Studies Toward 1,3-Enyne Cyclization for the Synthesis of Functionalized Pyrroles, Pyrazoles and Thiophenes

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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Dedicated To

My Family Members and

Dr. P. Jaisankar

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati   Bharathiraja G

August 2016

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Department of Chemistry

CERTIFICATE

This is to certify that Mr. Bharathiraja G has been working under my supervision since July 2011. I am forwarding his thesis entitled “Studies Toward 1,3-Enyne Cyclization for the Synthesis of Functionalized Pyrroles, Pyrazoles and Thiophenes” being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
August 2016

Prof. Tharmalingam Punniyamurthy
Supervisor

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Finally, I want to convey my sincere gratitude to my family members for their sustained help and encouragement in all my academic ventures. I feel deeply indebted to them for whatever I have achieved so far.

Bharathiraja G

List of Abbreviations

Ac	acetyl
Bz	benzoyl
Bn	benzyl
Bu	butyl
coe	cyclooctene
Cp	cyclopentadienyl
DAN	diazoacetonitrile
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DME	1,2-dimethoxyethane
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron wthdrawing group
FT-IR	fourier transform infrared spectroscopy
HMDS	hexamethyldisilazane
HRMS	high-resolution mass spectrometry
ICl	iodine monochloride
m/z	mass to charge ratio
mp	melting point
Me	methyl
MW	microwave
MS	molecular sieves
NBS	*N*-bromosuccinimide

NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolidone
DIPEA	*N*,*N*-diisopropylethylamine
DMEDA	*N*,*N'*-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
NMR	nuclear magnetic resonance
Oct	octanoate
Phen	phenanthroline
Pr	propyl
Ts	*p*-toluenesulfonyl
rt	room temperature
Boc	*tert*-butoxycarbonyl
TBAF	tetrabutylammonium fluoride
Bu_4NI	tetrabutylammonium iodide
HBF_4	tetrafluoroboric acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TCCA	trichloroisocyanuric acid
PCy_3	tricyclohexylphosphine
Et_3N	triethylamine
$HNTf_2$	triflimide
TFA	trifluoroacetic acid
TMS	trimethylsilyl
TIPS	triisopropylsilyl
PPh_3	triphenyphosphine
UV	ultraviolet

Abbreviations for intensities of ^{1}H-NMR signals

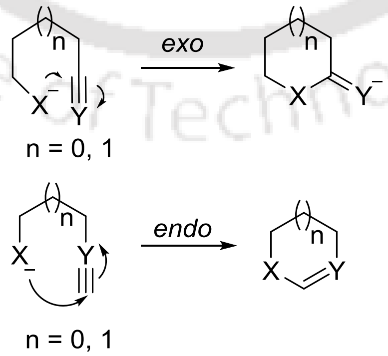
s	singlet
d	doublet
dd	doublet of doublet
dt	doublet of triplet
coe	cyclooctene
MHz	megahertz
t	triplet
q	quartet
m	multiplet
Hz	hertz

Abstract

The thesis contains four chapters. The first chapter describes general introduction of cyclization of alkynes for the synthesis of functionalized heterocycles. The second chapter deals with the synthesis of tetra- and penta-substituted pyrroles *via* domino iodine-promoted cyclization of 1,3-enynes with amine. The third chapter focuses on Cu-catalyzed inter/intramolecular cyclization of 1,3-enynes with amine for the synthesis of biologically important functionalized pyrroles and pyrazoles. The fourth chapter demonstrates base promoted domino synthesis of library of thiophene analogues from 1,3-enynes and 1,4-dithine-2,5-diol.

1. Cyclization of Alkynes to the Synthesis of Heterocycles

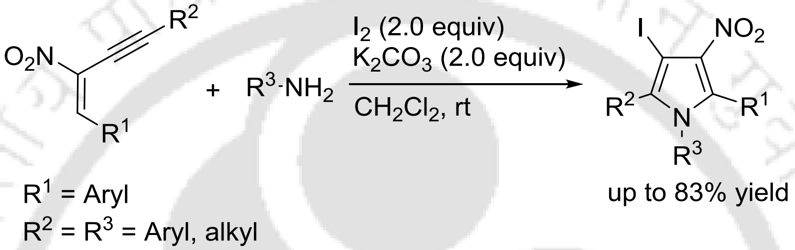
Heterocycles are important class of structural scaffolds in organic chemistry. They are abundant in natural as well as in synthetic products finding wide applications in drug discovery and material sciences. Due to their importance, the development of effective synthetic routes from the readily available starting materials with high selectivity and broad substrate scope are desirable. Iodine-promoted and metal-catalyzed cyclization of alkynes are found be a powerful synthetic tool for the construction of diverse heterocyclic compounds such as pyrroles, pyrazoles, furans, thiophenes, selenophenes, indoles, benzothiophenes, benzoselenophenes and tellurophenes. The reaction of alkynes containing heteroatom with electrophile/metal sources followed by an intramolecular heteroatom nucleophilic attack on the cationic intermediate *via* *endo*- or *exo-dig* cyclization depends on the chain length (Scheme 1). The chapter covers the recent development of the cyclization of alkynes.



Scheme 1. *Exo/Endo-dig* Cyclization

2. Iodine-Promoted 5-*Endo-dig* Cyclization of 1,3-Enynes with Amines: Domino Synthesis of Functionalized Pyrroles

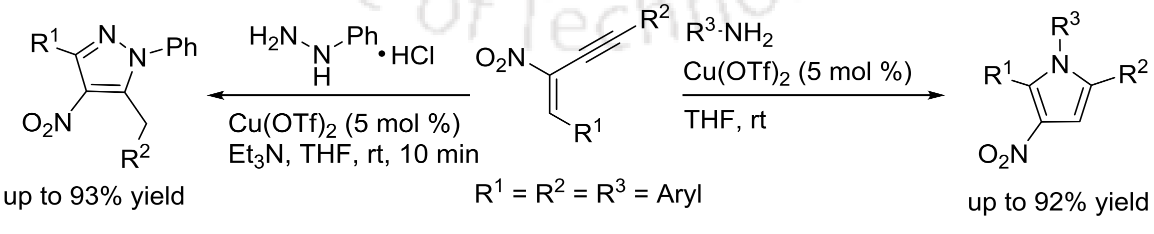
Pyrroles are widely distributed in nature and find numerous applications in the field of material, biological and pharmaceutical sciences. Herein we present a new and milder protocol for synthesis of tetra- and penta-substituted pyrroles from 1,3-enynes with amine using I_2 *via* a domino aza-Michael addition, iodocyclization and oxidative aromatization processes (Scheme 2). The protocol provides a potential route for the synthesis of pentasubstituted pyrroles.



Scheme 2. Synthesis of Functionalized Pyrroles

3. Cu-Catalyzed Cyclization of 1,3-Enynes with Amines and Hydrazines: Synthesis of Substituted Pyrroles and Pyrazoles

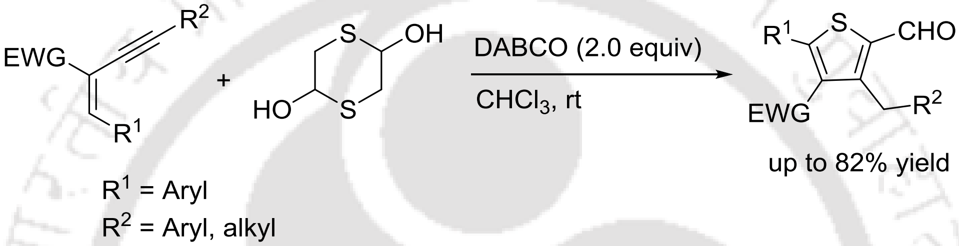
In this chapter, we present an efficient route for the synthesis of tetrasubstituted pyrroles from 1,3-enynes with amines using copper-catalyzed domino aza-Michael addition, cyclization and oxidative aromatization reaction sequence at room temperature (Scheme 3). This protocol is efficient, atom economical, tolerates an array of functionality and substantial steric hindrance. This protocol also provides a new avenue to construct medicinally significant tetrasubstituted pyrazole analogues in high yields.



Scheme 3. Synthesis of Tetrasubstituted Pyrroles and Pyrazoles

4. Synthesis of Functionalized Thiophenes from 1,3-Enynes with Mercaptoacetaldehyde

Functionalized thiophenes are widely found in bioactive natural products and pharmaceuticals. In this chapter, we present DABCO-mediated construction of tetrasubstituted thiophenes *via* the domino Michael addition, 5-*exo-dig* carboannulation and oxidation from 1,3-enynes and mercaptoacetaldehyde at room temperature (Scheme 4). This reaction affords the advantages of the direct introduction of the aldehyde and nitro/keto/ester functionalities in the thiophene ring with broad substrate scope.



Scheme 4. Synthesis of Highly Functionalized Thiophenes

Contents

Cyclization of Alkynes to the Synthesis of Heterocycles

Heterocycles are important class of structural scaffolds in organic chemistry. There are many heterocyclic compounds are well known and this number is still growing rapidly due to their synthetic utilities. Heterocycles are abundant in nature as well as in synthetic products and widely find applications in drug discovery, vitamins, bio and medicinally active compounds including antimalarial,[1a-c] antimicrobial,[1d] antibiotic,[1e] anticancer,[1f] anti-inflammatory,[1g-h] antidepressant,[1i] anti-HIV,[1j-k] antifungal,[1l] antibacterial,[1m] antiviral,[1n] herbicidal,[1o] antidiabetic,[1p] and insecticidal agents.[1q] In addition, they are utilized as building blocks in material sciences.[1r] Due to these importance, the development of new approaches for the construction of heterocyclic compounds using the readily accessible simple substrates with less number of steps, high selectivity, more substrate scope and easy purification procedure are still highly desirable. Consequently, electrophile promoted and metal-catalyzed cyclizations of alkynes are found be a powerful synthetic strategy for the construction of diverse heterocyclic compounds such as pyrroles, pyrazoles, furans, thiophenes, selenophenes, indoles, benzofurans, benzothiophenes, benzoselenophenes and tellurophenes. The reaction of alkynes containing heteroatom with electrophile/metal source followed by an intramolecular heteroatom nucleophilic attack on the cationic intermediate *via endo*- or *exo-dig* cyclization depends on the chain length (Scheme 1). The existence of cyclic structure in the rudimentary framework of numerous complex and biologically fascinating molecules has made their creation an essential method in synthetic organic chemistry. Therefore, ring-forming procedures have gathered the consideration of synthetic chemists for several years. A concise set of guidelines, which define the relative ease of ring formations, has been called as Baldwin's ring closure rules and historically served the most important device in the development of synthetic organic chemistry particularly in the field of cyclization of alkynes. Baldwin's rule classifies the cyclization processes by the following three norms (e.g., 5-*exo-dig*, Figure 1), first, '5' indicate the size of the ring formation (number of atom contributes in the ring), second is '*exo*' which describes the nature of breaking bond is towards outside the ring and third '*dig*' indicates hybridized state that affords ring closing reactions (*dig* = sp, *trig* = sp^2, *tet* = sp^3).

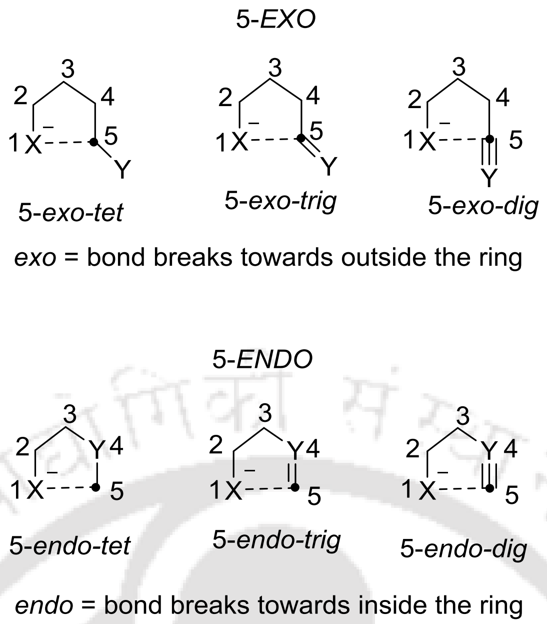
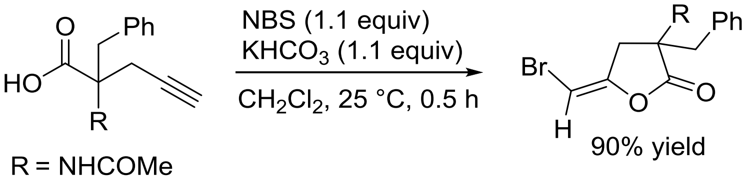


Figure 1. 5-Membered Ring Closure Baldwin Rule

Due to the rising prominence and efficacy of heterocycles in the field of organic chemistry, new notable findings and applications have been reported. The objective of this chapter is to demonstrate the importance of the cyclization reactions in the field of heterocycle synthesis. In this section, we present the synthetic methodologies based on electrophile mediated/metal catalyzed cyclization of alkynes, which include the coordination of electrophile/metal with triple bond of alkynes to form π-complexes that can readily undergo cyclization by intramolecular nucleophilic attack of the heteroatom to furnish the target heterocyclic products. This synthetic strategy has been used to prepare enormous oxygen, nitrogen, sulphur, selenium and tellurium containing heterocyclic compounds which are divided into the reactions involving electrophile promoted cyclization of alkyne and metal catalyzed cyclization of alkynes.

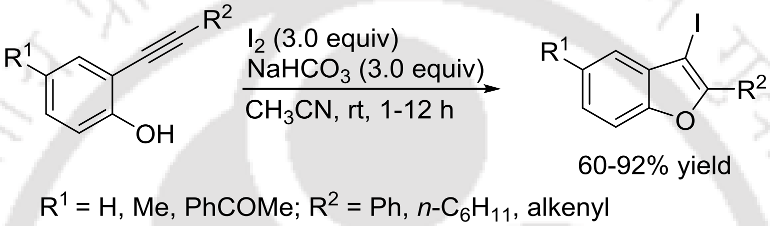
1.1 Electrophile Promoted Cyclization of Alkynes

Katzenellenbogen and co-workers reported NBS-promoted halolactonization process, which involves the conversion of 4-pentynoic acid into a (*E*)-N-(3-benzyl-5-(bromomethylene)-2-oxotetrahydrofuran-3-yl) acetamide in 90% yield (Scheme 1).[2a]



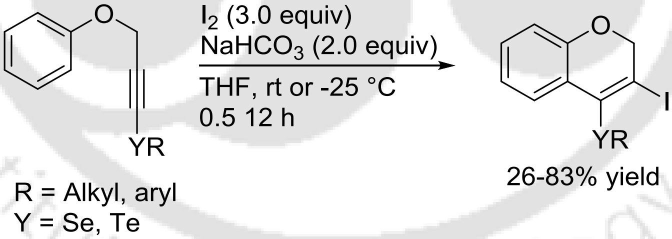
Scheme 1

5-*Endo-dig*-iodocyclization of *o*-alkynylphenols is reported to produce functionalized 2-substituted-3-iodobenzofurans using molecular iodine. The products would be useful for further elaboration to complex derivatives *via* cross-coupling reactions (Scheme 2).[2b]



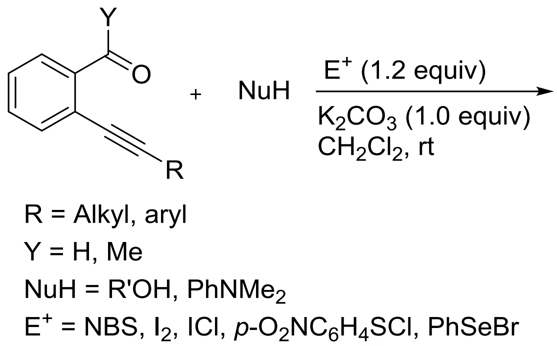
Scheme 2

Zeni and co-workers reported the synthesis of 3-iodo-4-chalcogen-2*H*-benzopyrans by intra molecular iodocyclization of propargyl aryl ethers, bearing the chalcogen group under mild reaction conditions (Scheme 3).[2c]



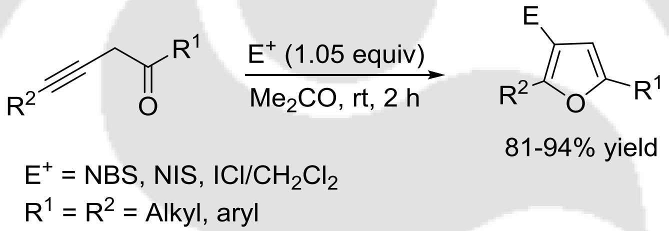
Scheme 3

Larock and co-workers demonstrated the synthesis of oxygen containing heterocycles by the reaction of *o*-(1-alkynyl)-substituted arene carbonyl compounds with various alcohols or *N*-centered nucleophiles in presence of an appropriate electrophile under mild reaction conditions (Scheme 4).[2d]



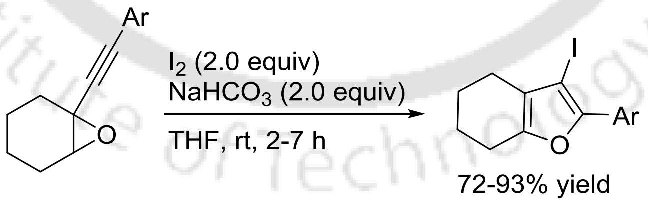
Scheme 4

Dembinski and co-workers reported a facile route to synthesize 3-halo-2,5-diarylfurans via 5-*endo-dig* electrophilic cyclization of 1,4-diaryl but-3-yn-1-ones with NBS, NIS or ICl under base free conditions (Scheme 5).[2e]



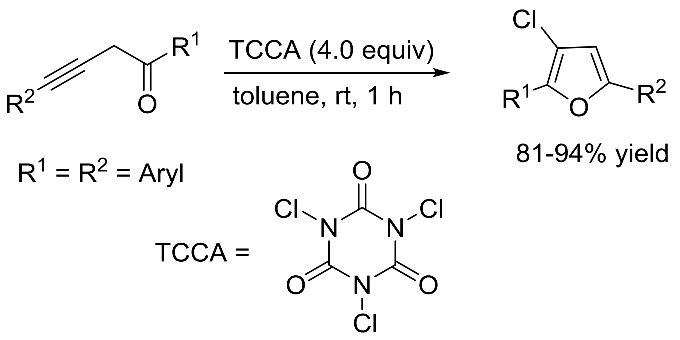
Scheme 5

Liu and co-workers designed an efficient synthesis of substituted iodofurans by I_2 mediated electrophilic cyclization of propargylic oxiranes. Consequently, functionalization of iodofuran to complex derivatives can be achieved using cross-coupling reactions (Scheme 6).[2f]



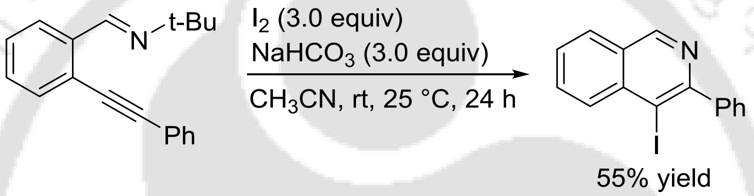
Scheme 6

Dembinski and co-workers found that 3-chloro furan can be derived using 5-*endo-dig* chlorocyclization of propargylic ketones with trichlorostriazinetrione under base free conditions. The utility of 3-chlorofuran is further explored by Suzuki–Miyaura coupling reactions (Scheme 7).[2g]



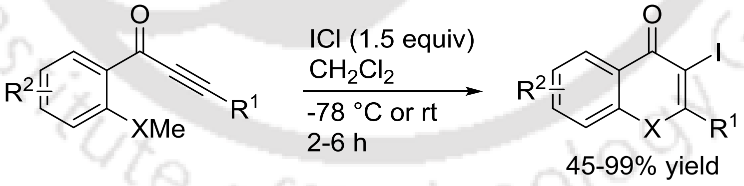
Scheme 7

Intramolecular cyclization of iminoalkynes is described with molecular iodine for the synthesis of substituted isoquinolines under mild reaction conditions (Scheme 8).[2h-i]



Scheme 8

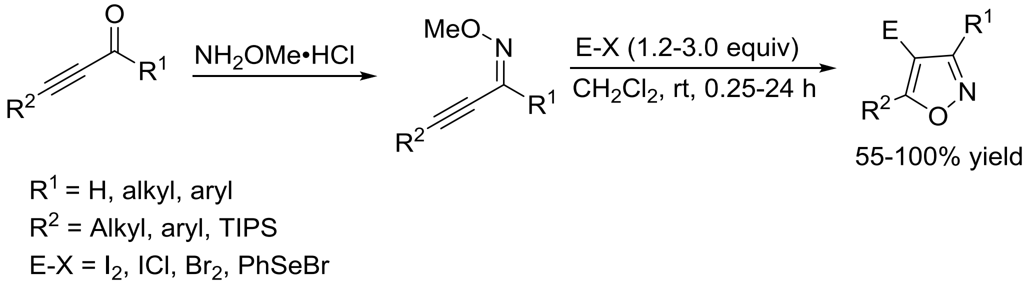
ICl-promoted intramolecular cyclization of heteroatom-substituted alkynones affords a novel approach to various 3-iodochromones and their analogues. This method features high functional group tolerance. The resulting 3-iodochromones can be converted into complex molecules using cross-coupling reactions (Scheme 9).[2j]



X = O, S, NMe
R^1 = Alkyl, aryl, TMS
R^2 = H, F, Br, MeO, NO_2

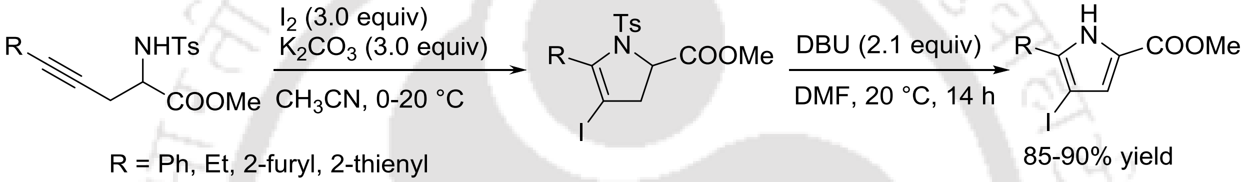
Scheme 9

Larock and co-workers disclosed rapid access to a variety of 4-halo(seleno)isoxazoles from 2-alkyn-1-one *o*-methyl oximes with ICl, I_2, Br_2 or PhSeBr under mild reaction conditions (Scheme 10).[3a-b]



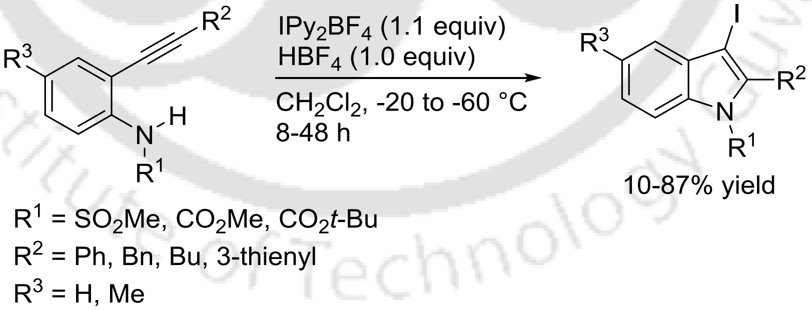
Scheme 10

Knight and co-workers reported 5-*endo-dig* iodocyclization of homopropargylic sulfonamides to afford iododihydropyrroles, which readily undergo elimination of sulfinic acid using DBU to yield the substituted pyrrole derivatives (Scheme 11).[3c]



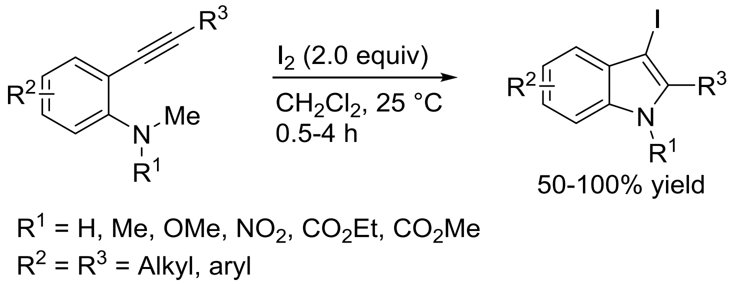
Scheme 11

Barluenga and co-workers achieved facile access to valuable 2-substituted-3-iodoindoles by intramolecular iodocyclization of readily available *N*-protected *o*-(alkynyl)anilines upon reaction with IPy$_2$BF$_4$ as iodinating agent (Scheme 12).[3d]



Scheme 12

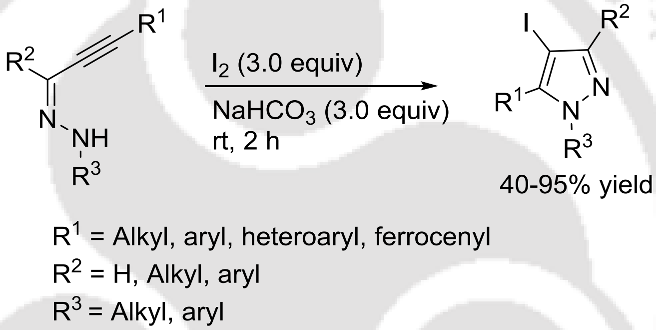
Larock and co-workers reported Sonagashira cross-coupling of *N*,*N*-dialkyl-*o*-iodoanilines with terminal alkynes to furnish *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines, which can be utilized for the synthesis of 3-iodoindoles using iodine-promoted electrophilic cyclization. The resulting 3-iodoindole can serve as valuable precursor in cross-coupling reactions (Scheme 13).[3e-g]



R^1 = H, Me, OMe, NO_2, CO_2Et, CO_2Me
R^2 = R^3 = Alkyl, aryl

Scheme 13

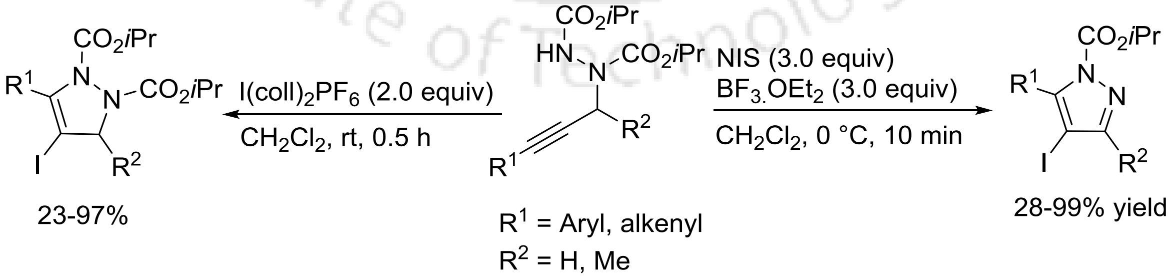
The reaction of hydrazines with propargyl aldehyde or ketone affords *α,β*-alkynic hydrazones, which can further undergo 5-*endo-dig* electrophilic cyclization using stoichiometric molecular iodine to yield 4-iodopyrazoles (Scheme 14).[3h]



R^1 = Alkyl, aryl, heteroaryl, ferrocenyl
R^2 = H, Alkyl, aryl
R^3 = Alkyl, aryl

Scheme 14

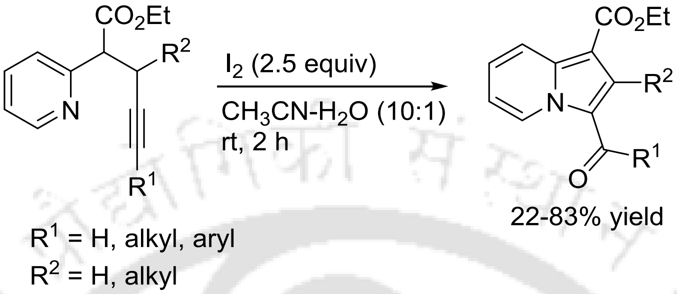
Wada and co-workers discovered reagent-controlled iodocyclization for the synthesis of dihydropyrazoles and pyrazoles from common propargylic hydrazides. This is the first report available in controlling the oxidative aromatization in iodocyclization for heterocycle synthesis and this method greatly utilizes the dual nature of iodine (Scheme 15).[3i]



R^1 = Aryl, alkenyl
R^2 = H, Me

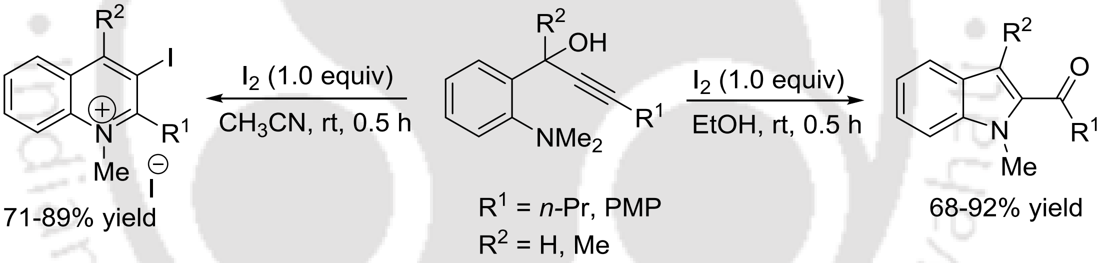
Scheme 15

Kim and co-workers developed an effective method to synthesize 3-acylated indolizine using iodine-promoted hydrative cyclization, which involves 5-*exo-dig* cyclization, deprotonation, incorporation of iodo group, deprotonation and subsequent replacement of the diiodo group using H_2O (Scheme 16).[3j]



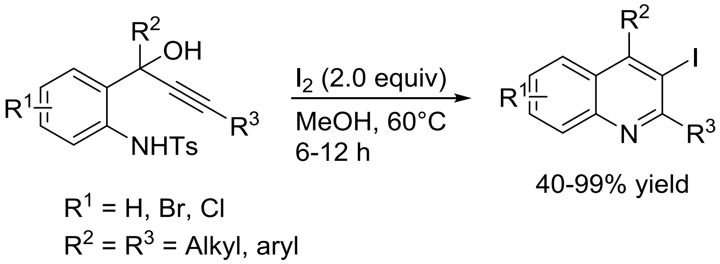
Scheme 16

Endo/*exo-dig* cyclization is found to be an efficient route for the synthesis of heterocyclic compounds such as indoles, quinolines and quinolinones using molecular iodine (Scheme 17).[4a]



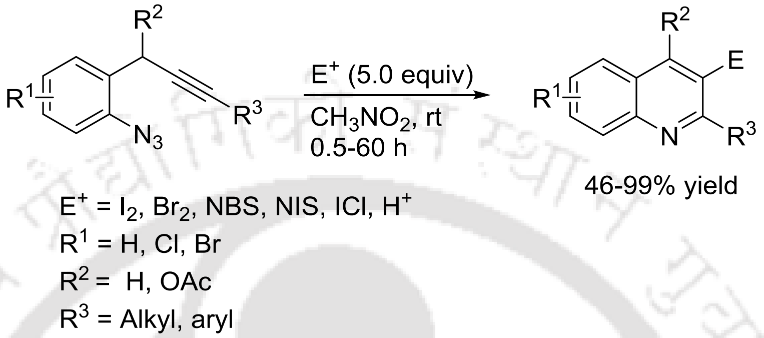
Scheme 17

Liang and co-workers designed 6-*endo-dig* iodocyclization of 2-tosylaminophenylprop-1-yn-3-ols to furnish substituted 3-iodoquinolines having dissimilar alkyl and aryl moieties using molecular iodine. The protocol is regioselective and the resulting 3-iodoquinolines can be further converted into complex derivatives using coupling partners (Scheme 18).[4b]



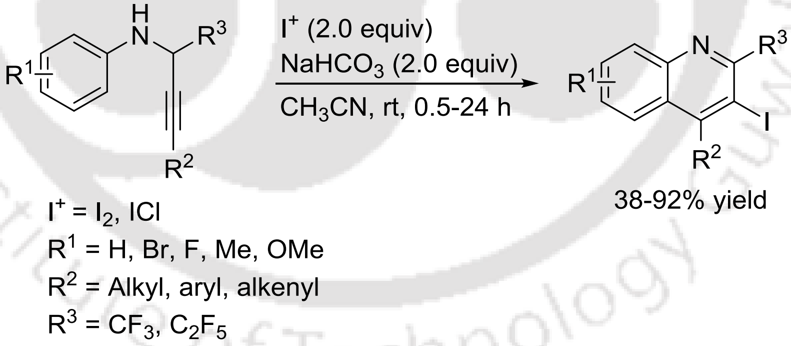
Scheme 18

The synthesis of substituted quinolines is reported *via* intramolecular electrophilic cyclization of 1-azido-2-(2-propynyl)benzene using various electrophilic sources such as I_2, Br_2, ICl, NBS, NIS and $HNTf_2$ under mild conditions (Scheme 19).[4c]



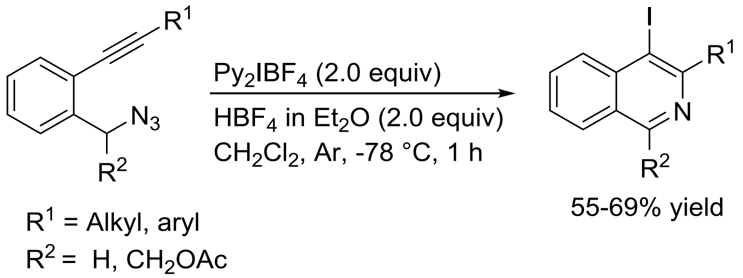
Scheme 19

Likhar and co-workers demonstrated the synthesis of 2-perfluoroalkyl-3-iodoquinolines from iodocyclization of perfluoroalkyl propargyl amines using I_2 or ICl. The substrates can be readily prepared using Sonogashira coupling of imidoyl iodides with alkynes followed by reduction with $NaBH_3CN$ (Scheme 20).[4d]



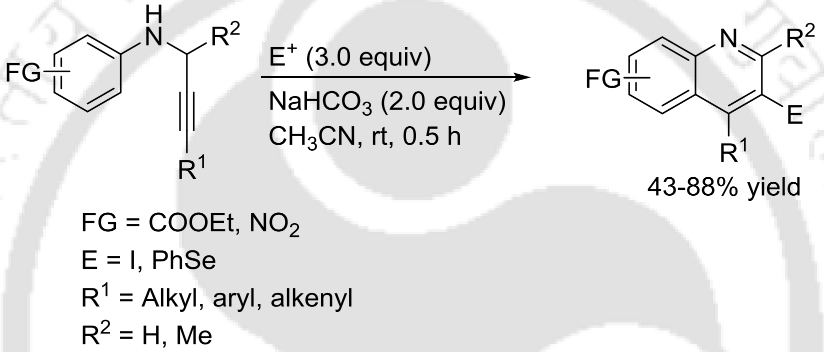
Scheme 20

2-Alkynyl benzyl azides can be readily converted into 1,3,4-trisubstituted isoquinolines using iodine source. Depending on the nature of the substrate, I_2, Barluenga reagent (Py_2IBF_4/HBF_4), or NIS is employed as I^+ source (Scheme 21).[4e]



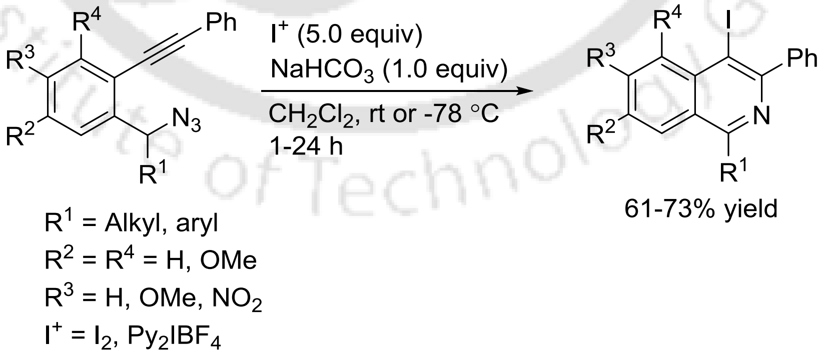
Scheme 21

Larock and co-workers revealed a prominent way for the synthesis of 3-iodo or phenylseleno quinoline derivatives from propargylic anilines with appropriate electrophiles (Scheme 22).[4f]



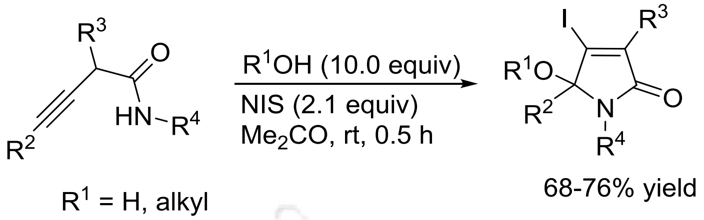
Scheme 22

Yamamoto and co-workers explored the cyclization of 2-alkynyl-1-methylene azide with iodine sources such as iodine, Barluenga reagent (Py_2IBF_4/HBF_4) and NIS to give the substituted 4-iodoisoquinolines in good to high yields (Scheme 23).[4g]



Scheme 23

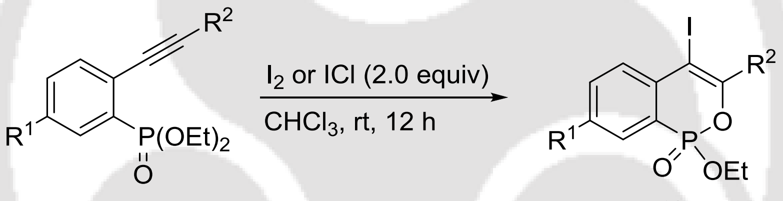
Zard group developed NIS induced 5-*endo-dig* cyclization of carboxamide branched alkynes to give iodopyrrolinones in the presence of oxygen centred nucleophiles (Scheme 24).[4h]



R^1 = H, alkyl
R^2 = R^3 = Aryl
R^4 = Alkyl

Scheme 24

Ding and co-workers showed the iodocyclization of 2-(1-alkynyl)phenylphosphonates to yield 4-iodophosphaisocoumarins with high regioselectivity. This method is the first example of a phosphonate iodocyclization of a C-C triple bond (Scheme 25).[4i-j]

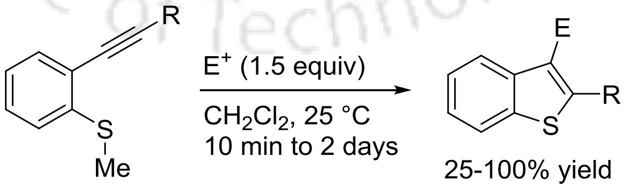


35-93% yield

R^1 = H, Cl, OMe
R^2 = H, alkyl, aryl

Scheme 25

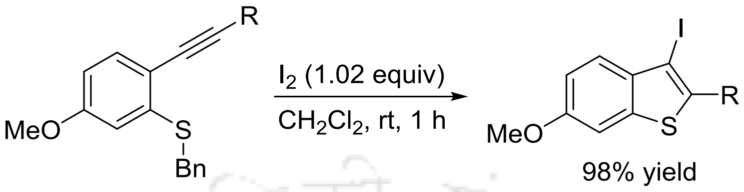
Larock and co-workers showed that 2,3-disubstituted benzothiophenes can be synthesized using Sonagashira cross-coupling of *o*-iodothioanisole with terminal alkynes, followed by electrophilic cyclization (Scheme 26).[5a-b]



E^+ = I_2, Br_2, NBS, *p*-$NO_2C_6H_4SCl$, PhSeCl
R = Ph, *n*-C_8H_{17}, TMS

Scheme 26

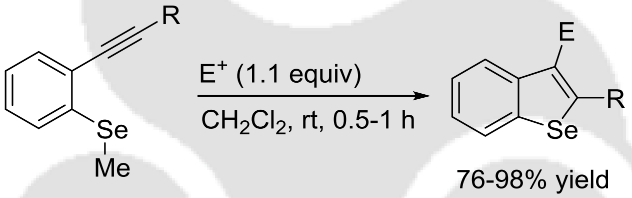
Flyn and co-workers reported 5-*endo-dig* iodocyclization of benzyl *o*-ethynylphenyl sulfides to produce 2,3-disubstituted benzothiophenes using molecular iodine. These iodides can be further converted into complex molecules using cross-coupling reactions (Scheme 27).[5c]



R = p-OMe-C_6H_4

Scheme 27

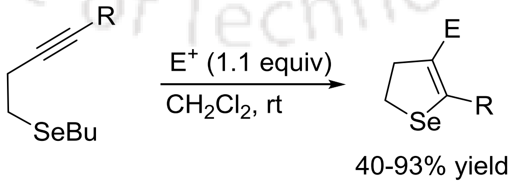
Electrophilic cyclization of 1-(1-alkynyl)-2-(methylseleno)arenes is demonstrated to provide 2,3-disubstituted benzoselenophenes using electrophiles such as Br_2, NBS, I_2, ICl, PhSeCl and PhSeBr (Scheme 28).[5d]



$E^+ = I_2$, ICl
R = Alkyl, vinyl, aryl

Scheme 28

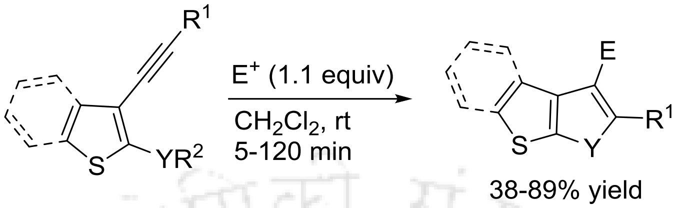
Zeni and co-workers reported the electrophilic cyclization of homopropargyl selenides to provide functionalized 2,3-dihydroselenophenes. I_2, ICl and PhSeBr are used as electrophiles (Scheme 29).[5e]



$E^+ = I_2$, ICl, PhSeBr
R = Alkyl, aryl, MeS, PhSe, BuSe, I, Br

Scheme 29

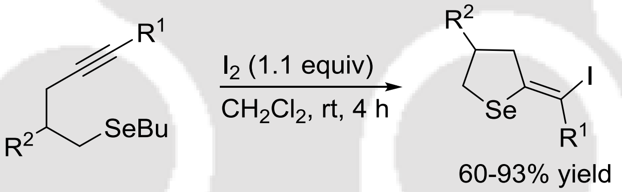
Zeni and co-workers showed the construction of fused 4-iodoselenophene[2,3-*b*]thiophenes by the electrophilic cyclization of 3-alkynylthiophenes with electrophiles such as I_2, ICl, and PhSeBr under mild reaction conditions (Scheme 30).[5f]



Y = Se, Te; E^+ = I_2, ICl, PhSeBr
R^1, R^2 = Alkyl, aryl

Scheme 30

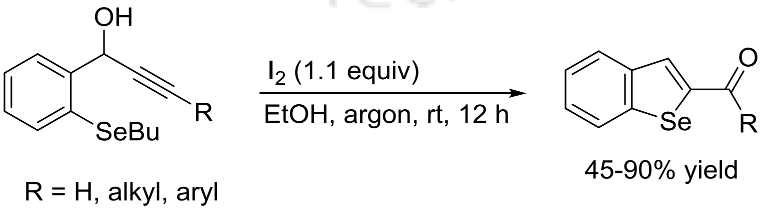
Zeni and co-workers designed the 1-butylseleno-4-alkynes which undergo cyclization to afford tetrahydroselenophene derivatives using molecular iodine under mild reaction conditions. The obtained tetrahydroselenophenes can be further transformed by cyanation, Suzuki and Ullmann cross-coupling reactions (Scheme 31).[5g]



R^1 = Alkyl, aryl, heteroaryl, SeBu, TMS, propargyl alcohol
R^2 = H, OH, OBz

Scheme 31

Zeni and co-workers demonstrated the synthesis of 2-acyl benzoselenophenes by I_2-promoted cyclization of [2-(butylselanyl)phenyl]propynols under mild conditions(Scheme 32).[5h]

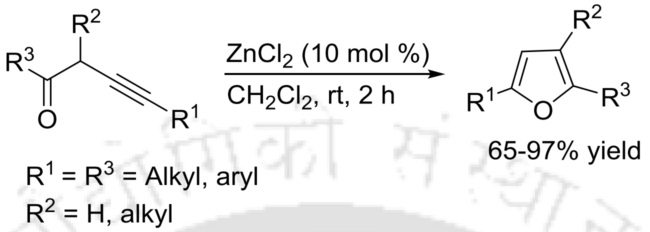


R = H, alkyl, aryl

Scheme 32

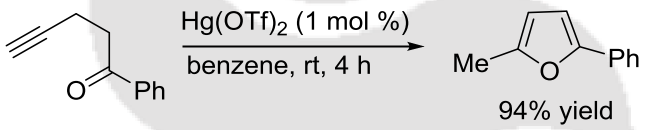
1.2 Transition-Metal-Catalyzed Cyclization of Alkynes

Dembinski and co-workers reported $ZnCl_2$ catalyzed synthesis of trisubstituted furans using 5-*endo-dig* cycloisomerization of the but-3-yn-1-ones at room temperature under base free conditions (Scheme 33).[6a-b]



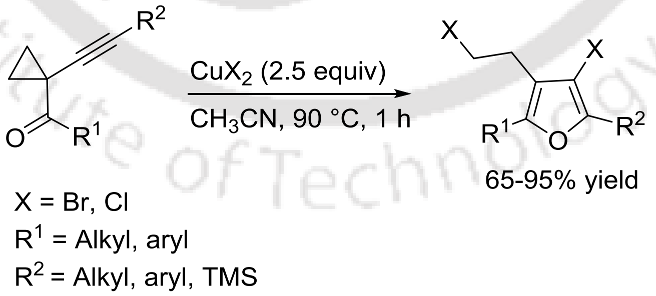
Scheme 33

Nishizawa and co-workers reported $Hg(OTf)_2$-catalyzed synthesis of 2-methylfurans by an 5-*exo-dig* cyclization of 1-alkyn-5-ones with high catalytic turnovers (Scheme 34).[6c]



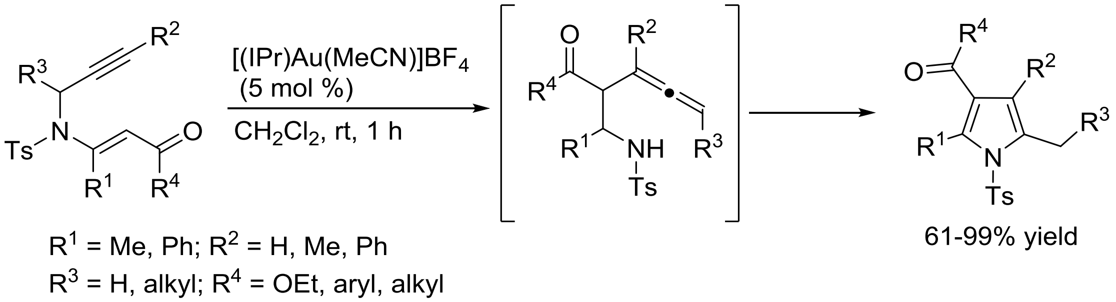
Scheme 34

Fu and co-workers established the synthesis of 3-halofurans using Cu-catalyzed cascade reaction of 1-(1-alkynyl)cyclopropyl ketones. The reaction involves consecutive C–O and C–X bonds formations (Scheme 35).[6d]



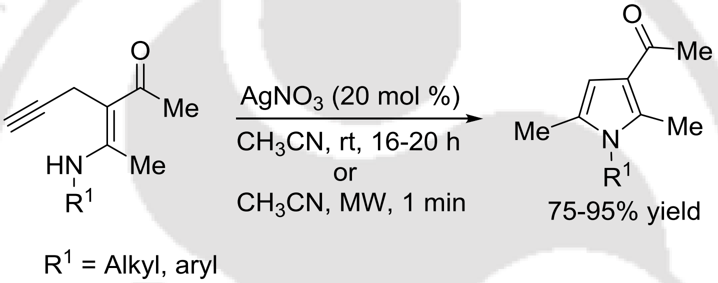
Scheme 35

Saito and co-workers reported Au-catalyzed cyclization of *N*-propargyl β-enaminone derivatives to furnish substituted pyrroles *via* the amino-Claisen rearrangement (Scheme 36).[6e]



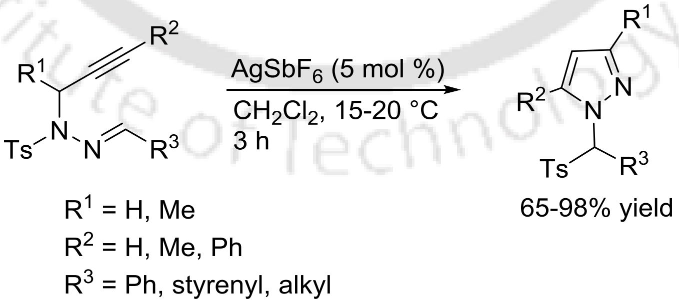
Scheme 36

Dovey and co-workers reported the synthesis of functionalized pyrroles via two-step sequence involving the propargylation of secondary enaminones using n-BuLi and propargyl bromide, followed by $AgNO_3$-catalyzed intramolecular hydroamination (Scheme 37).[6f]



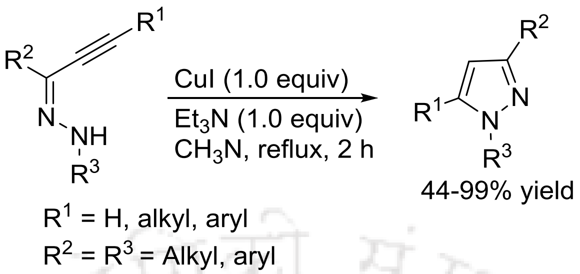
Scheme 37

Ag-catalyzed synthesis of pyrazoles is reported from propargyl *N*-sulfonylhydrazones *via* migration of sulfonyl group. This protocol has been demonstrated for the synthesis of 1,3- and 1,5-disubstituted and 1,3,5-trisubstituted pyrazoles (Scheme 38).[6g]



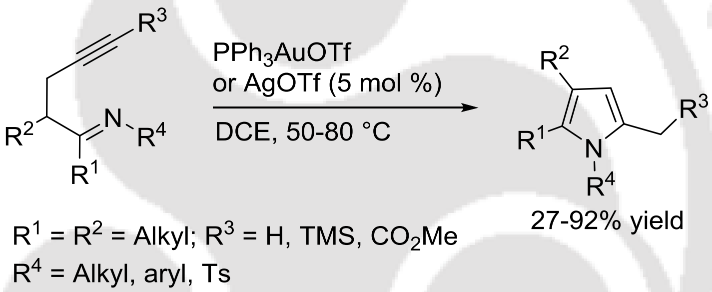
Scheme 38

Zora and co-workers disclosed Cu-catalyzed synthesis of pyrazoles via 5-*endo-dig* cyclization of α,β-alkynic hydrazones in the presence of Et_3N. The reaction tolerates aliphatic, aromatic and ferrocenyl moieties bearing electron-withdrawing and electron-donating substituents (Scheme 39).[6h]



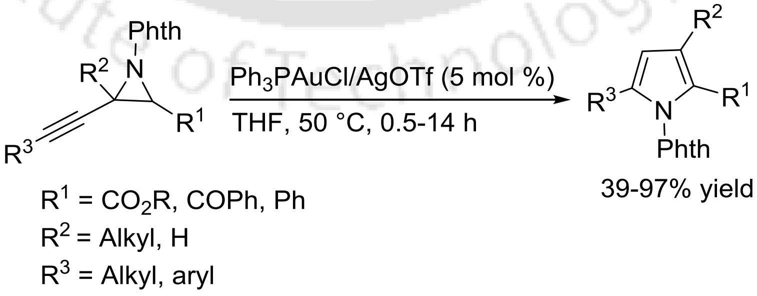
Scheme 39

Tetrasubstituted pyrroles can be synthesized by sequential amination/annulation of 2-propynyl-1,3-dicarbonyl compounds with primary amines in the presence of Au-catalyst (Scheme 40).[6i]



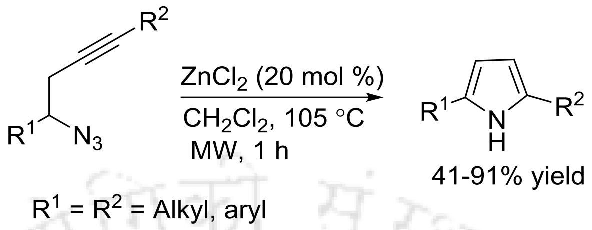
Scheme 40

The synthesis of *N*-phth pyrroles has been developed *via* Au-catalyzed cycloisomerization of *N*-phth alkynylaziridines. The resulting functionalized pyrroles can be further converted into *N*-amino pyrroles or 2-acyl pyrroles which are valuable synthetic intermediates (Scheme 41).[7a]



