Ipso Nucleophilic Substitution on Electron Deficient Arene Systems

A dissertation submitted in partial fulfillment for the degree of

Doctor of Philosophy

Submitted by

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STATEMENT

I do hereby declare that the matter embodied in this thesis entitled **"Ipso Nucleophilic Substitution on Electron Deficient Arene Systems"** is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the supervision of Prof. Bhubaneswar Mandal.

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

Sandip Mondal

Date: 11.01.2024

Place: IIT Guwahati

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CERTIFICATE

This is to certify that **Mr. Sandip Mondal** (Roll No. 166122007) has been working under my supervision since July 2016 as a regular registered Ph. D. student. His thesis entitled **"Ipso Nucleophilic Substitution on Electron Deficient Arene Systems"** is an authentic record of the results obtained from the research work in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding his thesis to submit for the Ph. D. degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis, and this work has not been submitted elsewhere for a degree.

Date: 11.01.2024

Place: IIT Guwahati

Prof. Bhubaneswar Mandal

(Thesis Supervisor)

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ABBREVIATION

T	Temperature	h	Hour(s)
°C	Degree Celsius	mL	Milliliter
δ	Chemical shifts	equiv.	Equivalent(s)
g	Grams	rt	Room temperature
mg	Milligram	IR	Infrared
mmol	Millimole	*m/z*	Mass to charge ratio
ppm	Parts per million	*e.g.*	For example
ESI-MS	Electrospray ionization mass spectrometry	*et al.*	and coworkers
HRMS	High-resolution mass spectrometry	etc.	Et cetera
Hz	Hertz	*i.e.*	namely
MHz	Megahertz	vs.	versus
NMR	Nuclear Magnetic Resonance	*via*	through
J	Spin – spin coupling constant	Me	Methyl
s	Singlet	OMe	Methoxy
d	Doublet	Et	Ethyl
dq	Doublet of Quartet	^{i}Pr	*iso*-propyl
dd	Doublet of Doublet	^{t}Bu	*tert*-butyl
t	Triplet	Cy	Cyclohexyl
q	Quartet	Ph	Phenyl
m	Multiplate	Ar	Aromatic
bs	Broad singlet	TOF	Turnover frequency
$CDCl_3$	Deuterated chloroform	EDG	Electron donating group
DMSO-d_6	Deuterated dimethyl sulfoxide	EWG	Electron withdrawing group
TMS	tetramethylsilane	Å	Angstrom

ABBREVIATION

SCXRD	Single crystal X-ray diffraction	*o*	ortho
DDQ	Dichloro dicyano benzoquinone	*p*	para
DBU	1,8-Diazabicyclo[5.4. 0]undec-7-ene	%	Percentage
TEA	Triethylamine	$FeCl_3$	Ferric chloride
DIPEA	N,N-Diisopropylethylamine	K_3PO_4	Tripotassium phosphate
K_2CO_3	Potassium cabonate	CF_3	Trifluoromethyl
Cs_2CO_3	Cesium cabonate	NO_2	Nitro
Na_2CO_3	Sodium cabonate	Cl	Chloride
NaOH	Sodium hydroxide	DFT	Density functional theory
KOH	Potassium hydroxide	EtOAc	Ethyl acetate
THF	Tetrahydrofuran	AcOH	Acetic acid
DCM	Dichloromethane	CH_3OH	Methanol
DMF	N,N-dimethylformamide	SO_2	Sulfur dioxide
CH_3CN	Acetonitrile	m. p	Melting point
HMPA	Hexamethylphosphoramide	PPh_3	Triphenylphosphine
DCE	1,2-Dichloroethane	^{1}H NMR	Proton NMR
API	Active pharmaceutical ingredients	^{13}C NMR	Carbon-13 NMR
ORTEP	Oak Ridge Thermal Ellipsoid Plot	^{19}F NMR	Fluorine-19 NMR
CCDC	Cambridge Crystallographic Data Center	MOF	Metal-organic framework
2,4-DNFB	2,4-Dinitrofluorobenzene	PTC	Phase-transfer catalyst
2,4-DNBSCl	2,4-Dinitrobenzene sulfonyl chloride	DNPC	Diniro phenyl cystine
2,4-DNBSA	2,4-Dinitrobenzene sulfonic acid	HOBt	1-Hydroxybenzotriazole
Q-TOF	Quadrupole time-of-flight	TLC	Thin layer chromatography

SYNOPSIS

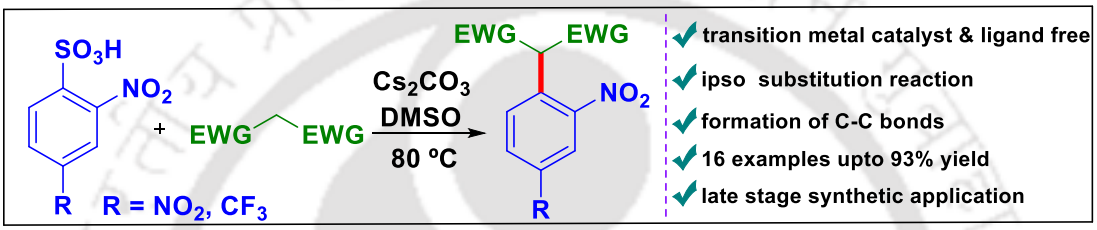
The contents of the present thesis entitled **''Ipso Nucleophilic Substitution on Electron Deficient Arene Systems"** has been divided into five chapters based on the results achieved from the experimental work carried out during the entire course of the Ph. D. program. Chapter I contains an introductory note of the thesis. It includes an overview of the important aspects of alkylation reactions and its synthesis using different approaches. Problems of the existing methods and defined objectives to solve some of the described problems are included. Chapter II describes C-C bond formation via ipso substitution of aryl sulfonic acid with active methylene compounds. Chapter III illustrates C-S bond formation strategy on the similar substrates with thiols. Chapter IV focuses on the N and S-alkylation of amines and thiols using aryl sulfonyl chlorides via intermolecular ipso aromatic nucleophilic substitution reaction. Chapter V contains the investigation of ipso nucleophilic substitution reaction of aryl benzotriazolyl derivative by an amine, thiol, and active methylene compounds.

Chapter I: A Brief Introduction of Ipso Nucleophilic Substitution and Various Alkylation Reactions

This introductory chapter consists of a concise literature survey on the alkylation reactions of active methylene compound, amine, and thiol nucleophiles to construct C-C, C-N, and C-S bond connectivity respectively. The products of these strategies exhibit a broad range of applications in natural products, pharmaceuticals, agrochemicals, polymers, and dyes. This inaugural chapter briefly focuses on the importance of the various alkylation strategies and aryl sulfonamides. Their existing synthetic protocols and drawbacks associated with the existing methods have been discussed precisely. The chapter ends by identifying and defining the scope of the thesis.

Chapter II: C-C Bond Formation via Ipso Nucleophilic Substitution of 2,4-Dinitrobenzene Sulfonic Acid with Active Methylene Compounds

Alkylation of active methylene group on an aromatic ring remains highly desirable and challenging topic for the organic chemists, due to its variety of use in the medicinal and pharmacology industries. To achieve this valuable goal, we have optimized the reaction using 2,4-dinitrobenzene sulfonic acid and dimethyl malonate.

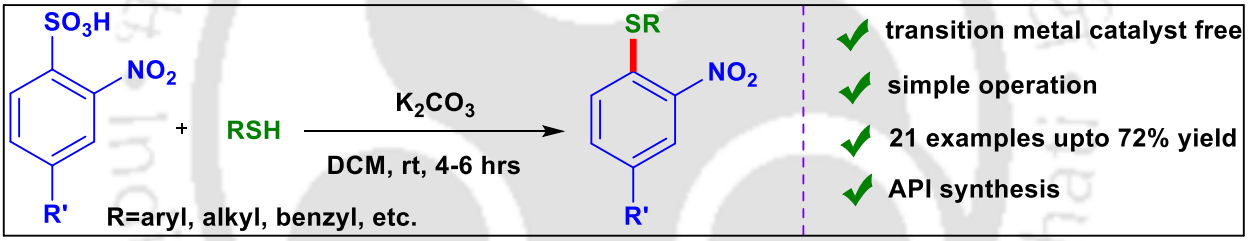


Scheme 1: *Schematic diagram of C-alkylation of active methylene compounds*

The sulfonic acid functionalization of sufficiently electron-deficient benzene sulfonic acids undergoes ipso nucleophilic substitution with various active methylene compounds leading to new C-C bond formation. Good to excellent yields are obtained under mild conditions without transition metal (Pd or Cu) catalyst, PTC, and ligand. No solid waste is generated. It is a highly effective strategy for incorporating various active methylene compounds into the *o*-nitro-substituted benzene ring. This method has been applied not only for synthesizing APIs but also in materials chemistry. It shows a novel route for creating heavily crowded all-carbon quaternary centers. Therefore, we have disclosed the strategy of carbon-carbon bond formation by substituting a sulfonic acid group.

Chapter III: Transition Metal-free C-S Bond Formation via Ipso Nucleophilic Substitution Reaction of Electron-Deficient Benzenesulfonic Acid with Thiols

Di-aryl thioethers are an essential class of reactive species because of their practical applications in biological and pharmaceutical research. Therefore, developing green and convenient strategies for constructing C-S bonds is a highly attractive and fundamental requirement in the research area of organic chemistry. In the past few decades, a massive exploration has been noticed in this area of synthesis using various transition metal catalysts. In this regard, mostly the starting materials are aryl halide, aryl boric acid, aryl trimethylsilyl compound, or aryl triflate. Herein, an efficient, cost-effective method for synthesizing 2,4-dinitro aryl thioether derivatives is achieved by ipso substitution of an aromatic sulfonic acid group by thiol to construct a new C-S bond.

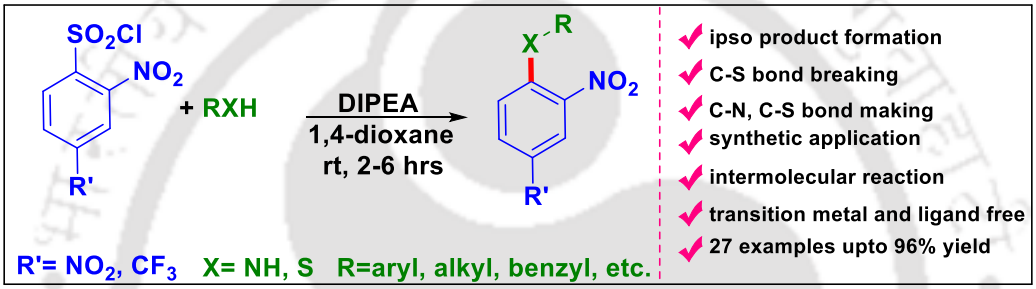


Scheme 2: *Schematic diagram of S-alkylation of thiols*

We have optimized the reaction and illustrated the substrate scope using various thiols In this reaction, a strong thiol nucleophile attacks on the ipso position of the aromatic ring, and desired product is obtained after the elimination of leaving group. This reaction goes via Meisenheimer adduct formation. This methodology neither requires the assistance of any transition metal catalyst nor harsh reaction conditions. We have also demonstrated its applications part.

Chapter IV: Formation of Smile Rearrangement Product by Mild Intermolecular Ipso Aromatic Nucleophilic Substitution

A novel and efficient procedure of amine and thiol produce Smile rearrangement products via ipso aromatic nucleophilic substitution reaction involving an in situ reduction of sufficiently electron deficient benzene sulfonyl chloride, leading to the generation of new C-N and C-S bonds. The optimal condition for this protocol has been attained after the investigation of several reaction conditions. Satisfactory to sufficiently high yields are obtained under

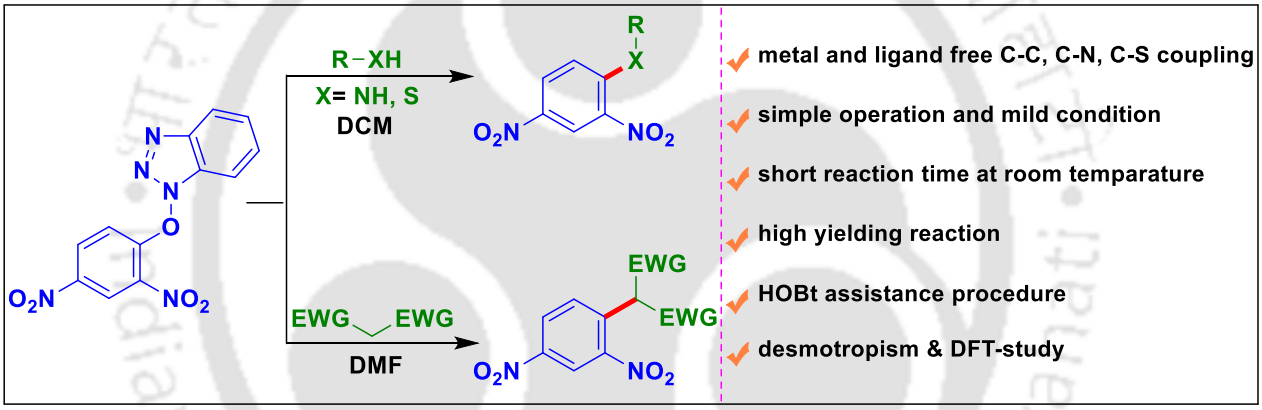


Scheme 3: *Schematic diagram of N and S-alkylation of amines and thiols on aryl sulfonyl chlorides*

transition metal free and mild reaction condition. A large number of various amine and thiols effectively produces corresponding desired diaryl amine and di aryl thioethers under optimized reaction conditions. Regio-selective attack of the nucleophile on benzene sulfonyl chloride derivatives can be controlled by varying the reaction conditions. A systematic mechanistic study has been investigated and established. This method has practical application for the formation of various organic synthons and biological potents.

Chapter V: Ipso Nucleophilic Substitution Reaction on Aryl Benzotriazolyl Derivative by Amine, Thiol and Active Methylene Compounds

Alkylation is an essential strategy in organic synthesis, since its required for the formation of essential biological active molecules and pharmaceutical compounds. We report an eminently high-yielding protocol for the alkylation of amine, thiol, and active methylene compounds on aryl benzotriazole derivatives in a mild reaction condition, which constructs C-N, C-S, and C-C bonds respectively. In this methodology, starting materials have been synthesized from electron deficient aryl sulfonyl chlorides, such as 2,4-dinitrobenzene sulfonyl chloride. The protocol is optimized



Scheme 4: *Schematic diagram of ipso substitution reaction of aryl benzotriazolyl analogs*

by varying several reaction conditions. This methodology does not require any expensive and toxic transition metal catalyst assistance. Moreover this protocol is good functional group tolerance. We have also demonstrated the desmotropic nature of aryl benzotriazolyl derivative by control experiments and Density Functional Theory calculations.

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Chapter I

A Brief Introduction of Ipso Nucleophilic Substitution and Various Alkylation Reactions

1.1. Background

Ipso nucleophilic substitution reaction of aromatic compounds is the most general and powerful pathway for functionalizing corresponding aromatic compounds, and these methodologies have been well established in the literature.[1-8] Carbon-Carbon and Carbon-heteroatom bond connectivity is the fundamental requirement in synthetic organic chemistry.[9-11] Those essential requirements can be accomplished by nucleophilic substitution reactions.[12-13] In this chapter, we have precisely described the alkylation reactions of various nucleophiles such as active methylene compounds, amines, and thiols by traditional ipso aromatic nucleophilic substitution reactions or transition metal-catalyzed cross-coupling reactions using different arene systems to produce diaryl derivatives, diaryl amines or diaryl thioethers. These structural frameworks are present in many biologically active molecules and pharmaceuticals.[14-16] Aryl sulfonamides are a highly valuable structural moiety in medicinal and organic chemistry. In this introductory chapter, a brief preview of the importance of above mentioned structural moieties has been elaborated, along with the existing synthetic methodologies. Also, the drawbacks of the existing methods have been discussed.

1.2. Alkylation Reaction

Alkylation is a process in which an alkyl group transfers from one molecule to another.[17] This alkyl group transfer may occur as a form of carbocation, carbanion, or free radical. Fridel-Craft alkylation is a well-known alkylation reaction that goes via electrophilic carbocation formation with the assistance of a strong Lewis acid catalyst.[18] Many alkylation reactions exist via radical alkyl formation assisted by the metal catalyst.[19] Another way of alkylation can happen by nucleophilic attack.[20] Alkylation on aromatic rings is a well-established area in organic chemistry. It is a highly demanding and valuable part of organic synthesis.

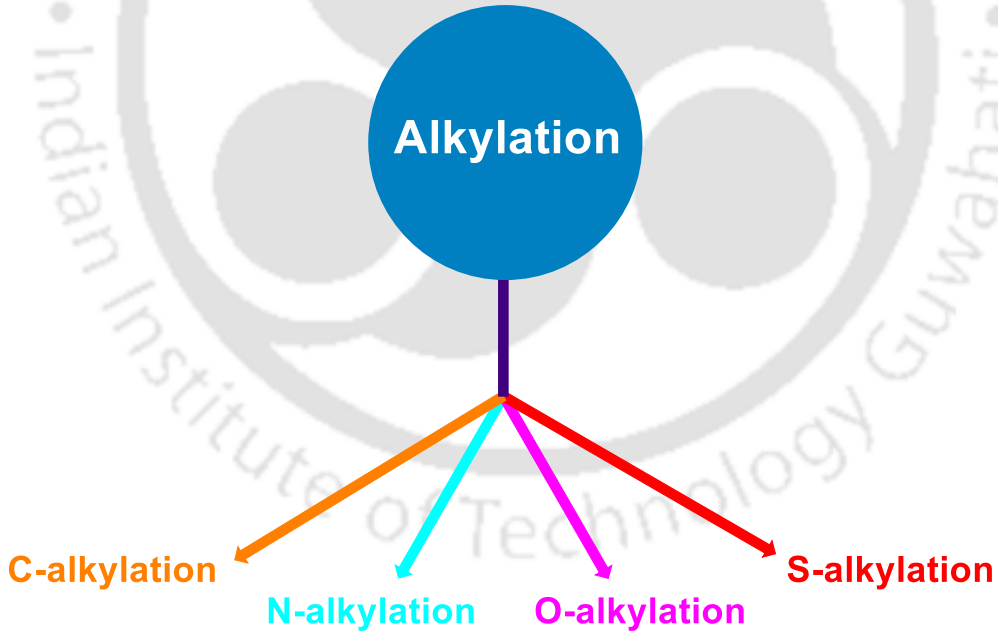


Figure 1.2.1: *Classification of alkylation based on new bond formation*

To prepare small molecules or natural products with complicated structure alkylation reaction is required. Therefore this fundamental process has become extensively valuable for organic synthetic chemistry. Based upon newly formed bonds, several types of

alkylation reactions exist, such as C-alkylation, N-alkylation, O-alkylation, S-alkylation, etc., where C-C, C-N, C-O, and C-S covalent bond forms respectively. A vast number of procedures have been developed for alkylation reactions. For example, Friedel-Crafts alkylation where alkylation occurs through C-C bond formation, have found many drawbacks like low yielding procedure, the toxic or expensive metal catalyst used, multiple by-product formation, harsh reaction condition requirement, etc.[21] Other alkylation procedure also has more or less similar difficulties. In significant cases, the starting material is an aromatic halide.[22]

1.3. Aromatic Nucleophilic Substitution Reaction

The aromatic nucleophilic substitution (S_NAr) reaction is a fundamental transformation in organic chemistry.[23] In this reaction, the aromatic ring is attacked by strong nucleophiles, and a good leaving group is displaced. This reaction is subjected only to aromatic compounds containing a powerful electron-withdrawing group and a leaving group with an ortho or para substituents relationship. This is an addition-elimination sequential reaction. In the first step, a nucleophile attack in the aromatic ring to generate a transition state called Meisenheimer adduct.[24-25] The S_NAr reaction mechanism's final step involves losing the leaving group to regain aromaticity.

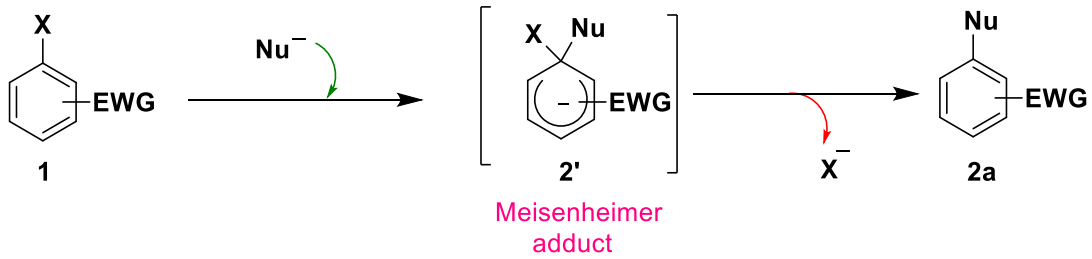


Figure 1.3.1: *S_NAr reaction mechanism*

1.4. Smile Rearrangement

Various rearrangement reactions can achieve all the above-discussed alkylation. One of the famous rearrangement reactions is Smile rearrangement.[26] There intra molecular nucleophiles participate in the reaction and cause the rearrangement. This is a neighboring group participation reaction. The nucleophilic center can form in situ.

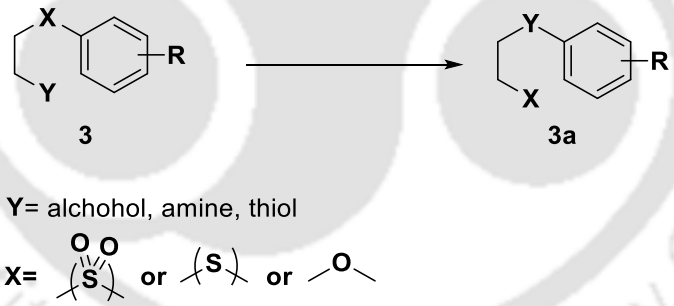


Figure 1.4.1: *Truce-Smile Rearrangement*

Most of the Truce-Smile rearrangement reactions undergo via in situ carbanion (nucleophile) generation,[27] which attack on the aromatic ring and forms a highly reactive Meisenheimer adduct, and finally, rearrangement occurs to give the final product.

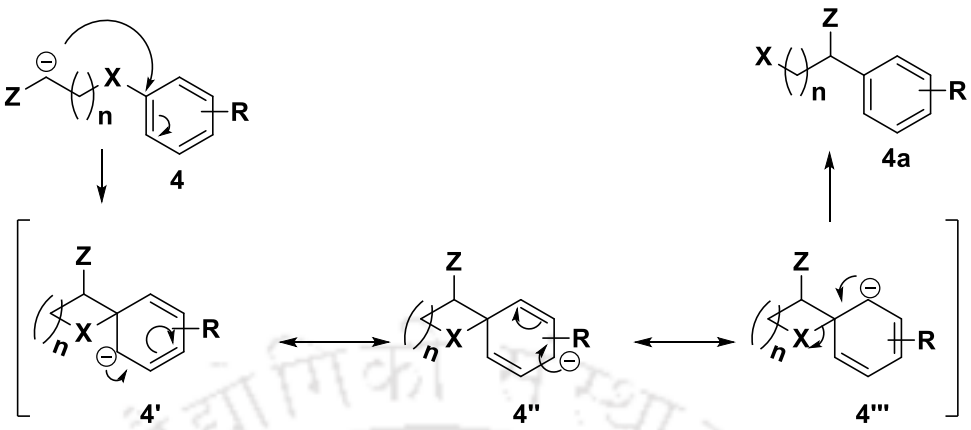


Figure 1.4.2: *Mechanistic pathway of Truce-Smile Rearrangement*

During working with benzene sulfonyl chloride derivative, we found some unusual behavior of nucleophiles which forms alkylating products. Here we discussed all the unique pathways of nucleophilic (N, O, S) reactions with benzene sulfonyl chloride analogs.

1.5. Ipso Substitution Reaction

Arene substitution patterns are classified based on the occupied position of the entering substituents. During ipso substitution[28] two substituents share the same ring position in an intermediate. And in the product, the substituent (e.g., nucleophile) occupies the same position as leaving group. Therefore, the above-described mechanism is an ipso aromatic nucleophilic substitution reaction.

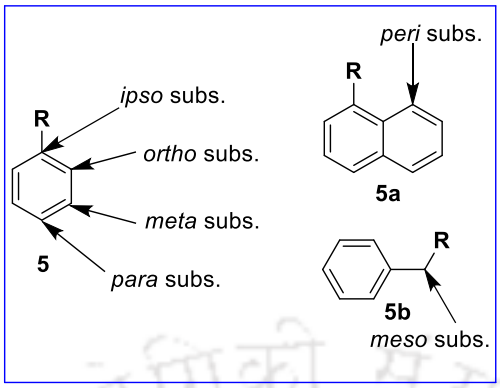


Figure 1.5.1: *Classification of S_NAr reaction*

In organic synthesis or medicinal chemistry, ipso substitution reaction is crucial as a functional group interchange or incorporating a new fragment. Besides all the above substitutions, there are other possibilities for substitution reactions, such as *cine* and *tele* substitution.

1.6. Importance of Sanger's Reagent, C-alkylation of Active Methylene Compounds, N-alkylation of Amines, S-alkylation of Thiols and Sulfonamides

1.6.1. Importance of Sanger's Reagent

2,4-dinitro fluorobenzene (2,4-DNFB), commonly called Sanger's reagent,[29] is a chemical species that can combine with the N-terminal amino acid of polypeptides and helps to identify the amino acid sequences. Alongside this significant application of Sanger's reagent, various applications were reported, such as establishing vast numbers of aromatic nucleophilic substitution (S_NAr) reactions in which fluoride ion act as a good leaving group.[30] There are structural similarities between Sanger's reagent and 2,4-dinitrobenzene

sulfonic acid, 2,4-dinitrobenzene sulfonyl chloride, and 2,4-dinitrobenzene benzotriazolyl analogs.

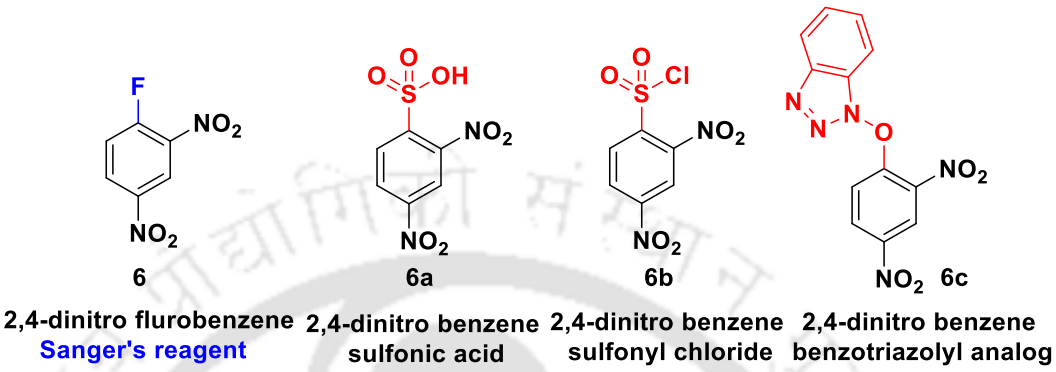


Figure 1.6.1.1: *Structural similarity between Sanger's reagent and its analog*

All reagents consist of two electron-withdrawing nitro functional groups and one leaving group, making them a suitable substrate for S_NAr reactions. Using this chemistry, we are exploring the scope of application of 2,4-dinitrobenzene sulfonic acid and 2,4-dinitrobenzene sulfonyl chloride. HOBt is a universal additive which is also a good leaving group. Aryl-OBt can easily synthesize from corresponding aryl halide or aryl sulfonyl chloride. Therefore we were curious about the aromatic nucleophilic substitution (S_NAr) reaction of aryl-OBt substrates.

During aromatic nucleophilic substitution (S_NAr) reaction of Sanger's reagent, hydrogen fluoride (HF) is generated as a byproduct. This highly acidic hydrogen fluoride (HF) can neutralize the nucleophile's efficiency and take part in other side reactions. Furthermore, hydrogen fluoride (HF) is toxic and can damage skin, eye, and lung tissues. Therefore, it is desirable to use such substrate which prevents the hydrogen fluoride (HF) generation during the reaction. There are no such possibilities if we use 2,4-dinitrobenzene sulfonic acid (6a) and 2,4-dinitrobenzene benzotrizolyl analogs or aryl-OBt (6c). Therefore,

developing methodologies using these reagents could be alternative and efficient pathways.

1.6.2. Importance of C-alkylation of Active Methylene Compounds

C-C bond formation is a fundamental transformation of synthetic organic chemistry. Therefore, developing efficient and practical methods for forming C–C bonds remains a topic of considerable interest for synthetic organic chemists.[31] Active methylene compounds are a particular class of organic synthons consisting of a highly acidic proton(s) and two electron-withdrawing groups such as malononitrile, ethyl cyanoacetate, diethyl malonate, and ethyl acetoacetate, etc.

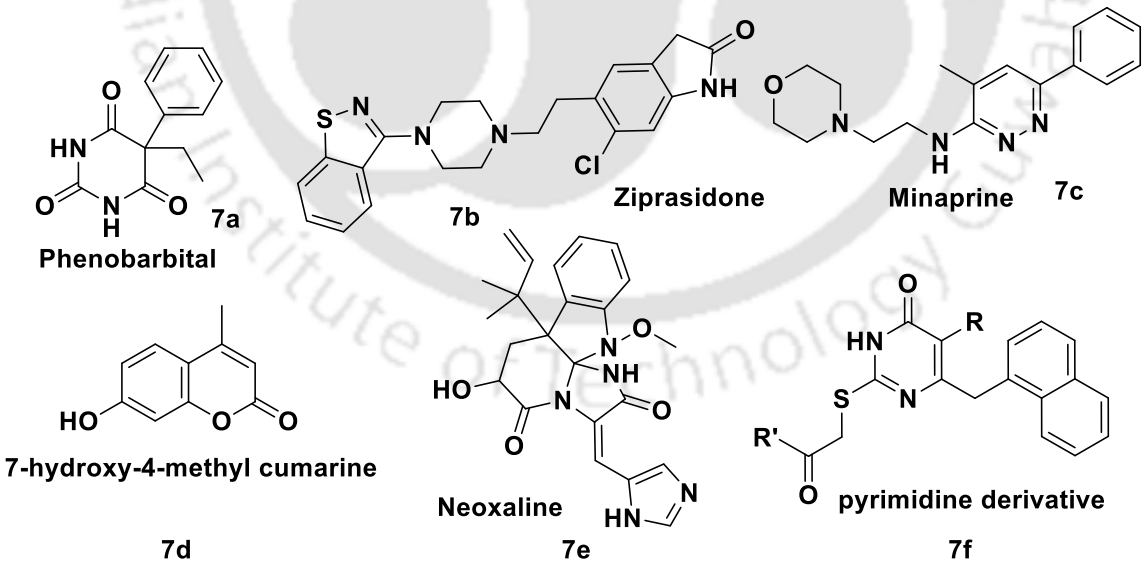


Figure 1.6.2.1: *Selected examples of biologically active molecules containing active methylene compounds*

Due to the structural diversity and distinct reactivity, active methylene compounds have many applications in organic syntheses, such as aldol condensation[32] Knoevenagel

reactions[33] and Michael addition.[34] Many biologically active molecules or natural products having structural framework consist of active methylene compounds. These molecules can be synthesized by hetero-cyclization of compounds containing an active methylene group, indicating that such compounds are valuable starting reagents for the selective synthesis of five- and six-membered mono and poly heterocyclic systems with various structures.[16] Therefore, the alkylation of active methylene compounds to an aromatic ring generates C-C bonds. This C-alkylation of active methylene compounds has been used for constructing isoquinoline, indole, pyrrole, and pyrimidine derivatives.[35] Several drug molecules, natural products, and dyes have these valuable structural moieties. Phenobarbital[36] is used during the treatment of insomnia, Ziprasidone[37] for mental illnesses like schizophrenia, Minaprine[38] is a psychotropic drug used as an antidepressant, and 7-hydroxy-4-methyl-cumarine[39] shows antifungal activity. At the same time, Neoxaline[40] is an effective anti-corrosion agent. Again pyrimidine derivatives 6-(1-Naphthylmethyl) pyrimidine-4 (3H)-ones is an anti-HIV agent.[41] Thus, C-alkylation of active methylene compounds is the critical area in organic synthesis.

1.6.3. Importance of N-alkylation of Amines

N-alkylation of nitrogen nucleophiles generates a carbon-nitrogen bond. Diaryl aromatic or heteroaromatic amines are an essential structural motif in organic chemistry, agrochemicals, and pharmaceuticals.[42] Therefore, cast around for synthetic methodologies for their preparation have been a field of interest for chemists over the decades. These structural motifs are extensively used in synthesizing dyes, fine chemicals, and polymers.

Various synthetic and naturally occurring diaryl amines are found in numerous well-known drugs. For example, Norfloxacin[43] is an essential constituent of the quinolone family and acts as an antibacterial, used to treat urinary tract infections and inflammation of the prostate gland. Linezolid[44] possessed antibiotic activity, tolfenamic acid[45] is an anti-inflammatory agent, and Vortioxetine[46] is used as an antidepressant. Folic acid[47] is vitamin B9, an essential component for daily human body functions, and helps the body convert food into energy. Primarily, it is necessary for pregnant women to prevent miscarriage and congenital disabilities of the baby's brain and spinal cord.[48]

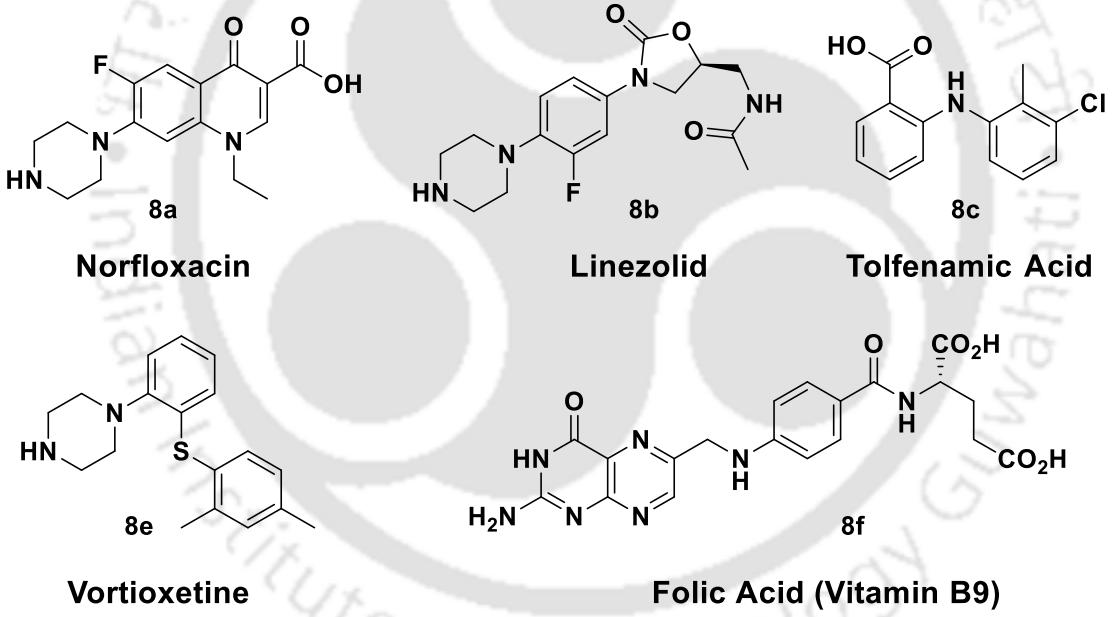


Figure 1.6.3.1: *Selected examples of some biologically active compounds*

1.6.4. Importance of S-alkylation of Thiols

S-alkylation is a familiar technique to generate new C-S bonds using various thiols, producing diaryl sulfides.[49] Due to their wide applications in numerous fields, designing

convenient methods for forming these molecules becomes an attractive research area. Diaryl sulfides or diaryl thioethers are essential in constructing many natural products, biologically active molecules, and pharmaceuticals. For example, Indometacine[50] is a non-steroidal anti-inflammatory agent. Butoconazole[51] is an imidazole-based antifungal used to treat yeast infections of the vagina. Nelfinavir[52] exhibits anti-HIV activity. Axitinib[53] is an anti-cancer drug. Again diaryl thioether is the crucial intermediate in organic synthesis.

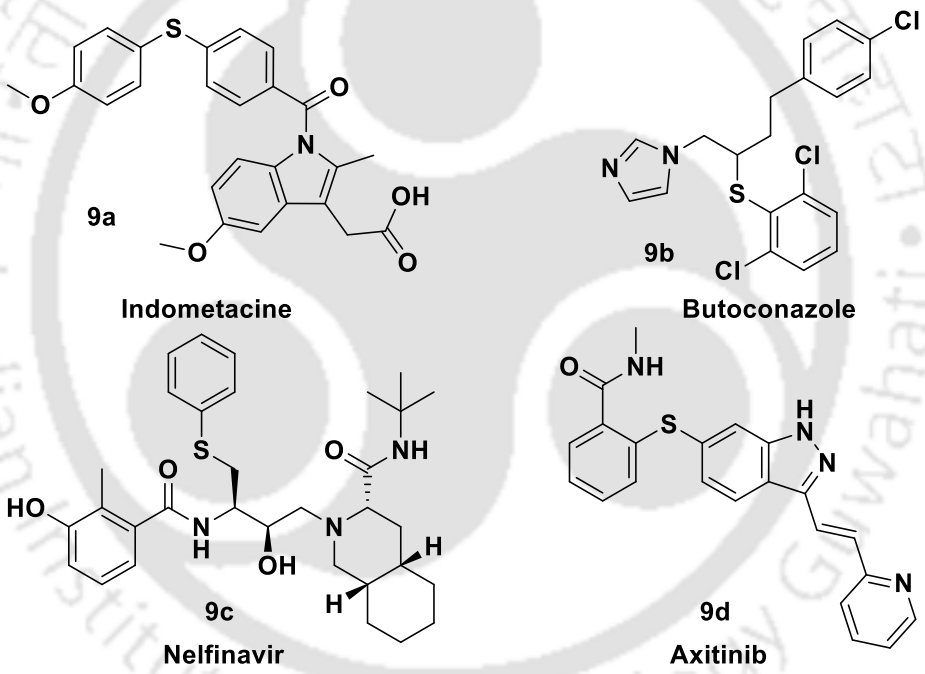


Figure 1.6.4.1: *Selected examples of some biologically active compounds contain thioethers*

1.6.5. Importance of Sulfonamides

Sulfonamides are a class of organic structural motifs commonly exhibiting antimicrobial activities.[54] Thus, it is widely used in the medicinal industry to treat human and animal

bacterial infections. For example, Sulfamethazine[55] is used to treat various types of bacterial infections. Sulfadiazine[56] is mainly used for urinary tract infections. Udenafil[57] is used for treating erectile dysfunction, and Celecoxib[58] is used for relieving pain and swelling. Probenecid[59] helps to lower the uric acid level. Tipranavir[60] is an anti-HIV agent.

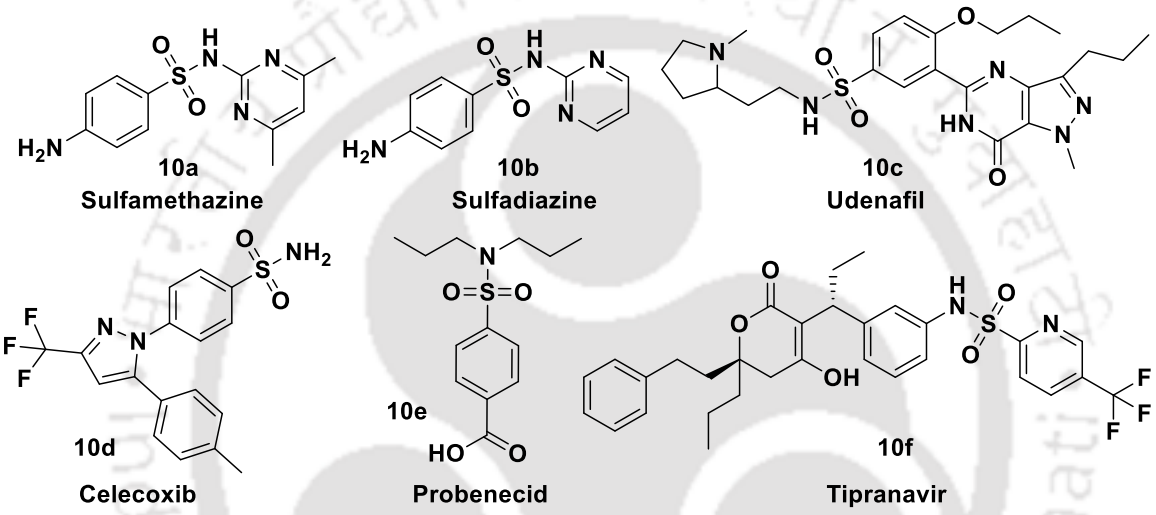
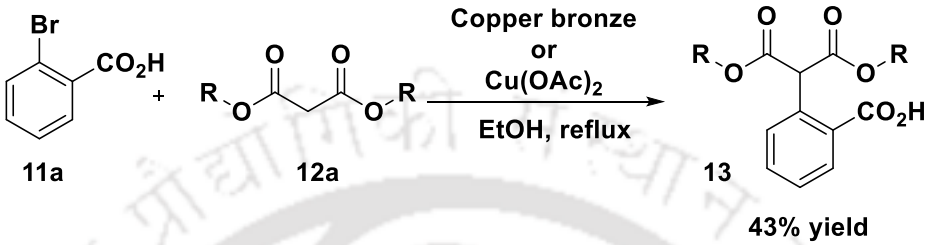


Figure 1.6.5.1: *Selected examples of some sulfonamide drugs*

1.7. Existing Methods of C-alkylation of Active Methylene Compounds, N-alkylation of Amines, S-alkylation of Thiols and Sulfonamides

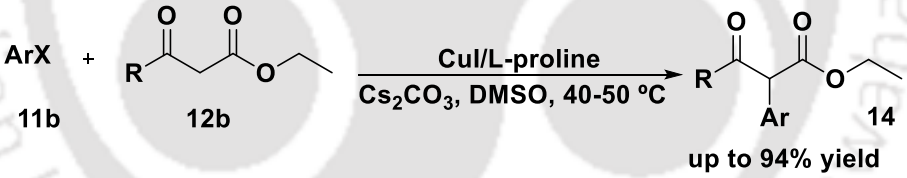
1.7.1. Existing Methods of C-alkylation of Active Methylene Compounds

In 1929, Hurtley first reported C-alkylation of active methylene compounds such as malonic esters with *ortho*-substituted aromatic halides using a catalytic amount of copper acetate [Scheme 1.7.1.1].[61]



Scheme 1.7.1.1: *C-alkylation of active methylene compounds by copper acetate*

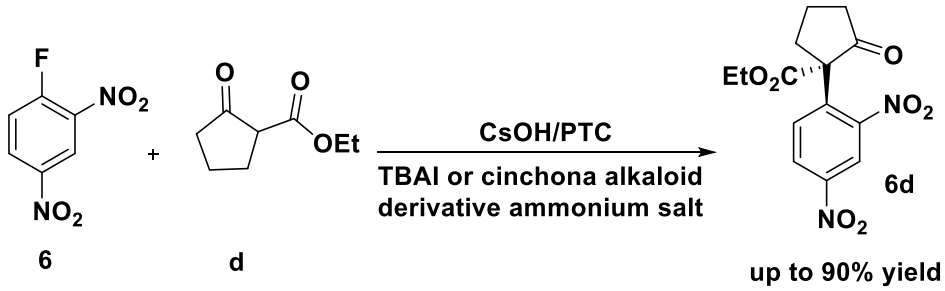
Later, Hurley's reaction was improved significantly using various metal catalysts. Such as Ma group has got highly high yield using CuI as a catalyst along with L-proline ligand [Scheme 1.7.1.2].[62]



Scheme 1.7.1.2: *CuI/L-proline catalyzed C-alkylation*

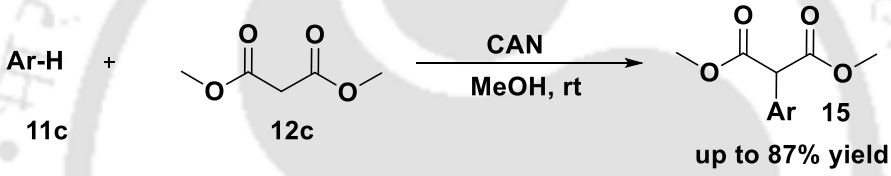
Again C-alkylation of active methylene compounds is reported using other transition metal catalysts such as Pd[63] and Re.[64]

Ipso substitution by active methylene compounds is also performed using PTC [Scheme 1.7.1.3].[65]



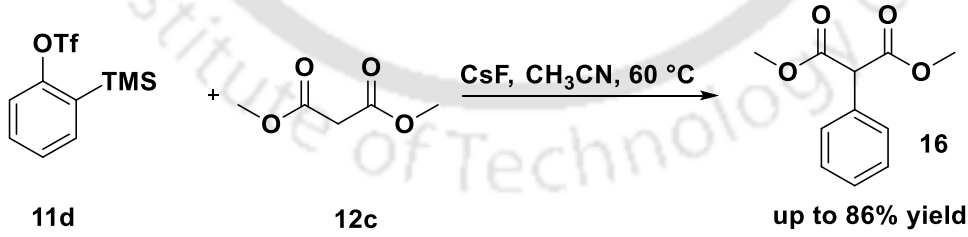
Scheme 1.7.1.3: *Organocatalytic regio and asymmetric C-Selective S_NAr Reactions*

CAN (cerium (IV) ammonium nitrate) mediated C-alkylation can occur on the aromatic ring of malonic esters [Scheme 1.7.1.4].[66]



Scheme 1.7.1.4: *CAN-mediated C-alkylation*

Chen *et al.* described monoarylation malonates with arynes by fluoride-induced elimination of Kobayashi's silylaryl triflates [Scheme 1.7.1.5].[67]

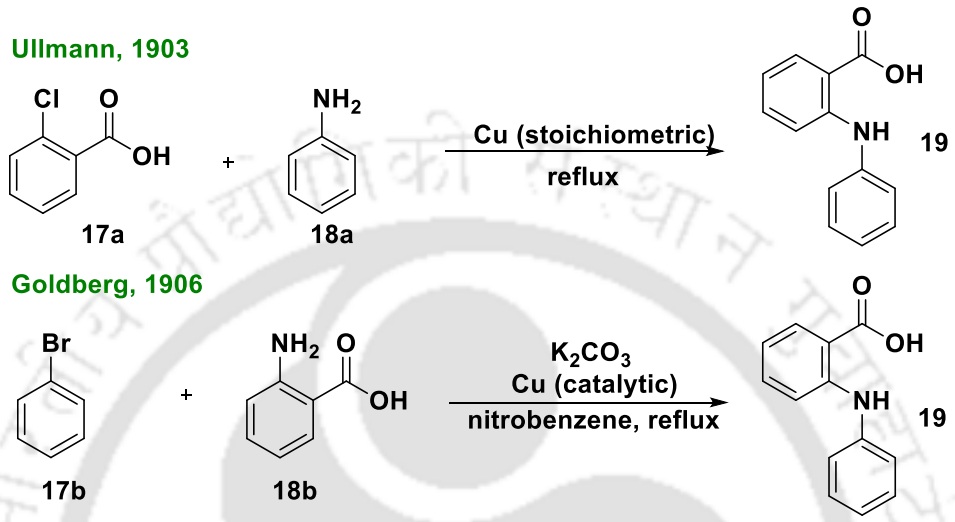


Scheme 1.7.1.5: *C-alkylation on silylaryl triflates*

1.7.2. Existing Methods of N-alkylation of Amines

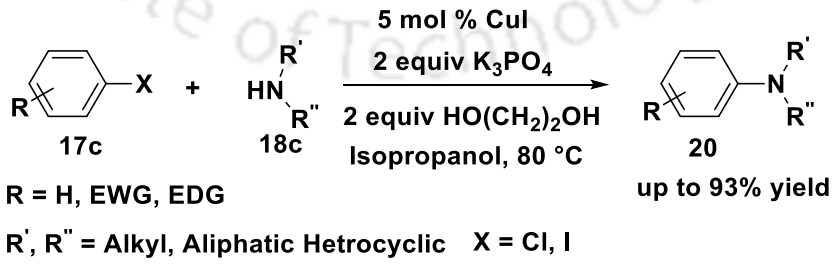
The past century was exciting for exploring chemical reactions using transition metal catalysts. Numerous strategies have been developed to construct C-N bonds by N-

alkylation of amines. The pioneering work reported by Ullmann[68(a)] and Goldberg[68(b)] at the beginning of the past century, in which N-alkylation of amines occurs with aryl halides by copper-mediated coupling reaction.



Scheme 1.7.2.1: *Pioneer N-alkylation of amines by cross-coupling reaction*

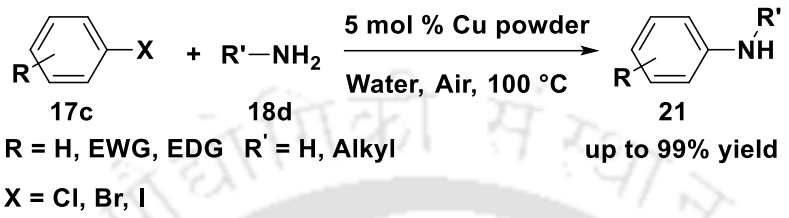
After understanding the detailed mechanism of the metal-catalyzed cross-coupling reaction and the development of various novel ligands, a massive exploration of the Ullmann reaction has been noticed. Several reviews have summarized the evolution of Ullmann's reaction.[69] Buchwald and co-workers have established the amination of aryl halides using copper iodide under mild reaction conditions in the open air.



Scheme 1.7.2.2: *Copper-catalyzed amination of aryl halide*

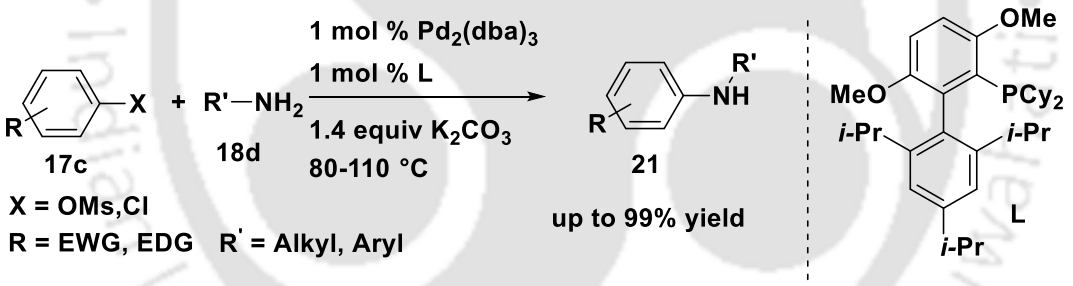
This N-alkylation protocol requires an ethylene glycol ligand [Scheme 1.7.2.2].[70]

Chen and co-workers have demonstrated an efficient and facile copper-catalyzed cross-coupling protocol for N-alkylation of amines on aryl halides in a water medium [Scheme 1.7.2.3].[71]



Scheme 1.7.2.3: *Copper powder catalyzed amination of aryl halide*

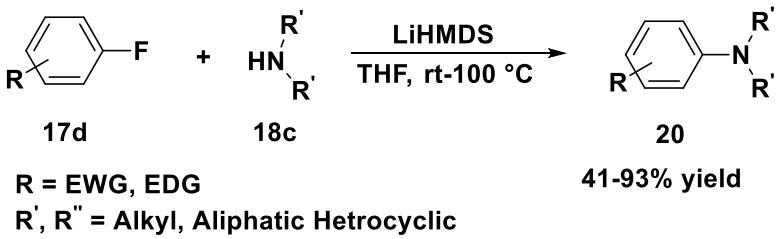
Buchwald and co-workers also have developed a palladium-catalyzed procedure for the synthesis of diarylamines from aryl chloride and aryl mesylates using brettphos ligand [Scheme 1.7.2.4].[72]



Scheme 1.7.2.4: *Palladium-catalyzed N-arylation of arylamines from aryl tosylates*

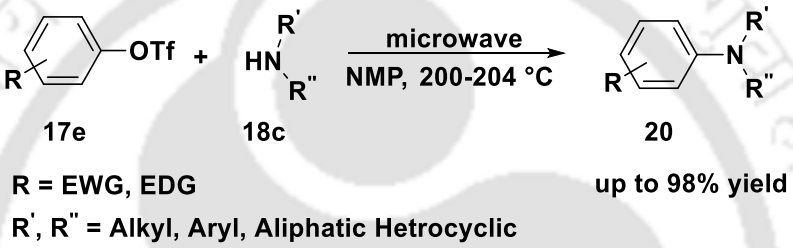
There are vast numbers of reports published for the N-alkylation of amines using other transition metal catalysts, such as Rhodium, Cobalt, and Nickel.[73]

Alongside many transition metal-catalyzed cross-coupling reactions, numerous transition metal-free methodologies have been developed for the N-alkylation of amines. Diness and co-workers have reported the transition metal-free N-arylation of amines using lithium bis(trimethylsilyl)amide as a base with fluorobenzene [Scheme 1.7.2.5].[74]



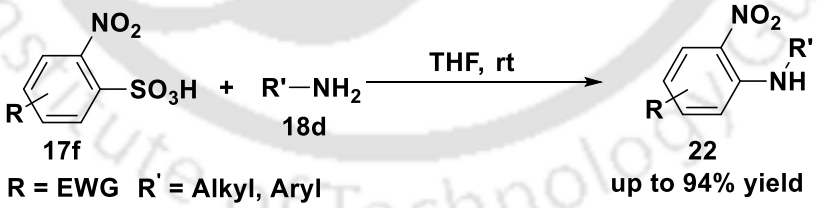
Scheme 1.7.2.5: *Transition metal-free Synthesis of arylamines from fluorobenzenes*

Xu and Wang established a microwave-assisted pathway of N-alkylation of amines using aryl triflates without any base and catalyst in NMP solvent [Scheme 1.7.2.6].[75]



Scheme 1.7.2.6: *Microwave-assisted N-alkylation of amines*

In 2019, Mandal and co-workers demonstrated N-alkylation of amines and amino acid esters using nitroaryl sulfonic acids via ipso nucleophilic substitution reaction [Scheme 1.7.2.7].[76]

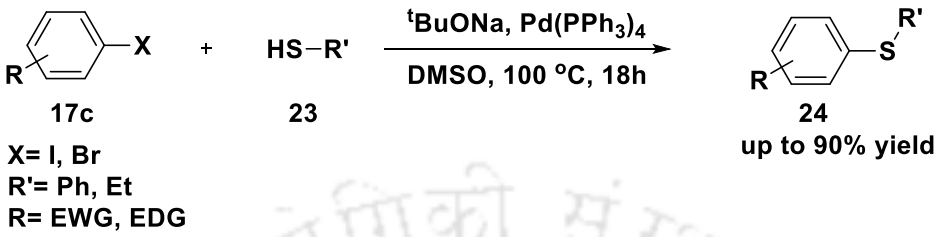


Scheme 1.7.2.7: *N-alkylation of amines using nitroaryl sulfonic acids*

1.7.3. Existing Methods of S-alkylation of Thiols

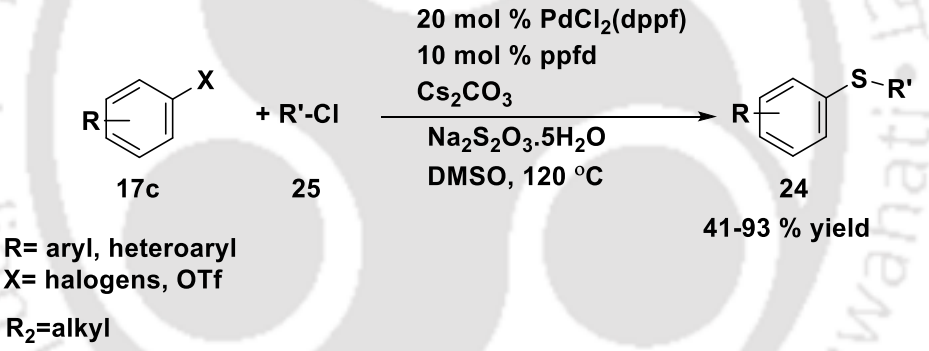
S-alkylation of thiols generates new C-S bonds, valuable bond connectivity in organic synthesis. Numerous strategies have been developed for the formation of C-S bonds. Migita group has established the method for the construction of a C-S bond, which occurs

between aryl halides and thiolates under high temperatures in the presence of sodium *tert*-butoxide and a catalytic amount of $Pd(PPh_3)_4$ [Scheme 1.7.3.1].[77]



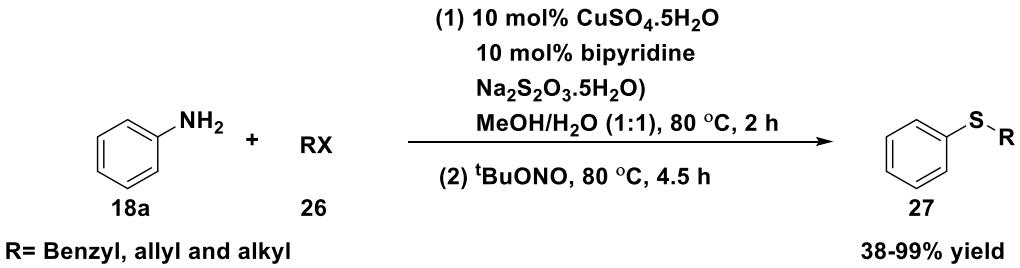
Scheme 1.7.3.1: *S-alkylation of thiols using Pd-catalyst*

In 2013, Qiao *et al.* achieved S-alkylation using sodium thiosulfate by Pd-catalyzed cross-coupling reaction with aryl halides and alkyl halides [Scheme 1.7.3.2].[78]



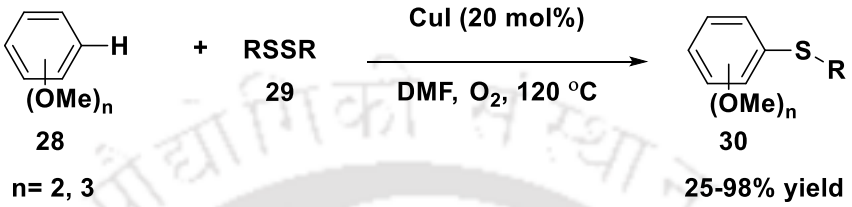
Scheme 1.7.3.2: *S-alkylation of thiols using Pd-catalyst and* $Na_2S_2O_3$

Jiang and co-workers have reported an efficient method to synthesize diaryl thioethers using sodium thiosulfate in the presence of Cu catalyst and *tert*-butyl nitrite [Scheme 1.7.3.3].[79]



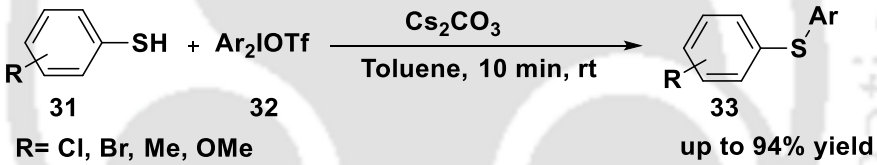
Scheme 1.7.3.3: *Cu-catalyzed S-alkylation of thiols*

Cheng group has established a protocol for thiolation of electron-rich arenes with diphenyl disulfides using a CuI [Scheme 1.7.3.4].[80]



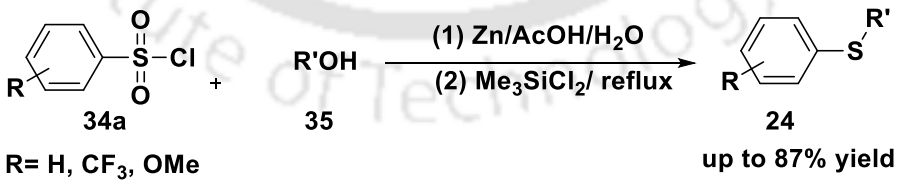
Scheme 1.7.3.4: *CuI catalyzed thiolation of di or tri methoxybenzenes*

Wang *et al*. have achieved C-S coupling in metal and ligand-free conditions using diaryliodonium salts in mild reaction conditions [Scheme 1.7.3.5].[81]



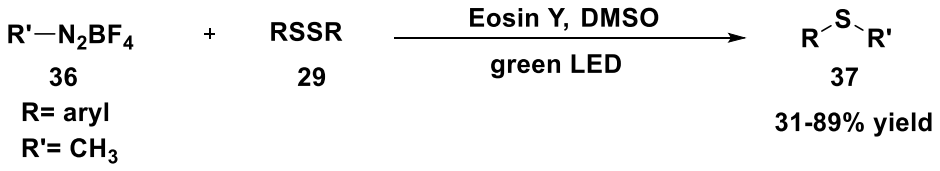
Scheme 1.7.3.5: *Transition metal and ligand-free S-alkylation*

Martin *et al*. have demonstrated the synthesis of thioethers from aromatic sulfonyl chloride and activated alcohol [Scheme 1.7.3.6].[82]



Scheme 1.7.3.6: *Synthesis of thioethers from sulfonyl chlorides*

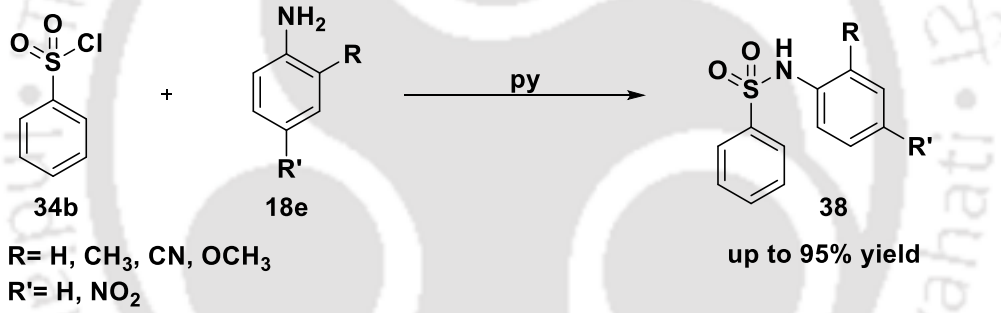
Recently C-S bond formation protocol has been developed using a photoredox catalyst.[83(a)] Jacobi von Wangelin and co-workers have reported a photocatalyzed protocol for S-alkylation of aryl sulfides using aryl diazonium salts and dimethyl disulfide [Scheme 1.7.3.7].[83(b)]



Scheme 1.7.3.7: *Photo-catalyzed pathway for S-alkylation*

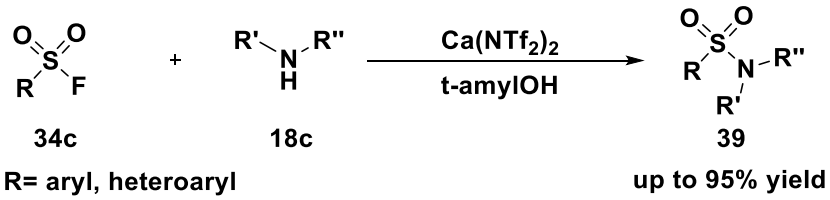
1.7.4. Existing Methods for Synthesis of Sulfonamides

Classical approaches to prepare sulfonamide have been done on benzene sulfonyl chloride with amines in the presence of pyridine base [Scheme 1.7.4.1].[84]



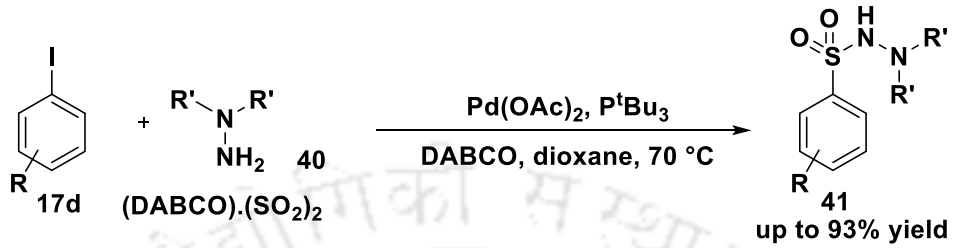
Scheme 1.7.4.1: *Classical approach of sulfonamides synthesis*

Mukherjee *et al.* have reported Lewis acid calcium triflimide [Ca-$(NTf_2)_2$] mediated sulfonamide synthesis without using strong base [Scheme 1.7.4.2].[85]



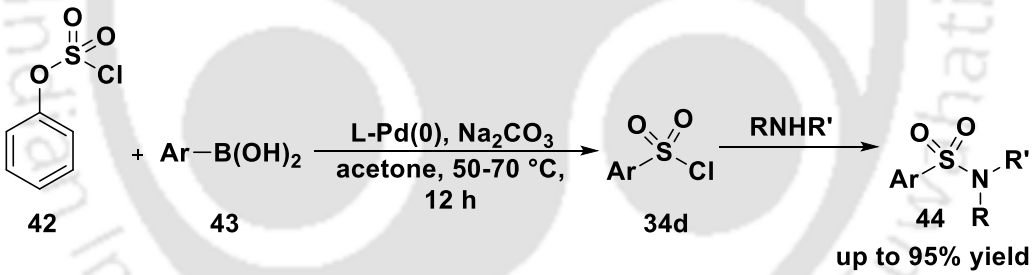
Scheme 1.7.4.2: *Lewis acid-mediated sulfonamide synthesis*

Willis *et al.* in 2010, achieved Pd-catalyzed N-amino-sulfonamides preparation from aryl iodides [Scheme 1.7.4.3].[86]



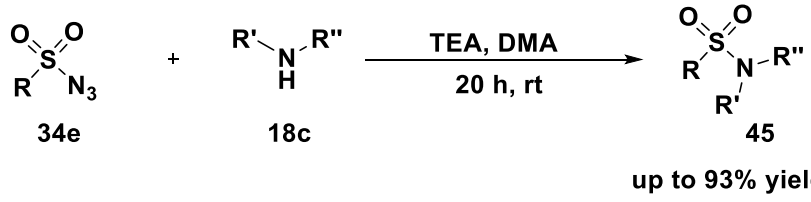
Scheme 1.7.4.3: *Pd-catalyzed sulfonamides synthesis*

Buchwald and co-workers have reported a unique pathway for the synthesis of various aryl sulfonamide from phenyl chlorosulfate using aryl boronic acids and amines via sulfonyl chloride intermediates by Pd-catalyst [Scheme 1.7.4.4].[87]



Scheme 1.7.4.4: *Pd-Catalyzed Chlorosulfonylation*

Odell and co-workers have synthesized sulfonamide complexes using sulfonyl azides as starting materials, with numerous amines in DMA medium [Scheme 1.7.4.5].[88]



Scheme 1.7.4.5: *Sulfonamides synthesis from sulfonyl azides*

Many other strategies than the above-discussed methodologies have been well established for the C-alkylation of active methylene compounds, N-alkylation of amines, S-alkylation of thiols, and sulfonamide synthesis.

