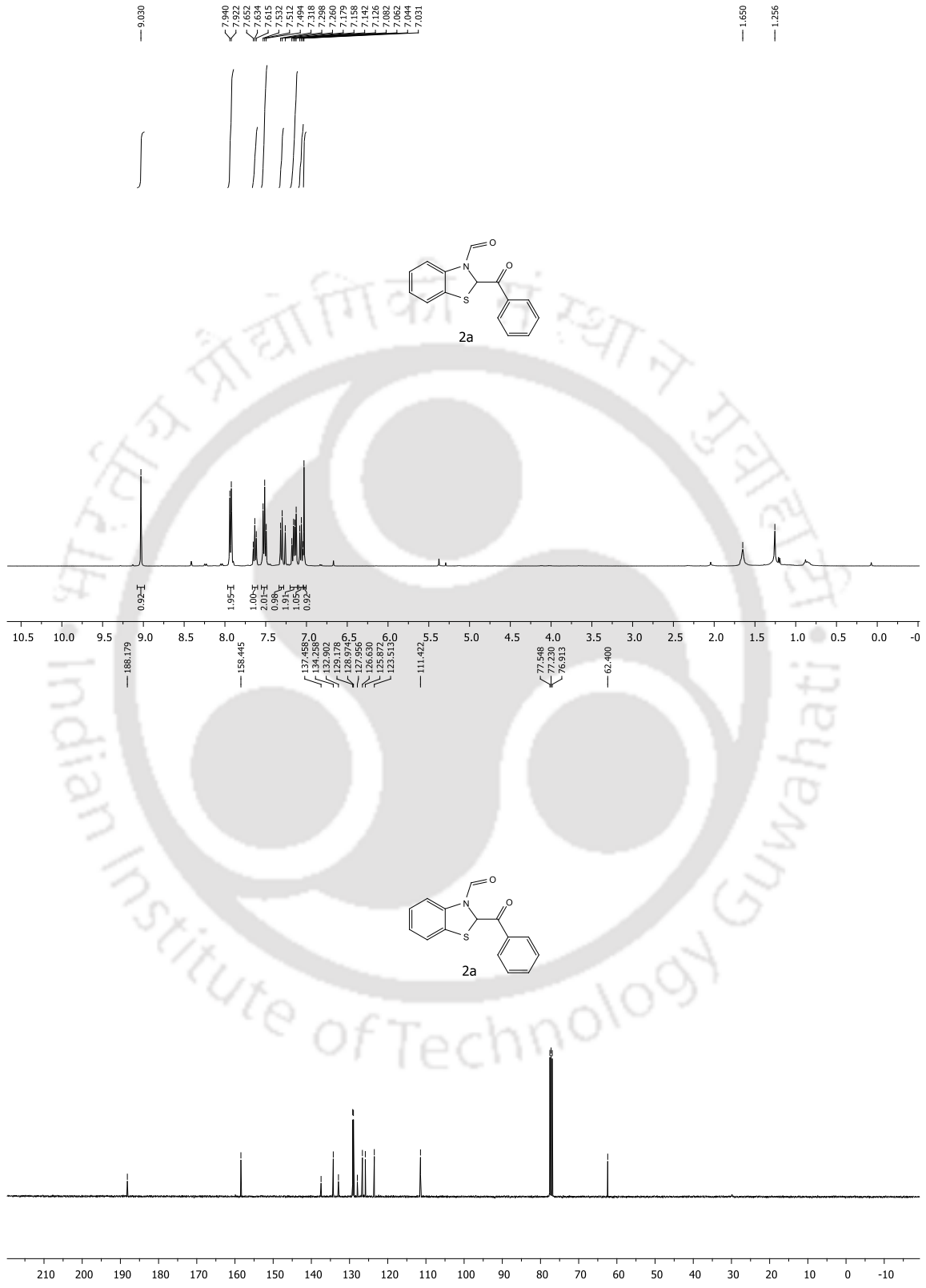
Light yellow sticky solid (yield 90%, 43.2 mg); R_f = 0.4 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.80 (s, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 1.34 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 154.0, 137.9, 134.8, 130.0, 127.2, 121.4, 112.0, 32.1, 30.3; **HRMS (ESI-TOF):** Calc for $C_{13}H_{17}N_2$ $[M+H]^+$ 201.1386; found: 201.1405.

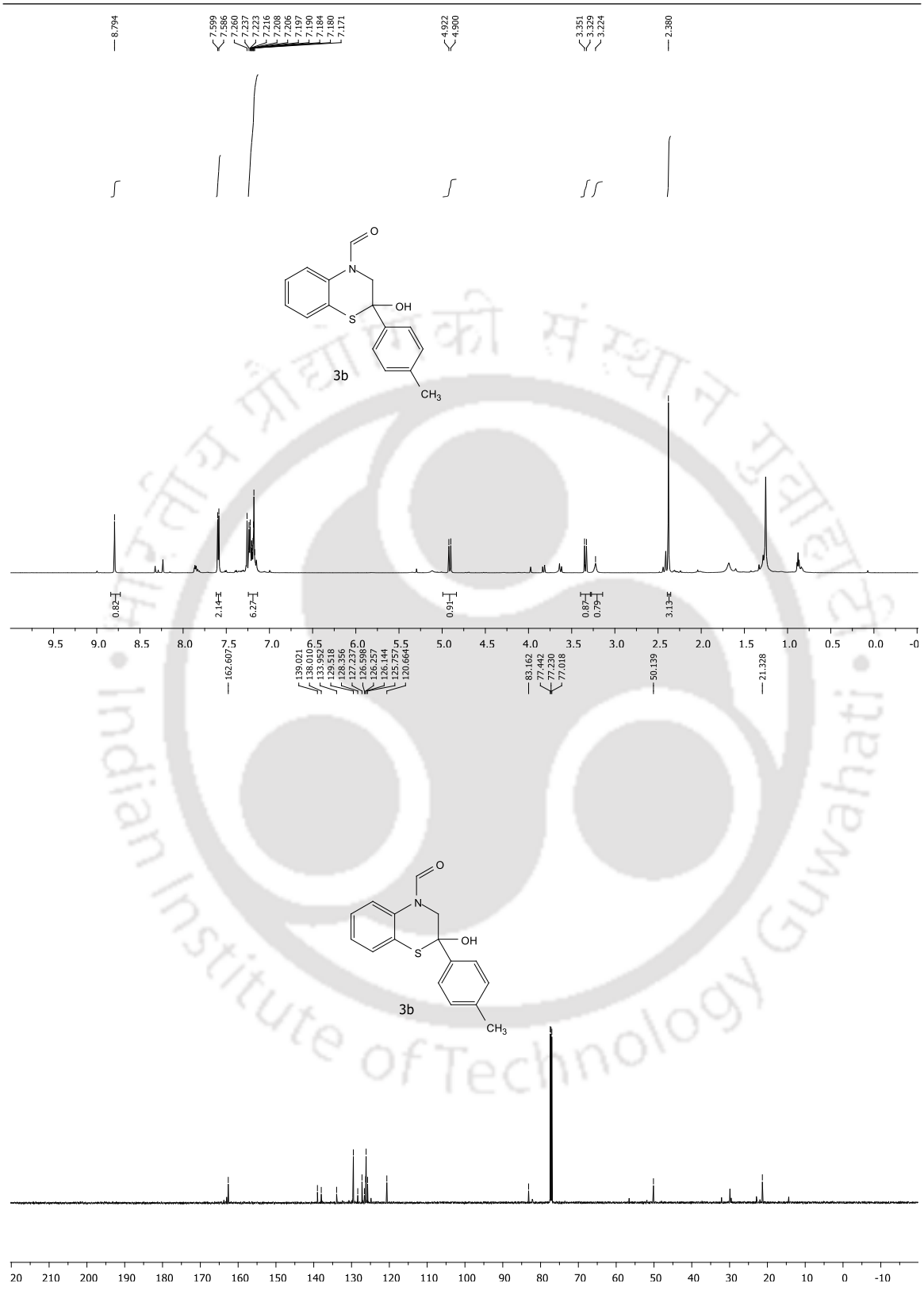
3.12 Selected spectra of products

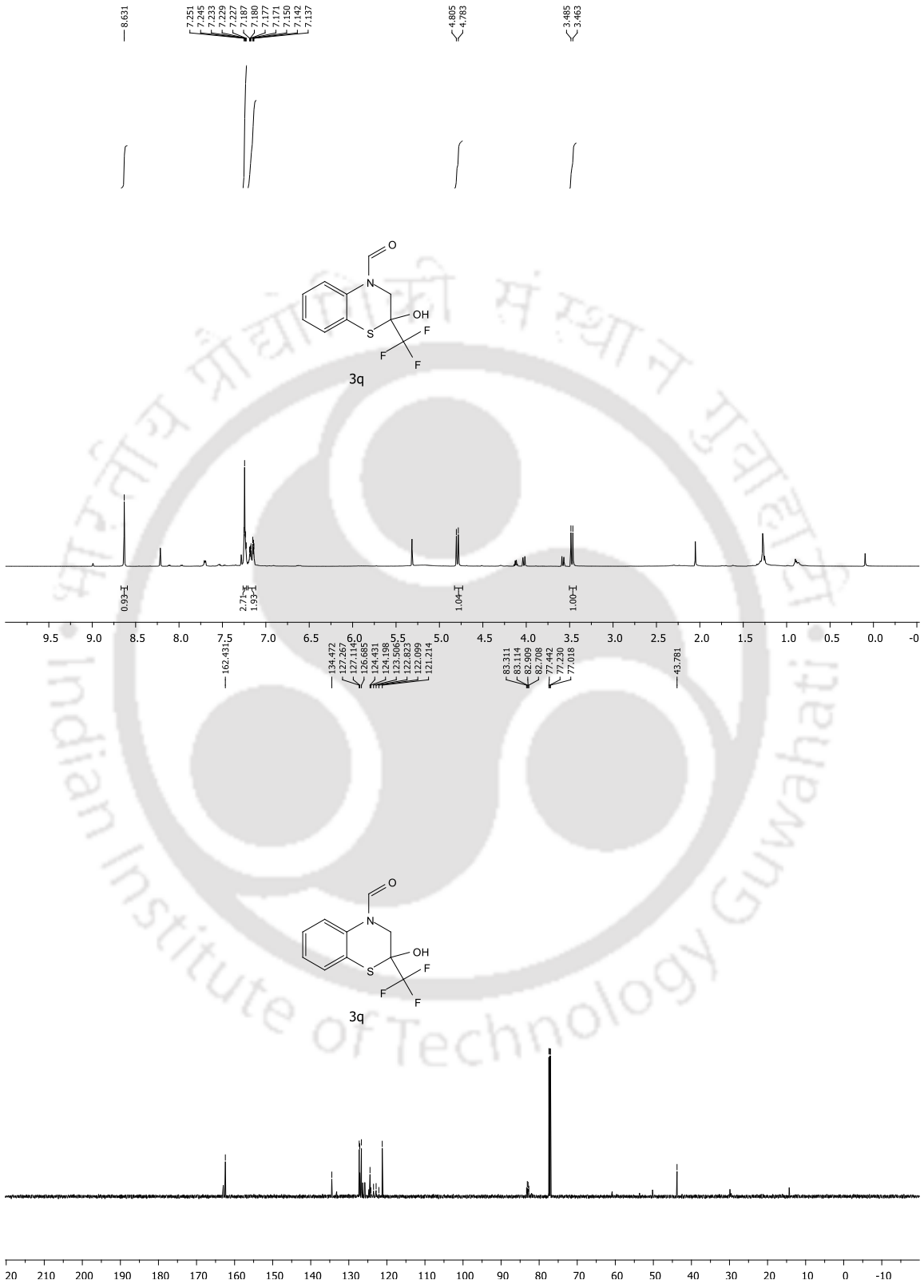


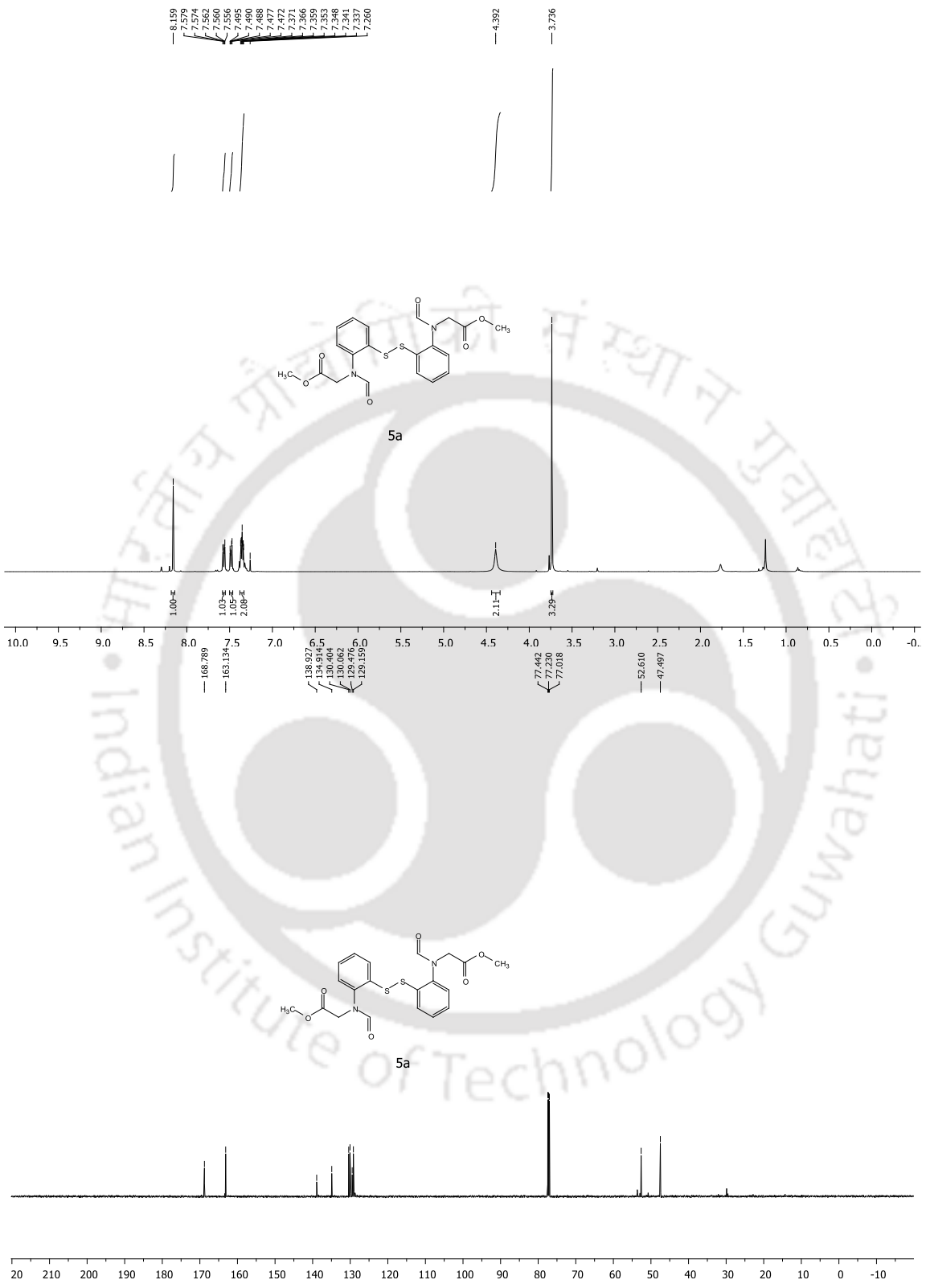
Sample Name	SCS-P14-H20-FREE	**Position**	P1-F5	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	20	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	SCS-P14-H20-FREE.d
ACQ Method	ESI ALS 100-600.m	**Comment**		**Acquired Time**	08-Jul-19 5:10:18 PM (UTC+05:30)

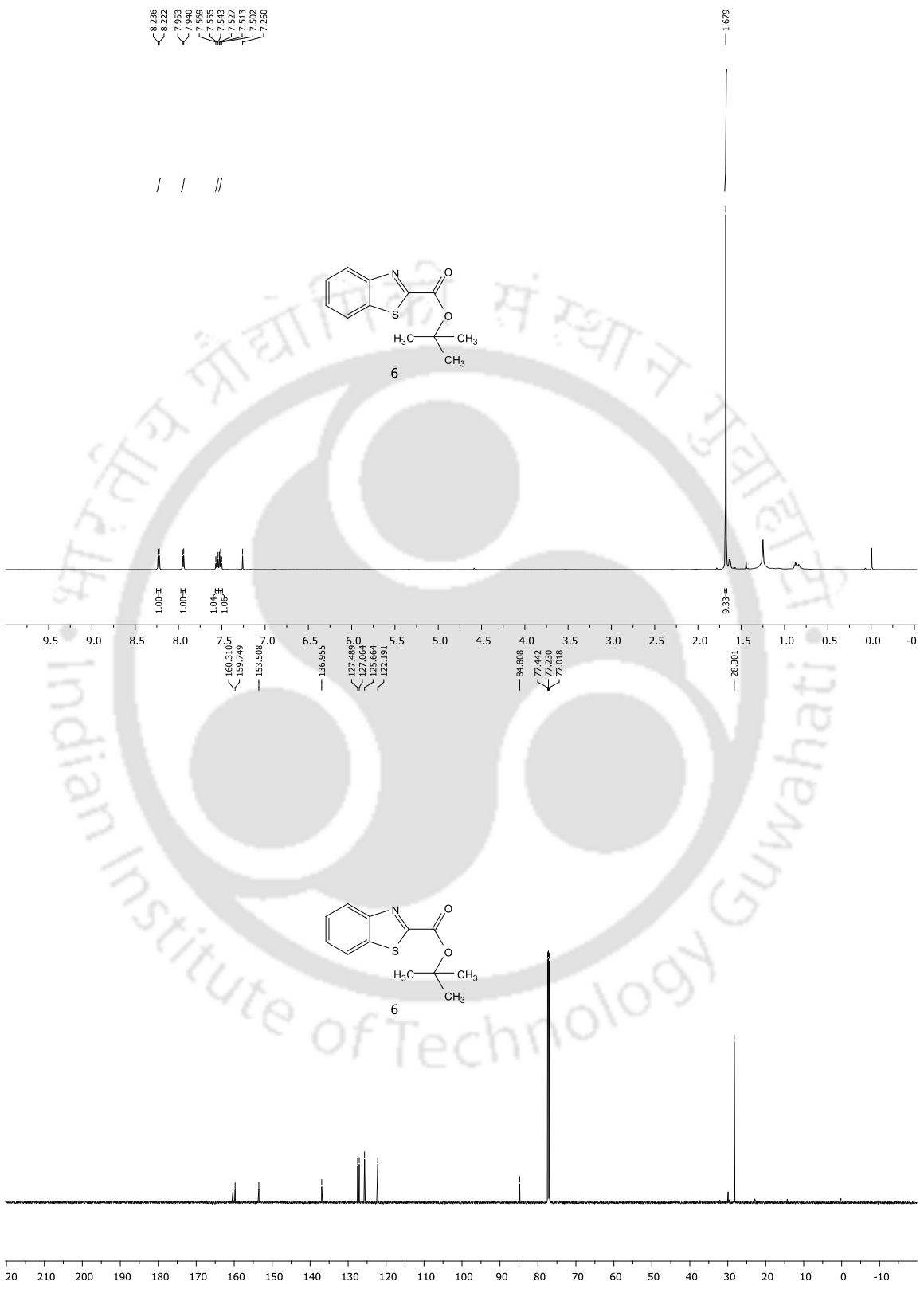


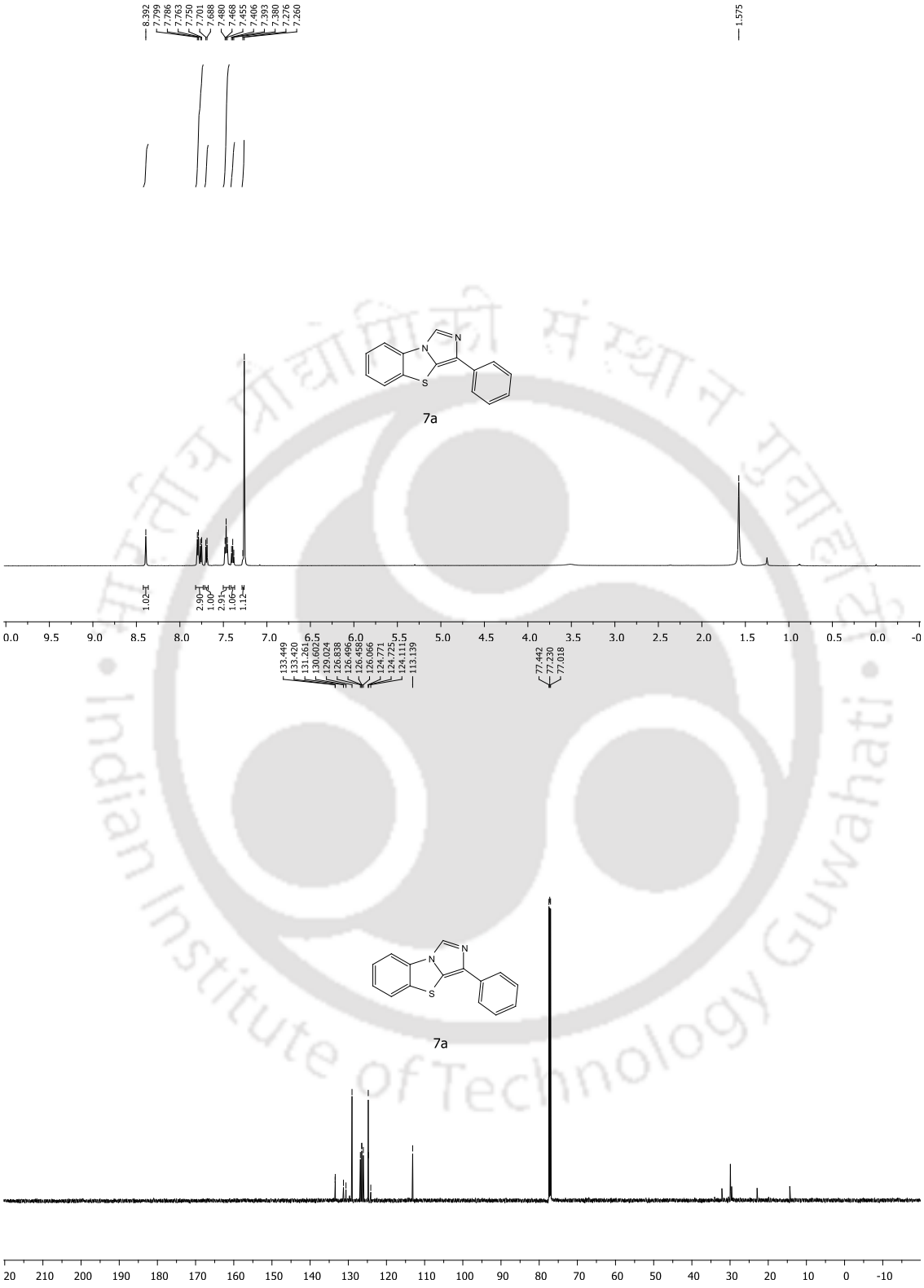


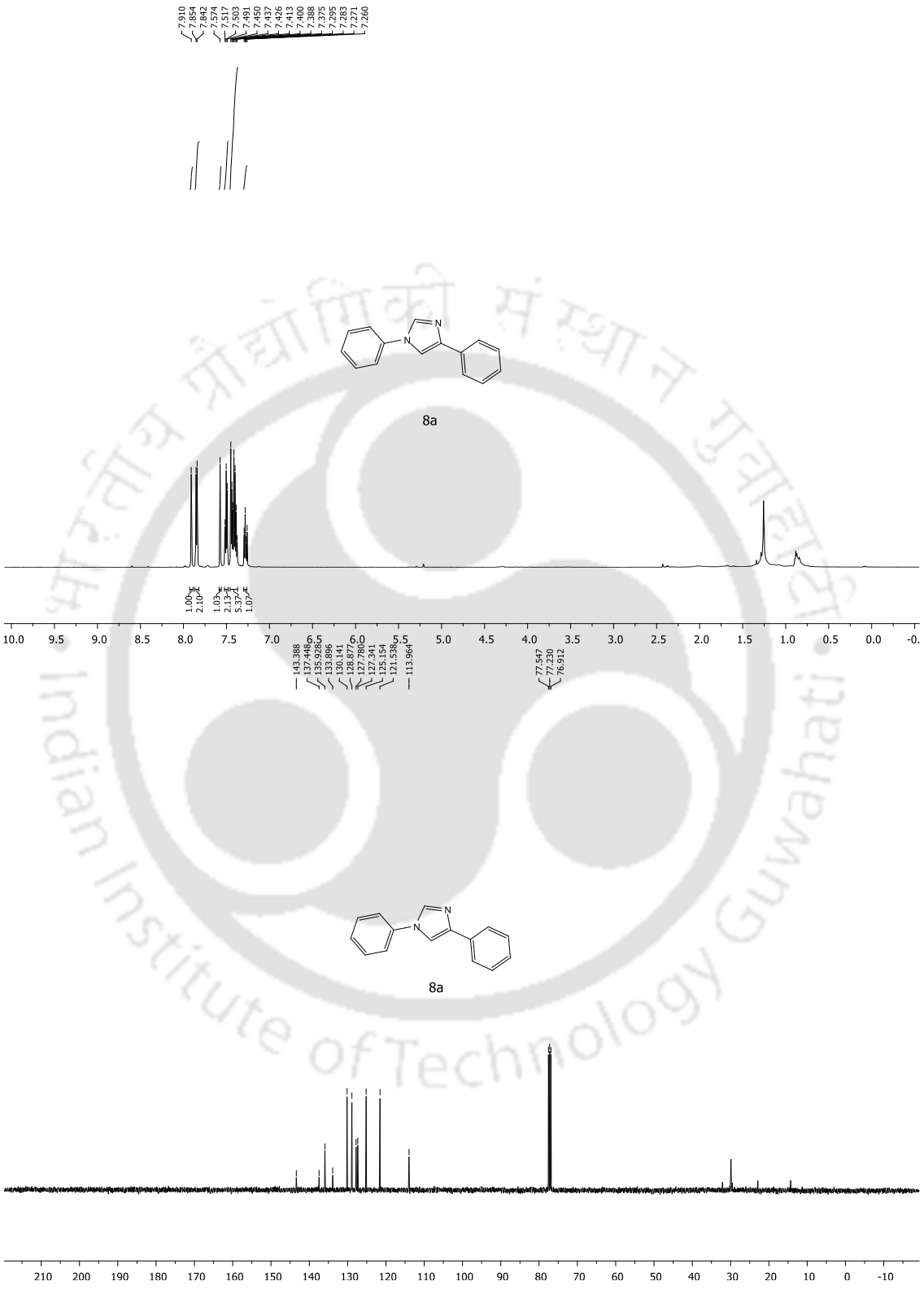


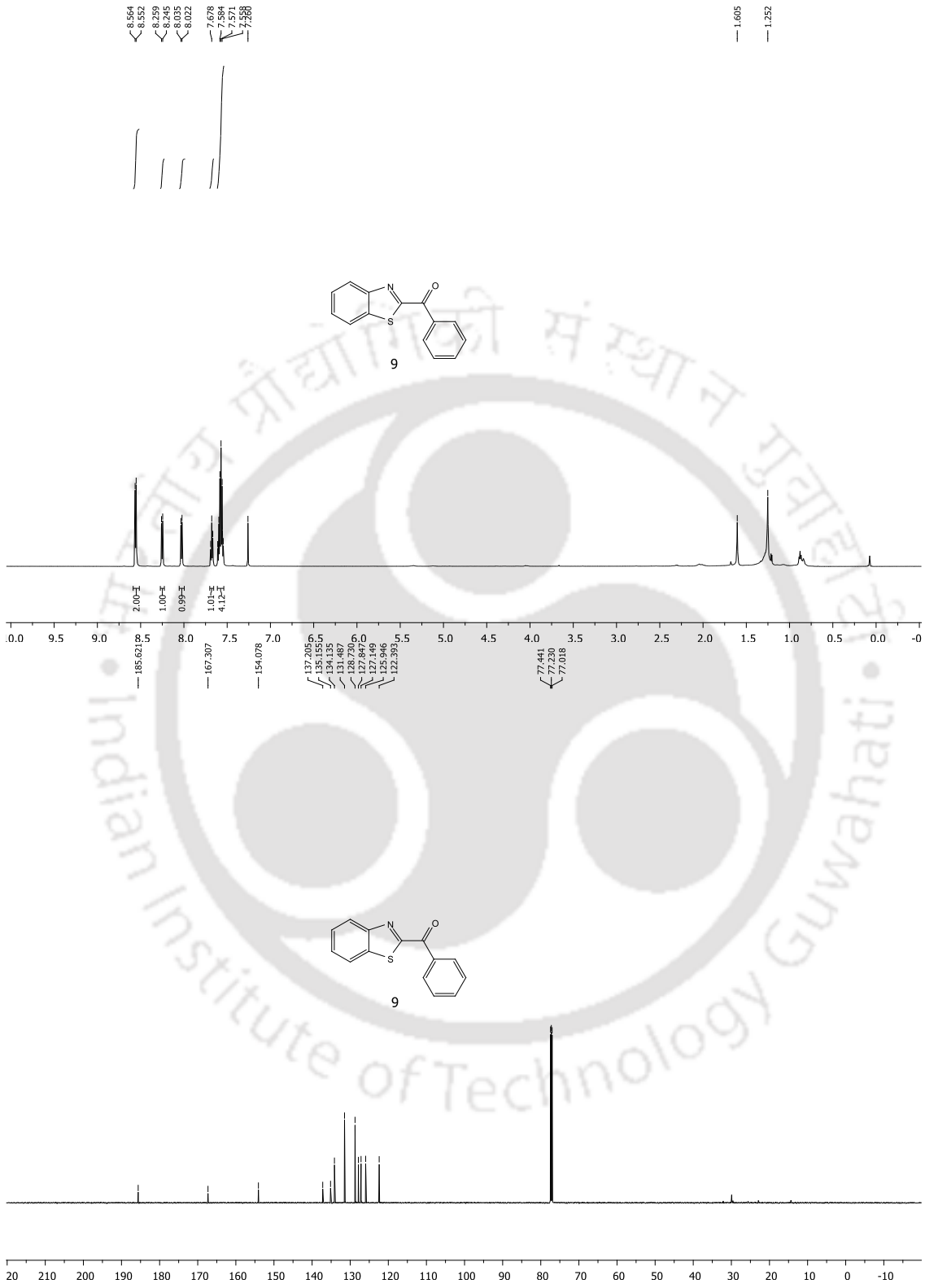


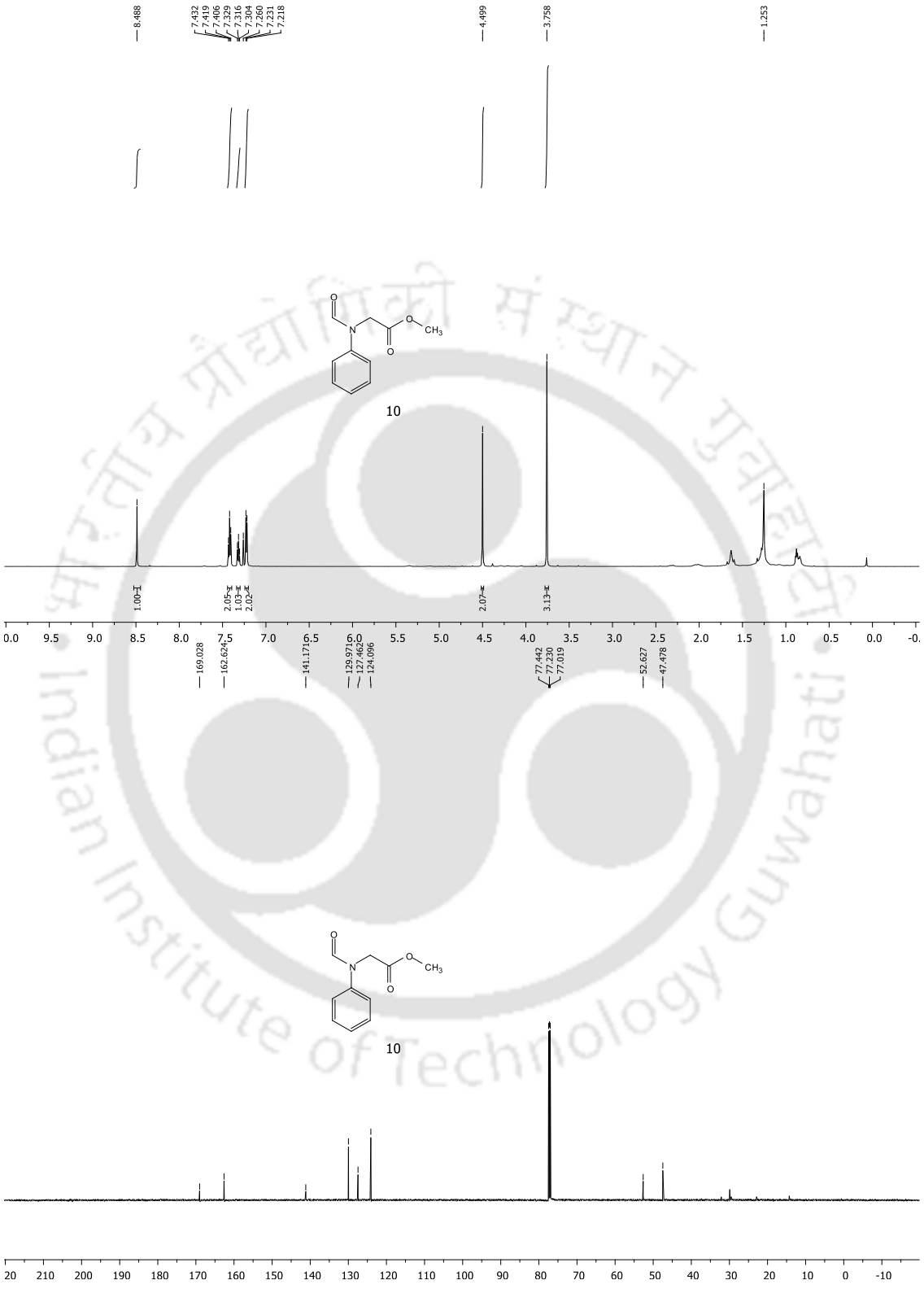






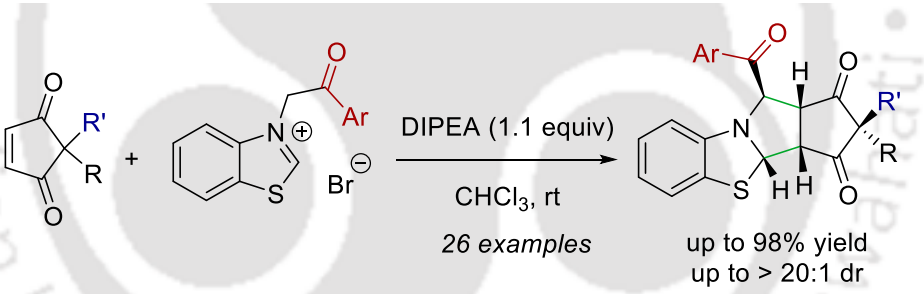






Chapter 4

[3+2] Cycloaddition Between N-Phenacylbenzothiazolium Bromides and Prochiral Cyclopentenones via Desymmetrization Strategy



4.1 Introduction

Modification of a molecule resulting loss of one or more symmetry elements is called desymmetrization. Traditionally, desymmetrization reactions have been used for the introduction of chirality because of sufficient reaction rate difference between the isomers. The desymmetrization reaction of *meso* or prochiral compounds has been considered as one of the powerful methodologies in organic synthesis.[1] It often leads to the formation of stereochemically fused complex molecules having multiple stereogenic centres in a single step.[1] In Figure 4.1, we have shown a few selective examples of bicyclic heterocycles fused cyclopentane moieties which demonstrate useful biological activities.[2]

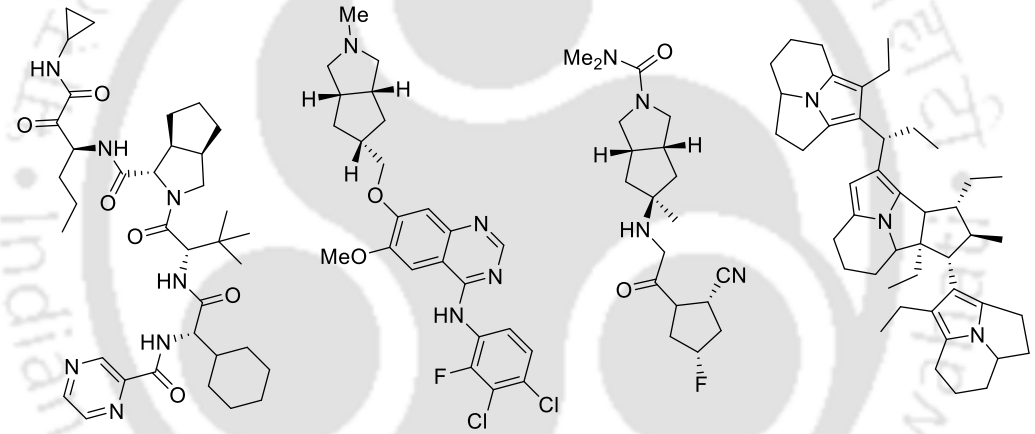
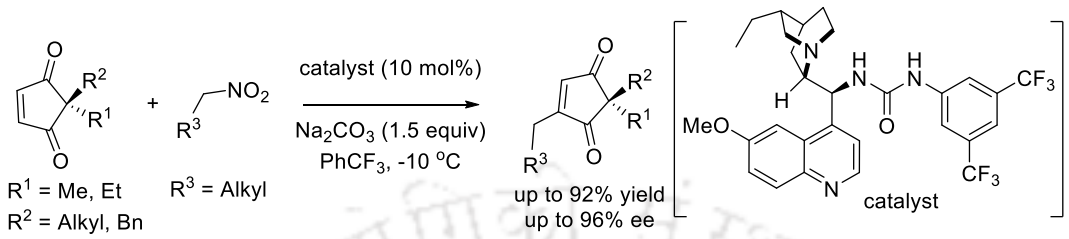


Figure 4.1: Selective examples of bioactive bicycles containing cyclopentane moieties.

