NEW METHODOLOGIES FOR C−C AND C−X (N, O & I) BOND FORMATION BY COPPER NANOPARTICLES AND TRICHLOROACETONITRILE

A THESIS SUBMITTED TO

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BY
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DEDICATED TO

…MY FAMILY

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CERTIFICATE

This is to certify that the research work presented in this thesis entitled **"New Methodologies for C−C and C−X (N, O & I) Bond Formation by Copper Nanoparticles and Trichloroacetonitrile"** submitted by **Mrs. Poshala Soumya** for the degree of Doctor of Philosophy in Chemistry, National Institute of Technology, Warangal (Telangana), under my supervision and that the same has not been submitted elsewhere for a degree.

Date: 19-12-2022
Place: NIT Warangal

Dr. K. Hari Prasad
Thesis Supervisor

DECLARATION

I hereby declare that the matter embodied in this thesis entitled **"New Methodologies for C−C and C−X (N, O & I) Bond Formation by Copper Nanoparticles and Trichloroacetonitrile"** is based entirely on the results of the investigations and research work carried out by me under the supervision of **Dr. K. Hari Prasad**, Department of Chemistry, National Institute of Technology, Warangal. I declare that this work is original and has not been submitted in part or full, for any degree or diploma to this or any other University.

Soumya

(Poshala Soumya)

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-Soumya

(Poshala Soumya)

ABBREVIATIONS

$(Bz)_2O_2$	:	Benzoyl peroxide
3D	:	Three dimensional
AcOH	:	Acetic acid
AIDS	:	Acquired immune deficiency syndrome
$AlCl_3$	:	Aluminium (III) chloride
ANO	:	Ammonium niobium oxalate
atm	:	Atmosphere
BF_3	:	Boron trifluoride
$BF_3.Et_2O$	:	Boron trifluoride diethyl etherate
BIMs	:	Bis(indolyl)methanes
Br_2	:	Bromine
Bu_2SnO	:	*n*-Dibutyltin oxide
Bu_3N	:	Tributylamine
Bu_4NI	:	Tetrabutylammonium iodide
CCl_3CN	:	Trichloroacetonitrile
CCl_4	:	Carbon tetrachloride
$CDCl_3$	:	Deuterated chloroform
$Ce_2(SO_4)_3$	:	Cerium(III) sulfate
$CeCl_3$	:	Cerium(III) chloride
CeO_2	:	Cerium(IV) oxide
CH_2Br_2	:	Dibromomethane
CH_3CN	:	Acetonitrile
CH_3SO_3H	:	Methanesulfonic acid
ChCl	:	Choline chloride
$CHCl_3$	:	Chloroform
CO	:	Carbon monoxide
CO_2	:	Carbon dioxide
$COCl_2$	:	Phosgene

Cs_2CO_3	:	Cesium carbonate
CSA	:	Camphorsulfonic acid
CTAB	:	Cetyltrimethylammonium bromide
Cu	:	Copper
$Cu(OAc)_2$	:	Copper(II) acetate
$Cu(OTf)_2$	:	Copper(II) trifluoromethanesulfonate
Cu_2O	:	Copper(I) oxide
Cu_2S	:	Copper(I) sulfide
CuAAC	:	Copper(I)-catalyzed alkyne-azide cycloaddition
$CuCl_2$	:	Copper(II) chloride
CuNPs	:	Copper nanoparticles
$CuSO_4$	:	Copper(II) sulfate
d	:	Doublet
DA	:	Diels–Alder reaction
DABCO	:	1,4-diazabicyclo[2.2.2]octane
DBU	:	1,8-Diazabicyclo 5.4.0 undec-7-ene
DCE	:	1,2-Dichloroethane
dd	:	Doublet of doublet
ddd	:	Doublet of doublet of doublet
DEAD	:	Diethyl azodicarboxylate
DEC	:	Diethyl carbonate
DIM	:	3,3'-Diindolylmethane
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMAP	:	4-Dimethylaminopyridine
DMC	:	Dimethyl carbonate
DMF	:	*N*, *N*-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
DMSO-*d6*	:	Deuterated dimethyl sulfoxide
DNA	:	Deoxyribonucleic acid
DTC	:	Ditetrahydrofurfuryl carbonate

EDG	:	Electron donating group
equiv.	:	Equivalent
Et_3N	:	Triethylamine (TEA)
EtOH	:	Ethanol
EWG	:	Electron withdrawing group
FDA	:	Food and drug administration
Fe_3O_4	:	Iron(II,III) oxide
$FeCl_3$	:	Iron(III) chloride
$FeSO_4$	:	Iron(II) sulfate
FTIR	:	Fourier transform infrared
GQD	:	Graphene quantum dots
h	:	Hour
H_2SO_4	:	Sulfuric Acid
H_5IO_6	:	Orthoperiodic acid
HBV	:	Hepatitis B virus
HIV	:	Human immunodeficiency virus
HTNT	:	Hydrogen trititanate nanotubes
GO	:	Graphene oxide
Hz	:	Hertz
$h\nu$	:	Photon
I_2	:	Iodine
Im	:	Imidazole
$InCl_3$	:	Indium(III) chloride
$i\mathrm{Pr}_2\mathrm{NEt}$	:	*N N*-Diisopropylethylamine
J	:	Coupling constant
JCPDS	:	Joint committee on powder diffraction standards
K_2CO_3	:	Potassium carbonate
$KHCO_3$	:	Potassium bicarbonate
KI	:	Potassium iodide
M	:	Multiplet

MeNO$_2$: Nitromethane

MeOH : Methanol

mg : Milligram

MHz : Megahertz

min : Minutes

mL : Millilitre

mmol : Milli mole

MOF : Metal–organic framework

mol : Mole

MoS$_2$: Molybdenum disulfide

MW : Microwave

MWCNT : Multi-walled carbon nanotubes

N$_2$H$_4$: Hydrazine

Na$_2$SO$_4$: Sodium sulfate

NaBH$_4$: Sodium borohydride

NaHCO$_3$: Sodium bicarbonate

NaI : Sodium iodide

NaN$_3$: Sodium azide

NaNO$_2$: sodium nitrite

NaOH : Sodium hydroxide

NaSCN : Sodium thiocyanate

Nb$_2$O$_5$: Niobium pentoxide

NBS : *N*-Bromosuccinimide

NHC : *N*-heterocyclic carbene

NMP : *N*-Methyl-2-pyrrolidone

NMR : Nuclear magnetic resonance

NMs : Nanomaterials

NPs : Nanoparticles

NRGO : *N*-doped reduced graphene oxide

Nu : Nucleophile

O_2	:	Oxygen
PPh_3	:	Triphenylphosphine
ppm	:	Parts per million
psi	:	Pounds of force per square inch of area
p-TSA	:	*p*-Toluene sulfonic acid
PVP	:	Polyvinylpyrrolidone
PVPP	:	Polyvinyl polypyrrolidone
PXRD	:	Powder X-ray diffraction
q	:	Quartet
RGO	:	Reduced graphene oxide
RNA	:	Ribonucleic acid
rt	:	Room temperature
$Ru(TMHD)_3$	:	Tris(2,2,6,6-tetramethyl-3,5-heptanedionato)ruthenium(III)
s	:	Singlet
SDS	:	Sodium dodecyl sulfate
SEM	:	Scanning electron microscopy
SiO_2	:	Silicon dioxide
$SnCl_2$	:	Tin(II) chloride
SXRD	:	Single-crystal X-ray diffraction.
t	:	Triplet
TBAB	:	Tetrabutylammonium bromide
TBAI	:	Tetrabutylammonium iodide
TBHP	:	*tert*-Butyl hydroperoxide
t-BuOH	:	*tert*-Butyl alcohol
TCE	:	Tetra chloroethylene
TFA	:	Trifluoroacetic acid
TfOH	:	Trifluoromethanesulfonic acid
THF	:	Tetrahydrofuran
TiO_2	:	Titanium dioxide
TLC	:	Thin layer chromatography

TMSOTf	:	Trimethylsilyl trifluoromethanesulfonate
TsIm	:	*N*-(Trimethylsilyl)imidazole
UV	:	Ultraviolet
$Yb(Otf)_3$	:	Ytterbium trifluoromethanesulfonate
$ZnCl_2$	:	Zinc Chloride
$ZnTiO_3$	:	Zinc titanate
ZrO_2	:	Zirconium dioxide
β-CD	:	β-Cyclodextrin
δ	:	Chemical shift
µmol	:	Micromoles

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CHAPTER I

INTRODUCTION

1.1. Introduction

Heterocyclic compounds are the most diverse and vast family of organic compounds. The name heterocyclic comes from the Greek word "heteros," which meaning "different." Heterocyclic compounds are cyclic organic compounds with at least one hetero atom, the most common hetero atoms being nitrogen, oxygen and sulphur, as well as other atoms.[1] Among them, nitrogen-containing heterocycles are very important in life science since they are plentiful in nature and can be found as subunits in a variety of natural products such as vitamins, hormones, and medicines. Serotonin,[2] thiamine,[3] atropine,[4] codeine,[5] papaverine,[6] notorious morphine,[7] coniine,[8] nicotine[9] and caffeine[10] are some representative *N*-containing natural products with diverse biological activities.

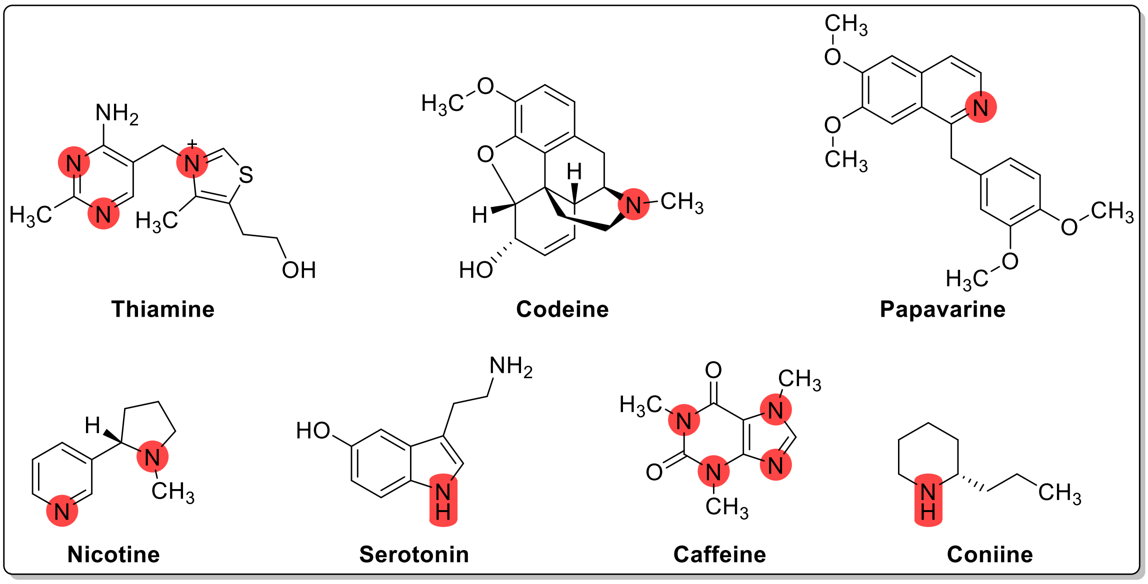


Figure 1.1. Some of examples of biologically active *N*-containing natural products.

Furthermore, they are found in a variety of pharmacologically active compounds. Purines, pyrimidines, and other *N*-heterocyclic compounds make comprise the base pairs of DNA and RNA (guanine, cytosine, adenine, and thymine).[11] *N*-heterocyclic compounds are not only present as the backbone in various natural products but also used as traditional medications or approved prescribed drugs, such as metronidazole, barbituric acid, diazepam, chlorpromazine, isoniazid, captopril, anti-pyrine, azidothymidine and chloroquinine.[12-13] Among the *N*-heterocyclic compounds, triazoles became thrust research area from last few decades due to this wide applications in pharmaceutical and materials industry.

1.1.1. Triazoles

Academics and industry have paid a lot of attention to 1,2,3-triazoles, a privileged structural motif. 1,2,3-triazoles are useful in organic synthesis, drug discovery, chemical biology, polymer chemistry, supramolecular chemistry, materials research, and fluorescent imaging, despite their rarity in nature.

Triazole and its derivatives have piqued interest due to their pharmaceutical and therapeutic applications such as anticonvulsant,[14-17] anticancer,[18-22] antiviral,[23] antimicrobial,[24-32] antiparasitic,[33-35] anti-acetylcholinesterase,[36] antioxidant,[37-40] anti-inflammatory,[41,42] antidepressant,[43] and anti-diabetic drugs.[44] Their capacity to generate a variety of non-covalent interactions to increase solubility and binding to bimolecular targets could explain their broad applicability.[45]

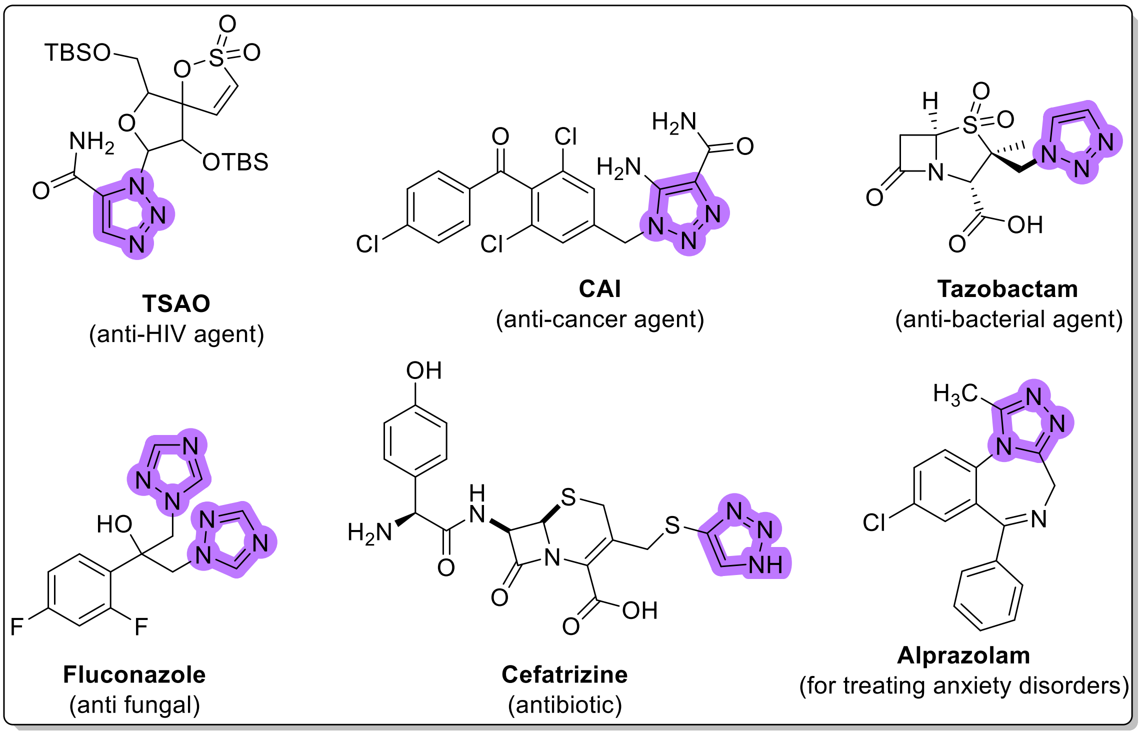


Figure 1.1.1. Some of examples of drugs containing triazoles.

Triazoles are utilised in the pre- and postharvest management of a number of fungal infections in fruits, vegetables, legumes, and grain crops.[46] 3-amino-1,2,4-triazole is a commercially available herbicide and cotton defoliant. S-3307, S-3308, triadimefon, and paclobutrazol are triazole compounds that are indicated for use as fungicides and plant growth regulators.[47]

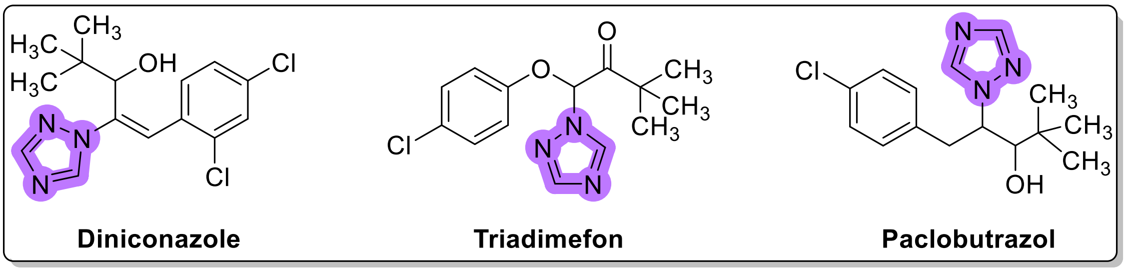


Figure 1.1.2. Some of examples of fungicides for plants containing triazoles.

The anticorrosive effects of triazoles have also been widely reported.[48] AMMT (4-amino-5-mercapto-3-methyl-1,2,4-triazole), AMET (4-amino-5-mercapto-3-ethyl-1,2,4-triazole), and AMPT (4-amino-5-mercapto-3-propyl-1,2,4-triazole) have been tested as new corrosion inhibitors for muntz alloy (Cu:Zn 60:40) corrosion in neutral and acidic solutions. Some triazole compounds were evaluated on an industrial basis as corrosion inhibitors for bronze with a patina layer.[49] Triazole compounds are also utilised as effective allylic alkylation catalysts. *N*-substituted triazoles are often utilised as catalysts in ligand synthesis due to their well-developed click chemistry. They are potent binding ligands even in their neutral state.

1.1.2. Bis(indolyl)methanes

Indole derivatives are abundant in nature and have beneficial biological properties such as antimicrobial[50,51] antifungal,[52] anti-inflammatory,[53,54] and anticancer properties.[55,56]

Delavirdine is an anti-retroviral medication based on indole that is used to treat HIV patients (Figure 1.1.3).[57] The Rauwolfia serpentina plant produces reserpine, an indole alkaloid. It has been used to treat high blood pressure as an antipsychotic and antihypertensive drug.[58] Novartis developed Panobinostat, an oral histone deacetylase inhibitor that is approved to treat multiple myeloma.[59]

Zafirlukast is the first orally active indole-like leukotriene-receptor antagonist for the treatment of asthma.[60] Another indole-based medication used to treat erectile dysfunction in men is tadalafil.[61] Pindolol is used as an antihypertensive and antidepressant drug.[62,63] Indomethacin is a nonsteroidal anti-inflammatory drug that is used to treat severe osteoarthritis, rheumatoid arthritis, gouty arthritis, and ankylosing spondylitis.[64]

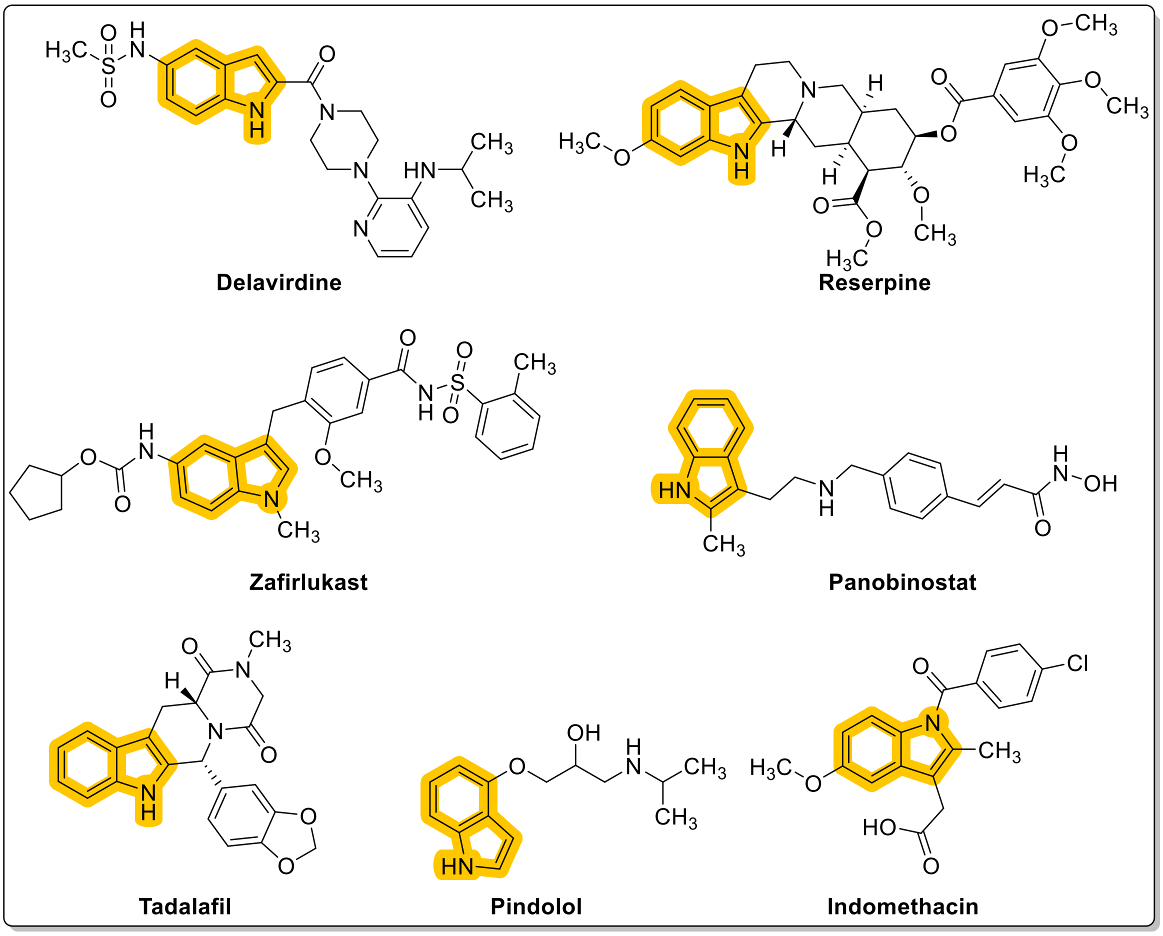


Figure 1.1.3. Indole scaffold in FDA (Food and Drug Administration) approved drugs.

Due to their occurrence in the core structure of numerous pharmacologically important natural compounds such as arundine, arsindoline A, barakacin, vibrindole A, etc., [65– 83] bis(3-indolyl)methanes (BIMs) are an important subgroup of indoles. Arundine has been identified as a good agent for breast cancer.[84] Irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome have all been successfully treated with vibrindole A.[85]

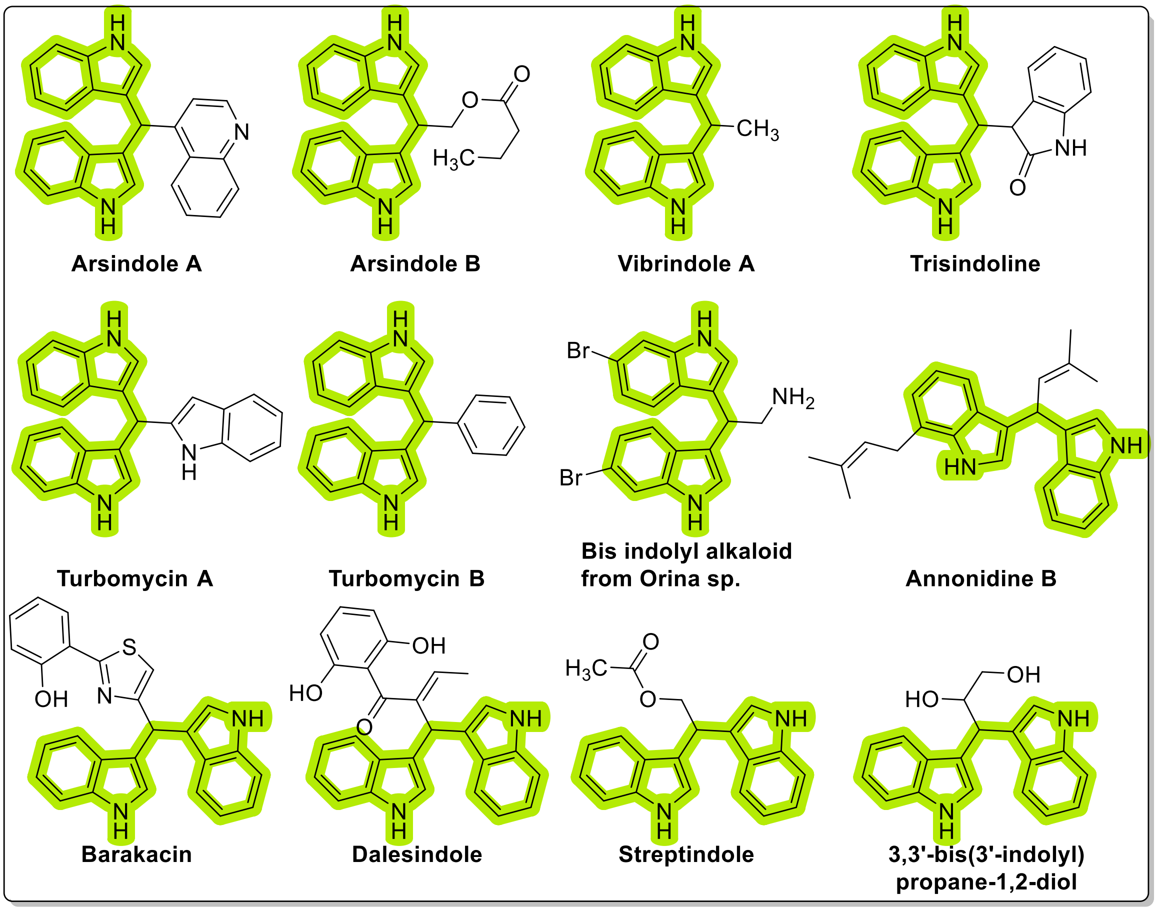


Figure 1.1.4. Some examples of biologically active naturally occurring bis(indolyl) methanes.

Bisindolylmethanes exhibit wide variety of biological activities including anti-fungal,[86-87] anti-inflammatory,[88] antioxidant,[89] cancer cell growth suppression through apoptosis and subsequent metastasis,[90] and glass fabrication of high-triplet energy materials properties.[91] Bisindolylmethanes are also utilised as dyes[92] and colorimetric sensors[93,94] in their oxidised form.

1.2. Copper nanoparticles

Materials with at least one dimension less than 100 nm are known as nanoparticles (NPs) or nanomaterials (NMs). Because of its small size, the material's properties differ from those of the bulk of the same composition. Indeed, when metallic elements like Cu, Fe, Ce, Ti, and Ag are induced by ionic forms rather than nanometric forms, the cellular responses are considerably different.[95] These additional qualities give the material an extra value that can be used in a variety of industries, including automotive, energy, pharmaceutical, medical, and agricultural.[96] A multitude of methods can be used to synthesize metal nanoparticles. Both top-down and bottom-up synthesis techniques have been identified and Figure 1.2.1 shows a more detailed classification.

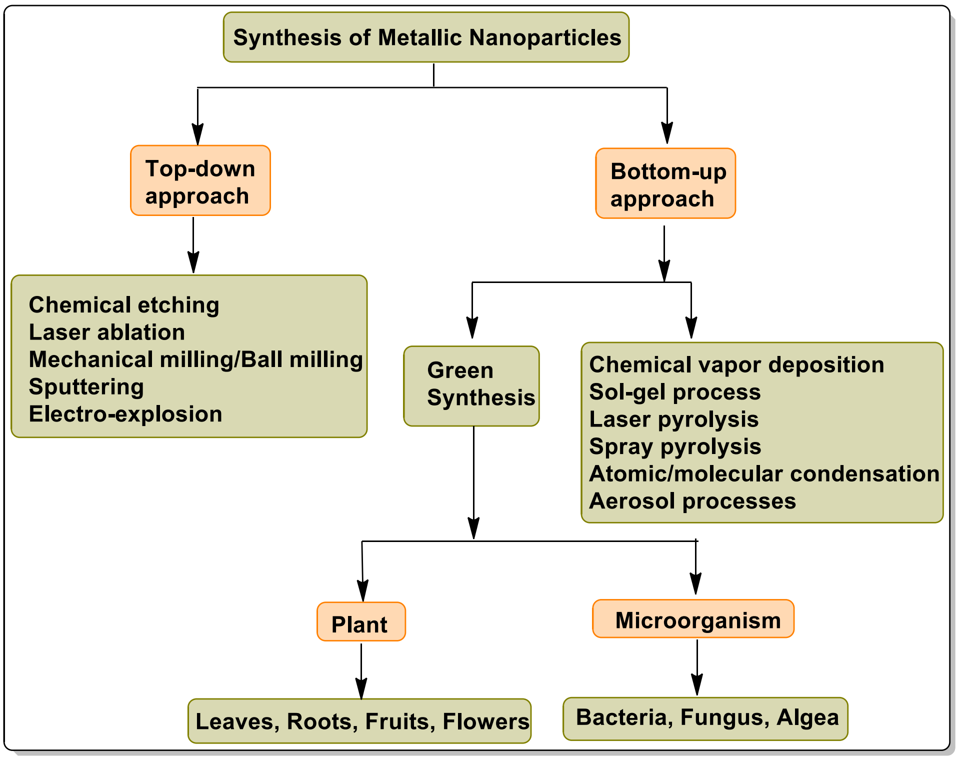


Figure 1.2.1. Different synthetic approaches for the preparation of metallic nanoparticles.

Due to their remarkable optical and electrical properties, there has been a burst of interest in the synthesis and uses of various metal nanoparticles, particularly gold, copper, and silver nanoparticles in recent years. Copper nanoparticles (CuNPs) have grown in popularity as a result of their unique physical, chemical, electrical and optical properties, as well as their low cost and availability.[97]

Cu-based nanocatalysts offer a wide range of applications in nanotechnology, including catalytic organic transformations, electrocatalysis, and photocatalysis, due to their unique traits and properties.[98-111] Anchoring CuNPs (e.g., Cu, CuO, or Cu_2O) on supports such iron oxides, SiO_2, carbon-based materials, or polymers is an inexpensive technique to make sophisticated Cu-based nanomaterials for catalysis. CuNPs boiling point and melting points are 2567 °C and 1083 °C, which makes it suitable for high-temperature and high-pressure chemical processes, such as continuous flow reactions, microwave-assisted reactions, vapour phase reactions, and a variety of organic transformations[112-116] as shown in Figure 1.2.2.

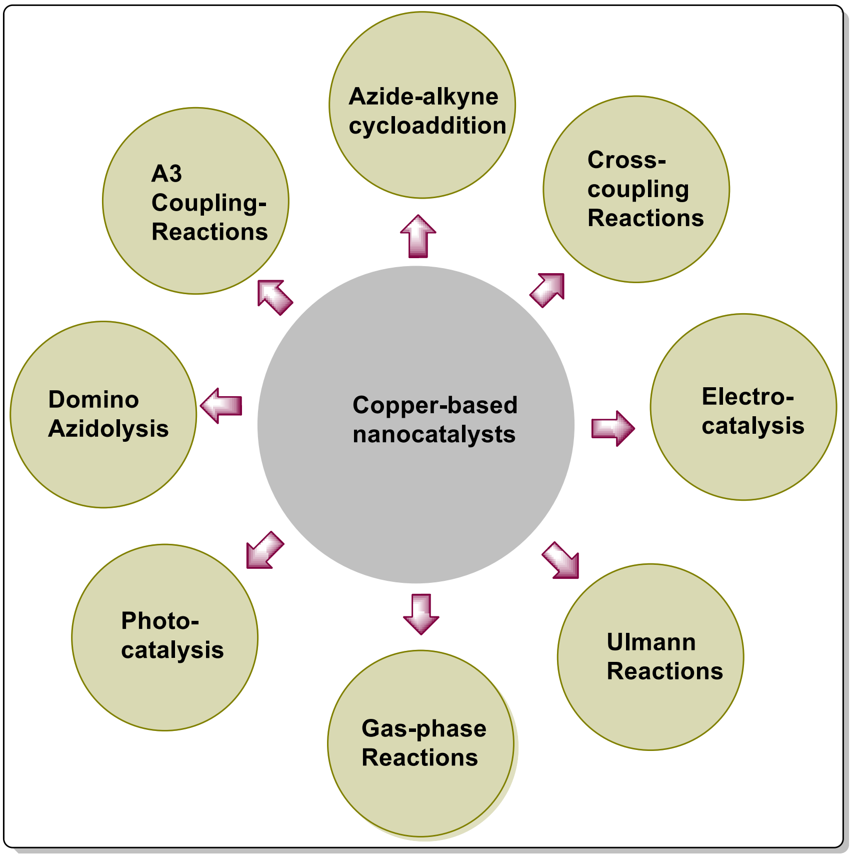


Figure 1.2.2. Applications of Cu-based nanocatalysts.

Particularly, copper nanoparticles (CuNPs) have drawn a lot of attention from all over the world because of its broad-spectrum of antimicrobial action. Copper is one of the most crucial minerals for plant growth and development. In agriculture, CuNP-based fertiliser and herbicide can be employed. CuNPs are easily absorbed by plants because of their tiny size.[117]And also CuNPs have the potential to be employed in food packaging to prevent the growth of bacteria that cause food spoiling.[118]

1.3. Phytochemicals

Non-nutritive plant compounds with disease-preventive or protective qualities are known as phytochemicals. There are over a thousand phytochemicals that have been identified. These molecules are produced by plants to protect themselves, but new study shows that they can also protect humans from disease. Phytochemicals, also known as phytonutrients, are found in fruits, whole grains, vegetables, herbs, legumes, beans, spices, seeds, and nuts and they are classified according to their chemical structures and functional properties[119] as shown in figure 1.3.1.

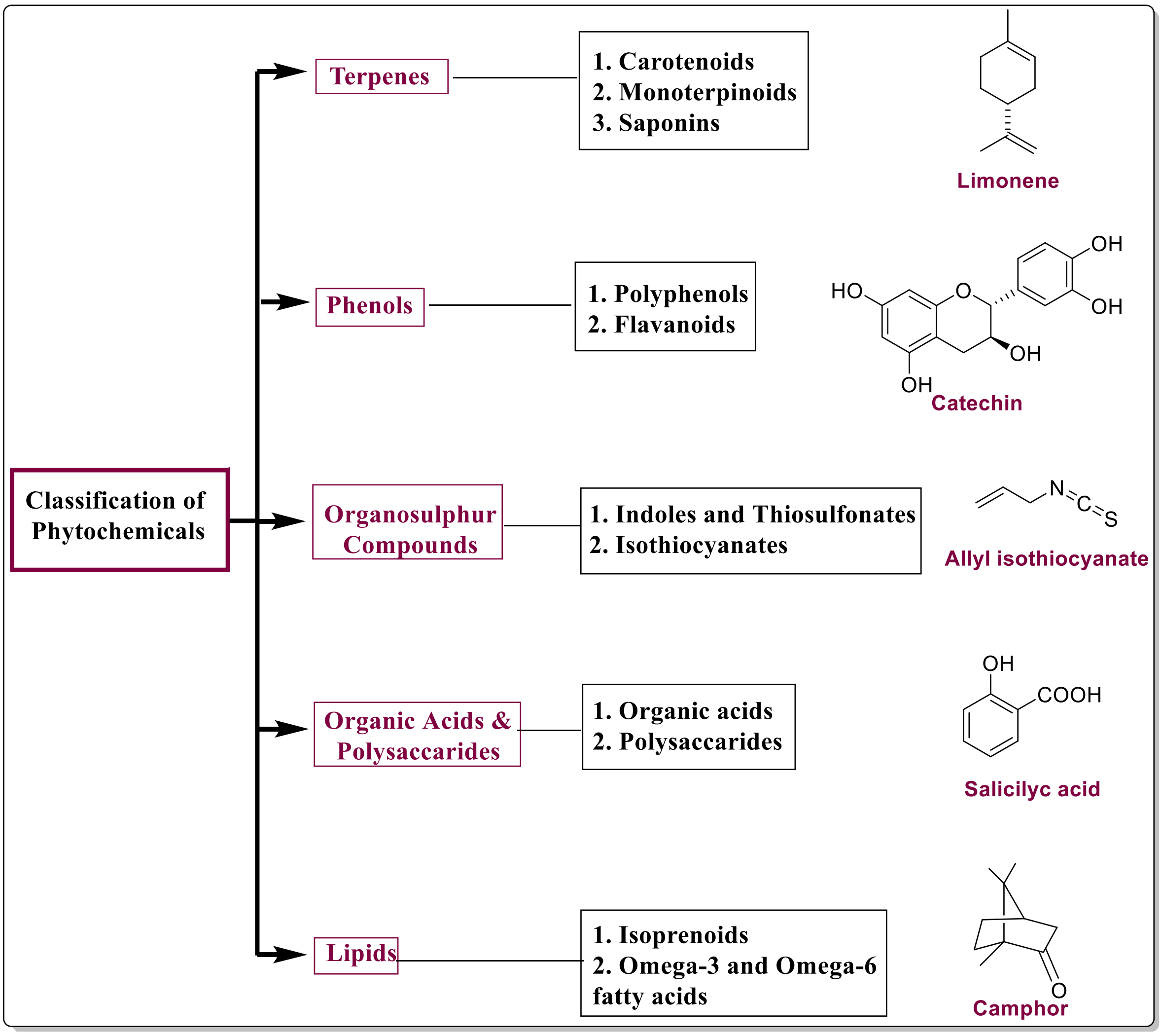


Figure 1.3.1. Classification of phytochemicals according to their chemical structures.

Each phytochemical has a unique function, and the following are some examples.

a. **Antioxidant** – Some phytochemicals have antioxidant activity, which means they protect cells from oxidative damage, lowering the risk of cancer, cardiovascular disease, and diabetes.[120]

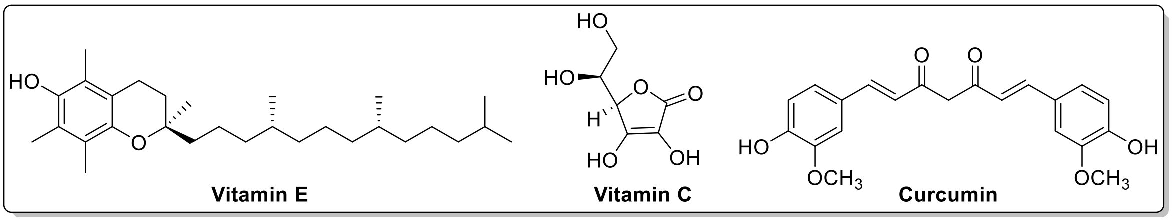


Figure 1.3.2

b. **Act as hormones** – Soy isoflavones and lignans, which imitate human estrogens, aid in the reduction of menopausal symptoms and osteoporosis. Phytoestrogens are another name for them.[121-122]

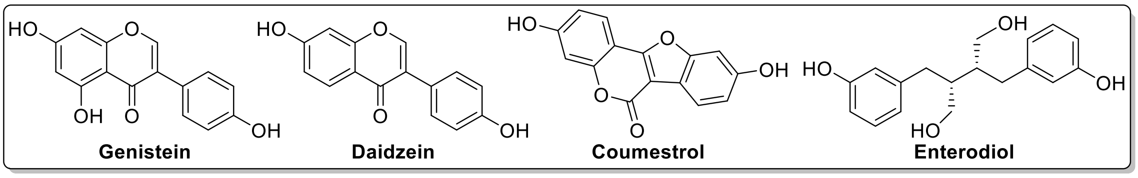


Figure 1.3.3

c. **Cancer preventing compounds** – Some phytochemicals found in foods having anti-cancer capabilities.[123-124]

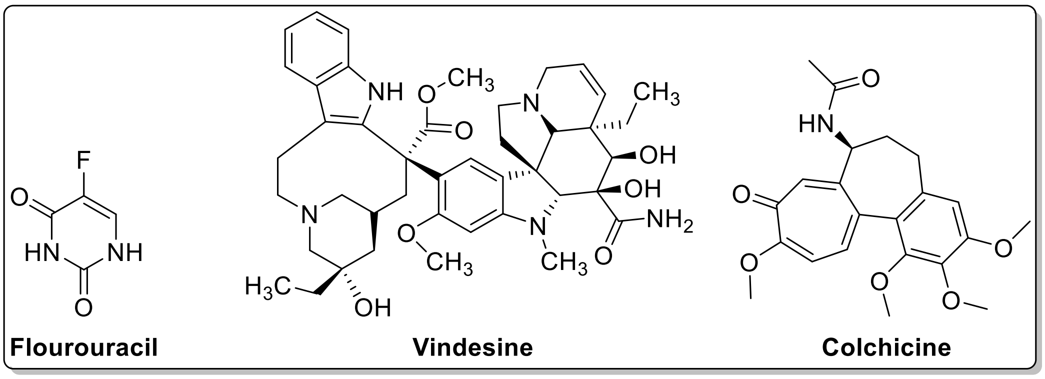


Figure 1.3.4

d. **Stimulation of enzymes** – Indoles activates enzymes that reduce the effectiveness of estrogen, potentially lowering the risk of breast cancer.[125-126]

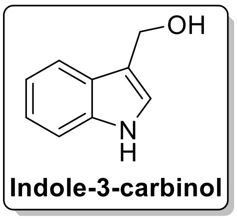


Figure 1.3.5

e. **Interference with DNA replication** – Bean saponins hinder cancer cells from proliferating by interfering with the reproduction of cell DNA. Peppers contain capsaicin, which protects DNA from carcinogens.[127-128]

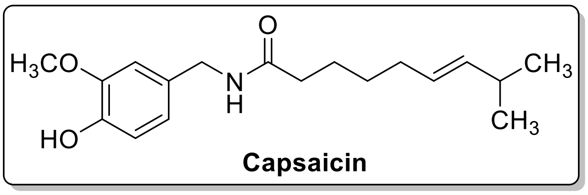


Figure 1.3.6

f. **Anti-bacterial effect** – Garlic's phytochemical allicin, as well as chemical compounds derived from spices, have antibacterial properties.[129-130]

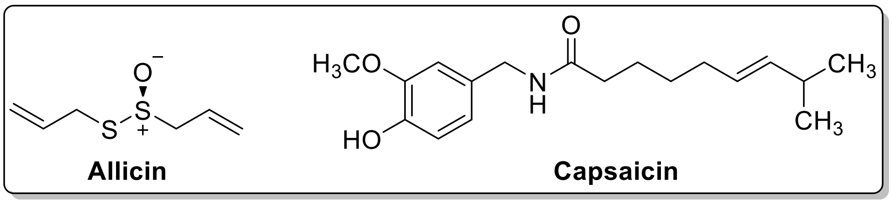


Figure 1.3.7

g. **Physical protective action** – Some phytochemicals bond to cell walls physically, preventing pathogens from adhering to human cell walls. Proanthocyanidins, for example, are responsible for the anti-adhesion effects of berries.[131-132]

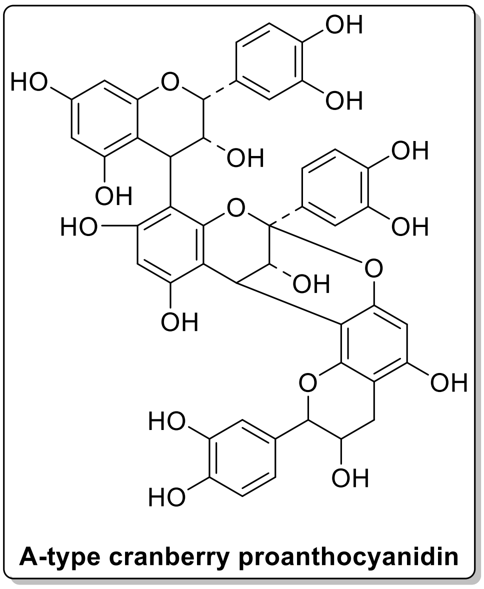


Figure 1.3.8

h. **Reduce the bioavailability of nutrients** – Iodine absorption is inhibited by goitrogens present in cabbage and iron, calcium absorption is inhibited by oxalic acid and phytic acid found in legumes. Anti-nutritional chemical substances are another name for them.[133]

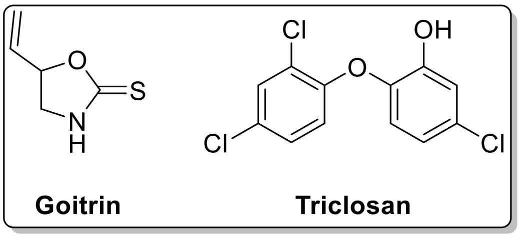


Figure 1.3.9

1.4. Rongalite

Sodium hydroxymethanesulfinate dihydrate also known as rongalite,[134] an industrial product used as a decolorizing agent for caramel, sugar juice, and so on, as well as a bleaching agent in the dyeing and printing industries.[135] It is also used as an antidote for heavy metal poisoning caused by Hg, Au, Cu, Ba, Sb, Pb, and Bi.[136] Also, acts as a green reducing agent for metal salts. It is used in veterinary medicines.[137] In recent years, it has also demonstrated its utility in material sciences for the preparation of copper nanoparticles (CuNps),[138] carbon nanotubes (CNTs),[139] ZnS nanoparticles,[140] PbSe films,[141] CdTe-quantum dots,[142] CdTe thin films,[143] $CoTe_2$,[144] Ag_2Se thin films,[145] Ag-Au hollow nanospheres[146] and CoSe nanoparticles.[147] Also, rongalite plays a crucial role in organic synthesis as a source of both the C1 unit donor and sulfone.[148-151]

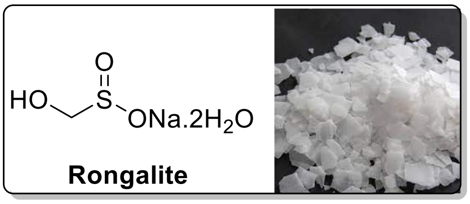


Figure. 1.4.1

Kotha and co-workers extensively used the multifarious reactivity of rongalite in variety of organic transformations. Rongalite has been widely used in synthetic organic chemistry for the preparation of sulfones and sultine moieties (acts as diene equivalents). They have used sulfone and sultine moieties for the synthesis of annulated benzocrown ethers, benzo-annulated indane-based α-amino acids, polycyclic aromatic compounds, cyclic sulfones, tetralin-based α-amino acid derivatives and other compounds *via* Diels–Alder and Suzuki–Miyaura cross-coupling reactions (Figure1.4.2).[152]

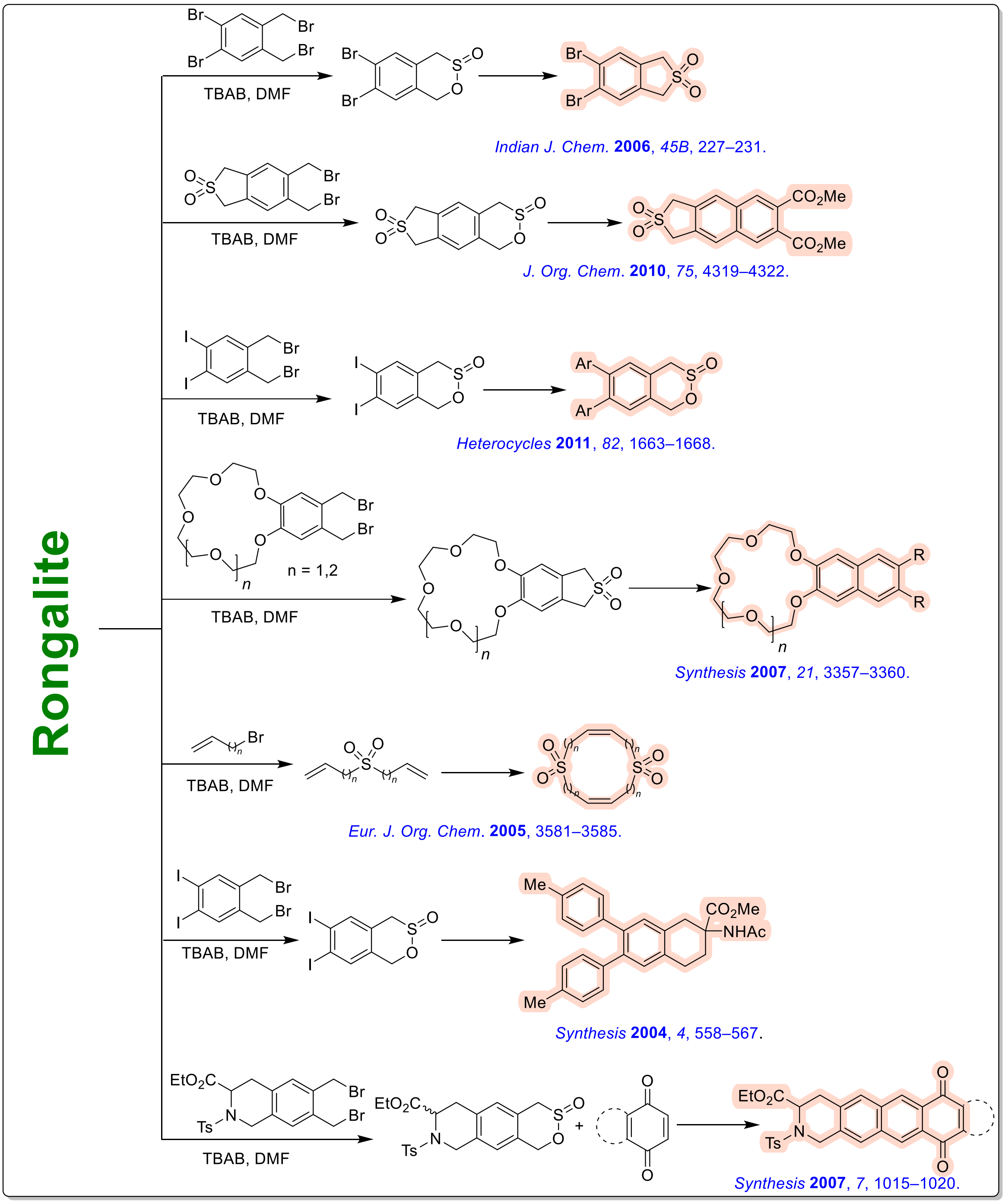
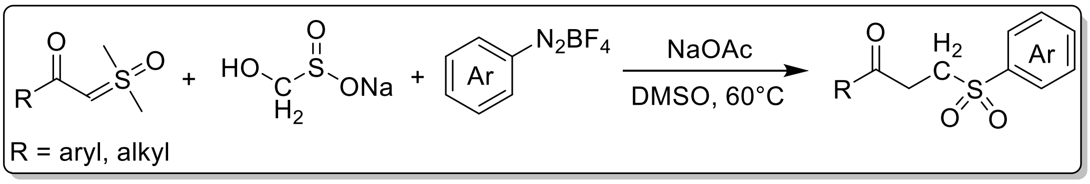


Figure 1.4.2. Some of organic transformations using sulfones and sultines produced *via* rongalite.

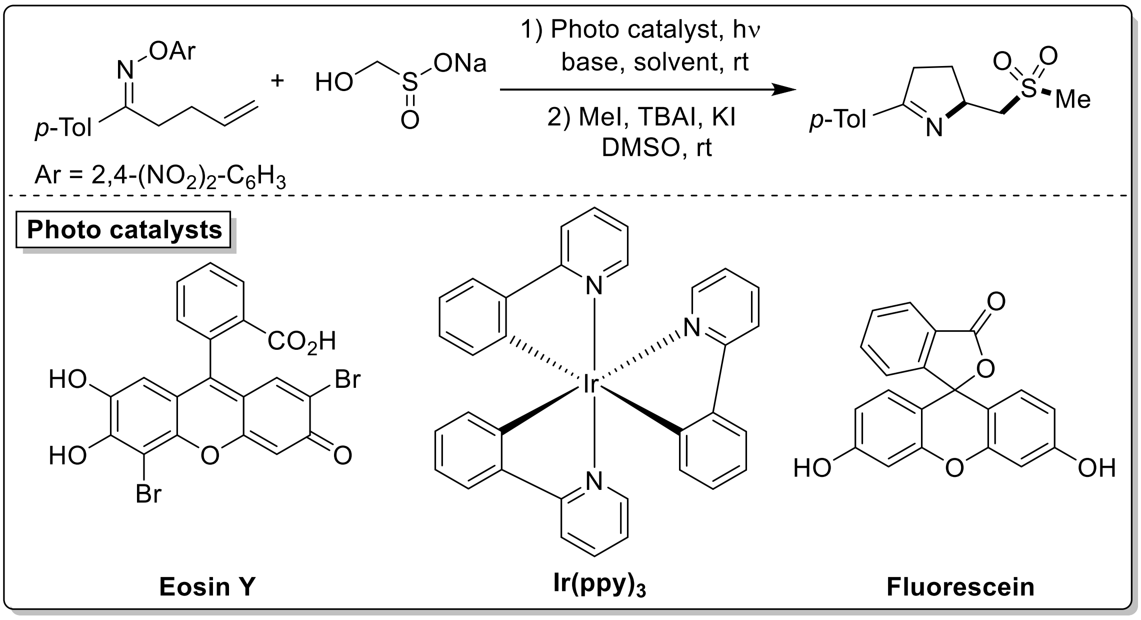
Some of other important organic transformations using rongalite are listed below.