1.8. Drawbacks of the Existing Methods

The literature descriptions unveiled the importance of C-C, C-N, and C-S bond formation and sulfonamide synthesis in various synthetic fields. In this regard, several procedures have been discovered and explored with modifications over the years. Most of the protocol involves different limitations, such as the requirement of transition metal catalysts, which are expensive and toxic. Therefore, those reagents produce a large amount of poisonous chemical waste, which is harmful to the environment. Most of the metal catalysis procedure demands suitable ligand that is also expensive. Again, for photochemical approaches, an expensive catalyst is necessary. C-alkylation of active methylene compounds does not tolerate various functionalization, requires elevated temperature, and is poor in yield. Many difficulties must be solved along with the metal catalyst and ligand requirement for the N-alkylation of amines. For example, the procedure requires prolonged time, inert reaction conditions, low tolerance of substrate functionalization, etc. S-alkylation of thiols by metal catalyst-mediated cross-coupling is prone to modifications that make the procedure inefficient and generate undesired products. Only some other methodologies require microwave assistance. In most systems, aryl halides, aryl boronic acids, silylaryl triflates, and diaryl iodonium salts are starting materials. The highly polar organic solvent is required for sulfonamide synthesis and to solve all these difficulties. Therefore, the invention of mild, straightforward,

environment-friendly methodologies with a high level of efficacy is highly desirable and challenging.

1.9. Objectives of Thesis

Based on the above observations, we proposed the following objectives to overcome the mentioned problems.

1. C-C Bond Formation *via* Ipso Nucleophilic Substitution of 2,4-Dinitrobenzene Sulfonic Acid with Active Methylene Compounds
2. Transition Metal-free C-S Bond Formation via Ipso Nucleophilic Substitution Reaction of Electron-Deficient Benzenesulfonic Acid with Thiols
3. Formation of Smile Rearrangement Product by Mild Intermolecular Ipso Aromatic Nucleophilic Substitution
4. Ipso Nucleophilic Substitution Reaction on Aryl Benzotriazolyl Derivative by Amine, Thiol, and Active Methylene Compounds

1.10. References

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Chapter II

C-C Bond Formation via Ipso Nucleophilic Substitution of 2,4-Dinitrobenzene Sulfonic Acid with Active Methylene Compounds

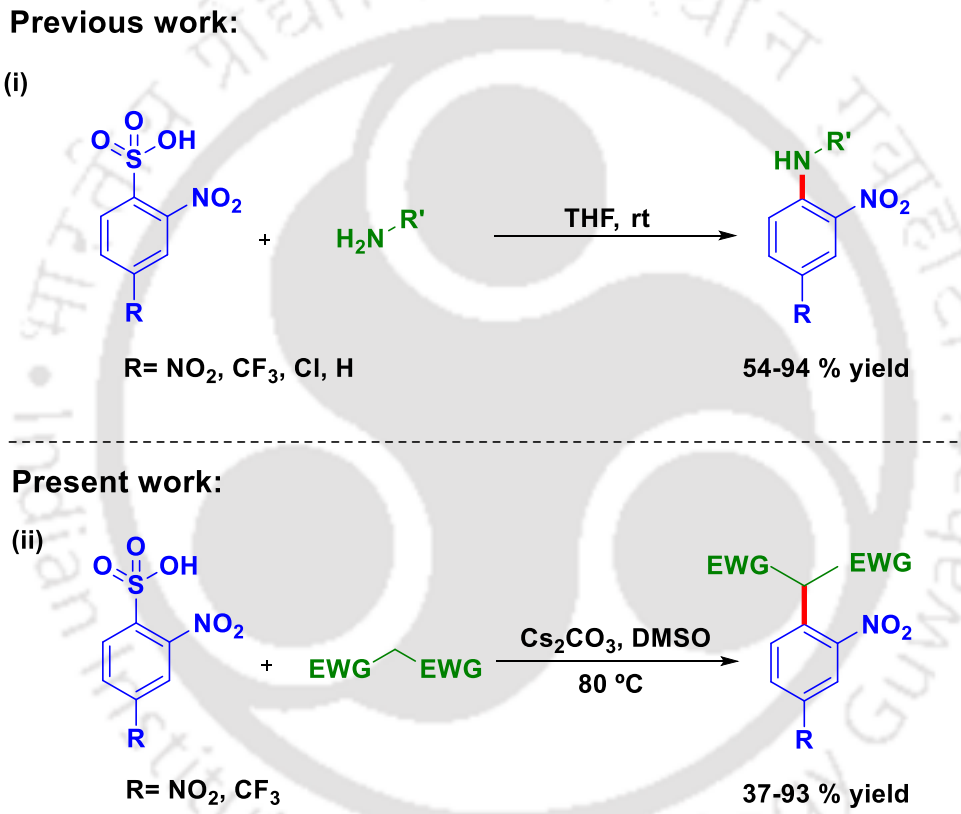
2.1. Introduction

Alkylation to an aromatic ring is a fundamental transformation in organic synthesis.[1] Friedel-Craft reaction (FCR) is widely used to achieve the alkylation of various substrates.[2] Although, it is not applicable for aromatic substrates with electron-withdrawing groups. Moreover, multi-directing alkylation is a significant drawback of FCR. Many transition metal-catalyzed alkylation or arylation have been established where carbon-carbon or carbon-heteroatom (N, O, S) bond construction occurs using aromatic halides.[3,4] Alternatively, carbon nucleophiles generated from active methylene compounds can be alkylated to an electron-deficient aromatic ring by ipso aromatic nucleophilic substitution reaction.[5] Existing methods for C-alkylation of active methylene compounds have been described in Chapter I [section 1.7.1]. However, using mainly halides as leaving groups, toxic transition metals as catalysts, and the requirements for chelating ligands limit the application scope of these transformations.

2.2. Objective

In this chapter, our motivation was to develop a transition metal-free protocol for the C-alkylation of active methylene compounds on electron-deficient aromatic rings. Previously our lab has demonstrated a highly efficient method for synthesizing arylamine

from aryl sulfonic acid derivatives via ipso substitution by amines [Scheme 2.1.1(i)].[6] In this chapter, we have described the new carbon-carbon bond formation via ipso nucleophilic substitution of sulfonic acid functionality of 2-nitrobenzene sulphonic acid analogs by active methylene compounds [Scheme 2.1.1(ii)]. In this ipso nucleophilic substitution reaction, the sulfonic acid group acts as a leaving group.



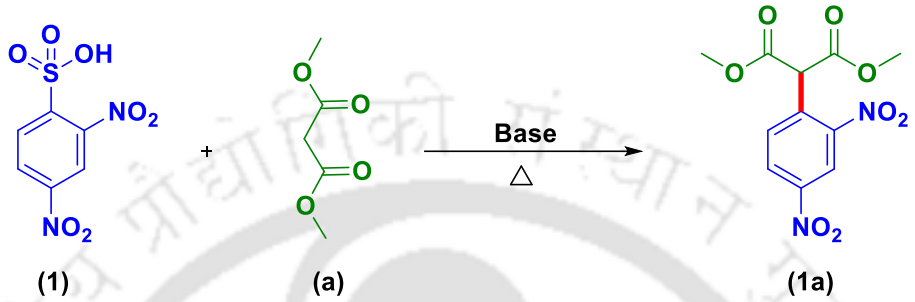
Scheme 2.1.1: *Ipso substitution on o-nitrobenzene sulfonic acid derivatives*

2.3. Results and Discussion

2.3.1. Optimization of the Reaction Conditions

We have chosen 2,4-dinitrobenzene sulfonic acid and dimethyl malonate as model substrates to optimize the reaction conditions. Several solvents, such as DMF, DMSO,

acetonitrile, MeOH, THF, EtOAc, DCE, DCM, acetone, and H_2O have been screened, keeping other variants fixed (entries 1-10), and we found that DMSO is the suitable solvent for this transformation.



Scheme 2.3.1.1: *Model reaction for optimization of the reaction conditions*

Again, several inorganic and organic bases have been screened. In the presence of Cs_2CO_3, the highest yield has been obtained. While no desired product was found with TEA and DIPEA in DCM, a 5% product yield was obtained using K_2CO_3 as a base in the DCM medium. However, Cs_2CO_3 performed better than K_2CO_3 (entry 14). Nitrogenous bases may substitute the sulfonic acid group.[6] Yield of this reaction increased with temperature till 80 °C (entries 14-16). Further increase in reaction temperature decreases the desired product formation (entries 17-18) by producing unwanted side products. We have also performed the methodology with a variant amount of base Cs_2CO_3 as well as with the substrate dimethyl malonate. This protocol shows its highest efficiency in the presence of two equivalents of the Cs_2CO_3 and dimethyl malonate. Further addition of dimethyl malonate (3.0 and 4.0 equivalent) does not enhance the yield.

Table 2.3.1.1. Optimization of the reaction conditions

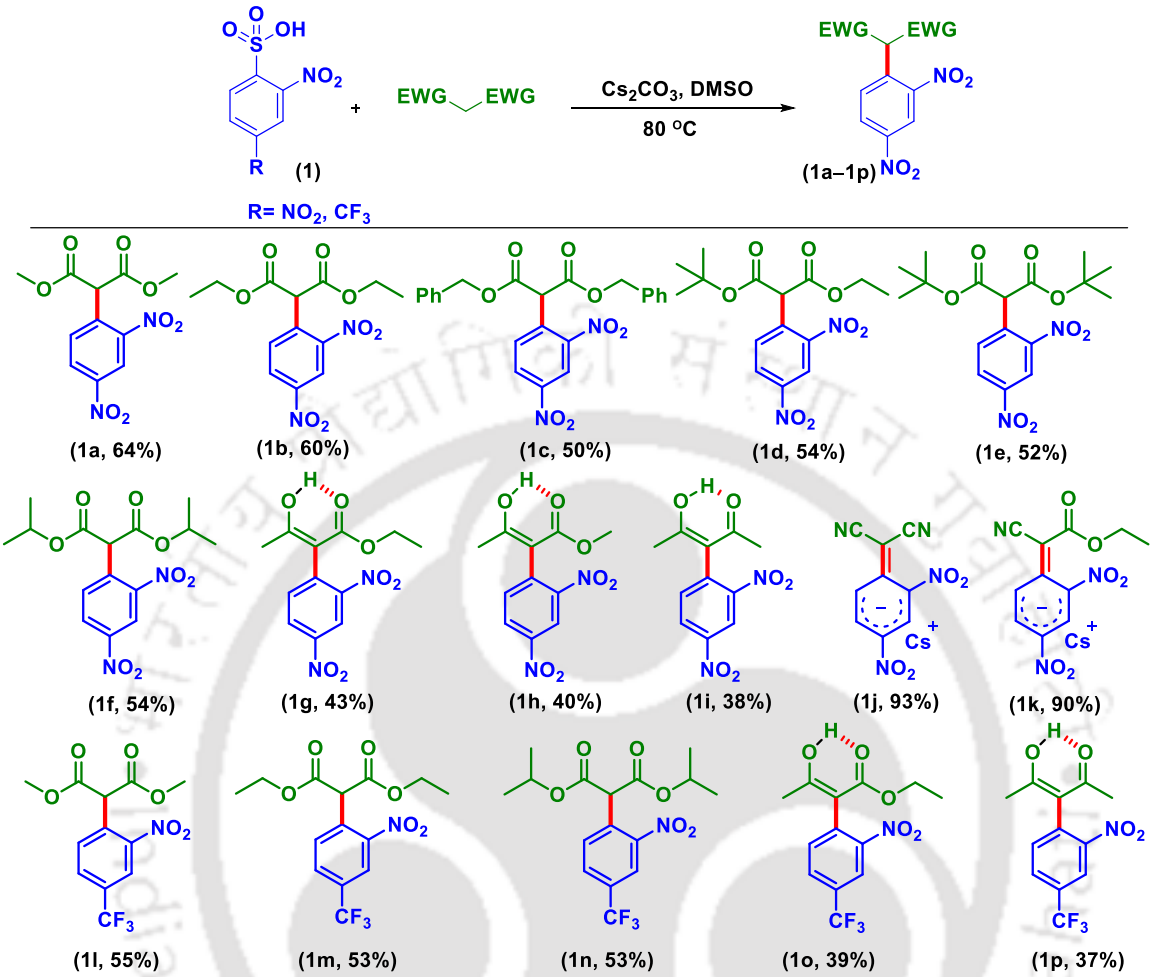
Entry	Solvent	Base (equiv.)	Temperature	Yield(%)[b]
1	DMF	K_2CO_3 (2.0)	80 °C	34
2	DMSO	,,	,,	49
3	CH_3CN	,,	,,	24
4	CH_3OH	,,	,,	27
5	THF	,,	,,	11
5	EtOAc	,,	,,	8
7	H_2O	,,	,,	n.r[c]
8	acetone	,,	,,	11
9	DCE	,,	,,	7
10	DCM	,,	40 °C	5
11	DCM	DIPEA (2.0)	,,	n.r[c]
12	DCM	TEA (2.0)	,,	n.r[c]
13	DMSO	Na_2CO_3 (2.0)	80 °C	24
14	,,	Cs_2CO_3 (2.0)	,,	64
15	,,	,,	60 °C	42
16	,,	,,	25 °C	34
17	,,	,,	120 °C	62
18	,,	,,	140 °C	57

[a]*Reaction conditions: Sulfonic acid (0.5 mmol), dimethyl malonate (1.0 mmol), reaction time 4 to 8 h.*

[b]*Isolated yield with respect to the sulphonic acid.* [c]*No reaction*

2.3.2. Substrate Scope

The scope of the reaction between 2,4-dinitrobenzene sulfonic acid and different active methylene compounds has been investigated under optimized conditions. Active methylene compounds with two ester groups (1a-1f) produced a higher yield. The products with ethyl acetoacetate (1g) and methyl acetoacetate (1h) are stable in enol form via forming a 6-membered ring through H-bonding. Acetylacetone also behaved similarly (1i), but a comparatively lower yield was obtained due to the formation of a byproduct. Interestingly, with malononitrile (1j) and ethyl cyanoacetate (1k), a reddish solid precipitate, crystallized in methanol, was noted upon adding DCM after the reaction. These two compounds are resonance stabilized in the anionic form in the presence of metal. However, cyclic active methylene compounds and substituted active methylene compounds did not react even at an elevated temperature (Table 2.3.2.1), probably for a steric reason. Substrate scope using 2,4-dinitrobenzene sulfonic acid analogs produced expected products with sufficiently high yield. Substrates bearing an *o*-nitro group and an electron-withdrawing group at the *para* position, such as the $–CF_3$, also produced similar yields (1l-1p). However, sulfonic acids without or with one nitro group are not sufficiently electron deficient in reacting (Table 2.3.2.1). The composition and the structure of compounds 1g and 1j were challenging to establish without the single-crystal X-ray diffraction analysis.



[a]*Reaction conditions: Sulfonic acid (1, 0.5 mmol), active methylene compound (1.0 mmol), cesium carbonate (1.0 mmol) reaction time 4 to 8 h at 80 °C.*

Scheme 2.3.2.1: *Substrate scope with 2,4-dinitrobenzene sulfonic acid*

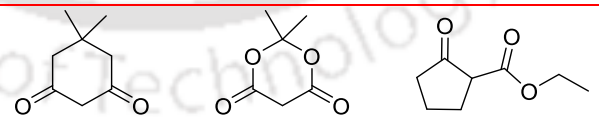
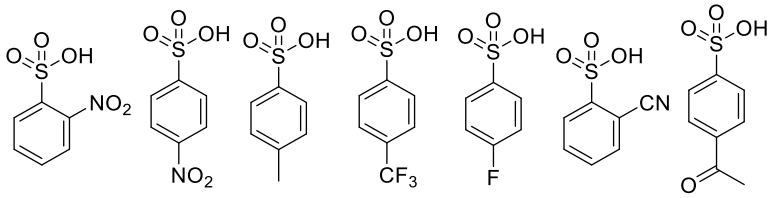
Active methylene compounds	
Aryl sulfonic acids	

Table 2.3.2.1: *The list of reagents those do not respond to this methodology*

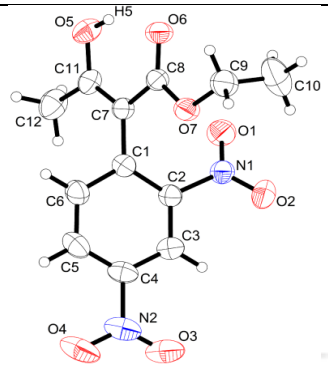
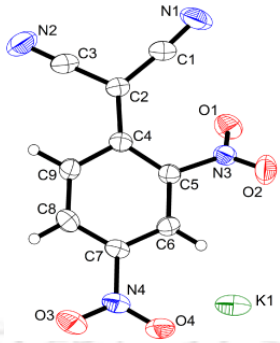
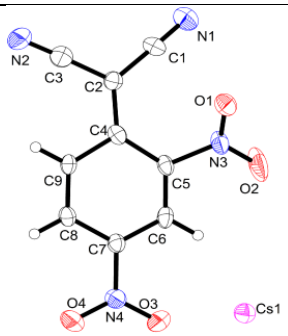
		
1g (CCDC No. 2155058)	**1j with potassium ion (CCDC No. 2155062)**	**1j with cesium ion (CCDC No. 2166732)**

Figure 2.3.2.1*: ORTEP Diagram with ellipsoid of 40% probability (a)* ***1g*** *(CCDC No. 2155058), (b)* ***1j*** *with potassium ion (CCDC No. 2155062), (c)* ***1j*** *with cesium ion (CCDC No. 2166732)*

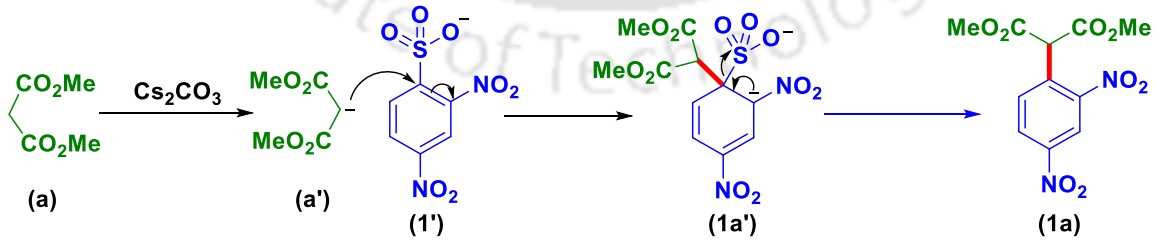
In the case of **1g,** the C-C bond lengths in the ring are comparable to the standard delocalized bonds in the benzene ring (1.40 Å; C_1-C_2 = 1.409 Å, C_2-C_3 = 1.382 Å, C_3-C_4 = 1.375 Å, C_4-C_5 = 1.376 Å, C_5-C_6 = 1.378 Å, C_6-C_1 = 1.397 Å). The exocyclic C_1-C_7 bond is slightly longer than the standard C_{sp2}-C_{sp2} bond length (1.455 Å) and close to the C-C single bond length. The C_7-C_8 bond (1.454 Å) length corresponds to the C-C single bond, and C_7-C_{11} is 1.369 Å, much closer to the C-C double bond. C_{11}-O_5 is 1.331 Å and C_8-O_6 is 1.232 Å. This close observation of the bond lengths indicates that the first one represents a C-O single bond, and the latter represents a C-O double bond. The above critical analysis of the bond lengths indicates enolization occurs via rearrangement of the active methylene proton over the keto group.[7]

In structure **1j** (potassium metal-organic framework, Figure 2.3.2.1:1b), the C_4-C_9 bond is strongly elongated, 1.424 Å. Similarly, C_4-C_5 is a longer, 1.420 Å. The remaining bonds in the benzene ring C_5-C_6 (1.384 Å), C_6-C_7 (1.376 Å), C_7-C_8 (1.382 Å), and C_8-C_9 (1.362

Å) are shorter than the standard delocalized bond in benzene ring (1.40 Å). These results indicate the absence of complete delocalization in the ring, and the –ve charge is distributed over C5-C6, C6-C7, C7-C8, and C8-C9 bonds.[8] C_2-C_4 is an exocyclic bond (1.421 Å), slightly smaller than the standard C_{sp2}-C_{sp2} single bond length (1.455 Å). C_1-C_2 (1.412 Å) and C_3-C_2 (1.410 Å) are longer than the standard C_{sp2}-C_{sp2} double bond length (1.34 Å), i.e., the partial double bond character exists. C_1-N_1 (1.140 Å) and C_3-N_2 (1.142 Å) bonds are comparable with standard CN triple bonds (1.13 Å). The structure of **1j** stabilized with cesium metal (Figure 2.3.2.1:1c) was similar to that of **1j** stabilized with potassium ion (Figure 2.3.2.1:1b).

2.3.3. Mechanism

According to established literature, a plausible reaction mechanism for the alkylation by active methylene compound on 2,4-dinitrobenzene sulfonic acid has been drawn.[9-11] This reaction undergoes Meisenheimer adduct[12] (**1a′**) formation, which is stabilized by resonance through the electron-withdrawing groups attached to the benzene ring.



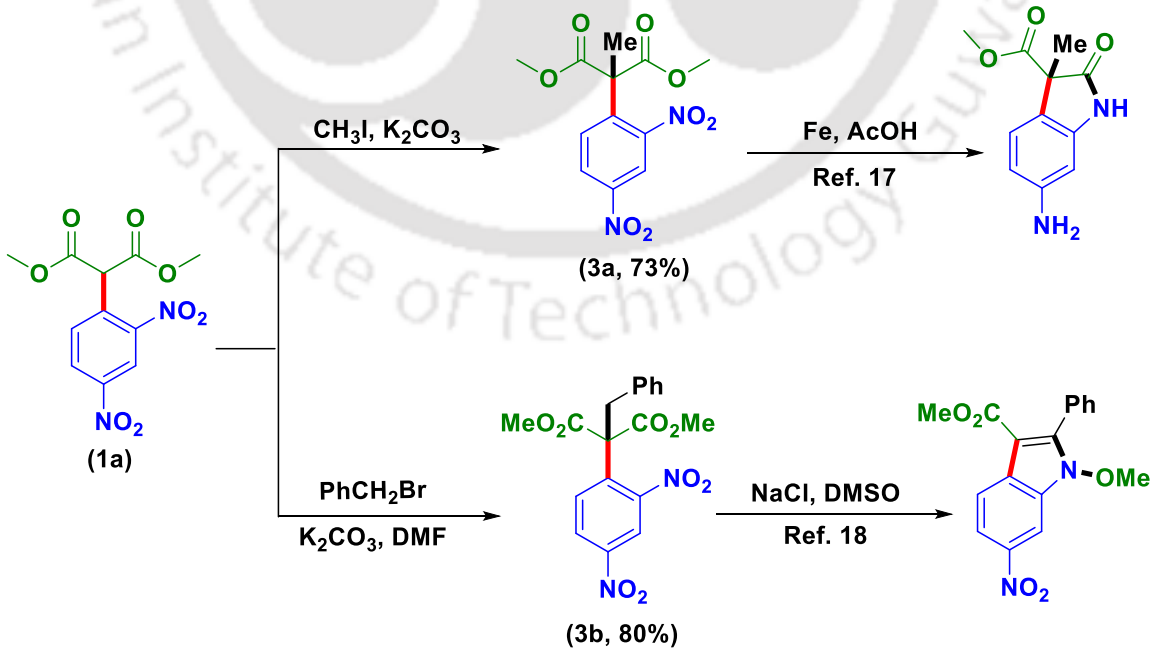
Scheme 2.3.3.1: *A plausible mechanism for alkylation on 2,4-dinitrobenzene sulfonic acid*

The *ortho* effect may stabilize the Meisenheimer adduct (**1a′**).[13] However, the possibility of nucleophilic replacement of hydrogen on the aromatic ring[14-16] can not be obviated.

However, no such side product formation could be noted so far in the present reaction conditions.

2.3.4. Applications

The current protocol has excellent potential in biologically active compound synthesis. For example, 2-oxoindole and 1-methoxyindole structural frameworks are valuable synthetic building blocks for many natural products and biologically active molecules.[17] Indoline and Ziprasidone are 2-oxoindole core-based successful pharmaceutical agents. Indoline is used in treating cardiovascular diseases and ischemic chest pain; Ziprasidone is used in treating mental illnesses like schizophrenia. Neoxalline is a 1-methoxyindole-based compound that stimulates the central nervous system. The nitro-diesters (**3a** and **3b**), crucial for synthesizing the above active pharmaceutical ingredients, can be easily accessed using this method.[18]



Scheme 2.3.4.1: *A representative post-synthetic application*

Metal-organic framework (MOF) is an exciting topic in the present research. Metal ions or clusters are linked with multiple organic moieties in a repetitive pattern to form a MOF structure. Due to their ordered pore structures, facile functionalization, and large surface areas, MOF is highly applicable for gas separation, semiconductors, radioactive waste absorption, biological imaging, and sensing. Using this protocol, we have synthesized MOFs where potassium and cesium ions are linked with 2-(2,4-dinitrophenyl)malononitrile moiety (**1j)**. The channel-like layer structure formation in solid-state stabilized though π-π stacking interaction between two benzene rings (centroid to centroid distance = 3.720 Å) and chelating interaction of potassium ion with ligand binding site such as two nitro as well as cyano group. (Figure 2) In this molecular structure, one potassium ion is bonded to nine donor atoms (six "O" and three "N")

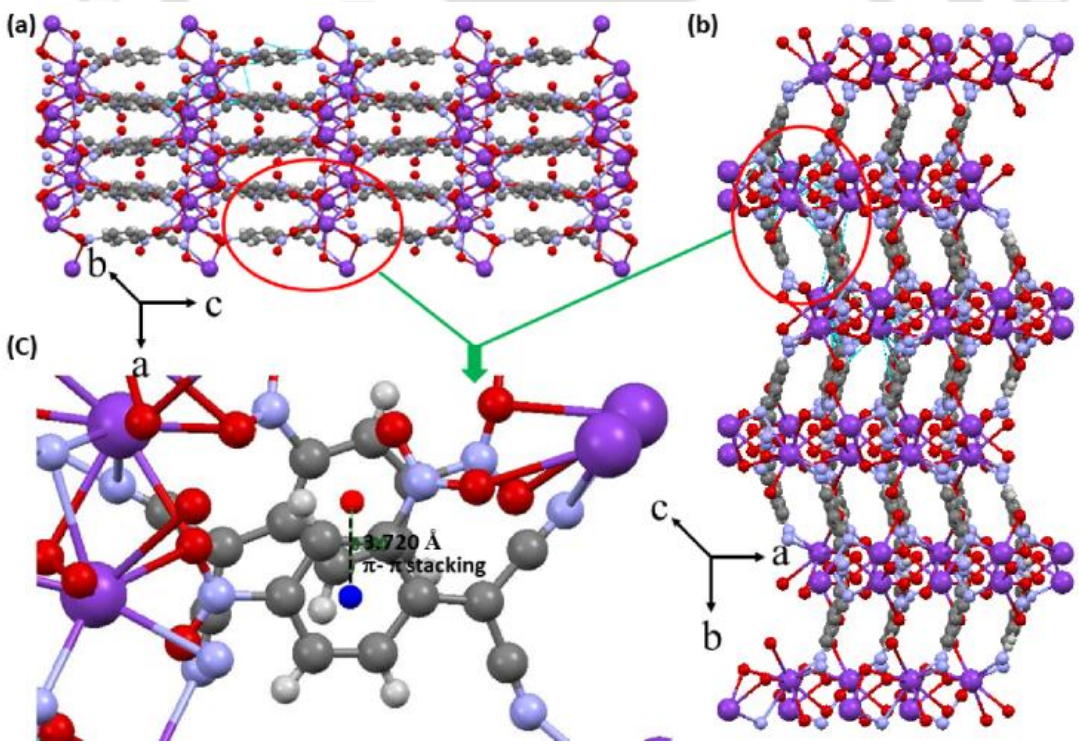


Figure 2.3.4.1: *(a) linear channel-like layer arrangement along the c-axis, (b) helical channel-like layer architecture along crystallographic b-axis in higher-order molecular packing, (c) π-π stacking interaction and Cs^+ ion binding interaction inside the channel of molecule 2-(2,4-dinitrophenyl)malononitrile*

2.4. Conclusion

In conclusion, we have disclosed a method for the C-alkylation of active methylene compounds by *o*-nitroaryl sulfonic acid derivatives. This method is an example of a C-C bond formation reaction by ipso substitution of a sulfonic acid group. No toxic transition metal catalyst, ligand, or PTC is required. Although this method works only for sufficiently electron-deficient aromatic sulfonic acids, the diverse derivatization possibilities make it an essential tool for API synthesis. Application possibilities in medicinal chemistry and material chemistry are demonstrated. This methodology opens up a novel route for accessing densely substituted quaternary carbon centers (**4a, 4b**). Moreover, no any acidic hydrogen halide (HX) byproduct formation occurs in this protocol unlike the case of halogen leaving group containing reagent.

2.5. Experimental Section

General Information

All reagents were purchased from commercial sources. NMR spectra were recorded on 400 MHz, 500 MHz, and 600 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) were reported in ppm, and spin-spin coupling constants (J) were given in Hz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dq (doublet of the quartet), and m (multiplet). $^{13}C\{^1H\}$ indicates the proton decoupled NMR experiment. Reactions were monitored using thin-layer chromatography with silica gel G254. The reaction products were purified by column

chromatography using silica gel (60-120 mesh) using eluent EtOAc/Hexane. Solvents were removed under reduced pressure using a Buchi rotary evaporator. Melting points were determined using a dedicated melting point measuring apparatus, and FT-IR spectra were recorded on an FT-IR spectrometer.

General procedure for the synthesis of arylated product

Active methylene compound (1.0 mmol) was taken in DMSO solvent (2 mL), and Cs_2CO_3 (1.0 mmol) was added to it. The mixture was stirred at room temperature for 10 minutes, and then sulfonic acid (0.5 mmol) was added. Then the temperature was increased to 80 ºC. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with ethyl acetate (15 mL) and washed with ice-cold water. The accumulated organic layer was washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 10-15% EtOAc/Hexane.

General procedure for the synthesis of 1j and 1k

Active methylene compound (2.0 mmol) was taken in DMSO solvent (2 mL), and Cs_2CO_3 (2.0 mmol) was added to it. The mixture was stirred at room temperature for 10 minutes, and then sulfonic acid (1.0 mmol) was added. Then stirring continued at 80 ºC. The progress of the reaction was monitored by TLC. After completion of the reaction, DCM was added to the reaction mixture. A large amount of precipitate was formed. This precipitate was separated by filter paper and dried at room temperature. No column chromatography purification was required in this procedure.

General procedure for the synthesis of 4a and 4b

Dimethyl 2-(2,4-dinitrophenyl)malonate (0.5 mmol) was taken in 50 mL RB in a DMF medium. K_2CO_3 (0.5 mmol) was added to this mixture and kept for stirring at room temperature for 10 minutes. Then alkyl halide (0.6 mmol) was added to the above reaction mixture and continued stirring overnight. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with ethyl acetate (15 mL) and washed with ice-cold water. The accumulated organic layer was washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The obtained residue was purified by column chromatography using 10-15% EtOAc/Hexane.

Procedure for large-scale synthesis of compound 3a

Dimethyl malonate (8.06 mmol) was taken in DMSO solvent (8 mL), and Cs_2CO_3 (8.06 mmol) was added to it. We stirred the mixture at room temperature for 10 minutes, and then 2,4-dinitrobenzene sulfonic acid (4.03 mmol) was added. Then continue the reaction at 80 ºC. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with ethyl acetate (30 mL) and washed with ice-cold water. The accumulated organic layer was washed with 5% HCl (2×20 mL), 5% $NaHCO_3$ (2×20 mL), saturated NaCl solution (2×20 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The obtained residue was purified by column chromatography using 10-15% EtOAc/Hexane. The pure product was a white crystalline solid (745mg. 2.5 mmol, 62%).

2.6. Characterization Data

Dimethyl 2-(2,4-dinitrophenyl)malonate (1a)[19]

As a white solid (85 mg, 64% yield, mp 90–92 °C); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, 1H, J = 2.4 Hz), 8.48 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.82 (d, 1H, J = 8.8 Hz), 5.41 (s, 1H), 3.82 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 166.7, 149.2, 147.9, 134.3, 133.5, 127.6, 120.8, 54.0, 53.8; IR (KBr, cm^{-1}): 3078, 2963, 2916, 2847, 1754, 1730, 1605, 1532, 1344, 1298, 1242, 1002, 837, 734; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{11}H_{11}N_2O_8$ $[M + H]^+$ 299.0510; found 299.0507.

Diethyl 2-(2,4-dinitrophenyl)malonate (1b)[20]

As a yellow liquid (98 mg, 60% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, 1H, J = 2.4 Hz), 8.47 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.82 (d, 1H, J = 8.8 Hz), 5.36 (s, 1H), 4.29 (dq, 4H, J_1 = 2.6 Hz, J_2 = 7.0 Hz), 1.29 (t, 6H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 166.3, 149.3, 147.8, 134.6, 133.4, 127.5, 120.7, 63.0, 54.4, 14.1; IR (KBr, cm^{-1}): 3105, 2984, 2919, 2853, 1732, 1607, 1532, 1466, 1346, 1298, 1175, 1023, 835, 723; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{13}H_{14}N_2O_8Na$ $[M + Na]^+$ 349.0642; found 349.0641.

Dibenzyl 2-(2,4-dinitrophenyl)malonate (1c)

As a yellow solid (112 mg, 50% yield, mp 88–90 °C); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, 1H, J = 2.4 Hz), 8.36 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.36–7.33 (m, 6H),

7.29–7.27 (m, 4H), 5.47 (s, 1H), 5.22 (s, 4H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.1, 149.1, 147.8, 134.7, 134.3, 133.4, 128.99, 128.89, 128.7, 127.5, 120.8, 68.7, 54.5; IR (KBr, cm^{-1}): 3078, 2953, 2921, 2852, 1744, 1725, 1601, 1526, 1495, 1454, 1344, 1295, 1175, 1020, 979, 836, 731, 694; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{23}H_{19}N_2O_8$ $[M + H]^+$ 451.1136; found 451.1144.

1-(*tert*-Butyl)3-ethyl(R)-2-(2,4-dinitrophenyl)malonate (1d)

As a yellow liquid (95 mg, 54% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, 1H, J_1 = 2.4 Hz), 8.47 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.81 (d, 1H, J = 8.8 Hz), 5.27 (s, 1H), 4.28 (dq, 2H, J_1 = 2.4 Hz, J_2 = 7.1 Hz), 1.48 (s, 9H), 1.30 (t, 3H, J = 7.2 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.7, 165.2, 149.3, 147.7, 135.1, 133.2, 127.4, 120.7, 84.4, 62.9, 55.5, 27.9, 14.2; IR (KBr, cm^{-1}): 3105, 2981, 2934, 2853, 1729, 1606, 1534, 1346, 1299, 1230, 1141, 1025, 835, 790, 727; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{15}H_{18}N_2O_8K$ $[M + K]^+$ 393.0695; found 393.0684.

Di-*tert*-butyl 2-(2,4-dinitrophenyl)malonate (1e)

As a yellow solid (99 mg, 52% yield, mp 97–99 °C); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, 1H, J = 2.4 Hz), 8.47 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.83 (d, 1H, J = 8.8 Hz), 5.18 (s, 1H), 1.49 (s, 18H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 165.6, 149.4, 147.5, 135.6, 133.0, 127.3, 120.6, 84.0, 56.4, 28.0; IR (KBr, cm^{-1}): 3105, 2979, 2930, 2850, 1728, 1606, 1535, 1346, 1249, 1136, 1066, 834, 748; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{17}H_{23}N_2O_8$ $[M + H]^+$ 383.1449; found 383.1438.

Diisopropyl 2-(2,4-dinitrophenyl)malonate (1f)

As a yellow solid (96 mg, 54% yield, mp 108–110 °C); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, 1H, J = 2.4 Hz), 8.46 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.79 (d, 1H, J = 8.8 Hz), 5.26–5.06 (m, 2H), 1.29–1.25 (m, 12H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 165.8, 149.2, 147.7, 134.9, 133.2, 127.4, 120.6, 70.9, 54.9, 21.6; IR (KBr, cm^{-1}): 3104, 2984, 2939, 2875, 1728, 1606, 1534, 1467, 1346, 1263, 1168, 1096, 834, 725; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{15}H_{19}N_2O_8$ $[M + H]^+$ 355.1136; found 355.1138.

Ethyl (*Z*)-2-(2,4-dinitrophenyl)-3-hydroxybut-2-enoate (1g)[7]

As a yellow crystalline (64 mg, 43% yield, mp 93–95 °C); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.15 (s, 1H), 8.84 (d, 1H, J = 2.4 Hz), 8.43 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.53 (d, 1H, J = 8.8 Hz), 4.24–4.19 (m, 1H), 4.07–4.02 (m, 1H), 1.92 (s, 3H), 1.12 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.5, 170.2, 149.9, 147.4, 136.8, 135.5, 126.9, 120.3, 100.0, 61.7, 20.3, 14.0; IR (KBr, cm^{-1}): 3075, 2963, 2921, 2852, 1729, 1640, 1603, 1531, 1467, 1344, 1218, 1098, 836, 729; ESI (m/z) calcd for $C_{12}H_{13}N_2O_7$ $[M + H]^+$ 297.0717; found 297.1045.

Methyl (*Z*)-2-(2,4-dinitrophenyl)-3-hydroxybut-2-enoate (1h)[21]

As a yellow liquid (61 mg, 43% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.98 (s, 1H), 8.82 (d, 1H, J = 2.4 Hz), 8.43 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 7.55 (d, 1H, J = 8.4 Hz), 3.63 (s, 3H), 1.90 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.5, 170.6, 149.6, 135.5, 127.0, 120.3, 99.6,

52.2, 20,1; IR (KBr, cm^{-1}): 3078, 2963, 2923, 2853, 1738, 1606, 1532, 1439, 1217, 1064, 835, 711; ESI (m/z) calcd for $C_{11}H_{10}N_2O_7Na$ $[M + Na]^+$ 305.0380; found 305.0494.

(*Z*)-3-(2,4-Dinitrophenyl)-4-hydroxypent-3-en-2-one (1i)[22]

As a yellow liquid (53 mg, 40% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 16.58 (s, 1H), 8.79 (d, 1H, J = 3.0 Hz), 8.50 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.5 Hz), 7.62 (d, 1H, J = 8.5 Hz), 1.86 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 189.9, 150.7, 148.0, 137.7, 135.7, 127.4, 120.2, 108.9, 24.3; IR (KBr, cm^{-1}): 3109, 2955, 2917, 2850, 1739, 1597, 1526, 1349, 1261, 1186, 1015, 905, 834, 798; ESI (m/z) calcd for $C_{11}H_{11}N_2O_6$ $[M + H]^+$ 267.0612; found 267.1738.

2-(2,4-Dinitrocyclohexylidene)malononitrile (1j)[8a] **[in reported compound cation is triethylammonium ion]**

As a reddish crystalline (169 mg, 93% yield, mp 267–269 °C); ^1H NMR (DMSO-d_6, 600 MHz): δ 8.37 (d, 1H, J = 2.4 Hz), 7.97 (dd, 1H, J_1 = 1.5 Hz, J_2 = 9.9 Hz), 7.18 (d, 1H, J = 9.0 Hz).; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 150 MHz): δ 142.1, 138.2, 135.8, 130.8, 125.7, 122.7, 122.7, 118.4; IR (KBr, cm^{-1}): 3114, 2974, 2919, 2853, 2201, 2173, 1738, 1563, 1480, 1287, 832.

Ethyl (Z)-2-cyano-2-(2,4-dinitrocyclohexylidene)acetate (1k)[8a] **[in reported compound cation is triethylammonium ion]**

As a reddish crystalline (185 mg, 90% yield, mp 258–260 °C); ^1H NMR (DMSO-d_6, 600 MHz): δ 8.29 (d, 1H, J = 2.4 Hz), 7.97 (dd, 1H, J_1 = 3.3 Hz, J_2 = 9.3 Hz), 7.59 (d, 1H, J = 9.6 Hz), 3.96 (q, 2H, J = 7.2 Hz), 1.14 (t, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 150

MHz): δ 166.3, 142.9, 140.5, 135.9, 125.3, 124.9, 122.8, 122.2, 58.2, 14.8; IR (KBr, cm^{-1}): 3344, 3098, 2977, 2950, 2183, 2155, 1516, 1566, 1299, 1089, 827.

Dimethyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate (2a)[23]

As a yellow liquid (88 mg, 55% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (d, 1H, J = 2.0 Hz), 7.92 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.73 (d, 1H, J = 8.4 Hz), 5.39 (s, 1H), 3.82 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 167.1, 149.0, 132.9, 131.8, 130.1 (q, J = 3.2 Hz), 124.1, 122.7 (q, J = 3.8 Hz), 121.4, 54.0, 53.6; ^{19}F NMR ($CDCl_3$): δ –63.1 (s); IR (KBr, cm^{-1}): 3105, 2962, 2916, 2851, 1760, 1732, 1634, 1539, 1440, 1329, 1242, 1128, 1088, 1009, 911, 700; ESI (m/z) calcd for $C_{12}H_{11}F_3NO_6$ $[M + H]^+$ 322.0533; found 322.0681.

Diethyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate (2b)[24]

As a yellow liquid (92 mg, 53% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, 1H, J = 2.0 Hz), 7.89 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.73 (d, 1H, J = 8.4 Hz), 5.34 (s, 1H), 4.28 (dq, 4H, J_1 = 2.0 Hz, J_2 = 7.2 Hz), 1.29 (t, 6H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 167.8, 149.1, 132.8, 132.1, 130.0 (q, J = 3.5 Hz), 124.1, 122.7 (q, J = 3.9 Hz), 121.5, 62.9, 54.4, 14.2; ^{19}F NMR ($CDCl_3$): δ –63.1 (s); IR (KBr, cm^{-1}): 3105, 2993, 2924, 2858, 1735, 1633, 1542, 1465, 1325, 1227, 1132, 1088, 1025, 862, 788; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{14}H_{15}F_3NO_6$ $[M + H]^+$ 350.0846; found 350.0846.

Diisopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate (2f)[25]

As a yellow liquid (100 mg, 53% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (d, 1H, J = 2.0 Hz), 7.88 (dd, 1H,

J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.72 (d, 1H, J = 8.0 Hz), 5.25 (s, 1H), 5.16–5.07 (m, 2H), 1.29–1.25 (m, 12H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.3, 149.2, 132.6, 132.1, 129.9 (q, J = 3.3 Hz), 124.2, 122.6 (q, J = 4.0 Hz), 121.5, 70.7, 54.9, 21.7; ^{19}F NMR ($CDCl_3$): δ –63.1 (s); IR (KBr, cm^{-1}): 3114, 2985, 2939, 2883, 1730, 1632, 1542, 1325, 1230, 1134, 1088, 904, 830, 787; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{16}H_{19}F_3NO_6$ $[M + H]^+$ 378.1159; found 378.1162.

Ethyl (*Z*)-3-hydroxy-2-(2-nitro-4-(trifluoromethyl)phenyl) but-2-enoate (2g)[26]

As a yellow liquid (62 mg, 39% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 13.06 (s, 1H), 8.24 (d, 1H, J = 2.0 Hz), 7.83 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.47 (d, J = 8.0 Hz, 1H), 4.23–4.17 (m, 1H), 4.06–3.99 (m, 1H), 1.87 (s, 3H), 1.10 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 174.1, 170.6, 149.9, 135.2, 134.1, 131.4, 131.1, 129.3 (q, J = 3.4 Hz), 124.1, 121.9 (q, J = 4.0, Hz), 100.3, 61.4, 20.0, 13.9; ^{19}F NMR ($CDCl_3$): δ –62.9 (s); IR (KBr, cm^{-1}): 3026, 2974, 2924, 2861, 1737, 1605, 1537, 1319, 1130, 1078, 709; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{13}H_{13}F_3NO_5$ $[M + H]^+$ 320.0740; found 320.0737.

(*Z*)-4-Hydroxy-3-(2-nitro-4-(trifluoromethyl)phenyl)pent-3-en-2-one (2h)[27]

As a yellow liquid (54 mg, 37% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 16.54 (s, 1H), 8.21 (d, 1H, J = 2.0 Hz), 7.91 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 1.85 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 190.1, 150.7, 135.2, 132.5, 132.2, 129.8 (q, J = 3.4 Hz), 124.2, 122.0 (q, J = 3.6 Hz), 109.4, 24.2; ^{19}F NMR ($CDCl_3$): δ –62.9 (s); IR (KBr, cm^{-1}):

3103, 2970, 2916, 2853, 1737, 1605, 1537, 1319, 1257, 1175, 1130, 1078, 847, 789; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{12}H_{11}F_3NO_4$ $[M + H]^+$ 290.0635; found 290.0627.

Dimethyl 2-(2,4-dinitrophenyl)-2-methylmalonate (3a)

As a yellow liquid (114 mg, 73% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, 1H, J = 2.4 Hz), 8.44 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.62 (d, 1H, J = 8.8 Hz), 3.76 (s, 6H), 2.06 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 169.4, 149.3, 147.4, 140.9, 130.9, 127.4, 121.5, 59.4, 53.7, 23.8; IR (KBr, cm^{-1}): 3136, 3095, 2955, 2923, 2853, 1730, 1711, 1603, 1531, 1435, 1347, 1245, 1123, 1068, 972, 810, 782, 721; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{12}H_{13}N_2O_8$ $[M + H]^+$ 313.0666; found 313.0723.

Dimethyl 2-benzyl-2-(2,4-dinitrophenyl)malonate (3b)

As a yellow liquid (155 mg, 80% yield); Purification over a column of silica gel (10–15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.73 (d, 1H, J = 2.4 Hz), 7.99 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz),7.12–7.05 (m, 3H), 6.96 (d, 2H, J = 8.0 Hz), 6.78 (d, 1H, J = 8.8 Hz), 4.01 (s, 2H), 3.78 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 168.5,138.2, 135.7, 134.4, 130.8, 128.4, 127.5, 125.2, 120.5, 65.6, 53.8, 40.8; IR (KBr, cm^{-1}): 3092, 3034, 2955, 2924, 2850, 1738, 1604, 1531, 1496, 1434, 1384, 1258, 1209, 1168, 1059, 907, 858, 725; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{18}H_{17}N_2O_8$ $[M + H]^+$ 389.0979; found 389.0979.