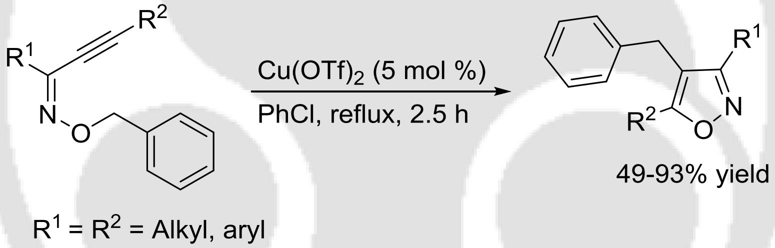
Scheme 41

Dembinski and co-workers showed ligand-free synthesis of substituted pyrroles using 5-*endo-dig* cyclization of 1,4- substituted but-3-yn-1-yl (homopropargyl) azides in the presence of zinc chloride (Scheme 42).[7b]



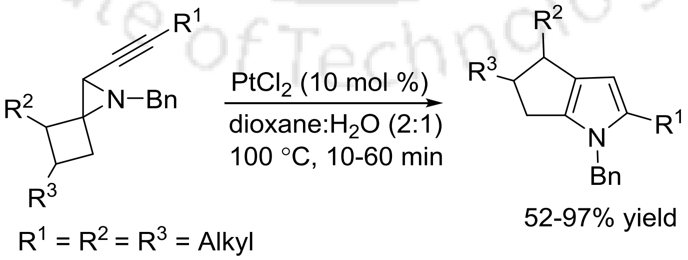
Scheme 42

The synthesis of 3,4,5-trisubstituted isoxazoles to 4-arylmethylisoxazoles is reported by the treatment of *o*-arylmethyl alkynyl oxime ethers with 5 mol % of Cu(OTf)$_2$ at reflux conditions. This protocol involves the sequential intramolecular addition of the oxime and subsequent 1,3-migration of the arylmethyl group to afford the target products (Scheme 43).[7c]



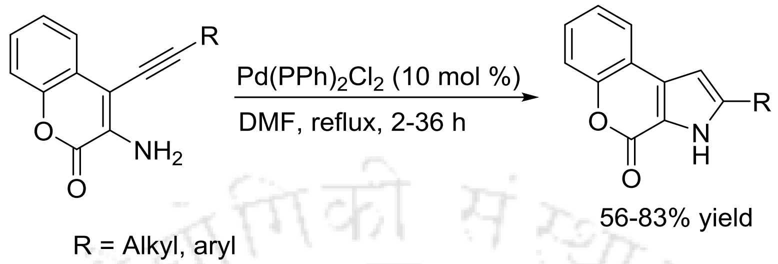
Scheme 43

Pt-catalyzed cyclization/ring expansion of 2-alkynyl-1-azaspiro[2.3]hexanes afforded 1,4,5,6-tetrahydrocyclopenta[b]pyrroles (Scheme 44).[7d]



Scheme 44

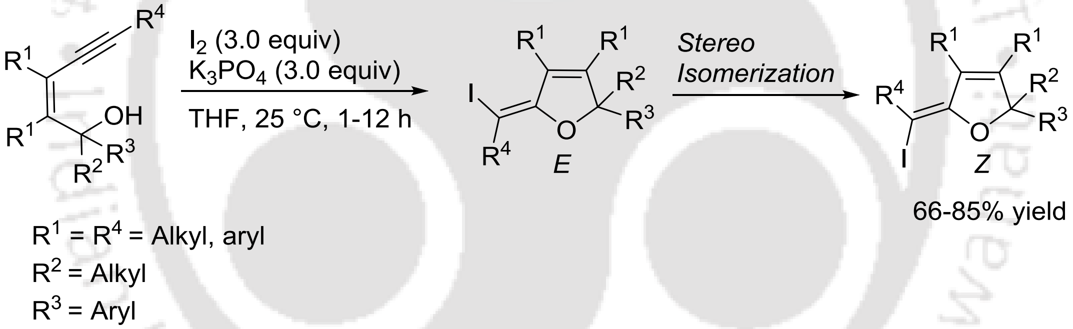
Xu and co-workers described the synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones using Pd-catalyzed coupling/cyclization reactions. The key step involves the formation of pyrrole ring through intramolecular hydroamination of acetylenic aminocoumarins (Scheme 45).[7e]



Scheme 45

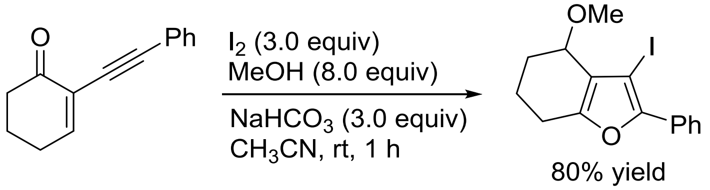
1.3 Cyclization of 1,3-Enynes

The synthesis of (*Z*)-5-(1-iodoylidene)-2,5-dihydrofurans is reported from (*Z*)-enynols using iodoelectrophilic cyclization under mild reaction conditions (Scheme 46).[8a]



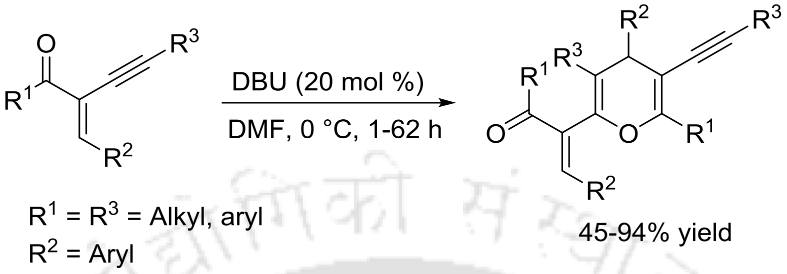
Scheme 46

Larock and co-workers described the I_2-mediated construction of furans using the coupling of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles. The resulting furans containing iodine can be further elaborated to complex derivatives using cross-coupling reactions (Scheme 47).[8b]



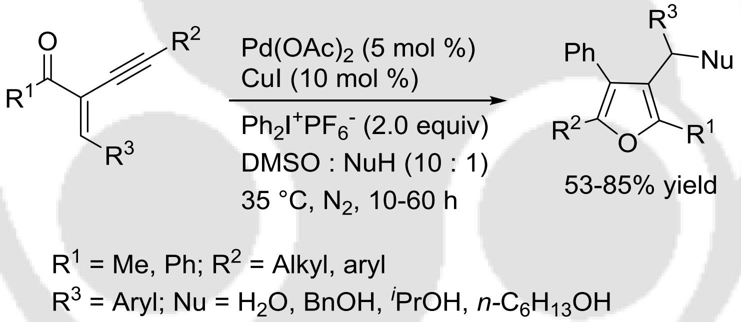
Scheme 47

Zhang and co-workers showed the synthesis of substituted 4*H*-pyrans from readily available 2-(1-alkynyl)-2-alkene-1-ones using DBU or *n*-Bu$_3$P-catalyzed hetero-[4+2] cycloaddition. 2-(1-Alkynyl)-2-alkene-1-ones act as both heterodiene and heterodinenophile (Scheme 48).[8c]



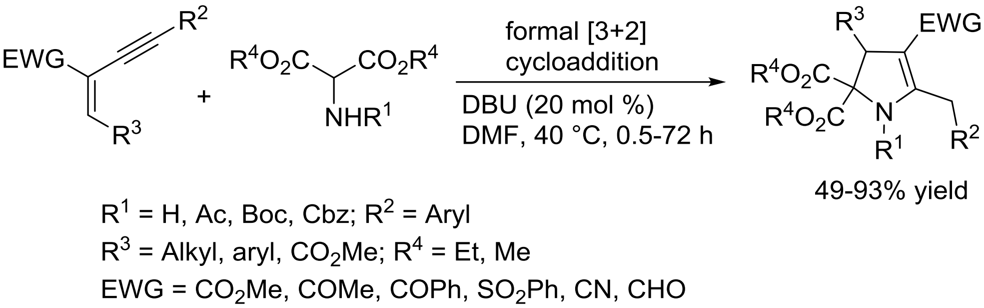
Scheme 48

Pd-catalyzed synthesis of substituted furans is demonstrated using three-component reaction of 2-(1-alkynyl)-2-alken-1-ones, nucleophiles and diaryliodonium salts in the presence of CuI as a co-catalyst (Scheme 49).[8d]



Scheme 49

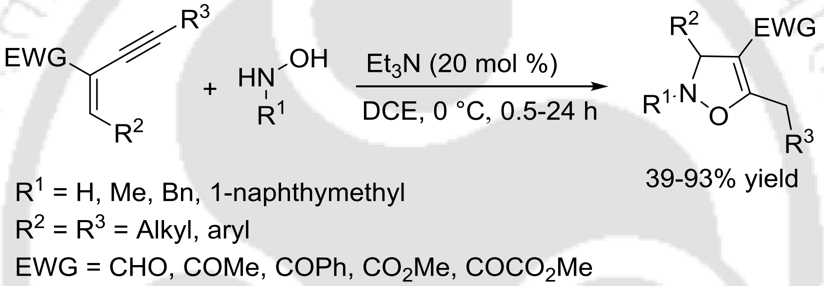
DBU-catalyzed tandem additions (a formal [3+2] cycloaddition) of electron-deficient 1,3-conjugated enynes with 2-aminomalonates has been shown to afford substituted 2-pyrrolines under mild conditions (Scheme 50).[8e]



R^1 = H, Ac, Boc, Cbz; R^2 = Aryl
R^3 = Alkyl, aryl, CO_2Me; R^4 = Et, Me
EWG = CO_2Me, COMe, COPh, SO_2Ph, CN, CHO

Scheme 50

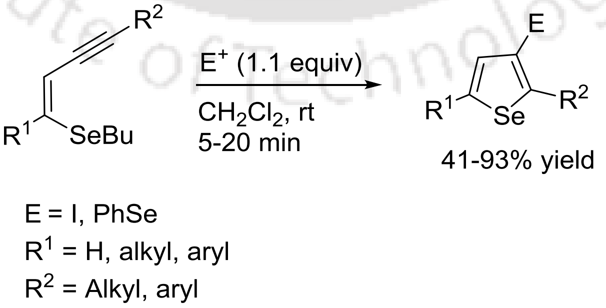
Et_3N-promoted tandem synthesis of substituted multifunctionalized 2,3-dihydroisoxazoles is reported using cyclization of electron-deficient 1,3-conjugated enynes with hydroxylamines under metal free conditions (Scheme 51).[8f]



R^1 = H, Me, Bn, 1-naphthymethyl
R^2 = R^3 = Alkyl, aryl
EWG = CHO, COMe, COPh, CO_2Me, $COCO_2Me$

Scheme 51

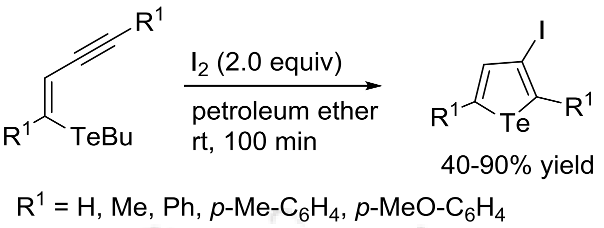
Zeni and co-workers reported the synthesis of 3-substituted selenophenes using electrophilic 5-*endo-dig* cyclization of (*Z*)-selenoenynes with various electrophiles such as I_2, ICl, PhSeBr, and PhSeCl under mild reaction conditions. The products can be readily transformed into complex derivatives using metal-catalyzed processes (Scheme 52).[8g]



E = I, PhSe
R^1 = H, alkyl, aryl
R^2 = Alkyl, aryl

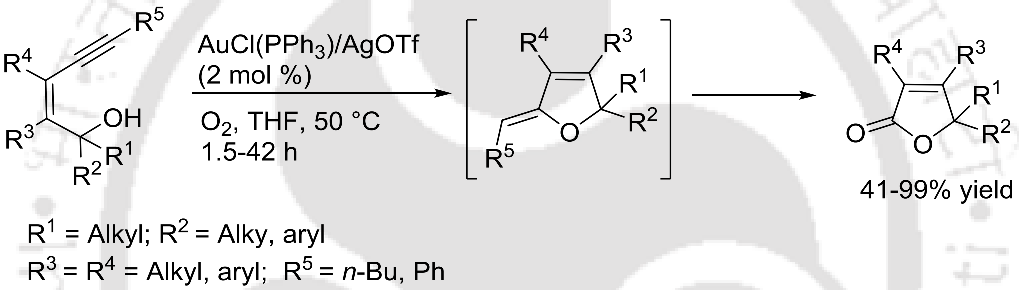
Scheme 52

Dabdoub and co-workers studied the 5-*endo-dig* iodocyclization of (*Z*)-tellurobutenynes to yield tellurophenes under mild reaction conditions (Scheme 53).[8h]



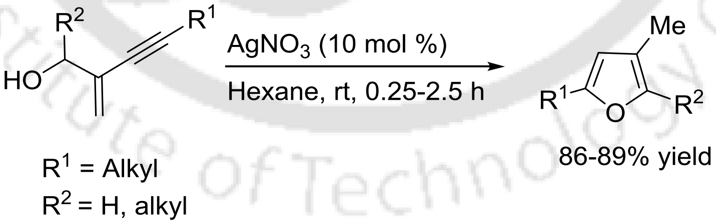
Scheme 53

Liu and co-workers discovered Au-catalyzed cyclization and oxidative cleavage of a dihydrofuran intermediate to afford butenolides in moderate to good yields (Scheme 54).[8i]



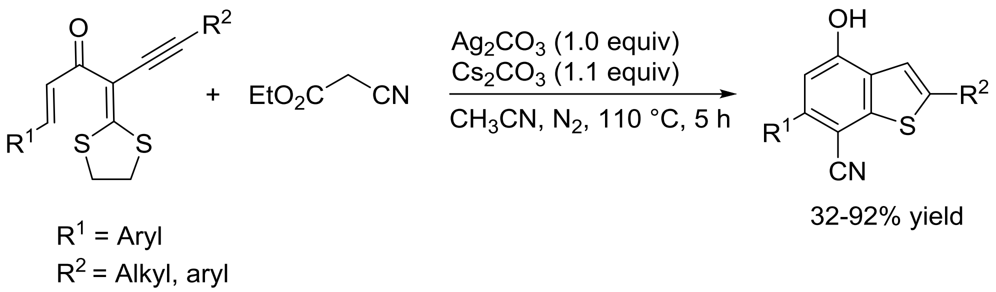
Scheme 54

Marshall and co-workers showed $AgNO_3$-catalyzed cyclization of *β*-alkynyl allylic alcohols to afford 2,3,5-tri substituted furan in good yields (Scheme 55).[8j]



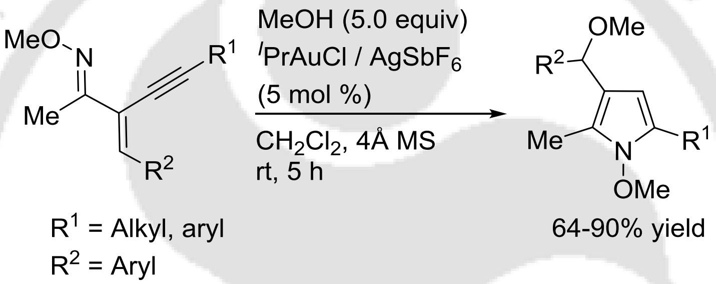
Scheme 55

Domino annulation is demonstrated for the synthesis of benzothiophenes from *α*-alkenoyl-*α*-alkynyl ketene dithioacetals and cyanoacetates using Ag_2CO_3 in the presence of Cs_2CO_3 (Scheme 56).[8k]



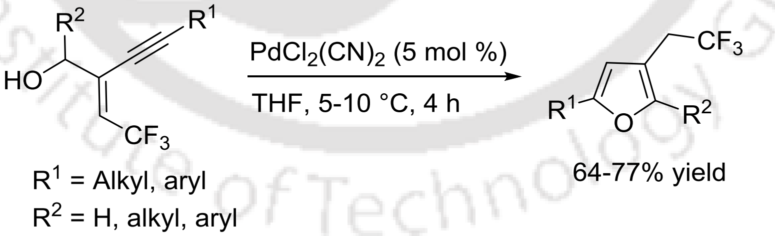
Scheme 56

Zhang and co-workers reported the synthesis of substituted *N*-alkoxypyrroles using gold-catalyzed cyclization of 2-(1-alkynyl)-alk-2-en-1-one oximes with MeOH which act as a nucleophile (Scheme 57).[8l]



Scheme 57

Qing and co-workers showed Pd-catalyzed cyclization-isomerization of (*Z*)-2-alkynyl- 3-trifluoromethyl allylic alcohols to furnish 3-trifluoroethylfurans (Scheme 58).[8m]



Scheme 58

In summary, we have described the recent developments of cyclization of alkynes using electrophiles and transition-metal-catalysts for the synthesis of diverse heterocycles. These strategies afford a simple and efficient route for the construction of diverse heterocycles with broad functional group toleraance under mild reaction conditions. Most of these cyclizations proceed stereo- and regioselectively.

1.4 References

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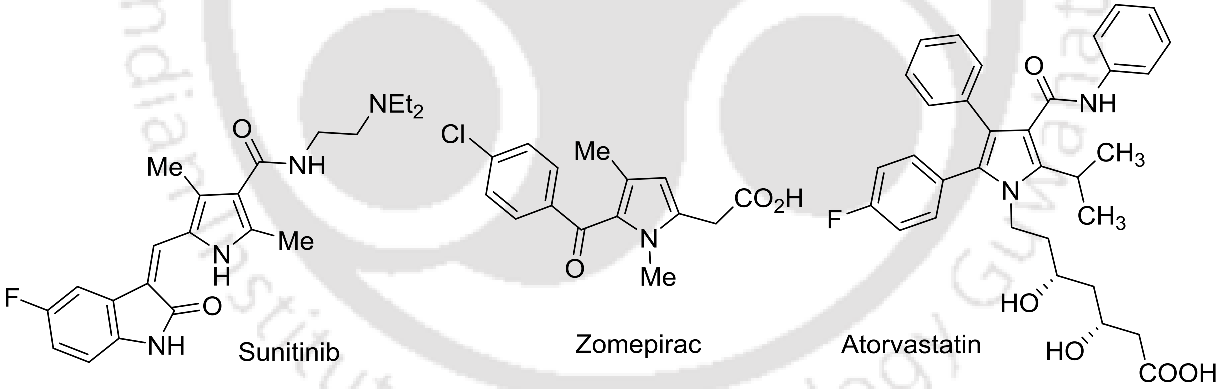
Iodine-Promoted 5-*Endo-dig* Cyclization of 1,3-Enynes with Amines: Domino Synthesis of Functionalized Pyrroles

Pyrroles are among one of the most important structural motifs of many natural products[1] and pharmaceuticals.[2] For examples, substituted pyrroles display many biological properties like anti-inflammatory,[3] antioxidant,[4] antibacterial,[5] antitumor,[6] anti-cancer drug and Lipitor[7] (Scheme 1). They also find widespread applications in material and supramolecular sciences.[8] Due to their long-standing significance in wide area, several classical and modern methods have been developed to the synthesis of pyrroles and their derivatives.[9-12] However, the strategies for the synthesis of highly substituted pyrroles from the readily available simple substrates is somewhat limited[13] due to lack of regioselectivity.[14] Recently, electrophilic iodocyclization of alkynes has been found to be a great device for the construction of carbocycles and heterocycles.[15] The designing of electron deficient 1,3-enynes[16] makes this manner very good-looking for the selective building of highly functionalized target heterocyclic compounds.

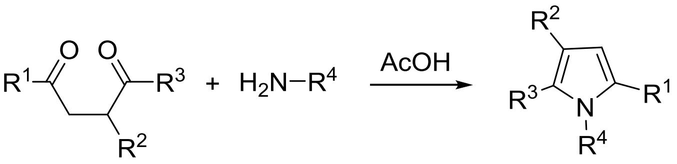


Scheme 1. Some Biologically Important Pyrrole Compounds

2.1 Classical Methods

Paal-Knorr Pyrrole Synthesis

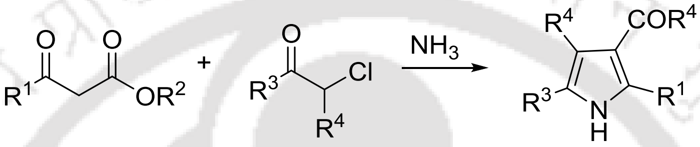
Paal and Knorr disclosed the condensation of 1,4-dicarbonyl compound with an excess of primary amine or ammonia to afford substituted pyrroles under acidic conditions (Scheme 2).[9a-b]



Scheme 2

Hantzsch Pyrrole Synthesis

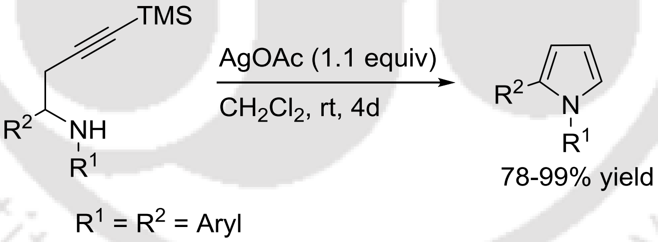
Hantzsch reported the synthesis of the substituted pyrroles by the reaction of *β*-ketoesters with ammonia followed by addition of *α*-haloketone (Scheme 3).[9c]



Scheme 3

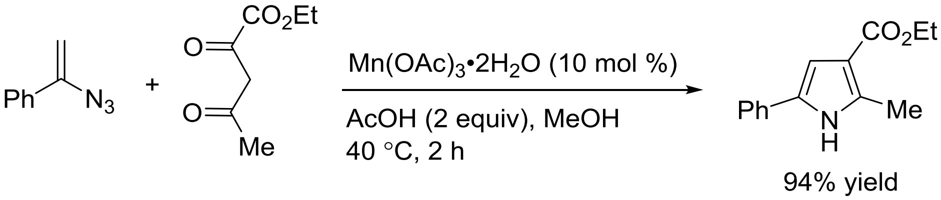
2.2 Modern Methods

AgOAc-mediated oxidative 5-*endo-dig* cyclization of homopropargylamines is reported for the synthesis of disubstituted pyrroles. The substrate precursors can be readily synthesized by the reaction of a propargyl Grignard reagent with Schiff bases (Scheme 4).[11a]



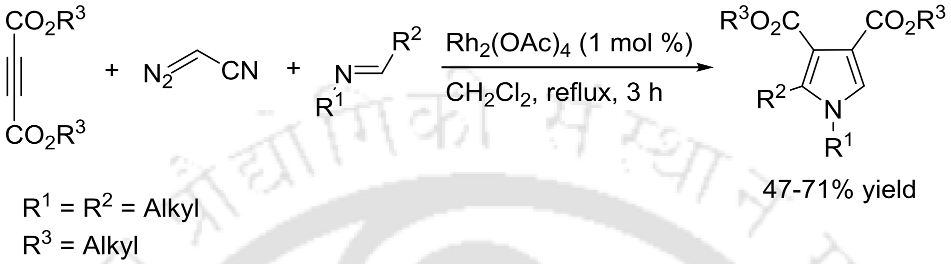
Scheme 4

Narasaka and co-workers developed Mn-catalyzed reaction of vinyl azides and 1,3-dicarbonyl compounds for the synthesis of tri- and tetrasubstituted pyrroles in high yields (Scheme 5).[11b]



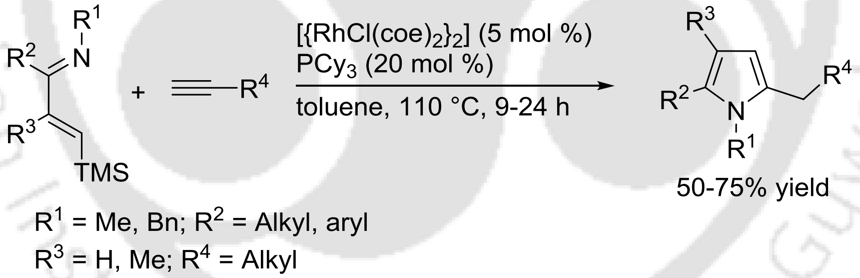
Scheme 5

Rh-catalyzed three-component reaction of an imine, diazoacetonitrile (DAN) and an activated alkyne affords substituted 1,2-diarylpyrroles. This reaction involves the formation of azomethine ylide and its cycloaddition with dipolarophiles (Scheme 6).[11c]

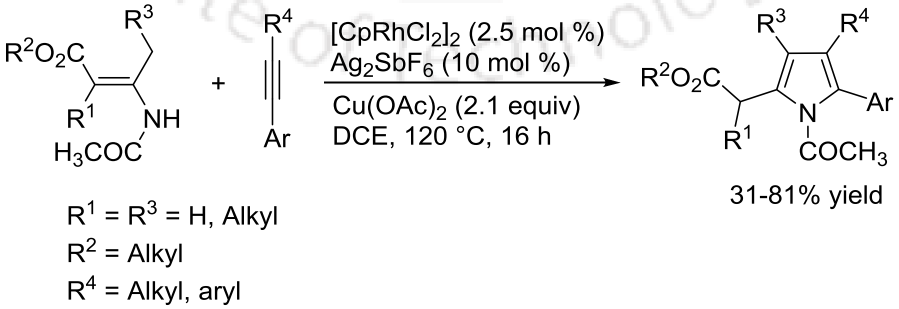


Scheme 6

Iwasawa group showed Rh-catalyzed synthesis of substituted pyrroles *via* intermolecular [4+1] cycloaddition of *α, β*-unsaturated imines with terminal alkynes. This protocol comprises of the addition of the imine nitrogen atom to the rhodium vinylidene complex to provide the target cyclic compounds (Scheme 7).[11d]



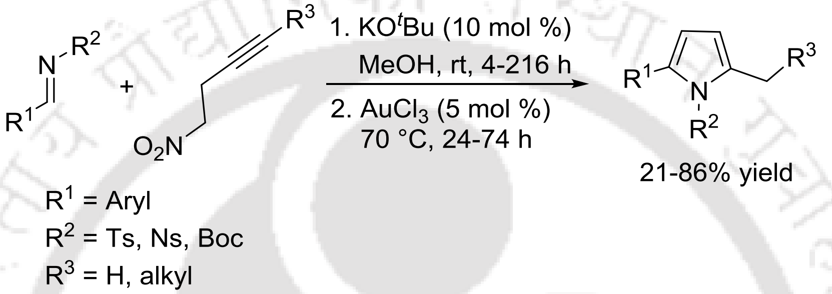
Scheme 7



Scheme 8

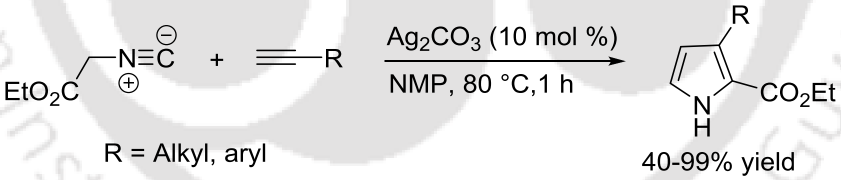
Glorius and co-workers reported Rh-catalyzed synthesis of polysubstituted pyrroles from enamines and unactivated alkynes under oxidative conditions. This strategy encompasses stimulating allylic sp^3 C-H activation of the enamine followed by the cyclization with the alkyne moieties (Scheme 8).[11e]

Dixon and co-workers reported cascade reaction of *p*-toluenesulfonyl protected imines with 4-nitrobut-1-yne to afford substituted pyrroles using combination of base and Au-catalysis (Scheme 9).[11f]



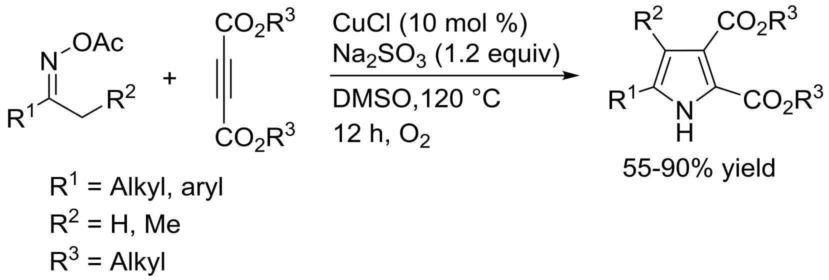
Scheme 9

Lei and co-workers described Ag-catalyzed click reaction for the construction of pyrroles from terminal alkynes and isocyanides. This method signifies an extremely simple, efficient, and atom-economic approach to substituted pyrroles (Scheme 10).[11g]



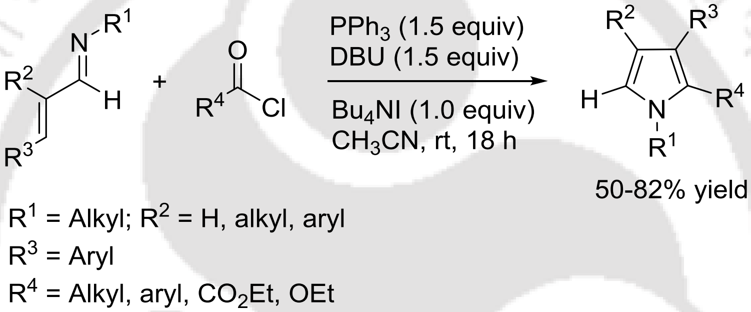
Scheme 10

An efficient facile access to the tetrasubstituted pyrroles was demonstrated by Jiang group using Cu-catalyzed condensation reaction of oxime acetates and dialkyl acetylenedicarboxylates under aerobic conditions (Scheme 11).[11h]



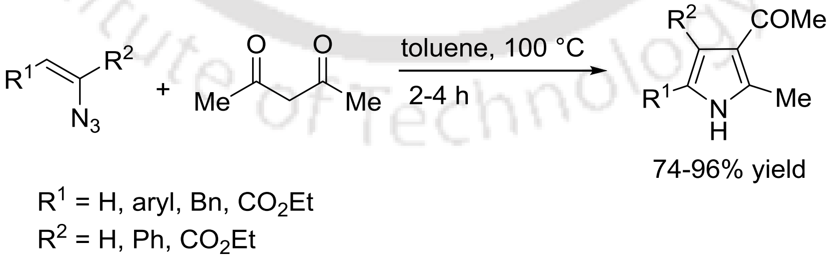
Scheme 11

Arndtsen and co-workers defined the one-step process to access highly substituted pyrroles with 50-82% yields from *α, β*-unsaturated imines and acid chlorides using triphenylphosphine, which induces cyclization by eliminating as phosphine oxide (Scheme 12).[11i]



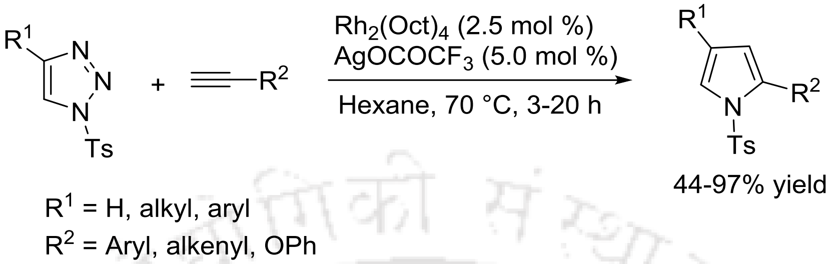
Scheme 12

Narasaka group reported the reaction of vinyl azides with 1,3-dicarbonyl compounds to afford the pyrrole derivatives in 74-96% yields. The reaction takes place *via* 1,2-addition of 1,3-dicarbonyl compounds to 2*H*-azirine intermediates formed *in situ* from vinyl azides (Scheme 13).[11j]



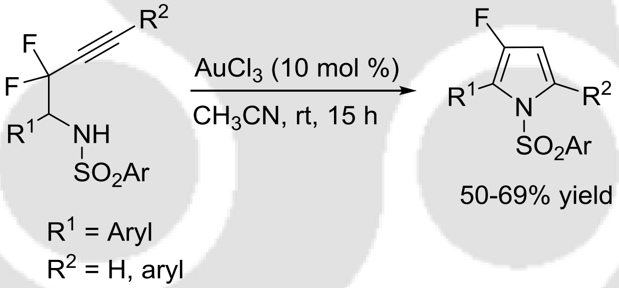
Scheme 13

Gevorgyan and co-workers developed $Rh_2(Oct)_4/AgOCOCF_3$ based binary catalytic system for the synthesis of trisubstituted pyrroles in 44-97% yields by the reaction of 1,2,3-triazoles with terminal alkynes (Scheme 14).[11k]



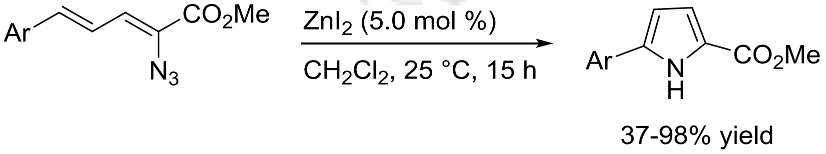
Scheme 14

Kimpe group reported Au-catalyzed cyclization followed by dehydrofluorination of *gem*-difluorohomopropargylamines to give fluorosubstituted pyrroles. The starting materials can be synthesized from *gem*-difluoropropargyllithium reagents with arylated *N*-tosylimines (Scheme 15).[11l]



Scheme 15

Driver and co-workers reported Zn-catalyzed intramolecular cyclization of dienyl azides to furnish 2,5-disubstituted pyrroles in high yields under mild conditions (Scheme 16).[11m]



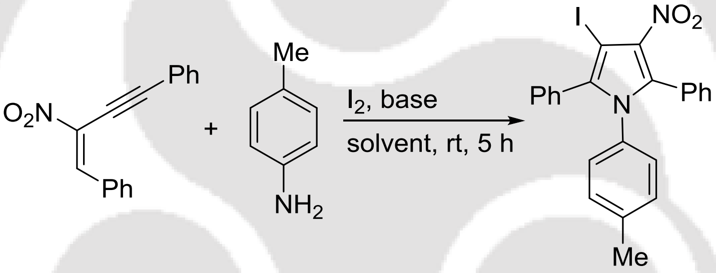
Scheme 16

2.3 Present Work

Herein we present the synthesis of tetra- and pentasubstituted pyrroles using molecular iodine from 1,3-enynes and amine *via* a sequential domino aza-Michael addition,[17] iodocyclization and oxidative aromatization. The protocol is simple and efficient to afford the target products at ambient conditions.

The optimization of the reaction was performed using various solvents and bases with (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne and *p*-toluidine as the standard substrates in the presence of molecular iodine (Table 1). We were delighted to observe that the reaction proceeded efficiently to give 3-iodo-4-nitro-2,5-diphenyl-1-*p*-tolyl-1*H*-pyrrole in 83% yield when the substrates were stirred with 2 equiv of iodine in the presence of K_2CO_3 in CH_2Cl_2 for 5 h at room temperature. CH_2Cl_2 was found to be the solvent of choice, whereas CH_3CN, THF and toluene provided the

Table 1. Optimization of the reaction conditions[a]



Entry	Solvent	Base	Yield (%)[b]
1	CH_3CN	$NaHCO_3$	17
2	Toluene	$NaHCO_3$	40
3	THF	$NaHCO_3$	50
4	CH_2Cl_2	$NaHCO_3$	52
5	CH_2Cl_2	NaOAc	31
6	CH_2Cl_2	K_2CO_3	58
7	CH_2Cl_2	K_3PO_3	37
8	**CH_2Cl_2**	**K_2CO_3**	**83**[c]

9	CH_2Cl_2	Et_3N	66[c]
10	CH_2Cl_2	DBU	73[c]
11	CH_2Cl_2	DIPEA	47[c]
12	CH_2Cl_2	K_2CO_3	62[d]
13	CH_2Cl_2	K_2CO_3	n.d.[e]

[a] Enyne (0.5 mmol), *p*-toluidine (0.5 mmol), I_2 (2.0 equiv), base (2.0 equiv) in solvent (3.0 mL) were stirred at room temperature under air for 5 h. [b]Isolated yield. [c]1.5 equiv of *p*-toluidine. [d]1.5 equiv of *p*-toluidine and 1.5 equiv of I_2 are used. [e] Without I_2. n.d. = not detected.

desired product in 17-52% yields (Entries 1-4). K_2CO_3 gave superior results compared to that of $NaHCO_3$, NaOAc and K_3PO_4, Et_3N, DBU and DIPEA (Entries 4-11). A complete disappearance of the (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne was observed with isolated yield of 83% when the amine quantity was increased to 1.5 equiv (Entry 8). The decrease of the amount of iodine to 1.5 equiv led to the formation of pyrrole in 62% yield (Entry 12). The control experiment conformed without iodine did not afford the target product (Entry 13).

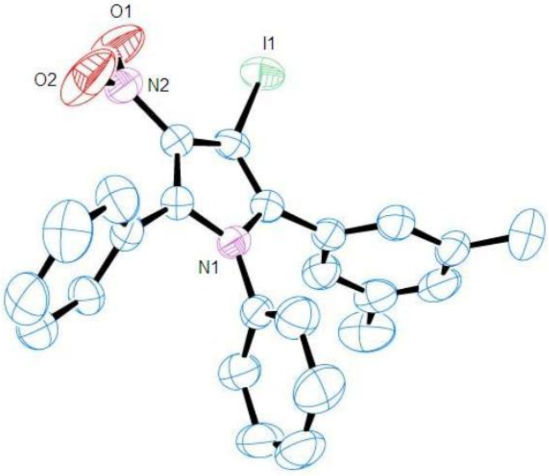
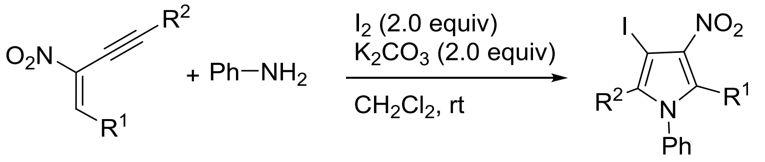
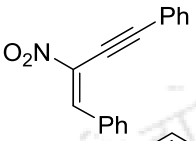
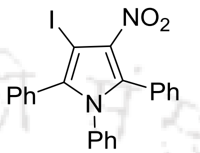
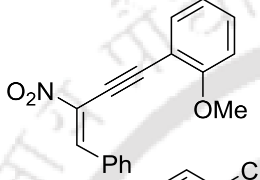
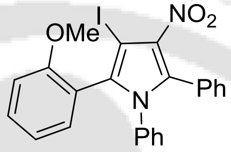
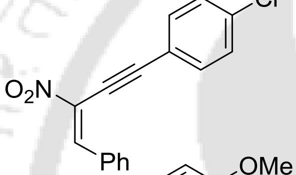
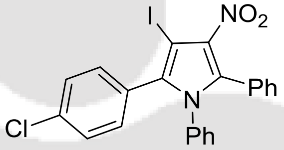
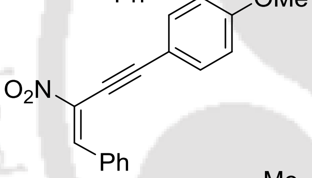
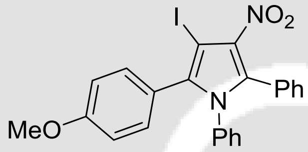
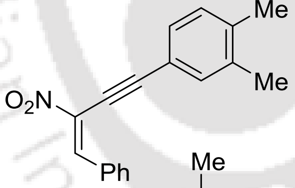
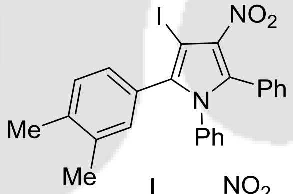
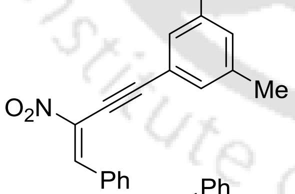
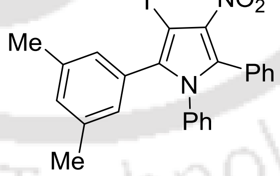
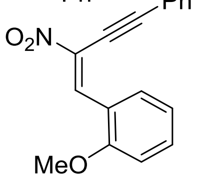
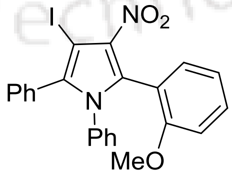
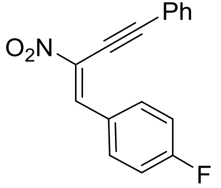
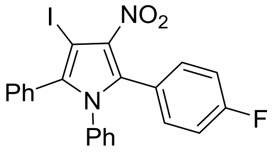


Figure 1. ORTEP diagram of 2-(3,5-dimethylphenyl)-3-iodo-4-nitro-1,5-diphenyl-1*H*-pyrrole. Thermal ellipsoids are drawn at a 50% probability level. *H*-atoms are omitted for clarity (CCDC 934526).

Table 2. Substrate Scope of Enynes[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			5	82
2			15	71
3			2	58
4			15	68
5			5	74
6			5	76
7			15	71
8			2	56

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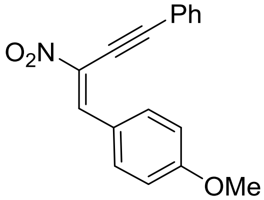
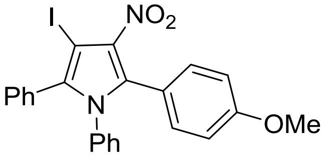
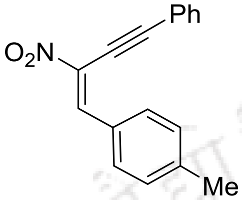
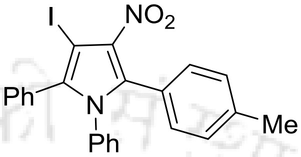
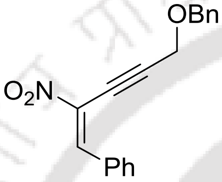
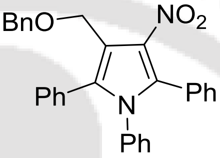
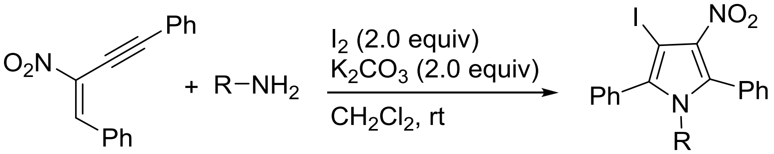
9			15	72
10			5	80
11			5	n.d.

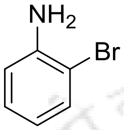
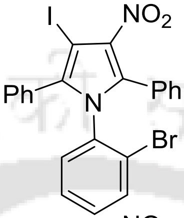
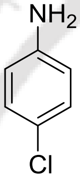
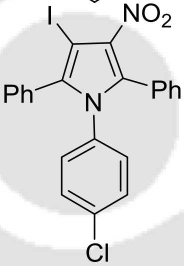
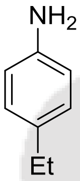
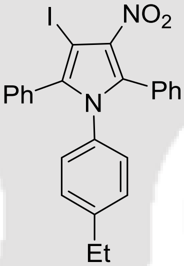
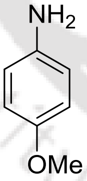
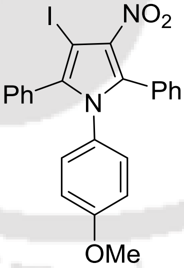
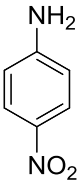
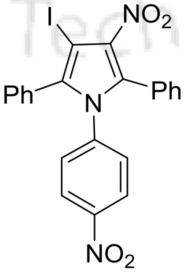
[a]Enyne (0.5 mmol), aniline (0.75 mmol), I_2 (2.0 equiv), base (2.0 equiv) in CH_2Cl_2 (3.0 mL) were stirred at room temperature for 5 h under air. [b]Isolated yield. n.d. = not detected.

Having the optimized reaction conditions, the scope of the protocol was scrutinized for the reactions of a series of substituted 1,3-enynes with aniline as a model substrate (Table 2). The reactions occurred readily to afford the pyrrole derivative in moderate to good yields. For instance, the substrate with R^1 and R^2 = Ph underwent reaction to give the target product in 82% yield (Entry 1). Similarly, the enynes bearing electron donating methoxy group in the aryl ring (R^1 or R^2) proceeded reaction to give the desired cyclic products in 68-72% yields (Entries 2, 4, 7 and 9), whereas enyne with electron withdrawing substituents in the aryl ring gave the corresponding pyrrole derivatives in 56% and 58% yield (Entries 3 and 8), respectively. While the enyne having mono- and dimethyl group in the aryl ring underwent reaction to furnish the desired pyrroles in high yields (Entries 5-6 and 10), whereas the benzyloxymethyl substituted enyne underwent decomposition, and the formation of the pyrrole was not observed (Entry 11). The crystallization of the 3-iodo-4-nitro pyrrole (Entry 6) in a 1:1 mixture of CH_3CN and MeOH gave crystals whose structure was determined by a single crystal X-ray analysis (Figure 1).

Next, the reaction of the (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene was explored with different substituted amines (Table 3). As anticipated, the amines underwent reaction exhibiting

Table 3. Substrate Scope of Amines[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			5	60
2			8	65
3			5	75
4			2	57
5			15	65

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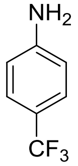
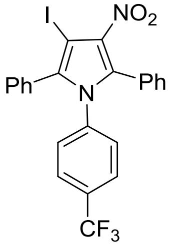
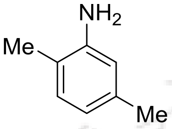
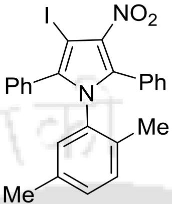
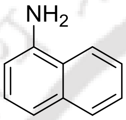
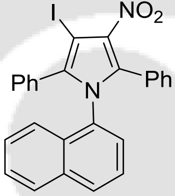
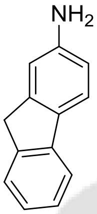
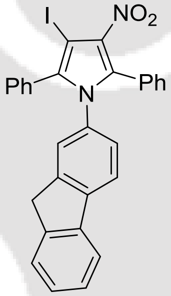
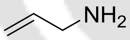
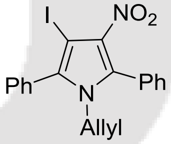
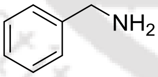
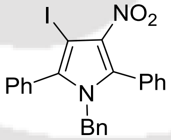
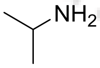
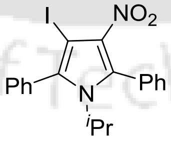
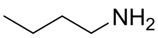
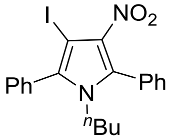
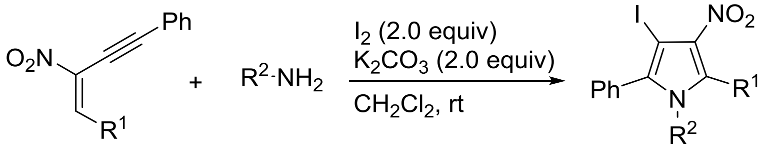
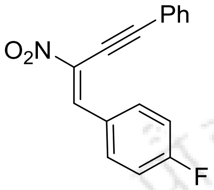
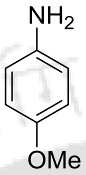
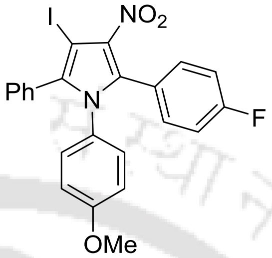
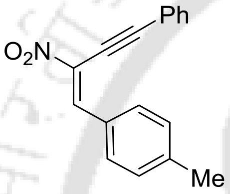
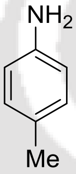
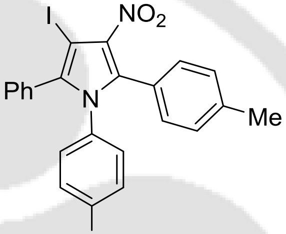
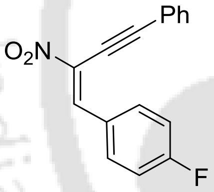
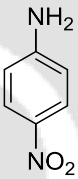
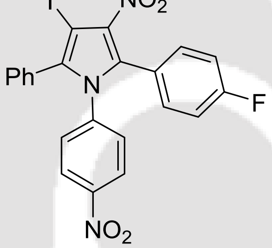
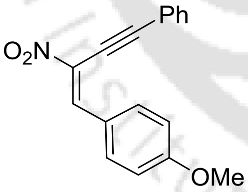
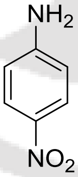
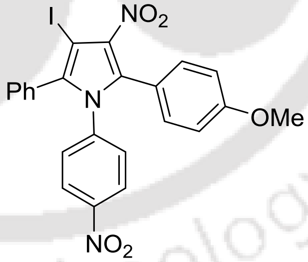
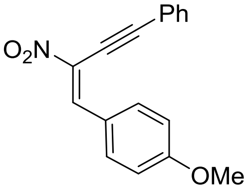
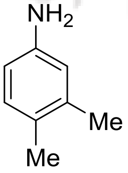
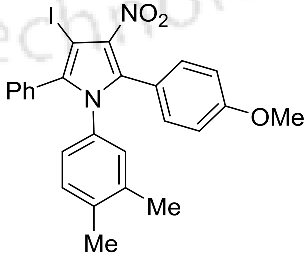
6			15	71
7			24	10
8			24	n.d.
9			24	18
10			5	47
11			5	33
12			5	35
13			5	30

[a]Enyne (0.5 mmol), amine (0.75 mmol), I_2 (2.0 equiv), base (2.0 equiv) in CH_2Cl_2 (3.0 mL) were stirred at room temperature under air. [b]Isolated yield. n.d. = not detected.

Table 4. Substrate Scope of 1,3-Enynes[a]

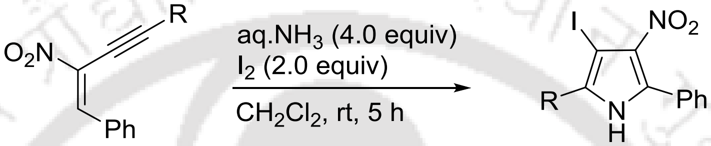


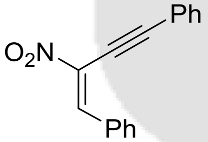
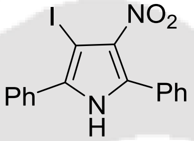
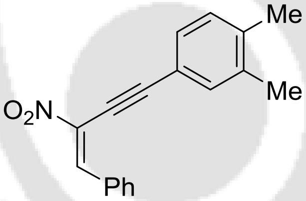
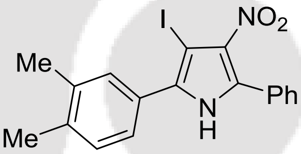
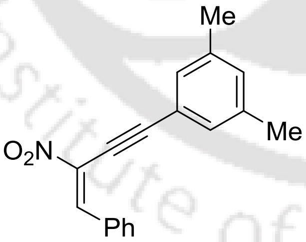
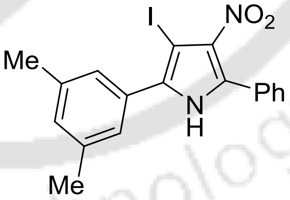
Entry	Enyne	Amine	Product	Time (h)	Yield (%)[b]
1				2	30
2				5	58
3				8	48
4				24	70
5				5	56

[a]Enyne (0.5 mmol), amine (0.75 mmol), I_2 (2.0 equiv), base (2.0 equiv) in CH_2Cl_2 (3.0 mL) were stirred at room temperature for 5 h. [b]Isolated yield.

a wide substrate compatibility and substituent tolerance. For instance, the aryl amines with electron withdrawing groups such as bromo, chloro, nitro and trifluoromethyl substituents proceeded reaction to give the corresponding substituted pyrroles in 60-71% yields (Entries 1-2 and 5-6). In addition, the aryl amines having electron donating groups such as ethyl and methoxy substituents on the aromatic rings underwent reaction to afford the target products in 57-75% yield (Entries 3-4). However, the bulky ortho substituted aryl amine with dimethyl substituent was less effective providing respective pyrrole in 10% yield (Entry 7).