Chen et al. reported an easy-to-handle, environmentally friendly, catalyst-free, and separate-embedding type sulfonylmethylation of sulfoxonium ylides in which rongalite simultaneously operated as a sulfone source, C1 synthon, radical initiator, and reducing reagent. In this reaction the C1 unit and sulfone core were assembled simultaneously in one step, eliminating the need for prefunctionalized sulfonylmethylation reagents (Scheme 1.4.1).[153]



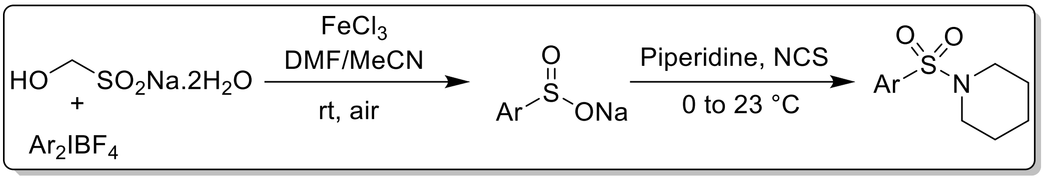
Scheme 1.4.1

He and co-workers reported a regioselective synthesis of diverse pyrrole-substituted aliphatic sulfones or sulphonamides using photoredox-catalyzed reaction of oximes, rongalite and electrophiles under mild conditions. Various electrophiles can trap the sulfinate produced *in situ* during the chemical process. This protocol is functionally compatible with a large number of groups (Scheme 1.4.2).[154]



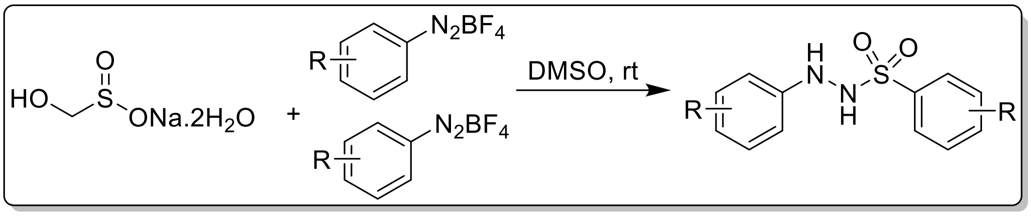
Scheme 1.4.2

Zhang et al. used an iron-catalyzed radical coupling reaction to establish a novel technique for installing sulfonyl fragments into arenes. At room temperature, arene radicals created from diaryliodoniums *via* a single electron transfer process interact with a sulfoxylate anion radical readily synthesised from commercially available rongalite to produce arylsulfinates. A wide range of functional groups are tolerated in this procedure, resulting in high yields (Scheme 1.4.3).[155]



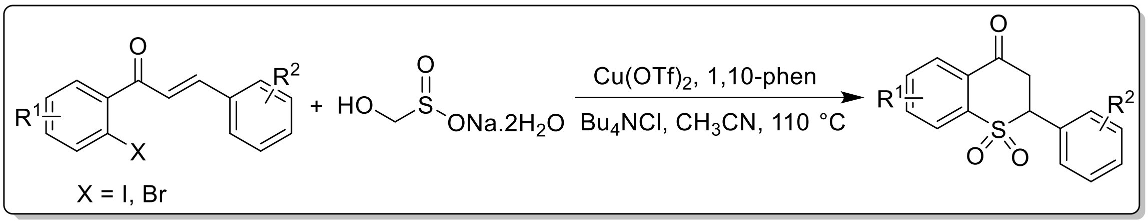
Scheme 1.4.3

Wang et al. reported a metal-free, oxidant-free, and convenient approach for N-aminosulfonamide synthesis through the cross-coupling of aryldiazonium tetrafluoroborates with rongalite at room temperature. The aryldiazonium tetrafluoroborate serves as an aryl radical as well as amine source in this approach. According to mechanistic studies, rongalite can operate as a radical initiator, a sulphur dioxide surrogate, and a reducing reagent simultaneously (Scheme 1.4.4).[156]



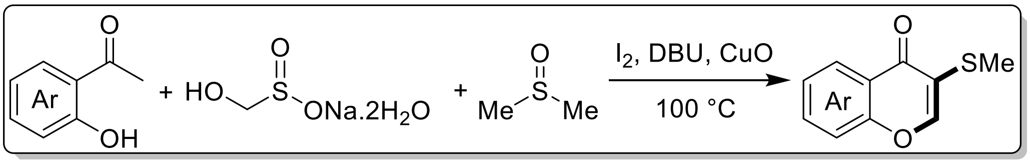
Scheme 1.4.4

Chen et al. developed a cost-effective, ecologically friendly, and copper-catalyzed sulphur dioxide inclusion cascade for the synthesis of 1-thiaflavanone sulfone derivatives. By forming two consecutive C-S bonds, this sulfonylation was able to achieve *in situ* inclusion of sulfone cores. Furthermore, this protocol avoids the use of expensive SO_2 surrogates and harmful SO_2 gas as sulfone sources (Scheme 1.4.5).[157]



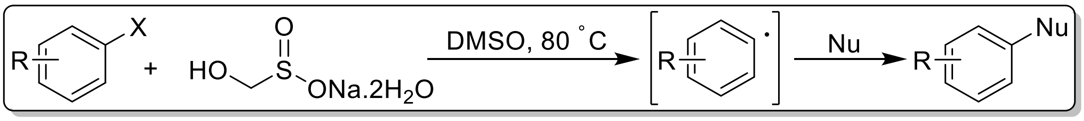
Scheme 1.4.5

Wu and co-workers synthesized of C3-sulfenylated chromones from *o*-hydroxyaryl methyl ketones, rongalite, and dimethyl sulfoxide using efficient I_2–DMSO reagent system-mediated multicomponent reaction stratagy. The C1 unit and sulphur source for the synthesis of C3-sulfenylated chromones were provided by the cleavages of double C–S bonds of rongalite and dimethyl sulfoxide, which were particularly crucial in this smooth transformation. According to preliminary mechanistic analyses, ***in** situ* produced HCHO and (2-(2-hydroxyphenyl)-2-oxoethyl)dimethylsulfonium iodine were likely the major stages in this transformation (Scheme 1.4.6).[158]



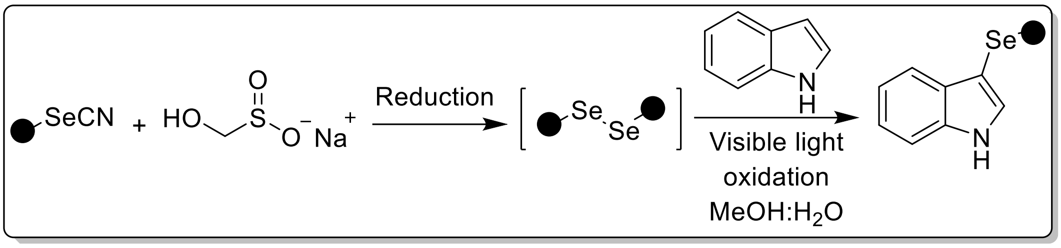
Scheme 1.4.6

Fazhi et al. exploited transition-metal free electron-catalyzed procedures in the presence of sodium formaldehyde sulfoxylate to obtain C-C, C-S, and C-P bonds from aryl halides *via* homolytic aromatic substitution or $S_{RN}1$ reactions. This protocol also used to synthesize quetiapine, an antipsychotic drug on a gram scale (Scheme 1.4.7).[159]



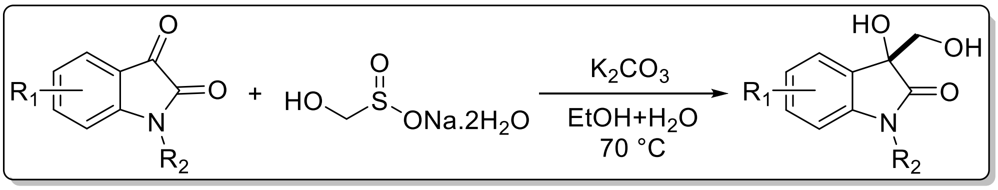
Scheme 1.4.7

Gabriela and co-workers developed a revolutionary multi-step continuous-flow technology to synthesise APIs, natural compounds, and fine chemicals. Selenylation of biologically relevant heterocyclic compounds was done using a continuous-flow technique that included chemical reduction and photochemical C(sp2)-H activation (Scheme 1.4.8).[160]



Scheme 1.4.8

Kokatla and co-workers developed a novel metal and hydride-free strategy for the synthesis of biologically active 3-hydroxy-3-(hydroxymethyl)indolin-2-ones and 3-amino-3-(hydroxymethyl)indolin-2-ones using isatins-derivatives and inexpensive rongalite *via* a reductive aldol reaction. In this methodology, rongalite serves as a reducing agent and a source of C1 unit. This approach also allows for the gram-scale production of 1-benzyl-3-((2,4-difluorophenyl)amino)-3-(hydroxymethyl)-5-ethylindolin-2-one, anti-cancer agent with high product yield (Scheme 1.4.9).[161]



Scheme 1.4.9

1.5. Trichloroacetonitrile

Trichloroacetonitrile (CCl_3CN) is a more reactive and versatile reagent. Although commercial samples are frequently brownish, it is a colourless liquid. Commercially, it is employed as a precursor to the fungicide etridiazole. Dehydration of trichloroacetamide is used to prepare CCl_3CN.[162] Trichloroacetonitrile is a bifunctional molecule that can react at both the trichloromethyl and nitrile groups. Electron-withdrawing action of trichloromethyl group activates the nitrile group for nucleophilic additions.

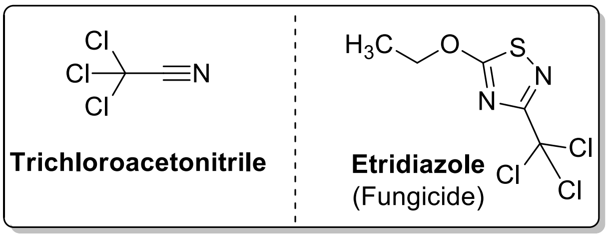
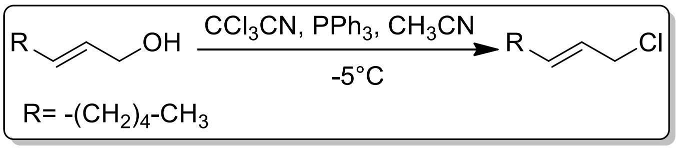


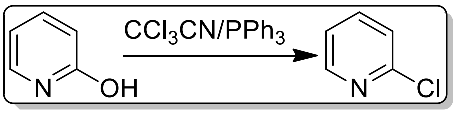
Figure 1.5.1

CCl_3CN/PPh_3 system can be used to convert allylic alcohols into allylic chlorides,[163] carboxylic acids to acylchlorides[164] and also converts sulfonic acids to sulfochlorides[165] due to strong reactivity of the chlorine atoms (Scheme 1.5.1).



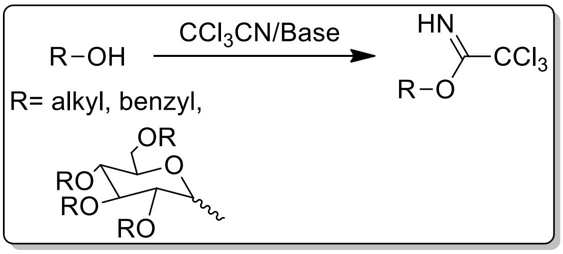
Scheme 1.5.1

CCl_3CN/PPh_3 reagent system also converts N-heteroaromatic hydroxy compounds into N-heteroaromatic chlorides under mild and acid-free conditions (Scheme 1.5.2).[166]



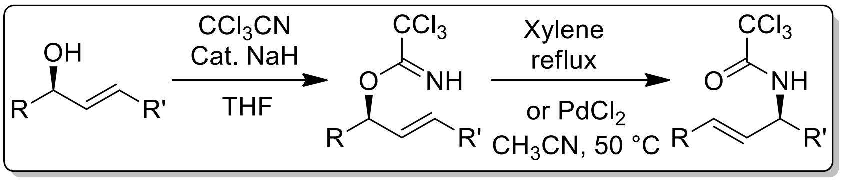
Scheme 1.5.2

Electron-withdrawing effect of the CCl_3 group activates the nitrile group of trichloroacetonitrile, allowing it to attack nucleophilic oxygen, nitrogen, and sulphur compounds. In the presence of a base, CCl_3CN produced *O*-alkyltrichloroacetimidates from alcohols[167] and also selectively activated the anomeric position of *O*-protected hexopyranoses, hexofuranoses, and pentopyranoses (Scheme 1.5.3).[168]



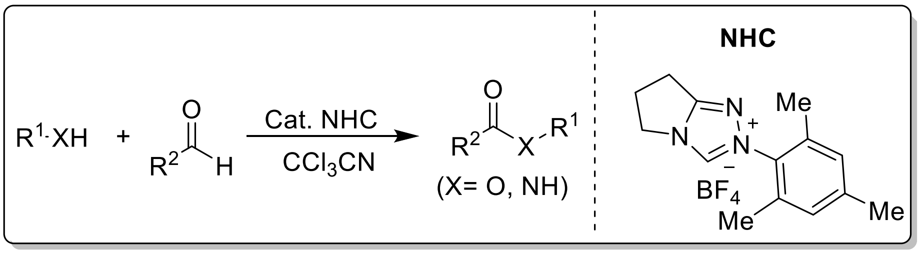
Scheme 1.5.3

In the Overman rearrangement, trichloroacetonitrile is employed as a reagent to convert allylic alcohols to allylic amines.[169-170] The reaction is based on a thermal [3,3]-sigmatropic rearrangement (Scheme 1.5.4).



Scheme 1.5.4

Trichloacetonitrile serves as a unique and flexible oxidant in the carbene-catalyzed acylation of dehydro-genative coupling reactions of aldehyde and alcohol, which involves a hydride transfer mechanism (Scheme 1.5.5).[171]



Scheme 1.5.5

1.6. References

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CHAPTER II (PART-A)

In Situ Generation of Copper Nanoparticles by Rongalite and Their Use as Catalyst for Click Chemistry in Water

2A.1. Introduction

Click chemistry, is a powerful tool for the synthesis of triazole containing five membered nitrogen heterocyclic architectures, which have a wide range of applications in medicine,[1–4] materials,[5–8] biological science,[4,6] and organic synthesis. Meldal[9] and Sharpless[10] independently introduced Copper(I)-catalyzed 1,3-dipolar cycloaddition of azide and alkynes in 2002, which significantly overcome the limitations of Huisgen cycloaddition such as higher temperatures and low regioselectivity, resulting in a mixture of 1,4 and 1,5-disubstituted 1,2,3-triazoles. Despite the fact that a variety of methods for accessing 1,2,3-triazole derivatives are known, the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction[11–15] remains the most efficient way to assemble the 1,2,3-triazole ring due to its 100 % atom economy, wide substrate scope, exquisite selectivity, mild reaction conditions, and simple product purification.

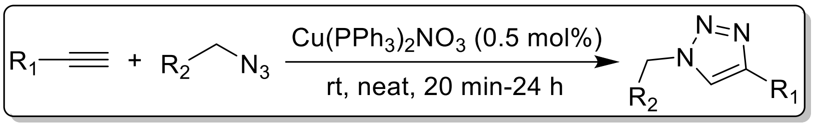
Many studies have shown that copper(I) acetylide species catalyse the 1,3-dipolar cycloaddition. However, because simple copper-(I) salts are unstable, active species are frequently produced *in situ* by reducing Cu(II) salts,[10] oxidation of Cu(0) metal,[16] or Cu(II)/Cu(0) comproportionation,[17,18] Cu(I)salts directly,[9] Cu(II) salts,[19,20] Cu(I) complexes,[21,22] copper containing nanoparticles,[23,24] *N*-heterocyclic carbene copper complexes,[25] $Cu_2S/h\upsilon$[26] and copper nanoclusters.[23] In some recent reports, copper species have been immobilized onto various supports such as activated charcoal,[27] amine-functionalized polymers,[28] and zeolites[29] to improve recovery and reusability of catalyst.

Since the discovery of copper metal (stoichiometric ratio of turnings or powder) as a source of the catalytic species hoping to implement green chemistry principles of reusability, efficiency, and operational simplicity compared to their traditional methods, copper nanoparticles (CuNPs) catalysed Click chemistry has increased exponentially. Following that, many methods for producing CuNPs from bulk copper metal and copper salts were disclosed. The majority of the procedures entailed reducing of copper salts using appropriate reducing agents, such as $NaBH_4$, Li, and $N_2H_4.H_2O$ etc.[30–32] As a result, a wide range of homogeneous[33,34] and heterogeneous[35–37] catalytic systems have arisen. CuNPs have recently been shown to speed up the one-pot click reaction involving the ring opening of an epoxide with azides followed by its cycloaddition with alkyne, as proven by Alonso et al.[38–42]

We discovered that the majority of CuAAC publications used CuNPs either directly from commercial sources or synthesised separately prior to use in the reactions. The latter involved the use of copper salts and reducing agents, the majority of which are environmentally toxic. As a result, there is a search for a cost-effective, ecologically friendly, and operationally straightforward approach for such cycloaddition reactions using green chemistry principles.

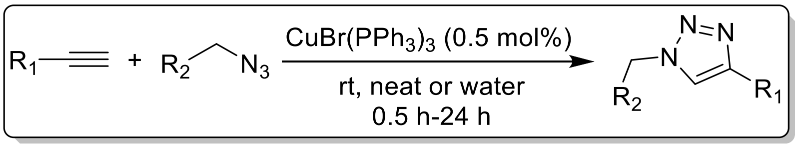
2A.1.1. Different synthetic approaches for the synthesis of 1,4-disubstituted-1,2,3-triazole derivatives

Chen and co-workers reported 1,3-dipolar Huisgen cycloaddition reaction of organic azides with terminal alkynes using $Cu(PPh_3)_2NO_3$ complex with low catalyst loading at room temperature (Scheme 2A.1).[43]



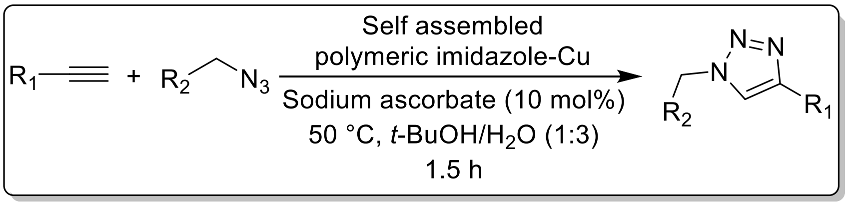
Scheme 2A.1

Lal et al. reported the synthesis of 1,2,3-triazoles and triazoles bearing glyco-substituents using $[CuBr(PPh_3)_3]$ under mild conditions and low catalyst loading at room temperature (Scheme 2A.2).[44]



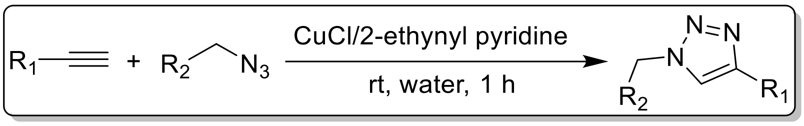
Scheme 2A.2

Yamada and co-workers synthesized metalloprotein-inspired self-assembled polymeric imidazole copper catalyst which promoted the Click reaction of alkynes and organic azides at 50 °C in 1.5 h (Scheme 2A.3).[45]



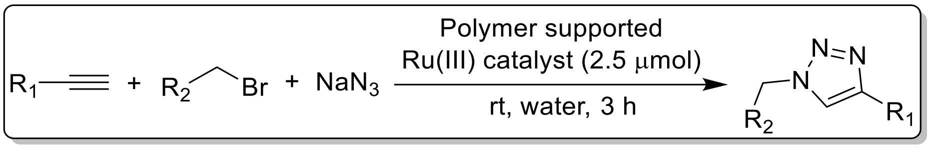
Scheme 2A.3

Fukuzawa and co-workers reported the combination of 2-ethynylpyridine and CuCl as an efficient catalyst for the copper catalysed azide alkyne cycloaddition reaction in water at room temperature (Scheme 2A.4).[46]



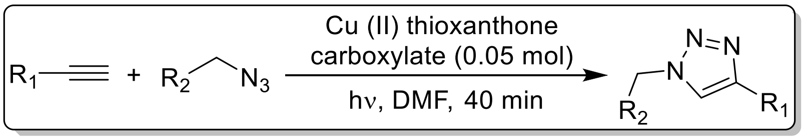
Scheme 2A.4

Islam and co-workers synthesised a polymer supported ruthenium catalyst and utilized its catalytic activity for the three-component coupling of alkynes, azides and alkyl halides to yield 1,4-disubstituted-1,2,3-triazoles in water medium at room temperature (Scheme 2A.5).[47]



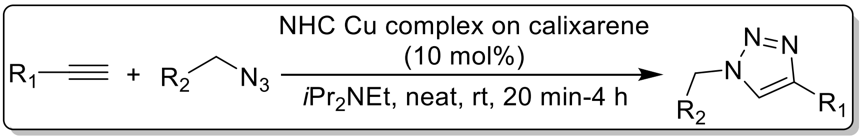
Scheme 2A.5

Yagci and co-workers reported the synthesis of copper(II) thioxanthone carboxylate and catalytic utility for the photo initiation of Click reaction (Scheme 2A.6).[48]



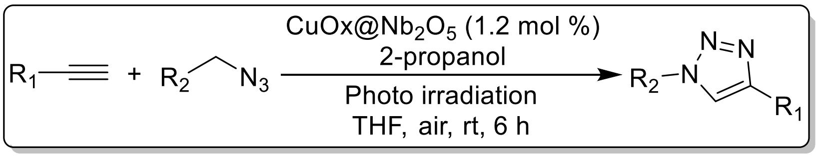
Scheme 2A.6

Bonnamour and co-workers reported the preparation and characterisation of air stable two NHC copper complexes bearing a calix[4]arene moiety. And also the catalytic activity of the complexes for CuAAC, under solvent-free conditions, at room temperature have been examined (Scheme 2A.7).[49]



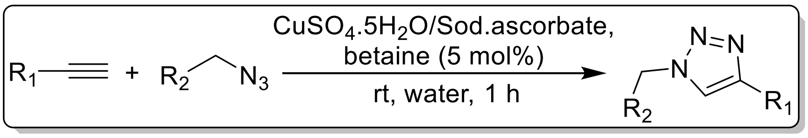
Scheme 2A.7

Scaiano and co-workers introduced an air stable, moisture-tolerant and reusable copper oxide nanostructures doped semiconductors (e.g. TiO_2 and Nb_2O_5). Upon irradiation, excited electrons from the semiconductor transferred to CuO nanoparticles to form Cu(I), which serve as effective catalyst for CuAAC (Scheme 2A.8).[50]



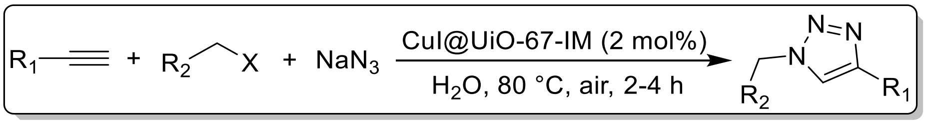
Scheme 2A.8

Lim and co-workers reported synthetic methodology for Click reaction using conventional Cu catalytic mixture ($CuSO_4$-Sodium ascorbate) accelerated by a simple zwitterionic additive, commercially available, biodegradable, and biocompatible surfactant, betaine at ambient temperature under 2.5–200 ppm levels of Cu(I) in aqueous medium (Scheme 2A.9).[51]



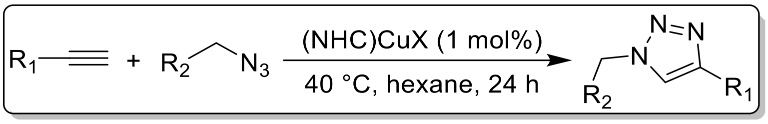
Scheme 2A.9

Dong and co-workers synthesised CuI-loaded and *n*-pentadecyl-attached imidazolium salt decorated UiO-67-type metal organic frameworks which serves as efficient phase-transfer catalyst for three component coupling of alkyne, halogenated compounds and sodium azide at 80 °C in water under open air conditions (Scheme 2A.10).[52]



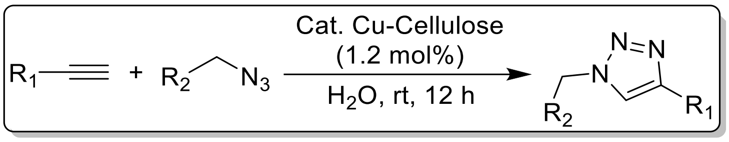
Scheme 2A.10

Topchiy et al. reported the synthesis of robust, and reproducible copper(I) complexes bearing NHC ligands decorated with bulky hexafluoroisopropylalkoxy group $[(CF_3)_2(OR)C\text{-}]$ and catalytic activity to promote Click reaction in hydrophobic solvents such as hexane, heptane and cyclohexane at 40 °C (Scheme 2A.11).[53]



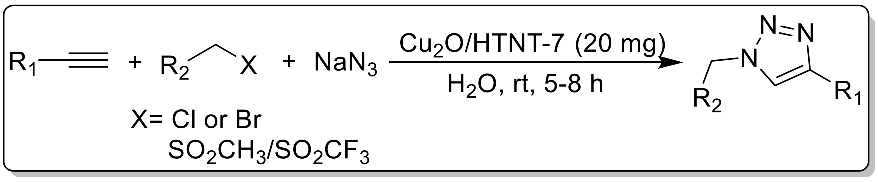
Scheme 2A.11

Bahsis and co-workers reported the preparation and characterisation of efficient, selective, reproducible copper catalysts supported on polysaccharide cellulose which exhibit catalytic activity towards the [3+2] cycloaddition reactions of alkyne and azides derivatives at room temperature in aqueous media (Scheme 2A.12).[54]



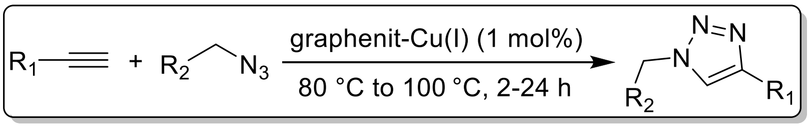
Scheme 2A.12

Bhoomireddy et al. reported the synthesis and characterisation of reusable heterogeneous catalyst Cu_2O nanoparticles supported on hydrogen trititanate nanotubes (Cu_2O/ HTNT). And also the catalytic efficiency of Cu_2O nanoparticles applied in the synthesis of 1,4-substituted triazoles in water at ambient temperature from different azide precursors (Scheme 2A.13).[55]



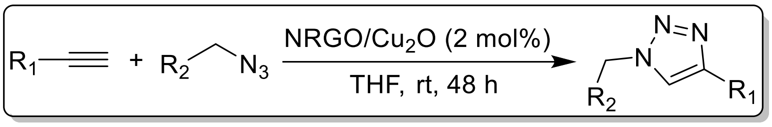
Scheme 2A.13

Angelis et al. prepared different heterogeneous graphene-based (GO, rGO, carbon black, and graphite nanoplatelets) Cu catalysts using conventional methods and compared the catalytic activities by using a Click reaction as a model. Among all Cu catalysts the material based on graphite nanoplatelets exhibited interesting properties such as stability for Cu(I) species and recyclability (Scheme 2A.14).[56]



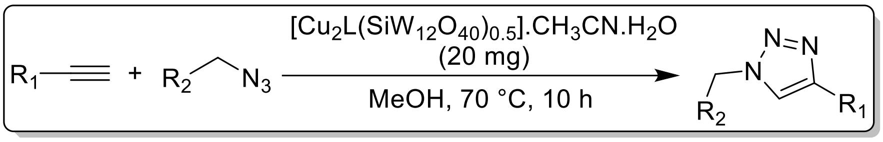
Scheme 2A.14

Michaud and co-workers reported the synthesis and characterization of copper nanoparticles stabilized by nitrogen-doped reduced graphene oxide (NRGO). Also described about the catalytic efficiency of NRGO/Cu_2O to promote Cu(I)-catalyzed Huisgen [3+2] cycloaddition at low temperature without any external oxidizing/reducing agents (Scheme 2A.15).[57]



Scheme 2A.15

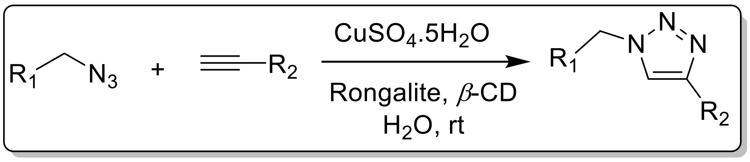
Yue et al. synthesized a new heterogeneous catalyst calix[4]arene-based polyoxometalate organic–inorganic hybrid *i.e.*, $[Cu_2L(SiW_{12}O_{40})_{0.5}].CH_3CN.2H_2O$ under solvothermal conditions and investigated the catalytic performance of catalyst for azide–alkyne cycloaddition reaction (Scheme 2A.16).[58]



Scheme 2A.16

2A.2. Present work

In this chapter, we have reported a green protocol for the *in situ* synthesis of CuNPs using sodium hydroxymethanesulfinate (Rongalite), a less expensive and environmentally friendly, reducing agent (Scheme 2A.17). Furthermore, this method eliminates some of the pre-stages required for the preparation of CuNPs, such as centrifugation, washing, drying, and further stabilisation of nanoparticles.

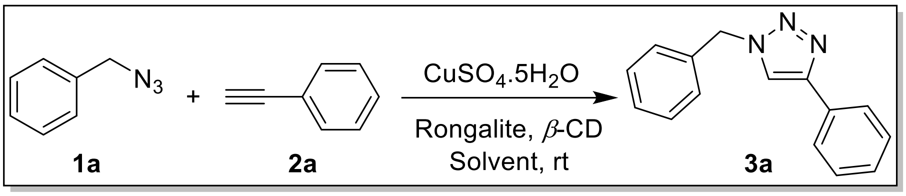


Scheme 2A.17

By applying above protocol for various azides and alkynes, we have synthesized a wide range of 1,4-disubstituted-1,2,3-triazoles with good to excellent yields.

2A.3. Results and discussion

Table 2A.1. Optimization of reaction conditions[a]



Entry	Solvent	CuSO$_4$.5H$_2$O (equiv.)	Rongalite (equiv.)	β-CD (equiv.)	Time	Yield[b] (%)
1	THF/H$_2$O	0.1	0.1	-	5 h	60
2	THF/H$_2$O	0.1	0.2	-	3 h	68
3	THF/H$_2$O	0.1	0.3		2h	70
4	THF/H$_2$O	0.1	0.5	-	1 h	70
5	DMF/H$_2$O	0.1	0.5	-	50 min	60
6	DMSO/H$_2$O	0.1	0.5	-	40 min	65
7	Dioxane/H$_2$O	0.1	0.5	-	40 min	80
8	EtOH/H$_2$O	0.1	0.5	-	1 h	50
9	CH$_3$CN/H$_2$O	0.1	0.5	-	12 h	15
10	*t*-BuOH/H$_2$O	0.1	0.5	-	1 h	70
11	H$_2$O	0.1	0.5	0.01	40 min	92
12	**H$_2$O**	**0.1**	**0.5**	**0.02**	**10 min**	**95**
13	H$_2$O	0.05	0.5	0.02	20 min	60

[a]Reaction conditions: benzyl azide **1a** (1.0 mmol), phenylacetylene **2a** (1.1 mmol), CuSO$_4$.5H$_2$O, β-CD and rongalite in solvent (1.0 mL). [b]Yields are of isolated pure products.

In this report, we have examined the feasibility to synthesize the copper nanoparticles from copper(II) salts *in situ* by green reducing agent rongalite, the potential catalyst for click ligation. For our initial screening experiments, the CuAAC reaction between benzyl azide, and phenyl acetylene was chosen as the model reaction (Table 2A.1). Initially, a reaction of the benzyl azide **1a** (1.0 mmol) with phenyl acetylene **2a** (1.1 mmol) catalyzed by *in situ* generated CuNPs from CuSO$_4$.5H$_2$O (0.1 equiv.) and rongalite (0.1 equiv.), in mixture of THF/ H$_2$O (1:1) (2 mL), for 5 h, was conducted to produce the corresponding 1,4-disubstituted-1,2,3-triazole **3a** in 60% yield (Table 2A.1, entry 1). These results prompted us to optimize the reaction conditions to improve the product yield.

Then, we have examined the effect of the reducing agent on reaction yield by increasing the loading of rongalite to 0.2 equiv., 0.3 equiv. and 0.5 equiv. (Table 2A.1, entries 2–4), surprisingly 0.5 equiv. of rongalite gave improved yield in less time (Table 2A.1, entry 4). Next, we have carried out the reaction in various solvents to assess their effect on the reaction efficiency. For this, we have performed the reactions in mixture of solvents such as DMF/H_2O, DMSO/H_2O, dioxane/H_2O, EtOH/H_2O, CH_3CN/H_2O, *t*-BuOH/H_2O (Table 2A.1, entries 5–10). These results proved that dioxane/H_2O solvent system is best for our reaction to furnish triazoles in good yield in less time (Table 2A.1, entry 7). Since the green chemistry principles are emerging to maximize the use of environmentally benign protocols toward the ecological and economic advantages, performing CuAAC in aqueous media is becoming popular, but remains challenging for chemists.[38,42,66–68] During the course of further optimization of the reaction conditions, we have noticed that addition of β-cyclodextrin as a phase transfer catalyst improved the yield and time with 95% and 10 min respectively (Table 2A.1, entry 12). These results were consistent with those reported by Lim et al.[69] However, lowering the CuNPs loading, decreases the product yield (Table 2A.1, entry 13).

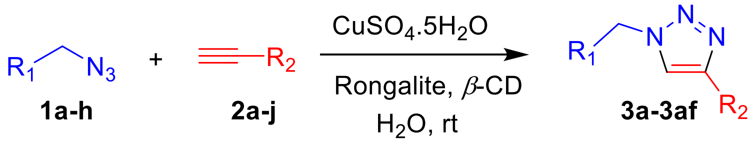
Table 2A.2. Optimization of reaction conditions with other sulphur-containing reducing Agents[a]

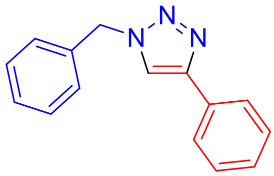
Entry	Copper salt	Reducing agent	Time	Yield[b] (%)
1	$CuSO_4.5H_2O$	Rongalite	10 min	95
2	$CuSO_4.5H_2O$	Sodium dithionite	24 h	50
3	$CuSO_4.5H_2O$	Thiourea dioxide	2 h	80
4	$CuCl_2$	Rongalite	20 min	60
5	$CuCl_2$	Sodium dithionite	24 h	30
6	$CuCl_2$	Thiourea dioxide	18 h	45
7	$Cu(OAc)_2.H_2O$	Rongalite	20 min	70
8	$Cu(OAc)_2.H_2O$	Sodium dithionite	24 h	40
9	$Cu(OAc)_2.H_2O$	Thiourea dioxide	1.5 h	87

[a]Reaction conditions: benzyl azide **1a** (1.0 mmol), phenylacetylene **2a** (1.1 mmol), copper salt (0.1 equiv.), β-CD (0.02 equiv.) and reducing agent (0.5 equiv.) in H_2O (1.0 mL). [b]Yields are of isolated pure products.

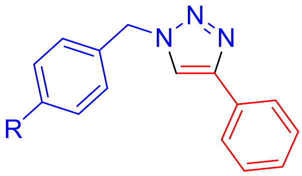
Further, we examined other sulphur-containing reducing agents for *in situ* generation of CuNPs from Cu(II) salts and click ligation, results are shown in Table 2A.2. Our data indicates that rongalite is the best reducing agent among the other sulphur-containing reducing agents (Table 2A.2, entry 1). Although, thiourea dioxide and sodium dithionite are capable of generating CuNPs, but they produce the 1,2,3-triazoles in less yield with longer time.

Table 2A.3. Click reaction of benzyl azides with various alkynes using *β*-Cyclodextrin (*β*-CD) and rongalite in water[a,b]

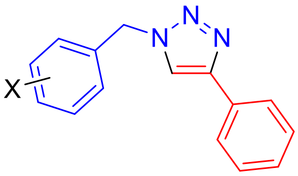




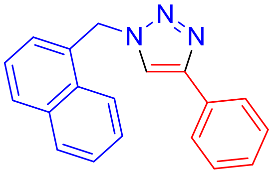
3a, 20 min, 95%



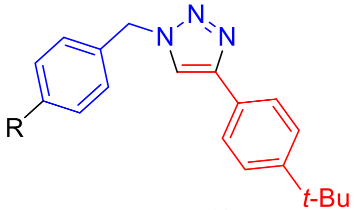
3b, R = CH_3, 30 min, 94%
3c, R = CN, 30 mn, 95%



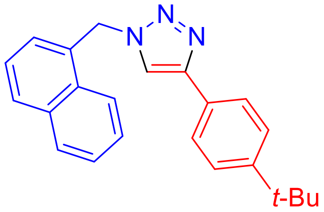
3d, X = 2-Cl, 30 min, 93%
3e, X = 3-Cl, 30 min, 80%
3f, X = 4-Cl, 30 min, 85%
3g, X = 2-Br, 30 min, 92%



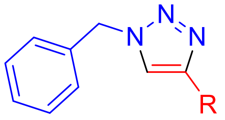
3h, 30 min, 99%



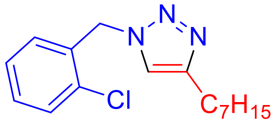
3i, R = H, 30 min, 91%
3j, R = CH_3, 30 min, 82%



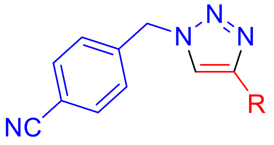
3k, 30 min,90%



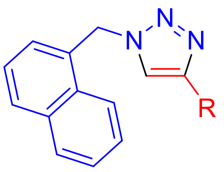
3l, R = C_6H_{13}, 30 min, 70%
3m, R = C_7H_{15}, 30 min, 68%



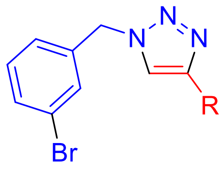
3n, 30 min, 95%



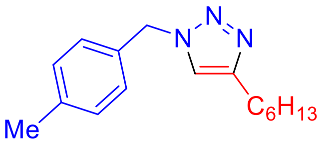
3o, R = C_6H_{13}, 30 min, 99%
3p, R = C_7H_{15}, 30 min, 85%



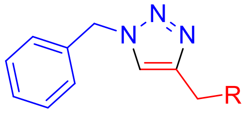
3q, R = C_6H_{13}, 30 min, 89%
3r, R = C_7H_{15}, 30 min, 85%



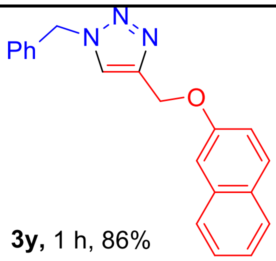
3s, R = C_6H_{13}, 30 min, 92%
3t, R = C_7H_{15}, 30 min, 85%



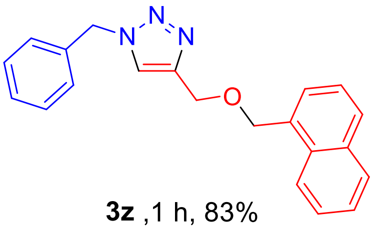
3u, 30 min, 89%



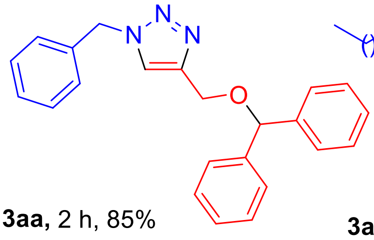
3v, R = OH, 1 h, 80%
3w, R = CH_2OH, 1 h, 75%
3x, R = 2-propanol, 1 h, 78%



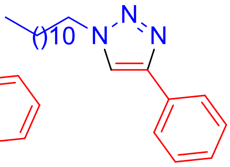
3y, 1 h, 86%



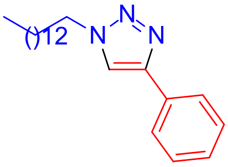
3z ,1 h, 83%



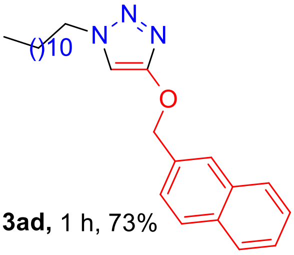
3aa, 2 h, 85%



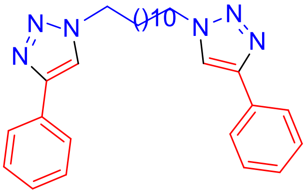
3ab, 30 min, 70%



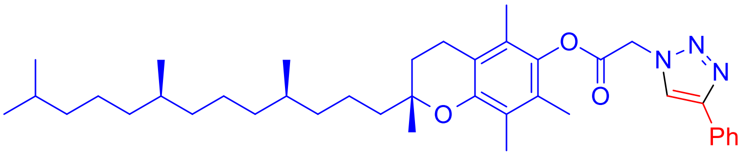
3ac, 30 min, 61%



3ad, 1 h, 73%



3ae, 2 h, 70%



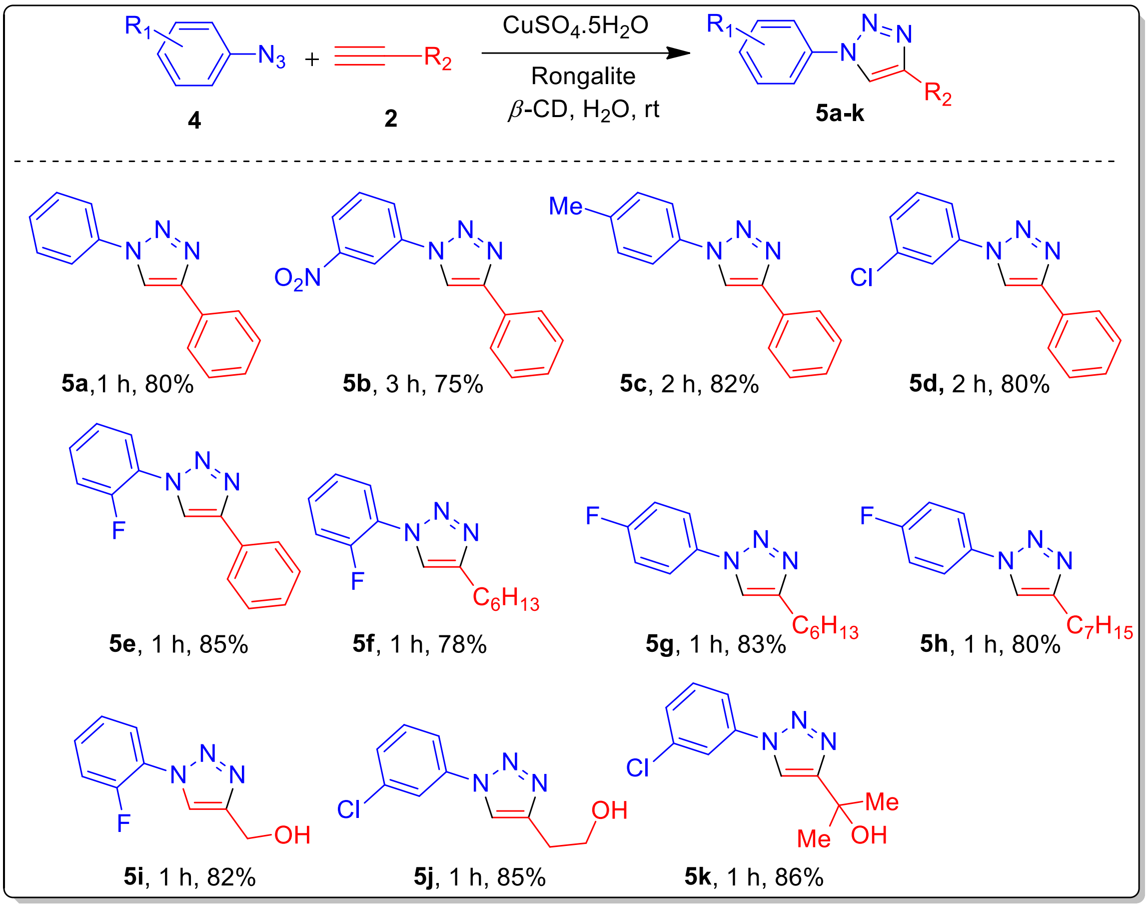
3af, 4 h, 60%

[a]Reaction conditions: azide **1a-h** (1.0 mmol), alkyne **2a-j** (1.1 mmol), $CuSO_4.5H_2O$ (0.1 equiv), β-CD (0.02 equiv.) and rongalite (0.5 equiv.) in H_2O (1.0 mL). [b]Yields are of isolated pure products.

With optimized reaction conditions (Table 2A.1, entry 12), we have applied same condition to various benzyl azides with substituted alkynes (Table 2A.3). Firstly, various benzyl azides were treated with phenyl acetylene and alkyl acetylenes (Table 2A.3). Benzyl azide reacted smoothly with phenyl acetylene to give 1,2,3-triazole **3a** in excellent yield (Table 2A.3). We have further investigated the effect of substituents on benzyl azide and found that a little effect on the product yields (Table 2A.3, **3b-c**). *Para* substitution of Me and CN groups did not affect the reaction outcome in terms of product yield. Halogen (at *ortho* as well as *para* positions) substituted benzyl azides also reacted smoothly to give the corresponding 1,2,3-triazoles in good yields (Table 2A.3, **3d-g**). 1-(Azidomethyl)naphthalene gave cycloadduct quantitatively with phenyl acetylene (Table 2A.3, **3h**). Notably, 4-tert-butyl-phenylacetylene gave less yield compared to phenyl acetylene (Table 2A.3, **3i-k**). Aliphatic long chain alkynes and alkynes containing polar groups also participated in our protocol for CuAAC reaction without any hurdle (Table 2A.3, **3l-x**). It is worth noting that increasing aromatic rings on alkynes did not alter the yields of the products (Table 2A.3, **3y-3aa**).

It is noteworthy that aliphatic long chain azides also participated in CuAAC reaction to afford triazole in good yield (Table 2A.3, **3ab-ac**). We have observed the downfall in reaction yields when chain length of aliphatic azides is increased, due to the solubility problem. To our delight, 1,12-diazido-dodecane also easily underwent click reaction with benzyl azide in 2 h to yield 70% of bis-triazole product (Table 2A.3, **3ae**). Bulky molecules like tocopherol is also tolerable with this new method (Table 2A.3, **3af**).

Table 2A.4. Click reaction of aryl azides with various alkynes using *β*-CD and rongalite in water[a,b]



[a] Reaction conditions: azide **4** (1.0 mmol), alkyne **2** (1.1 mmol), $CuSO_4.5H_2O$ (0.1 equiv), *β*-CD (0.02 equiv.) and rongalite (0.5 equiv.) in H_2O (1.0 mL). [b] Yields are of isolated pure products

Later, we applied our green protocol to aromatic azides and phenyl acetylenes and results are shown in (Table 2A.4). Unsubstituted phenyl azide and electron donating group containing phenyl azides gave corresponding triazoles in comparable yields, whereas electron withdrawing aromatic azides gave less yield in more time compare to phenyl azide (Table 2A.4, **5a-c**). Further, halogen containing phenyl azides also participated smoothly in cycloaddition reaction and gave 1,4-disubstituted-1,2,3-triazoles in good yields (Table 2A.4, **5d-e**). Also reactivity of aliphatic alkynes was comparable to the aromatic alkynes (Table 2A.4, **5f-k**).

Although, there are several reports on CuAAC reactions catalyzed by CuNPs and most of them require high temperatures (60-80 °C) and longer reaction times (2-24 h),[38,41–42] reactions using our method require ambient temperature and shorter reaction time (30 min-2 h) to furnish the triazoles in water. Further, we have investigated the reaction mechanism of CuAAC catalyzed by CuNPs. Also we found in the literature that rongalite is capable of converting copper(II) chloride into nanoparticles such as Cu and Cu_2O at higher temperature (70-100 °C).[63–65] These findings arose our interest to analyze the composition of copper complex to know the type of copper species present and responsible for click reaction. For this, CuNPs were prepared according to the following protocol: To a 20 mL of 0.5 molar $CuSO_4.5H_2O$ solution in a beaker were added *β*-cyclodextrin (0.02 equiv.) and rongalite (5 equiv.) and stirred at room temperature for 10 minutes.

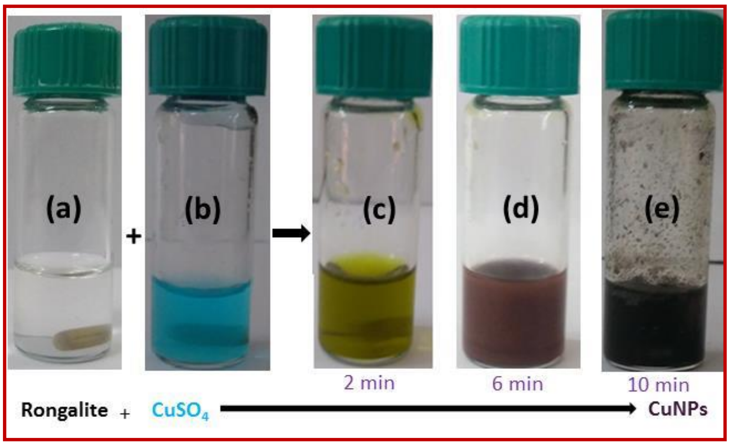


Figure 2A. 1. Color change observed during the copper nanoparticles formation

Finally, we have observed the formation of blackish brown colour precipitate from blue colour (Figure 2A.1, **a–e**), which was then centrifuged at 10000 rpm for 15 min, washed with water (5 times) and dried under inert condition. The dried powder was analyzed by powder XRD (PXRD).

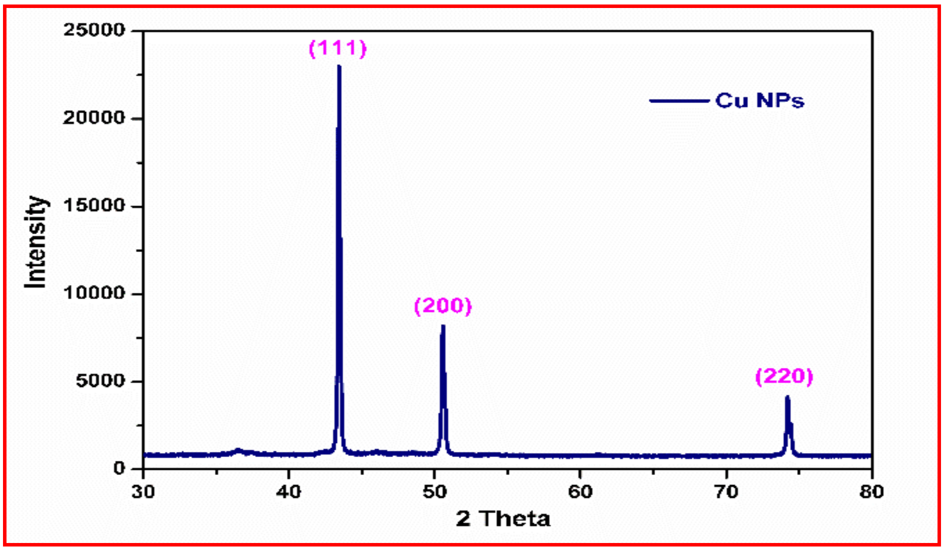


Figure 2A.2. Powder XRD pattern of synthesized Cu-NPs.

The powder XRD studies were carried out in order to investigate both the crystal structure and the average crystallite size of nanoparticles (Figure 2A.2). The PXRD patterns is indexed the presence of face centered cubic (f.c.c.) Cu (JCPDS, card no. 04–0836). The peaks at 43.36°, 50.48°, 74.35° belong to (111), (200), (220) planes of Cu nanoparticles. The average crystallite size was determined by using Scherrer’s equation.

Crystallite size = $k\lambda/\beta\cos\theta$. Where k is dimensionless shape factor = 0.9, λ is X-ray wavelength = 1.54 A°, β is full width of half maxima in radians, θ is angle of diffraction. The calculated average crystallite size of CuNPs is about to be 39 nm. Powder XRD data suggested that the sample contains only Copper(0) NPs (Figure 2A.2). Flores-López et al.[66] proved that cyclodextrins are good stabilizing agents in the formation of Cu nanoparticles and our results are consisting with reported method.

SEM was carried out to know the morphological characteristics of formed Cu nanoparticles (Figure 2A.3). Image of Figure 2A.3 (**a, b, c**) is the group of SEM images which clearly shows the formation of ‘Cu’ nanoparticles with irregular shape and the formed nanoparticles are agglomerated.

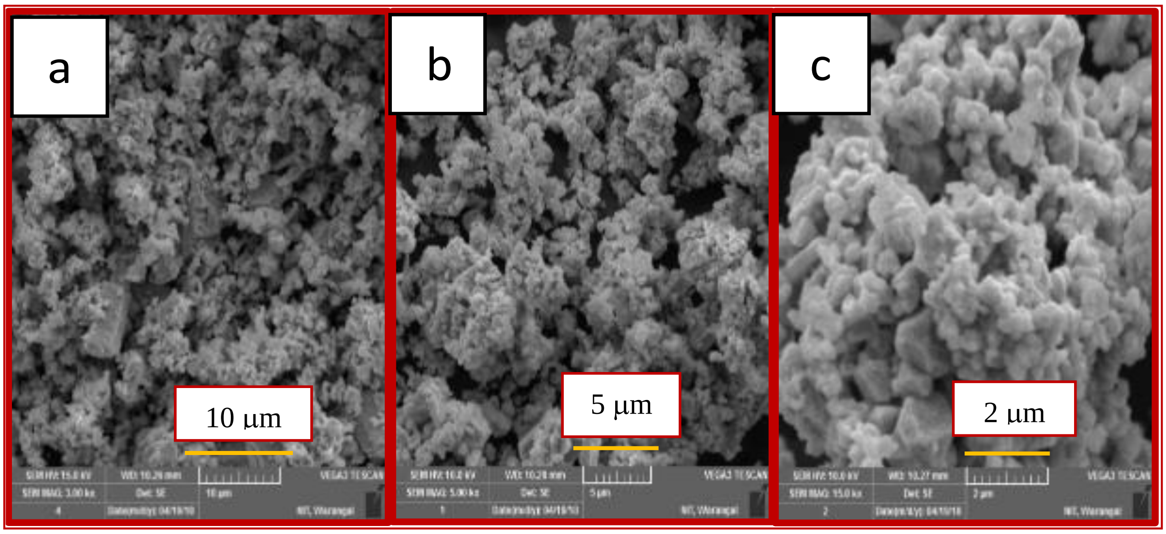
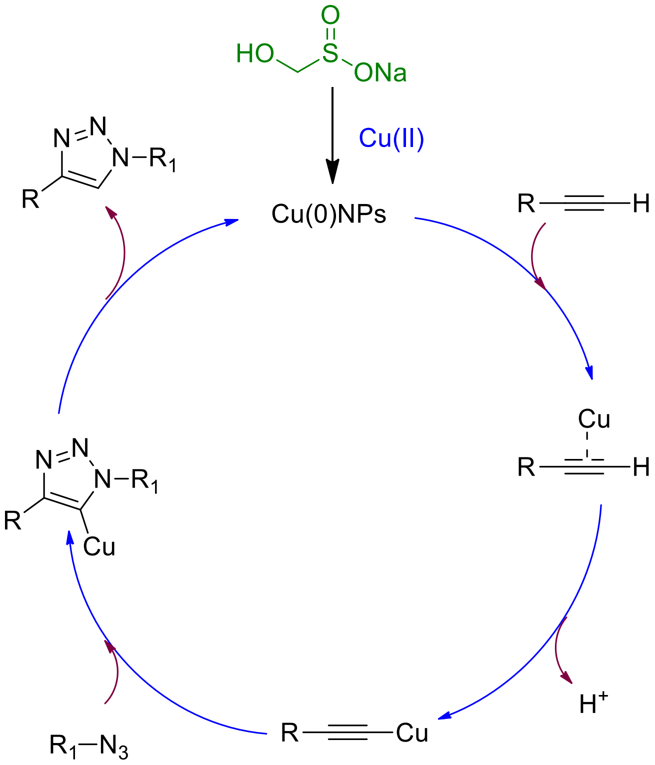


Figure 2A.3. SEM images of Cu-NPs in different magnifications (a) 10 µm (b) 5 µm (c) 2 µm



Scheme 2A. 18. Proposed mechanism for the CuAAC reaction.

The plausible reaction mechanism pathway proposed for the reaction is the same as in earlier reports.[10,16] The Cu(0)NPs were generated *in situ* by rongalite from copper salt *via* single electron transfer.[72] Then the Cu(0)NPs reacts with an alkyne to give a copper-acetylide. The 1,3-dipolar cyclization of the resulting Cu acetylide and an organic azide followed by the protonation provided the formation of a triazole and the regeneration of Cu(0) catalyst (Scheme 1).[67-68]

2A.4. Conclusions

In summary, a green protocol using $CuSO_4.5H_2O$/Rongalite catalyst system, which generates CuNPs *in situ* provides the regiospecific 1,4-disubstituted 1,2,3-triazoles in excellent yields with relatively short reaction times. Additionally, this protocol allows to a wide range of functional groups on both the alkyne and azide part. Here, *β*-cyclodextrin is playing dual role of both stabilizing agent as well as phase transfer catalyst. This method is also applicable for gram scale synthesis.

2A.5. Experimental Section

General information

Reactions were conducted in round bottom flasks. Thin layer chromatography was performed on 200 μm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. All other reagents were used as received from commercial suppliers. Aromatic and aliphatic azides were prepared according to reported methods. ^1H NMR spectra were obtained at 400 MHz in $CDCl_3$ and were referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ and were referenced to the solvent resonance. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) were in hertz (Hz). Standard abbreviations were used to designate resonance multiplicities.

Preparation of aryl azides[69]

In an oven dried round bottom flask, aniline derivative (13 mmol) was suspended in 80 mL hydrochloric acid (17%) at room temperature and then ethanol was added until a clear solution was obtained. The resulting solution was cooled to 0 °C and $NaNO_2$ (1.5 eq.) was added in small portions. After stirring at 0 °C for 15-30 min. NaN_3 (1.5 eq.) was slowly added and the mixture was stirred for additional 2 h at room temperature. The reaction mixture was extracted with diethyl ether (3 x 60 mL) and the combined organic fractions were washed with saturated $NaHCO_3$ solution (3 x 50 mL) and with brine (50 mL). After drying over Na_2SO_4 the ether was removed under reduced pressure and the desired azides were obtained without further purification.

Preparation of alkyl azides[70]

In an oven dried round bottom flask, alkyl bromide (1.0 eq.) was dissolved in DMSO (40 ml). Sodium azide (1.5 eq.) was added and the reaction was stirred at room temperature for 12 h. The mixture was allowed to stir at room temperature, until TLC indicated completion of reaction. Then the reaction mixture was diluted with water (70 mL) and extracted with diethyl ether (3 x 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was further used without purification.

General synthetic procedure for 1,4-disubstituted-1,2,3-triazoles (3a-af, 5a-k)

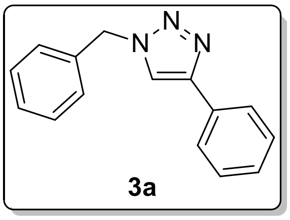
In an oven dried round bottom flask, azide **1a-h, 5a-f** (1.0 mmol) and alkyne **2a-j** (1.1 mmol) were added to a mixture of copper(II)sulfate pentahydrate (0.1 equiv.), rongalite (0.5 equiv.), and *β*-cyclodextrin (0.02 equiv.) in H_2O (1mL). The mixture was allowed to stir at room temperature, until TLC indicated completion of reaction. Then the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using 10% ethyl acetate in *n*-hexanes as an eluent.