2.7. Representative NMR Spectra

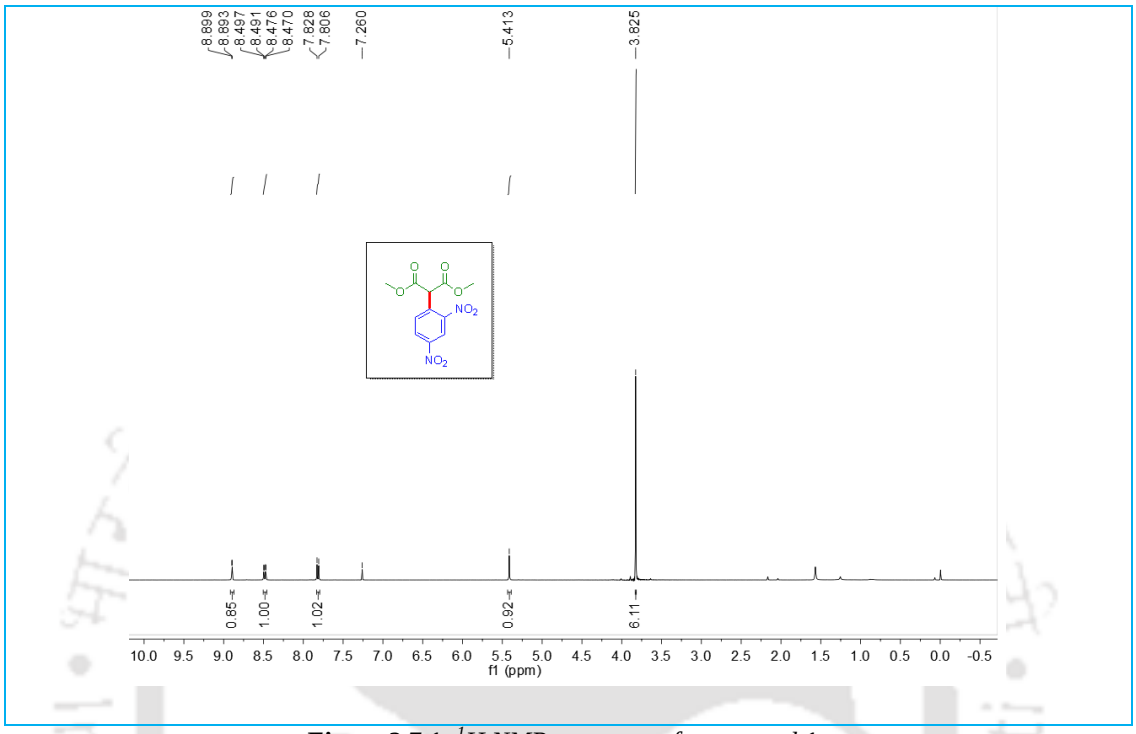


Figure 2.7.1: *^{1}H NMR spectrum of compound* ***1a***

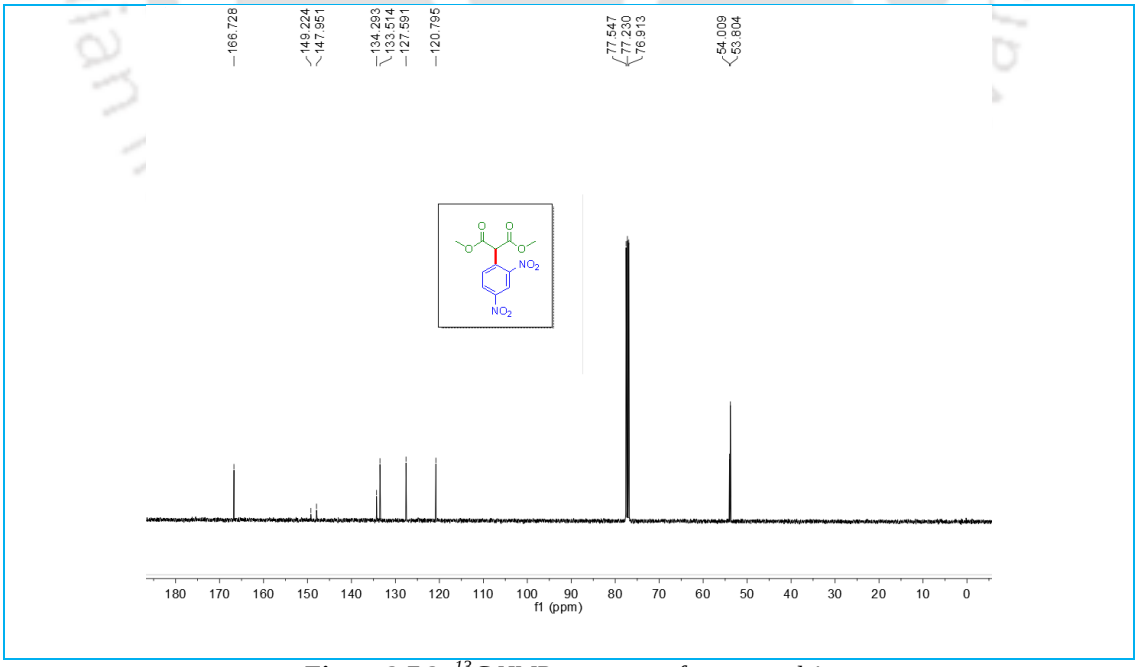


Figure 2.7.2: *^{13}C NMR spectrum of compound* ***1a***

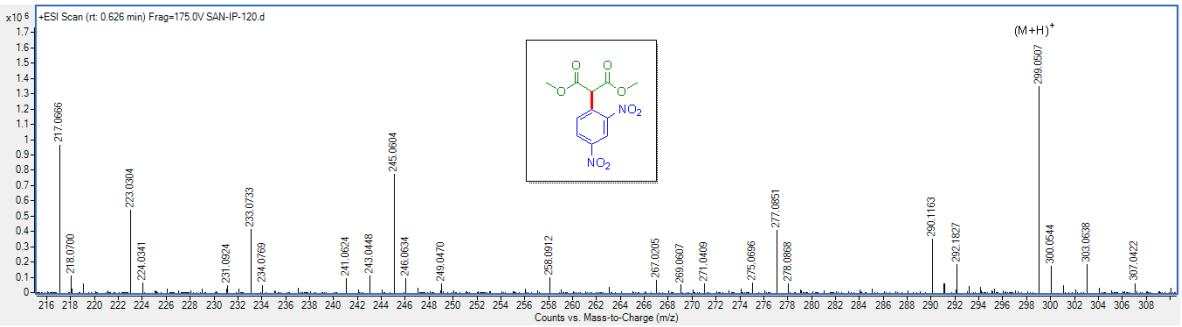


Figure 2.7.3: *HRMS spectrum of compound* ***1a***

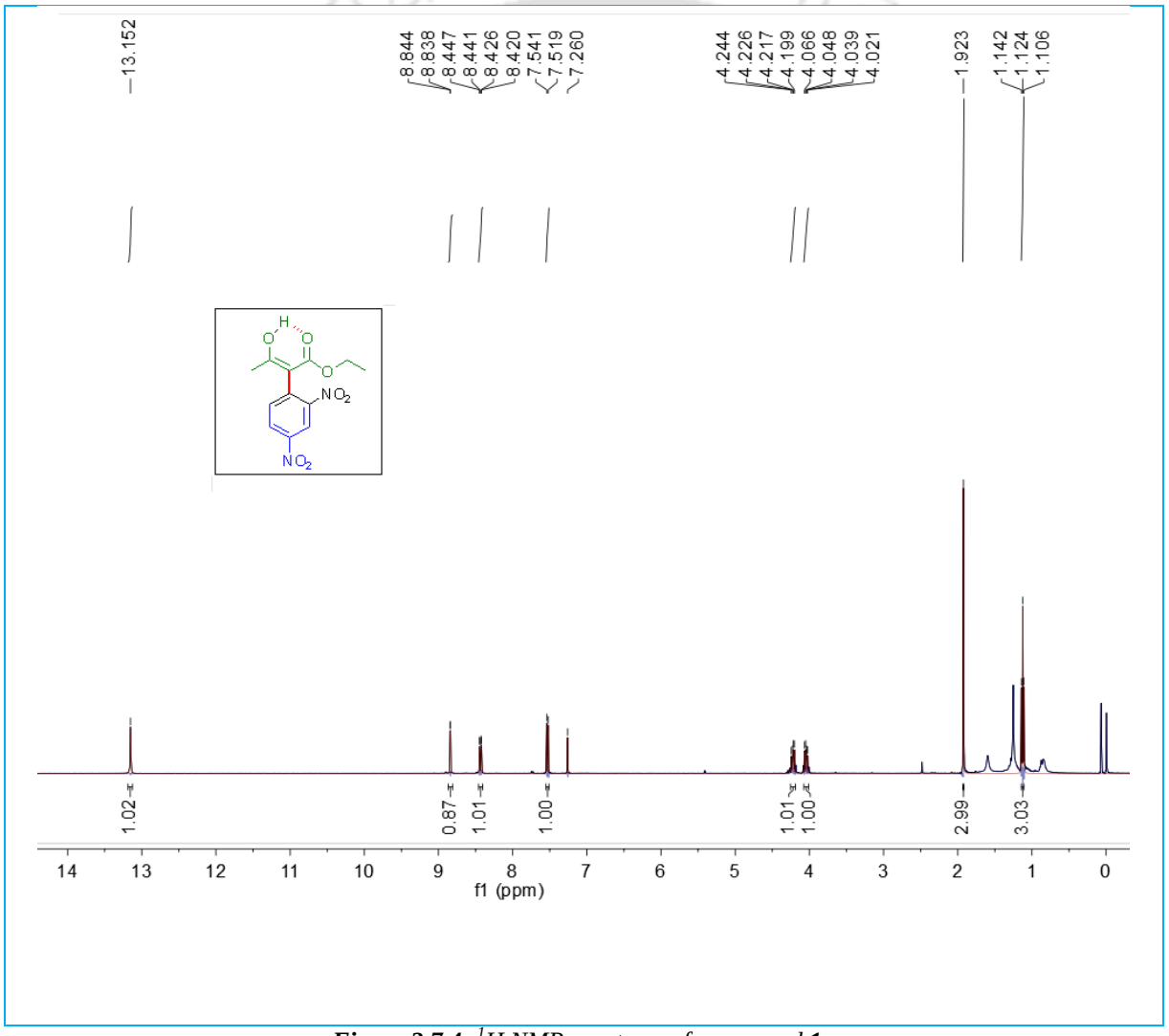


Figure 2.7.4: *^{1}H NMR spectrum of compound* ***1g***

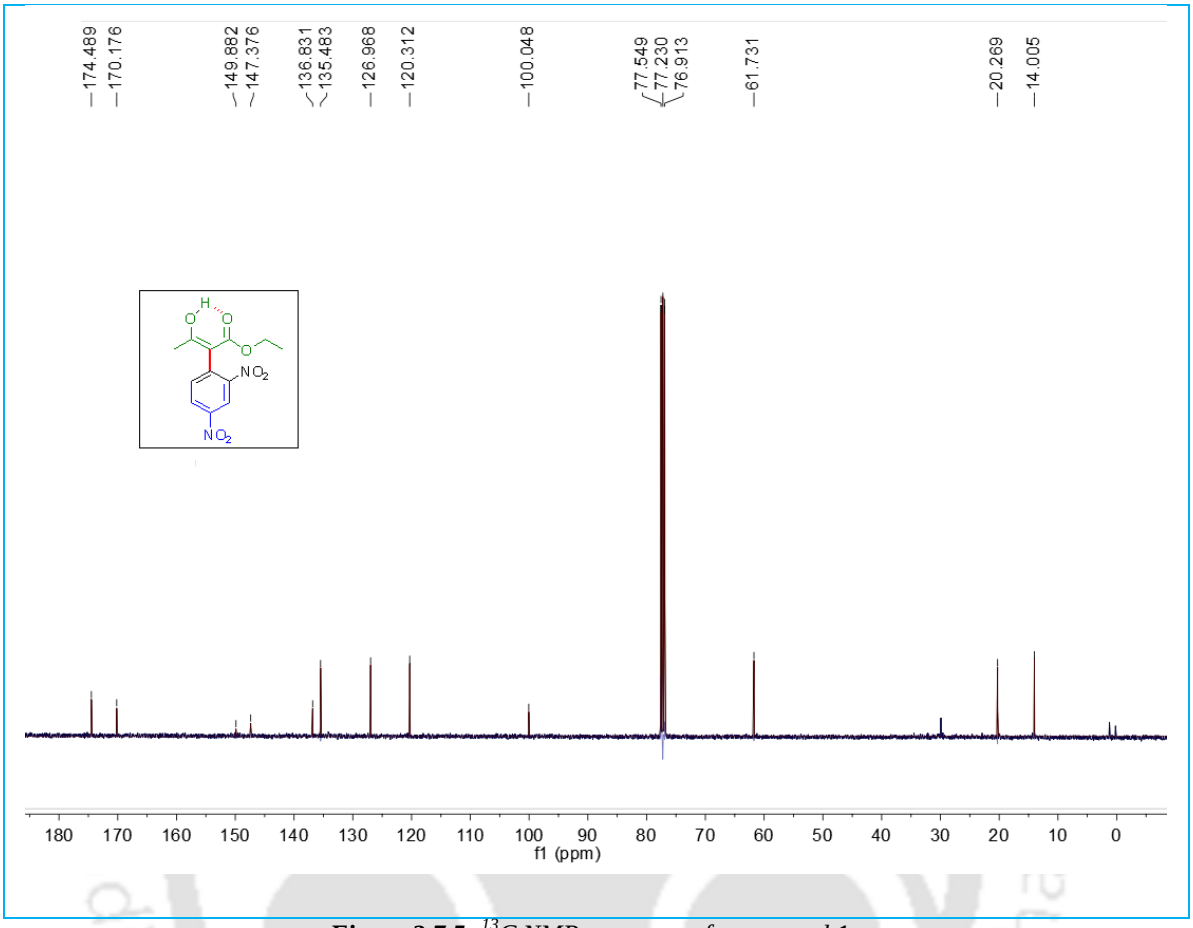


Figure 2.7.5: *^{13}C NMR spectrum of compound* ***1g***

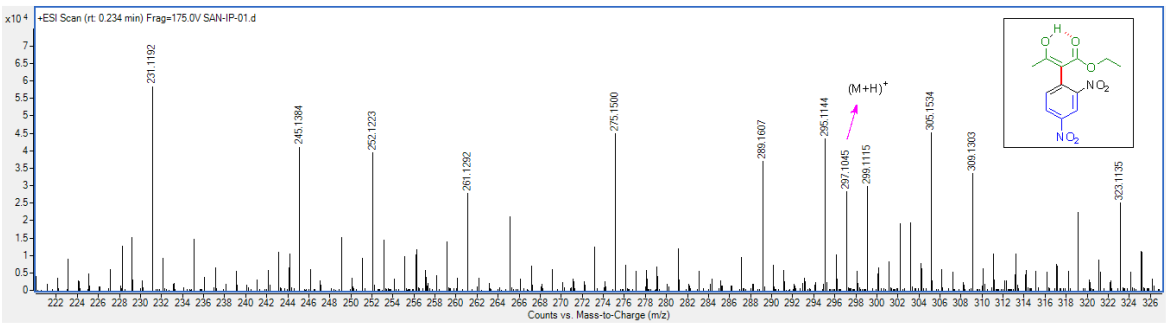


Figure 2.7.6: *HRMS spectrum of compound* ***1g***

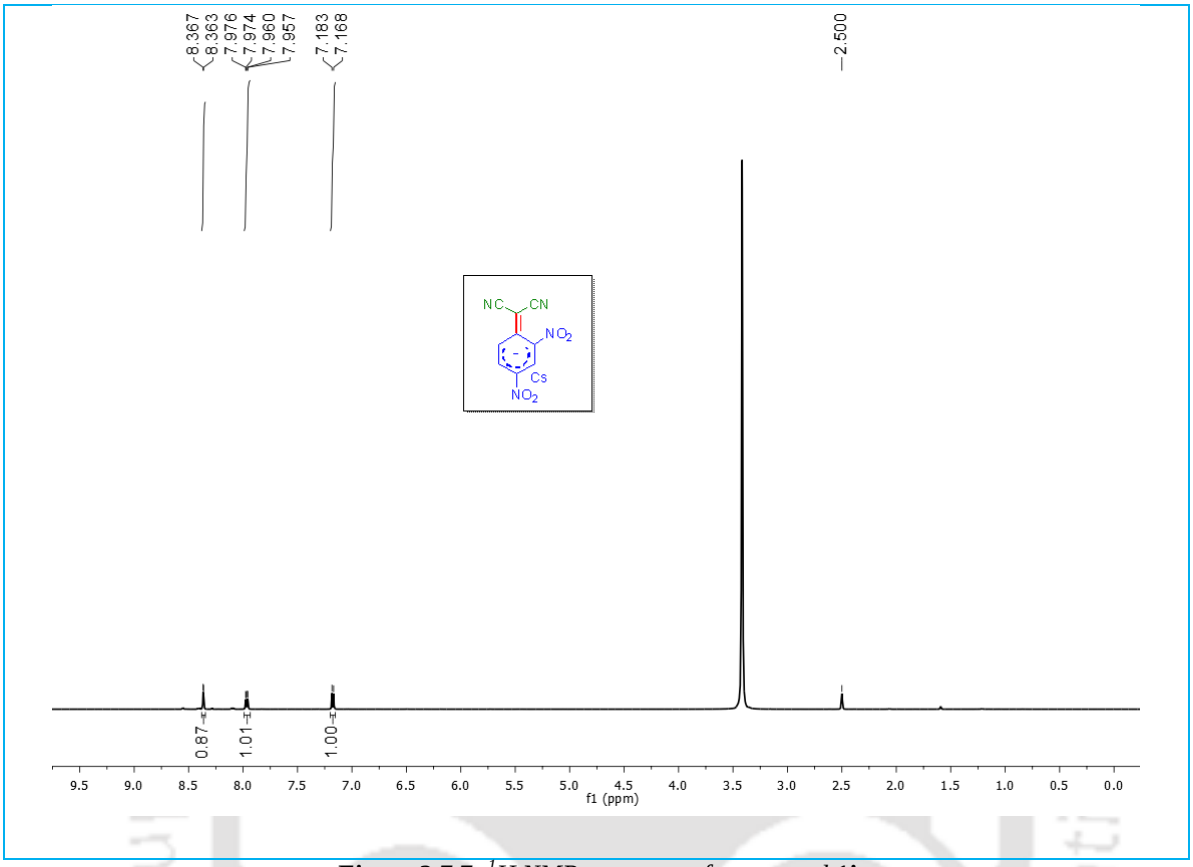


Figure 2.7.7: *^{1}H NMR spectrum of compound* ***1j***

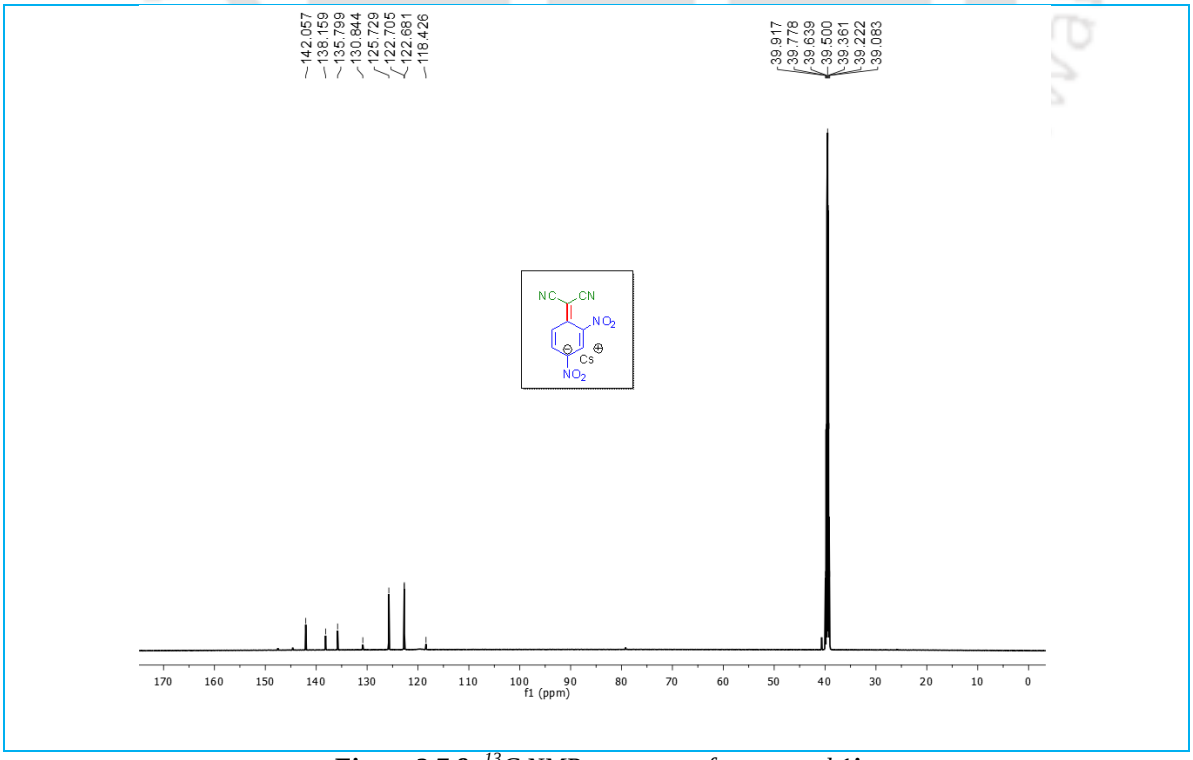


Figure 2.7.8: *^{13}C NMR spectrum of compound* ***1j***

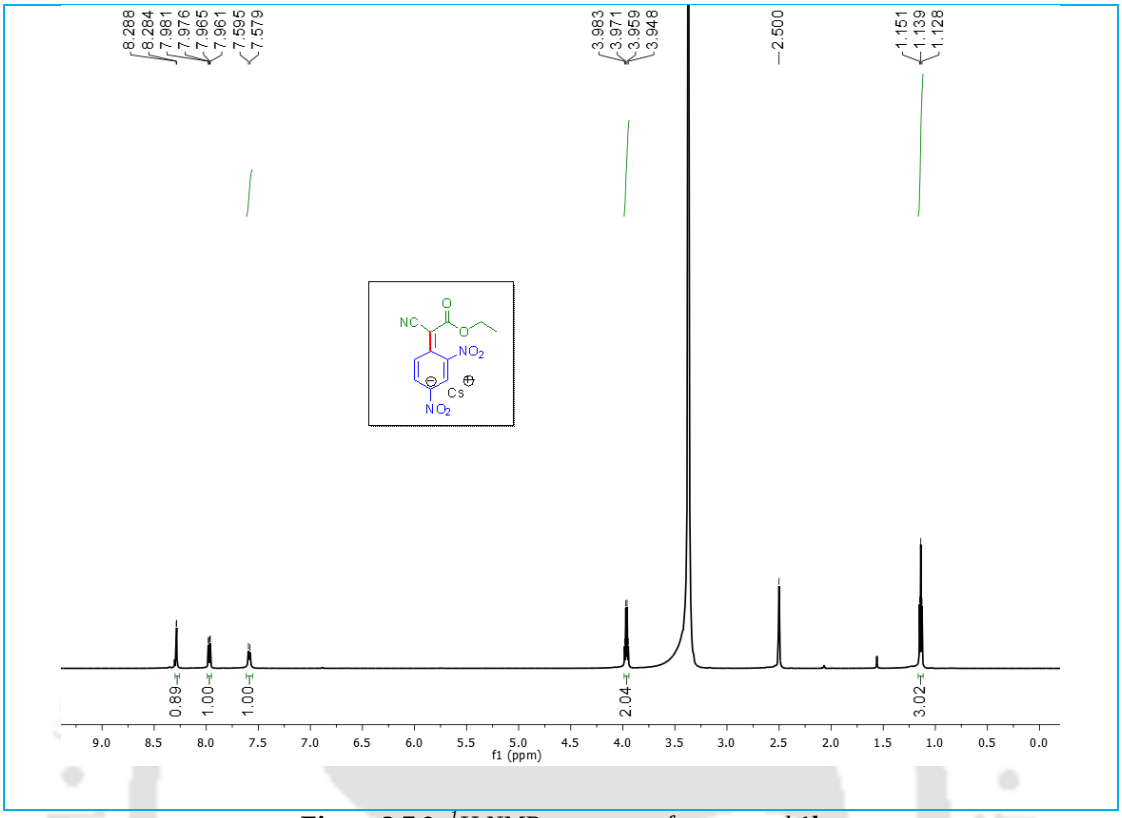


Figure 2.7.9: *^{1}H NMR spectrum of compound* ***1k***

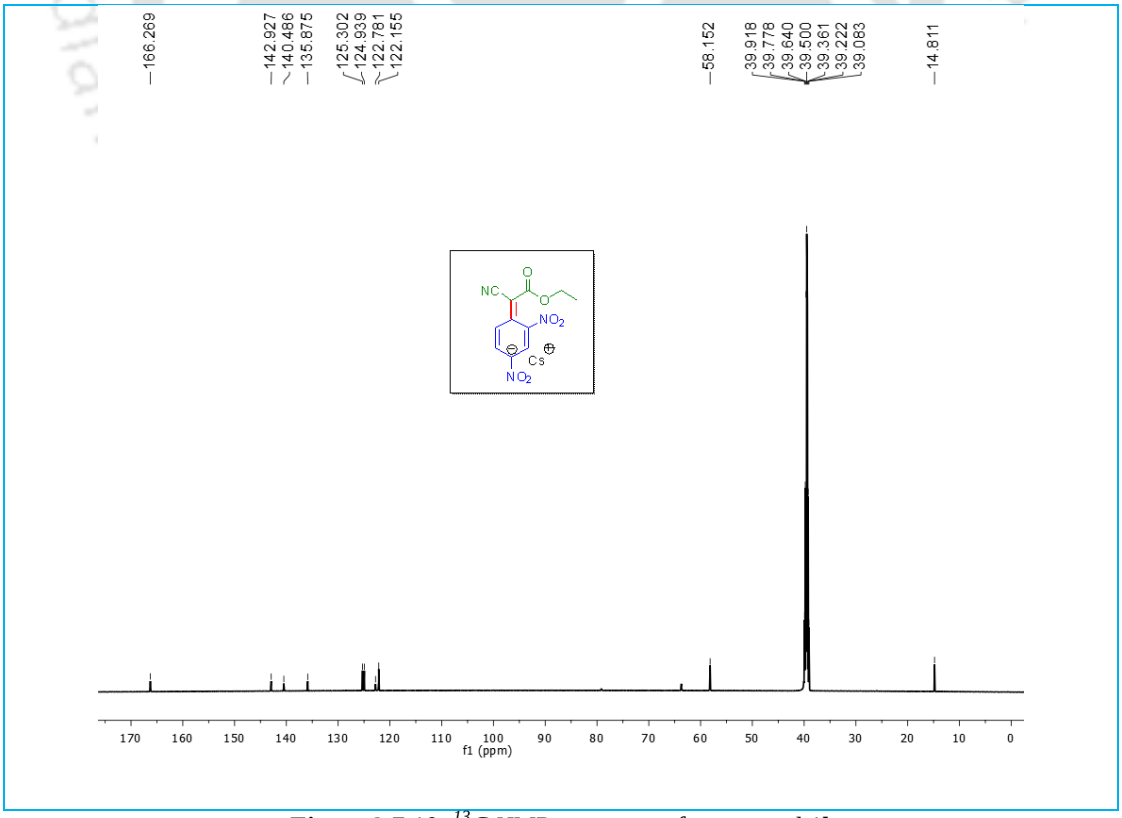


Figure 2.7.10: *^{13}C NMR spectrum of compound* ***1k***

2.8. Crystallographic Data

Compound No.	**1g**	**1j** (with K^+ ion)	**1j** (with Cs^+ ion)
Formula	$C_{12}H_{12}N_2O_7$	$C_9H_3KN_4O_5$	$C_9H_3CsN_4O_4$
CCDC No.	2155058	2155062	2166732
Formula. Wt.	296.24	268.25	364.06
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	P 21/n	P b c a	P 2(1)/c
a (Å)	8.241(7)	7.1133(3)	10.6287(5)
b (Å)	11.471(7)	14.9195(7)	6.8814(4)
c (Å)	14.849(10)	21.9730(8)	15.4115(8)
α(°)	90.00	90.00	90.00
β(°)	101.68(3)	90.00	97.706(2)
γ(°)	90.00	90.00	90.00
V/ $Å^3$	1374.8(17)	2331.93(17)	1117.02(10)
Z	4	8	4
Density/Mgm^{-3}	1.431	1.631	2.165
Abs. Coeff. /mm^{-1}	0.120	0.479	3.328
F(000)	308.0	1152.0	688.0
Total no. of reflections	17703	11364	36347
Reflections, $I > 2\sigma(I)$	0.0523	0.0471	0.0214
Max. 2θ/°	25.000	25.000	24.990
Ranges (h, k, l)	(9,13,17)	(8,17,26)	(12,8,18)
Complete to 2θ (%)	25.000	25.000	24.990
Data/ Restraints/Parameters	2413/0/193	2057/0/184	1961/0/163

Goof (F^2)	0.692	0.602	0.698
R indices [$I > 2\sigma(I)$]	0.0523	0.0471	0.0214
R indices (all data)	0.0740	0.0791	0.0230

2.9. References

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Chapter III

Transition Metal-free C-S Bond Formation via Ipso Nucleophilic Substitution Reaction of Electron-Deficient Benzenesulfonic Acid with Thiol

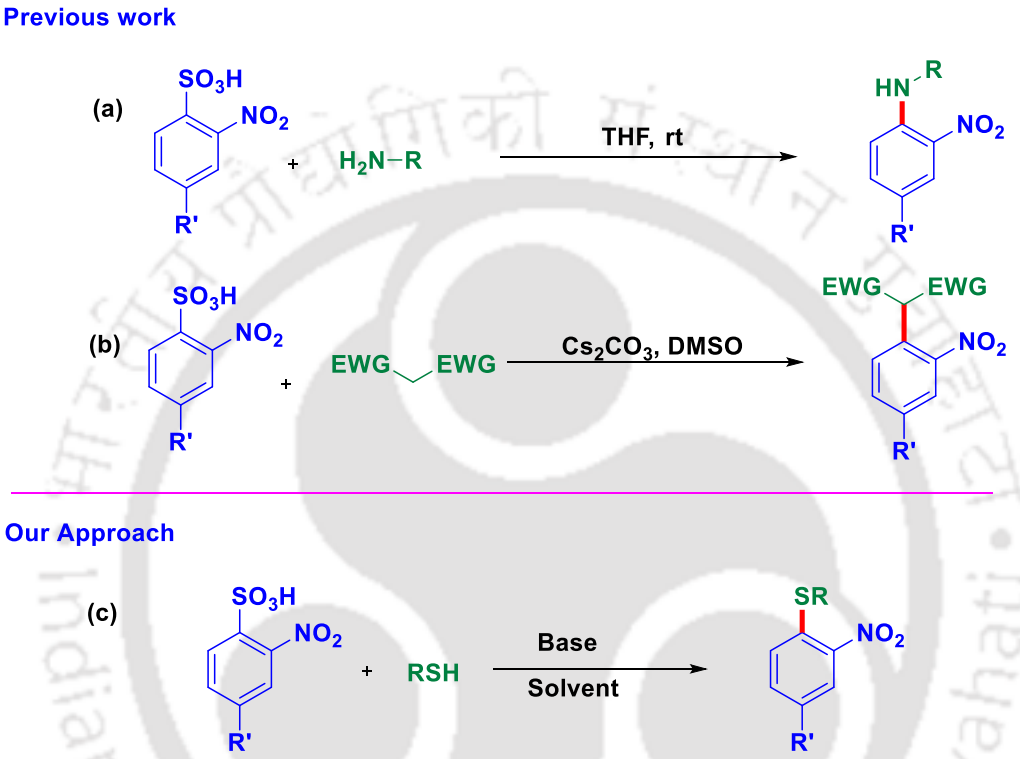
3.1. Introduction

Thioethers are an essential class of reactive species in organic synthesis because of their practical biological and pharmaceutical research applications.[1] It also acts as a reactive intermediate for synthesizing numerous classes of organic synthons. Aromatic nucleophilic substitution is the traditional method to achieve S-alkylation of thiols. The past few decades have witnessed a remarkable development in carbon-heteroatom bond construction.[2,3] Many procedures have been reported for C-N and C-O bond formation. In contrast, for C-S bond formation, it is moderate[4,5] due to the strong affinity of thiols toward catalytic modification and oxidative disulfide formation. We have elaborately described the importance of S-alkylation reactions and their existing procedures with drawbacks in Chapter I.

3.2. Objective

In 2019, Manne *et al.* demonstrated ipso nucleophilic substitution of dinitrobenzene sulfonic acids by amines [Scheme 3.2.1.1a].[6] In Chapter II, we have developed a strategy for the C-alkylation of active methylene compounds on aryl sulfonic acid [Scheme

3.2.1:1b]. Therefore, we were curious to investigate the reactivity of thiols over similar substrates. In this chapter, we describe aryl thioether synthesis using ipso nucleophilic substitution of the same [Scheme 3.2.1:1c].



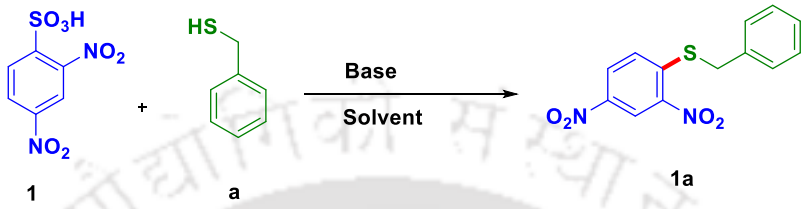
Scheme 3.2.1: *Objective of Chapter III*

3.3. Results and Discussion

3.3.1. Optimization of the Reaction Conditions

Our initial investigation started with 2,4-dinitrobenzene sulfonic acid (1) (1.0 equiv.) and benzyl mercaptan (1.0 equiv.) in the presence of K_2CO_3 (1.0 equiv.) in DMSO at room temperature.

Interestingly, we have isolated a decent amount of desired product (28% yield). Encouraged by this success, we have optimized this protocol using various reaction conditions to improve the yields.



Scheme 3.3.1.1: *Model reaction for optimization of the reaction conditions*

In the presence of base K_2CO_3 (1.0 equiv.), we performed the reaction in DMF, THF, DCE, DCM, 1,4-dioxane, $CHCl_3$, and acetone (entries 2-8). The highest yield of the ipso substituted product was obtained in DCM (entry 5). The product yield increased with the addition of more thiol. For the highest efficiency of this protocol, 1.5 equivalent of thiol is required (entry 10). After that, we screened various inorganic bases, such as Cs_2CO_3, Na_2CO_3, KOH, and K_3PO_4 (entries 12-15); the maximum yield was observed in the presence of K_2CO_3. Furthermore, we observed that product yield enhanced from 55 to 66% upon increasing the amount of K_2CO_3 from 1.0 to 1.5 equivalent (entries 10 and 17). Further increasing the base did not enhance the yield (entry 18). The reaction did not work in the absence of a base. Therefore, base plays a vital role in this S-alkylation reaction. But nitrogenous organic bases DIPEA and trimethylamine did not respond.[19] The product yield did not improve by increasing the temperature from 25 °C to 50 °C. Therefore, the optimized condition of our protocol requires 1.0 equivalent of 2,4-dinitrobenzene sulfonic acid, 1.5 equivalent of thiol (benzyl mercaptan), and 1.5 equivalent of K_2CO_3, and room temperature. Excess thiol (15.0 equivalent) produced a 95% yield in the optimized condition.

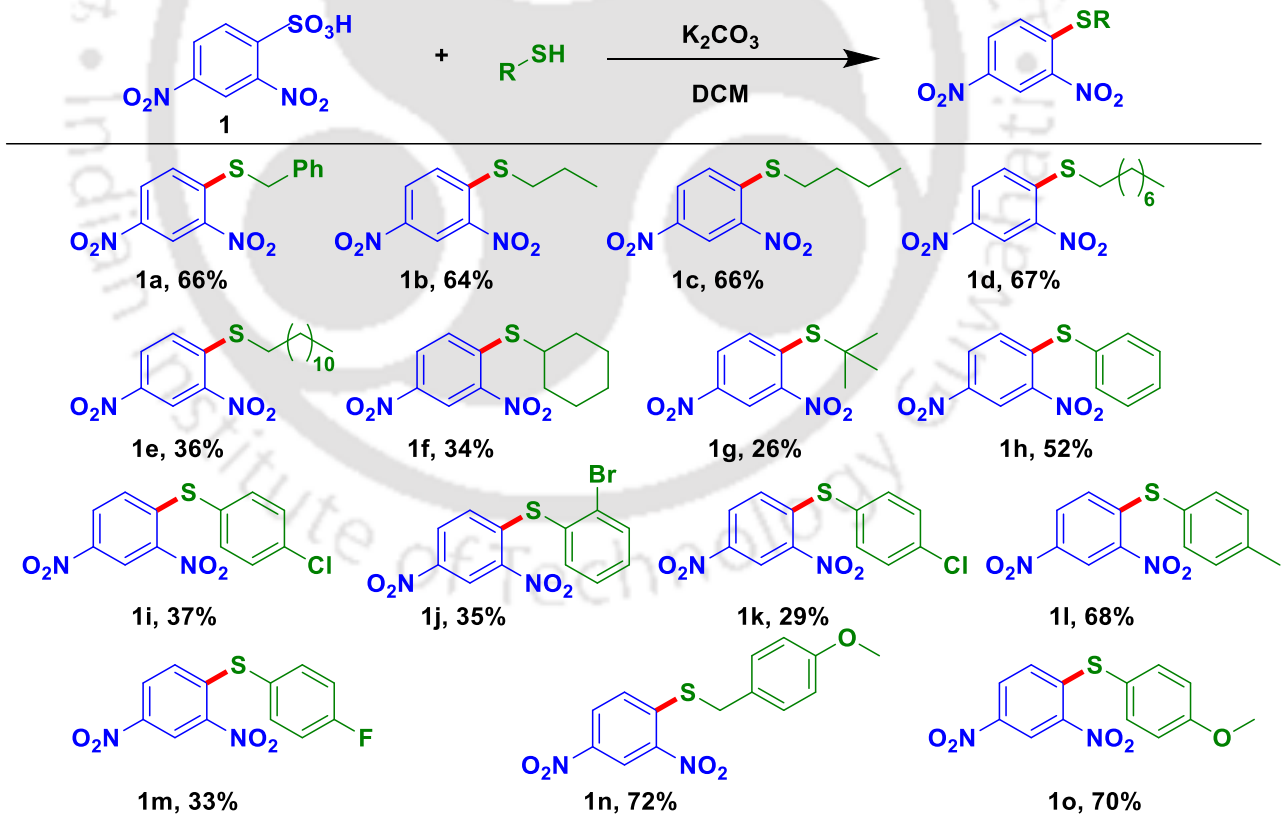
Table 3.3.1: Optimization of Reaction Conditions[a]

Entry	a (equiv.)	Base (equiv.)	Solvent	1a Yield (%)[b]
1	1.0	K_2CO_3 (1.0)	DMSO	28
2	,,	,,	DMF	31
3	,,	,,	THF	45
4	,,	,,	DCE	42
5	,,	,,	DCM	52
6	,,	,,	dioxane	35
7	,,	,,	$CHCl_3$	27
8	,,	,,	acetone	24
9	1.4	,,	DCM	54
10	1.5	,,	,,	55
11	2.0	,,	,,	55
12	1.5	Cs_2CO_3 (1.0)	,,	48
13	,,	Na_2CO_3 (1.0)	,,	22
14	,,	KOH (1.0)	,,	14
15	,,	K_3PO_4 (1.0)	,,	31
16	,,	K_2CO_3 (1.4)	,,	46
17	,,	K_2CO_3 (1.5)	,,	66
18	,,	K_2CO_3 (2.0)	,,	66
19	15	K_2CO_3 (1.5)	,,	95

[a]*2,4-dinitrobenzenesulfonic acid (**1**) (1.0 equiv.), benzyl mercaptan (a, varied amount), and different bases (varied amount) were stirred for 6 hours at room temperature.* [b]*Isolated yield.*

3.3.2. Substrate Scope

To explore the substrate scope, we reacted various thiols with 2,4-dinitrobenzene sulfonic acid (**1**) in optimized conditions (Scheme 3.3.2.1). Aliphatic primary thiols reacted efficiently and produced corresponding desired ipso substituted products (**1a-g**). The percentage yield of the product improved by increasing the chain length from 64 to 67% (**1b-d**). However, a significant drop in the yield was observed with further increasing the aliphatic chain length (**1e**). This is probably due to the increasing steric crowding. In addition, the product yield diminished in the presence of cyclohexyl thiol (**1f**, 34%) and tert-butyl thiol (**1g**, 26%). Various aryl thiols (**1h-o**)

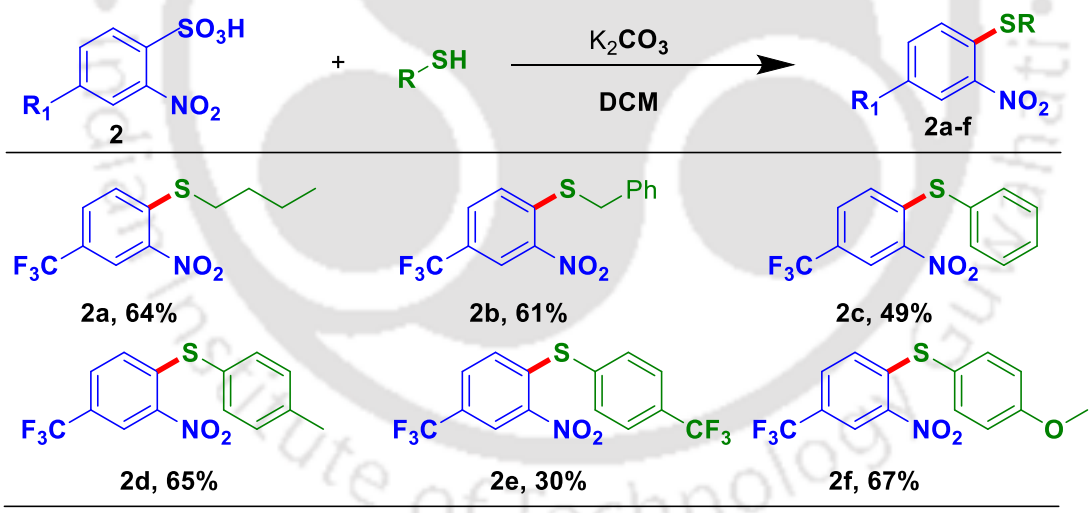


*[a]2,4-dinitrobenzene sulfonic acid (**1**) (1 equiv.), reacted with thiol (1.5 equiv.), K_2CO_3 (1.5 equiv.) at room temperature for 4-6 h, [b] Isolated yield.*

Scheme 3.3.2.1: *Facile aryl-thioether derivatives synthesis from 2,4-dinitrobenzene sulfonic acid[a,b]*

produced reasonable yield. Thiophenol (**1h**) produced 52% product. Adding an electron-withdrawing group (Cl, Br, CF_3, and F) at the benzene ring of the thiol produced 37, 35, 29, and 33% products, respectively. On the addition of the electron-donating groups, –Me and –OMe, the reaction yield increased (**1l, 1n-o**).

To explore the substrate scope further, 2-nitro-4-(trifluoromethyl) benzenesulfonic acid (**2**) was treated with various thiols producing reasonable yields. Here as well, the effect of electron-withdrawing and donating groups was similar. In the first case, product formation decreased to 30% (**2e**); in the second case (**2d** and **2f**), yields increased to 65 and 67%, respectively. However, aryl sulfonic acids with one nitro group or without a nitro group did not respond to this methodology.

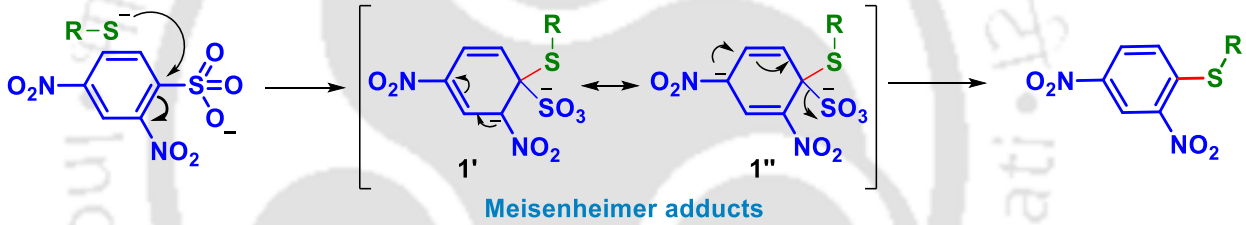


[a]2-nitro-4-(trifluoromethyl) benzenesulfonic acid (1 equiv.), reacted with various thiols (1.5 equiv.), K_2CO_3 (1.5 equiv.) at room temperature, 4-6 h, [b]Yields after column chromatography.

Scheme 3.3.2.2: *Facile arylthioether synthesis using 2-nitro-4-(trifluoromethyl) benzenesulfonic acid and various thiols[a,b]*

3.3.3. Mechanism

Based on the established literature, a plausible reaction mechanism for the S-alkylation of thiols on 2,4-dinitrobenzene sulfonic acid has been illustrated (Scheme 3.3.3.1).[7] Initially, thiolate ions were generated and attacked to the ipso position of 2,4-dinitrobenzene sulfonate ions to form Meisenheimer adducts (**1′** and **1″**).[8] This Meisenheimer adduct is resonance stabilized through a robust electron-withdrawing group in the benzene ring. The *ortho* effect also stabilized this reactive intermediate.[9] Finally, it gives rise to our desired product. Mąkosza *et al*. have explored the possibility of hydrogen displacement by thiolate ion.[10] However, we could not find any related product to date.

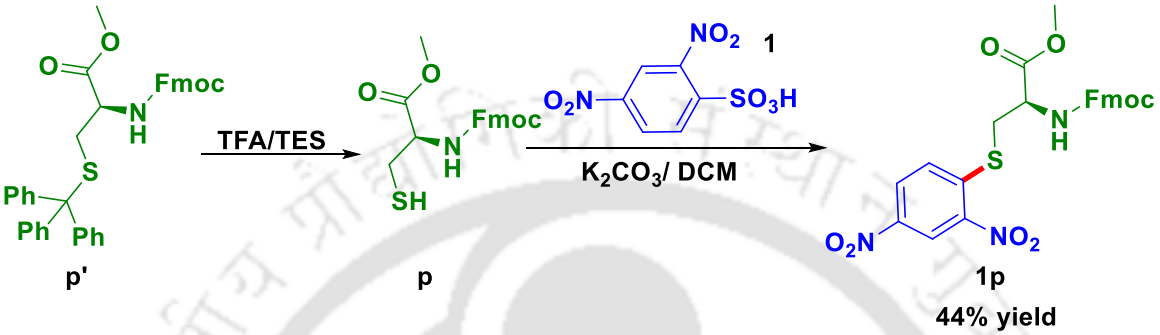


Scheme 3.3.3.1: *Established literature-based plausible reaction mechanism*

3.3.4. Applications

2,4-dinitrobenzene moiety is crucial for glutathione-mediated human metabolism as it easily gets attached to the cysteine side chain of glutathione by enzymatic reactions in the human body and produces 2,4-dinitrophenyl cysteine (DNPC).[11] DNPC is also used as a colorimetric sensor for Cu^{2+} detection.[12] DNPC can be easily incorporated into a peptide for chemical biology applications as a FRET partner.[22] Dinitro phenyl (DNP) core can be detcted using several fluoresence techniques, such as laser-induced fluoresence (LIF), etc. The modified cysteine i.e 2,4-dinitrophenyl cysteine (DNPC) can be use as a peptide residue for peptide lebelling. Generally, fluorescently labeled peptides are used for *in vivo*

biomedical imaging, localization studies, and protein binding. Fluorochrome-conjugated peptides can be visualized by fluorescence microscopy or other fluorescence visualization techniques. We could easily prepare protected DNPC (**1p)** using our methodology.



Scheme 3.3.4.1: *Side chain modification of cysteine*

The crude product of the reaction was purified by column chromatography technique using 5-12 % EtOAc/ hexane. The purity of sample **1p** was checked with RP-HPLC on Thermo Scientific analytical system, using C18 analytical column at a flow rate of 1 mL/min for a total run time of 15 min using a linear gradient of 5-95% ACN for 13 min, followed by 100% ACN for next 2 min, with the UV detector set at 214 and 254 nm. The chromatogram appeared with a single peak (Figure 3.3.4.2), and the collected sample was used for HRMS. We have obtained HRMS (Figure 3.3.4.3) corresponding to $[M(\mathbf{1p})+Na]^+$ and $[M(\mathbf{1p})+K]^+$.

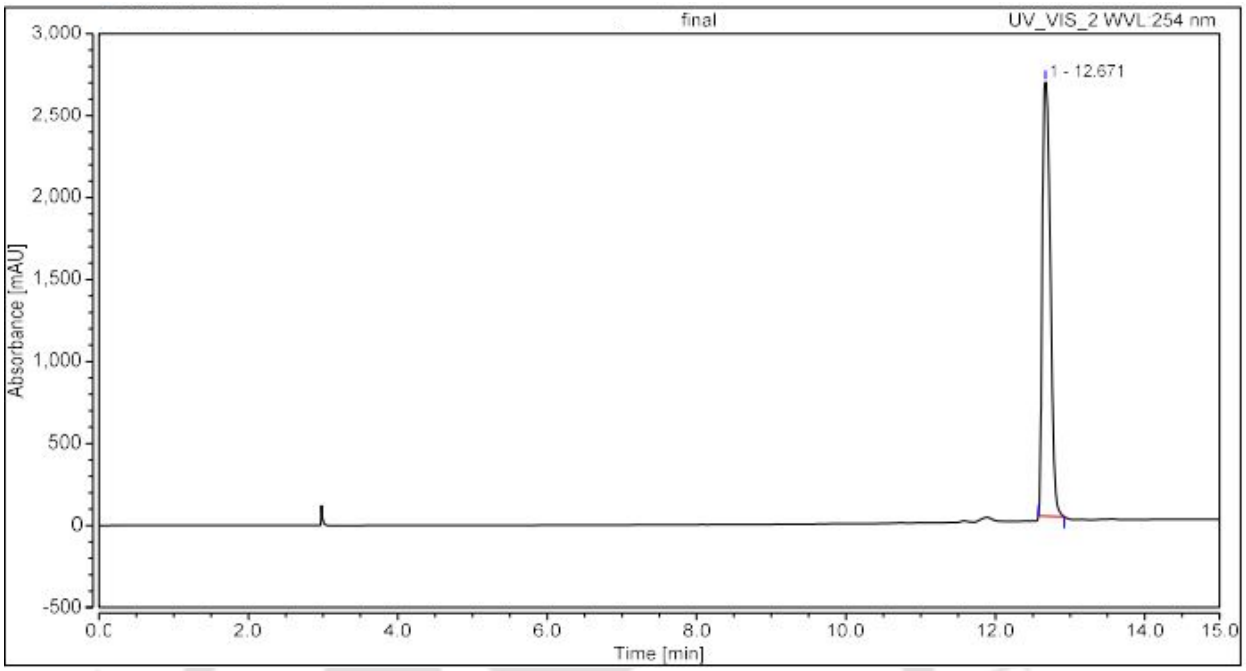


Figure 3.3.4.2: *HPLC profile of the final product (**1p**)*

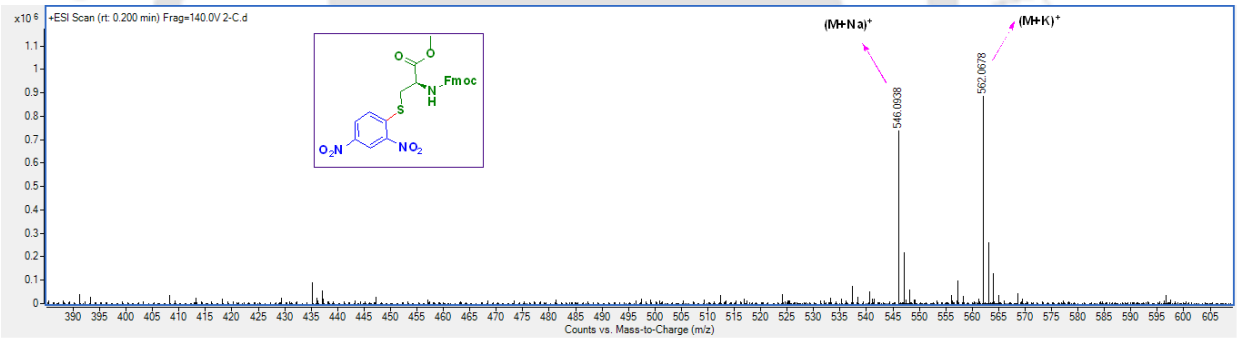
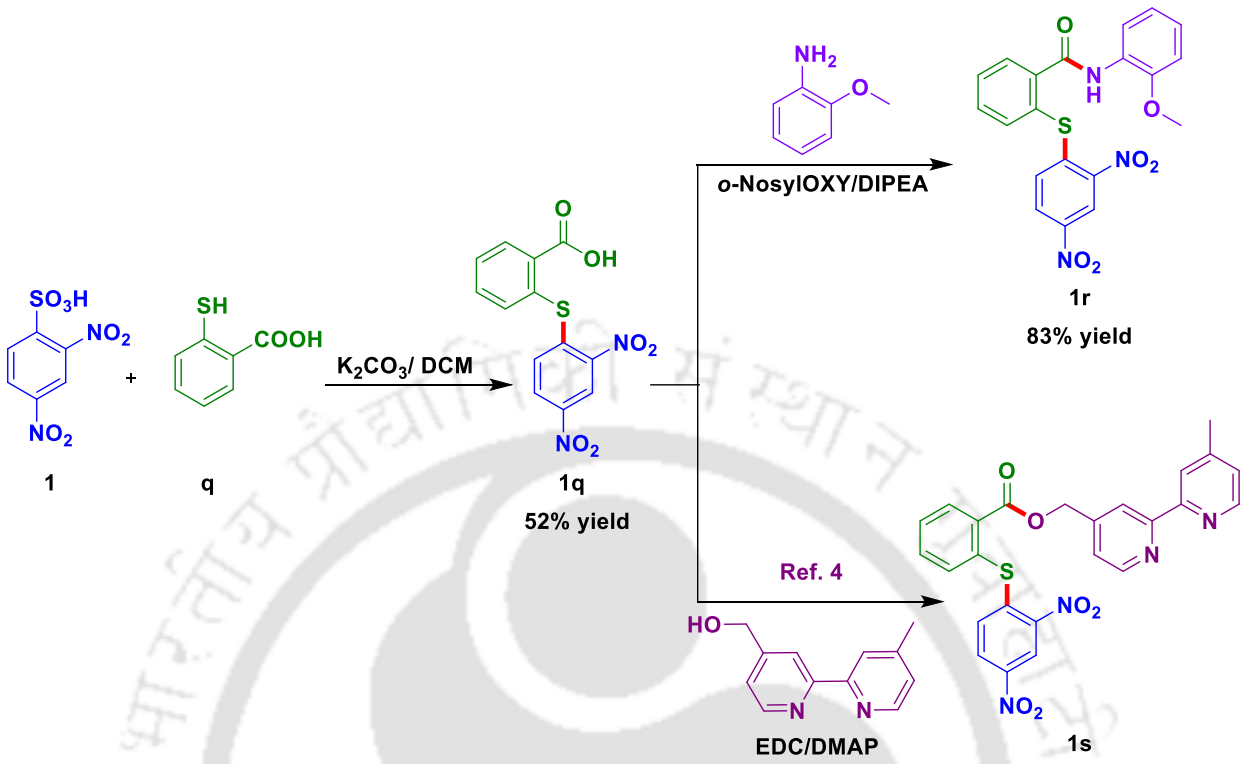


Figure 3.3.4.3: *HRMS spectra of the final product (**1p**)*

	Calculated	**Found**
[M(**1p**)+Na]$^+$	546.0942	546.0938
[M(**1p**)+K]$^+$	562.0681	562.0678

The current methodology is also helpful in synthesizing biologically or pharmaceutically active compounds. For example, **RN-18** analogs (**1r**) are efficient HIV-1 inhibitors.[13] We needed to synthesize the dinitro analog of **RN-18** for our ongoing research. We could achieve it from the benchtop reagent 2,4-dinitrobenzene sulfonic acid in the following way (Scheme 3.3.4.2). Similarly, MMB complex (**1s**) can be achieved via **1q**.



Scheme 3.3.4.2: *Synthesis route of API RN-18 analog (**1r**) and MMB complex (**1s**)*

First, this salicylic acid (**q**) produced an ipso substituted product (**1q**, 52% yield) from 2,4-dinitrobenzene sulfonic acid (**1**). Followed by the amidation of this thiolated product (**1q**) by *o*-anisidine with the assistance of a peptide coupling reagent *o*-NosylOXY,[23] we successfully obtained 83% yield of our targeted dinitro **RN-18** analog.

3.4. Conclusion

In conclusion, we have successfully developed a cost-effective method for constructing a C-S bond via ipso nucleophilic substitution reaction without any expensive and toxic transition metal catalysts. The main benefits of this protocol include a relatively short reaction time, reasonable yields, and less complexity in terms of operation. No any acidic

hydrogen halide (HX) byproduct formation occurs in this protocol unlike the case of halogen leaving group containing reagent. Moreover, this reaction is beneficial for the synthesis of biologically important molecules. Side chain modification on cysteine and API syntheses is demonstrated as an application of this methodology.

3.5. Experimental Section

General Information

All reagents were purchased from commercial sources. NMR spectra were recorded on 400 and 600 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) were reported in ppm, and spin-spin coupling constants (J) were given in Hz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), and m (multiplet). $^{13}C\{^{1}H\}$ indicates the proton decoupled NMR experiment. Reactions were monitored using thin-layer chromatography with silica gel G254. The reaction products were purified by column chromatography using silica gel (60-120 mesh) using eluent EtOAc/hexane. Solvents were removed under reduced pressure using a Buchi rotary evaporator. Melting points were determined using a dedicated melting point measuring apparatus, and FT-IR spectra were recorded on an FT-IR spectrometer.

General procedure for the synthesis of aryl thioether products

Thiol (0.75 mmol) was taken in DCM solvent (2 mL), and K_2CO_3 (0.75 mmol) was added to it. The mixture was stirred at room temperature for 10 minutes and then aryl sulfonic

acid (0.5 mmol) was added. The progress of the reaction was monitored by TLC. After completion of the reaction, DCM was evaporated, and ethyl acetate (10 mL) was added to it. Then the mixture was washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 1.0-5.0% EtOAc/hexane.

Procedure for compound 3a using excess benzyl mercaptan

Benzyl mercaptan (7.5 mmol) was taken in DCM solvent (5 mL), and K_2CO_3 (1.0 mmol) was added to it. The mixture was stirred at room temperature for 10 minutes, and then aryl sulfonic acid (0.5 mmol) was added. The progress of the reaction was monitored by TLC. After completion of the reaction, DCM was evaporated, and ethyl acetate (10 mL) was added to it. Then the mixture was washed with 5% HCl (2×10 mL), 5% $NaHCO_3$ (2×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 2-3% EtOAc/hexane.

Removal of the trityl group of cysteine

Protected L-cysteine (**p'**) (0.5 mmol) was taken in a 50 mL RB, and 7 mL of trifluoroacetic acid (TFA) was added slowly. To this mixture, 0.5 mL of triethylsilane (TES) was added and stirred at room temperature for 2 hours. After completion of the reaction, TFA was removed and washed with diethyl ether. Finally, the desired product was purified by column chromatography using 5-10% EtOAc/hexane solution.

Synthesis of compound 1p

Fmoc-L-cysteine methyl ester (**p**) (1.0 mmol) was taken in DCM solvent (5 mL), and K_2CO_3 (1.0 mmol) was added to it. The mixture was stirred at room temperature for 10 minutes, and then 2,4-dinitrobenzene sulfonic acid (0.5 mmol) was added. The progress of the reaction was monitored by TLC. After the reaction was completed (8 h), DCM was evaporated, and ethyl acetate (10 mL) was added to it. Then the mixture was washed with 5% HCl (2×10 mL) and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 5-12% EtOAc/hexane.

Synthesis of compound 1q

Thio salicylic acid (1.0 mmol) and K_2CO_3 (1.0 mmol) were taken in a 50 mL round bottom flask in DCM (4 mL). Stir the mixture for 10 min at room temperature, and then 2,4-dinitrobenzene sulfonic acid (0.5 mmol) was added to it. The reaction was monitored by TLC using 70% EtOAc/ Hexane solution. After 3 hours, the reaction mixture becomes dark yellow. Continue the reaction until complete consumption of starting materials (6 h). After the reaction, DCM was evaporated using a rotary evaporator, and EtOH (10 mL) was added to the mixture. Then the solution was filtered and concentrated by evaporating the ethanol. Now, 50 mL 5N HCl was added to this mixture, which gave rise to yellow precipitation. Collect this precipitate and wash it several times with diethyl ether.

Synthesis of compound 1r

In a 50 ml round bottom flask, **1q** (0.25 mmol) was taken along with *o*-NosylOXY (0.5 mmol) and DIPEA (1.0 mmol) in DMF. The mixture was stirred for 30 min at room

temperature, and then *o*-anisidine (0.5 mmol) was added. The reaction continued for 12 h. After completion of the reaction, the reaction mixture was diluted with 10 mL ethyl acetate and poured into a separating funnel containing ice-cold water. Then the organic layer was separated and again washed with ice-cold water (3 times). EtOAc was added to the combined aqueous layers and fractionated twice. The accumulated organic layer was washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. The product was purified by column chromatography using 10-15% EtOAc/ hexane solution.

3.6. Characterization Data

Benzyl(2,4-dinitrophenyl)sulfane (1a)[14]

As a yellow solid (96 mg, 66% yield, mp 126-128 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.08 (d, 1H, J = 2.8 Hz), 8.33 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.62 (d, 1H, J = 8.8 Hz), 7.44-7.33 (m, 5H), 4.30 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 147.1, 144.8, 144.1, 133.7, 129.3, 129.2, 128.5, 127.4, 127.3, 121.9, 37.9; IR (KBr, cm^{-1}): 3101, 2922, 2851, 1581, 1509, 1369, 1302, 1234, 1130, 1091, 832, 734.

(2,4-Dinitrophenyl)(propyl)sulfane (1b)[15]

As a yellow solid (79 mg, 64% yield, mp 92-94 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.07 (d, 1H, J = 2.4 Hz), 8.35 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.0 Hz), 7.56 (d, 1H, J = 9.2 Hz), 3.03 (t, 2H, J = 7.4 Hz), 1.88-1.79 (m, 2H), 1.14 (t, 3H, J = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 147.7,

143.8, 127.2, 127.0, 124.6, 121.9, 34.8, 21.2, 13.9; IR (KBr, cm^{-1}): 3122, 2965, 2929, 2872, 1586, 1504, 1463, 1339, 1303, 1052, 833; ESI (m/z) calcd for $C_9H_{10}N_2O_4SNa$ $[M + Na]^+$ 265.02; found 265.00.

Butyl(2,4-dinitrophenyl)sulfane (1c)[16]

As a yellow solid (85 mg, 66% yield, mp 67-68 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.06 (d, 1H, J = 2.4 Hz), 8.35 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.56 (d, 1H, J = 9.2 Hz), 3.04 (t, 2H, J = 7.4 Hz), 1.81-1.74 (m, 2H), 1.58-1.50 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 147.8, 144.9, 143.8, 127.2, 127.0, 121.9, 32.6, 29.6, 22.4, 13.8; IR (KBr, cm^{-1}): 3126, 3092, 2960, 2929, 2857, 1583, 1513, 1466, 1344, 1254, 1154, 1100, 918, 833.

(2,4-Dinitrophenyl)(octyl)sulfane (1d)[16]

As a yellow solid (105 mg, 67% yield, mp 74-76 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.08 (d, 1H, J = 2.4 Hz), 8.36 (dd, 1H, J_1 = 2.6 Hz, J_2 = 9.0 Hz), 7.55 (d, 1H, J = 8.8 Hz), 3.04 (t, 2H, J = 7.4 Hz), 1.83-1.75 (m, 2H), 1.55-1.48 (m, 2H), 1.35-1.24 (m, 8H), 0.88 (t, 3H, J = 6.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 147.8, 144.9, 143.8, 127.2, 127.0, 121.9, 32.9, 31.9, 29.29, 29.26, 29.2, 27.7, 22.8, 14.3; IR (KBr, cm^{-1}): 3121, 3088, 2955, 2917, 2856, 1599, 1586, 1517, 1369, 1341, 1104, 733.

(2,4-Dinitrophenyl)(dodecyl)sulfane (1e)[17]

As a yellow powder (66 mg, 36% yield, mp 84-86 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.08 (d, 1H, J = 2.8

Hz), 8.36 (dd, 1H, J_1 = 2.6 Hz, J_2 = 9.0 Hz), 7.55 (d, 1H, J = 8.8 Hz), 3.04 (t, 2H, J = 7.4 Hz), 1.83-1.75 (m, 2H), 1.55-1.48 (m, 2H), 1.35-1.25 (m, 16H), 0.88 (t, 3H, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 147.8, 145.0, 143.8, 127.2, 127.0, 121.9, 32.9, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 27.7, 22.9, 14.3; IR (KBr, cm^{-1}): 3120, 3087, 2954, 2915, 2851, 1586, 1517, 1471, 1103, 733; ESI (m/z) calcd for $C_{18}H_{31}N_3O_4S$ $[M + NH_3]^+$ 385.20; found 385.18.

Cyclohexyl(2,4-dinitrophenyl)sulfane (1f)[18]

As a yellow crystalline (48 mg, 34% yield, mp 142-144 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.03 (d, 1H, J = 2.4 Hz), 8.34 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.59 (d, 1H, J = 8.8 Hz), 3.43-3.39 (m, 1H), 2.13-2.09 (m, 2H), 1.89-1.86 (m, 2H), 1.74-1.69 (m, 1H), 1.58-1.45 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 146.4, 145.6, 143.8, 127.7, 126.9, 122.0, 44.6, 32.4, 26.1, 25.7; IR (KBr, cm^{-1}): 3117, 3102, 2937, 2851, 1593, 1525, 1505, 1334, 1131, 1050, 737; ESI (m/z) calcd for $C_{12}H_{16}N_2O_4S$ $[M + 2H]^+$ 284.08; found 284.10.

***tert*-Butyl(2,4-dinitrophenyl)sulfane (1g)[15]**

As a yellow sticky (34 mg, 26% yield); Purification over a column of silica gel (2-3% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, 1H, J = 2.4 Hz), 8.33 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.91 (d, 1H, J = 8.8 Hz), 1.48 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 151.9, 146.0, 140.0, 135.4, 125.5, 120.1, 49.9, 31.4; IR (KBr, cm^{-1}): 2952, 2922, 2852, 1632, 1457, 1384, 1336, 1108, 879.

(2,4-Dinitrophenyl)(phenyl)sulfane (1h)[19]

As a yellow powder (72 mg, 52% yield, mp 114-117 °C); Purification over a column of silica gel (0.5-1.0% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.09 (d, 1H, J = 2.4 Hz), 8.12 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.61-7.55 (m, 5H), 6.99 (d, 1H, J = 9.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 148.6, 146.5, 144.5, 136.1, 131.3, 130.9, 129.3, 129.0, 127.1, 121.6; IR (KBr, cm^{-1}): 3102, 2961, 2922, 2852, 1588, 1513, 1334, 1299, 1048, 831, 733.

(4-Chlorophenyl)(2,4-dinitrophenyl)sulfane (1i)[19]

As a yellow solid (58 mg, 37% yield, mp 120-122 °C); Purification over a column of silica gel (0.5-1.0% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.10 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.54 (s, 4H), 6.99 (d, 1H, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 147.8, 144.7, 144.1, 138.0, 137.4, 131.2, 128.9, 127.7, 127.2, 121.7; IR (KBr, cm^{-1}): 3104, 2957, 2923, 2852, 1596, 1506, 1474, 1360, 1341, 1090, 834, 735.

(2-Bromophenyl)(2,4-dinitrophenyl)sulfane (1j)[20]

As a yellow solid (62 mg, 35% yield, mp 60-62 °C); Purification over a column of silica gel (0.5-1.0% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.14 (d, 1H, J = 2.4 Hz), 8.17 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.84 (dd, 1H, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 7.77 (dd, 1H, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 7.53-7.44 (m, 2H), 6.88 (d, 1H, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 146.3, 144.8, 144.1, 138.4, 134.9, 133.0, 131.3, 130.6, 129.6, 128.6, 127.3, 121.9; IR (KBr, cm^{-1}): 2959, 2923, 2853, 1625, 1559, 1449, 1427, 1384, 1257, 1043, 739; ESI (m/z) calcd for $C_{12}H_7BrN_2O_4SK$ $[M + K]^+$ 392.89; found 392.12.

(2,4-Dinitrophenyl)(4-(trifluoromethyl) phenyl) sulfane (1k)

As a yellow sticky (50 mg, 29% yield); Purification over a column of silica gel (0.5-1.0% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.12 (d, 1H, J = 2.8 Hz), 8.18 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.83-7.74 (m, 4H), 6.99 (d, 1H, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 146.7, 144.9, 136.4, 134.2, 133.5, 133.1, 129.1, 127.7 (q, J = 3.6 Hz), 127.4, 122.3, 121.8; ^{19}F NMR ($CDCl_3$): δ -63.0 (s); IR (KBr, cm^{-1}): 3106, 2950, 2924, 2866, 1595, 1525, 1341, 1322, 1169, 1129, 833, 735; ESI (m/z) calcd for $C_{13}H_{10}F_3N_3O_4S$ $[M + NH_3]^+$ 361.03, found 361.17.

(2,4-Dinitrophenyl)(*p*-tolyl)sulfane (1l)[19]

As a yellow powder (99 mg, 68% yield, mp 99-100 °C); Purification over a column of silica gel (0.5-1.0% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.08 (d, 1H, J = 2.4 Hz), 8.11 (dd, 1H, J_1 = 2.6 Hz, J_2 = 9.0 Hz), 7.46 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.0 Hz), 6.99 (d, 1H, J = 8.8 Hz), 2.46 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 149.2, 144.4, 143.9, 141.9, 136.0, 131.7, 128.9, 126.9, 125.6, 121.6, 21.7; IR (KBr, cm^{-1}): 3108, 2961, 2923, 2852, 1739, 1584, 1508, 1448, 1331, 1297, 1048, 831, 731.

(2,4-Dinitrophenyl)(4-fluorophenyl)sulfane (1m)[20]

As a yellow crystalline (49 mg, 33% yield, mp 136-137 °C); Purification over a column of silica gel (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.11 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.62-7.58 (m, 2H), 7.28-7.24 (m, 2H), 6.97 (d, 1H, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 165.9, 163.4, 148.3, 144.4 (d, J = 55 Hz), 138.4 (d, J = 8.6 Hz), 128.8, 127.2, 124.6 (d, J = 3.7 Hz), 121.7, 118.4 (d, J = 22.0 Hz); ^{19}F NMR ($CDCl_3$): δ -107.6 (s); IR (KBr, cm^{-1}): 3118, 2957, 2922, 2852, 1747, 1590, 1487, 1331, 1227, 831, 733.

(2,4-dinitrophenyl)(4-methoxybenzyl)sulfane (1n)

As a yellow solid (141 mg, 72% yield, mp 99 °C); Purification over a column of silica gel (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.07 (d, 1H, J = 2.4 Hz), 8.33 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 7.62 (d, 1H, J = 8.8 Hz), 7.34 (d, 2H, J = 8.4 Hz), 6.89 (d, 2H, J = 8.8 Hz), 4.25 (s, 3H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 159.8, 147.3, 144.8, 144.1, 130.5, 127.35, 127.30, 125.3, 121.9, 114.7, 55.5, 37.5; IR (KBr, cm^{-1}): 3090, 2960, 2921, 2837, 1587, 1510, 1471, 1335, 1250, 823, 734; ESI (m/z) calcd for $C_{14}H_{15}N_3O_5S$ $[M + NH_3]^+$ 337.07, found 337.19.

(2,4-Dinitrophenyl)(4-methoxyphenyl)sulfane (1o)[21]

As a yellow crystalline (107 mg, 70% yield, mp 114-116 °C); Purification over a column of silica gel (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.05 (d, 1H, J = 2.4 Hz), 8.10 (dd, 1H, J_1 = 2.4 Hz, J_2 = 9.2 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.05 (d, 2H, J = 8.8 Hz), 6.99 (d, 1H, J = 8.8 Hz), 3.89 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.1, 149.7, 144.3, 143.8, 137.7, 128.9, 126.9, 121.5, 119.3, 116.4, 55.7; IR (KBr, cm^{-1}): 2958, 2923, 2853, 1738, 1618, 1591, 1527, 1494, 1323, 1247, 1086, 829, 712.

Butyl(2-nitro-4-(trifluoromethyl)phenyl)sulfane (2a)[22]

As a yellow solid (89 mg, 64% yield, mp 58 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 (d, 1H, J = 2.4 Hz), 7.75 (dd, 1H, J_1 = 2.2 Hz, J_2 = 8.6 Hz), 7.53 (d, 1H, J = 8.4 Hz), 2.99 (t, 2H, J = 7.4 Hz), 1.79-1.72 (m, 2H), 1.58-1.49 (m, 2H), 0.98 (t, 3H, J = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 145.6, 143.8, 133.1, 129.6 (q, J = 3.4 Hz), 127.2, 123.7 (q, J = 4.0 Hz), 121.9,

32.3, 29.9, 22.4, 13.8; ^{19}F NMR ($CDCl_3$): δ -62.7 (s); IR (KBr, cm^{-1}): 3088, 2959, 2930, 2876, 1620, 1559, 1525, 1327, 1249, 1086, 829, 713.

Benzyl(2-nitro-4-(trifluoromethyl)phenyl)sulfane (2b)[22]

As a yellow solid (96 mg, 61% yield, mp 129-131 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, 1H, J = 2.0 Hz), 7.73 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.44-7.32 (m, 5H), 4.25 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 145.3, 143.2, 134.3, 129.8 (q, J = 3.4 Hz), 129.24, 129.21, 128.3, 127.5, 124.5, 123.7 (q, J = 3.9 Hz), 121.8, 37.8; ^{19}F NMR ($CDCl_3$): δ -62.7 (s); IR (KBr, cm^{-1}): 3030, 2960, 2853, 2923, 1624, 1560, 1521, 1494, 1332, 1292, 1088, 837, 708.

(2-Nitro-4-(trifluoromethyl)phenyl)(phenyl)sulfane (2c)[23]

As a yellow crystalline (74 mg, 49% yield, mp 68 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, 1H, J = 2.0 Hz), 7.61-7.58 (m, 2H), 7.56-7.51 (m, 4H), 6.97 (d, 1H, J = 8.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 144.8, 144.5, 136.2, 130.9, 130.7, 129.9, 129.6 (q, J = 3.4 Hz), 129.1, 124.5, 123.3 (q, J = 4.0 Hz), 121.8; ^{19}F NMR ($CDCl_3$): δ -62.7 (s); IR (KBr, cm^{-1}): 2960, 2850, 2923, 1739, 1618, 1558, 1524, 1322, 1128, 1083, 833, 704.

(2-Nitro-4-(trifluoromethyl)phenyl)(p-tolyl)sulfane (2d)[24]

As a yellow crystalline (102 mg, 65% yield, mp 88-89 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, 1H, J = 2.4 Hz), 7.52 (dd, 1H, J_1 = 2.0 Hz, J_2 =8.8 Hz), 7.46 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 6.97 (d, 1H, J = 8.4 Hz), 2.45 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 145.4,

144.4, 141.4, 136.1, 131.5, 129.5 (q, J = 3.3 Hz), 129.0, 126.3, 124.5, 123.3 (q, J = 4.0 Hz), 121.8, 21.6; ^{19}F NMR ($CDCl_3$): δ -62.7 (s); IR (KBr, cm^{-1}): 2955, 2922, 2853, 1739, 1615, 1524, 1320, 1296, 1124, 1082, 811, 711.

(2-Nitro-4-(trifluoromethyl)phenyl)(4(trifluoromethyl)phenyl)sulfane (2e)

As a yellow solid (55 mg, 30% yield, mp 69-71 °C); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (d, 1H, J = 2.0 Hz), 7.77 (q, 4H, J = 8.4 Hz), 7.61 (dd, 1H, J_1 = 2.0 Hz, J_2 =8.4 Hz), 7.02 (d, 1H, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 144.9, 142.9, 136.2, 135.1, 132.8 (q, J = 32.8 Hz), 129.9 (q, J = 3.4 Hz), 129.3, 128.3 (q, J = 34.4 Hz), 127.4 (q, J = 3.7 Hz), 124.8 (d, J = 80.1 Hz), 123.4 (q, J = 4.0 Hz), 122.1 (d, J = 79.7 Hz); ^{19}F NMR ($CDCl_3$): δ -62.9 (s), -63.1 (s); IR (KBr, cm^{-1}): 2968, 2923, 2853, 1738, 1615, 1561, 1532, 1320, 1162, 1122, 838, 705; ESI (m/z) calcd for $C_{14}H_7F_6NO_2SK$ $[M + K]^+$ 405.97; found 405.21.