Table 5. Synthesis of Substituted Pyrroles using 30% Aqueous Ammonia[a]



Entry	Substrate	Product	Yield (%)[b]
1			52
2			59
3			55

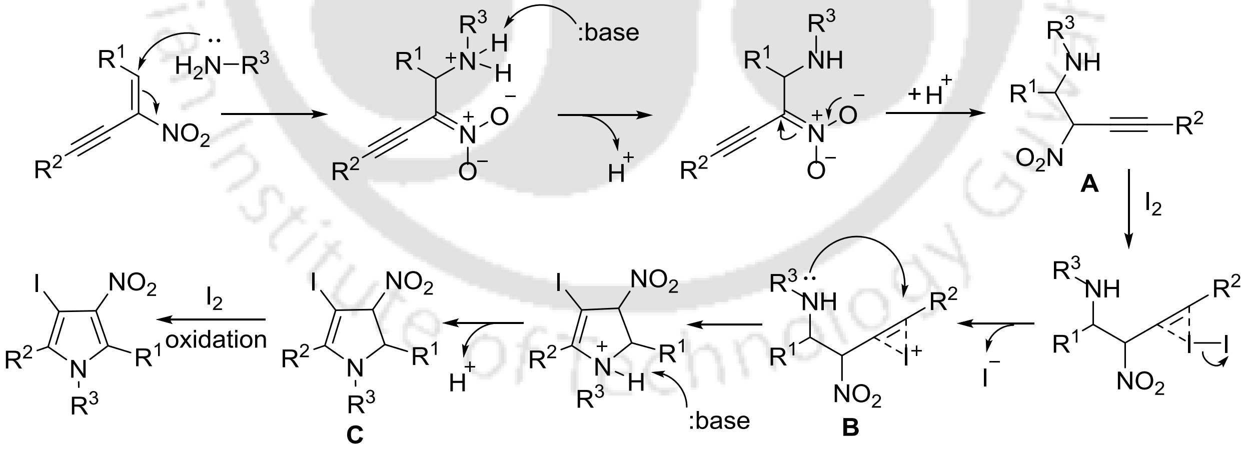
[a] Enyne (0.5 mmol), 2.0 mmol of aq.NH_3, I_2 (2.0 equiv) in CH_2Cl_2 (3.0 mL) were stirred at room temperature under air. [b] Isolated yield.

A similar result was observed with 2-fluorenyl amine supplying corresponding pyrrole derivative in 18% yield (Entry 9), whereas 1-naphthylamine showed no reaction and the starting material was recovered intact. Nevertheless, aliphatic amines such as allyl, benzyl, isopropyl and butyl amines were compatible providing the target products in moderate yields (Entries 10-13).

Next, the reaction of a series of substituted enynes with different substituted amines was studied (Table 4). The substrates bearing electron donating (methyl and methoxy) or electron withdrawing (fluoro and nitro) or the combination electron donating (methoxy) and electron withdrawing (fluoro and nitro) groups in the aryl rings readily proceeded reactions to afford the target products in moderate to good yields.

Finally, the compatibility of the protocol for the synthesis of tetrasubstituted pyrrole was studied employing various enynes with aqueous ammonia as amine source (Table 5). As above, the reaction readily occurred to afford the corresponding tetrasubstituted pyrroles in 52-59% yield (Entries 1-3). These observed results suggest that the protocol provides potential route for the synthesis of a library of highly substituted pyrroles by varying the substituents in the substrate precursors.

The proposed catalytic cycle is shown in Scheme 17. The intermolecular aza-Michael addition of the amine with the electron deficient conjugated 1,3-enyne in the presence of base leads to the formation of the intermediate **A**. The latter in the presence of iodine can give the iodonium intermediate[15j] **B**, which can undergo intramolecular cyclization to give the dihydropyrrole derivative **C**. The iodine mediated oxidative aromatization of **C** can lead to the formation of the target pyrrole products.



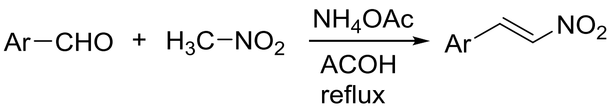
Scheme 17. Proposed Reaction Pathway

In summary, we have presented the synthesis of tetra- and pentasubstituted pyrroles from 1,3-enynes and amines using molecular iodine via aza-Michael addition, iodocyclization and oxidative aromatization. The results advise the electron deficient conjugated 1,3-enynes are hypothetically valuable class of substrates for the synthesis of desired cyclized compounds under mild reaction conditions.

2.4 Experimental Section

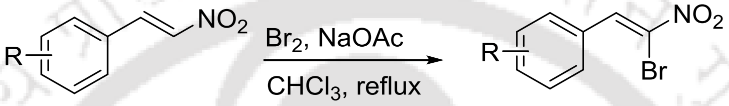
General Information. Amines, aldehydes, $Pd(PPh_3)_2Cl_2$ (98%), PPh_3 (99%) and CuI (98%)were purchased from Aldrich and used as received. Iodine (99.5%) purchaced from Rankem. The progress of the reaction was monitored by analytical TLC on Merck silica gel G/GF 254 plates. The column chromatography was performed with Rankem silica gel 60-120 mesh. NMR (^1H and ^{13}C) spectra were recorded on DRX-400 Varian spectrometer, Bruker Ultrashield^{TM} 300 using $CDCl_3$ as a solvent and chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. Elemental analyses were recorded using Perkin Elmer CHNS analyzer. Mass spectra were recorded on a ESI-MS TOF Instrument. For single crystal X-ray analysis the intensity data were collected using Bruker SMART APEX-II CCD diffractometer, equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structures were solved by direct methods using *SHELLX-97* (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-97.

General Procedure for Preparation of *β*-Nitrostyrene.[18] Aldehyde (10.0 mmol), nitromethane (12.0 mmol) and ammonium acetate (6.0 mmol) were added to 7 mL of glacial AcOH. The resulting solution was refluxed for 2 h and then poured into ice water and extracted with CH_2Cl_2 (3 x 20 mL). The extract was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate and hexane as eluent (Scheme 18).



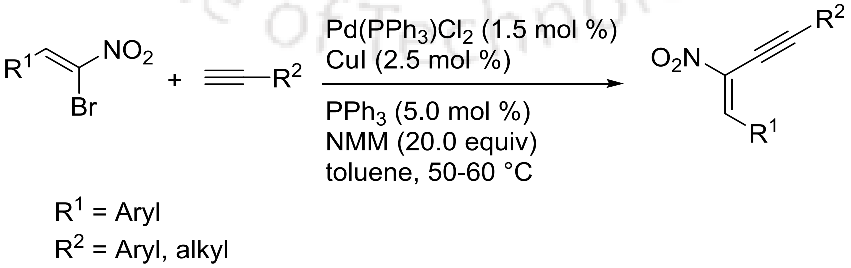
Scheme 18

General Procedure for Preparation of *β*-Bromonitroalkene.[16] To a stirred solution of *β*-nitrostyrene (10.0 mmol) in NaOAc (12.0 mmol) and $CHCl_3$ (10 mL) was added neat Br_2 (12.0 mmol) dropwise over 5 min at 0 °C. The cloudy yellow reaction was then heated to reflux and stirred for 5-8 h (monitored by TLC). The excess Br_2 was removed by washing with a saturated $Na_2S_2O_3$. The aqueous solution was then extracted by CH_2Cl_2 (3 x 20 mL), and the combined CH_2Cl_2 solution was dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent (Scheme 19).

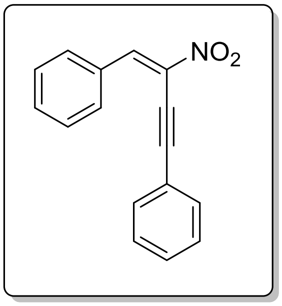


Scheme 19

General Procedure for Preparation of 1,3-Enynes.[16] To a solution of alkyne (2.8 mmol) in toluene (2 mL) was added CuI (2.5 mol %), and the reaction mixture was stirred at ambient temperature for 15 min. Meanwhile, a solution of *β*-bromonitroalkene (2.0 mmol) in toluene (2 mL) was added and the reaction mixture was stirred for 15 min. Next, $Pd(PPh_3)_2Cl_2$ (1.5 mol %) and PPh_3 (5.0 mol %) were added in one portion followed by *N*-methylmorpholine (8.0 mmol) over 1 min. The reaction mixture was slowly warmed to 50–60 °C and the progress of the reaction was monitored by TLC analysis using ethyl acetate and hexane. After completion, the reaction was cooled to ambient temperature and diluted with CH_2Cl_2 and filtered. The organic layer was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give 1,3-enynes (Scheme 20).



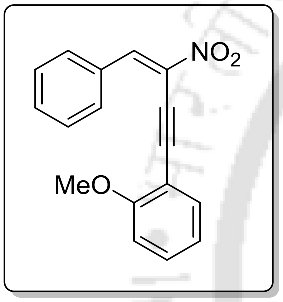
Scheme 20



(*E*)-(2-Nitrobut-1-en-3-yne-1,4-diyl)dibenzene.

Yellow liquid; yield: 72%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.61-7.57 (m, 2H), 7.53-7.38 (m, 6H).

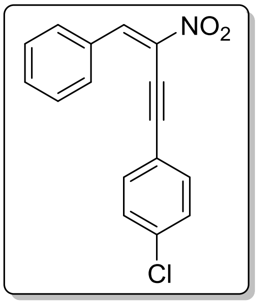


(*E*)-1-Methoxy-2-(3-nitro-4-phenylbut-3-en-1-ynyl)benzene.

Yellow liquid; yield: 68%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1H), 8.18 (d, *J* = 7.2, 2H), 7.54-7.45 (m, 4H), 6.98-6.91 (m, 3H), 3.93 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 137.5, 134.2, 133.4, 132.2, 131.5, 131.4, 130.7, 130.6, 128.8, 120.6, 110.8, 101.2, 83.2, 55.7.

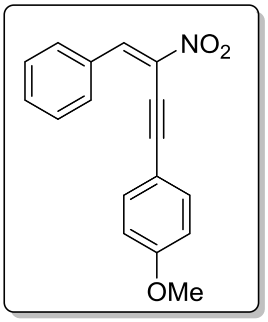


(*E*)-1-Chloro-4-(3-nitro-4-phenylbut-3-en-1-ynyl)benzene.

Yellow liquid; yield: 62%.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.33 (s, 1H), 8.04-7.98 (m, 2H), 7.61-7.32 (m, 7H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 139.1, 138.6, 136.1, 132.8, 132.3, 131.1, 130.9, 130.6, 129.1, 119.7, 102.1, 79.9.

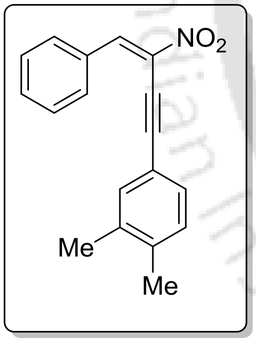


(*E*)-1-Methoxy-4-(3-nitro-4-phenylbut-3-en-1-ynyl)benzene.

Yellow liquid; yield: 66%.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.26 (s, 1H), 8.05-8.04 (m, 2H), 7.56-7.44 (m, 5H), 6.95 (d, *J* = 7.5 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 160.7, 137.1, 133.2, 133.0, 132.0, 130.9, 130.7, 128.8, 114.2, 113.0, 103.7, 78.3, 55.1.

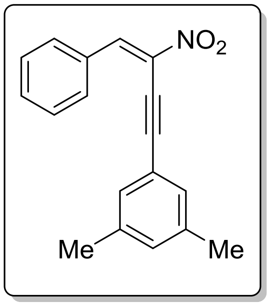


(*E*)-1,2-Dimethyl-4-(3-nitro-4-phenylbut-3-en-1-ynyl)benzene.

Yellow liquid; yield: 79%.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.26 (s, 1H), 8.04-8.02 (m, 2H), 7.54-7.33 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 2.29 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 139.1, 137.5, 137.0, 133.0, 132.5, 132.1, 131.0, 130.8, 129.9, 129.2, 129.0, 118.5, 103.9, 78.6, 19.7, 19.4.

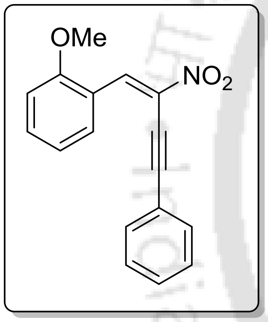


(*E*)-1,3-Dimethyl-5-(3-nitro-4-phenylbut-3-en-1-ynyl)benzene.

Yellow liquid; yield: 75%.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.20 (s, 1H), 7.97-7.95 (m, 2H), 7.42-7.39 (m, 3H), 7.14 (s, 2H), 6.98 (s, 1H), 2.25 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 138.1, 137.6, 132.0, 131.7, 131.0, 130.6, 129.2, 129.1, 128.9, 120.8, 103.8, 78.6, 20.8.

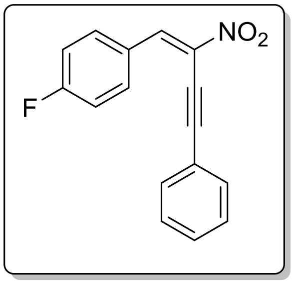


(*E*)-1-Methoxy-2-(2-nitro-4-phenylbut-1-en-3-ynyl)benzene.

Yellow liquid; yield: 66%.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.85 (s, 1H), 8.49 (d, *J* = 6.3 Hz, 1H), 7.58-7.37 (m, 6H), 7.06-6.92 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.0, 137.7, 133.9, 132.6, 131.5, 129.5, 129.1, 128.4, 128.3, 120.9, 119.3, 111.0, 102.4, 79.5, 55.5.

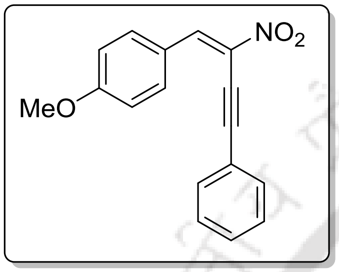


(*E*)-1-Fluoro-4-(2-nitro-4-phenylbut-1-en-3-ynyl)benzene.

Yellow liquid; yield: 51%.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.34 (s, 1H), 8.19-8.04 (m, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.62-7.40 (m, 5H), 7.37-7.06 (m, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.5, 163.1, 137.8, 136.9, 136.7, 133.4, 133.3, 131.7, 131.3, 131.1, 129.9, 128.6, 116.8, 116.5, 103.3.

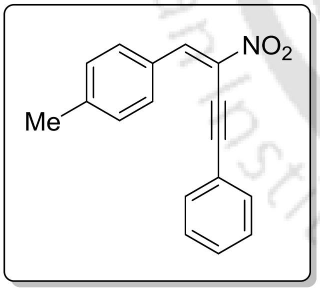


(*E*)-1-Methoxy-4-(2-nitro-4-phenylbut-1-en-3-ynyl)benzene.

Yellow liquid; yield: 72%.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.29 (s, 1H), 8.04 (dd, *J* = 7.2, 2.0 Hz, 2H), 7.61-7.58 (m, 2H), 7.41-7.39 (m, 3H), 6.89 (dd, *J* = 6.8, 2.0 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.1, 138.4, 133.4, 131.5, 130.6, 129.6, 128.6, 123.1, 121.5, 114.5, 102.9, 79.7, 55.4.

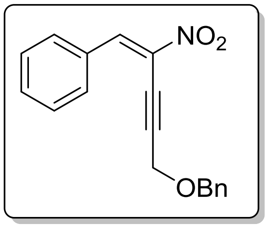


(*E*)-1-Methyl-4-(2-nitro-4-phenylbut-1-en-3-ynyl)benzene.

Yellow liquid; yield: 79%.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.31 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.62-7.60 (m, 2H), 7.43-7.41 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 143.4, 138.4, 131.9, 131.5, 131.2, 129.9, 129.7, 128.5, 127.8, 121.3, 103.1, 79.5, 21.6.

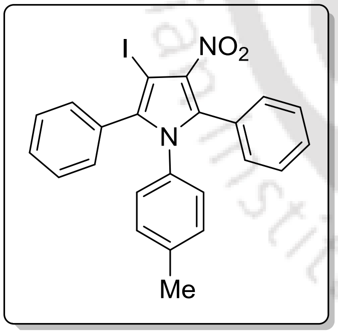


(*E*)-(5-(Benzyloxy)-2-nitropent-1-en-3-ynyl)benzene.

Yellow liquid; yield: 65%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.62-7.31 (m, 8H), 4.73 (s, 2H), 4.55 (s, 2H).

General Procedure for Synthesis of Pyrroles. To a stirred solution of 0.5 mmol of 1,3-enynes in CH_2Cl_2 (1.0 mL) at room temperature was added 2 equiv of I_2 dissolved in CH_2Cl_2 (1.5 mL). After 5 min, the reaction was treated with a solution of 0.75 mmol of amine in CH_2Cl_2 (0.5 mL) and the stirring continued at room temperature for the appropriate time. The excess I_2 was removed by washing with a saturated $Na_2S_2O_3$. The aqueous solution was then extracted by CH_2Cl_2 (2 x 10 mL), and the combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated to give a residue that was purified on silica gel column chromatography using hexane and ethyl acetate (19:1) as eluent.



3-Iodo-4-nitro-2,5-diphenyl-1-*p*-tolyl-1*H*-pyrrole (Table 1).

Yellow solid; yield: 83%; mp 238-239 °C.

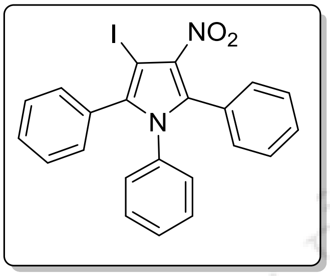
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.17 (m, 10H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 2.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 137.5, 136.1, 135.9, 134.1, 131.4, 131.0, 130.8, 129.4, 129.2, 129.0, 128.7, 128.3, 128.1, 128.0, 61.1, 21.1.

FT-IR (KBr): 3420, 3030, 2912, 1514, 1498, 1443, 1389, 1311, 1178, 1036, 916, 844, 764, 698, 725, 558 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_2$: C, 57.52; H, 3.57; N, 5.83. Found: C, 57.43; H, 3.59; N, 5.89.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{18}IN_2O_2$ 481.0413, found 481.0427.



3-Iodo-4-nitro-1,2,5-triphenyl-1*H*-pyrrole (Table 2, entry 1).

Yellow solid; yield: 82%; mp 219-220 °C.

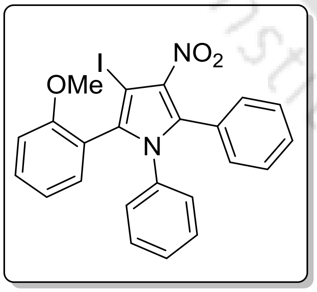
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.14 (m, 12H), 7.07 (dd, *J* = 14.8, 7.6 Hz, 2H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 136.7, 136.0, 131.4, 130.9, 129.1, 129.0, 128.7, 128.6, 128.5, 128.0, 61.2.

FT-IR (KBr): 3435, 3038, 1596, 1541, 1440, 1496, 1467, 1379, 1312, 1179, 1072, 1033, 913, 837, 795, 767, 696, 567 cm^{-1}.

Anal. Calcd for $C_{22}H_{15}IN_2O_2$: C, 56.67; H, 3.24; N, 6.01. Found: C, 56.58; H, 3.26; N, 6.06.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{16}IN_2O_2$ 467.0256, found 467.0277.



3-Iodo-2-(2-methoxyphenyl)-4-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, entry 2).

Yellow solid; yield: 71%; mp 187-188 °C.

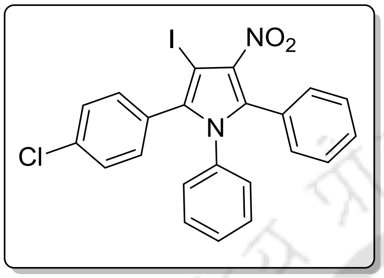
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.23 (m, 7H), 7.07-7.03 (m, 3H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 5.6 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 3.54 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 157.6, 137.0, 135.8, 135.6, 135.2, 133.4, 131.2, 130.9, 129.4, 128.9, 128.1, 128.0, 127.9, 120.4, 120.1, 110.9, 62.3, 55.1.

FT-IR (KBr): 3423, 2923, 1602, 1496, 1386, 1312, 1256, 1163, 1019, 839, 790, 759, 697 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_3$: C, 55.66; H, 3.45; N, 5.64. Found: C, 55.58; H, 3.46; N, 5.69.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{18}IN_2O_3$ 497.0362, found 497.0390.



2-(4-Chlorophenyl)-3-iodo-4-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, entry 3).

Yellow solid; yield: 58%; mp 157-158 °C.

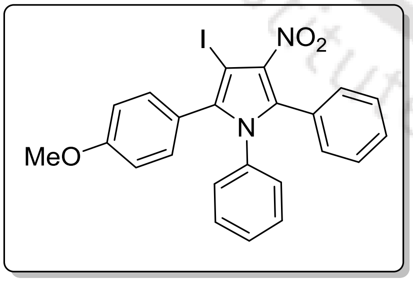
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28-7.23 (m, 5H), 7.20 (d, *J* = 6.4 Hz, 2H), 7.15-7.11 (m, 5H), 6.83 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.0, 136.3, 136.1, 135.9, 134.7, 132.5, 130.6, 129.9, 129.1, 129.0, 128.8, 128.7, 128.5, 128.3, 127.9, 61.5.

FT-IR (KBr): 3421, 2917, 1595, 1547, 1499, 1469, 1404, 1383, 1316, 1178, 1088, 1014, 839, 721, 696, 565 cm^{-1}.

Anal. Calcd for $C_{22}H_{14}ClIN_2O_2$: C, 52.77; H, 2.82; N, 5.59. Found: C, 52.87; H, 2.80; N, 5.52.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{22}H_{15}ClIN_2O_2$ 500.9867, found 500.9871.



3-Iodo-2-(4-methoxyphenyl)-4-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, entry 4).

Yellow solid; yield: 68%; mp 182-183 °C.

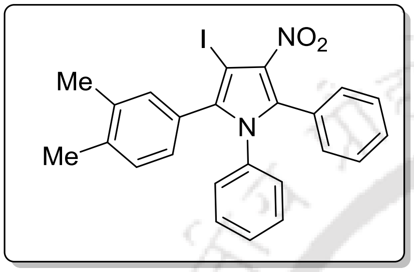
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.25-7.20 (m, 5H), 7.11-7.09 (m, 5H), 6.84 (d, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.7, 137.4, 136.9, 135.9, 132.7, 130.9, 129.2, 129.0, 128.8, 128.6, 128.4, 128.0, 123.0, 113.6, 61.3, 55.3.

FT-IR (KBr): 3423, 2922, 1610, 1533, 1497, 1467, 1384, 1311, 1289, 1256, 1178, 1032, 835, 795, 696, 570 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_3$: C, 55.66; H, 3.45; N, 5.64. Found: C, 55.57; H, 3.46; N, 5.71.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{18}IN_2O_3$ 497.0362, found 497.0390.



2-(3,4-Dimethylphenyl)-3-iodo-4-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, entry 5).

Yellow solid; yield: 74%; mp 204-205 °C.

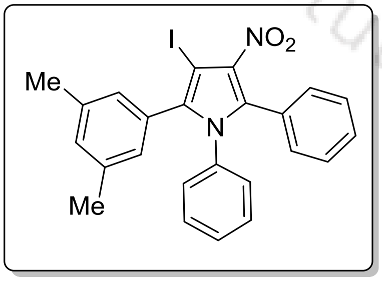
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.24-7.16 (m, 5H), 7.10-7.06 (m, 3H), 6.96 (t, *J* = 8.0 Hz, 2H), 6.86-6.80 (m, 3H), 2.18 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 137.7, 137.3, 136.8, 136.3, 135.9, 132.4, 130.8, 129.4, 129.2, 128.9, 128.7, 128.6, 128.3, 128.1, 127.9, 61.0, 19.7.

FT-IR (KBr): 3421, 2923, 1596, 1546, 1496, 1445, 1380, 1311, 1156, 886, 825, 795, 767, 721 cm^{-1}.

Anal. Calcd for $C_{24}H_{19}IN_2O_2$: C, 58.31; H, 3.87; N, 5.67. Found: C, 58.41; H, 3.85; N, 5.60.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{24}H_{20}IN_2O_2$ 495.0569, found 495.0590.



2-(3,5-Dimethylphenyl)-3-iodo-4-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, entry 6).

Yellow solid; yield: 76%; mp 212-213 °C.

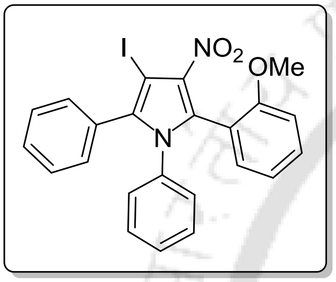
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.25-7.20 (m, 5H), 7.10-7.08 (m, 3H), 6.88 (s, 1H), 6.84 (dd, *J* = 7.2, 1.2 Hz, 2H), 6.78 (s, 2H), 2.19 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 137.8, 137.5, 136.9, 135.9, 130.9, 130.5, 130.4, 129.2, 129.1, 129.0, 128.6, 128.4, 128.0, 61.0, 21.2.

FT-IR (KBr): 3412, 2917, 1596, 1495, 1468, 1378, 1309, 1222, 1072, 1037, 857, 806, 718, 695 cm^{-1}.

Anal. Calcd for $C_{24}H_{19}IN_2O_2$: C, 58.31; H, 3.87; N, 5.67. Found: C, 58.40; H, 3.86; N, 5.61.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{20}IN_2O_2$ 495.0569, found 495.0558.



3-Iodo-5-(2-methoxyphenyl)-4-nitro-1,2-diphenyl-1*H*-pyrrole (Table 2, entry 7).

Yellow solid; yield: 71%; mp 185-186 °C.

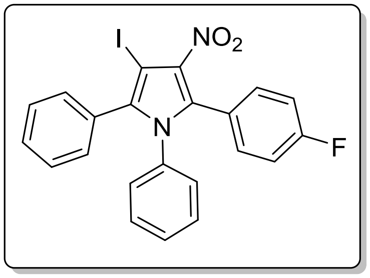
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.40-7.17 (m, 7H), 7.11-7.04 (m, 4H), 6.86-6.63 (m, 3H), 3.62 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 157.5, 137.0, 136.9, 133.3, 133.1, 131.9, 131.2, 130.9, 128.5, 128.2, 127.9, 120.1, 118.4, 112.3, 110.6, 60.9, 55.2.

FT-IR (KBr): 3433, 2953, 1605, 1481, 1377, 1301, 1264, 1168, 1001, 837, 785, 710 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_3$: C, 55.66; H, 3.45; N, 5.64. Found: C, 55.75; H, 3.43; N, 5.58.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{18}IN_2O_3$ 497.0362, found 497.0425.



2-(4-Fluorophenyl)-4-iodo-3-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, entry 8).

Yellow solid; yield: 56%; mp 217-218 °C.

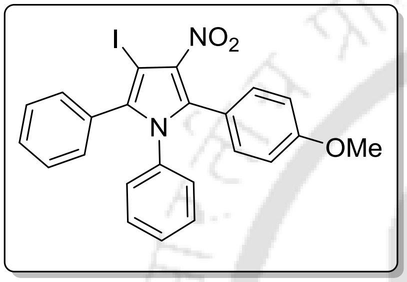
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31-7.29 (m, 4H), 7.27-7.09 (m, 7H), 7.00-6.91 (m, 2H), 6.83 (dd, *J* = 7.6, 0.8 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.2, 137.7, 136.7, 133.1, 133.0, 131.4, 130.8, 130.2, 129.0, 128.9, 128.7, 128.6, 128.5, 128.3, 124.9, 115.5, 115.3, 61.1.

FT-IR (KBr): 3436, 1606, 1503, 1382, 1313, 1219, 1157, 1023, 849, 763, 696 cm^{-1}.

Anal. Calcd for $C_{22}H_{14}FIN_2O_2$: C, 54.56; H, 2.91; N, 5.78. Found: C, 54.46; H, 2.92; N, 5.85.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{22}H_{15}FIN_2O_2$ 484.0084, found 485.0170.



3-Iodo-5-(4-methoxyphenyl)-4-nitro-1,2-diphenyl-1*H*-pyrrole (Table 2, entry 9).

Yellow solid; yield: 72%; mp 178-179 °C.

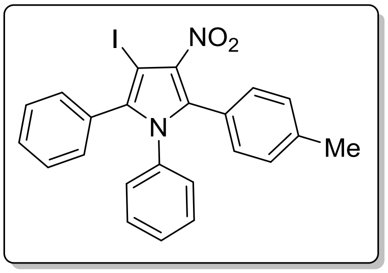
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.26-7.25 (m, 3H), 7.18-7.15 (m, 2H), 7.15-7.08 (m, 5H), 6.84 (dd, *J* = 7.6, 1.2 Hz, 2H), 6.76 (dd, *J* = 6.8, 2.0 Hz, 2H), 3.75 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 160.1, 137.4, 137.0, 136.1, 132.4, 131.5, 131.1, 129.0, 128.9, 128.8, 128.5, 128.2, 121.2, 113.6, 61.3, 55.4.

FT-IR (KBr): 3401, 2930, 1608, 1510, 1387, 1316, 1290, 1247, 1181, 1029, 1015, 843, 790, 767, 740, 703, 547 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_3$: C, 55.66; H, 3.45; N, 5.64. Found: C, 55.76; H, 3.43; N, 5.58.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{18}IN_2O_3$ 497.0362, found 497.0390.



3-Iodo-4-nitro-1,2-diphenyl-5-*p*-tolyl-1*H*-pyrrole (Table 2, entry 10).

Yellow solid; yield; 80%; mp 212-213 °C.

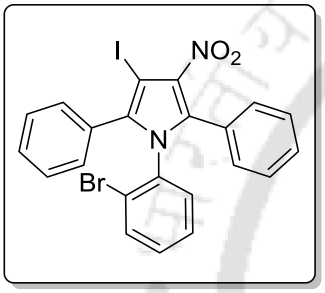
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21-7.20 (m, 4H), 7.13-7.12 (m, 2H), 7.07-6.97 (m, 6H), 6.79 (d, *J* = 6.8 Hz, 2H), 2.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 137.3, 136.9, 136.2, 136.0, 131.4, 131.0, 130.7, 128.9, 128.8, 128.7, 128.4, 128.1, 126.0, 61.3, 21.5.

FT-IR (KBr): 3423, 3028, 2918, 1594, 1549, 1504, 1471, 1376, 1310, 1184, 1111, 1072, 1025, 1002, 920, 841, 822, 789, 763, 738, 723, 698, 562 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_2$: C, 57.52; H, 3.57; N, 5.83. Found: C, 57.43; H, 3.58; N, 5.90.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{18}IN_2O_2$ 481.0413, found 481.0438.



1-(2-Bromophenyl)-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 1).

Yellow solid; yield: 60%; mp 208-209 °C.

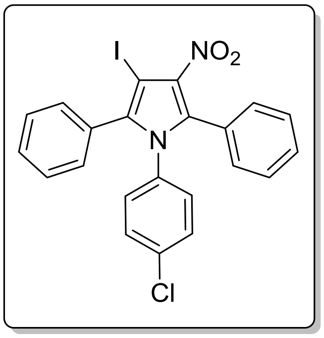
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30-7.19 (m, 10H), 7.17-7.09 (m, 3H), 7.03-6.98 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 136.3, 135.9, 133.2, 131.6, 131.3, 130.8, 130.5, 130.3, 129.3, 129.0, 128.7, 128.0, 127.9, 127.7. 123.2, 61.2.

FT-IR (KBr): 3432, 3059, 3021, 1549, 1494, 1479, 1442, 1380, 1310, 1179, 1027, 839, 765, 797, 731, 694 cm^{-1}.

Anal. Calcd for $C_{22}H_{14}BrIN_2O_2$: C, 48.47; H, 2.59; N, 5.14. Found: C, 48.56; H, 2.58; N, 5.07.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{22}H_{15}BrIN_2O_2$ 544.9362, found 544.9296.



1-(4-Chlorophenyl)-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 2).

Yellow solid; yield: 65%; mp 259-260 °C.

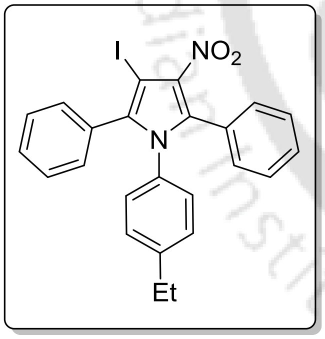
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.29-7.24 (m, 6H), 7.18-7.14 (m, 4H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 137.4, 135.9, 135.4, 134.5, 131.4, 130.9, 130.6, 129.8, 129.4, 129.1, 129.1, 128.8, 128.4, 128.3, 61.7.

FT-IR (KBr) 3057, 1544, 1490, 1467, 1376, 1307, 1171, 1087, 1009, 916, 842, 751, 725, 696 cm^{-1}.

Anal. Calcd for $C_{22}H_{14}ClIN_2O_2$: C, 52.77; H, 2.82; N, 5.59. Found: C, 52.66; H, 2.84; N, 5.65.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{18}IN_2O_2$ 500.9867, found 500.9856.



1-(4-Ethylphenyl)-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 3).

Yellow solid; yield: 75%; mp 206-207 °C.

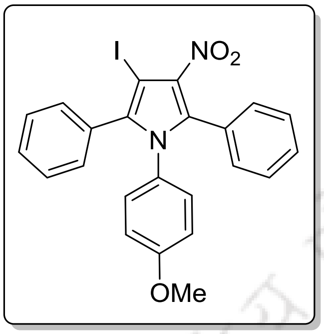
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.32-7.22 (m, 10H), 6.9 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.6, 137.5, 136.1, 135.9, 134.3, 131.4, 131.0, 130.9, 129.2, 128.9, 128.7, 128.3, 128.1, 128.0, 61.1, 28.2, 15.0.

FT-IR (KBr): 3422, 3029, 2965, 1546, 1497, 1468, 1443, 1381, 1308, 1178, 1035, 918, 849, 836, 759, 698, 559 cm^{-1}.

Anal. Calcd for $C_{24}H_{19}IN_2O_2$: C, 58.31; H, 3.87; N, 5.67. Found: C, 58.41; H, 3.85; N, 5.60.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{19}IN_2O_2$ 495.0569, found 495.0595.



3-Iodo-1-(4-methoxyphenyl)-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 4).

Yellow solid; yield: 57%; mp 220-221 °C.

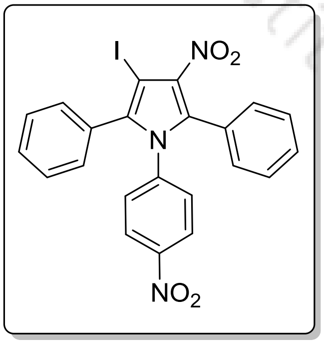
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26-7.21 (m, 6H), 7.19-7.15 (m, 4H), 6.74 (d, *J* = 9.2 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 3.64 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 137.7, 136.3, 131.5, 131.1, 130.9, 129.7, 129.6, 129.3, 129.0, 128.8, 128.2, 128.1, 113.9, 61.0, 55.4.

FT-IR (KBr): 3434, 2931, 2835, 1607, 1512, 1496, 1443, 1379, 1300, 1250, 1169, 1105, 1070, 1027, 845, 765, 731, 698 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_3$: C, 55.66; H, 3.45; N, 5.64. Found: C, 55.76; H, 3.43; N, 5.58.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{18}IN_2O_3$ 497.0362, found 497.0386.



3-Iodo-4-nitro-1-(4-nitrophenyl)-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 5).

Yellow solid; yield: 65%; mp 233-234 °C.

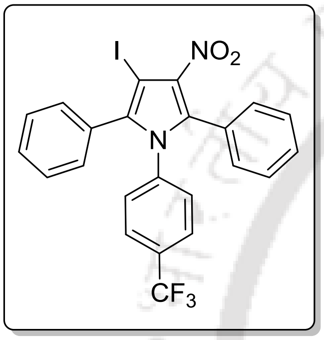
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.97 (d, *J* = 8.7 Hz, 2H), 7.36-7.26 (m, 6H), 7.22-7.16 (m, 4H), 7.02 (d, *J* = 7.8 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 146.9, 142.2, 137.2, 136.7, 135.6, 131.3, 130.9, 130.2, 129.7, 129.6, 129.4, 128.6, 128.5, 128.4, 124.1, 62.4.

FT-IR (KBr): 3412, 3082, 1613, 1593, 1551, 1520, 1504, 1470, 1446, 1381, 1343, 1309, 1181, 1108, 1014, 920, 863, 768, 745, 730, 710, 696 cm^{-1}.

Anal. Calcd for $C_{22}H_{14}IN_3O_4$: C, 51.68; H, 2.76; N, 8.22. Found: C, 51.59; H, 2.77; N, 8.29.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{15}IN_3O_4$ 512.0107, found 512.0093.



3-Iodo-4-nitro-2,5-diphenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (Table 3, Entry 6). Yellow solid; yield: 71%; mp 216-217 °C.

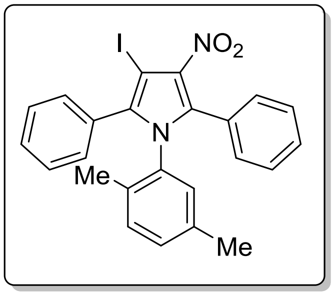
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.34 (d, *J* = 8.4 Hz, 3H), 7.29-7.22 (m, 7H), 7.18-7.13 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 139.9, 137.3, 136.4, 135.8, 131.4, 130.9, 130.5, 130.4, 130.2, 129.4, 129.2, 129.1, 128.6, 128.4, 128.3, 125.9, 62.0.

FT-IR (KBr): 3054, 1950, 1614, 1544, 1497, 1443, 1379, 1326, 1307, 1168, 1117, 1064, 1015, 919, 851, 763, 743, 718, 695 cm^{-1}.

Anal. Calcd for $C_{23}H_{14}F_3IN_2O_2$: C, 51.71; H, 2.64; N, 5.24. Found: C, 51.61; H, 2.66; N, 5.30.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{15}F_3IN_2O_2$ 535.0130, found 535.0135.



1-(2,5-Dimethylphenyl)-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 7).

Yellow solid; yield: 10%; mp 182-183 °C.

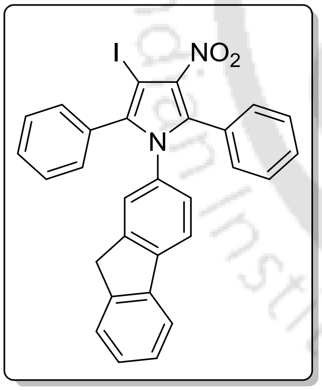
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.38 (s, 1H), 7.28-7.20 (m, 11H), 6.87 (s, 1H), 2.21 (s, 3H), 1.79 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 140.8, 139.6, 137.4, 136.1, 134.8, 131.1, 130.5, 130.4, 129.4, 129.1, 128.8, 128.3, 128.2, 128.1, 128.0, 102.0, 61.6, 28.0, 16.9.

FT-IR (KBr): 3422, 2912, 1544, 1498, 1443, 1384, 1310, 1193, 1174, 1088, 1028, 832, 766, 696 cm^{-1}.

Anal. Calcd for $C_{24}H_{19}IN_2O_2$: C, 58.31; H, 3.87; N, 5.67. Found: C, 58.39; H, 3.86; N, 5.61.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{20}IN_2O_2$ 495.0569, found 495.0582.



1-(9*H*-Fluoren-2-yl)-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 9).

Yellow semi solid; yield: 18%.

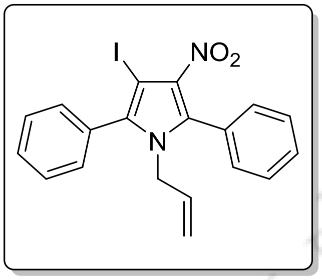
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.64 (d, *J* = 6.8 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 3H), 7.32-7.23 (m, 10H), 6.97 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 3.65 (s, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 143.5, 143.4, 141.7, 140.2, 137.4, 136.1, 135.8, 135.1, 131.3, 130.9, 130.8, 129.1, 128.9, 128.6, 128.1, 127.9, 127.4, 127.2, 127.0, 125.1, 120.2, 119.6, 61.2, 36.8.

FT-IR (neat): 3411, 3059, 2917, 1728, 1604, 1496, 1467, 1385, 1312, 1176, 1141, 1072, 1028, 916, 877, 837, 764, 737, 698 cm^{-1}.

Anal. Calcd for $C_{29}H_{19}IN_2O_2$: C, 62.83; H, 3.45; N, 5.05. Found: C, 62.74; H, 3.47; N, 5.11.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{19}IN_2O_2$ 555.0569, found 555.0547.



1-Allyl-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 10).

Yellow solid; yield: 47%; mp 159-160 °C.

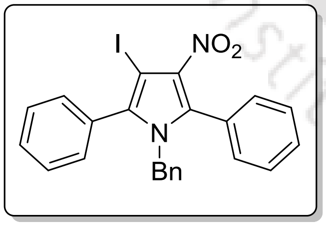
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.42 (m, 6H), 7.37-7.34 (m, 4H), 5.48-5.39 (m, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 4.60 (d, *J* = 17.2 Hz, 1H), 4.24 (d, *J* = 4.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.3, 135.9, 135.1, 132.7, 131.3, 131.0, 130.2, 129.7, 129.6, 129.5, 128.7, 128.6, 117.7, 60.9, 48.7.

FT-IR (KBr): 3417, 2923, 1728, 1548, 1530, 1493, 1467, 1415, 1348, 1309, 1221, 1155, 1073, 1037, 990, 931, 844, 754, 698 cm^{-1}.

Anal. Calcd for $C_{19}H_{15}IN_2O_2$: C, 53.04; H, 3.51; N, 6.51. Found: C, 53.13; H, 3.49; N, 6.45.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{16}IN_2O_2$ 431.2470, found 431.0283.



1-Benzyl-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 11).

Yellow solid; yield: 33%; mp 168-169 °C.

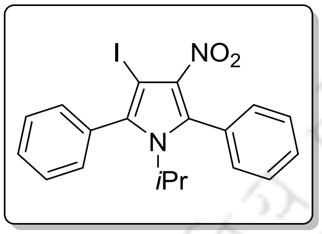
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.33 (m, 6H), 7.26-7.20 (m, 4H), 7.12-7.08 (m, 3H), 6.51 (d, *J* = 7.2 Hz, 2H), 4.88 (s, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 137.5, 136.3, 136.2, 135.3, 131.1, 130.9, 130.1, 129.5, 129.4, 129.3, 128.6, 128.4, 127.6, 126.1, 61.3, 50.0.

FT-IR (KBr): 3420, 3054, 3028, 1552, 1495, 1471, 1454, 1390, 1356, 1309, 1219, 1154, 1075, 1037, 922, 851, 781, 753, 698 cm^{-1}.

Anal. Calcd for $C_{23}H_{17}IN_2O_2$: C, 57.52; H, 3.57; N, 5.83. Found: C, 57.63; H, 3.55; 5.76.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{18}IN_2O_2$ 481.0413, found 481.0399.



3-Iodo-1-isopropyl-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 12).

Yellow solid; yield: 35%; mp 158-159 °C.

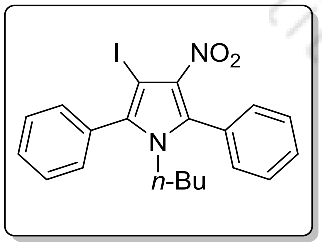
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49-7.46 (m, 6H), 7.42-7.35 (m, 4H), 4.24-4.20 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 136.6, 135.4, 135.0, 132.7, 132.0, 130.5, 130.3, 129.6, 129.5, 128.6, 128.5, 62.7, 51.9, 23.3.

FT-IR (KBr): 3412, 2977, 2928, 1494, 1465, 1443, 1390, 1378, 1311, 1216, 1070, 1033, 834, 769, 703 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}IN_2O_2$: C, 52.79; H, 3.96; N, 6.48. Found: C, 52.68; H, 3.98; N, 6.55.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{19}H_{19}IN_2O_2$ 433.0413, found 433.0413.



1-Butyl-3-iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 13).

Yellow liquid; yield: 30%.

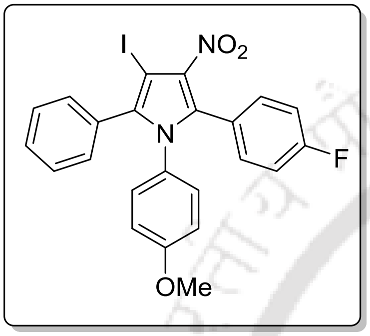
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.52-7.45 (m, 6H), 7.38-7.36 (m, 4H), 3.66 (t, *J* = 7.6 Hz, 2H), 1.18-1.14 (m, 2H), 0.85-0.79 (m, 2H), 0.48 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 136.7, 135.6, 134.8, 131.2, 131.0, 130.0, 129.6, 129.4, 129.3, 128.7, 128.6, 60.8, 46.1, 32.3, 19.1, 13.0.

FT-IR (KBr): 3390, 3061, 3029, 2960, 2932, 2872, 2232, 1958, 1890, 1719, 1668, 1551, 1495, 1470, 1393, 1368, 1311, 1217, 1178, 1108, 1074, 1036, 1020, 920, 849, 751, 699 cm^{-1}.

Anal. Calcd for $C_{20}H_{19}IN_2O_2$: C, 53.83; H, 4.29; N, 6.28. Found: C, 53.73; H, 4.31; N, 6.35.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{20}IN_2O_2$ 447.0569, found 447.0572.



2-(4-Fluorophenyl)-4-iodo-1-(4-methoxyphenyl)-3-nitro-5-phenyl-1*H*-pyrrole (Table 4, Entry 1).

Yellow solid; yield: 30%; mp 202-203 °C.

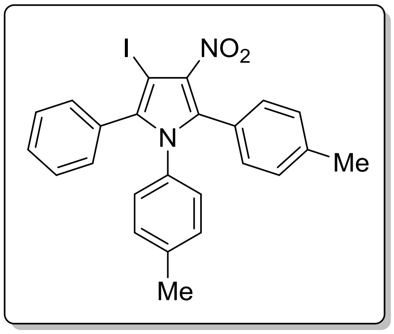
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.27-7.18 (m, 7H), 6.95 (t, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.7 Hz, 2H), 3.68 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.7, 161.3, 159.3, 137.9, 135.2, 133.0, 132.9, 131.4, 130.9, 129.6, 129.4, 128.9, 128.3, 125.3, 115.5, 115.2, 114.0, 61.1, 55.4.

FT-IR (KBr): 3428, 2932, 1609, 1513, 1501, 1442, 1381, 1301, 1250, 1170, 1027, 853, 837, 780, 698 cm^{-1}.

Anal. Calcd for $C_{23}H_{16}FIN_2O_3$: C, 53.71; H, 3.14; N, 5.45. Found: C, 53.80; H, 3.13; N, 5.38.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{17}FIN_2O_3$ 515.0268, found 515.0297.



3-Iodo-4-nitro-2-phenyl-1,5-di-*p*-tolyl-1*H*-pyrrole (Table 4, Entry 2).

Yellow solid; yield: 58%; mp 217-218 °C.

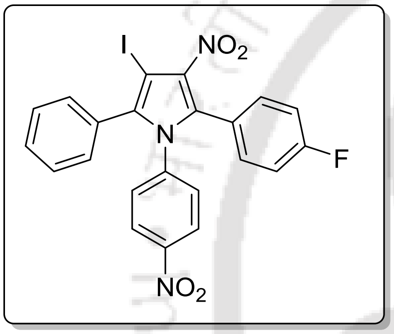
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.25 (d, *J* = 2.8 Hz, 3H), 7.18-7.11 (m, 2H), 7.07 (dd, *J* = 18.8, 7.6 Hz, 4H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 7.6 Hz, 2H), 2.28 (s, 3H), 2.18 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 139.0, 138.4, 137.3, 136.3, 134.2, 131.4, 131.1, 130.7, 129.4, 128.8, 128.7, 128.3, 128.1, 126.1, 114.5, 61.2, 21.5, 21.3.

FT-IR (KBr): 3421, 2918, 1630, 1504, 1472, 1378, 1309, 1210, 1184, 1111, 1021, 908, 849, 829, 774, 734, 694 cm^{-1}.

Anal. Calcd for $C_{24}H_{19}IN_2O_2$: C, 58.31; H, 3.87; N, 5.67. Found: C, 58.40; H, 3.86; N, 5.61.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{24}H_{20}IN_2O_2$ 495.0569, found 495.0546.



2-(4-Fluorophenyl)-4-iodo-3-nitro-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrrole (Table 4, Entry 3).

Yellow solid; yield: 48%; mp 204-205 °C.

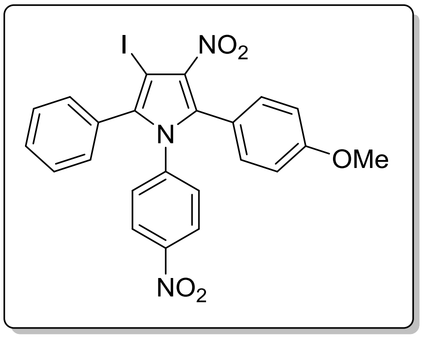
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.00 (d, *J* = 9.2 Hz, 2H), 7.34-7.30 (m, 3H), 7.23-7.15 (m, 4H), 7.04-6.96 (m, 4H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.9, 161.6, 147.1, 142.1, 137.4, 137.0, 134.5, 133.1, 133.0, 131.3, 130.1, 129.5, 128.7, 124.4, 124.3, 116.0, 115.7, 62.6.

FT-IR (KBr): 3423, 3071, 2923, 1594, 1507, 1470, 1382, 1342, 1310, 1235, 1158, 1103, 856, 694 cm^{-1}.

Anal. Calcd for $C_{22}H_{13}FIN_3O_4$: C, 49.93; H, 2.48; N, 7.94. Found: C, 49.83; H, 2.50; N, 8.00.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{22}H_{14}FIN_3O_4$ 530.0013, found 530.0028.



3-Iodo-5-(4-methoxyphenyl)-4-nitro-1-(4-nitrophenyl)-2-phenyl-1*H*-pyrrole (Table 4, Entry 4).

Yellow solid; yield: 70%; mp 206-207 °C.

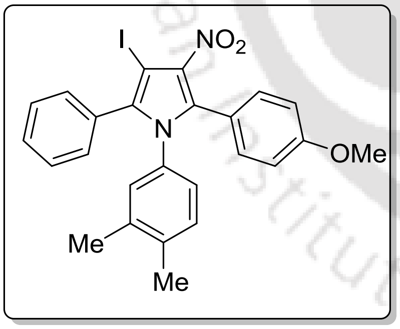
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.99 (d, *J* = 7.8 Hz, 2H), 7.32-7.26 (m, 3H), 7.17-7.11 (m, 4H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.81 (d, *J* = 7.8 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 160.5, 146.9, 142.4, 136.9, 135.6, 132.5, 131.3, 130.3, 129.5, 129.4, 128.7, 124.3, 120.1, 114.0, 62.6, 55.4.

FT-IR (KBr): 3435, 2923, 1610, 1519, 1504, 1374, 1347, 1310, 1253, 1174, 1110, 1032, 1015, 856, 701 cm^{-1}.

Anal. Calcd for $C_{23}H_{16}IN_3O_5$: C, 51.03; H, 2.98; N, 7.76. Found: C, 51.12; H, 2.97; N, 7.70.

MS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{23}H_{17}IN_3O_5$ 542.0213, found 542.0239.



1-(3,4-Dimethylphenyl)-3-iodo-5-(4-methoxyphenyl)-4-nitro-2-phenyl-1*H*-pyrrole (Table 4, Entry 5).

Yellow solid; yield: 56%; mp 203-204 °C.

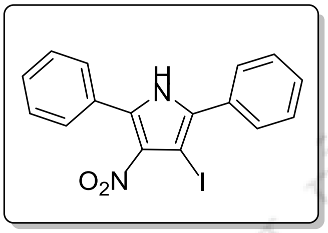
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.29-7.12 (m, 7H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.9, 137.2, 137.0, 136.1, 134.5, 132.3, 131.9, 131.8, 131.5, 131.3, 129.8, 129.5, 128.7, 128.1, 125.9, 121.4, 113.5, 61.1, 55.3, 19.7, 19.5.

FT-IR (KBr): 3439, 2924, 1609, 1499, 1383, 1310, 1246, 1176, 1036, 839, 762, 699 cm^{-1}.

Anal. Calcd for $C_{25}H_{21}IN_2O_3$: C, 57.26; H, 4.04; N, 5.34. Found: C, 57.17; H, 4.05; N, 5.41.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{22}IN_2O_3$ 525.0675, found 525.0699.



3-Iodo-4-nitro-2,5-diphenyl-1*H*-pyrrole (Table 5, Entry 1).

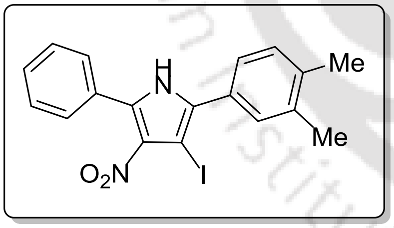
Yellow solid; yield: 52%; mp 174-175 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.88 (br s, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.52-7.33 (m, 8H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 134.4, 134.2, 130.8, 129.7, 129.4, 129.0, 128.8, 128.7, 128.6, 128.4, 124.6, 58.9; FT-IR (KBr): 3301, 2922, 2851, 1758, 1583, 1572, 1482, 1448, 1377, 1343, 1308, 1292, 1177, 1073, 1031, 912, 833, 769, 755, 695, 671, 531 cm^{-1}.