4.2 Known desymmetrization reactions with prochiral cyclopentene-1,3-diones

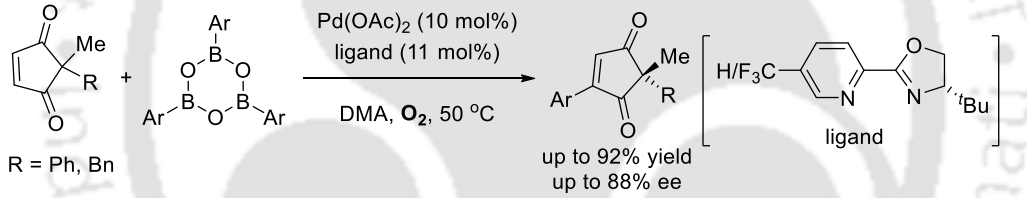
One of the prominent advantages of desymmetrization reactions is that the symmetric precursors are either readily available or can be prepared from simple starting materials in a few steps. As an instance, alkylative desymmetrization of prochiral cyclopentene-1,3-dione has proven to be an important method to provide valuable synthons for bioactive compounds. Recently, various groups documented a variety of desymmetrization reactions with prochiral cyclopentene-1,3-diones.[3]

Manna *et al*. reported an enantioselective formal C(sp^2)−H alkylation reaction using organocatalyst *via* desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones (Scheme 4.1).[3d]



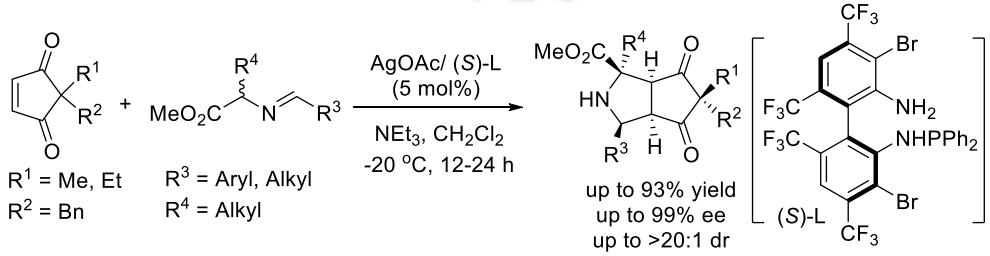
Scheme 4.1: Formal C(sp^2)−H alkylation of cyclopentene-1,3-diones

A new oxidative Heck-type desymmetrization strategy for 2,2-disubstituted cyclopentene-1,3-diones was demonstrated by Lee and co-workers. The reaction is very functional group tolerant and proceeds in the presence of unprotected alcohols, phenols, amides, acids and ketones (Scheme 4.2).[3f]



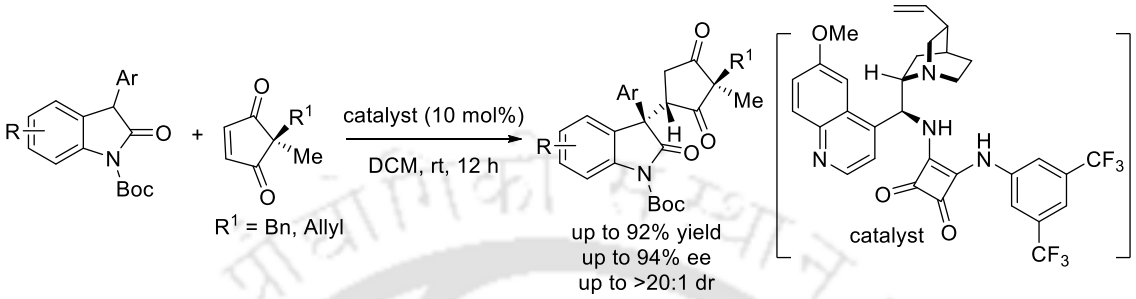
Scheme 4.2: Oxidative Heck coupling of substituted cyclopentene-1,3-diones

Wang group disclosed silver catalyzed 1,3 dipolar cycloaddition between azo-methine ylides and cyclopentene-1,3-diones, which delivered highly functionalized bicyclic pyrrolidine/cyclopentane derivatives with excellent stereoselectivities in good to high yields (Scheme 4.3).[2a] Similar work has also been reported independently by Singh group using silver(I)−ferrophox complex in the same year.[2b]



Scheme 4.3: Silver catalyzed cycloaddition reaction *via* desymmetrization strategy

Recently, Zhi *et al*. achieved a highly efficient enantioselective desymmetrization protocol for cyclopentene-1,3-diones and synthesized cyclopentane-substituted oxindoles *via* organocatalytic Michael addition of 3-substituted oxindoles (Scheme 4.4).[2h]

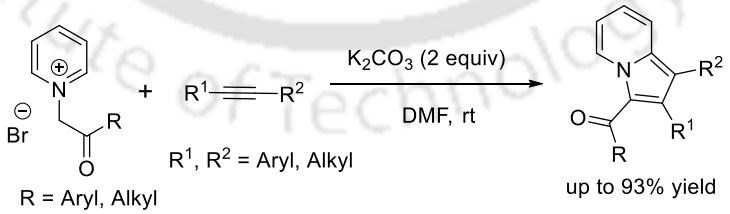


Scheme 4.4: Synthesis of cyclopentane-substituted oxindoles

4.3 Reaction with azo-methine ylides

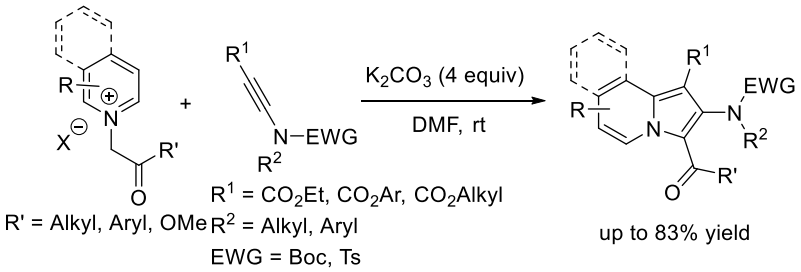
Pyridinium, quinolinium, isoquinolinium methylides, etc. are one class of reactive heteroaromatic azo-methine ylides, which can be easily prepared from alkylation of *aza*-aromatic heterocycles with active alkyl halides followed by deprotonation with some bases.[4] A wide variety of 1,3-diploar cycloaddition[5] reactions have been developed employing these azo-methine ylides and products such as polysubstituted pyridines, terpyridines and indolizines were obtained.[6]

For example, Shang group reported straightforward and convenient access to highly functionalized di- and tri-substituted indolizines *via* 1,3-dipolar cycloaddition reaction of pyridinium salts and alkynes in the presence of potassium carbonate (Scheme 4.5).[6b]



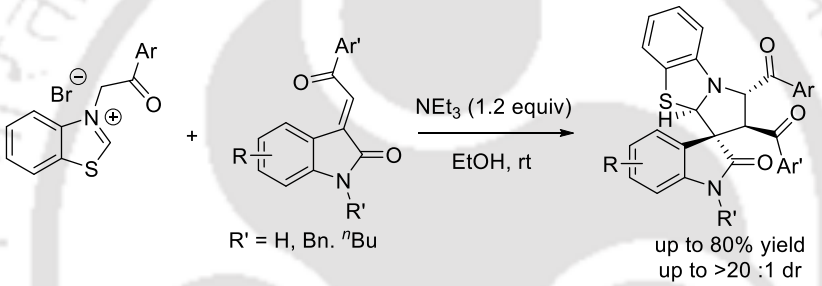
Scheme 4.5: Synthesis of substituted indolizines

Cossy group investigated 1,3-dipolar cycloaddition of stabilized pyridinium ylides with electron-deficient ynamides resulting in various *N*-fused heterocycles with a fully substituted pyrrole ring (Scheme 4.6).[6g]



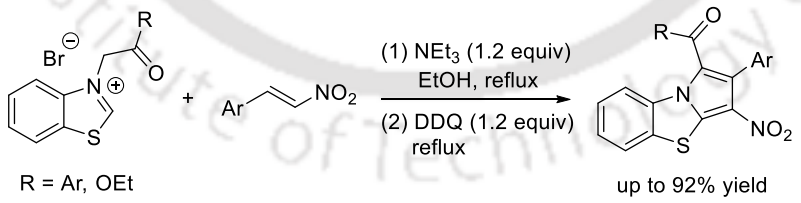
Scheme 4.6: [3 + 2] cycloaddition reaction with electron-deficient ynamides

Synthesis of spiro[benzo[*d*]pyrrolo[2,1-b]thiazole-3,3'-indolines] *via* [3+2] cyclo-addition reaction of *N*-phenacylbenzothiazolium bromides[7] with 3-methyleneoxindole was developed by Yan and co-workers using triethylamine with high diastereoselectivity (Scheme 4.7).[7c]



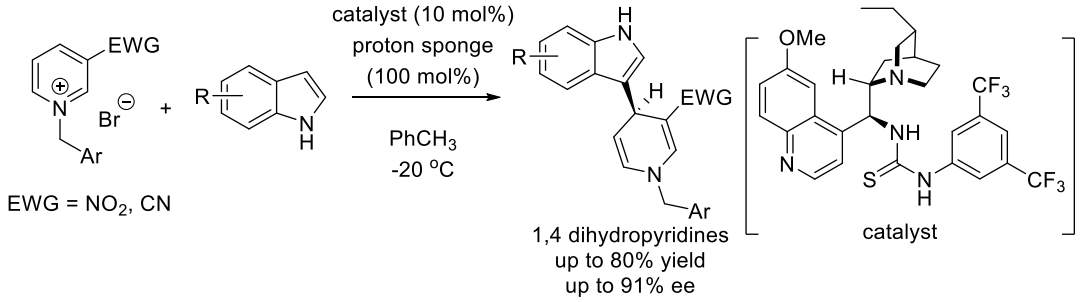
Scheme 4.7: Synthesis of *spiro*-oxindole derivatives

Yan group described triethylamine mediated stepwise 1,3-dipolar cycloaddition reaction of *N*-phenacylbenzothiazolium bromides with nitroalkenes in ethanol and synthesized tetrahydro-, dihydro- and benzo[*d*]pyrrolo[2,1-*b*]thiazoles (Scheme 4.8).[7e]



Scheme 4.8: Synthesis of substituted indolizines

Recently, Bertuzzi *et al.* published unusual C-4 regioselective addition of indoles to activated *N*-benzylpyridinium salts for the synthesis of optically active 1,4-dihydropyridines using organocatalyst (Scheme 4.9).[8]



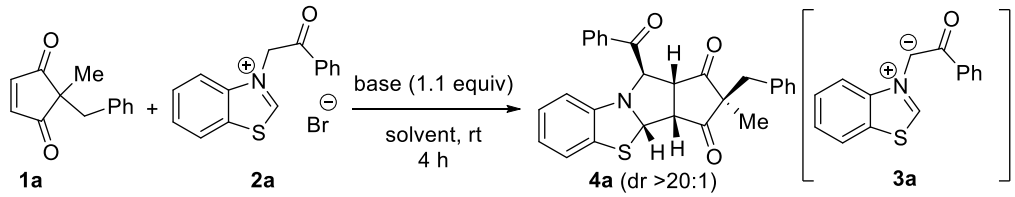
Scheme 4.9: Synthesis of chiral 1,4-dihydropyridines derivatives

4.4 Result and discussion

We became interested particularly in the cycloaddition reactions with *N*-phenacylbenzothiazolium bromides[7] as the resulting products are different derivatives of benzothiazoles[9] and could be potentially bioactive (discussed in chapter 3). Though different olefinic dipolarophiles were employed previously in the cycloaddition reaction with *N*-phenacylbenzothiazolium bromides, to the best of our knowledge, no report on desymmetrization reaction with a *meso* or prochiral dipolarophile has been documented. Herein, we disclose an organocatalytic highly diastereoselective desymmetrizing cycloaddition reaction between *N*-phenacylbenzothiazolium bromides and cyclopentene-1,3-diones.

Initially, we studied the model reaction between prochiral cyclopentene-1,3-dione **1a** and *N*-phenacylbenzothiazolium bromides **2a** in ethanol at room temperature (Table 4.1). It is expected that the active 1,3-dipole benzothiazolium *N*-phenacylide (**3a**) will be generated *in situ* from **2a** under basic medium. Delightfully, in the presence of pyridine, the desired cycloaddition product 2-benzyl-2-methyl-hexahydro-1benzo[*d*]cyclopenta[3,4]pyrrolo-[2,1-*b*]thiazol-10-yl) (phenyl) methanone **4a** was isolated as a single diastereomer in 70 % yield (Table 4.1, entry 1). The relative configuration of **4a** was determined by X-ray crystal structure.[10] Although DABCO could not improve the yield of the product, a higher yield of 80% was achieved with DBU. Interestingly, an enhancement in yield was observed with 1,1,3,3-tetramethylguanidine (TMG) (entry 4). Then triethylamine and diisopropylethylamine (DIPEA) were screened, and gratifyingly highest yield of 92% was obtained with DIPEA (entry 6). Inorganic bases such as K_2CO_3 and Cs_2CO_3 also

Table 4.1: Optimization of reaction condition



entry[a]	base	solvent	yield (%)[b]
1	pyridine	EtOH	70
2	DABCO	EtOH	72
3	DBU	EtOH	80
4	TMG	EtOH	85
5	Et_3N	EtOH	88
6	DIPEA	EtOH	92
7	K_2CO_3	EtOH	54
8	Cs_2CO_3	EtOH	51
9	^tBuOK	EtOH	0
10	DIPEA	CH_2Cl_2	91
11	DIPEA	$(CH_2Cl)_2$	93
12	**DIPEA**	**$CHCl_3$**	**98**
13	DIPEA	$PhCH_3$	84
14	DIPEA	DMSO	55
15	DIPEA	CH_3CN	78
16	DIPEA	$(C_2H_5)_2O$	40

[a]Reaction conditions: 0.05 mmol of **1a** and 0.05 mmol of **2a** was stirred with 0.055 mmol of base in 0.5 mL solvent. [b]Isolated yield after silica gel column chromatography.

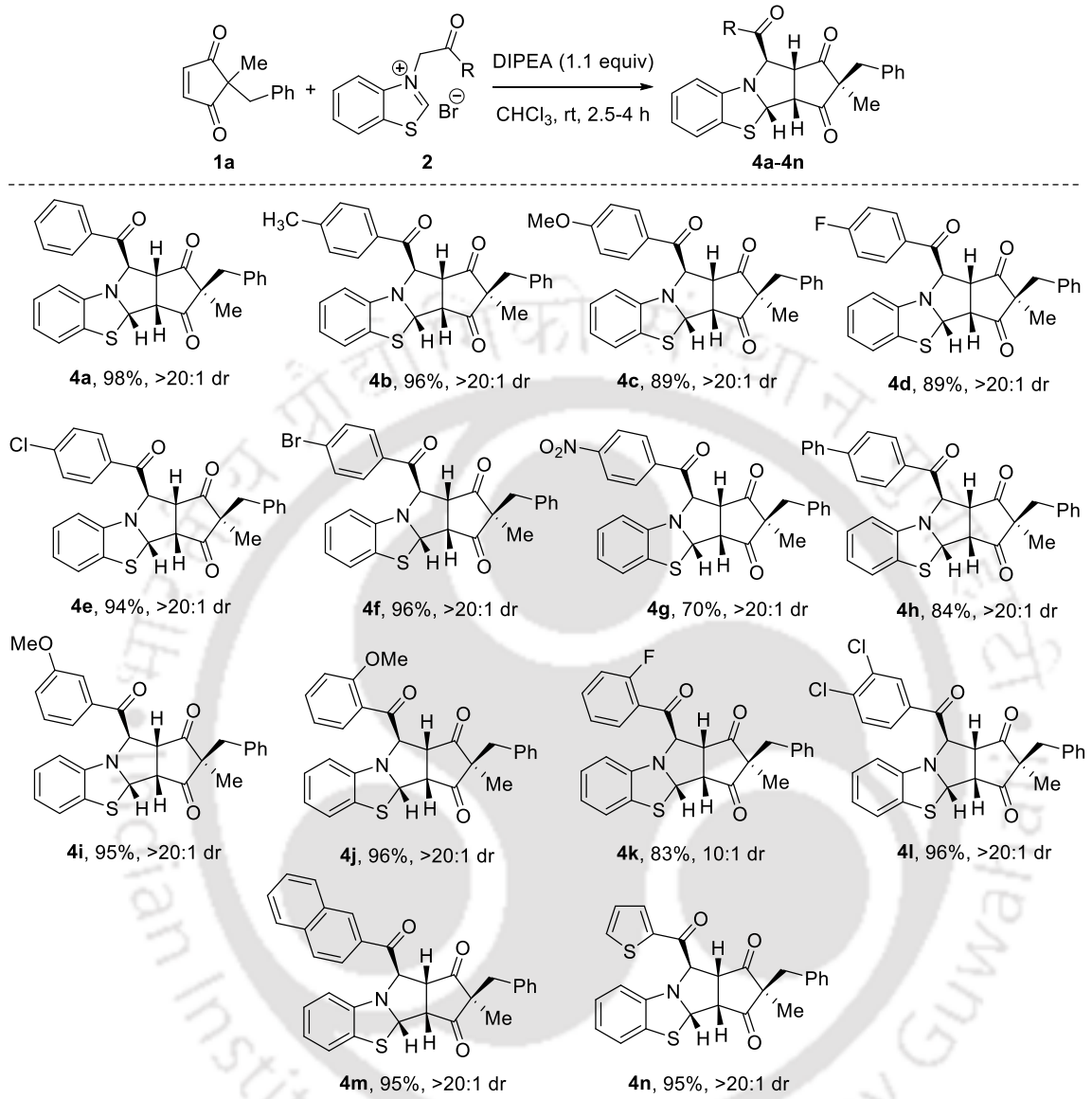
provided the product but lower yields were detected (entries 7-8). Unfortunately, no desired product was obtained with ^tBuOK (entry 9). After getting DIPEA as the best

catalyst, we started our solvent screening (entries 10-16). Initially different halogenated solvents were screened in the reaction (entries 10-12). Interestingly the yield got increased to 98% in chloroform solvent (entry 12). When the reaction was placed in toluene, the yield dropped to 84% (entry 13). Other solvents like DMSO, acetonitrile and diethyl ether were also screened, but the desired product was achieved with lower yields (entries 14-16).

4.5 Substrate scope

After establishing the optimized conditions, the generality and scope of the cycloaddition reaction were studied. Initially, *N*-phenacylbenzothiazolium bromides **2** having various aryl groups were tested with cyclopentene-1,3-dione **1a** (Scheme 4.10) and in most of the cases exclusive diastereoselectivity (>20:1) was observed as determined by ^{1}H NMR spectroscopy. At first, benzothiazolium bromides **2b**-**g** having different *para*-substitutions on the phenyl group were screened and very good results were achieved. *para*-Tolyl and *para*-anisyl derived benzothiazolium bromides **2b** and **2c** delivered the products **4b** and **4c** with high yields and excellent diastereoselectivities. Gratifyingly, 4-halo substituted aryl groups containing benzothiazolium bromides **2d**-**2f** also provided the corresponding products **4d**-**4f** in good to high yields. However, electron-poor benzothiazolium bromide **2g** having *para*-nitro substitution provided the product **4g** in slightly lower yield. Biphenyl group containing bromide **2h** also took part in the reaction and good yield of 84% was achieved for **4h**. Next, benzothiazolium bromide **2i** having *meta*-anisyl group was screened and the corresponding product **4i** was isolated in 95% yield and >20:1 diastereomeric ratio. Our methodology was also suitable for *o*-substituted aryl group containing benzothiazolium salts **2j**-**2k**. Product **4k** having *o*-fluoro substitution was isolated in 83% yield and 10:1 diastereomeric mixture. A disubstituted bromide such as **2l** was also tolerated in the reaction and 96% yield was achieved with excellent diastereoselectivity. A similar outcome was also observed with benzothiazolium salt **2m** having 2-naphthyl group. Finally, a heteroaromatic group containing bromide **2n** was employed and 95% yield was obtained for product **4n**.

Scheme 4.10: Scope of *N*-phenacylbenzothiazolium bromides[a,b,c]

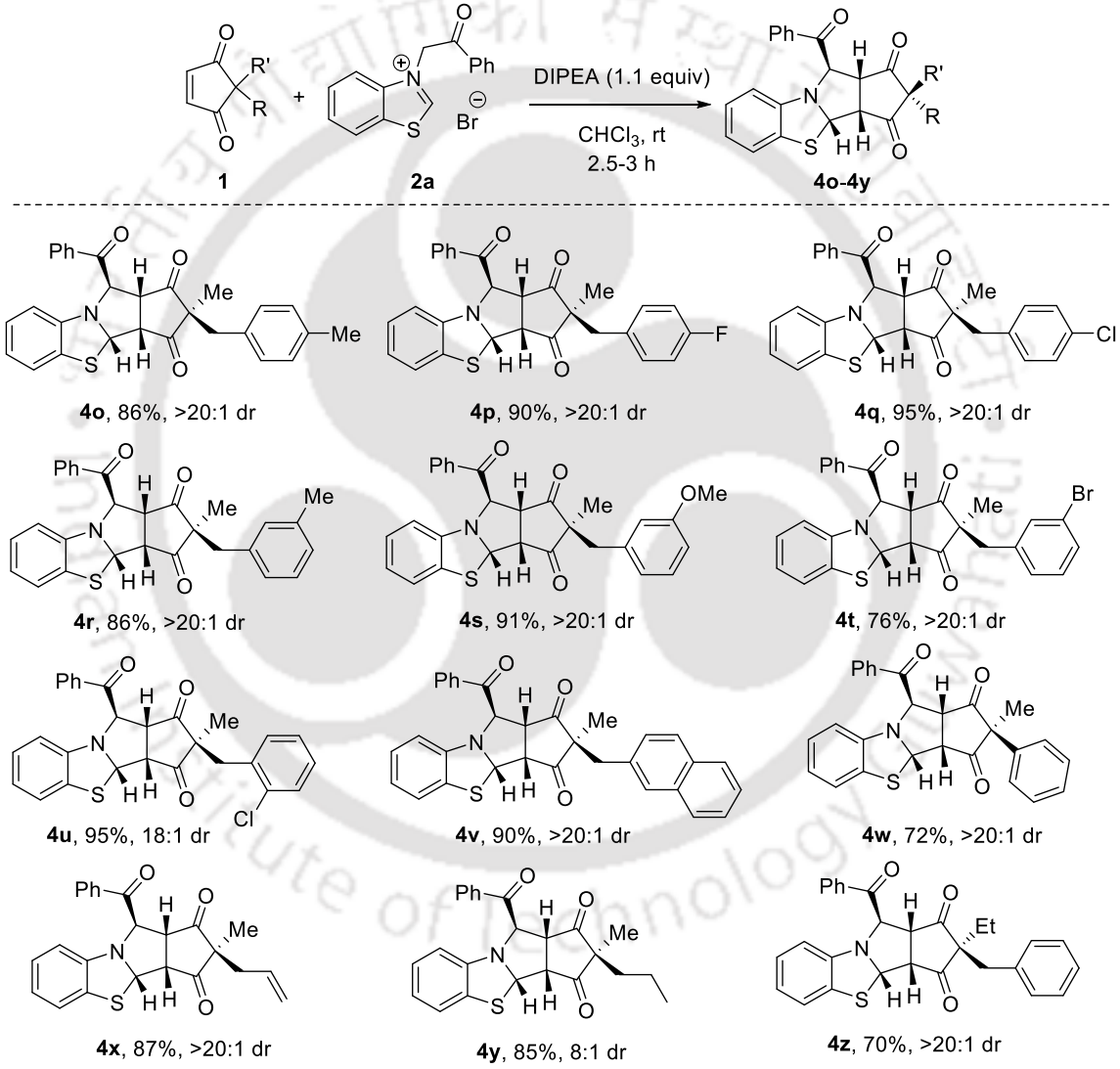


[a]Unless otherwise mentioned, reaction was carried out with 0.2 mmol of **1a** and 0.2 mmol of **2a** using 0.22 mmol of DIPEA at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

The scope of diastereoselective [3+2] cycloaddition was further explored on a range of cyclopentene-1,3-diones **2** (Scheme 4.11). Initially, a variety of substitutions on the phenyl group of the benzyl motif was checked and satisfactory results were obtained. In fact, the reaction was again compatible with electron-poor as well as electron-rich aryl groups having substitutions at the *ortho*, *meta* and *para* positions and excellent

diastereoselectivity (>20:1) was achieved. For example, *para*-xylyl cyclopentenedione **1b** delivered the product **4o** with 86% yield and excellent diastereoselectivity. Cyclopentenedione **1c** and **1d** having 4-halophenyl group also served as good substrate for this reaction and provided the corresponding products **4p** and **4q** in excellent yields. Excellent yield was also observed for product **4r** having 3-methyl substitution in the

Scheme 4.11: Scope of cyclopentenediones in the cycloaddition reaction[a,b,c]



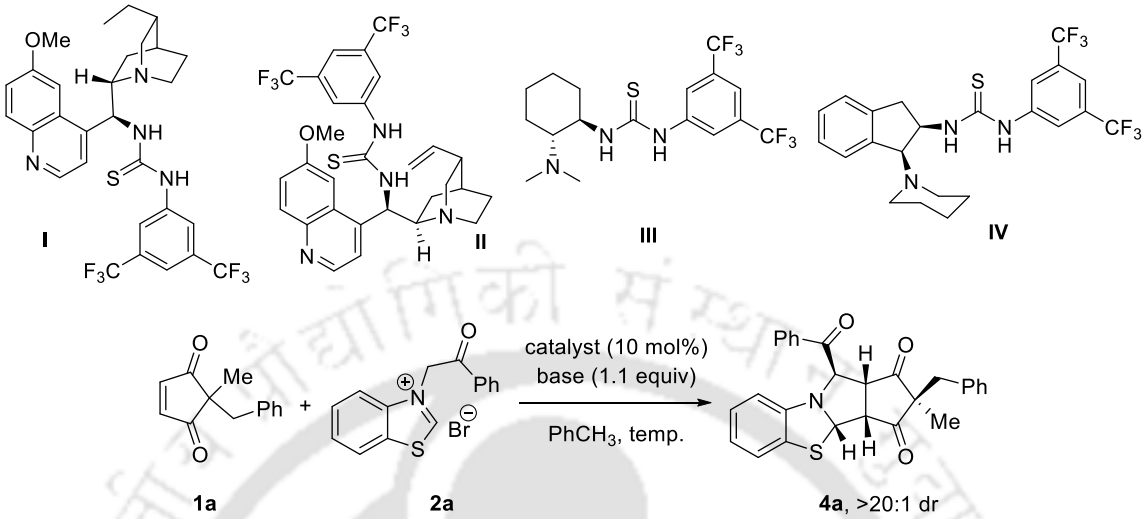
[a]Unless otherwise mentioned, reaction was carried out with 0.2 mmol of **1a** and 0.2 mmol of **2a** using 0.22 mmol of DIPEA at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

benzyl group. Though high yield was achieved for product **4s** having 3-methoxyphenyl group, slight less yield was detected for product **4t** having 3-bromophenyl group. The outcome was excellent with *ortho*-substituted cyclopentenedione **1h** albeit the product **4u** was obtained as 18:1 diastereomeric mixture. 2-Methylnaphthyl group was also well tolerated in the reaction and product **4v** was isolated in 87% yield. The reaction also proceeded well when benzyl group of **1a** was replaced with phenyl group and gratifyingly, a good yield of 72% was observed for the product **4w**. Then cyclopentenedione **1k** having allyl group was prepared and engaged in the reaction. To our delight, the desired cycloaddition product **4x** was formed in 87% yield. Interestingly, the diastereoselectivity was lower for product **4y** possibly due to the less steric difference between methyl and propyl groups. When the methyl group of **1a** was replaced by ethyl group, the outcome also did not change and the product **4z** was isolated in 70% yield.

4.6 Attempt for the asymmetric synthesis of 4a

For the development of an asymmetric variant, we started the optimization by screening different conditions (Table 4.2). Initially, the reaction of **1a** and **2a** in toluene was set in the presence of catalyst **I** (10 mol%). But only 20% yield of the product **4a** was observed having 0% ee (entry 1). This indicated that the catalyst is playing the role of base only instead of *H*-bonding. Then another reaction of **1a**, **2a** and catalyst **I** was set in toluene with one equivalent of $NaHCO_3/H_2O$ (0.5 mL) as additive at room temperature. Product **4a** was isolated with 80% yield and 15% ee (entry 2). When Amberlyst A21 was employed as an additive, racemic product was obtained. Then the temperature was decreased and interestingly 26% ee was observed at -20 ^oC (entry 5). Then Amberlyst A21 was replaced with proton sponge[8] and the reaction was observed under different temperature conditions (entries 7-9). Gratifyingly, 75% yield of product **4a** was detected with 26% ee at 0 ^oC. Other thiourea catalysts were also screened, but they were unable to improve enantiomeric excess of the product (entries 10-12). For example, Takemoto catalyst (**III**) and indane derived catalyst **IV** provided the product with excellent yields but almost racemic mixtures were isolated.

Table 4.2: Optimization of reaction condition for chiral product



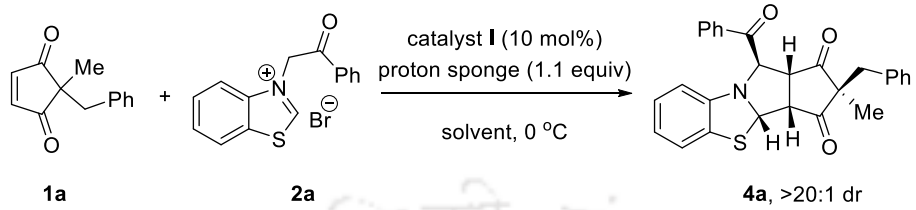
entry[a]	catalyst	base(1.1 equiv)	temperature	yield (%)[b]	ee (%)[c]
1	**I**	_	25 °C	20	0
2	**I**	Aq.$NaHCO_3$	25 °C	80	15
3	**I**	Amberlyst A21	25 °C	82	0
4	**I**	Amberlyst A21	0 °C	70	20
5	**I**	Amberlyst A21	-20 °C	65	26
6	**I**	Amberlyst A21	-40 °C	60	20
7	**I**	**Proton sponge**	**0 °C**	**75**	**26**
8	**I**	proton sponge	-20 °C	62	15
9	**I**	proton sponge	-40 °C	57	15
10	**II**	proton sponge	0 °C	84	11
11	**III**	proton sponge	0 °C	76	3
12	**IV**	proton sponge	0 °C	98	2

[a]Reactions were carried out with **1a** (0. 025 mmol) and **2a** (0.025 mmol) in 0.25 mL toluene for 4 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

After finding proton sponge as a suitable base, we optimized the reaction with different solvents at 0 °C (Table 4.3). Trifluorotoluene was found as the best solvent providing 62% yield and 43% ee of the product (entry 2). Moderate yield and enantiomeric excess

was achieved in MTBE solvent (entry 3). Chloroform and chlorobenzene were unable to improve the ee but provided the product with good yields (entries 4-5).

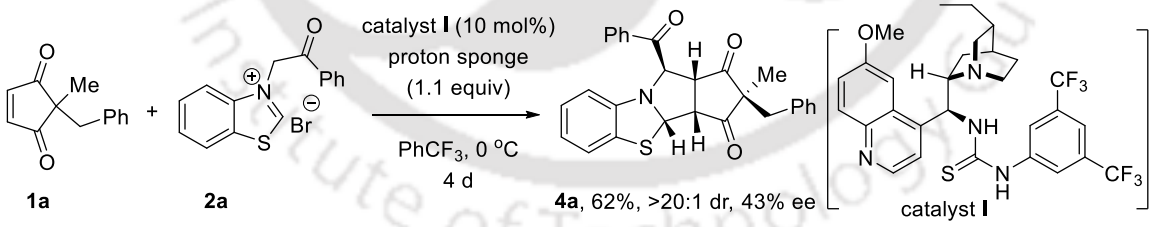
Table 4.3: Solvent screening for chiral product



entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	$PhCH_3$	75	26
2	**$PhCF_3$**	**62**	**43**
3	MTBE	55	40
4	$CHCl_3$	82	10
5	PhCl	76	10

[a]Reactions were carried out with **1a** (0. 025 mmol), **2a** (0.025 mmol) and catalyst **I** (10 mol%) in 0.25 mL solvent for 4 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

Thus, moderate enantiomeric excess (43% ee) was achieved with proton sponge as an additive in the presence of hydroquinine derived thiourea catalyst in $PhCF_3$ solvent at 0 °C (Scheme 4.12).



Scheme 4.12: Asymmetric synthesis of tetracycle

To explain the high diastereoselectivity of our product, we proposed plausible transition states (Figure 4.2). Plausible *endo*-TS **A** and **B** have been drawn to depict the stereochemical outcome of the reaction. In TS **A**, the steric effect is lower as the larger group of cyclopentenedione moiety stays away, whereas in TS **B** the steric hindrance could be seen.

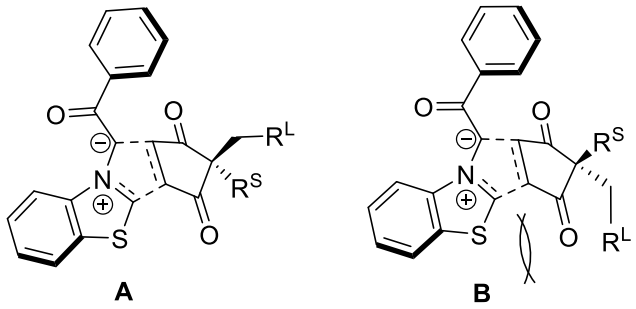
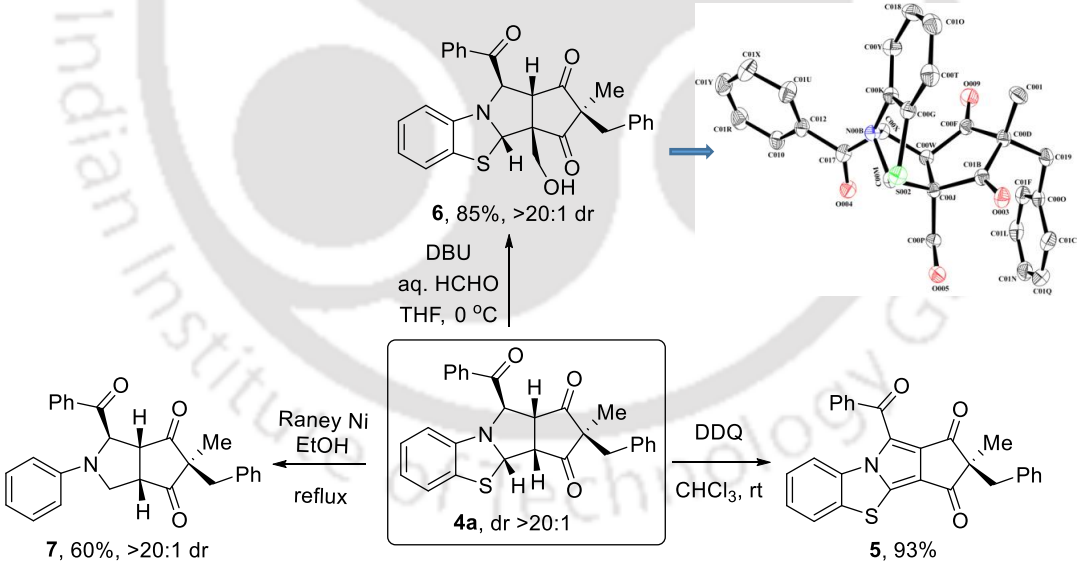


Figure 4.2: Plausible transition state.

To establish the synthetic utility of our method, a few reactions were envisaged using **4a** (Scheme 4.13). Initially, DDQ mediated oxidative reaction of **4a** was performed, which resulted in heteroaromatic compound **5** in 93% yield. Interestingly, regio- as well as diastereoselective mono-hydroxymethylation of **4a** with DBU/aq. HCHO provided alcohol **6** in 85% yield. The structure of **6** was confirmed by X-ray crystallography.[11] Finally desulfurization reaction with Raney nickel in ethanol[12] delivered fused pyrrolidine derivative **7** in 60% yield and diastereoselectivity was preserved.



Scheme 4.13: Synthetic transformations

In summary, we have developed a metal-free highly diastereoselective [3+2] cycloaddition reaction between *N*-phenacylbenzothiazolium bromides and prochiral cyclopentene-1,3-diones under mild reaction conditions. The corresponding tetracyclic products having five stereogenic centres could be useful in the development of new pharmaceuticals. The scope of the reaction is quite broad tolerating a variety of aryl and heteroaromatic groups. Interesting fused heterocyclic molecules have been synthesized from the product. A preliminary catalytic asymmetric approach has also been documented providing the product in moderate enantioselectivity.

4.7 Experimental section

A. General procedure for the synthesis 1,3-cyclopentenediones 1

1,3-Cyclopentenediones **1** were prepared according to reported procedures.[2c,2h]

B. General Procedure for the synthesis of *N*-arylbenzothiazolium bromides 2

N-Arylbenzothiazolium bromides salts **2** were prepared by refluxing benzothiazole with corresponding phenacyl bromides in ethanol (1M) for 2 hours. Then the solid was filtered and washed using diethyl ether/DCM.

C. General procedure for the synthesis of products 4a-4z

DIPEA (38 μL, 0.24 mmol) was added to a stirred solution of **1** (0.2 mmol) and **2** (0.2 mmol) in $CHCl_3$ (2 mL). After stirring for 2.5-4 hours at room temperature, 3 mL of water was added. The resulting mixture was extracted with EtOAc (3 X 2 mL). The combined organic phase was dried over anhyd. Na_2SO_4, evaporated in vacuum and purified by column chromatography (8%-10% EtOAc in hexane) to give compound **4**.

D. General procedure for the synthesis of asymmetric version of 4a

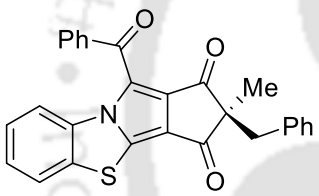
Proton sponge (23.5 mg, 0.11 mmol) and hydroquinine derived thiourea catalyst **I** (5.9 mg, 0.01 mmol) were added to the solution of **1a** (0.1 mmol) and **2a** (0.1 mmol) in trifluorotoluene (1 mL) respectively under argon atmosphere. After stirring for 4 days at 0 ^{o}C, 3 mL of water was added. The resulting mixture was extracted with EtOAc (3 X 2 mL). The combined organic phase was dried over anhyd. Na_2SO_4, evaporated in vacuum

and purified by column chromatography (8% EtOAc in hexane) to give 62% of compound **4a**.

HPLC information: Chiralpak IB column. Flow rate 1 mL/min. UV detection at 274 nm for major diastereomer; τ (major) = 12.2, τ (minor) = 19.8 min. using hexane:isopropanol = 95:5 as eluent, ee 43%.

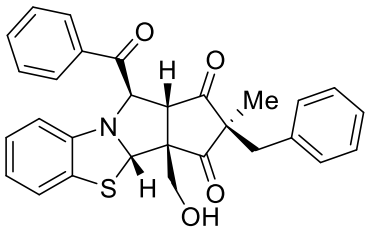
E. General procedure for the synthesis of *10-benzoyl-2-benzyl-2-methyl-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b] thiazole-1,3(2H)-dione* (5):

DDQ (56.7 mg, 0.25 mmol) was added to a solution of **4a** (45.3 mg, 0.1 mmol) in $CHCl_3$ (1 mL). After stirring for 3 hours at room temperature, 3 mL of water was added. The resulting mixture was extracted with DCM (3 x 2 mL). The combined organic phase was dried over anhyd. Na_2SO_4, evaporated in vacuum and purified by column chromatography (10% EtOAc in hexane) to give compound **5** as a yellow solid (41.7 mg, 93%); R_f = 0.45 (EtOAc/hexane 1:8); mp 181-184 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.30 (dd, *J* = 5.9, 3.6 Hz, 1H), 7.80 – 7.73 (m, 4H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.47 (dd, *J* = 6.2, 3.1 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.12 – 7.06 (m, 3H), 3.15 (d, *J* = 13.4 Hz, 1H), 2.99 (d, *J* = 13.4 Hz, 1H), 1.33 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.5, 194.7, 184.5, 139.6, 137.7, 136.5, 134.0, 133.8, 132.5, 130.3, 129.9, 128.4, 128.0, 127.0, 127.0, 124.0, 121.6, 121.2, 118.6, 62.6, 41.8, 21.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{20}NO_3S$ 450.1158; found: 450.1159.



***F*. General procedure for the synthesis of *10-benzoyl-2-benzyl-3a-(hydroxylmethyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione* (6)**:

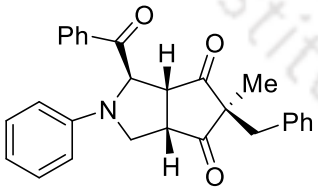
DBU (1.5 µL, 0.01 mmol) was added to a solution of **4a** (45.3 mg, 0.1 mmol) in dry THF (0.5 mL) at 0 ^oC under argon. After stirring for 1 hour, 0.17 ml (5 mmol) 37% formaldehyde solution was added dropwise and resulting solution was stirred for another 30 minutes at 0 ^oC. After consumption of **4a**, 1mL of water was added. Then the resulting mixture was extracted with EtOAc (3 x 2 mL). The combined organic phase was dried over anhyd. Na_2SO_4, evaporated in vacuum and purified by column



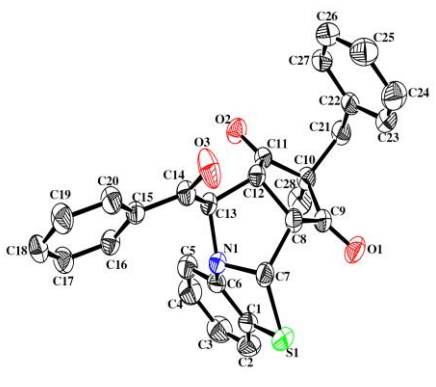
chromatography (15% EtOAc in hexane) to give compound **6** as a white solid (41 mg, 85%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:5); mp 170- 172 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.10 (d, *J* = 7.5 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.25 – 7.22 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.98 – 6.95 (m, 2H), 6.83 (dd, *J* = 17.9, 7.8 Hz, 2H), 5.89 (s, 1H), 5.35 (s, 1H), 3.36 – 3.31 (m, 1H), 3.16 (s, 1H), 3.03 (d, *J* = 10.8 Hz, 1H), 2.86 (s, 2H), 2.66 (s, 1H), 0.43 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 217.5, 216.5, 195.5, 145.5, 135.2, 134.2, 134.1, 129.9, 129.1, 128.9, 128.7, 127.8, 127.6, 126.3, 123.1, 123.0, 111.6, 78.3, 71.2, 66.6, 64.3, 60.2, 57.4, 44.3, 20.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_4S$ 484.1577; found: 484.1582.

***G.* General procedure for the synthesis of *1-benzoyl-5-benzyl-5-methyl-2-phenyltetrahydrocyclopenta[c]pyrrole-4,6(1H,5H) -dione* (7)**:

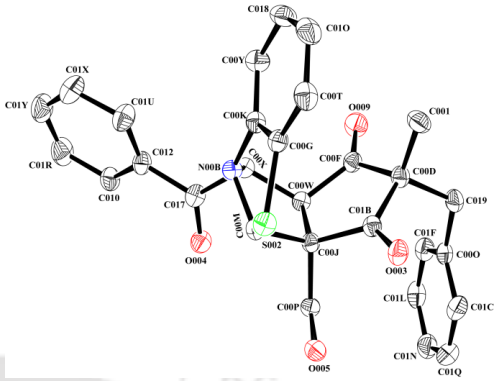
In a 5 mL round bottom flask, Raney nickel (600 mg, washed 6-7 times with dry ethanol) and **4a** (45.3 mg, 0.1 mmol) were taken in dry ethanol (2 mL). Then the round bottom flask was sealed with a condenser and placed in oil bath at 100 ^oC under argon for reflux. After consumption of **4a**, 1mL of water was added. Then the resulting mixture was extracted with EtOAc (3 x 2 mL). The combined organic phase was dried over anhyd. Na_2SO_4, evaporated in vacuum and purified by silica-gel (230-400 mesh) column chromatography (5% EtOAc in hexane) to give compound **7** as a red sticky solid (41 mg, 85%, >20:1 dr); R_f = 0.55 (EtOAc/hexane 1:15); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.15 (d, *J* = 7.4 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.26 (s, 2H), 7.17 – 7.11 (m, 5H), 7.02 (d, *J* = 6.9 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 2H), 5.82 (s, 1H), 3.94 – 3.89 (m, 2H), 3.02 (dd, *J* = 30.9, 13.0 Hz, 2H), 2.90 – 2.85 (m, 1H), 2.70 (d, *J* = 10.2 Hz, 1H), 1.24 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 218.0, 217.9, 197.7, 146.2, 135.1, 134.1, 129.3, 129.1, 128.8, 128.6, 127.7, 118.6, 113.9, 66.4, 60.0, 55.4, 52.8, 50.5, 44.6, 19.6; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{26}NO_3$ 424.1907; found: 424.1906.



H. Crystal structure of compound 4a and 6



(4a)



(6)

ORTEP crystal structure: (40% probability level) diagram of **4a** and **6** (all hydrogen atoms are omitted for clarity)

Table 4.4: Crystal data and structure refinement for 4a and 6.

Identification code	**4a**	**6**
formula	$C_{28}H_{23}NO_3S$	$C_{29}H_{25}NO_4S$
Formula weight	453.53	483.56
CCDC number	1540321	1566468
T (K)	296(2)	100(2)
Wavelength, λ(Å)	0.71073	0.71073
Crystal system	monoclinic	triclinic
Space group	$P2_1/n$	P-1
a (Å)	13.4330(10)	12.2788(5)
b (Å)	8.4143(6)	13.5044(5)
c (Å)	20.1570(14)	15.3335(4)
α (°)	90.00	105.770(3)
β (°)	90.985(7)	110.274(3)
γ (°)	90.00	90.739(3)
V (Å^3)	2278.0(3)	2279.07(15)
Z	4	4
D_{calcd} (g cm^{-3})	1.322	1.409

μ (mm^{-1})	0.173	0.181
F(000)	952.0	1016.0
Crystal size/mm^3	0.24×0.18×0.16	0.30×0.20×0.20
Reflections collected	9228	38001
Unique reflections	3990[R(int) = 0.0268]	12165
Goodness-of-fit (GOF)[a] on F^2	1.094	0.970
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.0483, 0.1185	0.0542, 0.1480
R_1[b], wR_2[c] (all data)	0.0708, 0.1335	0.0806, 0.1576

[a]GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined).[b]$R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0$, [c]$wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{½}$

4.8 References

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10. CCDC 1540321 contains the crystallographic data for **4a**.
11. CCDC 1566468 contains the crystallographic data for **6**. The crystallographic data can be obtained from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
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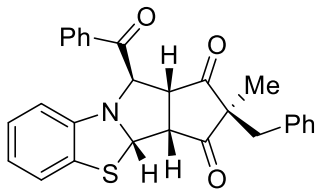
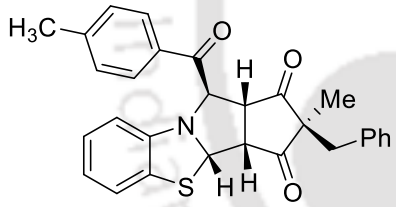
4.9 Characterization Data of Products

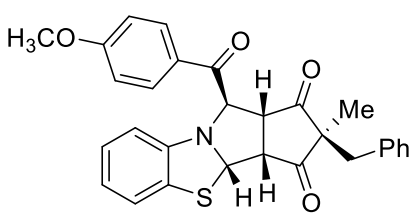
10-benzoyl-2-benzyl-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]-pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4a**): The title compound **4a** was prepared (4 h) as per the general procedure as a white solid (88.6 mg, 98%, >20:1 dr); R_f = 0.55 (EtOAc/hexane 1:9); mp 150-152 ^oC; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.06 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.20 – 7.16 (m, 3H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.03 (dd, *J* = 11.2, 4.3 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.86 – 6.79 (m, 2H), 5.86 (s, 1H), 5.28 – 5.23 (m, 1H), 2.90 (d, *J* = 12.6 Hz, 1H), 2.84 – 2.79 (m, 2H), 2.74 (d, *J* = 12.6 Hz, 1H), 0.41 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.8, 213.6, 194.8, 145.0, 135.2, 134.3, 134.1, 129.5, 129.1, 129.0, 128.9, 127.9, 127.4, 126.5, 123.4, 123.3, 112.2, 74.3, 70.2, 60.3, 56.1, 55.0, 46.5, 19.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{24}NO_3S$ 454.1471; found: 454.1471.