(4-Methoxyphenyl)(2-nitro-4-(trifluoromethyl)phenyl)sulfane (2f)[24]

As a yellow liquid (111 mg, 67% yield); Purification over a column of silica gel (2-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.50 (d, 1H, J = 2.5 Hz), 7.53 (dd, 1H, J_1 = 2.0 Hz, J_2 =8.5 Hz), 7.49 (d, 2H, J = 8.5 Hz), 7.03 (d, 2H, J = 9.0 Hz), 6.95 (d, 1H, J = 9.0 Hz), 3.89 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 161.8, 145.9, 144.2, 137.9, 132.9, 129.5 (q, J = 6.75 Hz), 128.7, 123.4 (q, J = 8.06 Hz), 120.2, 116.2, 114.8, 55.7; ^{19}F NMR ($CDCl_3$): δ -62.7 (s); IR (KBr, cm^{-1}): 2953, 2922, 2852, 1744, 1590, 1492, 1461, 1340, 1246, 1172, 1022, 827, 736.

Methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-L-cysteinate (p)[25]

As a white semi solid (145 mg, 82% yield, mp 117-118 °C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 7.5 Hz), 7.41 (t, 2H, J = 7.5 Hz), 7.33 (t, 2H, J = 7.5 Hz), 5.69 (d, 1H, J = 8.0 Hz), 4.69-4.66 (br, 1H), 4.47-4.41 (m, 2H), 4.24 (t, 1H, J = 6.75 Hz), 3.80 (s, 3H), 3.02-2.98 (m, 2H), 1.37 (t, 1H, J = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.6, 155.9, 144.0, 143.8, 141.6, 141.5, 128.0, 127.33, 127.31, 125.3, 125.2, 120.26, 120.23, 67.3, 55.4, 53.1, 47.4, 27.3; IR (KBr, cm^{-1}): 3316, 1735, 1689, 1531, 1446, 1321, 1274, 1086, 1008, 737; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{19}H_{20}NO_4S$ $[M + H]^+$ 358.1108, found 358.1124; calcd for $C_{19}H_{19}NO_4SNa$ $[M + Na]^+$ 380.0927, found 380.0943; calcd for $C_{19}H_{19}NO_4SK$ $[M + K]^+$ 396.0666, found 396.0681.

Methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(2,4-dinitrophenyl)-L-cysteinate (1p)

As a yellow crystalline (114 mg, 44% yield, mp 100-103 °C); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.01 (d, 1H, J = 2.5 Hz), 8.32 (dd, 1H, J_1 = 2.0 Hz, J_2 =9.5 Hz), 7.75-7.70 (m, 3H), 7.55 (d, 2H, J = 7.5 Hz), 7.38 (t, 2H, J = 7.5 Hz), 7.31-7.73 (m, 2H), 5.72 (d, 1H, J = 7.5 Hz), 4.71 (q, 1H, J = 6.33 Hz), 4.41 (d, 2H, J = 7.0 Hz), 4.18 (t, 1H, J = 7.25 Hz), 3.81 (s, 3H), 3.62-3.58 (m, 1H), 3.48-3.44 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.1, 155.9, 145.7, 144.9, 144.5, 143.7, 143.6, 141.5, 128.0, 127.5, 127.3, 127.2, 125.1, 121.8, 120.3, 67.6, 53.5, 52.9, 47.2, 34.8; IR (KBr, cm^{-1}): 3307, 3078, 2951, 1736, 1682, 1588, 1512, 1447, 1333, 1273, 1093, 1052, 736; HRMS (ESI/Q-TOF) (m/z) calcd for $C_{25}H_{22}N_3O_8S$ $[M + H]^+$ 524.1122, found 524.1125; calcd for $C_{25}H_{21}N_3O_8SNa$ $[M + Na]^+$ 546.0942, found 546.0949; calcd for $C_{25}H_{21}N_3O_8SK$ $[M + K]^+$ 562.0681, found 562.0686.

2-((2,4-dinitrophenyl)thio)benzoic acid (1q)[26]

As a yellow solid (98 mg, 52% yield, mp 184-187 °C); Purification done by washing with diethyl ether; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.49 (s, 1H), 7.94 (d, 2H, J = 8.0Hz), 7.66-7.59 (m, 3H), 7.17 (d, 1H, J = 8.4 Hz); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 167.4, 146.0, 141.5, 136.0, 132.7, 131.5, 130.78, 130.24, 129.9, 126.83, 126.49, 122.66, 121.6; IR (KBr, cm^{-1}): 2955, 2880, 2828, 1694, 1559, 1526, 1331, 1299, 1249, 1124, 1089, 757, 714.

2-((2,4-dinitrophenyl)thio)-N-(2-methoxyphenyl)benzamide (1r)

As a yellow solid (99 mg, 83% yield, mp 169-171 °C); Purification over a column of silica gel (10-15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (s, 1H), 8.38 (d, 1H, J = 2.0 Hz), 8.28 (dd, 1H, J_1 = 1.8 Hz, J_2 =8.2 Hz), 7.89 (dd, 1H, J_1 = 1.6 Hz, J_2 =7.6 Hz), 7.69-7.64 (m, 2H), 7.61-7.55 (m, 2H), 7.08-7.01 (m, 2H), 6.61-6.83 (m, 2H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.9, 148.2, 144.5, 143.1, 141.9, 137.7, 132.1, 131.5, 130.3, 129.8, 128.0, 127.52, 127.19, 124.5, 123.06, 123.01, 121.04, 119.9, 110.1, 55.6; IR (KBr, cm^{-1}): 3413, 3060, 2973, 2927, 2845, 1674, 1618, 1520, 1458, 1321, 1291, 1125, 747, 712; ESI (m/z) calcd for $C_{20}H_{15}N_3O_6S$ $[M]^+$ 425.06, found 425.09.

3.7. Representative NMR Spectra

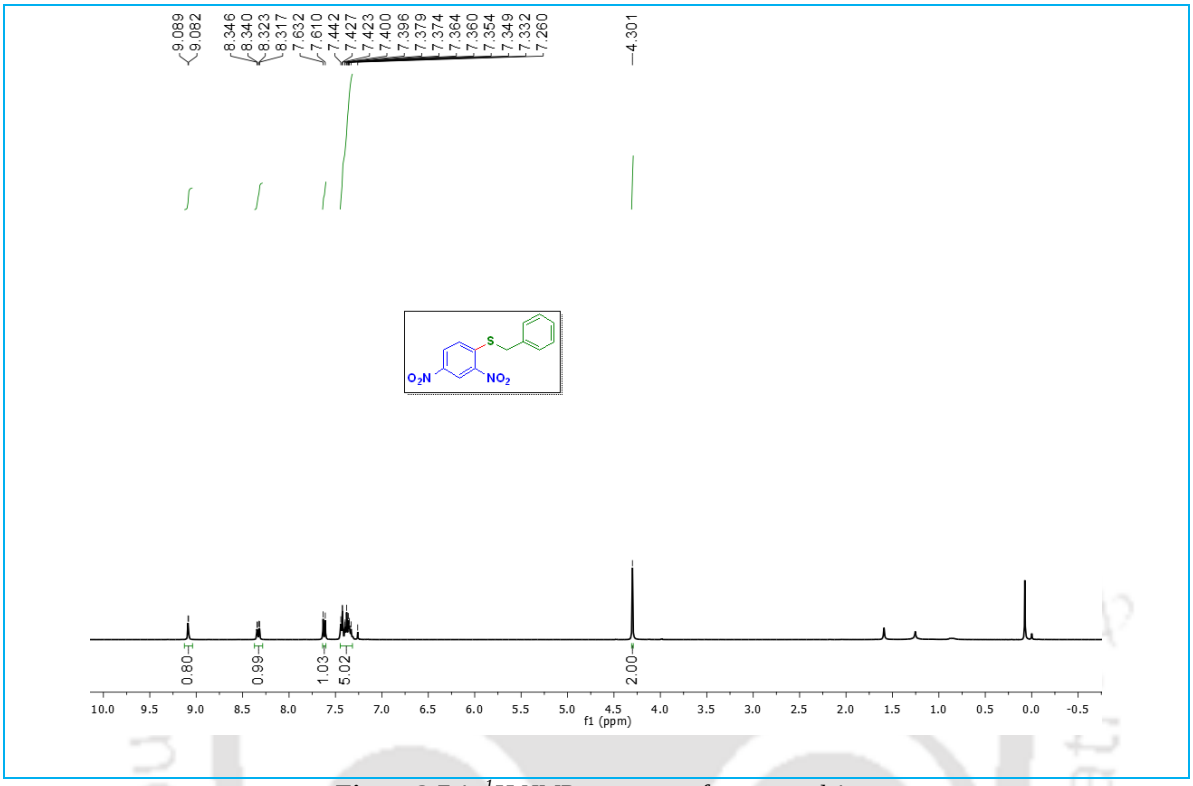


Figure 3.7.1: *^{1}H NMR spectrum of compound* ***1a***

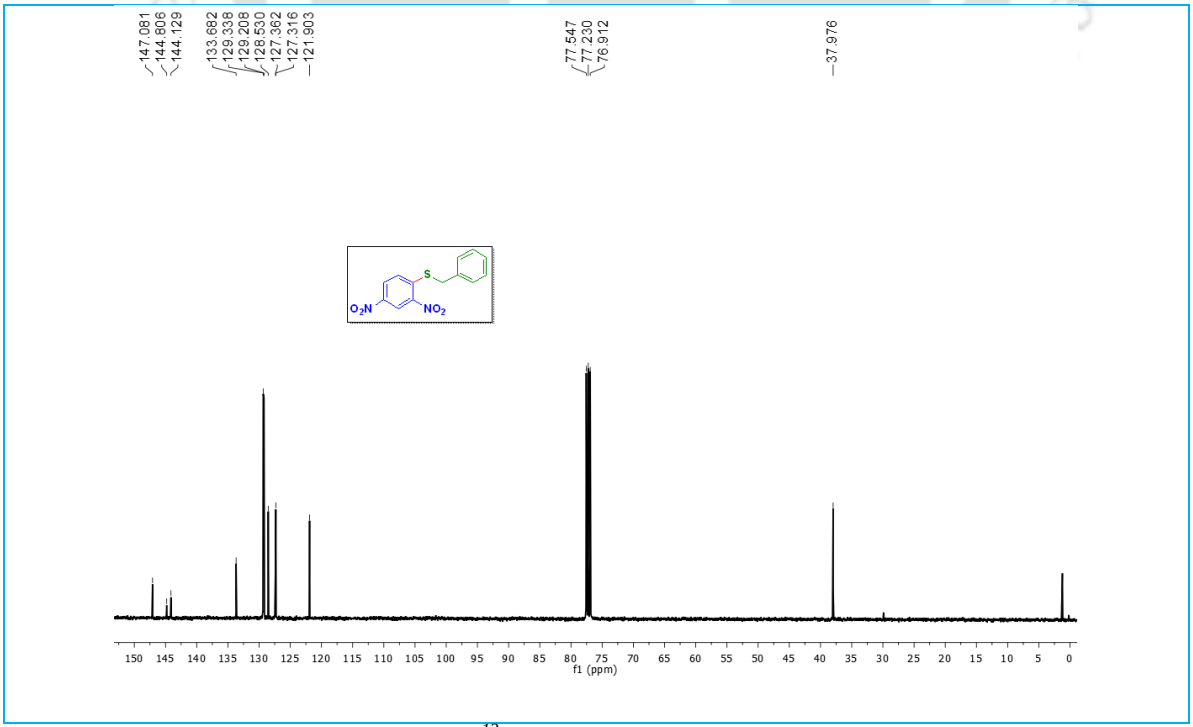


Figure 3.7.2: *^{13}C NMR spectrum of compound* ***1a***

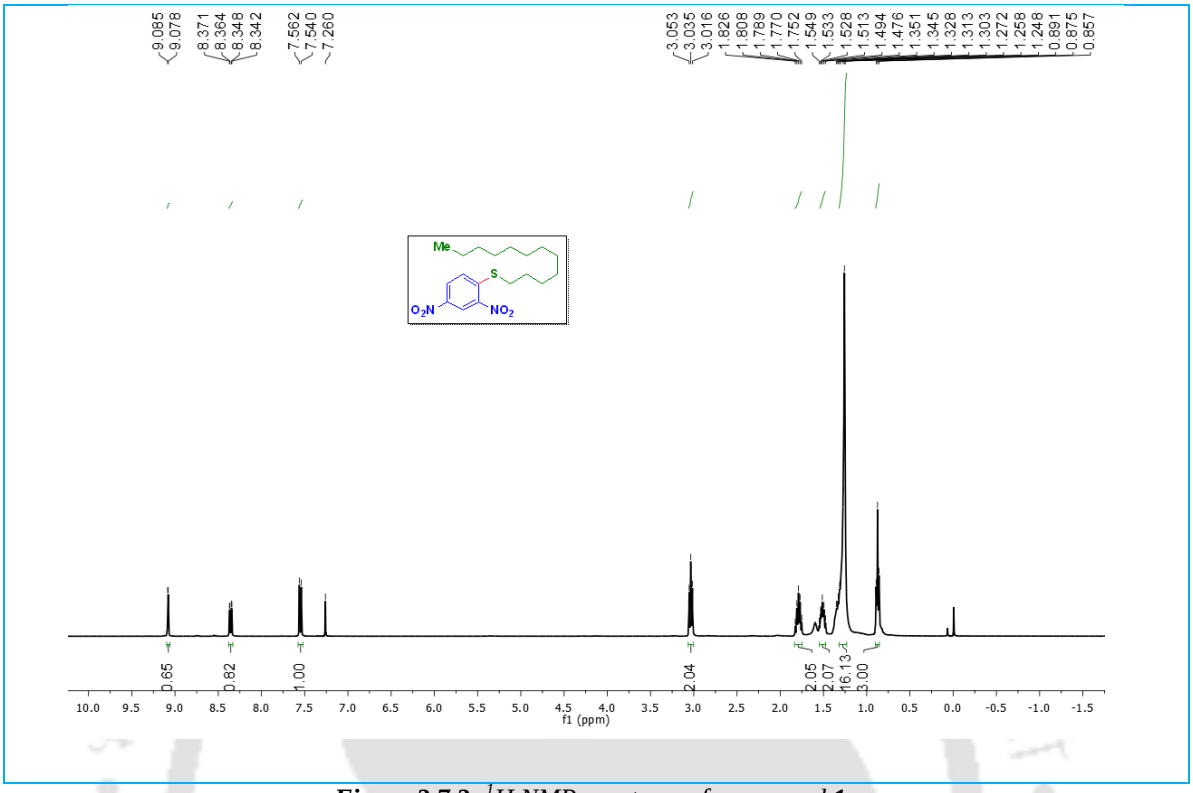


Figure 3.7.3: *^{1}H NMR spectrum of compound* ***1e***

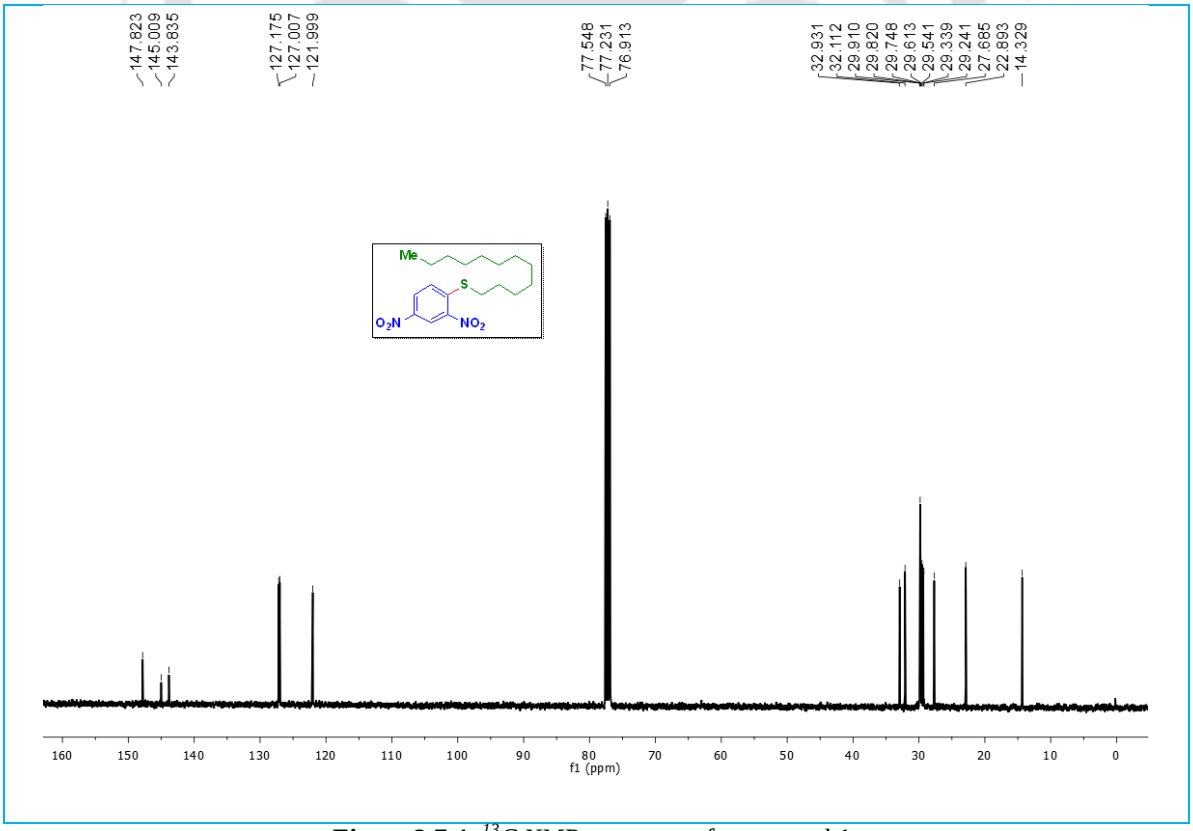


Figure 3.7.4: *^{13}C NMR spectrum of compound* ***1e***

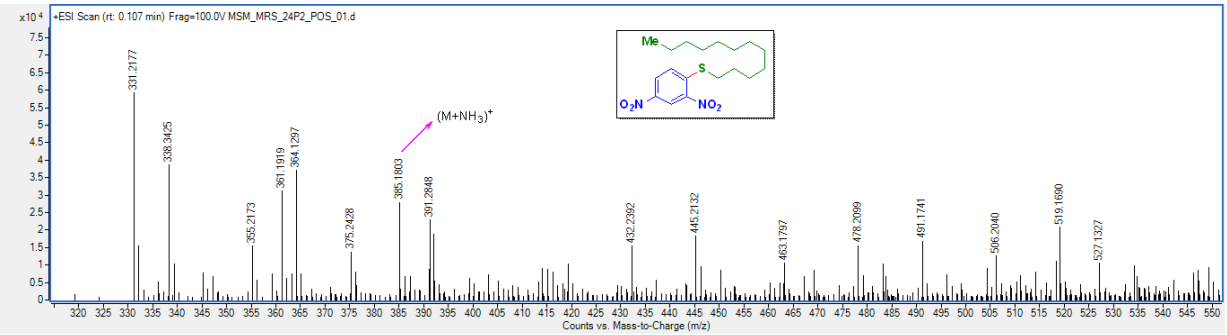


Figure 3.7.5: *ESI spectrum of compound* ***1e***

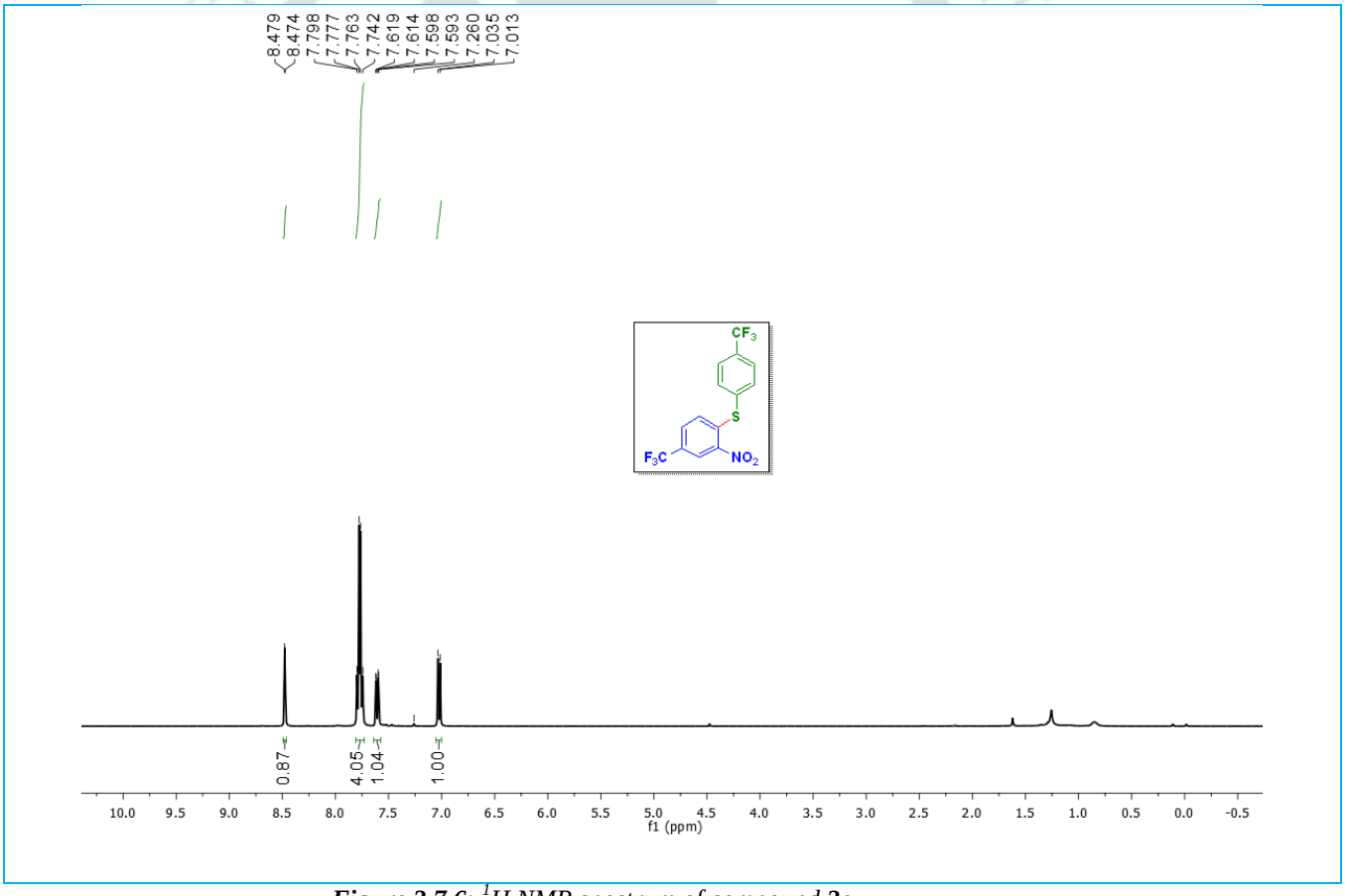


Figure 3.7.6: *^{1}H NMR spectrum of compound* ***2e***

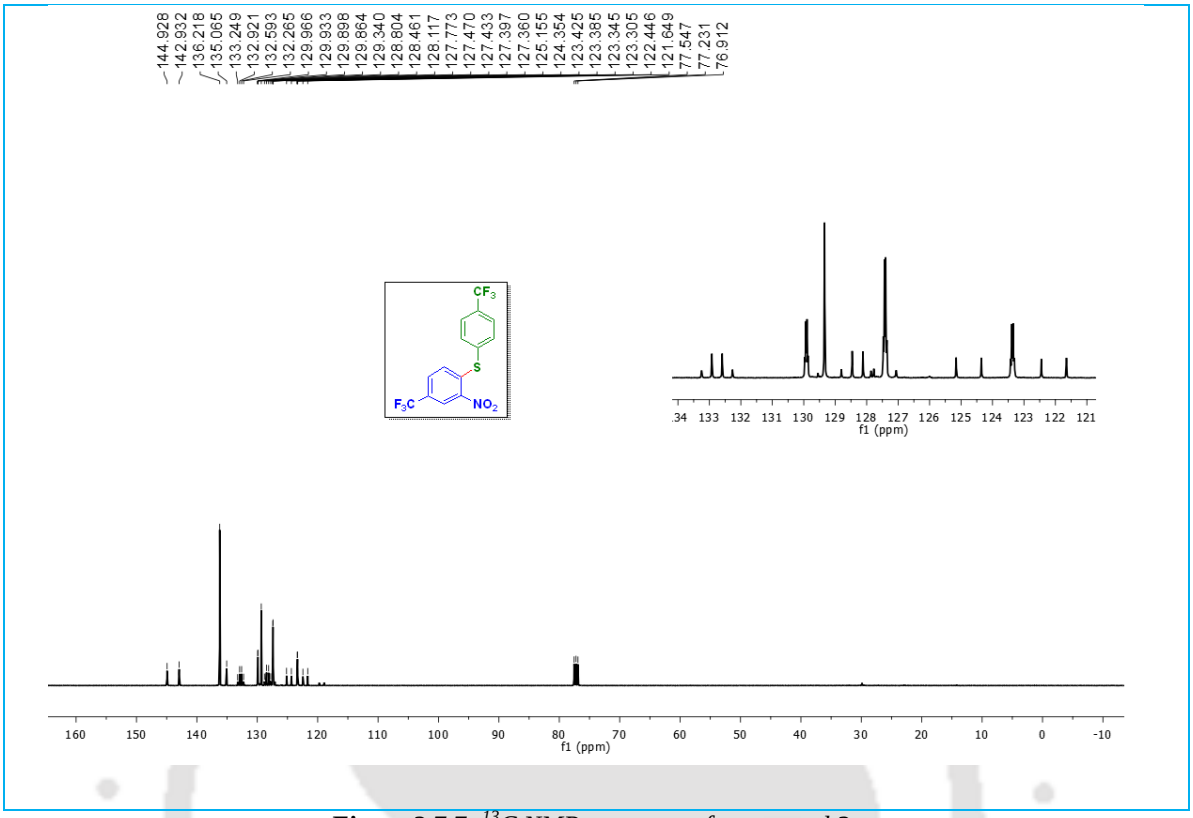


Figure 3.7.7: *^{13}C NMR spectrum of compound* ***2e***

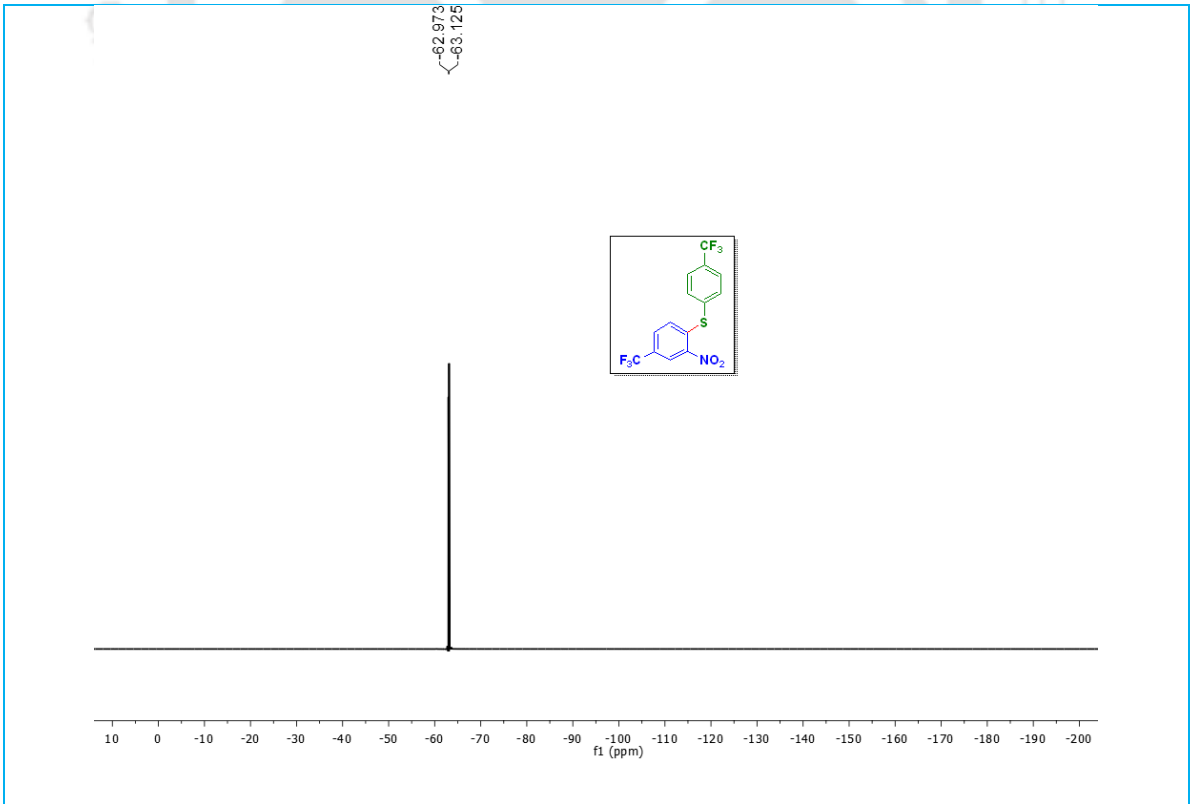


Figure 3.7.8: *^{19}F NMR spectrum of compound* ***2e***

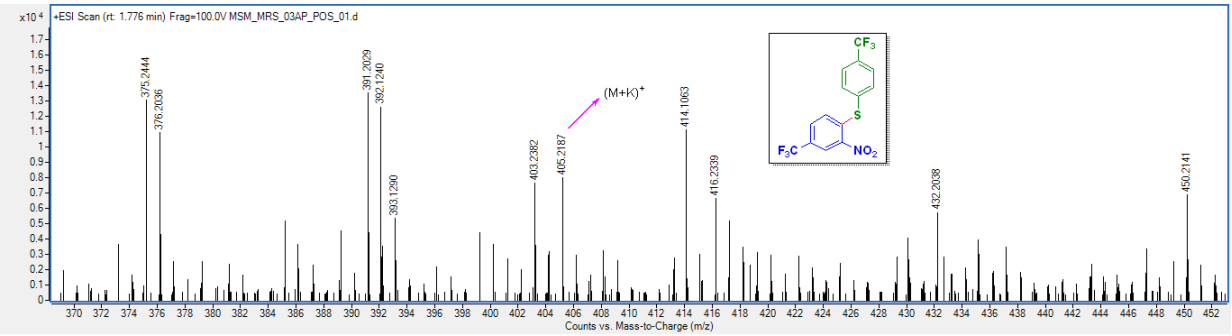


Figure 3.7.9: *ESI spectrum of compound* ***2e***

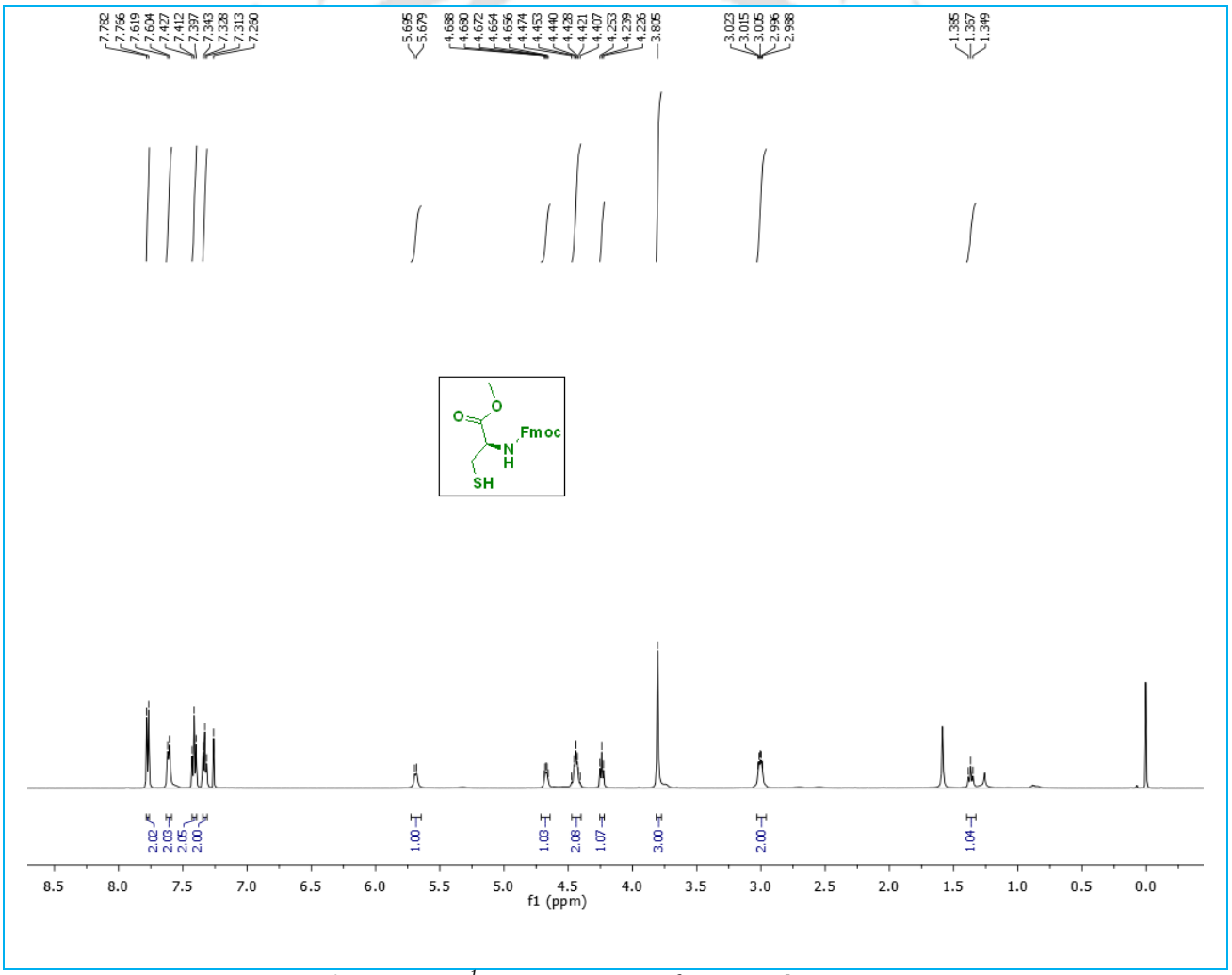


Figure 3.7.10: *^{1}H NMR spectrum of compound* ***p***

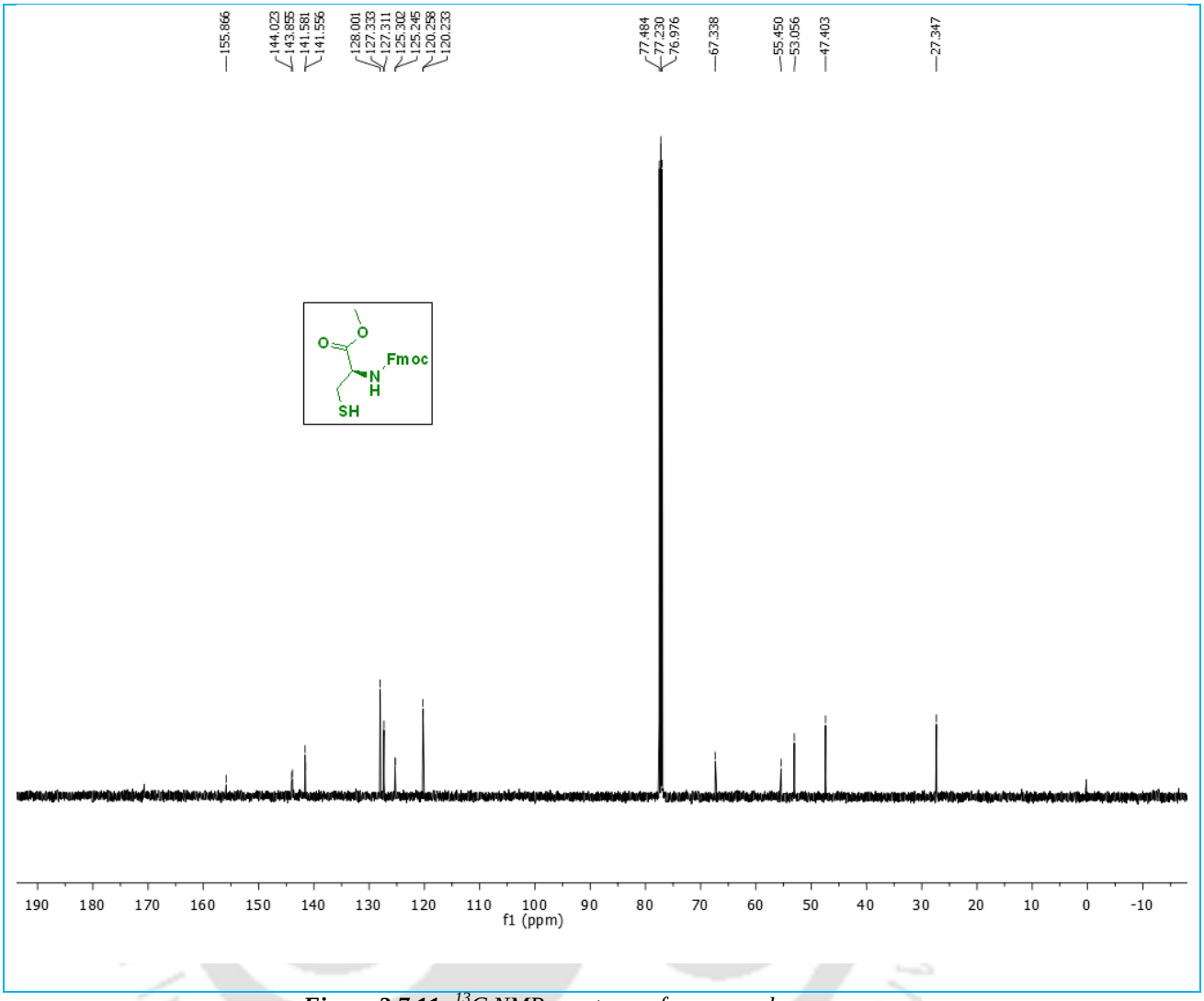


Figure 3.7.11: *^{13}C NMR spectrum of compound* ***p***

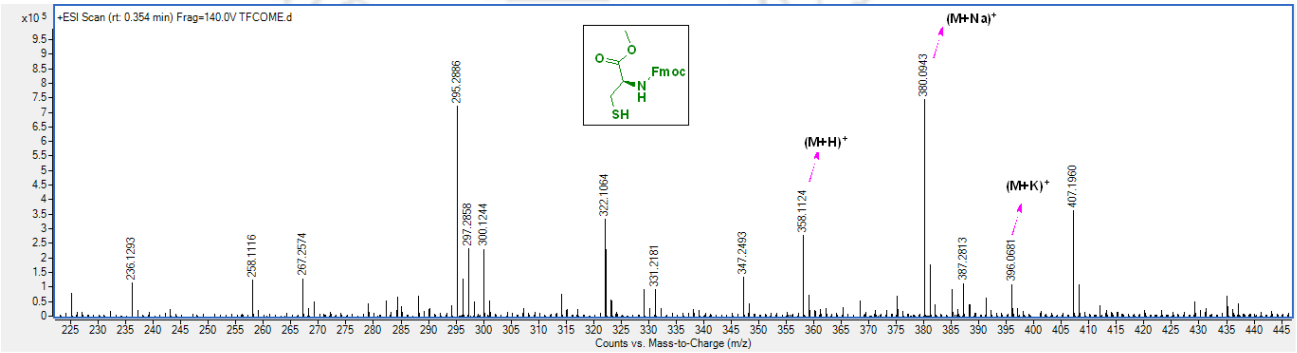


Figure 3.7.12: *HRMS spectrum of compound* ***p***

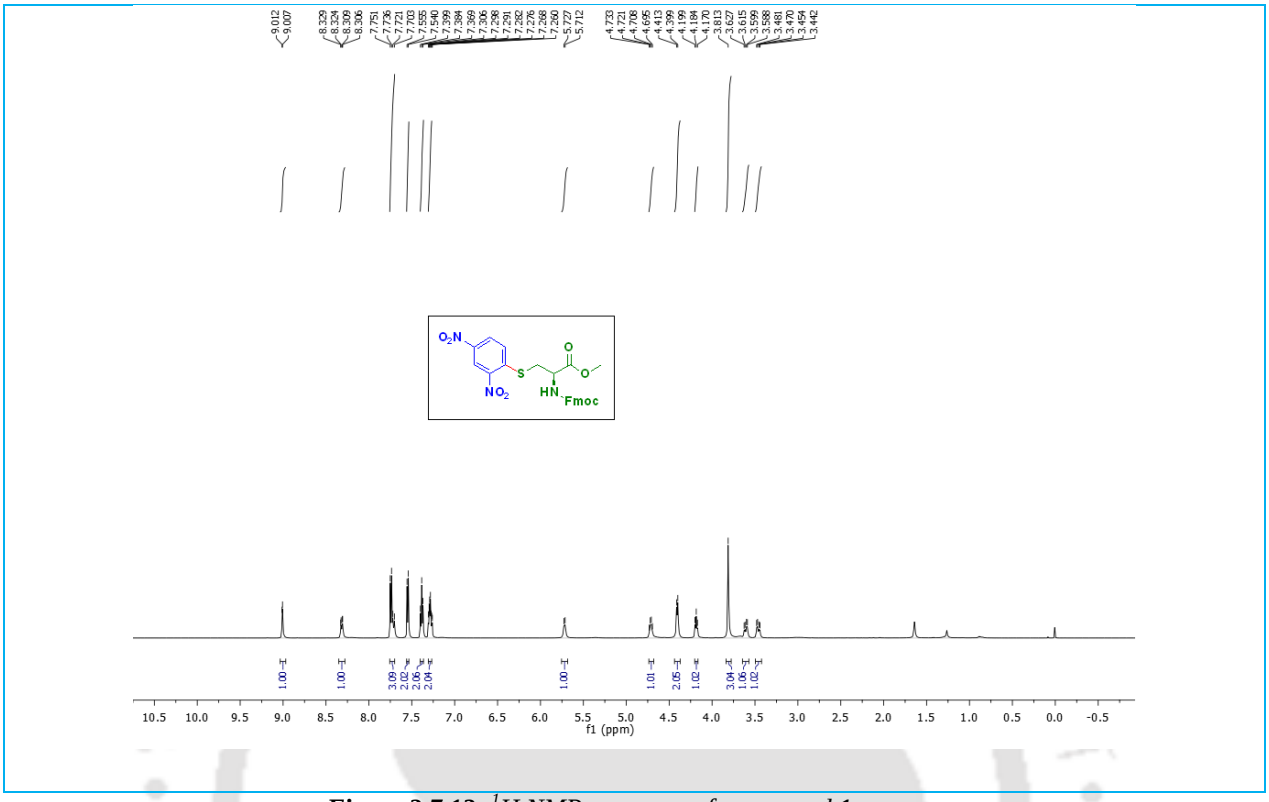


Figure 3.7.13: *^{1}H NMR spectrum of compound* ***1p***

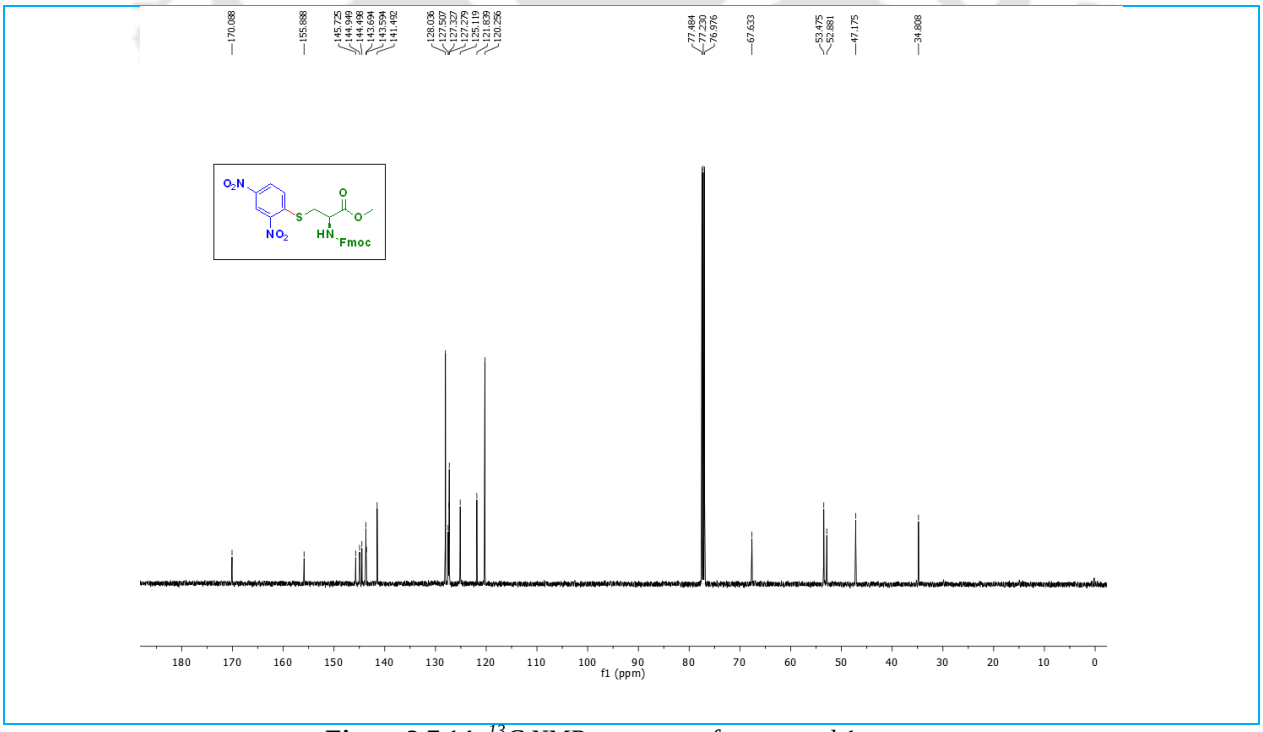


Figure 3.7.14: *^{13}C NMR spectrum of compound* ***1p***

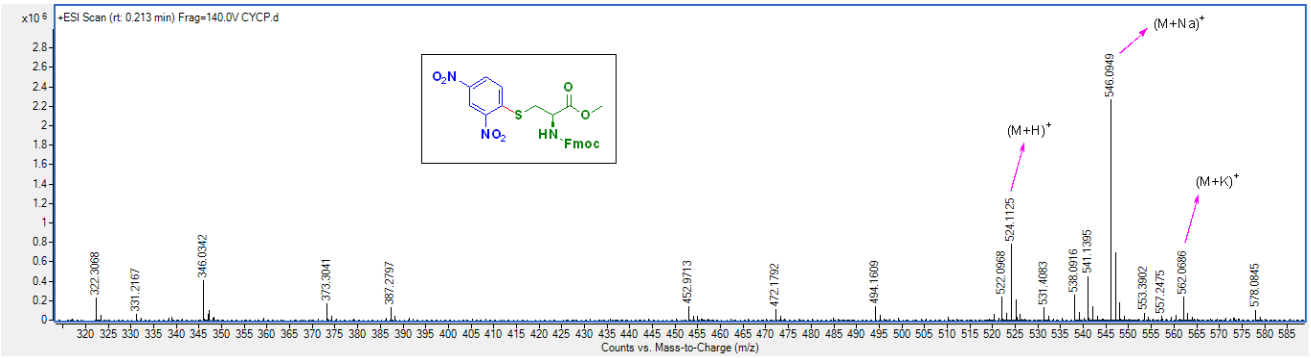


Figure 3.7.15: *HRMS spectrum of compound* ***1p***

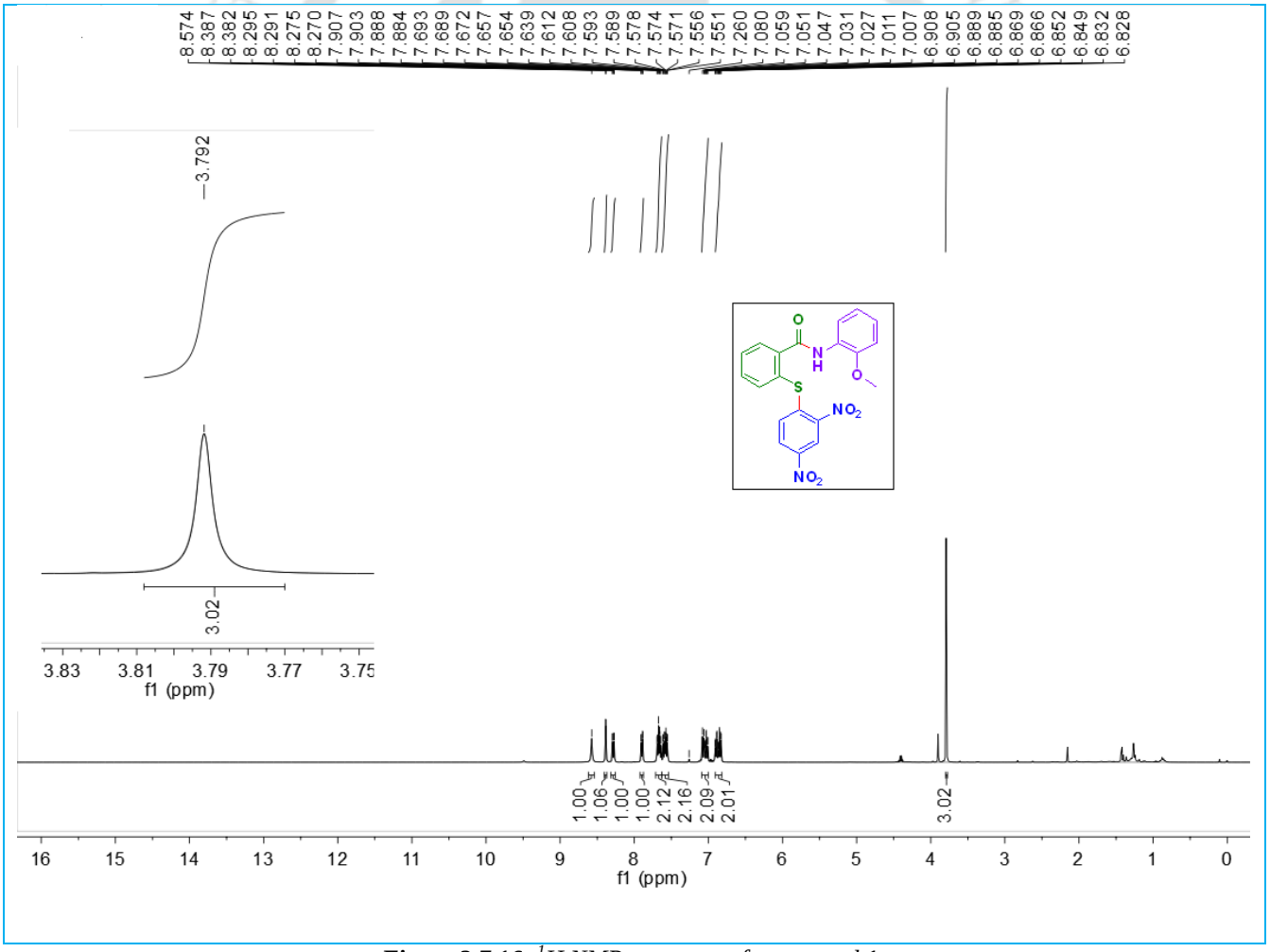


Figure 3.7.16: *^{1}H NMR spectrum of compound* ***1r***

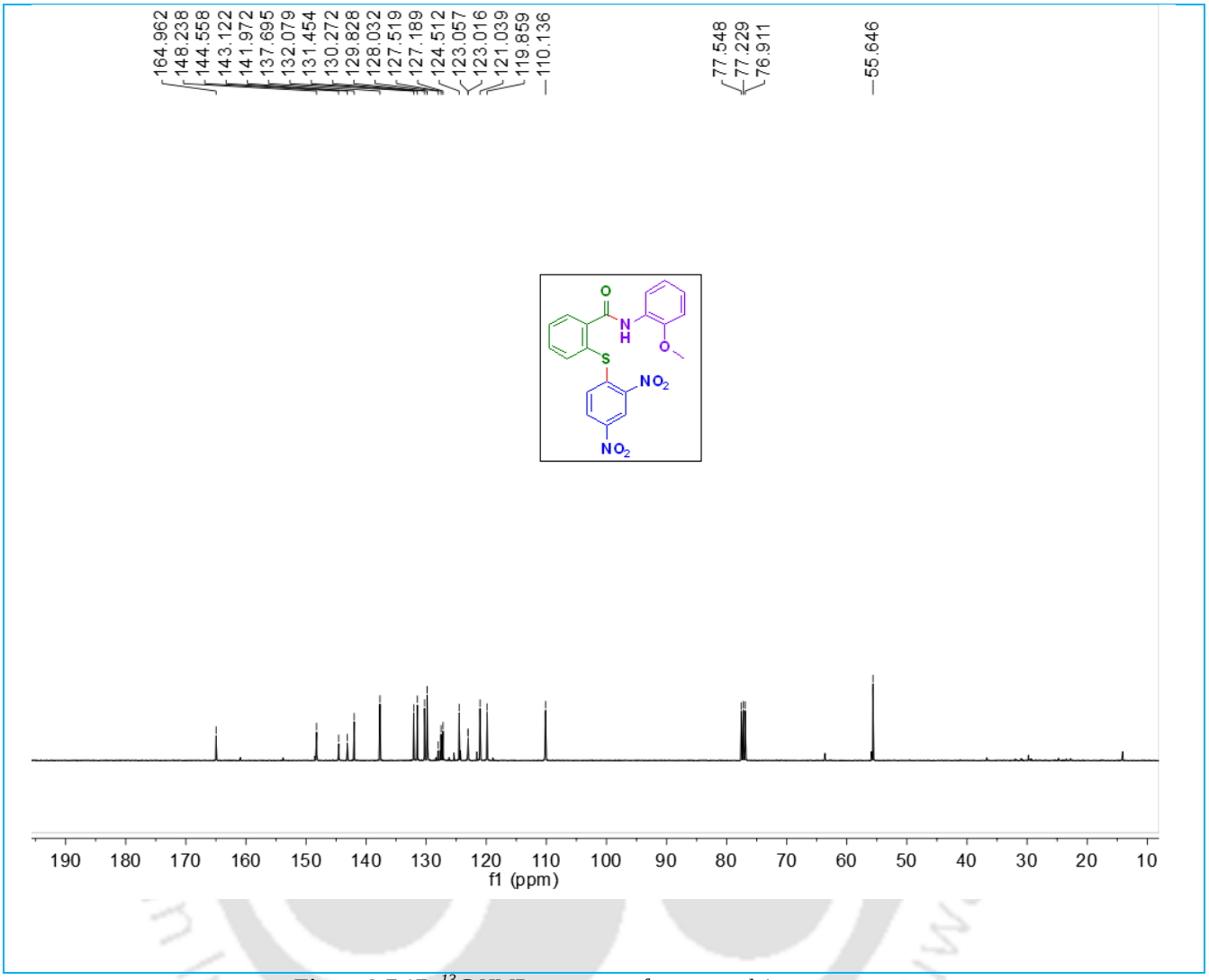


Figure 3.7.17: *^{13}C NMR spectrum of compound* ***1r***

3.8. Crystallographic Data

Compound No.	**1a**	**1p**
Formula	$C_{13}H_{10}N_2O_4S$	$C_{25}H_{21}N_3O_8S$
CCDC No.	2222280	2271987
Formula. Wt.	290.29	523.51
Crystal system	Monoclinic	Monoclinic
Space group	P 21/c	P 21
a (Å)	8.1262(10)	4.9587(5)
b (Å)	23.937(3)	13.0631(12)
c (Å)	7.3538(9)	18.7096(19)
α(°)	90.00	90.00
β(°)	114.786(3)	96.355(4)
γ(°)	90.00	90.00
V/ $Å^3$	1298.7(3)	1204.5(2)
Z	4	2
T(K)	273(2)	298(2)
Density/g cm^{-3}	1.485	1.443
Abs. Coeff. /mm^{-1}	0.264	0.191
F(000)	600.0	544.0
Total no. of reflections	32765	19572
Reflections, $I > 2\sigma(I)$	0.0350 (2069)	0.0575 (2921)
Max. 2θ/°	24.990	24.997
Ranges (h, k, l)	(9,28,8)	(5,15,22)
Complete to 2θ (%)	24.990	24.997
Data/ Restraints/Parameters	2255/0/181	4239/1/335
Goof (F^2)	1.117	1.047
R indices [$I > 2\sigma(I)$]	0.0350	0.0575
R indices (all data)	0.0387	0.0920

❖ **ORTEP Diagram with ellipsoid of 50% probability**

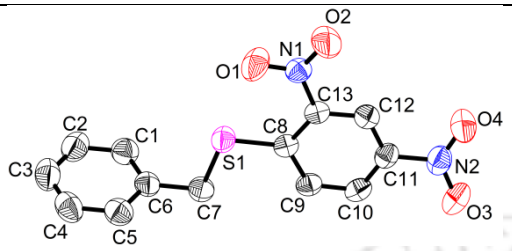
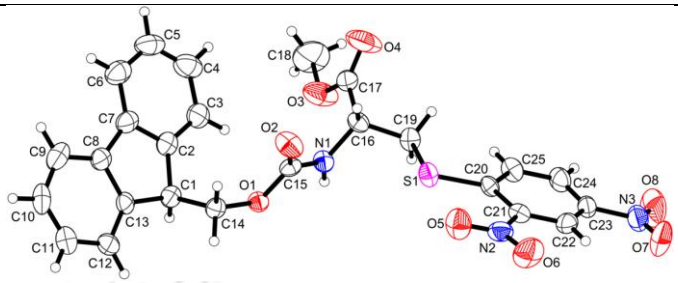
1a	**1p**
	
CCDC No. 2222280	CCDC No. 2271987

Figure 3.8.1: *ORTEP Diagrams*

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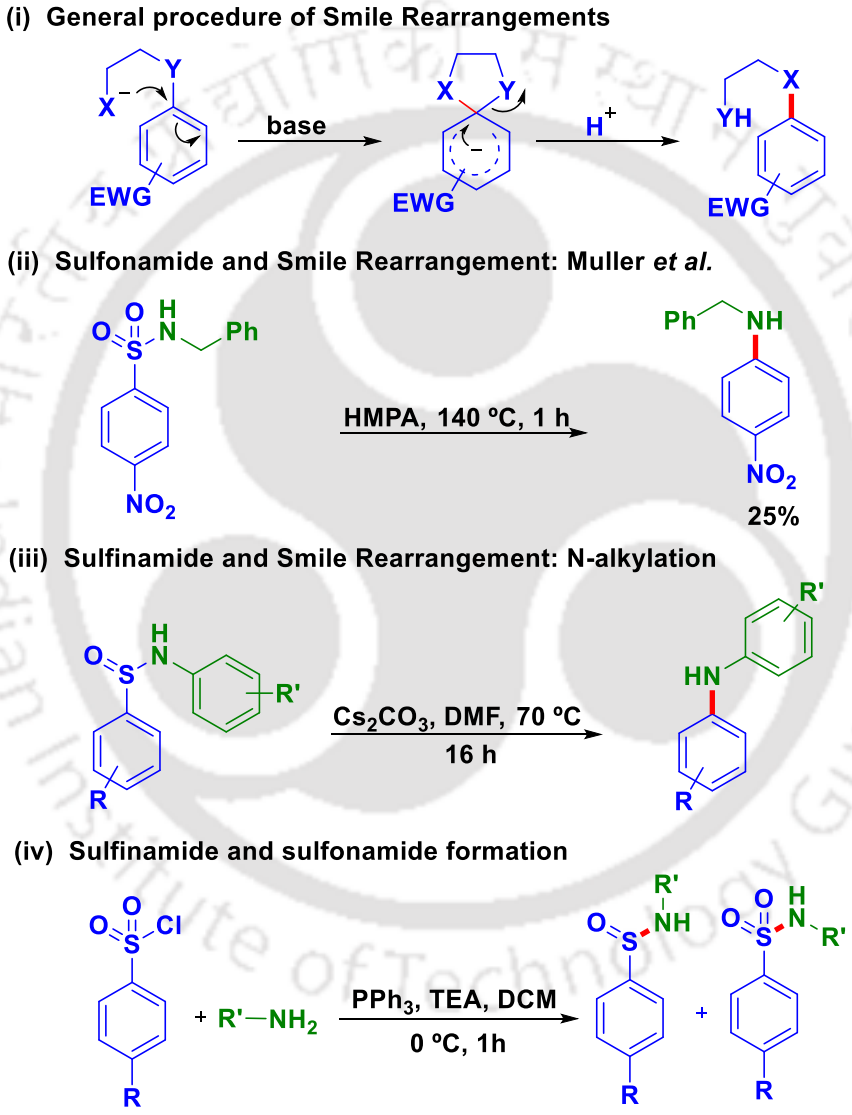
Chapter IV

Formation of Smile Rearrangement Product by Mild Intermolecular Ipso aromatic nucleophilic substitution

4.1. Introduction

Di-aryl amine or thioether and aryl sulfonamide are the critical class of organic synthons. These subunits are present in numerous drugs, biologically active molecules, and pharmaceuticals.[1-3] Therefore, massive efforts have been invested in the area of synthesis to form such connectivity, and various transition metal catalysts and ligands have been developed.[4] An intermolecular aromatic nucleophilic substitution reaction can achieve the alternative way of N-alkylation.[5] The existing methods have some inherent drawbacks, such as the use of toxic or expensive catalyst, elevated temperature, and harsh reaction conditions, which is not environment friendly. Moreover, in many cases, reaction efficiency and substrate scope limitation are significant drawbacks. N-alkylation of amine can be achieved by aryl sulfonamides or sulfonate esters in respectively mild conditions. Smile rearrangement[6] is one of the potential and alternative pathways by which N-alkylation of amines occurs in transition metal-free conditions. In the gas phase, SO_2 extrusion from sulfonamides by fragmentation pathway is well established in mass spectrometry.[7-8] In 1979, Muller *et al.*[9] found a single example of sulfonamide to N-arylated product via Smile rearrangement with 25% yield at high-temperature Scheme 4.1.1 (ii). We were curious to know the temperature and base effect in this particular reaction. Therefore, we investigated the reaction of 2,4-dinitro benzenesulfonyl chloride and benzylamine in the presence of base DIPEA, expecting to be a Smile rearrangement product via in situ formation of aryl sulfonamide. Surprisingly, at room temperature we

found two different products, aryl sulfonamide as a major product and a trace amount of N-arylated product as a minor product. In this condition, we tried to understand the mechanism of the reaction. We realized that the formation of the N-arylated product does not go via intramolecular Smile rearrangement although the product is similar to it.