Anal. Calcd for $C_{16}H_{11}IN_2O_2$: C, 49.25; H, 2.84; N, 7.18. Found: C, 49.35; H, 2.83; N, 7.11.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}IN_2O_2$ 390.9943, found 390.9956.



2-(3,4-Dimethylphenyl)-3-iodo-4-nitro-5-phenyl-1*H*-pyrrole (Table 5, Entry 2).

Yellow solid; yield: 59%; mp 186-187 °C.

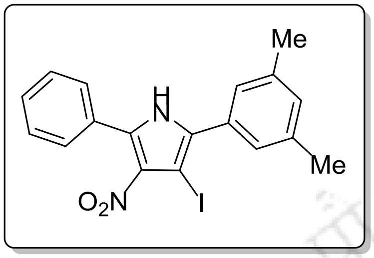
^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.84 (br s, 1H), 7.52-7.49 (m, 5H), 7.45-7.24 (m, 2H), 7.07 (s, 1H), 2.38 (s, 6H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 137.9, 137.2, 134.4, 134.1, 130.0, 129.6, 129.5, 129.3, 128.7, 128.6, 128.3, 128.1, 125.8, 58.4, 19.8, 19.7.

FT-IR (KBr): 3358, 2930, 2851, 1759, 1593, 1575, 1500, 1451, 1378, 1342, 1305, 1289, 1178, 1059, 1029, 918, 835, 781, 751, 696, 676, 549 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}IN_2O_2$: C, 51.69; H, 3.62; N, 6.70. Found: C, 51.60; H, 3.64; N, 6.78.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{16}IN_2O_2$ 419.0256, found 419.0271.



2-(3,5-Dimethylphenyl)-3-iodo-4-nitro-5-phenyl-1*H*-pyrrole (Table 5, Entry 3).

Yellow solid; yield: 55%; mp 194-195 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.86 (br s, 1H), 7.52-7.37 (m, 7H), 7.26-7.12 (m, 1H), 2.27 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4, 134.8, 134.4, 134.1, 130.7, 129.6, 129.4, 128.7, 128.6, 128.1, 126.0, 58.5, 21.2.

FT-IR (KBr): 3361, 2921, 2853, 1761, 1590, 1570, 1492, 1456, 1378, 1349, 1307, 1298, 1175, 1067, 1022, 917, 815, 771, 756, 690, 673 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}IN_2O_2$: C, 51.69; H, 3.62; N, 6.70. Found: C, 51.58; H, 3.65; N, 6.77.

MS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{16}IN_2O_2$ 419.0256, found 419.0241.

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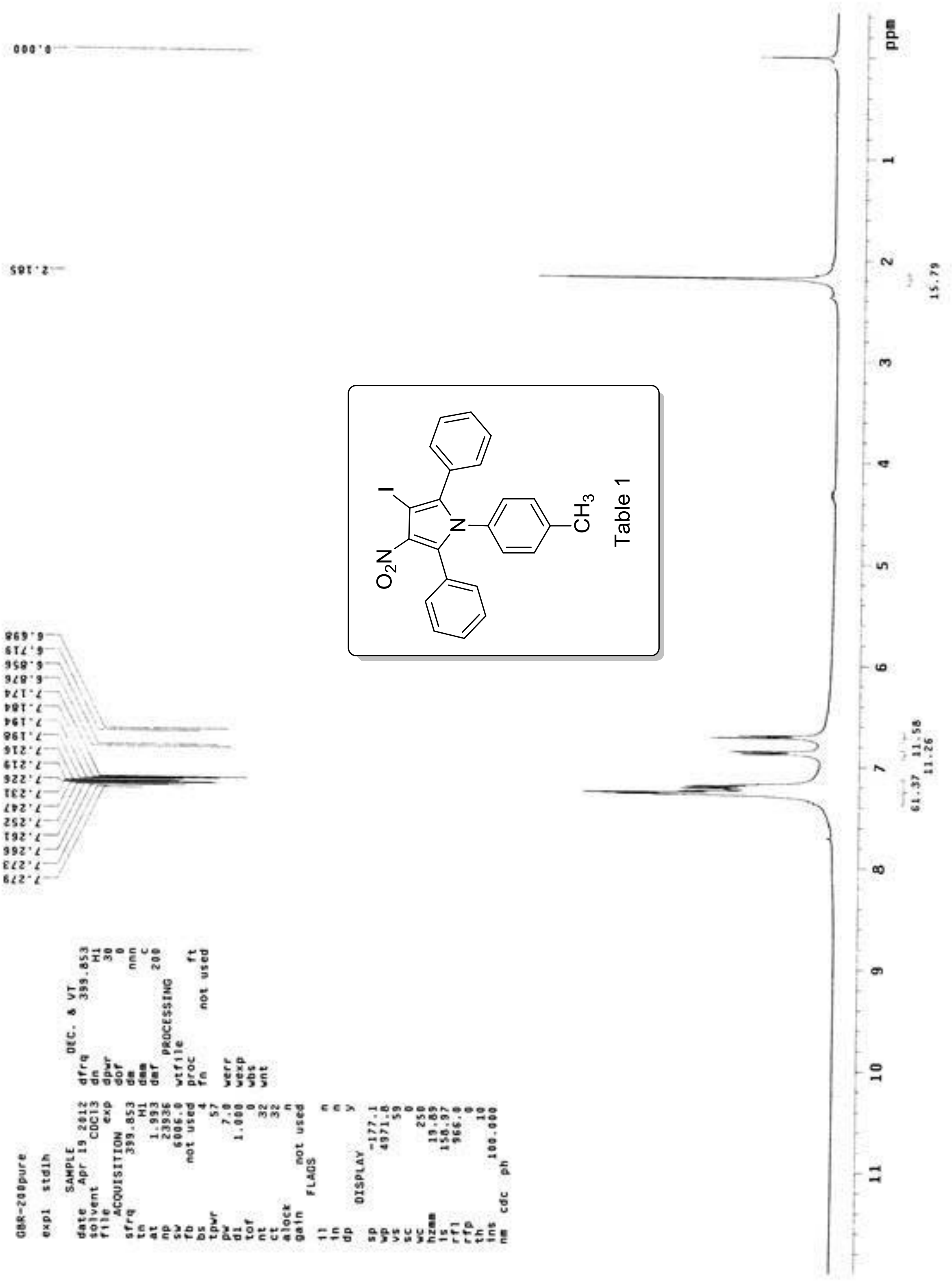
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SAMPLE
date Apr 19 2012
solvent CDCl3
file exp
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at 1.993
np 23936
sw 6006.0
fb not used
bs 4
tpwr 57
pw 7.0
d1 1.000
tof 0
nt 32
ct 32
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -177.1
wp 4971.8
vs 59
sc 0
wc 250
hzmm 19.89
is 158.97
rfl 966.0
rfp 0
th 10
ins 100.000
nm cdc ph
DEC. & VT
dfrq 399.853
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
0.000
2.185
6.698
6.719
6.856
6.876
7.174
7.184
7.194
7.198
7.216
7.219
7.226
7.231
7.247
7.252
7.261
7.266
7.273
7.279
I
O_2N
N
CH_3
Table 1
15.79
61.37
11.58
11.26
ppm
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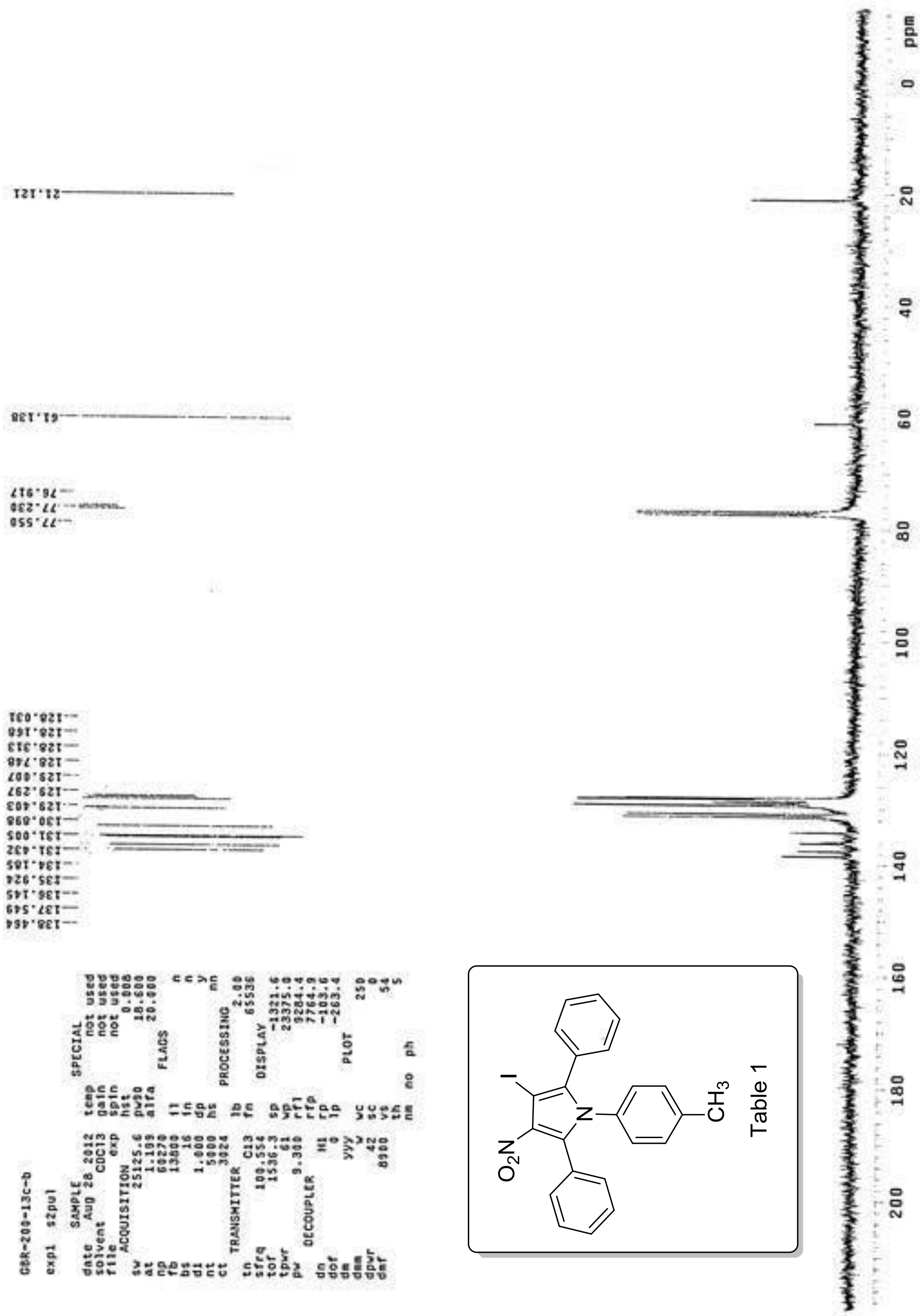
2
3
4
5
6
7
8
9
10
11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date Aug 28 2012
solvent CDCl3
file exp
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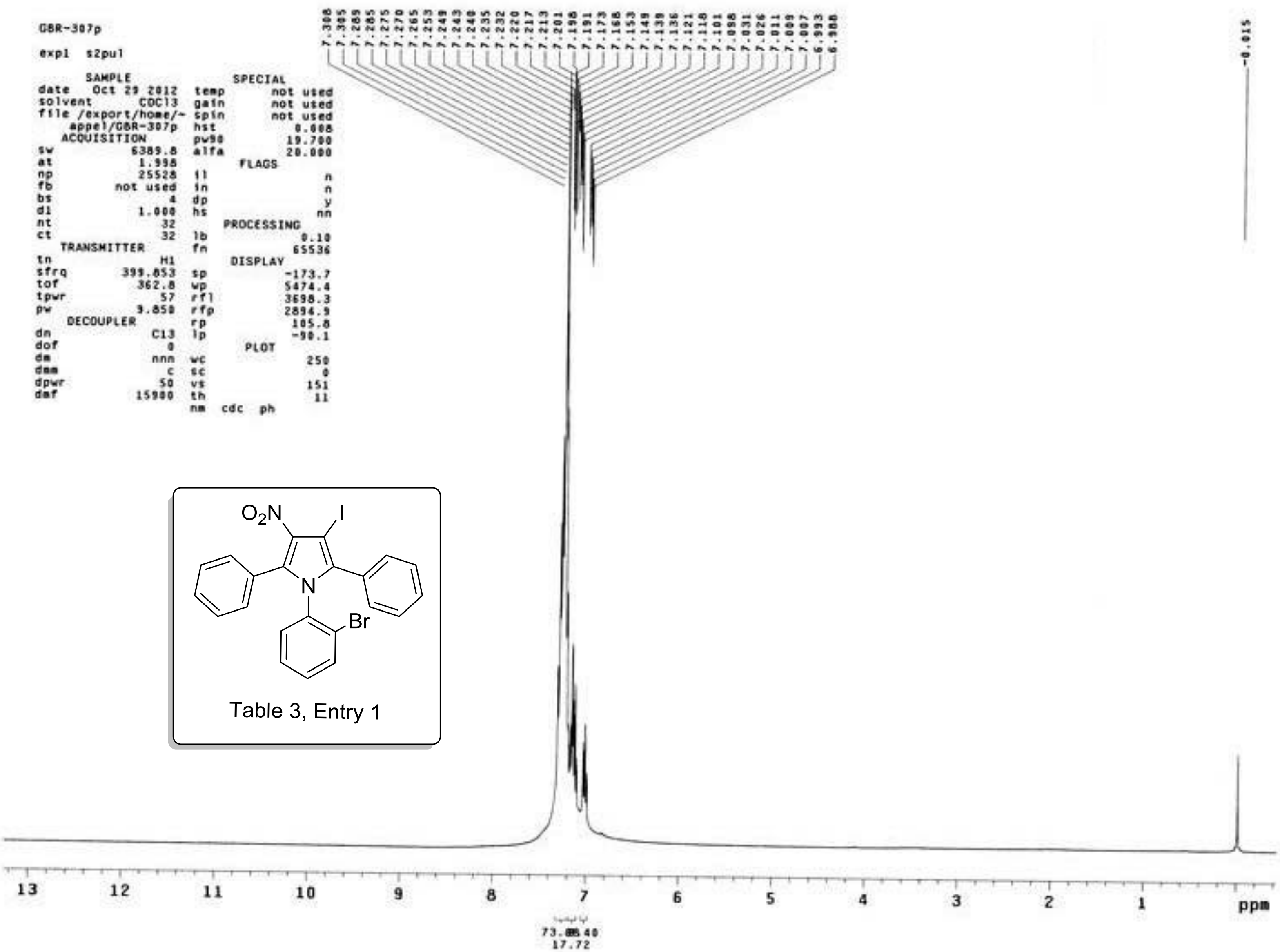
np 60270
fb 13800
bs 16
d1 1.000
nt 5000
ct 3024
TRANSMITTER
tn C13
sfrq 100.554
tof 1536.3
tpwr 61
pw 9.300
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 42
dmf 8900
SPECIAL
temp not used
gain not used
spin not used
hst 0.008
pw90 18.600
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 2.00
fn 65536
DISPLAY
sp -1321.6
wp 23375.0
rfl 9284.4
rfp 7764.9
rp -103.6
lp -263.4
PLOT
wc 250
sc 0
vs 54
th 5
nm no ph
21.121
61.138
76.917
77.230
77.550
128.031
128.168
128.313
128.748
129.007
129.297
129.403
130.898
131.005
131.432
134.185
135.924
136.145
137.549
138.464
I
O_2N
N
CH_3
Table 1
200
180
160
140
120
100
80
60
40
20
0
ppm



```
GBR-307p

expl  s2pul

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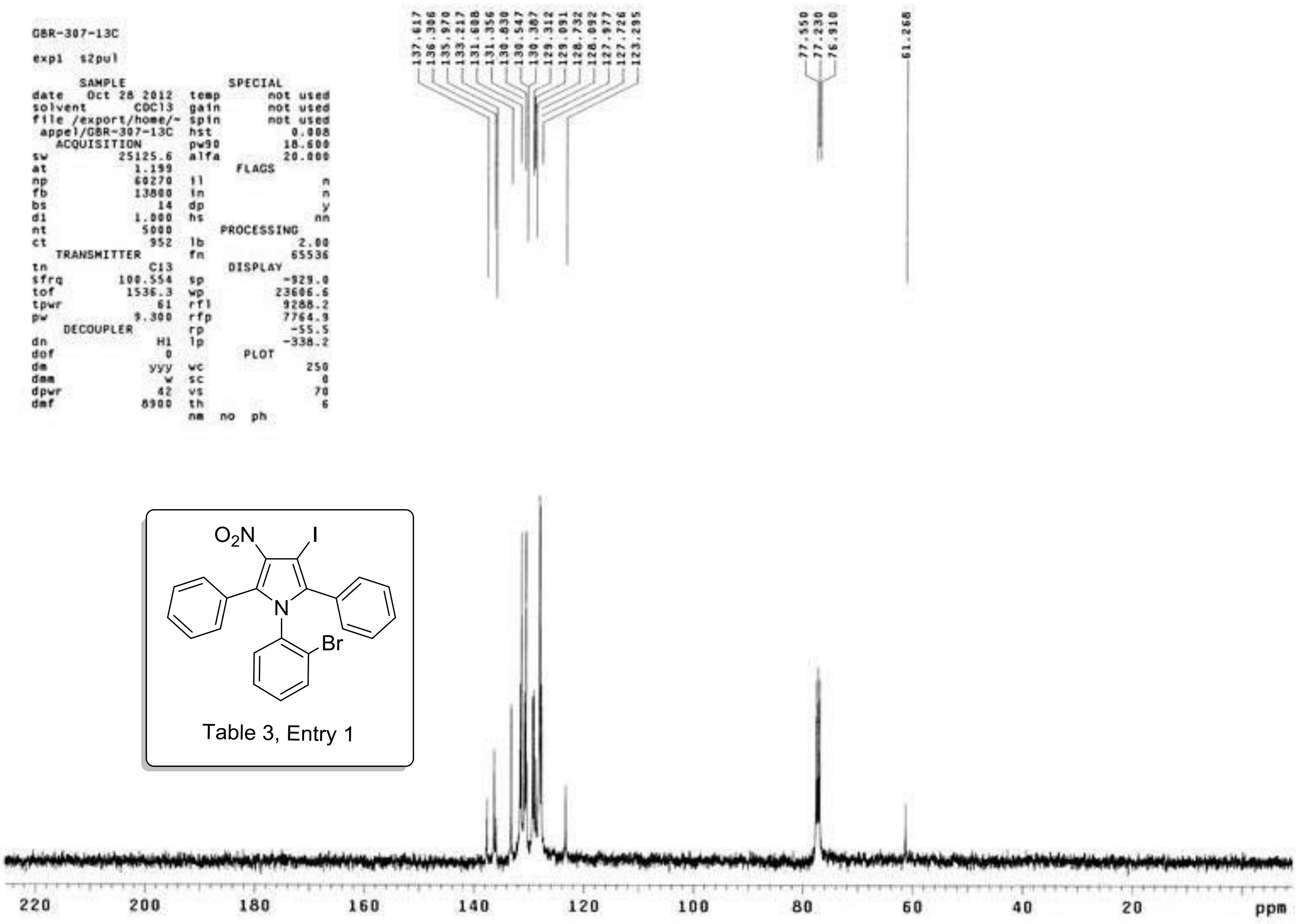
solvent       CDCl3  gain        not used
file /export/home/~ spin        not used
   appel/GBR-307p   hst            0.008
   ACQUISITION      pw90          19.700
sw            6389.8 alfa          20.000
at             1.998          FLAGS
np             25528 il                n
fb          not used in                n
bs                 4 dp                y
d1             1.000 hs               nn
nt                32        PROCESSING
ct                32 lb             0.10
   TRANSMITTER       fn            65536
tn                H1         DISPLAY
sfrq         399.853 sp           -173.7
tof            362.8 wp           5474.4
tpwr              57 rfl          3698.3
pw             9.850 rfp          2894.9
    DECOUPLER        rp            105.8
dn               C13 lp            -90.1
dof                0          PLOT
dm               nnn wc              250
dmm                c sc                0
dpwr              50 vs              151
dmf            15900 th               11
                     nm  cdc  ph
```

Table 3, Entry 1



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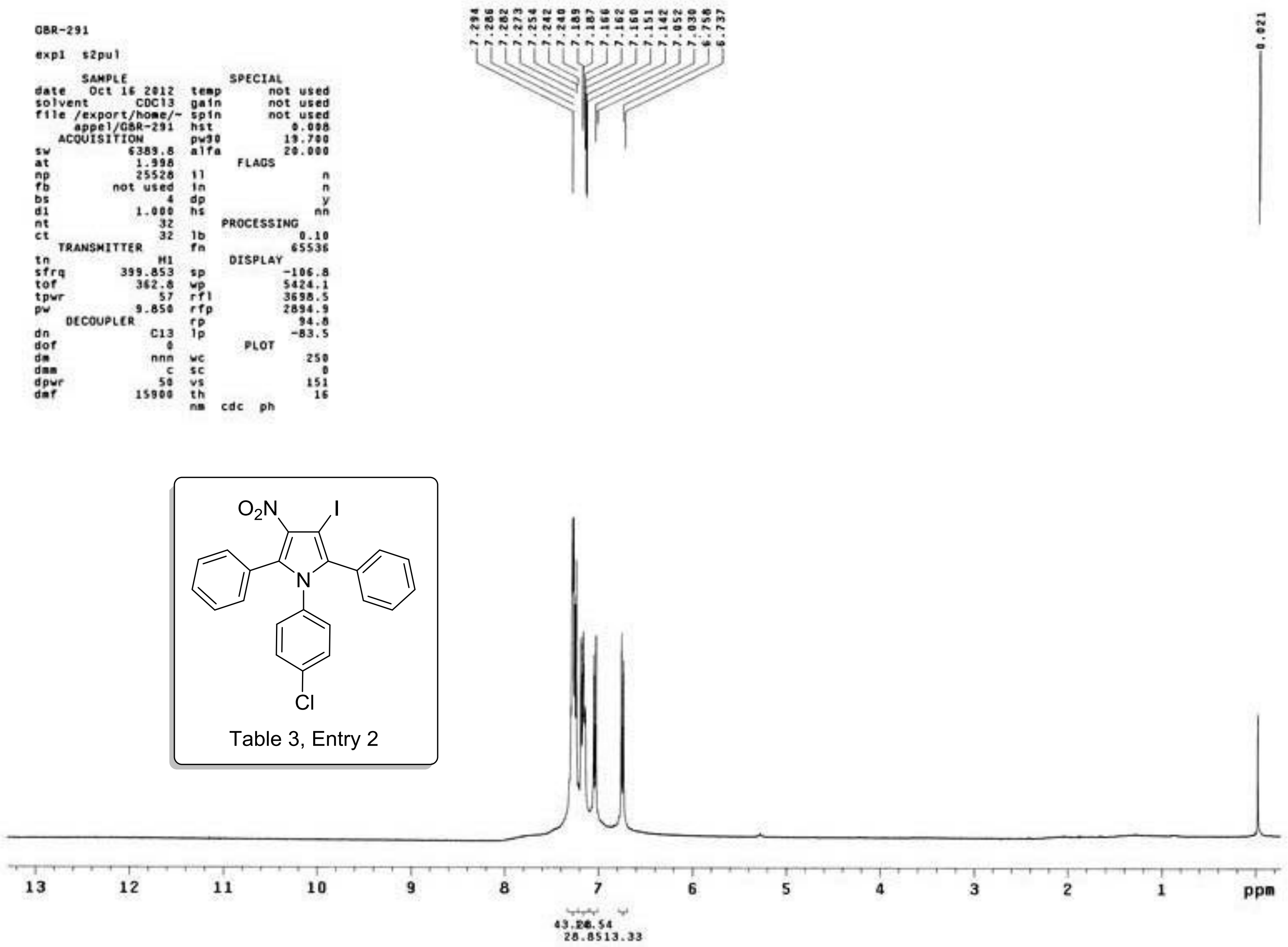

```
GBR-291

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date   Oct 16 2012  temp        not used
solvent       CDCl3  gain        not used
file /export/home/~  spin        not used
     appel/GBR-291  hst            0.008
   ACQUISITION      pw90          19.700
sw            6389.8  alfa          20.000
at             1.998           FLAGS
np             25528  il                n
fb          not used  in                n
bs                 4  dp                y
d1             1.000  hs               nn
nt                32        PROCESSING
ct                32  lb             0.10
   TRANSMITTER        fn            65536
tn                H1          DISPLAY
sfrq         399.853  sp            -106.8
tof            362.8  wp            5424.1
tpwr              57  rfl           3698.5
pw             9.850  rfp           2894.9
    DECOUPLER         rp              94.8
dn               C13  lp             -83.5
dof                0           PLOT
dm               nnn  wc              250
dmm                c  sc                0
dpwr              50  vs              151
dmf            15900  th               16
                      nm  cdc   ph
```

Table 3, Entry 2

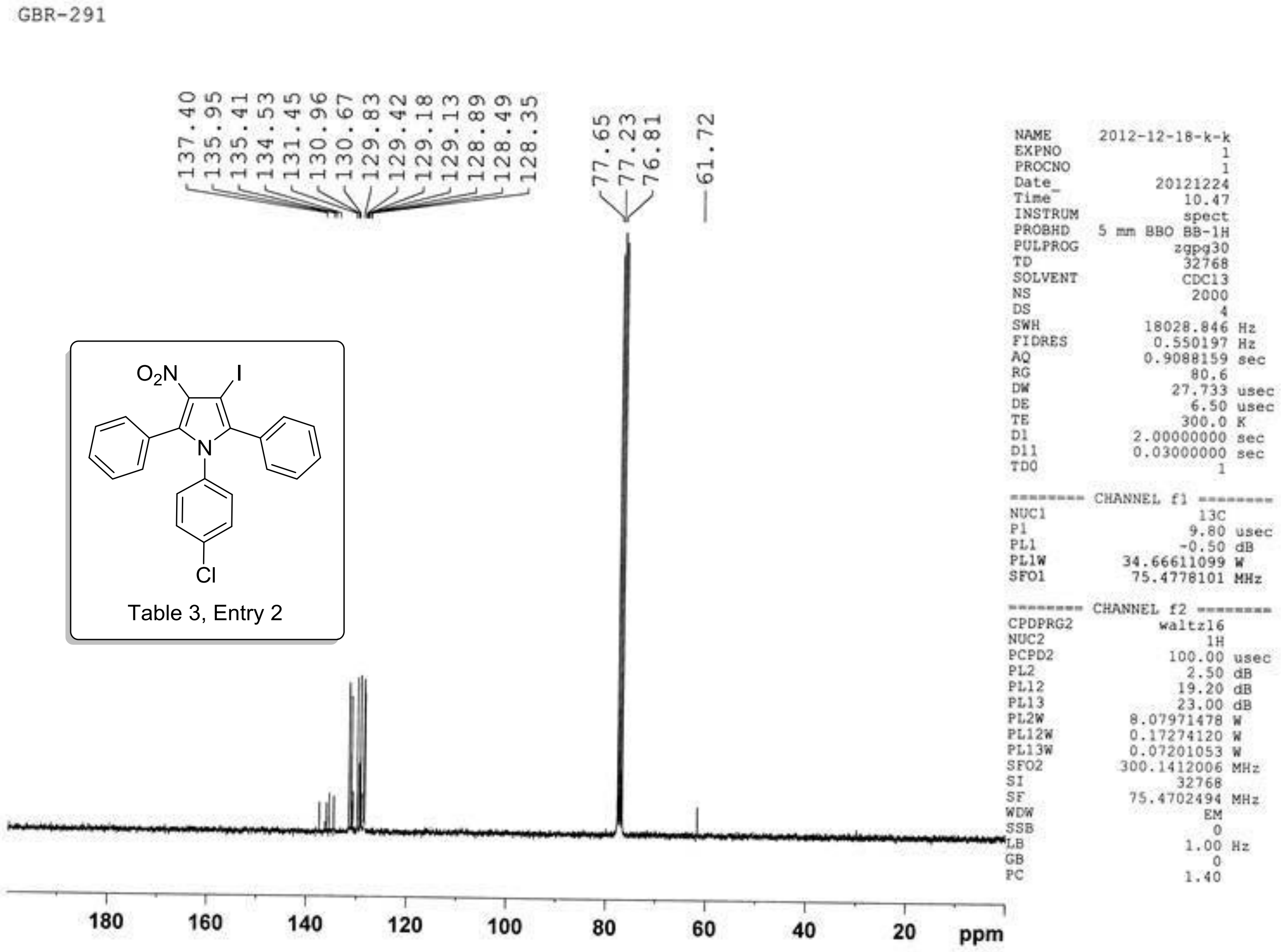

Table 3, Entry 2

```
NAME          2012-12-18-k-k
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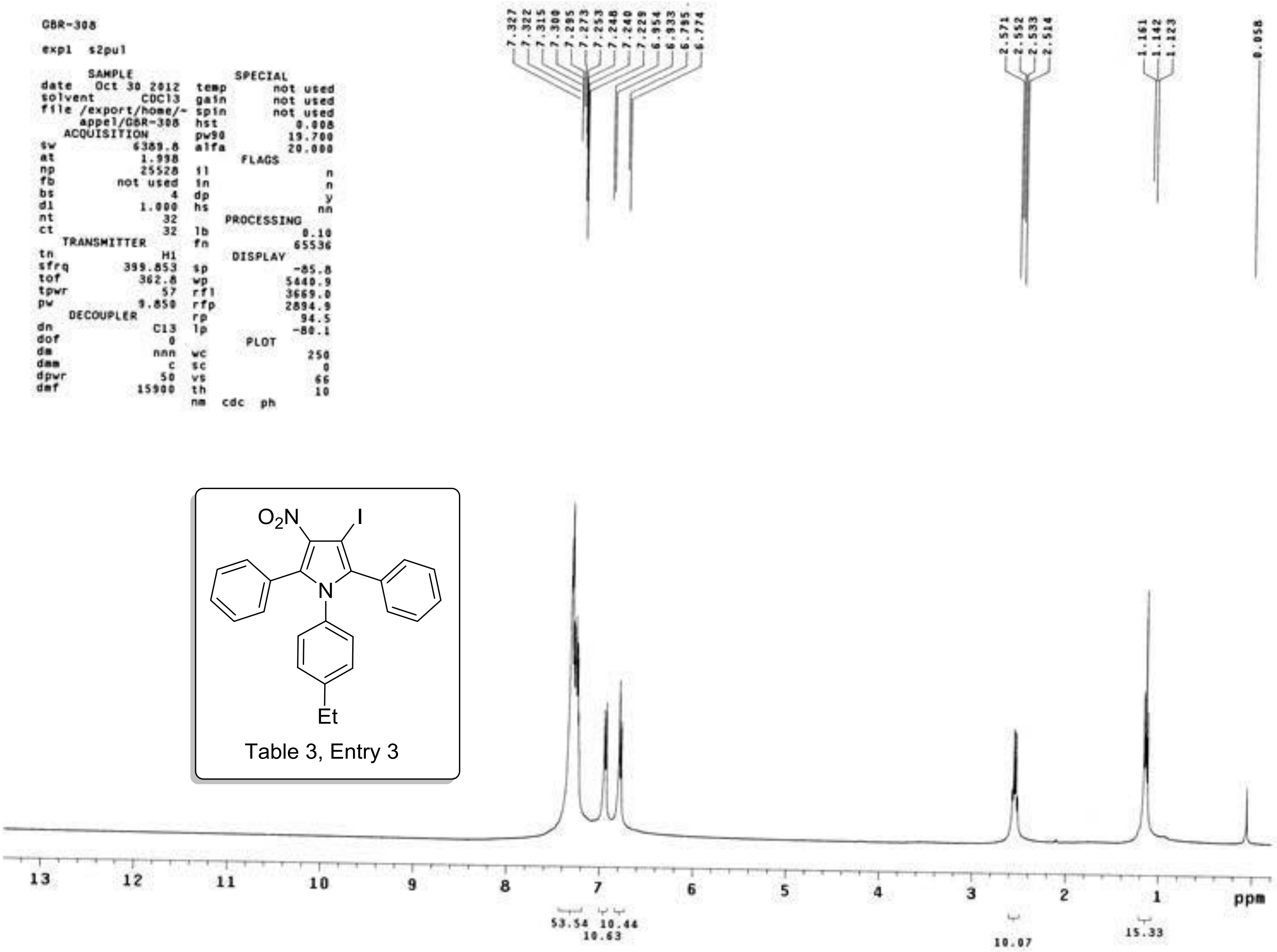
PROCNO                     1
Date_               20121224
Time_                  10.47
INSTRUM                spect
PROBHD     5 mm BBO BB-1H
PULPROG              zgpg30
TD                    32768
SOLVENT               CDCl3
NS                     2000
DS                        4
SWH               18028.846 Hz
FIDRES             0.550197 Hz
AQ                0.9088159 sec
RG                     80.6
DW                   27.733 usec
DE                     6.50 usec
TE                    300.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.80 usec
PL1                   -0.50 dB
PL1W            34.66611099 W
SFO1            75.4778101 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                    2.50 dB
PL12                  19.20 dB
PL13                  23.00 dB
PL2W             8.07971478 W
PL12W            0.17274120 W
PL13W            0.07201053 W
SFO2           300.1412006 MHz
SI                    32768
SF               75.4702494 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```