Procedure for gram scale synthesis of 3a.

In an oven dried round bottom flask, benzyl azide **1a** (5 g, 37.5 mmol) and phenyl acetylene **2a** (4.2 g, 41.3 mmol) were added to a mixture of copper(II)sulfate pentahydrate (0.937 g, 3.75 mmol), rongalite (2.89 g, 18.7 mmol), and *β*-cyclodextrin (0.85 g, 0.75 mmol) in H_2O (50 mL) at 0 °C. The mixture was then allowed to stir at room temperature for 10 min. After completion of reaction (TLC monitoring), the reaction mixture was diluted with water (150 mL) and extracted with ethyl acetate (3 x 150 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using 10% ethyl acetate in hexanes as an eluent to furnish **3a** (White solid, 85%).

2A.6. Spectral data

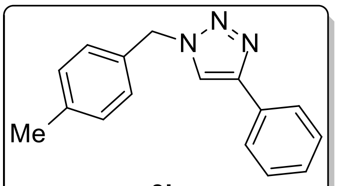
1-Benzyl-4-phenyl-1H-1,2,3-triazole (3a)[71]



3a

White solid (95%); FT-IR (KBr, cm^{-1}) 3121, 3051, 2949, 1612, 1495, 1466, 1357, 1223, 1074, 1047, 973, 766, 729, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (d, J = 7.2 Hz, 2H), 7.66 (s, 1H), 7.35–7.44 (m, 5H), 7.28–7.35 (m, 3H), 5.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 134.7, 134.7, 130.5, 129.2, 128.8, 128.2, 128.1, 125.7, 119.5, 54.3.

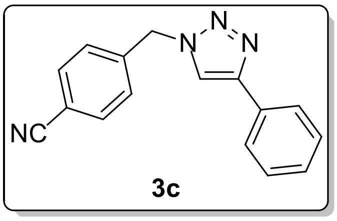
1-(4-Methylbenzyl)-4-phenyl-1H-1,2,3-triazole (3b)[72]



3b

White solid (94%); FT-IR (KBr, cm^{-1}) 3115, 3086, 2960, 2856, 1515, 1463, 1348, 1222, 1047, 1046, 973, 832, 762, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.8 Hz, 2H), 7.56 (s, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.10–7.17 (m, 4H), 5.46 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.8, 131.6, 130.6, 129.8, 128.8, 128.2, 125.7, 119.4, 54.1, 21.2.

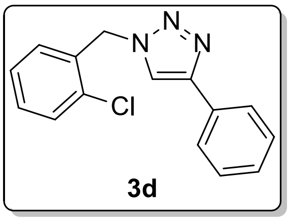
4-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl) benzonitrile (3c)[73]



3c

White solid (95%); FT-IR (KBr, cm^{-1}) 3135, 2925, 2227, 1463, 1431, 1347, 1223, 1186, 1076, 1043, 808, 765, 698, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.70 (d, J = 7.2 Hz, 2H), 7.67 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.38–7.24 (m, 5H), 5.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 139.9, 132.9, 130.1, 128.9, 128.5, 128.4, 125.7, 119.8, 118.2, 112.8, 53.5.

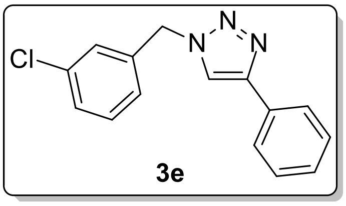
1-(2-Chlorobenzyl)-4-Phenyl-1*H*-1,2,3-triazole (3d)



3d

White solid (93%); FT-IR (KBr, cm^{-1}) 3112, 3060, 2961, 2948, 2924, 2853, 1704, 1550, 1445, 1328, 1219, 1050, 826, 726, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 2H), 7.80 (s, 1H), 7.50–7.40 (m, 3H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.27 (dd, *J* = 17.7, 6.4 Hz, 2H), 5.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 133.4, 132.6, 130.5, 130.3, 129.9, 128.8, 128.2, 127.7, 125.7, 119.9, 51.5.

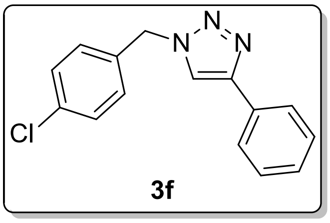
1-(3-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3e)[74]



3e

White solid (80%); FT-IR (KBr, cm^{-1}) 3098, 3124, 3060, 2924, 1560, 1464, 1357, 1219, 1208, 1081, 1045, 977, 824, 764, 750, 691; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.82 (d, *J* = 7.4 Hz, 2H), 7.77 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.33(d, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 4.0 Hz, 1H), 7.27 (d, *J* = 5.6 Hz, 1H), 7.23 (s, 1H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 148.2, 133.5, 132.6, 130.5, 130.3, 130.2, 130.0, 128.8, 128.2, 127.7, 125.7, 119.8, 51.5.

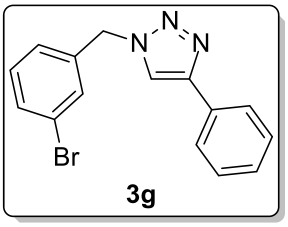
1-(4-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3f)[75]



3f

White solid (85%); FT-IR (KBr, cm^{-1}) 3108, 3083, 2925, 2850, 1550, 1461, 1220, 1092, 1080, 1016, 976, 845, 820, 804, 763, 688, 667; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.80 (d, *J* = 7.5 Hz, 2H), 7.67 (s, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 8.4 Hz, 3H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 148.4, 134.8, 133.2, 130.4, 129.4, 128.9, 128.3, 125.7, 119.5, 53.5.

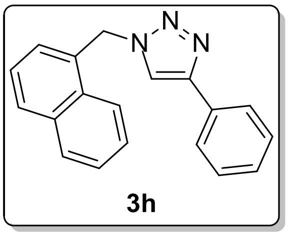
1-(3-Bromobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3g)[75]



3g

White solid (92%); FT-IR (KBr, cm^{-1}) 3115, 3084, 2920, 1570, 1480, 1432, 1343, 1223, 1192, 1071, 1046, 974, 910, 836, 809, 764, 750, 698, 671; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.74 (d, *J* = 7.3 Hz, 1H), 7.63 (s, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.23–7.14 (m, 3H), 5.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 148.5, 136.9, 132.0, 131.0, 130.8, 130.4, 128.9, 128.3, 126.6, 125.8, 123.2, 119.5, 53.5.

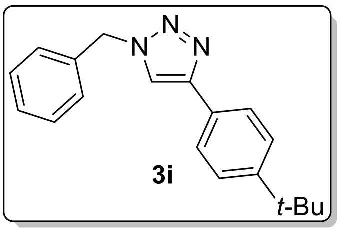
1-(Naphthalen-1-ylmethyl)-4-phenyl-1*H*-1,2,3-triazole (3h)[76]



3h

White solid (99%); FT-IR (KBr, cm^{-1}) 3117, 3086, 2966, 1597, 1510, 1480, 1342, 1213, 1193, 1081, 1047, 975, 778, 766, 721, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.89 (m, 1H), 7.79–7.85 (m, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 4.8 Hz, 3H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 2H), 7.21–7.15 (m, 1H), 5.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 134.0, 131.2, 130.5, 130.1, 129.9, 129.0, 128.8, 128.1, 127.9, 127.4, 126.5, 125.7, 125.4, 122.9, 119.5, 52.5.

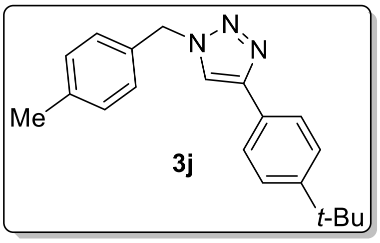
1-Benzyl-4-(4-(*tert*-butyl) phenyl)-1*H*-1,2,3-triazole (3i)[77]



3i

White solid (91%); FT-IR (KBr, cm^{-1}) 3115, 3087, 2958, 2865, 1604, 1495, 1457, 1363, 1218, 1070, 1040, 976, 827, 739, 717, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.57 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.28–7.32 (m, 3H), 7.20–7.24 (m, 2H), 5.50 (s, 2H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 134.8, 128.8, 128.0, 125.7, 125.5, 54.2, 34.7, 31.3.

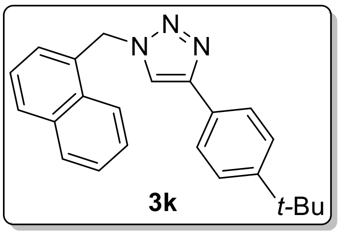
4-(4-(*tert*-Butyl) phenyl)-1-(4-methylbenzyl)-4-phenyl-1*H*-1,2,3-triazole (3j)[78]



3j

White solid (82%); FT-IR (KBr, cm^{-1}) 3120, 3090, 2960, 2928, 2865, 1514, 1494, 1454, 1347, 1219, 1203, 1071, 1047, 975, 823, 792, 751, 560; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 10.7 Hz, 2H), 7.09–7.15 (m, 4H), 5.45 (s, 2H), 2.28 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 148.6, 138.7, 131.8, 129.8, 128.1, 127.8, 125.7, 125.4, 119.2, 54.0, 34.7, 31.3, 21.2.

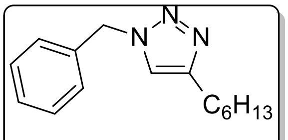
4-(4-(*tert*-Butyl) phenyl-1-(naphthalen-1-ylmethyl)-1*H*-1,2,3-triazole (3k)



3k

White solid (90%); FT-IR (KBr, cm^{-1}) 3108, 3055, 2963, 2956, 2863, 2850, 1555, 1469, 1345, 1220, 1193, 1065, 1043, 972, 845, 802, 790; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 6.1, 3.5 Hz, 1H), 7.78–7.85 (m, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.47–7.39 (m, 4H), 7.38 (d, J = 4.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H),), 5.92 (s, 2H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 134.0, 131.2, 130.1, 130.0, 129.0, 128.0, 127.7, 127.4, 126.5, 125.7, 125.4, 123.0, 119.3, 52.5, 34.7, 31.3.

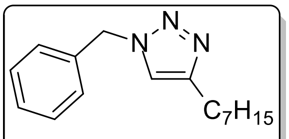
1-Benzyl-4-hexyl-1*H*-1,2,3-triazole (3l)[73]



3l

White solid (70%); FT-IR (KBr, cm^{-1}) 3113, 3064, 2954, 2927, 2854, 1552, 1494, 1456, 1326, 1213, 1177, 1073, 1053, 1030, 855, 747, 703, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.32 (m, 3H), 7.16–7.20 (m, 2H), 7.11 (s, 1H), 5.42 (s, 2H), 2.61 (t, J = 7.8 Hz, 2H), 1.56 (m, 2H), 1.10–1.29 (m, 6H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.0, 129.1, 128.6, 128.0, 120.5, 54.0, 31.5, 29.4, 28.9, 25.7, 22.5, 14.0.

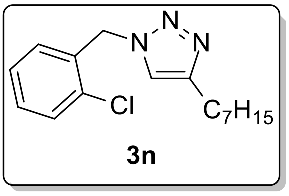
1-Benzyl-4-heptyl-1*H*-1,2,3-triazole (3m)[79]



3m

White solid (68%); FT-IR (KBr, cm^{-1}) 3113, 3064, 2956, 2920, 2852, 1551, 1468, 1455, 1337, 1212, 1052, 859, 703, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.41 (m, 3H), 7.25–7.29 (m, 2H), 7.20 (s, 1H), 5.50 (s, 2H), 2.70 (t, J = 7.8 Hz, 2H), 1.60–1.70 (m, 2H), 1.20–1.39 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.0, 129.0, 128.6, 127.9, 120.5, 54.0, 31.7, 29.4, 29.2, 29.0, 25.7, 22.6, 14.1.

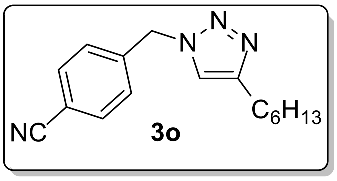
1-(2-Chlorobenzyl)-4-heptyl-1*H*-1,2,3-triazole (3n)



3n

White solid (95%); FT-IR (KBr, cm^{-1}) 3112, 3060, 2961, 2948, 2924, 2853, 1704, 1550, 1445, 1328, 1219, 1050, 826, 726, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.8 Hz, 1H), 7.26–7.15 (m, 3H), 7.06 (d, J = 7.5 Hz, 1H), 5.56 (s, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.63–1.52 (m, 2H), 1.32–1.13 (m, 8H), 0.79 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 133.3, 132.9, 130.1, 130.0, 129.9, 127.6, 120.9, 51.2, 31.7, 29.4, 29.2, 29.0, 25.7, 22.6, 14.1.

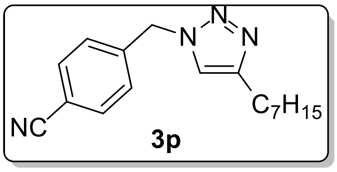
4-((4-Hexyl-1*H*-1,2,3-triazol-1-yl) methyl) benzo nitrile (3o)[79]



3o

White solid (99%); FT-IR (KBr, cm^{-1}) 3110, 3059, 2954, 2924, 2850, 2232, 1500, 1455, 1329, 1219, 1127, 1053, 868, 827, 781, 667, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.19 (s, 1H), 5.50 (s, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 1.63–1.53 (m, 2H), 1.27–1.23 (m, 6H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 140.3, 132.8, 128.3, 120.8, 118.2, 112.6, 53.3, 31.5, 29.3, 28.9, 25.7, 22.5, 14.0.

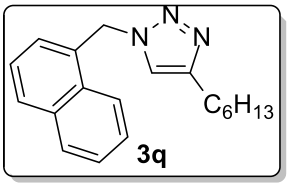
4-((4-Heptyl-1*H*-1,2,3-triazol-1-yl) methyl) benzo nitrile (3p)[79]



3p

White solid (85%); FT-IR (KBr, cm^{-1}) 3110, 3059, 2957, 2923, 2851, 2232, 1600, 1550, 1507, 1466, 1219, 1052, 1024, 868, 826, 781, 669, 553; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.19 (s, 1H), 5.50 (s, 2H), 2.63 (t, *J* = 7.9 Hz, 2H), 1.63–1.52 (m, 2H), 1.31–1.17 (m, 8H), 0.79 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 140.3, 132.8, 128.3, 120.8, 118.2, 112.6, 53.3, 31.7, 29.3, 29.2, 29.0, 25.7, 22.6, 14.1.

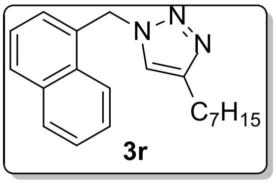
4-Hexyl-1-(naphthalen-1-ylmethyl)-1*H*-1,2,3-triazole (3q)[76]



3q

White solid (89%); FT-IR (KBr, cm^{-1}) 3107, 3054, 2951, 2926, 2857, 2847, 1600, 1510, 1464, 1213, 1133, 1050, 1018, 861, 780, 738, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 6.1, 3.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.43 (dd, *J* = 6.2, 3.1 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 6.9 Hz, 1H), 6.97 (s, 1H), 5.86 (s, 2H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.55–1.43 (m, 2H), 1.11–1.21 (m, 6H), 0.75 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 133.9, 131.2, 130.2, 129.9, 128.9, 127.7, 127.3, 126.4, 125.4, 123.0, 120.5, 52.2, 31.5, 29.3, 28.9, 25.7, 22.5, 14.0.

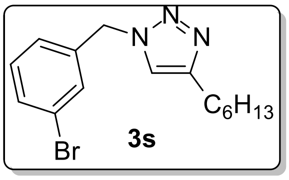
4-Heptyl-1-(naphthalen-1-ylmethyl)-1*H*-1,2,3-triazole (3r)



3r

White solid (85%); FT-IR (KBr, cm^{-1}) 3106, 3054, 2952, 2925, 2852, 1600, 1551, 1511, 1461, 1306, 1213, 1132, 1021, 1019, 863, 780, 739, 724; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 (dd, J = 6.0, 3.6 Hz, 1H), 7.86–7.79 (m, 2H), 7.41–7.47 (m, 2H), 7.39 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 6.9 Hz, 1H), 6.97 (s, 1H), 5.86 (s, 2H), 2.54 (t, J = 7.7 Hz, 2H), 1.44–1.54 (m, 2H), 1.25–1.06 (m, 8H), 0.76 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.8, 133.9, 131.2, 130.2, 129.9, 128.9, 127.7, 127.2, 126.4, 125.4, 123.0, 120.5, 52.3, 31.7, 29.3, 29.2, 29.0, 25.7, 22.6, 14.1.

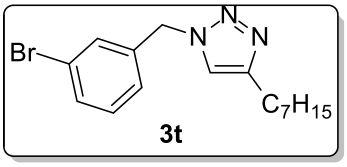
1-(3-Bromobenzyl)-4-hexyl-1*H*-1,2,3-triazole (3s)[80]



3s

White solid (92%); FT-IR (KBr, cm^{-1}) 3123, 3075, 2956, 2924, 2865, 1571, 1560, 1495, 1343, 1214, 1127, 1060, 1048, 855, 750, 726, 691; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, J = 7.9 Hz, 1H), 7.33 (s, 1H), 7.13–7.21 (m, 2H), 7.10 (d, J = 7.7 Hz, 1H), 5.39 (s, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.51–1.65 (m, 2H), 1.16–1.26 (m, 6H), 0.80 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.2, 137.2, 131.8, 130.9, 130.6, 126.4, 1 23.0, 120.6, 53.2, 31.5, 29.3, 28.9, 25.7, 22.5, 14.0.

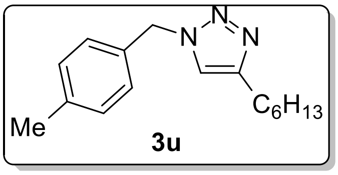
1-(3-Bromobenzyl)-4-heptyl-1*H*-1,2,3-triazole (3t)



3t

White solid (85%); FT-IR (KBr, cm^{-1}) 3124, 3073, 2956, 2924, 2855, 1571, 1550, 1485, 1323, 1215, 1127, 1070, 1048, 815, 770, 723, 688; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, J = 7.9 Hz, 1H), 7.33 (s, 1H), 7.08–7.20 (m, 2H), 7.10 (d, J = 7.6 Hz, 1H), 5.39 (s, 2H), 2.63 (t, J = 7.7 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.29–1.13 (m, 8H), 0.80 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.2, 137.2, 131.8, 130.9, 130.6, 126.4, 123.0, 120.6, 53.2, 31.7, 29.3, 29.2, 29.0, 25.7, 22.6, 14.1.

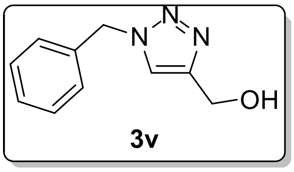
4-Hexyl-1-(4-methyl benzyl)-1*H*-1,2,3-triazole (3u)



3u

Colourless solid (89%); FT-IR (KBr, cm^{-1}) 3115, 3064, 2954, 2926, 2855, 1543, 1516, 1456, 1325, 1214, 1127, 1116, 839, 822, 786, 776, 756; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.06–7.12 (m, 5H), 5.37 (s, 2H), 2.60 (t, J = 7.8 Hz, 2H), 2.27 (s, 3H), 1.49–1.61 (m, 2H), 1.1–1.28 (m, 6H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.9, 138.5, 132.0, 129.7, 128.0, 120.4, 53.8, 31.5, 29.4, 28.9, 25.7, 22.5, 21.1, 14.0.

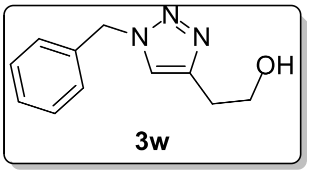
(1-Benzyl-1*H*-1,2,3-triazol-4-yl) methanol (3v)[81]



3v

White solid (80%); FT-IR (KBr, cm^{-1}) 3262, 3138, 3087, 3030, 2963, 2883, 1487, 1222, 1015, 719, 691; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (s, 1H), 7.33–7.16 (m, 5H), 5.43 (s, 2H), 4.67 (s, 2H), 3.42 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.1, 134.5, 129.2, 128.8, 128.2, 121.6, 77.4, 77.1, 76.7, 56.5, 54.2.

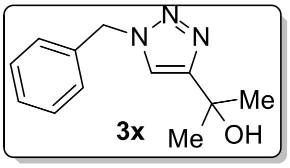
2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)ethanol (3w)[82]



3w

White solid (75%); FT-IR (KBr, cm^{-1}) 3355, 3134, 2935, 2830, 1539, 1456, 1173, 965, 830, 731; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 (s, 1H), 7.36–7.22 (m, 5H), 5.46 (s, 2H), 3.87 (t, J = 5.5 Hz, 2H), 3.35 (s, 1 H), 2.90 (t, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.0, 134.7, 129.1, 128.8, 128.1, 121.5, 77.4, 77.1, 76.8, 61.6, 54.1, 28.7.

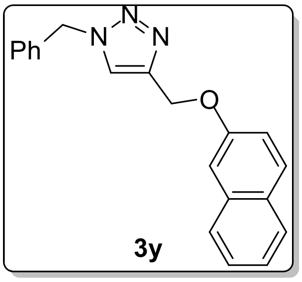
2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (3x)[83]



3x

White solid (78%); FT-IR (KBr, cm^{-1}) 3305, 3164, 2975, 2930, 1499, 1456, 1173, 961, 719, 731; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.36 (m, 4H), 7.31–7.27 (m, 2H), 5.51 (s, 2H), 2.96 (s, 1H), 1.62 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.1, 134.6, 129.1, 128.8, 128.2, 119.2, 68.5, 54.1, 30.4.

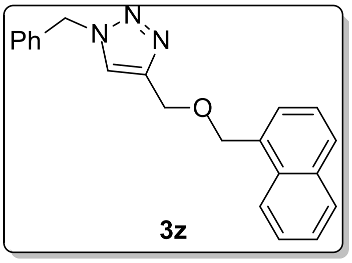
1-Benzyl-4-((naphthalen-2-yloxy)methyl)-1*H*-1,2,3-triazole (3y)[84]



3y

White solid (86%); FT-IR (KBr, cm^{-1}) 3145, 3034, 2872, 2815, 1628, 1457, 1258, 1219, 1045, 854, 824, 726; ^{1}H NMR (400 MHz, CDCl$_3$+DMSO-d_6) δ 7.67 (t, J = 9.4 Hz, 3H), 7.48 (s, 1H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 4H), 7.22–7.16 (m, 3H), 7.08 (dd, J = 9.0, 2.5 Hz, 1H), 5.45 (s, 2H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$+DMSO-d_6) δ 156.4, 143.4, 136.4, 134.7, 129.8, 129.2, 129.1, 128.6, 128.4, 128.0, 127.2, 126.9, 125.2, 124.2, 119.1, 107.7, 61.7, 53.4.

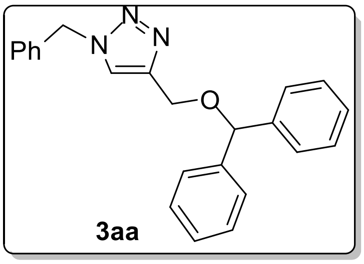
1-Benzyl-4-((naphthalen-1-ylmethoxy) methyl)-1*H*-1,2,3-triazole (3z)



3z

White solid (83%); FT-IR (KBr, cm^{-1}) 3114, 3071, 2955, 2863, 2781, 1457, 1097, 791, 777, 707; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.12–8.05 (m, 1H), 7.90–7.85 (m, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.55–7.48 (m, 3H), 7.44 (t, J = 7.6 Hz, 2H), 7.39 (d, J = 1.9 Hz, 1H), 7.38 (d, J = 1.8 Hz, 2H), 7.28 (dd, J = 7.1, 2.3 Hz, 2H), 5.52 (s, 2H), 5.06 (s, 2H), 4.76 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.7, 134.6, 1338, 133.3, 131.8, 129.1, 128.8, 128.8, 128.6, 128.1, 126.9, 126.3, 125.8, 125.2, 124.0, 122.5, 71.0, 63.8, 54.6.

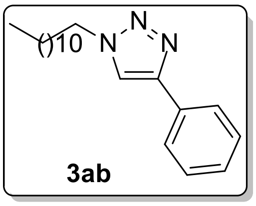
4-((Benzhydryloxy) methyl)-1-benzyl-1*H*-1,2,3-triazole (3aa)



3aa

White solid (85%); FT-IR (KBr, cm^{-1}) 3138, 3086, 3058, 3030, 2867, 2794, 1455, 1105, 756, 736, 704, 693; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 (s, 1H), 7.30–7.15 (m, 15H), 5.43 (s, 2H), 5.42 (s, 1H), 4.58 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.8, 141.7, 134.6, 129.2, 128.8, 128.5, 128.2, 127.6, 127.2, 122.6, 83.2, 77.4, 77.1, 76.8, 62.5, 54.2.

1-Dodecyl-4-phenyl-1*H*-1,2,3-triazole (3ab)[85]

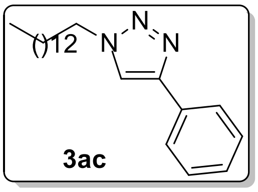


3ab

White solid (70%); FT-IR (KBr, cm^{-1}) 3119, 3081, 2954, 2917, 2846, 1609, 1464, 1356, 1216, 1078, 1053, 977, 839, 762, 723, 695; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, J = 7.2 Hz, 2H), 7.67

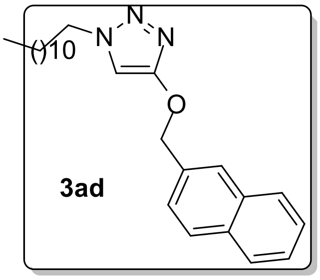
(s, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 4.32 (t, *J* = 7.2 Hz, 2H), 1.87 (p, *J* = 7.0 Hz, 2H), 1.35–1.08 (m, 18H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 130.7, 128.8, 128.1, 125.7, 119.4, 50.5, 31.9, 30.4, 29.5, 29.4, 29.3, 29.0, 26.5, 22.7, 14.1.

1-Tetradecyl-4-phenyl-1*H*-1,2,3-triazole (3ac)



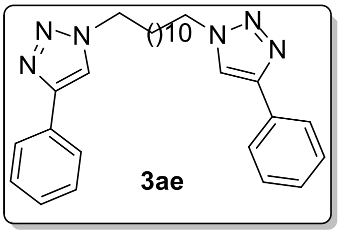
White solid (61%); FT-IR (KBr, cm^{-1}) 3119, 2954, 2917, 2846, 1609, 1464, 1216, 1078, 976, 839, 761, 723, 694, 527; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.67 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 4.32 (t, *J* = 7.2 Hz, 2H), 1.93–1.81 (m, 2H), 1.18 (s, 22H), 0.80 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 89.2, 77.4, 77.2, 77.1, 76.7, 75.3, 56.4, 53.5, 31.9, 29.7, 29.4, 22.7, 14.1.

1-Dodecyl-4-((naphthalen-2-yloxy) methyl)-1*H*-1,2,3-triazole (3ad)



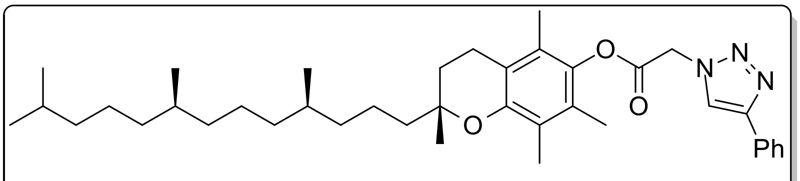
White solid (73%); FT-IR (KBr, cm^{-1}) 3133, 3098, 3058, 2948, 2848, 2818, 1600, 1469, 1215, 1000, 834, 813, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.74 (m, 3H), 7.64 (s, 1H), 7.49–7.44 (m, 1H), 7.39–7.34 (m, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.36 (s, 2H), 4.37 (t, *J* = 7.3 Hz, 2H), 1.99–1.88 (m, 2H), 1.38–1.22 (m, 18H), 0.90 (t, *J* = 6.9 Hz, 3H).

1, 12-bis (4-Phenyl-1*H*-1,2,3-triazol-1yl) dodecane (3ae)



White solid (70%); FT-IR (KBr, cm^{-1}) 3120, 3093, 2917, 2846, 1463, 1216, 1078, 762, 695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 4H), 7.76 (s, 2H), 7.44 (t, *J* = 7.5 Hz, 4H), 7.35 (t, *J* = 7.2 Hz, 2H), 4.43 (t, *J* = 7.2 Hz, 4H), 3.27 (t, *J* = 6.9 Hz, 4H), 1.99–1.93 (m, 4H), 1.73–1.56 (m, 4H), 1.40–1.27 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 130.8, 128.8, 128.1, 125.7, 119.4, 51.5, 50.4, 30.3, 29.4, 29.3, 29.1, 29.0, 28.8, 26.7, 26.5.

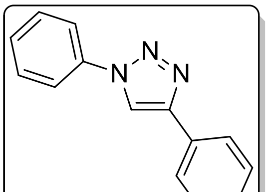
2,5,7,8-Tetramethyl-2-((4R, 8R)-4,8,12-trimethyltridecyl)chroman-6-yl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (3af)



3af

White solid (60%); FT-IR (KBr, cm^{-1}) 3133, 3097, 3057, 2924, 2849, 1765, 1468, 1205, 1182, 1001, 835, 764, 743; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.88 (dd, J = 8.3, 1.2 Hz, 2H), 7.49–7.43 (m, 2H), 7.40–7.34 (m, 1H), 5.52 (s, 2H), 2.60 (t, J = 6.7 Hz, 2H), 2.11 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.89–1.71 (m, 3H), 1.63–1.49 (m, 3H), 1.36–1.09 (m, 19H), 0.91–0.85 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 150.0, 148.4, 140.0, 130.3, 128.9, 128.4, 126.3, 125.9, 124.6, 123.4, 121.0, 117.7, 75.3, 50.8, 39.4, 37.4, 37.3, 32.8, 32.7, 31.0, 28.0, 24.8, 24.4, 22.7, 22.6, 21.0, 20.6, 19.8, 19.7, 13.0, 12.2, 11.8.

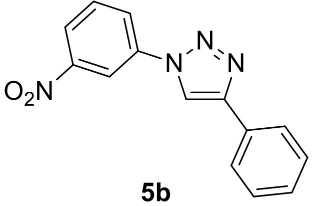
1,4-Diphenyl-1*H*-1,2,3-triazole (5a)[86]



5a

White solid (80%); FT-IR (KBr, cm^{-1}) 3120, 3096, 3055, 2923, 1576, 1504, 1227, 1041, 757, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.00–7.95 (m, 2H), 7.88–7.82 (m, 2H), 7.63–7.58 (m, 2H), 7.55–7.48 (m, 3H), 7.46–7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 129.8, 129.0, 128.8, 128.5, 125.9, 120.6, 117.6, 77.4, 77.0, 76.7.

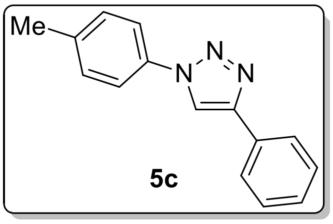
1-(3-Nitrophenyl)-4-phenyl-1*H*-1,2,3-triazole (5b)[86]



5b

Pale Yellow solid (78%); FT-IR (KBr, cm^{-1}) 3140, 3091, 2921, 1534, 1348, 1233, 1045, 870, 762, 745; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 9.53 (s, 1H), 8.80 (t, J = 2.0 Hz, 1H), 8.46 (dd, J = 8.1, 1.3 Hz, 1H), 8.33 (dd, J = 8.2, 1.4 Hz, 1H), 7.96 (d, J = 7.3 Hz, 2H), 7.91 (d, J = 8.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 149.0, 148.2, 137.8, 132.0, 130.4, 129.4, 128.8, 126.2, 125.9, 123.4, 120.3, 114.9.

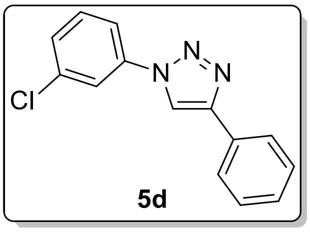
4-Phenyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole (5c)[81]



5c

White solid (82%); FT-IR (KBr, cm^{-1}) 3125, 3097, 3055, 1520, 1229, 1045, 817, 764, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.84 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 148.3, 139.0, 134.8, 130.3, 128.9, 128.4, 125.9, 120.5, 117.7, 117.7, 21.2.

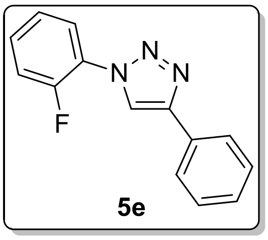
1-(3-Chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole (5d)[87]



5d

Yellow solid (80%); FT-IR (KBr, cm-1) 3120, 3098, 2923, 1589, 1227, 1041, 886, 791, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.88 (d, *J* = 5.6 Hz, 2H), 7.85 (s, 1H), 7.77–7.72 (m, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.38 (m, 3H), 7.30 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 130.9, 130.0, 129.0, 128.9, 128.7, 125.9, 120.8, 118.5, 117.4.

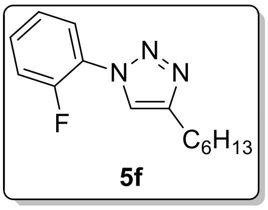
1-(2-Fluorophenyl)-4-phenyl-1*H*-1,2,3-triazole (5e)[88]



5e

White solid (85%); FT-IR (KBr, cm^{-1}) 3150, 3105, 3068, 1598, 1510, 1474, 1242, 1213, 1037, 817, 757, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 2.8 Hz, 1H), 7.99–7.93 (m, 1H), 7.85 (d, *J* = 7.1 Hz, 2H), 7.42–7.36 (m, 3H), 7.34–7.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 152.0, 148.2, 130.2, 130.1, 129.0, 128.5, 125.9, 125.4, 124.8, 120.7, 120.7, 117.2, 117.0.

1-(2-Fluorophenyl)-4-hexyl-1*H*-1,2,3-triazole (5f)

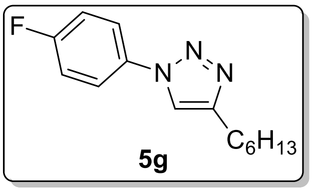


5f

White solid (78%); FT-IR (KBr, cm^{-1}) 3130, 3097, 2956, 2929, 2866, 1531, 1245, 1223, 1051, 840, 822, 533; ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.75 (d, *J* = 3.0 Hz, 1H), 7.37–7.31 (m, 1H), 7.27–7.18 (m, 2H), 2.74 (t, *J* = 7.7 Hz, 2H), 1.72–1.62 (m, 2H), 1.37–1.22 (m, 6H), 0.82 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 152.0, 148.8, 129.9, 129.8, 125.2, 124.8, 122.0, 121.9, 117.1, 116.9, 31.6, 29.3, 28.9, 25.6, 22.6, 14.1.

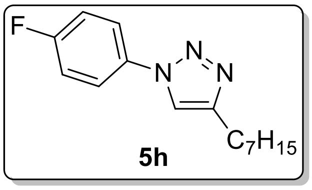
1-(4-Fluorophenyl)-4-hexyl-1*H*-1,2,3-triazole (5g)



5g

White solid (83%); FT-IR (KBr, cm^{-1}) 3131, 3095, 2956, 2919, 2856, 1521, 1245, 1224, 1051, 840, 822, 533; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.72 (m, 2H), 7.71 (s, 1H), 7.29–7.21 (m, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 1.84–1.74 (m, 2H), 1.40 (m, 6H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.0, 149.3, 133.6, 122.4, 122.3, 119.0, 116.7, 116.5, 31.6, 29.4, 28.9, 25.6, 22.6, 14.1.

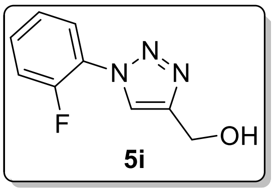
1-(4-Fluorophenyl)-4-heptyl-1*H*-1,2,3-triazole (5h)



5h

White solid (80%); FT-IR (KBr, cm^{-1}) 3132, 3096, 2955, 2917, 2871, 2848, 1524, 1468, 1245, 1224, 1047, 840, 819, 534; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 2H), 7.60 (s, 1H), 7.17–7.10 (m, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 1.69–1.62 (m, 2H), 1.38–1.15 (m, 8H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 163.5, 161.0, 149.3, 133.6, 122.4, 122.3, 119.0, 116.7, 116.5, 31.8, 29.4, 29.2, 29.1, 25.6, 22.6, 14.1.

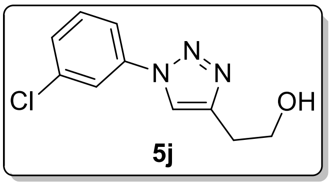
(1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl) methanol (5i)



5i

White solid (82%); FT-IR (KBr, cm^{-1}) 3268, 3101, 2939, 2875, 1595, 1489, 1239, 1046, 782, 674; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.68 (s, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.40–7.31 (m, 2H), 4.8 (s, 2H), 3.8 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 137.8, 135.6, 130.9, 128.9, 120.8, 120.1, 118.4, 56.2.

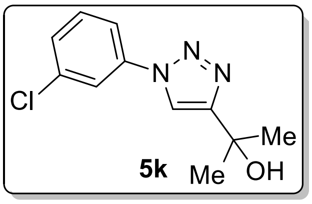
2-(1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethanol (5j)[89]



5j

White solid (85%); FT-IR (KBr, cm^{-1}) 3306, 3134, 3092, 3066, 2951, 2926, 2888, 1598, 1498, 1237, 1054, 786, 775, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.69 (s, 1H), 7.59–7.52 (m, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.35–7.31 (m, 1H), 3.95 (t, J = 5.7 Hz, 2H), 2.98 (t, J = 5.8 Hz, 2H), 2.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 137.8, 135.6, 130.8, 128.8, 120.7, 120.0, 118.4, 61.4, 28.7.

2-(1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl) propan-2-ol (5k)



5k

White solid (86%); FT-IR (KBr, cm^{-1}) 3252, 3142, 3063, 2979, 2963, 2927, 1596, 1495, 1374, 1231, 1177, 1055, 959, 907, 784, 772, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.79 (t, J = 2.0 Hz, 1H), 7.66 (ddd, J = 7.8, 1.9, 1.3 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.45–7.41 (m, 1H), 2.31 (s, 1H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 137.9, 135.6, 130.8, 128.8, 120.8, 118.5, 117.6, 68.7, 30.5.

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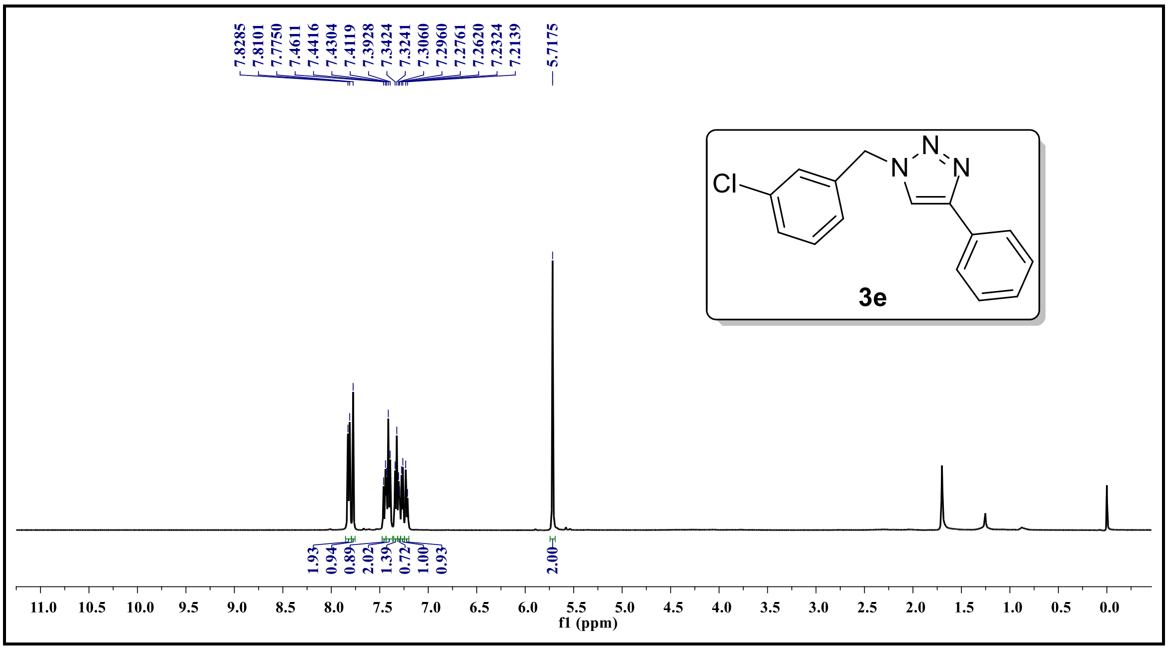
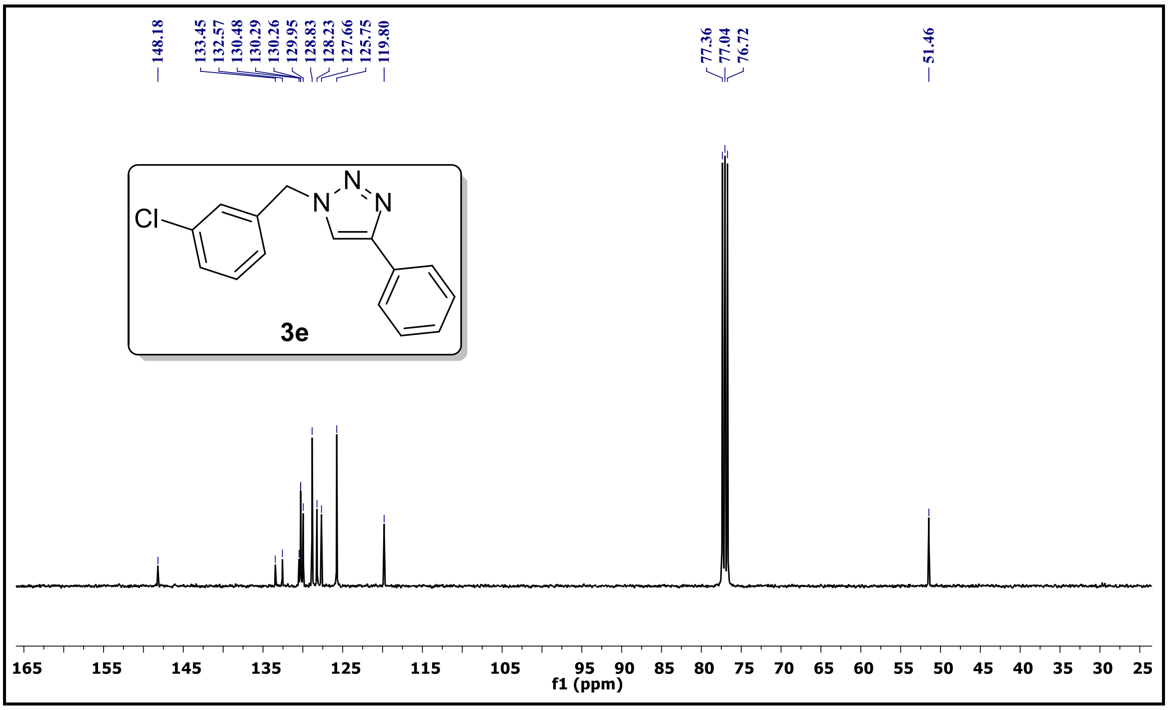
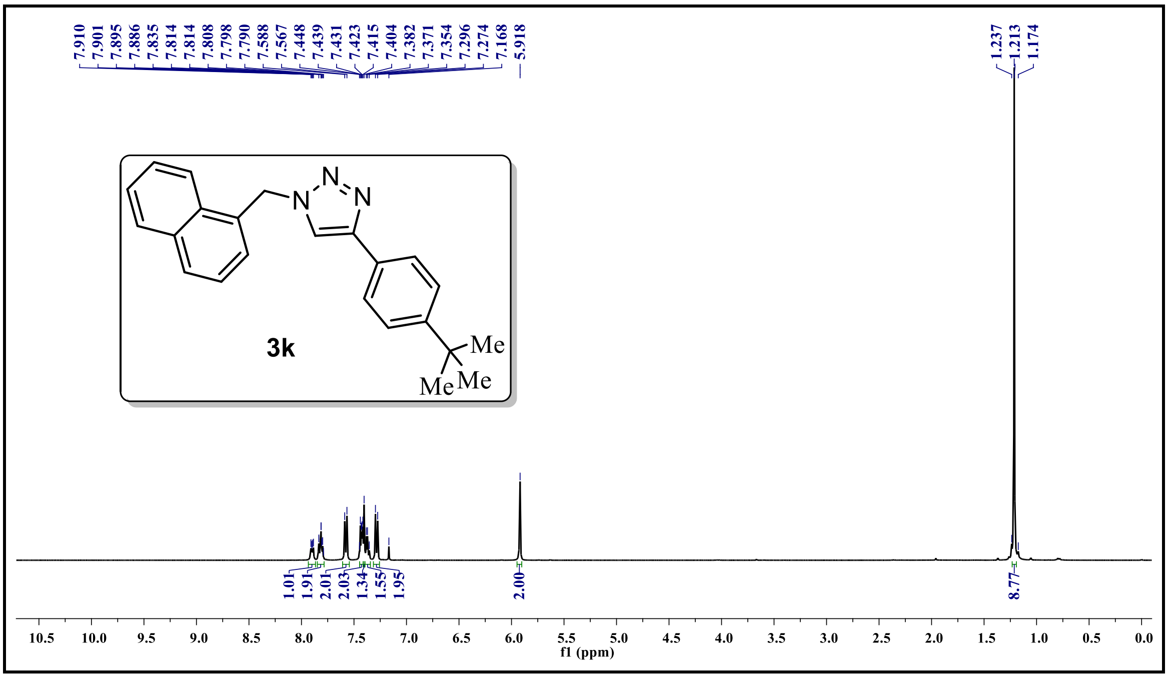
2A.8. Selected NMR (^{1}H and ^{13}C) spectra



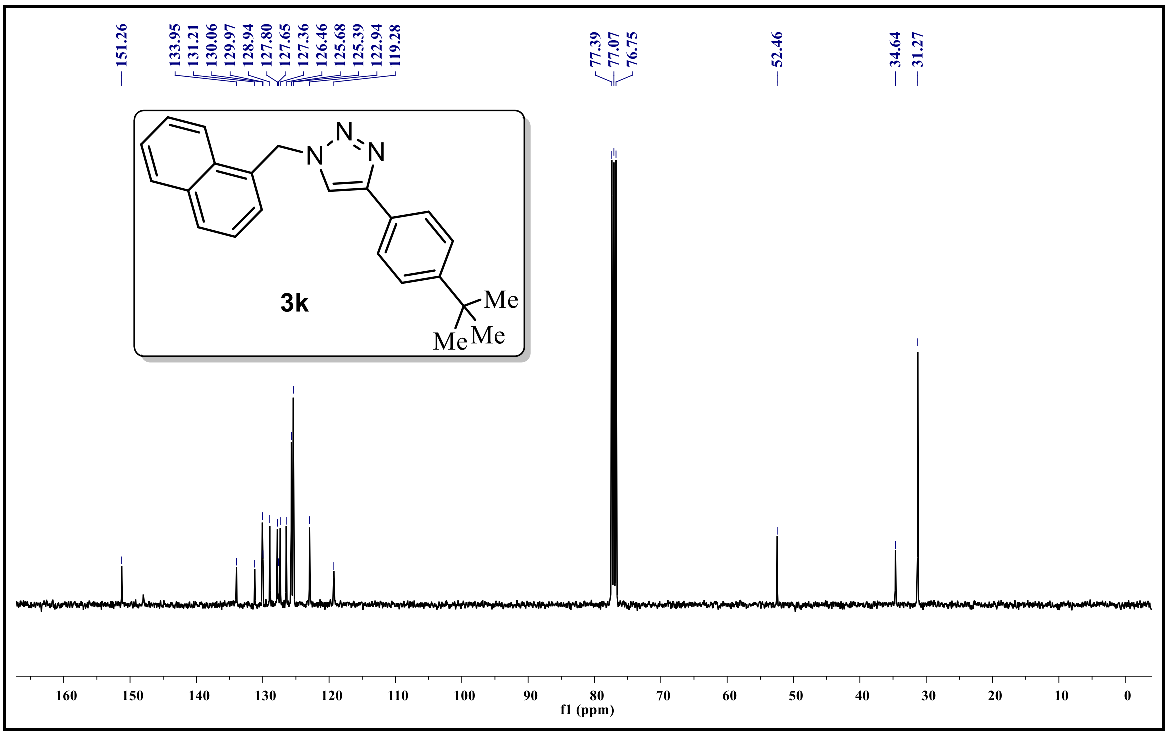
^{1}H NMR spectrum of compound **3e**



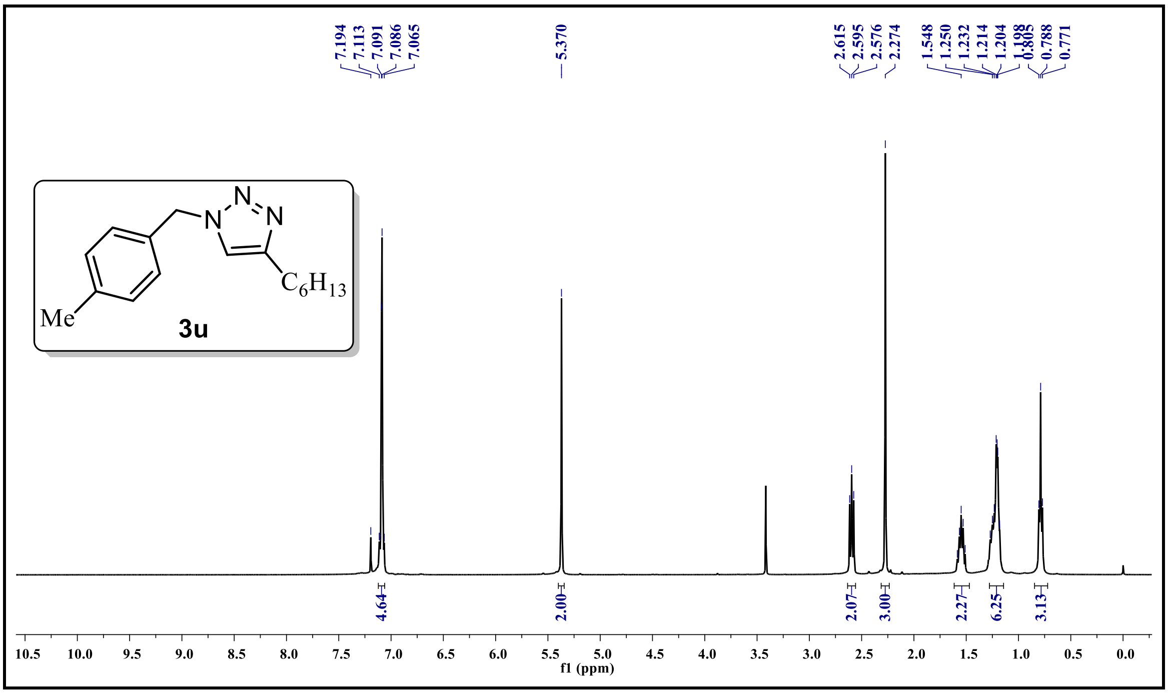
^{13}C NMR spectrum of compound **3e**



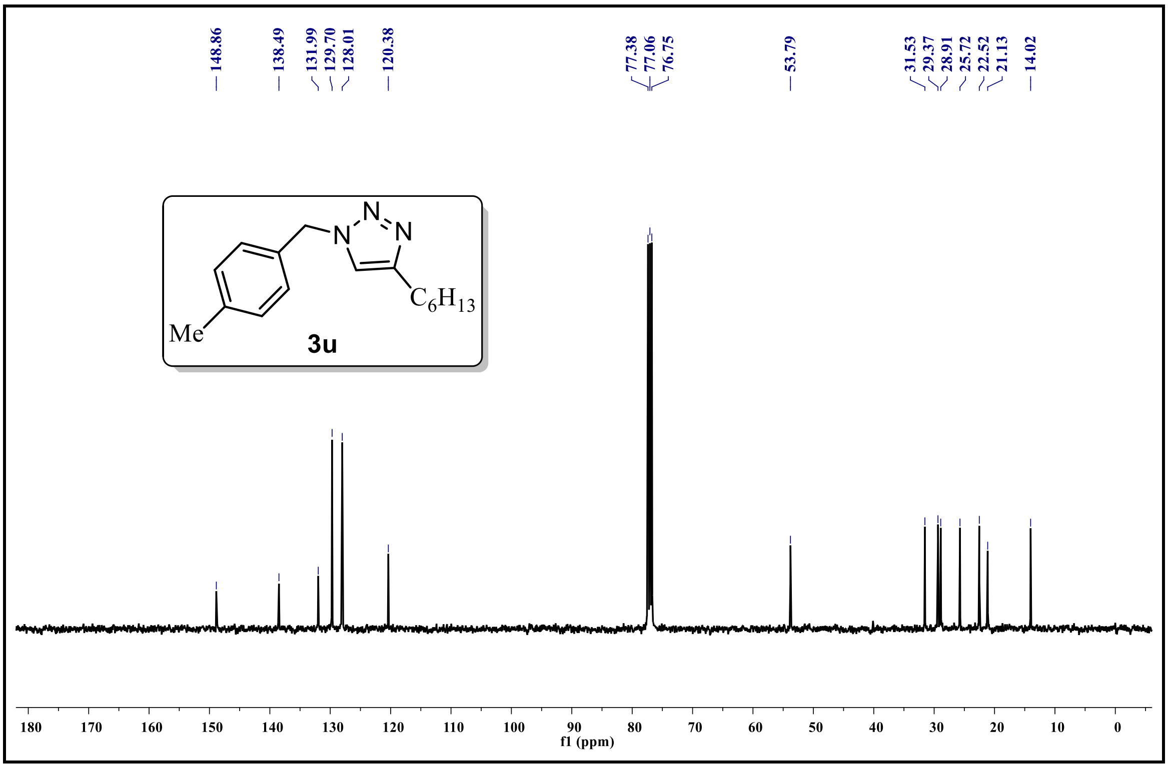
^{1}H NMR spectrum of compound **3k**



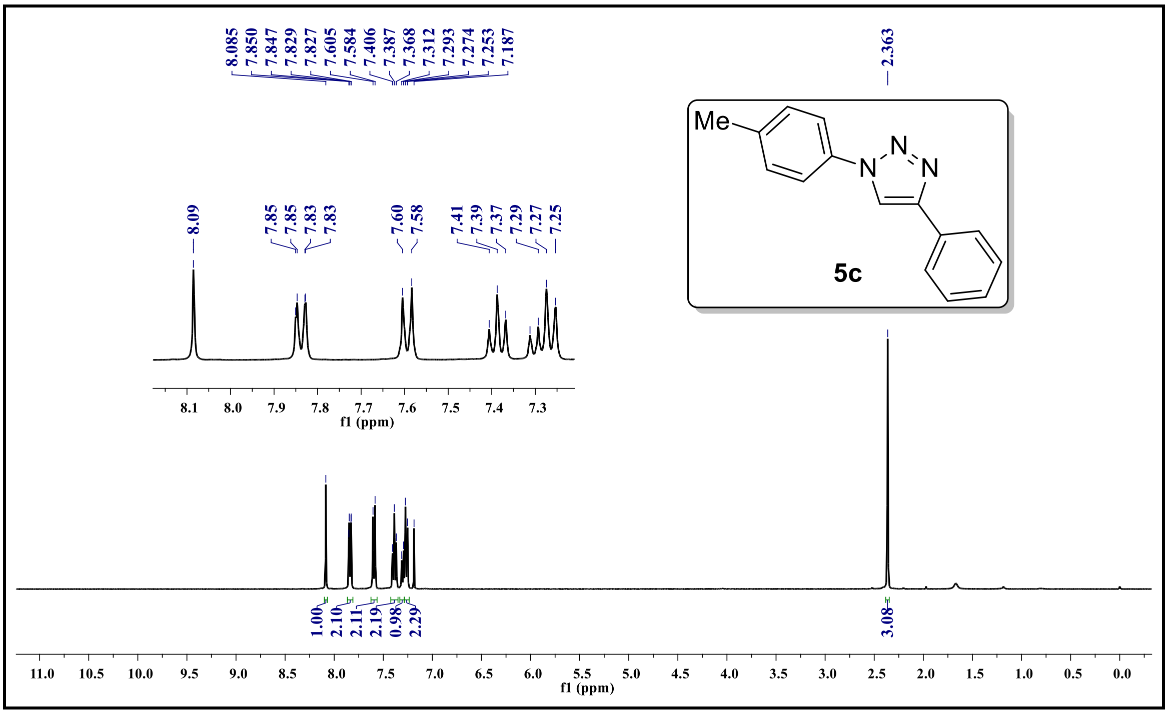
^{13}C NMR spectrum of compound **3k**



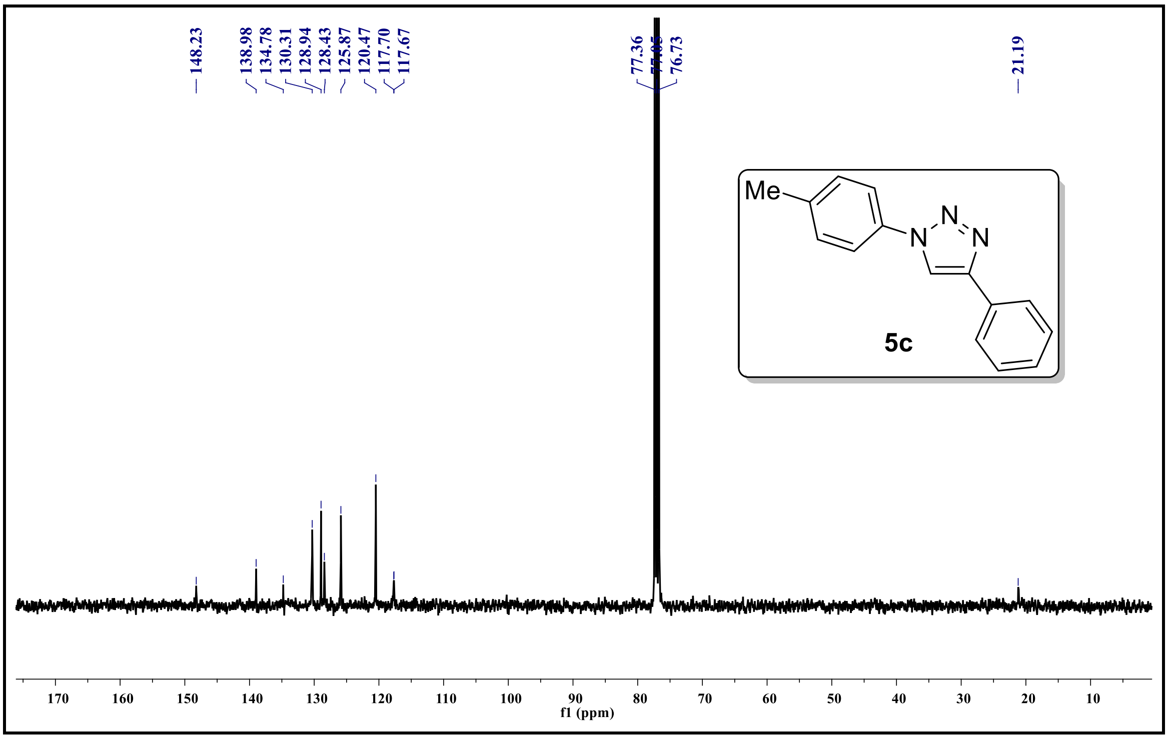
^{1}H NMR spectrum of compound **3u**



^{13}C NMR spectrum of compound **3u**



^{1}H NMR spectrum of compound **5c**



^{13}C NMR spectrum of compound **5c**

CHAPTER II (PART-B)

Facile Synthesis of 3,3’-Bis(indolyl)methanes using *in situ* Generated Copper Nanoparticles by Rongalite

2B.1. Introduction

Indoles and their derivatives are very important *N*-heterocyclic compounds, which have been readily found in various terrestrial and marine natural resources.[1–3] Bis(indolyl)methanes (BIMs) and their analogues show broad spectrum of biological and pharmacological activities such as antibiotic, antifungal, antibacterial, antioxidant, analgesic, antihyperglycemic, antiviral and anti-inflammatory.[4-10] The derivatives of BIMs exhibit anticancer activity through the inhibition of the growth of cell lines such as lung,[11] colon,[12] prostate,[13] and pancreatic[14]. In addition, the dimeric 3,3′-bis-(indolyl)methane efficiently reduces the growth of breast cancer cell lines.[15] Furthermore, BIMs are used as a *N,N'* donor ligands for the copper-catalyzed Sonogashira coupling reaction.[16]

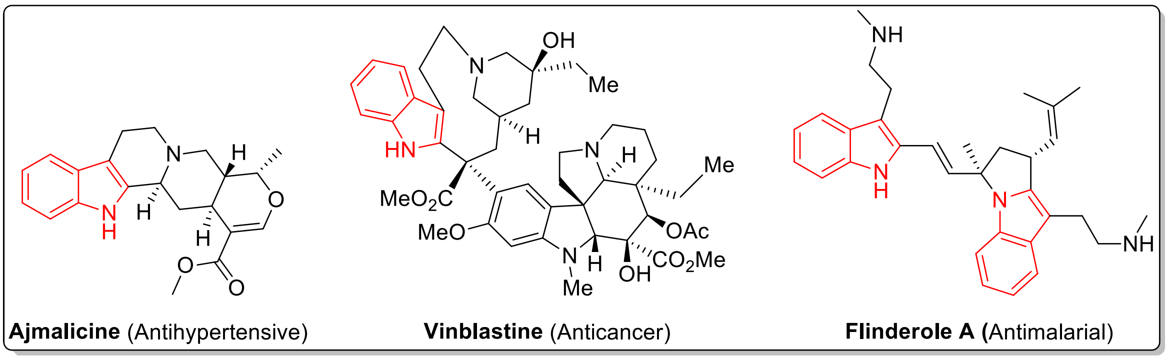
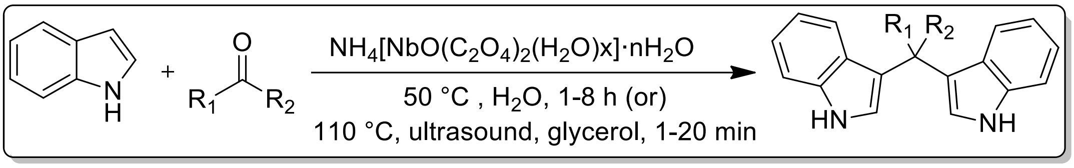


Figure 2B.1 Selective examples of medicinally active indole moieties

Conventionally, BIMs were synthesized by the electrophilic substitution of indoles with aldehydes or ketones in presence of broad range of acid catalysts.[17] Most of the reported methods require high temperatures, long reaction times and high catalyst loadings. Therefore, owing to their diverse biological and pharmacological activities, a great deal of interest has been focused on the development of efficient synthetic strategies for the synthesis of BIMs.