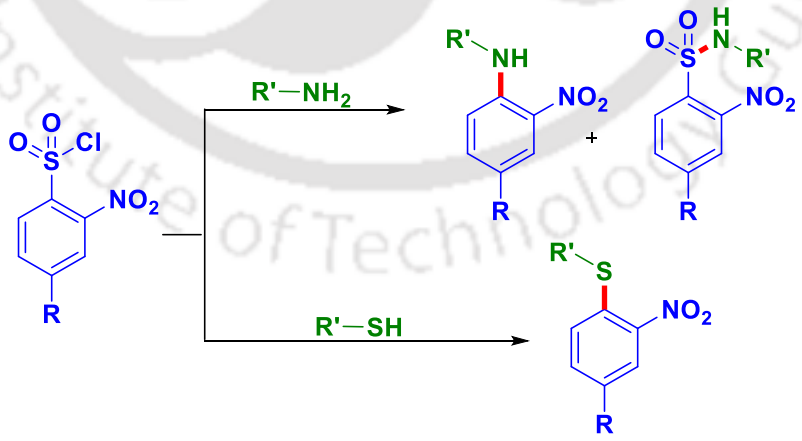
Scheme 4.1.1: *Smile rearrangements and substitution reactions*

We investigated various substrates and conditions, and in this chapter, we have briefly described our findings of N and S-alkylation, i.e., Smile rearrangement product via

intermolecular ipso aromatic nucleophilic substitution reaction, Scheme 4.1.1 (v). Recently, Sephton *et al.*[10] established the Smile rearrangement on aryl sulfonamides by SO extrusion Scheme 4.1.1 (iii). Related to this work another interesting work has been done by Hermata and the group.[11] They have described the formation of sulfinamide and sulfonamide from aryl sulfonyl chloride Scheme 4.1.1 (iv) using PPh_3 and TEA in DCM medium.

4.2. Objective

A novel and efficient procedure of amine and thiol produce Smile rearrangement products via ipso aromatic nucleophilic substitution reaction involving an in situ reduction of sufficiently electron deficient benzene sulfonyl chloride, leading to the generation of new C-N and C-S bonds. Satisfactory to sufficiently high yields are obtained under transition metal-free and mild reaction conditions. Many amines and thiols effectively produce corresponding desired diaryl amine and di aryl thioethers.



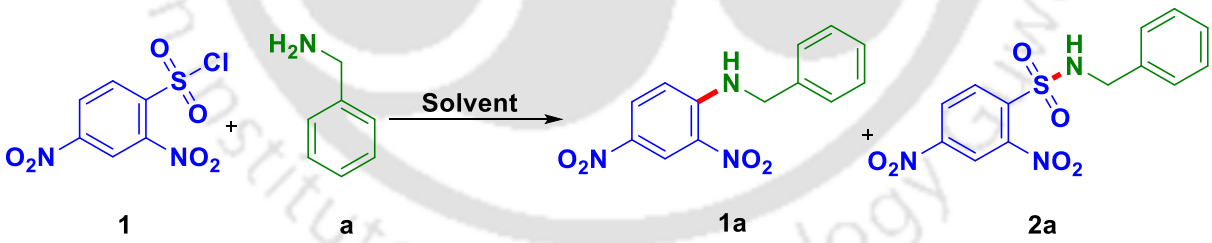
Scheme 4.2.1: *Ipso substitution on o-nitrobenzene sulfonic acid derivatives*

Regioselective attack of nucleophiles on benzene sulfonyl chloride derivatives can be controlled by varying the reaction conditions. This method has practical application for forming various organic synthons and biologically important compounds.

4.3. Results and Discussion

4.3.1. Preliminary Study and Sulfonamide Formation

Initially, we began our study with 2,4-dinitro benzene sulfonyl chloride as a model substrate. In the presence of 1.4 equivalent of amines, it produces corresponding sulfonamide products (2a) in a dioxane medium at room temperature with an extremely high yield of up to 96% (Table 4.3.1.1). The formation of aryl sulfonamides from aryl sulfonyl chloride is well documented in the literature. However, we have also observed the formation of a small amount of N-arylated product (1a) (Table 4.3.1.1), which is not well documented in the literature.



Scheme 4.3.1.1: *Model reaction for optimization of the reaction conditions*

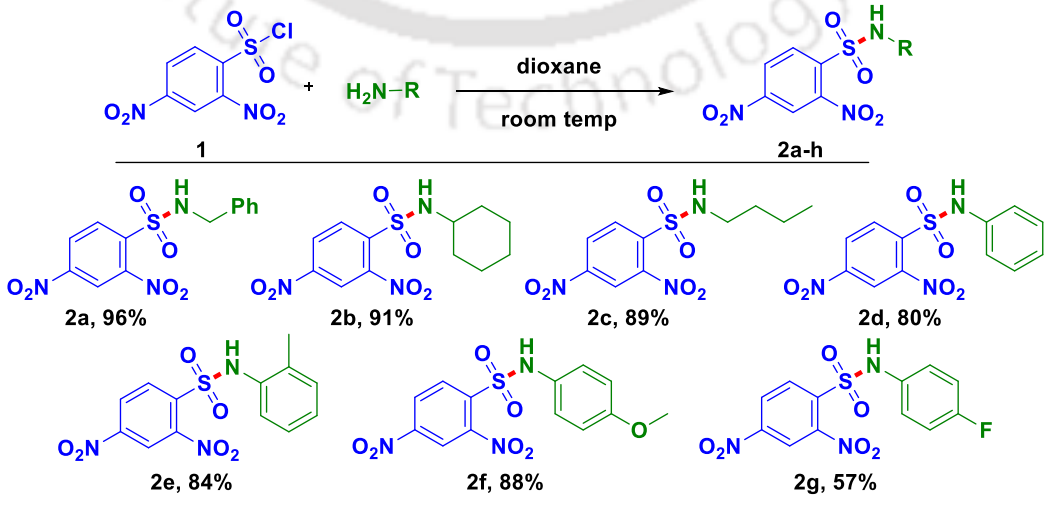
Table 4.3.1.1: Optimization of the reaction conditions of sulfonamide formation[a]

Entry	1 (equiv.)	a (equiv.)	Solvent	1a yield (%)[b]	2a yield (%)[b]
1	1.0	1.0	THF	7	40
2	,,	,,	DCM	5	70

3	,,	,,	dioxane	4	72
4	,,	,,	acetone	4	63
5	,,	,,	$CHCl_3$	-	68
6	,,	,,	DCE	-	63
7	,,	,,	DMSO	-	55
8	,,	,,	DMF	trace	64
9	,,	,,	ACN	trace	71
10	,,	1.2	dioxane	trace	89
11	,,	1.4	,,	-	96
12	,,	1.5	,,	-	96

[a]*Reaction condition: 2,4-dinitro benzene sulfonyl chloride (**1**, 1.0 equiv.) and benzylamine (**a**, varied amount) were stirred at room temperature for 30 min;* [b]*Isolated yields*

We have increased the substrate scope with various amines using the optimized reaction conditions and separated reasonable yields.



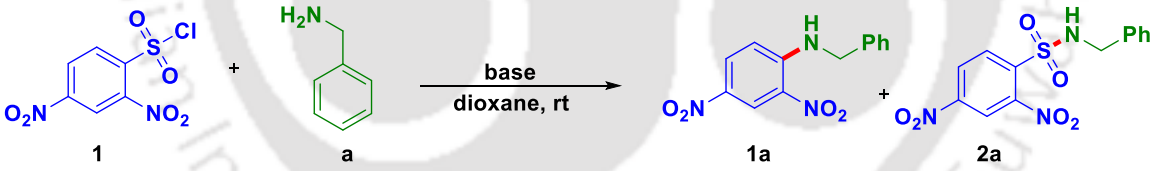
*Reaction condition: 2,4-dinitro benzenesulfonyl chloride (**1**, 1.0 equiv.), amine (1.4 equiv.), reaction time 30 min*

Scheme 4.3.1.2: *Formation of aryl sulfonamides*

The scenario changes in the presence of base, it produces both desired products of sulfonamide as well as N-arylated product with sufficient high yields. Therefore, we continued to reconnoiter this phenomenon with 2,4-dinitro benzene sulfonyl chloride and benzylamine as a model substrate.

4.3.2. Optimization for N-alkylation

During optimization of the reaction conditions, we found that an increase in the base (DIPEA) concentration from zero to 4.0 equivalent, the formation of an N-alkylated product increases, and aryl sulfonamide decrease (entry 1-6).



Scheme 4.3.2.1: *Model reaction for optimization of the reaction conditions*

We have screened various bases like DBU, TEA, K_2CO_3, and Cs_2CO_3 (entry 7-10), but DIPEA is a suitable candidate for this reaction. With the increase of amine concentration, the ipso product i.e. N-alkylated product formation gets enhanced (entry 11). In the presence of 4.0 equivalent of DIPEA at 4 hours it produces 95% yield. In those similar conditions, other bases require 6 to 24 hours of reaction time and produce similarly 95% yields. It has been noticed that the presence of 2.0 equivalent of benzylamine shows the highest efficiency in producing ipso product but other amines required 4.0 equivalent in

similar conditions and that's considered as the optimization condition of this reaction. Further increase of amine or DIPEA does not affect the yield of the reaction. We performed this reaction at higher temperatures (40 ºC and 80 ºC) but no significant change was observed.

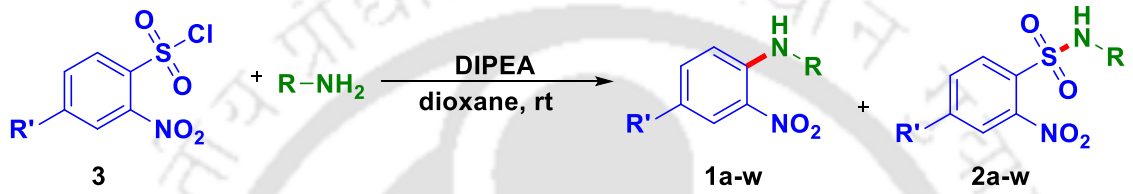
Table 4.3.2.1: Optimization of the reaction conditions[a]

entry	a (equiv.)	base (equiv.)	1a yield(%)[b]	2a yield(%)[b]
1.	1.5	-	trace	96
2.	,,	DIPEA (1.5)	25	70
3.	,,	DIPEA (2.0)	45	50
4.	,,	DIPEA (3.0)	57	39
5.	,,	DIPEA (3.5)	65	28
6.	,,	DIPEA (4.0)	70	20
7.	,,	DBU (4.0)	58	37
8.	,,	TEA (4.0)	60	34
9.	,,	K_2CO_3 (4.0)	50	45
10.	,,	Cs_2CO_3 (4.0)	53	45
11.	2.0	DIPEA (4.0)	95	-

[a]Reaction condition: 2,4-dinitro benzenesulfonyl chloride (1, 0.5 equiv.), amine (varied amount), base (varied amount) in dioxane medium at room temperature for 4 hours. [b]Isolated yield.

With this optimization condition in hand, we have illustrated the substrate scope with various amines and benzenesulfonyl chloride (Table 4.3.2.1) which produce reasonable yields.

4.3.3. Substrate Scope of N-alkylation[a]



entry	R′	RNH_2	1a-w: yield (%)[d]	2a-w: yield (%)[d]
1	NO_2	$PhCH_2NH_2$	1a: 95[b]	-
2	NO_2	*c*-hexyl-NH_2	1b: 91	trace
3	NO_2	*n*-Bu-NH_2	1c: 83	trace
4	NO_2	aniline	1d: 39	2d: 37
5	NO_2	*o*-toluidine	1e: 21	2e: 36
6	NO_2	*p*-anisidine	1f: 68	2f: 12
7	NO_2	*p*-F-aniline	1g: 33	-
8	NO_2	*p*-toluidine	1h: 71	2h: 18
9	NO_2	*o*-anisidine	1i: 25	2i: 46
10	NO_2	*i*-Bu-NH_2	1j: 76	-
11	NO_2	*p*-OMe-$BnNH_2$	1k: 80	-
12	NO_2	*n*-oclyl-NH_2	1l: 74	-

13	NO_2	*n*-dodecyl-NH_2	1m: 89	trace
14	NO_2	allylamine	1n: 75	-
15	NO_2	propargylamine	1o: 64	-
16	NO_2	*p*-Br-aniline	1p: 15	trace
17	NO_2	H_2N-Phg-OMe	1q: 15[c]	2q: 30[c]
18	NO_2	H_2N-Leu-OMe	1r: 36[c]	2r: 19[c]
19	CF_3	$PhCH_2NH_2$	1s: 40	2s: 48
20	CF_3	*p*-OMe-$BnNH_2$	1t: 46	2t: 41
21	CF_3	*n*-Bu-NH_2	1u: 39	2u: 49
22	CF_3	aniline	1v: 23	2v: 52
23	Cl	$PhCH_2NH_2$	Unidentified trace	2w: 62

*[a]Reactions were carried out using benzenesulfonyl chloride (**3**, 1.0 equiv.), amine (4.0 equiv.), and DIPEA (4.0 equiv.) and stirred for 4 h at room temperature. [b]This particular reaction was performed using 2.0 equiv. of amine with retaining other conditions. [c]For amino acid esters 6.0 equiv. of DIPEA were used. [d]Isolated yield.*

Table 4.3.3.1: *Substrate Scope*

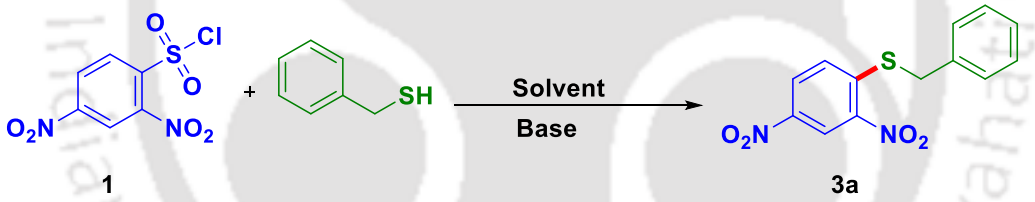
Aliphatic amines produce ipso products with sufficiently high yields (entries 1-3, 10, 12-15, 21), and in very few cases trace amounts of sulfonamide formation were noticed. Aromatic amines produce reasonable yields along with sulfonamide formation. Amino acid esters of phenyl glycine and leucine generated poor yields, 15% and 36% respectively (entries 17 and 18). Substrate 4-chloro-2-nitro-benzenesulfonyl chloride generates the corresponding sulfonamide product as a major product (62% yield, entry

23), and only a trace amount of unidentified product formation is noticed. Since the color of this unidentified trace was yellow and showed a similar R_f value as other N-alkylated products in TLC, it might be the corresponding ipso product.

4.3.4. Investigation for S-alkylation

Again we have investigated this protocol using thiol nucleophiles. For this case, 3.0 equivalent of both thiol and DIPEA is required (Table 4.3.2.1) at room temperature. Substrate scope has been increased using various thiols and benzenesulfonyl chlorides which produce up to 79% of yield.

Table 4.3.4.1. Optimization of the reaction conditions of S-alkylation reaction[a]



1 3a

Entry	Thiol (equiv.)	Base (equiv.)	Solvent	3a % yield[b]
1	1.0	DIPEA (1.0)	DMSO	27
2	,,	,,	DMF	35
3	,,	,,	THF	40
4	,,	,,	DCE	42
5	,,	,,	DCM	46
6	,,	,,	dioxane	47
7	,,	,,	$CHCl_3$	37

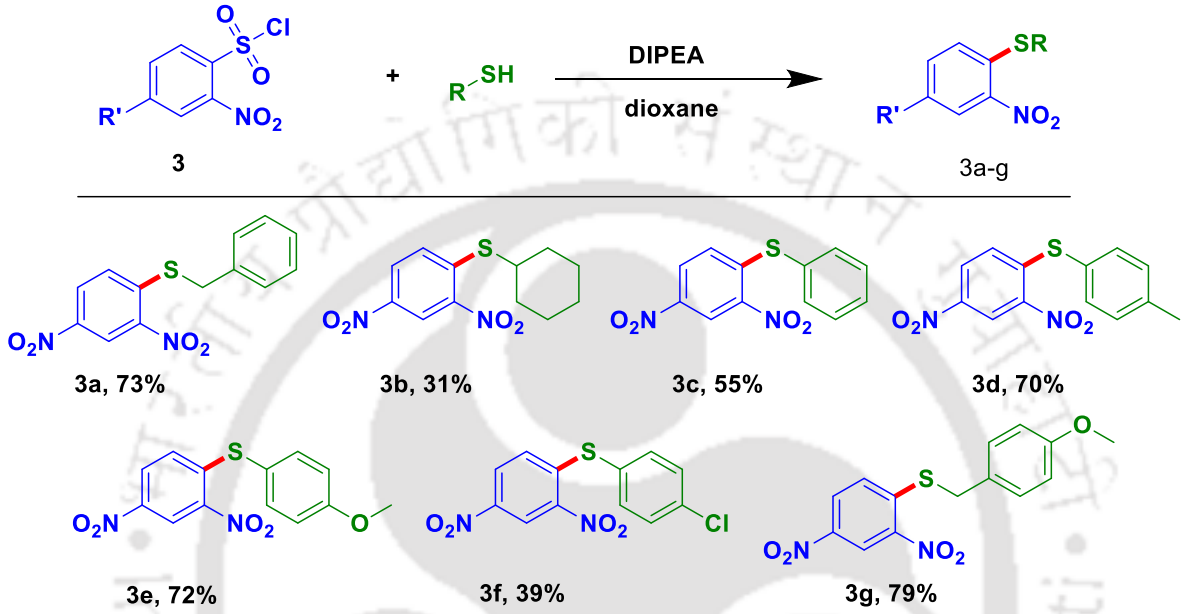
8	,,	,,	Acetone	43
9	,,	,,	ACN	45
10	2.0	,,	dioxane	54
11	3.0	,,	,,	59
12	4.0	,,	,,	60
13	3.0	K_2CO_3 (1.0)	,,	41
14	,,	Cs_2CO_3 (1.0)	,,	39
15	,,	Na_2CO_3 (1.0)	,,	29
16	,,	K_3PO_4 (1.0)	,,	35
17	,,	TEA (1.0)	,,	45
18	,,	DIPEA (3.0)	,,	73
19	,,	DIPEA (4.0)	,,	73

[a]*Reaction condition: 2,4-dinitro benzene sulphonyl chloride (**1**, 1.0 equiv.) and benzyl mercaptan (varied amount), base (varied amount) was stirred at room temperature for 6 hours;* [b]*yields after column chromatography.*

4.3.5. Substrate Scope for S-alkylation

In optimized condition, we have verified various thiol to increase the substrate scope (Scheme 4.3.5.1). Thiophenol produces 55% yield of the reaction (3c). It is found that the introducing an electron donating group (-Me, -OMe) in para position of thiol increases the formation of dithioethers (70% and 72% yield respectively) (3d, 3e). Whereas electron

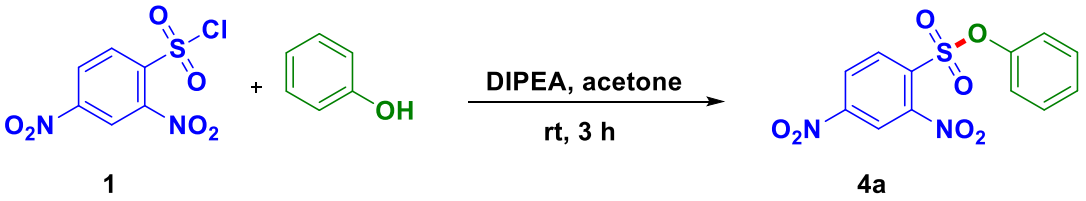
withdrawing group (-Cl) decreases the nucleophilicity of thiol, as a result its forms lower yield (39%, 3f). Aliphatic thiol generates sufficiently high yields (3a, 3g). Cyclohexyl thiol produces only 31% yield (3b). This is probably due to the steric hindrance.



*Reaction condition: benzenesulfonyl chloride derivative (**3**, 1.0 equiv.), thiol (3.0 equiv.) and DIPEA (3.0 equiv.) reaction time 4 to 6 hours at room temperature.*

Scheme 4.3.5.1: *Substrate Scope of diaryl thioether*

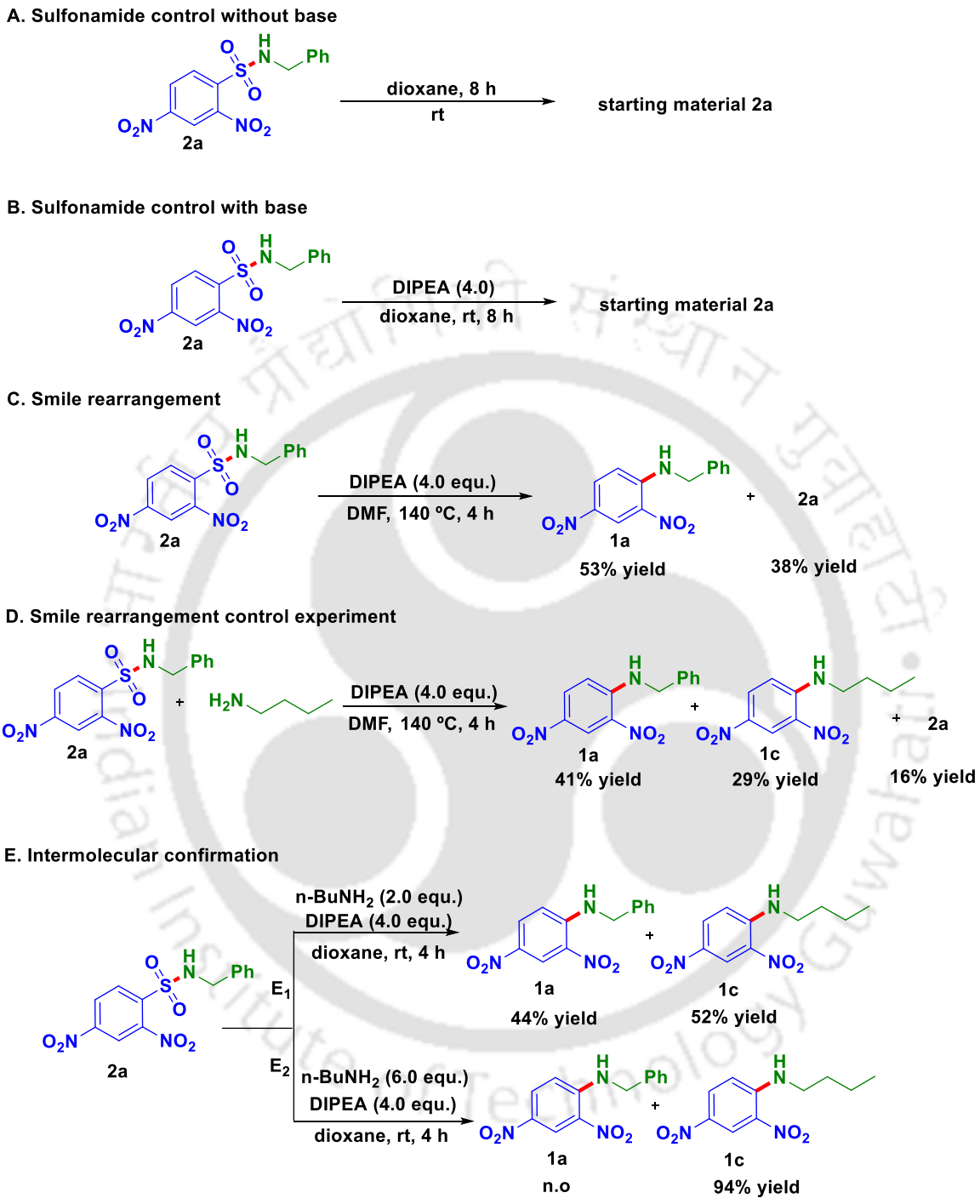
However, alcohol does not produce desired O-alkylated ipso product. It only substituted –Cl and formed the corresponding sulfonate ester product with an extremely high yield (99%). The product has been confirmed by SCXRD analysis. We have also verified this reaction with different bases and in various solvents but did not get an O-alkylated product.



Scheme 4.3.5.2: *Formation of sulfonate ester*

4.3.6. Mechanism

We then executed a series of reactions (Scheme 4.3.6.1) to understand the reaction mechanism. Since initially, sulfonamide formation occurs then ipso product formation started, (N-benzyl) 2,4-dinitro benzenesulfonamide (2a) was kept in observation without and with base for 8 h (Scheme 4.3.6.1A and 4.3.6.1B, respectively) in optimized conditions. No significant change was observed, which indicates the reaction does not follow the Smile rearrangement pathway at room temperature. Further, it was found that at higher temperatures (140 ºC) in the presence of a base, Smile rearrangement occurred and produced desired N-alkylated product (Scheme 4.3.6.1C). Surprisingly, in the crossover experiment, we isolated both possible products (1a and 1c) at high temperatures (Scheme 4.3.6.1D). That implies the Smile rearrangement and ipso aromatic substitution reaction occur simultaneously at higher temperatures. Another crossover experiment was performed at room temperature (Scheme 4.3.6.1E_1), where similar products were isolated as Scheme 4.3.6.1D. In the presence of excess n-$BuNH_2$, complete conversion occurred and 94% of 1c was obtained (Scheme 4.3.6.1E_2). Since, in the present condition no Smile rearrangement occurs, the reaction is going via an intermolecular pathway.



Scheme 4.3.6.1: *Mechanistic Investigations*

Time-dependent NMR Study

Sequential time-dependent ^{1}H NMR experiments were performed which also endorsed the intermolecular pathway for the formation of the ipso product (Figure 4.3.6.2- Figure 4.3.6.6). During the NMR titration proton signal shifted toward the downfield or upfield region. Interestingly, in the reaction medium, we found NMR signals (asterisk sign) that appear with the addition of benzylamine and increase with time, finally disappearing. These signals neither correspond to sulfonamide (2a) nor ipso product (1a). These transient signals are probably due to the formation of Meisenheimer adducts.

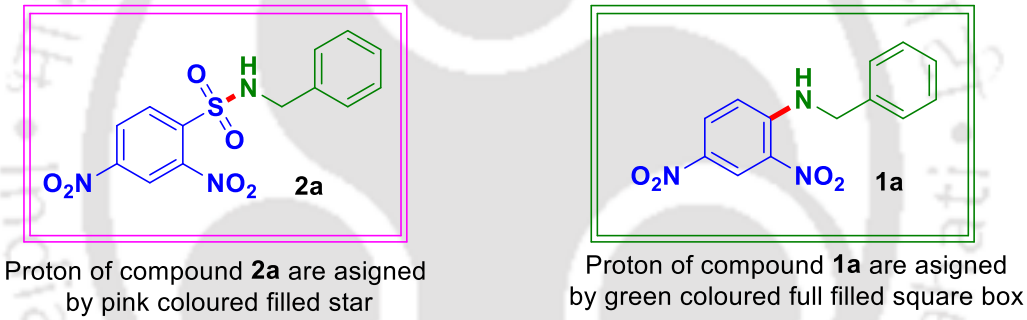


Figure 4.3.6.1: *Consideration of ^{1}H NMR signal colour and geometry*

(I) 2,4-DNBSCl + $BnNH_2$ + DIPEA

Experimental Procedure: Benzyl amine (21 mg, 0.2 mmol) and DIPEA (26 mg, 0.2 mmol) were taken in $CDCl_3$ medium. To this mixture 2,4-dinitrobenzene sulfonyl chloride (27 mg, 0.1 mmol) was added and started stirring. Immediately after adding, 0.5 mL of the reaction mixture was taken in a NMR tube and recorded proton NMR with various time (up to 180 min) at 400 MHz NMR.

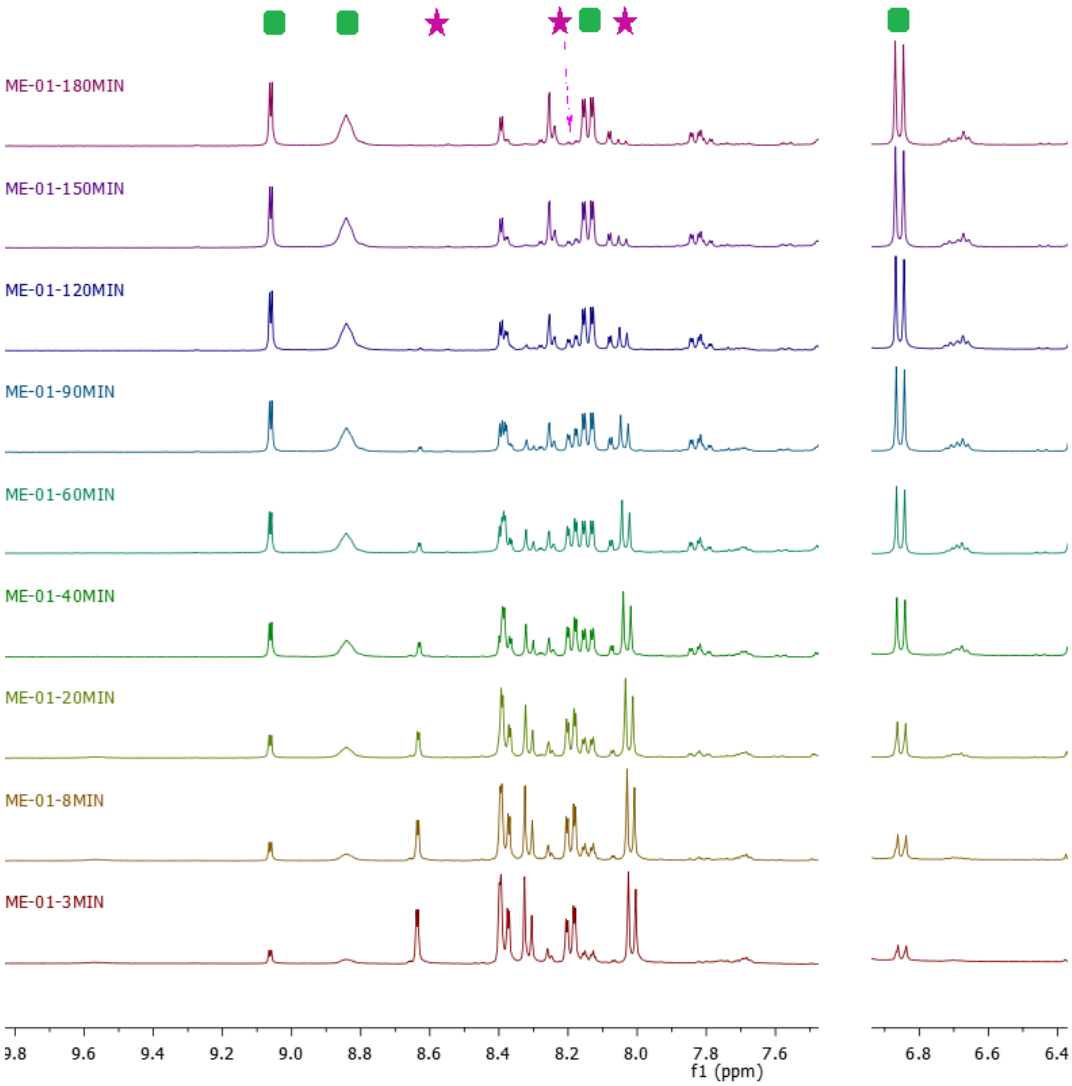


Figure 4.3.6.2: *Stacked ^1H NMR diagram for (2,4-DNBSCl + $BnNH_2$ + DIPEA)*

Explanation: With the addition of benzyl amine, sulfonamide product (2a) occurs exclusively immediately (at 3 min). All the protons for sulfonamide product (2a) are represented by pink coloured filled star. Along with that we have noticed relatively lower intensity peak (green coloured full filled square box) correspond to ipso product (1a). That indicates the ipso product (1a) formation started. The intensity of ipso product (1a) increases with time and maximum at 180 min. Reverse effect has been noticed for sulfonamide product (2a) which decreases with time and almost disappear after 180 min.

Therefore, in our methodology, first *in situ* formation of sulfonamide occurs by chloride displacement. Then nucleophile attack on the sulfonamide intermediate produces desired ipso product (1a).

(II) 2,4-DNBSCl + $BnNH_2$

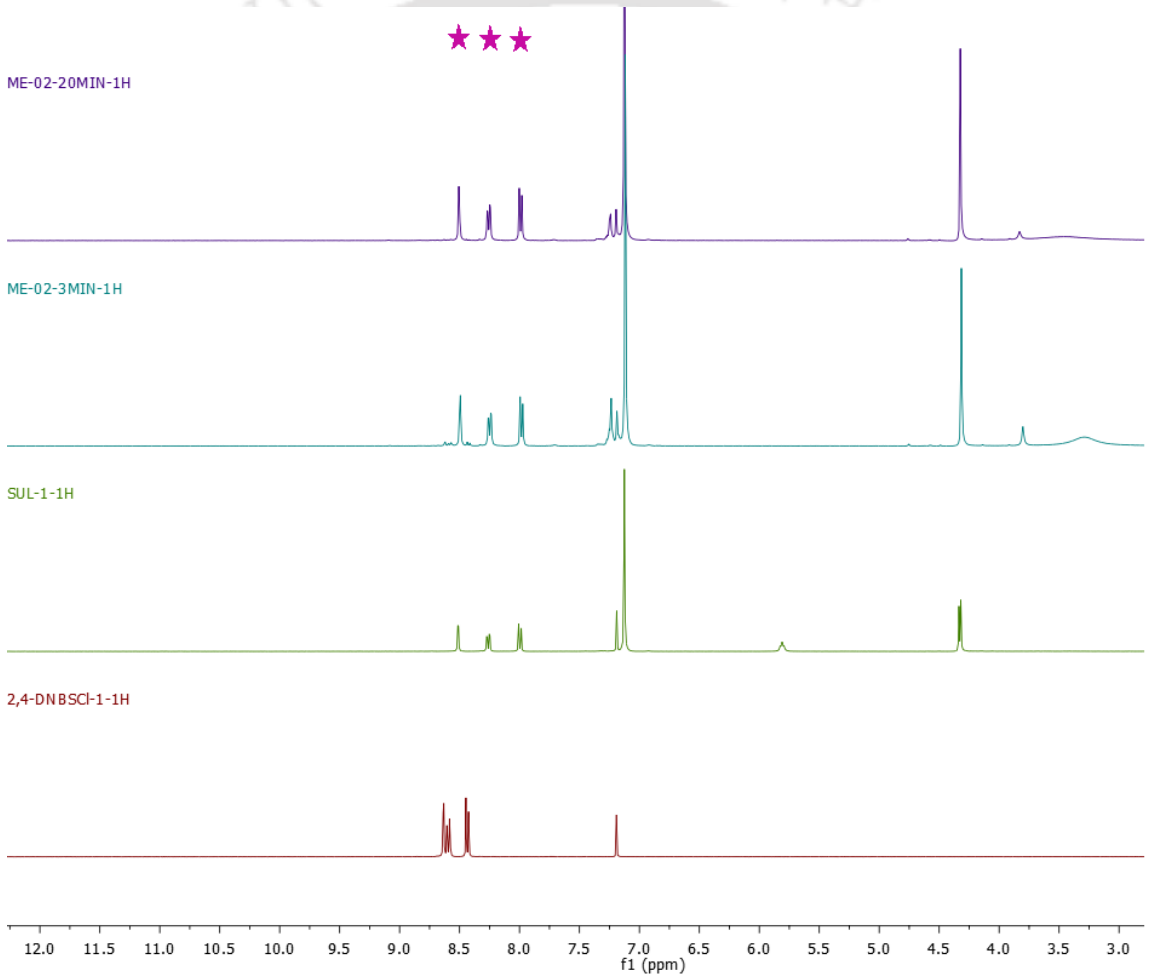


Figure 4.3.6.3: *Stacked ^1H NMR diagram for (2,4-DNBSCl + $BnNH_2$)*

Experimental Procedure: 2,4-dinitrobenzene sulfonyl chloride (27 mg, 0.1 mmol) was taken in $CDCl_3$ solvent. To this mixture benzyl amine (21 mg, 0.2 mmol) was added and

started stirring. Immediately after adding, 0.5 mL of the reaction mixture was taken in a NMR tube and recorded proton NMR at various time (up to 180 min) at 400 MHz NMR.

Explanation: In the Figure 4.3.6.4, lower two spectra are the reference of 2,4-dinitrobenzene sulfonyl chloride and sulfonamide product (2a). In this titration, in the absence of base only sulfonamide product (2a) was formed within 20 min. The newly generated peaks (of upper two spectra) are corresponding to sulfonamide product (2a) are compared with pure sulfonamide product (2a).

(III) (2,4-DNBSCl + $BnNH_2$) + DIPEA

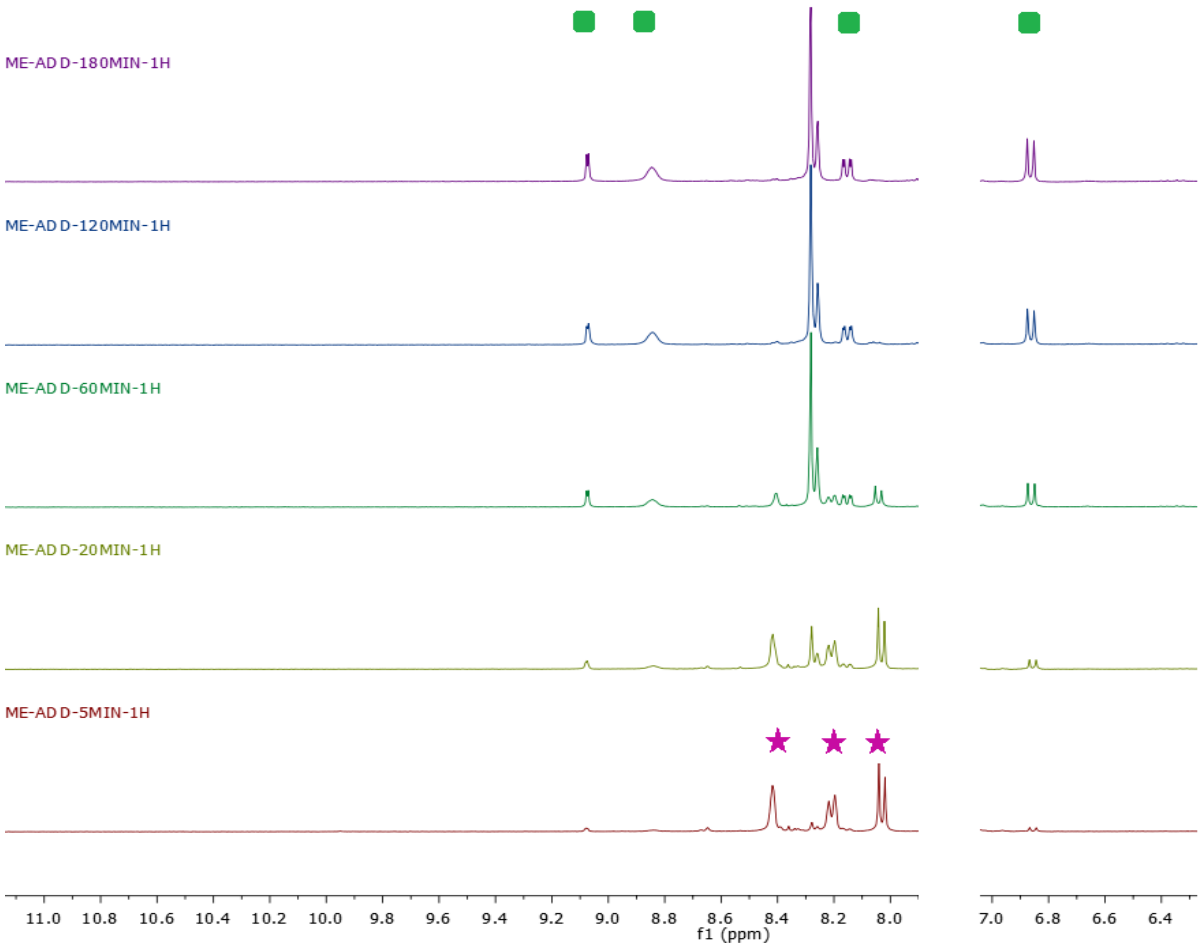


Figure 4.3.6.4: *Stacked ^1H NMR diagram for ((2,4-DNBSCl + $BnNH_2$) + DIPEA)*

Experimental Procedure: 2,4-dinitrobenzene sulfonyl chloride (27 mg, 0.1 mmol) and Benzyl amine (21 mg, 0.2 mmol) were taken in $CDCl_3$ solvent. Stirr the mixture for 30 min. To this mixture DIPEA (26 mg, 0.2 mmol) was added and started stirring again. Immediately after the addition, 0.5 mL of the reaction mixture was taken in a NMR tube and recorded proton NMR with various time (up to 180 min) at 400 MHz NMR.

Explanation: In 5 min we have notice the very lower intensity peak arises which are correspond to ipso product **(**1a**)**. Intensity of those peaks is increases with time indicate the formation of ipso product (1a) increases with time. At these mean times, peak intensity of sulfonamide product (2a) decreases and disappears after 120 min. Therefore, base plays an important role in our methodology. This base (DIPEA) enhances the nucleophilicity of the nucleophile (amine) to accelerate the reaction.

(IV) Compound 2a + $BnNH_2$

Experimental Procedure: 2,4-dinitrobenzene sulfonamide (32 mg, 0.1 mmol) was taken in $CDCl_3$ solvent. To this mixture and benzyl amine (21 mg, 0.2 mmol) was added and started stirring. Immediately after the addition, 0.5 mL of the reaction mixture was taken in a NMR tube and recorded proton NMR with various time (up to 15 h) at 400 MHz NMR.

Explanation: Here, with sulfonamide (2a) high concentration of benzyl amine (42 mg, 0.4 mmol) was added. From the Figure 4.3.6.6 it is clear that with the addition of benzyl amine the formation of ipso product started and increases very slowly. It requires 15 h to complete disappearing of sulfonamide peaks. Since benzyl amine is weakly basic in nature which abstracts the proton of another molecule of benzyl amine present in the

reaction mixture and produces corresponding anion. This anion attacks on sulfonamide (2a) and produced the final ipso product (1a).

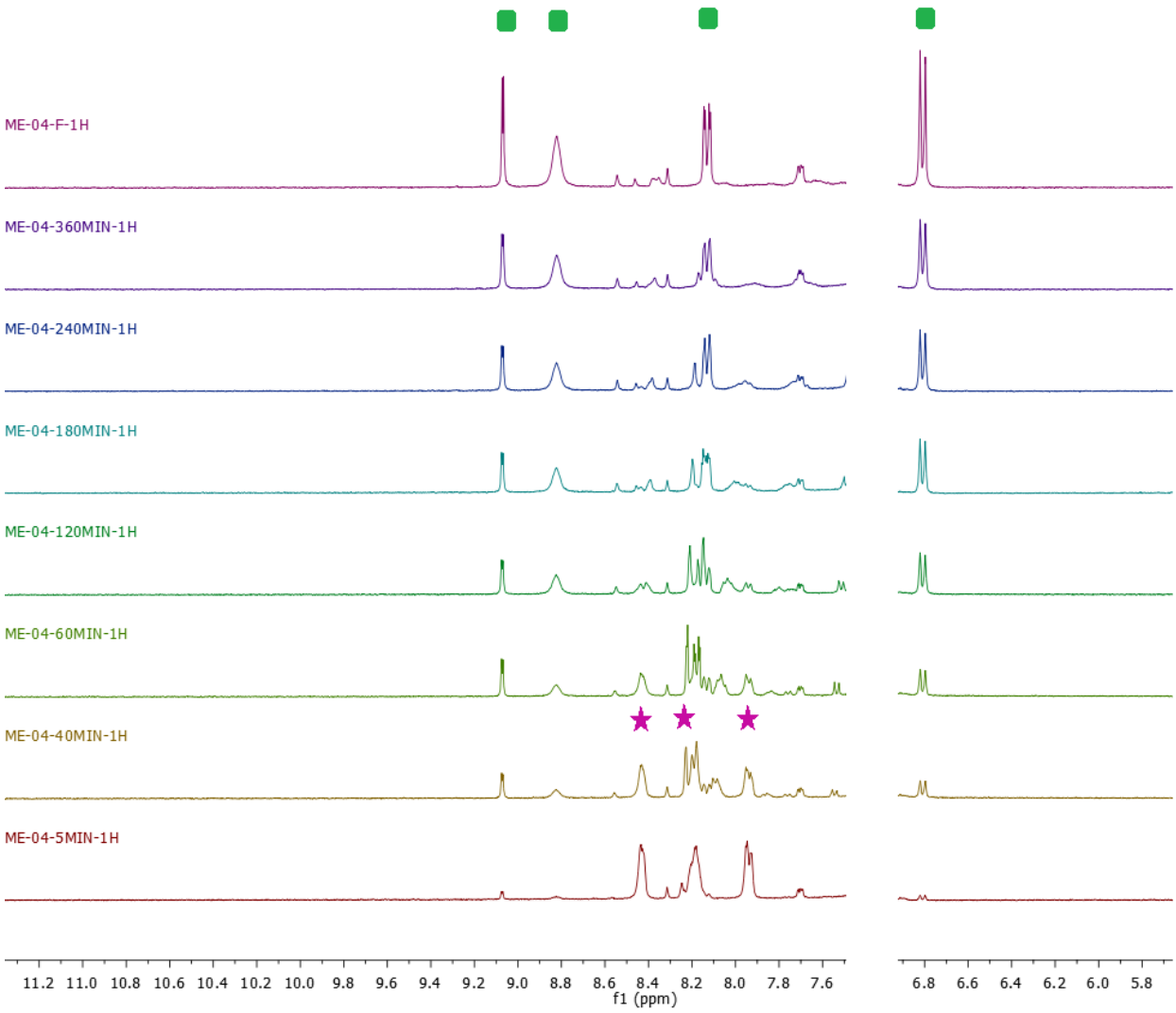


Figure 4.3.6.5: *Stacked ^{1}H NMR diagram for (Compound 2a + $BnNH_2$)*

(V) compound 2a + DIPEA (after 3 h, $BnNH_2$ added)

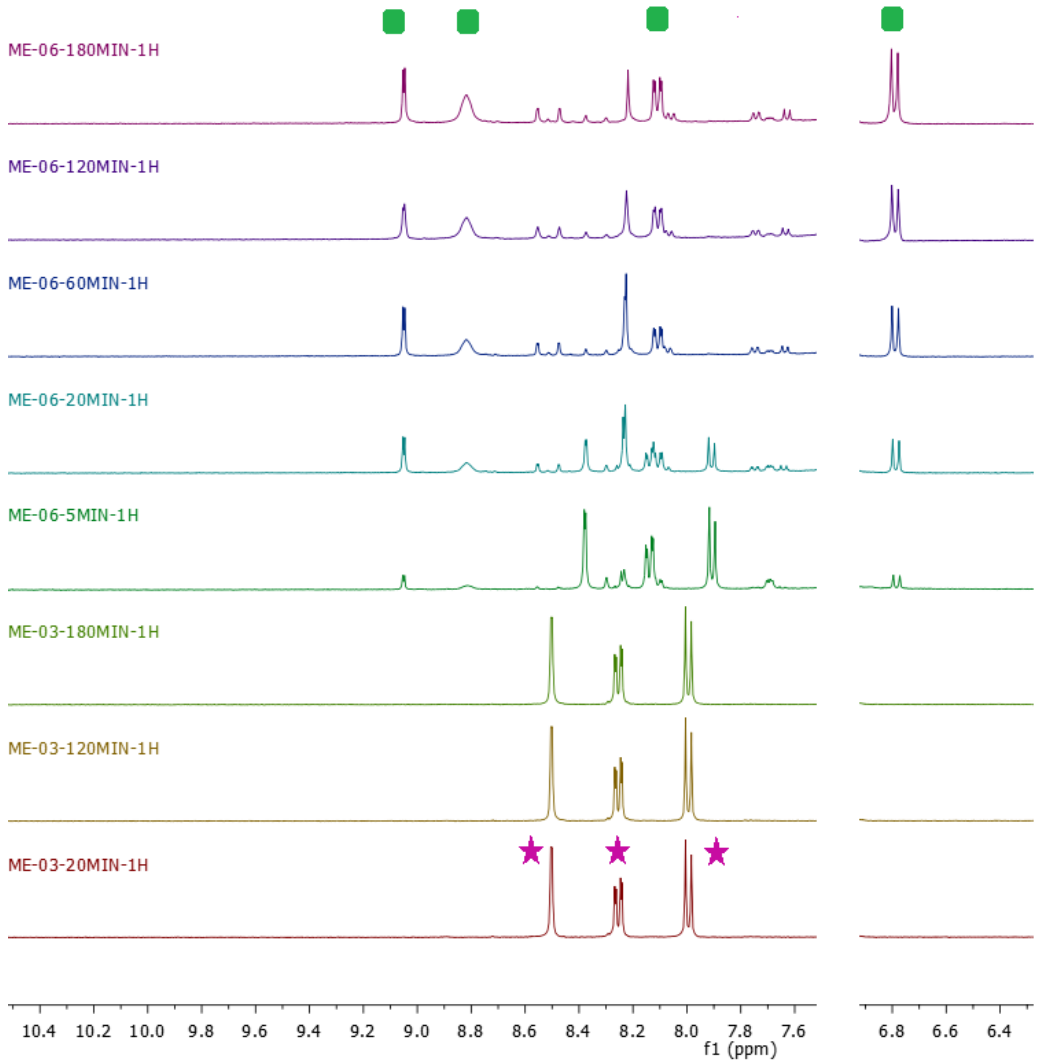


Figure 4.3.6.6: *Stacked ^1H NMR diagram for (compound 2a + DIPEA (after 3 h, $BnNH_2$ added))*

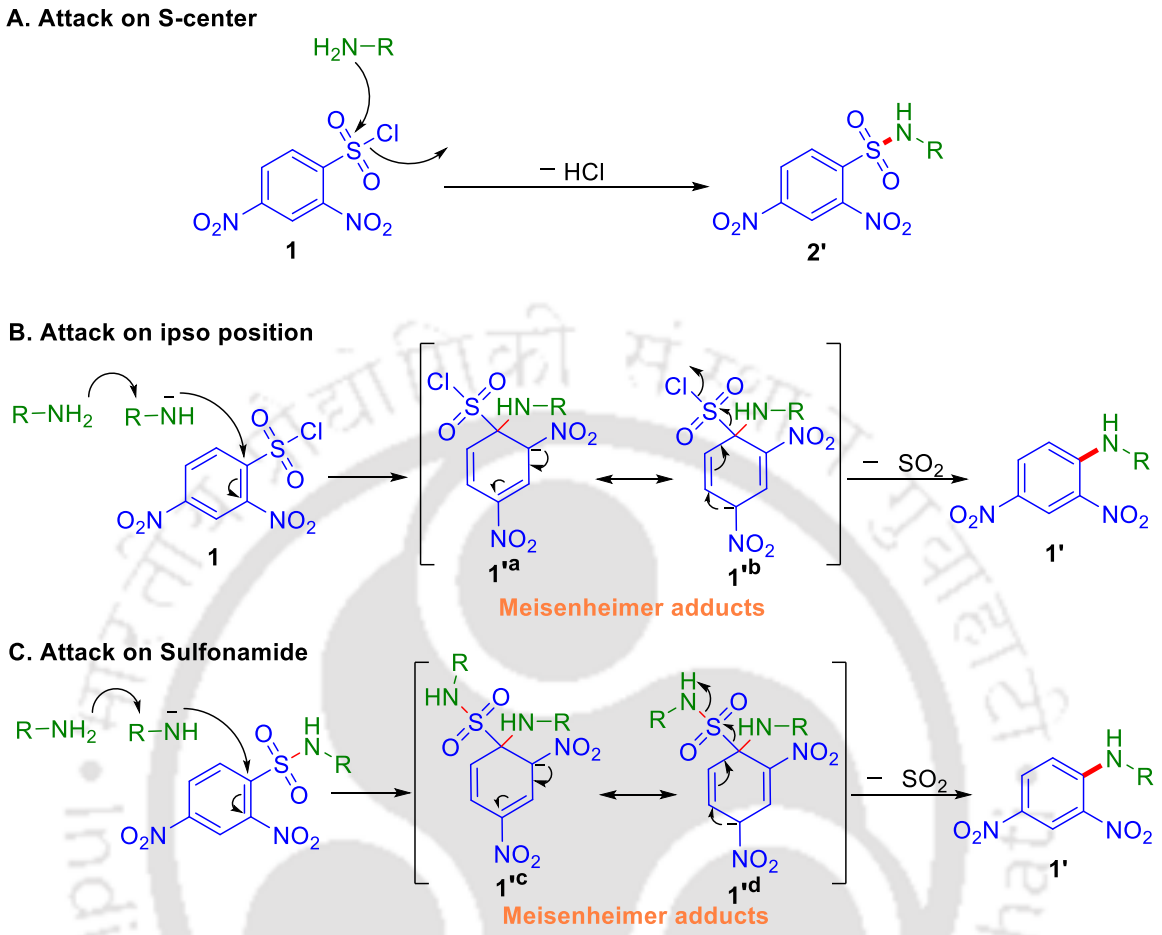
Experimental Procedure: 2,4-dinitrobenzene sulfonamide (32 mg, 0.1 mmol) and DIPEA (26 mg, 0.2 mmol) were taken in $CDCl_3$ solvent. Immediately after the addition of DIPEA, 0.5 mL of the reaction mixture was taken in a NMR tube and recorded proton NMR with various time (up to 3 h) at 400 MHz NMR. Then to the whole mixture, benzyl amine (21 mg, 0.2 mmol) was added and started stirring. Immediately after the addition,

0.5 mL of the reaction mixture was taken in a NMR tube and recorded in a similar fashion.

Explanation: In the first case, i.e., on the addition of DIPEA with sulfonamide (2a) no change in NMR spectra was observed. Also no new peaks correspond to ipso product was observed up to 3 h (lower 3 spectra). If our methodology goes via intra molecular Smile rearrangement pathway, then we should observe the new peaks generation for ipso product (**1a**) slowly from the beginning. Since no such phenomenon was observed, we can infer that our reaction is not intramolecular. As soon as we add benzyl amine to the mixture, the new peaks (with low intensity) for ipso product (1a) were observed within 5 min (4^{th} spectrum form below) and increases with time (5^{th} spectrum form below and all above). It signifies that the external nucleophile (benzyl amine) attacked the sulfonamide (2a) and produced the final ipso product (1a). Therefore, our protocol is following intermolecular pathway.

Proposed reaction Mechanism

Above mentioned experiments and existing literature indicates that sulfonamide formation occurs by the attack of amine on the S-center of the substrate with the departure of chloride ion, which further generates HCl (Scheme 4.3.6.2A).

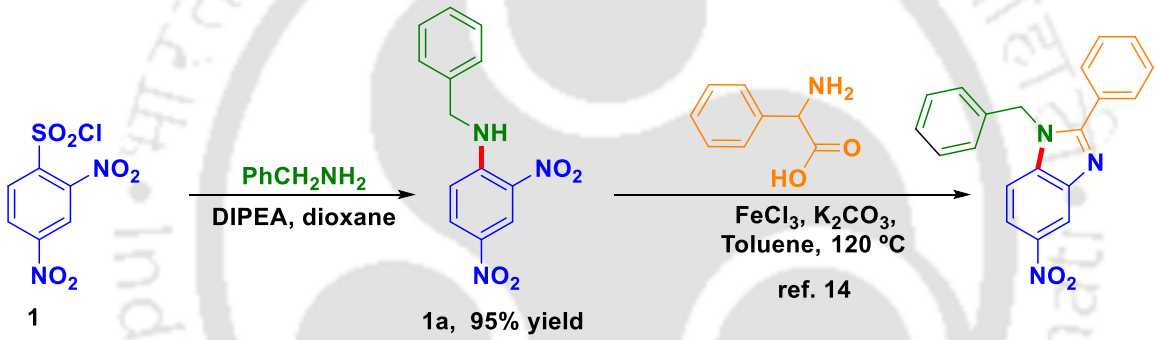


Scheme 4.3.6.2: *Plausible Reaction Mechanism*

Alternatively, nucleophiles may attack to the ipso position to produce an N-alkylated product by the ipso substitution mechanism with SO_2 extrusion (Scheme 4.3.6.2B) directly. The reaction goes via Meisenheimer adduct formation which may be stabilized by an additional ortho effect.[12] Similarly, thiol follows the later pathway. Also, first 2,4-DNBSCl can first form sulfonamide with amines in which amines attack the ipso position to produce an N-alkylated product (Scheme 4.3.6.2C).

4.3.7. Applications

The benzimidazole derivatives are crucial as therapeutic agents, such as antiulcer and anthelmintic drugs. Benzimidazole derivatives also exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory, analgesic, etc.[13] Herein, we have synthesized the important synthon (1a) which can react with phenyl glycine in the presence of the catalytic amount of $FeCl_3$ to construct dialkylbenzimidazoles (Scheme 4.3.7.1).[14]



***Scheme 4.3.7.1**: A representative post-synthetic application*

4.4. Conclusion

In summary, we have disclosed a transition metal-free strategy of diarylamine and diaryl thioether synthesis under mild reaction conditions by intermolecular ipso aromatic nucleophilic substitution. This method is applicable to highly electron-deficient aryl sulfonyl chlorides. A systematic mechanistic study revealed that although we have finally obtained the Smile rearrangement product no Smile rearrangement occurred. Application possibilities in medicinal chemistry are demonstrated.

4.5. Experimental Section

General Information

All reagents were purchased from commercial sources. NMR spectra were recorded on 400 MHz, 500 MHz, and 600 MHz spectrometers using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) were reported in ppm, and spin-spin coupling constants (J) were given in Hz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dq (doublet of the quartet), and m (multiplet). $^{13}C\{^{1}H\}$ indicates the proton decoupled NMR experiment. Reactions were monitored using thin-layer chromatography with silica gel G254. The reaction products were purified by column chromatography using silica gel (60-120 mesh) using eluent EtOAc/Hexane. Solvents were removed under reduced pressure using a Buchi rotary evaporator. Melting points were determined using a dedicated melting point measuring apparatus, and FT-IR spectra were recorded on an FT-IR spectrometer.

General procedure for the synthesis of aryl sulfonamide

Calculated amount of amine (0.7 mmol) was taken in 50 mL RB and dissolved it with 4 mL of dioxane. To this mixture 2,4-dinitro benzenesulfonyl chloride (0.5 mmol) was added. The whole mixture was stirred at room temperature for 30 minute. The progress of the reaction was monitored by TLC. After completion of the reaction, dioxane was evaporated under reduced pressure and diluted with ethyl acetate (10 mL). This solution was poured in to a separating funnel and washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After

that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 5-10% EtOAc/hexane solution.

General procedure for the synthesis of N-alkylated product

Calculated amount of amine (2.0 mmol) and DIPEA (2.0 mmol) was taken in 50 mL RB and dissolved it with 4 mL of dioxane. After 5 minutes, 2,4-dinitro benzenesulfonyl chloride (0.5 mmol) was added to this mixture. The whole mixture was stirred at room temperature for 4 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, dioxane was evaporated under reduced pressure and diluted with ethyl acetate (10 mL). This solution was poured in to a separating funnel and washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 5-10% EtOAc/hexane solution.

General procedure for the synthesis of S-alkylated product

Calculated amount of amine (1.5 mmol) and DIPEA (1.5 mmol) was taken in 50 mL RB and dissolved it with 4 mL of dioxane. After 5 minutes, 2,4-dinitro benzenesulfonyl chloride (0.5 mmol) was added to this mixture. The whole mixture was stirred at room temperature for 4-6 hours (reaction time required for the formation of **3a**, **3b** and **3g** is 4 hours, on the other hand for product **3c-f** 6 hours). The progress of the reaction was monitored by TLC. After completion of the reaction, dioxane was evaporated under reduced pressure and diluted with ethyl acetate (10 mL). This solution was poured in to a separating funnel and washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL),

saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 1-2% EtOAc/hexane solution.

General procedure for the synthesis of 4a

A calculated amount of phenol (1.0 mmol) and DIPEA (1.0 mmol) was taken in 50 mL RB and dissolved it with 4 mL of acetone. After 5 minutes, 2,4-dinitro benzenesulfonyl chloride (0.5 mmol) was added to this mixture. The whole mixture was stirred at room temperature for 1 hour. The progress of the reaction was monitored by TLC. After completion of the reaction, dioxane was evaporated under reduced pressure and diluted with ethyl acetate (10 mL). This solution was poured into a separating funnel and washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL), saturated NaCl solution (2×10 mL), and dried over anhydrous Na_2SO_4. After that reaction mixture was concentrated using a rotary evaporator. The residue was purified by column chromatography using 5-10% EtOAc/hexane solution.

4.6. Characterization Data

***N-Benzyl-2,4-dinitrobenzenesulfonamide* (2a)**[15]

As a white solid (161 mg, 96% yield, mp 127−128 ^oC); Purification over a column of silica gel (5-10% EtOAc in hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.58 (d, 1H, J = 2.0 Hz), 8.33 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 8.07 (d, 1H, J = 8.4 Hz), 7.22-7.17 (m, 5H), 5.89 (s, 1H), 4.39 (d, J = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 149.75,

139.93, 135.47, 132.73, 128.99, 128.57, 128.22, 126.94, 120.62, 48.30. IR (KBr, cm^{-1}): 3355, 3104, 3033, 3005, 2970, 1708, 1599, 1553, 1540, 1349, 1170, 905, 725.

***N-Cyclohexyl-2,4-dinitrobenzenesulfonamide* (2b)**

As a white solid (149 mg, 91% yield, mp 137–139 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, 1H, J = 2.4 Hz), 8.55 (dd, 1H, J_1 = 2.2 Hz, J_2 = 8.6 Hz), 8.39 (d, 1H, J = 8.8 Hz), 5.29 (d, 1H, J = 7.6 Hz), 3.44-3.37 (m, 1H), 1.82–1.79 (m, 2H), 1.69–1.66 (m, 2H), 1.58–1.54 (m, 2H), 1.31–1.27 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 149.93, 148.31, 141.06, 132.46, 127.40, 120.99, 54.25, 34.10, 25.16, 24.73; IR (KBr, cm^{-1}): 3333, 3104, 2933, 2856, 1737, 1604, 1536, 1423, 1347, 1167, 1070, 997, 746.

***N-Butyl-2,4-dinitrobenzenesulfonamide* (2c)[16]**

As a white solid (135 mg, 89% yield, mp 78-80^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, 1H, J = 2.0 Hz), 8.55 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 8.35 (d, 1H, J = 8.4 Hz), 5.36 (t, 1H, J = 6.0 Hz), 3.15 (q, 2H, J =6.6 Hz), 1.52 (quint, 2H, J = 7.4 Hz), 1.33 (sext, 2H, J = 7.28 Hz), 0.88 (t, 3H, J = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 149.9, 148.4, 139.5, 132.8, 127.3, 120.9, 43.9, 31.8, 19.8, 13.6; IR (KBr, cm^{-1}): 3366, 3104, 2962, 2925, 2875, 1738, 1551, 1539, 1417, 1347, 1265, 1169, 1077, 732.

***2,4-Dinitro-N-phenylbenzenesulfonamide* (2d)[15]**

As a white solid (129 mg, 80% yield, mp 107–108 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.66 (d, 1H, J = 2.4 Hz), 8.37 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 8.03 (d, 1H, J =9.0 Hz), 7.32–7.29 (m, 3H),

7.24 (d, 1H, J = 7.5 Hz), 7.20 (d, 2H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 150.3 148.7, 137.8, 134.7, 133.7, 129.9, 127.6, 126.9, 123.7, 120.8; IR (KBr, cm^{-1}): 3354, 3118, 2928, 2856, 1608, 1598, 1550, 1492, 1398, 1349, 11714, 1105, 901, 835, 737, 689.

***2,4-Dinitro-N-(o-tolyl)benzenesulfonamide* (2e)[16]**

As a brown solid (140 mg, 84% yield, mp 146–148 ^oC); Purification over a column of silica gel (5-10% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.69 (d, 1H, J = 2.0 Hz), 8.42 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 8.05 (d, 1H, J =9.0 Hz), 7.19–7.18 (m, 3H), 7.17–7.12 (m, 2H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 150.2, 148.5, 138.9, 133.9, 133.3, 133.1, 131.7, 128.2, 127.3, 127.1, 125.8, 120.9, 18.1; IR (KBr, cm^{-1}): 3321, 3113, 2951, 2922, 2851, 1605, 1539, 1493, 1458, 1393, 1343, 1170, 1107, 909, 833, 738, 710.