2-benzyl-2-methyl-10-(4-methylbenzoyl)-3a,3b,10,10a-tetrahydro-1H-benzo[d]-cyclopenta[3,4] pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4b**): The title compound **4b** was prepared (3 h) as per the general procedure as a white solid (89.5 mg, 96%, >20:1 dr); R_f = 0.50 (EtOAc/hexane 1:9); mp 160-163 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.21 – 7.17 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.04 – 7.00 (m, 1H), 6.95 (dd, *J* = 6.4, 2.9 Hz, 2H), 6.85 – 6.79 (m, 2H), 5.86 (s, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 2.89 (d, *J* = 12.7 Hz, 1H), 2.85 – 2.77 (m, 2H), 2.73 (d, *J* = 12.7 Hz, 1H), 2.42 (s, 3H), 0.38 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 218.9, 213.6, 194.3, 145.1, 144.9, 135.0, 131.6, 129.6, 129.4, 129.1, 128.8, 127.8, 127.1, 126.4, 123.3, 123.0, 112.0, 74.2, 70.0, 60.1, 56.0, 54.9, 46.3, 21.8, 19.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_3S$ 468.1628; found: 468.1631.

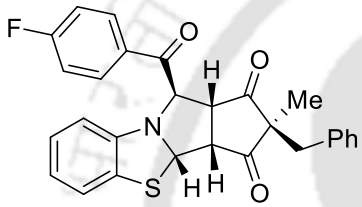


2-benzyl-10-(4-methoxybenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]-cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4c**): The title compound **4c** was prepared (3 h) as per the general procedure as a white sticky solid (85.9 mg, 89%, >20:1 dr); R_f = 0.40 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.07 (d, *J* = 8.9 Hz, 2H), 7.24 – 7.19 (m, 3H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.06 – 7.03 (m, 1H), 6.98 (dd, *J* = 9.2,



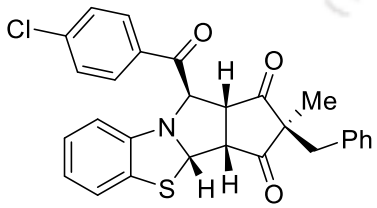
2.8 Hz, 4H), 6.87 – 6.81 (m, 2H), 5.86 (s, 1H), 5.26 (d, *J* = 9.1 Hz, 1H), 3.90 (s, 3H), 2.91 (d, *J* = 12.7 Hz, 1H), 2.88 – 2.78 (m, 2H), 2.75 (d, *J* = 12.7 Hz, 1H), 0.40 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 219.1, 213.7, 193.1, 164.2, 144.9, 135.0, 131.4, 129.3, 128.8, 127.7, 127.1, 127.0, 126.4, 123.3, 123.0, 114.1, 114.1, 114.1, 111.9, 74.2, 69.8, 60.2, 55.9, 55.6, 55.0, 46.3, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_4S$ 484.1577; found: 484.1575.

2-benzyl-10-(4-fluorobenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4d**): The title compound **4d** was



prepared (2.5 h) as per the general procedure as a white solid (83.8 mg, 89%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:9); mp 180-182 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.10 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.23 – 7.19 (m, 3H), 7.17 (t, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.96 (dd, *J* = 6.2, 2.7 Hz, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.80 (s, 1H), 5.22 (dd, *J* = 5.5, 3.5 Hz, 1H), 2.90 (d, *J* = 12.7 Hz, 1H), 2.82 – 2.78 (m, 2H), 2.74 (d, *J* = 12.7 Hz, 1H), 0.40 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 218.8, 213.4, 193.1, 167.2, 165.2, 144.7, 135.0, 131.8 (d, *J* = 10 Hz), 130.5, 129.3, 128.8, 127.8, 127.2, 126.5, 123.3 (d, *J* = 16.2 Hz), 116.1 (d, *J* = 21.2 Hz), 112.0, 74.2, 70.1, 60.2, 55.8, 54.8, 46.4, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}FNO_3S$ 472.1377; found: 472.1376.

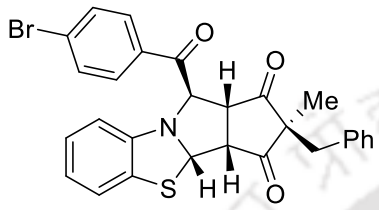
2-benzyl-10-(4-chlorobenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4e**): The title compound **4e** was



prepared (3 h) as per the general procedure as a light yellow solid (91.5 mg, 94%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:9); mp 172-175 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.22 – 7.17 (m, 3H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.95 (dd, *J* = 6.2, 2.7 Hz, 2H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.78 (s, 1H), 5.22 – 5.17 (m, 1H), 2.90 (d, *J* = 12.7 Hz, 1H), 2.79 (d, *J* = 5.2 Hz, 2H), 2.74 (d, *J* = 12.7 Hz,

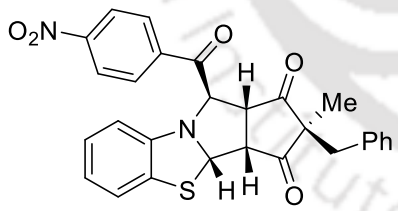
1H), 0.40 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 218.7, 213.4, 193.6, 144.7, 140.6, 135.0, 132.4, 130.4, 129.3, 129.2, 128.8, 127.8, 127.2, 126.5, 123.4, 123.3, 112.0, 74.2, 70.1, 60.2, 55.8, 54.7, 46.4, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}ClNO_3S$ 488.1082; found: 488.1084.

2-benzyl-10-(4-bromobenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4f**): The title compound **4f** was



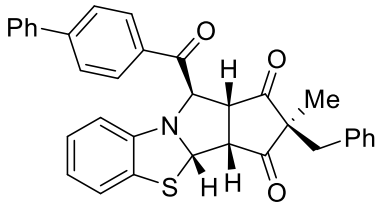
prepared (2.5 h) as per the general procedure as a brown solid (101.9 mg, 96%, >20:1 dr); R_f = 0.44 (EtOAc/hexane 1:9); mp 125-127 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.21 – 7.17 (m, 3H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.95 (dd, *J* = 6.3, 2.9 Hz, 2H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.78 (s, 1H), 5.21 – 5.16 (m, 1H), 2.89 (d, *J* = 12.7 Hz, 1H), 2.81 – 2.77 (m, 2H), 2.73 (d, *J* = 12.7 Hz, 1H), 0.39 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 218.7, 213.3, 193.8, 148.7, 144.7, 135.0, 132.8, 132.2, 130.5, 129.7, 129.4, 129.3, 128.8, 128.4, 127.8, 127.3, 126.5, 123.4, 123.3, 112.0, 74.2, 70.1, 60.2, 55.8, 54.7, 46.4, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}BrNO_3S$ 532.0577; found: 532.0582.

2-benzyl-2-methyl-10-(4-nitrobenzoyl)-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4] pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4g**): The title compound **4g** was



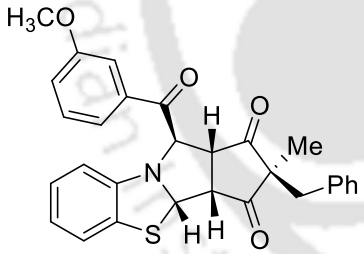
prepared (3 h) as per the general procedure as a yellow solid (69.7 mg, 70%, >20:1 dr); R_f = 0.35 (EtOAc/hexane 1:9); mp 188-190 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 7.25 – 7.20 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.98 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.82 (s, 1H), 5.16 (d, *J* = 8.5 Hz, 1H), 2.93 (d, *J* = 12.7 Hz, 1H), 2.86 – 2.80 (m, 2H), 2.77 (d, *J* = 12.7 Hz, 1H), 0.42 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 218.5, 213.0, 193.4, 150.7, 144.3, 138.7, 134.9, 130.1, 129.3, 128.8, 127.8, 127.3, 126.6, 124.0, 123.7, 123.6, 112.0, 74.1, 70.5, 60.2, 55.7, 54.4, 46.5, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}N_2O_5S$ 499.1322; found: 499.1321.

10-([1,1'-biphenyl]-4-carbonyl)-2-benzyl-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo-[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4h**): The title compound **4h**



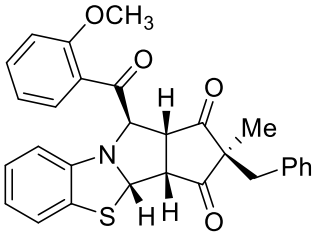
was prepared (2.5 h) as per the general procedure as a white solid (88.8 mg, 84%, >20:1 dr); R_f = 0.48 (EtOAc/hexane 1:9); mp 198-200 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.22 – 7.17 (m, 3H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.97 (dd, *J* = 5.9, 3.0 Hz, 2H), 6.85 (dd, *J* = 7.5, 5.0 Hz, 2H), 5.90 (s, 1H), 5.26 (d, *J* = 9.0 Hz, 1H), 2.90 (d, *J* = 12.7 Hz, 1H), 2.88 – 2.81 (m, 2H), 2.75 (d, *J* = 12.7 Hz, 1H), 0.41 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.9, 213.6, 194.2, 146.7, 144.8, 139.5, 135.0, 132.7, 129.6, 129.4, 129.1, 128.8, 128.5, 127.8, 127.5, 127.3, 127.2, 126.4, 123.4, 123.2, 112.0, 74.2, 70.1, 60.2, 55.9, 54.8, 46.4, 19.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{34}H_{28}NO_3S$ 530.1784; found: 530.1780.

2-benzyl-10-(3-methoxybenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4i**): The title compound **4i** was



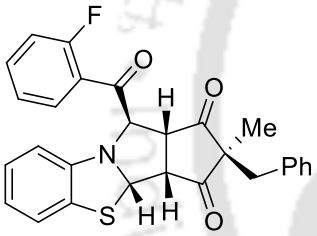
prepared (2.5 h) as per the general procedure as a white solid (91.7 mg, 95%, >20:1 dr); R_f = 0.41 (EtOAc/hexane 1:9); mp 152-155 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.59 – 7.57 (m, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.22 – 7.16 (m, 4H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.97 (dd, *J* = 6.1, 3.1 Hz, 2H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.86 (s, 1H), 5.31 (d, *J* = 8.9 Hz, 1H), 3.87 (s, 3H), 2.92 (d, *J* = 12.7 Hz, 1H), 2.83 (dt, *J* = 11.0, 10.4 Hz, 2H), 2.76 (d, *J* = 12.7 Hz, 1H), 0.45 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.7, 213.5, 194.5, 159.9, 144.9, 135.3, 135.0, 129.9, 129.3, 128.8, 127.8, 127.2, 126.4, 123.3, 123.2, 121.5, 120.8, 112.9, 112.1, 74.3, 70.2, 60.2, 55.9, 55.5, 55.0, 46.3, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_4S$ 484.1577; found: 484.1573.

2-benzyl-10-(2-methoxybenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4j**): The title compound **4j** was



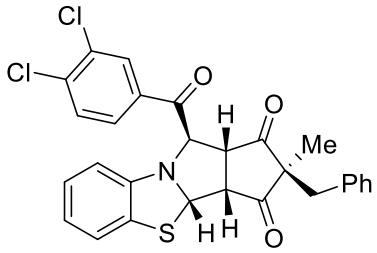
prepared (3 h) as per the general procedure as a light yellow sticky solid (92.7 mg, 96%, >20:1 dr); R_f = 0.40 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.64 (d, *J* = 6.0 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.23 – 7.19 (m, 3H), 7.01 (ddd, *J* = 24.1, 11.4, 5.2 Hz, 6H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 1H), 5.26 (dd, *J* = 5.7, 3.5 Hz, 1H), 4.00 (s, 3H), 2.91 (d, *J* = 12.7 Hz, 1H), 2.83 – 2.80 (m, 2H), 2.73 (d, *J* = 12.7 Hz, 1H), 0.42 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 218.2, 214.0, 198.1, 158.6, 145.4, 135.2, 134.6, 131.2, 129.3, 129.3, 128.7, 127.7, 126.6, 126.1, 125.3, 122.8, 122.5, 121.0, 112.4, 111.5, 73.9, 73.4, 60.0, 56.2, 55.7, 54.8, 46.3, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_4S$ 484.1577; found: 484.1577.

2-benzyl-10-(2-fluorobenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4k**): The title compound **4k** was



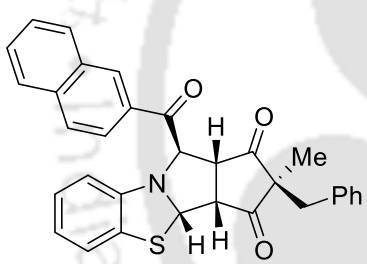
prepared (3 h) as per the general procedure as a yellow solid (78.1 mg, 83%, 10:1 dr); R_f = 0.45 (EtOAc/hexane 1:9); mp 170-172 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.83 (td, *J* = 7.7, 1.6 Hz, 0.13H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.55 (td, *J* = 7.5, 1.6 Hz, 1H), 7.23 (dd, *J* = 8.9, 5.6 Hz, 5H), 7.13 (dd, *J* = 11.1, 8.4 Hz, 1H), 7.02 (dd, *J* = 13.5, 7.4 Hz, 2H), 6.99 – 6.95 (m, 2H), 6.85 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 5.91 (d, *J* = 6.8 Hz, 0.11H), 5.87 (d, *J* = 2.0 Hz, 1H), 5.11 (d, *J* = 4.2 Hz, 0.1H), 4.93 (d, *J* = 9.5 Hz, 1H), 3.08 (t, *J* = 5.6 Hz, 0.20H), 2.97 (d, *J* = 10.3 Hz, 1H), 2.94 (d, *J* = 13.2 Hz, 0.17H), 2.87 (d, *J* = 12.6 Hz, 1H), 2.72 (dd, *J* = 16.2, 6.4 Hz, 2H), 1.43 (d, *J* = 11.4 Hz, 04H), 0.30 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 218.7, 213.6, 194.0 (d, *J* = 5 Hz), 161.9 (d, *J* = 253 Hz), 144.8, 135.6 (d, *J* = 9 Hz), 135.1, 131.3, 129.4, 128.8, 127.7, 126.6, 126.5, 124.8 (d, *J* = 3 Hz), 123.2, 123.1, 123.0, 116.9, 116.7, 112.8 (d, *J* = 5 Hz), 73.6, 73.1 (d, *J* = 6 Hz), 60.1, 55.8, 54.0, 46.5, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}FNO_3S$ 472.1377; found: 472.1382.

2-benzyl-10-(3,4-dichlorobenzoyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]-cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4l**): The title compound **4l** was prepared as (3 h) per the general procedure as a white sticky solid (100 mg, 96%, >20:1

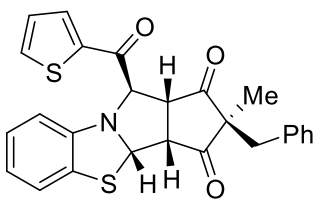


dr); R_f = 0.46 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.12 (d, *J* = 1.9 Hz, 1H), 7.89 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 4.8, 1.5 Hz, 3H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.95 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.72 (s, 1H), 5.19 (d, *J* = 9.0 Hz, 1H), 2.91 (d, *J* = 12.7 Hz, 1H), 2.82 – 2.78 (m, 1H), 2.77 – 2.72 (m, 2H), 0.42 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.4, 213.1, 192.7, 148.7, 144.6, 138.7, 134.9, 133.6, 133.6, 131.0, 129.3, 128.8, 127.9, 127.8, 127.4, 126.5, 123.5, 123.5, 112.1, 74.2, 70.2, 60.2, 55.7, 54.6, 46.4, 19.0; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{22}Cl_2NO_3S$ 522.0692; found: 522.0691.

10-(2-naphthoyl)-2-benzyl-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4m**): The title compound **4m** was prepared (3 h) as per the general procedure as a red solid (95.7 mg, 95%, >20:1 dr); R_f = 0.50 (EtOAc/hexane 1:9); mp 160-162 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.69 (s, 1H), 8.07 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.92 (dd, *J* = 15.7, 8.4 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.61 – 7.59 (m, 1H), 7.16 – 7.11 (m, 4H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.97 (dd, *J* = 7.2, 1.9 Hz, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.03 (s, 1H), 5.37 (dd, *J* = 6.3, 2.7 Hz, 1H), 2.94 (d, *J* = 12.6 Hz, 1H), 2.91 – 2.88 (m, 2H), 2.78 (d, *J* = 12.7 Hz, 1H), 0.49 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.7, 213.5, 194.7, 145.1, 135.9, 135.0, 132.4, 131.3, 131.2, 129.9, 129.3, 129.2, 128.8, 127.8, 127.7, 127.4, 127.1, 126.4, 124.1, 123.3, 123.2, 112.2, 74.4, 70.3, 60.2, 56.0, 55.2, 46.4, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{32}H_{26}NO_3S$ 504.1628; found: 504.1628.

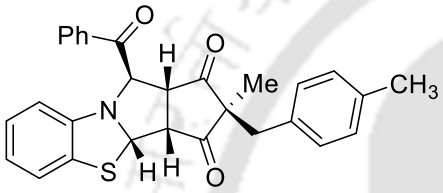


2-benzyl-2-methyl-10-(thiophene-2-carbonyl)-3a,3b,10,10a-tetrahydro-1H-benzo[d]-cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4n**): The title compound **4n** was prepared (3.5 h) as per the general procedure as a white solid (87.2 mg, 95%, >20:1 dr); R_f = 0.48 (EtOAc/hexane 1:9); mp 156-158 °C; **^{1}H NMR (600**

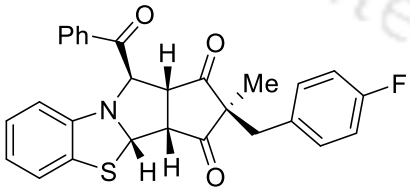


MHz, $CDCl_3$): δ 7.99 (d, *J* = 3.8 Hz, 1H), 7.70 (d, *J* = 4.9 Hz, 1H), 7.24 – 7.21 (m, 3H), 7.18 – 7.16 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 6.3, 3.0 Hz, 2H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.62 (s, 1H), 5.25 (d, *J* = 9.4 Hz, 1H), 2.92 (dd, *J* = 20.8, 11.5 Hz, 2H), 2.80 (t, *J* = 9.9 Hz, 1H), 2.75 (d, *J* = 12.7 Hz, 1H), 0.40 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 218.6, 213.5, 188.0, 144.8, 140.0, 135.4, 135.0, 134.2, 129.4, 128.8, 128.5, 127.8, 127.0, 126.4, 123.2, 112.1, 74.2, 71.3, 60.1, 55.8, 54.7, 46.3, 19.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{26}H_{22}NO_3S_2$ 460.1036; found: 460.1044.

10-benzoyl-2-methyl-2-(4-methylbenzyl)-3a,3b,10,10a-tetrahydro-1H-benzo[d]-cyclopenta [3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4o**): The title compound **4o** was prepared (2.5 h) as per the general procedure as a white solid (80.3 mg, 86%, >20:1 dr); R_f = 0.50 (EtOAc/hexane 1:9); mp 146-148 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.07 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.83 (dt, *J* = 10.2, 8.2 Hz, 4H), 5.86 (s, 1H), 5.28 (d, *J* = 8.4 Hz, 1H), 2.84 (dt, *J* = 13.7, 6.6 Hz, 3H), 2.70 (d, *J* = 12.7 Hz, 1H), 2.23 (s, 3H), 0.41 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.7, 213.6, 194.8, 145.0, 137.4, 134.1, 134.0, 131.9, 129.4, 129.2, 129.0, 128.9, 127.3, 126.4, 123.3, 123.2, 112.2, 74.2, 70.1, 60.2, 55.9, 55.0, 46.0, 21.0, 19.0; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_3S$ 468.1628; found: 468.1630.

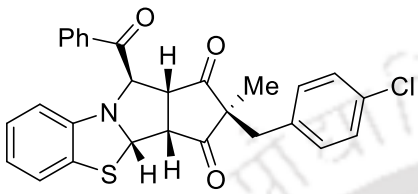


10-benzoyl-2-(4-fluorobenzyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclo-penta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4p**): The title compound **4p** was prepared (2.5 h) as per the general procedure as a white solid (84.8 mg, 90%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:9); mp 161-164 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.07 (d, *J* = 8.1 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 11.0, 4.6 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.92 – 6.86 (m, 4H), 6.86 – 6.81 (m, 2H), 5.90 (s, 1H), 5.25 (d, *J* = 9.3 Hz, 1H), 2.94 (d, *J* = 10.4 Hz, 1H), 2.87 – 2.82 (m, 2H), 2.71 (d, *J* = 12.9 Hz, 1H), 0.35 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.8, 213.4, 194.5, 163.4, 160.9, 144.7, 134.1, 134.1,



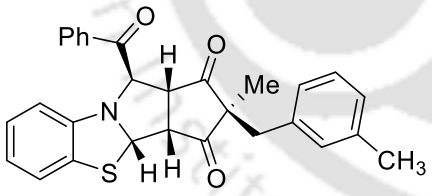
131.0, 130.9, 130.8, 129.0, 128.9, 127.1, 126.5, 123.4, 123.2, 115.8, 115.6, 111.9, 74.2, 70.1, 59.9, 55.9, 54.7, 45.2, 19.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}FNO_3S$ 472.1377; found: 472.1377.

10-benzoyl-2-(4-chlorobenzyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4q**): The title compound **4q** was



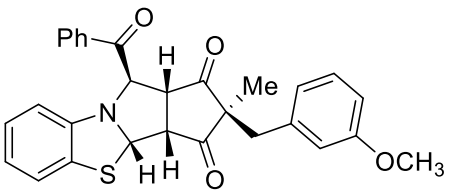
prepared (3 h) as per the general procedure as a white solid (92.5 mg, 95%, >20:1 dr); R_f = 0.44 (EtOAc/hexane 1:9); mp 166-168 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.10 (d, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.88 – 6.84 (m, 2H), 5.92 (s, 1H), 5.28 (d, *J* = 9.3 Hz, 1H), 3.00 (d, *J* = 10.4 Hz, 1H), 2.92 – 2.84 (m, 2H), 2.71 (d, *J* = 12.9 Hz, 1H), 0.37 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 218.6, 213.2, 194.5, 144.7, 134.1, 134.1, 133.7, 133.5, 130.8, 129.0, 128.9, 127.1, 126.5, 123.4, 123.2, 111.9, 74.2, 70.2, 59.8, 55.9, 54.7, 45.1, 19.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}ClNO_3S$ 488.1082; found: 488.1085.

10-benzoyl-2-methyl-2-(3-methylbenzyl)-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4r**): The title compound **4r** was



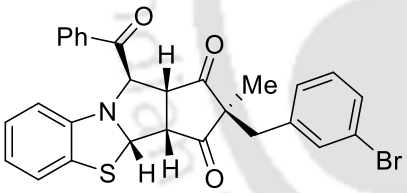
prepared (3 h) as per the general procedure as a white solid (80.3 mg, 86%, >20:1 dr); R_f = 0.52 (EtOAc/hexane 1:9); mp 142-145 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.10 (d, *J* = 7.5 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.11 – 7.02 (m, 3H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.90 (s, 1H), 5.30 (dd, *J* = 6.4, 2.7 Hz, 1H), 2.88 (d, *J* = 12.6 Hz, 1H), 2.85 – 2.81 (m, 2H), 2.72 (d, *J* = 12.6 Hz, 1H), 2.21 (s, 3H), 0.44 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.7, 213.5, 194.7, 145.0, 138.4, 134.9, 134.0, 130.0, 129.0, 128.9, 128.7, 128.5, 127.2, 126.4, 126.3, 123.3, 123.1, 112.1, 74.3, 70.1, 60.2, 55.9, 55.1, 46.4, 21.2, 19.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_3S$ 468.1628; found: 468.1633.

10-benzoyl-2-(3-methoxybenzyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4s**): The title compound **4s** was



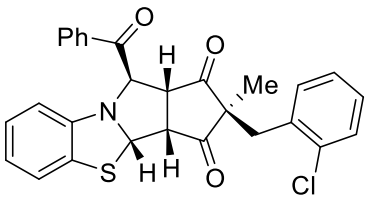
prepared (2.5 h) as per the general procedure as a brown solid (87.9 mg, 91%, >20:1 dr); R_f = 0.39 (EtOAc/hexane 1:9); mp 104-106 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.08 (d, *J* = 7.7 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.9 Hz, 2H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.71 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.53 (d, *J* = 7.5 Hz, 1H), 6.48 (s, 1H), 5.89 (s, 1H), 5.30 – 5.27 (m, 1H), 3.69 (s, 3H), 2.90 – 2.86 (m, 3H), 2.71 (d, *J* = 12.6 Hz, 1H), 0.40 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**; δ 218.7, 213.5, 194.7, 159.6, 144.9, 136.5, 134.0, 129.8, 129.0, 128.9, 127.2, 126.4, 123.3, 123.1, 121.5, 115.0, 113.1, 112.0, 74.2, 70.1, 60.0, 56.0, 55.1, 55.0, 46.4, 19.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_4S$ 484.1577; found: 484.1576.

10-benzoyl-2-(3-bromobenzyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4t**): The title compound **4t** was



prepared (2.5 h) as per the general procedure as a white solid (80.7 mg, 76%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:9); mp 146-148 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.08 (d, *J* = 8.2 Hz, 2H), 7.63 – 7.59 (m, 1H), 7.50 (t, *J* = 7.0 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.11 – 7.01 (m, 4H), 6.89 – 6.80 (m, 3H), 5.93 (s, 1H), 5.26 (d, *J* = 9.4 Hz, 1H), 2.97 (d, *J* = 10.4 Hz, 1H), 2.88 (t, *J* = 9.9 Hz, 1H), 2.82 (d, *J* = 12.8 Hz, 1H), 2.67 (d, *J* = 12.8 Hz, 1H), 0.35 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ 218.3, 213.0, 194.5, 144.7, 137.3, 134.1, 134.0, 132.3, 130.9, 130.3, 129.0, 129.0, 128.0, 127.0, 126.5, 123.4, 123.2, 122.8, 111.9, 74.2, 70.2, 59.7, 55.9, 54.8, 45.2, 19.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}BrNO_3S$ 532.0577; found: 532.0578.

10-benzoyl-2-(2-chlorobenzyl)-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4u**): The title compound **4u** was prepared (2.5 h) as per the general procedure as a white solid (92.5 mg, 95%, 18:1 dr); R_f = 0.44 (EtOAc/hexane 1:9); mp 126-128 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.19 (d, *J* =

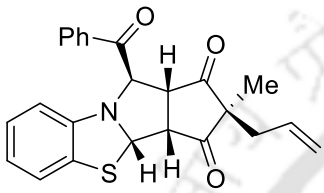


7.4 Hz, 0.13H), 8.13 – 8.09 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 0.13H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 3.6 Hz, 0.06H), 7.25 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 0.14H), 7.15 – 7.11 (m, 2H), 7.08 (d, *J* = 7.5 Hz, 0.10H), 7.04 (dd, *J* = 11.8, 5.2 Hz, 2H), 7.02 – 6.98 (m, 1H), 6.91 (d, *J* = 7.9 Hz, 0.09H), 6.84 – 6.79 (m, 2H), 6.09 (s, 0.06H), 5.98 (s, 1H), 5.61 (d, *J* = 9.3 Hz, 0.06H), 5.37 (d, *J* = 9.3 Hz, 1H), 3.97 (d, *J* = 10.8 Hz, 0.06H), 3.60 (t, *J* = 9.7 Hz, 0.06H), 3.51 (dd, *J* = 10.4, 0.6 Hz, 1H), 3.28 – 3.23 (m, 1H), 3.02 – 2.95 (m, 2H), 1.01 (s, 0.18H), 0.46 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 216.1, 211.7, 195.0, 145.0, 134.4, 134.1, 134.0, 132.6, 132.2, 129.9, 129.2, 129.1, 129.1, 129.0, 128.9, 127.4, 126.9, 126.4, 123.2, 123.2, 112.6, 74.5, 70.2, 58.5, 55.3, 54.4, 41.2, 17.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{28}H_{23}ClNO_3S$ 488.1082; found: 488.1082.

10-benzoyl-2-methyl-2-(naphthalen-2-ylmethyl)-3a,3b,10,10a-tetrahydro-1H-benzo[d]-cyclopenta[3,4]pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4v**): The title compound **4v** was prepared (3 h) as per the general procedure as a white solid (90.5 mg, 90%, >20:1 dr); R_f = 0.48 (EtOAc/hexane 1:9); mp 148-150 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.74 (dd, *J* = 5.9, 3.4 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 – 7.41 (m, 5H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.07 – 7.01 (m, 2H), 6.87 – 6.80 (m, 2H), 5.88 (s, 1H), 5.23 (d, *J* = 9.2 Hz, 1H), 3.05 (d, *J* = 12.8 Hz, 1H), 2.91 (d, *J* = 12.8 Hz, 1H), 2.84 (d, *J* = 10.4 Hz, 1H), 2.80 – 2.75 (m, 1H), 0.46 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 218.8, 213.5, 194.5, 144.9, 134.0, 133.2, 132.5, 128.9, 128.8, 128.5, 128.3, 127.7, 127.7, 127.2, 127.1, 126.5, 126.4, 126.2, 123.4, 123.2, 112.0, 74.3, 70.1, 60.2, 55.8, 54.9, 46.4, 19.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{32}H_{26}NO_3S$ 504.1628; found: 504.1631.

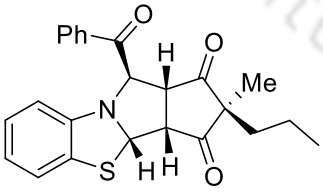
10-benzoyl-2-methyl-2-phenyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]-pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4w**): The title compound **4w** was prepared (3 h) as per the general procedure as a brown sticky solid (66.7 mg, 76%, >20:1 dr); R_f = 0.60 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$)**:

δ 8.16 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.15 (dd, *J* = 13.4, 7.5 Hz, 3H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.06 (s, 1H), 5.59 (d, *J* = 8.9 Hz, 1H), 3.95 (dd, *J* = 10.5, 1.2 Hz, 1H), 3.68 (dd, *J* = 10.3, 9.2 Hz, 1H), 0.90 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 213.4, 209.0, 195.4, 145.7, 136.5, 134.2, 132.4, 129.5, 129.1, 129.0, 128.3, 128.2, 126.3, 126.3, 123.7, 123.2, 117.2, 113.6, 75.0, 69.8, 62.8, 55.0, 54.0, 20.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{27}H_{22}NO_3S$ 440.1315; found: 440.1312.



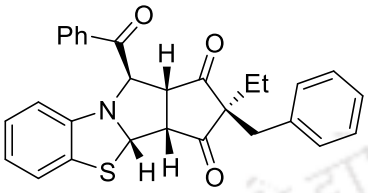
2-allyl-10-benzoyl-2-methyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]-pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4x**): The title compound **4x** was prepared (2.5 h) as per the general procedure as a brown sticky solid (70.1 mg, 87%, >20:1 dr); R_f = 0.58 (EtOAc/hexane 1:9); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.16 (d, *J* = 7.3 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 2H), 6.02 (s, 1H), 5.54 (dq, *J* = 10.0, 7.6 Hz, 1H), 5.42 (d, *J* = 9.3 Hz, 1H), 5.09 (d, *J* = 9.8 Hz, 1H), 5.03 (d, *J* = 15.9 Hz, 1H), 3.80 (d, *J* = 10.3 Hz, 1H), 3.40 (t, *J* = 9.8 Hz, 1H), 2.28 – 2.25 (m, 1H), 2.17 (dd, *J* = 13.1, 7.9 Hz, 1H), 0.32 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 217.6, 212.3, 194.9, 144.9, 134.1, 130.8, 129.1, 129.0, 127.2, 126.4, 123.3, 123.2, 120.5, 112.1, 74.4, 70.2, 58.2, 55.4, 54.4, 43.4, 17.6; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{22}NO_3S$ 404.1315; found: 404.1312.

10-benzoyl-2-methyl-2-propyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]-pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4y**): The title compound **4y** was prepared (2 h) as per the general procedure as a light yellow sticky solid (68.8 mg, 85%, 8:1 dr); R_f = 0.56 (EtOAc/hexane 1:9); **^{1}H NMR of major diastereomer (600 MHz, $CDCl_3$)**: δ 8.20 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.66 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.11 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.07 – 7.04 (m, 1H), 6.88 – 6.84 (m, 2H), 6.05 (s, 1H), 5.50 (d, *J* = 9.3 Hz, 1H), 3.91 (dd, *J* = 10.3, 1.1 Hz, 1H), 3.54 – 3.49 (m, 1H), 1.52 – 1.42 (m, 2H), 1.23 – 1.15 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H), 0.37 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 217.9, 212.6, 195.0, 145.0, 134.2, 134.1, 129.2, 129.0,

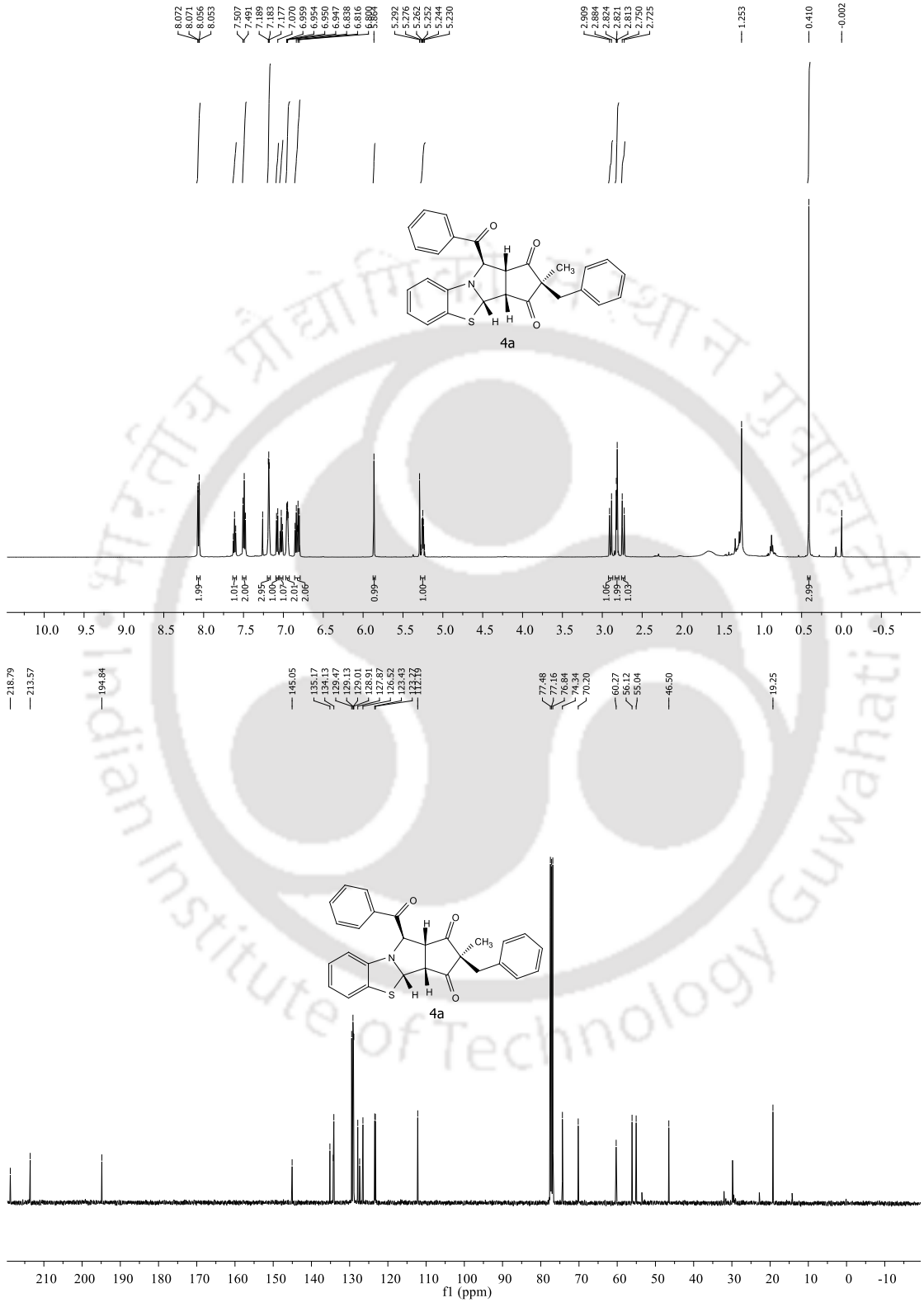


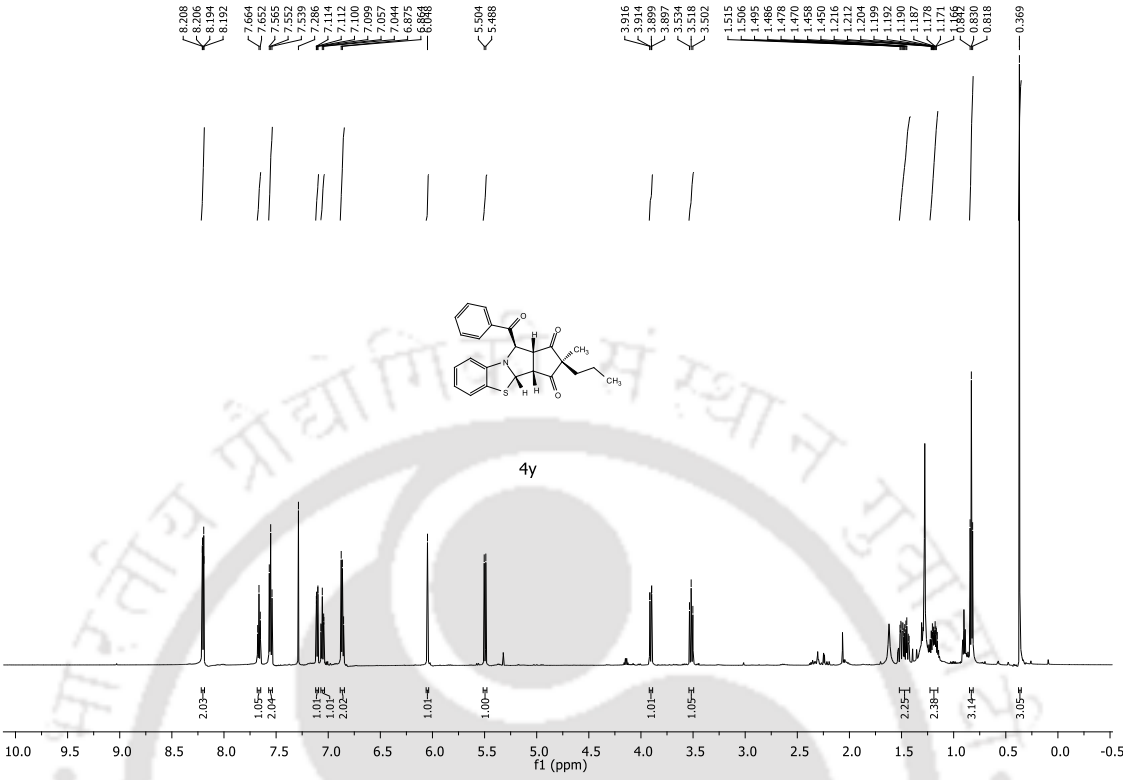
127.2, 126.3, 123.2, 123.2, 112.2, 74.5, 70.3, 57.9, 55.3, 54.1, 41.2, 17.9, 17.3, 14.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{22}NO_3S$ 406.1471; found: 406.1443.

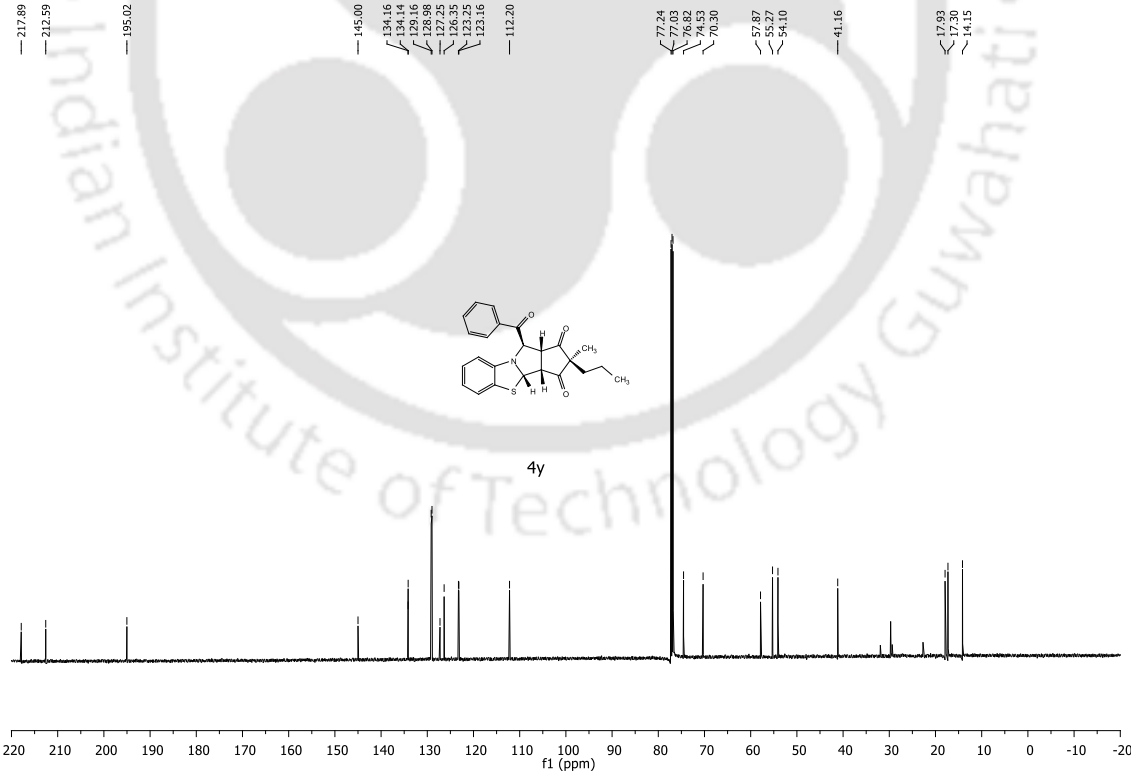
10-benzoyl-2-benzyl-2-ethyl-3a,3b,10,10a-tetrahydro-1H-benzo[d]cyclopenta[3,4]-pyrrolo[2,1-b]thiazole-1,3(2H)-dione (**4z**): The title compound **4z** was prepared (2.5 h) as per the general procedure as a white solid (65.3 mg, 70%, >20:1 dr); R_f = 0.50 (EtOAc/hexane 1:9); mp 106-108 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.10 (d, *J* = 7.3 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.22 – 7.19 (m, 3H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.98 (dd, *J* = 6.4, 2.9 Hz, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.83 (s, 1H), 5.36 (d, *J* = 8.9 Hz, 1H), 3.01 (d, *J* = 12.6 Hz, 1H), 2.86 – 2.79 (m, 3H), 0.99 (dq, *J* = 14.9, 7.5 Hz, 1H), 0.77 (dq, *J* = 14.7, 7.5 Hz, 1H), 0.56 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 218.6, 213.4, 195.1, 145.2, 135.4, 134.4, 134.3, 129.9, 129.3, 129.3, 129.2, 129.1, 128.0, 127.4, 126.6, 123.4, 123.0, 111.5, 74.2, 70.0, 64.0, 56.6, 55.3, 43.8, 27.7, 8.0; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{29}H_{26}NO_3S$ 468.1628; found: 468.1630.