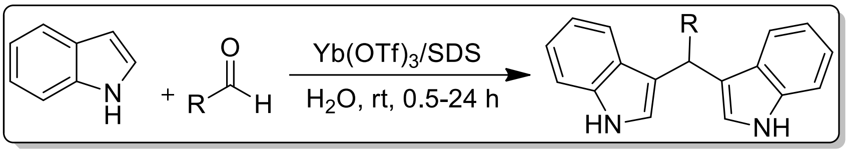
2B.1.1. Different synthetic approaches for the synthesis of 3,3'-Bis(indolyl)methanes derivatives

Mendes and co-workers used commercially available, air and moisture insensitive, ammonium niobium oxalate (ANO) $NH_4[NbO(C_2O_4)_2(H_2O)x]\cdot nH_2O$ as a green catalyst for the synthesis of BIMs under conventional heating (50 °C) in water or under sonication (110 °C) in glycerol solvent (Scheme 2B.1).[18]



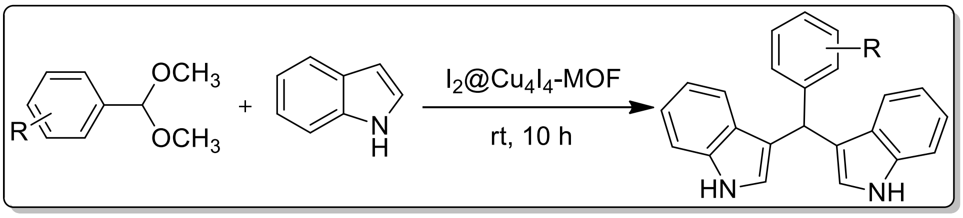
Scheme 2B.1

Tornquist et al. developed a new methodology for the synthesis of BIMs using recyclable and reusable, ytterbium triflate ($Yb(OTf)_3$)/sodium dodecyl sulfate (SDS) catalyst. In this report BIMs were produced by the reaction of indoles with aldehydes in presence of catalyst in aqueous media at ambient temperature (Scheme 2B.2).[19]



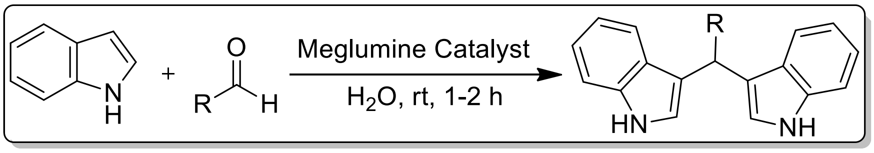
Scheme 2B.2

Zhu et al. reported solvent-free synthesis of BIMs using highly efficient heterogeneous catalyst, $I_2@Cu_4I_4$-MOF host–guest system by Friedel–Crafts alkylation of indoles with acetals in tandem at room temperature (Scheme 2B.3).[20]



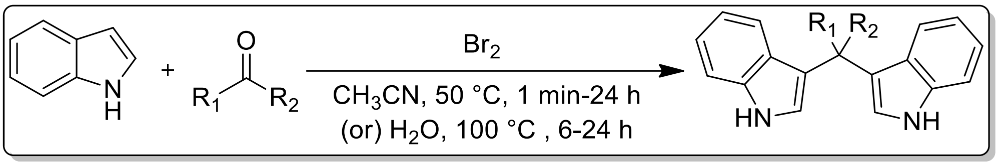
Scheme 2B.3

Nemallapudi et al. synthesized BIMs by the reaction of indoles with aldehydes in presence of meglumine catalyst at ambient temperature under aqueous media (Scheme 2B.4).[21]



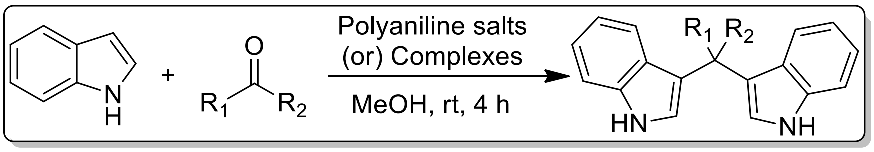
Scheme 2B.4

Liang and co-workers developed a new methodology for the synthesis of BIMs using a very cheap elemental bromine (Br_2) as potent Lewis acid catalyst. In this report indoles and carbonyl compounds were reacted in presence very less catalyst loading of Br_2 in either aqueous or organic solvents to afford BIMs (Scheme 2B.5).[22]



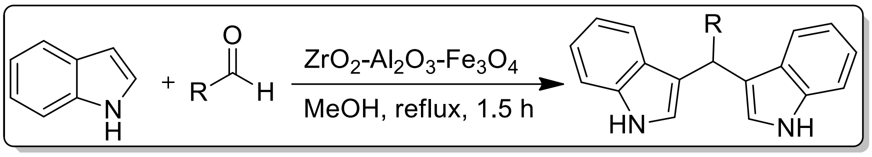
Scheme 2B.5

Palaniappan and co-workers prepared polyaniline salts and complexes using reported methods. Further, they have used these eco-friendly polyaniline salts or complexes as a catalyst for the efficient synthesis of BIMs at room temperature (Scheme 2B.6).[23]



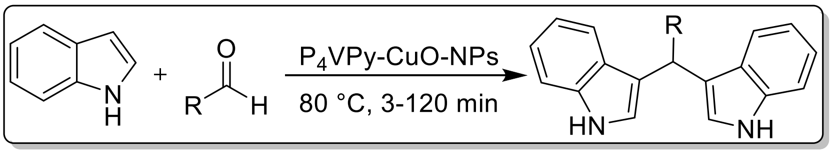
Scheme 2B.6

Wang et al. reported the synthesis and characterization of series of magnetically separable solid acid nano composites $ZrO_2–Al_2O_3–Fe_3O_4$. Further, they have investigated the catalytic behaviour of $ZrO_2–Al_2O_3–Fe_3O_4$ for the synthesis of BIMs (Scheme 2B.7).[24]



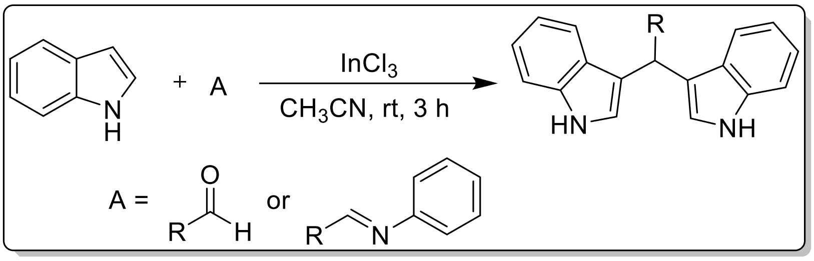
Scheme 2B.7

Shirini and co-workers synthesized CuO nanoparticles immobilized on poly(vinylpyridine polymer ($P_4VPy–CuO$) under ultrasound irradiation and used as a reusable solid acid catalyst for the solvent free synthesis of BIMs (Scheme 2B.8).[25]



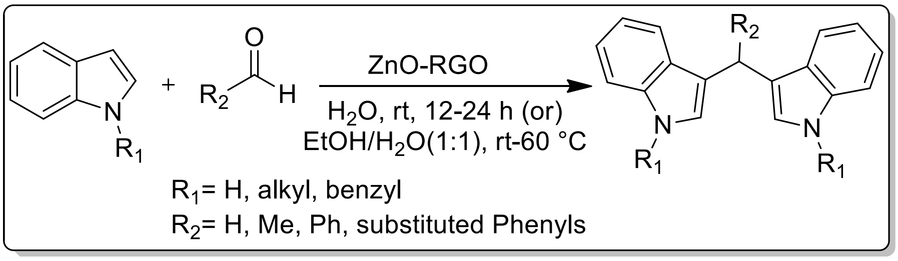
Scheme 2B.8

Babu et al. synthesized BIMs using Friedel crafts alkylation of indoles with aldehydes or Schiff bases in presence of anhydrous $InCl_3$ catalyst at room temperature (Scheme 2B.9).[26]



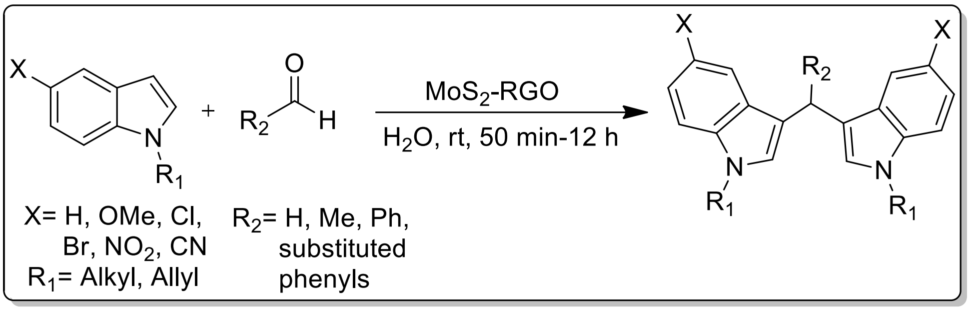
Scheme 2B.9

Krishnan and co-workers synthesized heterogeneous ZnO-RGO nanohybrid using hydrothermal method and reported the detailed characterization of ZnO-RGO using various techniques. In this report they described the catalytic activity of ZnO-RGO nanohybrid towards the synthesis of BIMs and indole alkaloids in water and ethanol as reaction medium (Scheme 2B.10).[27]



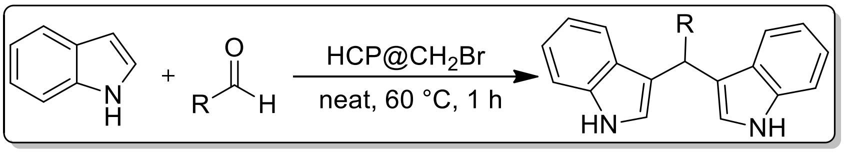
Scheme 2B.10

Bahuguna et al. synthesized MoS_2-RGO nanocomposite using hydrothermal method and also explained about the characterisation of MoS_2-RGO nanocomposite using various techniques. Further, they have investigated the efficiency of MoS_2-RGO nanocomposite as a heterogeneous catalyst for the one pot synthesis of indole alkaloids in water at room temperature (Scheme 2B.11).[28]



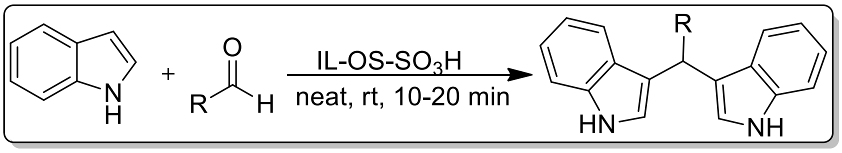
Scheme 2B.11

Kalla et al. synthesized environmentally benign and reusable hyper-cross-linked polyphenanthrene and polypyrene microspheres. Further, unreacted bromomethyl groups were decorated on the surface of the resultant microspheres. These microspheres were used as efficient catalysts for the electrophilic substitution of indoles with aldehydes (Scheme 2B.12).[29]



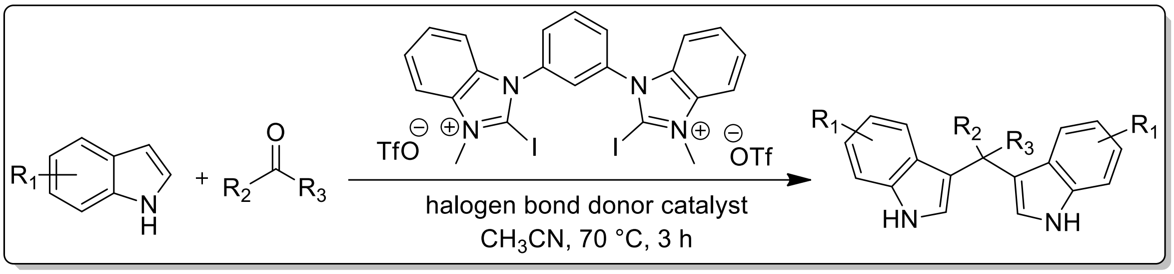
Scheme 2B.12

Norouzi et al. reported the synthesis and characterization of sulfonic acid-containing hybrid organic–inorganic material with ionic liquid framework (IL-OS-SO_3H). Later, they have applied IL-OS-SO_3H as an efficient reusable and recoverable catalyst for the solvent free synthesis of BIMs using indoles and aldehydes at room temperature (Scheme 2B.13).[30]



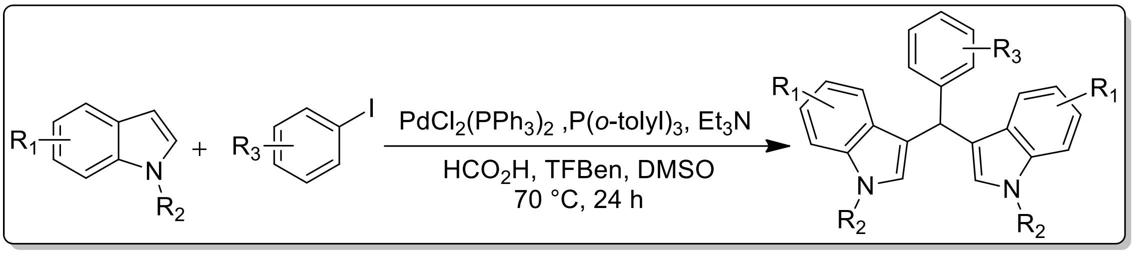
Scheme 2B.13

Liu et al. reported the bidentate halogen bond donor catalyzed electrophilic substitution of indoles with aldehydes and ketones to afford a wide range of BIMs in acetonitrile solvent at 70 °C (Scheme 2B.14).[31]



Scheme 2B.14

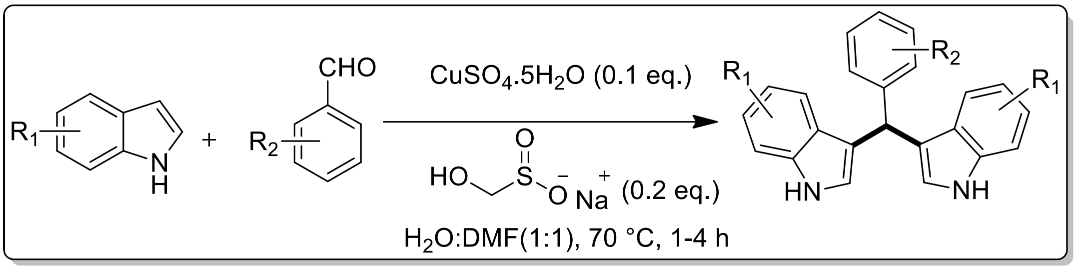
Qi et al. used benzene-1,3,5-triyl triformate (TFBen) as the solid CO source for the efficient palladium catalyzed synthesis BIMs using indoles and aryl iodides in DMSO solvent at 70 °C temperature (Scheme 2B.15).[32]



Scheme 2B.15

2B.2. Present work

There were numerous methods for the synthesis of BIMs using various nanoparticles in the literature, including sucrose nanoparticles on BF_3-grafted Fe_3O_4 core,[33] nano-Fe_3O_4,[34] L-proline modified magnetic nanoparticles,[35] hexamethylenetetramine on Fe_3O_4/SiO_2 core nanoparticles,[36] $H_5PW_{10}V_2O_{40}$/pyridino-Fe_3O_4 nanoparticles,[37] Fe_3O_4 on carbon core shell nanoparticles[38] etc. In all the cases they have prepared nanoparticles using different methods and investigated the efficiency of catalyst for the synthesis of BIMs. But in this chapter, we have generated Cu nanoparticles *in situ* by the reduction of $CuSO_4.5H_2O$ using rongalite. Further, these Cu nanoparticles used as an efficient catalyst for the electrophilic substitution of indoles with carbonyl compounds leads to form BIMs (Scheme 2B.16).



Scheme 2B.16

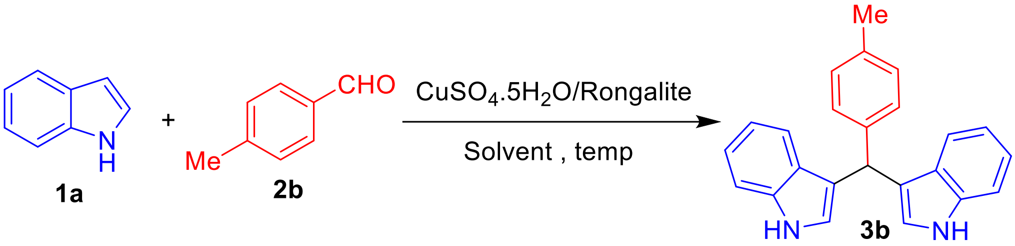
By applying above protocol for various indoles and carbonyl compounds, we have synthesized a wide range of bis(indolyl)methanes with good to excellent yields.

2B.3. Results and discussion

A series of reactions were carried out for the optimization of reaction conditions for the synthesis of BIMs and results were summarized in Table 2B.1. For the model reaction, we have selected indole **1a** and *p*-methyl benzaldehyde **2b** as substrates. Initially, indole **1a** and *p*-methyl benzaldehyde **2b** were reacted with each other at room temperature in presence of $CuSO_4.5H_2O$ (0.5 equiv.), rongalite (2.0 equiv.) in water (Table 2B.1, entry 1) and produced desired product **3b** with moderate yield. Then, we have investigated the reactions at different temperatures such as 50 °C and 70 °C (Table 2B.1, entries 2-3) to know the effect of temperature on the rate of reaction and reaction yield. From these experiments, we came to know that as we increasing the temperature of the reaction, we can obtain desired product in less time with better yields. To assess the effect of stoichiometry of rongalite, we have carried out a reaction using 1.0 equivalents of rongalite (Table 2B.1, entry 4) but there was no change in both reaction yield and rate of reaction observed.

Furthermore, we have investigated the reactions in various mixture of solvents in 1:1 ratio such as THF/ H_2O, MeOH/ H_2O, EtOH/ H_2O, CH_3CN/ H_2O, DMSO/ H_2O, Acetone/ H_2O, DMF/H_2O (Table 2B.1, entries 5-11) to know the effect of organic solvents. Among all the mixture of solvents, DMF/H_2O gave 95% of desired product (Table 2B.1, entry 11). This may be due to more solubility of the product in mixture of solvents. There was no effect on both reaction rate and product yield was observed by decreasing the concentrations of $CuSO_4.5H_2O$ and rongalite (Table 2B.1, entries 12-13). Finally, We have conducted one more control experiment with $CuSO_4.5H_2O$, which is give very little amount of the desired product after 24 h (Table 2B.1, entry 14).

Table 2B.1. Optimization of reaction conditions of synthesis of BIMs[a,b]

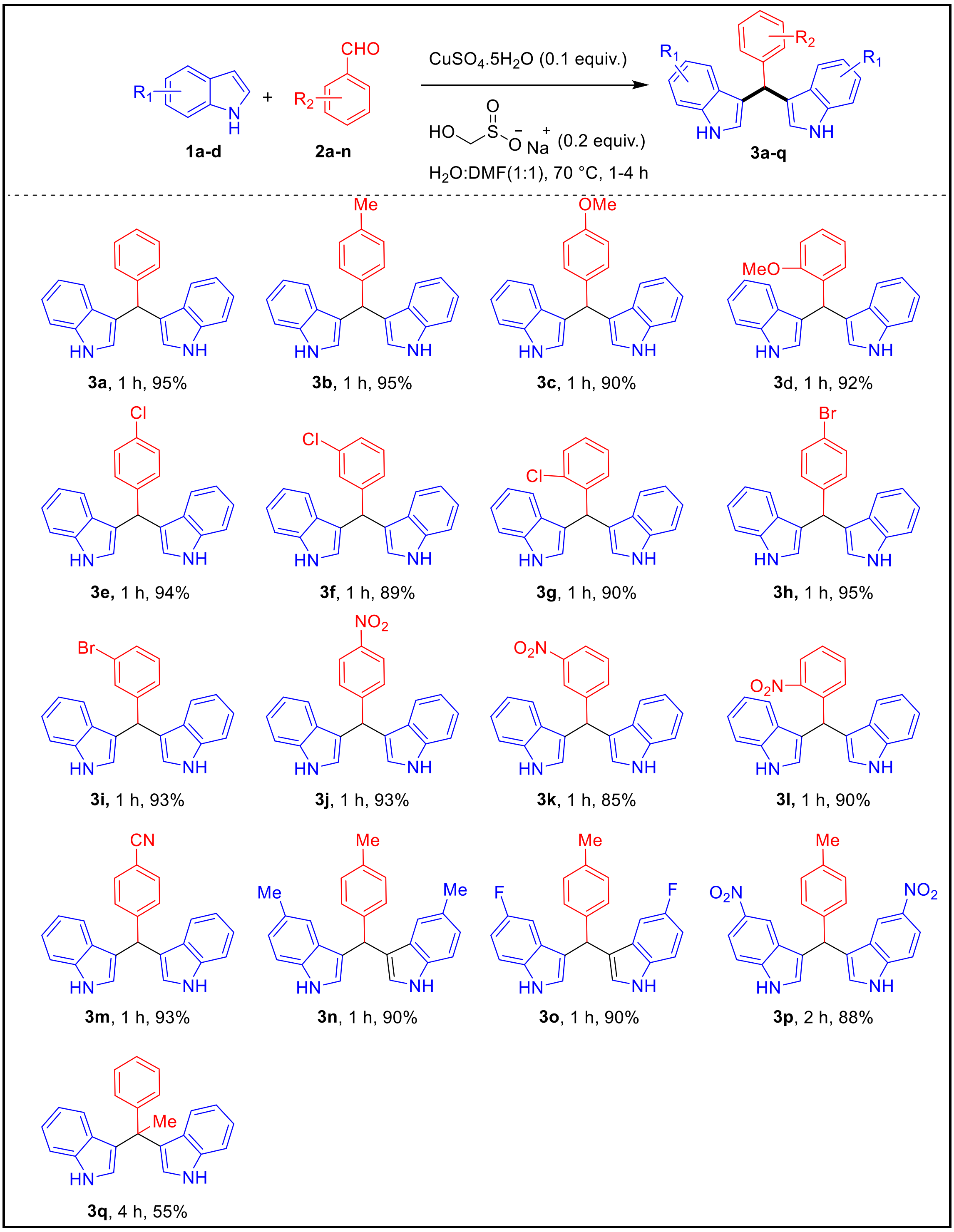


S.No	Solvent	$CuSO_4.5H_2O$ (equiv.)	Rongalite (equiv.)	Temperature (°C)	Time	Yield[b] (%)
1	H_2O	0.5	2.0	rt	6 h	42
2	H_2O	0.5	2.0	50	2 h	64
3	H_2O	0.5	2.0	70	1 h	85
4	H_2O	0.5	1.0	70	1 h	85
5	THF/ H_2O	0.5	1.0	70	3 h	70
6	MeOH/ H_2O	0.5	1.0	70	2 h	45
7	EtOH/ H_2O	0.5	1.0	70	2 h	56
8	CH_3CN/ H_2O	0.5	1.0	70	2.5 h	50
9	DMSO/ H_2O	0.5	1.0	70	1 h	65
10	Acetone/ H_2O	0.5	1.0	70	3 h	53
11	DMF/ H_2O	0.5	1.0	70	1 h	95
12	DMF/ H_2O	0.2	0.4	70	1 h	95
13	DMF/ H_2O	0.1	0.2	70	1 h	95
14	DMF/ H_2O	0.1	-	70	24 h	5

[a] Reaction conditions: Indole **1a** (1.0 mmol), *p*-methyl benzadehyde **2b** (0.6 mmol), $CuSO_4.5H_2O$ and rongalite in solvent (1.0 mL). [b] Yields are of isolated pure products.

Thus, the optimized reaction conditions are 1.0 mmol of indole **1a**, 0.6 mmol *p*-methyl benzaldehyde, $CuSO_4.5H_2O$ (0.1 equiv.) and rongalite (0.2 equiv.) in 1 mL of DMF/H_2O (1:1) at 70 °C for 1 h as shown in (Table 2B.1, entry 13).

Table 2B.2. Synthesis of Bis(indolyl)methane derivatives[a,b]



[a]Reaction conditions: Indole **1a-d** (1.0 mmol), benzadehyde **2a-n** (0.6 mmol), $CuSO_4.5H_2O$ (0.1 equiv.) and rongalite (0.2 equiv.) in DMF/H_2O (1.0 mL) in 1:1 ratio at 70 °C. [b]Yields are of isolated pure products.

To investigate the generality of the reaction, we have applied optimized condition (Table 2B.1, entry 13) to various substituted indoles **1a-d** and substituted benzaldehydes **2a-n** to afford corresponding BIMs and results were summarized in Table 2B.2. Indole was reacted with various benzaldehydes containing electron donating and electron withdrawing groups without any hurdle and afforded respective BIMs with good to excellent yields (Table 2B.2, **3b-d, 3j-m**). Similarly halogenated benzaldehydes (*ortho*-, *meta*-, *para*-) also underwent reaction smoothly with indoles to furnish the corresponding BIMs and showed little effect on product yields (Table 2B.2, **3e-i**).

Later, we have applied this protocol to various substituted indoles. It is worth to mention that electron donating and electron withdrawing groups on indoles did not hamper the reaction yields (Table 2B.2, **3n-p**). Finally, acetophenone also participated in our protocol without any difficulty and gave corresponding condensation product with comparatively less yield than benzaldehydes (Table 2B.2, **3q**). This may be due to the steric hindrance.

Next, we have focused on the synthesis of copper nanoparticles by rongalite in order to unveil the reaction mechanism for the synthesis of bisindolylmethanes (Figure 2B.1). The CuNPs were prepared according to the following protocol: To a 20 mL of 0.5 molar $CuSO_4.5H_2O$ solution in a round bottom flask were added rongalite (2 equiv.) and stirred at 70 °C for 20 minutes.

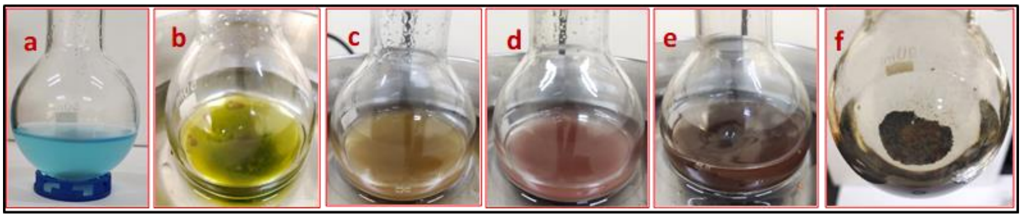


Figure 2B. 1. Synthesis of CuNPs with rongalite: Color change observed during the Cu-NPs formation in different time intervals with rongalite, (a) $CuSO_4.5H_2O$ (b) After addition of rongalite (c) 5 min (d) 10 min (e) 15 min (f) 20 min.

Finally, we have observed the formation of blackish brown colour precipitate from blue colour (Figure 2B.1, **a–f**), which was then centrifuged at 10000 rpm for 15 min, washed with water (5 times), dried under inert condition and analyzed by powder XRD (PXRD).

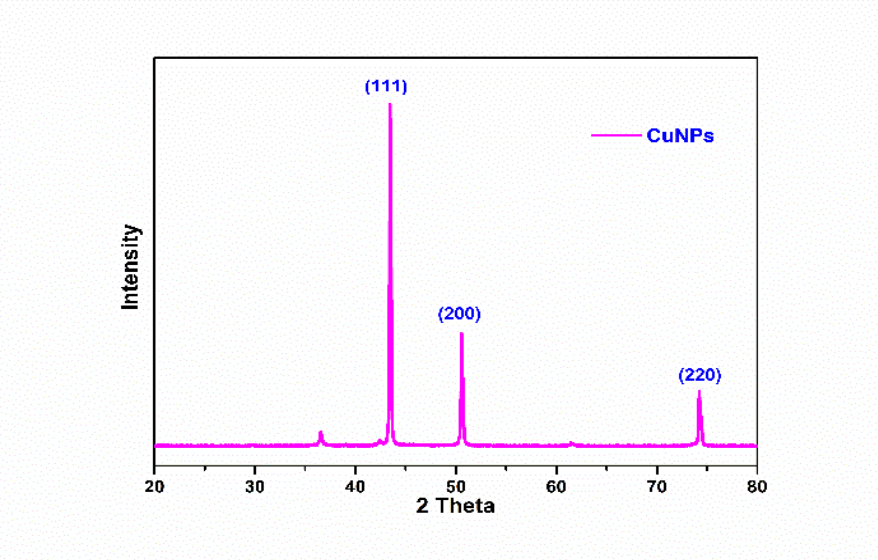
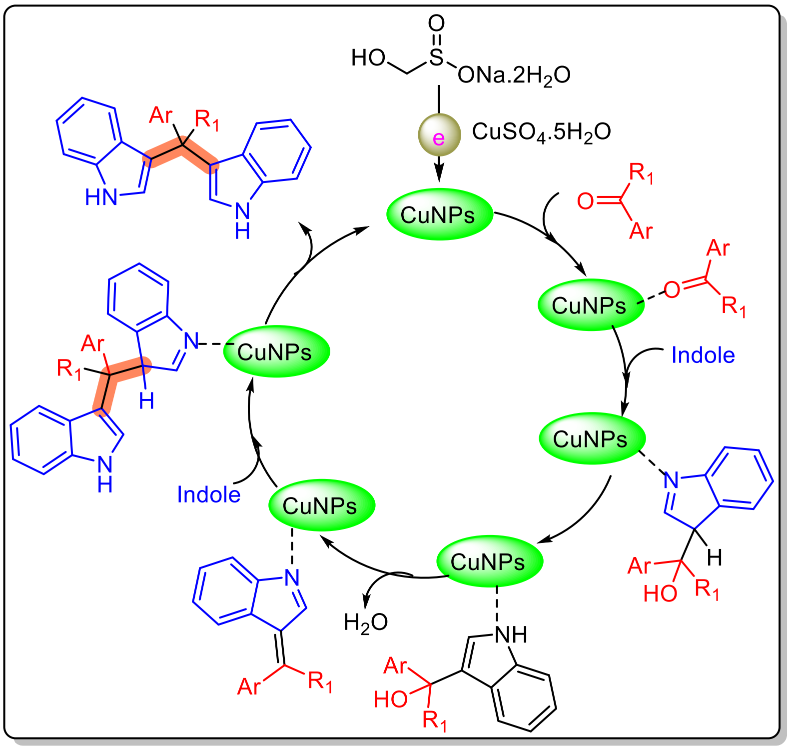


Figure 2B.2. Powder XRD pattern of synthesized CuNPs.

The PXRD studies were used to investigate both the crystal structure and the average crystallite size of nanoparticles (Figure 2B.2). The PXRD patterns is showed the presence of face centered cubic (f.c.c.) Cu (JCPDS, card no. 04–0836). The peaks at 43.45°, 50.57°, 74.24° belong to (111), (200), (220) planes of CuNps. The average crystallite size of CuNPs was determined by using Scherrer's equation that is about to be 32 nm. This PXRD data confirmed that the sample contains only Copper(0) NPs (Figure 2B.2).

A plausible tcondensation reaction mechanism is proposed in the Scheme 2B.17 based on our obervations and literature reports.[39] Initially, rongalite reduces $CuSO_4$ to form CuNPs *in situ via* single electron transfer. Further, In the presence of CuNPs, the electrophilicity of carbonyl carbon propably increased and it readily reacts with indole to afford the corresponding 3-arylidine-3H-indole intermediate *via* dehydration. This intermediate on reaction with second molecule of indole followed by rearrangement affords the final product.



Scheme 2B.17. Plausible mechanism for the synthesis of bisindolylmethanes.

2B.4. Conclusions

In this chapter we have developed a new synthetic strategy for the synthesis of bis(indolyl)methanes using *in situ* generated Cu nanoparticles. Less catalyst loading, less reaction time, high reaction yields are the advantages of this synthetic methodology. This protocol tolerates different substitutions (halogens, EDG and EWG) on Indole and as well as benzaldehydes. By applying this protocol to wide variety of indoles and carbonyl compounds, we have synthesized 17 compounds with 55–95 % of yield.

2B.5. Experimental Section

General Information. Substituted Indoles, benzaldehydes, $CuSO_4.5H_2O$ and rongalite were purchased from a commercial source and used as received. Reactions were conducted in round bottom flasks. Thin layer chromatography was performed on 200 µm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. ^1H NMR spectra were obtained at 400 MHz in $CDCl_3$ and were referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ and were referenced to the solvent resonance. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) were in hertz (Hz).

Standard abbreviations were used to designate resonance multiplicities. Melting points were determined with a melting point apparatus and are uncorrected.

General procedure for the synthesis of Bis(indolyl)methanes (3a-q) A mixture of Indole **1a-d** (1.0 mmol), carbonyl compound **2a-n** (0.6 mmol), $CuSO_4.5H_2O$ (0.1 equiv.) and rongalite (0.2 equiv.) in 1.0 mL of DMF/H_2O (1:1 ratio) was taken in an oven dried round bottom flask, equipped with a magnetic stirring bar. The resultant reaction mixture was stirred at 70 °C for 1 h to 4 h. After completion of reaction (monitored by TLC), reaction mixture was extracted with water and ethylacetate (3 x 20 mL). The extracted organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure using a rotatory evaporator. Purification of the crude reaction mixture was done by silica gel column chromatography using hexanes and ethylacetate as eluent.

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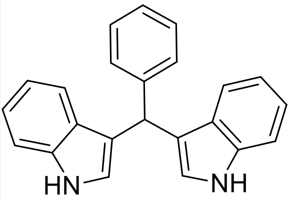
2B.6. Spectral data

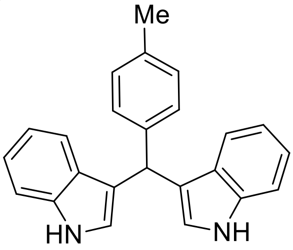
3,3'-(phenylmethylene)bis(1H-indole) (3a)[39c]



3a

White solid (95%); FT-IR (KBr, cm^{-1}) 3422, 2985, 2854, 1706, 1616, 1555, 1093, 953, 852, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.0 Hz, 2H), 7.28 (t, J = 7.0 Hz, 2H), 7.22–7.19 (m, 1H), 7.17 (t, J = 7.0 Hz, 2H), 7.00 (t, J = 7.5 Hz, 2H), 6.66 (s, 2H), 5.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 136.9, 128.9, 128.4, 127.2, 126.3, 123.8, 122.1, 120.1, 119.9, 119.4, 111.2, 40.4.

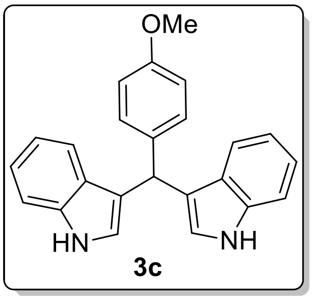
3,3'-(*p*-tolylmethylene)bis(1H-indole) (3b) [39]



3b

White solid (95%); FT-IR (KBr, cm^{-1}) 3409, 3050, 2919, 2854, 1703, 1606, 1455, 1415, 1336, 1217, 1091, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.26–7.17 (m, 2H), 7.14 (t, J = 7.2 Hz, 2H), 7.06 (d, J = 7.8 Hz, 2H), 7.01–6.95 (m, 2H), 6.59 (s, 2H), 5.83 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 136.7, 135.5, 129.0, 128.6, 127.1, 123.6, 121.9, 120.0, 119.9, 119.2, 111.1, 104.0, 39.8, 21.1.

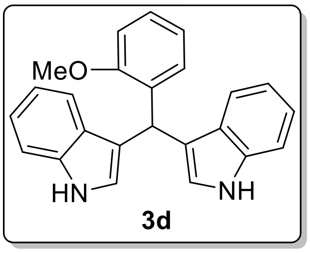
3,3'-((4-methoxyphenyl)methylene)bis(1H-indole) (3c)[39c]



3c

White solid (90%); FT-IR (KBr, cm^{-1}) 3410, 3052, 2926, 2854, 1712, 1601, 1455, 1216, 956, 787, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 2H), 7.38–7.35 (m, 4H), 7.26 (d, J = 8.6 Hz, 2H), 7.13 (t, J =7.6 Hz, 2H), 6.97 (t, J = 7.6 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.71 (s, 2H), 5.83 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 137.3, 136.9, 130.0, 127.5, 123.9, 122.4, 120.4, 120.2, 119.6, 114.0, 111.6, 55.7, 39.9.

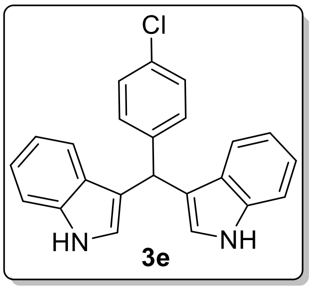
3,3'-((2-methoxyphenyl)methylene)bis(1H-indole) (3d)[40]



3d

White solid (92%); FT-IR (KBr, cm^{-1}) 3408, 3053, 2931, 2834, 1702, 1596, 1488, 1455, 1337, 1241, 1091, 1026, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.14–7.05 (m, 4H), 6.92 (t, J = 7.4 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.58 (s, 2H), 6.28 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 136.7, 132.4, 129.7, 127.3, 127.2, 123.5, 121.8, 120.4, 120.1, 119.6, 119.1, 111.0, 110.7, 55.8, 32.1.

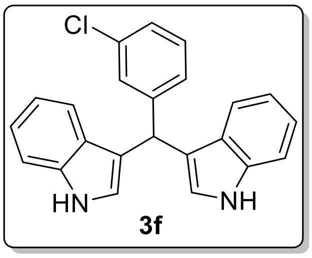
3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (3e)[39c]



3e

White solid (94%); FT-IR (KBr, cm^{-1}) 3407, 3054, 2923, 2855, 1702, 1612, 1487, 1455, 1416, 1088, 1012, 786, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.34 (t, J = 8.5 Hz, 4H), 7.29–7.20 (m, 4H), 7.16 (t, J = 7.6 Hz, 2H), 7.00 (t, J = 7.5 Hz, 2H), 6.59 (s, 2H), 5.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 136.7, 131.8, 130.1, 128.4, 126.9, 123.7, 122.1, 119.8, 119.4, 119.2, 111.2, 39.6.

3,3'-((3-chlorophenyl)methylene)bis(1H-indole) (3f)[41]

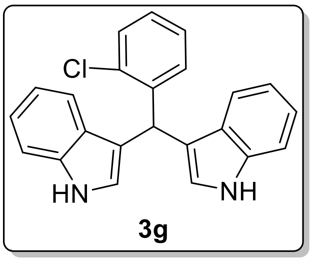


3f

White solid (89%); FT-IR (KBr, cm^{-1}) 3409, 3054, 1702, 1455, 1416, 1336, 1092, 794, 741, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.39 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.23–7.17 (m, 2H), 7.15 (d, J = 7.4 Hz, 2H), 7.13–7.05 (m, 2H), 7.01 (t, J = 7.5 Hz, 2H), 6.59 (s, 2H), 6.33 (s, 1H);

^{13}C NMR (100 MHz, CDCl$_3$) δ 141.3, 136.7, 134.0, 130.4, 129.5, 127.5, 127.0, 126.7, 123.8, 122.0, 119.9, 119.3, 118.4, 111.1, 36.6.

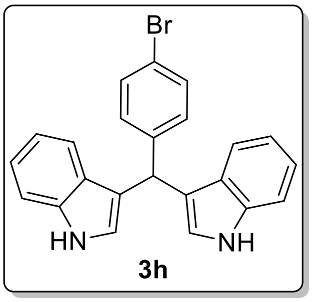
3,3'-((2-chlorophenyl)methylene)bis(1H-indole) (3g)[42]



3g

White solid (90%); FT-IR (KBr, cm^{-1}) 3408, 3036, 2920, 2865, 1705, 1601, 1545, 1123, 936, 852, 743; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.91 (s, 2H), 7.40–7.34 (m, 4H), 7.25–7.01 (m, 6H), 6.86 (d, J = 7.6 Hz, 2H), 6.63 (s, 2H), 6.34 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 141.2, 136.7, 133.9, 130.3, 129.5, 127.5, 127.0, 126.6, 123.7, 122.0, 119.8, 119.3, 118.4, 111.0, 36.6.

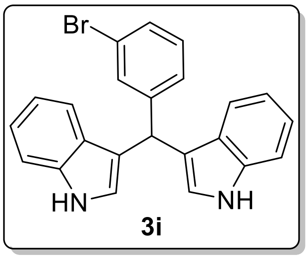
3,3'-((4-bromophenyl)methylene)bis(1H-indole) (3h)[42]



3h

White solid (95%); FT-IR (KBr, cm^{-1}) 3406, 3016, 2952, 2866, 1702, 1455, 1415, 1335, 1093, 742, 693; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (s, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.27 (dd, J = 17.3, 12.5 Hz, 4H), 7.04 (t, J = 7.4 Hz, 2H), 6.87 (d, J = 7.4 Hz, 2H), 6.83 (s, 2H), 5.83 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.2, 137.8, 132.4, 131.6, 128.4, 124.8, 123.2, 120.7, 119.9, 119.5, 119.1, 111.2, 39.9.

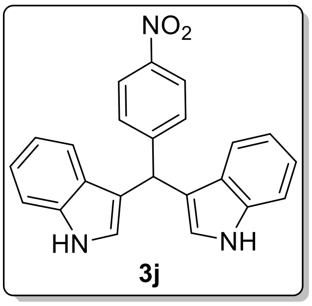
3,3'-((3-bromophenyl)methylene)bis(1H-indole) (3i)[43]



3i

White solid (93%); FT-IR (KBr, cm^{-1}) 3408, 3053, 2852, 1703, 1455, 1416, 1337, 1091, 741, 694, 679; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (s, 2H), 7.41 (s, 1H), 7.29 (d, J = 8.7 Hz, 3H), 7.18 (d, J = 9.7 Hz, 2H), 7.07 (dt, J = 15.8, 7.5 Hz, 4H), 6.94 (t, J = 7.5 Hz, 2H), 6.54 (s, 2H), 5.76 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.5, 136.7, 131.7, 129.9, 129.4, 127.4, 126.9, 123.7, 122.4, 122.1, 119.8, 119.4, 118.9, 111.2, 40.0

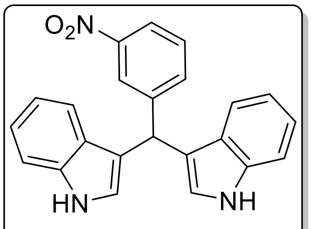
3,3'-((4-nitrophenyl)methylene)bis(1H-indole) (3j)[42]



3j

Yellow solid (93%); FT-IR (KBr, cm^{-1}) 3455, 3422, 3385, 2923, 2850, 1591, 1506, 1455, 1338, 1010, 745, 699; ^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-d_6) δ 9.90 (s, 2H), 8.09 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.12 (s, 2H), 6.94 (t, J = 7.6 Hz, 2H), 6.70 (s, 2H), 5.97 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-d_6) δ 147.9, 141.4, 132.1, 124.7, 121.7, 119.2, 118.5, 116.7, 114.3, 114.0, 112.3, 106.7, 39.1.

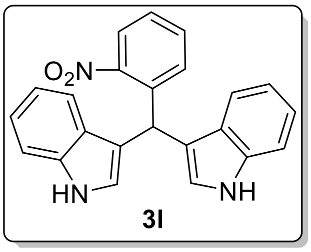
3,3'-((3-nitrophenyl)methylene)bis(1H-indole) (3k)[44]



3k

Pale yellow solid (85%); FT-IR (KBr, cm^{-1}) 3408, 3055, 2924, 2860, 1659, 1524, 1455, 1347, 1094, 793, 742, 729; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.31 (s, 2H), 8.11 (d, J = 8.4 Hz, 2H), 8.05 (s, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8 Hz, 2H), 7.37–7.40 (m, 4H), 7.29 (t, J = 7.6 Hz, 1H), 6.60 (s, 2H), 6.06 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.5, 146.4, 136.8, 134.9, 129.2, 126.7, 123.7, 123.6, 122.3, 121.5, 119.6, 118.3, 111.3, 40.0.

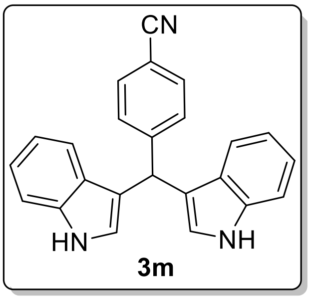
3,3'-((2-nitrophenyl)methylene)bis(1H-indole) (3l)[45]



3l

Yellow solid (90%); FT-IR (KBr, cm^{-1}) 3409, 3010, 2896, 1702, 1652, 1523, 1216, 1016, 958, 752; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (s, 2H), 7.80 (d, J = 7.8 Hz, 2H), 7.43–7.34 (m, 6H), 7.14 (t, J = 7.6 Hz, 2H) 6.90 (t, J = 7.6 Hz, 2H), 6.66 (s, 2H), 6.61 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.1, 138.5, 137.2, 132.9, 131.5,127.9, 127.2, 124.9, 124.4,122.7, 120.0, 119.9, 118.1, 111.7, 35.4.

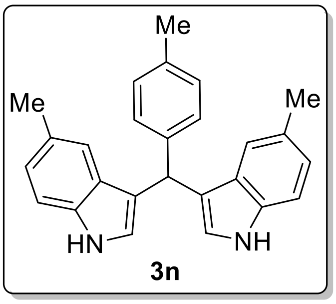
4-(di(1H-indol-3-yl)methyl)benzonitrile (3m)[39c]



3m

White solid (93%); FT-IR (KBr, cm^{-1}) 3430, 3368, 3058, 2921, 2846, 2224, 1602, 1456, 1417, 1336, 1214, 1091, 1008, 793, 739, 612; ^{1}H NMR (400 MHz, CDCl$_3$+DMSO-d_6) δ 10.76 (s, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.03 (t, J = 7.5 Hz, 2H), 6.86 (t, J = 7.5 Hz, 2H), 6.78 (s, 2H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$+DMSO-d_6) δ 150.6, 137.0, 132.0, 129.6, 126.7, 124.1, 121.5, 119.2, 118.7, 117.3, 111.6, 109.5, 40.4.

3,3'-(*p*-tolylmethylene)bis(5-methyl-1H-indole) (3n)[46]

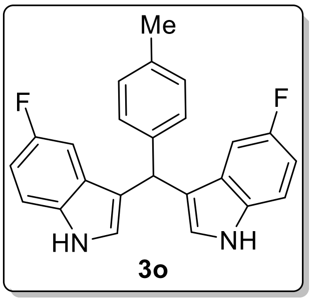


3n

White solid (90%); FT-IR (KBr, cm^{-1}) 3409, 3016, 2919, 2856, 1704, 1510, 1419, 1221, 1177, 1090, 869, 795, 776;

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74 (s, 2H), 7.26 (t, J = 7.6 Hz, 6H), 7.13 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 6.58 (s, 2H), 5.84 (s, 1H), 2.41 (s, 6H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 136.5, 130.6, 130.3, 124.2, 123.82, 123.6, 122.6, 119.1, 118.7, 114.7, 106.0, 34.9, 16.8, 16.4.

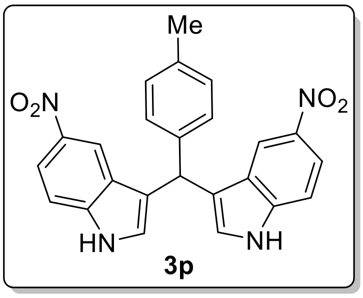
3,3'-(*p*-tolylmethylene)bis(5-fluoro-1H-indole) (3o)[47]



3o

White solid (90%); FT-IR (KBr, cm^{-1}) 3422, 2921, 2858, 1705, 1582, 1484, 1454, 1357, 1165, 937, 852, 799; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (s, 2H), 7.15–7.04 (m, 4H), 6.98 (d, J = 7.8 Hz, 2H), 6.89 (d, J = 9.7 Hz, 2H), 6.84–6.73 (m, 2H), 6.56 (s, 2H), 5.57 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.7, 140.3, 135.9, 133.2, 129.1, 128.5, 125.2, 119.7, 119.6, 111.7, 111.6, 110.5, 110.2, 104.9, 104.7, 39.8, 21.1.

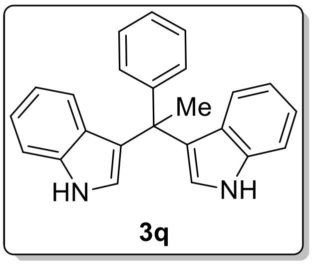
3,3'-(*p*-tolylmethylene)bis(5-nitro-1H-indole) (3p)[48]



3p

Yellow solid (88%); FT-IR (KBr, cm^{-1}) 3405, 3012, 2918, 2852, 1702, 1555, 1435, 1223, 1093, 869, 796, 697; Yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.68 (s, 2H), 7.80–7.73 (m, 4H), 7.32–7.28 (m, 2H), 7.22 (d, J = 7.6 Hz, 2H), 7.14 (d, J = 7.6 Hz, 2H), 6.72 (s, 2H), 5.90 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.6, 140.1, 139.8, 128.5, 128.1, 127.6, 126.6, 125.8, 120.4, 116.6, 116.1, 112.0, 38.4, 21.1.

3,3'-(1-phenylethane-1,1-diyl)bis(1H-indole) (3q)[49]



3q

White solid (55%); FT-IR (KBr, cm^{-1}) 3408, 3050, 2926, 2854, 1706, 1622, 1465, 1413, 1355, 1212, 1096, 856, 741; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (s, 2H), 7.42–7.39 (m, 5H), 7.36 (d, J = 8.2 Hz, 2H), 7.27–7.25 (m, 4H), 7.11–7.04 (m, 2H), 6.70 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.7, 137.7, 128.6, 128.2, 127.0, 126.4, 124.9, 123.8, 122.3, 122.0, 119.3, 111.7, 44.2, 29.3.