***N-(4-Methoxyphenyl)-2,4-dinitrobenzenesulfonamide* (2f)[15]**

As a yellowish solid (155 mg, 88% yield, mp 132–133 ^oC); Purification over a column of silica gel (5-10% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.44 (d, 1H, J = 2.0 Hz), 8.28 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 7.69 (d, 1H, J =9.0 Hz), 7.37–7.36 (m, 3H), 7.24–7.22 (m, 2H), 3.44 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 149.9, 139.8, 137.0, 133.7, 129.9, 128.9, 127.9, 125.6, 122.6, 119.6, 40.1; IR (KBr, cm^{-1}): 3316, 3108, 2959, 2922, 2853, 1593, 1556, 1530, 1492, 1453, 1360, 1300, 1264, 1182, 1153, 1060, 887, 833, 747, 695.

***N-(4-Fluorophenyl)-2,4-dinitrobenzenesulfonamide* (2g)**[17]

As a yellowish solid (95 mg, 57% yield, mp 138–140 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (d, 1H, J = 2.0 Hz), 8.40 (dd, 1H, J_1 = 8.75 Hz, J_2 = 2.25 Hz), 8.07 (d, 1H, J = 8.5 Hz), 7.46 (s, 1H), 7.34–7.31 (m, 2H), 7.25-7.22 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 150.2, 148.5, 137.7, 134.7, 133.6, 129.9, 127.4, 126.9, 123.6, 120.8; IR (KBr, cm^{-1}): 3328, 3105, 2923, 2893, 2856, 1605, 1537, 1505, 1391, 1347, 1170, 834, 747.

***N-Benzyl-2,4-dinitroaniline* (1a)**[18]

As a yellow solid (130 mg, 96% yield, mp 113–115 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.17 (d, 1H, J = 2.5 Hz), 8.90 (s, 1H), 8.23 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.42–7.39 (m, 2H), 7.37–7.33 (m, 3H), 6.91 (d, 1H, J = 9.5 Hz), 4.65 (d, 2H, J = 5.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 148.4, 136.8, 135.8, 131.0, 130.6, 129.5, 129.2, 127.3, 124.4, 114.6, 47.8; IR (KBr, cm^{-1}): 3378, 3103, 2942, 2876, 1610, 1579, 1491, 1414, 1328, 1257, 1146, 1070, 917, 830, 743, 712, 694.

***N-Cyclohexyl-2,4-dinitroaniline* (1b)**[18]

As a yellow solid (120 mg, 91% yield, mp 152–154 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.14 (d, 1H. J = 3.0 Hz), 8.62 (s, 1H), 8.24 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.93 (d, 1H, J = 9.5 Hz), 3.62–3.61 (m, 1H), 2.09–2.07 (m, 2H), 1.84–1.82 (m, 2H), 1.72–1.68 (m, 1H), 1.48–1.44

(m, 4H), 1.36–1.33 (m, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 147.7, 135.9, 130.42, 130.38, 124.9, 114.4, 52.1, 32.6, 25.5, 24.6; IR (KBr, cm^{-1}): 3350, 3108, 2943, 2854, 1617, 1513, 1419, 1324, 1251, 1131, 1087, 1049, 920, 829, 744, 714.

***N-Butyl-2,4-dinitroaniline* (1c)[18]**

As a yellow solid (99 mg, 83% yield, mp 86–88 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.15 (d, 1H, J = 2.5 Hz), 8.55 (s, 1H), 8.28 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.92 (d, 1H, J = 10.0 Hz), 3.41 (q, 2H, J = 3.0 Hz), 1.80–1.74 (m, 2H), 1.53–1.49 (m, 2H), 1.01 (t, 3H, J = 7.2 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 148.6, 130.9, 130.6, 130.5, 124.6, 114.1, 43.6, 30.9, 20.4, 13.9; IR (KBr, cm^{-1}): 3356, 3111, 2954, 2871, 1616, 1583, 1518, 1417, 1328, 1268, 1221, 1110, 1070, 921, 830, 743, 701.

***2,4-Dinitro-N-phenylaniline* (1d)[18]**

As a orange solid (50 mg, 39% yield, mp 101–102 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.98 (s, 1H), 9.19 (d, 1H, J = 2.5 Hz), 8.17 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.51 (t, 2H, J = 8.0 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.31 (d, 2H, J = 7.5 Hz), 7.17 (d, 1H, J = 9.5 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 147.3, 136.9, 130.5, 130.1, 127.9, 125.8, 124.3, 116.2; IR (KBr, cm^{-1}): 3315, 3113, 2963, 2853, 1617, 1595, 1581, 1516, 1495, 1321, 1257, 1144, 1121, 1058, 921, 844, 743, 684.

***2,4-Dinitro-N-(o-tolyl)aniline* (1e)[19]**

As a yellow solid (29 mg, 21% yield, mp 112–114 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.82 (s, 1H), 9.21 (d, 1H, J = 3.0 Hz), 8.16 (dd, 1H, J_1 = 9.5 Hz, J_2 = 3.0 Hz), 7.41–7.39 (m, 1H), 7.34–7.32 (m, 2H), 7.26 (d, 1H, J = 9.0 Hz), 6.82 (d, 1H, J = 9.5 Hz), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.7, 142.3, 135.4, 135.2, 133.6, 132.1, 130.3, 128.7, 127.9, 127.0, 124.4, 116.1, 14.3; IR (KBr, cm^{-1}): 3329, 2955, 2920, 2851, 1731, 1616, 1585, 1462, 1360, 1255, 1126, 918, 741.

***N-(4-Methoxyphenyl)-2,4-dinitroaniline* (1f)[18]**

As an orange solid (98 mg, 68% yield, mp 135–137 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.87 (br: s, 1H), 9.18 (d, 1H, J = 2.8 Hz), 8.14 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.8 Hz), 7.22 (d, 2H, J = 8.8 Hz), 7.01 (d, 3H, J = 9.2 Hz), 3.87 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 159.3, 148.2, 137.3, 130.9, 130.1, 129.4, 127.7, 124.3, 116.2, 115.6, 55.8; IR (KBr, cm^{-1}): 3309, 3103, 2922, 2852, 1615, 1581, 1459, 1420, 1316, 1275, 1245, 1121, 1057, 927, 832, 742, 699.

***N-(4-Fluorophenyl)-2,4-dinitroaniline* (1g)[20]**

As a orange solid (37 mg, 33% yield, mp 165–167 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.87 (s, 1H), 9.19 (d, 1H, J = 2.5 Hz), 8.18 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.32–7.28 (m, 2H), 7.21 (t, 2H, J = 8.5 Hz), 7.03 (d, 1H, J = 9.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 161.9 (d, J = 247.1 Hz), 147.6, 137.7, 132.8 (d, J = 3.2 Hz), 131.3, 130.2, 128.1 (d, J = 8.5 Hz), 124.3,

117.5 (d, J = 22.6 Hz), 115.9; IR (KBr, cm^{-1}): 3306, 3106, 2921, 2856, 1615, 1582, 1500, 1426, 1334, 1232, 1122, 1097, 925, 832, 783, 740, 662.

2,4-Dinitro-N-(p-tolyl)aniline **(1h)**[21]

As a orange solid (96 mg, 71% yield, mp 139–140 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.92 (s, 1H), 9.18 (d, 1H, J = 3.0 Hz), 8.14 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.30 (d, 2H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.5 Hz), 7.11 (d, 1H, J = 9.5 Hz), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.7, 138.1, 137.4, 134.2, 131.2, 131.0, 130.1, 125.8, 124.3, 116.3, 21.3; IR (KBr, cm^{-1}): 3061, 2924, 2853, 1588, 1481, 1454, 1378, 1293, 1218, 1151, 1071, 924, 774, 690.

N-(2-methoxyphenyl)-2,4-dinitroaniline **(1i)**[19]

As a orange solid (35 mg, 25% yield, mp 146–148 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.87 (s, 1H), 9.18 (d, 1H, J = 3.0 Hz), 8.16 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.11 (d, 1H, J = 9.5 Hz), 7.07–7.04 (m, 2H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 161.6, 149.6, 138.2, 132.7, 129.9, 128.7, 125.7, 124.3, 121.3, 116.5, 112.5, 112.3, 55.9; IR (KBr, cm^{-1}): 3336, 3102, 2923, 2853, 1619, 1592, 1534, 1464, 1338, 1280, 1144, 1048, 833, 748, 735, 697.

N-iso-Butyl-2,4-dinitroaniline **(1j)**[19]

As a yellow solid (90 mg, 76% yield, mp 79–81 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.15 (d, 1H, J = 3.0 Hz),

8.66 (s, 1H), 8.26 (dd, 1H, J_1 = 9.5 Hz, J_2 = 3.0 Hz), 6.91 (d, 1H, J = 9.5 Hz), 3.23 (t, 2H, J = 6.2 Hz), 2.11–2.03 (m, 1H), 1.09 (d, 6H, J = 6.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 148.8, 136.2, 130.5, 124.6, 114.1, 51.3, 28.2, 20.5; IR (KBr, cm^{-1}): 3350, 3101, 2956, 2922, 2853, 1617, 1583, 1519, 1468, 1417, 1308, 1230, 1132, 1066, 922, 824, 793, 743.

***N-(4-Methoxybenzyl)-2,4-dinitroaniline* (1k)**[22]

As a yellow solid (120 mg, 80% yield, mp 107–109 ^oC); Purification over a column of silica gel (5-10% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.15 (d, 1H, J = 3.0 Hz), 8.82 (s, 1H), 8.24 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.27 (d, 2H, J = 8.5 Hz), 6.94–6.92 (m, 3H), 4.57 (d, 2H, J = 5.5 Hz), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.8, 148.3, 136.6, 130.9, 130.5, 128.8, 127.6, 124.4, 114.8, 114.5, 55.6, 47.4; IR (KBr, cm^{-1}): 3377, 3111, 2918, 2839, 1613, 1589, 1515, 1495, 1330, 1277, 1178, 1077, 1029, 917, 811, 743, 709.

***2,4-Dinitro-N-octylaniline* (1l)**[23]

As a yellow liquid (109 mg, 74% yield); Purification over a column of silica gel (0.5-2.0% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.11 (d, 1H, J = 3.0 Hz), 8.54 (s, 1H), 8.25 (dd, 1H, J_1 = 9.5 Hz, J_2 = 3.0 Hz), 6.91 (d, 1H, J = 10.0 Hz), 3.41–3.37 (m, 2H), 1.79–1.73 (m, 2H), 1.46–1.42 (m, 2H), 1.31–1.23 (m, 8H), 0.87 (t, 3H, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 148.6, 136.1, 130.5, 130.4, 124.5, 114.1, 53.6, 43.8, 31.9, 29.3, 28.9, 27.1, 22.8, 14.2; IR (KBr, cm^{-1}): 3366, 3106, 2954, 2924, 2854, 1619, 1589, 1523, 1466, 1425, 1333, 1310, 1135, 1082, 922, 832, 744, 712.

N-Dodecyl-2,4-dinitroaniline **(1m)**

As a yellow solid (155 mg, 89% yield, mp 64–66 ^{o}C); Purification over a column of silica gel (0.5-2.0% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.15 (d, 1H, J = 2.5 Hz), 8.55 (s, 1H), 8.27 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.91 (d, 1H, J = 9.5 Hz), 3.40 (q, 2H, J = 6.5 Hz), 1.81–1.75 (m, 2H), 1.49–1.43 (m, 2H), 1.38–1.26 (m, 16H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 148.6, 136.2, 130.6, 124.6, 114.1, 43.8, 32.1, 29.8, 29.73, 29.66, 29.5, 29.4, 28.9, 27.2, 22.9, 14.3; IR (KBr, cm^{-1}): 3339, 3103, 2954, 2916, 2849, 1613, 1583, 1500, 1468, 1415, 1331, 1299, 1255, 1136, 1090, 1055, 921, 817, 797, 702.

N-Allyl-2,4-dinitroaniline **(1n)**[24]

As a yellow solid (83 mg, 75% yield, mp 73–75 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.15 (d, 1H, J = 2.5 Hz), 8.68 (s, 1H), 8.27 (dd, 1H, J_1 = 9.5 Hz, J_2 = 3.0 Hz), 6.91 (d, 1H, J = 9.5 Hz), 5.99–5.92 (m, 1H), 5.36–5.32 (m, 2H), 4.09 (t, 2H, J = 5.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 148.5, 136.6, 131.8, 130.8, 130.5, 124.4, 118.5, 114.5, 45.9; IR (KBr, cm^{-1}): 3361, 3106, 2920, 2849, 1617, 1582, 1518, 1416, 1312, 1231, 1157, 1132, 1068, 988, 923, 821, 763, 708.

2,4-Dinitro-N-(prop-2-yn-1-yl)aniline **(1o)**[25]

As a yellow solid (70 mg, 64% yield, mp 148–151 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.17 (d, 1H, J = 2.5 Hz), 8.66 (s, 1H), 8.36 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.07 (d, 1H, J = 9.5 Hz),), 8.24

(dd, 2H, J_1 = 5.5 Hz, J_2 = 2.5 Hz), 2.38 (t, 1H, J = 2.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 147.6, 137.3, 131.5, 130.6, 124.3, 114.5, 77.4, 73.8, 33.3; IR (KBr, cm^{-1}): 3373, 3275, 3103, 2954, 2921, 2849, 1612, 1582, 1497, 1408, 1333, 1307, 1252, 1228, 1126, 1081, 1052, 914, 820, 744, 697.

***N-(4-Bromophenyl)-2,4-dinitroaniline* (1p)**[18]

As a orange solid (26 mg, 15% yield, mp 153–155 ^oC); Purification over a column of silica gel (5-10% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.88 (s, 1H), 9.18 (d, 1H, J = 2.5 Hz), 8.20 (dd, 1H, J_1 = 9.5 Hz, J_2 = 3.0 Hz), 7.63 (d, 2H, J = 8.5 Hz), 7.20 (d, 2H, J = 8.5 Hz), 7.14 (d, 1H, J = 9.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 146.8, 136.1, 133.7, 133.4, 130.3, 127.5, 127.3, 124.3, 121.3, 116.1; IR (KBr, cm^{-1}): 3330, 3101, 2923, 2853, 1619, 1585, 1488, 1335, 1280, 1146, 1011, 972, 832, 743, 706.

***Methyl 2-((2,4-dinitrophenyl)amino)-2-phenylacetate* (1q)**

As a yellow solid (25 mg, 15% yield, mp 163–166 ^oC); Purification over a column of silica gel (5-15% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.68 (d, 1H, J = 5.5 Hz), 9.15 (d, 1H, J = 2.5 Hz), 8.13 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.48-7.38 (m, 5H), 6.64 (d, 1H, J = 9.5 Hz), 5.29 (d, 1H, J = 6.0 Hz), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 169.9, 146.3, 137.1, 134.9, 131.7, 130.4, 129.7, 129.6, 127.2, 124.3, 114.9, 60.5, 53.8; IR (KBr, cm^{-1}): 3339, 3105, 2958, 2922, 2852, 1742, 1618, 1523, 1425, 1346, 1295, 1149, 924, 738.

***methyl (2,4-dinitrophenyl)leucinate* (1r)**

As a yellow liquid (55 mg, 36% yield); Purification over a column of silica gel (5-15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.16 (d, 1H, J = 3.0 Hz), 8.73-8.69 (m, 1H), 8.28 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.81 (d, 1H, J = 9.5 Hz), 4.32 (q, 1H, J = 7.0 Hz), 3.79 (s, 3H), 1.90-1.76 (m, 3H), 1.04 (d, 3H, J = 6.5 Hz), 0.96 (d, 3H, J = 6.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.9, 147.6, 130.8, 128.9, 128.0, 124.5, 114.0, 55.0, 53.1, 41.5, 25.2, 22.8, 22.2; IR (KBr, cm^{-1}): 3327, 3106, 2958, 2924, 2872, 1740, 1605, 1538, 1426, 1348, 1172, 1147, 748.

***N-Benzyl-2-nitro-4-(trifluoromethyl)aniline* (1s)[26]**

As a yelow solid (59 mg, 40% yield, mp 94–96 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.65 (s, 1H), 8.50 (d, 1H, J = 2.0 Hz), 7.57 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.40-7.33 (m, 5H), 6.91 (d, 1H, J =9.0 Hz), 4.60 (d, 2H, J = 5.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 146.9, 136.6, 132.40, 132.38, 129.4, 128.3, 127.2, 125.1 (q, J = 4.3 Hz), 118.0, 115.1, 47.5; IR (KBr, cm^{-1}): 3383, 3108, 2924, 2869, 1642, 1574, 1537, 1429, 1414, 1305, 1252, 1147, 10825, 914, 830, 763, 744.

***N-(4-Methoxybenzyl)-2-nitro-4-(trifluoromethyl)aniline* (1t)[27]**

As a yelow solid (74 mg, 46% yield, mp 125–127 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.56 (s, 1H), 8.49 (s, 1H), 7.58 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 7.26 (d, 2H, merged with $CDCl_3$, J = 8.5 Hz), 6.94–6.90 (m, 3H), 4.51 (d, 2H, J = 5.5 Hz), 3.81 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$,

125 MHz): δ 159.6, 146.8, 132.3 (q, J = 3.1 Hz), 131.5, 128.6, 128.4, 125.1 (q, J = 4.3 Hz), 117.9 (d, J = 34.2 Hz), 115.1, 114.7, 55.6, 47.0; ^{19}F NMR ($CDCl_3$,): δ –61.94 (s); IR (KBr, cm^{-1}): 3383, 2961, 2925, 2854, 1634, 1574, 1537, 1434, 1322, 1237, 1153, 1081, 1033, 899, 765, 691.

***N-Butyl-2-nitro-4-(trifluoromethyl)aniline* (1u)[21]**

As a yellow solid (50 mg, 39% yield, mp 60–62 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.47 (d, 1H, J = 2.5 Hz), 8.26 (s, 1H), 7.61 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 6.94 (d, 1H, J = 9.0 Hz), 3.34 (q, 2H, J = 6.5 Hz), 1.77–1.71 (m, 2H), 1.53–1.46 (m, 2H), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.2, 140.7, 132.3 (q, J = 3.1 Hz), 131.0, 125.2 (q, J = 4.2 Hz), 114.7, 43.2, 31.0, 20.4, 13.9; IR (KBr, cm^{-1}): 3378, 2959, 2928, 2856, 1637, 1577, 1538, 1438, 1326, 1274, 1159, 1123, 1081, 916, 816, 692.

***2-Nitro-N-phenyl-4-(trifluoromethyl)aniline* (1v)[10]**

As an orange solid (32 mg, 23% yield, mp 116–118 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.98 (s, 1H), 9.19 (d, 1H, J = 2.5 Hz), 8.17 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.51 (t, 2H, J = 8.0 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.31 (d, 2H, J = 7.5 Hz), 7.17 (d, 1H, J = 9.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.3, 136.9, 130.5, 130.1, 127.9, 125.8, 124.3, 116.2; IR (KBr, cm^{-1}): 3370, 3096, 2956, 2925, 2854, 1554, 1486, 1373, 1322, 1184, 1149, 1087, 943, 882, 793, 694.

***N-(2-methoxyphenyl)-2,4-dinitrobenzenesulfonamide* (2i)**[17]

As a white solid (80 mg, 46% yield, mp 167–170 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (d, 1H, J = 2.5 Hz), 8.36 (dd, 1H, J_1 = 8.75 Hz, J_2 = 2.25 Hz), 8.07 (d, 1H, J = 8.5 Hz), 7.94-7.73 (br, s, 1H), 7.57 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.12 (dt, 1H, J_1 = 7.75 Hz, J_2 = 1.67 Hz), 6.94 (dt, 1H, J_1 = 7.75 Hz, J_2 = 1.67 Hz), 6.74 (dd, 1H, J_1 = 8.25 Hz, J_2 = 1.25 Hz), 3.60 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 150.9, 150.1, 148.3, 138.8, 133.2, 127.5, 126.9, 124.1, 123.9, 121.5, 120.9, 111.1, 55.9; IR (KBr, cm^{-1}): 3334, 3103, 2953, 2922, 2852, 1618, 1584, 1504, 1425, 1331, 1258, 1115, 1023, 742.

Methyl ((2,4-dinitrophenyl)sulfonyl)leucinate (2r)

As a brown liquid (35 mg, 19% yield); Purification over a column of silica gel (5-15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.75 (d, 1H, J = 2.0 Hz), 8.52 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz), 8.27 (d, 1H, J = 8.5 Hz), 6.02 (br. s, 1H), 4.29-4.26 (m, 1H), 3.51 (s, 3H), 1.85 (nonet, 1H, J = 6.87 Hz), 1.67-1.62 (m, 2H), 4.34-4.26 (m, 1H), 0.96 (q, 6H, J = 3.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.2, 149.9, 148.1, 140.0, 132.2, 127.3, 121.2, 55.9, 52.8, 41.9, 24.6, 22.9, 21.4; IR (KBr, cm^{-1}): 3352, 3108, 2955, 2923, 2853, 1742, 1618, 1523, 1429, 1333, 1160, 833, 743.

***N-Benzyl-2-nitro-4-(trifluoromethyl)benzenesulfonamide* (2s)**

As a white solid (86 mg, 48% yield, mp 198–200 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.64 (s, 1H), 8.48 (d, 1H, J = 2.0 Hz), 7.56 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.40-7.33 (m, 5H), 6.91 (d, 1H, J =9.0 Hz), 4.59 (d, 2H, J = 5.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.9, 137.8, 135.5 (t,

J = , 132.1, 129.5 (q, *J* = 3.5 Hz), 128.9, 128.4, 128.2, 123.2, 122.6 (q, *J* = 3.7 Hz), 121.1, 48.2; IR (KBr, cm^{-1}): 3339, 3091, 2956, 2919, 2856, 1580, 1549, 1493, 1422, 1367, 1318, 1189, 1085, 1053, 893, 715, 693.

N-(4-Methoxybenzyl)-2-nitro-4-(trifluoromethyl)benzenesulfonamide **(2t)**

As a yellow liquid (80 mg, 41% yield); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (d, 2H, *J* = 10.5 Hz), 7.81 (d, 1H, *J* = 9.0 Hz), 7.09 (d, 2H, *J* =8.5 Hz), 6.70 (d, 2H, *J* = 9.0 Hz), 5.79 (s, 1H), 4.30 (s, 2H), 3.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.7, 147.9, 137.9, 135.4 (q, *J* = 34.6 Hz), 135.2, 129.6, 129.5 (q, *J* = 3.5 Hz), 127.5, 123.3, 122.6 (q, *J* = 3.8 Hz), 121.1, 114.2, 55.4, 47.8; IR (KBr, cm^{-1}): 3318, 3093, 2959, 2924, 2851, 1610, 1548, 1515, 1425, 1365, 1324, 1253, 1168, 1152, 1088, 817, 716.

N-Butyl-2-nitro-4-(trifluoromethyl)benzenesulfonamide **(2u)**

As a yellow liquid (80 mg, 49% yield); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.29 (d, 1H, *J* = 8.0 Hz), 8.10 (s, 1H), 7.99 (d, 1H, *J* = 7.5 Hz), 5.32 (s, 1H), 3.12 (t, 2H, *J* =7.3 Hz), 1.56–1.49 (m, 2H), 1.37–1.29 (m, 2H), 0.88 (t, 3H, *J* = 7.3 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 160.1, 148.4, 137.6, 135.8 (q, *J* = 34.8 Hz), 132.2, 129.4 (q, *J* = 3.4 Hz), 125.5, 123.3, 122.9 (q, *J* = 3.6 Hz), 121.1, 118.9, 43.9, 31.8, 19.8, 13.6; IR (KBr, cm^{-1}): 3314, 3088, 2961, 2933, 2875, 1660, 1547, 1459, 1419, 1320, 1185, 1148, 1080, 977, 892, 795, 714.

***N-Benzyl-4-chloro-2-nitrobenzenesulfonamide* (2w)**

As a white solid (101 mg, 62% yield, mp 100–102 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (d, 1H, J = 8.5 Hz), 7.78 (d, 1H, J = 2.0 Hz), 7.56 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 7.24-7.19 (m, 5H), 5.72 (s, 1H), 4.32 (d, 2H, J = 6.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 148.3, 139.8, 135.7, 132.84, 132.77, 132.4, 128.9, 128.3, 128.1, 125.6, 48.1; IR (KBr, cm^{-1}): 3341, 3088, 2959, 2921, 2849, 1588, 1549, 1496, 1461, 1365, 1340, 1156, 1107, 1049, 885, 827, 771, 748, 700.

***Benzyl(2,4-dinitrophenyl)sulfane (3a)*[29]**

As a yellow solid (105 mg, 73% yield, mp 127-128 °C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, 1H, J = 2.5 Hz,), 8.33 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz), 7.61 (d, 1H, J = 9.0 Hz), 7.43 (d, 2H, J = 7.5 Hz), 7.38 (t, 2H, J = 7.5 Hz), 7.34 (d, 1H, J = 7.5 Hz), 4.30 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.0, 144.9, 144.2, 133.7, 129.4, 129.2, 128.6, 127.4, 127.3, 121.9, 38.0. IR (KBr, cm^{-1}): 3087, 2957, 2922, 2852, 1713, 1588, 1514, 1453, 1337, 1051, 917, 734.

***Cyclohexyl(2,4-dinitrophenyl)sulfane (3b)*[30]**

As a yellow solid (55 mg, 31% yield, mp 142-143 °C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (d, 1H, J = 2.5 Hz,), 8.34 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.59 (d, 1H, J = 9.0 Hz), 3.43-3.39 (m, 1H), 2.13-3.09 (m, 2H), 1.89-1.86 (m, 2H), 1.74-1.70 (m, 1H), 1.59-1.43 (m, 5H); ^{13}C{^{1}H}

NMR (125 MHz, $CDCl_3$) δ 146.4, 145.6, 143.8, 127.7, 126.9, 122.1, 44.7, 32.4, 26.1, 25.7; IR (KBr, cm^{-1}): 3102, 2926, 2853, 1592, 1527, 1450, 1339, 1132, 1051, 915, 735.

(2,4-Dinitrophenyl)(phenyl)sulfane (3c)[31]

As a yellow solid (75 mg, 55% yield, mp 115-117 °C); Purification over a column of silica gel (1-2% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, 1H, J = 2.5 Hz,), 8.12 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.61–7.54 (m, 5H), 6.99 (d, 1H, J = 9.0 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 148.6, 144.5, 144.0, 136.1, 131.3, 130.9, 129.7, 129.24, 129.21, 129.0, 127.1, 121.6; IR (KBr, cm^{-1}): 3104, 2956, 2923, 2853, 1593, 1518, 1440, 1337, 1134, 1049, 917, 734.

(2,4-Dinitrophenyl)(p-tolyl)sulfane (3d)[31]

As a yellow solid (101 mg, 70% yield, mp 99-100 °C); Purification over a column of silica gel (1-2% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.08 (d, 1H, J = 2.5 Hz,), 8.11 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.47 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.0 Hz), 6.99 (d, 1H, J = 9.0 Hz), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 149.2, 144.4, 143.9, 141.9, 136.0, 131.7, 129.0, 126.9, 125.6, 121.6, 21.7; IR (KBr, cm-1): 3103, 2958, 2923, 2853, 1588, 1513, 1451, 1334, 1133, 1048, 916, 733.

(2,4-Dinitrophenyl)(4-methoxyphenyl)sulfane (3e)[32]

As a yellow solid (109 mg, 72% yield, mp 115-117 °C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.08 (d, 1H, J = 2.5

Hz,), 8.12 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.50 (d, 2H, J = 8.5 Hz), 7.06 (d, 2H, J = 8.5 Hz), 6.99 (d, 1H, J = 9.0 Hz), 3.90 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.1, 149.7, 144.4, 143.9, 137.8, 128.9, 126.9, 121.6, 119.4, 116.5, 55.8; IR (KBr, cm^{-1}): 3103, 2965, 2924, 2840, 1592, 1518, 1493, 1339, 1252, 1133, 1049, 917, 735.

(4-Chlorophenyl)(2,4-dinitrophenyl)sulfane (3f)[32]

As a yellow solid (60 mg, 39% yield, mp 121-122 °C); Purification over a column of silica gel (1-2% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, 1H, J = 1.0 Hz,), 8.16 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.5 Hz), 7.54 (s, 4H), 6.99 (d, 1H, J = 9.0 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.8, 144.7, 144.2, 138.1, 137.4, 131.3, 128.9, 127.7, 127.2, 121.4; IR (KBr, cm^{-1}): 3103, 2953, 2923, 2853, 1591, 1512, 1335, 1134, 1088, 916, 830, 734.

(2,4-dinitrophenyl)(4-methoxybenzyl)sulfane (3g)

As a yellow solid (125 mg, 79% yield, mp 98-100 °C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, 1H, J = 2.5 Hz,), 8.33 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.62 (d, 1H, J = 8.5 Hz), 7.34 (d, 2H, J = 8.5 Hz), 6.90 (d, 2H, J = 8.5 Hz), 4.25 (s, 2H), 3.81 (s, 3H).; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.8, 147.3, 144.9, 144.1, 130.5, 127.34, 127.31, 125.3, 121.9, 114.8, 55.6, 37.6; IR (KBr, cm^{-1}): 3091, 2953, 2924, 2853, 1590, 1336, 1248, 1176, 1153, 1051, 918, 832, 734..

Phenyl 2,4-dinitrobenzenesulfonate (4a)[28]

As a yellow solid (137 mg, 99% yield, mp 111°C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, 1H, J = 2.0 Hz,), 8.47 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 8.17 (d, 1H, J = 8.5 Hz), 7.39–7.19 (m, 3H), 7.20 (d, 2H, J = 7.5 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 151.1, 149.1, 134.1, 133.9, 130.5, 128.4, 126.5, 122.2, 120.5.IR (KBr, cm^{-1}): 3103, 2955, 2913, 2853, 1607, 1585, 1527, 1477, 1342, 1266, 1188, 1067, 757.