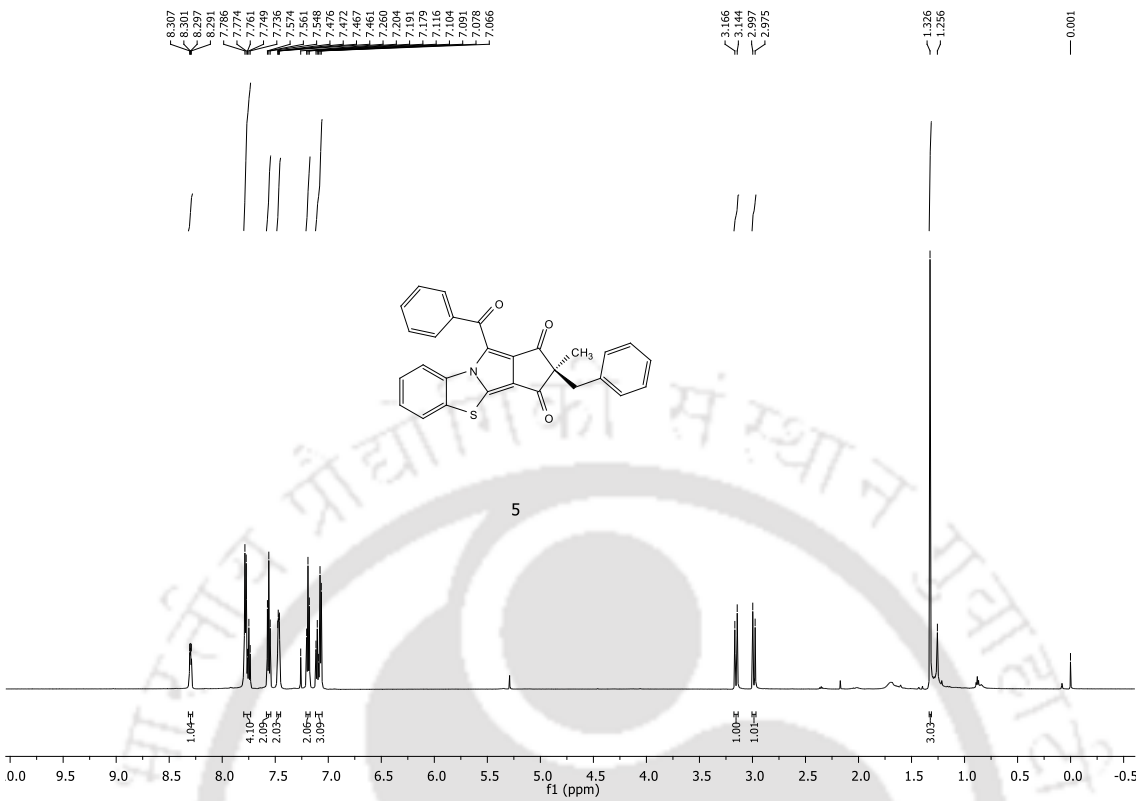


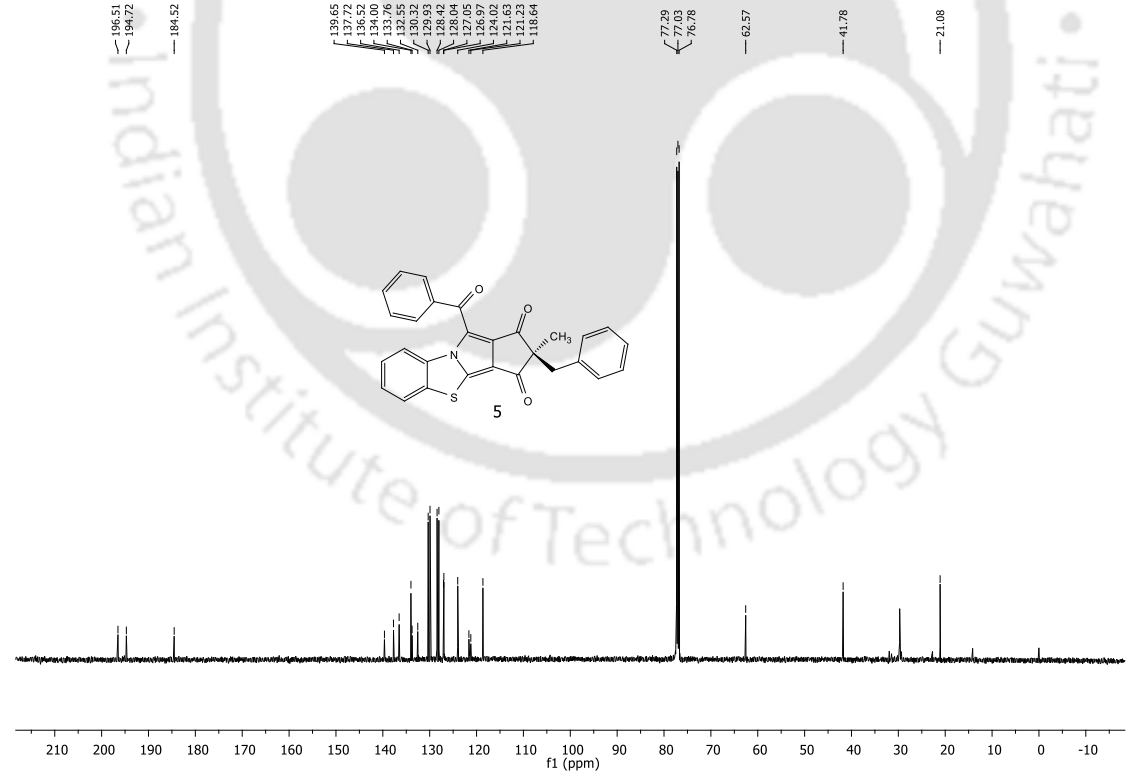
4.10 Selected spectra of products

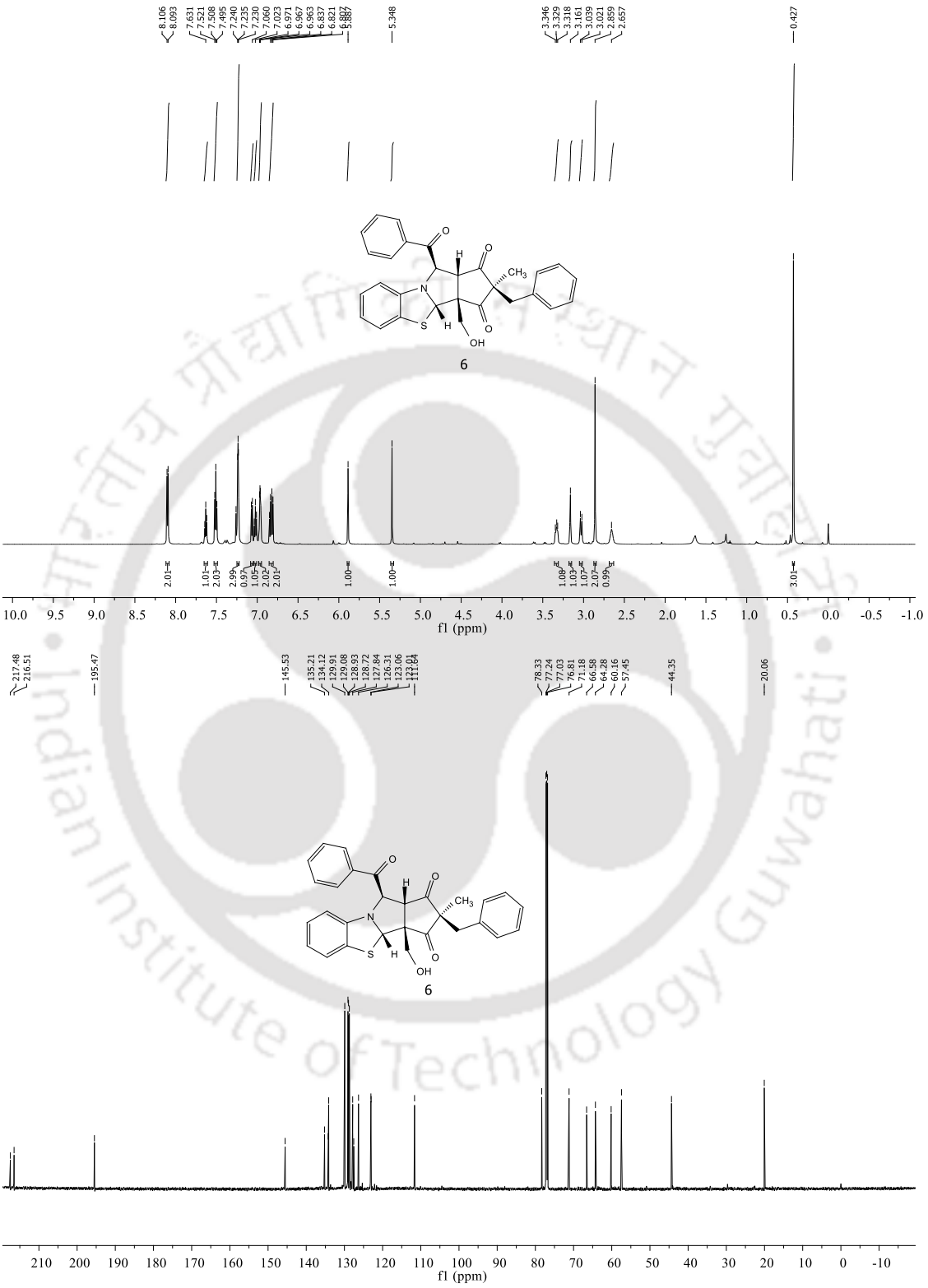


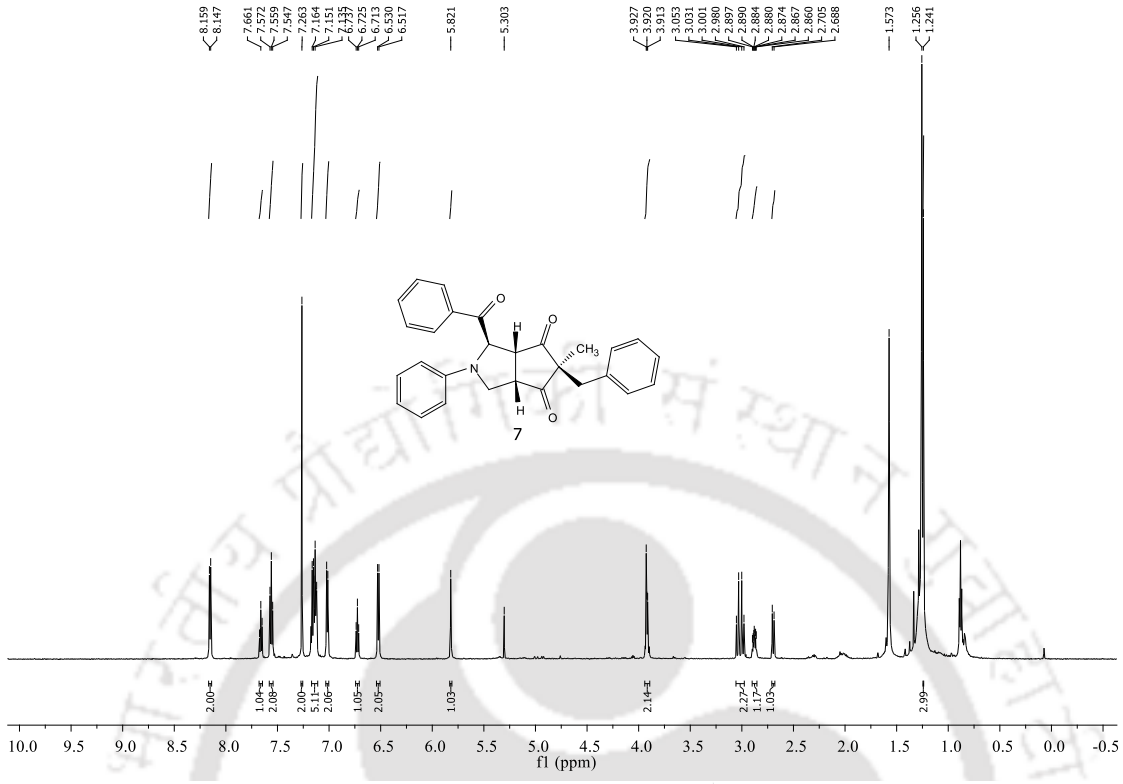


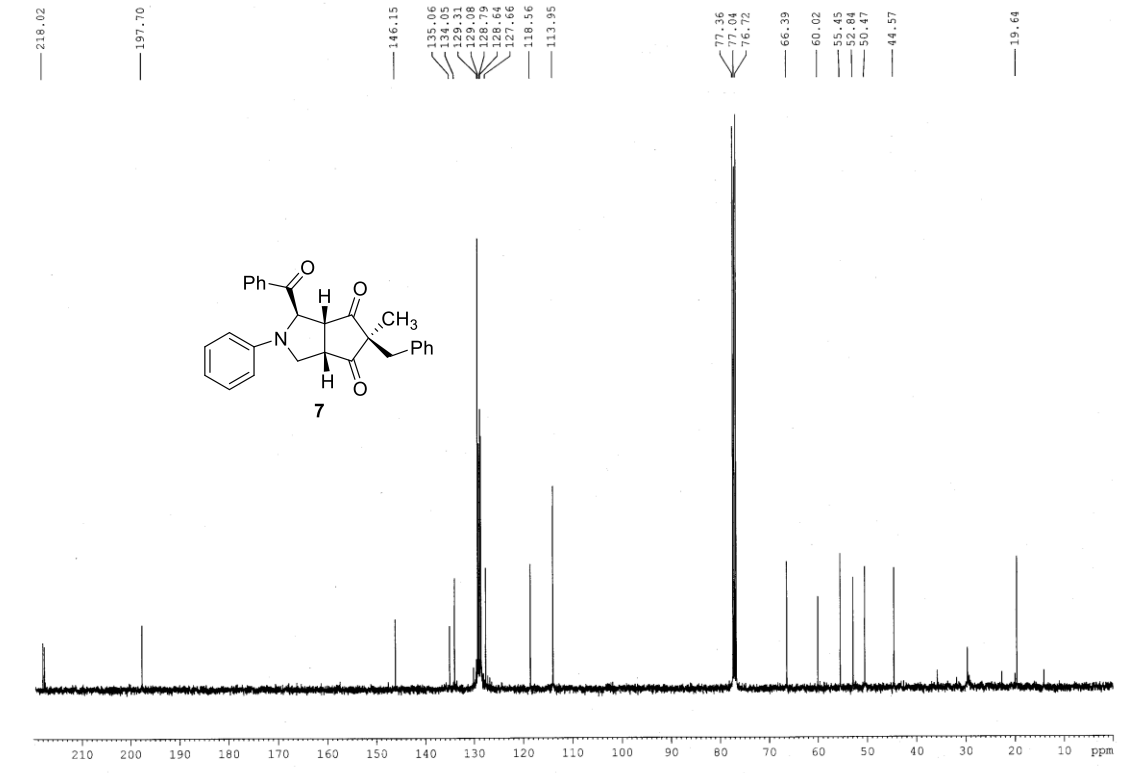




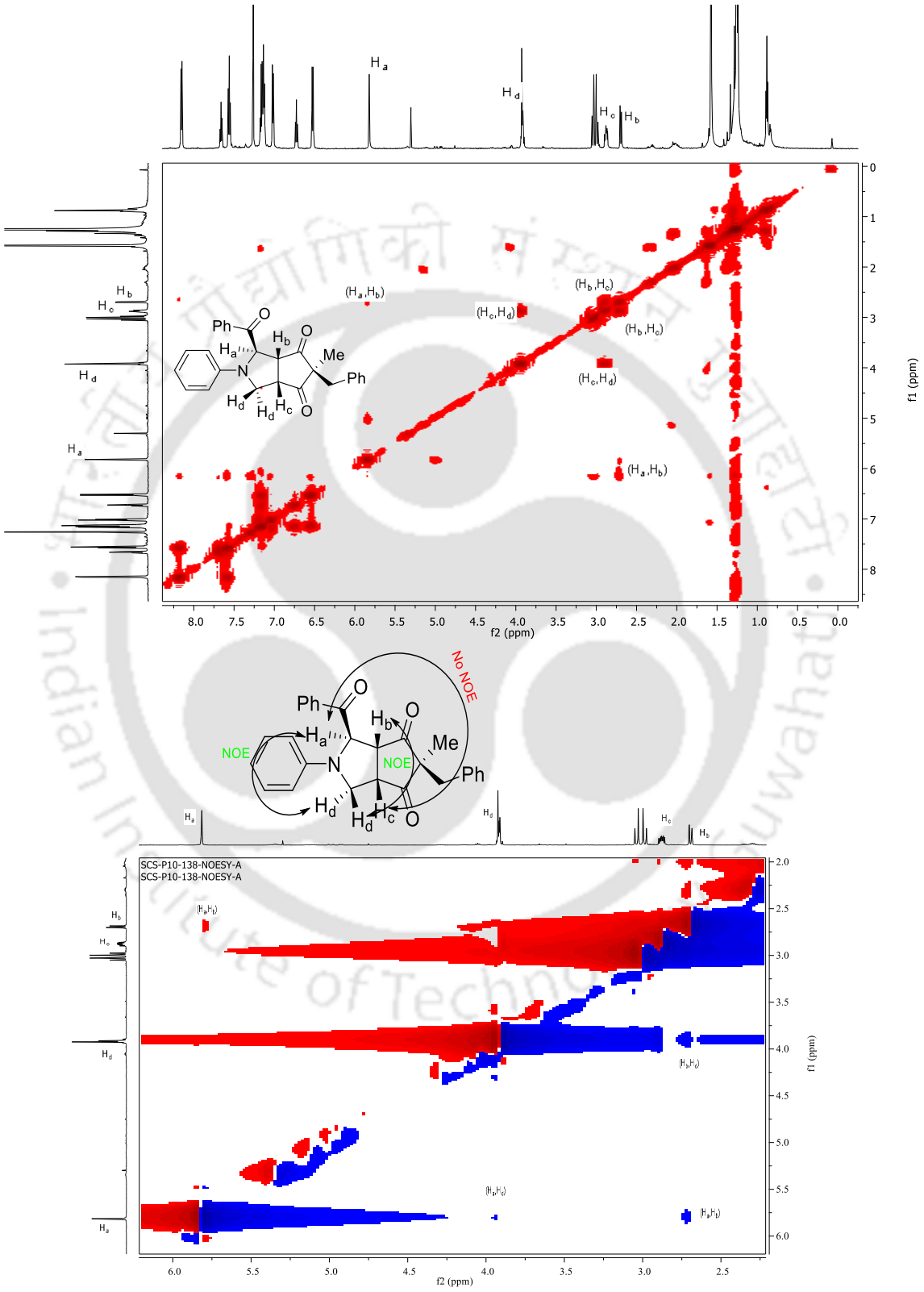






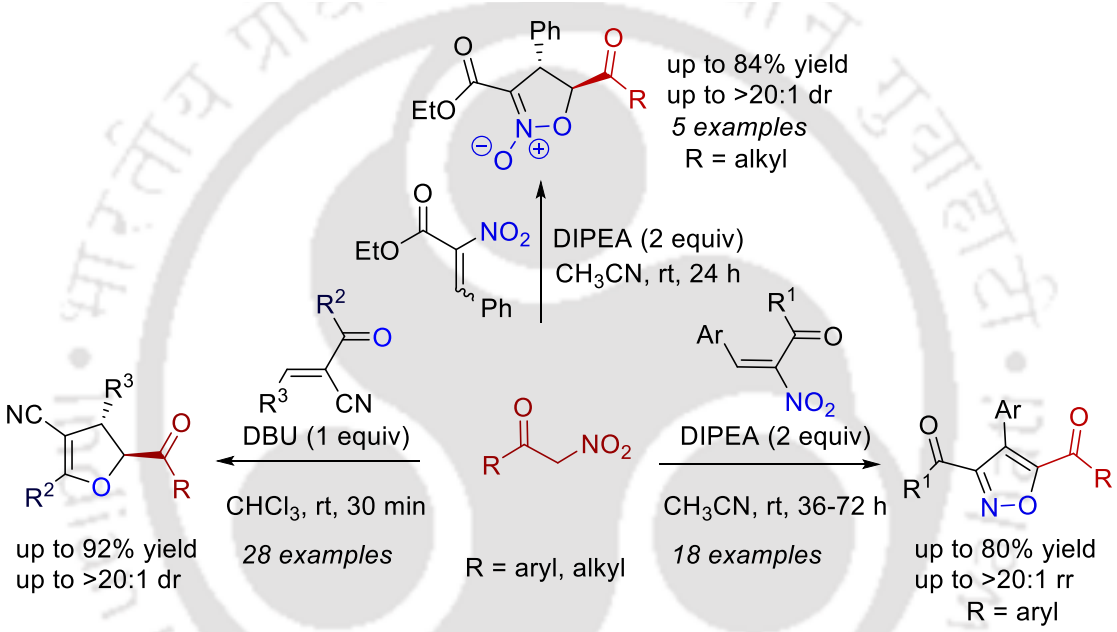


4.10 COSY and NOESY spectra for stereochemistry of product 7



Chapter 5

Synthesis of Heterocyclic Molecules by Denitration of α-Nitroketones



5.1 Introduction

As per name, *α*-nitroketones[1] has two electron withdrawing functionalities, one is carbonyl group, and the other is nitro group at the *α*-carbon adjacent to the carbonyl group. Because of the two electron withdrawing groups, it serves as excellent Michael donor in the primary step. Other two functionalities show their versatile nature depending on the opponent reactive partners (Figure 5.1).[1d] The flexible nature of *α*-nitroketones made it more applicable starting material in many organic synthesis.

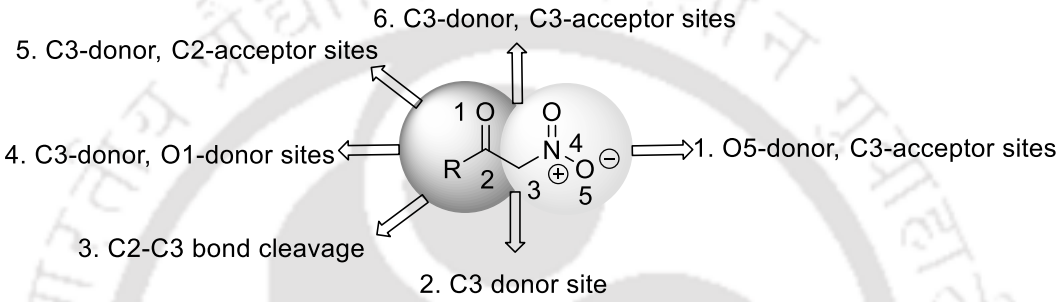


Figure 5.1: Flexible reactive sites of *α*-nitroketones.

α-Nitroketones serve as important building blocks for a range of valuable synthetic transformations.[2,3] Herein, we have shown transformation of *α*-nitroketones to isoxazole and dihydrofuran *via* base mediated denitration strategy.

Isoxazoles, important five-membered aromatic heterocycles, are often found in natural products and biologically active compounds as well as used as building blocks in organic synthesis.[4] In particular, 3,4,5-trisubstituted oxazoles have drawn attention in view of their biological activities[5] such as activation of PPARδ, BET protein antagonism, antibacterial and antifugal activities and inhibition of casein kinase (Figure 5.2). These bioactivities have prompted the development for the synthesis of a variety of trisubstituted isoxazoles.[6]

Substituted dihydrofurans are also one class of important heterocycles frequently found in numerous natural products (e.g., azadirachtin, austocystin D, etc.) and in a number of pharmaceuticals (e.g., aflatoxin B1, clerodin, etc.). In addition they display important biological activities, and are extensively applied in the pharmaceutical industry (Figure 5.2).[7,8] Due to their diverse applications in organic synthesis, a large number of synthetic chemists became interested to develop many synthetic methodologies.[9]

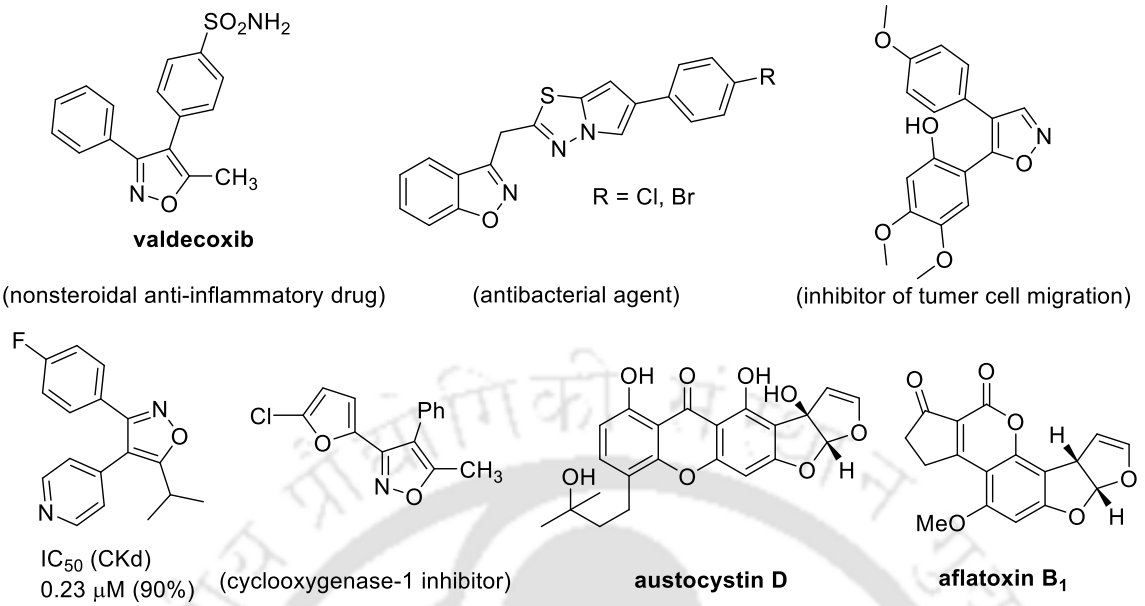


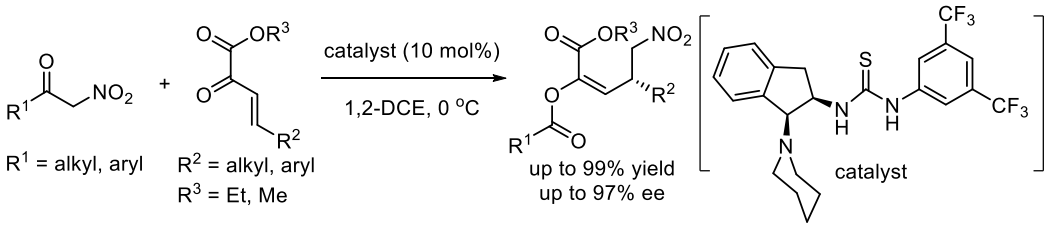
Figure 5.2: Selective examples of bioactive heterocyclic compounds containing isoxazole and dihydrofuran moieties.

Nitro compounds can be considered as versatile building blocks in organic synthesis. Due to the activating effect of the nitro group and its facile transformations into various functionalities, importance of nitro compounds has been extended in the preparation of complex molecules.[10]

5.2 Known strategies for Michael and acyl transfer reactions

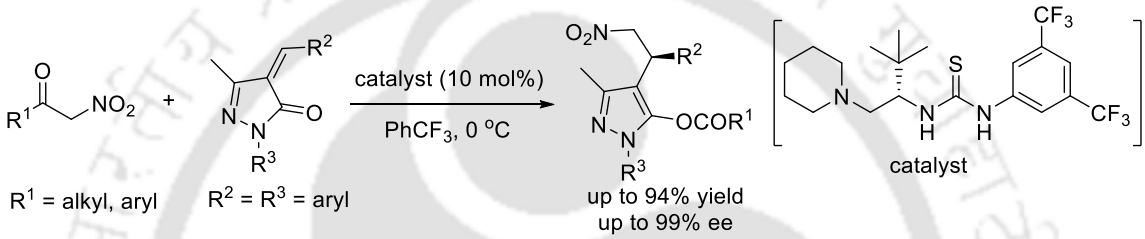
Recently, a variety of methods have been developed for the highly enantioselective Michael addition[11,12] reactions of nitroalkanes and nitro-esters with α,β-unsaturated systems.[13] However as an active nucleophilic reagent, α-nitroketones were less explored. Previously, few groups independently have disclosed the organocatalytic asymmetric conjugate addition of α-nitroketones followed by acyl transfer reaction. Our group also contributed well to the asymmetric acyl transfer zone.[14]

For example, Wang *et al*. reported bifunctional indane amine-thiourea catalyzed asymmetric organocatalytic Michael and hemiketalization followed by retro-aldol reaction between β,γ-unsaturated ketoesters and α-nitroketones (Scheme 5.1).[13a] Similar protocol was also utilized by Yan and Kwong groups.[13b,13c]



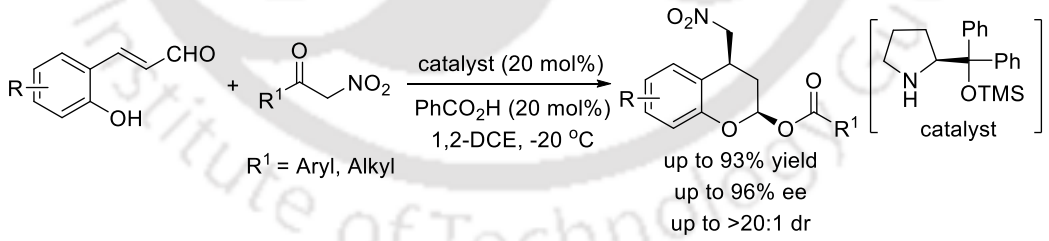
Scheme 5.1: Indane derived thiourea catalyzed Michael/acyl transfer reaction

Our group demonstrated the synthesis of highly enantioselective 3-acyloxy pyrazoles *via* Michael/hemiketalization followed by retro-aldol reaction between *α*-nitroketones with unsaturated pyrazolones by using bifunctional thiourea catalyst (Scheme 5.2).[14a]



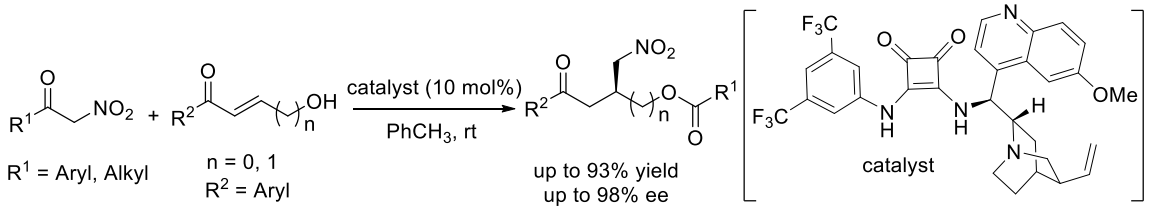
Scheme 5.2: Organocatalytic asymmetric Michael/Hemiketalization/Retro-aldol reaction

In 2018, our group established an efficient methodology for the construction of highly diastereo- and enantiopure 2,4-disubstituted chromans from 2-hydroxycinnamaldehydes and *α*-nitroketones using prolinol TMS ether catalyst and benzoic acid as an additive (Scheme 5.3).[14b]



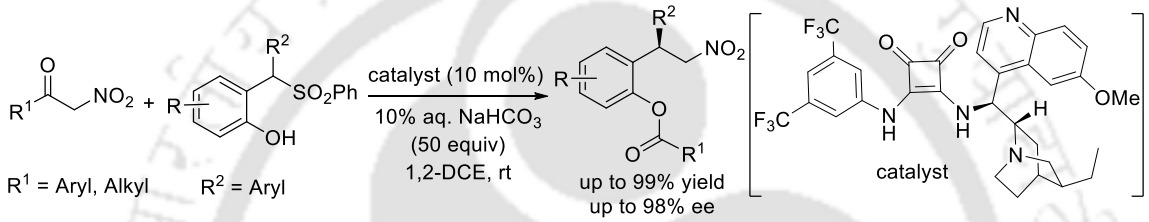
Scheme 5.3: Prolinol TMS ether catalyzed asymmetric Michael/acyl transfer reaction

In the same year, cinchona derived bifunctional squaramide catalysed another acyl transfer sequence was developed by using *α*-nitroketones and *γ/δ*-hydroxyenones (Scheme 5.4).[14c]



Scheme 5.4: Quinine derived squaramide catalyzed Michael/acyl transfer reaction

Our group successfully explored hydroquinine derived squaramide catalysed domino Michael/acyl transfer reaction between *α*-nitroketones and *in situ* generated *ortho*-quinone methides (Scheme 5.5).[14d]



Scheme 5.5: Hydroquinine derived squaramide catalyzed Michael/acyl transfer reaction

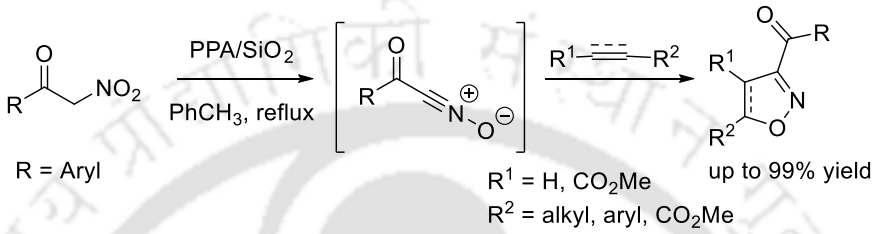
5.3 Known strategies for cycloaddition and denitration reactions

Mostly nitro compounds have become corporate source of nitrile oxides since it can be dehydrated and become important precursors in the synthesis of heterocyclic compounds *via* 1,3-dipolar cycloaddition.[15] Another synthetic protocol is based on the conversion of the nitro compounds into alkyl or silyl nitronates, followed by cycloaddition/ elimination. Other methods need treatment of the nitro compounds with acylating agents or the reagents must be heated in the presence of strong acids. Nonetheless, under heating condition; activated nitro compounds undergo cycloaddition reaction even without an acid catalyst.

In the reports that involve the use of acylating agents for the dehydration of nitro compounds, several authors have proposed mechanisms in which an acyl derivative of nitronic acid is suggested as the intermediate which collapses to nitrile oxide. But bases could be used for the dehydration of primary nitro compounds. Machetti group demonstrated that the use of a dehydrating agent can be avoided and tertiary diamine

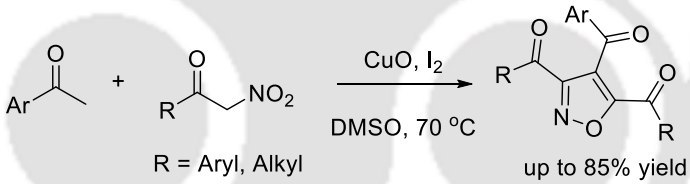
bases, such as DABCO or TMEDA promote the dehydration of the nitro compounds as a thermodynamically favored process.[15b]

In 2011, Itoh *et al*. demonstrated silica gel supported polyphosphoric acid catalysed reaction of *α*-nitroacetophenone with suitable alkynes and alkenes to provide isoxazoles/isoxazolines (Scheme 5.6).[15d] Similar protocol was executed by Wang and Pal groups by using $Cu(OAc)_2$/DDQ and PEG/H_2O respectively.[15e, 15f]



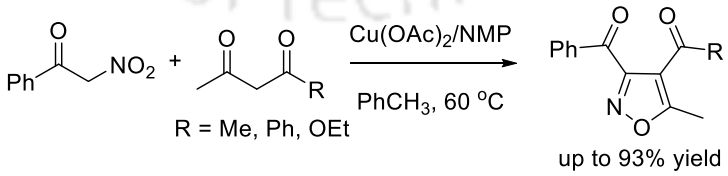
Scheme 5.6: Acid catalysed cycloaddition reaction

Wu group synthesised trisubstituted isoxazoles from *α*-nitroketones and acetophenone *via in situ* phenylglyoxal formation followed by Knoevenagel condensation and denitration (Scheme 5.7).



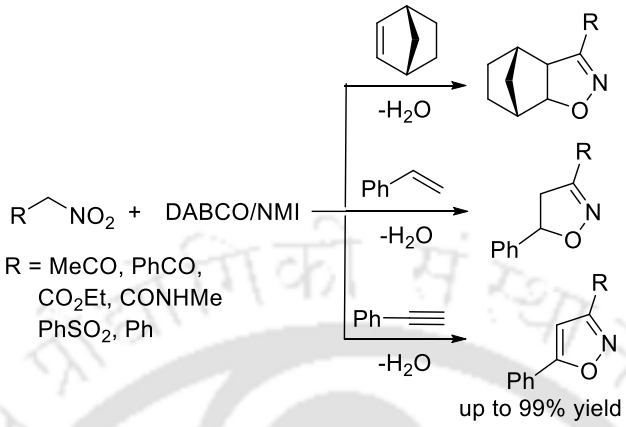
Scheme 5.7: Synthesis of trisubstituted isoxazoles using acetophenones

Machetti group reported a synthesis of substituted isoxazoles utilizing *N*-methylpiperidine (NMP) as base and Cu(II) catalyst through cycloaddition followed by condensation reaction of *α*-nitroketone with 1,3-dicarbonyl compounds (Scheme 5.8).[16]



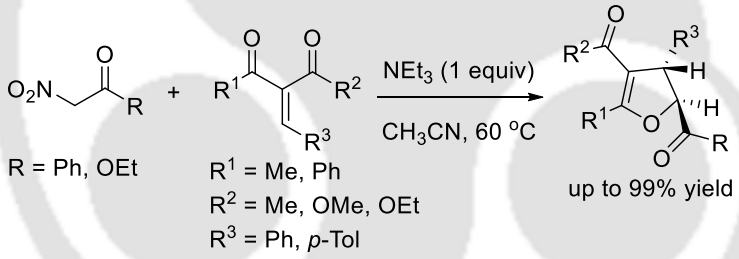
Scheme 5.8: Cycloaddition reaction using $Cu(OAc)_2$/NMP

Machetti group later synthesized isoxazole derivatives from primary nitro compounds *via* base catalyzed cycloaddition reaction (Scheme 5.9).[15b]



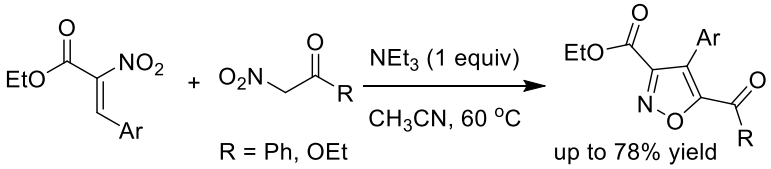
Scheme 5.9: Cycloaddition reaction in presence of base

Chuang group reported base mediated synthesis of 2,3-dihydrofurans from α-nitro carbonyl compounds and 3-benzylidene-2,4-pentanedione (Scheme 5.10).[17]



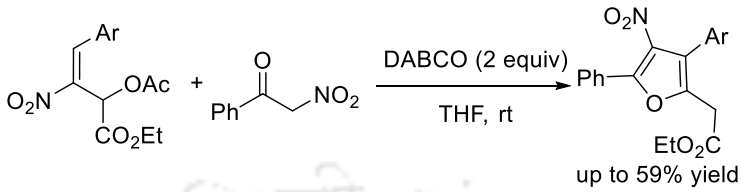
Scheme 5.10: Base mediated synthesis of dihydrofuran

A new methodology was also developed by Chuang group for the synthesis of highly functionalized isoxazoles from α-nitro carbonyl compounds and ethyl α-nitrocinnamates (Scheme 5.11).[18]



Scheme 5.11: Base mediated synthesis of isoxazoles

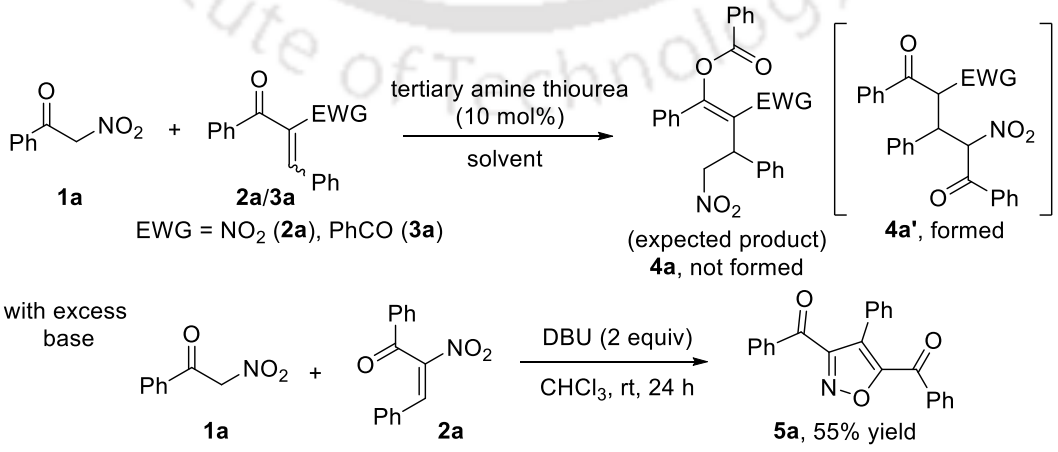
Namboothiri and co-workers developed a convenient approach for the regioselective synthesis of *tetra*-substituted furans using Morita-Baylis-Hillman acetate (MBH acetate) and *α*-nitroacetophenone (Scheme 5.12).[19]



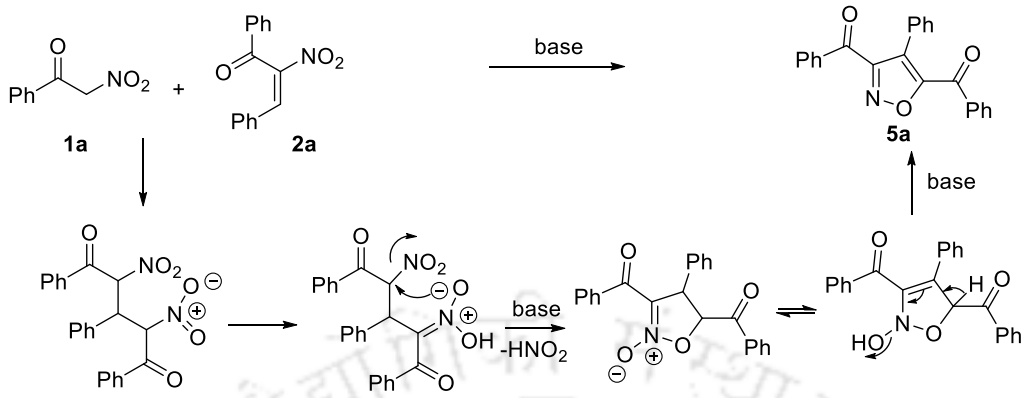
Scheme 5.12: DABCO mediated synthesis of furan

5.4 Result and discussion

According to literature, *α*-nitroketone **1** shows unusual character in the presence of different reacting partners. Therefore, initially we set a model reaction of *α*-nitro chalcones **2a** and 2-benzylidene-1,3-diphenylpropane-1,3-dione **3a** with *α*-nitroketone **1a** in the presence of an achiral catalyst expecting the acyl transfer product **4a** (Scheme 5.13). Other withdrawing groups like cyano, acetyl were also employed. But unfortunately we obtained the single Michael attack product **4a′** as the major and another unidentified minor product. When we increased the catalyst amount in the reaction of *α*-nitro chalcones with *α*-nitroketone, the minor unidentified product became major one and was isolated. The isoxazole **5a** product was characterized from NMR and mass spectrometry. Nitroketone **1a** first gets deprotonated by base which undergoes conjugate addition reaction to *α*-nitro chalcone **2a** to form isoxazoline *N*-oxide. Finally, product **5a** was formed *via* base mediated rearrangements and aromatization (Scheme 5.13).