```
GBR-308

exp1  s2pul

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solvent       CDCl3  gain        not used
file /export/home/~ spin        not used
     appel/GBR-308  hst            0.008
   ACQUISITION      pw90          19.700
sw          6389.8  alfa          20.000
at           1.998          FLAGS
np           25528  il                 n
fb        not used  in                 n
bs               4  dp                 y
d1           1.000  hs                nn
nt              32         PROCESSING
ct              32  lb              0.10
   TRANSMITTER      fn             65536
tn              H1          DISPLAY
sfrq       399.853  sp             -85.8
tof          362.8  wp            5440.9
tpwr            57  rfl           3669.0
pw           9.850  rfp           2894.9
    DECOUPLER       rp              94.5
dn             C13  lp             -80.1
dof              0           PLOT
dm             nnn  wc               250
dmm              c  sc                 0
dpwr            50  vs                66
dmf          15900  th                10
                    nm   cdc   ph
```

Table 3, Entry 3

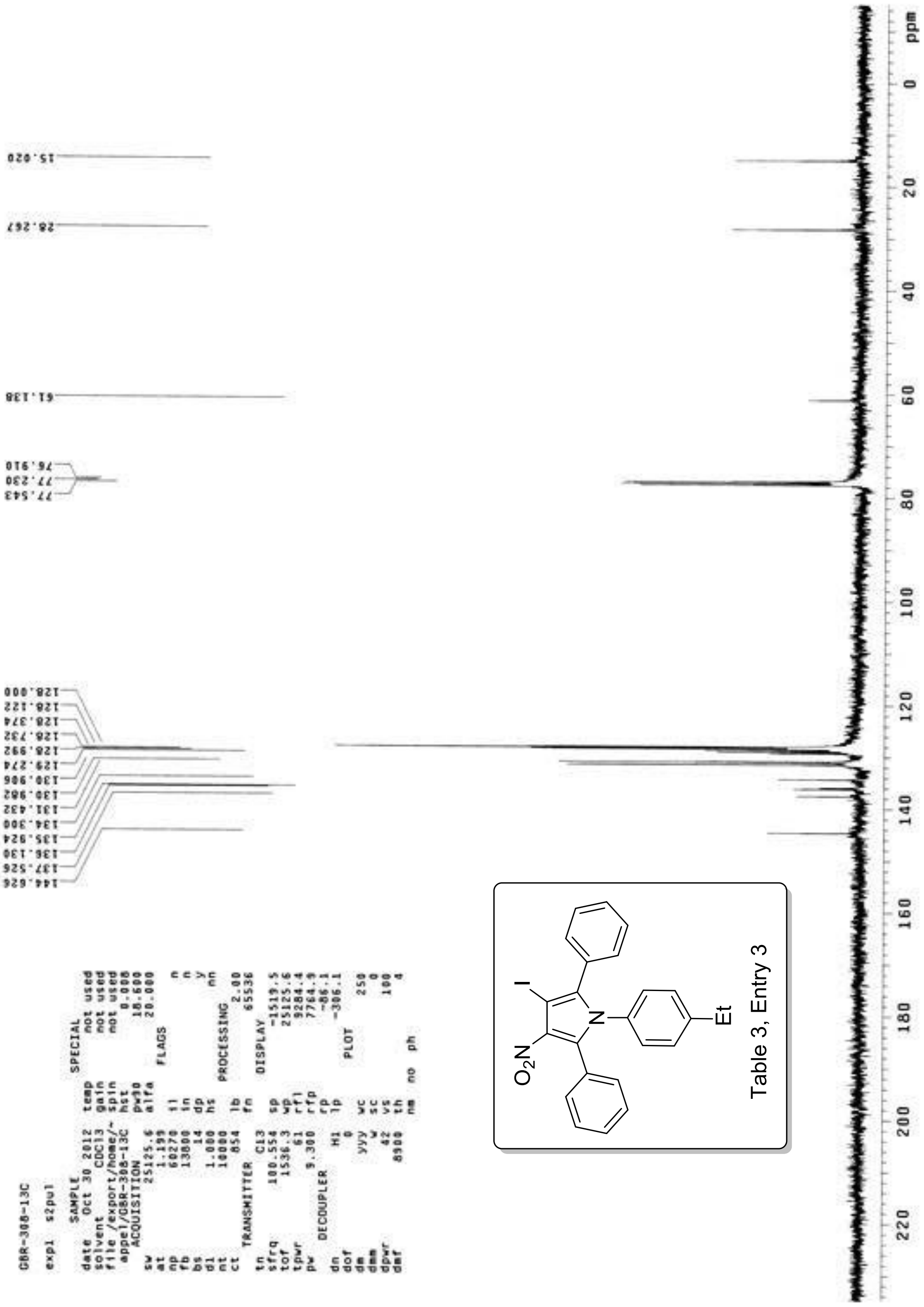

Table 3, Entry 3

GBR-287

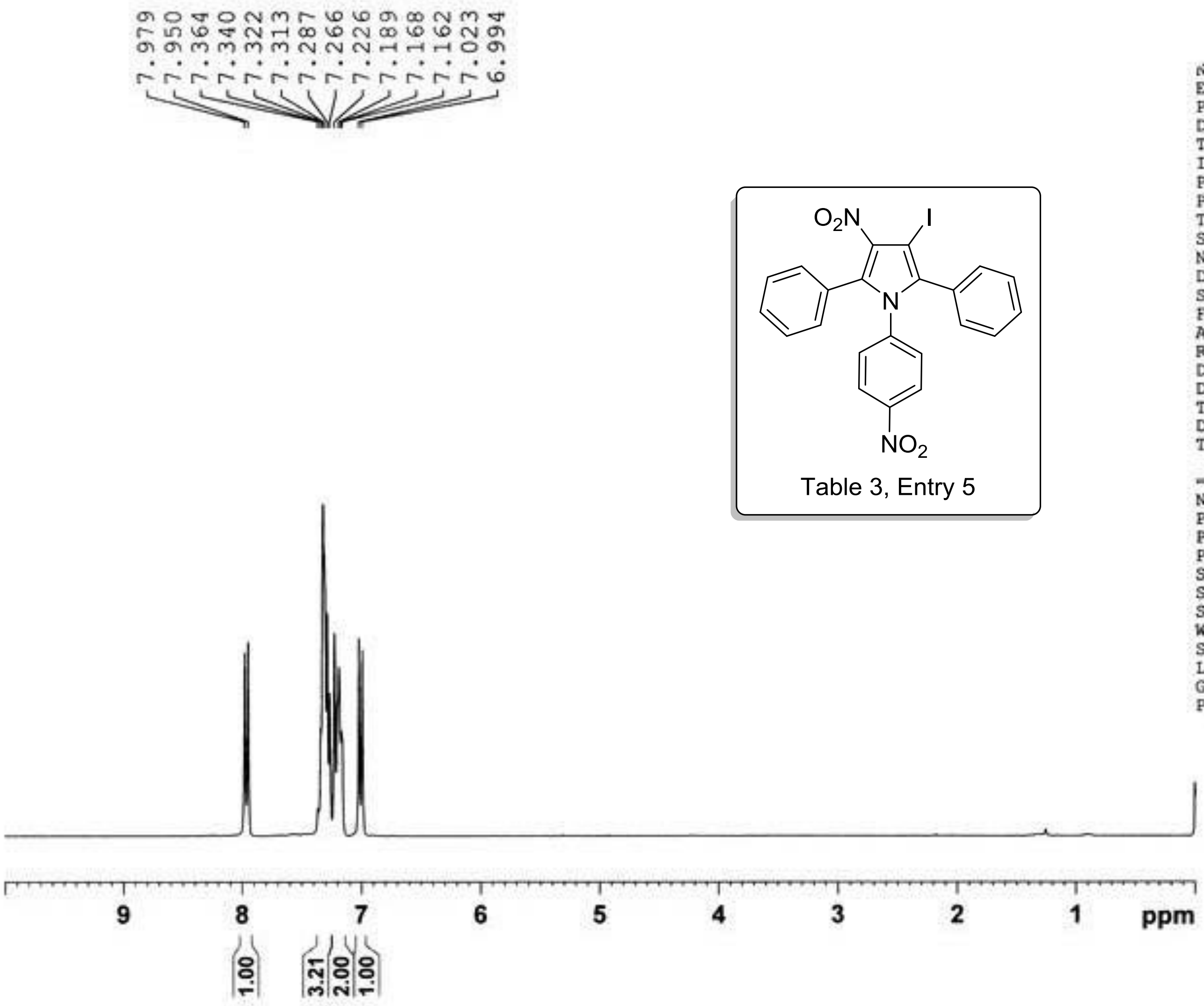

Table 3, Entry 5

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PROCNO                  1
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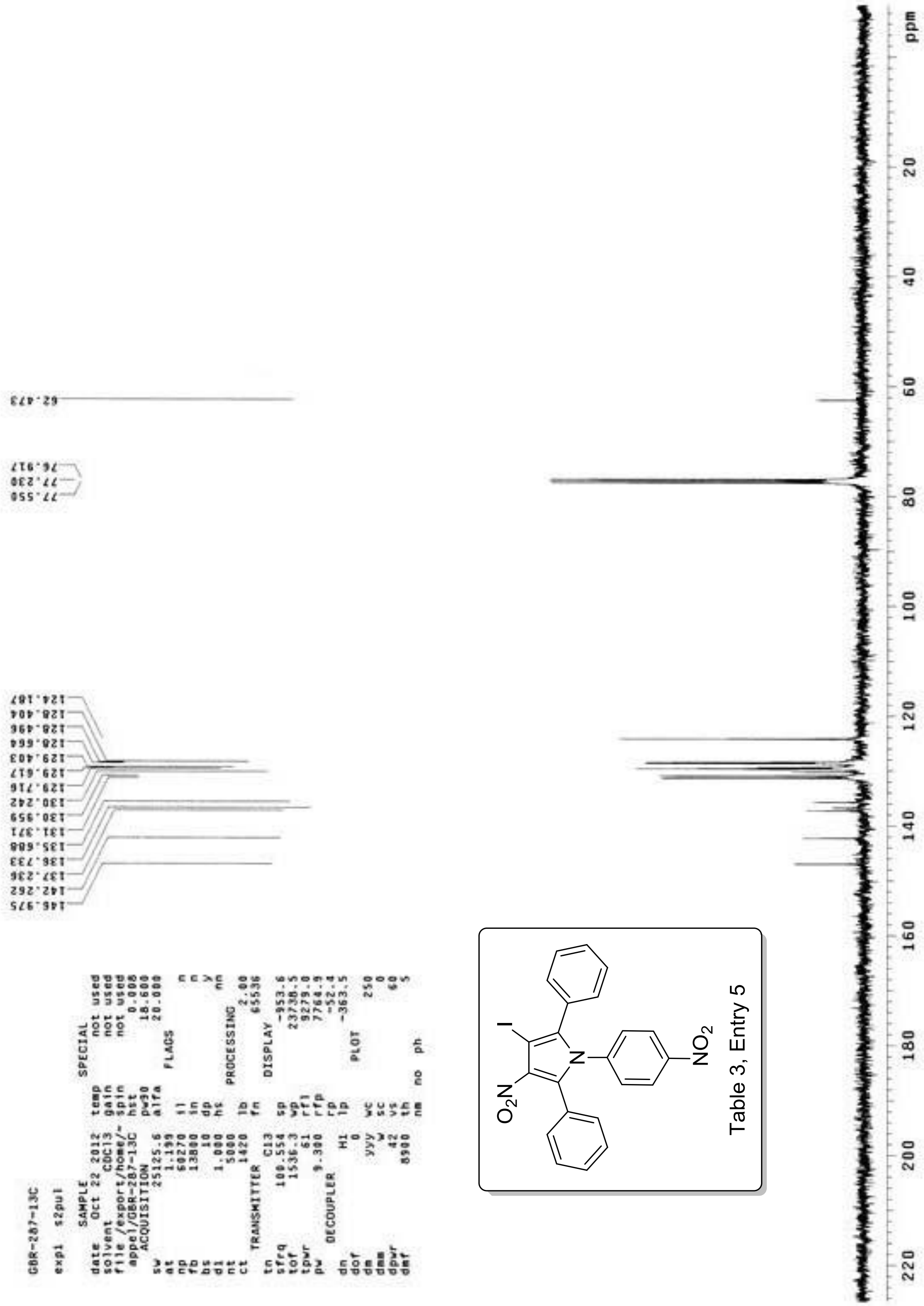
INSTRUM             spect
PROBHD   5 mm BBO BB-1H
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              6188.119 Hz
FIDRES           0.188846 Hz
AQ              2.6477044 sec
RG                     10
DW                 80.800 usec
DE                   6.50 usec
TE                  300.0 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.75 usec
PL1                  2.50 dB
PL1W           8.07971478 W
SFO1          300.1418535 MHz
SI                  16384
SF            300.1400000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```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date Oct 22 2012
solvent CDCl3
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TRANSMITTER
DECOUPLER
SPECIAL
FLAGS
PROCESSING
DISPLAY
PLOT
146.975
142.262
137.236
136.733
135.688
131.371
130.959
130.242
129.716
129.617
129.403
128.664
128.496
128.404
124.187
77.550
77.230
76.917
62.473
O_2N
I
N
NO_2
Table 3, Entry 5
220
200
180
160
140
120
100
80
60
40
20
ppm

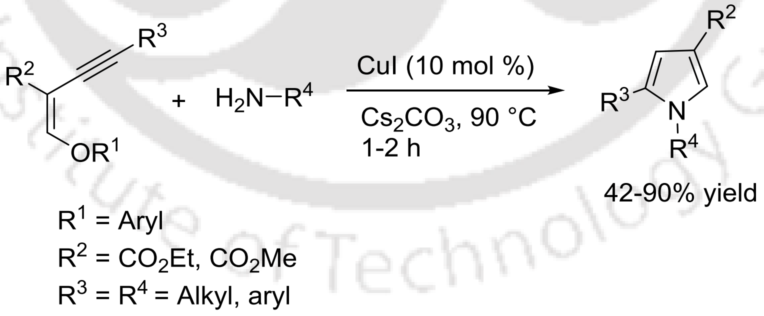
Cu-Catalyzed Cyclization of 1,3-Enynes with Amines and Hydrazine: Synthesis of Substituted Pyrroles and Pyrazoles

Development of new and efficient protocols towards the construction of functionalized pyrroles and pyrazoles[1-2] garnered considerable attention in academia and pharmaceutical industries. The strategies for the synthesis of highly substituted pyrroles with diverse substituents are unfamiliar till date due to poor functional group tolerance, longer reaction time, limited substrate scopes and harsh reaction conditions. Transition metal-catalyzed reactions somewhat tackled the above mentioned drawbacks to construct the highly functionalized biological heterocyclic scaffolds. Among these, Cu-catalyzed[3] processes have attracted significant interest for the carbon-carbon and carbon-heteroatom bonds formation due to high abundance, low-toxicity with high efficiency and milder the reaction conditions with high functional group tolerance.

The importance of pyrroles and pyrazoles derivatives has motivated the development of several methods with diverse substitution patterns.

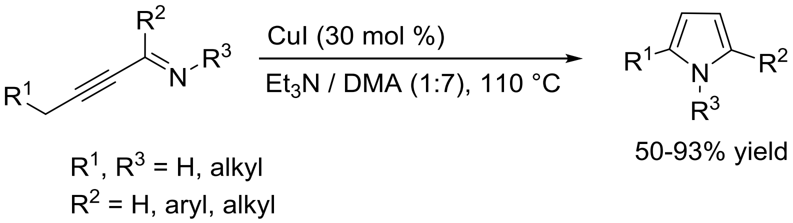
3.1 Cu-Catalyzed Pyrrole Synthesis

Li and co-workers developed regioselective synthesis of 1,2,4-trisubstituted pyrroles using Cu-catalyzed cascade reaction of aryloxyenynes with amines (Scheme 1).[3a]



Scheme 1

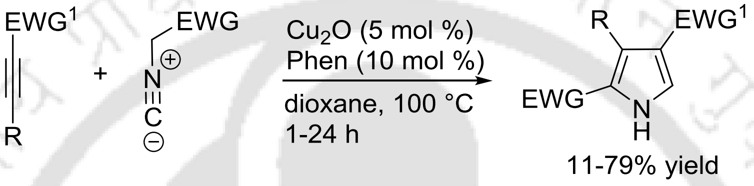
Gevorgyan group demonstrated that the 2,5-disubstituted pyrroles can be readily synthesized using Cu-assisted cycloisomerization of readily available alkynyl imines (Scheme 2).[3b]



R^1, R^3 = H, alkyl
R^2 = H, aryl, alkyl

Scheme 2

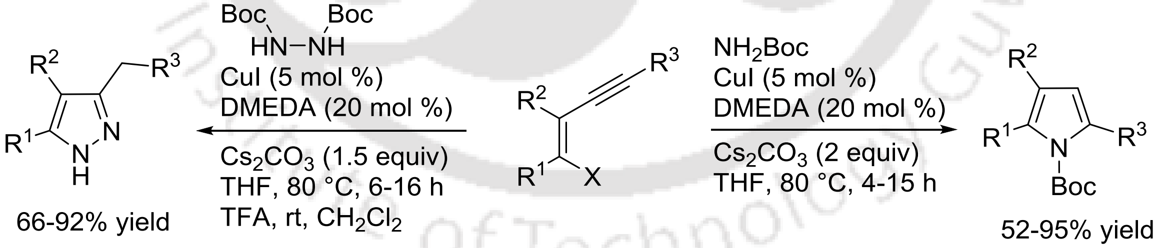
Cu-catalyzed formal [3+2] cycloaddition of isocyanides with electron-deficient alkynes provides tri-substituted pyrroles (Scheme 3).[3c]



R = H, alkyl, aryl
EWG = CO_2Et, CO_2Me, CO_2t-Bu, $CONEt_2$, $PO(OEt)_2$, Ph
EWG^1 = CO_2Et, CO_2Me, CN, SO_2Ph, CO_2Et

Scheme 3

Buchwald and co-workers reported Cu-catalyzed domino *C-N* coupling/hydroamidation of 1,3-enyne with amine to produce pyrroles and pyrazoles in high yields. In this reaction, metal encompasses dual roles of amidation and hydroamidation (Scheme 4).[3d]

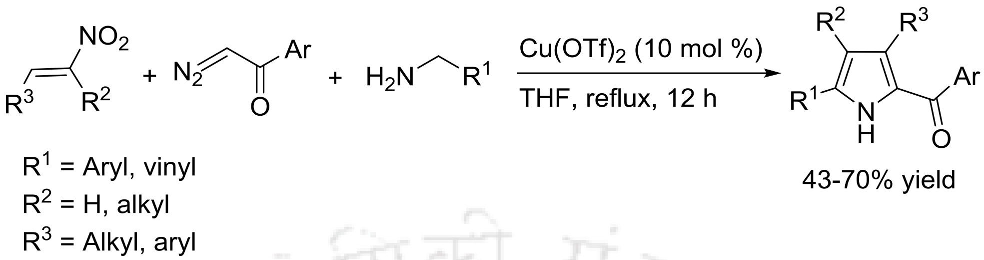


X = I, Br
R^1 = Alkyl, vinyl, CO_2Me, TBS
R^2 = R^3 = H, alkyl, aryl

Scheme 4

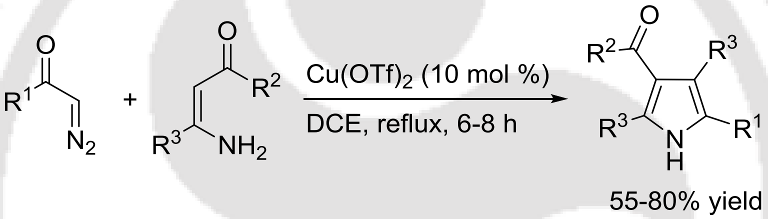
Cu-catalyzed substituted pyrroles can be readily synthesized from three-component reaction of α-diazoketones, nitroalkenes and amines under aerobic conditions. This strategy encompasses an

N-H insertion of carbene, oxidative dehydrogenation of amine and [3+2] cycloaddition of azomethine ylide (Scheme 5).[3e]



Scheme 5

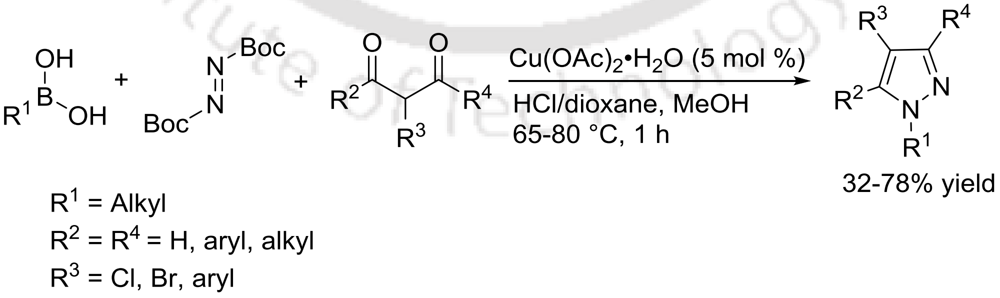
Cu(OTf)$_2$-catalyzed synthesis of trisubstituted pyrrole has been shown from the coupling of *α*-diazoketones with *β*-enaminoketones under reflux conditions (Scheme 6).[3f]



Scheme 6

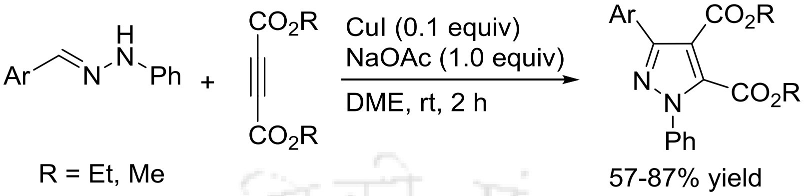
3.2 Pyrazole Synthesis

Beveridge group reported the synthesis of substituted pyrazoles using Cu-catalyzed boronic acid coupling followed by cyclization. The diversity of aryl and heteroaryl *N*-functionalized pyrazoles has been demonstrated (Scheme 7).[2a]



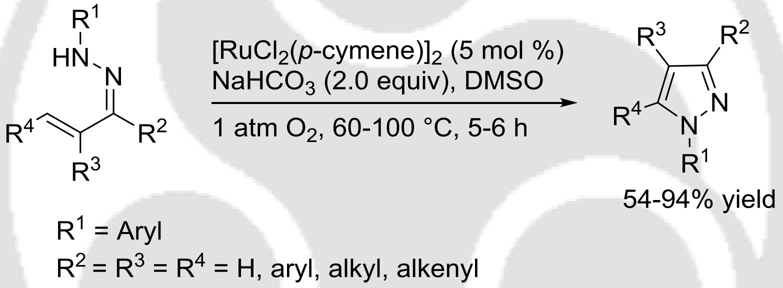
Scheme 7

Ma and co-workers showed the synthesis of tetrasubstituted pyrazoles using Cu-catalyzed reaction of phenylhydrazine with dialkyl ethylenedicarboxylates. The construction of a series of pyrazoles has been presented with diverse functionalities (Scheme 8).[2b]



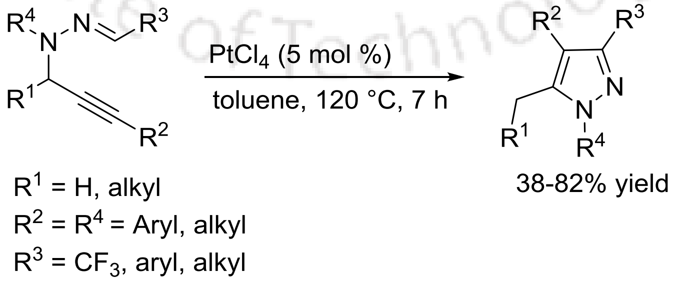
Scheme 8

Rao group showed Ru-catalyzed intramolecular oxidative *C-N* coupling reaction for the synthesis of substituted pyrazoles. The reaction uses of oxygen as the oxidant and the products are formed in high yields (Scheme 9).[2c]



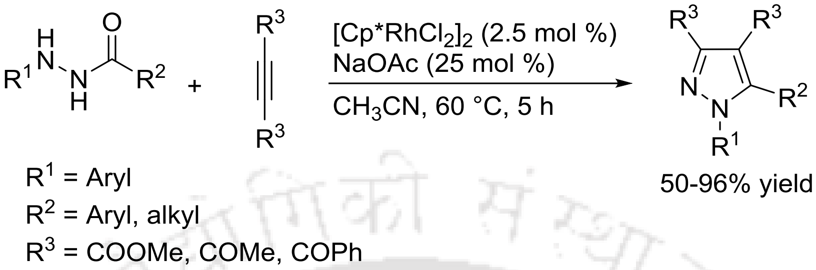
Scheme 9

Zhan and co-workers presented Pt-catalyzed reaction of *N*-propargylhydrazones to furnish pyrazoles *via* [3,3]-sigmatropic rearrangement/cascade cyclization. The method affords a convenient route to a diversity of highly substituted pyrazole derivatives (Scheme 10).[2d]



Scheme 10

Liu and co-workers demonstrated Rh-catalyzed addition-cyclization of hydrazine with alkyne to give substituted pyrazoles. The cascade cyclization comprises addition of the *C−N* bond of hydrazines to alkynes *via* *C−N* bond cleavage and intramolecular dehydration (Scheme 11).[2e]



Scheme 11

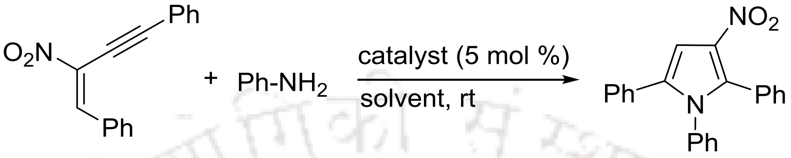
3.3 Present Work

Herein we present an aerobic Cu-catalyzed domino aza Michael addition, cyclization and oxidative aromatization of 1,3-enynes with amines. This protocol is simple, efficient, atom economical and tolerates an array of functionality and substantial steric hindrance.

First, the optimization of the reaction conditions was performed employing (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne and aniline as the model substrates in the presence of Cu-catalysts in different solvents under air (Table 1). To our pleasure, the reaction expeditiously occurred to deliver the target 3-nitro-1,2,5-triphenyl-1*H*-pyrrole in 0.5 h with up to 99% conversion when the substrates were stirred with 5 mol % $Cu(OTf)_2$ in THF at room temperature under air. In a set of copper sources screened, $Cu(OTf)_2$ displayed the superior results, while CuCl, CuBr, CuI and $Cu(OAc)_2$ required somewhat longer reaction (2 h) to give similar conversions (Entries 1-4). In contrast, $CuSO_4$ was less effective affording the target product in 25% conversion (Entry 6). THF was found to be solvent of choice, whereas CH_3CN, CH_2Cl_2 and toluene led to the formation of target pyrrole in 74-88% conversions (Entries 7-9). Control experiment confirmed that the target product was not formed in the absence of the Cu-catalyst.

With the optimal conditions in hand, the scope of the protocol was studied for the reaction of substituted 1,3-enyne derivatives with aniline as a standard substrate (Table 2). The reactions occurred in high yields. For instance, the enyne with electron withdrawing chloro and flouro groups in aryl ring readily underwent reaction to give target pyrrole in good yields (Entries 1and 9), whereas enynes bearing electron donating methoxy group required slightly longer reaction time to give the desired pyrroles in 80-83% yields (Entries 2,7and 10). In addition, the mono and dimethyl substituted enynes proceeded reaction in 72-79% yields (Entries 3-4, 6, 8 and 11). Also, the reactions of the enynes containing naphthyl substituent produced the pyrrole derivatives (Entries 5and 12) in 63% and 82% yields, respectively.

Table 1. Optimization of the Reaction Conditions[a]

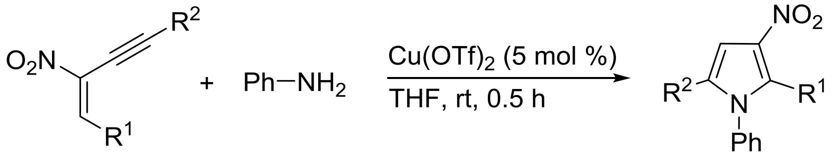


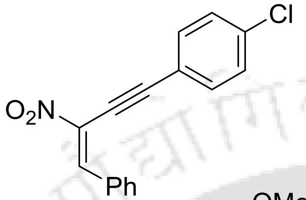
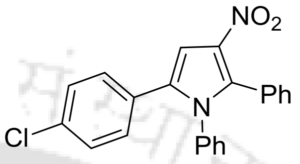
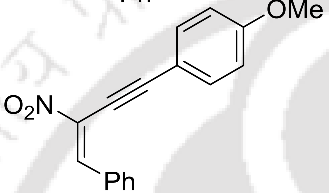
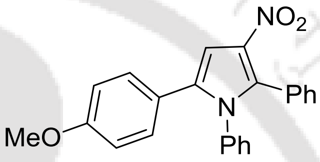
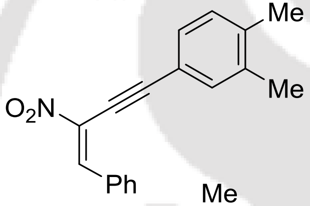
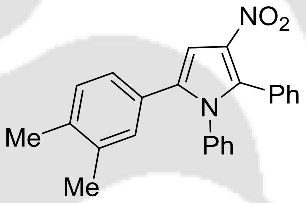
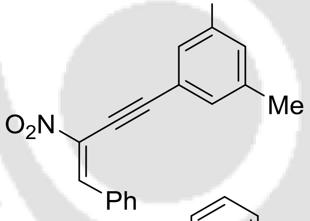
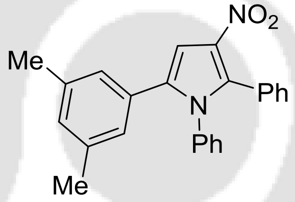
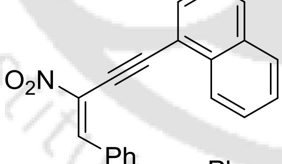
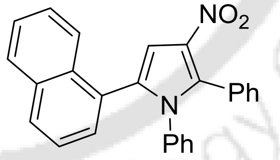
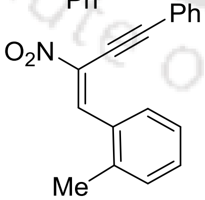
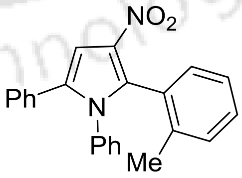
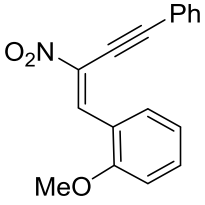
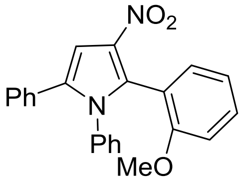
Entry	Catalyst	Solvent	Conversion (%)[b]
1	CuCl	THF	84
2	CuI	THF	89
3	CuBr	THF	92
4	$Cu(OAc)_2$	THF	95
5	**$Cu(OTf)_2$**	**THF**	**99[c] (87[d])**
6	$CuSO_4$	THF	25
7	$Cu(OTf)_2$	CH_3CN	74
8	$Cu(OTf)_2$	Toluene	88
9	$Cu(OTf)_2$	CH_2Cl_2	81
10	-	THF	n.d.

[a]Enyne (0.5 mmol), aniline (0.6 mmol), catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for 2 h. [b]Determined by ^{1}H NMR spectroscopic analysis. [c]The reaction completed at 0.5 h. [d]Isolated yield. n.d. = not detected.

Next, the reaction of different substituted amines was studied using (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne as a standard substrate (Table 3). As above, the reactions readily occurred in high yields. For instance, aryl amines with electron withdrawing substituents such as chloro, iodo, and nitro groups took slightly longer reaction time to afford the target cyclized

Table 2. Cu-Catalyzed Cyclization of Different 1,3-Enynes with Aniline[a]



Entry	Substrate	Product	Yield (%)[b]
[c]1			69
[d]2			80
3			75
4			72
5			63
6			74
[d]7			80

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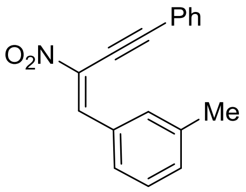
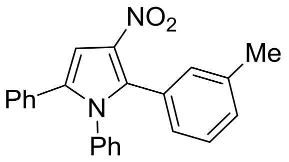
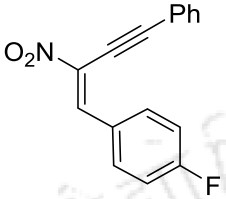
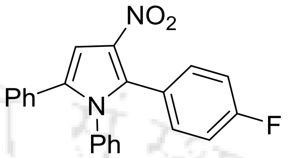
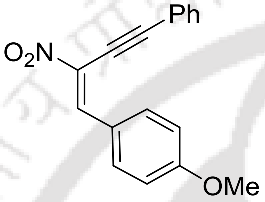
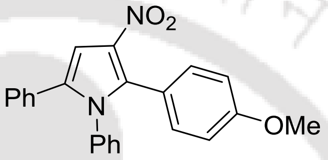
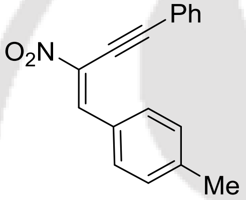
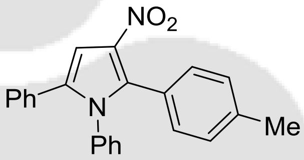
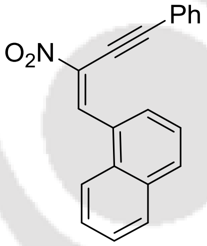
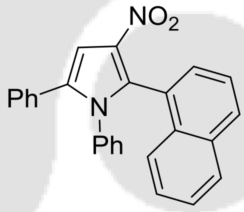
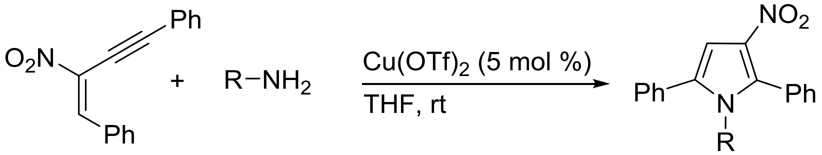
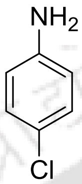
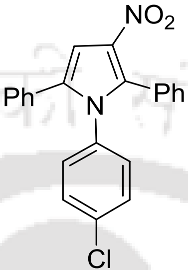
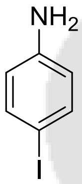
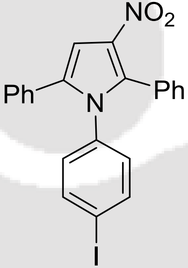
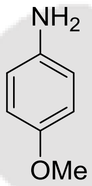
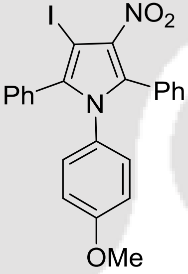
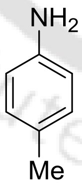
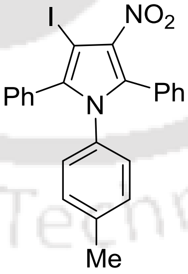
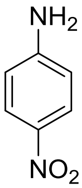
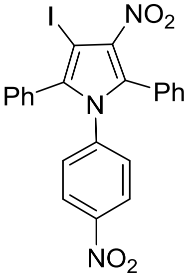
8			79
[c]9			81
[d]10			83
11			76
12			82

[a] Enyne (0.5 mmol), amine (0.6 mmol), catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for 0.5 h. [b]Isolated yield. [c]Reaction time for 10 min. [d]Reaction time for 1 h.

compounds in 76-82% yields (Entries 1-2 and 5), whereas electron donating methoxy, mono and dimethyl groups readily underwent reaction to give the corresponding substituted pyrroles in good yields (Entries 3-4 and 6-8). The crystallization of the 1-(4-Iodophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole in MeOH gave single crystals whose structure was deetermined by X-ray analysis (Fig. 1). Furthermore, amine with diazophenyl group proceeded reaction with 76% yield (Entry 9), whereas the reaction of 2-fluorenyl amine furnished the target pyrrole derivative in 53% yield (Entry 10). In contrast, the reaction with aliphatic amine (Entry 11) showed no

Table 3. Cyclization of (*E*)-2-Nitro-1,4-diphenylbut-1-en-3-yne with Amines[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			1.5	78
2			1.0	82
3			0.5	71
4			0.5	92
5			18	76

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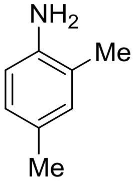
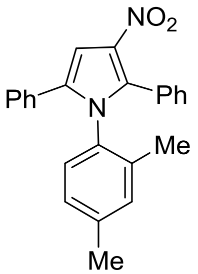
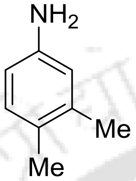
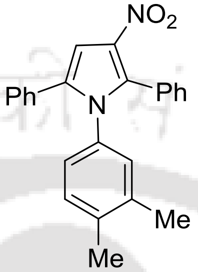
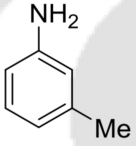
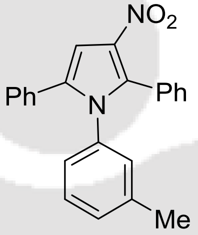
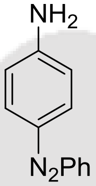
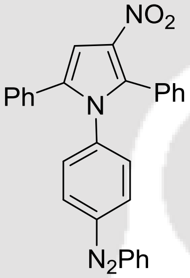
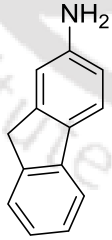
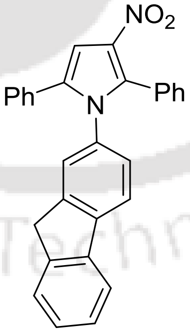
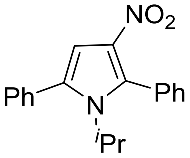
6			0.5	88
7			0.5	90
8			0.5	77
9			0.5	76
10			0.5	53
11	NH_2 ^{i}Pr		24	n.d.

[a]Enyne (0.5 mmol), amine (0.6 mmol), catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for appropriate time. [b]Isolated yield.

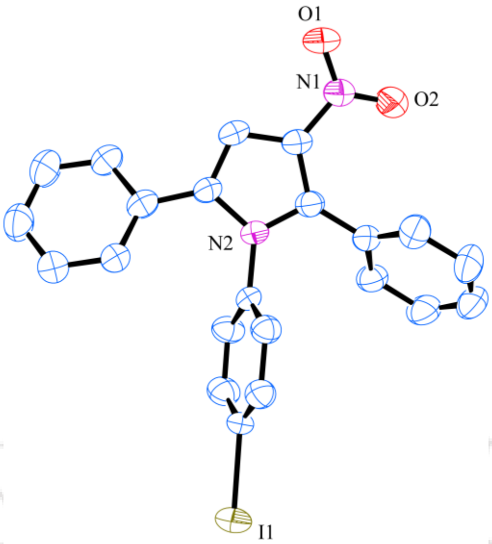


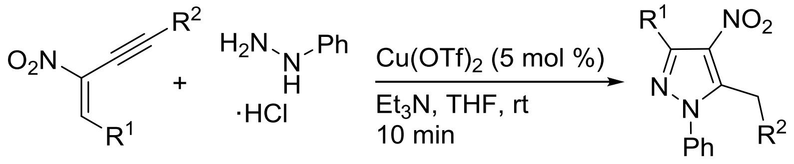
Figure 1. ORTEP diagram of 1-(4-iodophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole. Thermal ellipsoids are drawn at a 50% probability level. Hydrogen atoms have omitted for clarity (CCDC 1025795).

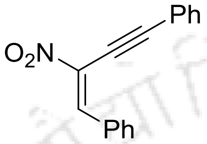
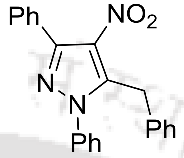
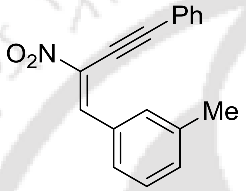
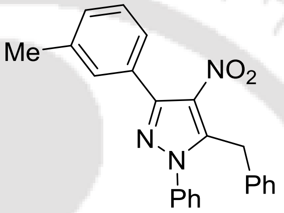
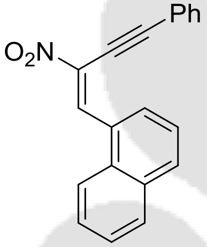
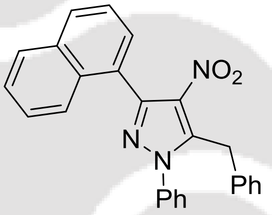
product formation, which may be due to the complex formation with $Cu(OTf\ )_2$.

Finally, the compatibility of the protocol was explored for the synthesis of analogue substituted pyrazoles using phenylhydrazine hydrochloride in the presence of base (Table 4). As predicted, the reaction readily occurred in high yields. For examples, the enynes underwent reaction to give the corresponding pyrazole derivatives in 75-93% yields (Entries 1-3). This reaction showed greater reactivity compared to that of the pyrrole synthesis. These results suggest that this strategy can be utilized for the synthesis of tetrasubstituted pyrroles and pyrazoles with wide substrate scope and substantial steric hindrance at mild reaction conditions. The scale of the procedure was examined using (*E*)-(2-nitrobut-1-en-3-yne-1,4-diyl)dibenzene and 4-methylaniline as representative examples (Scheme 12). The reaction readily occurred to afford the target product in 86% yield.

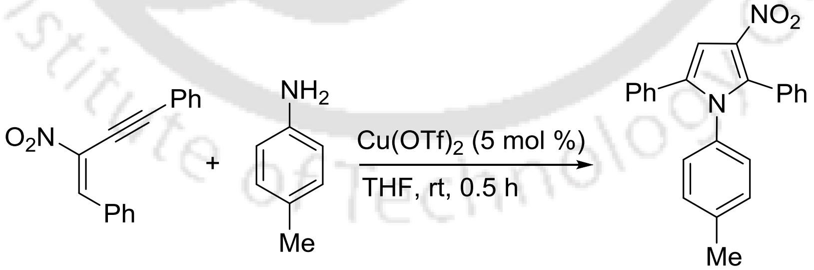
The synthetic utility of the pyrrole derivatives was studied for the preparation of an azo dye (Scheme 13). Treatment of 3-nitro-2,5-diphenyl-1-(*p*-tolyl)-1*H*-pyrrole with 15 equiv of Zn dust in the presence of HCl in EtOH gave amine derivative in 81% yield, which underwent diazotization followed by coupling with 2-naphthol to produce red dye in 63% yield.

Table 4. Cu-Catalyzed Cyclization 1,3-Enynes with Phenylhydrazine[a]



Entry	Substrate	Product	Yield (%)[b]
1			93
2			86
3			75

[a]Enyne (0.5 mmol), phenyl hydrazine hydrochloride (0.6 mmol), Et_3N (2.0 equiv) catalyst (5 mol %) in solvent (3.0 mL) were stirred at room temperature under air for 10 min. [b]Isolated yield.

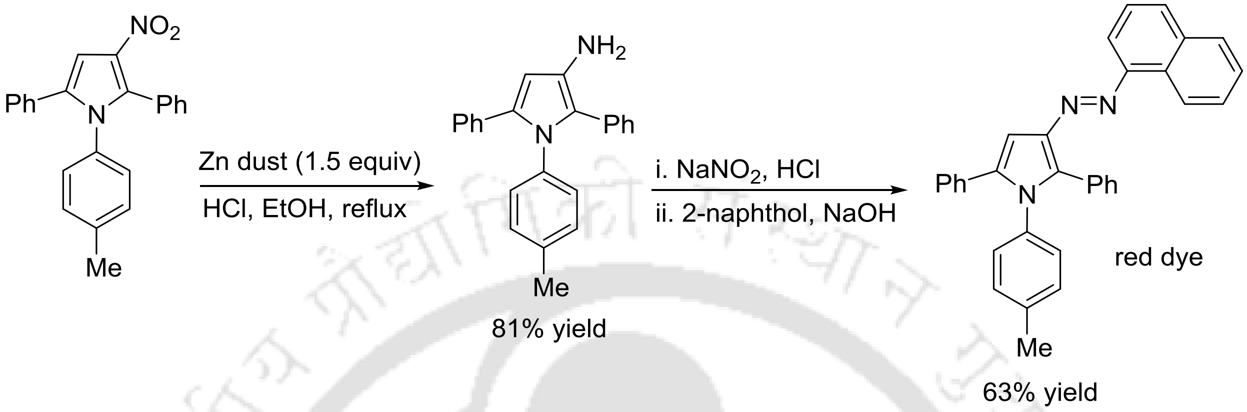


5 mmol, 1.24 g   6 mmol, 0.64 g   1.52 g (86%)

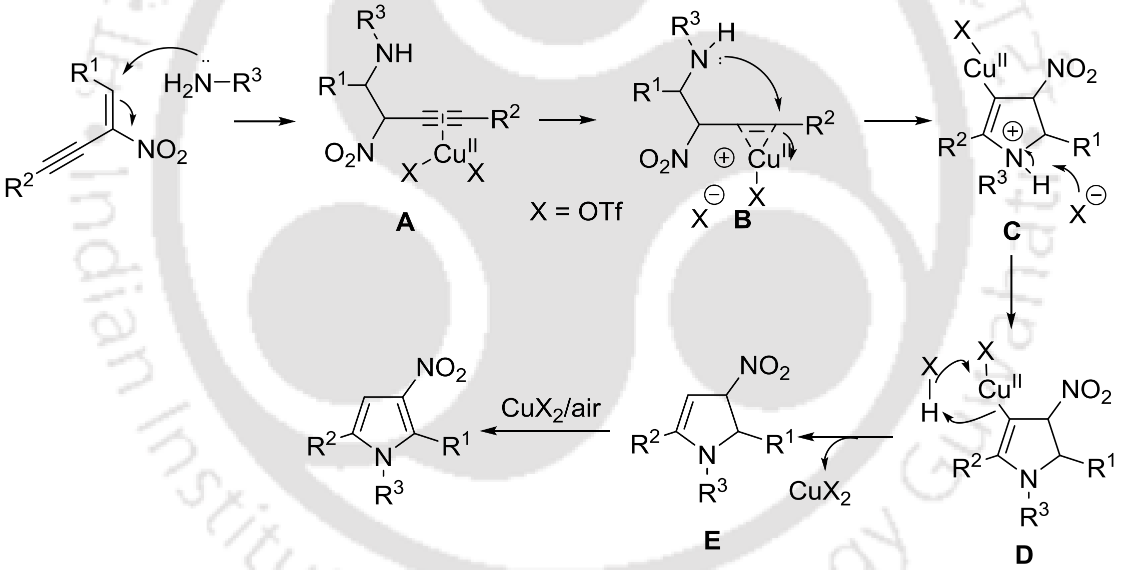
Scheme 12. Gram Scale Synthesis

The proposed catalytic cycle is shown in Scheme 14. Aza-Michael addition of amines with 1,3-enynes in the presence of Cu-catalyst may lead to the formation of the intermediate **B** *via* **A**.

Intramolecular 5-*endo-dig* cyclization of **B** can give intermediate **C** that can convert into intermediate **D**. The latter can transform into dihydropyrrole derivative **E** and CuX_2, which can produce the target heterocycle by oxidation.



Scheme 13. Preparation of Azo Dye



Scheme 14. Proposed Catalytic Cycle.

In summary, we developed Cu-catalyzed cascade inter/intramolecular cyclization of 1,3-enynes with amines for the synthesis of tetrasubstituted pyrroles/pyrazoles. This reaction shows wide substrate scope, atom economy, mild reaction conditions, eco-friendliness and shorter reaction time to produce the target heterocycles good yields.

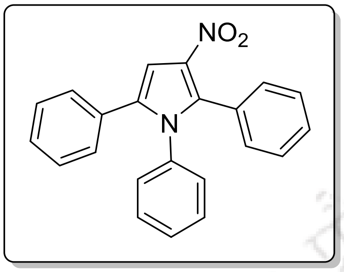
3.4 Experimental Section

General Information. Amines, aldehydes, $Pd(PPh_3)_2Cl_2$ (98%), PPh_3 (99%), CuCl (99%), CuBr (98%), CuI (98%), $Cu(OTf)_2$ (98%) and $Cu(OAc)_2$ (98%) were purchased from Aldrich and used as received. $CuSO_4 \cdot 5H_2O$ (99%) was obtained from rankem. The progress of the reaction was monitored by analytical TLC on Merck silica gel G/GF 254 plates. The column chromatography was performed with Rankem silica gel 60-120 mesh. NMR (^1H and ^{13}C) spectra were recorded on 400 and 600 MHz instruments using $CDCl_3$ as a solvent and Me_4Si as internal standard. Chemical shifts (δ) were reported in ppm, and spin−spin coupling constants (J) were given in Hz. The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. High-resolution mass spectra were recorded on a QTof ESI-MS instrument. For single crystal X-ray analysis the intensity data were collected using Bruker SMART APEX-II CCD diffractometer, equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structures were solved by direct methods using *SHELLX-97* (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-97. 1,3-Enynes were prepared according to the reported procedure.[4a]

General Procedure for Synthesis of Pyrroles. To a stirred solution of amine (0.6 mmol) and $Cu(OTf)_2$ (5 mol %) in THF (2 mL) was added a solution of 1,3-enynes (0.5 mmol) in THF (1.0 mL) at room temperature under air, and the stirring was continued until completion of the reaction. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as the eluent. The resulting mixture was then concentrated using a rotary evaporator to give a residue, which was purified by silica gel column chromatography using hexane and ethyl acetate (19:1) as the eluent.

General Procedure for Synthesis of Substituted Pyrazoles. To a mixture of phenyl hydrazine hydrochloride (0.6 mmol) and Et_3N (1.0 mmol) dissolved in THF (1mL) was added $Cu(OTf)_2$ (5 mol %) at room temperature under air. After 5 min, a solution of 1,3-enynes (0.5 mmol) in THF (1.0 mL) was added and the stirring was continued until completion of the reaction. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as the solvent.

Evaporation of the solvent gave a residue that was treated with water (5 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated on a rotary evaporator to give a residue, which was purified by silica gel column chromatography using hexane and ethyl acetate (19:1) as the eluent.



3-Nitro-1,2,5-triphenyl-1*H*-pyrrole (Table 1).

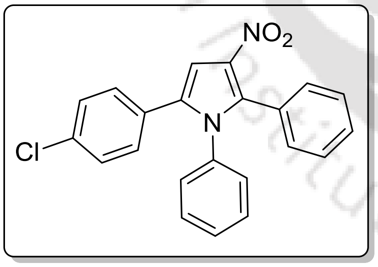
Yellow solid; yield: 87%; mp 179-180 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.17 (m, 11H), 7.10-7.08 (m, 3H), 6.94 (dd, *J* = 7.6, 0.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 135.2, 134.9, 134.4, 131.2, 131.0, 129.5, 129.4, 129.0, 128.9, 128.8, 128.5, 128.4, 128.0, 127.9, 106.0.

FT-IR (KBr): 3114, 3072, 3034, 2923, 1551, 1527, 1495, 1468, 1449, 1397, 1375, 1321, 1305, 1183, 1027, 833, 782, 762, 755, 697 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}N_2O_2$ 341.1290, found 341.1292.



5-(4-Chlorophenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole (Table 2, Entry 1).

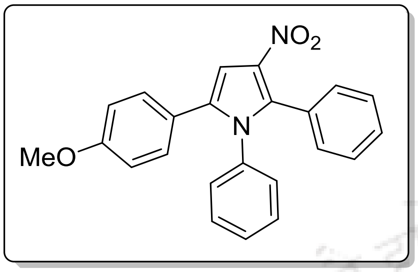
Yellow solid; yield: 69%; mp 206-207 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29-7.16 (m, 10H), 7.08 (s, 1H), 7.01-6.98 (m, 2H), 6.92-6.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 135.5, 134.9, 134.0, 133.1, 131.1, 130.1, 129.5, 129.3, 129.2, 129.0, 128.8, 128.7, 128.0, 106.2.

FT-IR (KBr): 3134, 3056, 1554, 1526, 1492, 1468, 1447, 1418, 1388, 1317, 1308, 1189, 1092, 1011, 919, 835, 804, 770, 756, 742, 698 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{15}ClN_2O_2$ 375.0900, found 375.1010.



5-(4-Methoxyphenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole (Table 2, Entry 2).

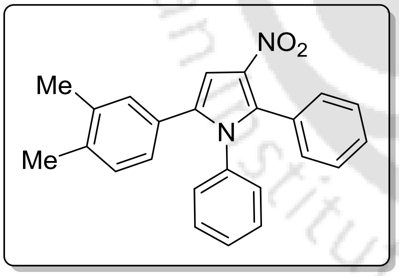
Yellow solid; yield: 80%; mp 147-148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26-7.17 (m, 8H), 7.01(d, *J* = 8.0 Hz, 3H), 6.93 (d, *J* = 7.6 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 3.75 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 136.6, 134.4, 133.9, 130.8, 129.9, 129.1, 128.6, 128.5, 128.4, 128.0, 127.5, 123.1, 113.5, 104.9, 54.9.