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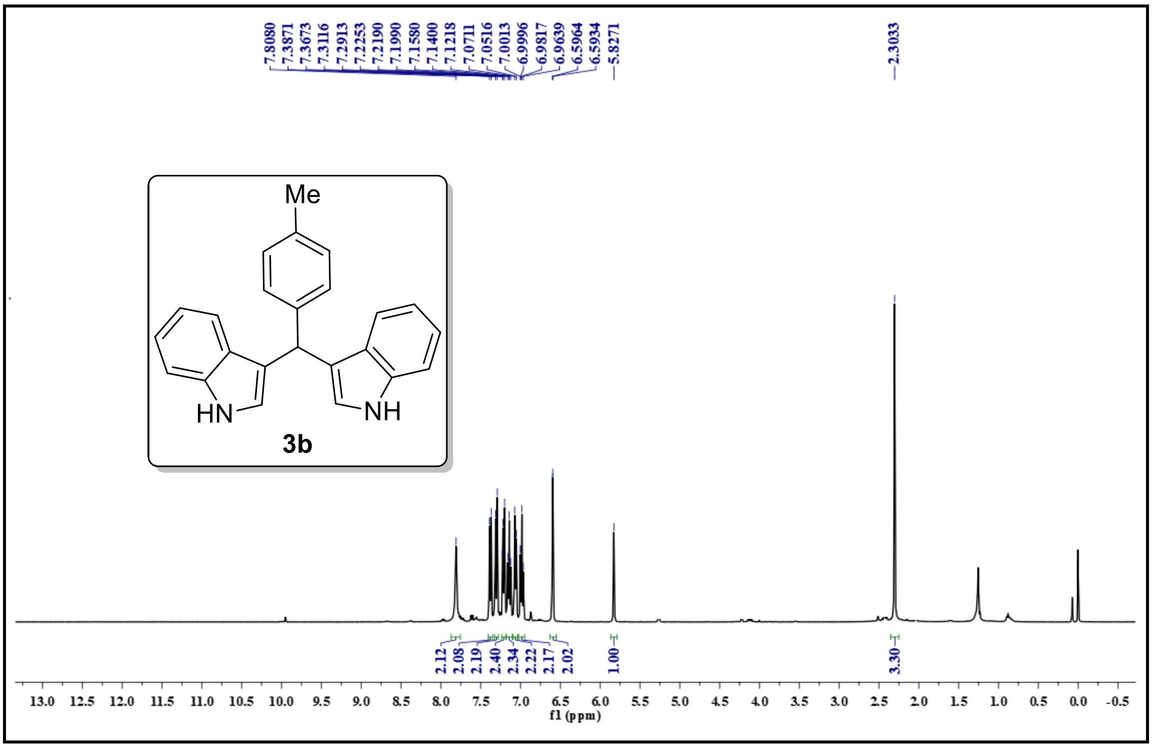
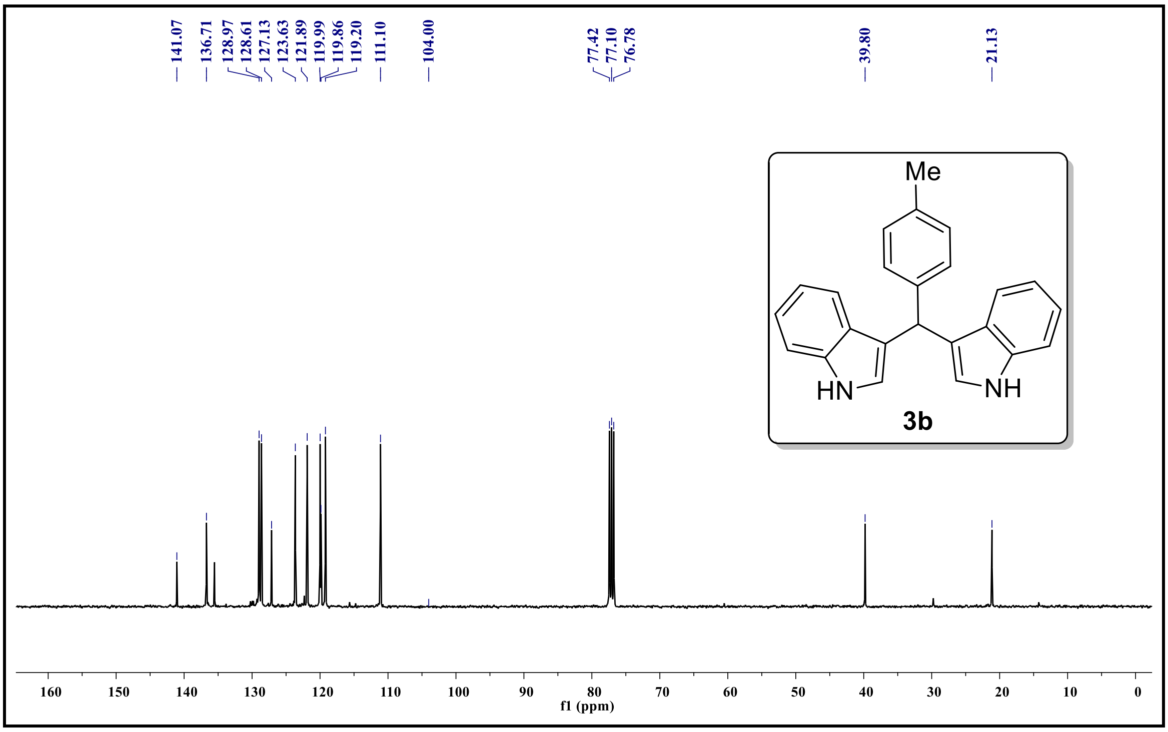
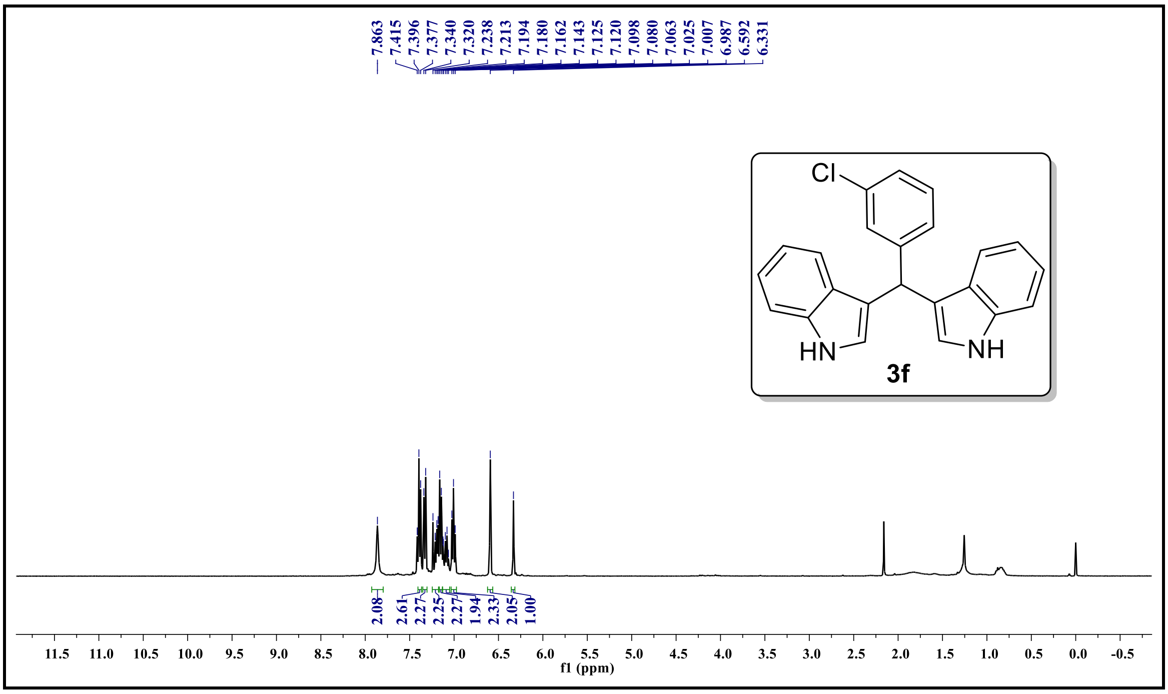
2B.8. Selected NMR (^{1}H and ^{13}C) spectra



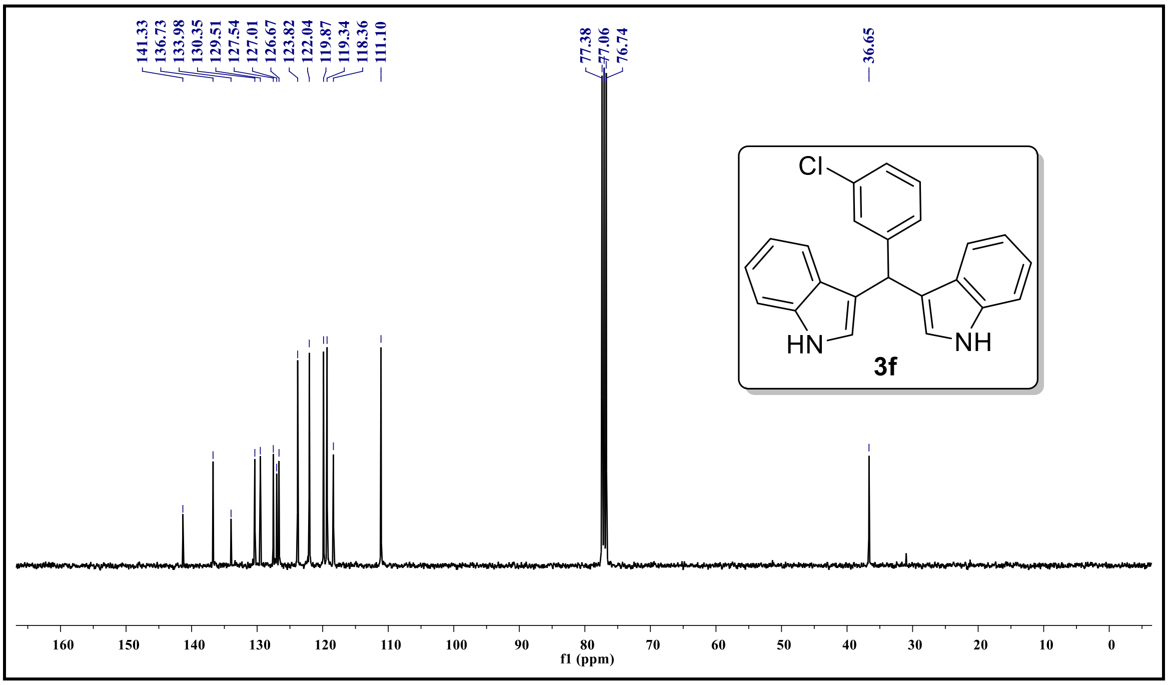
^{1}H NMR spectrum of compound **3b**



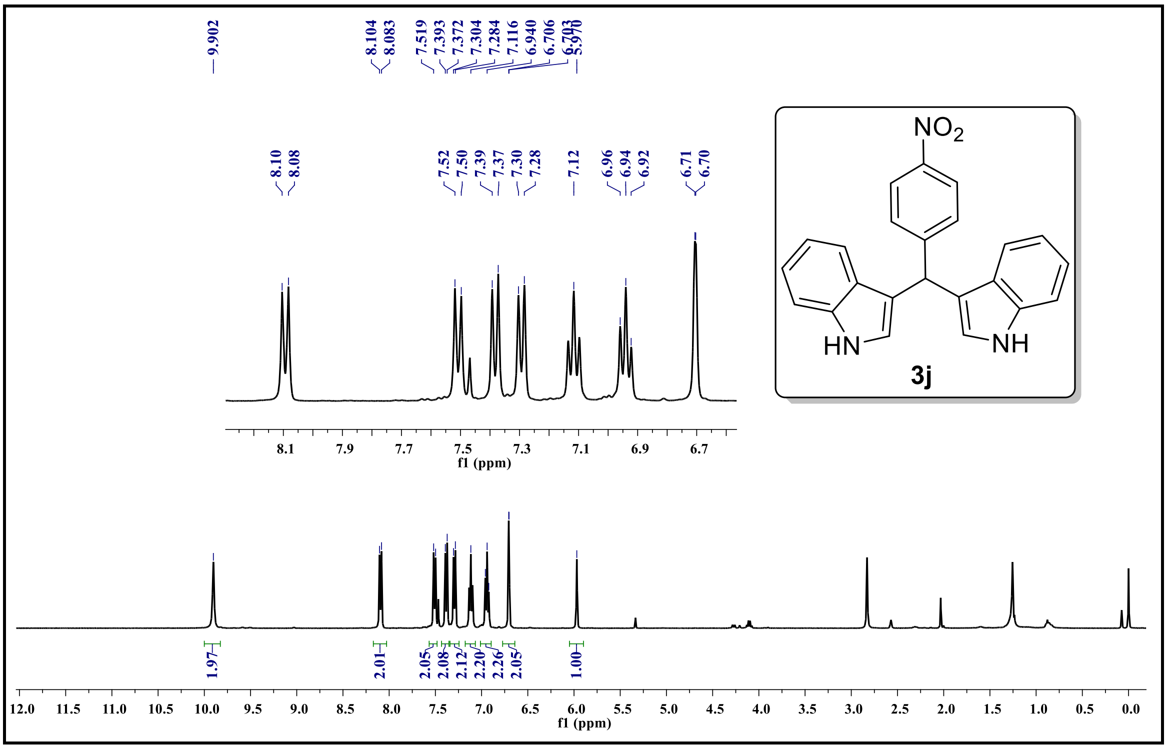
^{13}C NMR spectrum of compound **3b**



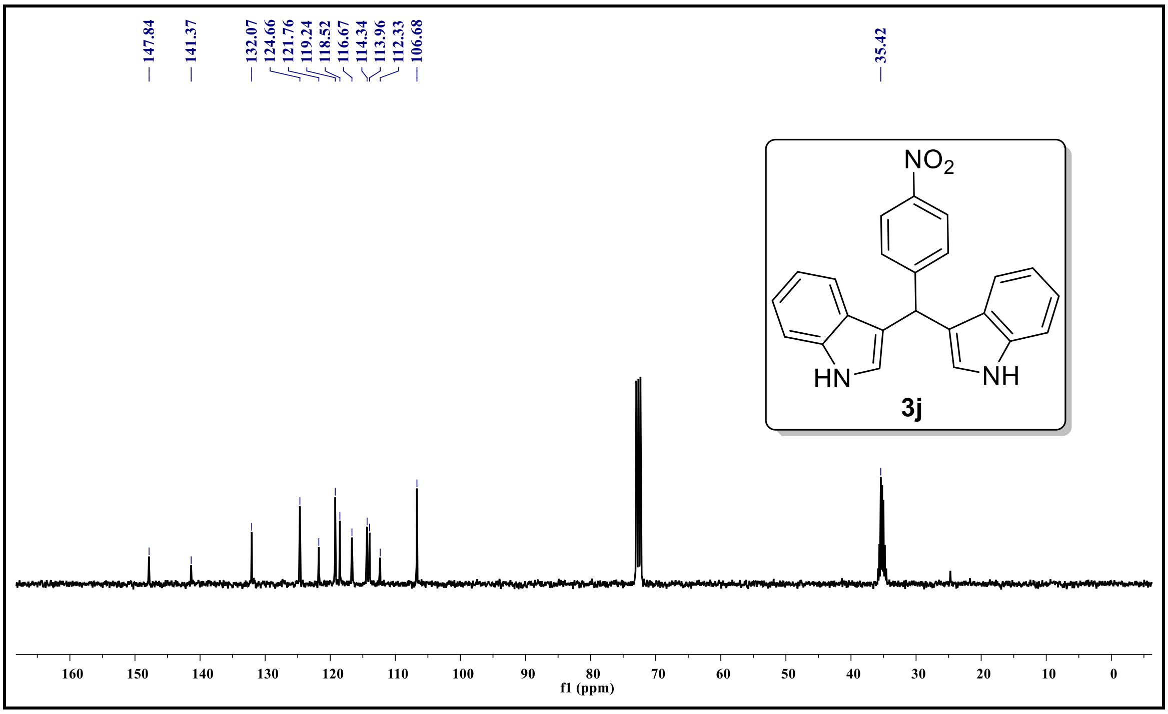
^{1}H NMR spectrum of compound **3f**



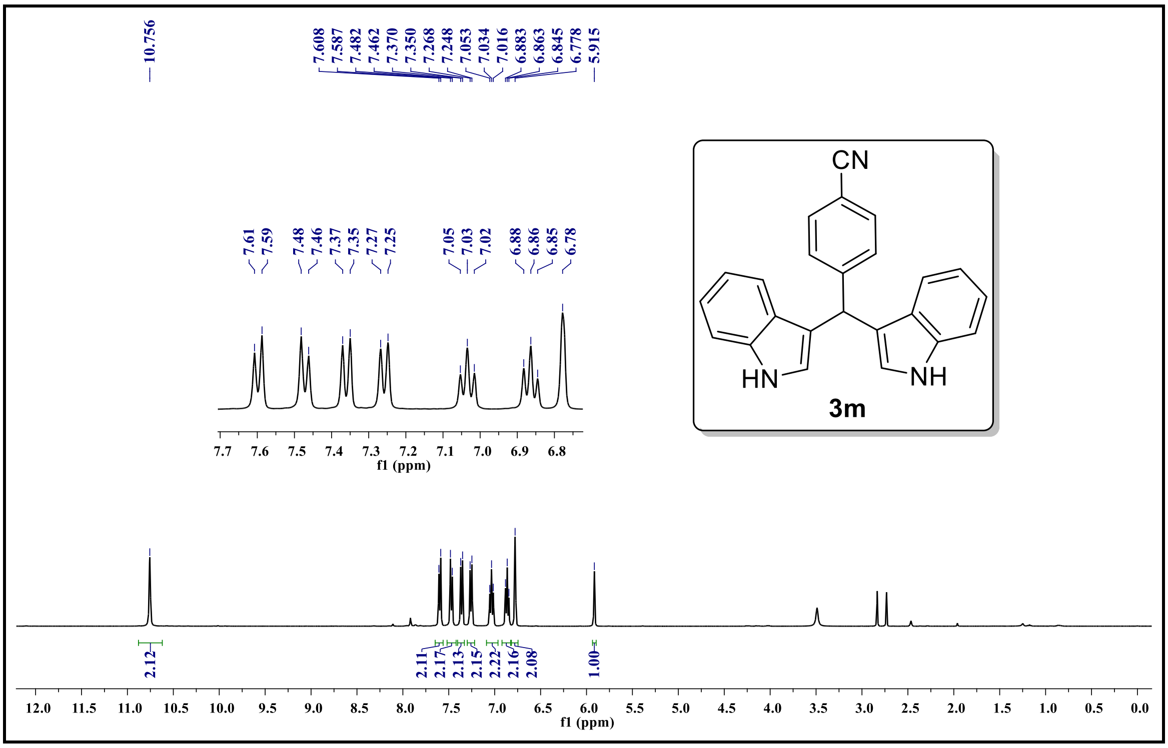
^{13}C NMR spectrum of compound **3f**



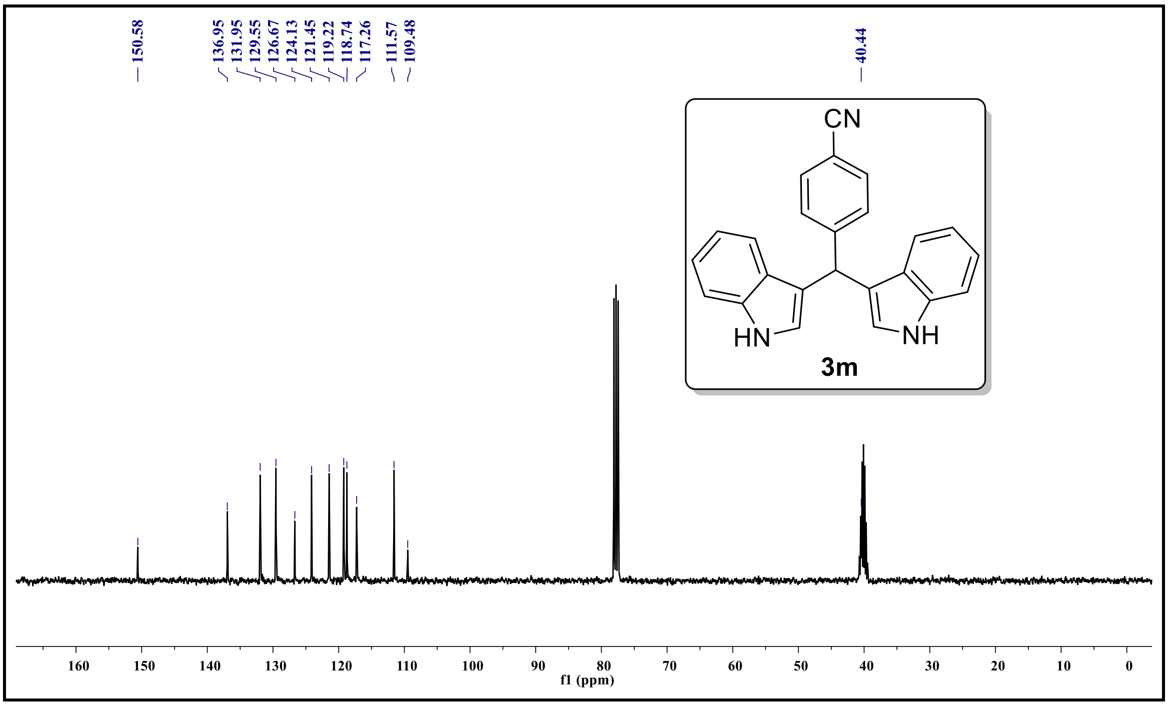
^{1}H NMR spectrum of compound **3j**



^{13}C NMR spectrum of compound **3j**



^{1}H NMR spectrum of compound **3m**



^{13}C NMR spectrum of compound **3m**

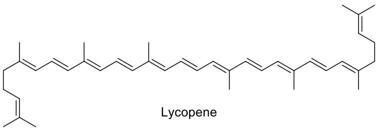
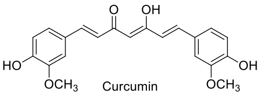
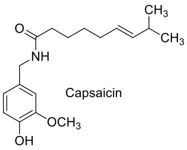
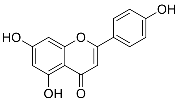
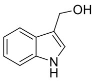
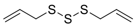
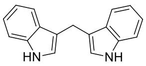
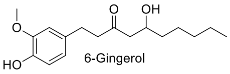
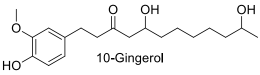
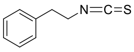
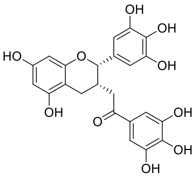
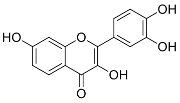
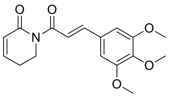
CHAPTER III

Phytochemicals Promoted Copper Catalyzed Azide Alkyne Cycloaddition Reactions in Water

3.1. Introduction

Phytochemicals are the chemical compounds which are produced from plants. These chemicals protect plants from viral, fungal, bacterial infections. Scientists have identified thousands of various phytochemicals, found in fruits, vegetables, whole grains, beans, nuts, seeds and legumes. Most of the phytochemicals have been used as traditional medicines and some as poisons. Phytochemicals stimulates the human immune system against viruses, bacteria and other disease-causing agents and also reduce oxidation, the damage to cells that occurs with aging and exposure to pollution. They will help to regulate hormones, such as insulin and estrogen. Excess levels of these hormones are leads to increase risk for breast and colon cancer.

Table.3.1. Some examples of phytochemicals and their sources

	 Lycopene		 Curcumin
	 Capsaicin		 Apigenin
	 Indole-3-carbinol		 Dially trisulfide
	 Di-indolylmethane		 6-Gingerol  10-Gingerol
	 Phenethyl isothiocyanate		 Epigallocatechin gallate (EGCG)
	 Fisetin		 Piperlongumine

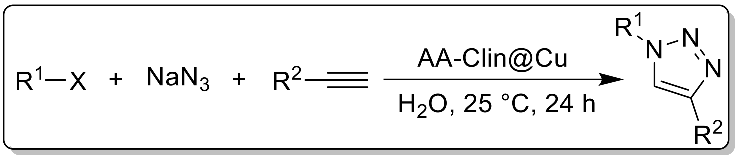
Some of the phytochemicals present in respective species were tabulated in table 3.1. Eucalyptus bark has high content of extractives rich in phenolics, flavonoids and tannins such as polyphenol, tannin, polygalloyl glucoses, catechin, epicatechin, ellagic acid, quercetin-3-o-rhamnoside, and isorhamnetin.[1a-b] Tamarindus indica bark extracts indicated the presence of n-hexacosane, eicosanoic acid, β-sitosterol, octacosanylferulate, 21-oxobehenic acid, and (+)-pinitol, lupeol, sterols and triterpenes.[1c] The phytochemicals present in Neem bark extracts were contains saponins, sterols, triterpenes, phenolic diterpenoids, glycosides and tannins etc.[1d] Teak contains triterpenoids, steroids, lignans, fatty esters and phenolic compounds etc.[1e]

Among all the phytochemicals, the potential phytochemicals providing health benefits are polyphenols, terpenoids, carotenoids, flavonoids, isoflavonoids, anthocyanidins, phytosterols, glucosinolates, phytoestrogens, fibers, and limonoids. These phytochemicals used not only for health benefits but also for the synthesis of different nanoparticles.

Green synthesis of metal nanoparticles using phytochemicals have received considerable attention due to their catalytic activities. From the literature survey, the copper nanoparticles were synthesized using different plant extracts including ageratum houstonianum mill. leaf extract, [2a] cassia occidetalis, [2b] the leaves of euphorbia esula L,[3] cissus vitiginea,[4] allium sativum L. roots,[5] tea leaf,[6] tomato,[7] Murraya Koenigii leaves,[8] Punica granatum peel extract,[9] Eclipta prostrata leaves,[10] and Aegle marmelos leaf,[11] Moringa oleifera Leaves.[12] Most of the literature reports reveal that copper nanoparticles have easily synthesized using phytochemicals and further, separated copper nanoparticles used as catalysts for the Click reaction but to the best of our knowledge, no one used *in situ* generated copper nanoparticles for click reaction. Hence, we are the first to report the Click reaction catalyzed by *in situ* generated copper nanoparticles using phytochemicals.

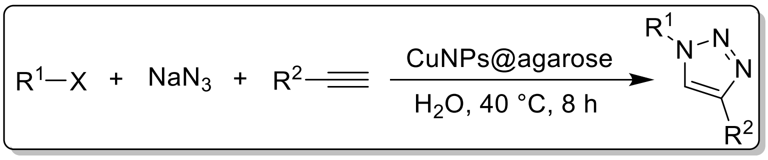
3.1.1. Different synthetic approaches for the synthesis of 1,2,3-triazoles

Gholinejad and co-workers reported the synthesis and characterization of acid activated clinochlore supported copper nanoparticles (AA-Clin@Cu). Further they have investigated the catalytic efficiency for the synthesis of 1,2,3-triazoles at ambient temperature in water (Scheme 3.1).[13]



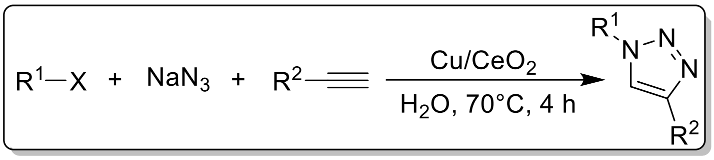
Scheme 3.1

Jeddi et al. synthesized copper nanoparticles supported on bioorganic and degradable polysaccharide i.e., agarose (CuNPs@agarose) and assessed the catalytic activity in the click reaction for the synthesis of 1,4-disubstituted-1,2,3-triazoles in water (Scheme 3.2).[14]



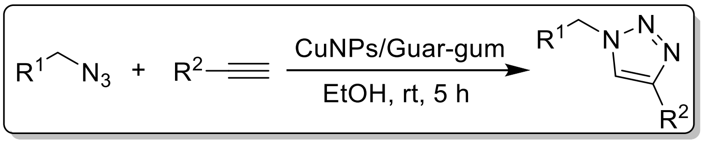
Scheme 3.2

Amini and co-workers reported the synthesis and characterization of CeO_2 supported copper nanoparticles and which were further investigated for the synthesis of 1,2,3-triazoles in water as reaction medium (Scheme 3.3).[15]



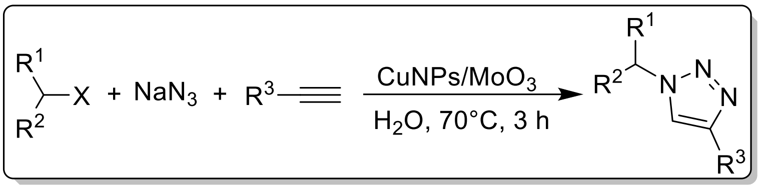
Scheme 3.3

Mozumdar and co-workers used Cu-nanoparticles entrapped within the viscous mesh of Guar-gum for the heterogeneous catalysis of Cu catalysed azide alkyne cycloaddition reaction in ethanol at room temperature (Scheme 3.4).[16]



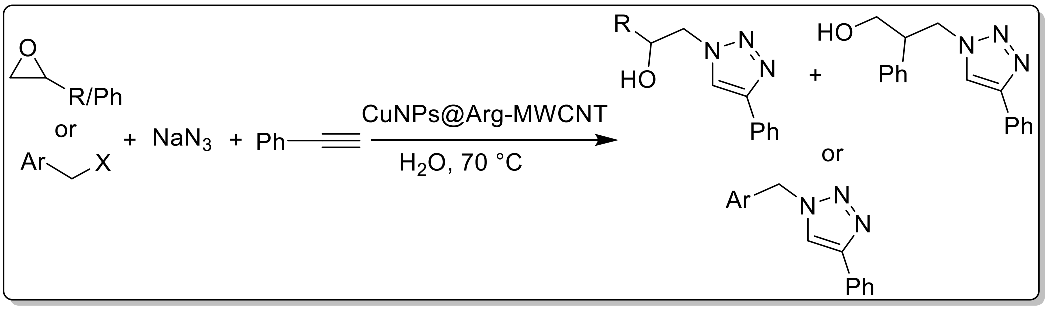
Scheme 3.4

Janmohammadi et al. reported the green synthesis of copper nanoparticles supported on MoO_3 ($CuNPs/MoO_3$) using sun spurge leaf extract and characterized using different analytical techniques. Further, catalytic activity was tested to synthesize 1,2,3-triazoles at 70 °C in water (Scheme 3.5).[17]



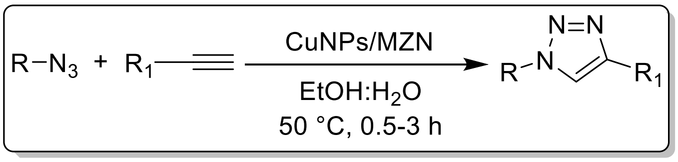
Scheme 3.5

Eshghi and co-workers reported the functionalization of multi-walled carbon nanotube with L-arginine (Arg-MWCNT) and synthesized CuNPs anchored on functionalized MWCNTs. Furthermore, they have investigated the catalytic efficiency of Cu@Arg-MWCNT towards the synthesis of 1,2,3-triazoles in water (Scheme 3.6).[18]



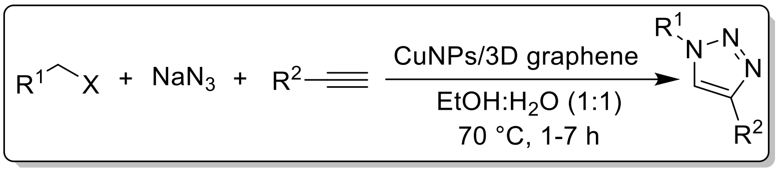
Scheme 3.6

Siuki et al. used Cu nanoparticles, which were decorated on the surface of modified clinoptilolite/Fe_3O_4 nanocomposite with epichlorohydrine and ethylenediamine species (CuNPs/ MZN) as an efficient catalyst for the synthesis of 1,4-disubstituted-1,2,3-triazoles under ultrasonic conditions (Scheme 3.7).[19]



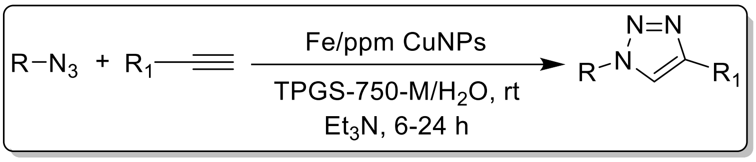
Scheme 3.7

Dabiri and co-workers reported the 1,3-dipolar cycloaddition reaction using Cu nanoparticles decorated on the surface of three-dimensional graphene nanocomposite **(**Cu NPs/3D Graphene) (Scheme 3.8).[20]



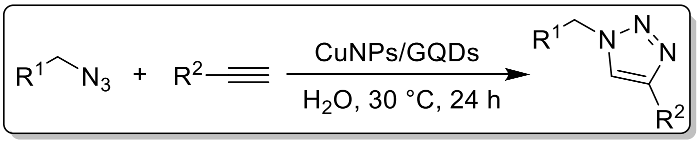
Scheme 3.8

Adenot et al. reported an efficient synthesis of 1,2,3-triazoles catalyzed by iron-based nanoparticles doped with ppm levels of CuOAc in presence of a surfactant, DL-α Tocopherol methoxypolyethylene glycol succinate (TPGS-750-M) at ambient temperatures in water (Scheme 3.9).[21]



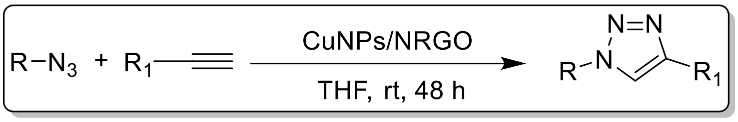
Scheme 3.9

Liu and co-workers reported the synthesis and characterization of copper nanoparticles stabilized by graphene quantum dots (GQDs). Further, they have investigated the catalytic efficiency of CuNPs for the catalysis of click reaction in water (Scheme 3.10).[22]



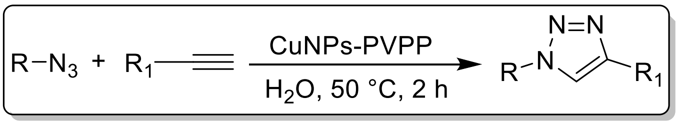
Scheme 3.10

Sanka et al. synthesized recyclable copper nanoparticles stabilized by using nitrogen-doped reduced graphene oxide (NRGO) and tested the catalytic behaviour of CuNPs for CuAAC reaction at ambient temperature (Scheme 3.11).[23]



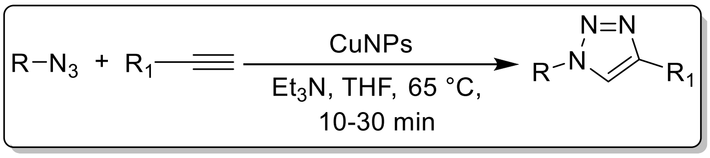
Scheme 3.11

Bahsis and co-workers reported the synthesis and characterization of copper nanoparticles stabilized by polyvinylpolypyrrolidone (PVPP). Further, these CuNPs-PVPP were investigated for the synthesis of 1,4-disustibuted-1,2,3-triazoles at 50 °C in water (Scheme 3.12).[24]



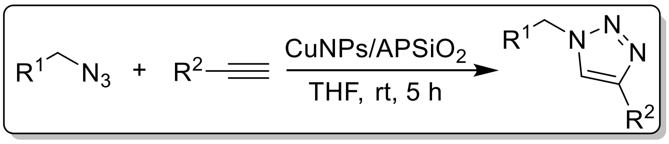
Scheme 3.12

Alonso and co-workers reported the new methodology for the synthesis of 1,2,3-triazoles using readily prepared copper nanoparticles in presence of triethylamine (Et_3N) (Scheme 3.13).[25]



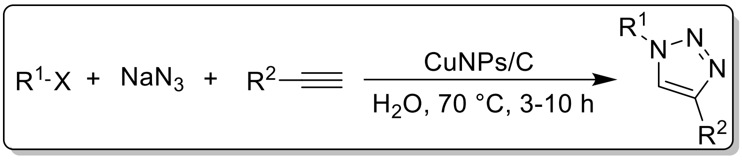
Scheme 3.13

Jumde et al. reported the synthesis and characterization of copper nanoparticles immobilized on functionalized 3-aminopropyl- silica ($APSiO_2$). In addition, they have scrutinized the catalytic efficiency of CuNPs-$APSiO_2$ towards 1,3-dipolar cycloaddition reaction at room temperature (Scheme 3.14).[26]



Scheme 3.14

Moglie et al. developed a new and efficient method for the synthesis of 1,4-disustituted-1,2,3-triazoles using copper nanoparticles supported on activated carbon in water (Scheme 3.15).[27]

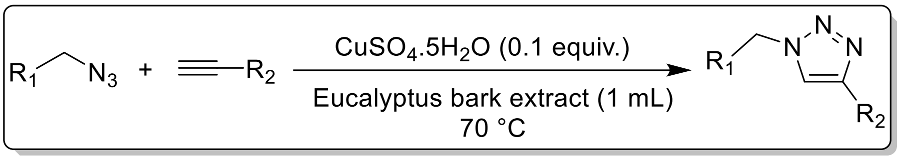


Scheme 3.15

3.2. Present work

A plenty of methods were reported in the literature for the synthesis of 1,4-disustituted-1,2,3-triazoles using copper nanoparticles via Click reaction. From these reports, we found that most of the people using commercially available copper nanoparticles or synthesized separately using different techniques such as vacuum vapour deposition,[28] exploding wire method,[29] microemulsion,[30] laser irradiation[31] and metal vapours synthesis[32] etc. These techniques need high temperature, pressure, radiation, toxic chemicals, stabilizing agents and capping agents. Therefore there is a search for the cost effective, green, eco-friendly and easy methods for the Click reaction.

Therefore, in this chapter we have reported the synthesis of 1,4-disustituted-1,2,3-triazoles by using *in situ* generated copper nanoparticles using a very cheap, green, easily available Eucalyptus bark extract and low catalyst loading of $CuSO_4.5H_2O$ (Scheme 3.16). Furthermore, this method avoids the use of stabilizing agents, capping agents and toxic chemicals.



Scheme 3.16

We have synthesized library of 1,4-disustituted-1,2,3-triazoles by applying above protocol to various azides and alkynes.

3.3. Results and discussion

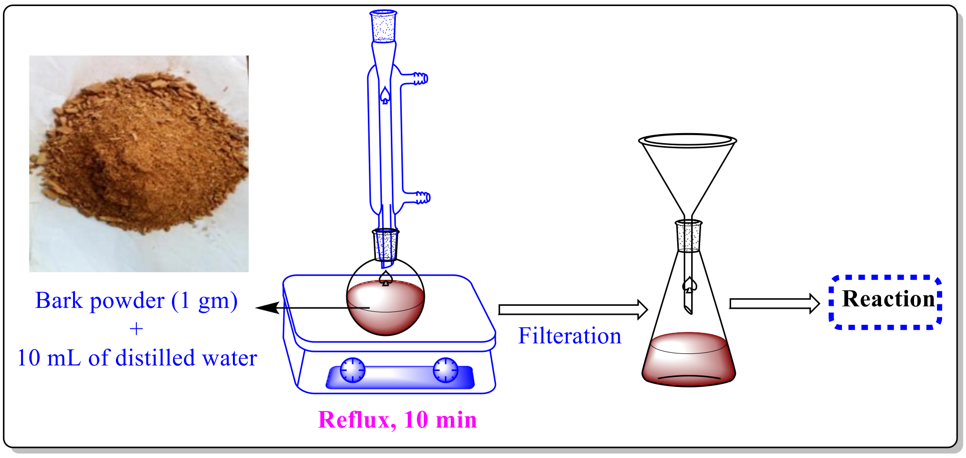
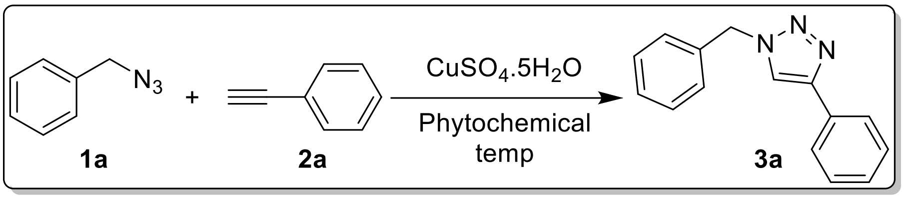


Figure 3.1. Extraction of phytochemicals from the barks of trees

Extraction of Phytochemicals. The barks of various trees were freshly collected and washed initially with tap water and then double distilled water to remove all the contaminants present on the surface of species. The washed and dried barks were crushed into fine powder. Further, 10 mL of distilled water was added to 1 gm of bark powder in a round bottom flask and refluxed for 10 minutes. Then, the extract was filtered through Whatman filter no. 1, stored at 5 °C in a refrigerator for the further analyses.

Optimization reactions of synthesis of triazoles were summarized in the Table 3.2. Benzyl azide **1a** and phenyl acetylene **2a** were chosen as model substrates for the optimization to afford corresponding triazole **3a**. Initially, benzyl azide (1.0 equiv.), phenyl acetylene (1.1 equiv.), $CuSO_4.5H_2O$ (0.5 equiv.), eucalyptus bark extract (1 mL), β-CD (0.02 equiv.) were taken in one pot and stirred at room temperature for 4 h to produce triazole with 94% of yield (Table 3.2, entry 1). Further, to know the effect of concentration of $CuSO_4.5H_2O$, we have conducted reactions using less quantities (0.2 equiv, 0.1 equiv.) of $CuSO_4.5H_2O$ at room temperature (Table 3.2, entries 2-3). Surprisingly, there is no change in the product yield and rate of reaction was observed.

Table 3.2. Optimisation of reaction conditions[a]



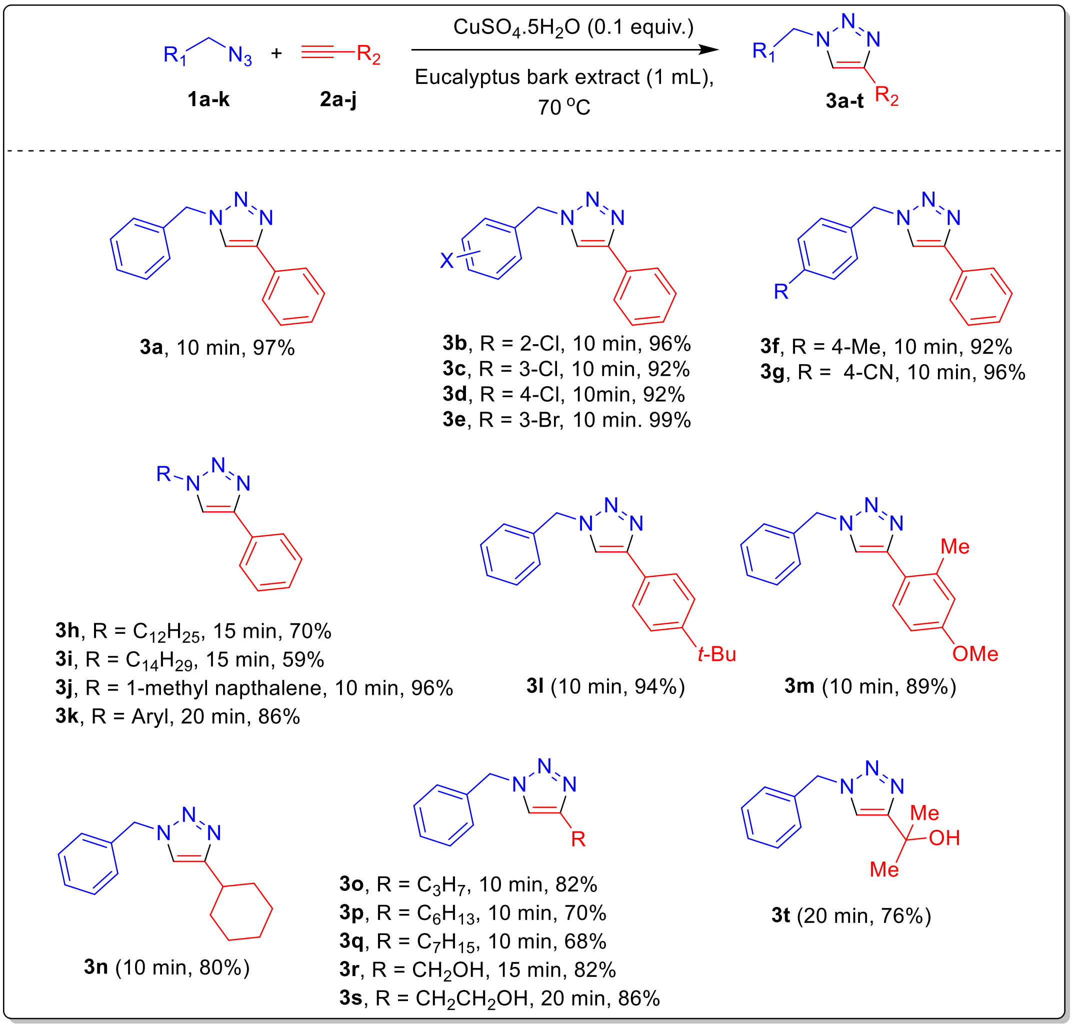
S. No	$CuSO_4.5H_2O$ (equiv.)	Name of Plant	Volume of extract	*β*–CD (equiv.)	Temp (°C)	Time	Yield[b] (%)
1	0.5	Eucalyptus	1.0 mL	0.02	rt	4 h	94
2	0.2	Eucalyptus	1.0 mL	0.02	rt	4 h	95
3	0.1	Eucalyptus	1.0 mL	0.02	rt	4 h	95
4	0.1	Eucalyptus	1.0 mL	0.02	50	40 min	97
5	0.1	Eucalyptus	1.0 mL	0.02	60	20 min	97
6	0.1	Eucalyptus	1.0 mL	0.02	70	10 min	97
7	**0.1**	**Eucalyptus**	**1.0 mL**	**-**	**70**	**10 min**	**97**
8	0.1	Eucalyptus	2.0 mL	-	70	10 min	97[c]
9	0.1	Tamarind	1.0 mL	-	70	30 min	55
10	0.1	Teak	1.0 mL	-	70	1 h	82
11	0.1	Neem	1.0 mL	-	70	1 h	65

[a] Reaction Conditions: Benzyl azide **1a** (1.0 equiv.), phenyl acetylene **2a** (1.1 equiv.), $CuSO_4.5H_2O$ (0.5 equiv.), *β*-CD (0.02 equiv.), Eucalyptus bark extract (1.0 mL) at 70 °C. [b] Yields are of isolated pure products. [c] Eucalyptus bark extract (2.0 mL).

Optimization reactions of synthesis of triazoles were summarized in the Table 3.2. Benzyl azide **1a** and phenyl acetylene **2a** were chosen as model substrates for the optimization to afford corresponding triazole **3a**. Initially, benzyl azide (1.0 equiv.), phenyl acetylene (1.1

equiv.), $CuSO_4.5H_2O$ (0.5 equiv.), eucalyptus bark extract (1 mL), *β*-CD (0.02 equiv.) were taken in one pot and stirred at room temperature for 4 h to produce triazole with 94% of yield (Table 3.2, entry 1). Further, to know the effect of concentration of $CuSO_4.5H_2O$, we have conducted reactions using less quantities (0.2 equiv, 0.1 equiv.) of $CuSO_4.5H_2O$ at room temperature (Table 3.2, entries 2-3). Surprisingly, there is no change in the product yield and rate of reaction was observed. To assess the effect of temperature on the reaction, we have carried out reactions at different temperatures such as 50 °C, 60 °C, 70 °C (Table 3.2, entries 4-6). From these experiments, we observed that as increasing the temperature of reaction, the reaction time was decreased as well as product yield was increased. Further, a control experiment in absence of *β*-CD, showed no change in results (Table 3.2, entry 7).

Table 3.2. Substrate scope.



1a-k **2a-j** **3a-t**

3a, 10 min, 97%

3b, R = 2-Cl, 10 min, 96%
3c, R = 3-Cl, 10 min, 92%
3d, R = 4-Cl, 10min, 92%
3e, R = 3-Br, 10 min. 99%

3f, R = 4-Me, 10 min, 92%
3g, R = 4-CN, 10 min, 96%

3h, R = $C_{12}H_{25}$, 15 min, 70%
3i, R = $C_{14}H_{29}$, 15 min, 59%
3j, R = 1-methyl napthalene, 10 min, 96%
3k, R = Aryl, 20 min, 86%

3l (10 min, 94%)

3m (10 min, 89%)

3n (10 min, 80%)

3o, R = C_3H_7, 10 min, 82%
3p, R = C_6H_{13}, 10 min, 70%
3q, R = C_7H_{15}, 10 min, 68%
3r, R = CH_2OH, 15 min, 82%
3s, R = CH_2CH_2OH, 20 min, 86%

3t (20 min, 76%)

[a]Reaction Conditions: alkyl azide **1a-k** (1.0 equiv.), alkyne **2a-j** (1.1 equiv.), $CuSO_4.5H_2O$ (0.1 equiv.), eucalyptus bark extract (1.0 mL) at 70 °C. [b]Yields are of isolated pure products.

Aliphatic long chain alkyl azides underwent cycloaddition reaction smoothly and gave less yields of triazoles as compared to benzyl azides (Table 3.3, **3h-i**). Notably, bulky naphthyl azide also participated in our protocol to produce triazole moiety with excellent yield (Table 3.3, **3j**). It is worth mentioning that, aryl azides also underwent reaction smoothly (Table 3.3, **3k**) and gave moderate yield of triazole as compared to benzyl azides.

Later, we have applied our protocol to various substituted aliphatic and aromatic alkynes. Substituted phenyl acetylenes underwent cycloaddition reaction without any hurdle and gave 1,2,3-triazoles with excellent yields (Table 3.3, **3l-m**). 1-ethynylcyclohexane also participated smoothly in 1,3-dipolar cycloaddition reaction to afford 1,4-disubstituted-1,2,3-triazole in good yield (Table 3.3, **3l-m**). Finally, aliphatic alkynes gave desired triazoles with moderate to good yields (Table 3.3, **3o-t**). It is noteworthy that as chain length increased or as polar group substitutions increased on aliphatic alkyne, the reaction yield was decreased.

3.4. Conclusions

In this chapter, we have developed a green approach for the synthesis of triazoles. In this protocol copper nanoparticles generated in *in situ* using $CuSO_4.5H_2O$, aqueous extract of eucalyptus bark and further used to catalyse the cycloaddition reaction. Simple synthetic procedure, usage of less toxic chemicals, short reaction times and high reaction yields are the advantages of this methodology. This protocol tolerates various substitutions (halogens, EDG and EWG) on benzyl azide, various substitutions on phenyl acetylene and aliphatic alkynes. By applying this protocol to wide range of azides and alkynes, we have synthesized 20 compounds with 68–99 % of yield.

3.5. Experimental Section

General Information. Anilines, Alkyl bromides, Hydrochloric acid, $NaNO_2$, NaN_3 and $CuSO_4.5H_2O$ were purchased from a commercial source and used as received. Reactions were conducted in round bottom flasks. Thin layer chromatography was performed on 200 µm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. ^1H NMR spectra were obtained at 400 MHz in $CDCl_3$ and were referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ and were referenced to the solvent resonance. Chemical shifts (*δ*) were reported in parts per million (ppm) and coupling constants (*J*) were in hertz (Hz). Standard abbreviations were used to designate resonance multiplicities. Melting points were determined with a melting point apparatus and are uncorrected.

Preparation of aryl azides. In an oven dried round bottom flask, aniline derivative (13 mmol) was suspended in 80 mL hydrochloric acid (17%) at room temperature and then ethanol was added until a clear solution was obtained. The resulting solution was cooled to 0 °C and $NaNO_2$ (1.5 eq.) was added in small portions. After stirring at 0 °C for 15-30 min. NaN_3 (1.5 eq.) was slowly added and the mixture was stirred for additional 2 h at room temperature. The reaction mixture was extracted with diethyl ether (3 x 60 mL) and the combined organic fractions were washed with saturated $NaHCO_3$ solution (3 x 50 mL) and with brine (50 mL). After drying over Na_2SO_4 the ether was removed under reduced pressure and the desired azides were obtained without further purification.

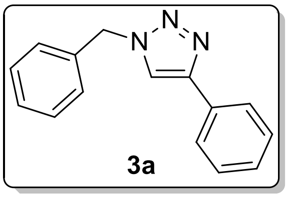
Preparation of alkyl azides. In an oven dried round bottom flask, alkyl bromide (1.0 eq.) was dissolved in DMSO (40 ml). Sodium azide (1.5 eq.) was added and the reaction was stirred at room temperature for 12 h. The mixture was allowed to stir at room temperature, until TLC indicated completion of reaction. Then the reaction mixture was diluted with water (70 mL) and extracted with diethyl ether (3 x 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was further used without purification.

General procedure for the one-pot synthesis of 1,4-substituted-1,2,3-triazoles (3a-t).

In an oven dried round bottom flask, benzyl azide/aryl azide **1a-k** (133 mg, 1.0 mmol), alkyne **2a-j** (112 mg, 1.1 mmol), copper(II)sulfate pentahydrate (24.9 mg, 0.1 mmol) and 1 mL of eucalyptus bark extract were added. The mixture was allowed to stir at 70 °C temperature, until TLC indicated completion of reaction. Then the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using ethyl acetate in *n*-hexanes as an eluent.

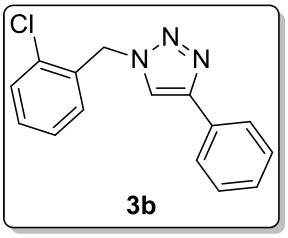
3.6. Spectral data

1-Benzyl-4-phenyl-1H-1,2,3-triazole (3a)[33]


3a

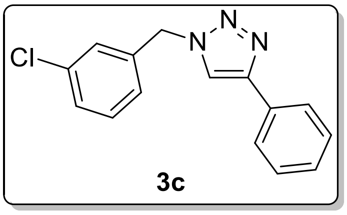
White solid (97%); FT-IR (KBr, cm^{-1}) 3121, 3051, 2949, 1612, 1495, 1466, 1357, 1223, 1074, 1047, 973, 766, 729, 693; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.8 (d, J = 7.2 Hz, 2H), 7.66 (s, 1H), 7.35–7.44 (m, 5H), 7.28–7.35 (m, 3H), 5.57 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.2, 134.7, 134.7, 130.5, 129.2, 128.8, 128.2, 128.1, 125.7, 119.5, 54.3.

1-(2-Chlorobenzyl)-4-Phenyl-1*H*-1,2,3-triazole (3b)


3b

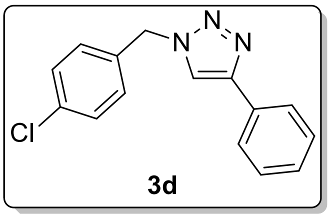
White solid (93%); FT-IR (KBr, cm^{-1}) 3112, 3060, 2961, 2948, 2924, 2853, 1704, 1550, 1445, 1328, 1219, 1050, 826, 726, 681; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (d, J = 7.6 Hz, 2H), 7.80 (s, 1H), 7.50–7.40 (m, 3H), 7.35 (t, J = 7.4 Hz, 2H), 7.27 (dd, J = 17.7, 6.4 Hz, 2H), 5.74 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.2, 133.4, 132.6, 130.5, 130.3, 129.9, 128.8, 128.2, 127.7, 125.7, 119.9, 51.5.

1-(3-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3c)[34]


3c

White solid (92%); FT-IR (KBr, cm^{-1}) 3098, 3124, 3060, 2924, 1560, 1464, 1357, 1219, 1208, 1081, 1045, 977, 824, 764, 750,691; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, J = 7.4 Hz, 2H), 7.77 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.7 Hz, 2H), 7.33(d, J = 7.3 Hz, 1H), 7.30 (d, J = 4.0 Hz, 1H), 7.27 (d, J = 5.6 Hz, 1H), 7.23 (s, 1H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.2, 133.5, 132.6, 130.5, 130.3, 130.2, 130.0, 128.8, 128.2, 127.7, 125.7, 119.8, 51.5.