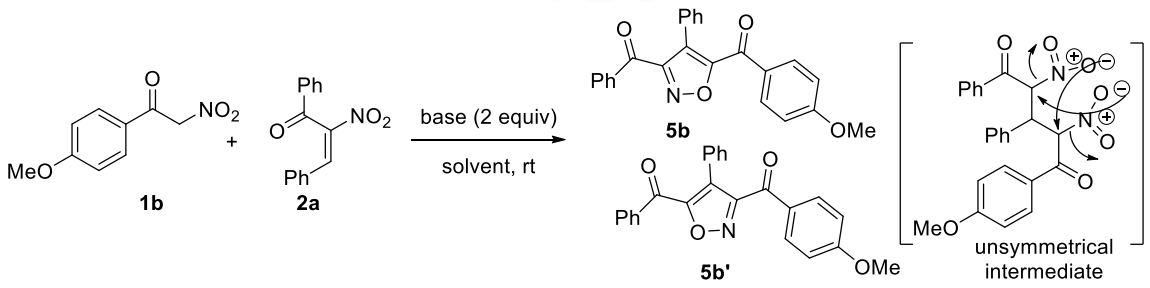
Mechanism:



Scheme 5.13: Primary analysis

Therefore, we planned to synthesize isoxazoles regioselectively by varying the *α*-nitroketone **1**. We have selected *para*-anisyl nitroketone **1b** for determining the regioisomeric ratio (rr) (Table 5.1). When we set reaction of **1b** and **2a** in the presence of DBU in chloroform solvent, the desired isoxazole product **5b** was isolated in 3:1 ratio along with the regioisomer **5b'** (entry 1). A complex reaction mixture was formed in the presence of DABCO catalyst (entry 2). Improved yield as well as good regioselectivity was observed with DIPEA (entry 3). Then attention was given on the solvent optimization. In toluene, smooth conversion was also observed but regioselectivity of the product got decreased (entry 4). Whereas, DMSO was not at all a good solvent and only 5% yield was attained (entry 5). Gratifyingly, a decent yield of 72% with high regioselectivity (5:1) was achieved in acetonitrile (entry 6). The yield and regioselectivity got slightly decreased when the reaction temperature was increased to 60 ^{o}C (entry 7).

Table 5.1: Optimization of reaction conditions



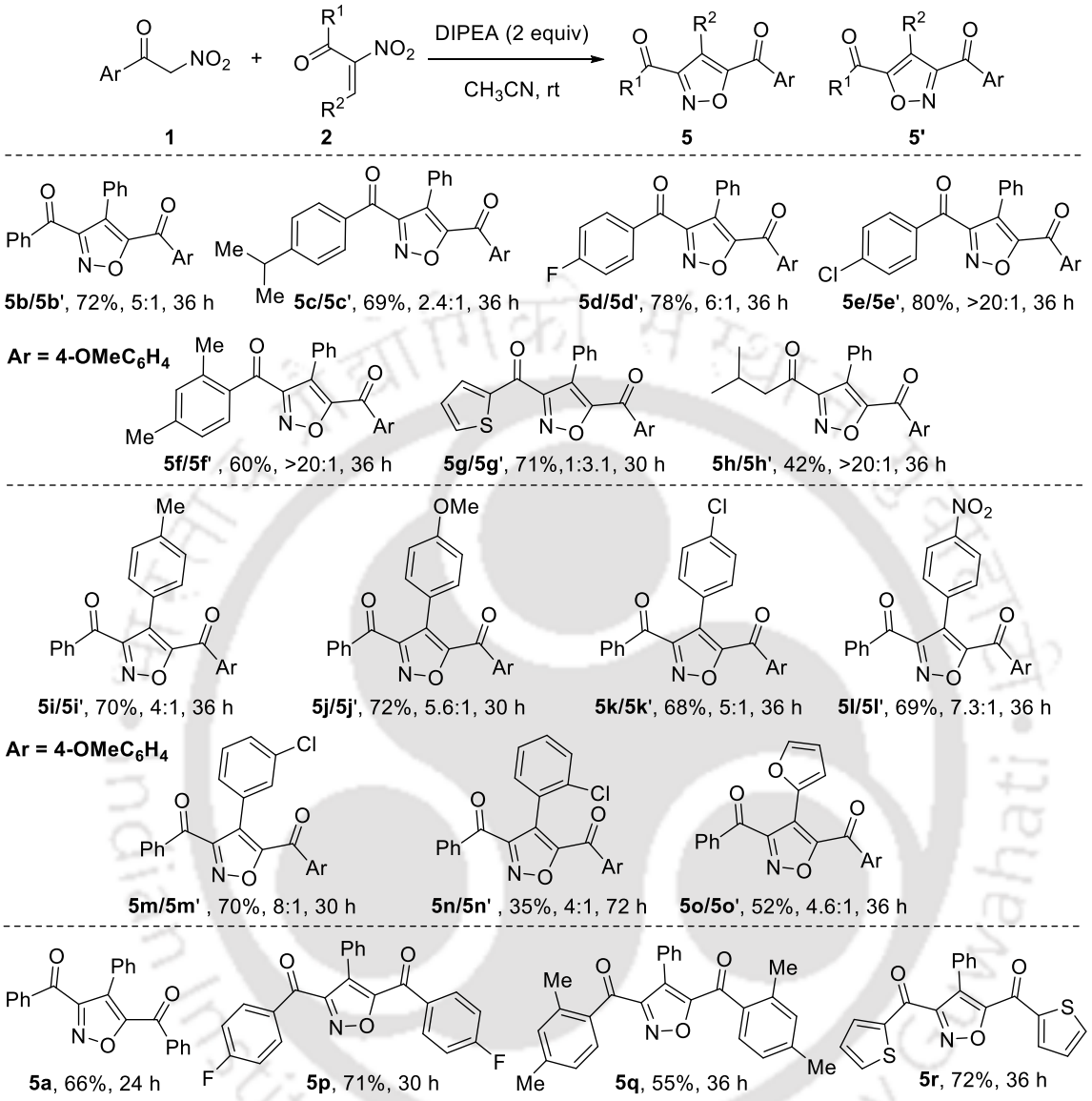
entry[a]	base	solvent	time (h)	yield (%)[b]	rr (5b/5b′)[c]
1	DBU	$CHCl_3$	24	68	3:1
2	DABCO	$CHCl_3$	24	mixture	-
3	DIPEA	$CHCl_3$	36	71	3.5:1
4	DIPEA	$PhCH_3$	36	55	2:1
5	DIPEA	DMSO	36	5	-
6	**DIPEA**	**CH_3CN**	**36**	**72**	**5:1**
7[d]	DIPEA	CH_3CN	20	70	4.6:1

[a]Reaction condition: 0.05 mmol of **1b** and 0.05 mmol of **2a** in 0.5 mL solvent using 2 equivalents base at rt. [b]Isolated yield (combined yield). [c]Determined by ^{1}H NMR. [d]Reaction at 60 ^{o}C.

5.5 Substrate scope of isoxazoles

After the best reaction conditions was established, the scope and generality of the isoxazole product was checked. Initially the keto-functionality of *α*-nitro-*α,β*-unsatutared ketone **2** was varied and the results are shown in Scheme 5.14. At the beginning, different electron donating and withdrawing groups substitution at *para* position were tested and the products **5c**-**5e** were obtained in good yields and excellent regioselectivities. In particular, product **5e** having 4-chloro substitution was isolated as single regioisomer in 80% yield. Then enone **2e** having 2,4-dimethylphenyl group was employed and delightfully here also the product **5f** was obtained as a single regioisomer. Smooth conversion was also seen with 2-thienyl enone **2f** but in this case the opposite regioisomer **5g'** was formed as the major product because of more electron density on thiophene ring. Alphatic enone **2g** was also tolerated in the reaction, albeit slight lower yield of product **5h** was observed with excellent regioselectivity because of the difference in electron withdrawing properties between aliphatic and aromatic carbonyls. Then, the optimization of the reaction was further carried out with different groups of the olefin functionality in enone **2** (Scheme 5.14). Thus enones **2h**-**2k** having variations in *para*-substititions were initially engaged in the reaction. The corresponding products **5i**-**5l** were isolated in acceptable yields and good regioselectivities. For example, enone **2h**

Scheme 5.14: Substrate scope of isoxazoles [a,b,c]



[a]Reaction condition: 0.1 mmol of **1**, 0.1 mmol of **2** and 0.2 mmol of DIPEA in 1 mL CH_3CN. [b]Isolated yields (combined yield). [c]Regioisomeric ratio was determined by ^1H NMR.

having 4-methyl group delivered product **5i** with 70% yield and 4:1 regioisomeric ratio. Products **5j** and **5k** having 4-methoxy and 4-chloro substituents respectively were obtained with 5.6:1 and 5.1:1 regioisomeric ratios. Also, high regioselectivity and acceptable yield was observed for the product **5l** having 4-nitroaryl group. Higher regioselectivity (8:1) was observed for product **5m** having *meta*-chloro substitutions with good yield. For *ortho*-chloro derivative lower yield as well as lower regioselectivity was

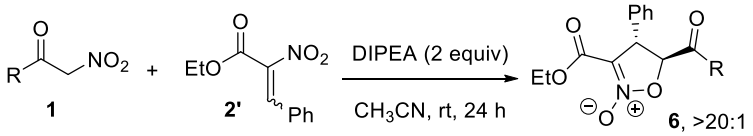
observed after longer reaction time. A heteroaromatic furyl group was also screened and the regioisomeric product **5o** was obtained as 4.6:1 mixture. The single regioisomer was prepared from pyridinium salt according to the reported procedure[18] and spectral data was compared.

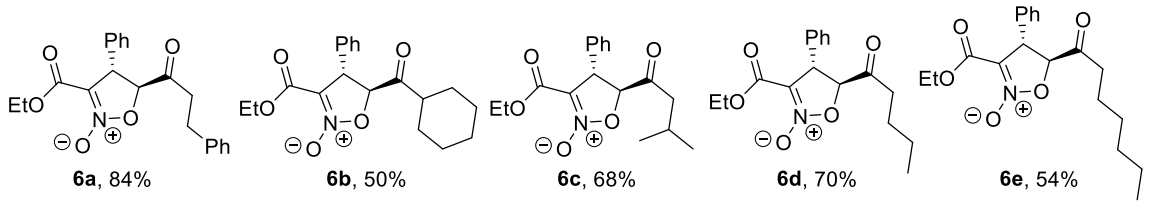
The generality of the reaction was further established by preparing isoxazoles with same ketofunctionalities (Scheme 5.14). Product **5a** was again synthesized under this reaction condition and 66% yield of the product was detected. Similarly other products **5p**-**5r** were isolated in good yields. In these cases, the cyclization happened through a symmetrical intermediate. Gratifyingly, smooth conversions were observed for products **5p** and **5q** with 4-fluoro and 2,4-dimethyl functionalities respectively. Heteroaromatic enone with heteroaromatic nitroketone was also tested in the reaction and 72% yield of the product **5r** was observed.

5.6 Substrate scope of isoxazoline *N*-oxide

Next, we became interested to employ *α*-nitrocinnamates in the reaction. Though Chuang and co-workers earlier employed aromatic nitroketones with *α*-nitrocinnamates in their reaction, to our best knowledge aliphatic *α*-nitroketones were not studied. Thus we reacted aliphatic nitroketone **1** with *α*-nitrocinnamate **2′** and this resulted in the formation of single isoxazoline *N*-oxide **6** (Scheme 5.15) instead of isoxazole because of more electron withdrawing nature of aliphatic carbonyls than aromatic one. Linear and branched aliphatic substituted nitroketones participated well in the reaction to provide decent yields of the products **6a-6e**. 1-Nitro-4-phenylbutan-2-one provided 84% yield of the product **6a**. Branched *α*-nitroketones having cyclohexyl and ^{i}butyl group delivered the products **6b**-**6c** with 50% and 68% yields respectively. ^{n}Butyl and ^{n}hexyl substituted *α*-nitroketones were also employed in the reaction and good yields of the products **6d**-**6e** were observed.

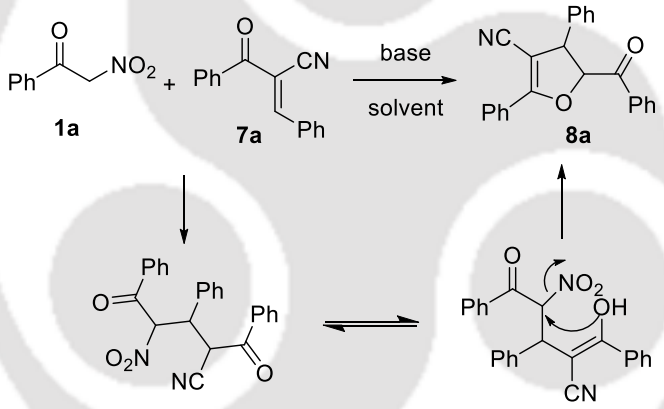
Scheme 5.15: Substrate scope of isoxazoline *N*-oxide using aliphatic nitroketones [a,b,c]





[a]Reaction condition: 0.1 mmol of **1**, 0.1 mmol of **2′** and 0.2 mmol of DIPEA in 1 mL CH_3CN. [b]Isolated yields after silica gel column chromatography. [c]dr determined by ^1H NMR.

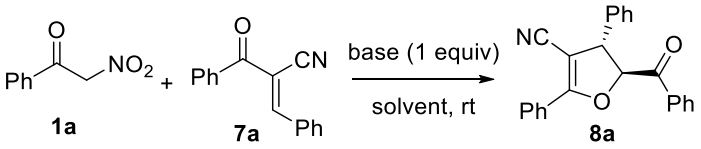
Cyano group is as an important motif in organic synthesis which can be transferred to amine, ester etc. and thus useful in natural product synthesis. After realizing the importance of cyano group we changed our reacting partner and treated *α*-cyano-*α,β*-unsatutared ketone **7a** with *α*-nitroketone **1a** in the presence of base catalyst. Tetra-substituted dihydrofuran **8a** was obtained as the product and it was characterized from NMR and mass spectrometry (Scheme 5.16).



Scheme 5.16: Primary analysis of *α*-nitroketone with *α*-cyano-*α,β*-unsatutared ketone

After finding the dihydrofuran product, we began our investigation by reacting nitroketone **1a** and *α*-cyano-*α,β*-unsatutared ketone **7a** (Table 5.2). Unfortunately, the desired product was not obtained in suitable quantity with DABCO and K_2CO_3 in chloroform at room temperature (entries 1-2). When DBU was employed as the base catalyst, product **8a** was isolated with 92% yield in short reaction time (entry 3). After finding the best catalyst, different varieties of solvents i.e. toluene, DMSO, acetonitrile and ethanol were screened. But in all of the cases we got good quantities of the product only after longer reaction period (entries 5-8). Hence, DBU was finalized to be the best catalyst in chloroform solvent for this reaction.

Table 5.2: Optimization of reaction condition



entry[a]	base	solvent	time	yield (%)[b]	dr[c]
1	DABCO	$CHCl_3$	24 h	<10	
2	K_2CO_3	$CHCl_3$	24 h	0	
3	**DBU**	**$CHCl_3$**	**20 min**	**92**	**>20:1**
4	DIPEA	$CHCl_3$	2 h	85	>20:1
5	DBU	$PhCH_3$	2 h	90	>20:1
6	DBU	DMSO	2 h	85	>20:1
7	DBU	CH_3CN	2 h	72	>20:1
8	DBU	EtOH	2 h	80	>20:1

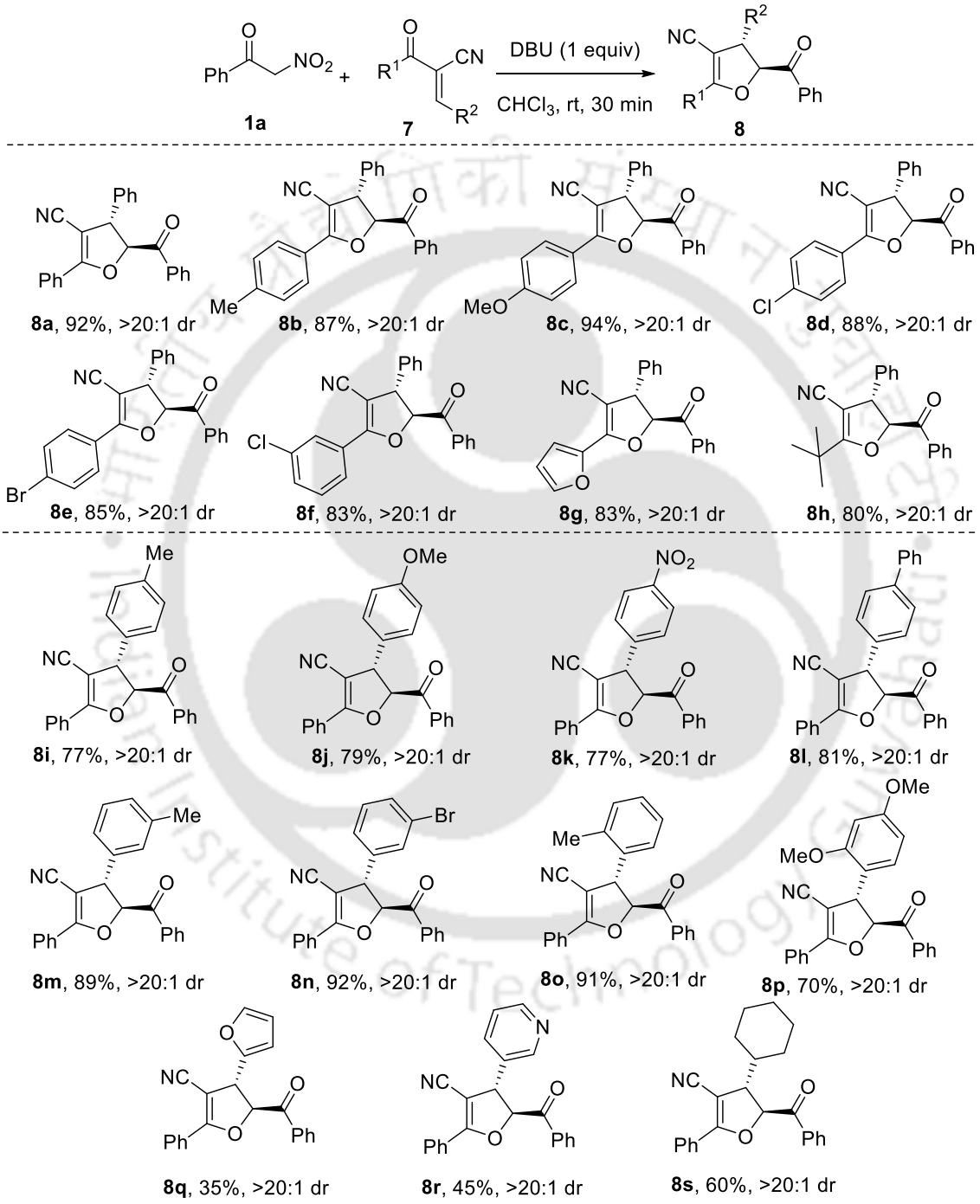
[a]Reactions were carried out with **1a** (0.05 mmol) and **7a** (0.05 mmol) in 0.5 mL solvent using 1 equivalent of base at rt. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR.

5.7 Substrate scope of dihydrofuran

After that, the scope of the *α*-cyano-*α,β*-unsatutared ketone **7** was studied and pleasingly a variety of groups including aliphatic functionalities were tolerated and excellent results (>20:1 dr) were achieved (Scheme 5.17). Initially, the aryl group of ketone motif in **7** was varied. At first, enones **7b-7e** having *para*-substitutions were evaluated and good results was achieved. 4-Methyl substituted aryl enone **7b** was screened under the reaction conditions and product **8b** was obtained with 87% yield. Enone **7c** having 4-anisyl group reacted efficiently to provide 94% yield of the product **8c**. Then halo substituted enones **7d-7f** were tested in the reaction and the corresponding products **8d-8f** were isolated with good yields. 4-Chloro substituted enone was also well tolerated and 88% yield of the product **8d** was observed. The reactions worked well with *meta*-chloro substituted enone **7f** and product **8f** was isolated in 83% yield. Heteroaromatic group containing

enone **7g** was also employed to obtain 83% yield of the product **8g**. Also, aliphatic enone **7h** was well tolerated in our reaction delivering 80% yield of the product **8h**.

Scheme 5.17: Scope of *α*-cyano-*α,β*-unsaturated ketones for dihydrofuran[a,b,c]



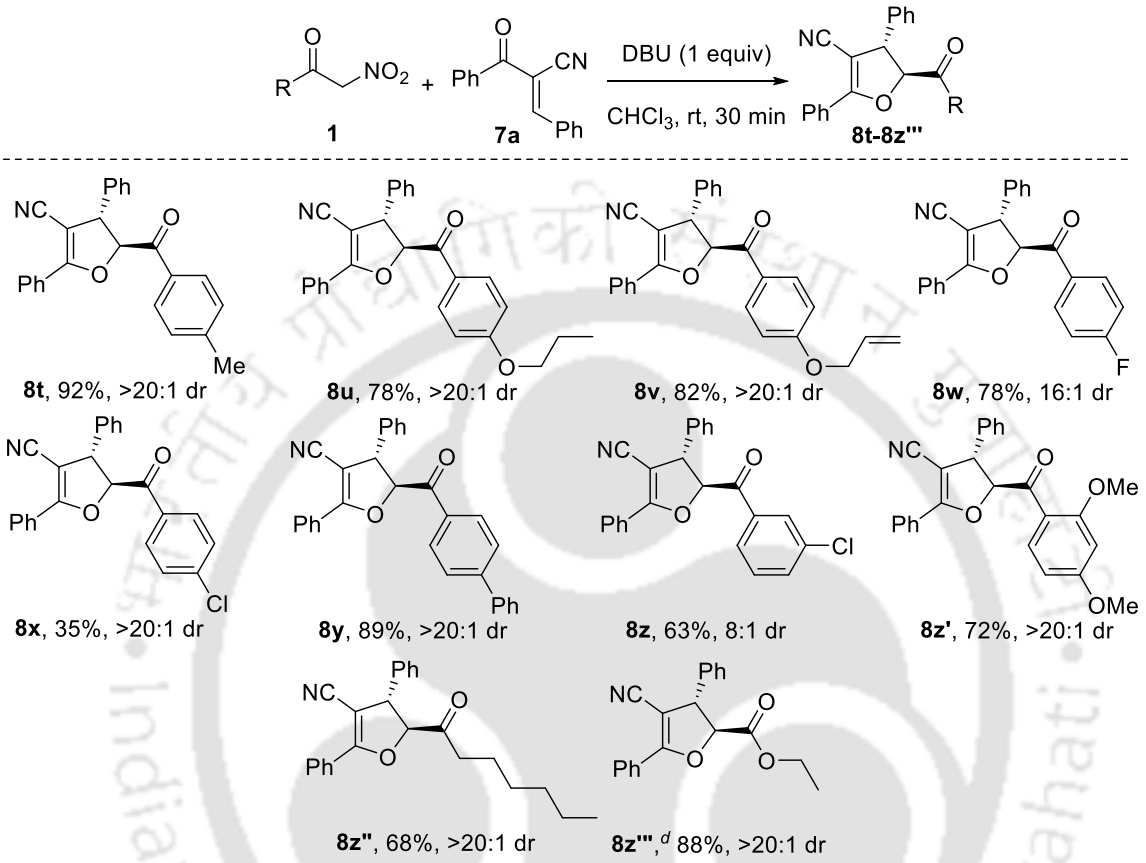
[a]Reactions condition: 0.3 mmol of **1a** and 0.3 mmol of **7** using 0.3 mmol DBU in 3 mL $CHCl_3$ at rt for 30 min. [b]Isolated yield. [c]dr determined by ^{1}H NMR.

Then we turned our attention to change the olefin aryl group of enone **7**. A range of substitutions were incorporated at the *para*, *meta* and *ortho* positions on the different aryl groups of the olefin functionality in enone irrespective of their electronic nature. Different substitution at the *para* position of the aryl ring did not influence considerably on the yield of the products. 4-Methyl and 4-methoxy substituted enones **7i-7j** were subjected under the reaction conditions and acceptable yields were attained. Electron deficient NO_2 group was also tolerated and product **8k** was isolated in 77% yield. Biphenyl group containing enone **7l** also participated in the reaction to deliver product **8l** in 81% yield. Then *meta*-substitutions were checked and to our delight, better results were achieved. Product **8m** (CCDC 1887603)[20] having *meta*-tolyl substitution was isolated in 89% yield. Excellent yield (92%) was observed for *meta*-bromo substituted enone. Product **8o** was obtained from *ortho*-methyl substituted aryl enone **7o** in 91% yield. 2,4-Disubstituted aryl group containing enone **7p** was employed and product **8p** was obtained in acceptable yield. However lesser yields were detected when heteroaromatic groups i.e 2-furyl and 3-pyridyl motifs were incorporated in the reaction. Finally, an aliphatic cyclohexyl substituted enone **7s** was engaged in the reaction and moderate yield was obtained.

Afterwards, different *α*-nitroketones were evaluated under similar reaction conditions and pleasingly here also, good results were achieved (Scheme 5.18). Initially 4-methyl substituted *α*-nitroketone was tested and the product **8t** was isolated in 92% yield. Our methodology was also suitable for 4-alkoxy substituted *α*-nitroketones and good yields were achieved for products **8u** and **8v**. 4-Fluoro substituted nitroketone provided 78% yield of the desired product **8w**. Poor yield was observed for **8x** having 4-chloro substitution. Then, biphenyl motif containing nitroketone was employed and gratifyingly high yield of 89% was attained for product **8y**. Moderate yield with 8:1 dr of the product **8z** was attained for 3-chloro substituted nitroketone. This methodology was also suitable for 2,4-disubstituted aryl group containing nitroketones and the corresponding product **8z′** was isolated in 72% yield. An aliphatic nitroketone having ^{n}hexyl group was prepared and employed in the reaction. The reaction progressed well to deliver product **8z′′** in 68% yield. Finally, we employed ethyl nitroacetate **1′** in the

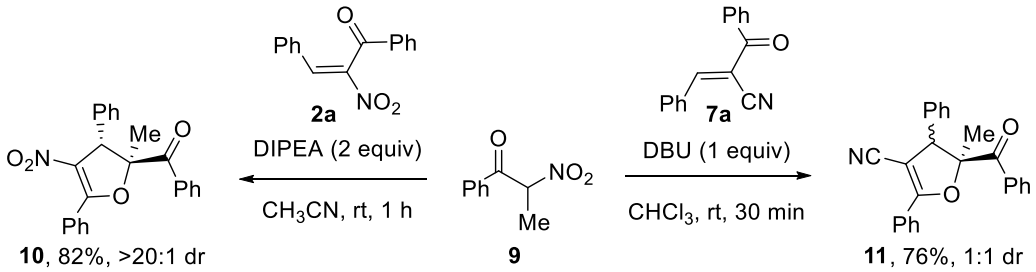
reaction and gratifyingly, product **8z‴** was isolated in good yield with excellent diastereomeric ratio.

Scheme 5.18: Scope of α-nitroketones for dihydrofuran[a,b,c]



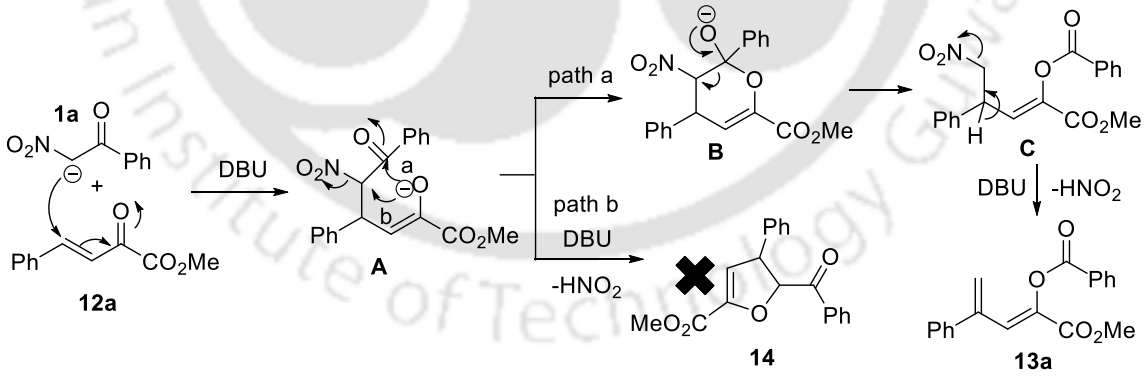
[a]Reactions condition: 0.3 mmol of **1** and 0.3 mmol of **7a** using 0.3 mmol DBU in 3 mL $CHCl_3$ at rt for 30 min. [b]Isolated yield. [c]dr determined by ^{1}H NMR. [d]**1′** used instead of **1a**.

Then α-nitrochalcones **2a** and α-cyanochalcones **7a** were treated with α-methyl nitroketone **9**. Gratifyingly the reaction progressed well in both cases to deliver tetrasubstituted furan products **10** and **11** in good yields. Though the diastereoselectivity of the product **10** was excellent, product **11** was obtained as a mixture of diastereomers (Scheme 5.19).



Scheme 5.19: Reaction of *α*-methyl nitroketones for dihydrofuran

After that, we thought to change the position of electron withdrawing group and thus reacted *β,γ*-unsaturated *α*-ketoester **12a** with *α*-nitroketone **1a** in the presence of DBU base (1 equivalent) in chloroform solvent. Interestingly, conjugated diester **13a** was isolated instead of the expected dihydrofuran product **14** (Scheme 5.20). It can be expected that DBU will first deprotonate nitroketone **1a** and conjugate addition happens to *β,γ*-unsaturated *α*-ketoester **12a** to generate **A**. Hemiketalization of **A** affords **B** (*via* path a) which on retro-Henry reaction provides **C**. Finally, DBU mediated elimination of HNO_2 from **C** delivers **13a**. There is also a possibility for the formation of product **14** *via* denitration of intermediate **A** (*via* path b). After investigating the reaction mechanism, we concluded that the acyl transfer reaction[13] is quite faster and the product **13a** was obtained after denitration of the acyl transfer intermediate **C**.



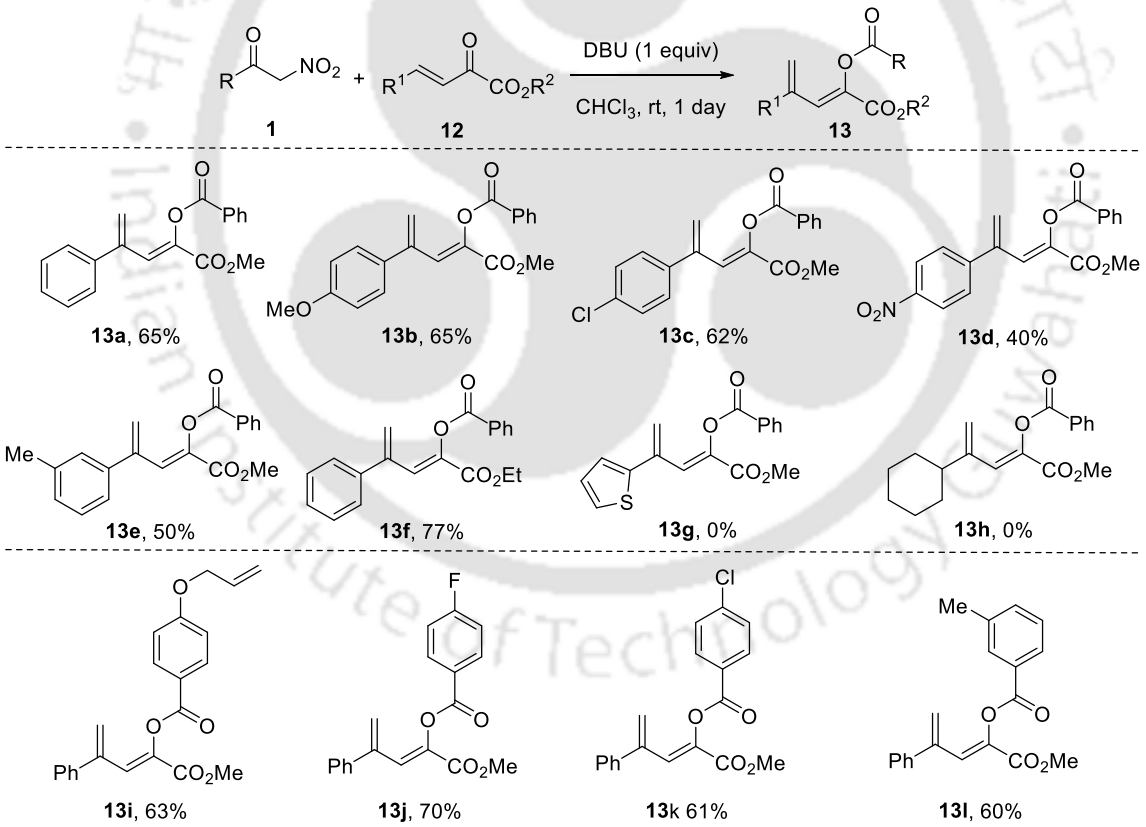
Scheme 5.20: Plausible mechanism for *β,γ*-unsaturated diester product

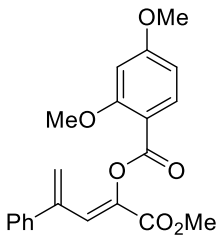
5.8 Substrate scope of *β,γ*-unsaturated diester

The generality of the reaction was further established by utilizing differently substituted *β,γ*-unsaturated ketoesters **12** and *α*-nitroketones **1** (Scheme 5.21). At first, we employed

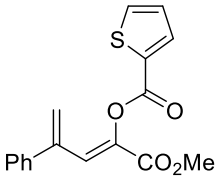
a range of unsaturated ketoesters **12** in the reaction. The reaction worked well with ketoesters **12b-12c** having methoxy and chloro substitutions at the *para*-position of the aryl group. The products **13b** and **13c** were isolated in acceptable yields. Slightly lower yield was observed for product **13d** having 4-nitro substitution. Ketoester **12e** having *meta*-substituted aryl group also participated in the reaction and moderate yield was detected for **13e**. Then an ethyl ester was screened and interestingly, the yield got enhanced for the product **13f**. We also checked ketoester **12g** having 2-thienyl group and cyclohexyl substituted ketoester **12h**. However, no desired product was formed in both cases. 2-Thienyl derived ketoester was unable to deliver the desired product because of the high electron donor ability of the ring. Aliphatic ketoester **12h** was also not suitable for our methodology because of unavailability of acidic benzylic proton.

Scheme 5.21: Substrate scope of *β,γ*-unsaturated diester [a,b]

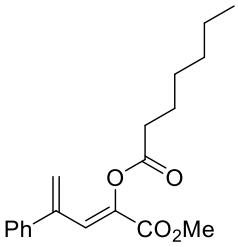




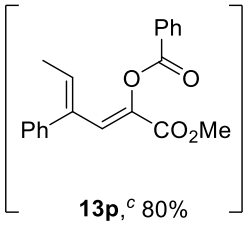
13m, 72%



13n, 73%



13o, 77%



13p,[c] 80%

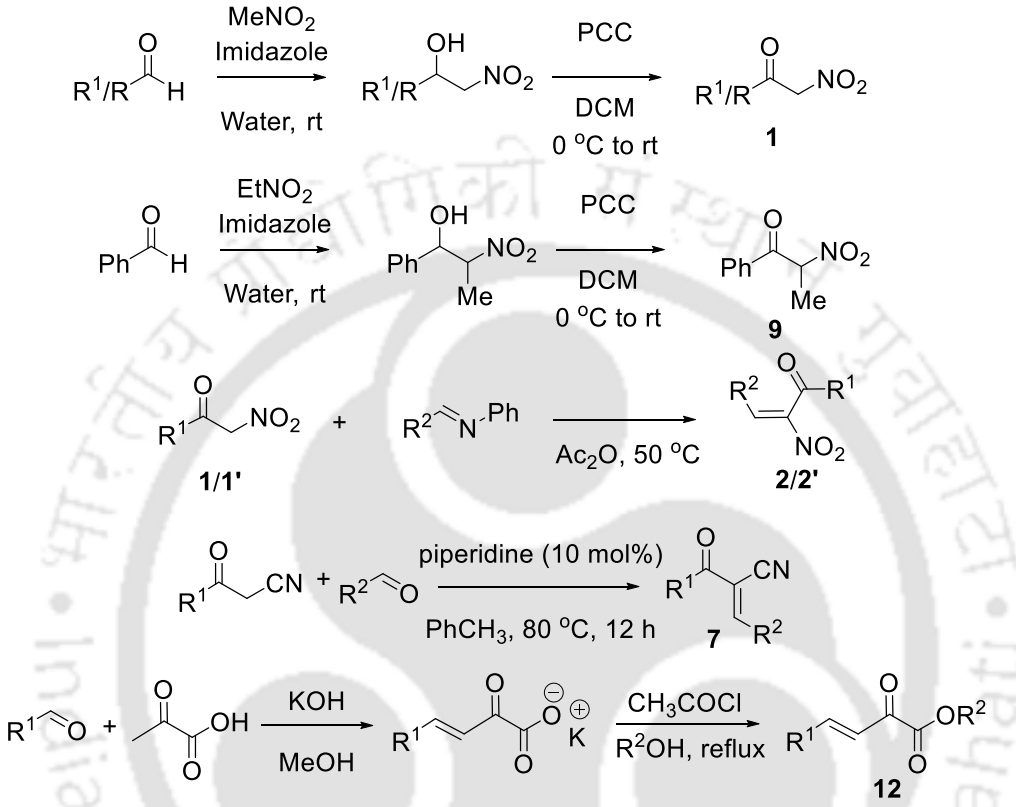
[a]Reactions condition: 0.3 mmol of **1** and 0.3 mmol of **12** using 0.3 mmol DBU in 3 mL $CHCl_3$ at rt for 1 day. [b]Isolated yield. [c]**9** used instead of **1a**.

Then we turned our attention to engage different *α*-nitroketones **1** in this reaction (Scheme 5.21). Initially different *para*-substituted aryl group containing *α*-nitroketones were investigated and to our delight the products **13i-13k** were isolated in acceptable yields. Smooth conversion was observed for product **13i** having 4-allyloxy substitution. 4-Fluoro aryl nitroketone was also engaged in the reaction and the desired product **13j** was obtained with 70% yield. 4-Chloro aryl nitroketone afforded the product **13k** with 61% yield. Similar yield was detected for product **13l** having *meta*-methyl substitution. Gratifyingly, 2,4-disubstituted nitroketone was also tolerated and product **13m** was isolated in 72% yield. Moreover, heteroaryl and aliphatic nitroketones could also be employed and the corresponding products **13n** and **13o** were obtained in good yields. Finally, *α*-methyl nitroketone **9** was screened to deliver the product **13p** in 80% yield with perfect selectivity.

In conclusion, different denitration reactions of *α*-nitroketones have been successfully presented. Versatile nature of *α*-nitroketones triggered the construction of various heterocyclic molecules. Regioselective synthesis of isoxazoles and isoxazoline *N*-oxides has been developed. A variety of tetrasubstituted dihydrofurans has also been synthesized with good to high yields and excellent diastereoselectivities. Some unsaturated diesters have also been prepared which might have pharmaceutical and industrial use.

5.9 Experimental section

DIPEA and DBU were purchased from spectrochem and used without further purification. Ethyl nitroacetate **1′** was purchased from aldrich.



Scheme 5.22: Synthesis of starting materials

A. General procedure for the synthesis of *α*-nitroketones 1

α-Nitroketones **1**/**9** were prepared according to the reported procedure.[14b, 21]

B. General procedure for the synthesis of *α*-nitro enones 2 and *α*-nitrocinnamate 2′

α-Nitro enones **2** and *α*-nitrocinnamate **2′** were prepared according to literature procedure.[22]

C. General procedure for the synthesis of *α*-cyano enones 7

α-Cyano enones **7** were prepared according to reported procedure.[23]

D. General procedure for the synthesis of *β,γ*-unsaturated ketoesters 12

β,γ-Unsaturated ketoesters **12** were prepared according to reported procedure.[24]

E. General procedure for the synthesis of isoxazoles (5a- 5r)

DIPEA (34 μL, 0.2 mmol) was added to a stirred solution of α-nitroketones **1** (0.1 mmol) and α-nitro enones **2** (0.1 mmol) in CH_3CN (1 mL) and stirring was maintained at room temperature. After consumption of starting materials, 3 mL of water was added. The resulting mixture was extracted with EtOAc (3 X 2 mL). The combined organic phase was dried with Na_2SO_4, evaporated in vacuum and purified by column chromatography (4%-8% EtOAc in Hexane) to give compound **5**.

F. General procedure for the synthesis of isoxazoline *N*-oxide 6

DIPEA (34 μL, 0.2 mmol) was added to a stirred solution of aliphatic α-nitroketones **1** (0.1 mmol) and α-nitrocinnamate **2′** (0.1 mmol) in CH_3CN (1 mL) and stirring was maintained at room temperature for 24 hours. After consumption of starting materials, 3 mL of water was added. The resulting mixture was extracted with EtOAc (3 X 2 mL). The combined organic phase was dried with Na_2SO_4, evaporated in vacuum and purified by column chromatography (15%-20% EtOAc in Hexane) to give compound **6**.

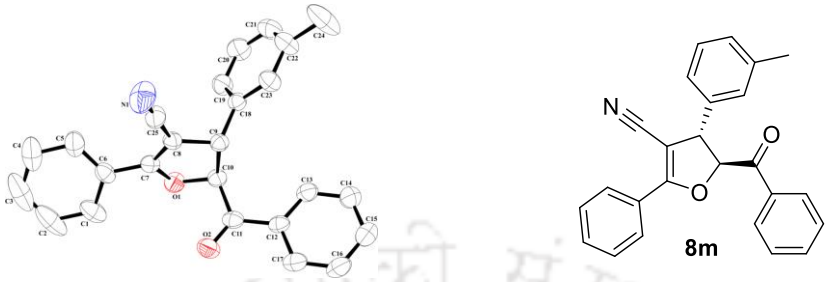
G. General procedure for the synthesis of dihydrofurans (8, 10, 11)

DBU (45 μL, 0.1 mmol) was added to solution of α-nitroketones **1**/**1′**/**9** (0.3 mmol) and α-cyano/α-nitro enones **7**/**2a** (0.3 mmol) in $CHCl_3$ (3 mL). After stirring for 30 minutes at room temperature, 5 mL of water was added. The resulting mixture was extracted with DCM (3 X 5 mL). The combined organic phase was dried with Na_2SO_4, evaporated in vacuum and purified by column chromatography (5%-10% EtOAc in Hexane) to give dihydrofuran products.