4.7. Representative NMR Spectra

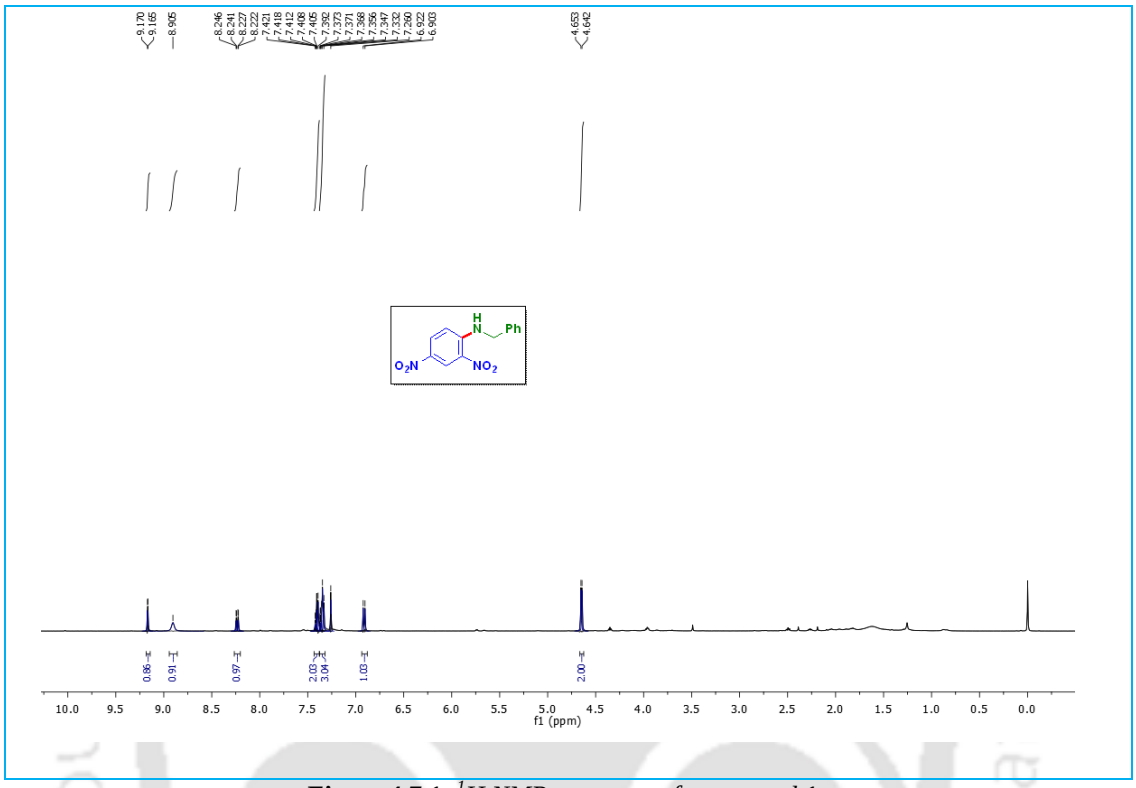


Figure 4.7.1: *^{1}H NMR spectrum of compound* ***1a***

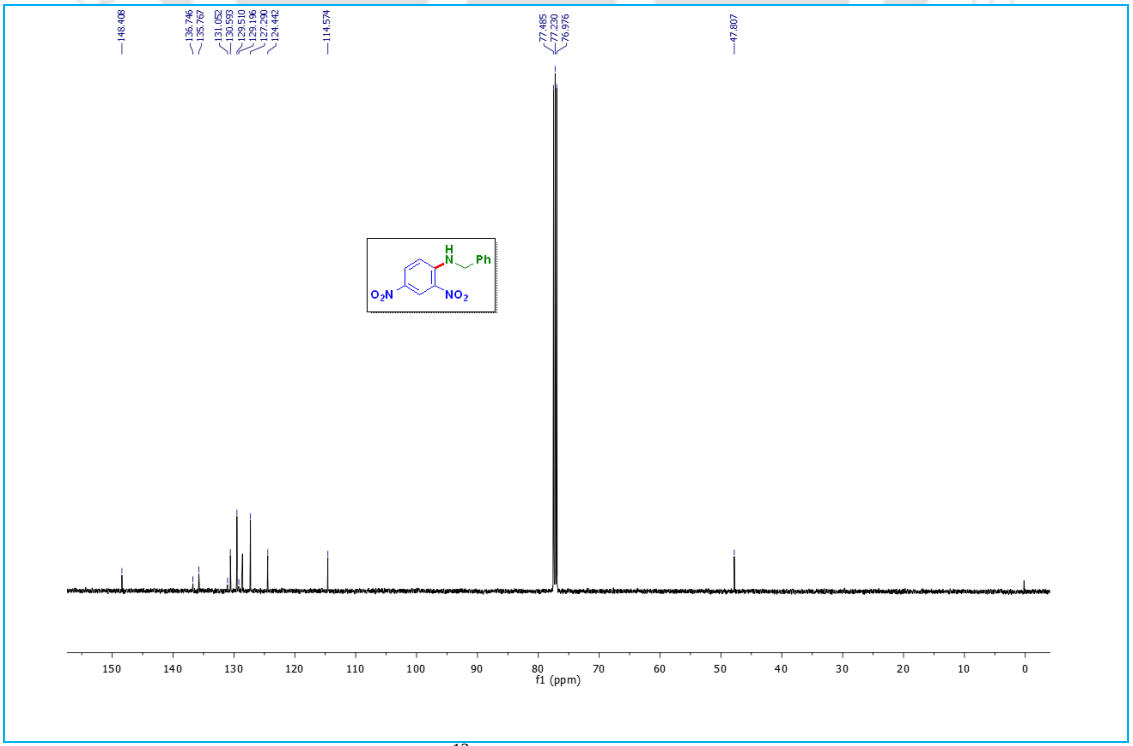


Figure 4.7.2: *^{13}C NMR spectrum of compound* ***1a***

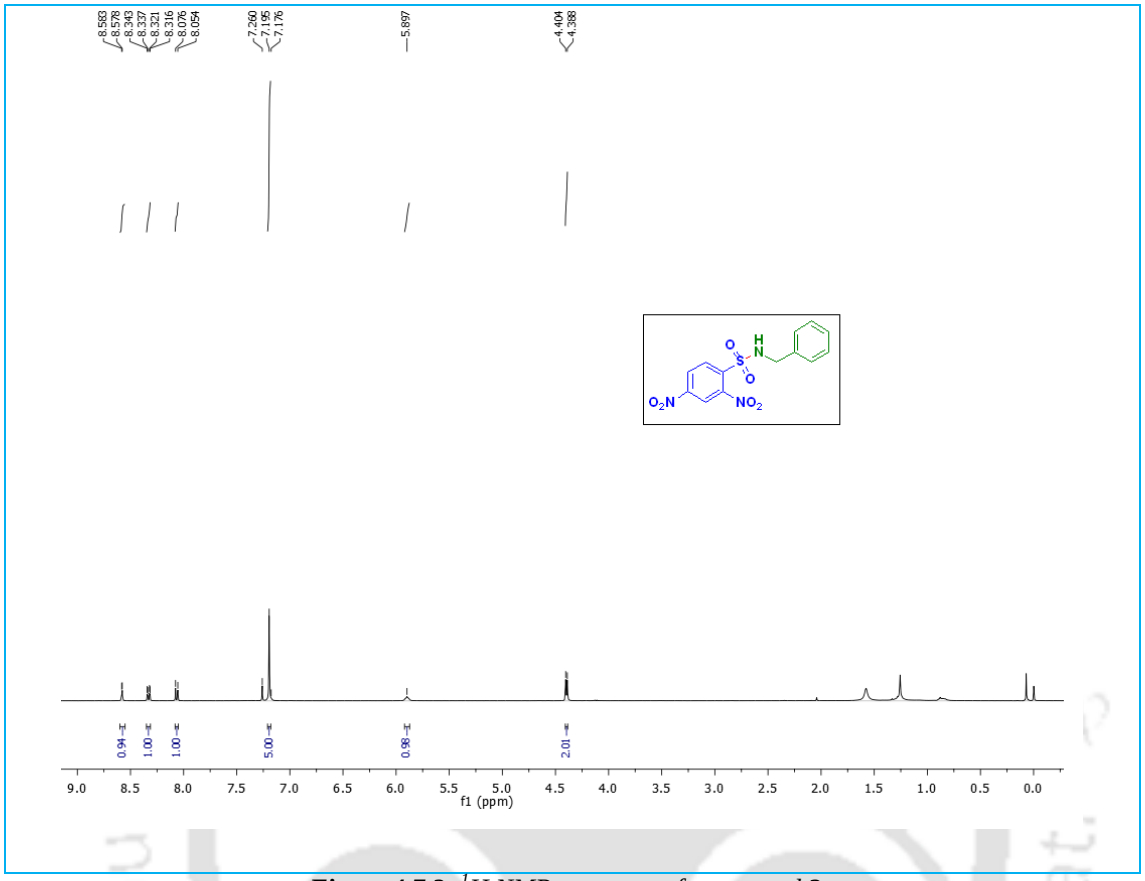


Figure 4.7.3: *^{1}H NMR spectrum of compound* ***2a***

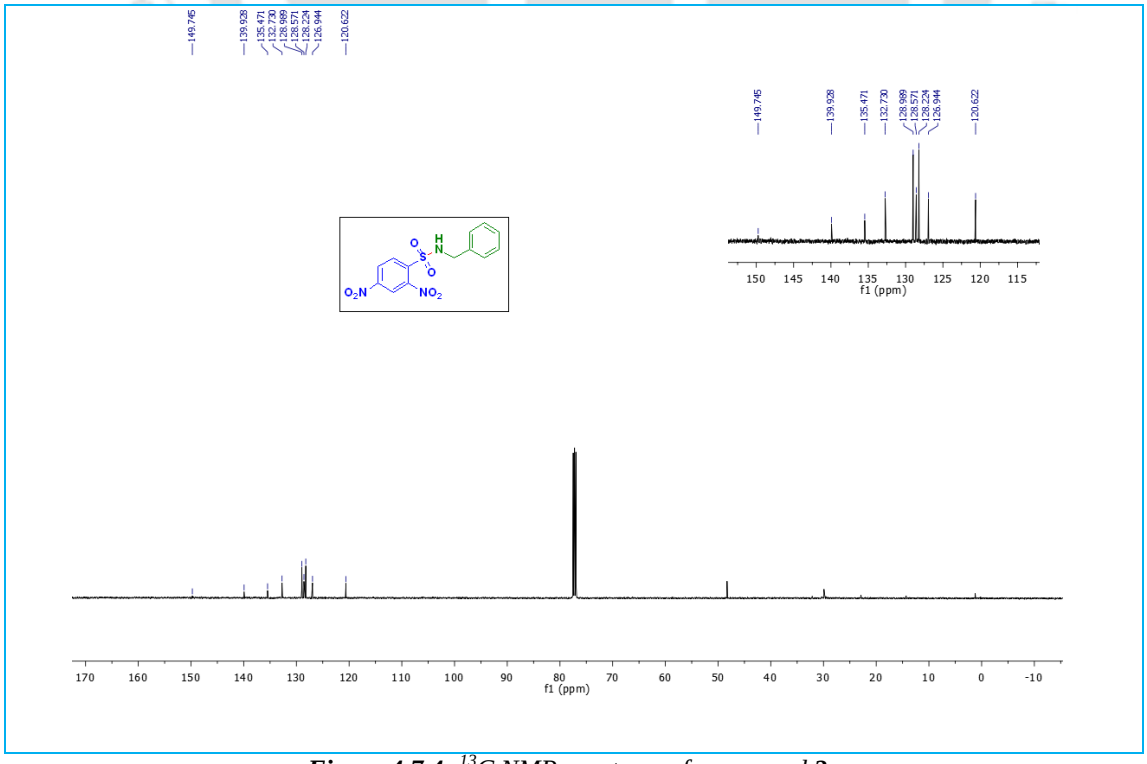


Figure 4.7.4: *^{13}C NMR spectrum of compound* ***2a***

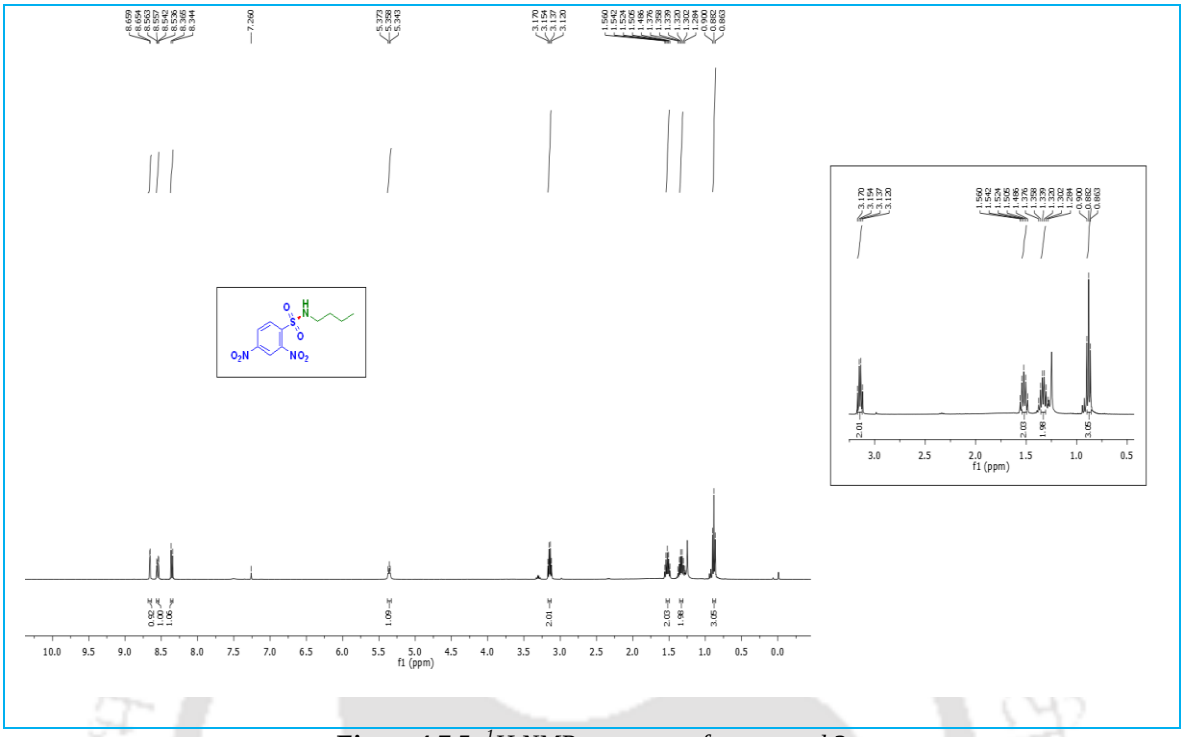


Figure 4.7.5: *^{1}H NMR spectrum of compound* ***2c***

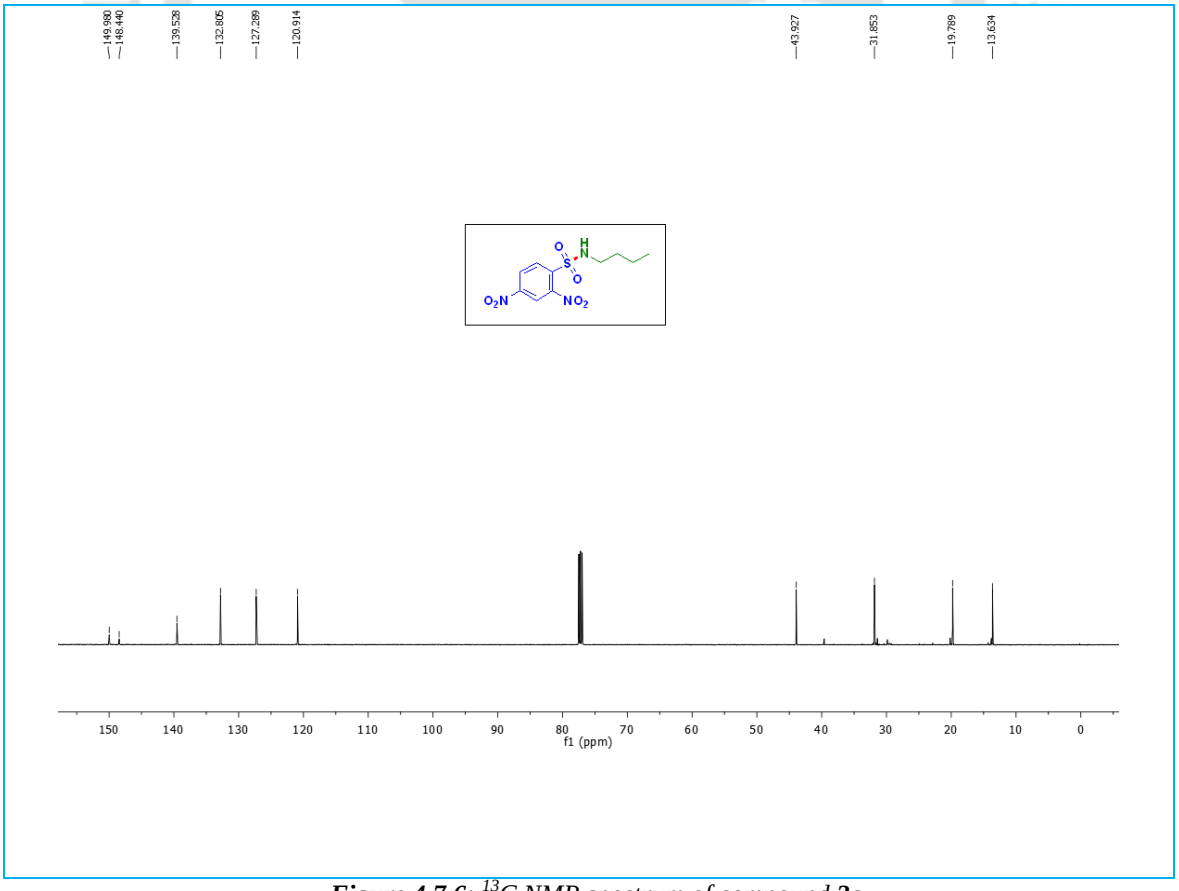


Figure 4.7.6: *^{13}C NMR spectrum of compound* ***2c***

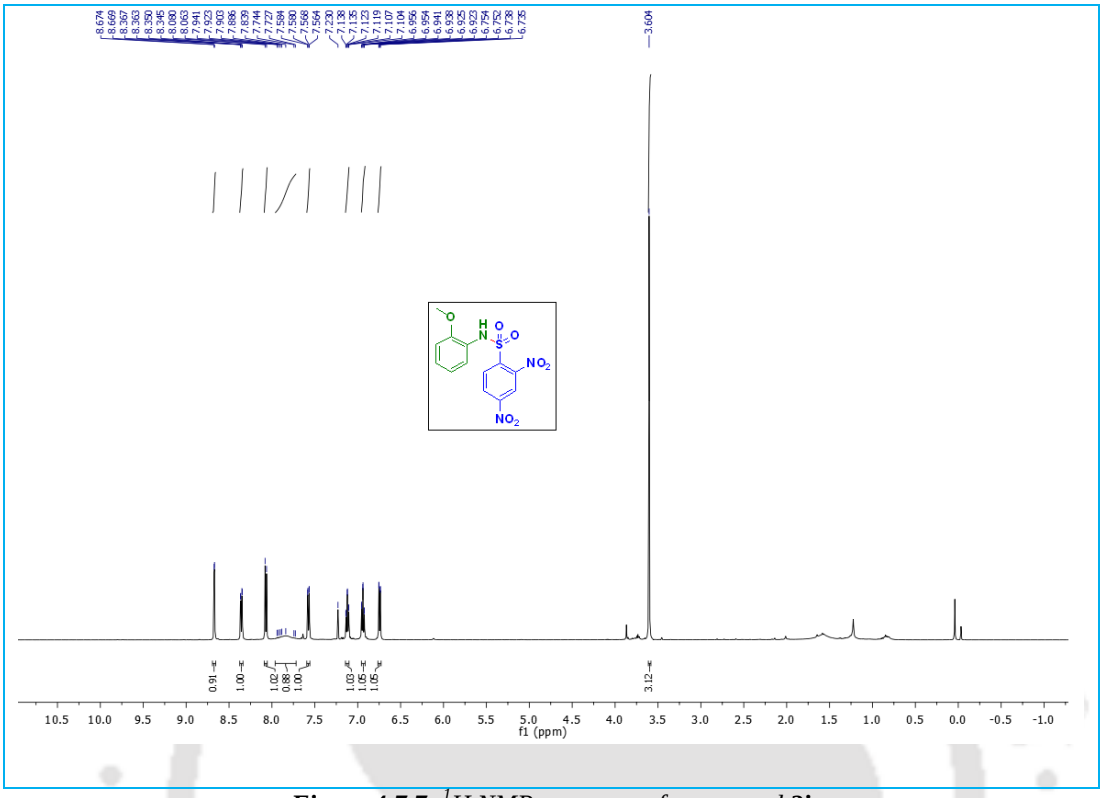


Figure 4.7.7: *^{1}H NMR spectrum of compound* ***2i***

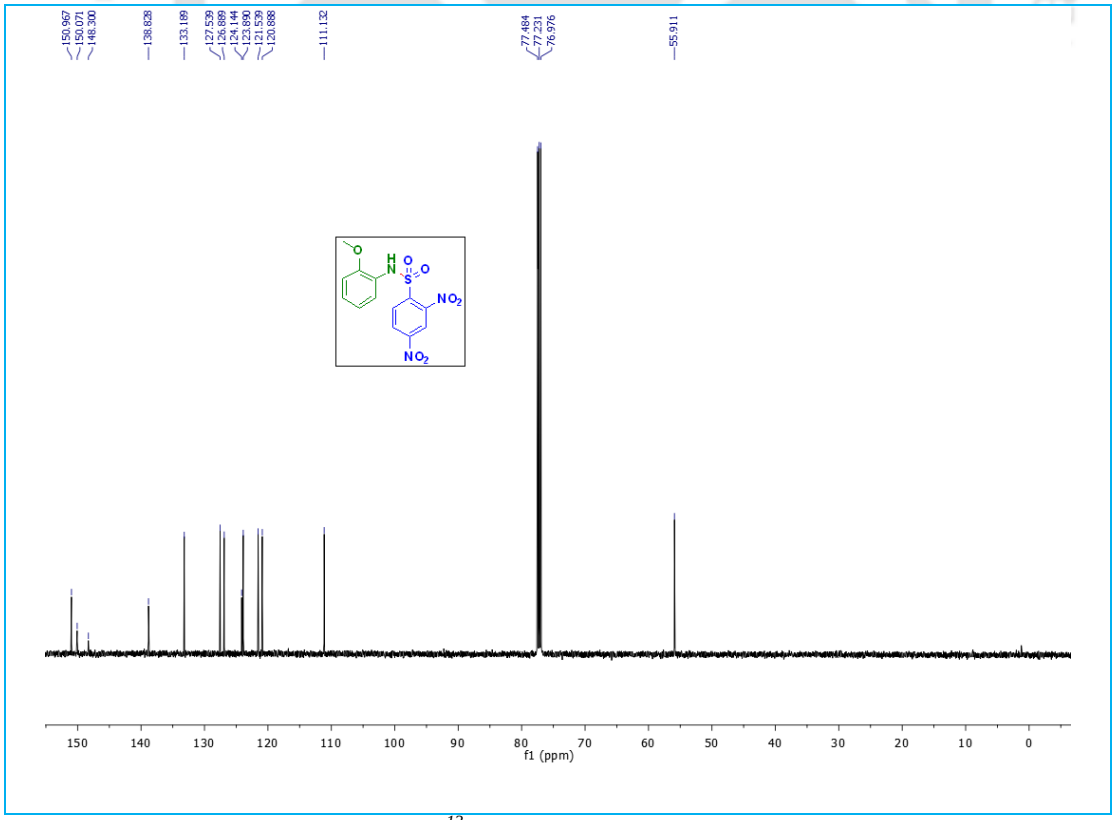


Figure 4.7.8: *^{13}C NMR spectrum of compound* ***2i***

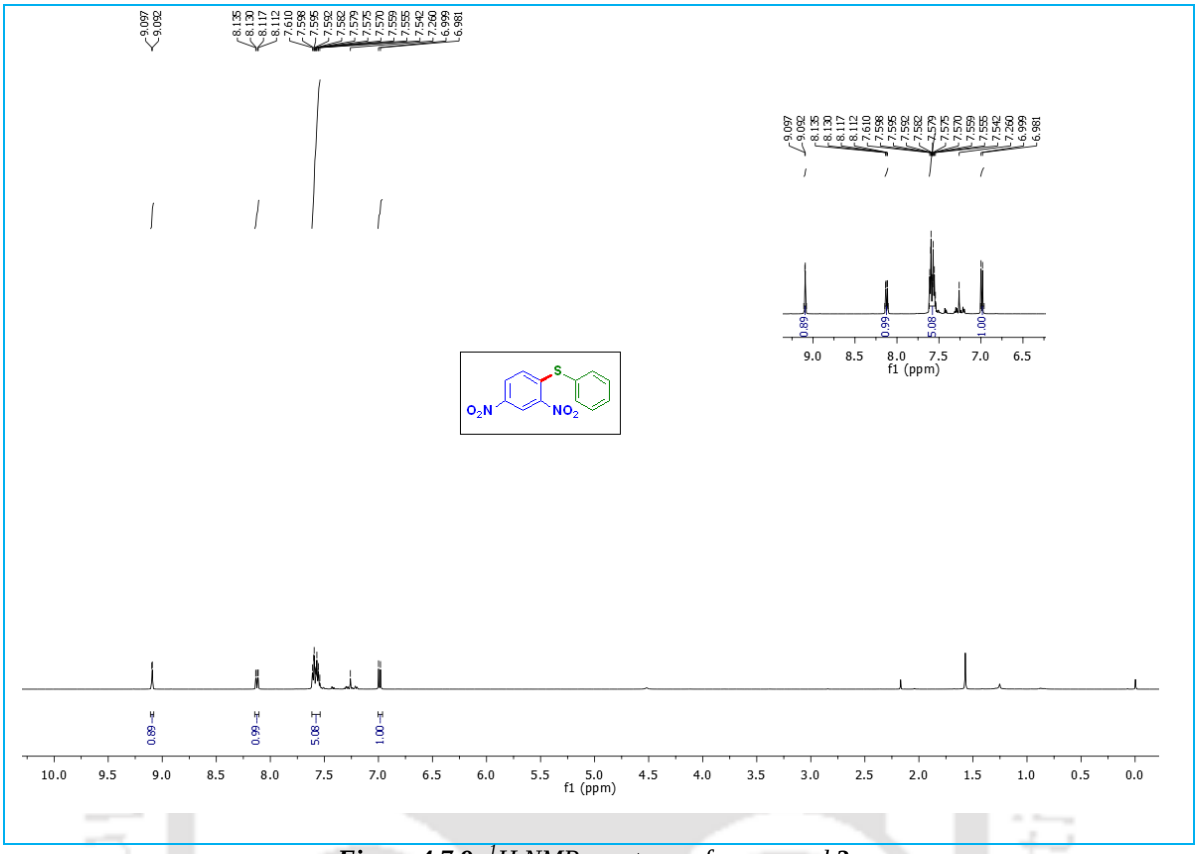


Figure 4.7.9: *^{1}H NMR spectrum of compound* ***3c***

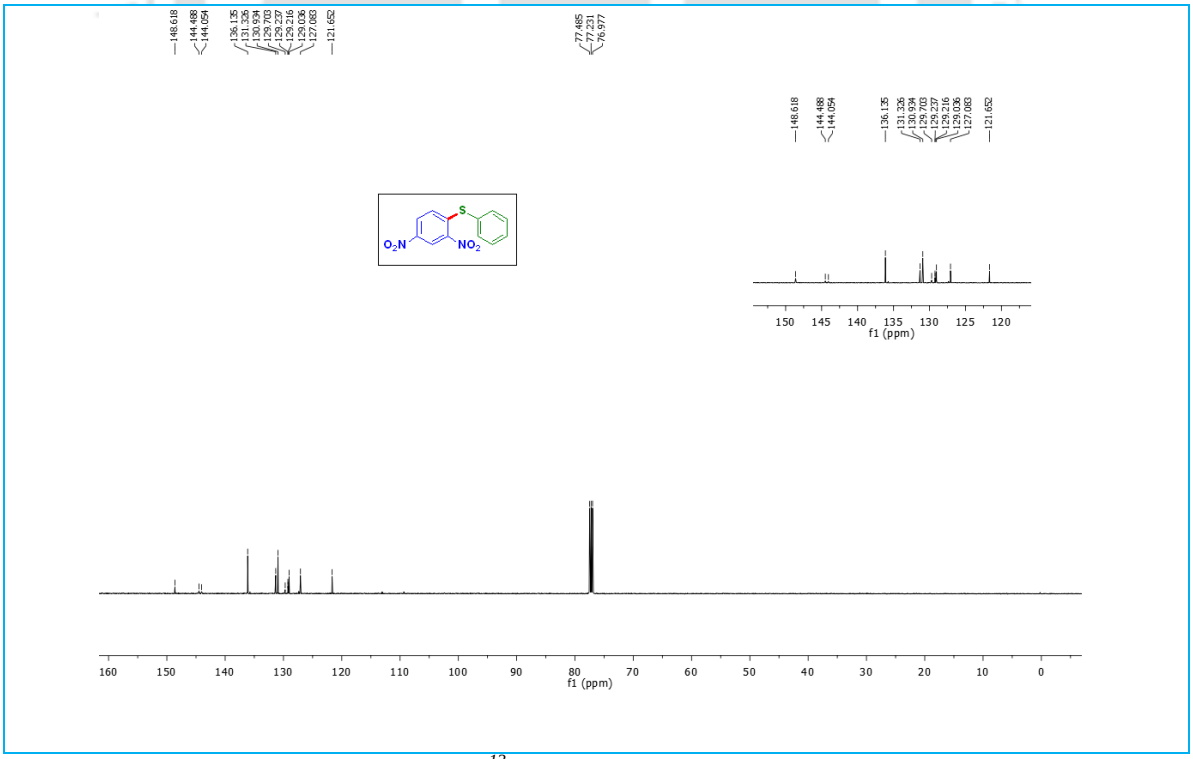


Figure 4.7.10: *^{13}C NMR spectrum of compound* ***3c***

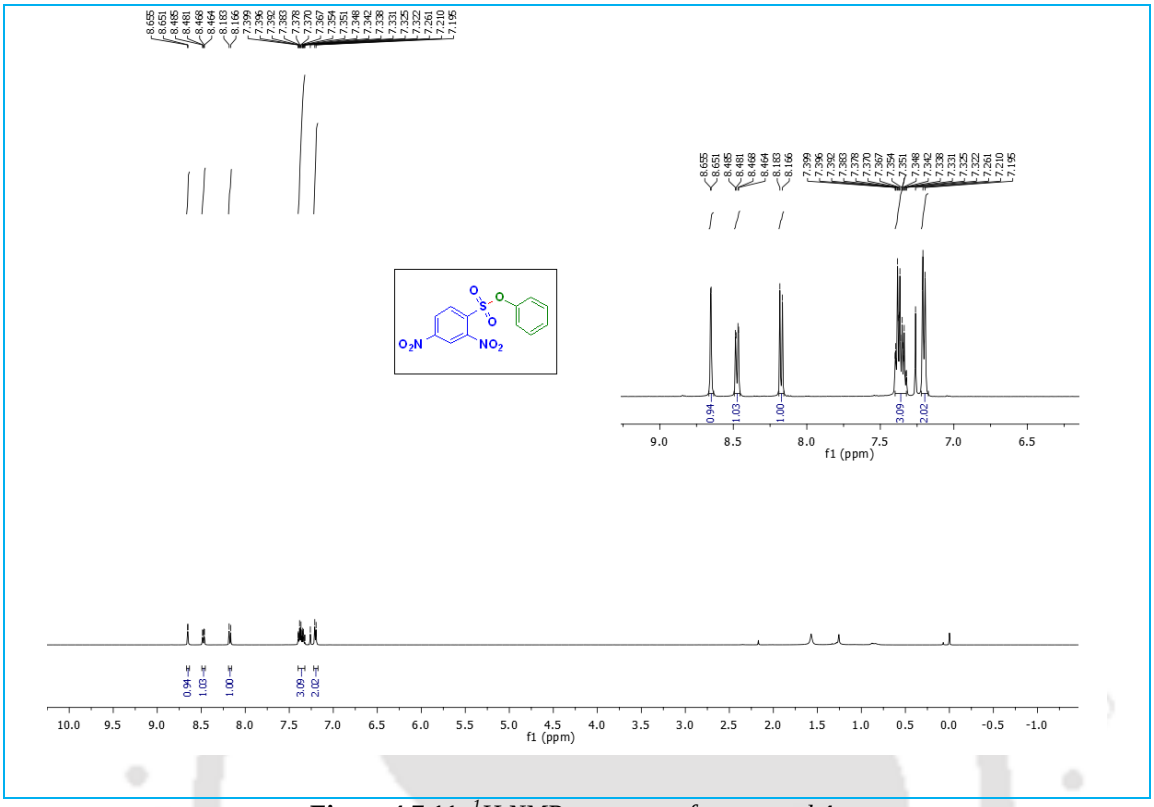


Figure 4.7.11: *^{1}H NMR spectrum of compound* ***4a***

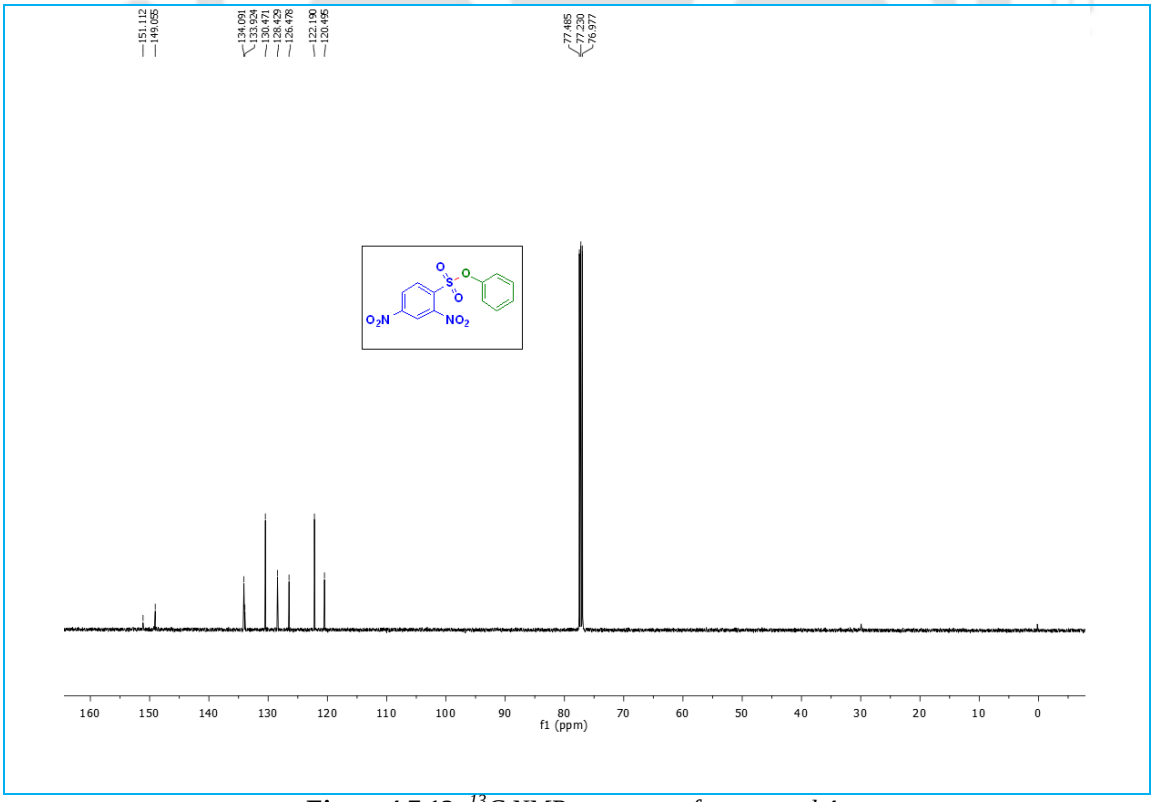


Figure 4.7.12: *^{13}C NMR spectrum of compound* ***4a***

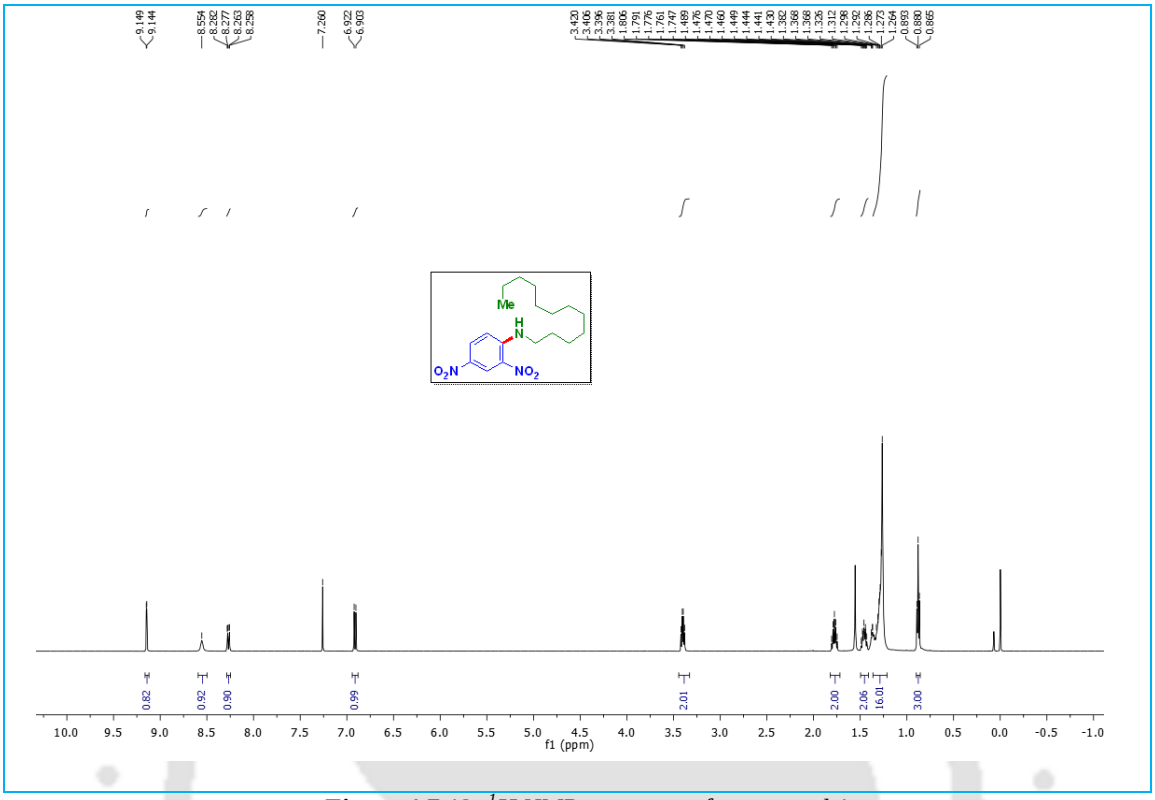


Figure 4.7.13: *^{1}H NMR spectrum of compound* ***1m***

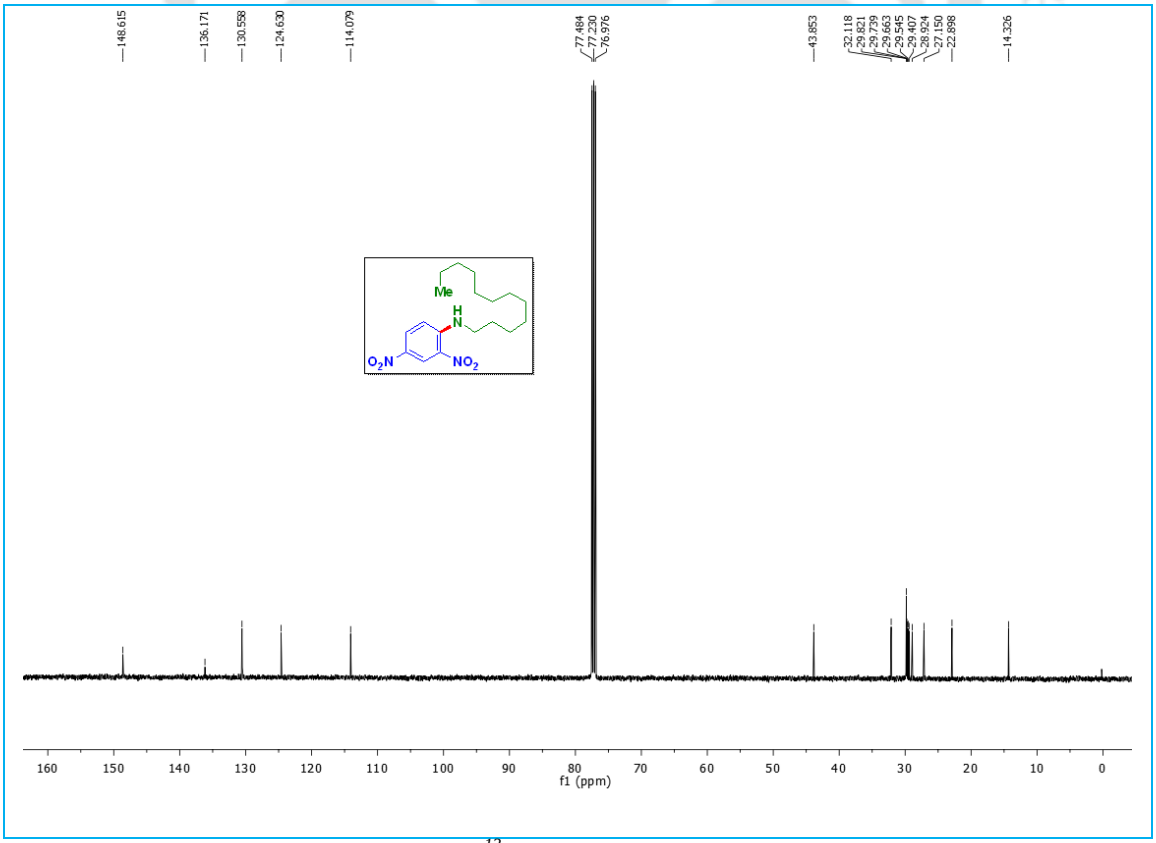


Figure 4.7.14: *^{13}C NMR spectrum of compound* ***1m***

4.8. Crystallographic Data

Compound No.	**1a**	**2a**	**3a**	**4a**
Formula	$C_{13}H_{11}N_3O_4$	$C_{13}H_{11}N_3O_6S$	$C_{13}H_{10}N_2O_4S$	$C_{12}H_8N_2O_7S$
CCDC No.	2259694	2259704	2259703	2259695
Formula. wt.	273.25	337.31	290.29	324.26
Crystal system	Triclinic	Orthorhombic	Monoclinic	Orthorhombic
Space group	P -1	P 21 21 21	P 21/c	P 21 21 21
a (Å)	7.1265(6)	7.3386(7)	8.1205(5)	6.4488(3)
b (Å)	8.2619(7)	7.6263(7)	23.9374(14)	10.9089(6)
c (Å)	11.1826(9)	25.689(4)	7.3502(4)	19.5171(10)
α(°)	84.588(2)	90	90	90
β(°)	84.009(2)	90	114.746(2)	90
γ(°)	73.008(2)	90	90	90
V/ $Å^3$	624.82(9)	1437.7(3)	1297.56(13)	1373.01(12)
Z	2	4	4	4
Density/Mgm^{-3}	1.452	1.558	1.486	1.569
Abs. Coeff. /mm^{-1}	0.110	0.262	0.264	0.274
F(000)	284	696.0	600.0	664.0
Total no. of reflections	13409	3269	29733	13729
Reflections, $I > 2\sigma(I)$	0.0727	0.0736	0.0451	0.03770
Max. 2θ/°	25.000	24.499	24.996	24.997
Ranges (h, k, l)	(8,9,13)	(8,8,29)	(9,28,8)	(7,12,23)
Complete to 2θ (%)	25.000	24.499	24.996	24.997
Data/ Restraints/Parameters	2194/0/184	2092/0/208	2286/0/181	2406/0/199

Goof (F^2)	1.037	0.938	1.000	1.130
R indices [$I > 2\sigma(I)$]	0.0727	0.0736	0.0451	0.0377
R indices (all data)	0.1086	0.1990	0.0495	0.0446

❖ **ORTEP Diagram with ellipsoid of 50% probability**

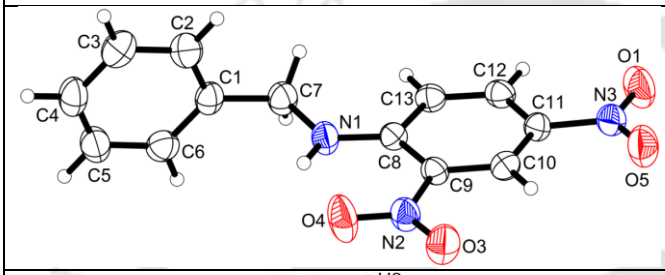
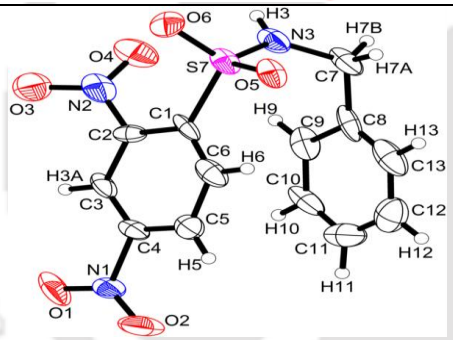
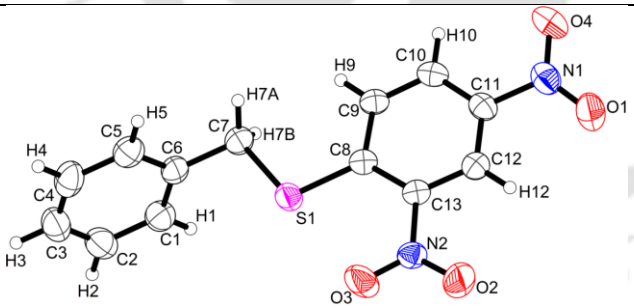
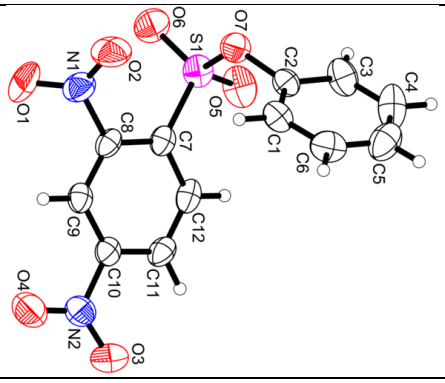
ORTEP Diagram	Compound	CCDC No.
	**1a**	2259694
	**2a**	2259704
	**3a**	2259703
	**4a**	2259695

Figure 4.8.1: *ORTEP Diagrams*

4.9. References

1. (a) Soussi, M. A.; Provot, O.; Bernadat, G.; Bignon, J.; Wdzieczak-Bakala, J.; Desravines, D.; Dubois, J.; Brion, J. D.; Messaoudi, S.; Alami, M. Discovery of Azaisoerianin Derivatives as Potential Antitumors Agents, *Eur. J. Med. Chem.*, **2014**, *78*, 178-189. (b) Qin, B.; Jiang, X.; Lu, H.; Tian, X.; Barbault, F.; Huang, L.; Qian, K.; Chen, C. H.; Huang, R.; Jiang, S.; Lee, K. H. Diarylaniline Derivatives as a Distinct Class of HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors, *J. Med. Chem.*, **2010**, *53*, 4906-4916.

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Chapter V

Ipso Nucleophilic Substitution of Aryl Benzotriazoles by Amine, Thiol, and Active Methylene Compounds

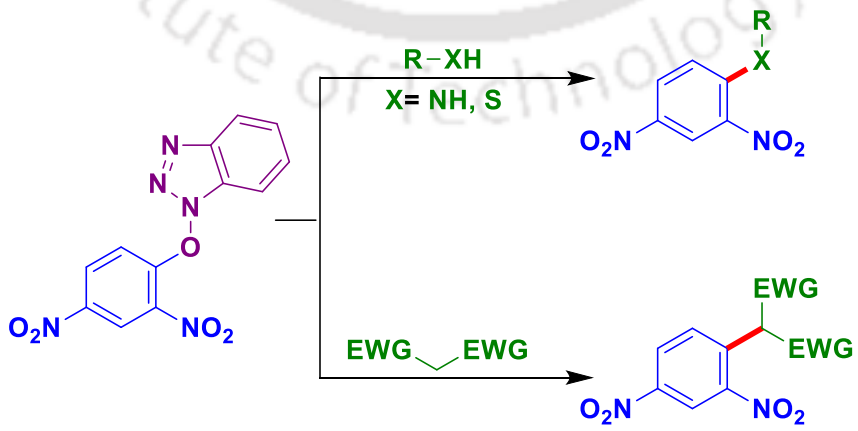
5.1. Introduction

Alkylation reactions mainly construct carbon-carbon and carbon-heteroatom bonds, which is the fundamental requirement in organic chemistry.[1,2] Therefore, alkylation reaction has attracted significant research interest because of its wide application in the area of medicinal chemistry, the dye sector, the food industry, and materials.[3] Many biologically active molecule synthesis requires methods for constructing C-C, C-N, and C-S bonds. Numerous strategies have been developed in this field. The Knoevenagel condensation[11] is one of the most used methods for alkylating active methylene compounds. Alkylation of active methylene compounds can be achieved by nucleophilic substitution,[12] DDQ[13] or $FeCl_3$[14] catalyst, transition metal catalyst,[15] and microwave assistance.[16] Similarly, the formation of C-N and C-S bonds attained much interest due to their important function in many chemical fields. Transition metal catalysts retain their dominance in this particular area of synthesis. At the beginning of the past century, early work was done by Ullmann,[17] Goldberg,[18] and Hurtley[19]. Later on, Migita,[20] Buchward,[21] Hatwig,[22] Suzuki,[23] Chan,[24] Evans,[25] and Lam[26] have got remarkable success in this field. They have mainly developed C-N bonds between aryl halide or aryl boronic acid with amines in the presence of transition metal (Cu, Pd, etc.) catalysts. Beletskaya and Ananikov got success with C-S coupling.[27] Alongside many transition metal-free procedures have been developed for N-alkylation and S-alkylation of amines and thiols,

such as S_NAr reaction,[28] photocatalytic pathways,[29] microwave assisted[30] procedures, etc. In all cases starting materials are mainly aryl halide, aryl boronic acid, aryl triflate, or diaryl iodonium salts, which makes limitations of those procedures. The major drawbacks of the existing procedures are expensive as well as toxic metal catalysts and ligands, elevated temperature, and harsh reaction condition requirements. Therefore, producing a green method for the alkylation of active methylene compounds, amines, and thiols is highly desired.

5.2. Objective

Alkylation is an essential strategy in organic synthesis because of its presence in essential biological active molecules and pharmaceutical compounds. We report an eminently high-yielding protocol for the alkylation of amine, thiol, and active methylene compounds on aryl benzotrizolyl derivatives in a mild reaction condition, which constructs C-N, C-S, and C-C bonds, respectively. This methodology does not require any expensive and toxic transition metal catalyst assistance. Moreover, this protocol is good for functional group tolerance.

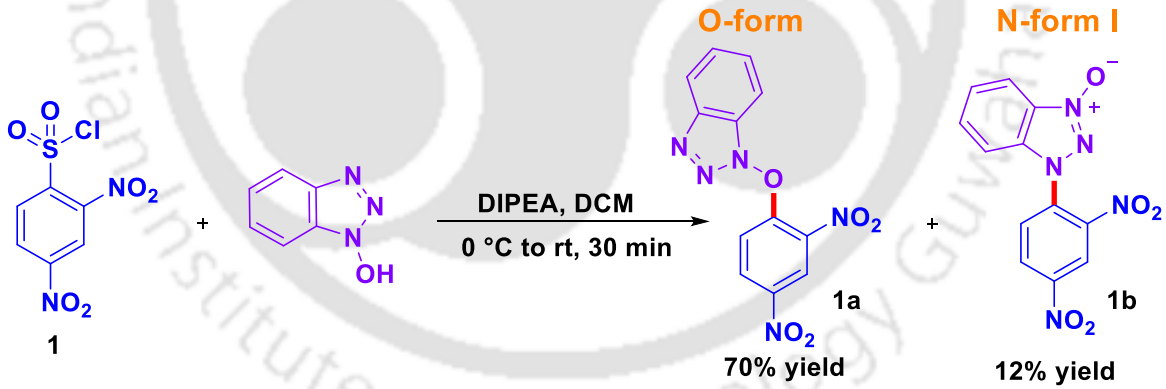


Scheme 5.2.1: *Objective of Chapter V*

5.3. Results and Discussion

5.3.1. Desmotropic nature of HOBt

1-Hydroxybenzotriazole (HOBt)[31] is a well-known additive and acts as a good leaving group. Therefore, it can be used during ipso substitution by various nucleophiles. In 2012, Khattab *et al.*[32] reported only three examples of N-alkylation of amine on aryl benzotrizolyl derivatives (cyclohexylamine, morpholine, and aniline) with 70-80% yield. In this chapter, we have optimized and described the alkylation of active methylene compounds, amines, and thiols using aryl benzotriazolyl derivatives (yield up to 99%). We have observed the desmotropic nature of our starting materials aryl benzotriazolyl derivatives. A systematic DFT calculation has been done.



Scheme 5.3.1.1: *Synthesis of aryl benzotriazolyl derivatives*[a]

[a]*Reaction condition: 2,4-dinitro benzene sulfonyl chloride (4.0 mmol), HOBt (4.0 mmol), and DIPEA (4.0 mmol) were stirred at 0 °C to room temperature for 30 minutes*

2,4-dinitro benzenesulfonyl chloride (1), on treatment with HOBt in the presence of base DIPEA produces two aryl benzotriazolyl isomers as **O-form** and **N-form I** with 70% and 12% yield, respectively. Similar desmotropism has been established in literature by acyl and immonium sulfonyl groups with HOBt.[33] In our case, the desmotropic behavior of

HOBt is observed with an aryl group. The aryl dance can be possible through three different positions (shown in Figure 5.3.1.1) **N-form II** is theoretically postulated, it has not been separated yet. We also did not obtain the **N-form II**.

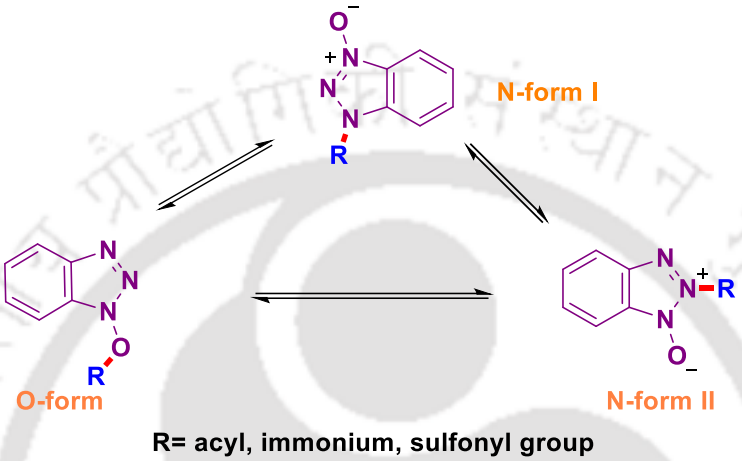
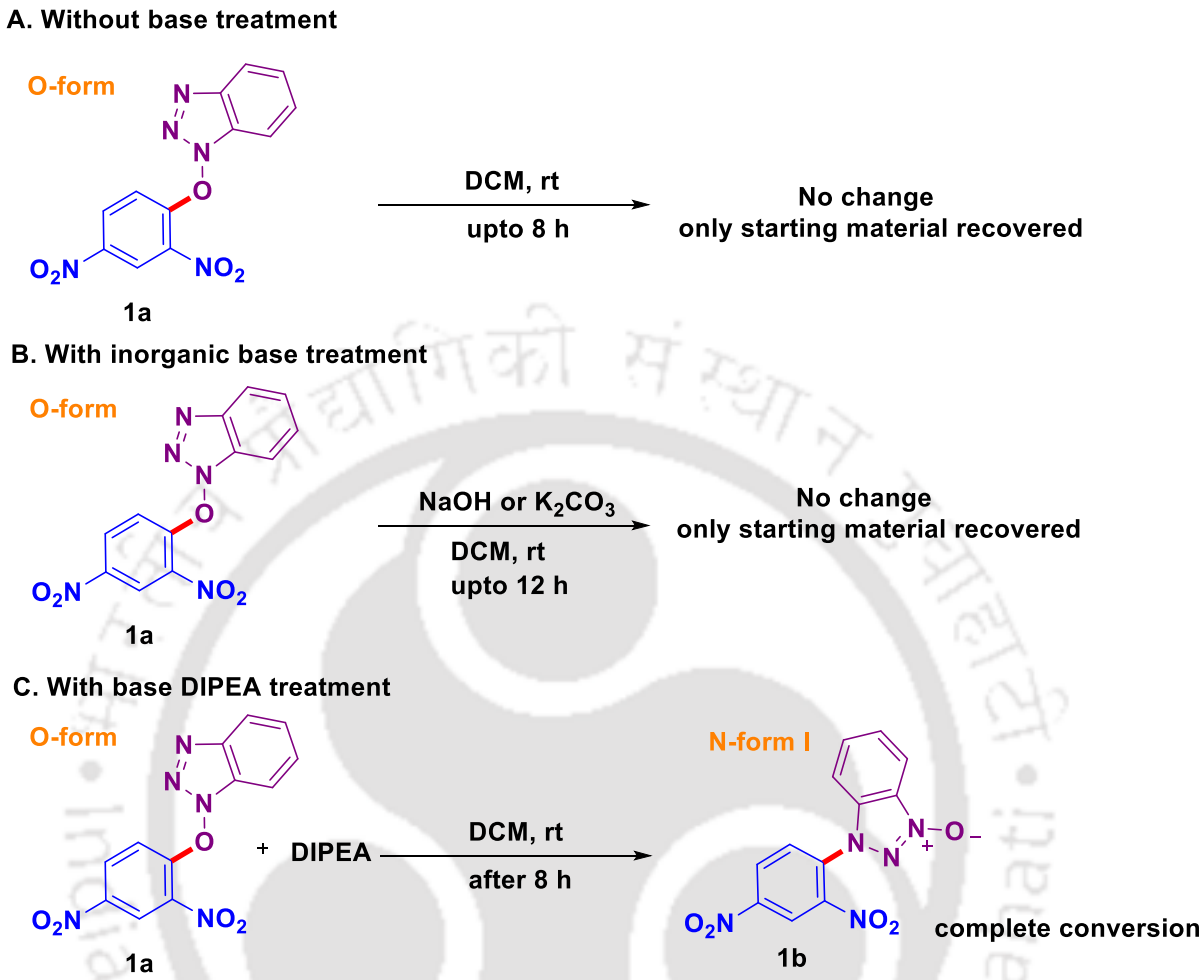


***Figure 5.3.1.1**: Desmotropic nature of HOBt*

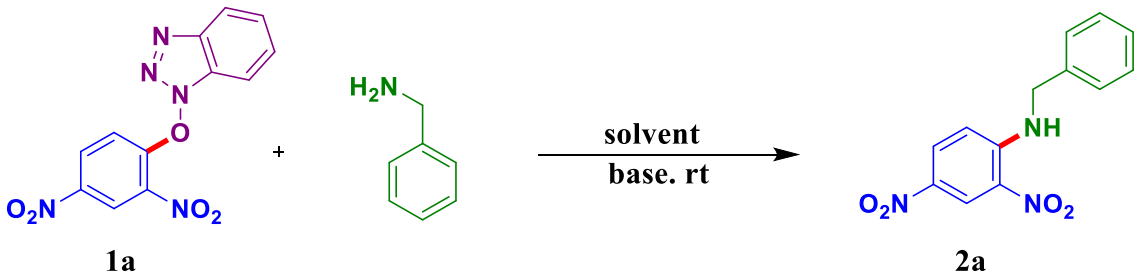
Among all three possible isomers, **N-form I** is the most stable conformer. We have demonstrated the inter-conversion between **O-form** and **N-form** with control reactions (Scheme 5.3.1.2). We have observed that the pure **O-form** converted into **N-form I** after keeping it for several weeks at room temperature. **N-form I** is a more stable isomer among all three possibilities. This phenomenon is described at the end of this chapter with some theoretical calculations. We stirred **O-form** in DCM medium at room temperature for 8 h. No **N-form I** was detected during and after this experiment. Again we kept this reaction for 24 h. There also **N-form I** formation does not occur. Next **O-form** is treated with different bases, such as sodium hydroxide and potassium carbonate in DCM solvent at room temperature for up to 12 h. Each time we got the only starting material, **O-form**. Surprisingly, in the presence of DIPEA in the identical reaction condition complete conversion into **N-form I** have been observed (Scheme 5.3.1.2C).



Scheme 5.3.1.2: *Inter-conversion between O-form and N-form of aryl benzotriazolyl derivative*

5.3.2. Optimization of the Reaction Conditions

Firstly, we have investigated the nucleophilic behavior of amines on aryl benzotriazolyl derivative. For optimization of the reaction conditions corresponding **O-form** (1a) and benzyl amine have been chosen as model substrates (Scheme 5.3.2.1).



1a **2a**

Scheme 5.3.2.1: *Model reaction for optimization of the reaction conditions*

During optimization, we screened several solvents such as DMSO, DMF, MeOH, $CHCl_3$, EtoAc, DCM, H_2O, and THF. We obtained the highest yield in the DCM medium. The reaction was performed in the presence of the different bases (DBU, DABCO, DMAP, TEA, DIPEA), where we found that 2.0 equivalent of DIPEA is required for the highest efficiency of the reaction along with a little excess of amine (1.3 equiv.) and it produces 99% yield at room temperature.

Table 5.3.2.1: Optimization of Reaction Conditions[a]

Entry	$BnNH_2$ (equiv.)	Base (equiv.)	Solvent	1a Yield (%)[b]
1	1.0	-	DMF	48
2	,,	-	DMSO	45
3	,,	-	MeOH	47
4	,,	-	$CHCl_3$	45
5	,,	-	EtOAc	25
6	,,	-	ACN	56
7	,,	-	DCM	59
8	,,	-	H_2O	20

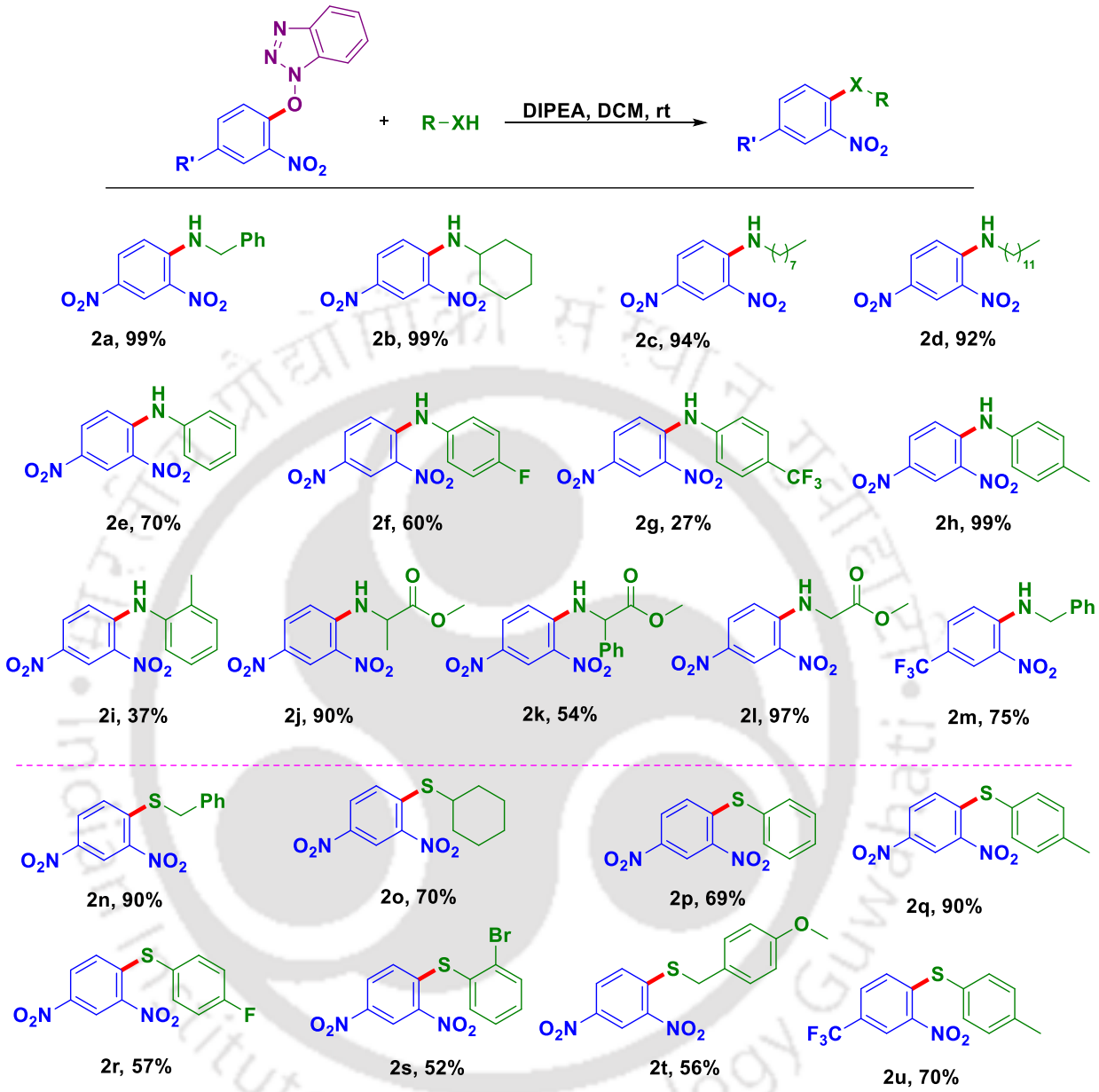
9	,,	-	THF	42
10	,,	DBU (1.0)	DCM	65
11	,,	DABCO (1.0)	,,	67
12	,,	DMAP (1.0)	,,	65
13	,,	Et_3N (1.0)	,,	70
14	,,	DIPEA (1.0)	,,	72
15	,,	DIPEA (1.5)	,,	74
16	,,	DIPEA (2.0)	,,	77
17	,,	DIPEA (2.2)	,,	77
18	1.2	DIPEA (2.0)	,,	85
19	1.3	,,	,,	99

[a]*Reaction condition: 2,4-dinitrophenoxy benzotriazole (1a) (0.25 mmol), benzylamine (varied amount), and base (varied amount) was stirred at room temperature for 2 h.* [b]*Isolated yield.*

5.3.3. Substrate Scope

With the optimal reaction parameters, the *ipso* nucleophilic substitution of 2,4-dinitro phenyl benzotriazoles was examined with various primary amines as appropriate nucleophiles. Aliphatic amines such as benzylamine, cyclohexyl amine, long-chain amines viz. octyl amine, and dodecyl amine successfully underwent this base-mediated *ipso* S_NAr to provide corresponding N-alkylated products, 2a-2d, in excellent yields. The protocol also generated diaryl amine 2e in 70% yields with aniline as an aromatic amine nucleophile. Next, other aniline derivatives with different substituents were investigated

and it was observed that the presence of the electron-withdrawing group (*para*-F, and *para*-CF_3) decreased the yields of the products, (2f, 60%) and (2g, 27%), respectively. On the other hand, electron-donating *para*-Me produced the corresponding product in excellent yield (2h, 99%). However, when *ortho*-toluidine was used as a nucleophile, a lower yield of 37% of the corresponding diaryl amine 2i was observed. Interestingly, a few amino acid esters such as alanine, phenylglycine, and glycine worked as efficient N-nucleophiles in this ipso-S_NAr reaction to deliver amino acid containing diaryl amines 2j-2l. Further, the reaction was equally successful when 2-nitro-4-trifluoromethyl phenyl benzotriazole was coupled with benzylamine in the presence of DIPEA to give the N-arylated product 2m in 75% yield. Further, the alkylation reaction using **N-form I** occurred with a sufficiently high yield, 90%, with benzylamine.



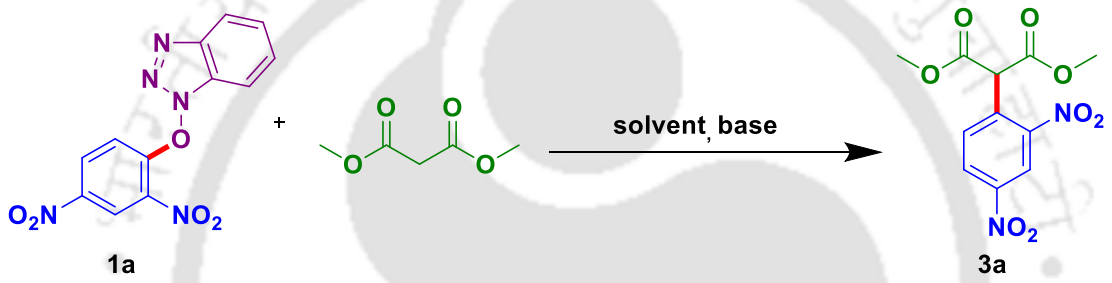
Scheme 5.3.3.1: *Substrate scope of N and S-alkylation*

Reaction condition: O-form (1a) of aryl benzotriazolyl analog (1.0 equiv.), DIPEA (2.0 equiv.), amine, or thiol (1.3 equiv.) were stirred in DCM at room temperature for 2-6 h.

In a similar condition, we have treated various thiols to illustrate the substrate scope. There also we have isolated reasonable yields (up to 91%). The presence of electron-

withdrawing and donating groups influences the formation of desired products similarly (2n-u).

Next, we have explored the possibility of C-alkylation of active methylene compounds via ipso nucleophilic substitution reaction. To optimize the reaction conditions, we have chosen O-form (1a) of aryl benzotriazolyl analog and dimethyl malonate as model substrates.



Scheme 5.3.3.2: *Model reaction for optimization of the C-alkylation of active methyl compounds*

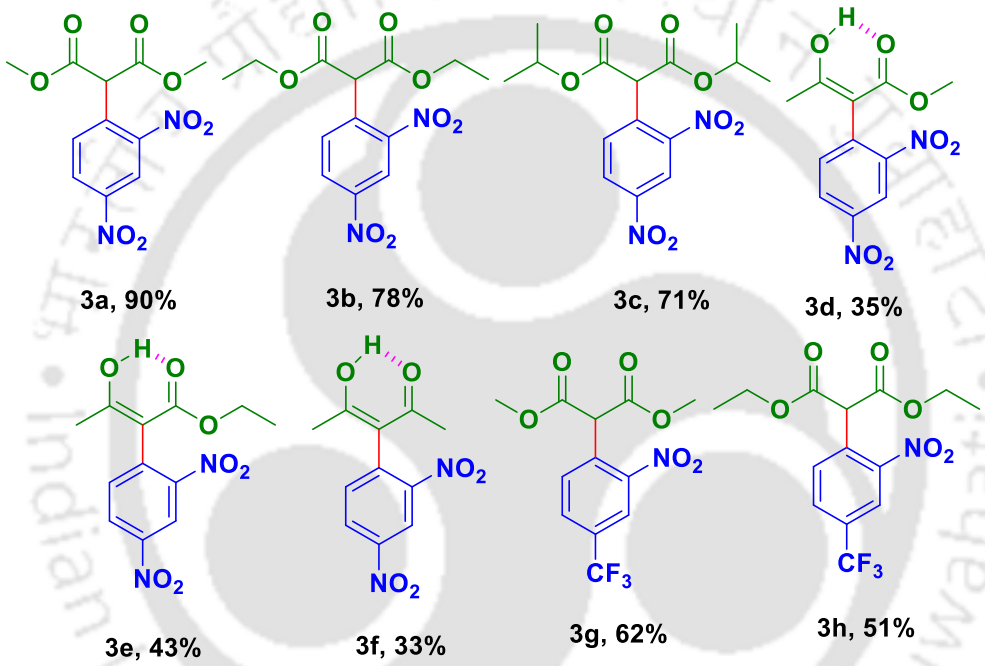
From optimization of the reaction, we have screened several solvents such as DMF, DMSO, acetonitrile, dioxane, acetone, THF, DCM, and MeOH (Table 5.3.3.1: entry 1-8) keeping all other components constant. We have found that DMF is the suitable solvent for this conversion. Then we verified this protocol in the presence of various other bases, like Cs_2CO_3, Na_2CO_3, and DIPEA (Table 5.3.3.1: entry 9-11) but no increment of yield % occurs. Therefore, the reaction produces the highest yield in the presence of 2.0 equiv. of both base K_2CO_3 and active methylene compounds at 80 °C. Further increase in reaction temperature does not improve the yields.

Table 5.3.3.1: Optimization table for C-alkylation of active methylene compound

Entry	DEM(equiv.)	Base (equiv.)	Solvent	Temp[n] (°C)	3a Yield (%)[b]
1	2.0	K_2CO_3 (2.0)	DMSO	80 °C	88
2	,,	,,	DMF	,,	90
3	,,	,,	ACN	,,	41
4	,,	,,	dioxane	,,	81
5	,,	,,	acetone	50 °C	80
6	,,	,,	THF	80 °C	31
7	,,	,,	DCM	25 °C	10
8	,,	,,	MeOH	80 °C	71
9	,,	Cs_2CO_3 (2.0)	DMF	,,	86
10	,,	Na_2CO_3 (2.0)	,,	,,	48
11	,,	DIPEA (2.0)	,,	,,	25
12	1.0	K_2CO_3 (2.0)	,,	,,	54
13	1.5	,,	,,	,,	70
14	1.8	,,	,,	,,	79
15	2.0	K_2CO_3 (1.8)	,,	,,	67
16	,,	K_2CO_3 (2.2)	,,	,,	90
17	,,	K_2CO_3 (2.0)	,,	25 °C	72
18	,,	,,	,,	60 °C	79

[a]*Reaction conditions: 2,4-dinitro benzotriazolyl derivative (O-form) (0.25 mmol), dimethyl malonate (various amount), reaction time 5 h.* [b]*Isolated yield*

With the optimized conditions in hand, we have increased the substrate scope, where we obtained moderate to high yields. Dialkyl malonates effectively respond to this methodology, producing up to 90% yield (3a-c, 3g-h). The product generated by using methyl acetoacetate, ethyl acetoacetate, and acetylacetone is stable in enol forms by the formation of a 6-member cyclic ring through H-bonding (3d-f).



Scheme 5.3.3.3: Substrate scope of C-alkylation

Reaction conditions: 2,4-dinitro benzotriazolyl derivative (O-form) (1.0 equiv.), dimethyl malonate (2.0 equiv.), K_2CO_3 (2.0 equiv.) was stirred in DMF at 80 °C for 5 h.

5.3.4. Computational Work

The molecular geometries of O-form or isomers 1, and N-form I or isomer 2 were constructed using the available X-ray crystal structures. However, for N-form II or isomer 3, we have built the molecular structure manually. The optimized structures of all the

isomers performed at the B3LYP-D3BJ/def2-TZVP level of theory are presented in Figure 5.3.4.1.

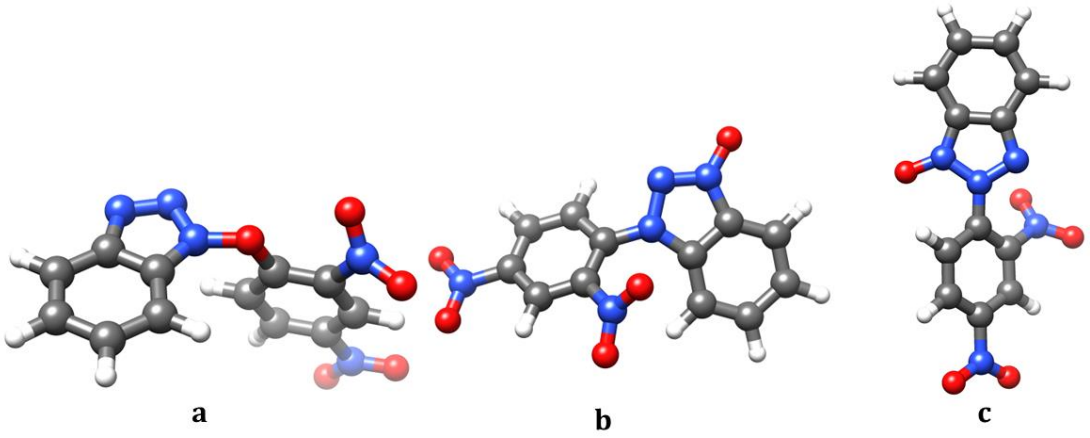


Figure 5.3.4.1: *Optimized molecular geometries (**a**) O-form or isomer 1, (**b**) N-form I or isomer 2, and (**c**) N-form II or isomer 3 were obtained at the B3LYP-D3BJ/def2-TZVP level of theory.*

Further, we have compared the optimized structures of O-form or isomers 1 and N-form I or isomer 2 with the experimental crystallographic structures. The agreement between the DFT-optimized geometric structures and experiment data from the X-ray analysis is fully satisfactory as shown in Figure 5.3.4.2.

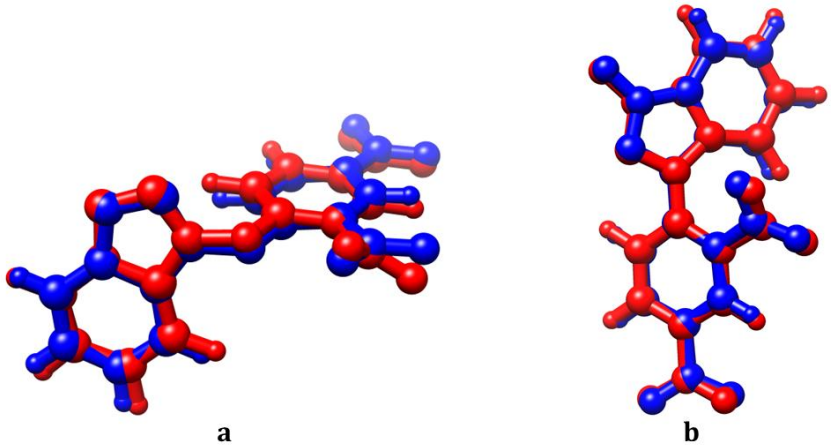


Figure 5.3.4.2: *Superimposed crystallographic (blue) and B3LYP-D3BJ/def2-TZVP calculated (red) of (**a**) O-form or isomer 1 and (**b**) N-form I or isomer 2*

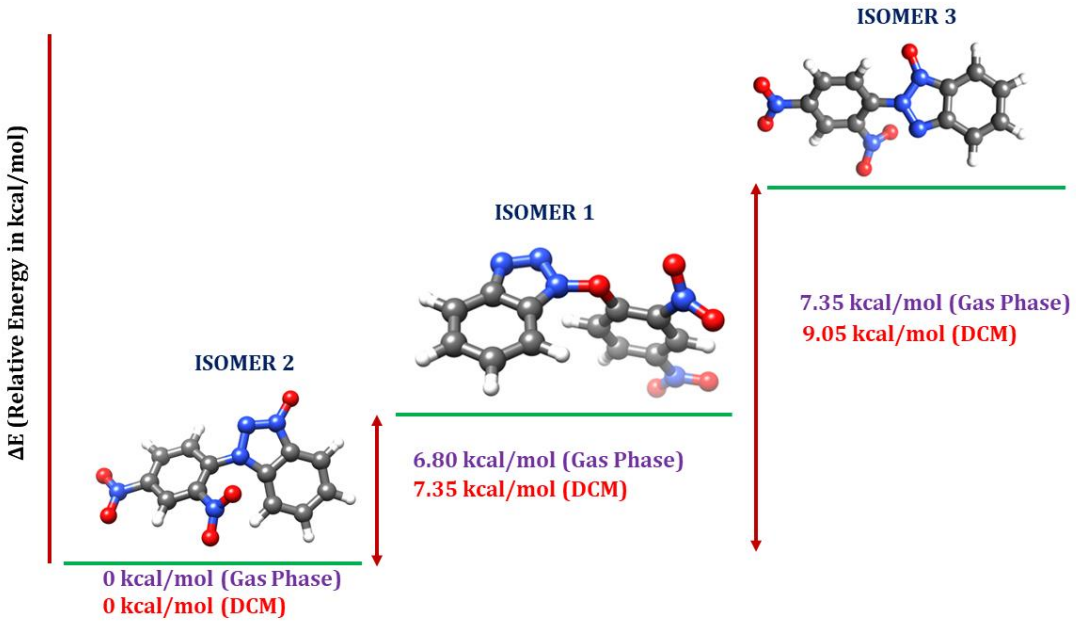


Figure 5.3.4.3: *Relative energies (kcal/mol) in the gas and solvent dichloromethane (DCM) phases of isomers 1, 2, and 3 obtained at the B3LYP-D3BJ/def2-TZVP level of theory.*

Table 5.3.4.1 Total energies in Hartree of isomers calculated at the B3LYP-D3BJ/def2-TZVP Level.

	O-form or Isomer 1	**N-form I or Isomer 2**	**N-form II or Isomer 3**
Gas phase	-1111.5601	-1111.5709	-1111.5592
Solvent (DCM)	-1111.5755	-1111.5872	-1111.5728

The calculated total energies (Table 5.3.4.1) of the isomeric structures revealed that N-form I or isomer 2 is more stable than the others. As seen in Figure 5.3.4.3, N-form I or isomer 2 is relatively more stable than isomers 1 and 3 by 6.80 kcal/mol and 7.35 kcal/mol, respectively, in the gas phase. In addition, a similar trend in the energy barrier was observed in the solvent dichloromethane (DCM) with the energy difference between isomers 2 and 1 of 7.35 kcal/mol and isomers 2 and 3 of 9.05 kcal/mol. Moreover, at this particular level of theory, the energy difference between isomers 1 and 3 is very small.

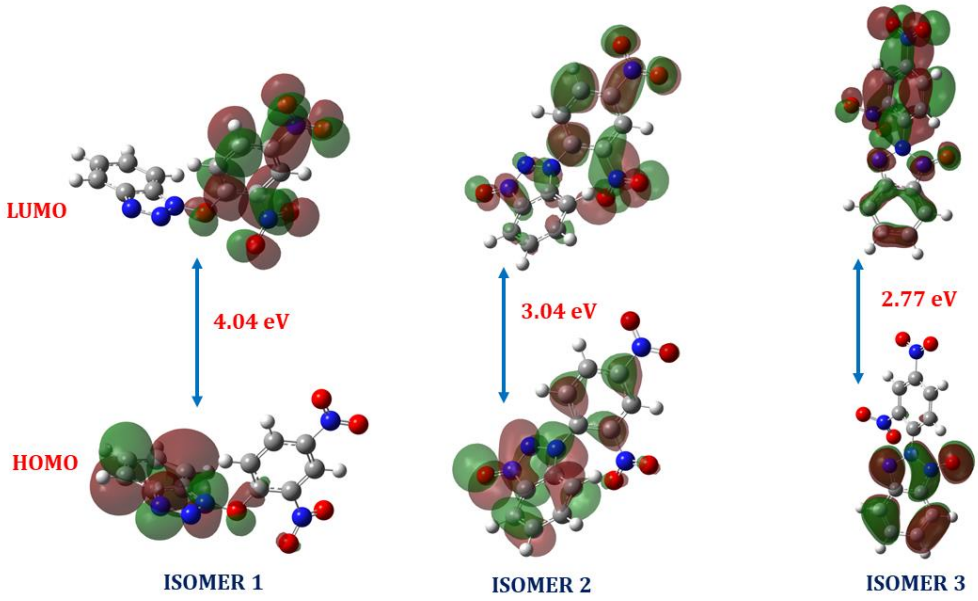


Figure 5.3.4.4: *Frontier molecular orbitals and HOMO-LUMO energy gap for isomers 1, 2, and 3 were calculated at the B3LYP-D3BJ/def2-TZVP level of theory.*

The frontier molecular orbitals of all the isomers are calculated at the B3LYP-D3BJ/def2-TZVP level of theory and shown in Figure 5.3.4.4. The HOMO-LUMO energy gap reduces from isomers 1 to 3. In isomer 1, the HOMO molecular orbital is localized on the benzotriazolyl unit, while the LUMO is distributed around the 2,4-dinitrophenoxy region. In the case of isomer 2, the HOMO and LUMO molecular orbitals are distributed on the entire system. Further, in isomer 3, the HOMO resides in the benzotriazolyl region, while the LUMO is localized in the benzotriazolyl and 2,4-dinitrophenoxy regions.

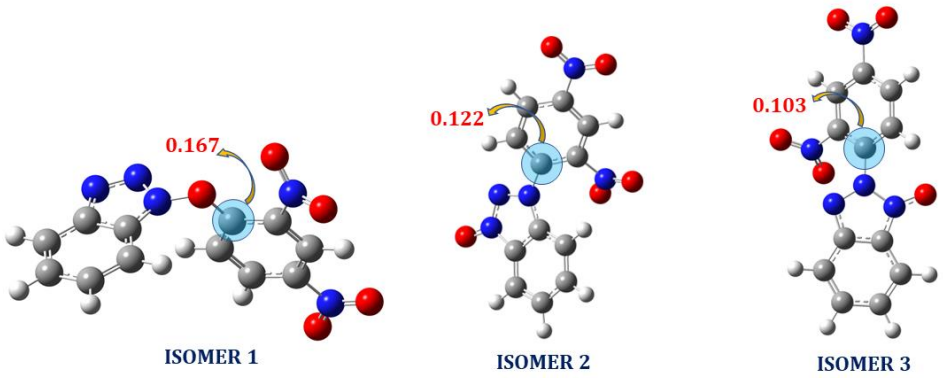
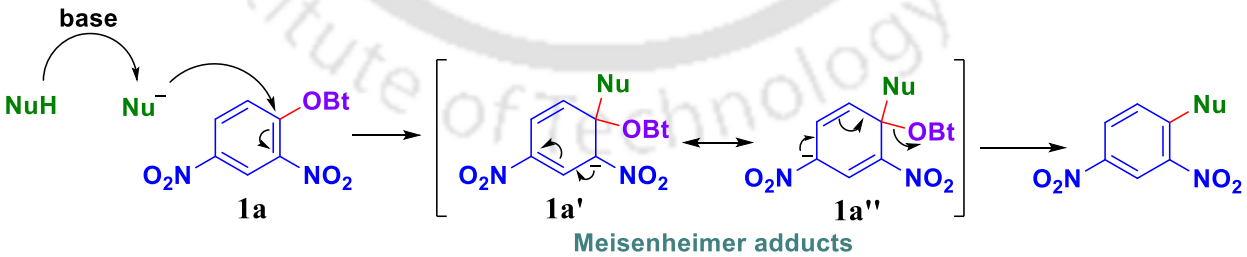


Figure 5.3.4.5: *Mulliken charges (e) on C-atom of isomers 1, 2, and 3 calculated at the B3LYP-D3BJ/def2-TZVP level of theory.*

The atomic charge (Figure 5.3.4.5) on the carbon center (C-O) of isomer 1 (0.167 e) is appreciably greater than that of (C-N) isomer 2 (0.122 e), and (C-N) isomer 3 (0.103 e). These charge variations suggest that the nucleophile is more likely to attack isomer 1. Therefore, we observed the reactions to occur with isomer 1.

5.3.5. Mechanism

The reaction mechanism and kinetics study for aryl benzotriazolyl analog with amine has been well established in the literature. Here we have illustrated a plausible reaction mechanism for C, N, and S-alkylation of active methylene compound, amine, and thiol on aryl benzotriazolyl analog.[32] Initially, the base abstracted the acidic hydrogen of the nucleophile which attacked the ipso position of the aryl benzotriazolyl analog to form the Meisenheimer adduct.[34] This Meisenheimer adduct has resonance stabilization through a strong electron-withdrawing group present in the benzene ring. The Meisenheimer adduct is also stabilized by the *ortho* effect.[35] Finally, by elimination of OBt^- anion it produces the desired alkylated product.



Scheme 5.3.5.1: *Literature-based plausible reaction mechanism*

5.3.6. Applications

The importance of alkylation of active methylene compounds, amines, and thiols is described in Chapter 2, Chapter 3, and Chapter 4 respectively with some practical applications. Where we have developed strategies for 1-methoxy indole, RN-18 analogs, and DNPC derivatives, and all of these can be achieved using our current methodology also.

5.4. Conclusion

In summary, we have successfully alkylated active methylene compounds, amines, and thiols on aryl benzotriazolyl analog via ipso aromatic nucleophilic substitution reaction with a very high yield. This is an example of a toxic and expensive transition metal catalyst-free C-C, C-N, and C-S bond formation reaction in mild conditions. This protocol requires a shorter reaction time and produces high yields without any complex operation strategies involvement. Moreover, no any acidic hydrogen halide (HX) byproduct formation occurs in this protocol specially during amine attack step unlike the case of halogen leaving group containing reagent. We have also explored the desmotropic behavior of the arylated HOBt. Systematic DFT calculations have been performed. The results explain the stability of the isomer 2 and reactivity of the isomer 1.

5.5. Experimental Section

General Information

All reagents were purchased from commercial sources. NMR spectra were recorded on 400, 500, and 600 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as solvent and

tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) were reported in ppm, and spin-spin coupling constants (J) were given in Hz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), and m (multiplet). $^{13}C\{^{1}H\}$ indicates the proton decoupled NMR experiment. Reactions were monitored using thin-layer chromatography with silica gel G254. The reaction products were purified by column chromatography using silica gel (60-120 mesh) using eluent EtOAc/hexane. Solvents were removed under reduced pressure using a Buchi rotary evaporator. Melting points were determined using a dedicated melting point measuring apparatus, and FT-IR spectra were recorded on an FT-IR spectrometer.

Computational Methods

Geometry optimization of isomers 1, 2, and 3 was performed using the B3LYP-D3BJ level of theory with the def2-TZVP basis set.[36-40] Moreover, employing the same level of theory, frequency calculation was conducted to confirm that the optimized geometry corresponds to the minimum energy. Further, the calculations were extended in the dichloromethane (DCM) solvent by implementing the integral equation formalism polarizable continuum model (IEF-PCM).[41-43] All the calculations were performed in the Gaussian 16 software package.[44] The molecular pictures of the isomers were generated by using Gauss View and UCSF Chimera software.[45]

General procedure for the synthesis of aryl benzotriazolyl analogs (1a, 1b)

1-hydroxy benzotriazole (HOBt) (4.0 mmol) was taken in a 200 mL round bottom flask in a DCM medium. DIPEA (4.0 mmol) was added to the RB. The mixture was stirred for 5

minutes. To the RB 2,4-dinitrobenzenesulfonyl chloride (4.0 mmol) was added at 0°C. The reaction was stirred with a magnetic stirrer for 30 minutes till the complete consumption of 2,4-dinitrobenzenesulfonyl chloride was confirmed by TLC. At the end of the reaction acid workup was done with 5% HCl (3×20 mL) followed by basic workup using 5% $NaHCO_3$ (3×20 mL). Finally, the compounds were purified by silica gel column chromatography with 1-15 % EtOAc in hexane as eluent, concentrated the solution under reduced pressure to afford the purified product.

General synthetic procedure of N-alkylation of amines

In a 50 mL RB amines (1.3 equiv.) were taken in DCM medium and DIPEA (2.0 equiv.) was added to it. This mixture was stirred for 5 minutes at room temperature. Then aryl benzotriazolyl analog (1a) (1.0 equiv., 0.25 mmol) was added to it. The whore mixture was continued stirring at room temperature for 2 hours. After completion of the reaction acidic workup was done by 5% HCl (3×10 mL) followed by a basic workup by 5% $NaHCO_3$ (3×10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, the compounds were purified by silica gel column chromatography with 5-10 % EtOAc in hexane as eluent, concentrated the solution under reduced pressure to afford the purified products.

The general synthetic procedure of S-alkylation of thiols

In a 50 mL RB thiols (1.3 equiv.) were taken in DCM medium and DIPEA (2.0 equiv.) was added to it. This mixture was stirred for 5 minutes at room temperature. Then aryl benzotriazolyl analog (1a) (1.0 equiv., 0.25 mmol) was added to it. The whore mixture was continuing to stir at room temperature for 2-6 hours. After completion of the reaction

acidic workup was done by 5% HCl (3×10 mL) followed by a basic workup by 5% $NaHCO_3$ (3×10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, the compounds were purified by silica gel column chromatography with 1-3 % EtOAc in hexane as eluent, concentrated the solution under reduced pressure to afford the purified products.

General synthetic procedure of C-alkylation of active methylene compounds

K_2CO_3 (2.0 equiv., 0.50 mmol) and active methylene compound (2.0 equiv., 0.5 mmol) were taken in an RB flask in DMF solvent and placed on a magnetic stirrer. After 5 mins of pre-activation of the active methylene group, aryl benzotrizolyl analog (1a) (1.0 equiv., 0.25 mmol) was added to RB flask. The reaction was kept for 4-6 hours under reflux conditions. After completion of the reaction 10 mL EtOAc was added to the reaction mixture and DMF was removed by ice-cold water wash (3 times). All collected organic layer was placed in a separating funnel. Then acidic workup was done using 5% HCl (3×10 mL) followed by a basic workup using 5% $NaHCO_3$ (3×10 mL) and finally, wash by brine solution (2×10 mL). Subsequently, the organic portion was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Finally, the compounds were purified by silica gel column chromatography with 5-12 % EtOAc in hexane as eluent, concentrated the solution under reduced pressure to afford the purified products.

General procedure for inter-conversion between O-form and N-form of aryl benzotriazolyl derivative

Aryl benzotrizolyl analog (1a) (1.0 equiv., 0.50 mmol) was taken in a 50 mL RB in DCM solvent. Various base (0 or 2.0 equiv., 1.0 mmol) was added to the above solution. The

above mixture was stirred for several hours (8 to 24 h) with TLC monitoring. Finally, an acidic workup was done using 5% HCl (3×10 mL) solution. The collected organic layer was concentrated under reduced pressure and the product was washed with hexane.

5.6. Characterization Data

***1-(2,4-dinitrophenoxy)-1H-benzo[d][1,2,3]triazole* (1a)**[32]

As a pale yellow solid (850 mg, 70% yield, mp 133–136 ^{o}C); Purification over a column of silica gel (1-15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.02 (d, 1H, J = 2.5 Hz), 8.39 (dd, 1H, J_1 = 9.25 Hz, J_2 = 2.75 Hz), 8.17 (d, 1H, J = 8.5 Hz), 7.63–7.60 (m, 2H), 7.54 (dt, 1H, J_1 = 7.625 Hz, J_2 = 1.375 Hz), 7.00 (d, 1H, J = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 155.9, 144.2, 143.6, 137.9, 130.3, 129.8, 127.9, 126.2, 122.7, 121.2, 116.8, 108.5; IR (KBr, cm^{-1}): 3096, 3066, 3028, 2923, 1604, 1560, 1525, 1472, 1337, 1155, 1127, 915, 768, 702.

***1-(2,4-dinitrophenyl)-1H-benzo[d][1,2,3]triazole 3-oxide* (1b)**

As a yellow solid (140 mg, 12% yield, mp 135–138 ^{o}C); Purification over a column of silica gel (1-15% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.02 (d, 1H, J = 2.5 Hz), 8.70 (dd, 1H, J_1 = 8.75 Hz, J_2 = 2.75 Hz), 8.12 (d, 1H, J = 8.5 Hz), 8.05 (d, 1H, J = 8.5 Hz), 7.74 (t, 1H, J = 7.75 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.37 (d, 1H, J = 8.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 134.2, 133.3, 132.6, 132.1, 130.3, 129.4, 128.9, 126.8, 126.2, 122.4, 117.0, 110.5 ; IR (KBr, cm^{-1}): 3086, 1605, 1530, 1498, 1458, 1341, 1159, 908, 740.

***N-Benzyl-2,4-dinitroaniline* (2a)[46]**

As a yellow solid (67 mg, 99% yield, mp 112–115 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.15 (d, 1H, J = 2.5 Hz), 8.91 (s, 1H), 8.22 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.42–7.39 (m, 2H), 7.36–7.34 (m, 3H), 6.92 (d, 1H, J = 9.5 Hz), 4.66 (d, 2H, J = 5.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 148.4, 136.6, 135.8, 130.9, 130.5, 129.4, 128.5, 127.3, 124.4, 114.6, 47.8; IR (KBr, cm^{-1}): 3375, 2924, 1610, 1579, 1491, 1331, 1257, 1233, 1121, 1072, 1047, 918, 830, 744, 695.

***N-Cyclohexyl-2,4-dinitroaniline* (2b)[46]**

As a yellow solid (65 mg, 99% yield, mp 152–154 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.12 (d, 1H. J = 2.5 Hz), 8.60 (s, 1H), 8.22 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.93 (d, 1H, J = 9.5 Hz), 3.63-3.59 (m, 1H), 2.08–2.06 (m, 2H), 1.85-1.82 (m, 2H), 1.71-1.67 (m, 1H), 1.48-1.44 (m, 4H), 1.37-1.32 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.7, 135.8, 130.4, 130.3, 124.8, 114.4, 52.1, 32.6, 25.5, 24.5; IR (KBr, cm^{-1}): 3351, 2943, 2855, 1617, 1585, 1418, 1253, 1130, 1087, 1050, 921, 829, 744, 653.