FT-IR (KBr): 3125, 3050, 3006, 2973, 2928, 2842, 1612, 1560, 1498, 1469, 1453, 1445, 1397, 1321, 1306, 1287, 1247, 1183, 1028, 833, 807, 795, 778, 728, 707, 702 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1396.



5-(3,4-Dimethylphenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole (Table 2, Entry 3).

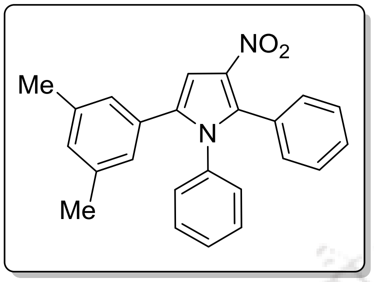
Yellow solid; yield: 75%; mp 174-175 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.16 (m, 8H), 7.04 (s, 1H), 6.93 (s, 4H), 6.71 (d, *J* = 7.6 Hz, 1H), 2.18 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 136.7, 136.5, 135.0, 134.9, 134.7, 131.2, 130.2, 129.6, 128.9, 128.8, 128.5, 128.4, 127.9, 126.3, 105.5, 19.8, 19.6.

FT-IR (KBr): 3142, 3059, 3009, 2961, 2911, 2853, 1596, 1526, 1494, 1469, 1445, 1417, 1388, 1320, 1306, 1201, 1168, 918, 821, 802, 774, 763, 754, 701, 691 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1601.



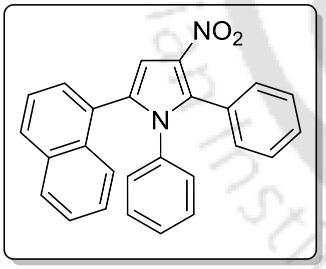
5-(3,5-Dimethylphenyl)-3-nitro-1,2-diphenyl-1*H*-pyrrole (Table 2, Entry 4).

Yellow solid; yield: 72%; mp 216-217 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ =7.28-7.16 (m, 8H), 7.06 (s, 1H), 6.93-6.92 (m, 2H), 6.85 (s, 1H), 6.68 (s, 2H), 2.16 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 137.1, 135.0, 134.9, 134.7, 131.2, 130.8, 129.6, 129.0, 128.9, 128.4, 127.9, 126.8, 105.7, 21.3; FT-IR (KBr): 3070, 2909, 2848, 1598, 1560, 1536, 1493, 1483, 1470, 1395, 1323, 1310, 1230, 1080, 1007, 857, 810, 778, 770, 754, 710, 696 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1595.



5-(Naphthalen-1-yl)-3-nitro-1,2-diphenyl-1*H*-pyrrole (Table 2, Entry 5).

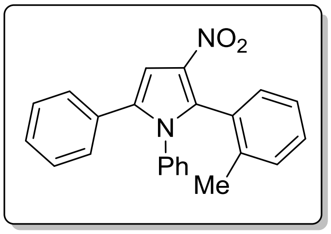
Yellow solid; yield: 63%; mp 242-243 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98-7.97 (m, 1H), 7.81 (dd, *J* = 7.2, 3.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.50-7.46 (m, 2H), 7.31-7.26 (m, 6H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.15 (s, 1H), 7.00-6.98 (m, 1H), 6.94 (t, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 134.7, 133.5, 132.9, 132.2, 131.2, 129.9, 129.5, 129.2, 128.9, 128.6, 128.4, 128.3, 128.1, 128.0, 126.8, 126.2 125.7, 124.9, 108.1.

FT-IR (KBr): 3056, 1826, 1497, 1491, 1478, 1469, 1445, 1395, 1318, 1305, 848, 802, 768, 756, 714, 701, 696 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{18}N_2O_2$ 391.1447, found 391.1446.



3-Nitro-1,5-diphenyl-2-(*o*-tolyl)-1*H*-pyrrole (Table 2, Entry 6).

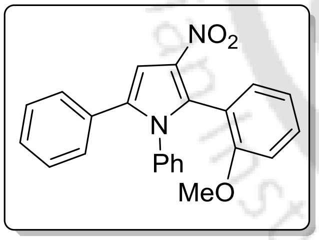
Yellow solid; yield: 74%; mp 166-167 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22-7.19 (m, 5H), 7.16-7.10 (m, 6H), 7.06 (d, *J* = 4.0 Hz, 2H), 6.92 (s, 2H), 2.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 137.0, 135.4, 135.3, 134.4, 131.1, 129.9, 129.5, 129.4, 128.9, 128.8, 128.6, 128.5, 128.3, 127.9, 125.4, 105.7, 20.1.

FT-IR (KBr): 3131, 3070, 2917, 2845, 1598, 1559, 1490, 1473, 1456, 1445, 1401, 1317, 1306, 1284, 1254, 1188, 1132, 1080, 1027, 955, 919, 839, 802, 782, 766, 758, 733, 701, 696 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1445.



2-(2-Methoxyphenyl)-3-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, Entry 7).

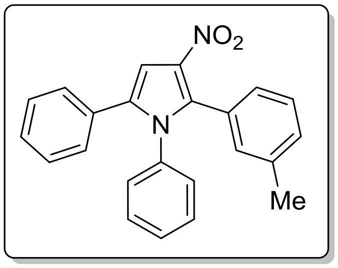
Yellow solid; yield: 80%; mp 171-172 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30-7.27 (m, 1H), 7.21-7.08 (m, 10H), 6.95 (d, *J* = 7.2, 2H), 6.86 (t, *J* = 7.2, 1H), 6.79 (d, *J* = 8.4, 1H), 3.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 137.3, 134.3, 132.5, 132.4, 131.2, 130.9, 128.9, 128.8, 128.6, 128.4, 128.3, 127.9, 127.7, 120.3, 119.0, 110.9, 105.9, 55.5.

FT-IR (KBr): 3125, 3050, 2961, 2925, 2837, 1611, 1596, 1560, 1491, 1478, 1460, 1446, 1404, 1321, 1309, 1275, 1247, 1047, 1024, 836, 780, 770, 753, 700 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1394.



3-Nitro-1,5-diphenyl-2-(*m*-tolyl)-1*H*-pyrrole (Table 2, Entry 8).

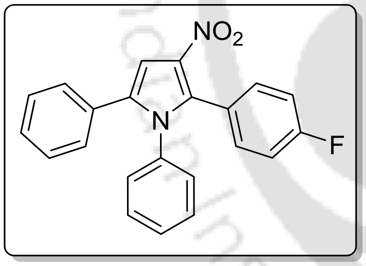
Yellow solid; yield: 79%; mp 190-191 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22-7.15 (m, 6H), 7.13-7.00 (m, 7H), 6.94 (d, *J* = 6.8 Hz, 2H), 2.25 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 137.0, 135.5, 134.8, 134.3, 131.8, 131.1, 129.7, 129.3, 129.0, 128.98, 128.90, 128.5, 128.4, 128.2, 127.9, 127.8, 106.0, 21.4.

FT-IR (KBr): 3120, 3047, 3014, 2914, 2850, 1601, 1551, 1526, 1490, 1477, 1446, 1393, 1322, 1307, 1171, 1018, 930, 857, 822, 818, 798, 768, 697 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1443.



2-(4-Fluorophenyl)-3-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, Entry 9).

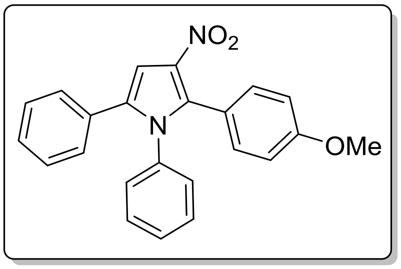
Yellow solid; yield: 81%; mp 186-187°C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.23-7.18 (m, 8H), 7.08-7.07 (m, 3H), 6.96-6.91 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (d, $J_{C\text{-}F}$ = 248.6 Hz), 136.8, 135.1, 134.6, 134.0, 133.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 130.9, 129.2, 129.0, 128.8, 128.7, 128.4, 128.0, 125.4, 115.3 (d, $J_{C\text{-}F}$ = 22.1 Hz), 106.0.

FT-IR (KBr): 3139, 3061, 3022, 1599, 1508, 1497, 1448, 1418, 1398, 1325, 1226, 1187, 1163, 1026, 846, 824, 811, 784, 763, 752, 734, 703, 695 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{15}FN_2O_2$ 359.1196, found 359.1189.



2-(4-Methoxyphenyl)-3-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, Entry 10).

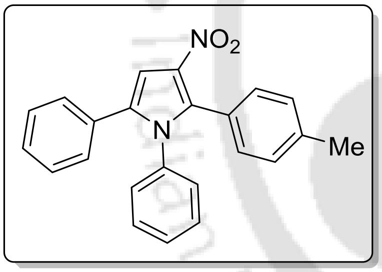
Yellow solid; yield: 83%; mp 186-187 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21-7.08 (m, 11H), 6.93 (d, *J* = 6.8 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 137.0, 135.2, 134.9, 134.2, 132.6, 131.1, 129.1, 129.0, 128.9, 128.5, 128.4, 127.9, 121.4, 113.5, 106.1, 55.3.

FT-IR (KBr): 3134, 3061, 2939, 2842, 1608, 1574, 1506, 1477, 1463, 1445, 1415, 1399, 1319, 1304, 1289, 1253, 1176, 1026, 843, 827, 781, 769, 760, 737, 698 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1393.



3-Nitro-1,5-diphenyl-2-(*p*-tolyl)-1*H*-pyrrole (Table 2, Entry 11).

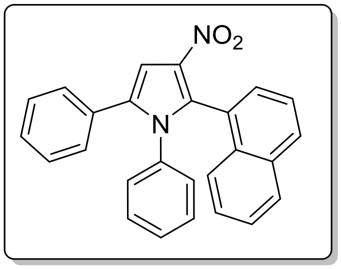
Yellow solid; yield: 76%; mp 176-177 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.23-7.16 (m, 6H), 7.10-7.05 (m, 7H), 6.93 (d, *J* = 7.8 Hz, 2H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 137.0, 135.4, 134.9, 134.3, 131.1, 131.0, 129.0, 128.9, 128.7, 128.5, 128.4, 127.9, 126.3, 106.1, 21.5.

FT-IR (KBr): 3117, 3081, 3050, 3022, 2928, 1560, 1506, 1473, 1446, 1415, 1393, 1377, 1321, 1315, 1306, 1177, 1016, 845, 823, 785, 768, 758, 733, 702, 696 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1445.



2-(Naphthalen-1-yl)-3-nitro-1,5-diphenyl-1*H*-pyrrole (Table 2, Entry 12).

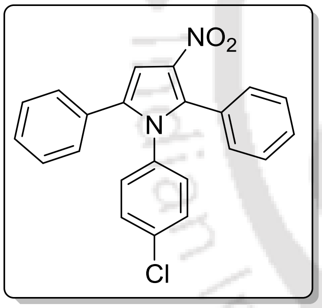
Yellow solid; yield: 82%; mp 160-161 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.83-7.79 (m, 2H), 7.68-7.67 (m, 1H), 7.48-7.45 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.24-6.99 (m, 11H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 136.9, 136.2, 134.8, 133.7, 133.2, 133.0, 131.0, 129.7, 129.5, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.6, 127.0, 126.2, 125.1, 124.8, 105.7.

FT-IR (KBr): 3150, 3045, 1596, 1559, 1534, 1508, 1497, 1481, 1454, 1447, 1407, 1319, 1305, 1264, 1217, 1068, 917, 807, 793, 781, 772, 756, 726, 697 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{26}H_{18}N_2O_2$ 391.1447, found 391.1449.



1-(4-Chlorophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 1).

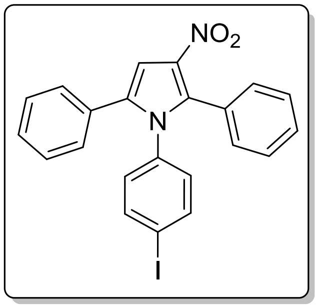
Yellow solid; yield: 78%; mp 156-157 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31-7.19 (m, 8H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.06 (s, 3H), 6.86 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 135.4, 135.0, 134.5, 134.4, 131.1, 130.7, 130.0, 129.3, 129.1, 129.0, 128.6, 128.1, 106.2.

FT-IR (KBr): 3134, 3097, 3056, 3039, 1560, 1497, 1470, 1449, 1444, 1400, 1320, 1310, 1182, 1094, 1010, 952, 846, 818, 758, 727, 700 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{22}H_{15}ClN_2O_2$ 375.0900, found 375.0862.



1-(4-Iodophenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 2).

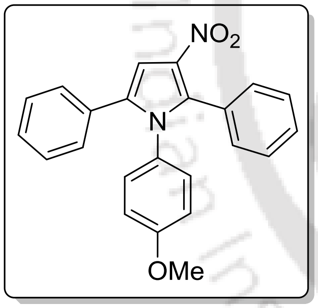
Yellow solid; yield: 82%; mp 189-190 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48 (d, *J* = 7.2 Hz, 2H), 7.29-7.18 (m, 8H), 7.06 (s, 3H), 6.65 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 138.2, 136.6, 134.9, 134.3, 131.2, 130.7, 130.5, 129.2, 129.1, 129.0, 128.6, 128.2, 106.3, 94.0.

FT-IR (KBr): 3145, 3081, 3042, 2964, 1601, 1552, 1491, 1472, 1448, 1402, 1318, 1306, 1279, 1259, 1008, 821, 774, 759, 733, 723, 694 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{22}H_{15}IN_2O_2$ 467.0256, found 467.0247.



1-(4-Methoxyphenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 3).

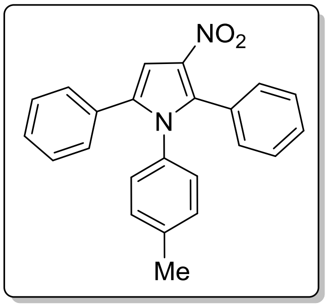
Yellow solid; yield: 71%; mp 130-131 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28-7.21 (m, 8H), 7.11-7.09 (m, 2H), 7.07 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 3.72 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.3, 135.4, 134.8, 134.5, 131.23, 131.20, 129.8, 129.7, 129.6, 129.0, 128.8, 128.4, 128.0, 127.8, 114.1, 105.8, 55.5.

FT-IR (KBr): 3150, 3059, 2978, 2925, 2828, 1612, 1561, 1515, 1494, 1447, 1405, 1387, 1324, 1297, 1252, 1178, 1168, 1022, 846, 831, 813, 799, 763, 753, 734, 697 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{23}H_{18}N_2O_3$ 371.1396, found 371.1378.



3-Nitro-2,5-diphenyl-1-(*p*-tolyl)-1*H*-pyrrole (Table 3, Entry 4).

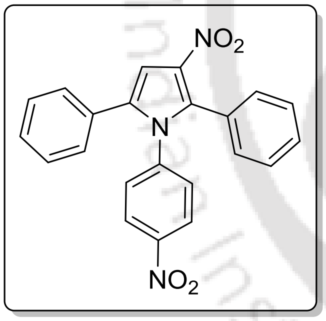
Yellow solid; yield: 92%; mp 181-182 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26-7.19 (m, 8H), 7.09-7.06 (m, 3H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 2.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 135.3, 134.8, 134.4, 134.2, 131.2, 131.1, 129.6, 129.5, 128.9, 128.8, 128.5, 128.4, 127.9, 127.8, 105.9, 21.2.

FT-IR (KBr): 3120, 3067, 3039, 2920, 2956, 2853, 1554, 1513, 1500, 1448, 1403, 1324, 1186, 840, 819, 760, 731, 696, 546 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1443.



3-Nitro-1-(4-nitrophenyl)-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 5).

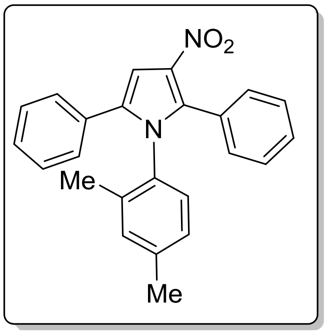
Yellow solid; yield: 76%; mp 165-166 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 9.0 Hz, 2H), 7.33-7.19 (m, 9H), 7.08-7.04 (m, 4H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.0, 142.4, 135.6, 134.8, 134.4, 131.1, 130.3, 129.7, 129.5, 129.1, 128.8, 128.7, 128.5, 128.4, 124.3, 106.8.

FT-IR (KBr): 3145, 3120, 3064, 3039, 2859, 1613, 1597,1523, 1498, 1474, 1448, 1400, 1346, 1320, 1182, 1107, 909, 864, 854, 831, 775, 753, 733, 716, 701 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{15}N_3O_4$ 386.1141, found 386.1150.



1-(2,4-Dimethylphenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 6).

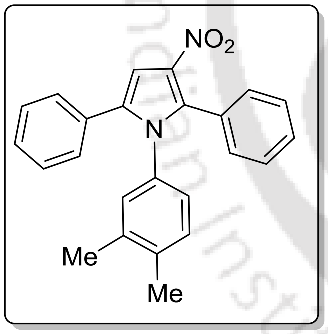
Yellow solid; yield: 88%; mp 185-186 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.24-7.19 (m, 8H), 7.09 (s, 3H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 2.20 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 139.2, 135.7, 135.3, 134.7, 134.6, 133.4, 131.6, 131.2, 130.8, 129.6, 129.4, 128.9, 128.4, 127.9, 127.2, 105.6, 21.2, 17.7.

FT-IR (KBr): 3134, 3056, 3031, 2911, 1604, 1565, 1535, 1494, 1471, 1448, 1405, 1319, 1261, 1236, 1187, 1027, 837, 820, 763, 738, 698 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1596.



1-(3,4-Dimethylphenyl)-3-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 7).

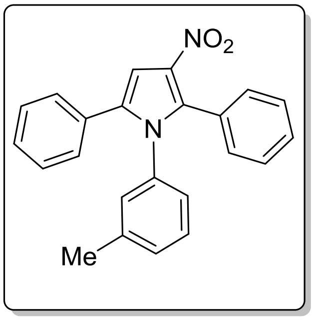
Yellow solid; yield: 90%; mp 179-180 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.25-7.20 (m, 8H), 7.09-7.05 (m, 3H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.66-6.62 (m, 2H), 2.13 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 137.4, 137.0, 135.3, 134.7, 134.4, 131.2, 131.1, 129.9, 129.7, 129.6, 128.9, 128.7, 128.3, 127.9, 127.7, 126.0, 105.8, 19.7, 19.5.

FT-IR (KBr): 3120, 3053, 3031, 2973, 2914, 2853, 1602, 1579, 1553, 1530, 1496, 1472, 1404, 1375, 1322, 1309, 1190, 1029, 918, 889, 875, 839, 821, 774, 759, 731, 707, 692 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{20}N_2O_2$ 369.1603, found 369.1572.



3-Nitro-2,5-diphenyl-1-(*m*-tolyl)-1*H*-pyrrole (Table 3, Entry 8).

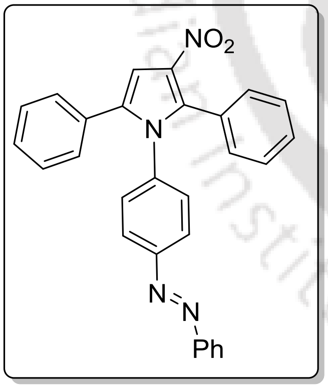
Yellow solid; yield: 77%; mp 164-165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.20 (m, 8H), 7.08-6.98 (m, 5H), 6.70 (s, 2H), 2.13 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 136.8, 135.2, 134.8, 134.4, 131.2, 131.1, 129.5, 129.4, 129.2, 129.0, 128.9, 128.7, 128.4, 127.93, 127.90, 125.9, 105.9, 21.2.

FT-IR (KBr): 3147, 3056, 3034, 2917, 1604, 1559, 1469, 1448, 1402, 1281, 1267, 1180, 1163, 1074, 1027, 921, 861, 822, 792, 694 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}N_2O_2$ 355.1447, found 355.1440.



(*E*)-3-Nitro-2,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1*H*-pyrrole (Table 3, Entry 9).

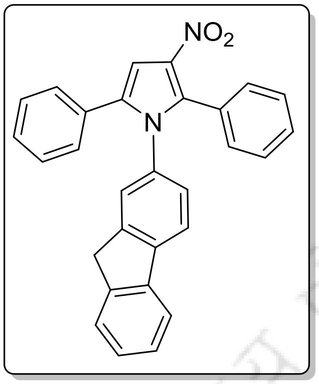
Yellow solid; yield: 76%; mp 154-155 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 6.49 (s, 3H), 7.28-7.23 (m, 8H), 7.14-7.12 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 151.6, 138.8, 135.1, 134.4, 131.8, 131.2, 130.8, 129.6, 129.3, 129.2, 129.18, 129.12, 128.6, 128.1, 123.4, 123.1, 106.3.

FT-IR (KBr): 3120, 3072, 3025, 2959, 1500, 1485, 1473, 1443, 1404, 1324, 1261, 1180, 1153, 1096, 1068, 1027, 1016, 923, 857, 829, 810, 778, 768, 764, 757, 741, 718, 699, 686 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{20}N_4O_2$ 445.1665, found 445.1652.



1-(9*H*-Fluoren-2-yl)-3-nitro-2,5-diphenyl-1*H*-pyrrole (Table 3, Entry 11).

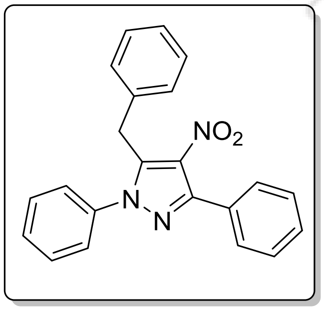
Yellow liquid; yield: 53%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.26 -7.23 (m, 5H), 7.20-7.18 (m, 3H), 7.14-7.08 (m, 3H), 7.08 (s, 1H), 6.95 (dd, *J* = 7.8, 1.8 Hz, 1H), 3.72 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 143.7, 141.9, 140.5, 135.45, 135.41, 134.9, 134.5, 131.2, 131.1, 129.6, 129.0, 128.9, 128.4, 128.0, 127.9, 127.7, 127.6, 127.2, 125.5, 125.3, 120.4, 120.0, 106.0, 36.9.

FT-IR (neat): 3136, 3057, 2900, 2792, 1606, 1558, 1496, 1470, 1458, 1448, 1403, 1320, 1264, 1190, 1071, 1029, 1002, 952, 917, 875, 837, 757, 737, 721, 697 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{20}N_2O_2$ 429.1603, found 429.1605.



5-Benzyl-4-nitro-1,3-diphenyl-1*H*-pyrazole (Table 4, Entry 1).

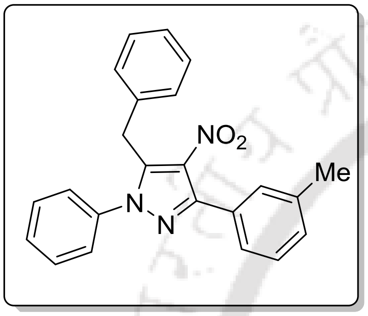
Yellow liquid; yield: 93%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 7.2, 3.2 Hz, 2H), 7.49-7.46 (m, 5H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.28-7.26 (m, 4H), 7.05 (d, *J* = 6.8 Hz, 2H), 4.47 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 143.1, 138.1, 136.0, 130.6, 130.0, 129.6, 129.5, 129.0, 128.6, 128.3, 128.2, 127.2, 126.3, 125.5, 31.5.

FT-IR (neat): 3062, 3030, 2925, 2850, 1596, 1552, 1496, 1453, 1438, 1422, 1379, 1357, 1200, 1074, 1027, 1003, 989, 918, 833, 734, 694 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{17}N_3O_2$ 356.1399, found 356.1402.



5-Benzyl-4-nitro-1-phenyl-3-(*m*-tolyl)-1*H*-pyrazole (Table 4, Entry 2).

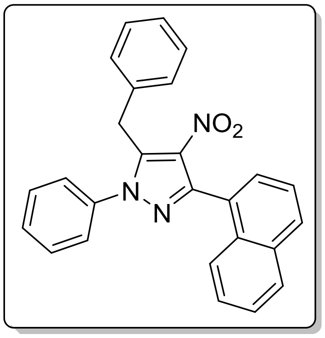
Yellow liquid; yield: 86%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.50 (m, 5H), 7.40-7.25 (m, 7H), 7.07 (d, *J* = 7.2 Hz, 2H), 4.48 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 143.1, 138.1, 138.0, 136.0, 130.4, 130.2, 129.9, 129.9, 129.6, 128.9, 128.2, 128.2, 127.2, 126.5, 126.3, 125.4, 31.5, 21.5.

FT-IR (neat): 3062, 3030, 2928, 2856, 1596, 1551, 1495, 1457, 1423, 1357, 1279, 1235, 1173, 1073, 1030, 1015, 907, 829, 791, 766, 734, 694 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{19}N_3O_2$ 370.1556, found 370.1567.



5-Benzyl-3-(naphthalen-1-yl)-4-nitro-1-phenyl-1*H*-pyrazole (Table 4, Entry 3).

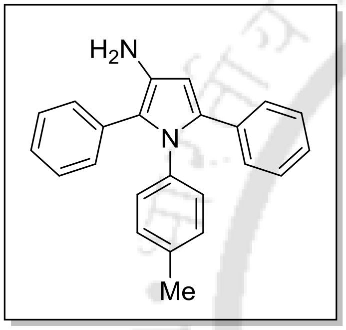
Yellow liquid; yield: 75%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 6.8 Hz, 1H), 7.55 (t, 1H), 7.51-7.42 (m, 7H), 7.30-7.23 (m, 3H), 7.08 (d, *J* = 7.2 Hz, 2H), 4.55 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 142.6, 138.1, 136.1, 133.6, 132.1, 130.0, 129.9, 129.6, 129.0, 128.7, 128.3, 128.2, 127.2, 126.8, 126.2, 126.1, 125.2, 125.0, 124.6, 31.5.

FT-IR (neat): 3059, 3025, 2934, 1596, 1552, 1494, 1454, 1443, 1387, 1357, 1261, 1225, 1172, 1125, 1070, 1023, 964, 917, 864, 843, 804, 778, 733, 695 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{19}N_3O_2$ 406.1556, found 406.1559.



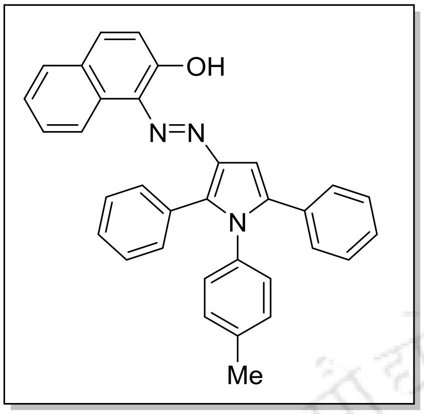
2,5-Diphenyl-1-*p*-tolyl-1*H*-pyrrol-3-amine. To a stirred solution of 3-nitro-2,5-diphenyl-1-(*p*-tolyl)-1*H*-pyrrole (2 mmol) in ethanol (35 mL) was added zinc dust (30 mmol) and 6 M HCl (10 mL).[4b] After refluxing the mixture for 2 h, it was cooled to room temperature and diluted with CH_2Cl_2 (10 mL). Excess zinc was filtered and the solvent was evaporated on a rotary evaporator. The residue was neutralized with 15% NaOH (pH 10) and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine (5 mL × 1), water (5 mL × 1) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was crystallized in hot ethanol.

Yellow solid; yield: 81%; mp 165-166 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.23 (t, J = 7.8 Hz, 2H), 7.17–7.11 (m, 4H), 7.07–7.05 (m, 4H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.14 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 136.6, 136.5, 133.4, 133.3, 132.3, 130.2, 129.8, 129.3, 128.8, 127.7, 128.3, 128.0, 126.2, 125.9, 120.5, 102.6, 21.2.

FT-IR (KBr): 3450, 2959, 2922, 2854, 1654, 1600, 1509, 1457, 1418, 1387, 1310, 1261, 1096, 1025, 912, 805, 760, 696 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{20}N_2$ 325.1705, found 325.1708.



(*E*)-1-((2,5-Diphenyl-1-*p*-tolyl-1*H*-pyrrol-3-yl)diazenyl)naphthalen-2-ol. To a stirred solution of $NaNO_2$ (2 mmol) in water (0.5 mL) was added 2,5-diphenyl-1-*p*-tolyl-1*H*-pyrrol-3-amine (1 mmol) in 6 N HCl (0.5 mL) at 0 °C. After 10 min, the mixture was treated with a solution of 2-naphthol (1 mmol) in 10% NaOH (1 mL).[4c] The resulting red solid was stirred for about 0.5 h and filtered, washed with water, and dried and purified by silica gel column chromatography using hexane and ethyl acetate (49 : 1) as the eluent.

Red solid; yield: 63%; mp 189-190 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 9.6 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.33-7.29 (m, 5H), 7.25-7.23 (m, 3H), 7.21-7.18 (m, 2H), 7.13 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 151.8, 139.7, 137.9, 137.2, 136.5, 135.2, 133.1, 133.0, 132.3, 130.7, 130.3, 130.0, 129.7, 129.1, 128.6, 128.4, 128.2, 128.1, 127.4, 124.2, 122.2, 120.1, 99.1, 21.3.

FT-IR (KBr): 3444, 3034, 2922, 2852, 1619, 1597, 1546, 1512, 1485, 1472, 1452, 1418, 1383, 1337, 1210, 1171, 1144, 1016, 813, 776, 730, 696 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{25}N_3O$ 480.2076, found 480.2071.

3.5 References

1. (a) Haque, T. S.; Tadesse, S.; Marcinkeviciene, J.; Rogers, M. J.; Sizemore, C.; Kopcho, L. M.; Amsler, K.; Ecret, L. D.; Zhan, D. L.; Hobbs, F.; Slee, A.; Trainor, G. L.; Stern, A.

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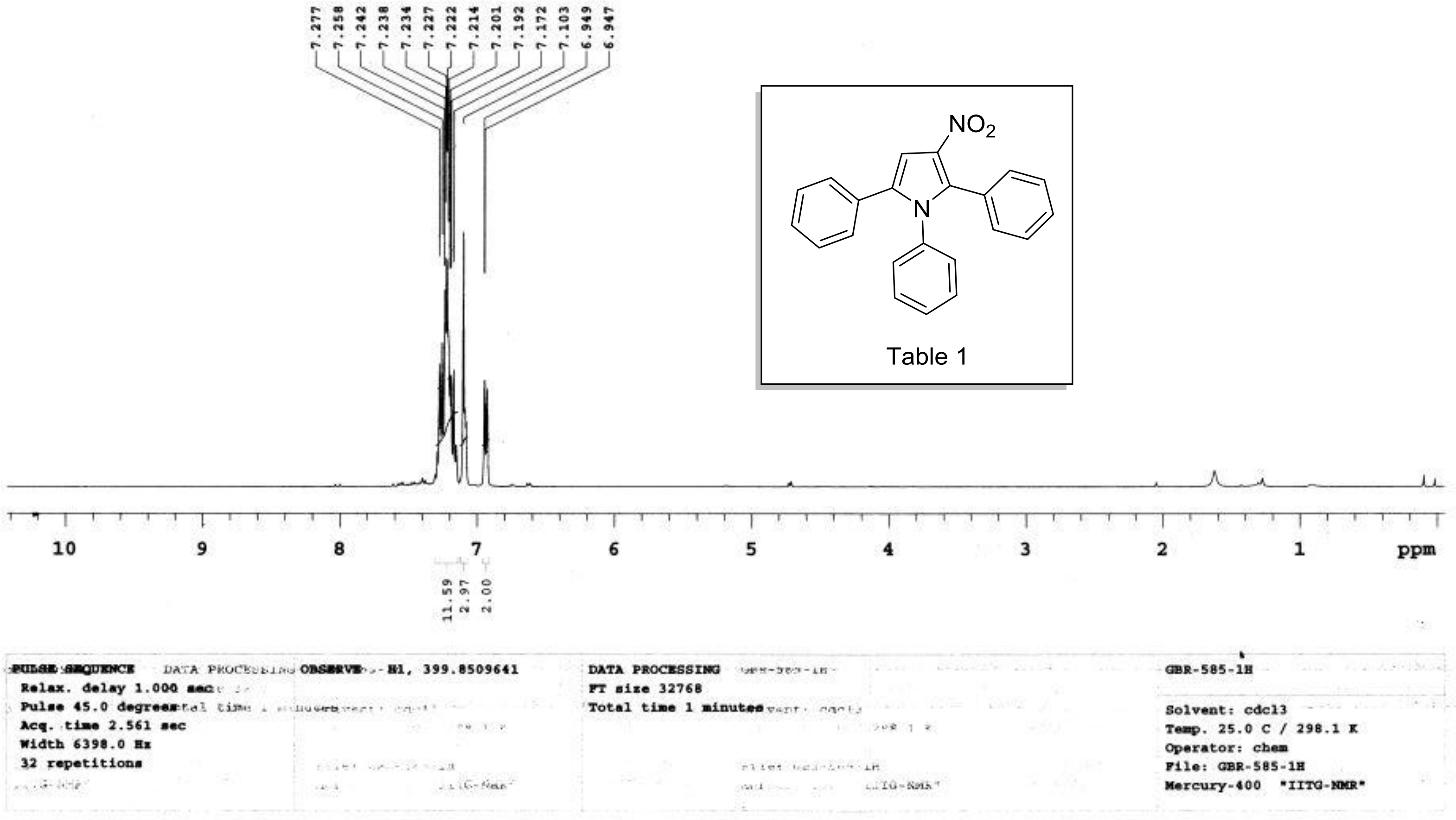

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32 repetitions

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Total time 1 minutes

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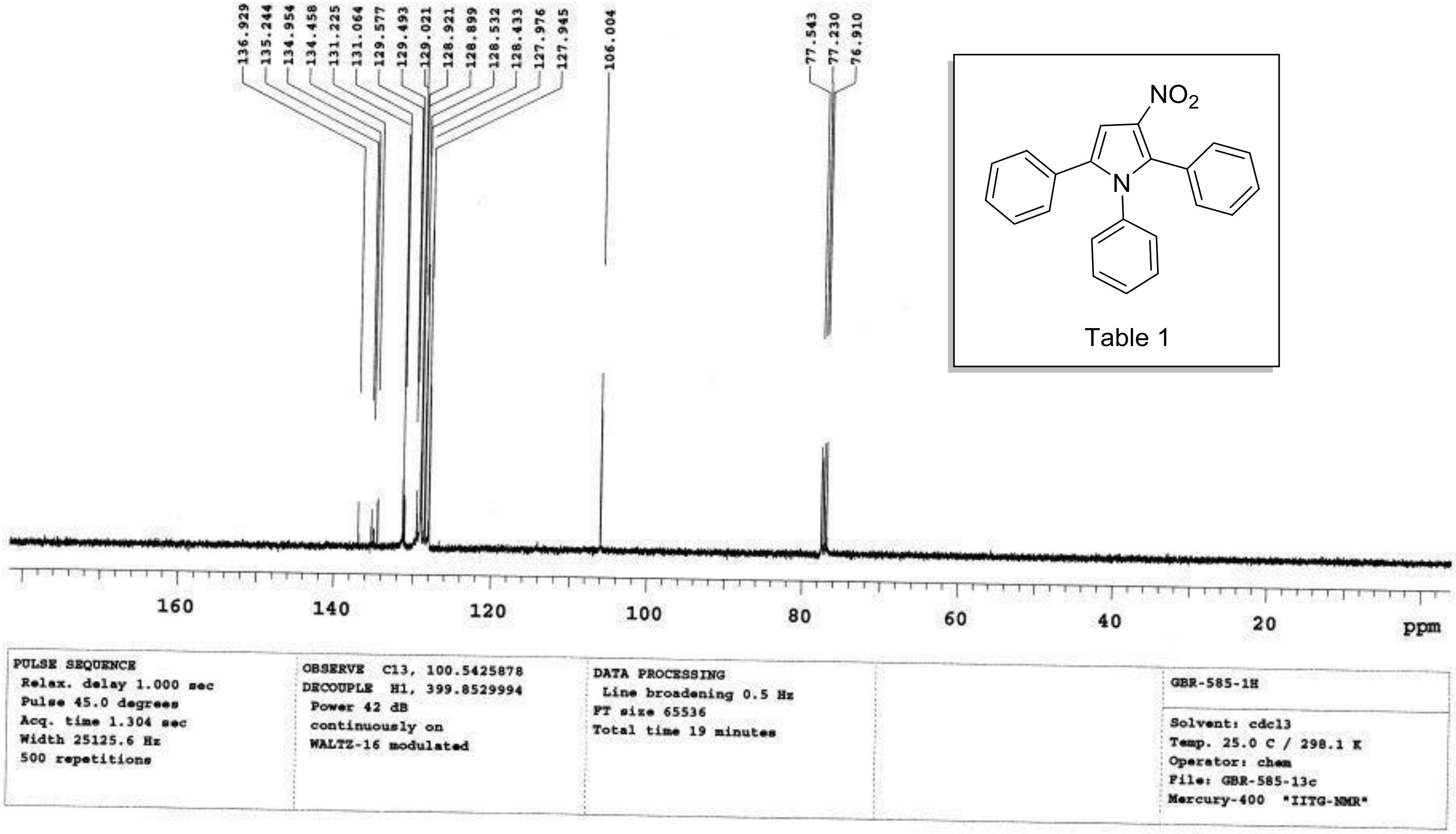
File: GBR-585-1H
Mercury-400 "IITG-NMR"



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500 repetitions

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Power 42 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
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GBR-585-1H

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Temp. 25.0 C / 298.1 K
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File: GBR-585-13c
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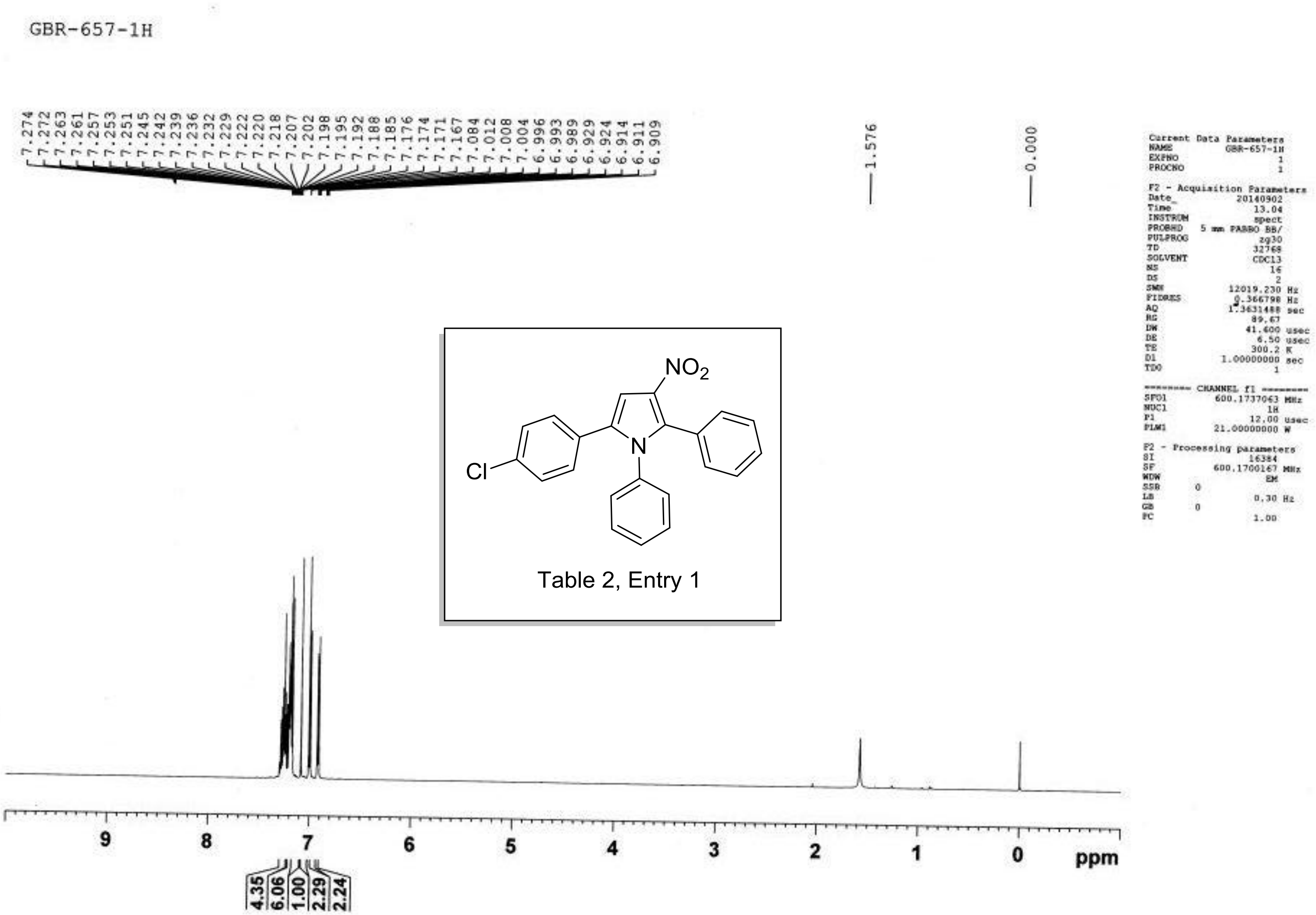

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PROCNO                 1

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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
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FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                 89.67
DW                41.600 usec
DE                  6.50 usec
TE                 300.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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NUC1                  1H
P1                 12.00 usec
PLW1         21.00000000 W

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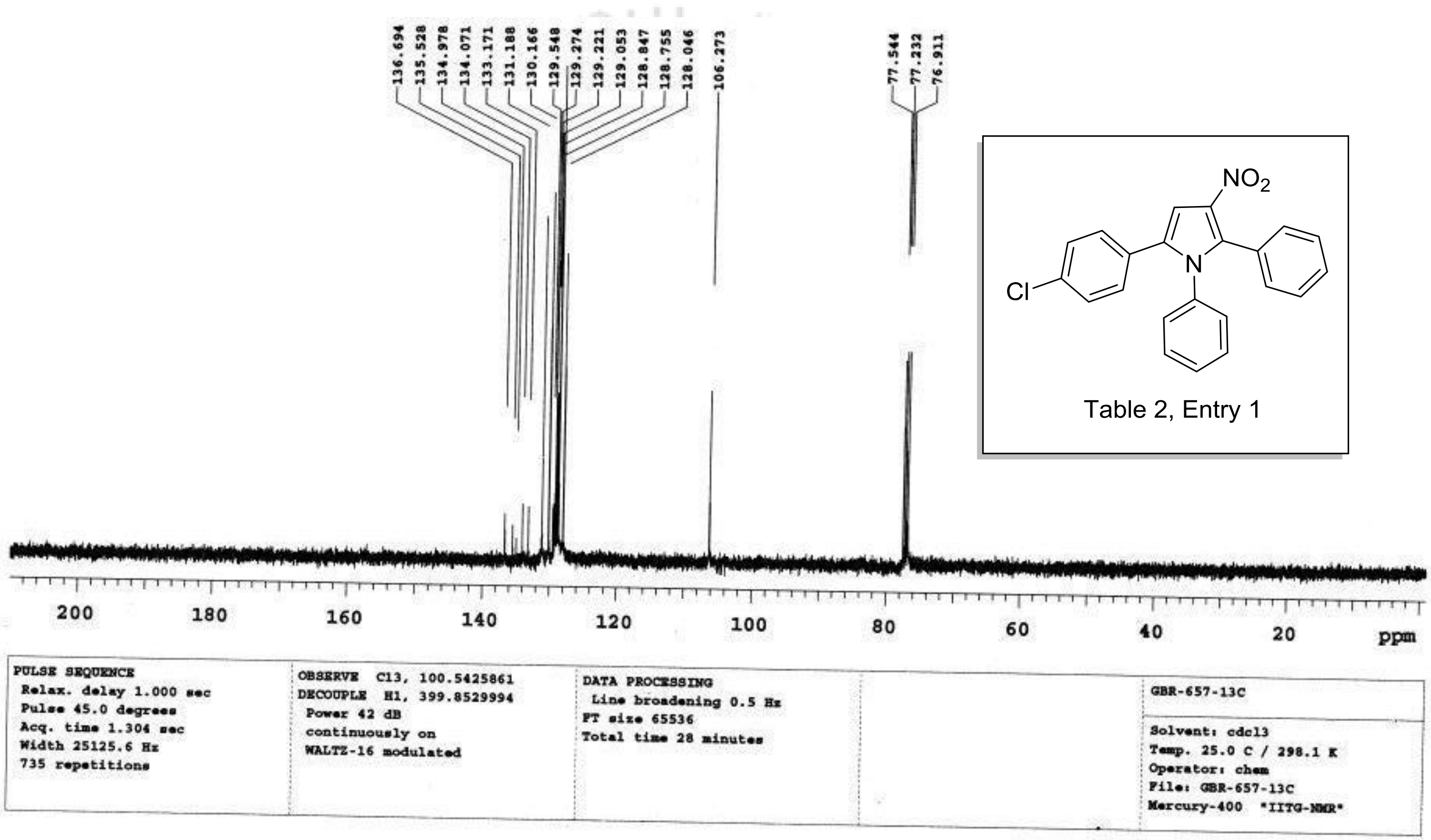

Table 2, Entry 1

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DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
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FT size 65536