H. General procedure for the synthesis of unsaturated diesters 13

DBU (45 μL, 0.3 mmol) was added to a stirred solution of α-nitroketones **1**/**9** (0.3 mmol) and β,γ-unsaturated ketoesters **12** (0.3 mmol) in $CHCl_3$ (3 mL) and stirring was maintained at room temperature for 24 hours. After consumption of starting materials, 5 mL of water was added. The resulting mixture was extracted with DCM (3 X 5 mL). The combined organic phase was dried with Na_2SO_4, evaporated in vacuum and purified by column chromatography (4%-8% EtOAc in Hexane) to give compound **13**.

I. Crystal structure of compound 5-benzoyl-2-phenyl-4-(m-tolyl)-4,5-dihydro-furan-3-carbonitrile (8m)



ORTEP crystal structure of 8m (35% probability level)

Table 5.3. Crystal data and structure refinement for compound 8m

Empirical formula	C25H19NO2
Formula weight	365.41
CCDC Number	1887603
Crystal habit, Colour	Block, White
Crystal size (mm^3)	0.24×0.18×0.16
Temperature, T	293(2)
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	P21/n
Unit cell dimensions	a = 10.8449(4) Å
	b = 16.9400(7) Å
	c = 11.0749(4) Å
	α = 90.00°, β = 96.952(4)°, γ = 90.00°
Volume, V ($Å^3$)	2019.64(13)
Z	4
Calculated density, $g \cdot cm^{-3}$	1.202
μ (mm^{-1})	0.076
F(000)	768.0
Limiting indices	$-12 \leq h \leq 12$, $-19 \leq k \leq 20$, $-13 \leq l \leq 11$
Reflection collected/unique	3548/2570
Completeness to θ	99.8% (θ = 25°)
Data/restraints/parameters	3548/0/254
Goodness-of-fit (GOF)[a] on F^2	1.064
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	R1 = 0.0500, wR2 = 0.1122
R_1[b], wR_2[c] (all data)	R1 = 0.0721, wR2 = 0.1274

[a]GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined).[b]$R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0$, [c]$wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{½}$

5.10 References

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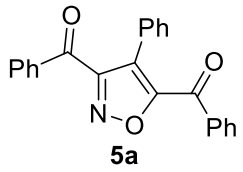
5.11 Characterization Data of Products

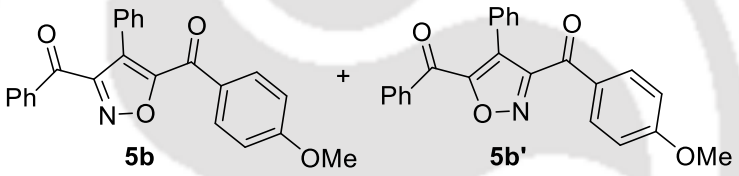
(4-phenylisoxazole-3,5-diyl)bis(phenylmethanone) **(5a)**



5a

Pale yellow sticky solid (23.3 mg, 66%); R_f = 0.6 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.10 – 8.07 (m, 2H), 8.01 – 7.97 (m, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.35 (m, 2H), 7.32 – 7.28 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 186.6, 183.0, 162.4, 160.3, 136.0, 135.6, 134.9, 134.6, 130.8, 130.4, 130.1, 129.2, 129.0, 128.9, 128.6, 127.0, 125.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{23}H_{16}NO_3^+$ 354.1125; found: 354.1125.

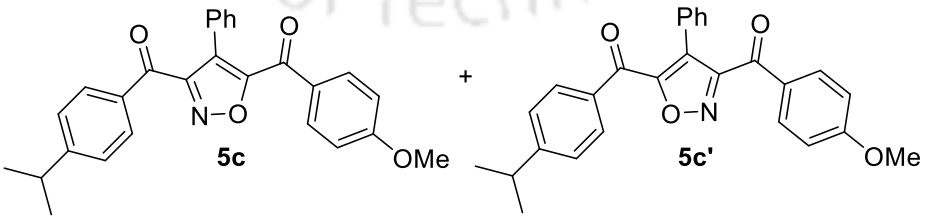
(3-benzoyl-4-phenylisoxazol-5-yl)(4-methoxyphenyl)methanone **(5b/5b′)**



5b **5b'**

Pale yellow sticky solid (25.7 mg, 72%); R_f = 0.5 (EtOAc/hexane 1:19); Regioisomeric ratio = 5:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.09 – 8.06 (m, 2.4H), 8.01 – 7.98 (m, 2.4H), 7.65 (t, *J* = 7.4 Hz, 1.3H), 7.51 (dd, *J* = 8.1, 7.6 Hz, 2.4H), 7.38 – 7.35 (m, 2.4H), 7.31 – 7.29 (m, 3.5H), 6.95 (d, *J* = 9.0 Hz, 2.3H), 3.90 (s, 0.6H), 3.89 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 186.8, 181.4, 164.9, 162.9, 160.2, 136.0, 134.9, 133.3, 133.0, 130.8, 130.4, 130.0, 129.1, 129.0, 128.9, 128.6, 128.6, 127.1, 124.3, 114.3, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{18}NO_4^+$ 384.1230; found: 384.1244.

(3-(4-isopropylbenzoyl)-4-phenylisoxazol-5-yl)(4-methoxyphenyl)methanone **(5c/5c′)**

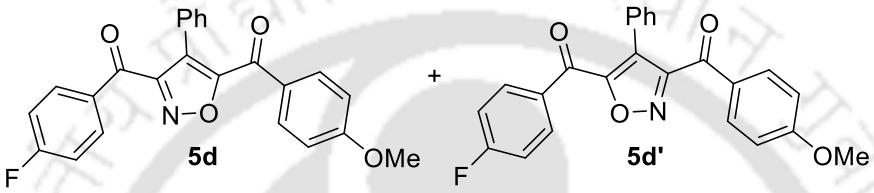


5c **5c'**

Yellow sticky solid (29.4 mg, 69%); R_f = 0.55 (EtOAc/hexane 1:19); Regioisomeric ratio = 2.4:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.06 (d, *J* = 9.0 Hz, 0.97H), 8.03 – 7.98 (m,

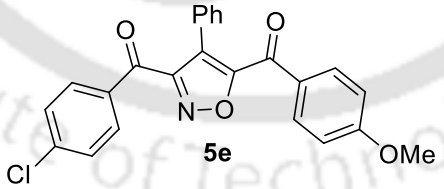
4.44H), 7.92 (d, *J* = 8.4 Hz, 0.89H), 7.40 – 7.34 (m, 5.7H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.31 – 7.27 (m, 4.45H), 6.97 (d, *J* = 9.0 Hz, 0.88H), 6.96 – 6.92 (m, 2.28H), 3.89 (s, 1.2H), 3.89 (s, 3H), 3.01 – 2.98 (m, 1.59H), 1.29 – 1.25 (m, 8.89H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 186.3, 185.0, 182.8, 181.5, 165.1, 164.9, 162.8, 162.5, 160.5, 160.3, 156.8, 156.5, 133.9, 133.3, 133.0, 131.1, 130.7, 130.0, 130.0, 129.0, 128.6, 128.6, 128.5, 127.2, 127.2, 127.1, 124.6, 124.3, 114.3, 114.3, 55.9, 34.6, 23.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{18}NO_4^+$ 426.1700; found: 426.1700.

***(3-(4-fluorobenzoyl)-4-phenylisoxazol-5-yl)(4-methoxyphenyl)methanone* (5d/5d′)**



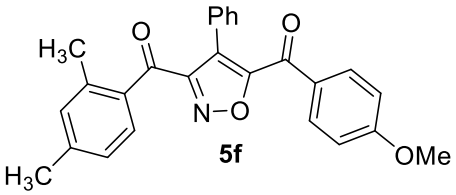
Pale yellow sticky solid (31.3 mg, 78%); R_f = 0.45 (EtOAc/hexane 1:19); Regioisomeric ratio = 6:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.16 (dd, *J* = 8.9, 5.4 Hz, 2H), 8.08 – 8.06 (m, 0.6H), 8.01 (d, *J* = 9.0 Hz, 2H), 7.40 – 7.37 (m, 2.3H), 7.33 (dd, *J* = 5.0, 1.9 Hz, 3.5H), 7.20 (t, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 0.5H), 3.91 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 185.0, 181.4, 167.0 (d, *J* = 257 Hz), 165.0, 163.1, 159.9, 133.6 (d, *J* = 10.5 Hz), 133.3, 133.0, 132.5, 132.4, 130.0, 129.1, 128.6, 128.5, 127.0, 124.3, 116.3 (d, *J* = 22.5 Hz), 114.3, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}FNO_4^+$ 402.1136; found: 402.1134.

***(3-(4-chlorobenzoyl)-4-phenylisoxazol-5-yl)(4-methoxyphenyl)methanone* (5e/5e′)**



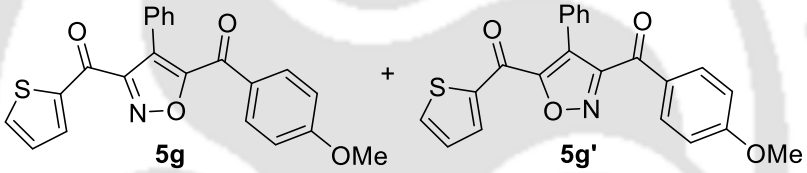
Pale yellow sticky solid (33.4 mg, 80%); R_f = 0.44 (EtOAc/hexane 1:19); Regioisomeric ratio = >20:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.08 – 8.02 (m, 2H), 8.02 – 7.97 (m, 2H), 7.51 – 7.46 (m, 2H), 7.39 – 7.34 (m, 2H), 7.34 – 7.28 (m, 3H), 6.97 – 6.92 (m, 2H), 3.89 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 185.4, 181.3, 165.0, 163.1, 159.8, 141.6, 134.3, 133.0, 132.1, 130.0, 129.4, 129.2, 128.6, 128.5, 127.0, 124.4, 114.3, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}ClNO_4^+$ 418.0841; found: 418.0854.

***(3-(2,4-dimethylbenzoyl)-4-phenylisoxazol-5-yl)(4-methoxyphenyl)methanone* (5f/5f′)**



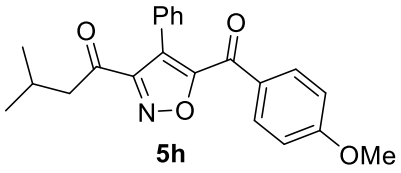
Pale yellow sticky solid (24.7 mg, 60%); R_f = 0.5 (EtOAc/hexane 1:19); Regioisomeric ratio = >20:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.02 – 7.97 (m, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.31 – 7.28 (m, 3H), 7.13 – 7.06 (m, 2H), 6.96 – 6.92 (m, 2H), 3.89 (s, 3H), 2.56 (s, 3H), 2.37 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 188.4, 181.5, 164.9, 162.7, 161.7, 144.6, 141.1, 133.5, 133.3, 133.0, 132.9, 129.9, 129.0, 128.6, 128.6, 127.3, 126.6, 124.1, 114.3, 55.9, 21.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{26}H_{22}NO_4^+$ 412.1543; found: 412.1556.

***(5-(4-methoxybenzoyl)-4-phenylisoxazol-3-yl)(thiophen-2-yl)methanone* (5g/5g′)**



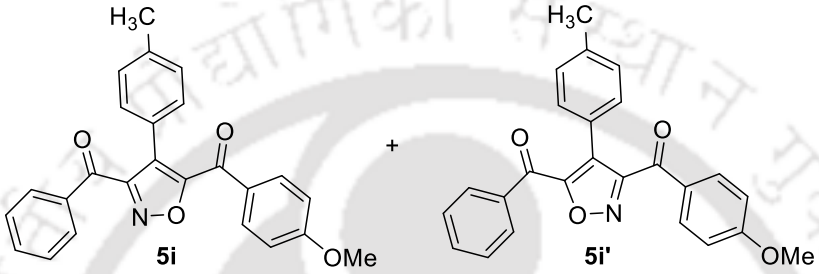
Pale yellow sticky solid (27.6 mg, 71%); R_f = 0.39 (EtOAc/hexane 1:19); Regioisomeric ratio = 1:3.1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.22 – 8.20 (m, 1H), 8.11 – 8.10 (m, 0.3H), 8.06 – 8.02 (m, 2H), 7.99 – 7.95 (m, 0.6H), 7.83 – 7.81 (m, 1.3H), 7.45 – 7.42 (m, 2H), 7.42 – 7.39 (m, 0.6H), 7.36 – 7.32 (m, 3.7H), 7.23 (dd, *J* = 4.7, 4.1 Hz, 1H), 7.21 (dd, *J* = 4.8, 4.1 Hz, 0.3H), 6.98 – 6.95 (m, 2H), 6.93 (d, *J* = 8.9 Hz, 0.56H), 3.89 (s, 3H), 3.88 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**; δ 184.8, 181.4, 177.7, 173.6, 165.1, 164.9, 163.3, 161.2, 161.0, 159.5, 142.8, 142.4, 139.5, 137.4, 137.1, 136.8, 136.3, 133.2, 133.0, 130.2, 130.1, 129.2, 129.1, 129.0, 128.9, 128.5, 128.4, 127.0, 127.0, 125.4, 124.2, 114.3, 114.3, 55.9, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{16}NO_4S^+$ 390.0795; found: 390.0793.

***1-(5-(4-methoxybenzoyl)-4-phenylisoxazol-3-yl)-3-methylbutan-1-one* (5h/5h′)**



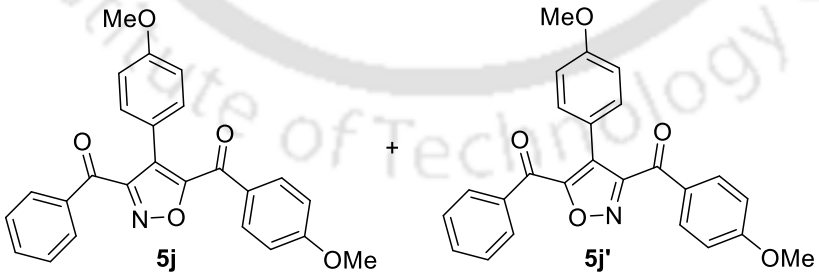
White sticky solid (15.3 mg, 42%); R_f = 0.45 (EtOAc/hexane 1:19); Regioisomeric ratio = >20:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.93 – 7.89 (m, 2H), 7.37 – 7.31 (m, 5H), 6.93 – 6.88 (m, 2H), 3.87 (s, 3H), 2.98 (d, *J* = 6.9 Hz, 2H), 2.31 – 2.29 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.5, 181.3, 164.8, 164.0, 159.3, 132.9, 130.3, 129.0, 128.5, 128.3, 127.2, 123.4, 114.2, 55.8, 50.6, 24.8, 22.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{22}NO_4^+$ 364.1543; found: 364.1567.

***(3-benzoyl-4-(p-tolyl)isoxazol-5-yl)(4-methoxyphenyl)methanone* (5i/5i′)**



White sticky solid (27.8 mg, 70%); R_f = 0.44 (EtOAc/hexane 1:19); Regioisomeric ratio = 4:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.10 – 8.07 (m, 2H), 8.06 (d, *J* = 8.9 Hz, 0.5H), 8.03 – 8.00 (m, 2.5H), 7.65 (t, *J* = 7.4 Hz, 1.3H), 7.51 (t, *J* = 7.8 Hz, 2.3H), 7.27 (s, 1.2H), 7.26 (s, 1.2H), 7.11 (d, *J* = 8.0 Hz, 2.5H), 6.98 (s, 0.5H), 6.96 (dd, *J* = 6.4, 4.6 Hz, 2H), 3.89 (s, 3.8H), 2.30 (s, 3.8H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 186.9, 181.5, 164.9, 162.7, 160.2, 139.1, 136.0, 134.9, 133.3, 133.0, 130.8, 130.4, 129.9, 129.4, 129.3, 129.0, 128.9, 128.7, 124.5, 124.1, 114.3, 55.9, 21.5; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{20}NO_4^+$ 398.1387; found: 398.1363.

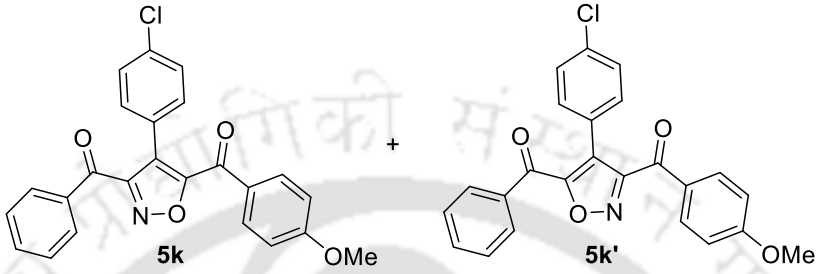
***(3-benzoyl-4-(4-methoxyphenyl)isoxazol-5-yl)(4-methoxyphenyl)methanone* (5j/5j′)**



Yellow sticky solid (29.8 mg, 72%); R_f = 0.4 (EtOAc/hexane 1:19); Regioisomeric ratio = 5.6:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.09 – 8.06 (m, 2H), 8.06 – 8.04 (m, 0.35H), 8.02 – 7.99 (m, 2H), 7.65 (t, *J* = 7.4 Hz, 1.2H), 7.51 (t, *J* = 7.9 Hz, 2.2H), 7.34 – 7.32 (m, 2.1H), 6.97 – 6.93 (m, 2.1H), 6.84 – 6.81 (m, 2.1H), 3.89 (s, 3.3H), 3.76 (s, 3.3H); **^{13}C**

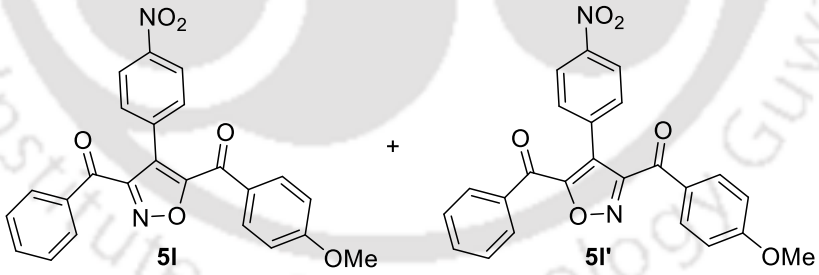
NMR (150 MHz, $CDCl_3$): δ 187.0, 181.5, 164.9, 162.5, 160.2, 160.2, 136.0, 134.9, 133.3, 133.0, 131.5, 131.4, 130.8, 130.4, 129.3, 129.0, 128.9, 128.7, 126.1, 124.2, 119.2, 114.3, 114.1, 55.9, 55.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{20}NO_5^+$ 414.1336; found: 414.1338.

***(3-benzoyl-4-(4-chlorophenyl)isoxazol-5-yl)(4-methoxyphenyl)methanone* (5k/5k′)**



Yellow sticky solid (28.4 mg, 68%); R_f = 0.5 (EtOAc/hexane 1:19); Regioisomeric ratio = 5.1:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.11 – 8.07 (m, 2H), 8.07 (d, *J* = 9.0 Hz, 0.4H), 8.04 – 7.99 (m, 2.3H), 7.70 – 7.66 (m, 1.1H), 7.53 (dd, *J* = 8.2, 7.6 Hz, 2.1H), 7.36 – 7.33 (m, 2.2H), 7.31 – 7.28 (m, 2.4H), 7.00 – 6.96 (m, 2.4H), 3.90 (s, 3.6H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 186.5, 181.1, 165.1, 163.1, 159.9, 135.8, 135.3, 135.0, 133.3, 133.0, 131.5, 130.8, 130.4, 129.1, 129.0, 128.8, 128.4, 125.7, 123.5, 114.4, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}ClNO_4^+$ 418.0841; found: 418.0850.

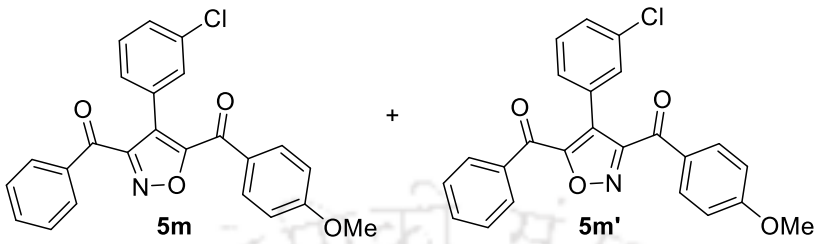
***(3-benzoyl-4-(4-nitrophenyl)isoxazol-5-yl)(4-methoxyphenyl)methanone* (5l/5l′)**



Brown sticky solid (29.6 mg, 69%); R_f = 0.3 (EtOAc/hexane 1:19); Regioisomeric ratio = 7.3:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.23 – 8.20 (m, 2H), 8.20 (s, 0.26H), 8.16 – 8.12 (m, 2.1H), 8.11 (s, 0.25H), 8.08 – 8.05 (m, 2H), 8.04 (d, *J* = 1.3 Hz, 0.24H), 7.72 – 7.68 (m, 1.23H), 7.61 – 7.58 (m, 2.3H), 7.55 (dd, *J* = 8.1, 7.5 Hz, 2.3H), 7.02 – 6.98 (m, 2.3H), 3.92 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 185.9, 180.5, 173.3, 165.3, 163.9, 159.6, 148.0, 135.6, 135.3, 134.3, 133.4, 133.1, 131.2, 130.9, 130.4, 130.1, 129.1, 128.9,

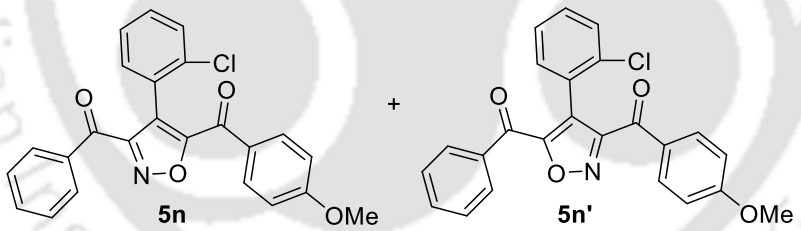
128.2, 123.7, 123.0, 114.6, 56.0; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}N_2O_6^+$ 429.1081; found: 429.1084.

***(3-benzoyl-4-(3-chlorophenyl)isoxazol-5-yl)(4-methoxyphenyl)methanone* (5m/5m′)**



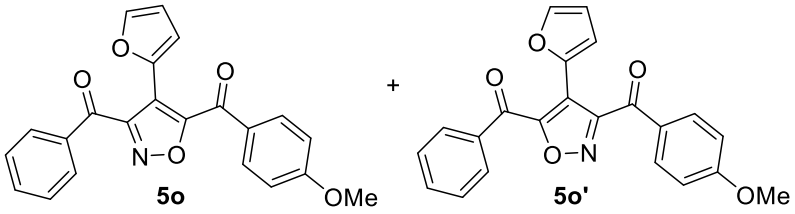
Yellow sticky solid (29.2 mg, 70%); R_f = 0.5 (EtOAc/hexane 1:19); Regioisomeric ratio = 8:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.12 – 8.08 (m, 2H), 8.03 – 8.00 (m, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 0.15H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.7 Hz, 0.24H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.36 – 7.34 (m, 0.12H), 7.31 – 7.28 (m, 1H), 7.28 – 7.25 (m, 2.3H), 7.00 (s, 0.19H), 6.99 – 6.96 (m, 2H), 3.90 (s, 3.3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 186.3, 181.0, 165.1, 163.4, 159.8, 135.9, 135.0, 134.4, 133.0, 130.8, 130.1, 129.8, 129.2, 129.1, 129.0, 128.4, 128.3, 123.3, 114.4, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}ClNO_4^+$ 418.0841; found: 418.0846.

***(3-benzoyl-4-(2-chlorophenyl)isoxazol-5-yl)(4-methoxyphenyl)methanone* (5n/5n′)**



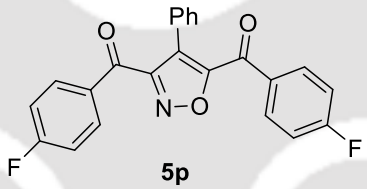
White sticky solid (14.6 mg, 35%); R_f = 0.45 (EtOAc/hexane 1:19); Regioisomeric ratio = 4:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.19 – 8.15 (m, 2H), 8.06 – 8.02 (m, 2H), 8.02 – 8.00 (m, 0.5H), 7.66 (t, *J* = 7.4 Hz, 1.3H), 7.53 (t, *J* = 7.8 Hz, 2.3H), 7.41 – 7.36 (m, 2.2H), 7.31 – 7.26 (m, 2.2H), 6.99 (d, *J* = 8.9 Hz, 0.5H), 6.98 – 6.93 (m, 2H), 3.89 (s, 2.8H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 185.7, 180.6, 164.9, 163.8, 160.2, 135.6, 134.7, 132.9, 132.2, 130.9, 130.5, 129.7, 128.9, 128.4, 127.2, 127.1, 114.3, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}ClNO_4^+$ 418.0841; found: 418.0860.

***(3-benzoyl-4-(furan-2-yl)isoxazol-5-yl)(4-methoxyphenyl)methanone* (5o/5o′)**



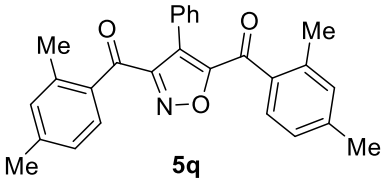
Brown sticky solid (19.4 mg, 52%); R_f = 0.55 (EtOAc/hexane 1:19); Regioisomeric ratio = 4.6:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.11 – 8.07 (m, 2.1H), 8.08 – 8.03 (m, 2H), 7.69 – 7.65 (m, 1.2H), 7.52 (dd, *J* = 8.1, 7.6 Hz, 2.3H), 7.23 – 7.21 (m, 1H), 7.03 – 7.00 (m, 2H), 6.99 – 6.98 (m, 0.4H), 6.43 – 6.40 (m, 1.2H), 3.92 (s, 3.3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 186.8, 180.9, 164.9, 161.1, 159.2, 144.0, 141.5, 139.5, 135.9, 134.9, 132.9, 130.5, 129.0, 128.8, 115.1, 114.4, 113.9, 112.0, 55.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{22}H_{16}NO_5^+$ 374.1023; found: 374.1028.

***(4-phenylisoxazole-3,5-diyl)bis((4-fluorophenyl)methanone)* (5p)**



White sticky solid (27.6 mg, 71%); R_f = 0.50 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.16 – 8.12 (m, 2H), 8.06 – 8.01 (m, 2H), 7.38 – 7.30 (m, 5H), 7.19 – 7.13 (m, 4H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 184.7, 181.2, 167.0 (d, *J* = 257 Hz, 1H), 166.7 (d, *J* = 3.4 Hz, 1H), 162.22, 160.08, 133.6 (d, *J* = 9 Hz, 1H), 133.2 (d, *J* = 10.5 Hz, 1H), 130.06, 129.38, 128.64, 126.76, 125.36, 116.4 (d, *J* = 7.5 Hz, 1H), 116.3 (d, *J* = 6 Hz, 1H); **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{23}H_{14}F_2NO_3^+$ 390.0936; found: 390.0941.

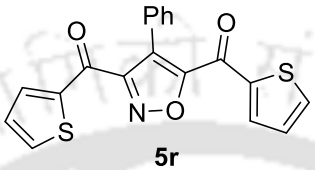
***(4-phenylisoxazole-3,5-diyl)bis((2,4-dimethylphenyl)methanone)* (5q)**



Yellow sticky solid (22.5 mg, 55%); R_f = 0.50 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.31 (m, 2H),

7.29 – 7.25 (m, 3H), 7.08 (t, *J* = 10.9 Hz, 3H), 7.00 (d, *J* = 8.0 Hz, 1H), 2.55 (s, 3H), 2.49 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 188.3, 185.0, 163.0, 161.8, 144.6, 143.9, 141.1, 140.0, 133.5, 133.3, 132.9, 132.8, 132.8, 131.7, 129.8, 128.9, 128.5, 127.2, 126.6, 126.5, 124.3, 21.8, 20.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{27}H_{24}NO_3^+$ 410.1751; found: 410.1755.

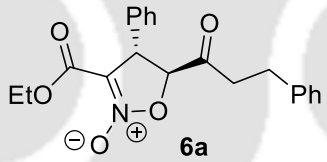
(4-phenylisoxazole-3,5-diyl)bis(thiophen-2-ylmethanone) **(5r)**



5r

White sticky solid (26.3 mg, 72%); R_f = 0.55 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.21 – 8.18 (m, 1H), 8.10 – 8.07 (m, 1H), 7.85 – 7.81 (m, 2H), 7.48 – 7.44 (m, 2H), 7.42 – 7.37 (m, 3H), 7.24 – 7.20 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 177.4, 173.4, 161.8, 160.0, 142.8, 142.4, 137.4, 137.2, 136.9, 136.3, 130.3, 129.3, 129.1, 128.9, 128.4, 126.8, 125.5; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{12}NO_3S_2^+$ 366.0253; found: 366.0255.

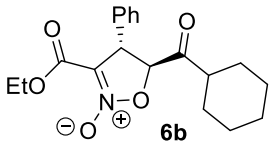
3-(ethoxycarbonyl)-4-phenyl-5-(3-phenylpropanoyl)-4,5-dihydroisoxazole 2-oxide **(6a)**



6a

White sticky solid (30.8 mg, 84%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:4); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.41 – 7.37 (m, 2H), 7.38 – 7.35 (m, 1H), 7.33 – 7.30 (m, 2H), 7.29 – 7.24 (m, 2H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 4.94 (d, *J* = 2.6 Hz, 1H), 4.85 (d, *J* = 2.5 Hz, 1H), 4.35 – 4.30 (m, 2H), 3.25 – 3.17 (m, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 189.8, 168.0, 140.3, 137.9, 129.4, 128.7, 128.5, 128.5, 127.0, 126.2, 117.5, 79.1, 62.7, 52.5, 42.8, 29.02, 14.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{21}H_{22}NO_5^+$ 368.1492; found: 368.1495.

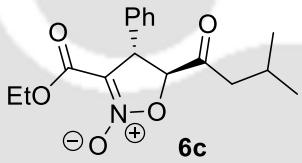
5-(cyclohexanecarbonyl)-3-(ethoxycarbonyl)-4-phenyl-4,5-dihydroisoxazole 2-oxide **(6b)**



6b

White sticky solid (17.2 mg, 50%, >20:1 dr); R_f = 0.55 (EtOAc/hexane 1:4); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.40 (t, *J* = 7.3 Hz, 2H), 7.37 – 7.34 (m, 1H), 7.34 – 7.31 (m, 2H), 4.92 (d, *J* = 2.6 Hz, 1H), 4.87 (d, *J* = 2.6 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.28 – 3.21 (m, 1H), 1.87 (d, *J* = 12.7 Hz, 1H), 1.83 – 1.74 (m, 3H), 1.69 (d, *J* = 13.1 Hz, 1H), 1.39 (s, 1H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.36 – 1.28 (m, 3H), 1.22 – 1.07 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 194.1, 168.5, 138.4, 129.7, 128.9, 127.2, 117.4, 79.2, 62.9, 53.3, 47.0, 30.0, 28.0, 27.3, 26.1, 26.0, 25.6, 14.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{24}NO_5^+$ 346.1649; found: 316.1645.

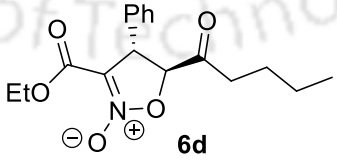
3-(ethoxycarbonyl)-5-(3-methylbutanoyl)-4-phenyl-4,5-dihydroisoxazole 2-oxide **(6c)**



6c

White sticky solid (21.7 mg, 68%, >20:1 dr); R_f = 0.55 (EtOAc/hexane 1:4); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.38 (dd, *J* = 7.9, 6.5 Hz, 2H), 7.35 – 7.31 (m, 3H), 4.92 (d, *J* = 2.6 Hz, 1H), 4.85 (d, *J* = 2.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.81 – 2.79 (m, 1H), 2.69 – 2.66 (m, 1H), 2.12 – 2.09 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 190.9, 168.5, 138.3, 129.7, 129.0, 127.2, 117.9, 79.2, 63.0, 53.0, 49.8, 30.0, 24.4, 22.9, 22.5, 14.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{17}H_{22}NO_5^+$ 320.1492; found: 392.1497.

3-(ethoxycarbonyl)-5-pentanoyl-4-phenyl-4,5-dihydroisoxazole 2-oxide **(6d)**

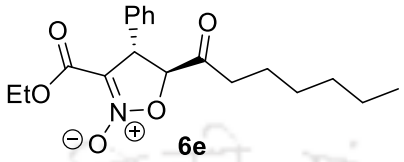


6d

White sticky solid (22.3 mg, 70%, >20:1 dr); R_f = 0.65 (EtOAc/hexane 1:4); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.39 (dd, *J* = 7.9, 6.5 Hz, 2H), 7.36 – 7.31 (m, 3H), 4.93 (d, *J* = 2.6 Hz, 1H), 4.84 (d, *J* = 2.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.87 (td, *J* = 7.1, 1.4 Hz, 2H), 1.55 – 1.52 – 1.47 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.29 (d, *J* = 7.7 Hz, 2H), 0.88

(d, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 191.3, 168.4, 138.3, 129.7, 129.0, 127.3, 117.7, 79.3, 63.0, 53.0, 41.2, 25.3, 22.4, 14.4, 14.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{17}H_{22}NO_5^+$ 320.1492; found: 392.1499.

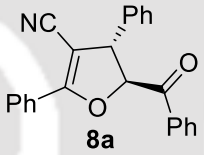
***3-(ethoxycarbonyl)-5-heptanoyl-4-phenyl-4,5-dihydroisoxazole 2-oxide* (6e)**



6e

White sticky solid (26.3 mg, 72%, >20:1 dr); R_f = 0.55 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.42 – 7.39 (m, 2H), 7.38 – 7.32 (m, 3H), 4.95 (d, *J* = 2.6 Hz, 1H), 4.86 (d, *J* = 2.5 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 1.58 – 1.54 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.30 (s, 4H), 0.93 – 0.84 (m, 5H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 191.3, 168.4, 138.3, 129.7, 129.0, 127.3, 117.7, 79.3, 63.0, 53.0, 41.5, 31.8, 30.0, 28.9, 23.2, 22.8, 14.4, 14.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{26}NO_5^+$ 348.1805; found: 348.1799.

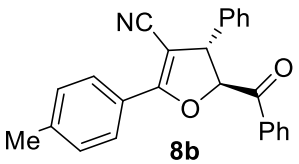
***trans-5-benzoyl-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile* (8a)**



8a

Pale yellow solid (97 mg, 92%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:12); mp 125-128 ^{o}C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.06 (d, *J* = 7.3 Hz, 2H), 7.94 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.47 (m, 5H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 7.1 Hz, 2H), 5.92 (d, *J* = 5.6 Hz, 1H), 4.76 (d, *J* = 5.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.6, 166.6, 139.4, 134.5, 133.6, 132.1, 129.6, 129.3, 129.1, 129.0, 128.7, 127.8, 127.6, 127.3, 116.5, 89.6, 85.3, 52.6; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{18}NO_2^+$ 352.1332; found: 352.1332.

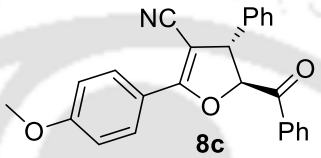
***trans-5-benzoyl-4-phenyl-2-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile* (8b)**



8b

White solid (95.3 mg, 87%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:12); mp 135-137 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.94 (t, *J* = 7.7 Hz, 4H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.39 – 7.33 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.89 (d, *J* = 5.6 Hz, 1H), 4.75 (d, *J* = 5.6 Hz, 1H), 2.42 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.8, 166.8, 142.8, 139.6, 134.5, 133.7, 129.7, 129.6, 129.4, 129.2, 128.7, 127.9, 127.6, 124.6, 116.8, 89.6, 84.4, 52.7, 21.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{20}NO_2^+$ 366.1489; found: 366.1490.

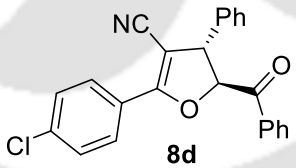
trans-5-benzoyl-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydrofuran-3-carbonitrile (**8c**)



8c

White solid (107.4 mg, 94%, >20:1 dr); R_f = 0.35 (EtOAc/hexane 1:12); mp 125-127 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.02 (d, *J* = 8.9 Hz, 2H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.32 (m, 3H), 6.99 – 6.95 (m, 2H), 5.88 (d, *J* = 5.6 Hz, 1H), 4.72 (d, *J* = 5.6 Hz, 1H), 3.87 (d, *J* = 0.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 192.8, 166.5, 162.6, 139.7, 134.4, 133.7, 129.6, 129.5, 129.3, 129.1, 128.6, 127.8, 119.9, 117.1, 114.4, 89.6, 83.1, 55.7, 52.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{20}NO_3^+$ 382.1438; found: 382.1440.

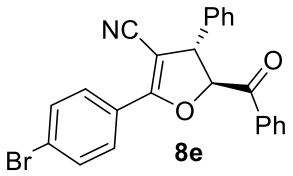
trans-5-benzoyl-2-(4-chlorophenyl)-4-phenyl-4,5-dihydrofuran-3-carbonitrile (**8d**)



8d

White solid (101.5 mg, 88%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:12); mp 155-158 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.47 – 7.41 (m, 4H), 7.40 - 7.37 (m, 1H), 7.34 (d, *J* = 7.1 Hz, 2H), 5.93 (d, *J* = 5.6 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.4, 165.5, 139.2, 138.2, 134.6, 133.5, 129.7, 129.3, 129.3, 129.2, 129.0, 128.8, 127.8, 125.8, 116.3, 89.6, 85.9, 52.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}ClNO_2^+$ 386.0942; found: 386.0942.

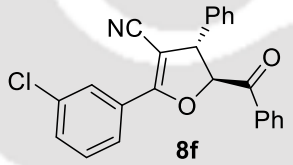
***trans-5-benzoyl-2-(4-bromophenyl)-4-phenyl-4,5-dihydrofuran-3-carbonitrile* (8e)**



8e

White solid (109.3 mg, 85%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:12); mp 172-174 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.94 (d, *J* = 8.7 Hz, 4H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.1 Hz, 2H), 5.95 (d, *J* = 5.6 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.4, 165.5, 139.1, 134.6, 133.5, 132.3, 129.7, 129.3, 129.2, 129.1, 128.8, 127.8, 126.7, 126.2, 116.3, 89.6, 86.0, 52.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{17}BrNO_2^+$ 430.0437; found: 430.0444.

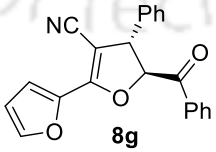
***trans-5-benzoyl-2-(3-chlorophenyl)-4-phenyl-4,5-dihydrofuran-3-carbonitrile* (8f)**



8f

Pale yellow solid (95.8 mg, 83%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:12); mp 110-112 ^oC; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.03 – 7.98 (m, 2H), 7.94 – 7.90 (m, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 3H), 7.46 – 7.38 (m, 4H), 7.36 – 7.31 (m, 2H), 5.94 (d, *J* = 5.6 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 192.3, 165.0, 139.1, 135.2, 134.7, 133.4, 132.1, 130.4, 129.7, 129.3, 129.2, 129.0, 128.9, 127.8, 127.6, 125.8, 116.0, 89.6, 86.7, 52.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{17}ClNO_2^+$ 386.0942; found: 386.0946.

***trans-5-benzoyl-4-phenyl-4,5-dihydro-[2,2'-bifuran]-3-carbonitrile* (8g)**

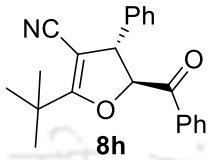


8g

White solid (84.5 mg, 83%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:12); mp 140-142 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.90 (d, *J* = 7.2 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.34 – 7.31 (m, 2H), 7.11 (d, *J* = 3.5 Hz, 1H), 6.59 – 6.56 (m, 1H), 5.90 (d, *J* = 5.7 Hz, 1H), 4.71 (d, *J* = 5.7

Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.4, 157.7, 146.0, 143.0, 139.1, 134.6, 133.5, 129.7, 129.4, 129.2, 128.8, 127.9, 115.5, 115.3, 112.3, 90.3, 84.0, 52.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{16}NO_3^+$ 342.1125; found: 342.1121.

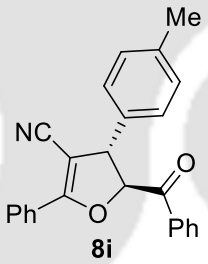
trans-5-benzoyl-2-(tert-butyl)-4-phenyl-4,5-dihydrofuran-3-carbonitrile (**8h**)



8h

White sticky solid (79 mg, 80%, >20:1 dr); R_f = 0.6 (EtOAc/hexane 1:12); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.85 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 2H), 5.74 (d, *J* = 4.9 Hz, 1H), 4.42 (d, *J* = 4.9 Hz, 1H), 1.41 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.9, 179.5, 139.8, 134.4, 133.4, 129.6, 129.2, 129.1, 128.6, 127.6, 116.2, 114.3, 89.3, 84.6, 52.9, 28.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{22}NO_2^+$ 332.1645; found: 332.1651.

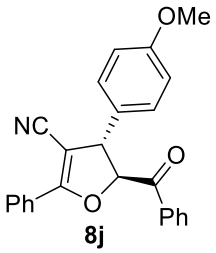
trans-5-benzoyl-2-phenyl-4-(p-tolyl)-4,5-dihydrofuran-3-carbonitrile (**8i**)



8i

White solid (84.3 mg, 77%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:12); mp 106-108 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.07 (d, *J* = 7.4 Hz, 2H), 7.94 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.54 – 7.47 (m, 5H), 7.24 (s, 4H), 5.92 (d, *J* = 5.6 Hz, 1H), 4.70 (d, *J* = 5.6 Hz, 1H), 2.39 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 192.7, 166.5, 138.5, 136.4, 134.5, 133.6, 132.0, 130.3, 129.3, 129.1, 129.0, 127.7, 127.6, 127.4, 116.6, 89.7, 85.5, 52.5, 21.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{25}H_{20}NO_2^+$ 366.1489; found: 366.1495.

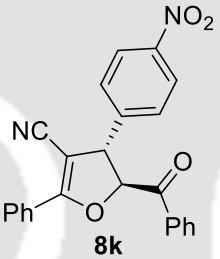
***trans-5-benzoyl-4-(4-methoxyphenyl)-2-phenyl-4,5-dihydrofuran-3-carbonitrile* (8j)**



8j

White solid (90.3 mg, 79%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 132-134 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 – 7.39 (m, 5H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.83 (d, *J* = 5.7 Hz, 1H), 4.62 (d, *J* = 5.7 Hz, 1H), 3.77 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 192.7, 166.3, 159.9, 134.5, 133.6, 132.0, 131.4, 129.3, 129.1, 129.0, 127.6, 127.4, 116.6, 115.0, 89.7, 85.6, 55.5, 52.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{20}NO_3^+$ 382.1438; found: 382.1439.

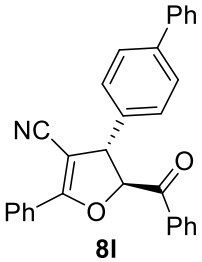
***trans-5-benzoyl-4-(4-nitrophenyl)-2-phenyl-4,5-dihydrofuran-3-carbonitrile* (8k)**



8k

The title compound **3k** was prepared as per the general procedure as a brown solid (91.4 mg, 77%, >20:1 dr); R_f = 0.35 (EtOAc/hexane 1:12); mp 115-117 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.27 (d, *J* = 7.4 Hz, 2H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.57 – 7.52 (m, 5H), 7.48 (t, *J* = 7.7 Hz, 2H), 5.87 (d, *J* = 6.0 Hz, 1H), 5.04 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 191.9, 167.1, 148.1, 146.5, 134.8, 133.6, 132.6, 129.5, 129.3, 129.1, 129.0, 127.7, 126.8, 124.9, 116.0, 89.1, 84.3, 51.7; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{16}N_2O_4^+$ 397.1183; found: 397.1176.