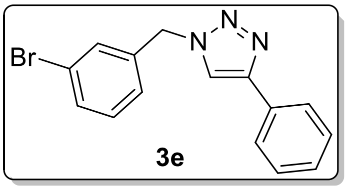
1-(4-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3d)[35]



3d

White solid (92%); FT-IR (KBr, cm^{-1}) 3108, 3083, 2925, 2850, 1550, 1461, 1220, 1092, 1080, 1016, 976, 845, 820, 804, 763, 688, 667; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 (d, J = 7.5 Hz, 2H), 7.67 (s, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 8.4 Hz, 3H), 7.24 (d, J = 8.1 Hz, 2H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.4, 134.8, 133.2, 130.4, 129.4, 128.9, 128.3, 125.7, 119.5, 53.5.

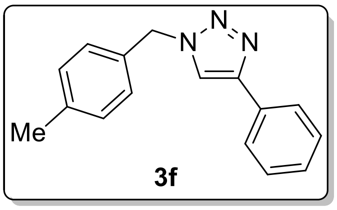
1-(3-Bromobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3e)[35]



3e

White solid (99%); FT-IR (KBr, cm^{-1}) 3115, 3084, 2920, 1570, 1480, 1432, 1343, 1223, 1192, 1071, 1046, 974, 910, 836, 809, 764, 750, 698, 671; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74 (d, J = 7.3 Hz, 1H), 7.63 (s, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.40 (s, 1H), 7.35 (t, J = 7.7 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.23–7.14 (m, 3H), 5.48 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.5, 136.9, 132.0, 131.0, 130.8, 130.4, 128.9, 128.3, 126.6, 125.8, 1 23.2, 119.5, 53.5.

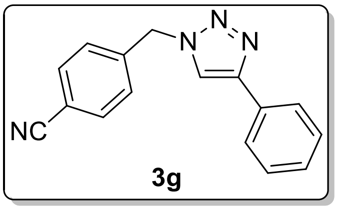
1-(4-Methylbenzyl)-4-phenyl-1H-1,2,3-triazole (3f)[36]



3f

White solid (92%); FT-IR (KBr, cm^{-1}) 3115, 3086, 2960, 2856, 1515, 1463, 1348, 1222, 1047, 1046, 973, 832, 762, 690; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, J = 7.8 Hz, 2H), 7.56 (s, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.10–7.17 (m, 4H), 5.46 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.2, 138.8, 131.6, 130.6, 129.8, 128.8, 128.2, 125.7, 119.4, 54.1, 21.2.

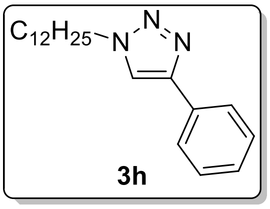
4-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl) benzonitrile (3g)[37]



3g

White solid (96%); FT-IR (KBr, cm^{-1}) 3135, 2925, 2227, 1463, 1431, 1347, 1223, 1186, 1076, 1043, 808, 765, 698, 554; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76–7.70 (d, J = 7.2 Hz, 2H), 7.67 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.38–7.24 (m, 5H), 5.56 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.7, 139.9, 132.9, 130.1, 128.9, 128.5, 128.4, 125.7, 119.8, 118.2, 112.8, 53.5.

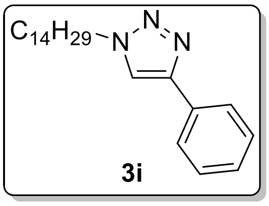
1-Dodecyl-4-phenyl-1*H*-1,2,3-triazole (3h)[38]



3h

White solid (70%); FT-IR (KBr, cm^{-1}) 3119, 3081, 2954, 2917, 2846, 1609, 1464, 1356, 1216, 1078, 1053, 977, 839, 762, 723, 695; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, J = 7.2 Hz, 2H), 7.67 (s, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 4.32 (t, J = 7.2 Hz, 2H), 1.87 (p, J = 7.0 Hz, 2H), 1.35–1.08 (m, 18H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.7, 130.7, 128.8, 128.1, 125.7, 119.4, 50.5, 31.9, 30.4, 29.5, 29.4, 29.3, 29.0, 26.5, 22.7, 14.1.

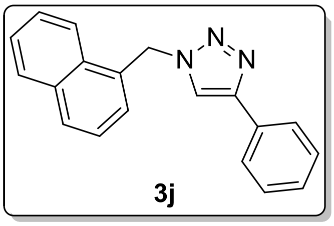
1-Tetradecyl-4-phenyl-1*H*-1,2,3-triazole (3i)



3i

White solid (59%); FT-IR (KBr, cm^{-1}) 3119, 2954, 2917, 2846, 1609, 1464, 1216, 1078, 976, 839, 761, 723, 694, 527; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, J = 7.4 Hz, 2H), 7.67 (s, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 4.32 (t, J = 7.2 Hz, 2H), 1.93–1.81 (m, 2H), 1.18 (s, 22H), 0.80 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.3, 89.2, 77.4, 77.2, 77.1, 76.7, 75.3, 56.4, 53.5, 31.9, 29.7, 29.4, 22.7, 14.1.

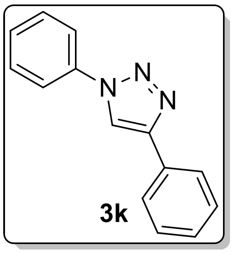
1-(Naphthalen-1-ylmethyl)-4-phenyl-1*H*-1,2,3-triazole (3j)[39]



3j

White solid (96%); FT-IR (KBr, cm^{-1}) 3117, 3086, 2966, 1597, 1510, 1480, 1342, 1213, 1193, 1081, 1047, 975, 778, 766, 721, 693; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94–7.89 (m, 1H), 7.79–7.85 (m, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.43 (t, J = 4.8 Hz, 3H), 7.39 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.4 Hz, 2H), 7.21–7.15 (m, 1H), 5.92 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.0, 134.0, 131.2, 130.5, 130.1, 129.9, 129.0, 128.8, 128.1, 127.9, 127.4, 126.5, 125.7, 125.4, 122.9, 119.5, 52.5.

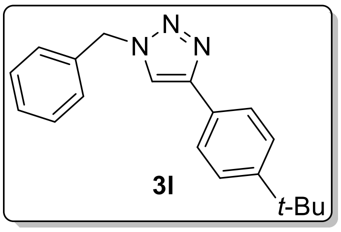
1,4-Diphenyl-1*H*-1,2,3-triazole (3k)[40]



3k

White solid (86%); FT-IR (KBr, cm^{-1}) 3120, 3096, 3055, 2923, 1576, 1504, 1227, 1041, 757, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.00–7.95 (m, 2H), 7.88–7.82 (m, 2H), 7.63–7.58 (m, 2H), 7.55–7.48 (m, 3H), 7.46–7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 129.8, 129.0, 128.8, 128.5, 125.9, 120.6, 117.6, 77.4, 77.0, 76.7.

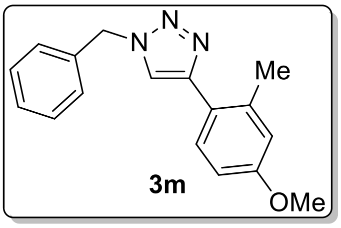
1-Benzyl-4-(4-(*tert*-butyl) phenyl)-1*H*-1,2,3-triazole (3l)[41]



3l

White solid (94%); FT-IR (KBr, cm^{-1}) 3115, 3087, 2958, 2865, 1604, 1495, 1457, 1363, 1218, 1070, 1040, 976, 827, 739, 717, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.57 (s, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.28–7.32 (m, 3H), 7.20–7.24 (m, 2H), 5.50 (s, 2H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 134.8, 128.8, 128.0, 125.7, 125.5, 54.2, 34.7, 31.3.

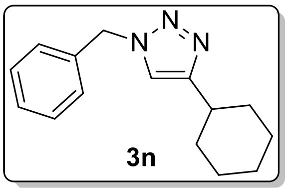
1-Benzyl-4-(4-methoxy-2-methylphenyl)-1H-1,2,3-triazole (3m)



3m

White solid (89%); FT-IR (KBr, cm^{-1}) 3125, 3080, 2928, 2855, 1601, 1492, 1447, 1368, 1212, 1060, 1045, 970, 823, 736, 713, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.41–7.34 (m, 3H), 7.30 (d, J = 7.2 Hz, 2H), 6.79 (d, J = 7.2 Hz, 2H), 5.58 (s, 2H), 3.81 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 147.4, 137.1, 134.9, 130.2, 129.1, 128.7, 128.0, 122.7, 121.1, 116.2, 111.4, 55.2, 54.1, 21.6.

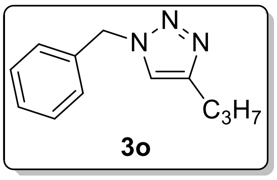
1-Benzyl-4-cyclohexyl-1H-1,2,3-triazole (3n)



3n

White solid (80%); FT-IR (KBr, cm^{-1}) 3124, 3060, 2925, 2856, 1600, 1462, 1447, 1368, 1212, 1060, 1045, 975, 826, 746, 712, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.29 (m, 3H), 7.28–7.23 (m, 2H), 7.16 (s, 1H), 5.49 (s, 2H), 2.79–2.70 (s, 1H), 2.03 (d, J = 7.2 Hz, 2H), 1.84–1.74 (m, 2H), 1.70 (d, J = 12.8 Hz, 1H),1.51–1.29 (m, 4H), 1.29–1.16 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.2, 135.0, 129.1, 128.6, 128.0, 119.2, 54.0, 35.3, 33.0, 26.1, 26.0.

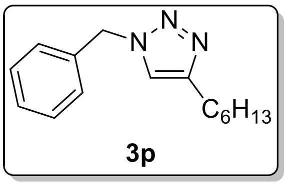
1-Benzyl-4-propyl-1H-1,2,3-triazole (3o)



3o

White solid (82%); FT-IR (KBr, cm^{-1}) 3111, 3054, 2944, 2927, 2856, 1554, 1494, 1456, 1326, 1212, 1177, 1073, 1063, 1030, 855, 747, 695; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39–7.30 (m, 3H), 7.27–7.22 (m, 2H), 7.21 (s, 1H), 5.48 (s, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.74–1.58 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.7, 135.0, 129.0, 128.6, 127.9, 120.7, 53.9, 27.7, 22.6, 13.8.

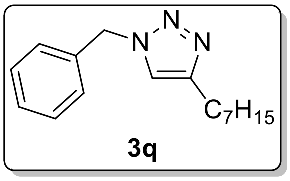
1-Benzyl-4-hexyl-1*H*-1,2,3-triazole (3p)[37]



3p

White solid (70%); FT-IR (KBr, cm^{-1}) 3113, 3064, 2954, 2927, 2854, 1552, 1494, 1456, 1326, 1213, 1177, 1073, 1053, 1030, 855, 747, 703, 692; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26–7.32 (m, 3H), 7.16–7.20 (m, 2H), 7.11 (s, 1H), 5.42 (s, 2H), 2.61 (t, J = 7.8 Hz, 2H), 1.56 (m, 2H), 1.10–1.29 (m, 6H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.0, 135.0, 129.1, 128.6, 128.0, 120.5, 54.0, 31.5, 29.4, 28.9, 25.7, 22.5, 14.0.

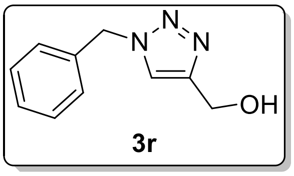
1-Benzyl-4-heptyl-1*H*-1,2,3-triazole (3q)[42]



3q

White solid (68%); FT-IR (KBr, cm^{-1}) 3113, 3064, 2956, 2920, 2852, 1551, 1468, 1455, 1337, 1212, 1052, 859, 703, 692; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35–7.41 (m, 3H), 7.25–7.29 (m, 2H), 7.20 (s, 1H), 5.50 (s, 2H), 2.70 (t, J = 7.8 Hz, 2H), 1.60–1.70 (m, 2H), 1.20–1.39 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.0, 135.0, 129.0, 128.6, 127.9, 120.5, 54.0, 31.7, 29.4, 29.2, 29.0, 25.7, 22.6, 14.1.

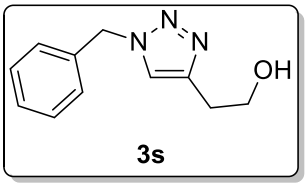
(1-Benzyl-1*H*-1,2,3-triazol-4-yl) methanol (3r)[43]



3r

White solid (82%); FT-IR (KBr, cm^{-1}) 3262, 3138, 3087, 3030, 2963, 2883, 1487, 1222, 1015, 719, 691; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (s, 1H), 7.33–7.16 (m, 5H), 5.43 (s, 2H), 4.67 (s, 2H), 3.42 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.1, 134.5, 129.2, 128.8, 128.2, 121.6, 77.4, 77.1, 76.7, 56.5, 54.2.

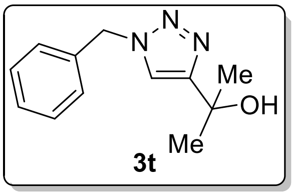
2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)ethanol (3s)[44]



3s

White solid (86%); FT-IR (KBr, cm^{-1}) 3355, 3134, 2935, 2830, 1539, 1456, 1173, 965, 830, 731; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 (s, 1H), 7.36–7.22 (m, 5H), 5.46 (s, 2H), 3.87 (t, J = 5.5 Hz, 2H), 3.35 (s, 1 H), 2.90 (t, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.0, 134.7, 129.1, 128.8, 128.1, 121.5, 77.4, 77.1, 76.8, 61.6, 54.1, 28.7.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (3t)[45]



3t

White solid (76%); FT-IR (KBr, cm^{-1}) 3305, 3164, 2975, 2930, 1499, 1456, 1173, 961, 719, 731; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.36 (m, 4H), 7.31–7.27 (m, 2H), 5.51 (s, 2H), 2.96 (s, 1H), 1.62 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.1, 134.6, 129.1, 128.8, 128.2, 119.2, 68.5, 54.1, 30.4.

3.7. References

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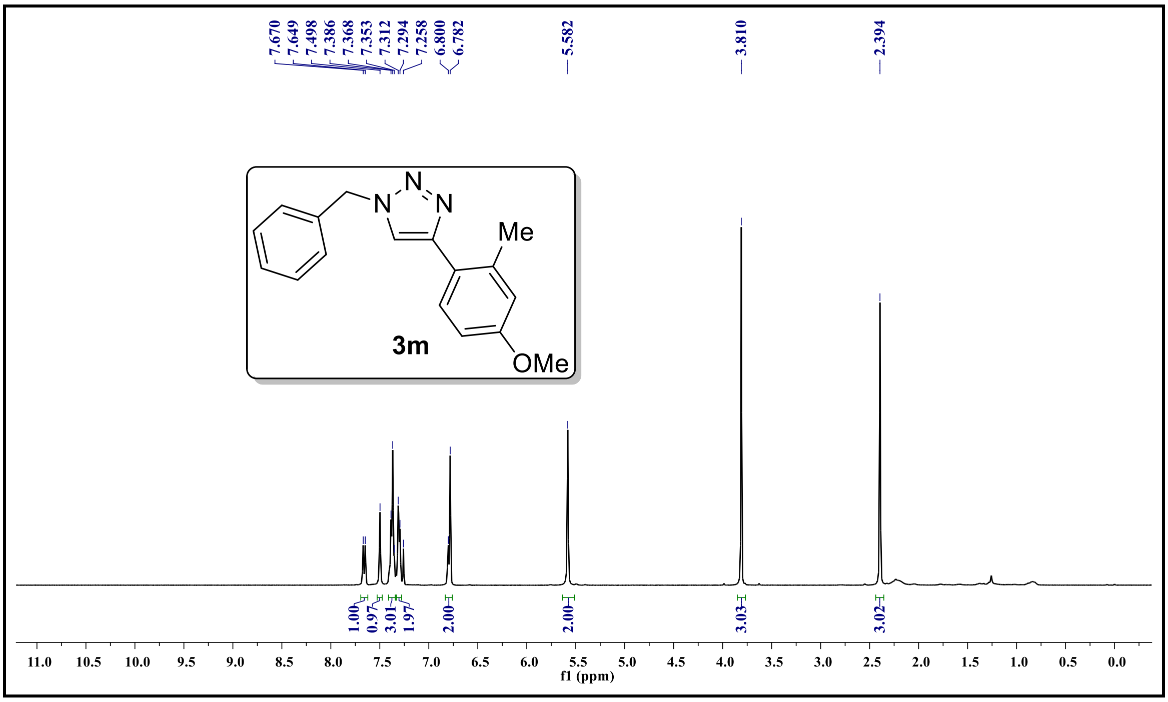
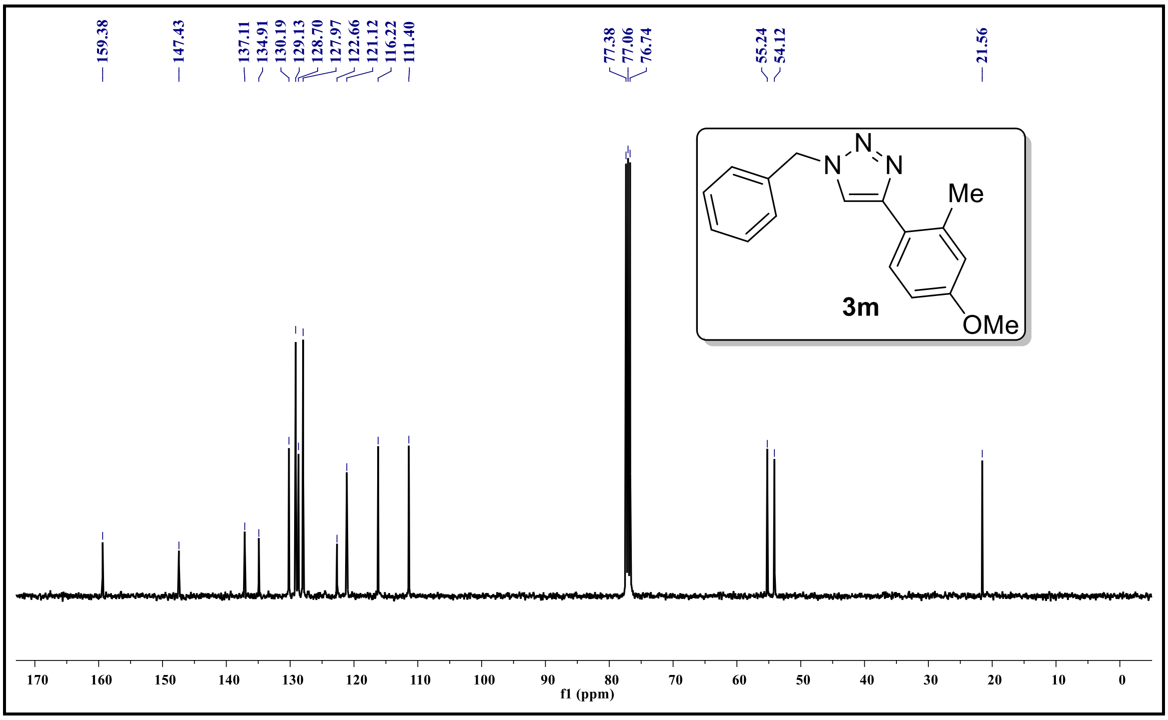
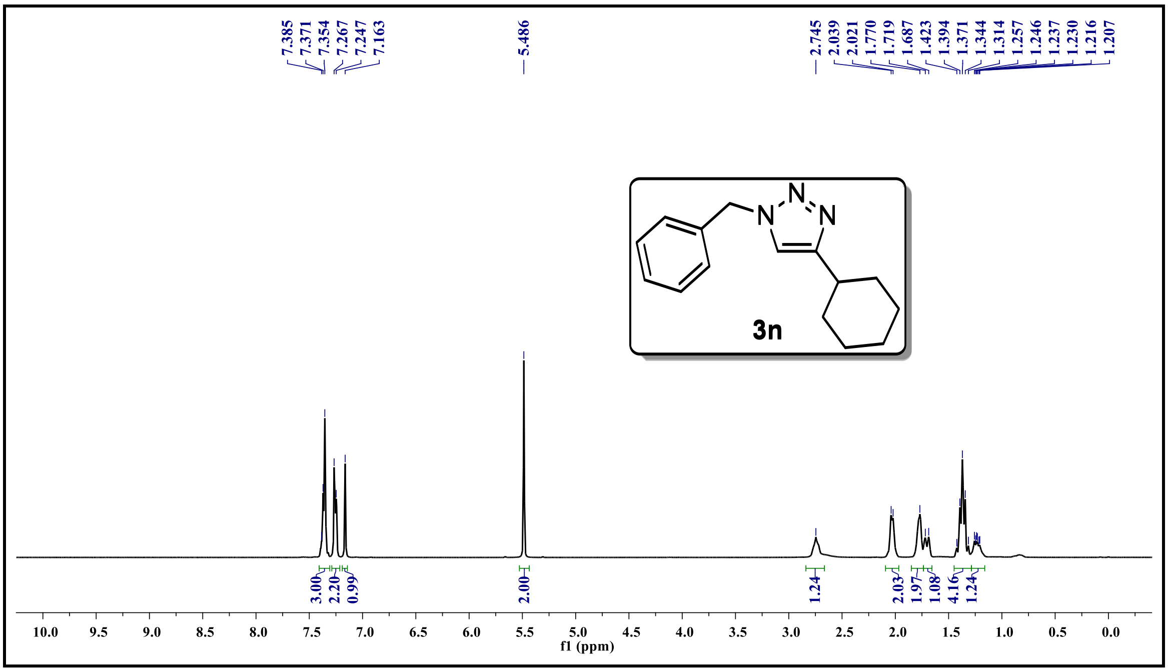
3.8. Selected NMR (^{1}H and ^{13}C) Spectra



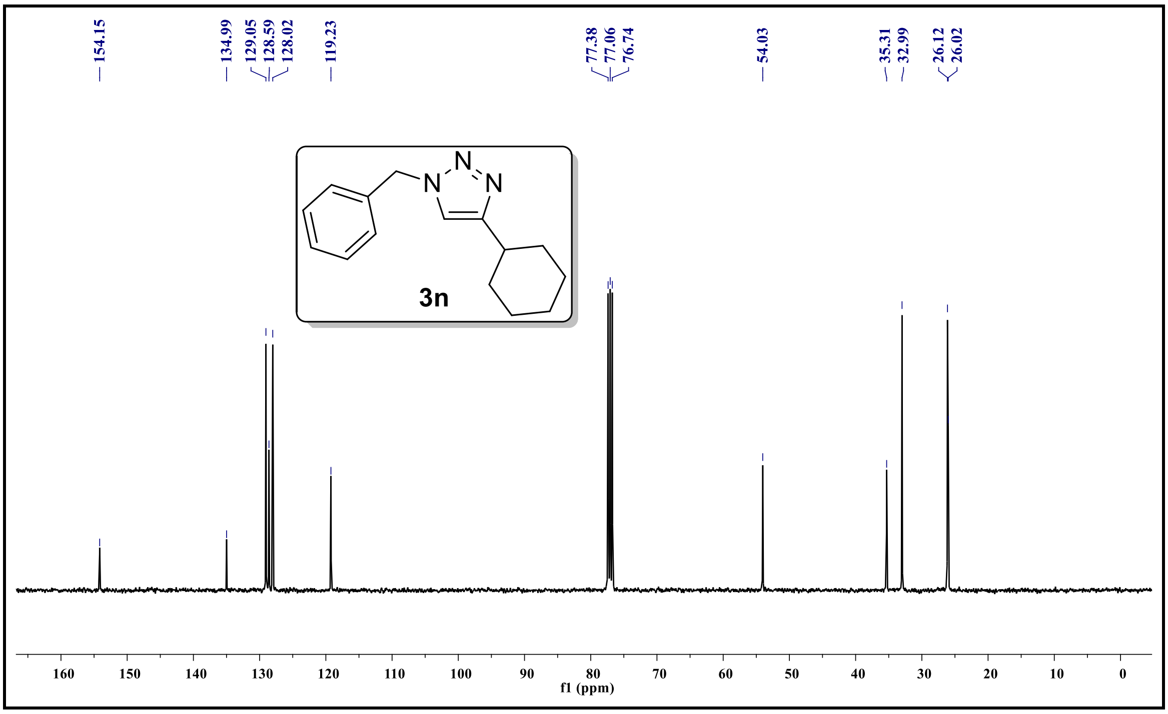
^{1}H NMR spectrum of compound **3m**



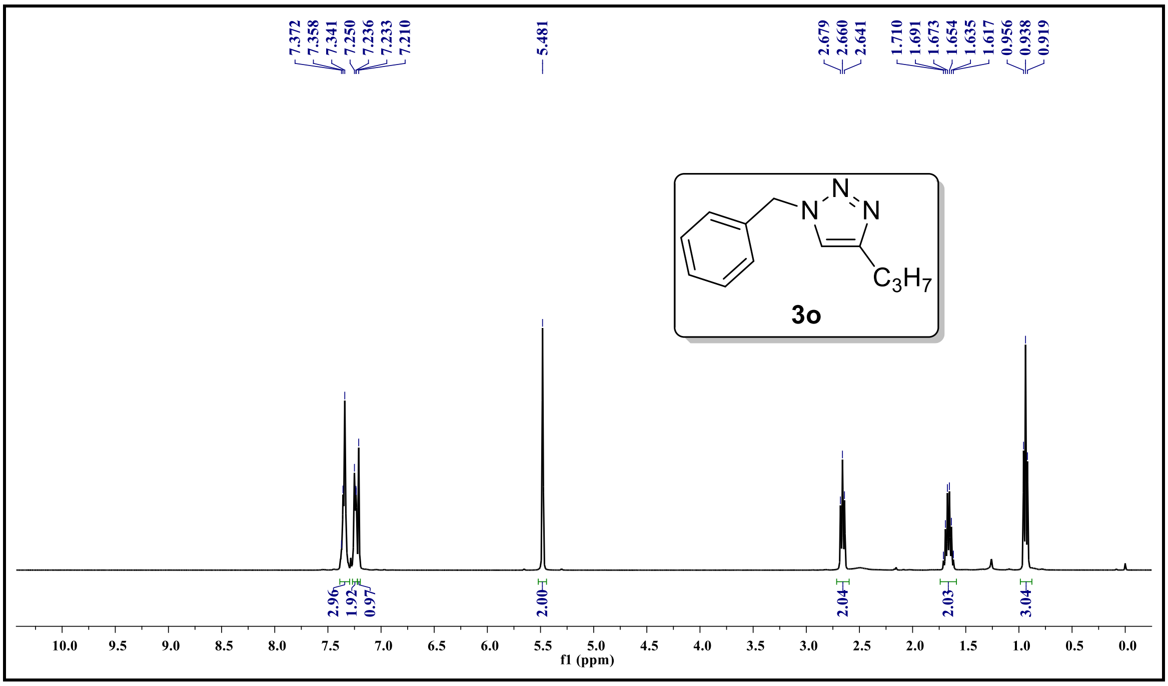
^{13}C NMR spectrum of compound **3m**



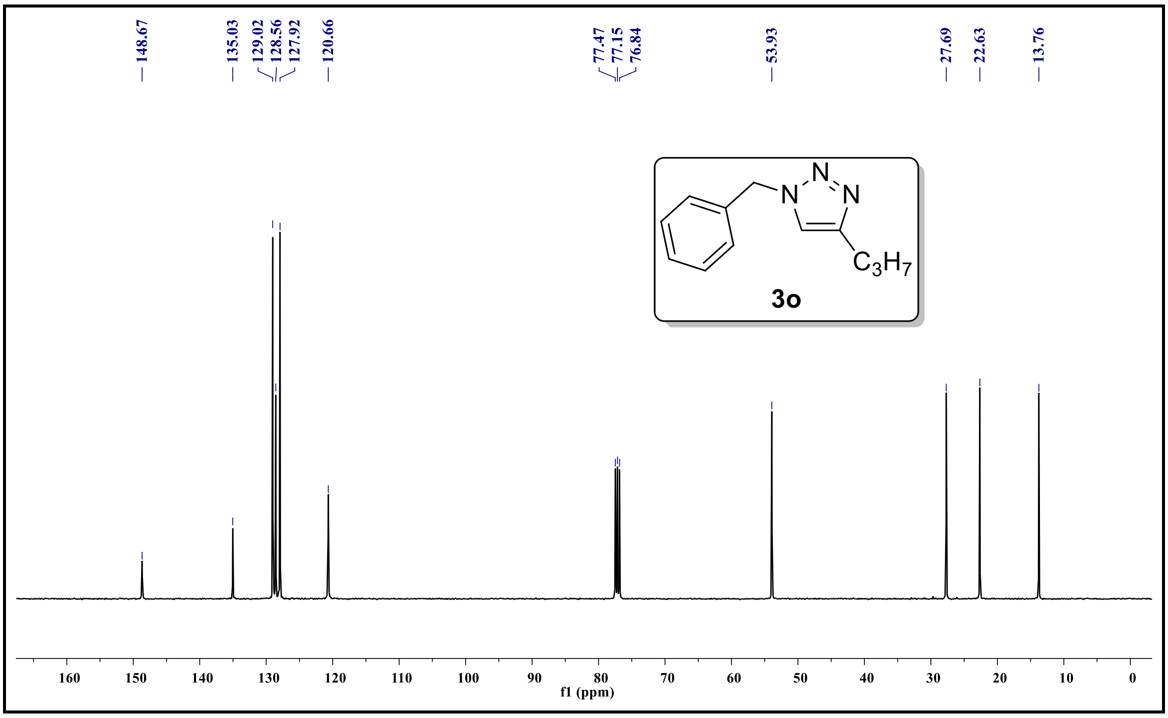
^{1}H NMR spectrum of compound **3n**



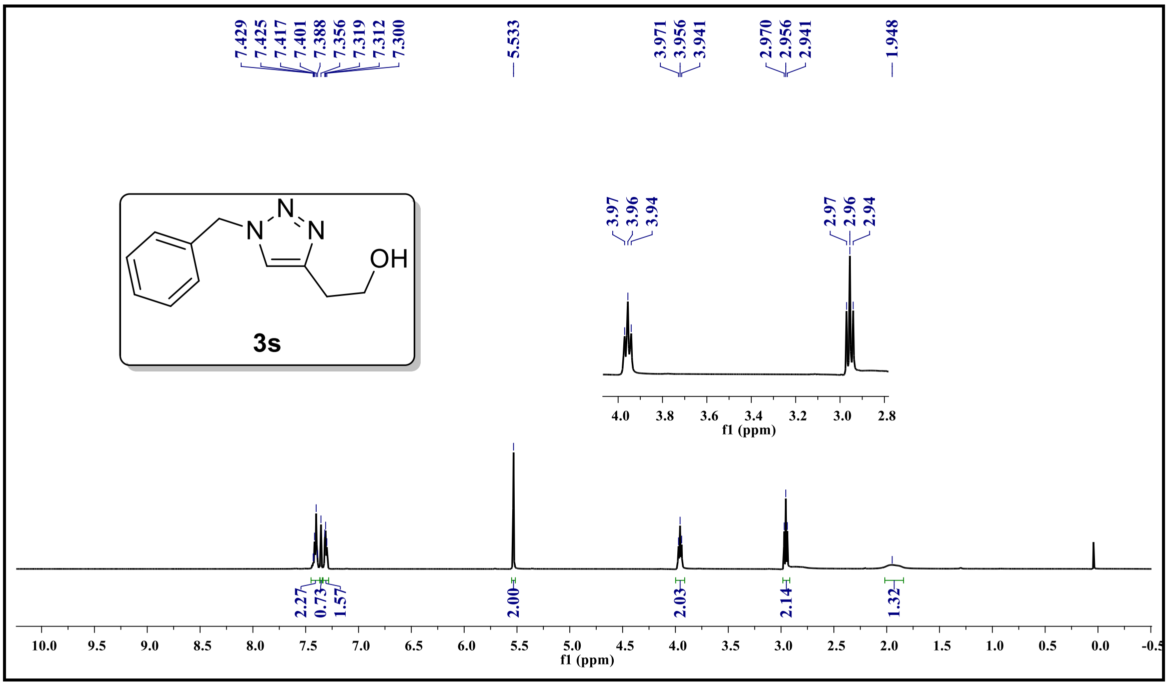
^{13}C NMR spectrum of compound **3n**



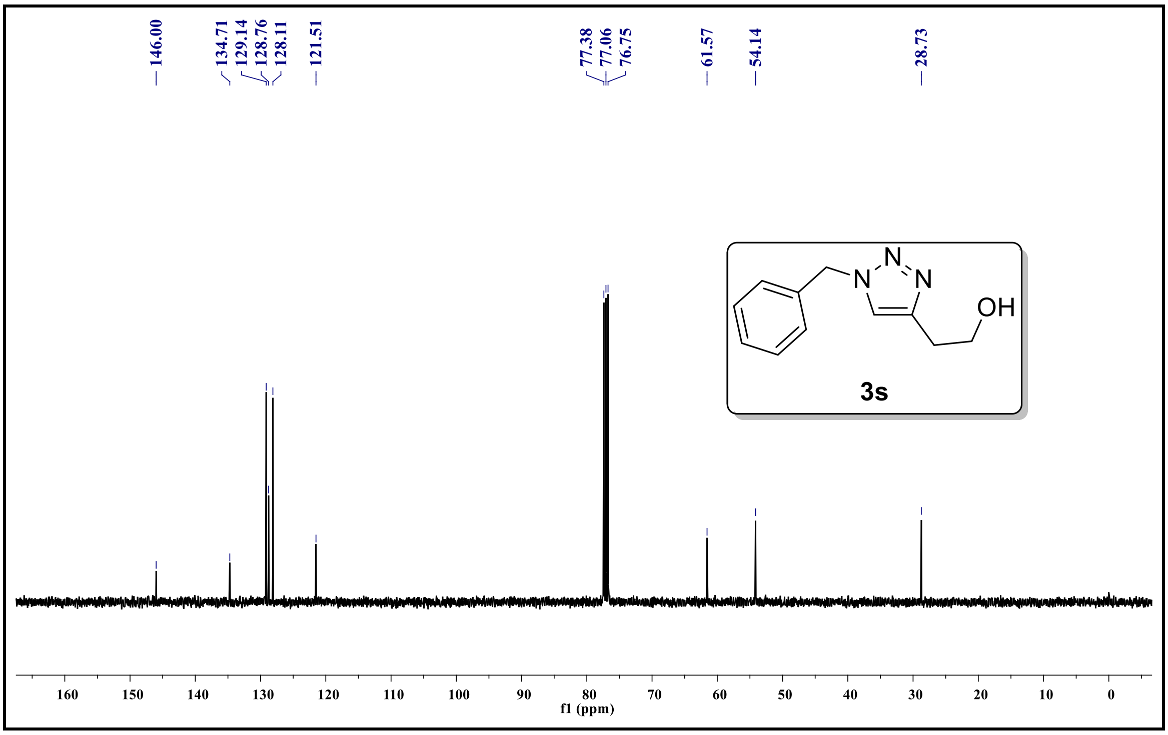
^{1}H NMR spectrum of compound **3o**



^{13}C NMR spectrum of compound **3o**



^{1}H NMR spectrum of compound **3s**



^{13}C NMR spectrum of compound **3s**

CHAPTER IVA

Acid-Catalyzed Benzylation of Arenes with *O*-Benzyl Trichloroacetamidates: Synthesis of Diarylmethanes

4A.1. Introduction

Friedel–Crafts alkylation, which has been known since 1877, is one of the most fundamental processes in organic synthesis. Particularly, diphenylmethane obtained through Friedel–Crafts alkylation of benzene with benzyl chloride, is used in the fragrance industry as a fixative and in the scenting of soaps, as well as in the dye industry as a solvent to improve dyeing characteristics.[1-2]

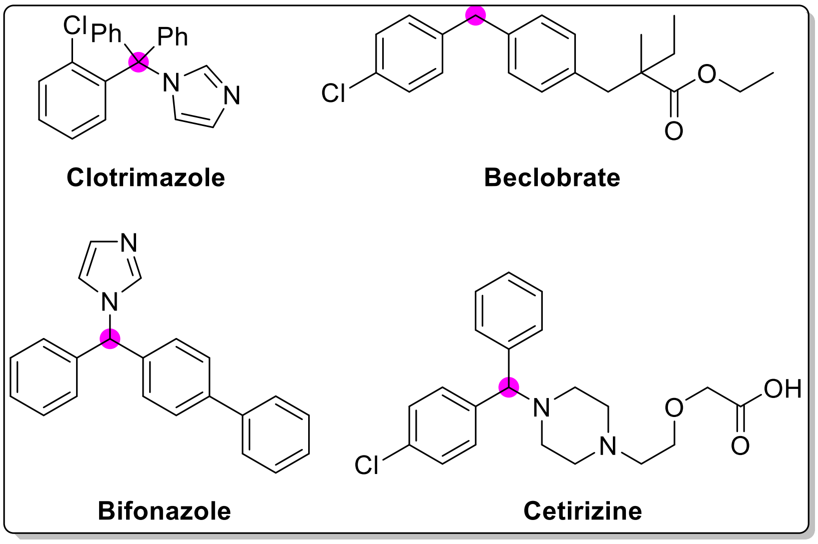


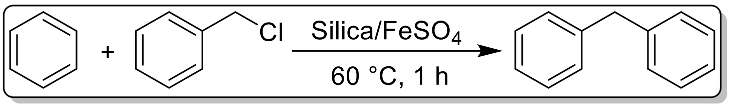
Figure 4A.1. Some examples of pharmaceuticals containing diphenylmethane moiety

Traditionally, Friedel–Crafts alkylation of arenes was carried out using benzyl halide in the presence of Lewis acids such as $AlCl_3$, $FeCl_3$, BF_3, $ZnCl_2$ and H_2SO_4 as catalysts.[3] Although, these catalysts are very active, they are suffer from some disadvantages such as toxicity, corrosion, difficult separation and recovery. To overcome these difficulties heterogeneous catalysts such as supported metal triflates,[4-5] clay materials,[6-7] zeolites[8-9] and mesoporous solid acid catalysts[10-11] were used in place of homogeneous catalysts. Most of these catalysts require longer reaction times and are not selective.

Literature reports revealed that various alkylating reagents were used in Friedel–Crafts alkylation such as benzyl halides,[12] alkenes,[13] benzyl alcohols,[14] aromatic aldehydes,[15-16] benzyl hydroxamates,[17] and benzyl trichloroacetamidates.[18] Although great progress has been achieved in Friedel–Crafts alkylation reactions, nontoxic, green, cheap reagents and simple synthetic procedures still need to be developed.

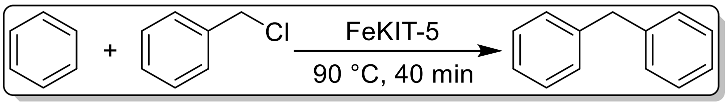
4A.1.1. Different synthetic approaches for the synthesis of diarylmethanes derivatives.

Nuzhdin and co-workers synthesized silica supported $FeSO_4$ by the impregnation of silica with aqueous $FeSO_4$ and investigated the catalytic activity for the benzylation of benzene using benzyl chloride to access diphenylmethane (Scheme 4A.1).[19]



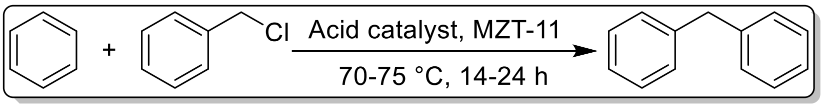
Scheme 4A.1

Anand and co-workers synthesized cage type FeKIT-5 cubic structures with varying n_{Si}/n_{Fe} ratios and characterized using a variety of advanced techniques. These FeKIT-5 catalysts were discovered to be highly efficient for Friedel–Crafts alkylation and the amount of iron incorporated in the KIT-5 silica framework was found to improve the reaction rate (Scheme 4A.2).[20]



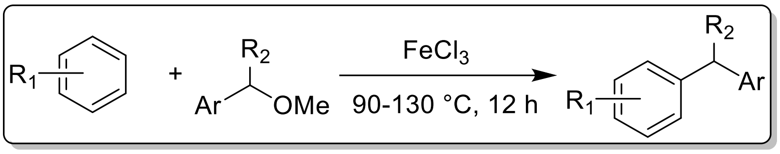
Scheme 4A.2

Bhaumik and co-workers have been reported the synthesis and characterization of mesoporous perovskite $ZnTiO_3$ having cubic pore wall structure. Further, they also investigated the catalytic efficiency of perovskite $ZnTiO_3$ towards the Friedel-Crafts benzylation of aromatics at temperatures ranging from 70 to 75 °C (Scheme 4A.3).[21]



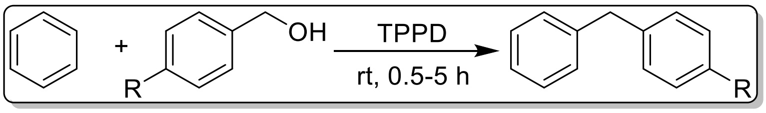
Scheme 4A.3

Zhao and co-workers reported $FeCl_3$-catalyzed Friedel–Crafts alkylation of benzene using various benzyl ethers at 90-130 °C (Scheme 4A.4).[22]



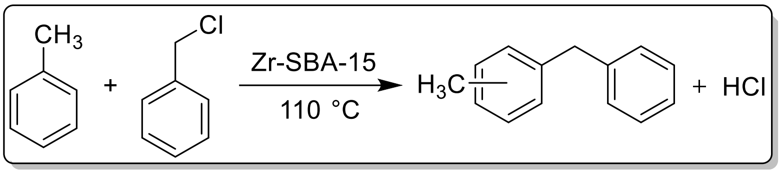
Scheme 4A.4

Khodaei and co-workers developed a new methodology for the synthesis of diarylalkanes using triphenylphosphine ditriflate (TPPD), which was discovered to be an effective promoter for Friedel–Crafts benzylation of arenes with benzyl alcohols in CH_2Cl_2 at ambient temperature (Scheme 4A.5).[23]



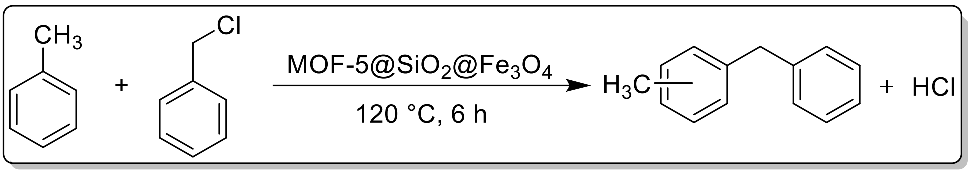
Scheme 4A.5

Gracia et al. synthesized Zr-SBA-15 materials and tested their catalytic activity in the alkylation of aromatics with benzyl chloride. While Zr-SBA-15 materials required more than 12 hours of time to accomplish quantitative conversion of reactant, recovered catalyst showed extremely strong catalytic activity, achieving quantitative conversion in less than 1 hour (Scheme 4A.6).[24]



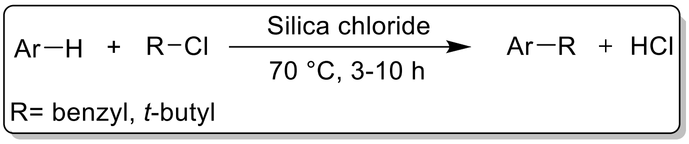
Scheme 4A.6

Li et al. prepared a new magnetic MOFs by encapsulating MOF-5 on the surface of SiO_2 coated Fe_3O_4. By varying the contents of MOF-5, they have prepared a series of MOF-5@SiO_2@Fe_3O_4 catalysts. Further, they evaluated the catalytic activities of the magnetic MOF-5@SiO_2@Fe_3O_4 catalysts for the Friedel–Crafts alkylation of toluene with benzyl chloride to access corresponding diaryl alkane (Scheme 4A.7).[25]



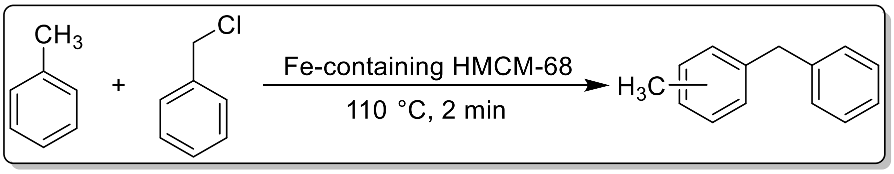
Scheme 4A.7

Mohanazadeh and co-workers developed a simple and easy methodology for Friedel–Crafts alkylation of electron rich aromatic compounds by benzyl and tert-butyl chloride using inexpensive silica chloride as catalyst (Scheme 4A.8).[26]



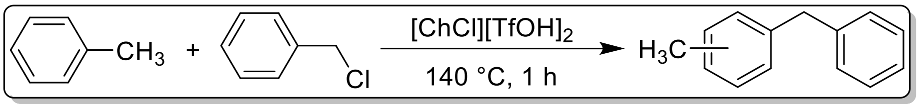
Scheme 4A.8

Liu and co-workers synthesized Fe-containing HMCM-68 by impregnation of HMCM-68 with several iron precursors such as Fe_2O_3/HMCM-68, $FeCl_3$/HMCM-68 and characterised their structure by various analytical techniques. Moreover, Fe-containing HMCM-68 showed high catalytic efficiency and selectivity towards the benzylation of toluene with benzyl chloride in a short reaction time (Scheme 4A.9).[27]



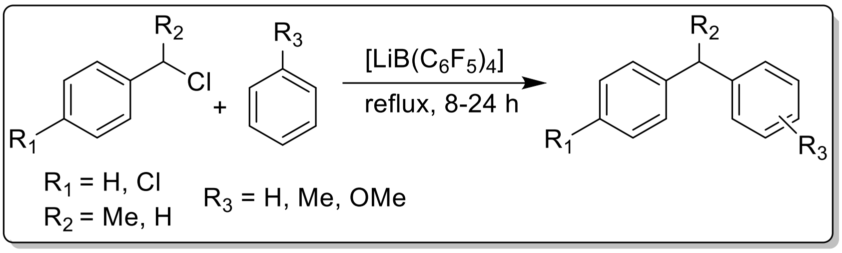
Scheme 4A.9

Ghiaci and co-workers prepared brønsted acidic deep eutectic solvent, [ChCl][TfOH]$_2$, by combining choline chloride (ChCl) with trifloromethanesulfonic acid (TfOH) in a molar proportion of 2:1. [ChCl][TfOH]$_2$ showed excellent catalytic activity, selectivity in the Friedel–Crafts benzylation using benzyl Alcohol as a benzylating agent (Scheme 4A.10).[28]



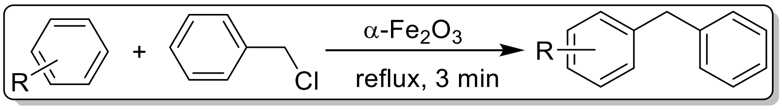
Scheme 4A.10

Mukaiyama et al. utilized Lithium tetrakis(pentafluorophenyl)borate [$LiB(C_6F_5)_4$], a neutral salt to effectively synthesise diaryl alkanes from aromatic compounds with benzyl chloride or mesylate. In the presence of magnesium oxide, these $LiB(C_6F_5)_4$-catalyzed reactions proceeded more efficiently (Scheme 4A.11).[29]



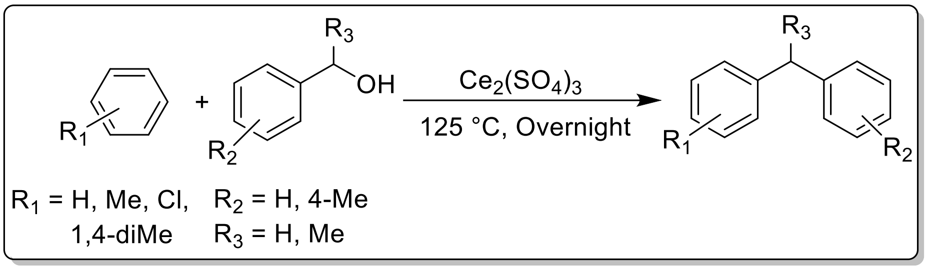
Scheme 4A.11

Cuong et al. used a hydrothermal technique to synthesise nanoporous hematite nanoparticles (α-Fe_2O_3) and studied their catalytic performance in the benzylation of benzene and various aromatic compounds in the manufacture of diaryl alkane with good selectivity (Scheme 4A.12).[30]



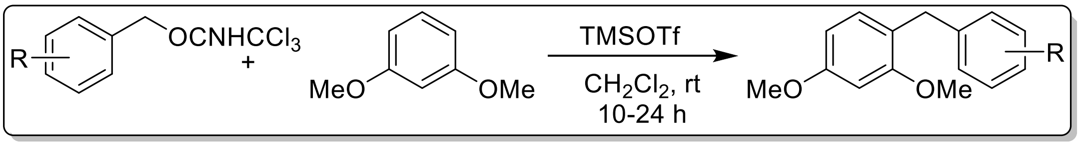
Scheme 4A.12

Li and co-workers devised a new approach for Friedel Crafts alkylation of aromatic compounds with benzyl alcohols, including primary and secondary benzyl alcohols, as well as allyl alcohol, using $Ce_2(SO_4)_3$ as a catalyst. The catalyst was also recycled and used three cycles without losing substantial catalytic activity (Scheme 4A.13).[31]



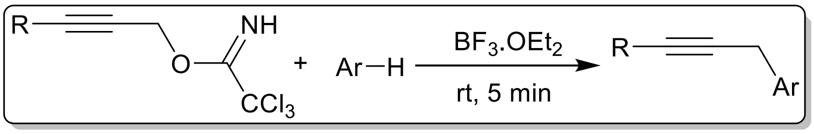
Scheme 4A.13

Schmidt and co-workers reported an efficient method for the synthesis of diarylmethanes by the benzylation of arenes using corresponding *O*-benzyl trichloroacetimidates having only electron-withdrawing substituents in the presence of catalytic amounts of TMSOTf afford the corresponding diarylmethane derivatives at room temperature (Scheme 4A.14).[18]



Scheme 4A.14

Wang and co-workers demonstrated a highly efficient methodology to synthesize 1,3-diarylpropynes at room temperature in the presence of a catalytic amount of cheap and readily available $BF_3.OEt_2$ in good to excellent yields (Scheme 4A.15).[32]

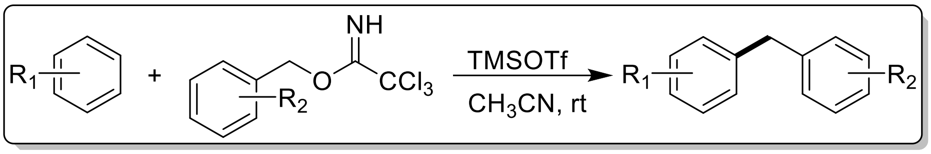


Scheme 4A.15

4A.2. Present work

Friedel crafts alkylation reaction has been studied extensively. Alkyl halides, alkyl ethers, alcohols, and alkyl trichloroacetamidates were utilised as alkylating agents, and Lewis, Bronsted acid catalysts were used as catalysts in this literature. Despite the huge success of the reported methods using alcohols, ketones, alkyl halides, and alkyl ethers, there are still significant flaws such as long reaction times, reflux or high temperatures and the use of rare and expensive transition metal catalysts. Therefore, to overcome these problems, the development of new methodologies is desirable.

However, there is only one report using benzyl trichloroacetamidates as benzylating agent, which suffers from the lack of substrate scope and requires EDG on trichloroacetamidate. Thus, herein we report an efficient one-pot synthesis of diaryl methanes from alkyl trichloroacetamidates with arenes in acetonitrile at ambient temperature within short reaction times (Scheme 4A.16).



Scheme 4A.16

By applying above protocol to various substituted alkyl trichloroacetamidates and substituted arenes, we have synthesized library of diaryl methanes.

4A.3. Results and discussion

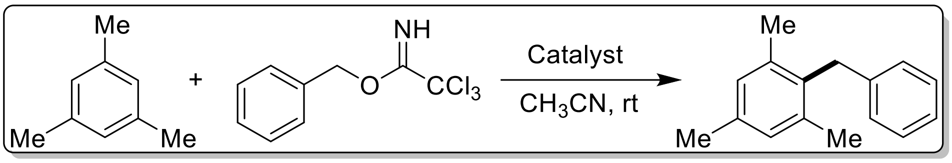


Table 4A.1. Optimisation of reaction conditions[a]

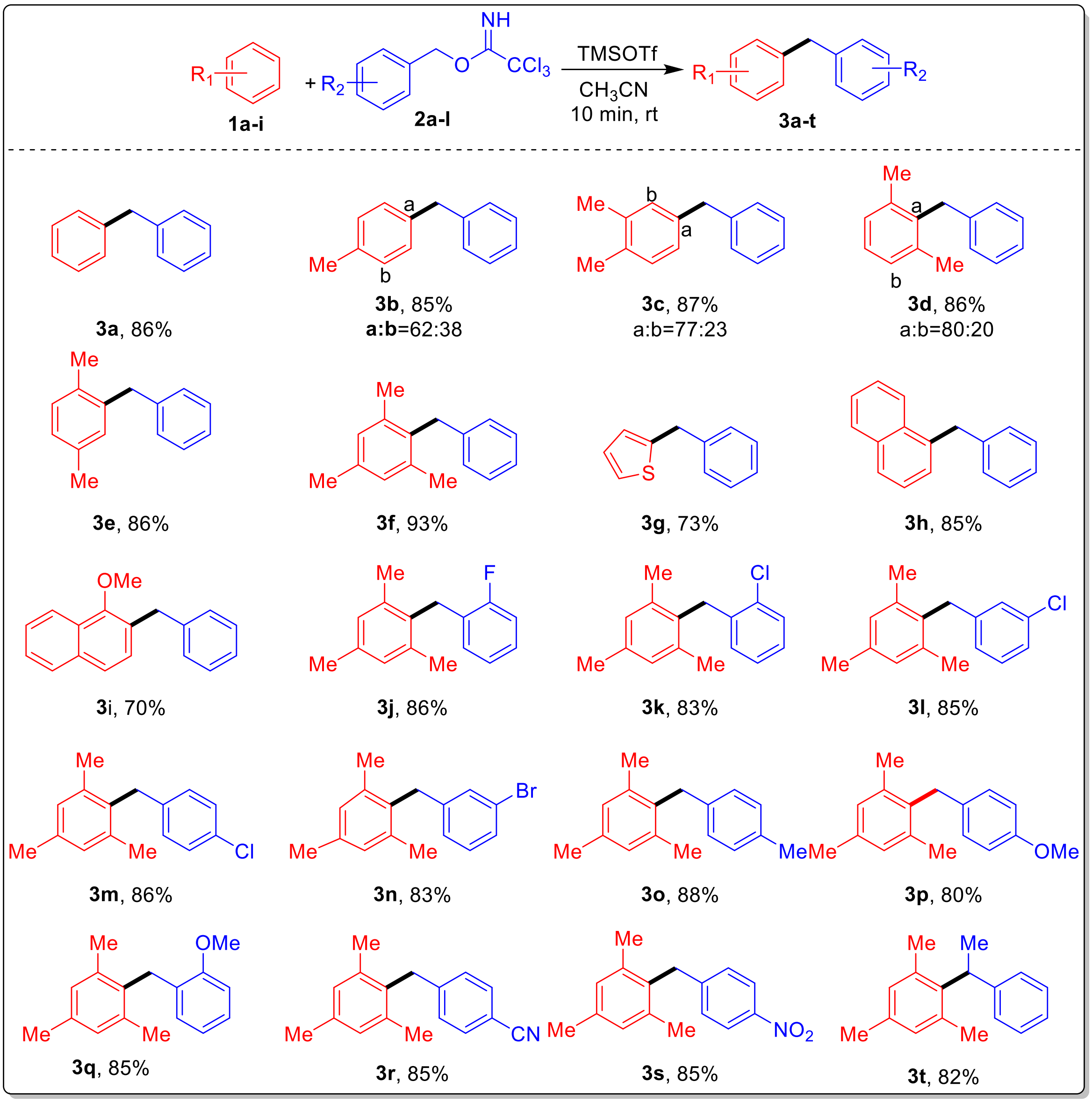
S.NO	Solvent	Catalyst	Catalyst (equiv.)	Time (Min)	Yield[b] (%)
1	MeOH	TMSOTf	1.0	10	0
2	Acetone	TMSOTf	1.0	10	46
3	Diethylether	TMSOTf	1.0	10	55
4	CH_2Cl_2	TMSOTf	1.0	10	79

5	DCE	TMSOTf	1.0	10	65
6	1,4-dioxane	TMSOTf	1.0	10	10
7	CH_3CN	TMSOTf	1.0	10	93
8	DMF	TMSOTf	1.0	10	68
9	CH_3CN	$AlCl_3$	1.0	20	62
10	CH_3CN	$FeCl_3$	1.0	20	89
11	CH_3CN	TfOH	1.0	20	64
12	CH_3CN	$BF_3.Et_2O$	1.0	20	78
13	CH_3CN	$SnCl_2$	1.0	25	57
14	CH_3CN	TMSOTf	0.5	10	92[c]
15	CH_3CN	TMSOTf	0.2	10	93[d]
16	**CH_3CN**	**TMSOTf**	**0.1**	**10**	**93**[e]

[a]Reaction Conditions: Mesitylene **1f** (1.0 equiv.), benzyl-2,2,2-trichloroacetamidate **2a** (1.0 equiv.), acid catalyst, solvent (1.0 mL) at room temperature. [b]Yields are of isolated pure products. [c]TMSOTf (0.5 equiv.). [d]TMSOTf (0.2 equiv.). [e]TMSOTf (0.1 equiv.).