***2,4-dinitro-N-octylaniline* (2c)[49]**

As a yellow liquid (69 mg, 94% yield); Purification over a column of silica gel (0.5-2.0% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.14 (d, 1H, J = 3.0 Hz), 8.55 (s, 1H), 8.27 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.91 (d, 1H, J = 9.5 Hz), 3.43–3.35 (m, 2H), 1.77 (t, 2H, J = 7.5 Hz), 1.47–1.43 (m, 2H), 1.30–1.24 (m, 8H), 0.88 (t, 3H, J = 7.0 Hz);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 148.6, 136.1, 130.5, 130.4, 124.5, 114.1, 43.8, 31.9, 29.33, 29.28, 28.9, 27.1, 22.8, 14.2; IR (KBr, cm^{-1}): 3358, 3331, 2952, 2920, 2851, 1620, 1589, 1488, 1335, 1134, 816, 744 .

***N-Dodecyl-2,4-dinitroaniline* (2d)**

As a yelloy solid (80 mg, 92% yield, mp 64–67 ^{o}C); Purification over a column of silica gel (0.5-2.0% EtOAc in hexane δ 9.14 (d, 1H, J = 2.5 Hz), 8.54 (s, 1H), 8.26 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.90 (d, 1H, J = 9.5 Hz), 3.40 (q, 2H, J = 6.5 Hz), 1.81–1.75 (m, 2H), 1.49–1.42 (m, 2H), 1.38–1.26 (m, 16H), 0.89 (t, 3H, J = 7.0 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 148.6, 140.2, 136.2, 130.5, 124.6, 114.1, 43.8, 42.3, 33.8, 32.1, 29.9, 29.7, 29.6, 27.1, 22.9, 14.3; IR (KBr, cm^{-1}): 3365, 3104, 2956, 2925, 2855, 1618, 1523, 1467, 1331, 1270, 1134, 921, 844.

***2,4-Dinitro-N-phenylaniline* (2e)[47]**

As a orange solid (45 mg, 70% yield, mp 152–154 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.98 (s, 1H), 9.18 (d, 1H, J = 3.0 Hz), 8.17 (dd, 1H, J_1 = 9.6 Hz, J_2 = 3.0 Hz), 7.51 (t, 2H, J = 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.31 (d, 2H, J = 7.8 Hz), 7.17 (d, 1H, J = 9.6 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 147.3, 137.6, 136.9, 130.5, 130.1, 127.9, 125.7, 124.3, 116.2; IR (KBr, cm^{-1}): 3315, 2922, 2852, 1616, 1595, 1494, 1319, 1253, 1144, 1057, 921, 742, 683.

***N-(4-Fluorophenyl)-2,4-dinitroaniline* (2f)**

As a orange solid (41 mg, 60% yield, mp 166–168 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.87 (s, 1H), 9.18 (d, 1H, J = 2.5 Hz), 8.18 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.32–7.28 (m, 2H), 7.21 (t, 2H, J = 8.2 Hz), 7.04 (d, 1H, J = 9.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 161.9 (d, J = 247.1 Hz), 147.6, 137.7, 132.8 (d, J = 3.2 Hz), 131.3, 130.2, 128.1 (d, J = 8.5 Hz), 124.3, 117.5 (d, J = 22.6 Hz), 115.9; ^{19}F NMR ($CDCl_3$): δ -112.7 (s); IR (KBr, cm^{-1}): 3308, 2921, 2852, 1615, 1582, 1501, 1335, 1234, 1122, 1060, 926, 819, 783, 689.

***2,4-Dinitro-N-(4-(trifluoromethyl)phenyl)aniline* (2g)[50]**

As a yellow solid (22 mg, 27% yield, mp 116–118 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 10.0 (s, 1H), 9.20 (d, 1H, J = 3.0 Hz), 8.25 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.4 Hz), 7.77 (d, 2H, J = 7.8 Hz), 7.45 (d, 2H, J = 7.8 Hz), 7.29 (d, 1H, J = 9.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 146.0, 140.4, 138.6, 136.6, 132.3, 130.4, 127.7 (q, J = 3.5 Hz), 120.0, 124.2, 116.2; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –62.5 (s), IR (KBr, cm^{-1}): 3309, 2921, 2852, 1602, 1585, 1523, 1318, 1225, 1163, 1062, 927, 833, 741, 707.

***2,4-Dinitro-N-(p-tolyl)aniline* (2h)[46]**

As a orange solid (67 mg, 99% yield, mp 130–132 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.92 (s, 1H), 9.17 (d, 1H, J = 2.4 Hz), 8.14 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.4 Hz), 7.30 (d, 2H, J = 7.8 Hz), 7.18 (d, 2H, J = 7.8 Hz), 7.11 (d, 1H, J = 9.6 Hz), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 147.7, 138.1, 137.4, 134.2, 131.1, 131.0, 130.1, 125.8, 124.3, 116.3, 21.3; IR

(KBr, cm^{-1}): 3309, 2922, 2851, 1607, 1579, 1514, 1421, 1331, 1254, 1139, 1057, 918, 821, 740, 690.

***2,4-Dinitro-N-(o-tolyl)aniline* (2i)**

As a yellow solid (25 mg, 37% yield, mp 110–114 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.82 (s, 1H), 9.20 (d, 1H, J = 3.0 Hz), 8.15 (dd, 1H, J_1 = 9.5 Hz, J_2 = 3.0 Hz), 7.40–7.37 (m, 1H), 7.34–7.33 (m, 2H), 7.26 (d, 1H merge with $CDCl_3$, J = 9.0 Hz), 6.82 (d, 1H, J = 9.5 Hz), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.7, 142.3, 135.4, 135.2, 133.6, 132.1, 130.3, 128.7, 127.9, 127.0, 124.4, 116.1, 14.3; IR (KBr, cm^{-1}): 3329, 2955, 2920, 2851, 1731, 1616, 1585, 1462, 1360, 1255, 1126, 918, 741.

***Methyl (2,4-dinitrophenyl)alaninate* (2j)[46]**

As a yellow liquid (60 mg, 90% yield); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.13 (d, 1H, J = 2.4 Hz), 8.89 (d, 1H, J = 6.8 Hz), 8.27 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.8 Hz), 6.80 (d, 1H, J = 9.6 Hz), 4.45–4.34 (m, 1H), 3.82 (s, 3H), 1.66 (d, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 171.9, 147.1, 136.9, 131.3, 130.6, 124.4, 114.1, 53.3, 51.7, 18.5; IR (KBr, cm^{-1}): 3339, 2918, 2850, 1740, 1616, 1588, 1522, 1424, 1331, 1294, 1229, 1117, 1055, 916, 832, 743, 715.

***Methyl 2-((2,4-dinitrophenyl)amino)-2-phenylacetate* (2k)**

As a yellow solid (44 mg, 54% yield, mp 134–136 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.69 (d, 1H, J = 6.0 Hz), 9.15 (d, 1H, J = 2.4 Hz), 8.14 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 7.47 (d, 2H, J = 7.2

Hz), 7.43–7.37 (m, 3H), 6.64 (d, 1H, J = 9.6 Hz), 5.30 (d, 1H, J = 5.4 Hz), 3.81 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz): δ 169.9, 146.4, 137.1, 134.9, 131.7, 130.4, 129.8, 129.6, 127.2, 124.3, 114.9, 60.5, 53.9; IR (KBr, cm^{-1}): 3106, 3079, 3029, 2923, 2854, 1622, 1561, 1521, 1325, 1229, 1119, 914, 893.

***Methyl (2,4-dinitrophenyl)glycinate* (2l)**[46]

As a yellow solid (61 mg, 97% yield, mp 120–122 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.18 (d, 1H, J = 3.0 Hz), 8.95 (s, 1H), 8.32 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 6.78 (d, 1H, J = 9.5 Hz), 4.20 (d, 2H, J = 5.0 Hz), 3.87 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 168.7, 147.5, 137.2, 130.7, 124.4, 114.1, 53.3, 44.9; IR (KBr, cm^{-1}): 3347, 2916, 2847, 1754, 1618, 1587, 1434, 1324, 1235, 1154, 1058, 915, 828, 730, 698.

***N-Benzyl-2-nitro-4-(trifluoromethyl)aniline* (2m)**[48]

As a yellow solid (55 mg, 75% yield, mp 126–128 ^{o}C); Purification over a column of silica gel (5-10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.65 (s, 1H), 8.50 (d, 1H, J = 2.5 Hz), 7.57 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.0 Hz), 7.41–7.36 (m, 2H), 7.35–7.32 (m, 3H), 6.92 (d, 1H, J = 9.0 Hz), 4.60 (d, 2H, J = 5.5 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 146.9, 136.6, 132.4 (q, J = 3.2 Hz), 131.5, 129.3, 128.3, 127.2, 125.1 (q, J = 4.3 Hz), 124.8, 115.1, 47.4; IR (KBr, cm^{-1}): 3382, 2922, 2853, 1639, 1574, 1428, 1305, 1250, 1146, 1079, 899, 744, 700.

***Benzyl(2,4-dinitrophenyl)sulfane* (2n)[51]**

As a yellow solid (65 mg, 90% yield, mp 122–124 ^{o}C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.09 (d, 1H, J = 2.5 Hz), 8.33 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.61 (d, 1H, J = 9.0 Hz), 7.43 (d, 2H, J = 7.0 Hz), 7.38 (t, 2H, J = 7.3 Hz), 7.33 (t, 1H, J = 7.3 Hz), 4.30 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.0, 144.9, 144.2, 133.7, 129.4, 129.2, 128.6, 127.4, 127.3, 121.9, 38.0; IR (KBr, cm^{-1}): 3100, 2920, 2851, 1578, 1506, 1495, 1455, 1331, 1232, 1089, 916, 830, 732, 692.

***Cyclohexyl(2,4-dinitrophenyl)sulfane* (2o)[52]**

As a yellow solid (49 mg, 70% yield, mp 141–143 ^{o}C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.03 (d, 1H. J = 2.5 Hz), 8.34 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.59 (d, 1H, J = 9.0 Hz), 3.43-3.39 (m, 1H), 2.13–2.09 (m, 2H), 1.90-1.86 (m, 2H), 1.75-1.71 (m, 1H), 1.53-1.43 (m, 4H), 1.39-1.34 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 146.4, 145.6, 143.8, 127.7, 126.9, 122.1, 44.7, 32.4, 26.1, 25.7; IR (KBr, cm^{-1}): 3116, 2937, 2851, 1584, 1503, 1448, 1331, 1260, 1093, 1050, 917, 831, 736, 677.

***(2,4-Dinitrophenyl)(phenyl)sulfane* (2p)[53]**

As a yellow solid (47 mg, 69% yield, mp 115–117 ^{o}C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.10 (d, 1H. J = 2.5 Hz), 8.13 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.53-7.49 (m, 5H),; 6.80 (d, 1H, J = 8.5 Hz), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 147.5, 144.9, 142.7, 135.0, 131.1, 130.9, 129.1,

128.8, 127.5, 121.4; IR (KBr, cm^{-1}): 3112, 2957, 2920, 2853, 1591, 1514, 1336, 1297, 1052, 833, 735.

***(2,4-Dinitrophenyl)(p-tolyl)sulfane* (2q)**[53]

As a yellow solid (64 mg, 90% yield, mp 98–100 °C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.09 (d, 1H. J = 2.5 Hz), 8.11 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.47 (d, 2H, J = 7.0 Hz), 7.30 (d, 2H, J = 8.0 Hz), 6.99 (d, 1H, J = 9.0 Hz), 2.46 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 149.2, 144.4, 143.9, 141.9, 136.0, 131.7, 128.9, 126.9, 125.6, 121.6, 21.7; IR (KBr, cm^{-1}): 3083, 2922, 2852, 1588, 1509, 1448, 1330, 1298, 1129, 1079, 907, 830, 743, 674.

***(2,4-Dinitrophenyl)(4-fluorophenyl)sulfane* (2r)**

As a yellow solid (42 mg, 57% yield, mp 135–138 °C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.10 (d, 1H, J = 2.4 Hz), 8.15 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 7.61–7.59 (m, 2H), 7.26 (t, 2H, J = 8.4 Hz), 6.97 (d, 1H, J = 9.0 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz): δ 164.7 (d, J = 252.2 Hz), 148.3, 144.6, 144.1, 138.4 (d, J = 8.7 Hz), 128.8, 127.2, 124.6 (d, J = 3.6 Hz), 121.7, 118.4 (d, J = 22.0 Hz); ^{19}F NMR ($CDCl_3$): δ -107.6 (s); IR (KBr, cm^{-1}): 3118, 2922, 2853, 1589, 1526, 1487, 1332, 1222, 1130, 1083, 915, 831, 733, 677.

***(2-Bromophenyl)(2,4-dinitrophenyl)sulfane* (2s)**

As a yellow solid (45 mg, 52% yield, mp 59–62 °C); Purification over a column of silica gel (1-3% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.13 (d, 1H, J = 2.5 Hz),

8.17 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.83 (d, 1H, J = 8.0 Hz), 7.76 (d, 1H, J = 7.5 Hz), 7.52–7.44 (m, 2H), 6.88 (d, 1H, J = 9.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 146.3, 144.8, 144.2, 138.4, 134.9, 133.0, 131.3, 130.6, 129.6, 128.6, 127.3, 121.9; IR (KBr, cm^{-1}): 3115, 2922, 2852, 1591, 1505, 1447, 1337, 1303, 1247, 1153, 1050, 905, 831, 732, 673.

***(2,4-Dinitrophenyl)(4-methoxybenzyl)sulfane* (2t)**

As a light yellow solid (44 mg, 56% yield, mp 98–101 ^oC); Purification over a column of silica gel (1-3% EtOAc in hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.09 (d, 1H, J = 2.5 Hz), 8.33 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 7.62 (d, 1H, J = 9.0 Hz), 7.34 (d, 2H, J = 8.5 Hz), 6.90 (d, 2H, J = 8.5 Hz), 4.25 (s, 2H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.8, 147.3, 144.8, 144.1, 130.5, 127.33, 127.32, 125.3, 121.9, 114.8, 55.6, 37.6; IR (KBr, cm^{-1}): 3089, 2954, 2919, 2851, 1741, 1587, 1509, 1335, 1299, 1098, 835, 734.

***(2-Nitro-4-(trifluoromethyl)phenyl)(p-tolyl)sulfane* (2u)[54]**

As a yellow solid (54 mg, 70% yield, mp 88–90 ^oC); Purification over a column of silica gel (1-3% EtOAc in hexane); ^1H NMR ($CDCl_3$, 600 MHz): δ 8.52 (d, 1H, J = 1.8 Hz), 7.54 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.47 (d, 2H, J = 7.8 Hz), 7.15 (d, 2H, J = 7.8 Hz), 6.99 (d, 1H, J = 8.4 Hz), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ 145.2, 144.1, 141.2, 135.9, 131.3, 129.3 (q, J = 3.3 Hz), 128.8, 126.1, 124.4, 123.1 (q, J = 4.2 Hz), 122.1, 21.1; ^{19}F NMR ($CDCl_3$): δ -62.7 (s); IR (KBr, cm^{-1}): 2955, 2920, 2868, 1618, 1561, 1492, 1323, 1296, 1132, 1086, 810, 759, 712.

***Dimethyl 2-(2,4-dinitrophenyl)malonate* (3a)[55]**

As a white solid (67 mg, 90% yield, mp 92–93 ^{o}C); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.90 (d, 1H, J = 2.4 Hz), 8.48 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 7.81 (d, 1H, J = 8.4 Hz), 5.41 (s, 1H), 3.82 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 166.7, 149.2, 147.9, 134.3, 133.5, 127.6, 120.8, 54.0, 53.8; IR (KBr, cm^{-1}): 3105, 2984, 2927, 1732, 1607, 1533, 1466, 1346, 1223, 1151, 1024, 835, 724.

***Diethyl 2-(2,4-dinitrophenyl)malonate* (3b)[56]**

As a yellow liquid (63 mg, 78% yield); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.89 (d, 1H. J = 1.8 Hz), 8.48 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.82 (d, 1H, J = 8.4 Hz), 5.36 (s, 1H), 4.32–4.25 (m, 4H), 1.30 (t, 6H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 166.3, 149.2, 147.8, 134.6, 133.4, 127.5, 120.7, 63.1, 54.4, 14.2; IR (KBr, cm^{-1}): 3100, 2929, 2985, 2856, 1734, 1607, 1447, 1299, 1152, 1026, 743.

***Diisopropyl 2-(2,4-dinitrophenyl)malonate* (3c)**

As a yellow solid (62 mg, 71% yield, mp 109–112 ^{o}C); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.86 (d, 1H, J = 2.4 Hz), 8.46 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.80 (d, 1H, J = 8.4 Hz), 5.27 (s, 1H), 5.15–5.08 (m, 2H), 1.28 (d, 6H, J = 6.0 Hz), 1.26 (d, 6H, J = 6.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 166.3, 149.2, 147.8, 134.6, 133.4, 127.5, 120.7, 63.1, 54.5, 14.2; IR (KBr, cm^{-1}): 3104, 2984, 2938, 1728, 1606, 1534, 1346, 1227, 1097, 906, 834.

Methyl (Z)-2-(2,4-dinitrophenyl)-3-hydroxybut-2-enoate **(3d)**[57]

As a yellow liquid (24 mg, 35% yield); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 12.99 (s, 1H), 8.83 (d, 1H, J = 2.4 Hz), 8.43 (dd, 1.40H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 7.54 (d, 1H, J = 8.4 Hz), 3.64 (s, 3H), 1.89 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 174.5, 170.6, 149.8, 136.6, 127.7, 120.3, 99.6, 52.3, 20.1; IR (KBr, cm^{-1}): 3080, 2966, 2924, 2850, 1741, 1610, 1533, 1441, 1059, 833, 712.

Eethyl (Z)-2-(2,4-dinitrophenyl)-3-hydroxybut-2-enoate **(3e)**[58]

As a yellow solid (31 mg, 43% yield, mp 93–94 ^{o}C); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 13.15 (s, 1H), 8.84 (d, 1H, J = 2.4 Hz), 8.43 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.53 (d, 1H, J = 8.4 Hz), 4.25–4.19 (m, 1H), 4.07–4.02 (m, 1H), 1.92 (s, 3H), 1.13 (t, 3H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 174.5, 170.2, 169.3, 147.4, 136.8, 135.5, 126.9, 120.3, 100.0, 61.7, 20.3, 14.0; IR (KBr, cm^{-1}): 3105, 2955, 2897, 1740, 1656, 1605, 1520, 1441,1342, 1273, 1219, 909, 731.

3-(2,4-Dinitrophenyl)pentane-2,4-dione **(3f)**[59]

As a yellow liquid (22 mg, 33% yield); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.79 (d, 1H, J = 2.4 Hz), 8.50 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.62 (d, 1H, J = 8.4 Hz), 4.27 (s, 1H), 1.86 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 189.9, 137.7, 135.7, 135.0, 127.7, 127.4, 120.9, 120.2, 108.9,

48.7, 24.3; IR (KBr, cm^{-1}): 3104, 2923, 2853, 1720, 1599, 1528, 1400, 1348, 1162, 909, 736.

***Dimethyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate* (3g)**[60]

As a yellow liquid (46 mg, 62% yield); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.32 (d, 1H, J = 2.4 Hz), 7.90 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.4), 7.72 (d, 1H, J = 7.8 Hz), 5.38 (s, 1H), 3.81 (s, 6H); 13C{1H} NMR ($CDCl_3$, 150 MHz): δ 167.1, 149.0, 132.9, 132.3, 131.8, 130.1 (q, J = 3.45 Hz), 122.7 (q, J = 3.9 Hz), 54.0, 53.6; IR (KBr, cm^{-1}): 2958, 2915, 2850, 1738, 1632, 1542, 1507, 1301, 1325, 1268, 1133, 1088, 737.

***Diethyl 2-(2-nitro-4-(trifluoromethyl)phenyl)malonate* (3h)**[61]

As a yellow liquid (45 mg, 51% yield); Purification over a column of silica gel (5-12% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.32 (s, 1H), 7.90 (d, 1H, J = 8.4 Hz), 7.73 (d, 1H, J = 8.4 Hz), 5.34 (s, 1H), 4.30-4.26 (m, 4H), 1.29 (t, 6H, J = 7.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 166.8, 149.1, 132.8, 132.1, 130.0 (q, J = 3.3 Hz), 123.7, 122.7 (q, J = 3.6 Hz), 121.9, 62.9, 54.5, 14.2; IR (KBr, cm^{-1}): 2985, 2925, 2856, 1734, 1633, 1507, 1466, 1300, 1226, 1177, 1133, 799.

5.7. Representative NMR Specta

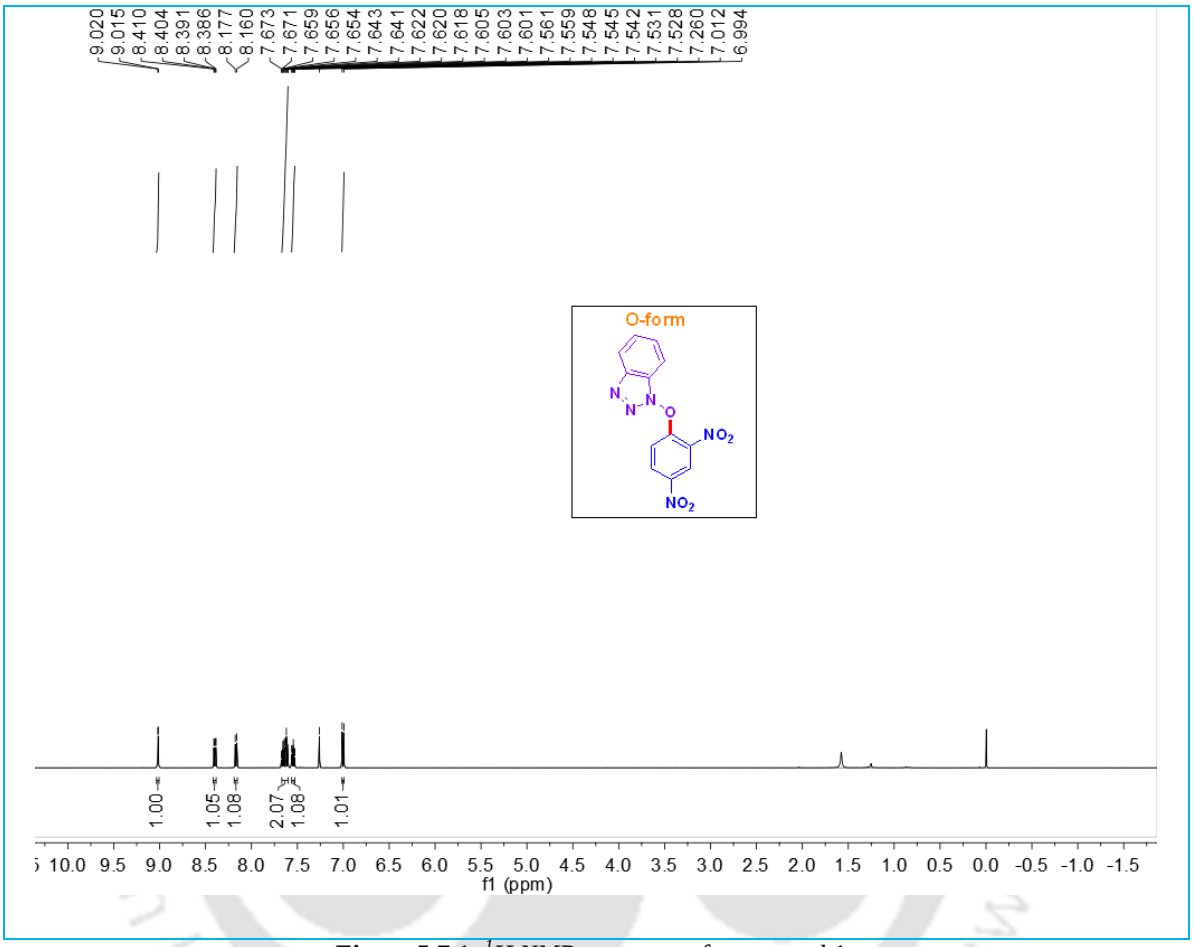


Figure 5.7.1: *^{1}H NMR spectrum of compound* ***1a***

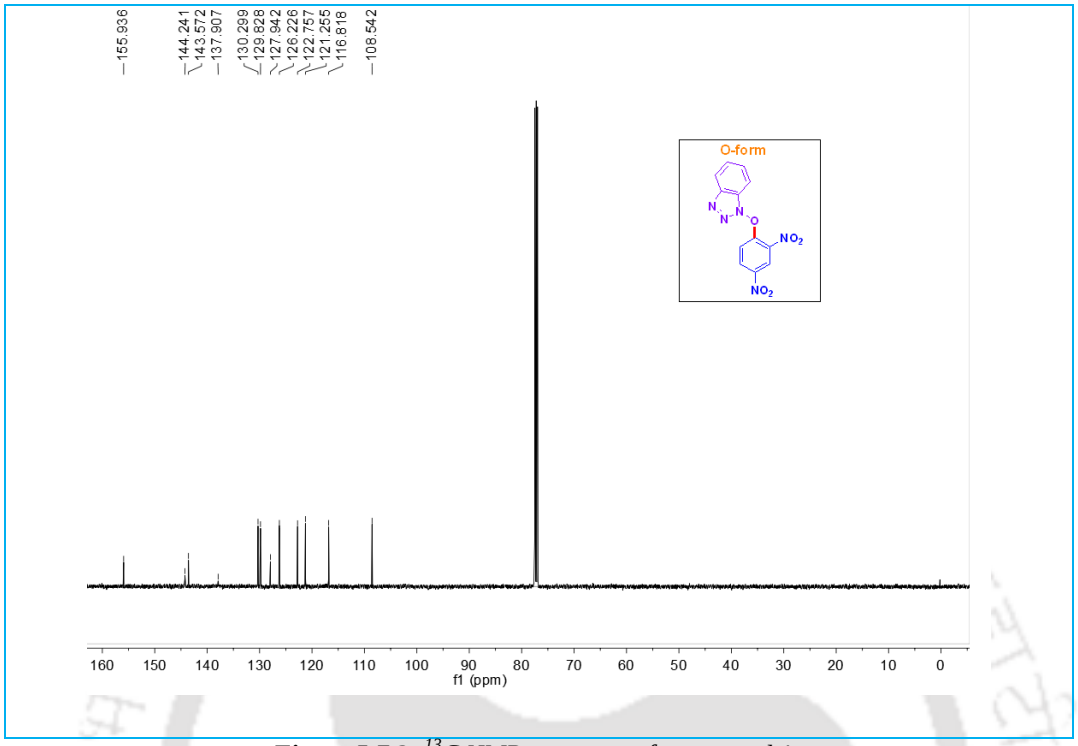


Figure 5.7.2: *^{13}C NMR spectrum of compound* ***1a***

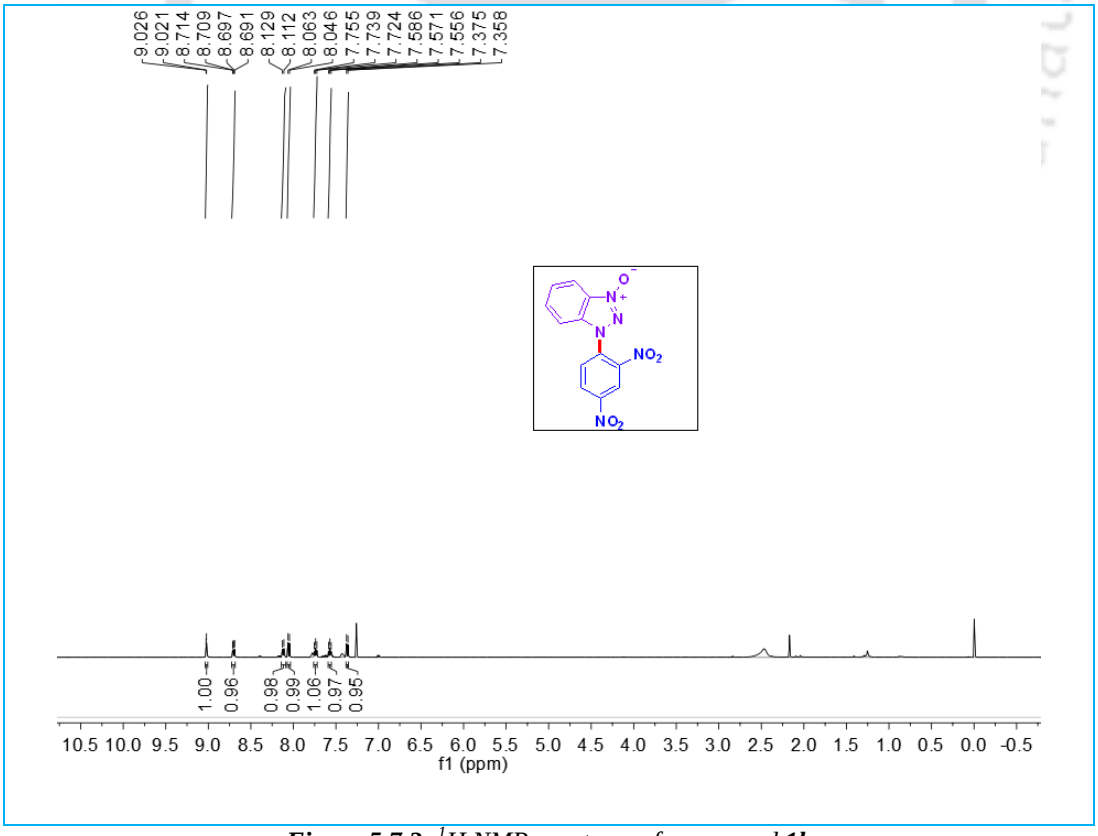


Figure 5.7.3: *^{1}H NMR spectrum of compound* ***1b***

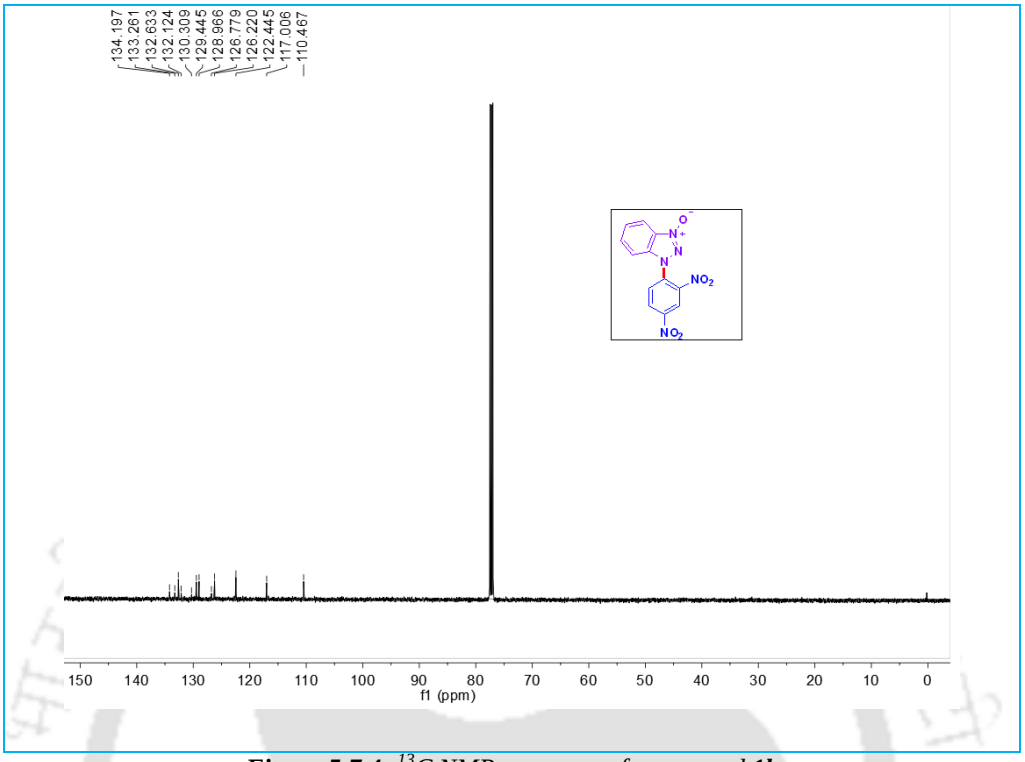


Figure 5.7.4: *^{13}C NMR spectrum of compound* ***1b***

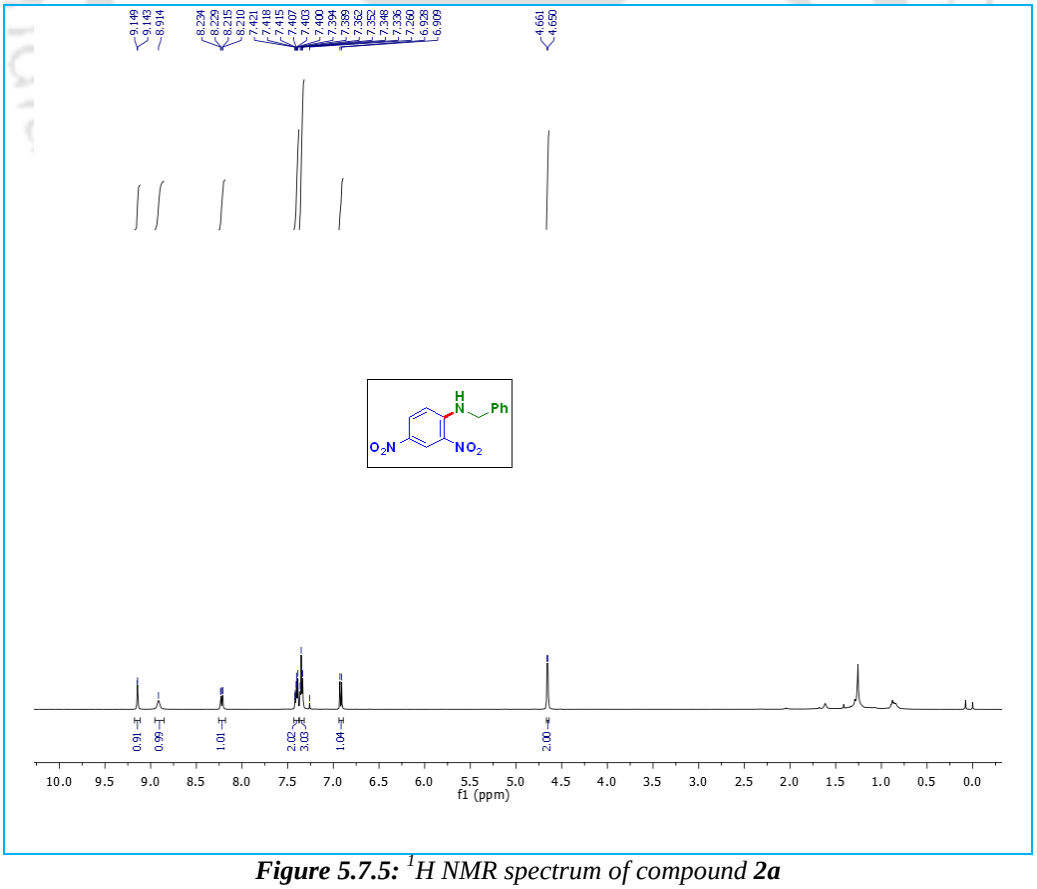


Figure 5.7.5: *^{1}H NMR spectrum of compound* ***2a***

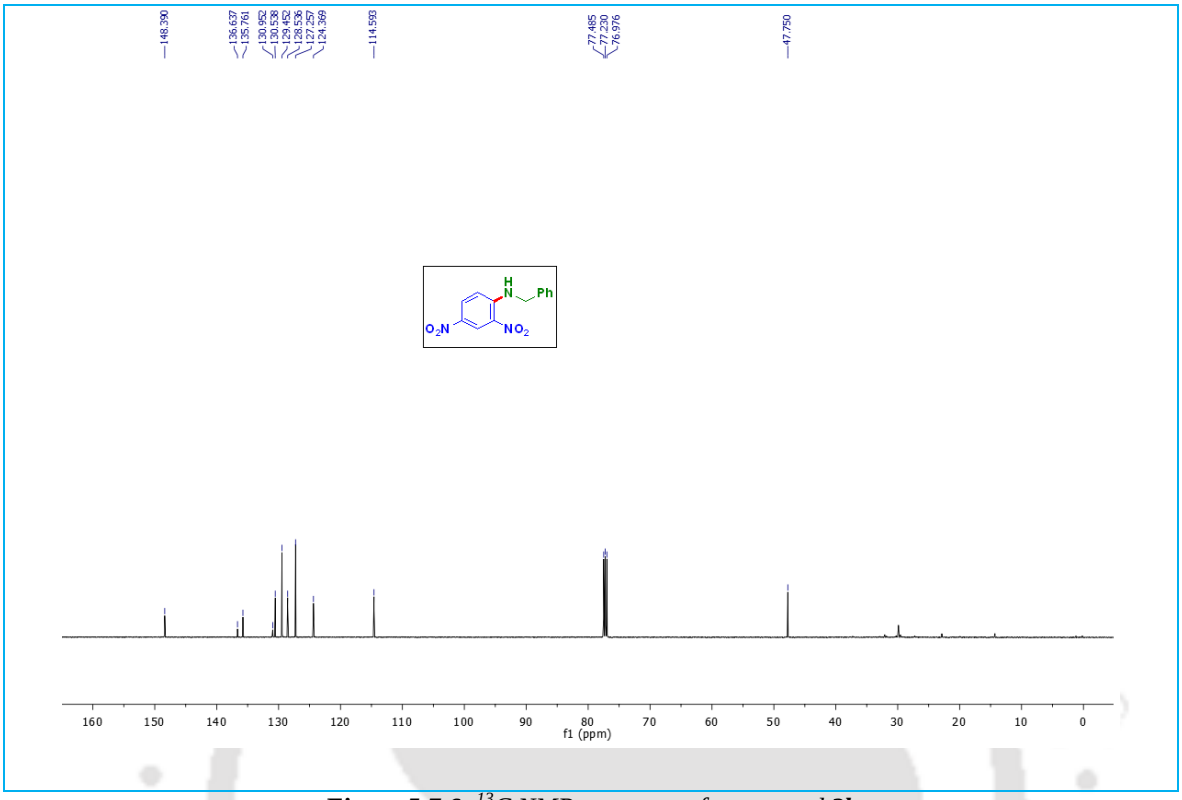


Figure 5.7.6: *^{13}C NMR spectrum of compound* ***2b***

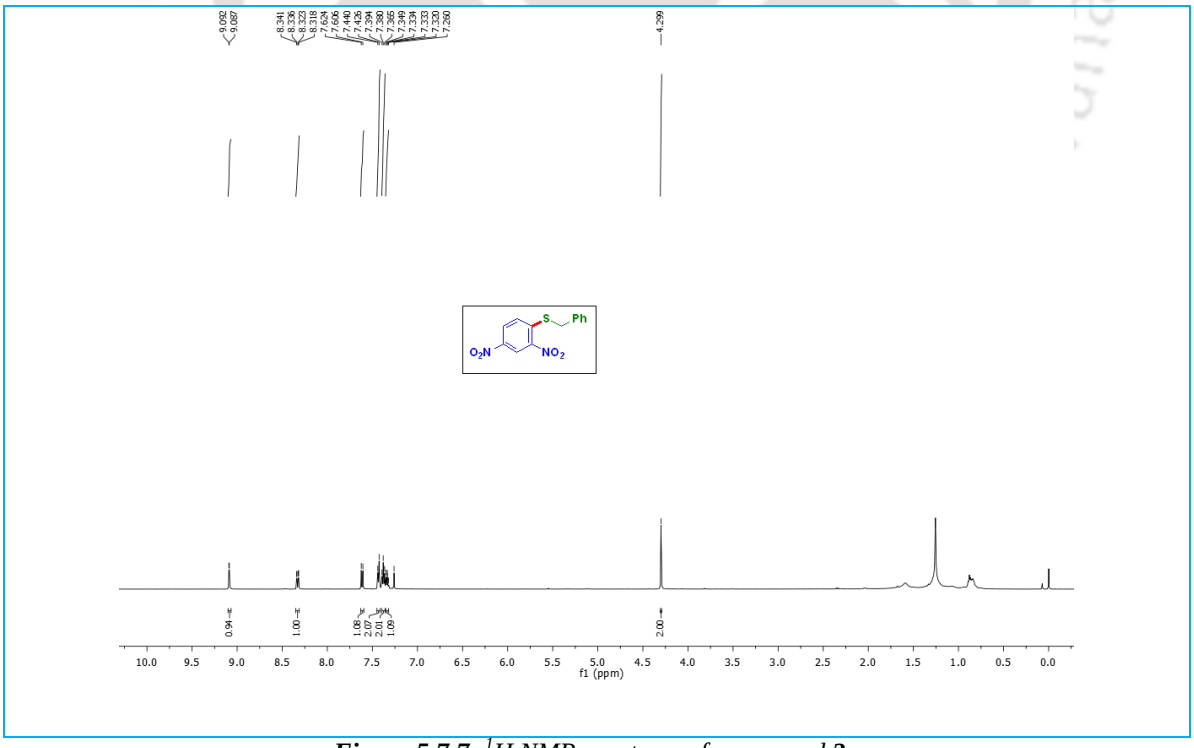


Figure 5.7.7: *^{1}H NMR spectrum of compound* ***2n***

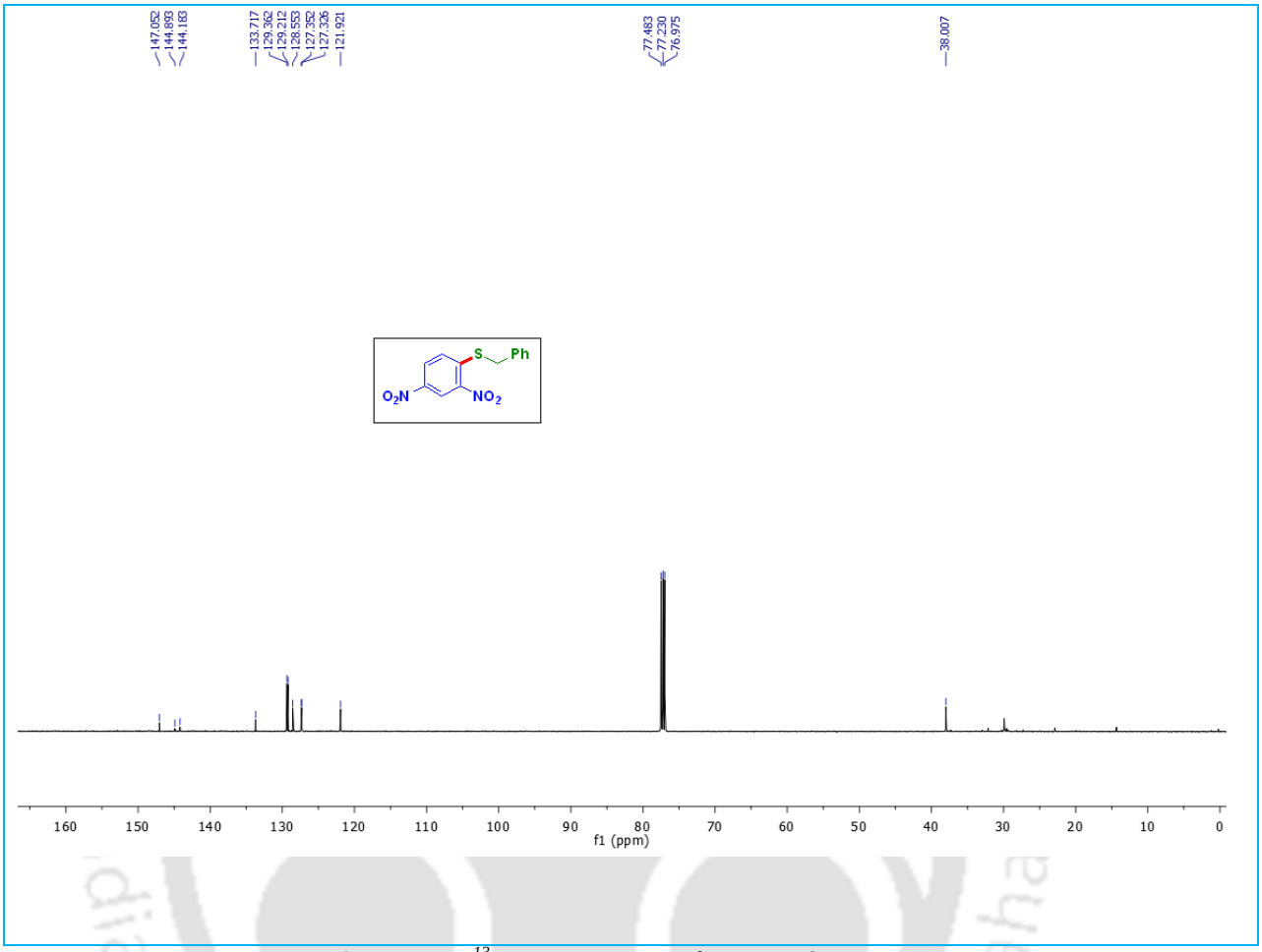


Figure 5.7.8: *^{13}C NMR spectrum of compound* ***2n***

5.8. Crystallographic Data

Compound No.	**1a**	**1b**	**2a**
Formula	$C_{12}H_7N_5O_5$	$C_{12}H_7N_5O_5$	$C_{13}H_{11}N_3O_4$
CCDC No.	2261267	2261268	2259705
Formula. wt.	301.23	301.23	273.25
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	P 21/c	P-1	P-1
a (Å)	5.9664(17)	6.5572(5)	7.1191(4)
b (Å)	9.137(3)	10.4905(7)	8.2564(5)
c (Å)	23.831(7)	18.6503(13)	11.1831(6)
α(°)	90.00	96.330(2)	84.604(2)
β(°)	96.055(9)	93.416(2)	84.013(2)
γ(°)	90.00	97.450(2)	73.046(2)
V/ $Å^3$	1291.9(6)	1260.78(16)	623.92(6)
Z	4	4	2
T(K)	297(2)	297(2)	296(2)
Density/g cm^{-3}	1.549	1.587	1.454
Abs. Coeff. /mm^{-1}	0.125	0.128	0.111
F(000)	616.0	616.0	284.0
Total no. of reflections	31763	27984	25602
Reflections, $I > 2\sigma(I)$	0.0482 (2130)	0.0470 (3107)	0.0498(1658)
Max. 2θ/°	26.338	24.999	24.994
Ranges (h, k, l)	(7,11,29)	(7,12,22)	(8,9,13)
Complete to 2θ (%)	25.242	24.999	24.994
Data/ Restraints/Parameters	2641/0/199	4435/0/397	2194/0/181
Goof (F^2)	1.073	1.008	0.684
R indices [$I > 2\sigma(I)$]	0.0482	0.0470	0.0498
R indices (all data)	0.0586	0.0736	0.0629

❖ **ORTEP Diagram with ellipsoid of 50% probability**

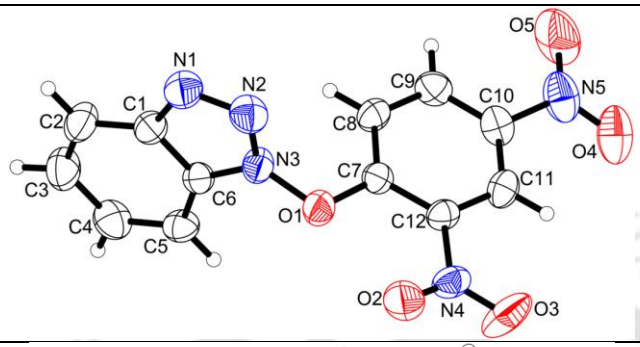
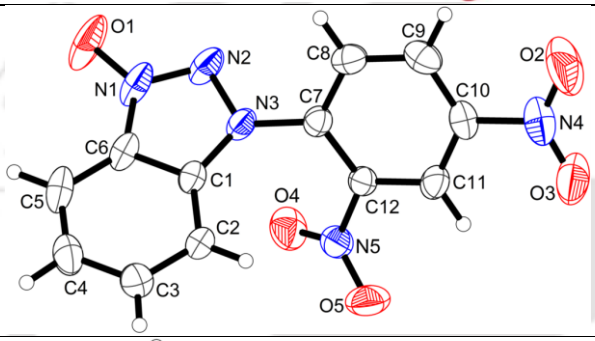
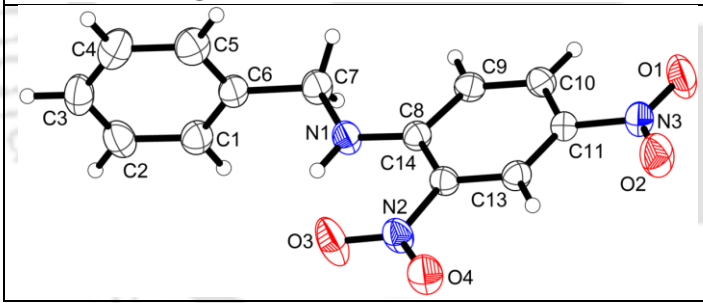
ORTEP Diagram	Compound	CCDC No.
	**1a**	2261267
	**1b**	2261268
	**2a**	2259705

Figure 5.8.1: *ORTEP Diagrams*

5.9. References

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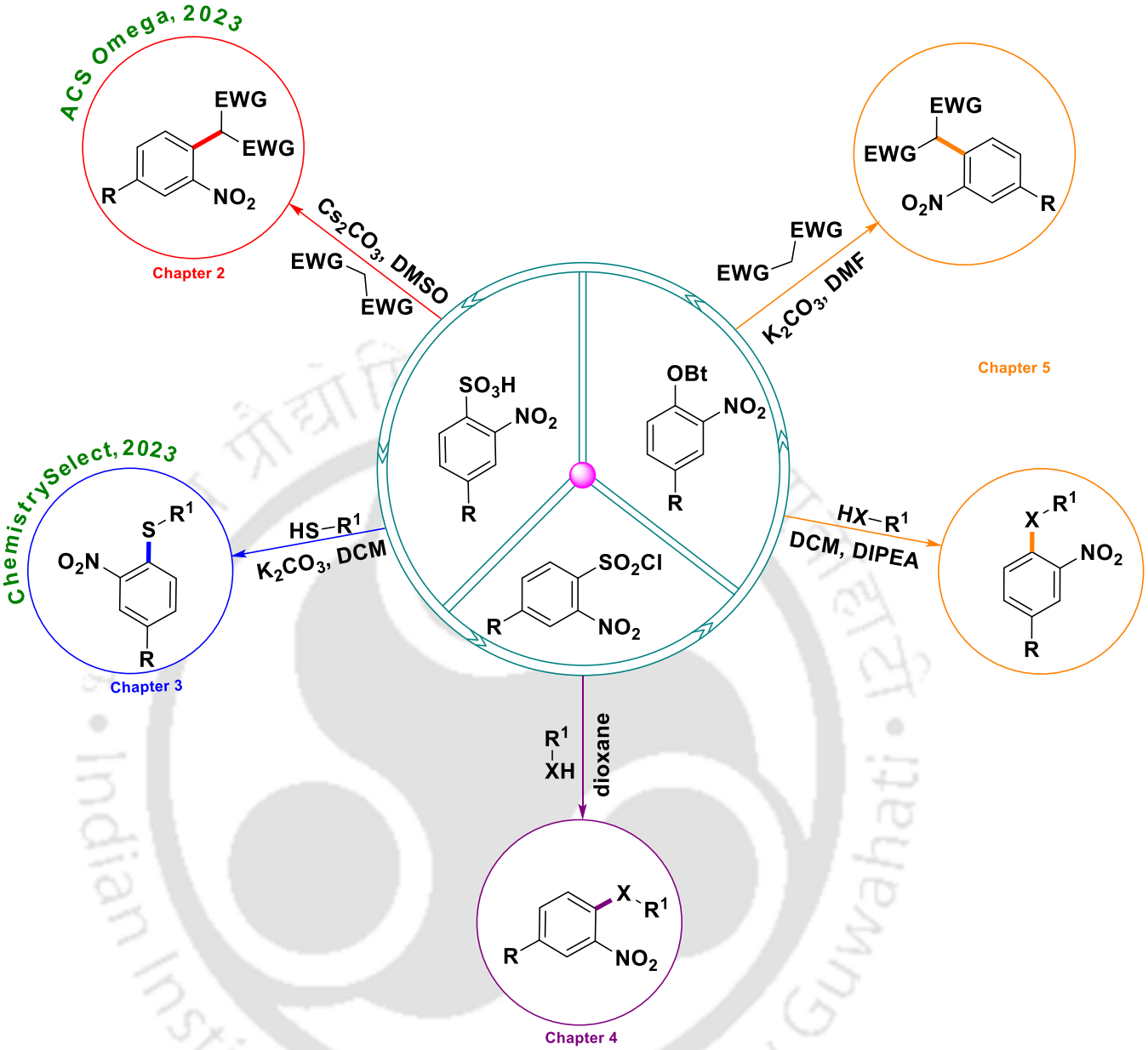
Conclusion and Future Directions

Conclusion

This thesis work is aimed to investigate and explore different types of alkylation reactions on various electron-deficient arene systems and develop convenient strategies for the C-alkylation of active methylene compounds, N-alkylation of amines, and S-alkylation of thiols. The importance of those strategies to produce respective alkylated or arylated products and their existing synthetic methods and drawbacks are precisely discussed in Chapter 1. Also, associated sulfonamide formation has been duly addressed in relevant chapters. In Chapter 2, we have unveiled and demonstrated a new strategy for the C-alkylation of active methylene compounds on aryl sulfonic acid derivatives via ipso aromatic nucleophilic substitution reaction and its feasible applications. In continuation, the S-alkylation of thiols on electron-deficient benzene sulfonic acids under mild reaction condition and its practical applications has been demonstrated in Chapter 3. Next, in Chapter 4, we have described a transition metal-free versatile methodology for synthesizing diarylamines and diaryl thioethers under mild reaction conditions by intermolecular ipso aromatic nucleophilic substitution reaction using aryl sulfonyl chlorides. Eventually, in Chapter 5, we devised and described a highly efficient HOBt-mediated protocol for the alkylation of active methylene compounds, amines, and thiols via ipso substitution reaction. The entire structure of the thesis is depicted in Scheme 1.



Scheme 1: *Thesis overview*

Future Directions

Only some alkylation methodologies have been investigated and disclosed for highly electron-deficient various arene systems (aryl sulfonic acids, sulfonyl chlorides, and benzotriazolyl analogs) in my Ph. D. tenure. The substrate scope can further be increased by surveying for each methodology using discussed nucleophile analogs and electrophilic arene derivatives. O-alkylation or unsaturated system alkylation is the other possibility that can be investigated on similar substrates.

Research Outcome

❖ List of Publications

1. **Mondal, S.**; Sikdar, A.; Singh, H. K.; Paul, A.; Roy, R.; Sarma, M.; Mandal, B. Ipso Nucleophilic Substitution Reaction on Aryl Benzotriazolyl Derivative by Various Nucleophiles (Manuscript to be submitted).
2. **Mondal, S.**; Boder, A.; Sikdar, A.; Roy, S.; Paul, A.; Mandal, B. Formation of Smile Rearrangement Product by Mild Intermolecular Ipso Aromatic Nucleophilic Substitution (Manuscript to be submitted).
3. **Mondal, S.**; Mukherjee, P.; Paul, A.; Sikdar, A.; Mandal, B. Carbon-Sulfur Bond Formation via Ipso Nucleophilic Substitution of Electron-Deficient Benzenesulfonic Acid with Thiol, *ChemistrySelect*, **2023**, *8*, e202303212.
4. **Mondal, S.**; Dolai, G.; Mandal, B. Unprecedented C-C Bond Formation *via* Ipso Nucleophilic Substitution of 2,4-Dinitrobenzene Sulfonic Acid with Active Methylene Compounds, *ACS Omega*, **2023**, *8*, 1401–1409.
5. Kalita, T.; Dev, D.; **Mondal, S.**; Giri, R. S.; Mandal, B. Ethyl-2-Cyano-2-(2-Nitrophenylsulfonyloximino)Acetate (ortho-NosylOXY) Mediated One-Pot Racemization Free Synthesis of Ureas, Carbamates, and Thiocarbamates via Curtius Rearrangement, *A. J. Org. Chem.* **2021**, *10*, 1523-1529.
6. Chandra, J.; Manne, S. R.; **Mondal, S.**; Mandal, B. (*E*)-Ethyl-2-cyano-2-(((2,4,6-trichlorobenzoyl)oxy)imino)acetate: A Modified Yamaguchi Reagent for Enantioselective Esterification, Thioesterification, Amidation and Peptide Synthesis, *ACS Omega*, **2018**, *3*, 6120–6133.

7. Chandra, J.; Chaudhuri, R.; Manne, S. R.; **Mondal, S.**; Mandal, B. Direct Synthesis of Sulphonates of Alcohol, Oxyma-O-sulphonates and Oxime-O-sulphonates under Microwave Irradiation, *ChemistrySelect*, **2017**, *2*, 8471–8477.

❖ Patent

1. Indian Patent Application (complete specifications), filed on 14.12.2017, Title: "A Novel Coupling Reagent for Esterification, Thioesterification, Amidation and Peptide Synthesis". Application No. 201731045011 Inventors: Dr. Bhubaneswar Mandal, Jyoti Chandra, Srinivasa Rao Manne and **Sandip Mondal**

❖ Conference Attended

1. Participated in a poster presentation on the topic of 'Unprecedented C-C Bond Formation *via* Ipso Nucleophilic Substitution of 2,4-Dinitrobenzene Sulfonic Acid with Active Methylene Compounds' in an international conference on Frontiers in Chemical Sciences (FICS-2022) organized by Indian Institute of Technology Guwahati, Page 115, Dated on 03.12.2022
2. Participated in an oral presentation on the topic of "Ipso Substitution on 2,4-Dinitrobenzene Sulfonic Acid by Various Nucleophiles" in an International Conference on Emerging Trends in Chemistry (ICETC-2023) organized by Don Bosco University, Page 88, Dated on 03.03.2023
3. Participated in a poster presentation on the topic of "Transition Metal-free C-S Bond Formation via Ipso Nucleophilic Substitution Reaction of Electron-Deficient Benzenesulfonic Acid with Thiol" in National Conference on Emerging Dimension

in Chemical Sciences (EDCS-2023) organized by Kalyani University, Page 64, Dated on 28.03.2023

4. Participated in poster presentation on the topic of "Replacement of Sulfonic Acid Functionality by Amines, Thiols and Active Methylene Compounds of Highly Electron Deficient Benzene Sulfonic Acids" in a Conference on Research & Industrial Conclave (RIC-2023) organized by IIT Guwahati, Dated on 15.05.2023
5. Participated in a poster presentation on the topic of "Ipso Nucleophilic Substitution Reaction on Aryl Benzotriazolyl Derivative by Amines, Thiols and Active Methylene Compounds" in P. C. Ray Memorial International Conference on Contemporary Ideas, Innovations & Initiatives in Chemical Sciences (CI3CS-2023) organized by Presidency University, Page 87, Dated on 23.08.2023
6. Participated in a poster presentation on the topic of "Ipso Substitution on Electron-Deficient Aryl Sulfonic Acids and Sulfonyl Chlorides by Various Nucleophiles" in XVIII J-NOST Conference 2023 for Young Researchers in Organic Chemistry (J-NOST 2023) organized by Indian Institute of Science Education and Research, Pune, Page 109, Dated on 10.10.2023
7. Participated in an oral presentation on the topic of "Ipso Substitution on Electron-Deficient Aryl Sulfonic Acids and Sulfonyl Chlorides by Various Nucleophiles" in an International Conference on Interface of Chemistry, Material Chemistry and Pharmaceutical Sciences (ICMCPS-2023) jointly organized by The Assam Royal Global University and Cotton University, Page 59, Dated on 10.11.2023

❖ Workshop Attended

1. Participated in workshop on "Procedures & Applications of XRD, XRF & Single Crystal XRD" organized by SAIF, Guwahati, sponsored by DST, Government of India from 27.07.2018 to 01.08.2018
2. Participated in the online workshop " Nuclear Magnetic Resonance: Technique and its Application" organized by North East Centre for Biological Sciences and Healthcare Engineering, Indian Institute of Technology Guwahati, Assam, in collaboration with Bruker, India with support of Department of Biotechnology, Government of India during 23.08.2021 to 24.08.2021

CURRICULUM VITAE

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EDUCATION

2023
Doctor of Philosophy (Ph. D.) in organic chemistry
Indian Institute of Technology Guwahati, India-781039
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2016
Master of Science (M. Sc.) in Chemistry
School of Chemistry, University of Hyderabad, India-500046

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Bachelor of Science (B. Sc.) in Chemistry
Presidency College, University of Calcutta, India-700073

WORK EXPERIENCE

Thesis Title: Synthesis of Functionalized Pyrrole Derivatives (M. Sc. Project)
Supervisor: Dr. Pradeepta K. Panda
School of Chemistry, University of Hyderabad, India-500046
Duration: January-April, 2016

PROFESSIONAL SKILL

Field: 400 MHz NMR instrumental duty as an operator
Department of Chemistry, Indian Institute of Technology Guwahati
Duration: January 2018-March, 2023
Used a wide range of analytical instruments such as HRMS, LCMS, FT-IR, UV-visible spectrometer, NMR, HPLC, Microwave reactor, SC-XRD, Koelar distillation apparatus
Familiar with Origin, Adobe Illustrator, MS-office, Chemdraw, Mestrenova, Mercury, SHELXL, Mass Hunter, EndNote

TEACHING EXPERIENCE

- ✓ Teaching Assistantship (TA) in the undergraduate lab at the Department of Chemistry, IIT Guwahati, in July-November 2017 semester
- ✓ Mentored one Ph. D., three M. Sc., and one B. Tech. students during Ph. D. period

RESEARCH INTEREST

- Synthetic Organic Chemistry
- Solution Phase Peptide Synthesis
- Newer Methodology in Organic Synthesis (Photochemical & Electrochemical)

ACADEMIC ACHIEVEMENTS

- Qualified Graduate Aptitude Test in Engineering (GATE) organized by the Department of Higher Education, Ministry of Human Resources Development (MHRD), Government of India [2016]
- Qualified Joint Admission Test for Masters (JAM) organized by IIT Roorkee on behalf of the Ministry of Human Resources Development (MHRD), Government of India [2014]
- Qualified UoH Entrance Examination for Masters [2014]
- Qualified Visva-Bharati University Entrance Examination for Masters [2014]
- Qualified Presidency College Entrance Examination for UG [2009]
- Qualified Visva-Bharati University Entrance Examination for UG [2009]

SCHOLARSHIPS AWARDED

- Received Sitaram Jindal Scholarship sponsored by Sitaram Jindal Foundation [2011]
- Received Anant Merit Scholarship sponsored by Infinity Group [2011]
- Received Foundation for Academic Excellence & Access (FAEA) Scholarship sponsored by the Confederation of Indian Industry [2010]
- Received Merit Cum Means Scholarship awarded by the Government of West Bengal [2009]
- Received Merit Cum Means Scholarship awarded by the Government of West Bengal [2007]

VOLUNTEER ACTIVITY

- Participated as a volunteer during North-East Research Conclave-2022 & Assam Biotech Conclave-2022, during May 20-22, 2022, at the Indian Institute of Technology Guwahati
- Participated as a volunteer in both inter IIT sports meet and inter IIT aquatics meet 2018