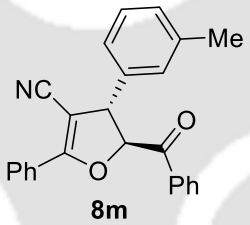
***trans-4-([1,1'-biphenyl]-4-yl)-5-benzoyl-2-phenyl-4,5-dihydrofuran-3-carbonitrile* (8l)**



8l

White solid (103.7 mg, 81%, >20:1 dr); R_f = 0.45 (EtOAc/hexane 1:12); mp 144-146 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.12 – 8.06 (m, 2H), 8.01 – 7.95 (m, 2H), 7.67 (t, *J* = 7.0 Hz, 3H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.56 – 7.45 (m, 7H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 5.96 (d, *J* = 5.7 Hz, 1H), 4.83 (d, *J* = 5.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.6, 166.6, 141.7, 140.6, 138.3, 134.5, 133.6, 132.1, 129.4, 129.2, 129.0, 129.0, 128.3, 128.3, 127.8, 127.7, 127.4, 127.3, 116.6, 89.6, 85.3, 52.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{30}H_{22}NO_2^+$ 428.1645; found: 428.1644.

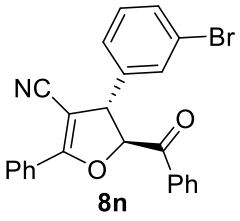
trans-5-benzoyl-2-phenyl-4-(m-tolyl)-4,5-dihydrofuran-3-carbonitrile (**8m**)



8m

Light yellow solid (97.7 mg, 89%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:12); mp 130-133 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.07 (d, *J* = 7.5 Hz, 2H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.47 (m, 5H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 6.5 Hz, 2H), 5.92 (d, *J* = 5.6 Hz, 1H), 4.72 (d, *J* = 5.6 Hz, 1H), 2.39 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.7, 166.5, 139.4, 139.4, 134.5, 133.6, 132.1, 129.5, 129.4, 129.1, 129.0, 128.4, 127.6, 127.4, 124.9, 116.6, 89.7, 85.4, 52.7, 21.7; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{25}H_{20}NO_2^+$ 366.1489; found: 366.1483.

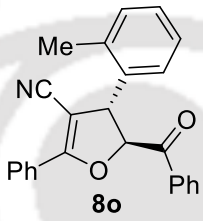
trans-5-benzoyl-4-(3-bromophenyl)-2-phenyl-4,5-dihydrofuran-3-carbonitrile (**8n**)



8n

Pale yellow solid (118.4 mg, 92%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 135-137 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.47 (m, 7H), 7.31 – 7.28 (m, 2H), 5.86 (d, *J* = 5.8 Hz, 1H), 4.80 (d, *J* = 5.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.2, 166.8, 141.7, 134.7, 133.6, 132.3, 131.9, 131.2, 130.9, 129.4, 129.2, 129.1, 127.7, 127.1, 126.7, 123.7, 116.3, 89.4, 84.8, 52.0; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{17}BrNO_2^+$ 430.0437; found: 430.0442.

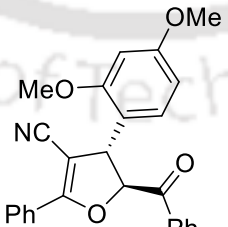
trans-5-benzoyl-2-phenyl-4-(o-tolyl)-4,5-dihydrofuran-3-carbonitrile (**8o**)



8o

White solid (99.5 mg, 91%, >20:1 dr); R_f = 0.5 (EtOAc/hexane 1:12); mp 125-128 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.54 – 7.45 (m, 5H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 5.92 (d, *J* = 5.4 Hz, 1H), 5.15 (d, *J* = 5.4 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.7, 166.1, 138.0, 136.3, 134.5, 133.8, 132.0, 131.2, 129.3, 129.2, 129.0, 128.4, 127.6, 127.6, 127.4, 116.6, 89.7, 85.7, 48.2, 19.7; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{25}H_{20}NO_2^+$ 366.1489; found: 366.1488.

trans-5-benzoyl-4-(2,4-dimethoxyphenyl)-2-phenyl-4,5-dihydrofuran-3-carbonitrile **(8p**)

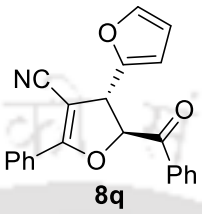


8p

Brown solid (86.3 mg, 70%, >20:1 dr); R_f = 0.25 (EtOAc/hexane 1:12); mp 130-132 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.04 (d, *J* = 7.1 Hz, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.63 – 7.61 (m, 1H), 7.51 – 7.45 (m, 5H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.53 – 6.51 (m, 1H), 6.48 (d,

J = 2.4 Hz, 1H), 5.88 (d, *J* = 5.7 Hz, 1H), 5.03 (d, *J* = 5.7 Hz, 1H), 3.83 (s, 3H), 3.63 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 193.2, 166.8, 161.1, 158.2, 134.1, 131.8, 129.5, 129.3, 128.9, 127.5, 119.7, 117.0, 105.1, 99.1, 88.3, 84.2, 55.6, 55.5, 46.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{26}H_{22}NO_4^+$ 412.1543; found: 412.1540.

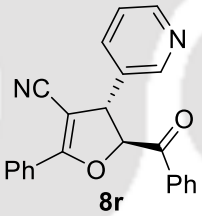
trans-2'-benzoyl-5'-phenyl-2',3'-dihydro-[2,3'-bifuran]-4'-carbonitrile **(8q)**



8q

Light yellow sticky solid (35.8 mg, 35%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.05 – 8.00 (m, 4H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.49 – 7.45 (m, 3H), 6.44 – 6.39 (m, 2H), 6.08 (d, *J* = 5.6 Hz, 1H), 4.97 (d, *J* = 5.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.1, 167.1, 151.1, 143.5, 134.6, 133.6, 132.2, 129.5, 129.2, 129.0, 127.7, 127.3, 116.3, 111.1, 108.7, 86.3, 82.5, 45.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{22}H_{16}NO_3^+$ 342.1125; found: 342.1121.

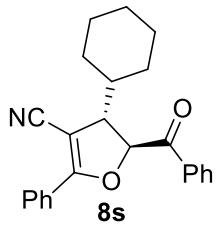
trans-5-benzoyl-2-phenyl-4-(pyridin-3-yl)-4,5-dihydrofuran-3-carbonitrile **(8r)**



8r

Light brown sticky solid (47.2 mg, 45%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:4); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.66 – 8.61 (m, 2H), 8.03 (d, *J* = 7.3 Hz, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 7.73 – 7.71 (m, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.57 – 7.51 (m, 3H), 7.50 – 7.45 (m, 2H), 7.40 – 7.38 (m, 1H), 5.87 (d, *J* = 5.7 Hz, 1H), 4.89 (d, *J* = 5.7 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: 191.9, 166.9, 150.0, 149.3, 135.3, 134.9, 134.6, 133.4, 132.3, 129.2, 129.1, 128.9, 127.5, 126.8, 124.3, 116.0, 114.1, 89.1, 84.2, 49.7; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{23}H_{17}N_2O_2^+$ 353.1285; found: 353.91.

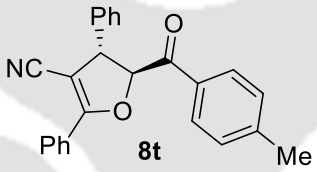
trans-5-benzoyl-4-cyclohexyl-2-phenyl-4,5-dihydrofuran-3-carbonitrile (**8s**)



8s

Yellow sticky liquid (64.2 mg, 60%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 6.8 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.49 – 7.40 (m, 3H), 5.69 (d, *J* = 4.8 Hz, 1H), 3.69 (t, *J* = 4.4 Hz, 1H), 1.78 (m, 7H), 1.36 – 1.27 (m, 3H), 1.17 (d, *J* = 3.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 194.2, 166.5, 134.3, 134.2, 131.8, 129.3, 129.1, 128.9, 127.6, 127.5, 117.7, 85.2, 82.9, 51.8, 41.4, 29.9, 29.4, 26.4, 26.4, 26.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{24}NO_2^+$ 358.1802; found: 358.1798.

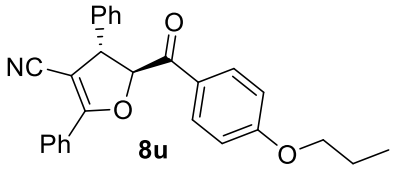
trans-5-(4-methylbenzoyl)-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile (**8t**)



8t

White solid (100.7 mg, 92%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 164-166 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.06 (d, *J* = 7.3 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.53 – 7.50 (m, 1H), 7.49 – 7.46 (m, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.37 – 7.34 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.90 (d, *J* = 5.6 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 2.44 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.2, 166.7, 145.7, 139.5, 132.1, 131.1, 129.9, 129.6, 129.5, 129.0, 128.6, 127.9, 127.7, 127.4, 116.6, 89.6, 85.3, 52.8, 22.0; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{25}H_{20}NO_2^+$ 366.1489; found: 366.1494.

trans-2,4-diphenyl-5-(4-propoxybenzoyl)-4,5-dihydrofuran-3-carbonitrile (**8u**)

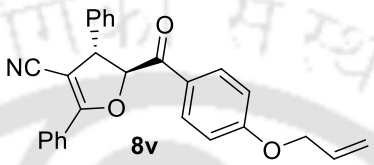


8u

Light yellow solid (95.5 mg, 78%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 163-165 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 2H),

7.52 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.38 – 7.34 (m, 3H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.87 (d, *J* = 5.8 Hz, 1H), 4.77 (d, *J* = 5.8 Hz, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 191.0, 166.6, 164.3, 139.6, 132.0, 131.8, 129.6, 129.0, 128.6, 127.9, 127.7, 127.5, 126.3, 116.7, 114.8, 89.5, 85.4, 70.1, 52.8, 22.6, 10.7; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{27}H_{24}NO_3^+$ 410.1751; found: 410.1758.

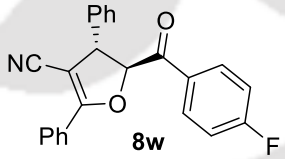
trans-5-(4-(allyloxy)benzoyl)-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile (**8v**)



8v

White solid (100 mg, 82%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 165-167 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 7.54 – 7.50 (m, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.39 – 7.33 (m, 3H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.05 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.87 (d, *J* = 5.8 Hz, 1H), 5.47 – 5.40 (m, 1H), 5.36 – 5.33 (m, 1H), 4.77 (d, *J* = 5.8 Hz, 1H), 4.63 (d, *J* = 5.3 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 191.0, 166.6, 163.6, 139.6, 132.4, 132.0, 131.7, 129.6, 129.0, 128.6, 127.9, 127.6, 127.5, 126.7, 118.6, 116.7, 115.1, 89.5, 85.4, 69.2, 52.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{27}H_{22}NO_3^+$ 408.1594; found: 408.1586.

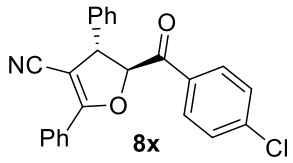
trans-5-(4-fluorobenzoyl)-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile (**8w**)



8w

Yellow solid (56.5 mg, 78%, 9:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 175-178 °C; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.04 (d, *J* = 7.7 Hz, 2H), 7.99 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.18 (t, *J* = 8.5 Hz, 2H), 5.86 (d, *J* = 5.8 Hz, 1H), 5.79 (d, *J* = 6.0 Hz, 0.07H), 4.85 (d, *J* = 6.0 Hz, 0.06H), 4.80 (d, *J* = 5.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 191.1, 166.5 (d, *J* = 256 Hz), 166.4, 139.3, 132.2 (d, *J* = 6 Hz), 132.2, 130.2 (d, *J* = 3 Hz), 129.7, 129.1, 128.8, 127.9, 127.62 127.3, 116.5 (d, *J* = 16.5 Hz), 89.6, 85.5, 52.5; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{17}FNO_2^+$ 370.1238; found: 370.1247.

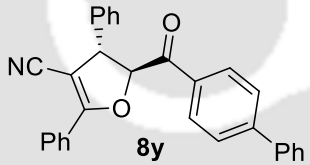
trans-5-(4-chlorobenzoyl)-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile **(8x)**



8x

Pale yellow solid (40.4 mg, 35%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 185- 187 ^oC; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.03 (d, *J* = 6.9 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.52 – 7.47 (m, 4H), 7.45 – 7.39 (m, 3H), 7.36 (dd, *J* = 8.3, 6.8 Hz, 3H), 5.85 (d, *J* = 5.8 Hz, 1H), 4.79 (d, *J* = 5.7 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 191.6, 166.4, 141.2, 139.3, 132.2, 132.0, 130.8, 129.7, 129.6, 129.1, 128.8, 127.9, 127.6, 127.3, 116.4, 89.6, 85.5, 52.5; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{17}ClNO_2^+$ 386.0942; found: 386.0938.

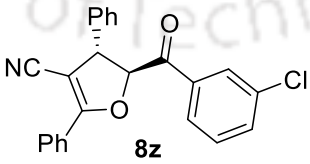
trans-5-([1,1'-biphenyl]-4-carbonyl)-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile **(8y)**



8y

White solid (113.4 mg, 35%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 162-164 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.07 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.54 – 7.51 (m, 1H), 7.51 – 7.47 (m, 4H), 7.43 (q, *J* = 7.4 Hz, 3H), 7.43 – 7.36 (m, 3H), 5.94 (d, *J* = 5.7 Hz, 1H), 4.80 (d, *J* = 5.7 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.2, 166.6, 147.2, 139.6, 139.5, 132.3, 132.1, 130.0, 129.7, 129.3, 129.0, 128.8, 128.7, 127.9, 127.8, 127.7, 127.5, 127.4, 116.6, 89.7, 85.4, 52.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{30}H_{22}NO_2^+$ 428.1645; found: 428.1555.

trans-5-(3-chlorobenzoyl)-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile **(8z)**

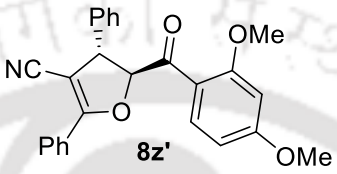


8z

Brown solid (72.5 mg, 63%, 8:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); mp 155-157 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.03 (dd, *J* = 5.3, 3.4 Hz, 2H), 8.01 (t, *J* = 1.7 Hz, 0.12H), 7.96 (t, *J* = 1.8 Hz, 0.12H), 7.94 (t, *J* = 1.8 Hz, 1H), 7.83 (dd, *J* = 5.1, 4.0 Hz, 0.14H), 7.82 – 7.79 (m, 1H), 7.63 – 7.60 (m, 1H), 7.55 – 7.51 (m, 1H), 7.51 – 7.48 (m, 2H), 7.47

(d, *J* = 7.4 Hz, 1H), 7.44 (dd, *J* = 7.7, 6.3 Hz, 3H), 7.40 – 7.38 (m, 1H), 7.36 – 7.34 (m, 2H), 5.83 (d, *J* = 5.8 Hz, 1H), 5.78 (d, *J* = 5.8 Hz, 0.12H), 4.84 (d, *J* = 5.8 Hz, 0.12H), 4.79 (d, *J* = 5.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 191.6, 166.4, 139.1, 135.6, 135.2, 134.4, 132.2, 130.5, 129.7, 129.5, 129.1, 128.8, 127.9, 127.6, 127.4, 127.2, 116.4, 89.7, 85.4, 52.5; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{17}ClNO_2^+$ 386.0942; found: 386.0941.

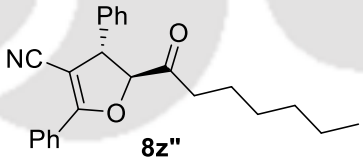
trans-5-(2,4-dimethoxybenzoyl)-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile (**3z′**)



8z'

White solid (88.6 mg, 72%, >20:1 dr); R_f = 0.25 (EtOAc/hexane 1:12); mp 185-187 ^oC; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.09 (d, *J* = 6.9 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.52 – 7.46 (m, 3H), 7.42 – 7.38 (m, 2H), 7.35 – 7.31 (m, 3H), 6.64 – 6.61 (m, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 6.17 (d, *J* = 4.2 Hz, 1H), 4.28 (d, *J* = 4.1 Hz, 1H), 3.87 (s, 3H), 3.20 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.0, 167.3, 166.0, 161.2, 141.8, 134.3, 131.8, 129.2, 128.9, 128.1, 127.9, 127.8, 127.2, 117.1, 116.5, 106.4, 98.1, 91.7, 85.6, 55.9, 55.0, 54.1; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{26}H_{12}NO_4^+$ 412.1543; found: 412.1550.

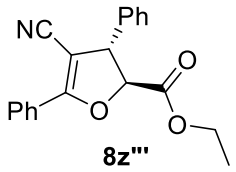
trans-5-heptanoyl-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile (**3z′′**)



8z"

Yellow sticky liquid (73.2 mg, 68%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.08 (d, *J* = 6.7 Hz, 2H), 7.53 (ddd, *J* = 12.5, 7.3, 5.9 Hz, 3H), 7.42 – 7.37 (m, 2H), 7.33 (t, *J* = 6.5 Hz, 3H), 4.98 (d, *J* = 5.7 Hz, 1H), 4.60 (d, *J* = 5.7 Hz, 1H), 2.75 – 2.57 (m, 2H), 1.67 – 1.61 (m, 2H), 1.28 (s, 6H), 0.89 – 0.87 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 207.2, 166.2, 139.7, 132.3, 129.6, 129.2, 128.5, 127.6, 127.5, 127.4, 116.5, 92.5, 85.2, 52.9, 39.1, 31.7, 29.0, 23.2, 22.6, 14.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{26}NO_2^+$ 360.1958; found: 360.1963.

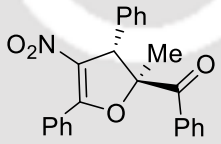
***trans- ethyl -4-cyano-3,5-diphenyl-2,3-dihydrofuran-2-carboxylate* (3z‴)**



8z‴

Reaction performed in 0.2 mmol scale. Yellow sticky solid (56.3 mg, 88%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:12); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.08 (d, *J* = 6.7 Hz, 2H), 7.53 (ddd, *J* = 12.5, 7.3, 5.9 Hz, 3H), 7.42 – 7.37 (m, 2H), 7.33 (t, *J* = 6.5 Hz, 3H), 4.98 (d, *J* = 5.7 Hz, 1H), 4.60 (d, *J* = 5.7 Hz, 1H), 2.75 – 2.57 (m, 2H), 1.67 – 1.61 (m, 2H), 1.28 (s, 6H), 0.89 – 0.87 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 169.2, 167.1, 139.3, 132.2, 129.5, 129.0, 128.6, 127.7, 127.4, 127.3, 116.5, 86.2, 84.7, 62.4, 54.2, 14.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{20}H_{18}NO_3^+$ 320.1281; found: 320.1283.

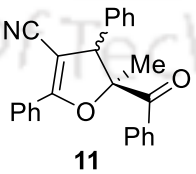
***(2-methyl-4-nitro-3,5-diphenyl-2,3-dihydrofuran-2-yl)(phenyl)methanone* (10)**



10

Reaction performed in 0.2 mmol scale. Light yellow sticky solid (63 mg, 82%, >20:1 dr); R_f = 0.4 (EtOAc/hexane 1:15); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.20 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 2H), 7.55 – 7.51 (m, 3H), 7.42 – 7.35 (m, 7H), 5.63 (s, 1H), 1.38 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 199.2, 184.7, 135.6, 134.7, 134.2, 133.6, 133.5, 130.5, 129.4, 129.0, 128.9, 128.6, 118.4, 114.3, 89.7, 55.7, 20.6; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{24}H_{20}NO_4^+$ 386.1387; found: 386.1390.

***5-benzoyl-5-methyl-2,4-diphenyl-4,5-dihydrofuran-3-carbonitrile* (11)**

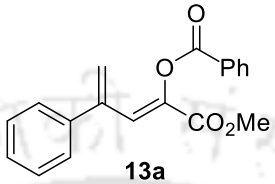


11

Reaction performed in 0.2 mmol scale. Yellow sticky solid (55.3 mg, overall yield 88%, 1:1 dr); R_f = 0.4 (EtOAc/hexane 1:15); NMR data of one diastereomer given; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.23 (d, *J* = 6.8 Hz, 2H), 7.57 – 7.50 (m, 4H), 7.42 (dt, *J* = 16.0, 7.0 Hz, 4H), 7.26 (s, 1H), 7.22 (dd, *J* = 8.2, 7.6 Hz, 2H), 7.08 (d, *J* = 7.2 Hz, 2H), 4.58

(s, 1H), 1.96 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 185.7, 165.2, 136.3, 135.4, 134.5, 132.6, 132.3, 130.6, 129.7, 129.2, 129.2, 128.9, 128.7, 127.9, 127.1, 116.5, 111.4, 103.9, 85.4, 60.8, 28.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{25}H_{20}NO_2^+$ 366.1489; found: 366.1490.

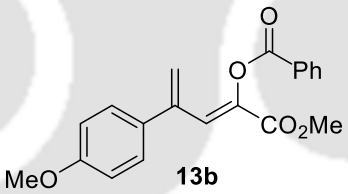
(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl benzoate **(13a)**



13a

Pale yellow sticky solid (60 mg, 65%); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.76 – 7.71 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 8.1, 7.6 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.28 (s, 1H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 5.68 (d, *J* = 0.9 Hz, 1H), 5.58 (d, *J* = 1.2 Hz, 1H), 3.83 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.3, 163.2, 142.1, 139.8, 138.1, 133.7, 130.2, 128.5, 128.4, 128.4, 128.3, 127.8, 127.1, 123.2, 52.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{17}O_4^+$ 309.1121; found: 309.1123.

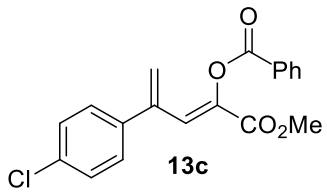
(Z)-1-methoxy-4-(4-methoxyphenyl)-1-oxopenta-2,4-dien-2-yl benzoate (**13b**)



13b

Yellow sticky solid (65.9 mg, 65%); R_f = 0.55 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.83 – 7.76 (m, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 8.2, 7.6 Hz, 2H), 7.31 (d, *J* = 0.7 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.63 (d, *J* = 1.0 Hz, 1H), 5.55 (d, *J* = 1.3 Hz, 1H), 3.85 (s, 3H), 3.65 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 164.4, 163.2, 159.4, 141.5, 137.9, 133.7, 132.3, 130.2, 128.7, 128.3, 128.3, 122.0, 113.8, 55.3, 52.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{20}H_{19}O_5^+$ 339.1227; found: 339.1225.

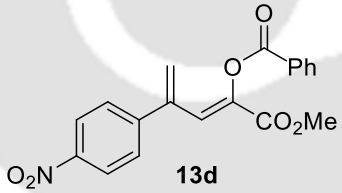
(Z)-4-(4-chlorophenyl)-1-methoxy-1-oxopenta-2,4-dien-2-yl benzoate **(13c)**



13c

Pale yellow sticky solid (63.6 mg, 62%); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.73 – 7.68 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 1.0 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 5.68 (s, 1H), 5.54 (d, *J* = 1.0 Hz, 1H), 3.82 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 164.3, 163.1, 141.3, 138.3, 138.2, 133.9, 133.8, 130.1, 128.6, 128.6, 128.5, 128.3, 127.9, 123.9, 52.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{16}ClO_4^+$ 343.0732; found: 343.0743.

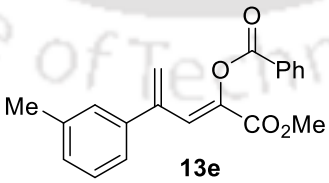
(Z)-1-methoxy-4-(4-nitrophenyl)-1-oxopenta-2,4-dien-2-yl benzoate **(13d)**



13d

Pale yellow sticky solid (42.4 mg, 40%); R_f = 0.35 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.96 (d, *J* = 8.8 Hz, 2H), 7.69 – 7.63 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.30 (dd, *J* = 9.9, 5.8 Hz, 3H), 5.82 (s, 1H), 5.61 (s, 1H), 3.84 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 164.0, 162.8, 147.2, 146.5, 141.1, 138.4, 134.2, 130.0, 128.4, 128.3, 127.9, 127.1, 126.1, 123.7, 53.0; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{16}NO_6^+$ 354.0972; found: 354.0973.

(Z)-1-methoxy-1-oxo-4-(m-tolyl)penta-2,4-dien-2-yl benzoate **(13e)**

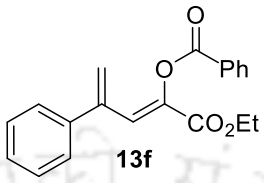


13e

Colourless sticky solid (48.3 mg, 50%); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.74 – 7.68 (m, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 0.8 Hz, 1H), 7.07 (dd, *J* = 7.2, 3.3 Hz, 2H), 6.85 (d, *J* = 6.3 Hz, 1H), 5.66 (d, *J* = 1.0 Hz, 1H), 5.56 (d, *J* = 1.3 Hz, 1H), 3.83 (s, 3H), 2.17 (s, 3H); **^{13}C NMR (150**

MHz, $CDCl_3$): δ 164.3, 163.2, 142.4, 139.8, 138.0, 137.9, 133.7, 130.2, 128.5, 128.5, 128.5, 128.4, 128.3, 127.9, 124.2, 123.3, 52.9, 21.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{20}H_{19}O_4^+$ 323.1278; found: 323.1279.

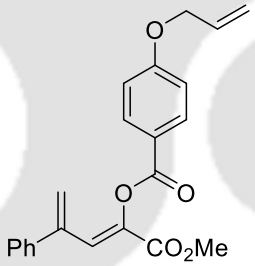
(Z)-1-ethoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl benzoate (**13f**)



13f

Pale yellow sticky solid (74.3 mg, 77%); R_f = 0.4 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.77 – 7.72 (m, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.30 (s, 1H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 5.68 (s, 1H), 5.58 (d, *J* = 1.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.31 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**; δ 166.7, 164.4, 142.2, 139.9, 138.4, 133.6, 130.2, 129.0, 128.4, 128.3, 127.9, 127.8, 127.1, 123.0, 62.0, 14.3; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{20}H_{19}O_4^+$ 323.1278; found: 323.1280.

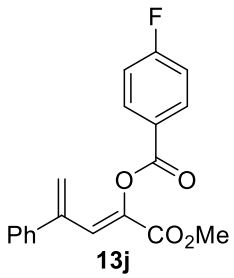
(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl 4-(allyloxy)benzoate (**13i**)



13i

Pale yellow sticky solid (68.7 mg, 63 %); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.69 (d, *J* = 8.9 Hz, 2H), 7.31 – 7.25 (m, 3H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.04 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.68 (s, 1H), 5.58 (d, *J* = 1.2 Hz, 1H), 5.45 – 5.39 (m, 1H), 5.34 – 5.31 (m, 1H), 4.58 (dt, *J* = 5.2, 1.4 Hz, 2H), 3.82 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.0, 163.3, 163.0, 142.1, 140.0, 138.2, 132.6, 132.4, 128.4, 128.0, 127.8, 127.1, 123.0, 121.0, 118.4, 114.4, 69.1, 52.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{21}O_5^+$ 365.1384; found: 365.1387.

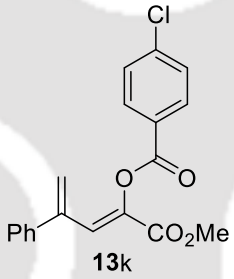
(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl 4-fluorobenzoate (**13j**)



13j

Pale yellow sticky solid (68.4 mg, 70%); R_f = 0.44 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.71 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.31 (d, *J* = 0.7 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.18 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.67 (s, 1H), 5.57 (d, *J* = 1.2 Hz, 1H), 3.83 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 166.1 (d, *J* = 243 Hz), 163.31, 163.09, 142.29, 139.84, 137.77, 132.8 (d, *J* = 9 Hz), 128.48, 128.40, 127.79, 127.19, 124.76, 124.74, 123.65, 115.5 (d, *J* = 22 Hz), 52.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{16}FO_4^+$ 327.1027; found: 327.1030.

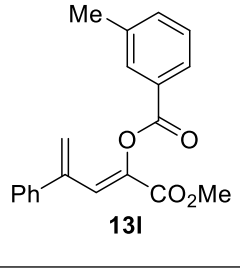
(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl 4-chlorobenzoate (**13k**)



13k

Yellow sticky solid (62.5 mg, 61%); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.61 (d, *J* = 8.7 Hz, 4H), 7.31 – 7.28 (m, 6H), 7.27 – 7.25 (m, 5H), 7.18 (t, *J* = 7.7 Hz, 4H), 7.09 (t, *J* = 7.4 Hz, 2H), 5.66 (d, *J* = 1.0 Hz, 2H), 5.56 (d, *J* = 1.2 Hz, 2H), 3.82 (s, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 163.5, 163.0, 142.3, 140.2, 139.8, 137.7, 131.5, 128.7, 128.5, 128.4, 127.8, 127.2, 126.9, 123.8, 52.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{16}ClO_4^+$ 343.0732; found: 343.0735.

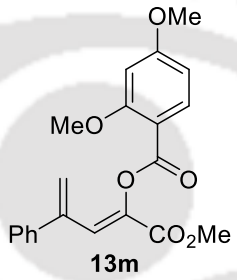
(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl 3-methylbenzoate (**13l**)



13l

Yellow sticky solid (57.9 mg, 60%); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.28 (m, 3H), 7.25 – 7.19 (m, 3H), 7.11 (t, *J* = 7.4 Hz, 1H), 5.68 (d, *J* = 1.0 Hz, 1H), 5.58 (d, *J* = 1.2 Hz, 1H), 3.83 (s, 3H), 2.34 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 164.5, 163.2, 142.1, 139.9, 138.1, 134.5, 130.7, 128.4, 128.3, 128.2, 127.8, 127.4, 127.1, 123.2, 52.9, 21.4; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{20}H_{19}O_4^+$ 323.1278; found: 323.1276.

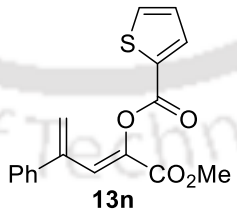
(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl 2,4-dimethoxybenzoate (13**m**)



13m

Pale yellow sticky solid (79.4 mg, 72%); R_f = 0.3 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.49 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* = 5.1, 3.2 Hz, 2H), 7.24 (dd, *J* = 10.8, 4.2 Hz, 3H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.38 – 6.35 (m, 1H), 5.72 (d, *J* = 1.0 Hz, 1H), 5.60 (d, *J* = 1.2 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.2, 163.5, 162.6, 162.3, 141.9, 140.2, 138.5, 134.9, 128.4, 127.8, 127.5, 127.1, 122.4, 110.1, 104.7, 98.8, 56.1, 55.7, 52.8; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{21}H_{21}O_6^+$ 369.1333; found: 369.1337.

(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl thiophene-2-carboxylate (**13n**)

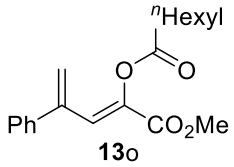


13n

Yellow sticky solid (68.7 mg, 73%); R_f = 0.5 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.57 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.55 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.30 – 7.28 (m, 3H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.02 (dd, *J* = 4.9, 3.8 Hz, 1H), 5.70 (d, *J* = 1.0 Hz, 1H), 5.61 (d, *J* = 1.2 Hz, 1H), 3.83 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 163.1, 159.6, 142.0, 139.8, 137.7, 135.0, 133.8, 131.7, 128.6, 128.4,

127.9, 127.8, 127.1, 123.4, 52.9; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{17}H_{15}O_4S^+$ 315.0686; found: 315.0687.

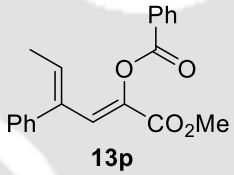
(Z)-1-methoxy-1-oxo-4-phenylpenta-2,4-dien-2-yl heptanoate (**13o**)



13o

Colourless sticky liquid (73 mg, 77%); R_f = 0.45 (EtOAc/hexane 1:19); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.35 – 7.26 (m, 5H), 7.18 (d, *J* = 0.8 Hz, 1H), 5.62 (s, 1H), 5.56 (d, *J* = 1.3 Hz, 1H), 3.81 (s, 3H), 1.94 (t, *J* = 7.6 Hz, 2H), 1.21 (m, 6H), 0.83 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.5, 163.2, 142.4, 139.9, 137.8, 128.4, 128.0, 127.9, 127.4, 123.3, 52.8, 33.4, 32.1, 28.8, 24.4, 22.6, 14.2; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{25}O_4^+$ 317.1747; found: 317.1744.

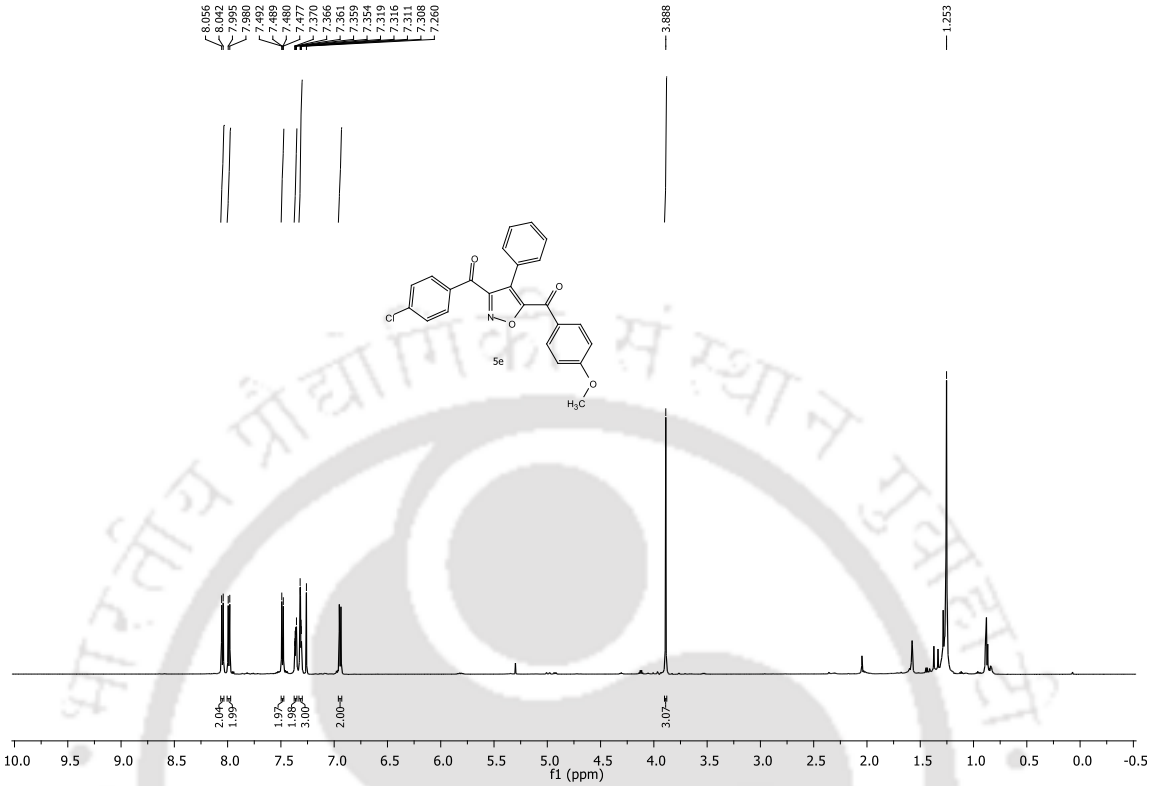
(2Z,4Z)-1-methoxy-1-oxo-4-phenylhexa-2,4-dien-2-yl benzoate (**13p**)

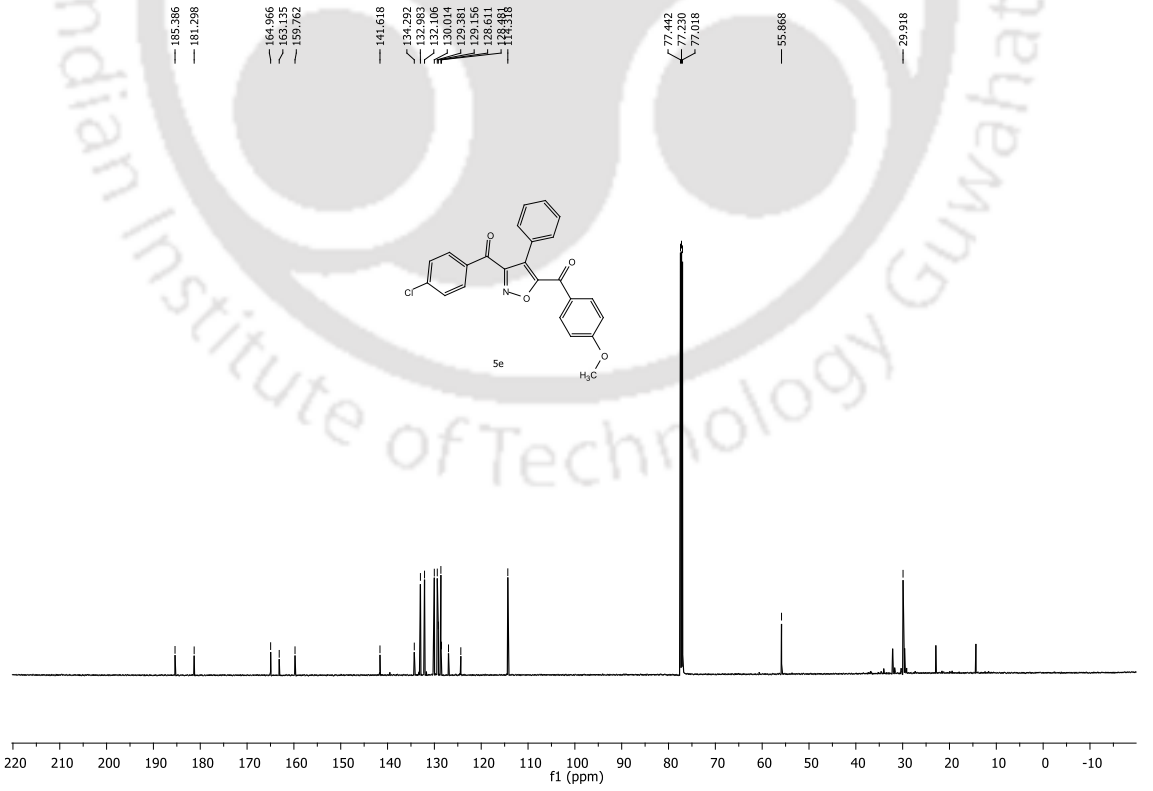


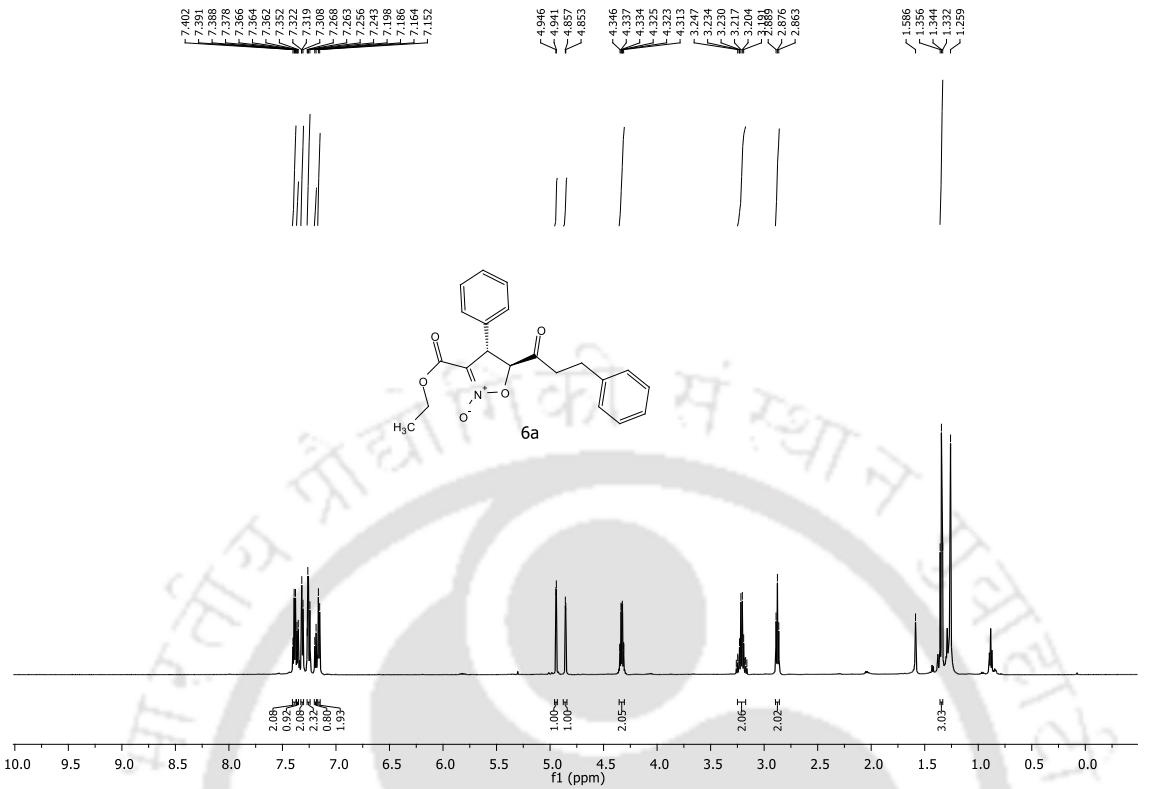
13p

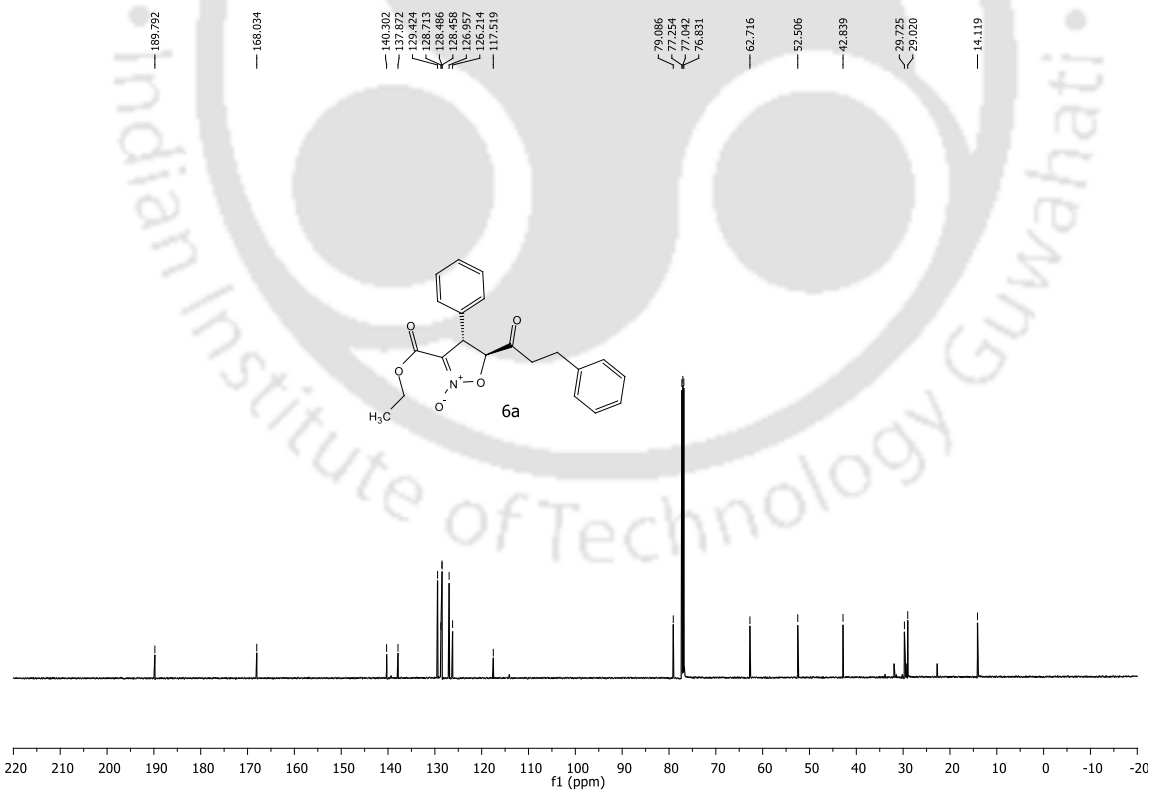
Light yellow sticky liquid (77.2 mg, 80%); R_f = 0.55 (EtOAc/hexane 1:19); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.60 – 7.45 (m, 8H), 7.49 (t, *J* = 7.4 Hz, 5H), 7.28 (dd, *J* = 5.9, 2.2 Hz, 9H), 7.25 (s, 4H), 7.08 – 7.06 (m, 14H), 6.85 (ddd, *J* = 8.8, 5.0, 3.8 Hz, 4H), 6.37 – 6.32 (m, 4H), 3.79 (s, 12H), 1.63 (d, *J* = 7.2 Hz, 13H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.5, 163.8, 138.5, 137.7, 137.6, 134.3, 133.3, 131.1, 130.1, 128.6, 128.5, 128.3, 127.9, 126.9, 52.6, 15.6; **HRMS (ESI-TOF) m/z:** $[M+H]^+$ $C_{22}H_{16}NO_5^+$ 323.1278; found: 323.1280.