Table 4A.1 summarises the optimization reactions for diarylmethane production. Mesitylene **1f** and benzyl-2,2,2- trichloroacetamidate **2a** were chosen as model substrates for the optimization to obtain corresponding diarylmethane **3f**. Initially, Mesitylene (1.0 equiv.), benzyl-2,2,2-trichloroacetate (1.0 equiv.), TMSOTf (1.0 equiv.) and methanol were mixed at room temperature but no product was observed (Table 4A.1, entry 1). Furthermore, we studied the reaction conditions utilising various solvents such as acetone, diethyl ether, DCM, DCE, 1,4-dioxane, CH_3CN, and DMF to determine the influence of solvents (Table 4A.1, entries 2-8). From this study we found that diphenylmethane was produced with a high yield only in the presence of CH_3CN (Table 4A.1, entry 7). Later, to assess the efficiency of catalysts, reaction was investigated by using various acid catalysts such as $AlCl_3$, $FeCl_3$, TfOH, $BF_3.Et_2O$, $SnCl_2$ (Table 4A.1, entries 9-13). Among all tested catalysts, TMSOTf showed efficient catalytic activity toward trichloroacetamidate to afford excellent yield of diphenylmethane (Table 4A.1, entry 7). Finally, we have conducted another set of reactions, to determine the role stoichiometry of TMSOTf on the product yield (Table 4A.1, entries 14-16). These reactions demonstrated that the reaction rate, product yield are unaffected and 0.1 equivalents of TMSOTf is enough to get the desired product in 10 min (Table 4A.1, entry 16).

Table 4A.2. Synthesis of diaryl methane derivatives[a, b]



3a, 86%
3b, 85% a:b=62:38
3c, 87% a:b=77:23
3d, 86% a:b=80:20
3e, 86%
3f, 93%
3g, 73%
3h, 85%
3i, 70%
3j, 86%
3k, 83%
3l, 85%
3m, 86%
3n, 83%
3o, 88%
3p, 80%
3q, 85%
3r, 85%
3s, 85%
3t, 82%

[a]Reaction Conditions: Arene **1a-i** (1.0 equiv.), alkyl trichloroacetamidate **2a-l** (1.0 equiv.), TMSOTf (0.1 equiv.), CH_3CN (1.0 mL) at room temperature. [b]Yields are of isolated pure products.

Various substituted benzyl trichloroacetamidates and substituted arenes were used to produce corresponding diaryl methanes to evaluate the substrate scope and generality of our synthetic approach and results are summarized in Table 4A2. Benzene and toluene easily underwent alkylation reaction to afford corresponding diarylmethanes with high yields (Table 4A.2, **3a-b**).

Di methyl substituted arenes such *o*-xylene, *m*-xylene, *p*-xylene were also reacted with benzyl trichloroacetamidate to form the corresponding alkylated products in good yields (Table 4A.2, **3c-e**). Tri methyl substituted arene *i.e.*, mesitylene underwent reaction smoothly and gave excellent yield of diaryl methane (Table 4A.2, **3f**). It is worth mentioning that compounds like thiophene, substituted naphthalene easily produced respective diaryl methanes in 73%, 85% and 70% respectively (Table 4A.2, **3g-i**).

Further, we also investigated the alkylation reaction using various substituted alkyl trichloroacetamidates. It is worth noting that halogen (-F, -Cl, -Br) substitutions in the *ortho*, *meta*, and *para* positions of benzyl trichloroacetamidate undergo alkylation reactions without any difficulty and have minimal effect on reaction yields (Table 4A.2, **3j-n**). Electron donating groups like –Me, -MeO substituted benzyl trichloroacetamidates (Table 4A.2, **3o-q**) and electron withdrawing groups like –CN, -NO_2 substituted benzyl trichloroacetamidates (Table 4A.2, **3r-s**) underwent reaction smoothly to form corresponding diarylmethanes in good reaction yields. Surprisingly, secondary alkyl trichloroacetamidate also underwent a smooth reaction to give good yields of corresponding diaryl methane (Table 4A.2, **3t**).

4A.4. Conclusions

In this chapter, we have developed a new methodology for the synthesis of diaryl methanes using benzyl trichloroacetamidate and arenes in presence of TMSOTf at room temperature. Short reaction times, high reaction yields, and simple synthetic procedure are the advantages of this method. This protocol tolerates various substitutions (halogens, EDG and EWG) on benzyl trichloroacetamidate, and various substitutions on arene. We have synthesized 20 compounds with 68–93 % of yield using variety of arenes and alkyl trichloroacetamidates.

4A.5. Experimental Section

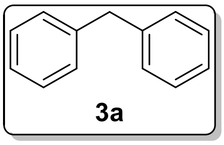
General Information. Alcohols, CCl_3CN, DBU, Lewis acids and aromatic compounds were purchased from a commercial source and used as received. Reactions were conducted in round bottom flasks. Thin layer chromatography was performed on 200 µm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. ^1H NMR spectra were obtained at 400 MHz in $CDCl_3$ and were referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ and were referenced to the solvent resonance. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) were in hertz (Hz). Standard abbreviations were used to designate resonance multiplicities. Melting points were determined with a melting point apparatus and are uncorrected.

Procedure for the preparation of trichloroacetamidate (2a-l). In an oven dried round bottom flask, benzyl alcohol (1.0 equiv.) and DBU (0.1 equiv.) were stirred in dichloromethane for 5 minutes at 0 °C, then trichloroacetonitrile (1.5 equiv.) was added drop wise to the reaction mixture and allowed to stir until trichloroacetamidate was formed (monitored by TLC). After completion, the organic layer was separated, dried with Na_2SO_4, and evaporated to yield a residue that was purified using ethyl acetate and *n*-hexanes as an eluent on a silica gel column chromatography.

General procedure for the synthesis of diaryl methane (3a-t). A round bottom flask charged with arene **1a-i** (1.0 equiv.), alkyl trichloroacetamidate **2a-l** (1.0 equiv.) in CH_3CN (1.0 mL). Then, TMSOTf (0.1 equiv.) was added drop wise at 0 °C and stirring was continued at room temperature for 10 min. After completion (monitored by TLC), reaction mixture was extracted with water and ethylacetate (3 x 20 mL). The extracted organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure using a rota evaporator. Purification of the crude reaction mixture was done by silica gel column chromatography using hexanes and ethylacetate as eluent.

4A.6. Spectral data

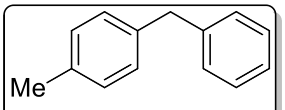
Diphenylmethane (3a)[33]



3a

Colorless liquid (86%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38–7.31 (m, 4H), 7.29–7.22 (m, 6H), 4.05 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.1, 129.0, 128.5, 126.1, 77.3, 42.0.

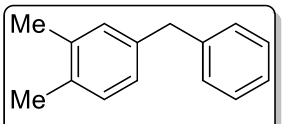
1-Benzyl-4-methylbenzene (3b)[33]



3b

Colorless liquid (85%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39–7.34 (m, 2H), 7.30–7.23 (m, 5H), 7.21 (d, J = 8.4 Hz, 2H), 4.03 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.5, 140.5, 139.1, 138.2, 136.8, 135.7, 130.4, 130.1, 129.3, 129.0, 128.9, 128.9, 128.6, 128.5, 127.0, 126.6, 126.1, 126.0, 41.7, 39.6, 21.1, 19.8.

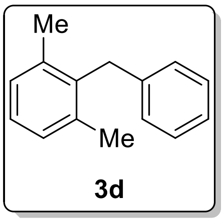
4-Benzyl-1,2-dimethylbenzene (3c)[34]



3c

Colorless liquid (87%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42–7.18 (m, 8H), 4.03 (s, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.6, 140.9, 138.8, 138.6, 137.1, 136.6, 135.3, 134.3, 130.3, 129.8, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.5, 126.4, 126.0, 125.9, 125.5, 41.6, 40.1, 20.8, 19.8, 19.4, 15.5.

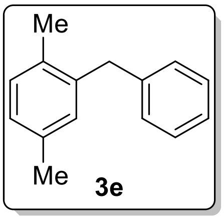
2-Benzyl-1,3-dimethylbenzene (3d)[35]



3d

Colorless liquid (86%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.29 (m, 2H), 7.19 (d, J = 7.2 Hz, 2H), 7.11–7.01 (m, 4H), 4.02 (s, 2H), 2.38 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.8, 137.2, 136.5, 136.0, 131.2, 130.0, 128.8, 128.4, 128.2, 127.9, 126.7, 126.4, 125.9, 125.8, 39.1, 35.1, 21.0, 20.3, 19.7.

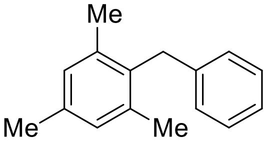
2-Benzyl-1,4-dimethylbenzene (3e)[33]



3e

Colorless liquid (86%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.17 (t, J = 7.4 Hz, 2H), 7.11–7.05 (m, 1H), 7.03 (d, J = 7.4 Hz, 2H), 6.96 (d, J = 7.6 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.84 (s, 1H), 3.85 (s, 2H), 2.19 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 136.0, 134.0, 130.7, 128.8, 126.1, 125.5, 124.0, 123.7, 122.4, 121.2, 34.8, 16.3, 14.5.

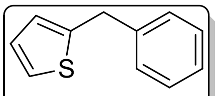
2-Benzyl-1,3,5-trimethylbenzene (3f)[33]



3f

Colorless liquid (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, J = 7.4 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 6.91 (d, J = 7.2 Hz, 2H), 6.79 (s, 2H), 3.92 (s, 2H), 2.19 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 135.5, 132.4, 131.0, 129.2, 124.3, 124.0, 123.8, 123.3, 121.1, 30.1, 16.3, 15.5.

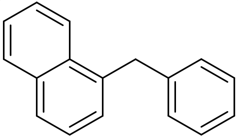
2-Benzylthiophene (3g)[36]



3g

Colorless liquid (73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.30 (m, 6H), 6.99 (s, 2H), 4.22 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 139.3, 136.8, 135.9, 135.7, 124.1, 123.9, 123.9, 123.9, 122.1, 121.8, 121.5, 120.9, 120.5, 119.2, 116.5, 31.8, 31.3.

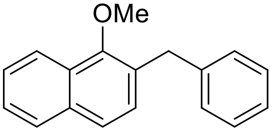
1-Benzylnaphthalene (3h)[33]



3h

Colorless liquid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.85 (m, 2H), 7.79−7.69 (m, 2H), 7.63−7.50 (m, 3H), 7.33−7.26 (m, 5H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 140.7, 138.7, 136.7, 134.0, 133.7, 132.2, 129.1, 128.8, 128.8, 128.6, 128.5, 128.2, 127.7, 127.6, 127.4, 127.2, 127.2, 126.2, 126.1, 126.1, 125.6, 125.4, 124.4, 42.2, 39.1.

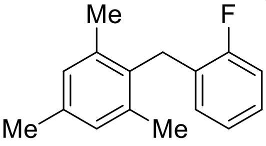
2-Benzyl-1-methoxynaphthalene (3i)[37]



3i

Colorless liquid (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 6.3, 3.3 Hz, 2H), 7.36–7.29 (m, 3H), 7.28–7.21 (m, 5H), 6.82 (d, J = 8.0 Hz, 1H), 4.44 (s, 2H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 141.2, 133.0, 128.7, 128.5, 127.3, 126.6, 126.0, 125.0, 124.2, 122.6, 103.4, 55.5, 38.7.

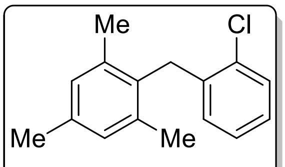
2-(2-fluorobenzyl)-1,3,5-trimethylbenzene (3j)



3j

Colorless liquid (86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90–6.84 (m, 3H), 6.83–7.78 (d, J = 4.9 Hz, 3H), 3.89 (s, 2H), 2.21 (s, 3H), 2.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 160.0, 136.9, 135.9, 135.7, 135.6, 133.7, 129.2, 129.1, 129.0, 115.2, 115.0, 33.9, 20.9, 20.1.

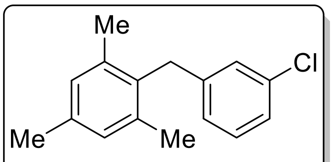
2-(2-chlorobenzyl)-1,3,5-trimethylbenzene (3k)



3k

Colorless liquid (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 8.0, 1.2 Hz, 1H), 7.05–6.99 (m, 1H), 6.94 (td, J = 7.6, 1.2 Hz, 1H), 6.82 (s, 2H), 6.49 (dd, J = 8.0, 0.8 Hz, 1H), 3.95 (s, 2H), 2.22 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.3, 136.0, 134.4, 132.6, 129.1, 129.0, 128.2, 127.1, 126.9, 32.4, 21.0, 19.9.

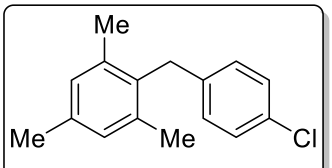
2-(3-chlorobenzyl)-1,3,5-trimethylbenzene (3l)



3l

Colorless liquid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 –7.11 (m, 2H), 7.04–7.01 (d, J = 0.8 Hz, 1H), 6.91 (s, 3H), 3.99 (s, 2H), 2.31 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 137.0, 136.1, 134.5, 133.0, 129.7, 129.2, 128.1, 126.2, 126.2, 34.6, 21.1, 20.3.

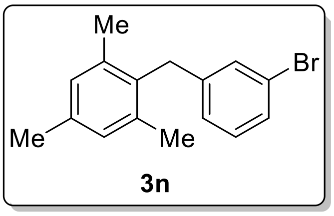
2-(4-chlorobenzyl)-1,3,5-trimethylbenzene (3m)[38]



3m

Colorless liquid (86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.08 (m, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.81 (s, 2H), 3.89 (s, 2H), 2.21 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 136.9, 136.0, 133.3, 131.4, 129.2, 129.0, 128.5, 34.1, 20.9, 20.1.

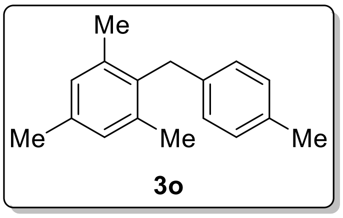
2-(3-bromobenzyl)-1,3,5-trimethylbenzene (3n)



3n

Colorless liquid (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 11.0 Hz, 3H), 4.06 (s, 2H), 2.37 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 132.2, 131.3, 128.1, 126.2, 125.2, 124.3, 124.2, 121.8, 117.9, 29.7, 16.2, 15.4.

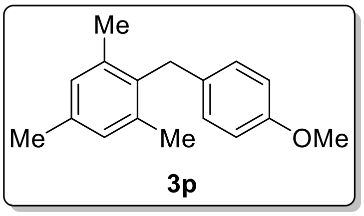
1,3,5-trimethyl-2-(4-methylbenzyl)benzene (3o)[38]



3o

Colorless liquid (88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.6 Hz, 2H), 7.04 (d, J = 9.6 Hz, 4H), 4.12 (s, 2H), 2.43 (s, 6H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 130.9, 130.4, 129.3, 124.4, 124.2, 123.0, 29.6, 16.3, 16.2, 15.4.

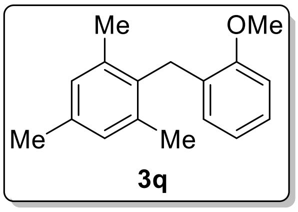
2-(4-methoxybenzyl)-1,3,5-trimethylbenzene (3p)[39]



3p

Colorless liquid (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84–6.79 (m, 2H), 6.78 (s, 2H), 6.69–6.64 (m, 2H), 3.84 (s, 2H), 3.63 (s, 3H), 2.18 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 137.0, 135.6, 134.3, 132.1, 129.8, 129.0, 128.8, 113.8, 55.3, 33.9, 21.0, 20.2.

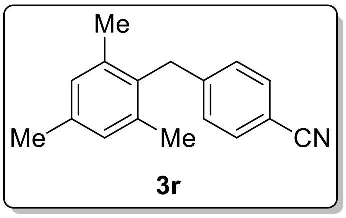
2-(2-methoxybenzyl)-1,3,5-trimethylbenzene (3q)



3q

Colorless liquid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, J = 8.0 Hz, 1H), 6.81 (s, 2H), 6.79 (d, J = 8.0 Hz, 1H), 6.66 (t, J = 7.2 Hz, 1H), 6.43 (d, J = 7.6 Hz, 1H), 3.85 (s, 2H), 3.82 (s, 3H), 2.22 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 137.4, 135.5, 133.5, 128.8, 128.2, 127.5, 126.7, 120.5, 109.6, 55.3, 28.4, 21.0, 19.9.

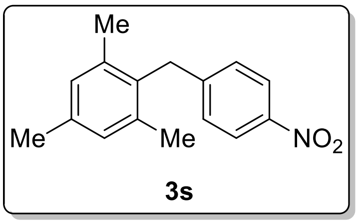
4-(2,4,6-trimethylbenzyl)benzonitrile (3r)



3r

Colorless liquid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.83 (s, 2H), 3.98 (s, 2H), 2.22 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 136.9, 136.4, 132.2, 132.2, 129.2, 128.6, 119.1, 109.7, 34.9, 20.9, 20.1.

1,3,5-trimethyl-2-(4-nitrobenzyl)benzene (3s)[40]

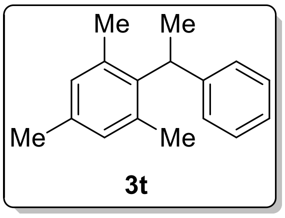


3s

Colorless liquid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.83 (s, 2H), 4.01 (s, 2H), 2.21 (s, 3H), 2.09 (s, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 148.3, 146.3, 136.9, 136.5, 132.1, 129.2, 128.6, 123.7, 34.8, 20.9, 20.1.

1,3,5-trimethyl-2-(1-phenylethyl)benzene (3t)[41]



3t

Colorless liquid (82%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (m, 2H), 7.51 (d, J = 7.2 Hz, 2H), 7.47 (t, J = 7.0 Hz, 1H), 7.16 (s, 2H), 4.98 (q, J = 7.2 Hz, 1H), 2.59 (s, 3H), 2.45 (s, 6H), 1.99 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 140.4, 136.7, 135.6, 130.4, 128.5, 127.1, 125.6, 38.1, 21.4, 21.1, 17.2.

4A.7. References

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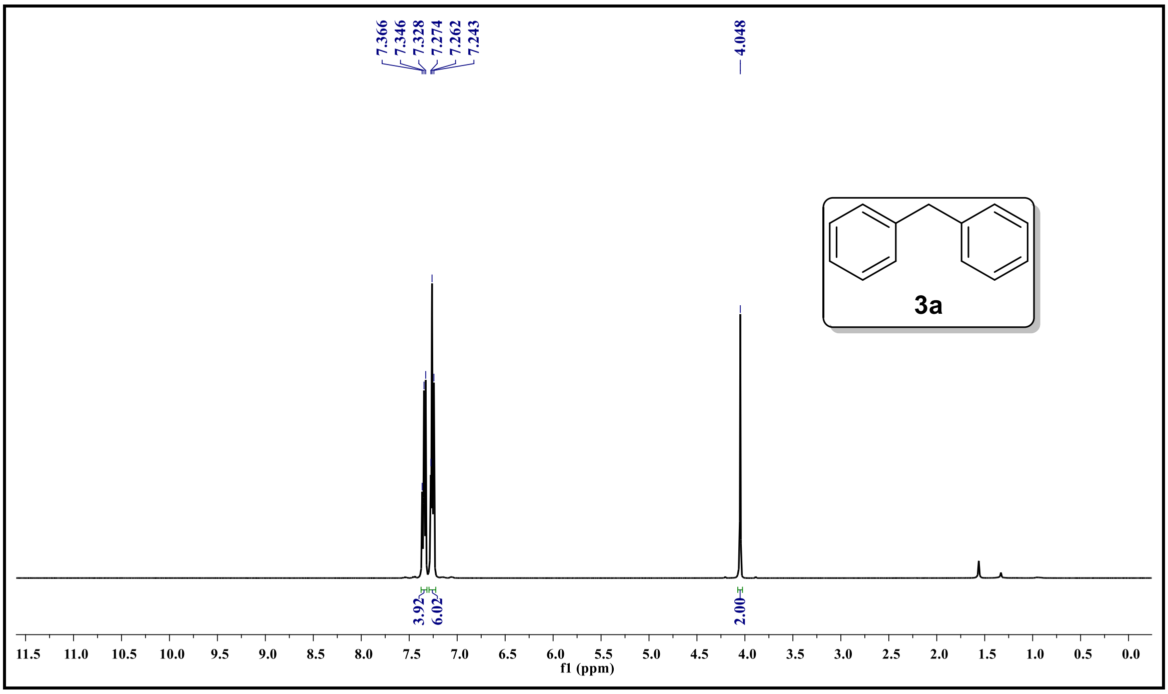
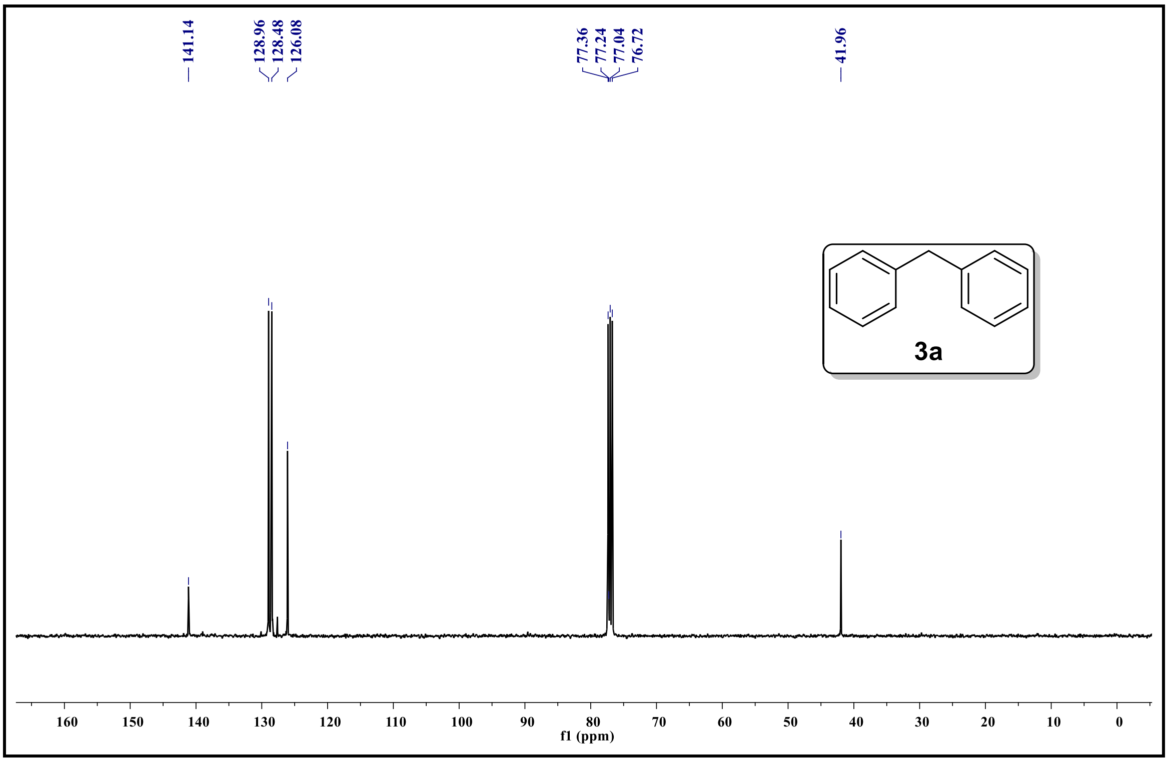
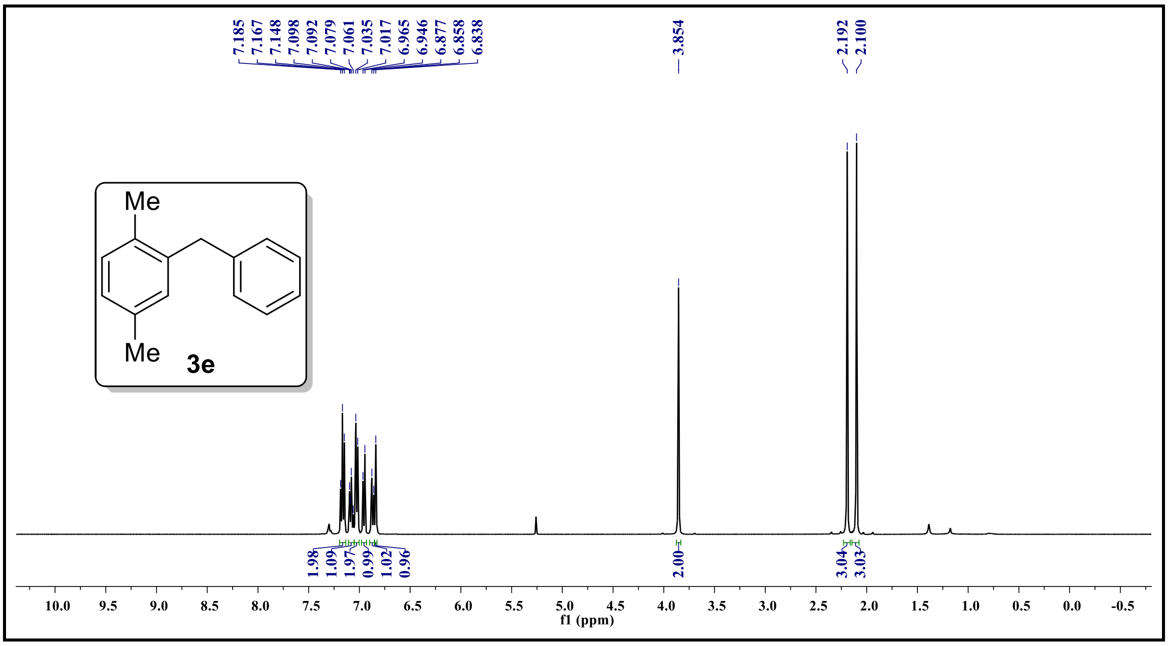
4A.8. Selected ^{1}H and ^{13}C NMR Spectra



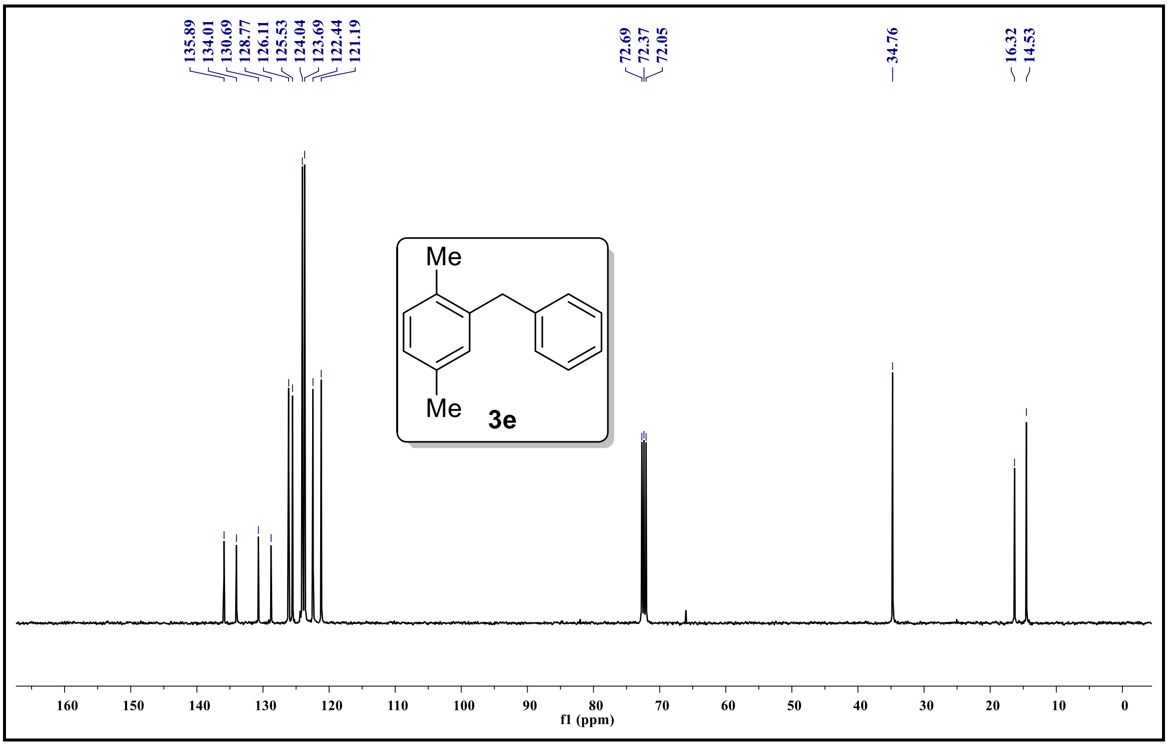
^{1}H NMR spectrum of compound **3a**



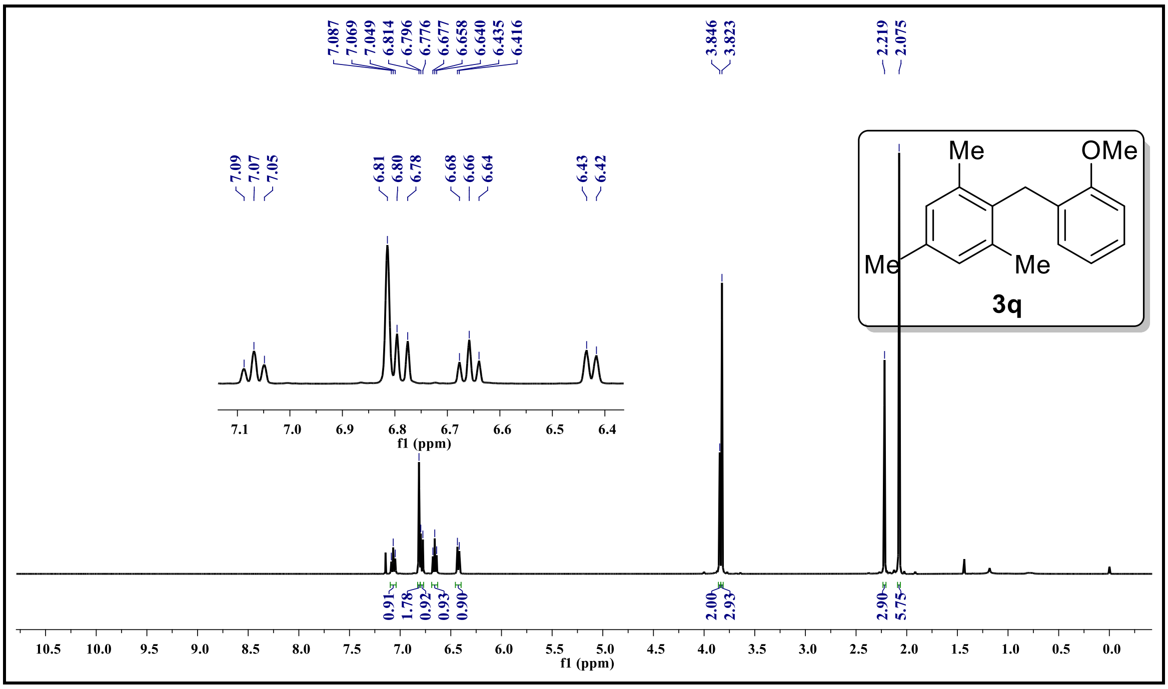
^{13}C NMR spectrum of compound **3a**



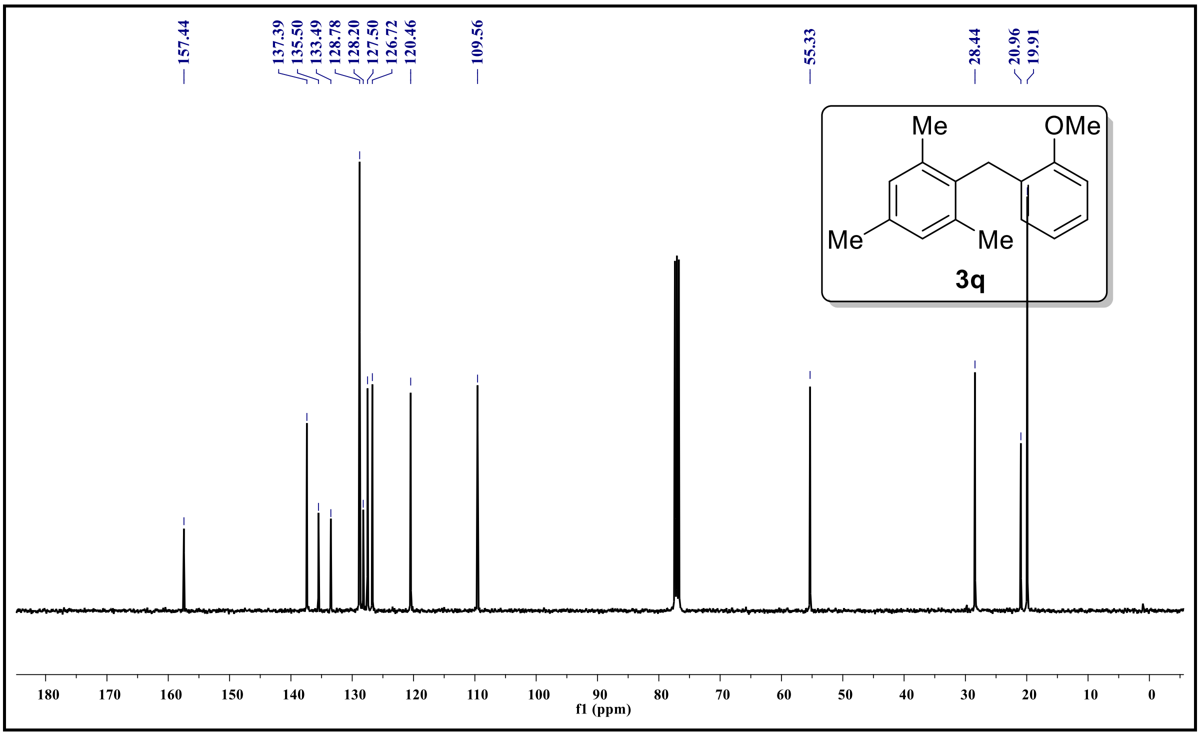
^{1}H NMR spectrum of compound **3e**



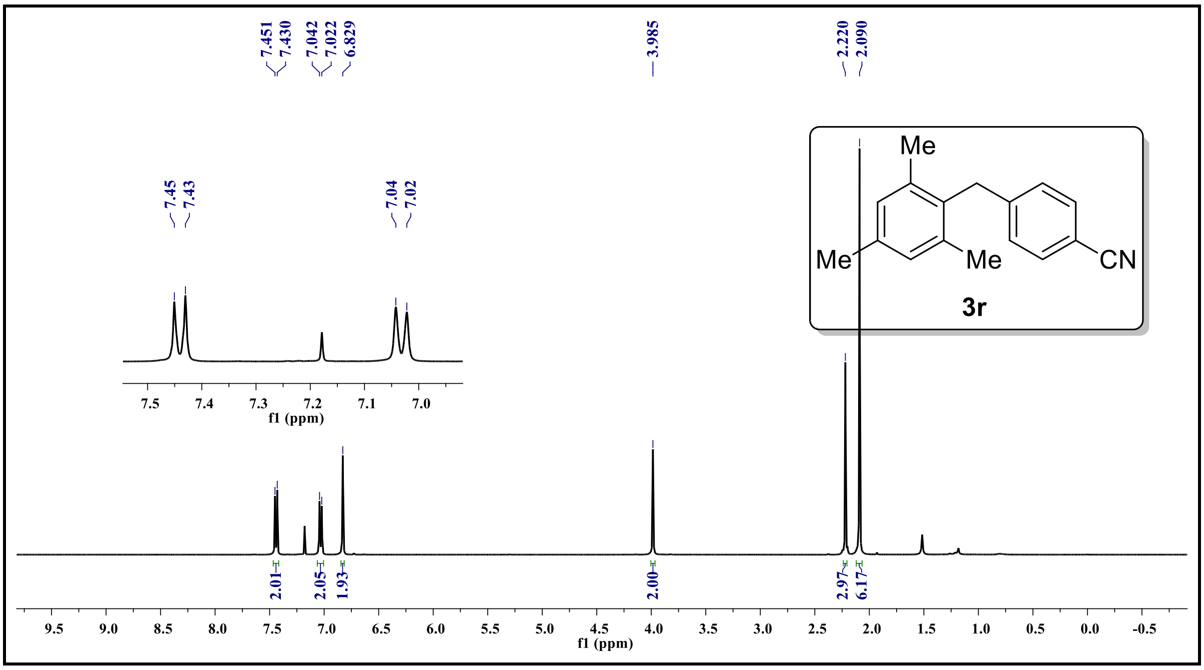
^{13}C NMR spectrum of compound **3e**



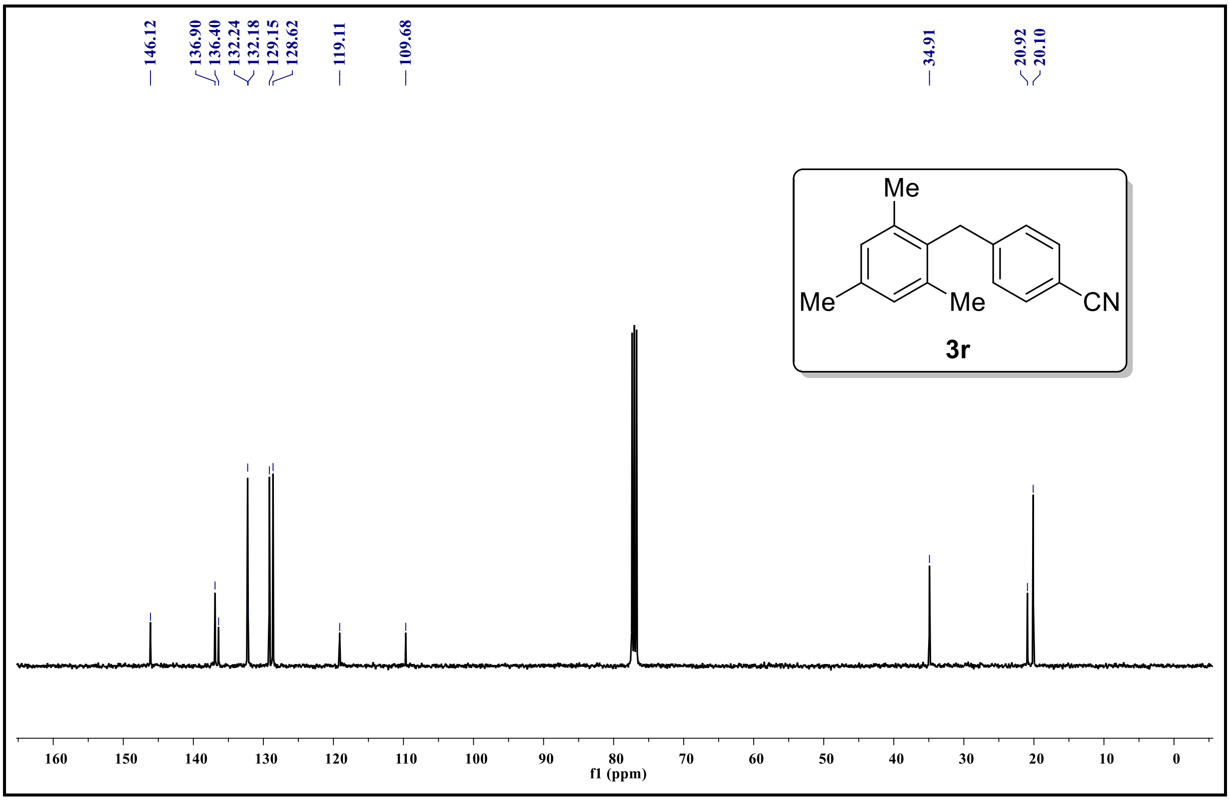
^{1}H NMR spectrum of compound **3q**



^{13}C NMR spectrum of compound **3q**



^{1}H NMR spectrum of compound **3r**



^{13}C NMR spectrum of compound **3r**

CHAPTER IV (PART-B)

A Facile One-Pot Synthesis of 2,2,2-Trichloroacetates through Acid-Catalyzed Deimination

4B.1. Introduction

Halogens are widely distributed and are present in a wide range of natural products and biologically active substances.[1] Because of its abundant presence in naturally occurring compounds as well as its inclusion in the repertoire of medicines and agrochemicals, substitution with chlorine, particularly the one involving fully chlorinated trichloromethyl group (CCl_3), has aroused the curiosity of chemists all over.[2] Also, trichloromethyl group (CCl_3) plays a pivotal role in the biological activity of many molecules, such as larvicidal activity, to treat anxiety disorders and anti-Alzheimer's Salubrinal (Figure 4B.1).[3–5]

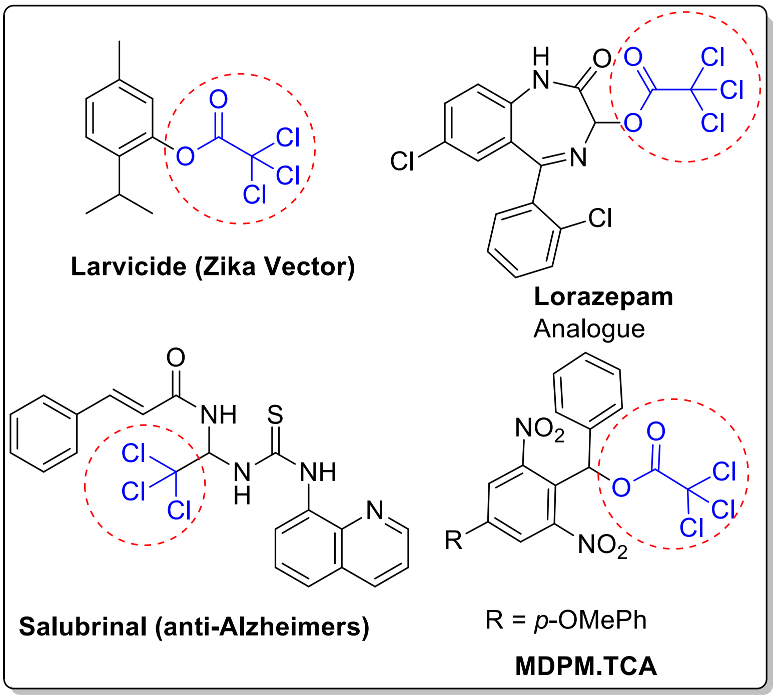
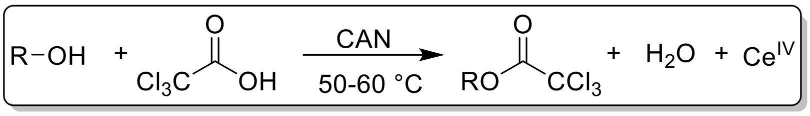


Figure 4B.1. Some of the important trichloromethyl and trichloroacetates

The trichloroacetate synthon is very important intermediate in the synthetic organic chemistry.[6] The trichloroacetate core is used as solvents, buffers, and found in many biologically relevant molecules.[7] It has been used as a good leaving group in carbohydrate chemistry,[8] and also used as carbenes source[9] which are precursors in the Mannich-type of reactions.[10] Corey and Link developed a novel synthetic approach 'Jocic reaction' for preparation of chiral-amino acids, *via* trichloromethylcarbinol as an intermediate.[11] Also, Consequently, the development of methods towards the synthesis of trichloroacetate compounds is of continued interest.

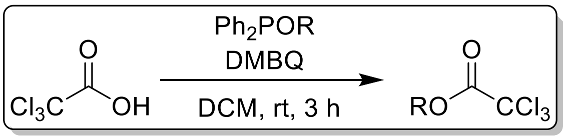
4B.1.1. Different synthetic approaches for the synthesis of ester derivatives

Papori et al. developed a method for the esterification of alcohols and carboxylic acids using ceric ammonium nitrate (CAN) as a catalyst, in excellent yields under mild reaction conditions (Scheme 4B.1).[12]



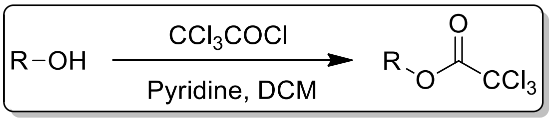
Scheme 4B.1

Shintou et al. prepared alkoxydiphenylphosphines having primary, secondary or tertiary alkoxy groups and used for the redox condensation proceeded to afford carboxylic acid alkyl esters. In this synthesis 2,6-dimethyl-1,4-benzoquinone (DMBQ) used as a mild oxidant (Scheme 4B.2).[13]



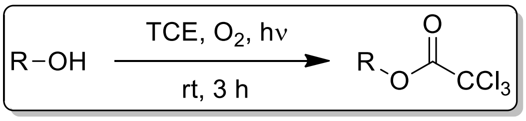
Scheme 4B.2

Kunz and co-workers synthesised trichloroacetates using the corresponding alcohols with trichloroacetyl chloride and pyridine in dichloromethane (Scheme 4B.3).[14]



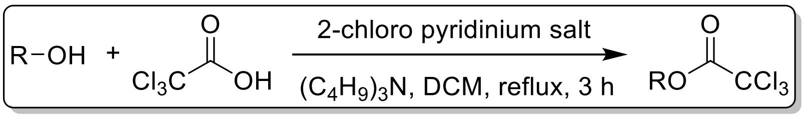
Scheme 4B.3

Zhang et al. developed a synthetic method which produced mixture of toxic compounds such as chlorine, carbon dioxide, epoxides, trichloroacetyl chloride (TCAC) and phosgene by the oxidative photodecomposition of tetrachloroethylene (TCE) without using any harsh conditions. Further, acyl chlorides and $COCl_2$ reacted *in situ* with alcohols to produce esters in high yields (Scheme 4B.4).[15]



Scheme 4B.4

Mukaiyama and co-workers reported a method for the synthesis of carboxylic esters from carboxylic acids and alcohols in high yields using an efficient coupling reagent 2-chloro or 2-bromo pyridinium salt (Scheme 4B.5).[16]

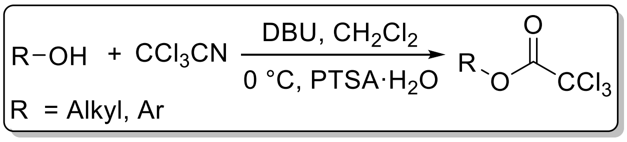


Scheme 4B.5

4B.2. Present work

The presence of a stoichiometric amount or more of a base in any of above esterification methods results in the creation of a significant amount of unwanted chemical waste. Moreover, due to the high reactivity of these acylating agents, selectivity among the different types of alcohols are generally not satisfactory. The reported methods also have drawbacks such as employing harsh reagents and operating at high temperatures.

According to green chemistry principles,[17] it would be useful to develop a metal-free, less toxic, inexpensive, and environmentally benign synthesis of trichloroesters from readily available alcohols and trichloroacetonitrile under mild conditions. In order to simplify the synthesis, herein we report an efficient one-pot synthesis of trichloroacetates from trichloroacetonitrile with various alcohols in mild reaction conditions *via* trichloroacetamidate intermediate (Scheme 4B.6).

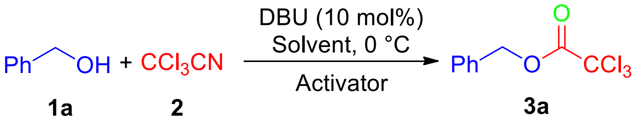


Scheme 4B.6

By applying above protocol to various substituted alkyl, aryl trichloroacetamidates we have synthesized library of trichloroesters.

4B.3. Results and discussion

Table 4B.1. Optimisation of reaction conditions[a]

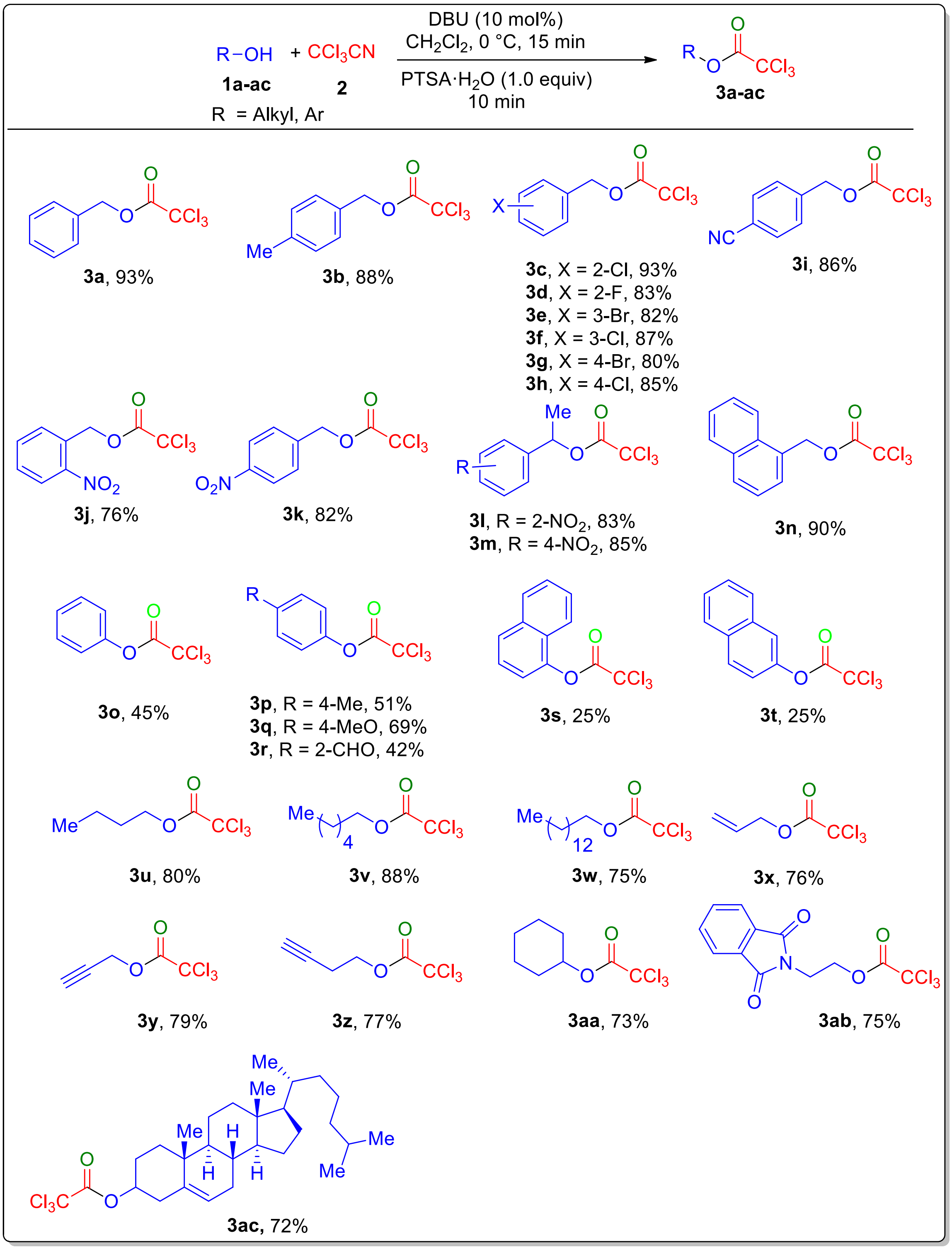


Entry	Activator (equiv.)	Solvent	Time (h)	Yield (%)[b]
1	$BF_3 \cdot OEt_2$	CH_2Cl_2	24	5
2	$FeCl_3$	CH_2Cl_2	3	65
3	$AlCl_3$	CH_2Cl_2	0.5	0
4	TFA	CH_2Cl_2	1.5	80
5	SiO_2	CH_2Cl_2	24	10
6	(±) CSA	CH_2Cl_2	1	73
7	**PTSA·H_2O**	**CH_2Cl_2**	**10 min**	**93**
8	PTSA·H_2O	CH_2Cl_2	4	86[c]
9	PTSA·H_2O	CH_2Cl_2	6	72[d]
10	PTSA·H_2O	$MeNO_2$	0.5	82
11	PTSA·H_2O	Toluene	1	80
12	PTSA·H_2O	DMF	1.5	85
13	-	CH_2Cl_2	24	0

[a]Reaction Conditions: Benzyl alcohol **1a** (1.0 mmol), CCl_3CN **2** (1.5 mmol), DBU (10 mol%), activator (1.0 mmol), solvent (1.0 mL) at 0 °C. [b]Yields are of isolated pure products. [c]PTSA·H_2O (0.5 mmol); [d]PTSA·H_2O (0.2 mmol).

In order to test our hypothesis, a reaction was conducted between benzyl alcohol **1a** as a model substrate and trichloroacetonitrile **2** in presence $BF_3 \cdot OEt_2$ as an activator in CH_2Cl_2 to transform into the corresponding trichloroacetates. To our delight the formation of **3a** was observed in 5% in CH_2Cl_2 at 0 °C (Table 4B.1, entry 1). These results provoked us to optimize the reaction conditions to improve the product yield. Then $FeCl_3$ gave the trichloroester **3a** in 65%, whereas $AlCl_3$ was inefficient for the transformation (Table 4B.1, entries 2–3). Further, the acids, SiO_2, TFA, (±) CSA and PTSA·H_2O were screened and found that the PTSA·H_2O was the best catalyst for the transformation (Table 4B.1, entries 4–7). It was observed that of all the solvents examined, CH_2Cl_2 was the most efficient (Table 4B.1, entries 7–12). A control experiment was also carried out in absence of catalyst, showed inferior results (Table 4B.1, entry 13). With optimized reaction conditions (Table 4B.1, entry 7), then we have validated the scope of the substrates with our one-pot operation. Firstly, various benzyl alcohols were treated with DBU in CH_2Cl_2 followed by the hydrolysis of trichloroacetamidate to the trichloroester in presence of PTSA.

Table 4B.2. Synthesis of trichloroacetate derivatives[a,b]



[a]Reaction Conditions: Alcohol **1a-ac** (1.0 mmol), CCl_3CN **2** (1.5 mmol), DBU (10 mol%), PTSA·H_2O (1.0 mmol), CH_2Cl_2 (1.0 mL) at 0 °C. [b]Yields are of isolated pure products.

We have further investigated the effect of substituents on benzyl alcohols and found that a little effect on the product yields (Table 4B.2). Methyl, halogen (at *ortho*, *meta* and *para* positions) substituted benzyl alcohols also reacted smoothly to give the corresponding 2,2,2-trichloroacetates (Table 4B.2, **3b-h**). Electron withdrawing groups such as -CN, -NO_2 did not hamper the product yields (Table 4B.2, **3i-k**). Also, secondary alcohols and naphthalen-1-ylmethanol undergo reaction without any difficulty to produce the respective 2,2,2-trichloroacetates (Table 4B.2, **3l-n**). Furthermore, we have extended our protocol to the aromatic alcohols. It is worth mentioning that, aromatic alcohols gave corresponding trichloroacetate comparatively low yields than benzyl alcohols (Table 4B.2, **3o-t**). Later, we applied our one-pot procedure to other aliphatic alcohols and observed good yields (Table 4B.2, **3u-ab**). Next, we put our forward effort to check the compatibility of our method with complex molecules such as cholesterol (Table 4B.2, **3ac**). Notably, cholesterol afforded corresponding tricholoroester **3ac** product in good in 72% yield.

Apart from the traditional FTIR, ^{1}H and ^{13}C NMR spectral analysis, the formation of trichloroester was also confirmed by single crystal X-ray diffraction of compound **3ab** (Figure 4B.2).