Total time 28 minutes

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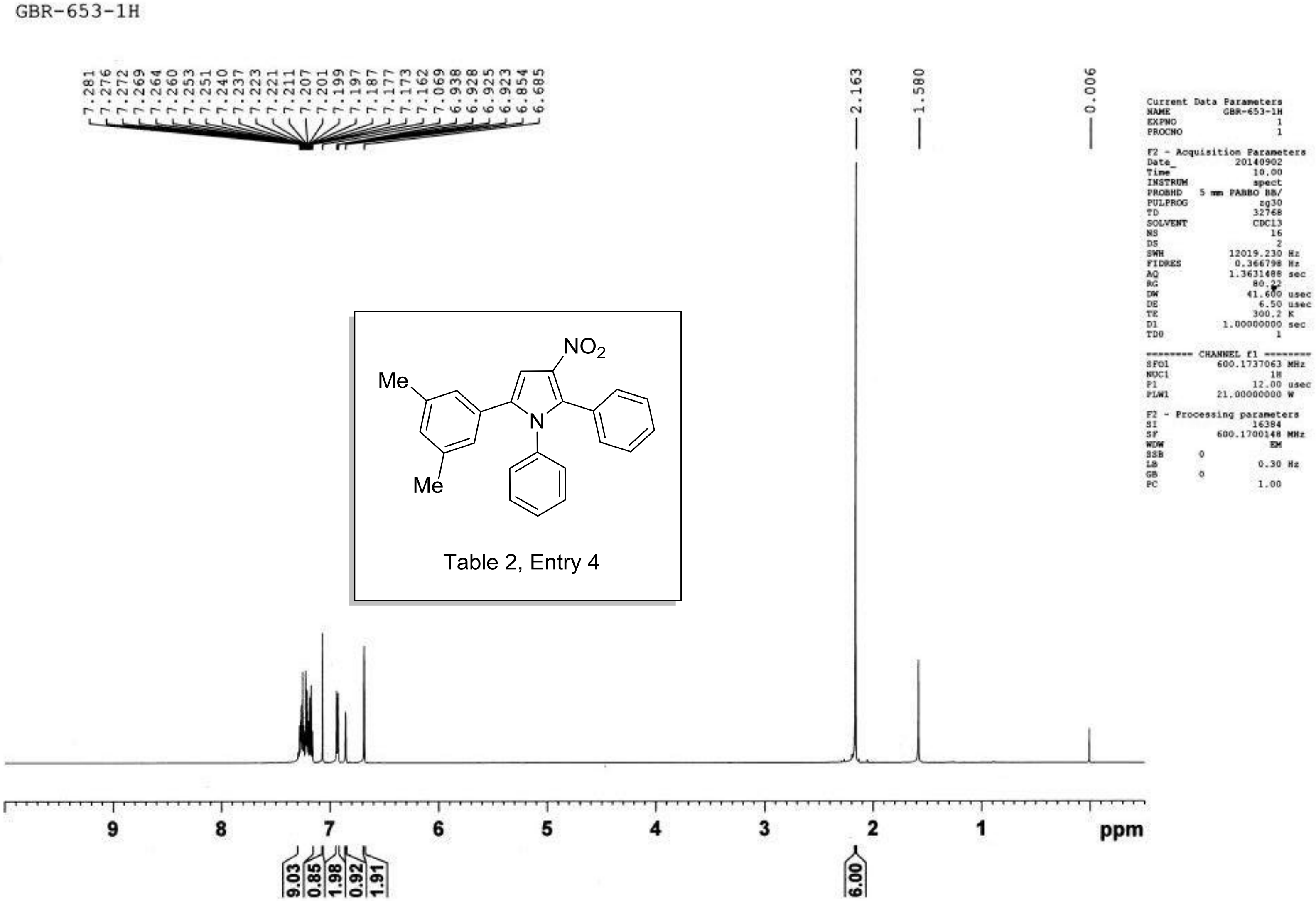
File: GBR-657-13C
Mercury-400 "IITG-NMR"



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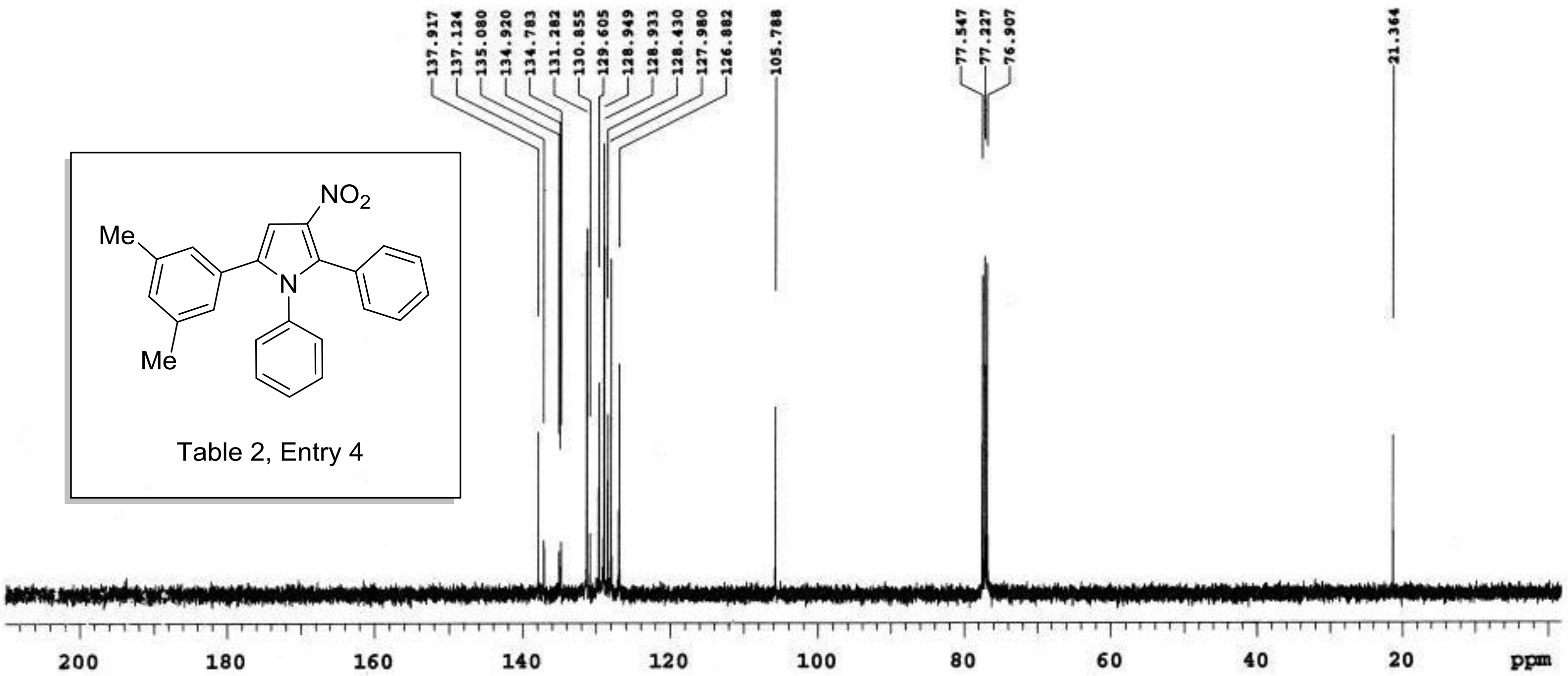

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 1110 repetitions
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DECOUPLE  H1, 399.8529994
 Power 42 dB
 continuously on
 WALTZ-16 modulated
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DATA PROCESSING
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Mercury-400  "IITG-NMR"
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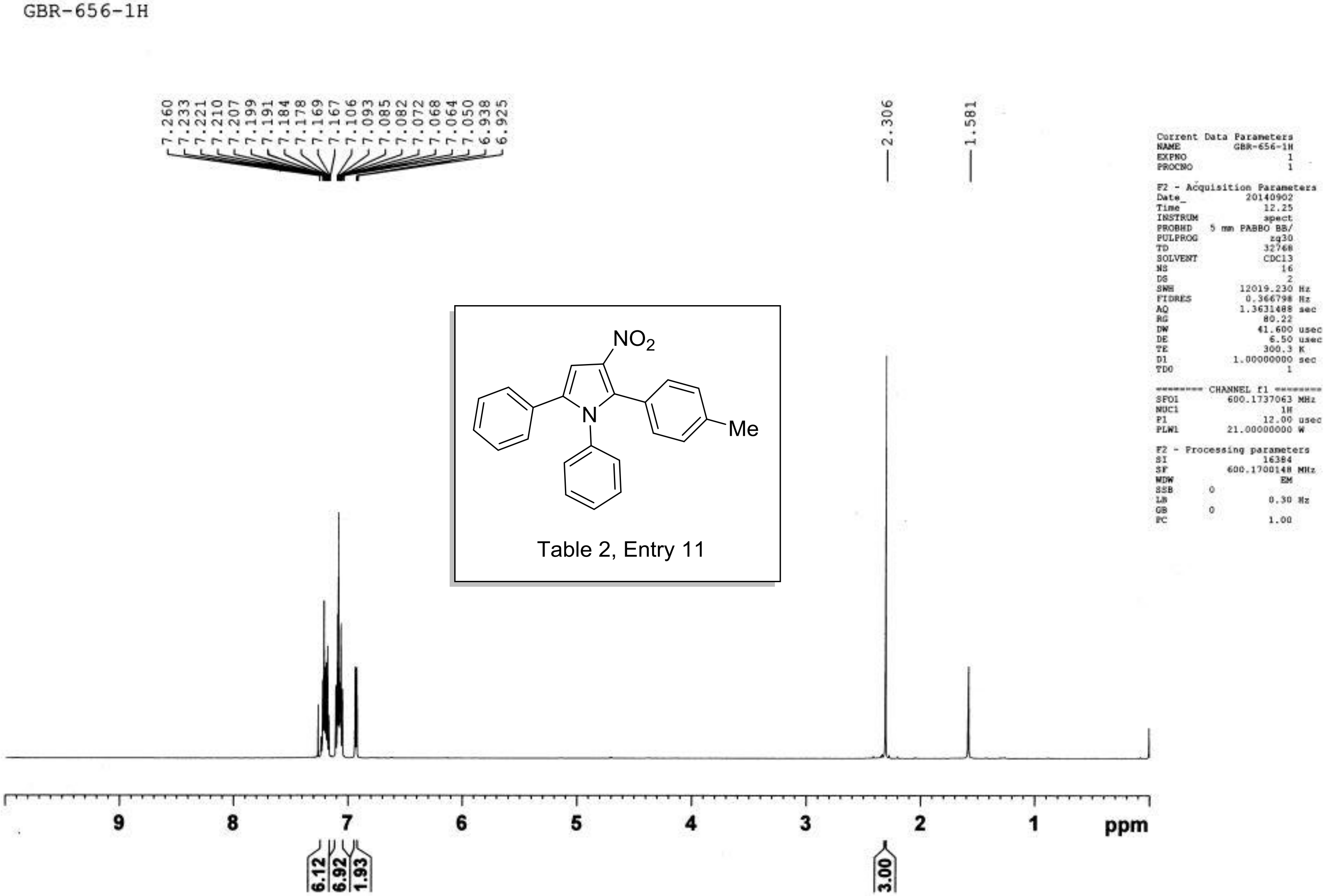

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PROCNO                 1

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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
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DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             1.3631488 sec
RG                 80.22
DW                41.600 usec
DE                  6.50 usec
TE                 300.3 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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NUC1                  1H
P1                 12.00 usec
PLW1         21.00000000 W

F2 - Processing parameters
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WDW                   EM
SSB      0
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GB       0
PC                  1.00
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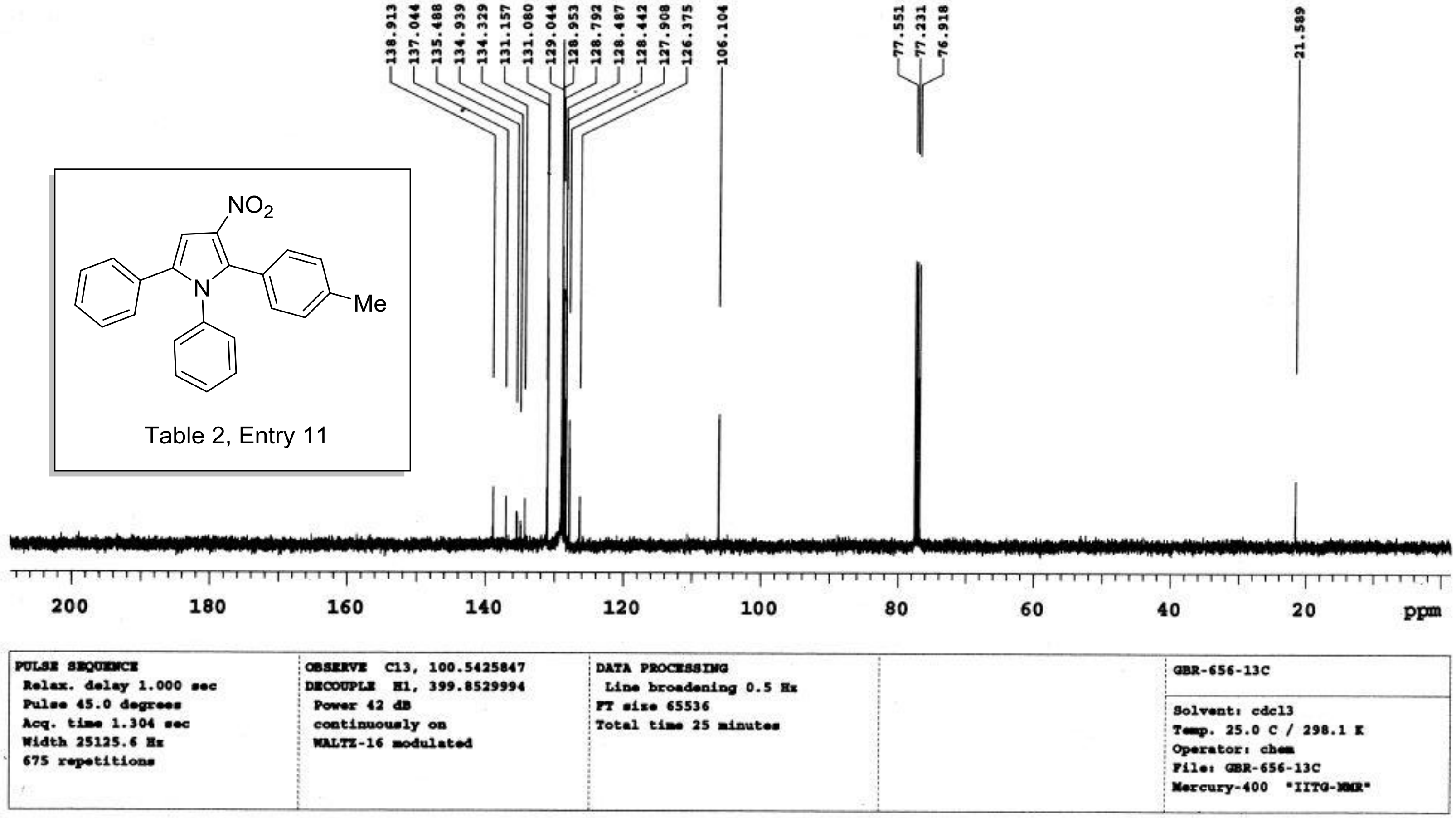

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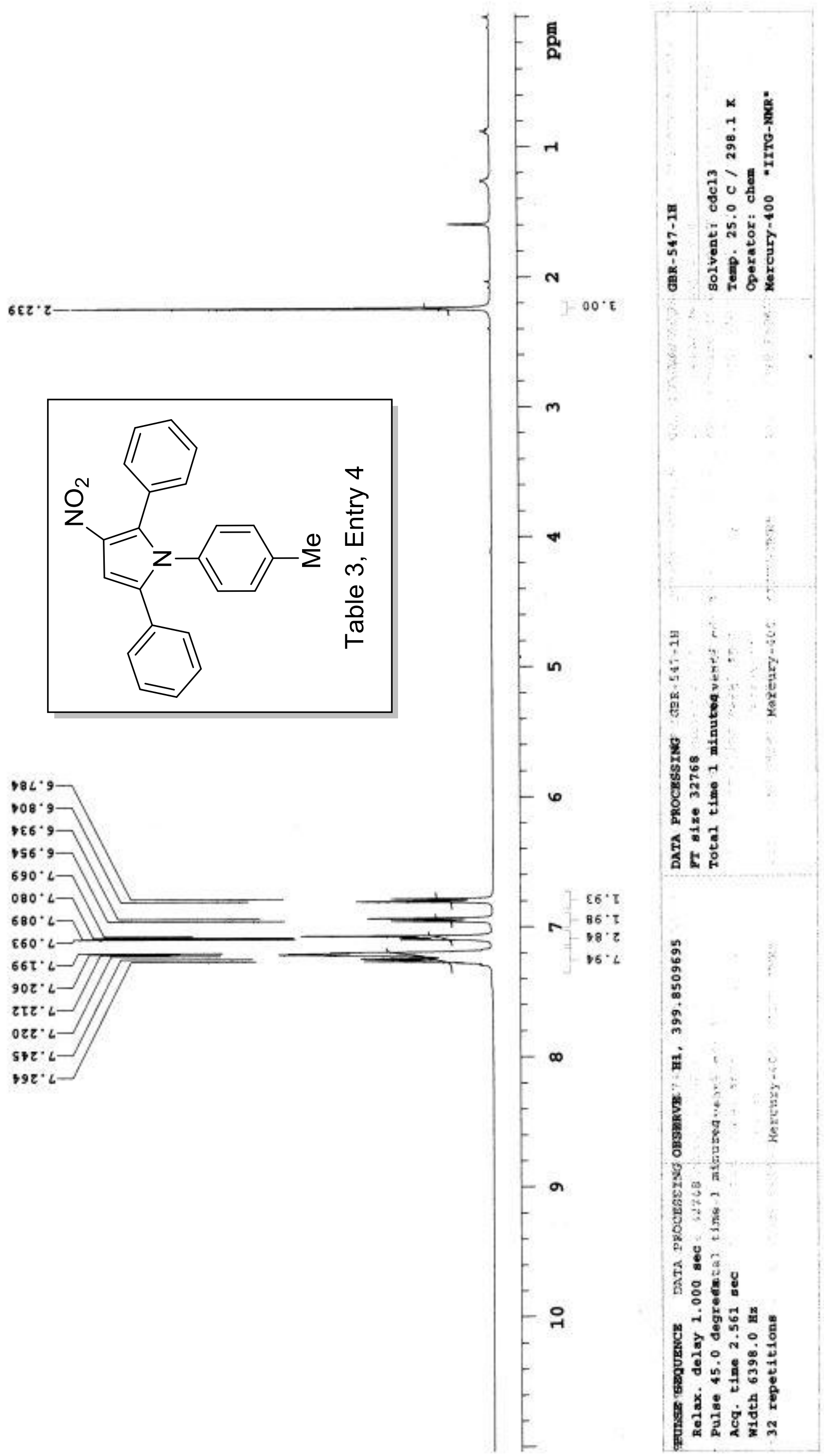
Width 25125.6 Hz
675 repetitions

OBSERVE C13, 100.5425847
DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 25 minutes

GBR-656-13C

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
File: GBR-656-13C
Mercury-400 "IITG-NMR"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7.069
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6.784
2.239
7.94
2.84
1.98
1.93
3.00
10
9
8
7
6
5
4
3
2
1
ppm
NO2
N
Me
Table 3, Entry 4
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 6398.0 Hz
32 repetitions
OBSERVE H1, 399.8509695
DATA PROCESSING
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Solvent: cdcl3
Temp. 25.0 C / 298.1 K
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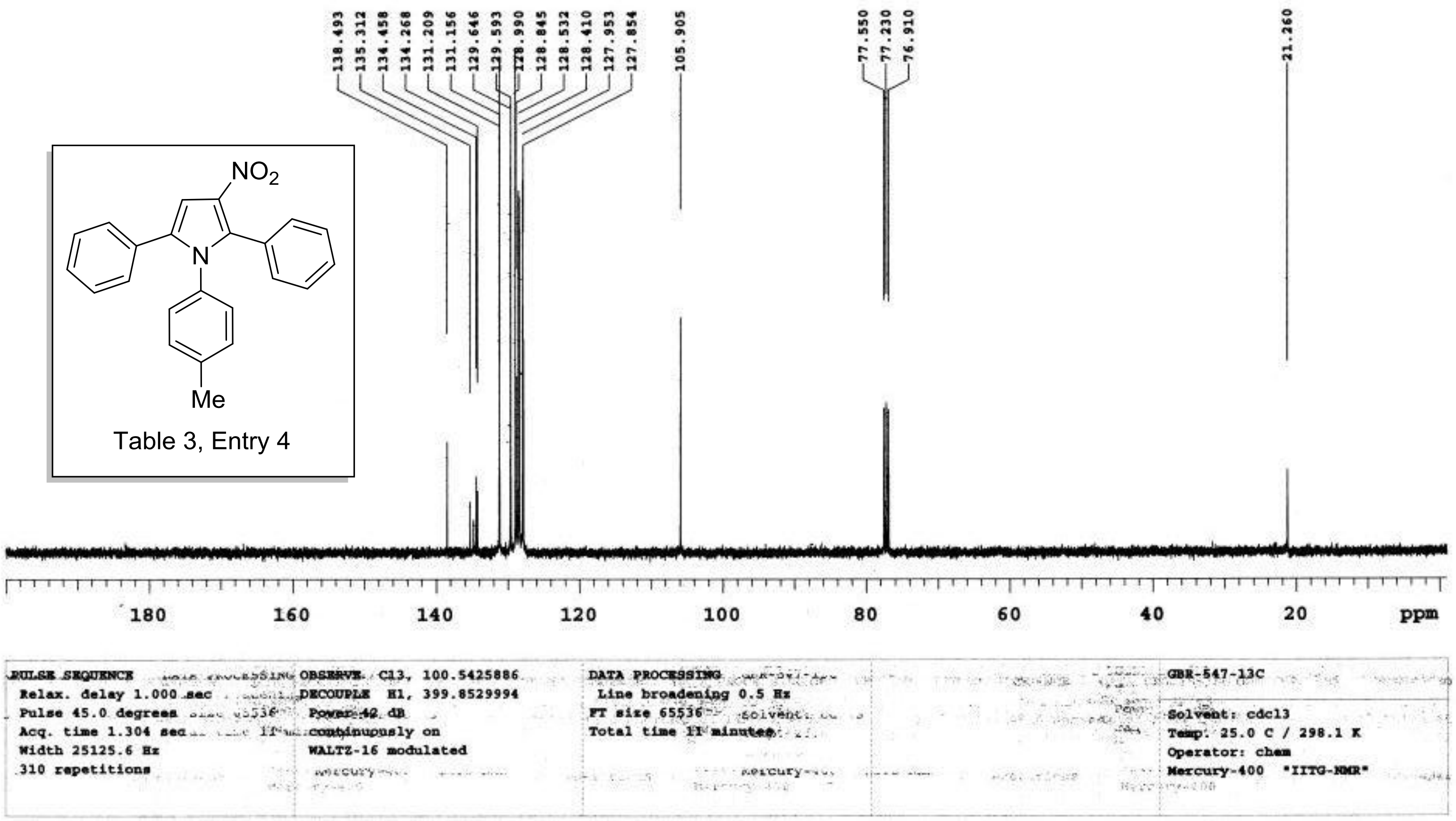
Mercury-400 "IITG-NMR"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127.854
105.905
77.550
77.230
76.910
21.260
NO2
N
Me
Table 3, Entry 4
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160
140
120
100
80
60
40
20
ppm
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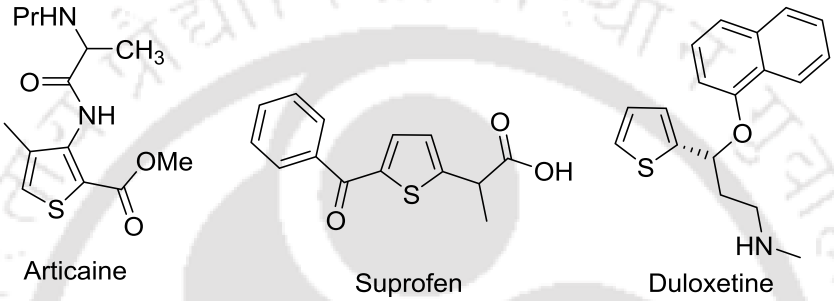
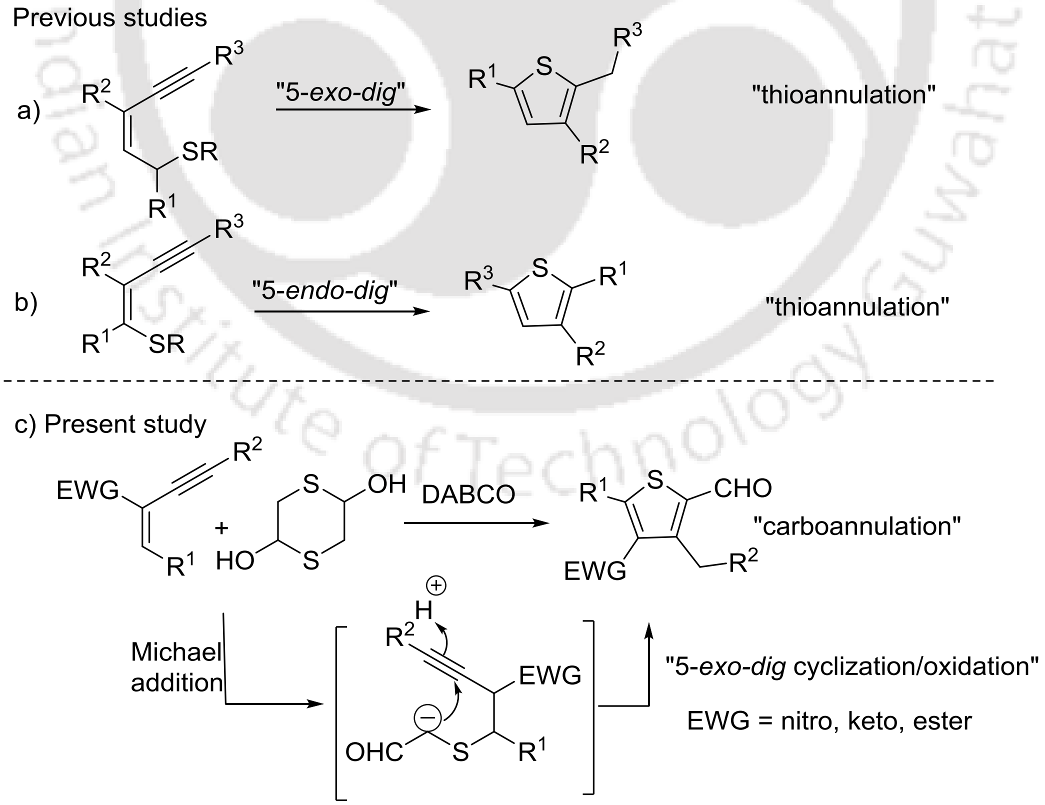
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
310 repetitions
OBSERVE C13, 100.5425886
DECOUPLE H1, 399.8529994
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 11 minutes
GBR-547-13C
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: chem
Mercury-400 "IITG-NMR"

Synthesis of Functionalized Thiophenes from 1,3-Enynes with 2-Mercaptoacetaldehyde

Functionalized thiophenes are significant structural skeletons in numerous bioactive natural products and pharmaceuticals (Scheme 1).[1] In addition, they find wide applications in material sciences as building blocks: for instances, in the assemblage of organic semiconductor, field



Scheme 1. Some Pharmaceutically Active Thiophenes

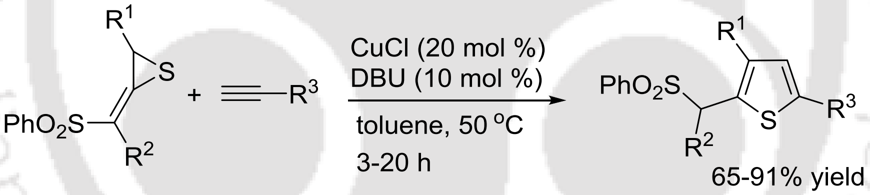


Scheme 2. Enynes in Functionalized Thiophene Synthesis

effect transistor, light emitting diode, photovoltaic material, etc.[2] Substantial efforts have thus been made on the development of effective methods for the construction of substituted thiophenes *via* either the *α*-metalation/*β*-halogenation of the thiophene ring or the thioannulation of the suitably substituted acyclic precursors.[3-5] Amongst these, the annulation of the enynes are very attractive as they afford effective synthetic routes for the building of thiophenes with diverse substitution pattern. For instances, the annulation of 2-en-4-yne-1-thiols was accomplished via 5-*exo-dig* cyclization (Scheme 2a),[6] while the cyclization of thiobutenynes was attained via 5-*endo-dig* cyclization (Scheme 2b).[7] The importance of thiophene derivatives has driven the development of several methods for the synthesis of various substituted thiophenes. Some of the recent examples follow.

4.1 Thiophene Synthesis

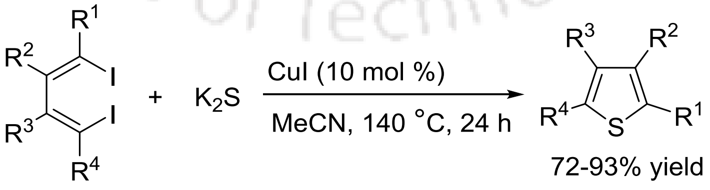
Ma group described Cu-catalyzed tandem addition/cycloisomerization of 1-phenylsulfonyl alkylidenethiiranes with terminal alkynes to give thiophenes (Scheme 3).[4a]



R^1 = H, alkyl; R^2 = alkyl; R^3 = aryl

Scheme 3

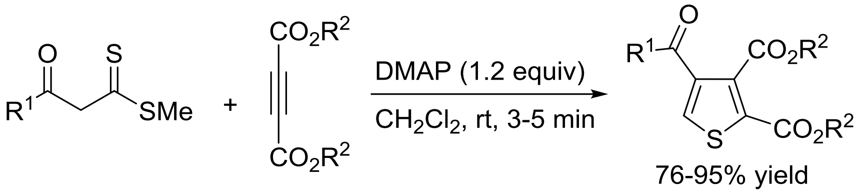
Xi and co-workers established Cu-catalyzed tandem S-alkenylation of potassium sulfide with 1,4-diiodo-1,3-dienes to afford substituted thiophenes in 72-93% yield (Scheme 4).[4b]



R^1, R^2, R^3, R^4 = H, alkyl, aryl, heteroaryl

Scheme 4

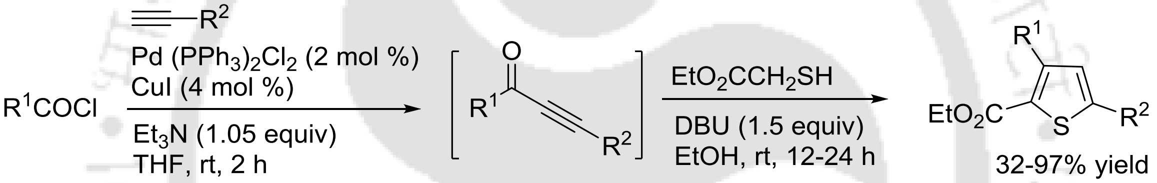
Sing and co-workers demonstrated DMAP-mediated synthesis of substituted thiophenes from β-oxodithioester and dialkyl acetylenedicarboxylate (Scheme 5).[4c]



R^1 =Aryl, 2-furyl, 2-thienyl, 3-pyridyl, ferrocenyl, isopropyl
R^2 = Me, Et

Scheme 5

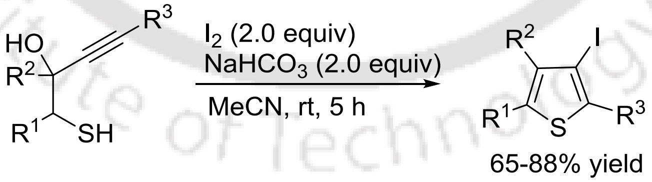
Muller group reported the synthesis of 2,4-disubstituted thiophene 5-carboxylates using three-component reaction of aroyl chlorides, alkynes and ethyl 2-mercapto acetate in 32-97% yields (Scheme 6).[4d]



R^1 = aryl, 2-thienyl
R^2 = alkyl, aryl, 2-thienyl, 2-pyridyl, ferrocenyl

Scheme 6

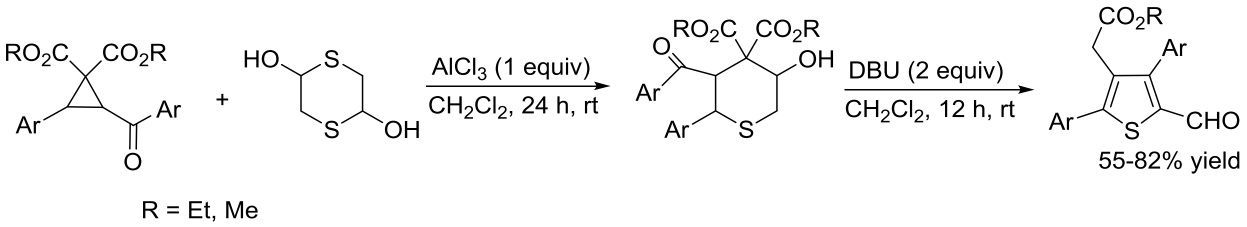
Iodine-mediated synthesis of 3-iodothiophenes is presented using the direct iodocyclization of alkynylthiol derivatives in the presence of $NaHCO_3$ at room temperature (Scheme 7).[4e]



R^1, R^2 = H, Me
R^3 = alkyl, aryl

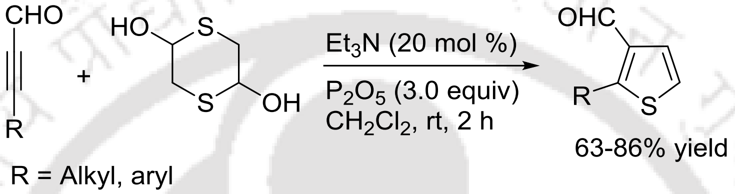
Scheme 7

Srinivasan and co-workers reported $AlCl_3$-promoted [3+3] annulation of cyclopropane derived 1,3-zwitterionic intermediate with mercaptoacetaldehyde to give tetrahydrothiopyranols, which is converted into thiophenecarbaldehyde in the presence of DBU (Scheme 8).[4f]



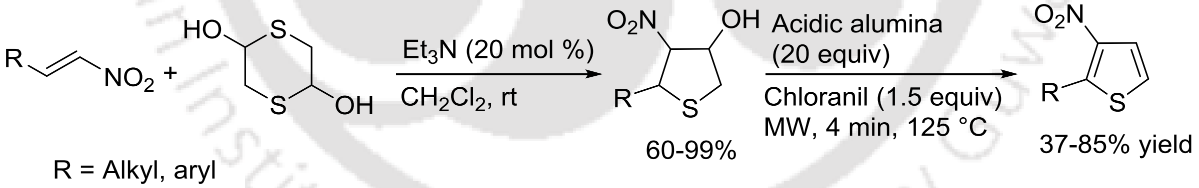
Scheme 8

Et_3N-promoted the [3+2]-cycloaddition of 2-mercaptoacetaldehyde with ynal to afford thiophenecarbaldehdyes at room temperature (Scheme 9).[4g]



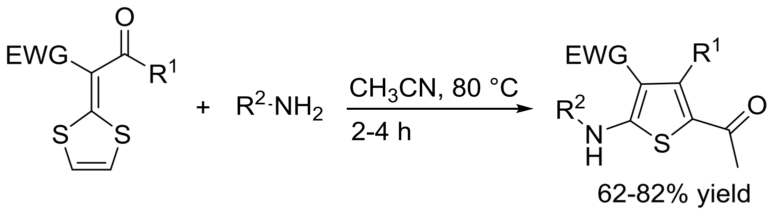
Scheme 9

Southern and co-workers showed Et_3N-catalyzed synthesis of 3-nitro-2-substituted thiophenes from *β*-nitrostyrene and 1,4-dithane-2,5-diol. This reaction involves tandem Michael addition followed by intramolecular Henry reaction to give tetrahydrothiophene derivatives that undergo dehydration and aromatization using microwave irradiation on acidic alumina to form substituted thiophenes (Scheme 10).[4h]



Scheme 10

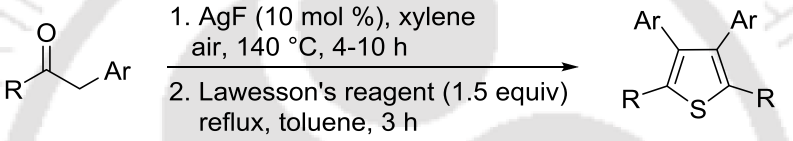
Liang and co-workers reported amine-promoted ring-opening of triggered 2-methylene-1,3-dithioles to highly substituted thiophenes *via* ring opening of 1,3-dithiols, intramolecular annulation and amine substitution under mild reaction conditions (Scheme 11).[4i]



R^1 = H, Me, Ph
R^2 = Alkyl
EWG = COMe, CO_2Et, CO_2Me, COPh

Scheme 11

Wang and co-workers reported AgF-catalyzed synthesis of tetrasubstituted thiophenes using benzoin which undergoes cyclization with Lawesson's reagent to afford the desired thiophenes (Scheme 12).[4j]

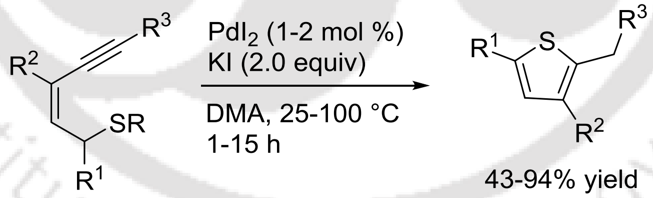


R = Aryl

Scheme 12

4.2 5-*Exo-dig* Thioannulation

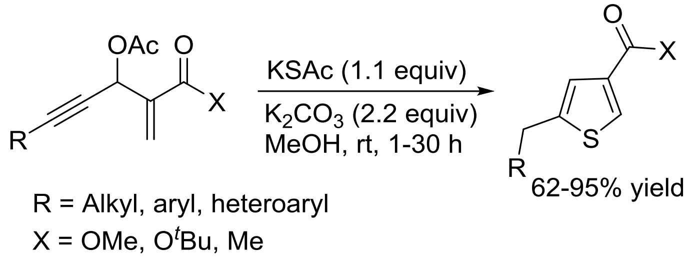
Gabriele and coworkers reported the synthesis of trisubstituted thiophenes using Pd-catalyzed 5-*exo-dig* cyclization of (*Z*)-2-en-4-yne-1-thiols in *N, N*-dimethylacetamide (Scheme 13).[6a]



R^1 = H, Et, Ph
R^2 = H, Me
R^3 = H, Bu, Ph

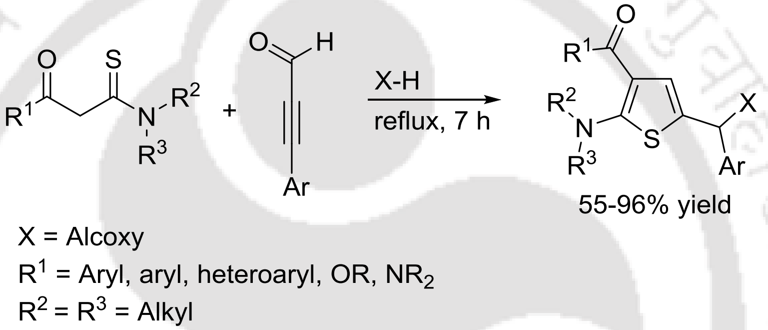
Scheme 13

Reddy and co-workers described base-promoted thioannulation of Morita–Baylis–Hillman acetates of acetylenic aldehydes with KSAc to provide the substituted thiophenes. This reaction invovles an allylic substitution/deacetylative 5-*exo-dig*-thiocycloisomerization under metal-free reaction conditions (Scheme 14).[6b]



Scheme 14

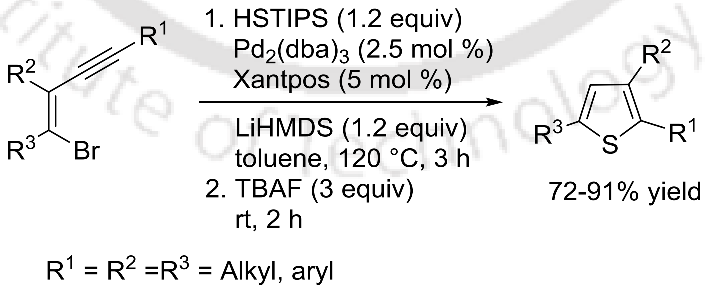
The synthesis of 2-aminothiophene is reported using the reaction of 2-ynals with thioamides. This reaction involves aldol condensation/regioselective intramolecular cyclization/conjugate addition to provide the 2,3,5-trisubstituted 2-aminothiophenes (Scheme 15).[6c]



Scheme 15

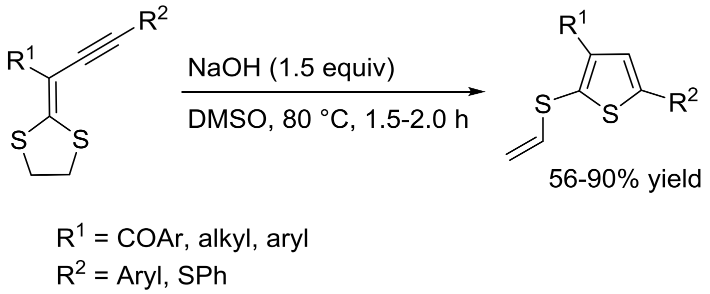
4.3 5-*Endo-dig* Thioannuation

Sanz and coworkers demonstrated the synthesis of thiophenes from bromoenynes derivatives. This protocol involves Pd-catalyzed *C-S* bond formation with a hydrogen sulfide surrogate followed by a *5-end-dig* cyclization (Scheme 16).[7a]



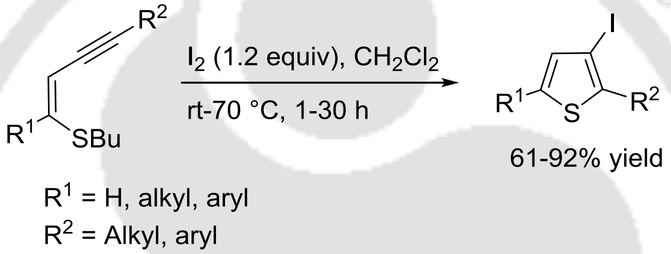
Scheme 16

Base-mediated synthesis of thiophenes is demonstrated from gem-dialkylthio enynes via 5-*endo-dig* cyclization (Scheme 17).[7b]



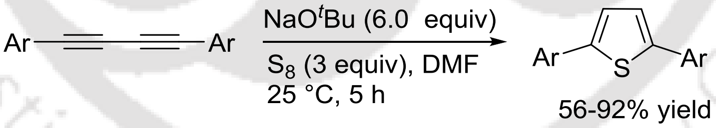
Scheme 17

Baroni and co-workers presented iodine-mediated 5-*endo*-*dig* cyclization of (*Z*)-thioenynes to furnish 3-iodothiophenes, which can further be elaborated to complex derivatives using cross-coupling reactions (Scheme 18).[7c]



Scheme 18

Lei and co-workers described base-promoted synthesis of thiophenes from 1,3-diynes and polysulfide (Scheme 19).[7d]



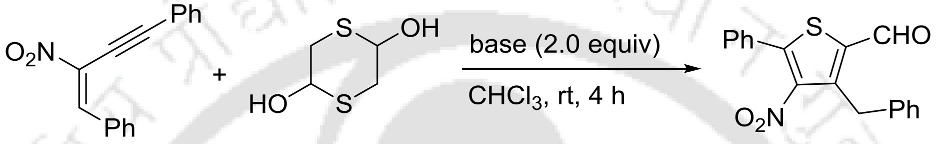
Scheme 19

4.4 Present Work

Herein we present the construction of highly functionalized thiophenes *via* the domino Michael addition, 5-*exo-dig carboannulation* and oxidation of 1,3-enynes with 2-mercaptoacetaldehyde using DABCO at room temperature (Scheme 2). This reaction affords the advantages of the direct introduction of the aldehyde and nitro/keto/ester functionalities in the thiophene ring with broad substrate scope under metal-free mild reaction conditions.

First, optimization of the reaction conditions was performed using (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne as a model substrate with 1,4-dithiane-2,5-diol in the presence of different bases and solvents under air. The reaction occurred efficiently to furnish the target3-benzyl-4-nitro-5-phenylthiophene-2-carbaldehyde in 4 h with >99% conversion and 100% selectivity when the substrates (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne and 1,4-dithiane-2,5-diol were stirred with 2.0 equiv of DABCO in $CHCl_3$ at room temperature in an open vessel. In a set of bases screened, DABCO displayed superior results compared to DBU, Et_3N and $^iPr_2NH$ (Entries 1-4). Inorganic

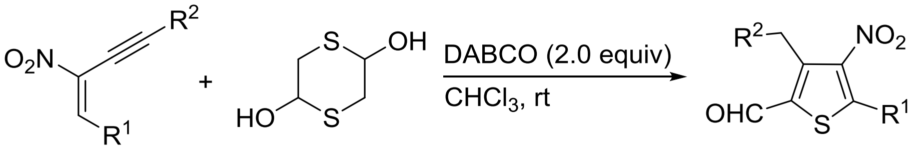
Table 1. Optimization of the Reaction Conditions[a]

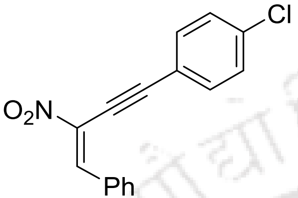
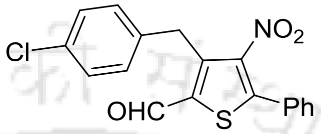
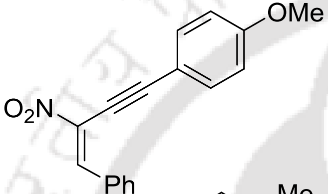
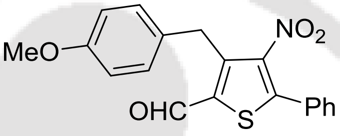
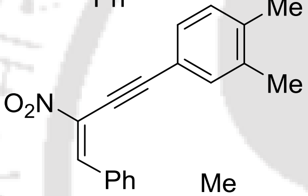
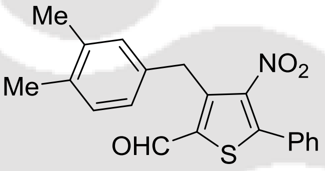
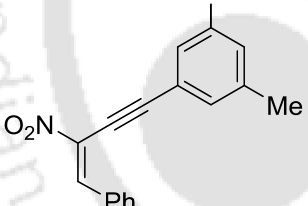
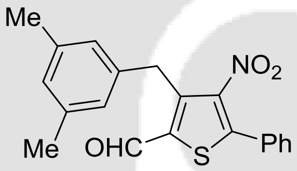
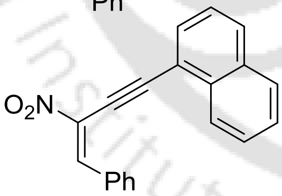
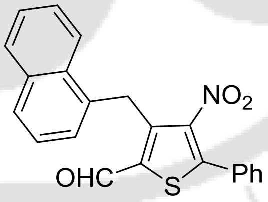
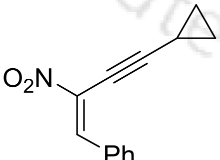
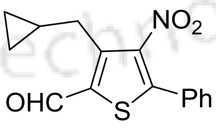
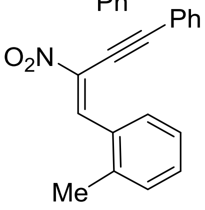
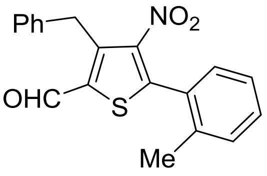


Entry	Base	Solvent	Conversion (%)[b]
1	DBU	CH_2Cl_2	trace
2	DABCO	CH_2Cl_2	89
3	Et_3N	CH_2Cl_2	81
4	$^iPr_2NH$	CH_2Cl_2	62
5	K_2CO_3	CH_2Cl_2	n.d.
6	$NaHCO_3$	CH_2Cl_2	n.d.
7	Cs_2CO_3	CH_2Cl_2	n.d.
8	DABCO	Dioxane	52
9	DABCO	Toluene	87
10	DABCO	DCE	58
11	**DABCO**	**$CHCl_3$**	**>99**
12	DABCO	$CHCl_3$	77[c]
13	DABCO	$CHCl_3$	55[d]
14	-	$CHCl_3$	n.d.

[a] Enyne (0.5 mmol), 1,4-dithiane-2,5-diol (0.35 mmol), base (2.0 equiv) in solvent (3.0 mL) were stirred at room temperature under air for 4 h. [b] Determined by ^1H NMR spectroscopic analysis. DABCO = [c] 1.5 equiv. [d] 1.0 equiv. n.d. = not detected.

Table 2. Reaction of 1,3-Enyne bearing Nitro Functionality with 2-Mercaptoacetaldehyde[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			3	78
2			12	66
3			4	79
4			4	81
5			12	68
6			24	29
7			12	66

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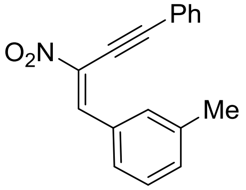
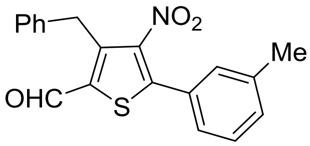
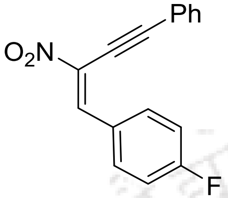
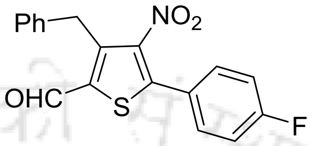
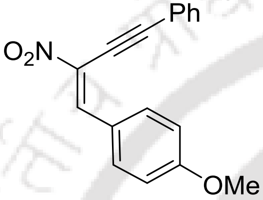
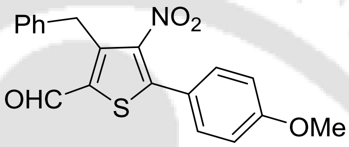
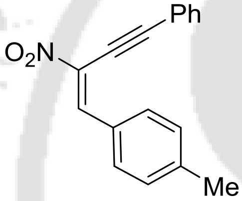
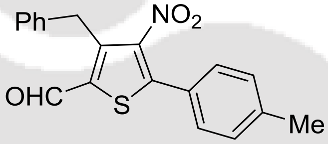
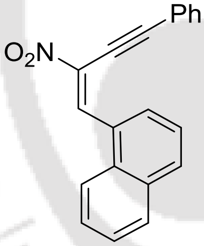
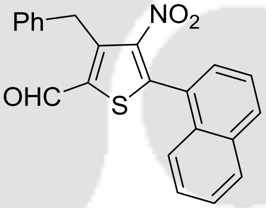
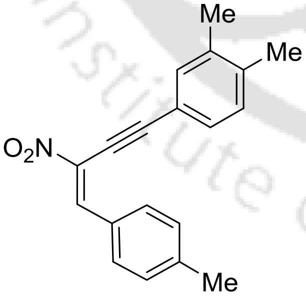
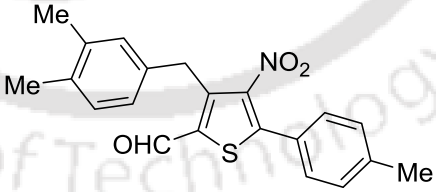
8			4	73
9			2	74
10			15	69
11			4	77
12			18	62
13			3	60

[a]Enyne (0.5 mmol), 1,4-dithiane-2,5-diol (0.35 mmol), DABCO (1 mmol) in $CHCl_3$ (3.0 mL) were stirred at room temperature under air. [b]Isolated yield.

---

bases such as K_2CO_3, $NaHCO_3$ and Cs_2CO_3 failed to produce the target product (Entries 5-7). $CHCl_3$ was found to be the solvent of choice, whereas CH_2Cl_2, dioxane, toluene and DCE produced desired product in 52-89% (Entries 2 and 8-11). Decreasing the amount of DABCO (1.5 equiv) led to drop in the yield to $\leq$ 77%. Control experiment confirmed that the desired thiophene was not formed without addition of base and the starting materials were recovered intact.

With optimized reaction conditions in hand, the scope of the protocol was explored for the reaction of several substituted 1,3-enynes bearing nitro functionality (Table 2). The substrates with electron withdrawing groups in the aryl rings exhibited greater reactivity compared to that containing electron donating groups. For instances, the substrates bearing chloro and fluoro substituents underwent reaction to provide desired heterocycle in 78 and 74% yield, respectively, (Entries 1 and 9), whereas enyne with methoxy group in aryl rings required slightly longer reaction time to afford thiophenes in 66 and 69% yields, respectively, (Entries 2 and 10). The reactions of mono-, di- and tri-methyl substituted enynes gave the corresponding substituted thiophenes in 60-81% yields (Entries 3-4, 8, 11 and 13). In addition, the enynes bearing *ortho*-methyl and naphthyl groups underwent reaction to give target cyclic compounds in 62-68% yields (Entries 5, 7 and 12), while the reaction of aliphatic enyne produced thiophine in 29% yield (Entry 6). Recrystallization of 3-(4-chlorobenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde provided single crystals whose structure was confirmed by X-ray analysis (Figure 1).

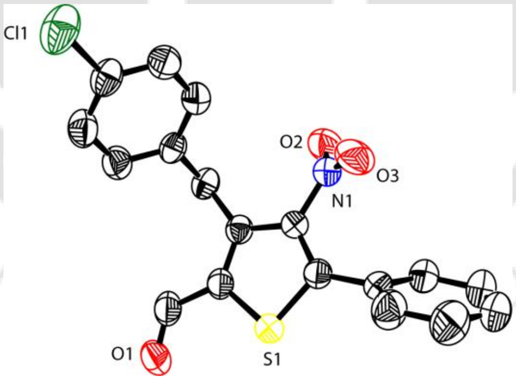
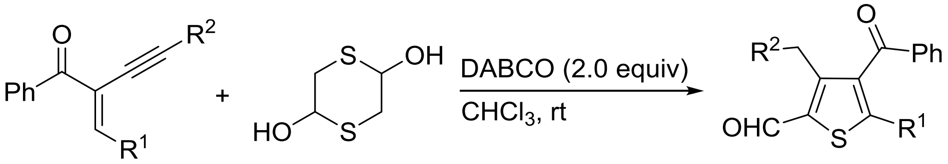
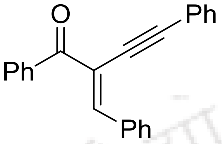
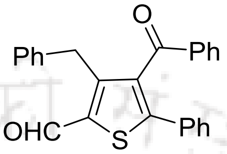
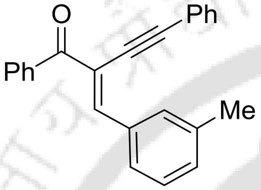
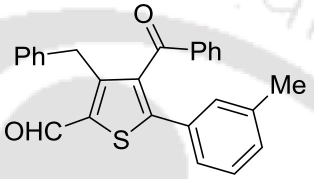
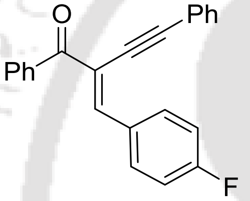
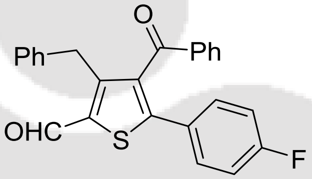
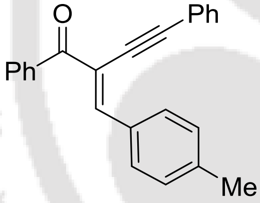
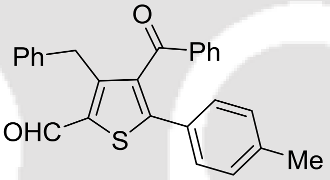
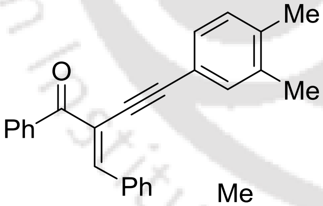
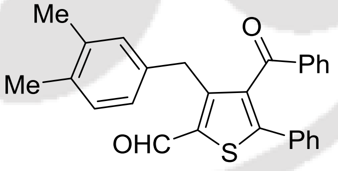
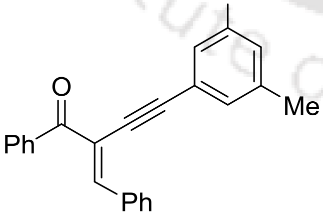
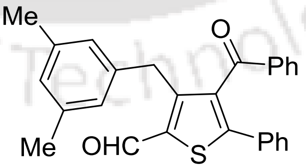


Figure 1. ORTEP diagram of 3-(4-chlorobenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 2, Entry 1). Thermal ellipsoids are drawn at a 50% probability level. Hydrogen atoms are omitted for clarity (CCDC 1444602).

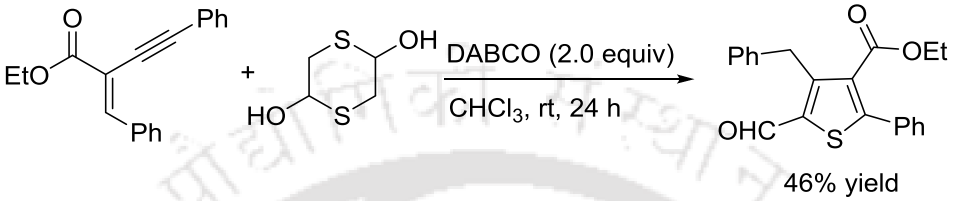
Table 3. Reaction of 1,3-Enyne bearing Ketone Functionality with 2-Mercaptoacetaldehyde[a]



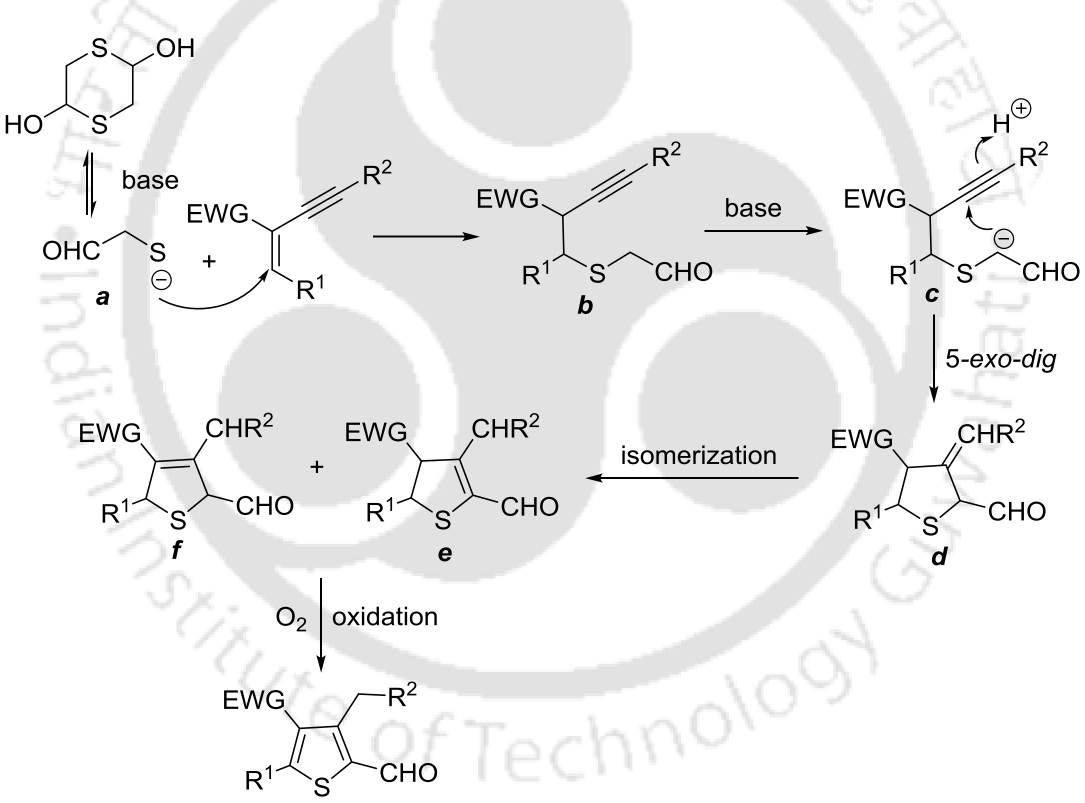
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			12	71
2			12	61
3			8	73
4			12	69
5			12	63
6			12	66

[a]Enyne (0.5 mmol), 1,4-dithiane-2,5-diol (0.35 mmol), DABCO (1 mmol) in $CHCl_3$ (3.0 mL) were stirred at room temperature under air. [b]Isolated yield

Next, the reaction of 1,3-enynes containing ketone functionality was investigated (Table 3). These substrates required somewhat longer time (8-12 h) compared to that of the nitro compounds. For instance, the substrate with R^1 and R^2 = Ph underwent reaction to give thiophene derivative in 71% yield (Entry 1). The reaction of the enyne with electron-withdrawing 4-fluoro group in the aryl ring gave target heterocyclic compounds in 73% yield (Entry 3). In addition, mono- and di-methyl substituted aryl groups in the enynes could be transformed into the thiophene derivatives in 61-69% yields (Entries 2 and 4-6).



Scheme 20. Reaction of 1,3-Enyne bearing Ester with 2-Mercaptoacetaldehyde



Scheme 21. Proposed Reaction Pathway

Finally, the compatibility of the protocol was examined for the reaction of 1,3-enyne bearing ester functionality (Scheme 20). The substrate required longer reaction time (24 h) compared to that of the enyne bearing nitro and keto functionalities. For instance, the enyne having ethyl ester underwent reaction to deliver desired cyclic compounds with 46% yield. These results suggest that wide-ranging of enynes can be coupled with 2-mercaptoacetaldehyde to yield highly functionalized thiophene-2-carbaldehdyes under mild reaction conditions.

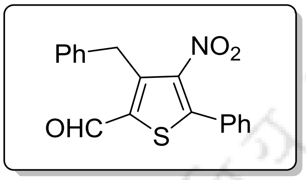
The proposed reaction pathway is displayed in Scheme 21. 1,4-Dithiane-2,5-diol with DABCO can produce ***a*** that may undergo Michael addition with 1,3-enyne to furnish carbanion intermediate ***b***. The latter may transform into ***c*** that can be stabilized by "CHO" as well as vacant *d* orbital of "S". 5-*Exo-dig* carboannulation[9-10] of ***c*** may lead to the formation of ***d*** that may undergo isomerization to furnish ***e*** and ***f***, which may undergo oxidation[11] using air to yield the target product. The proposed reaction pathway also explains the necessity of excess DABCO to produce the target products in good yields.

In summary, we presented DABCO-mediated domino[12] reaction of 1,3-enynes with 2-mercaptoacetaldehyde to furnish highly functionalized thiophenes under mild conditions *via* a sequential Michael addition, carboannulation, and oxidative aromatization. The use of a mild organic base, wide substrate scope and metal-free conditions are the significant practical advantages.

4.5 Experimental Section

General Information. $Pd(PPh_3)_2Cl_2$ (98%), CuI (98%), DABCO (98%) and 1,4-dithiane-2-5-diol (97%) were purchased from commercial sources. 1,3-Enynes were synthesized according to reported procedure.[13-14] The progress of the reaction was monitored by analytical TLC on silica gel G/GF 254 plates. The column chromatography was performed with silica gel 60-120 mesh. NMR (^1H and ^{13}C) spectra were recorded on DRX- 400 and 600 MHz instruments using $CDCl_3$ as a solvent and Me_4Si as an internal standard. Chemical shifts (δ) were reported in ppm, and spin−spin coupling constants (*J*) were given in Hz. The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet. Melting points were determined by melting point apparatus and are uncorrected. FT-IR spectra were recorded using an IR Spectrometer. High-resolution mass spectra were recorded on a QTof ESI-MS instrument. For single crystal X-ray analysis the intensity data were collected using CCD diffractometer using Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structures were solved by direct methods using SHELXL-97 (Göttingen, Germany).

General Procedure for the Synthesis of Substituted Thiophenes. To a stirred solution of 1,4-dithiane-2,5-diol **2** (0.35 mmol) and enyne (0.5 mmol) in $CHCl_3$ (2 mL), DABCO (1.0 mmol) in $CHCl_3$ (1.0 mL) was added under air. The stirring was continued until completion of the reaction. The progress of the reaction was monitored using TLC with hexane and ethyl acetate as eluent. The solvent was then evaporated in a rotary evaporator and the residue was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford analytically pure products.



3-Benzyl-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 1).

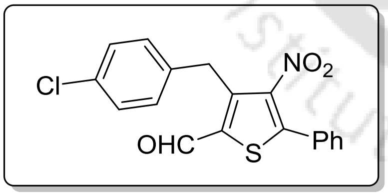
Yellow liquid; yield: 82% (132 mg)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.06 (s, 1H), 7.49-7.43 (m, 5H), 7.32-7.29 (m, 2H), 7.25-7.23 (m, 1H), 7.18 (d, J = 7.2 Hz, 2H), 4.49 (s, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 181.8, 149.7, 142.7, 137.2, 137.0, 130.8, 129.6, 129.3, 129.1, 128.6, 128.4, 127.3, 32.1.

FT-IR (neat): 3417, 3029, 2923, 2853, 1665, 1602, 1558, 1546, 1518, 1494, 1453, 1443, 1384, 1349, 1216, 1056, 1028, 794, 744, 695, 663 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{14}NO_3S$ 324.0689, found 324.0696.



3-(4-Chlorobenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 2, Entry 1).

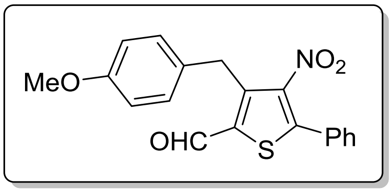