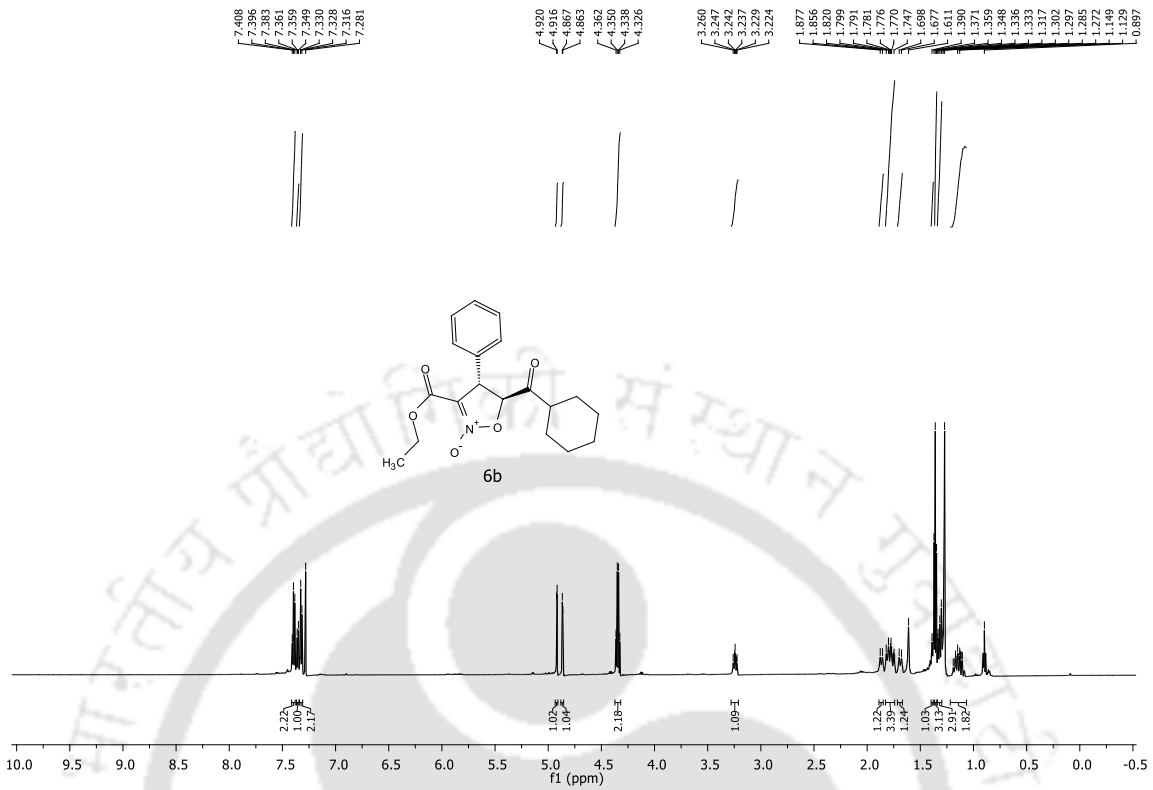
5.12 Selected spectra of products

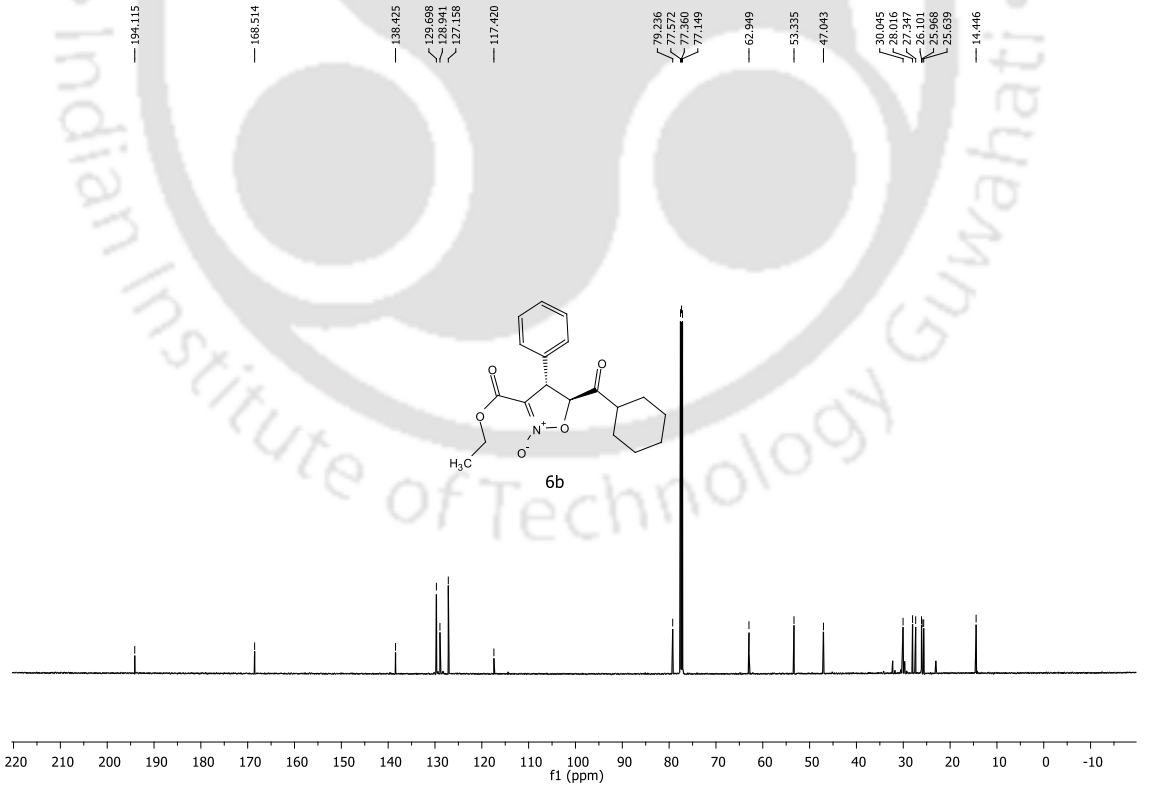


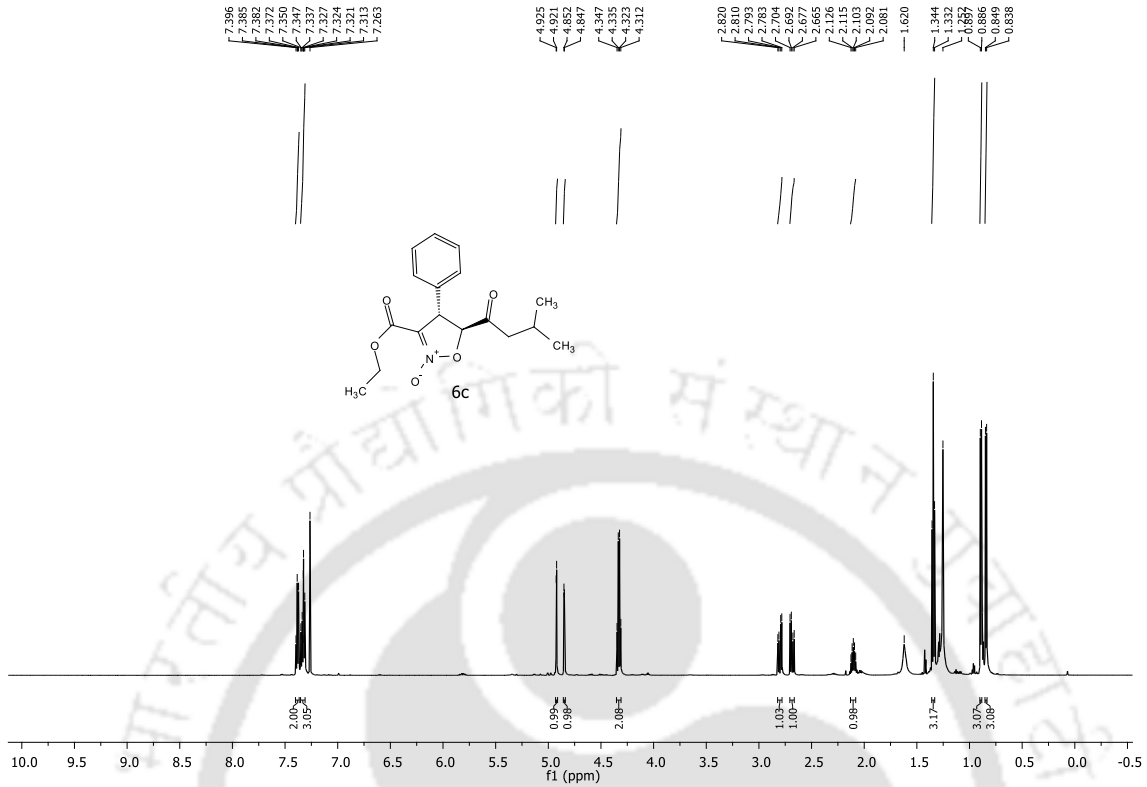


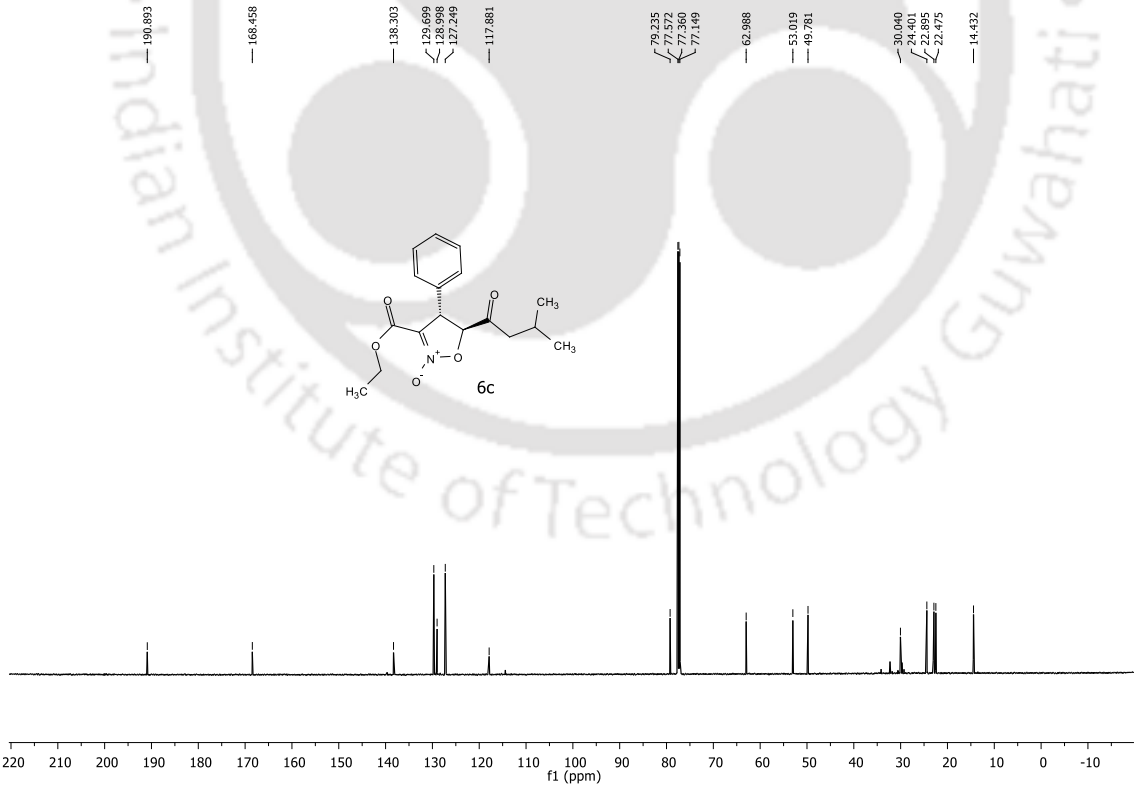


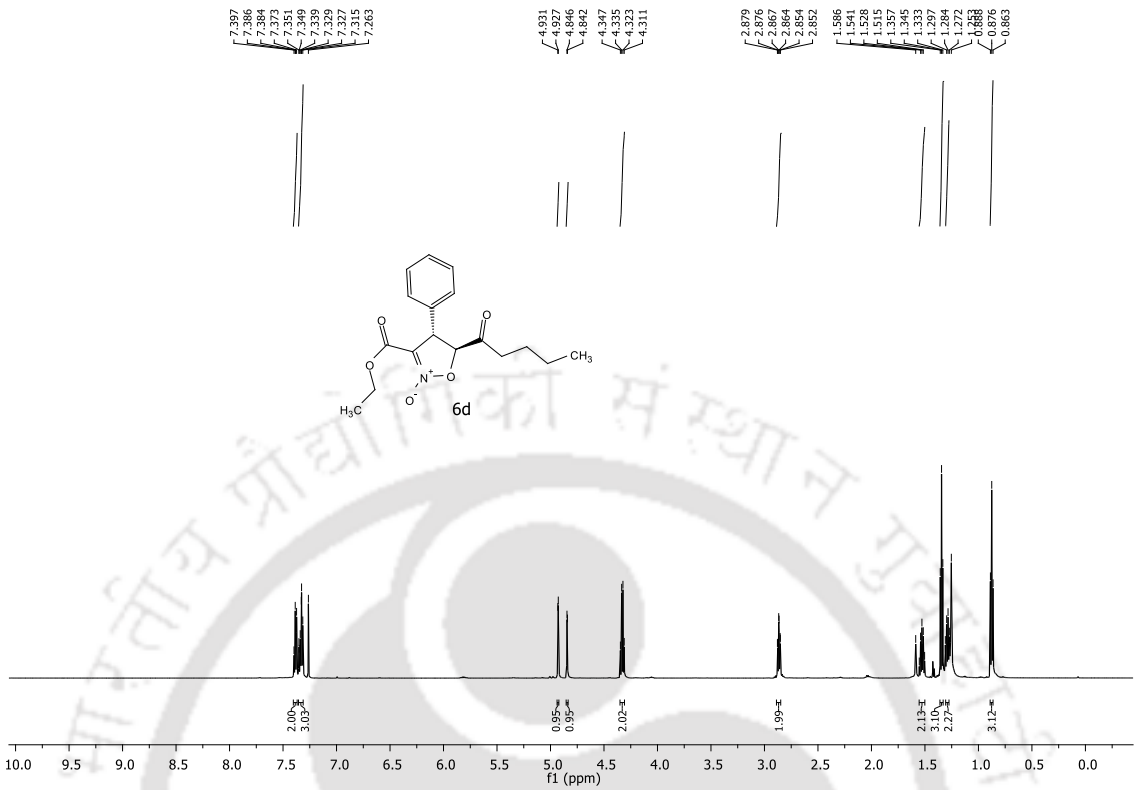


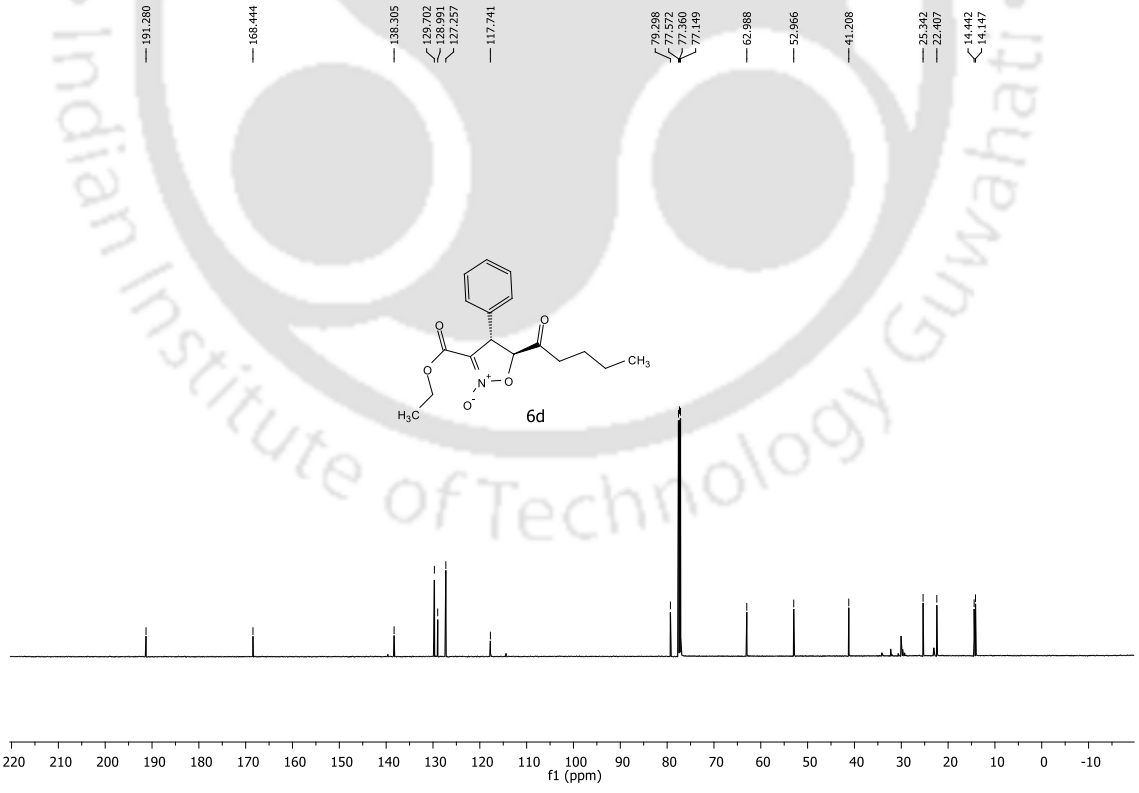


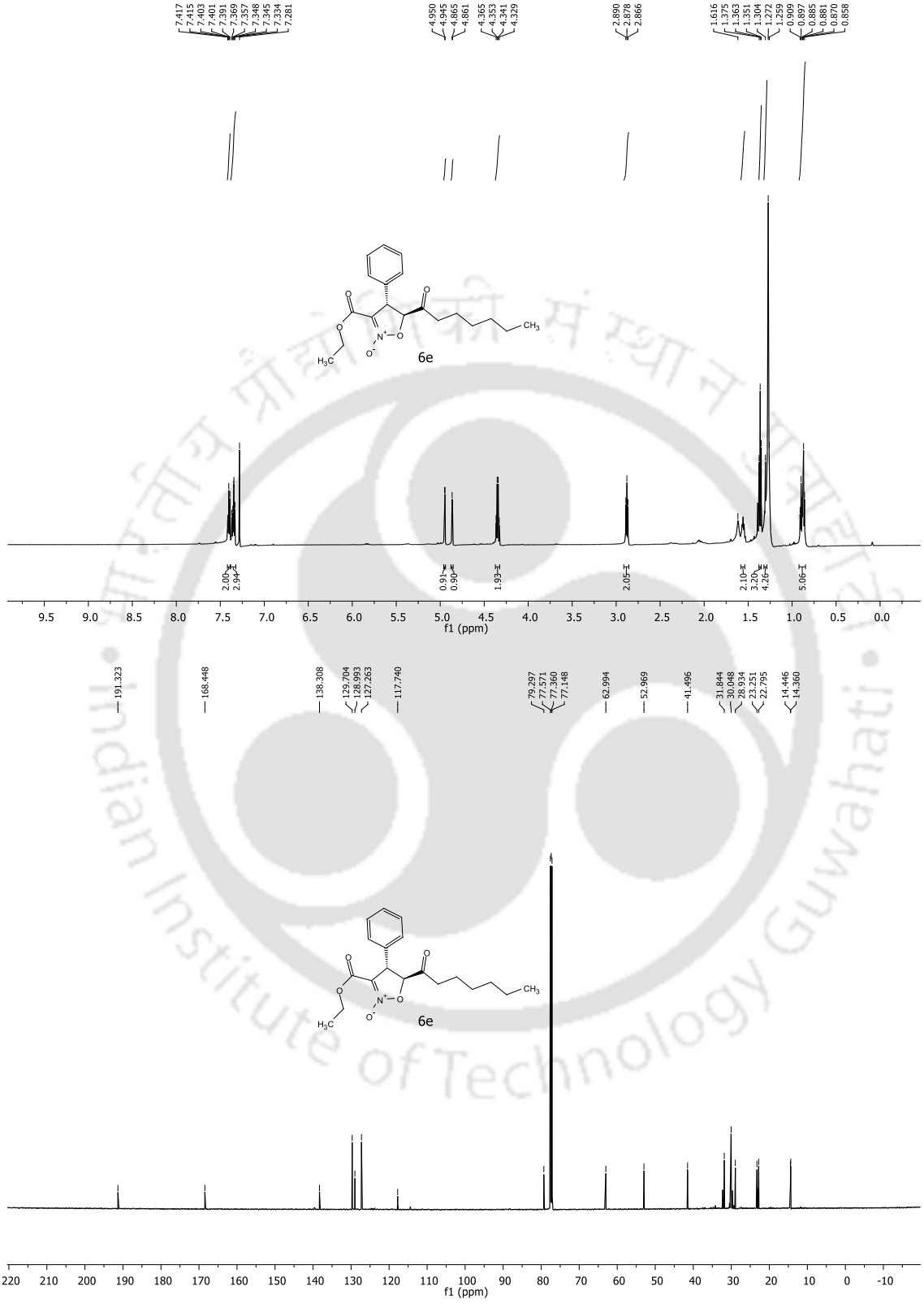


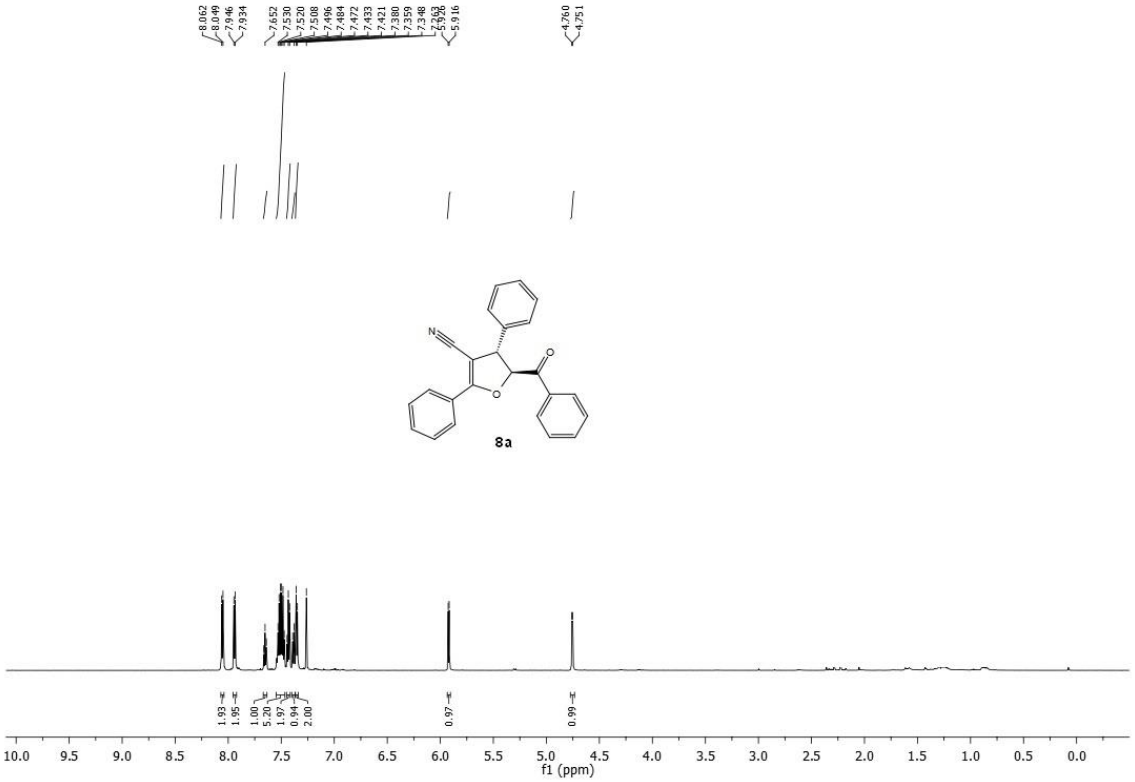


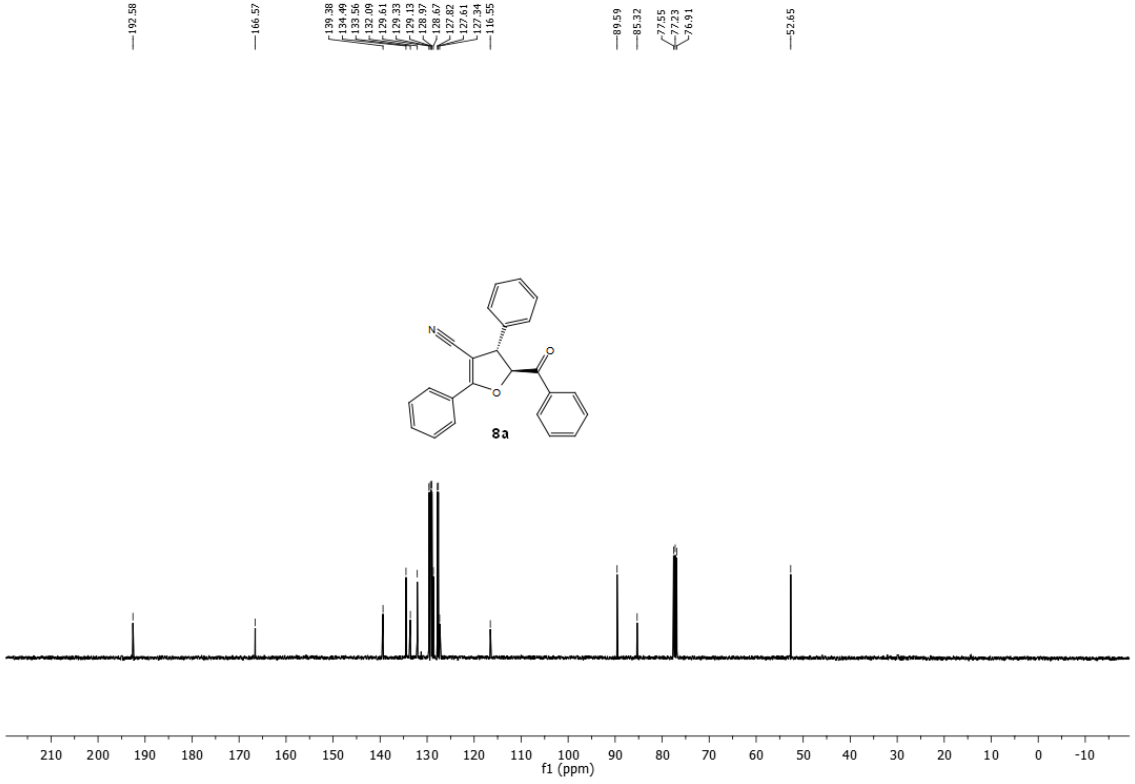


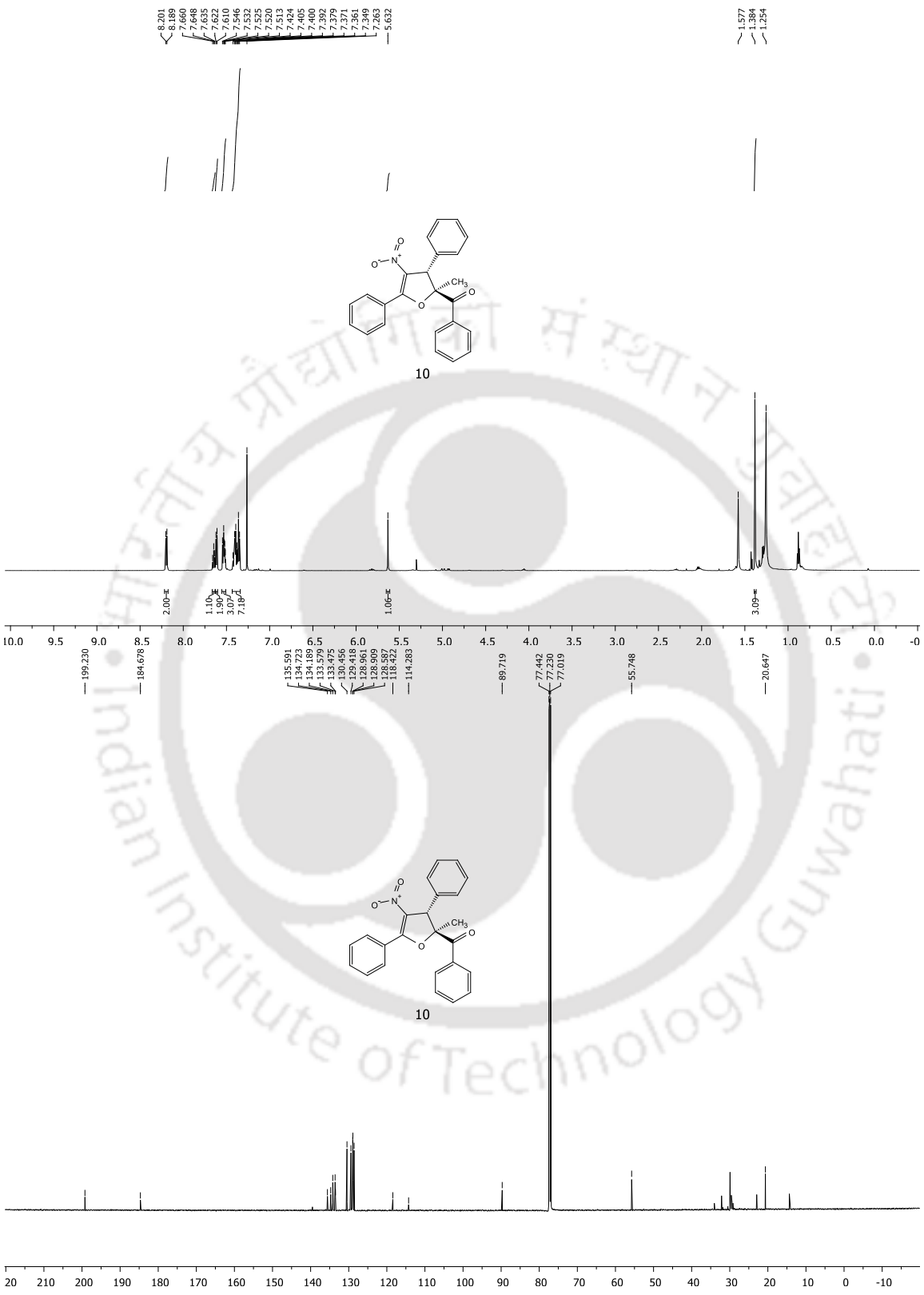


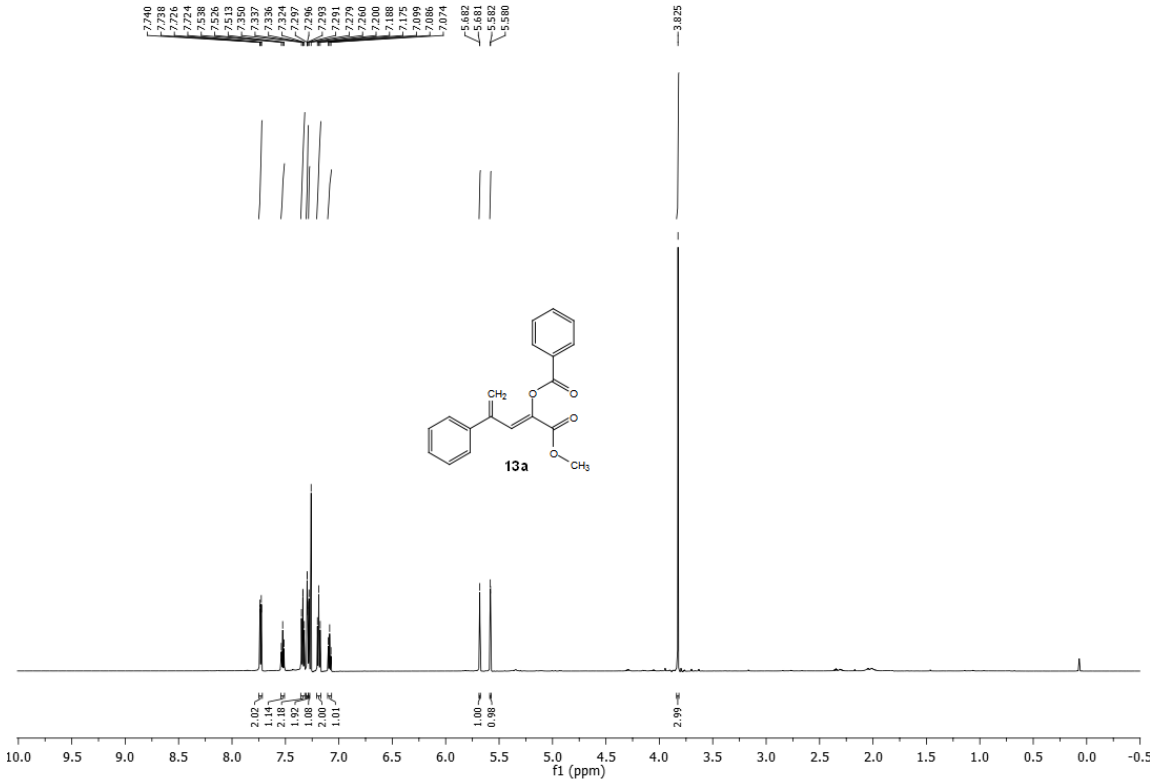


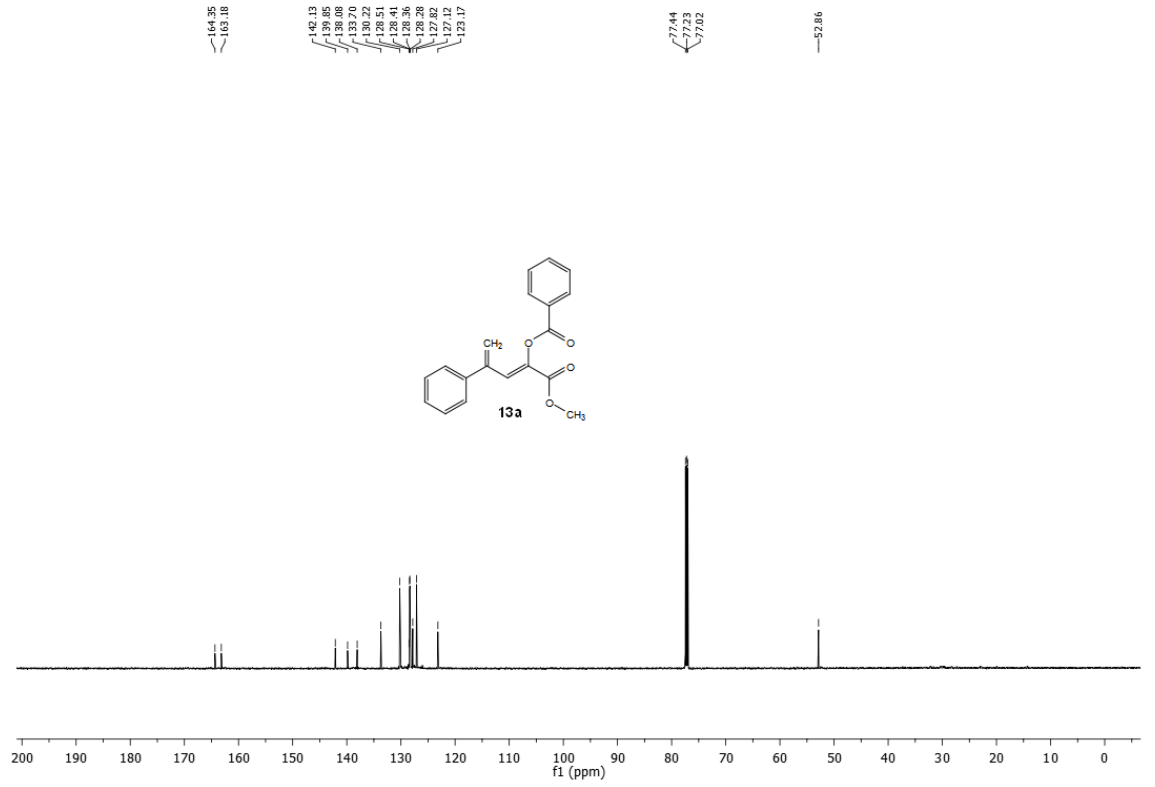












Thesis Conclusion

Importantly, the thesis describes synthesis of various heterocyclic compounds without any transition metal or external oxidant. In chapter 1, importance of heterocyclic molecules and their synthesis by different strategies have been discussed. Chapter 2 highlights synthesis of heterocycles *via* aerobic oxidation of 2-hydroxyacetophenones. Catalytic amount of base/acid has been added for continuation of some reaction but has no role in the oxidation process. Chapter 3 represents an unusual aerobic hydrolysis-cascade reaction for the synthesis of *N*-formyl-2-benzoyl benzothiazolines, 2-substituted benzothiazoles and disulfides. The reaction proceeds *via* base mediated aerobic formation of iminium ion intermediate. Chapter 4 describes metal-free highly diastereoselctive [3+2] cycloaddition reaction between *N*-phenacylbenzothiazolium bromides and prochiral cyclopentene-1,3-diones which results a tetracyclic product with five stereogenic centres. Interesting fused heterocyclic molecules have been synthesized from the tetracyclic product. A preliminary catalytic asymmetric approach has also been documented. Lastly, chapter 5 demonstrates base mediated denitration reactions of nitroketones. We have been able to synthesize isoxazoles in regioselective manner, isoxazoline *N*-oxides and dihydrofurans with excellent diastereomeric ratio and *β*,*γ*-unsaturated diesters.

List of publications and presentations

1. $^{n}Bu_4NI$-Catalyzed α-Benzoxylation of Ketones with Terminal Aryl Alkenes, Buddhadeb Mondal, **Subas Chandra Sahoo** and Subhas Chandra Pan*, *Eur. J. Org. Chem.* **2015**, 3135.
2. Organocatalytic Asymmetric Michael-Hemiacetalization Reaction Between 2-Hydroxyacetophenones and Enals: A Route to Chiral β,γ-Disubstituted γ-Butyrolactones, Megha Balha, Buddhadeb Mondal, **Subas Chandra Sahoo** and Subhas Chandra Pan*, *J. Org. Chem.* **2017**, *82*, 6409.
3. Direct Aerobic Oxidative Reactions of 2-Hydroxyacetophenones, **Subas Chandra Sahoo**, Utpal Nath and Subhas Chandra Pan*, *Eur. J. Org. Chem.* **2017**, 44434.
4. Diastereoselective Desymmetrization of Prochiral Cyclopentenediones via Cycloaddition Reaction with *N*-Phenacylbenzothiazolium Bromides, **Subas Chandra Sahoo**, Mayank Joshi and Subhas Chandra Pan*, *J. Org. Chem.* **2017**, *82*, 12763.
5. Catalytic Enantioselective Synthesis of 3,4,5-Trisubstituted Isoxazoline *N*-Oxides and Regioselective Synthesis of 3,4,5-Trisubstituted Isoxazoles, **Subas Chandra Sahoo** and Subhas Chandra Pan*, *Eur. J. Org. Chem.* **2019**, 1385.
6. DBU-Mediated Addition of α-Nitroketones to α-Cyano-enones and α,β-Unsaturated α-Ketoesters: Synthesis of Dihydrofurans and Conjugated Dienes, **Subas Chandra Sahoo**, Rajendra Maity and Subhas Chandra Pan*, *ACS Omega.* **2019**, *4*, 2792.
7. Organocatalytic Asymmetric Michael-Acyl Transfer Reaction of α-Nitroketones with 2-Hydroxybenzylidene Ketones, Rajendra Maity, **Subas Chandra Sahoo** and Subhas Chandra Pan*, *Eur. J. Org. Chem.* **2019**, 2297.
8. Synthesis of *N*-Formyl-2-Benzoyl Benzothiazolines, 2-Substituted Benzothiazoles and Symmetrical Disulfides from *N*-Phenacylbenzothiazolium Bromides, **Subas Chandra Sahoo** and Subhas Chandra Pan*, *Org. Lett.* **2019**, *21*, 6208.
9. α-Nitro-α,β-Unsaturated Ketones: An Electrophilic Acyl Transfer Reagent in Catalytic Asymmetric Friedel-Crafts and Michael Reactions, Chandrakanta

Parida, Rajendra Maity, **Subas Chandra Sahoo** and Subhas Chandra Pan*, *Org. Lett.* **2019**, *21*, 6700.

10. Organocatalytic Asymmetric Domino [3+2]-Cycloaddition-Acyl Transfer Reaction between Azomethine Ylides and *α*-Nitro-*α*,*β*-Unsaturated Ketones, **Subas Chandra Sahoo** and Subhas Chandra Pan*, *manuscript under preparation*.

Presentations

- National Conference on Frontiers in Chemical Sciences (**FICS-2016**), December 8-10, 2016, Indian Institute of Technology Guwahati, India (Poster presentation).
- International Conference on Frontiers in Chemical Sciences (**FICS-2018**), December 6-8, 2018, Indian Institute of Technology Guwahati, India (Poster presentation).
- International Conference on XV J-NOST Conference for Research Scholars (**J-NOST-2019**), October 18-21, 2019, University of Delhi, Delhi, India (Poster presentation).