Colorless solid; yield: 78% (139 mg); mp 117–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.61 (s, 1H), 8.04-7.97 (m, 5H), 7.83-7.80 (m, 2H), 7.67 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 181.6, 150.0, 144.1, 142.0, 137.0, 135.6, 133.3, 131.0, 129.8, 129.5, 129.4, 129.3, 128.6, 31.5.

FT-IR (KBr): 3452, 2936, 2853, 1666, 1546, 1517, 1491, 1408, 1384, 1347, 1263, 1216, 1093, 1057, 1029, 1014, 807, 748, 694, 668 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{13}ClNO_3S$ 358.0299, found 358.0299.



3-(4-Methoxybenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 2, Entry 2).

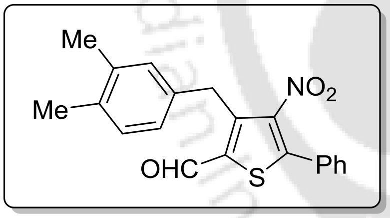
Yellow liquid; yield: 66% (116 mg).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.07 (s, 1H), 7.48-7.44 (m, 5H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.41 (s, 2H), 3.77 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 181.9, 158.8,149.6, 144.3, 143.4, 136.9, 130.9, 129.7, 129.6, 129.3, 129.2, 128.6, 114.6, 55.4, 31.3.

FT-IR (neat): 3443, 2929, 2837, 1665, 1609, 1584, 1558, 1526, 1511, 1458, 1442, 1384, 1350, 1303, 1249, 1217, 1177, 1031, 818, 757, 740, 694, 667 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{16}NO_4S$ 354.0795, found 354.0786.



3-(3,4-Dimethylbenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 2, Entry 3).

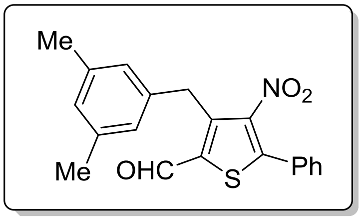
Yellow liquid; yield: 79% (138 mg).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.06 (s, 1H), 7.49-7.44 (m, 5H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.93 (s, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 4.41 (s, 2H), 2.22 (s, 3H), 2.21 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 182.0, 149.5, 144.3, 143.3, 137.4, 137.0, 135.7, 134.6, 130.8, 130.3, 129.6, 129.3, 128.6, 125.8, 31.7, 20.0, 19.5.

FT-IR (neat): 3442, 2921, 2850, 1665, 1546, 1519, 1443, 1384, 1349, 1216, 1057, 1028, 1001, 814, 774, 757, 694, 663 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_3S$ 352.1002, found 352.1002.



3-(3,5-Dimethylbenzyl)-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 2, Entry 4).

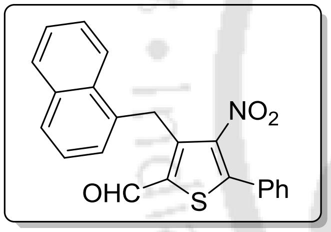
Yellow liquid; yield: 81% (142 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 10.05 (s, 1H), 7.50-7.45 (m, 5H), 6.87 (s, 1H), 6.76 (s, 2H), 4.39 (s, 2H), 2.27 (s, 6H).

^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ = 182.1, 149.5, 144.3, 143.1, 138.8, 137.1, 137.0, 130.8, 129.7, 129.3, 129.0, 128.6, 126.2, 32.0, 21.5.

FT-IR (neat): 3408, 2919, 2854, 1665, 1601, 1547, 1520, 1489, 1443, 1384, 1349, 1281, 1216, 1163, 1053, 1029, 1000, 843, 796, 750, 694 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{18}NO_3S$ 352.1002, found 352.1000.



3-(Naphthalen-1-ylmethyl)-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 2, Entry 5).

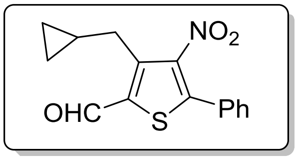
Yellow liquid; yield: 68% (127 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 9.79 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.61-7.48 (m, 7H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 6.6 Hz, 1H), 4.92 (s, 2H).

^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ = 181.9, 149.5, 144.6, 142.1, 137.7, 133.9, 133.7, 131.5, 130.9, 129.6, 129.4, 129.2, 128.7, 128.2, 126.9, 126.4, 125.7, 125.5, 122.9, 29.5.

FT-IR (neat): 3451, 3058, 2922, 2852, 1664, 1598, 1547, 1516, 1443, 1398, 1384, 1347, 1221, 1028, 797, 771, 754, 737, 694, 667 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{22}H_{16}NO_3S$ 374.0845, found 374.0848.



3-(Cyclopropylmethyl)-4-nitro-5-phenylthiophene-2-carbaldehyde (Table 2, Entry 6).

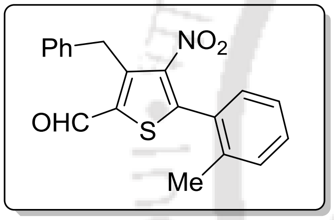
Yellow liquid; yield: 29% (42 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 10.05 (s, 1H), 7.48-7.45 (m, 5H), 3.02 (d, J = 6.6 Hz, 2H), 1.06 (t, J = *6.0* Hz, 1H), 0.58 (d, J = 7.2 Hz, 2H), 0.28 (d, J = 4.8 Hz, 2H).

^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ = 181.7, 149.1, 145.0, 136.6, 130.8, 129.8, 129.4, 128.6, 126.8, 30.8, 12.6, 5.5.

FT-IR (neat): 3442, 3003, 2962, 2854, 1665, 1546, 1519, 1443, 1384, 1349, 1260, 1237, 1210, 1079, 1054, 1020, 792, 762, 746, 694, 663 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{15}H_{14}NO_3S$ 288.0689, found 288.0686.



3-Benzyl-4-nitro-5-(*o*-tolyl)thiophene-2-carbaldehyde (Table 2, Entry 7).

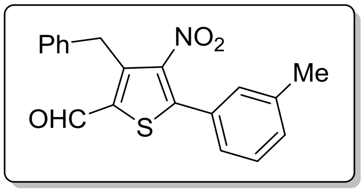
Yellow liquid; yield: 66% (111 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 10.11 (s, 1H), 7.40-7.37 (m, 1H), 7.33-7.29 (m, 3H), 7.28-7.23 (m, 3H), 7.19 (d, J = 7.2 Hz, 2H), 4.60 (s, 2H), 2.20 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ = 182.0, 151.1, 145.2, 142.6, 137.7, 137.5, 137.2, 130.6, 130.5, 129.7, 129.3, 129.1, 128.4, 127.3, 126.1, 32.3, 20.0.

FT-IR (neat): 3440, 3062, 3028, 2924, 2853, 1667, 1602, 1548, 1515, 1495, 1453, 1383, 1347, 1288, 1233, 1216, 1160, 1076, 1056, 1030, 983, 908, 804, 749, 718, 700, 660 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{16}NO_3S$ 338.0845, found 338.0854.



3-Benzyl-4-nitro-5-(*m*-tolyl)thiophene-2-carbaldehyde (Table 2, Entry 8).

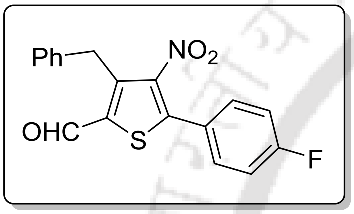
Yellow liquid; yield: 73% (123 mg).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.05 (s, 1H), 7.30-7.24 (m, 7H), 7.17-7.15 (d, J = 7.6 Hz, 2H), 4.47 (s, 2H), 2.38 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 181.8, 150.0, 142.7, 139.3, 137.3, 136.9, 131.7, 129.5, 129.3, 129.2, 128.4, 127.3, 125.7, 32.1, 21.5.

FT-IR (neat): 3443, 3029, 2922, 2854, 1665, 1602, 1546, 1519, 1494, 1453, 1384, 1349, 1220, 1030, 780, 698, 662 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{16}NO_3S$ 338.0845, found 338.0858.



3-Benzyl-5-(4-fluorophenyl)-4-nitrothiophene-2-carbaldehyde (Table 2, Entry 9).

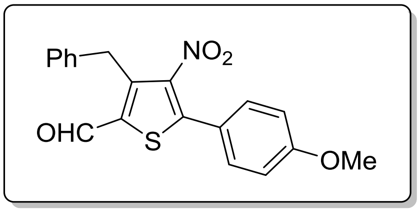
Yellow liquid; yield 74% (126 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 10.07 (s, 1H), 7.45-7.43 (m, 2H), 7.32-7.30 (m, 2H), 7.24 (d, J = 7.8 Hz, 1H), 7.17-7.13 (m, 4H), 4.49 (s, 2H).

^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ = 179.2, 162.5 (d, $J_{C\text{-}F}$ = 251.2 Hz), 160.9, 146.0, 141.8, 140.3, 134.6, 128.4 (d, $J_{C\text{-}F}$ = 8.7 Hz), 128.3, 126.7, 125.9, 124.9, 123.1, 114.2 (d, $J_{C\text{-}F}$ = 88.2 Hz), 114.0, 29.6.

FT-IR (neat): 3440, 2922, 2852, 1665, 1602, 1549, 1519, 1495, 1453, 1412, 1384, 1347, 1223, 1161, 1054, 1015, 837, 814, 786, 744, 700, 672, 668 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{18}H_{13}FNO_3S$ 342.0595, found 342.0590.



3-Benzyl-5-(4-methoxyphenyl)-4-nitrothiophene-2-carbaldehyde (Table 2, Entry 10).

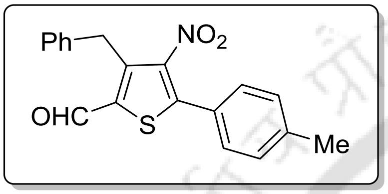
Yellow liquid; yield: 69% (122 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 10.04 (s, 1H), 7.40-7.38 (m, 2H), 7.31-7.29 (m, 2H), 7.25-7.22 (m, 1H), 7.17 (d, J = 7.2 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 4.46 (s, 2H), 3.85 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ = 181.8, 161.8, 149.9, 143.8, 142.9, 137.3, 136.2, 130.2, 129.1, 128.5, 127.3, 121.8, 114.8, 55.6, 32.1.

FT-IR (neat): 3449, 2921, 2850, 1663, 1604, 1558, 1545, 1518, 1494, 1454, 1438, 1384, 1346, 1299, 1259, 1217, 1179, 1028, 803, 832, 779, 745, 700, 667 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^{+}$ calcd for $C_{19}H_{16}NO_4S$ 354.0795, found 354.0791.



3-Benzyl-4-nitro-5-(*p*-tolyl)thiophene-2-carbaldehyde (Table 2, Entry 11).

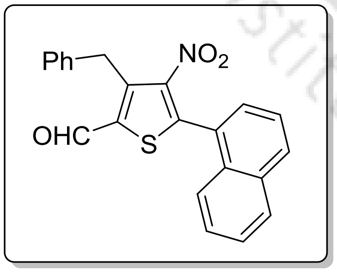
Yellow liquid; yield: 77% (130 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 10.05 (s, 1H), 7.34-7.29 (m, 4H), 7.25-7.22 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 4.47 (s, 2H), 2.40 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ = 181.8, 150.0, 144.1, 142.8, 141.4, 137.3, 136.7, 130.1, 129.1, 128.5, 128.5, 127.3, 126.7, 32.1, 21.6.

FT-IR (neat): 3441, 3029, 2923, 2856, 1722, 1665, 1603, 1547, 1520, 1495, 1453, 1410, 1384, 1349, 1280, 1219, 1187, 1123, 1075, 1029, 1019, 816, 800, 778, 745, 700, 663 cm^{-1}.

HRMS (ESI) *m/z*: [M + H]$^{+}$ calcd for $C_{19}H_{16}NO_3S$ 338.0845, found 338.0850.



3-Benzyl-5-(naphthalen-1-yl)-4-nitrothiophene-2-carbaldehyde (Table 2, Entry 12).

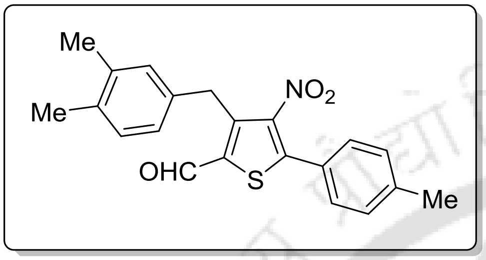
Yellow liquid; yield: 62% (116 mg).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 10.14 (s, 1H), 7.97 (d, J = 6.6 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.55-7.47 (m, 5H), 7.33-7..31 (m, 2H), 7.24-7.20 (m, 3H), 4.63 (s, 2H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 182.0, 149.6, 145.9, 142.6, 138.1, 137.5, 133.5, 131.2, 131.1, 129.2, 128.9, 128.5, 128.4, 127.8, 127.4, 127.3, 126.9, 125.1, 124.2, 32.4.

FT-IR (neat): 3406, 3058, 2924, 2854, 1665, 1602, 1546, 1515, 1494, 1472, 1453, 1439, 1391, 1346, 1265, 1218, 1109, 1029, 908, 800, 776, 738, 700 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO_3S$ 374.0845, found 374.0850.



3-(3,4-Dimethylbenzyl)-4-nitro-5-(*p*-tolyl)thiophene-2-carbaldehyde (Table 2, Entry 13).

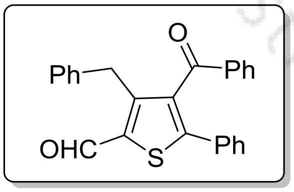
Yellow liquid; yield: 60% (110 mg).

^1H NMR (600 MHz, $CDCl_3$): δ = 10.06 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 7.8 Hz, 1H), 694 (s, 1H), 6.90 (d, J = 7.8 Hz, 1H), 4.40 (s, 2H), 2.41 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 182.0, 149.8, 144.1, 143.3, 141.3, 137.4, 136.5, 135.6, 134.6, 130.3, 130.0, 129.7, 128.4, 126.8, 125.8, 31.7, 21.6, 20.0, 19.5.

FT-IR (neat): 3449, 2920, 2856, 1664, 1609, 1546, 1521, 1447, 1411, 1383, 1349, 1219, 1187, 1125, 1054, 1020, 815, 766, 737, 667 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_3S$ 366.1158, found 366.1157.



4-Benzoyl-3-benzyl-5-phenylthiophene-2-carbaldehyde (Table 3, Entry 1).

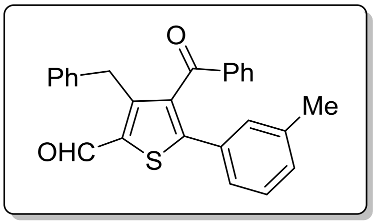
Yellow liquid; yield: 71% (136 mg).

^1H NMR (600 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.34-7.31 (m, 3H), 7.20-7.18 (m, 3H), 7.15 (t, J = 7.8 Hz, 2H), 7.10-7.07 (m, 2H), 7.03-7.02 (m, 3H), 4.33 (s, 2H);

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 194.4, 182.7, 182.6, 152.7, 149.9, 139.2, 138.6, 138.3, 136.7, 133.7, 132.3, 129.7, 129.6, 129.0, 128.8, 128.7, 128.3, 126.7, 32.9.

FT-IR (neat): 3441, 3060, 3028, 2849, 1659, 1596, 1579, 1529, 1494, 1453, 1432, 1383, 1312, 1279, 1216, 1173, 1067, 1029, 1001, 981, 841, 759, 737, 692, 643 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{19}O_2S$ 383.1100, found 383.1105.



4-Benzoyl-3-benzyl-5-(*m*-tolyl)thiophene-2-carbaldehyde (Table 3, Entry 2).

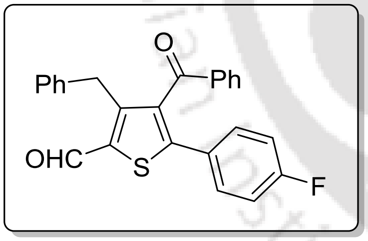
Yellow liquid; yield: 61% (121 mg).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.34-7.31 (m, 1H), 7.16-7.12 (m, 3H), 7.10-7.06 (m, 4H), 7.04-6.99 (m, 4H), 4.33 (s, 2H), 2.19 (s, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 194.5, 182.6, 153.09, 149.9, 139.0, 138.7, 138.4, 136.9, 133.5, 132.2, 130.4, 129.6, 129.5, 128.8, 128.8, 128.7, 128.3, 126.7, 125.9, 32.8, 21.3.

FT-IR (neat): 3449, 3060, 3028, 2922, 2851, 1958, 1659, 1596, 1579, 1528, 1494, 1449, 1383, 1313, 1287, 1218, 1173, 1070, 1029, 1019, 1001, 983, 926, 850, 781, 734, 692, 670 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{21}O_2S$ 397.1257, found 397.1256.



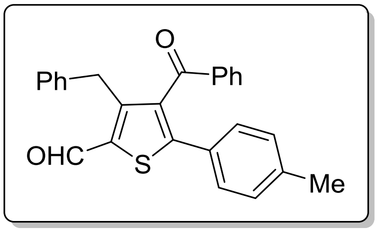
4-Benzoyl-3-benzyl-5-(4-fluorophenyl)thiophene-2-carbaldehyde (Table 3, Entry 3).

Yellow liquid; yield: 73% (146 mg).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.37-7.34 (m, 1H), 7.31-7.29 (m, 3H), 7.16 (t, J = 7.8 Hz, 2H), 7.09-7.07 (m, 2H), 7.03-7.01 (m, 2H), 6.89-6.86 (m, 2H), 4.31 (s, 2H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 194.3, 182.5, 164.2 (d, J_{C-F} = 249.7 Hz), 162.6, 151.2, 149.8, 139.3, 138.6, 138.2, 136.6, 133.8, 130.7 (d, J_{C-F} = 8.7 Hz), 130.6, 129.6, 128.8, 128.7, 128.4, 126.8, 116.2 (d, J_{C-F} = 21.7 Hz), 116.1, 32.9.

FT-IR (neat): 3463, 3062, 2850, 1659, 1600, 1579, 1558, 1530, 1508, 1494, 1453, 1407, 1383, 1313, 1279, 1216, 1160, 1101, 1066, 1029, 1014, 1001, 982, 834, 808, 790, 735, 692, 667 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{18}FO_2S$ 401.1006, found 401.1006.



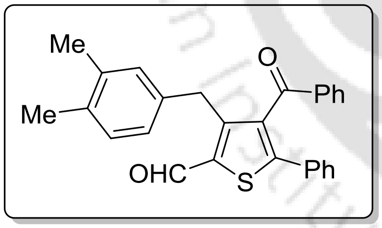
4-Benzoyl-3-benzyl-5-(*p*-tolyl)thiophene-2-carbaldehyde (Table 3, Entry 4).

Yellow liquid; yield: 69% (137 mg).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.11 (s, 1H), 7.50 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.16 (t, J = 7.8 Hz, 2H), 7.09-7.06 (m, 2H),7.02-6.98 (m, 5H), 4.30 (s, 2H), 2.22 (s, 3H).

^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 194.8, 182.6, 152.9, 149.8, 140.0, 138.8, 138.3, 138.2, 136.7, 129.8, 129.7, 129.6, 129.4, 128.8, 128.6, 128.4, 128.4, 126.7, 32.9, 21.4.

FT-IR (neat): 3448, 3060, 3027, 2921, 2851, 1657, 1596, 1579, 1532, 1507, 1494, 1453, 1381, 1312, 1283, 1217, 1173, 1114, 1066, 1019, 1001, 980, 912, 843, 815, 791, 734, 690, 667 cm^{-1}. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{21}O_2S$ 397.1257, found 397.1257.



4-Benzoyl-3-(3,4-dimethylbenzyl)-5-phenylthiophene-2-carbaldehyde (Table 3, Entry 5).

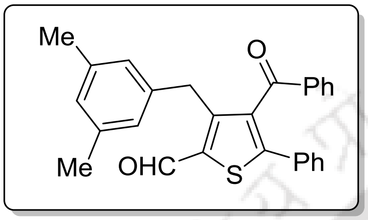
Yellow liquid; yield: 63% (129 mg).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.34-7.32 (m, 3H), 7.20-7.13 (m, 5H), 6.83 (d, J = 7.8 Hz, 1H), 6.75-6.72 (m, 2H), 4.25 (s, 2H), 2.03 (s, 3H), 1.98 (s, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 194.5, 182.8, 152.2, 150.6, 139.2, 138.4, 136.8, 136.7, 135.6, 134.8, 133.4, 132.3, 130.3, 129.9, 129.7, 129.6, 128.9, 128.7, 128.2, 126.3, 32.4, 19.7, 19.3.

FT-IR (neat): 3442, 3059, 2921, 2853, 2729, 1660, 1596, 1579, 1529, 1503, 1448, 1433, 1381, 1312, 1280, 1174, 1068, 1024, 1000, 981, 909, 841, 758, 728, 713, 691, 643 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{23}O_2S$ 411.1413, found 411.1414.



4-Benzoyl-3-(3,5-dimethylbenzyl)-5-phenylthiophene-2-carbaldehyde (Table 3, Entry 6).

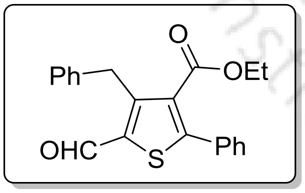
Yellow liquid; yield: 66% (135 mg).

^1H NMR (600 MHz, $CDCl_3$): δ = 10.16 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.34-7.31 (m, 3H), 7.19-7.18 (m, 3H), 7.15 (t, *J* = 7.8 Hz, 2H), 6.59 (d, *J* = 4.2 Hz, 3H), 4.25 (s, 2H), 2.06 (s, 6H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 194.5, 182.8, 152.3, 150.5, 139.2, 138.5, 138.2, 138.0, 136.7, 132.3, 129.7, 129.6, 128.9, 128.8, 128.7, 128.2, 126.8, 126.6, 32.7, 21.2, 21.1.

FT-IR (neat): 3450, 3059, 2919, 2851, 1659, 1597, 1579, 1529, 1448, 1433, 1383, 1312, 1280, 1215, 1172, 1069, 1026, 1000, 987, 911, 844, 759, 728, 689, 672, 643 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{23}O_2S$ 411.1413, found 411.1410.



Ethyl 4-benzyl-5-formyl-2-phenylthiophene-3-carboxylate.

Colorless liquid; yield: 46% (81 mg).

^1H NMR (600 MHz, $CDCl_3$): δ = 10.09 (s, 1H), 7.44-7.40 (m, 5H), 7.29-7.26 (m, 2H), 7.20-7.15 (m, 3H), 4.53 (s, 2H), 4.01 (q, *J* = 6.6 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 182.6, 164.4, 155.7, 149.6, 139.0, 138.6, 133.0, 132.0, 129.7, 128.9, 128.8, 128.7, 128.6, 126.8, 61.4, 32.8, 13.7.

FT-IR (neat): 3441, 2958, 2852, 1716, 1662, 1601, 1533, 1496, 1453, 1403, 1384, 1285, 1207, 1077, 1016, 965, 754, 696, 661 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{19}O_3S$ 351.1049, found 351.1048.

4.6 References

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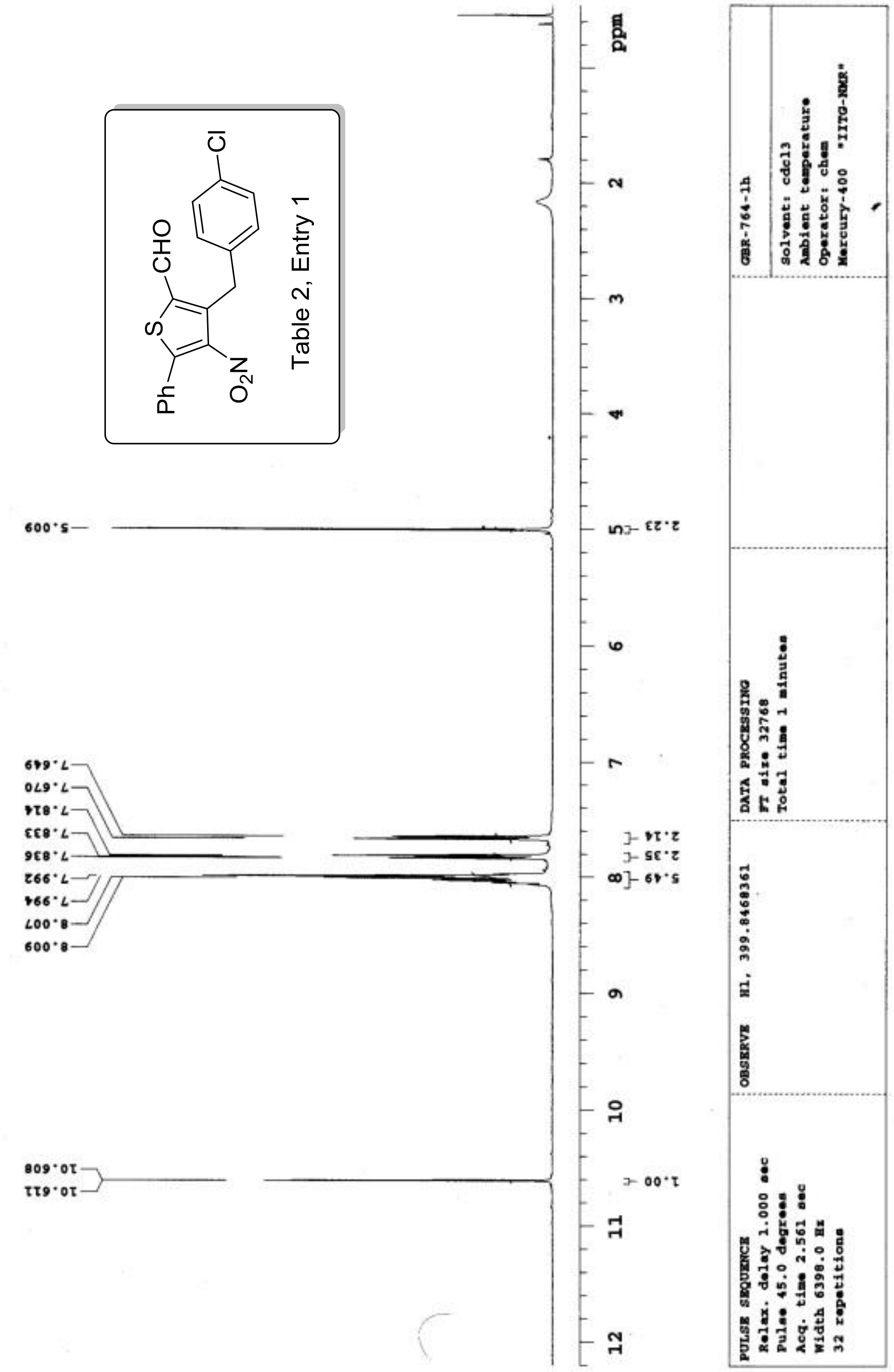
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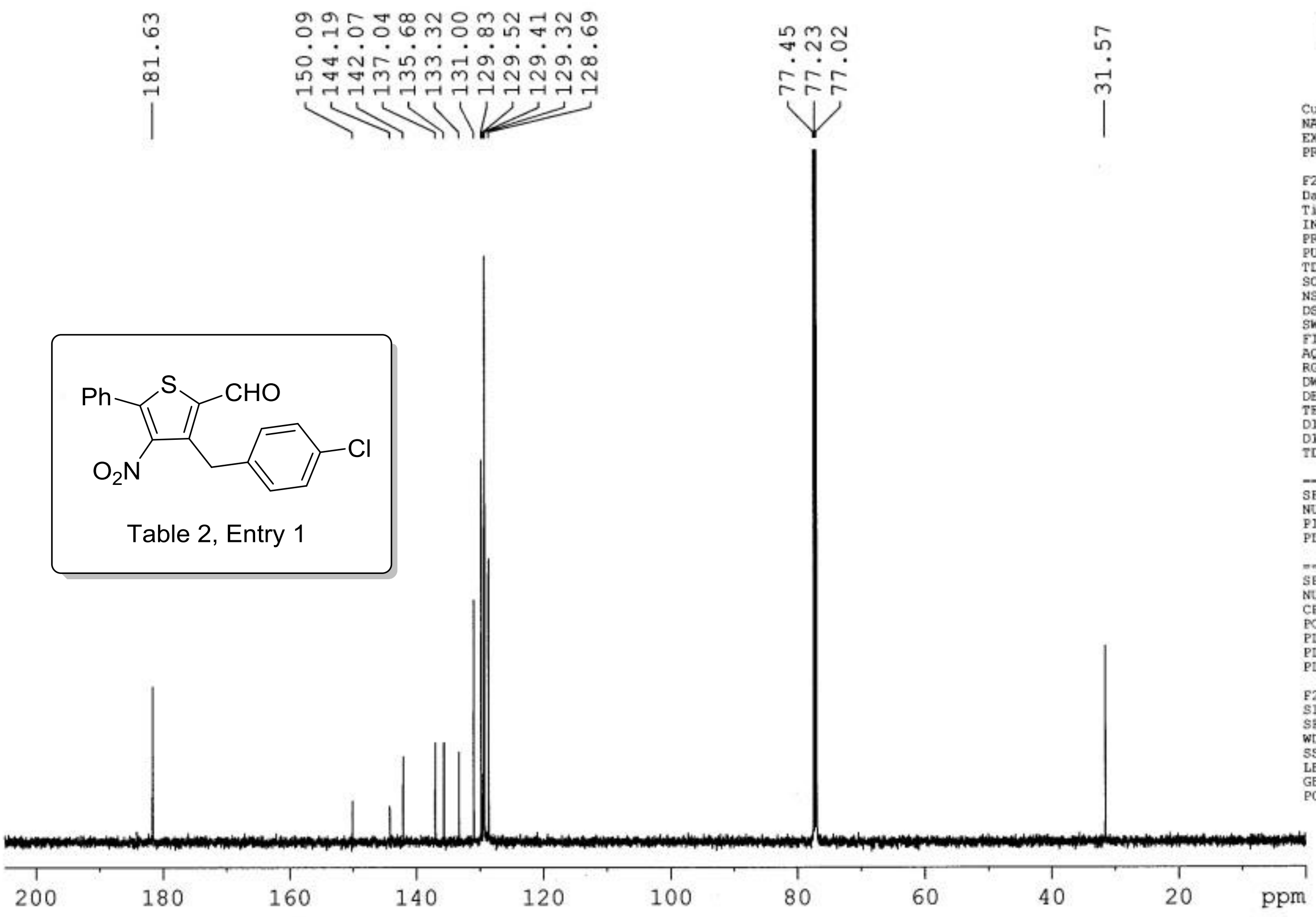

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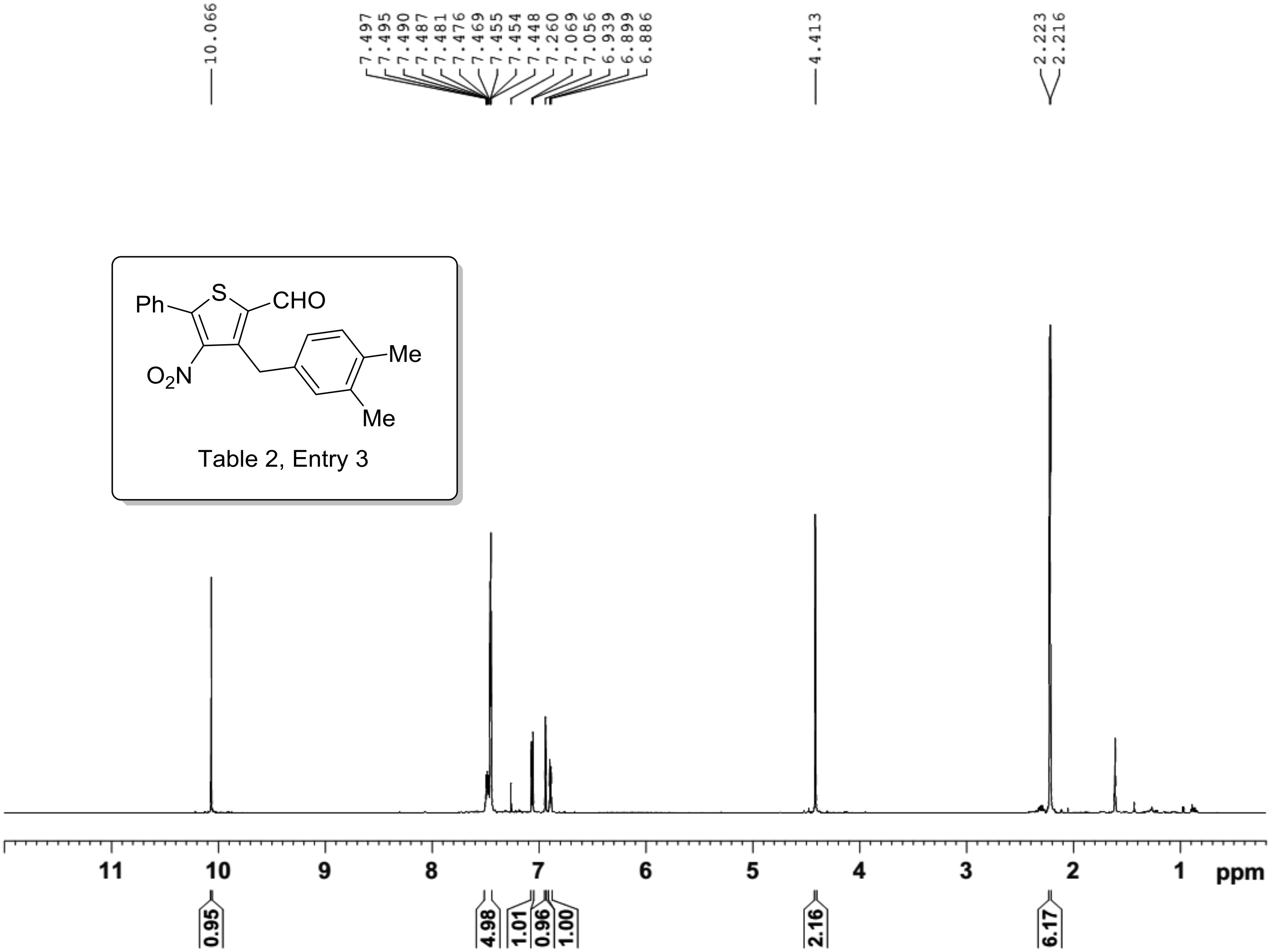

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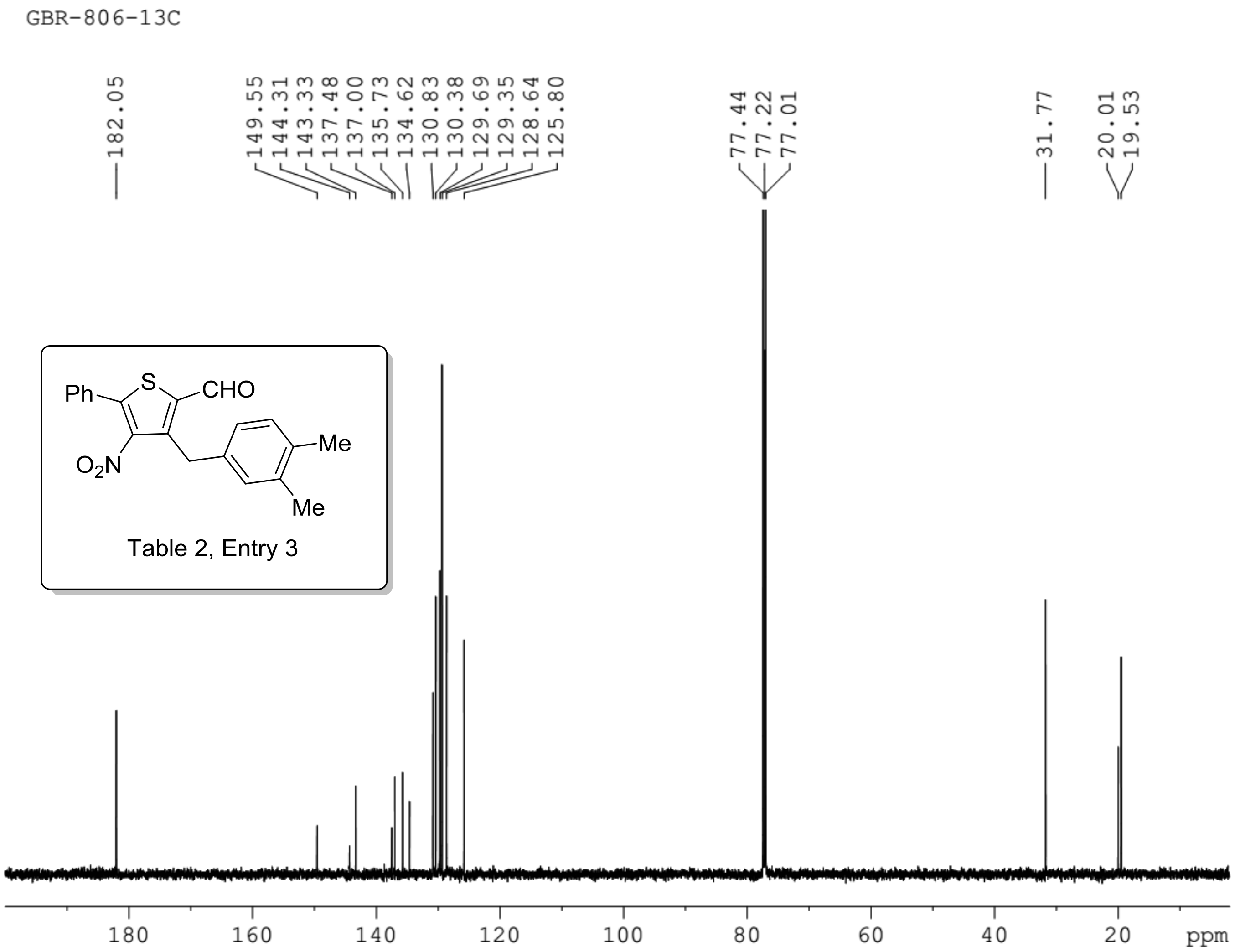

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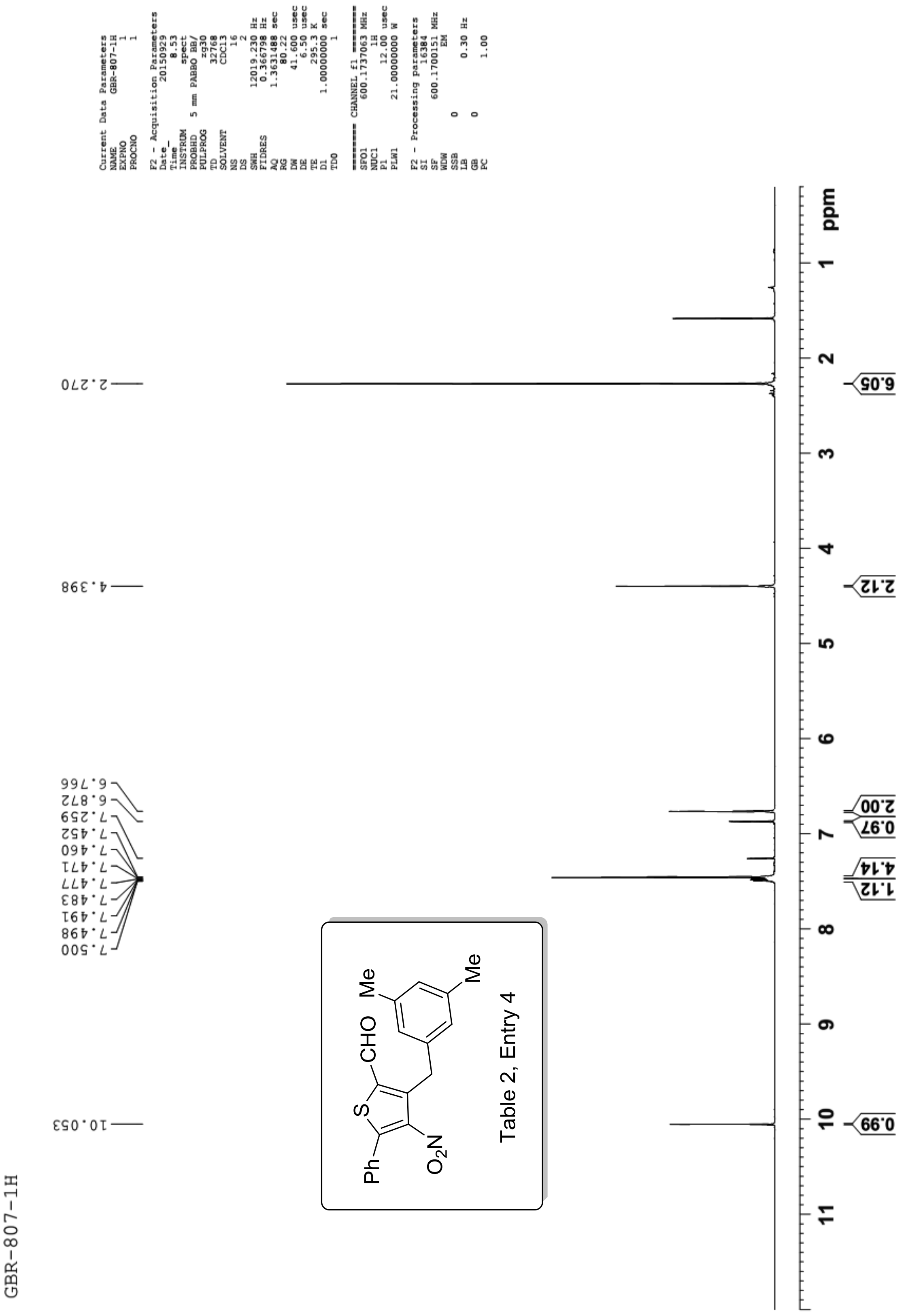
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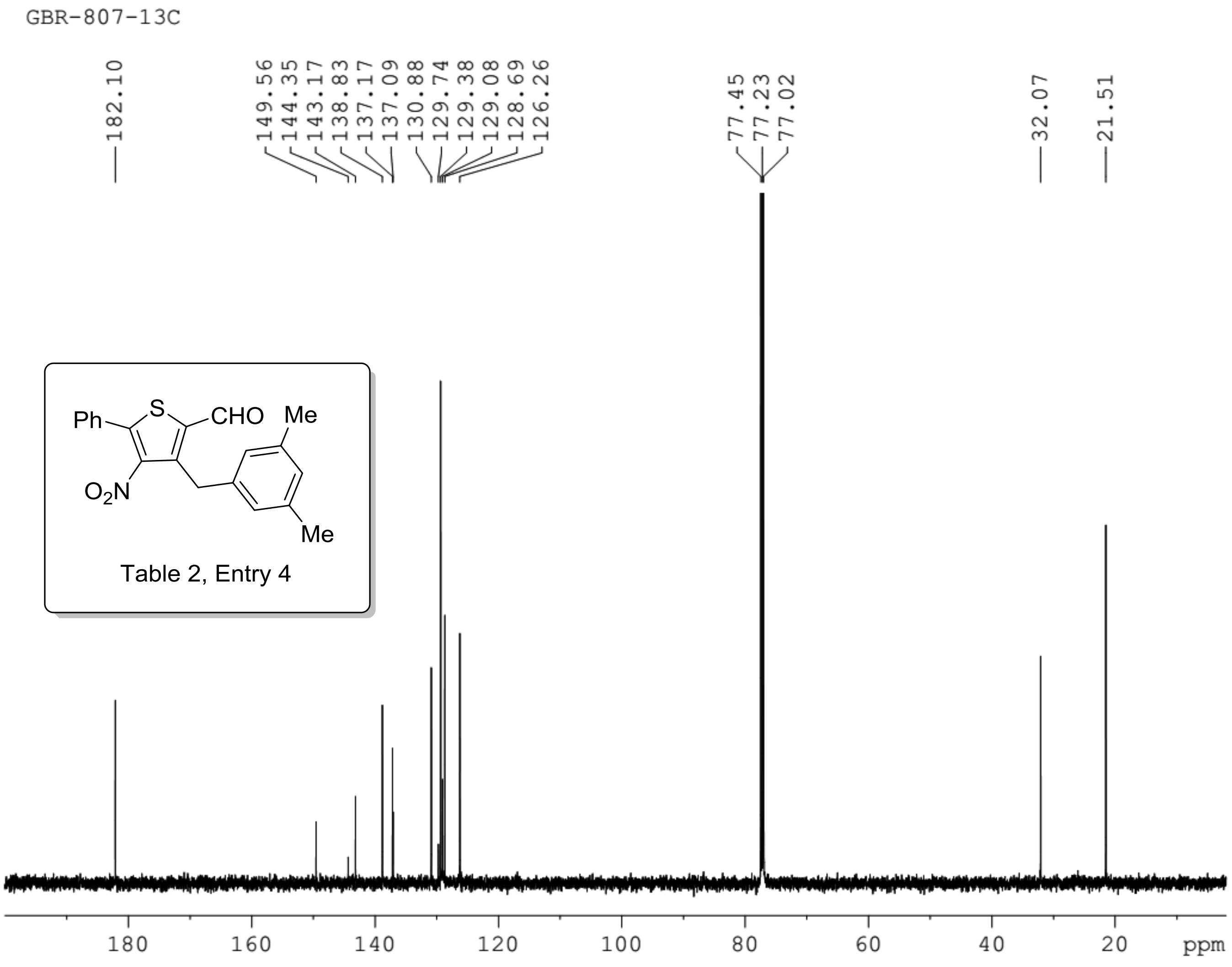

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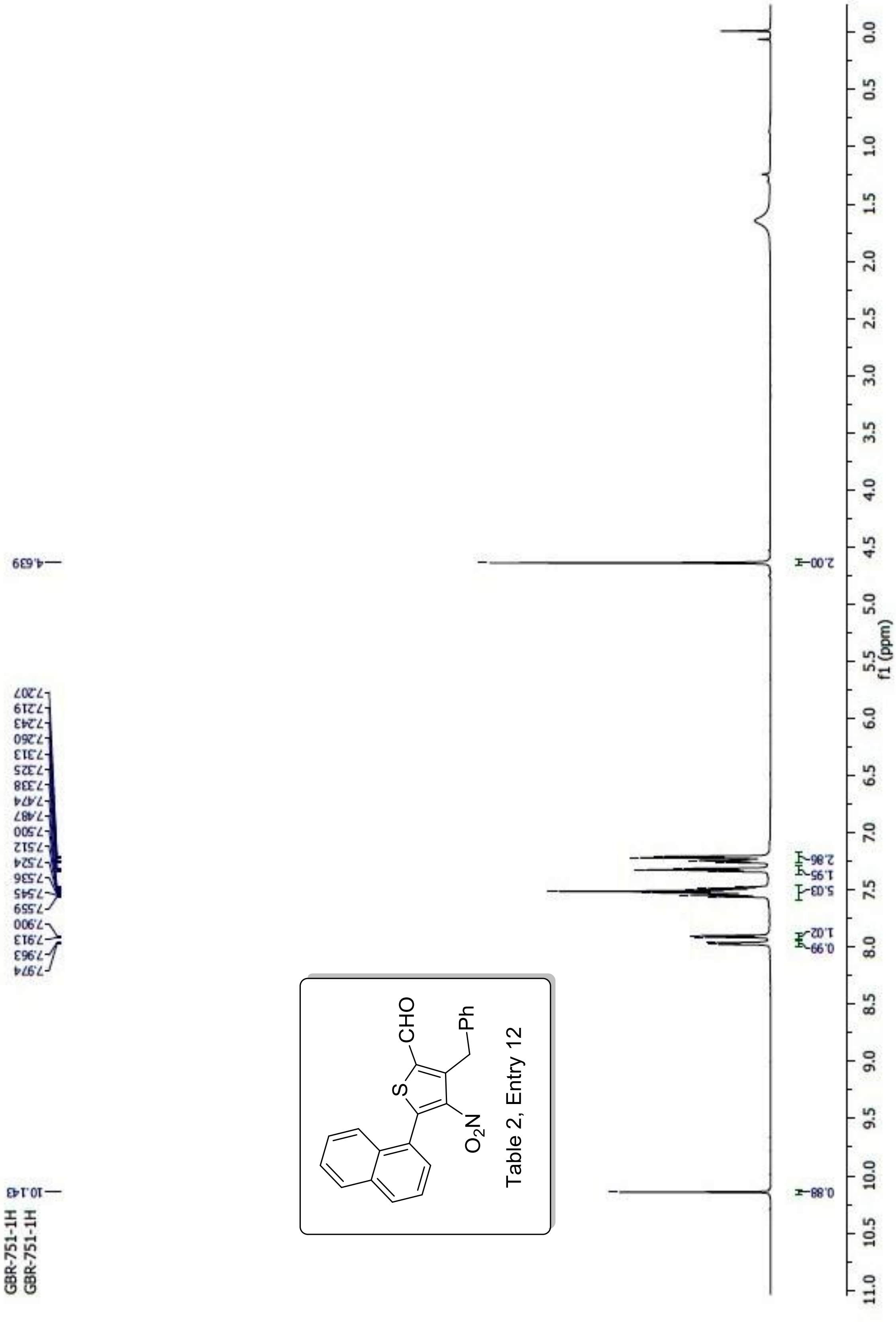
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2.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

GBR-751-13C

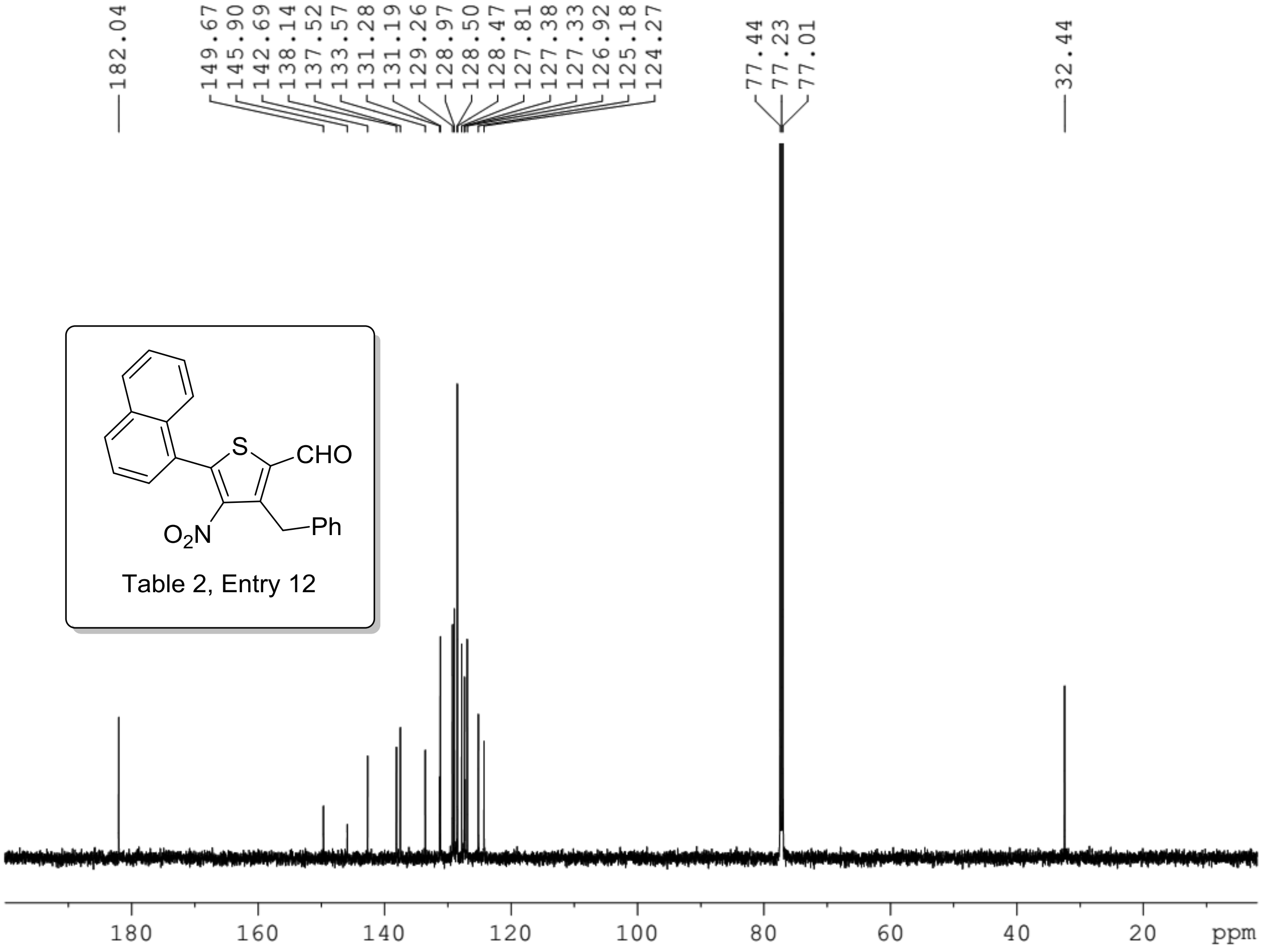

Table 2, Entry 12

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Current Data Parameters
NAME          GBR-751-13C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150826
Time                14.09
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 32768
SOLVENT            CDCl3
NS                   493
DS                     2
SWH            42613.637 Hz
FIDRES          1.300465 Hz
AQ             0.3844779 sec
RG                 65.24
DW                11.733 usec
DE                  6.50 usec
TE                 293.9 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9279571 MHz
NUC1                 13C
P1                 10.50 usec
PLW1         95.00000000 W

======== CHANNEL f2 ========
SFO2         600.1724007 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              70.00 usec
PLW2         21.00000000 W
PLW12         0.61714000 W
PLW13         0.30239999 W

F2 - Processing parameters
SI                 16384
SF           150.9128391 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
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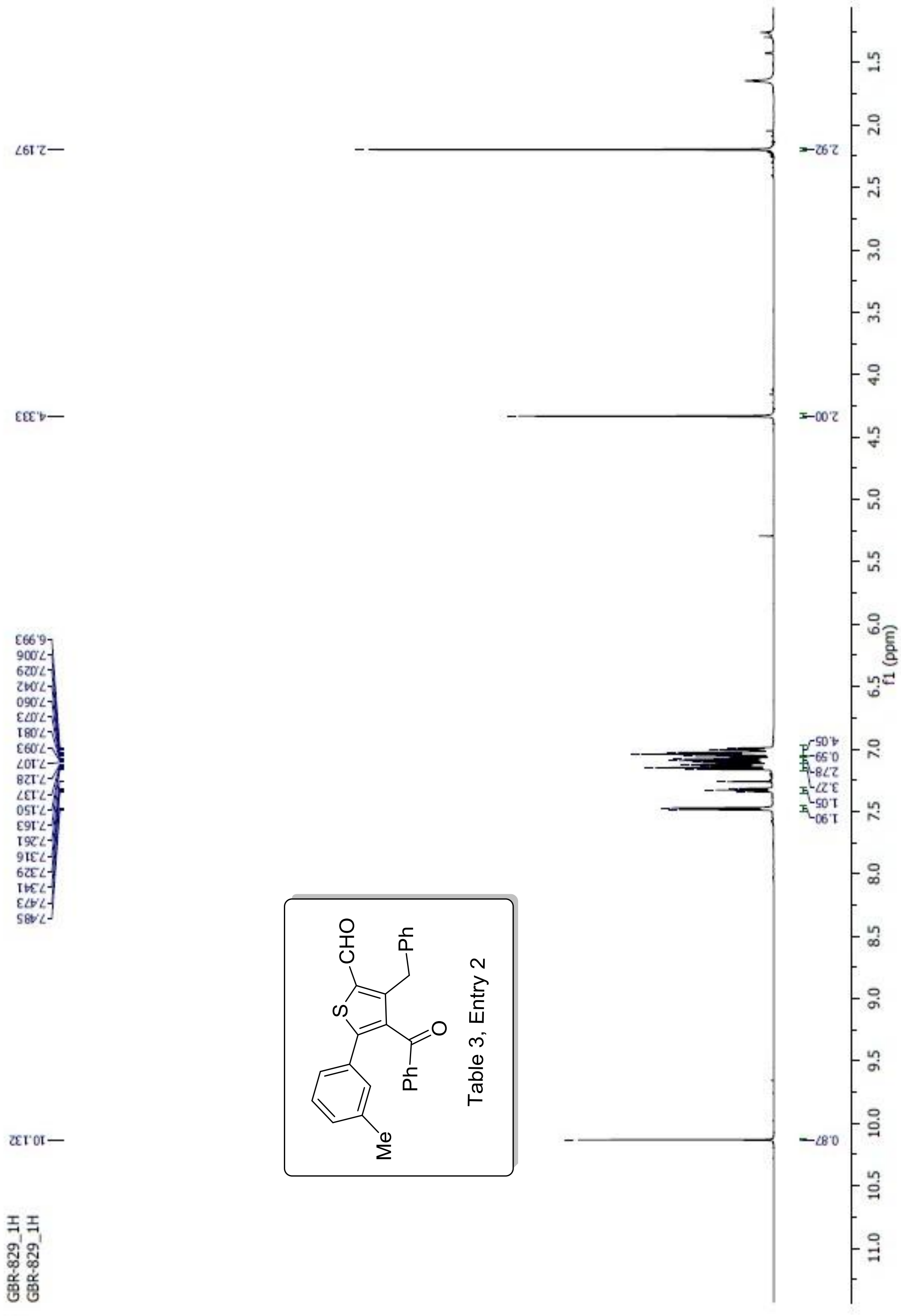
GBR-829_1H
GBR-829_1H
10.132
7.485
7.473
7.341
7.329
7.316
7.261
7.163
7.150
7.137
7.128
7.107
7.093
7.081
7.073
7.060
7.042
7.029
7.006
6.993
4.333
2.197
0.87
1.90
1.05
3.27
2.78
0.59
4.05
2.00
2.92
f1 (ppm)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
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2.0
1.5
Me
S
CHO
Ph
Ph
O
Table 3, Entry 2

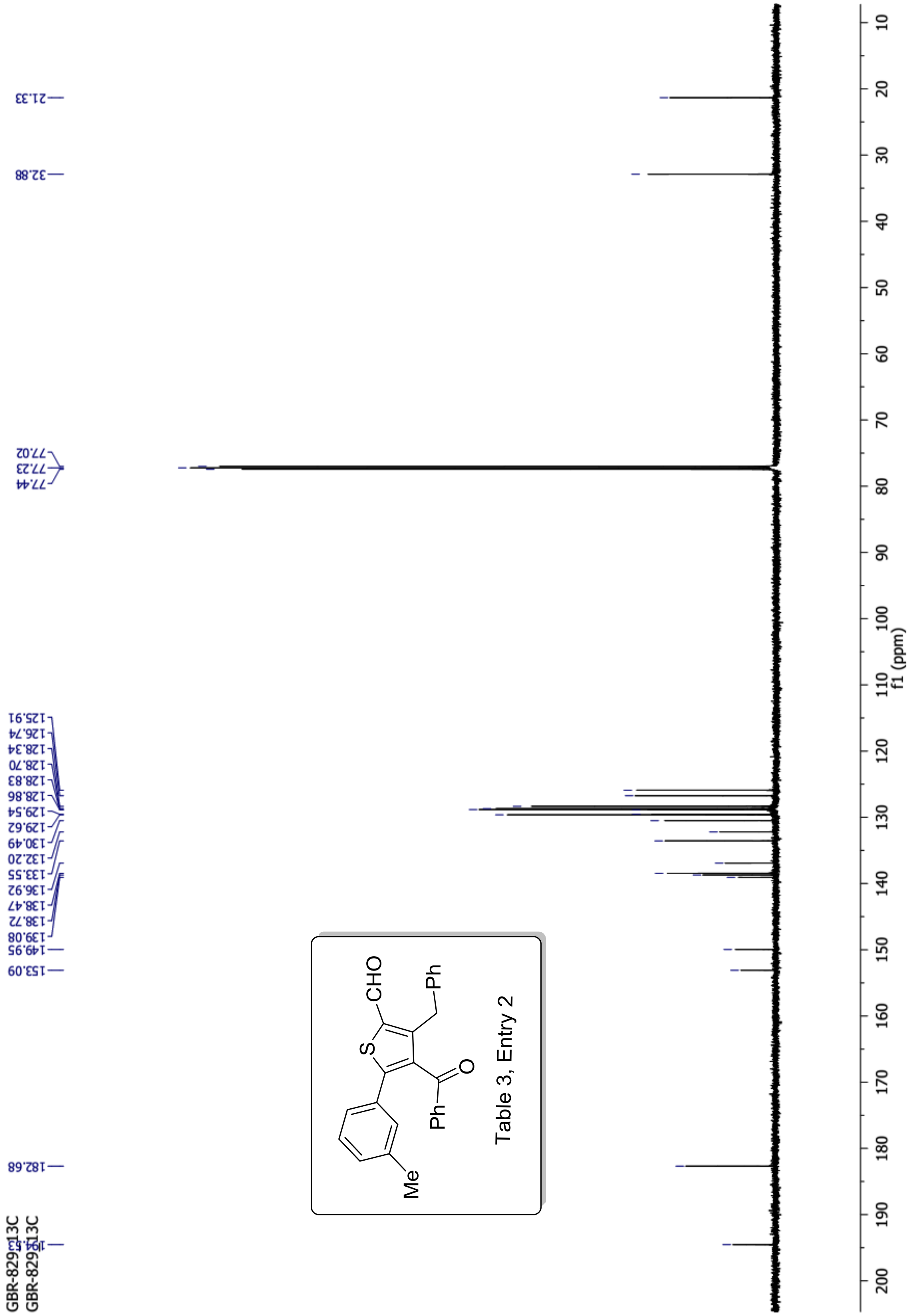

Table 3, Entry 2

Conclusions

In first chapter, we presented the recent developments of alkyne cyclization reactions using electrophiles and transition metal catalysts for the construction of diverse heterocycles. These protocols allow a wide variety of functional groups compatibility under mild reaction conditions. Most of these alkyne cyclizations proceed stereo- and regioselectively. In recent times, there are countless methods on the synthesis of heterocycles *via endo*/*exo-dig* cyclization of alkynes.

In second chapter, we established a new route for the synthesis of tetra- and pentasubstituted pyrroles from 1,3-enynes and amines using molecular iodine *via* aza-Michael addition, iodocyclization and oxidative aromatization sequence under mild conditions. The results suggest that the electron deficient conjugated 1,3-enynes are hypothetically useful class of substrates for the synthesis of desired cyclized compounds. The presence of iodine and nitro groups may facilitate further amplification of the products into the complex derivatives.

In third chapter, we presented Cu-catalyzed domino 5-*endo-dig* cyclization of 1,3-enynes with amines for the synthesis of pyrroles/pyrazoles using air. Widespread substrate scope, atom economy, mild reaction conditions, eco-friendliness and shorter reaction time are the significant practical advantages.

In fourth chapter, DABCO-promoted domino cyclization of 1,3-enynes with 2-mercaptoacetaldehyde is presented to assemble functionalized thiophenes at room temperature *via* sequential Michael addition, 5-*exo-dig* carboannulation and oxidation. The use of mild organic base, wide substrate scope and metal-free conditions are the significant practical advantages. In addition, the aldehyde, ketone, nitro and ester functionalities can be further converted into valuable derivatives which may be of immense interest in biological and material sciences.

List of Publications

1. A Novel Tandem Sequence to Pyrrole Syntheses by 5-*Endo-dig* Cyclization of 1,3-Enynes with Amines

   Bharathiraja, G.; Sakthivel, G.; Sengoden, M.: Punniyamurthy, T. *Org. Lett.* **2013**, *15*, 1334.

2. Expedient synthesis of tetrasubstituted pyrroles *via* copper-catalyzed cascade inter-/intramolecular cyclization of 1,3-enynes carry a nitro group with amines

   Bharathiraja, G.; Sengoden, M.; Kannan, M.; Punniyamurthy, T. *Org. Biomol. Chem*. **2015**, *13*, 2786.

3. Domino synthesis of tetrasubstituted thiophenes from 1,3-enynes with mercaptoacetaldehyde

   Bharathiraja, G.; Sathishkannan, G.; Punniyamurthy, T. *J. Org. Chem*. **2016**, *81*, 2670.

Conferences

1. A Novel Domino Sequence to Pyrrole Syntheses by 5-*endo-dig* Cyclization of 1,3-Enynes with Amines. **Bharathiraja, G**.; Sakthivel, G.; Sengoden, M.: Punniyamurthy, T. *16th Chemical Research Society of India (CRSI) National Symposium in Chemistry*, organized by IIT Bombay, February 07-09, 2014.
2. Copper-Catalyzed Synthesis of Pyrroles by Inter/Intramolecular Cyclization of 1,3-Enynes with Amines. **Bharathiraja, G**.; Sengoden, M.; Kannan, M.; Punniyamurthy, T. International Conference on *Nascent Developments in Chemical Sciences: Opportunities for Academia-Industry Collaboration* organized by BITS Pilani, October 16-18, 2015.
3. Synthesis of Highly Functionalized Thiophenes via 5-*exo-dig* Cyclization of 1,3-enynes with Mercaptoacetaldehyde. **Bharathiraja, G**.; Sathishkannan, G.; Punniyamurthy, T. *19th Chemical Research Society of India (CRSI) National Symposium in Chemistry*, organized by University of North Bengal, July 14-16, 2016.