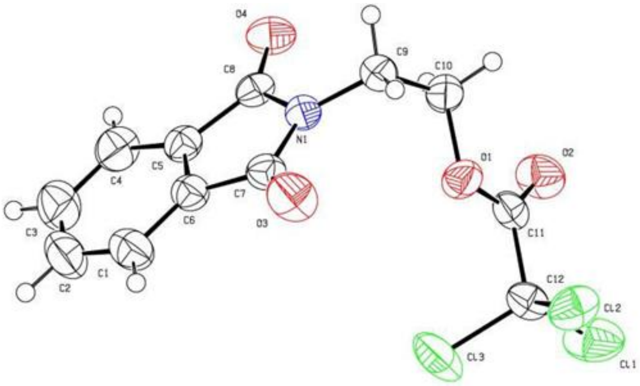
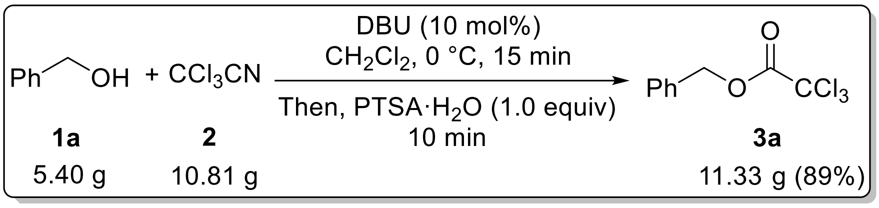


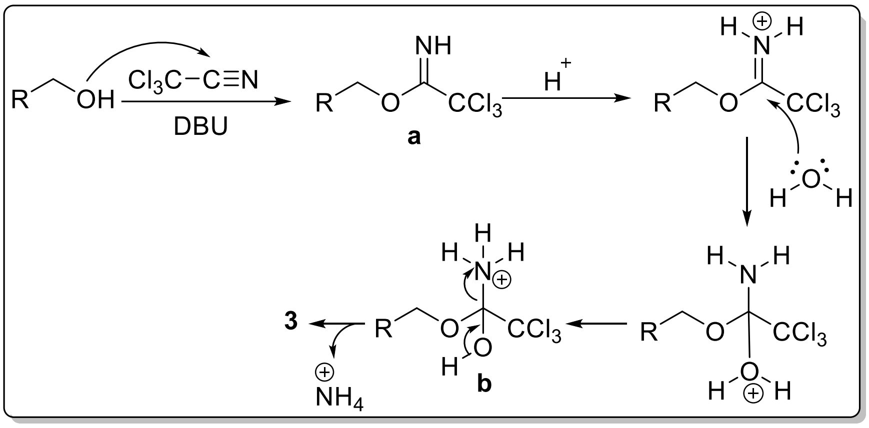
Figure 4B.2. ORTEP representation of 2-(1,3-dioxoisoindolin-2-yl)ethyl 2,2,2-trichloroacetate **3ab** with 50% ellipsoid (CCDC 1920925).

In addition, the reaction was investigated in gram-scale using benzyl alcohol **1a** as a model substrate (Scheme 4B.1) and found to produce the corresponding benzyl 2,2,2-trichloroacetate **3a** in 89%. The reaction suggest that the protocol is scalable.



Scheme 4B.7. Gram-Scale synthesis of benzyl trichloroacetate

The plausible reaction mechanism pathway is proposed for the reaction in scheme 4B.2. The alcohols react with trichloroacetonitrile in presence of DBU to form trichloroacetamidate intermediate **a**. Then the intermediate **a** gets protonation with acid followed by addition of water and elimination of ammonia occurs sequentially to yield the corresponding trichloroester.



Scheme 4B.8. Plausible reaction mechanism

4B.4. Conclusions

To summarise, we have presented a unique one-pot method for producing 2,2,2-trichloroacetates using commercially available trichloroacetonitrile and a wide range of substituted alcohols.

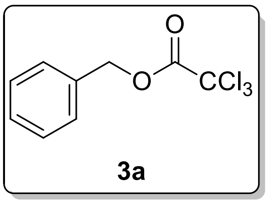
4B.5. Experimental Section

General Information. Alcohols, CCl_3CN, DBU, Lewis acids were purchased from a commercial source and used as received. Reactions were conducted in round bottom flasks. Thin layer chromatography was performed on 200 µm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. ^1H NMR spectra were obtained at 400 MHz in $CDCl_3$ and were referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ and were referenced to the solvent resonance. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) were in hertz (Hz). Standard abbreviations were used to designate resonance multiplicities. Melting points were determined with a melting point apparatus and are uncorrected.

General procedure for the one-pot synthesis of trichloroacetates 3a-ac. In an oven dried round bottom flask, benzyl alcohol (1 mmol) and DBU (10 mol %) were stirred in dichloromethane for 5 minutes at 0 °C, then trichloroacetonitrile (1.5 mmol) was added drop wise to the reaction mixture and allowed to stir until trichloroacetamidate was formed (monitored by TLC). Then, PTSA·H_2O (1.0 mmol) was added and allowed the reaction for appropriate reaction timings. The progress of the reaction was monitored by TLC. After completion, the organic layer was separated, dried with Na_2SO_4, and evaporated to give a residue that was purified on a silica gel column chromatography using ethyl acetate and *n*-hexanes as an eluent.

4B.6. Spectral data

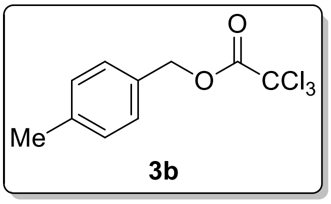
Benzyl 2,2,2-trichloroacetate (3a)[12]



3a

Colourless liquid (93%); FT-IR (neat, cm^{-1}) 3067, 3036, 2961, 1767, 1713, 1456, 1226, 996, 828, 696, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 5H), 5.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 133.8, 129.1, 128.8, 128.3, 89.8, 70.7.

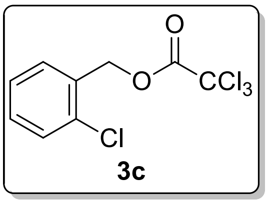
4-Methylbenzyl 2,2,2-trichloroacetate (3b)



3b

Colourless liquid (88%); FT-IR (neat, cm^{-1}) 2924, 2959, 1765, 1617, 1519, 1226, 982, 961, 827, 803, 680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.7 Hz, 2H), 5.32 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 139.1, 130.8, 129.5, 128.6, 89.9, 70.8, 29.7, 21.3.

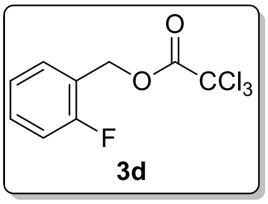
2-Chlorobenzyl 2,2,2-trichloroacetate (3c)



3c

Colourless liquid (93%); FT-IR (neat, cm^{-1}) 3067, 2963, 1768, 1597, 1479, 1227, 1059, 1002, 969, 827, 754, 680; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (dd, J = 6.8, 2.4 Hz, 1H), 7.43 (dd, J = 7.4, 1.8 Hz, 1H), 7.36–7.29 (m, 2H), 5.48 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.7, 133.9, 131.6, 130.4, 130.0, 129.8, 127.1, 89.7, 68.0.

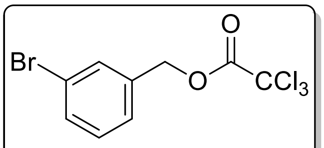
2-Fluorobenzyl 2,2,2-trichloroacetate (3d)



3d

Colourless liquid (83%); FT-IR (neat, cm^{-1}) 3057, 2960, 1769, 1595, 1479, 1227, 1055, 1001, 969, 829, 754, 680; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (dd, J = 8.4, 5.4 Hz, 2H), 7.09 (t, J = 8.6 Hz, 2H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 164.4, 161.9, 161.8, 130.6, 130.5, 129.6, 129.6, 116.0, 115.7, 89.7, 77.3, 77.0, 76.7, 70.0.

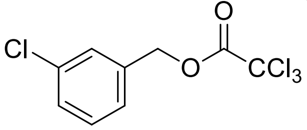
3-Bromobenzyl 2,2,2-trichloroacetate (3e)



3e

Colourless liquid (82%); FT-IR (neat, cm^{-1}) 3280, 2965, 1768, 1610, 1226, 1002, 960, 826, 754, 680; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.7, 135.9, 132.2, 131.2, 130.4, 126.8, 122.8, 89.6, 69.6.

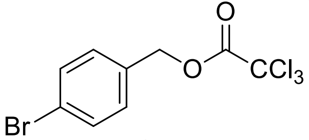
3-Chlorobenzyl 2,2,2-trichloroacetate (3f)



3f

Colourless liquid (87%); FT-IR (neat, cm^{-1}) 3284, 2964, 1765, 1600, 1226, 1002, 970, 826, 754, 682; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (dd, J = 6.9, 2.2 Hz, 1H), 7.48–7.44 (m, 1H), 7.39–7.31 (m, 2H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.7, 133.9, 131.6, 130.4, 130.0, 129.8, 127.1, 89.7, 68.0.

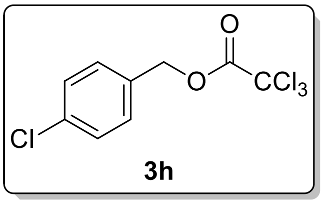
4-Bromobenzyl 2,2,2-trichloroacetate (3g)



3g

Colourless liquid (80%); FT-IR (neat, cm^{-1}) 3068, 3036, 2961, 1758, 1450, 1225, 998, 824, 750, 696; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.8, 132.7, 132.1, 130.0, 123.3, 89.6, 69.9.

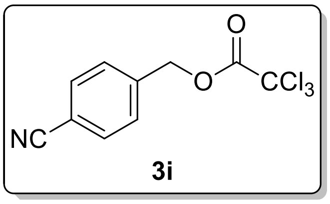
4-Chlorobenzyl 2,2,2-trichloroacetate (3h)



3h

Colourless liquid (85%); FT-IR (neat, cm^{-1}) 3384, 2930, 2098, 1764, 1600, 1494, 1225, 1093, 830, 811, 752, 682; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43–7.36 (m, 4H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.8, 135.1, 132.2, 129.8, 129.1, 89.7, 69.8.

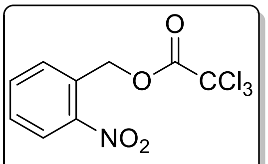
4-Cyanobenzyl 2,2,2-trichloroacetate (3i)



3i

Colourless liquid (86%); FT-IR (neat, cm^{-1}) 2998, 2894, 1768, 1540, 1228, 1002, 849, 754, 681; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.6, 138.9, 132.7, 128.4, 118.3, 113.0, 89.4, 69.2.

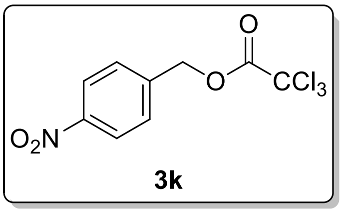
2-Nitrobenzyl 2,2,2-trichloroacetate (3j)[18]



3j

Colourless liquid (76%); FT-IR (neat, cm^{-1}) 3224, 3081, 1768, 1589, 1225, 1020, 846, 832, 754, 681; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (d, J = 8.3 Hz, 1H), 7.78–7.69 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 5.81 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.4, 147.1, 134.3, 130.2, 129.6, 128.7, 125.4, 89.5, 67.3.

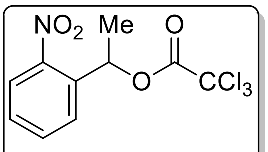
4-Nitrobenzyl 2,2,2-trichloroacetate (3k)



3k

Colourless liquid (82%); FT-IR (neat, cm^{-1}) 3116, 3091, 1764, 1604, 1518, 1348, 1228, 1002, 846, 822, 737, 678; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.28 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 5.49 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.6, 148.2, 140.8, 128.5, 124.1, 89.4, 68.9.

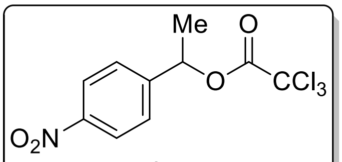
1-(2-Nitrophenyl)ethyl 2,2,2-trichloroacetate (3l)[18]



3l

Colourless liquid (83%); FT-IR (neat, cm^{-1}) 2986, 2933, 2784, 1766, 1600, 1517, 1243, 1001, 854, 827, 753, 699, 682; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.26 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 6.06 (q, J = 6.6 Hz, 1H), 1.73 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.9, 148.0, 146.5, 126.8, 124.1, 89.7, 76.7, 21.8.

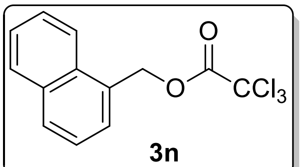
1-(4-Nitrophenyl)ethyl 2,2,2-trichloroacetate (3m)



3m

Colourless liquid (85%); FT-IR (neat, cm^{-1}) 2990, 2936, 2864, 1765, 1607, 1525, 1348, 1243, 1061, 1001, 857, 827, 751, 697, 682; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.21 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 6.05 (q, J = 6.6 Hz, 1H), 1.71 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.8, 147.9, 146.6, 126.8, 124.1, 89.7, 76.8, 21.8

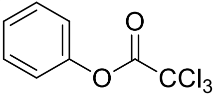
Naphthalen-1-ylmethyl 2,2,2-trichloroacetate (3n)



3n

White solid (90%); FT-IR (KBr, cm^{-1}) 3042, 2974, 2923, 2854, 1767, 1692, 1685, 1593, 1363, 1040, 784, 757; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.63–7.58 (m, 1H), 7.59–7.55 (m, 1H), 7.54–7.49 (m, 1H), 5.85 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.9, 133.8, 131.5, 130.2, 129.2, 128.9, 128.2, 127.0, 126.2, 125.2, 123.3, 89.9, 69.4.

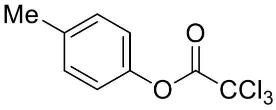
Phenyl 2,2,2-trichloroacetate (3o)[19]



3o

Colourless liquid (45%); FT-IR (neat, cm^{-1}) 2930, 1778, 1590, 1225, 1165, 870, 822, 757; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.6, 150.6, 129.9, 127.1, 120.5, 89.7.

p-Tolyl 2,2,2-trichloroacetate (3p)[19]

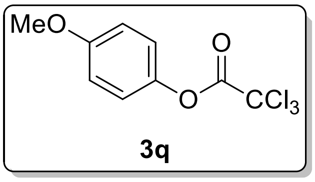


3p

Colourless liquid (51%); FT-IR (neat, cm^{-1}) 2929, 1779, 1490, 1225, 1165, 875, 823, 747; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.21–

7.09 (m, 3H), 7.06–7.01 (m, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 149.1, 131.6, 129.9, 127.3, 127.3, 120.8, 89.8, 15.9.

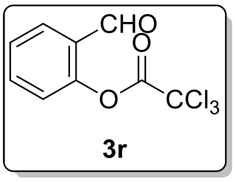
4-Methoxyphenyl 2,2,2-trichloroacetate (3q)[19]



3q

Colourless liquid (69%); FT-IR (neat, cm^{-1}) 3004, 2928, 2839, 1780, 1599, 1504, 1218, 1180, 1033, 837, 676; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 9.2 Hz, 2H), 6.84 (d, J = 9.2 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.1, 144.1, 121.3, 114.7, 89.7, 55.7.

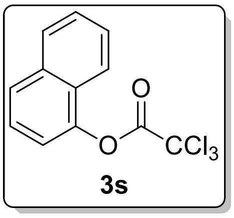
2-Formylphenyl 2,2,2-trichloroacetate (3r)[20]



3r

White solid (42%); FT-IR (KBr, cm^{-1}) 3415, 2927, 2960, 1768, 1644, 1502, 1223, 1150, 804, 758, 641; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.05 (s, 1H), 7.50–7.37 (m, 1H), 7.37–7.28 (m, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 160.4, 153.3, 135.8, 128.3, 122.7, 115.3, 113.5, 101.5, 99.9, 92.2.

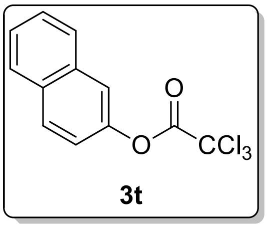
Naphthalen-1-yl 2,2,2-trichloroacetate (3s)[19]



3s

White solid (25%); FT-IR (KBr, cm^{-1}) 3063, 2923, 1775, 1590, 1388, 1226, 1034, 839, 761, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.89 (m, 1H), 7.82–7.77 (m, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.50–7.42 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 146.3, 134.8, 128.2, 127.3, 127.2, 127.0, 126.1, 125.3, 120.6, 117.2, 89.9.

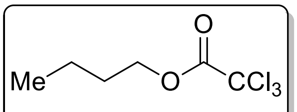
Naphthalen-2-yl 2,2,2-trichloroacetate (3t)[19]



3t

White solid (25%); FT-IR (KBr, cm^{-1}) 2924, 2853, 1778, 1509, 1234, 971, 820, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.9 Hz, 1H), 7.81–7.70 (m, 2H), 7.63 (s, 1H), 7.50–7.37 (m, 2H), 7.24 (dd, J = 8.9, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 148.2, 133.6, 132.0, 130.1, 127.9, 127.9, 127.1, 126.5, 119.4, 118.0, 89.7.

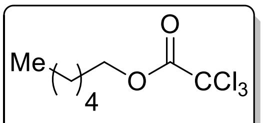
Butyl 2,2,2-trichloroacetamidate (3u)[21]



3u

Colourless liquid (80%); FT-IR (neat, cm^{-1}) 2963, 1768, 1632, 1462, 1248, 1029, 828, 681; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, J = 6.5 Hz, 2H), 1.85–1.69 (m, 2H), 1.52–1.41 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 90.0, 69.3, 30.2, 18.9, 13.6.

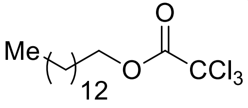
Hexyl 2,2,2-trichloroacetate (3v)



3v

Colourless liquid (88%); FT-IR (neat, cm^{-1}) 2933, 2960, 2861, 1768, 1467, 1246, 990, 828, 681; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (t, J = 6.6 Hz, 2H), 1.83–1.71 (m, 2H), 1.47–1.38 (m, 2H), 1.37–1.29 (m, 4H), 0.90 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 90.0, 69.5, 31.2, 28.1, 25.2, 22.4, 13.9.

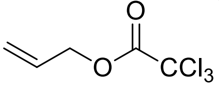
Tetradecyl 2,2,2-trichloroacetate (3w)



3w

Colourless liquid (75%); FT-IR (neat, cm^{-1}) 2926, 2855, 1768, 1631, 1466, 1248, 987, 838, 681; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (t, J = 6.6 Hz, 2H), 1.86-1.69 (m, 2H), 1.50–1.17 (m, 22H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 90.0, 69.6, 31.9, 29.7, 29.6, 29.5, 29.4, 29.4, 29.1, 28.2, 25.6, 22.7, 14.1.

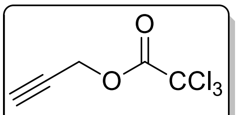
Allyl 2,2,2-trichloroacetate (3x)



3x

Colourless liquid (76%); FT-IR (neat, cm^{-1}) 2971, 2928, 1769, 1621, 1242, 1001, 828, 685, 652; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96–5.84 (m, 1H), 5.40 (dd, J = 17.2, 0.8 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 4.77 (d, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 130.0, 120.3, 89.8, 69.4.

Prop-2-yn-1-yl 2,2,2-trichloroacetate (3y)[22]

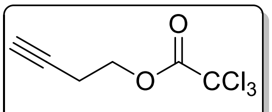


3y

Colourless liquid (79%); FT-IR (neat, cm^{-1}) 2951, 2925, 1767, 1643, 1212, 996, 858, 671, 652; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (d, J =

2.7 Hz, 2H), 2.65 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.3, 89.1, 77.2, 75.3, 56.4.

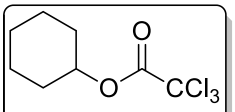
But-3-ynyl 2,2,2-trichloroacetate (3z)



3z

Colourless liquid (77%); FT-IR (neat, cm^{-1}) 2971, 2925, 2855, 1769, 1641, 1242, 999, 828, 681, 652; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.47 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 6.6 Hz, 2H), 2.06 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.8, 89.6, 78.4, 70.8, 66.5, 18.7.

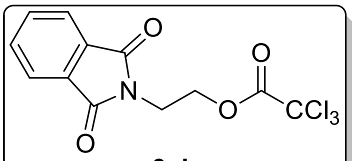
Cyclohexyl 2,2,2-trichloroacetate (3aa)[23]



3aa

Colourless liquid (52%); FT-IR (neat, cm^{-1}) 2941, 2862, 1762, 1451, 1242, 1007, 980, 851, 681; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.01–4.92 (m, 1H), 1.96-1.86 (m, 2H), 1.84–1.73 (m, 2H), 1.71–1.60 (m, 2H), 1.60–1.50 (m, 1H), 1.50–1.32 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.4, 90.4, 78.5, 30.7, 25.1, 23.1.

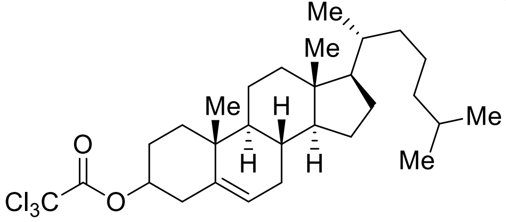
2-(1,3-dioxoisoindolin-2-yl)ethyl 2,2,2-trichloroacetate (3ab)



3ab

White solid (73%); FT-IR (KBr, cm^{-1}) 3320, 2926, 1775, 1704, 1466, 1439, 1390, 1263, 1014, 871, 845, 821, 718, 675; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91–7.85 (m, 2H), 7.79–7.72 (m, 2H), 4.62 (t, J = 5.3 Hz, 2H), 4.11 (t, J = 5.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.8, 161.9, 134.3, 131.8, 123.5, 89.3, 65.8, 36.2.

(8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl) 2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 2,2,2-trichloroacetate (3ac)[24]



3ac

White solid (72%); FT-IR (KBr, cm^{-1}) 2950, 2867, 1764, 1467, 1247, 1002, 982, 993, 837, 754; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.45 (d, J = 3.8 Hz, 1H), 4.93–4.72 (m, 1H), 2.60–2.42 (m, 2H), 2.13–1.01 (m, 29H), 0.94 (d, J = 6.4

Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 138.7, 123.7, 90.3, 79.8, 56.7, 56.1, 50.0, 42.3, 39.7, 39.5, 37.3, 36.8, 36.6, 36.2, 35.8, 34.7, 34.5, 31.9, 31.8, 28.2, 28.0, 27.1, 26.9, 25.3, 24.3, 23.8, 22.8, 22.6, 21.1, 20.7, 19.3, 18.7, 14.1, 11.9.

4B.7. References

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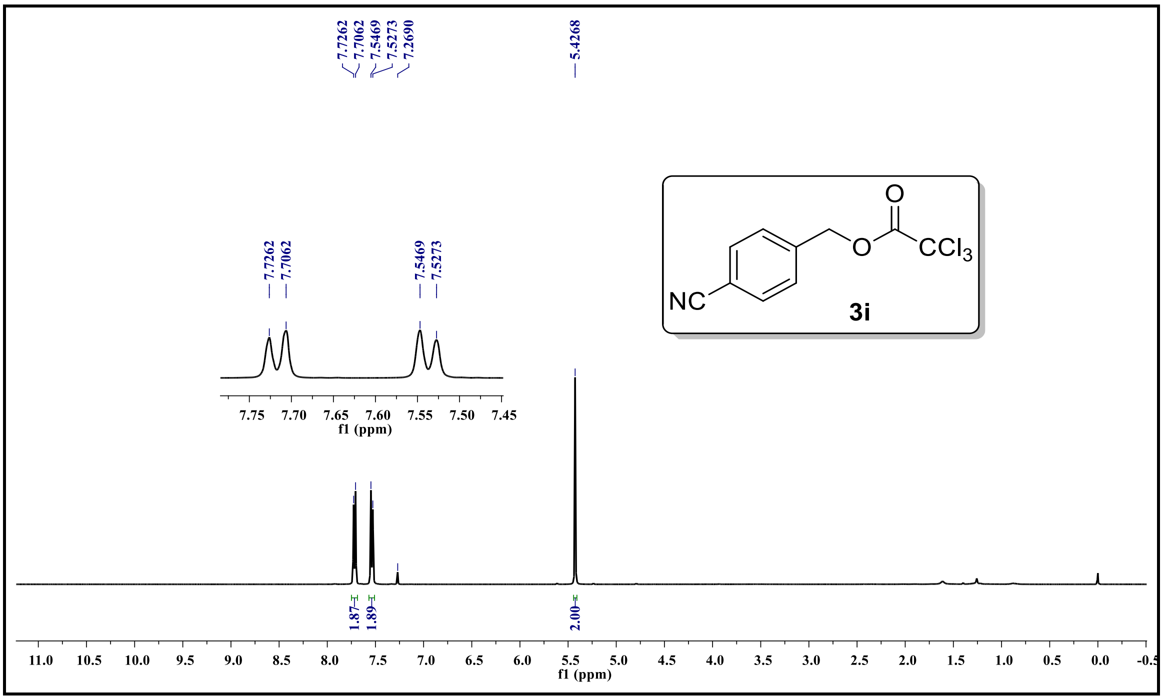
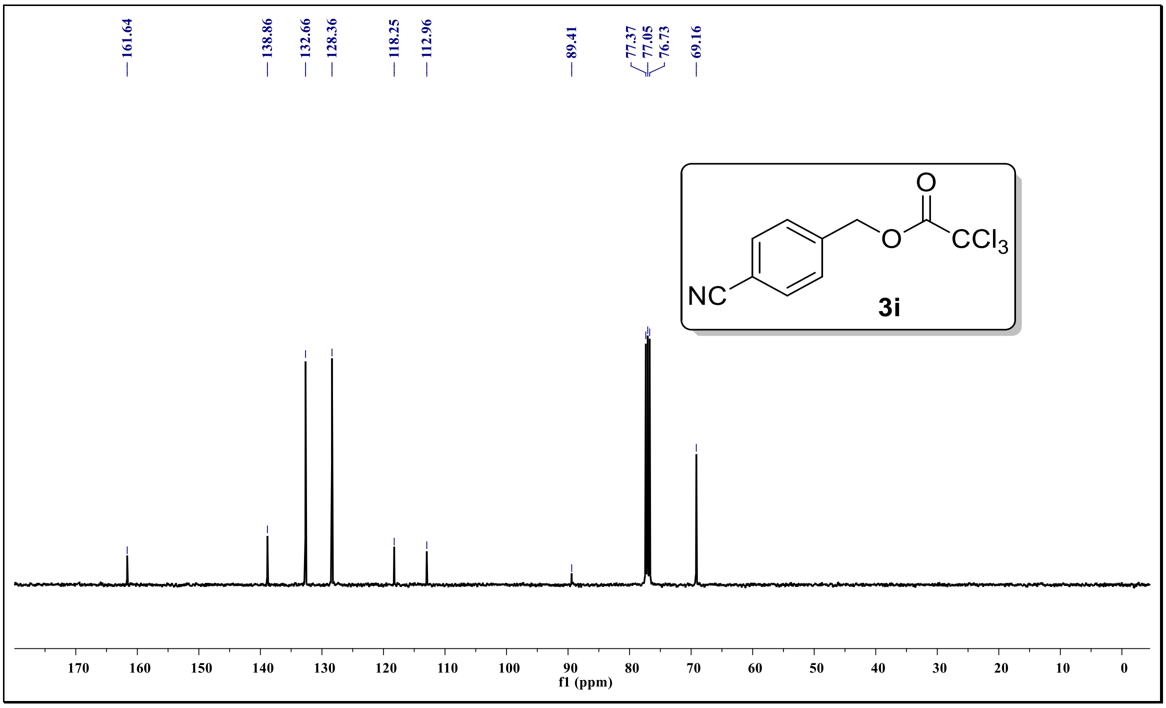
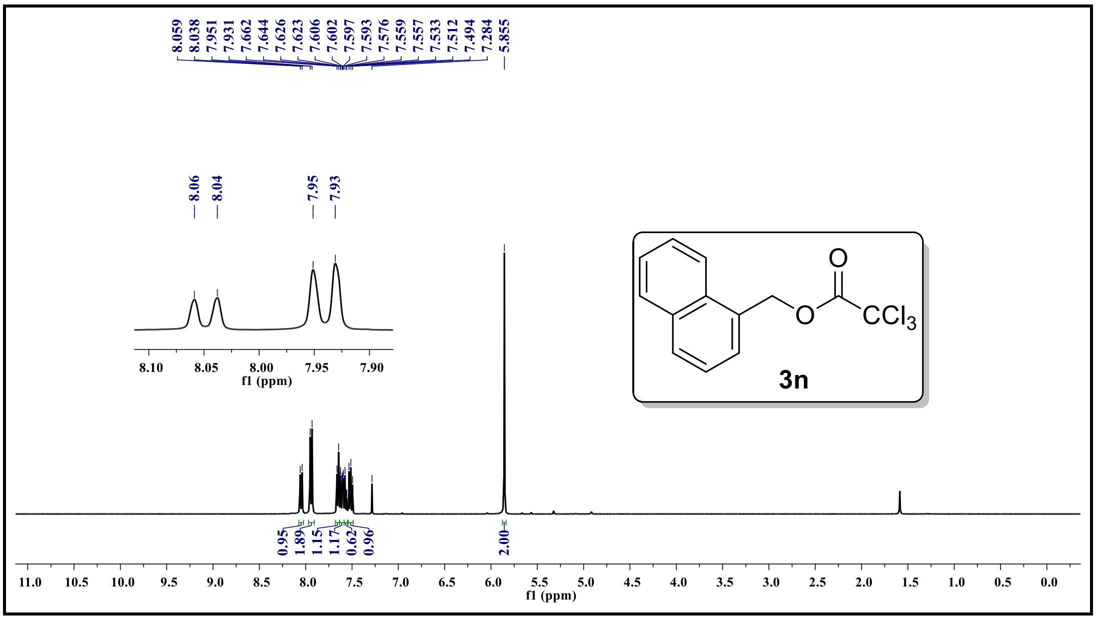
4B.8. Selected NMR (^{1}H and ^{13}C) Spectra



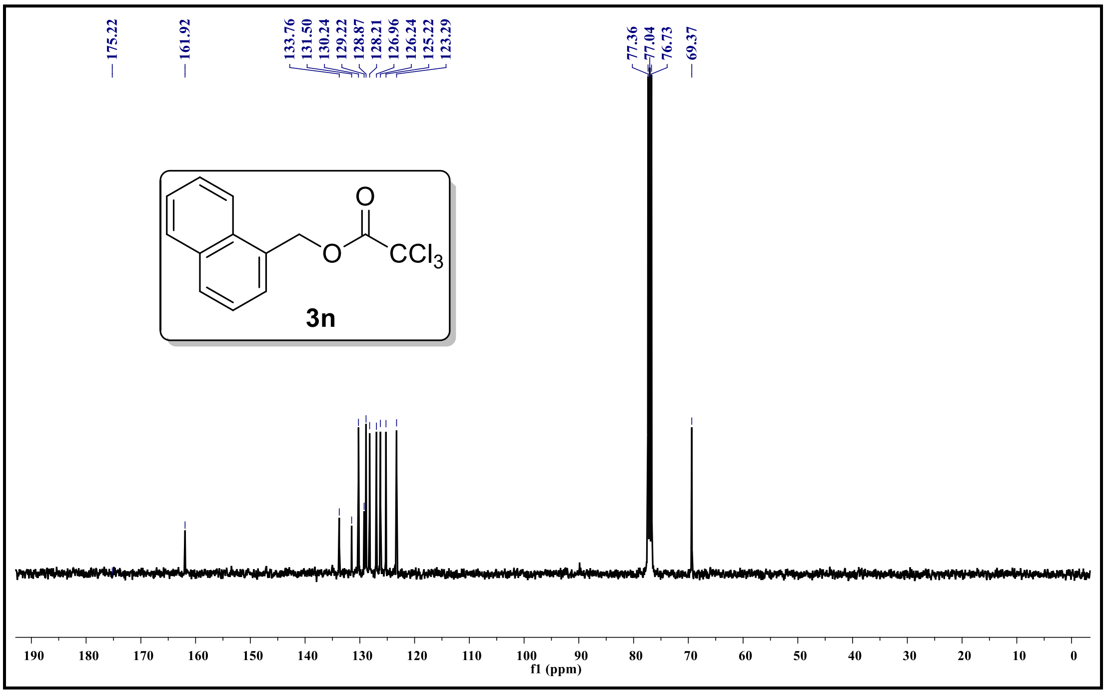
^{1}H NMR spectrum of compound **3i**



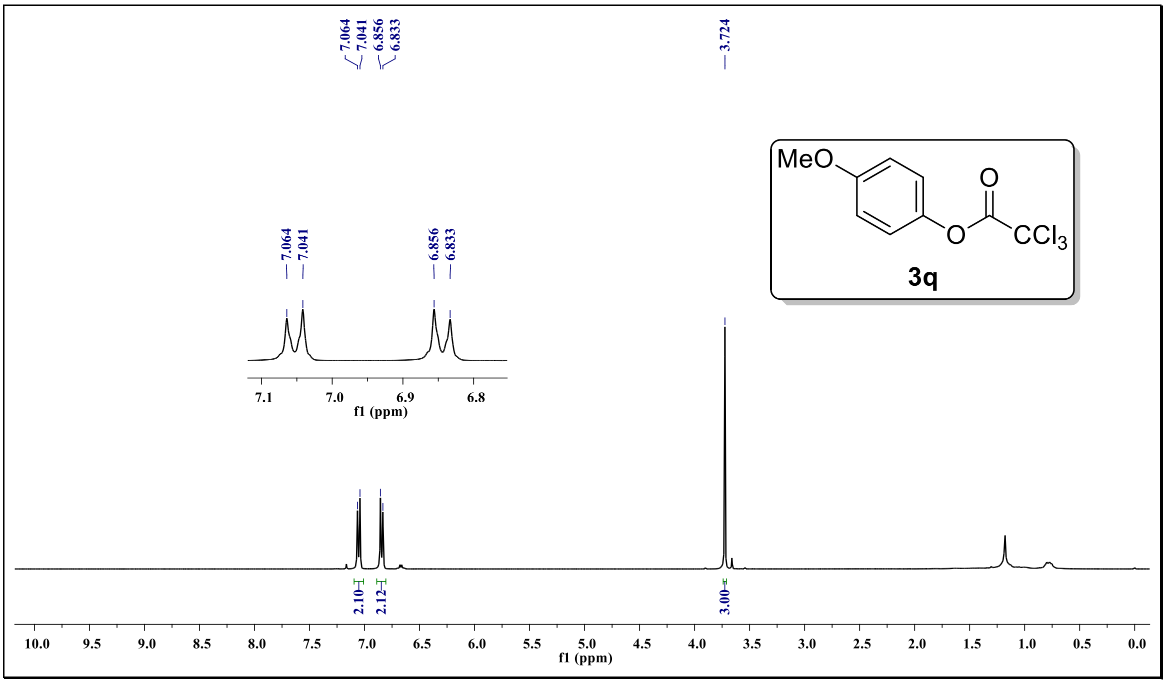
^{13}C NMR spectrum of compound **3i**



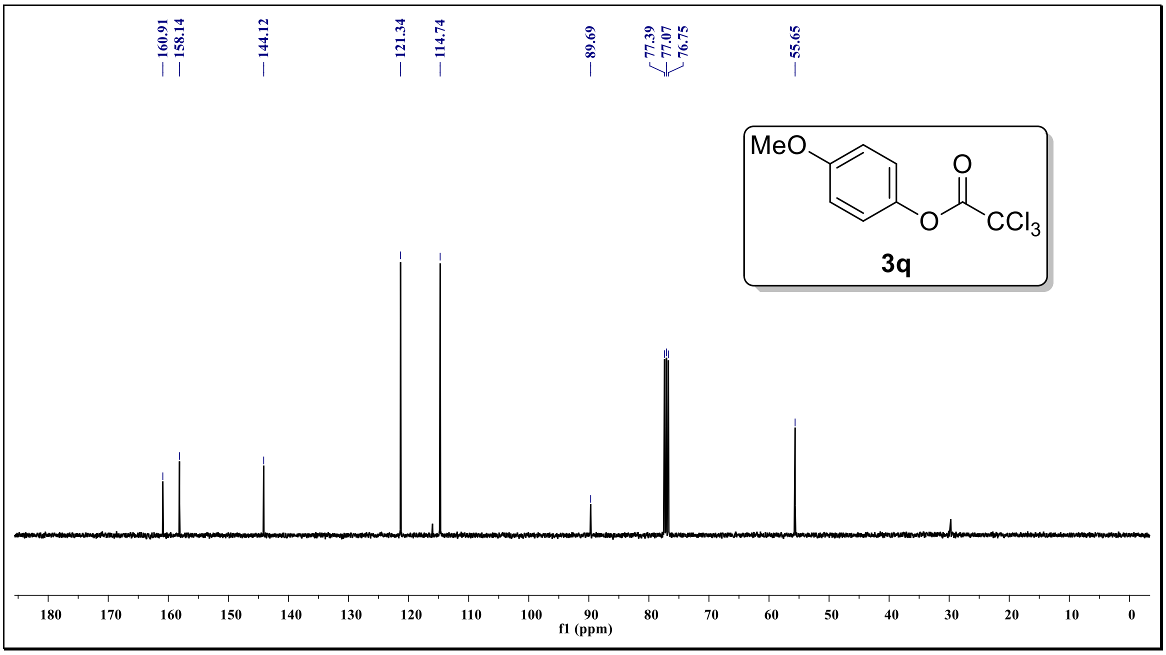
^{1}H NMR spectrum of compound **3n**



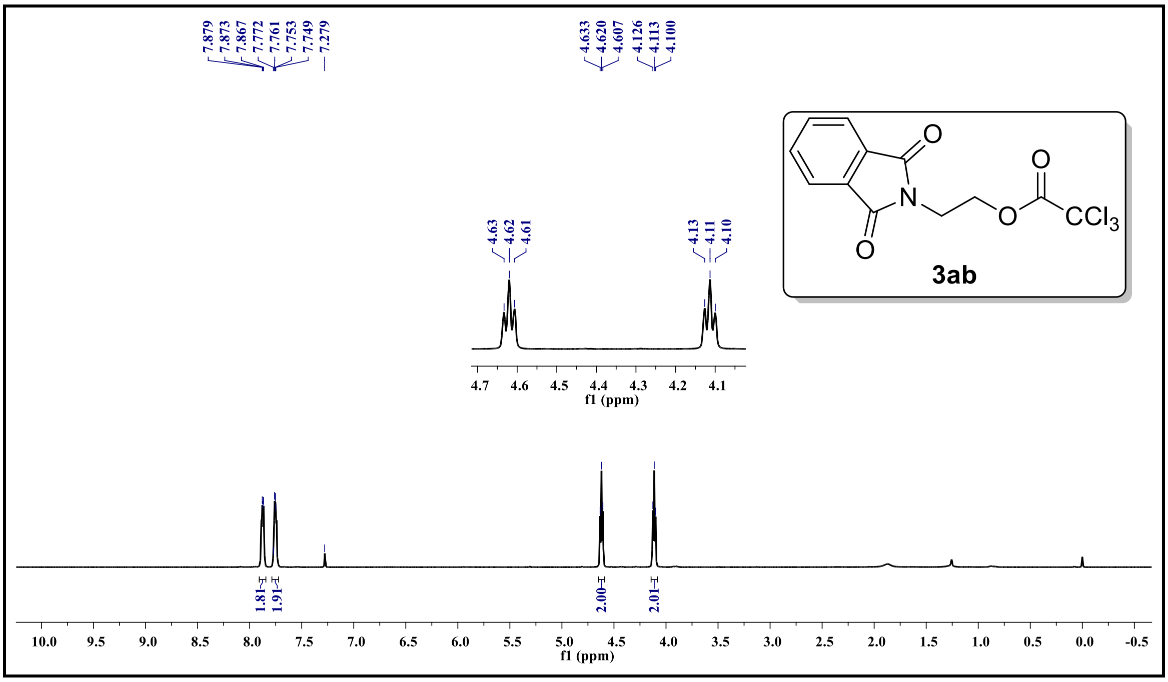
^{13}C NMR spectrum of compound **3n**



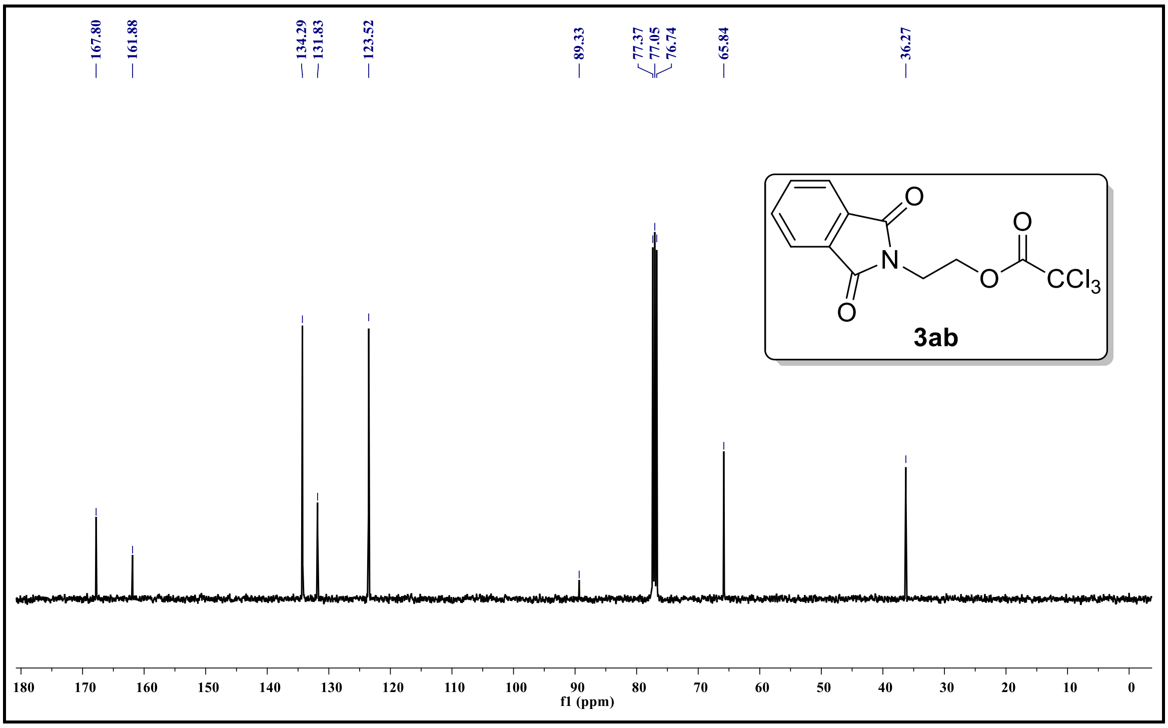
^{1}H NMR spectrum of compound **3q**



^{13}C NMR spectrum of compound **3q**

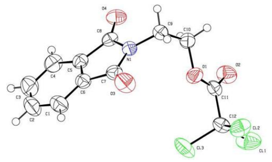


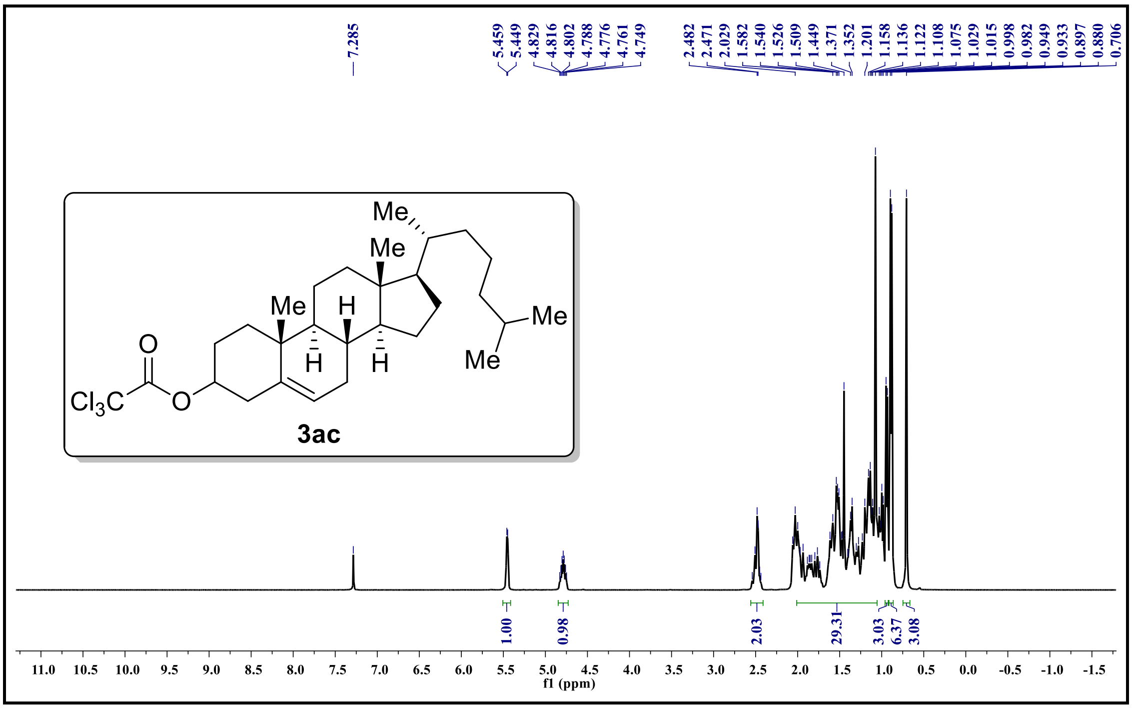
^{1}H NMR spectrum of compound **3ab**



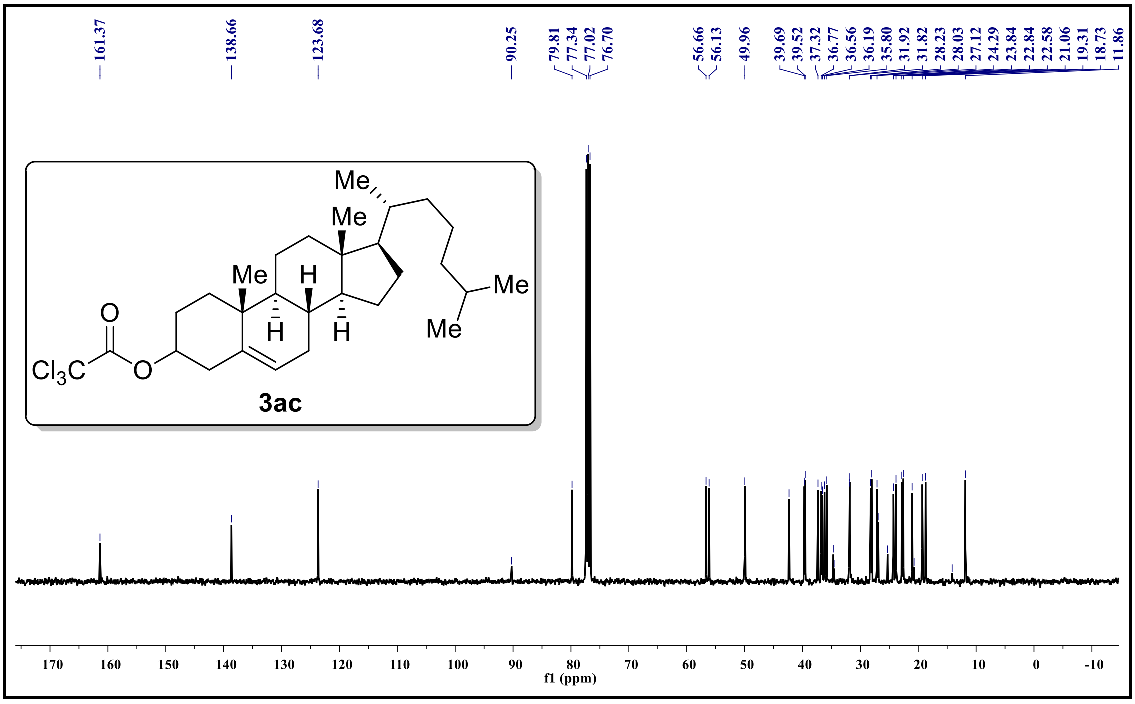
^{13}C NMR spectrum of compound **3ab**

Single Crystal X-ray Diffraction Data of 3ab

Identification code	shelx 
Empirical formula	$C_{12}H_8Cl_3NO_4$
Formula weight	336.54
Crystal habit, colour	Block, colourless
Temperature (K)	296(2)
Radiation	MoKα (λ = 0.71073)
Crystal system	orthorhombic
Space group	‘P 21 21 21’
Wavelength, λ/Å	0.71073
a/Å	9.7782(6)
b/Å	10.9915(7)
c/Å	13.1393(8)
α/°	90.00°
β/°	90.00°
γ/°	90.00°
Volume/$Å^3$	1412.17(15)
Crystal size (mm^3)	0.35 × 0.30 × 0.30
Z	4
Density (Mg /m^{-3})	1.583
Final R [I>2σ(I)]	R_1 = 0.0382, wR_2 = 0.1110
R (all data)	R_1 = 0.0484, wR_2 = 0.1302
Reflections collected/Unique	3532/ 2934
Theta range for data collection	2.42 to 28.34°
Absorption coefficient (mm^{-1})	0.659
Refinement method	SHELXL-97 (Sheldrick, 1997)'
Goodness of fit on F^2	0.982
CCDC No.	1920925



^{1}H NMR spectrum of compound **3ac**



^{13}C NMR spectrum of compound **3ac**

CHAPTER V (PART-A)

Base Promoted Synthesis of Dialkyl Carbonates From 2,2,2-Trichloroacetates

5A.1. Introduction

Symmetric and unsymmetric dialkyl carbonates are most important key intermediates in synthetic organic chemistry. Nowadays, production and usage of dialkyl carbonates (dimethyl, ethylene or propylene carbonate) taking place in multiton scale because of low production cost, low toxicity and its applications in various fields. Dialkyl carbonates extensively used as lubricating oils,[1,2] photo resistors,[3] packaging materials,[4] condensers and batteries.[5] Furthermore, dialkyl carbonates such as dimethyl carbonate (DMC), diethyl carbonate (DEC), ditetrahydrofurfuryl carbonate (DTC) have been used as fuel additives[6] due to mutual solubility with the fuel and high oxygen content.

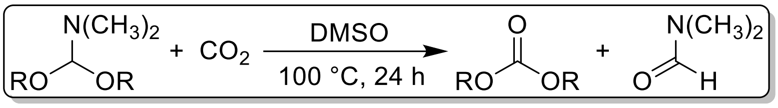
DMC used as a green solvent and also used in organic synthesis in place of most toxic chemicals such as phosgene, methyl halides and dimethylsulfate. Short chain dialkyl carbonates were act as good alkylating and alkoxy carbonylating agents for alcohols, amines and aryl acetonitriles.[7-12]

Only a very few number of carbonates are commercially available. Literature reports revealed that the synthesis of dimethyl carbonate and other acyclic carbonate include (a) dehydrative condensation of alcohols under CO_2 atmosphere,[13] (b) reactions of alkyl halide with metal carbonates,[14] (c) reactions of alkyl halide, alcohol with CO_2,[15] (d) transesterification of cyclic carbonates[16] and (e) reactions of alcohol and dimethyl carbonate in presence of heterogeneous catalysts.[17-20]

In the conventional synthetic process of dialkyl carbonates either phosgene[21-23] or carbon monoxide or carbon dioxide or inorganic carbonates were used as the carbonate source. The toxicity and flammability of phosgene and carbon monoxide are very high so they are very harmful to environment. Although, carbon dioxide and metal carbonates are environmentally benign, the chemical reaction using carbon dioxide need specially equipped setup and the chemical reaction using metal carbonates need high temperature due to low solubility, reactivity issues. Therefore, a great deal of research should focused on the synthesis of dialkyl carbonates.

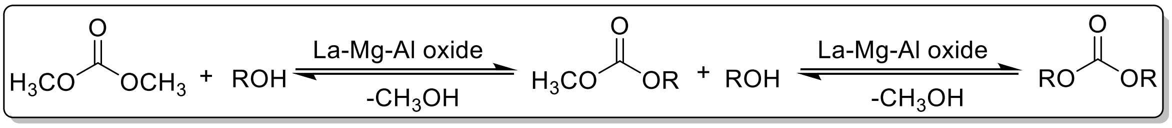
5A.1.1. Different synthetic approaches for the synthesis of dialkyl carbonate derivatives

Saito and co-workers developed a method for the synthesis of dialkyl carbonates using acetals of *N*, *N*-dimethylformamide and CO_2 in DMSO solvent at 100 °C (Scheme 5A.1).[24]



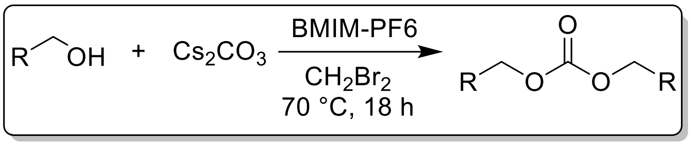
Scheme 5A.1

Srinivas and co-workers reported the synthesis and characterization of ternary oxides (La-Mg-Al-oxide) derived through the calcination of rare earth modified hydrotalcite. And also they investigated the catalytic activity of prepared ternary oxides for the synthesis of dialkyl carbonates by transesterification of ethylene carbonate and dimethyl carbonate with alcohols. This reaction was carried out at 80-150 °C for 6 hours (Scheme 5A.2).[25]



Scheme 5A.2

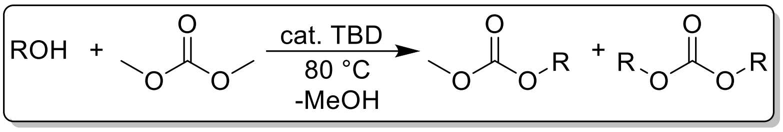
Lim et al. reported direct coupling of alcohols with Cs_2CO_3 at 70 °C in a mixture of dibromomethane and 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM-PF_6) to synthesize dialkyl carbonates (Scheme 5A.3).[26]



Scheme 5A.3

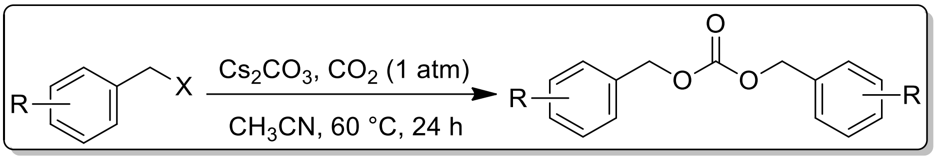
Mutlu et al. reported a simple and mild approach for the synthesis of symmetric, unsymmetric alkyl carbonates and polycarbonates using 1,5,7-triazabicyclo [4.4.0] dec -

5-ene (TBD) catalyst in combination with dimethyl carbonate (DMC) at 80 °C (Scheme 5A.4).[27]



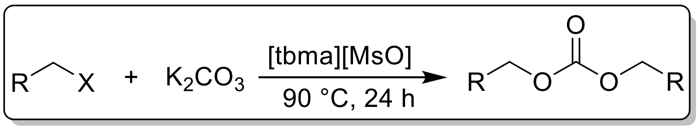
Scheme 5A.4

Zhou and co-workers developed a simple method for the synthesis of organic carbonates from benzyl halides with Cs_2CO_3 under the atmospheric pressure of CO_2 at 60 °C temperature using anhydrous CH_3CN as solvent (Scheme 5A.5).[28]



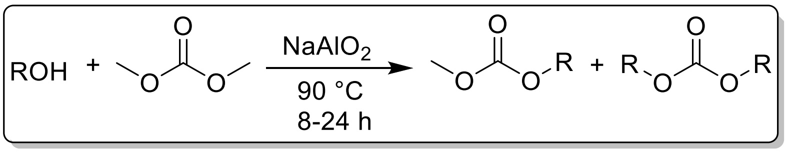
Scheme 5A.5

Goracci et al. developed easy and simple methodology for the synthesis of symmetric organic carbonates by nucleophilic substitution of potassium carbonate on alkyl halides in presence of an ionic liquid tributylmethylammonium methanesulfonate ([tbma][MsO] at 90 °C for 24 hours (Scheme 5A.6). [29]



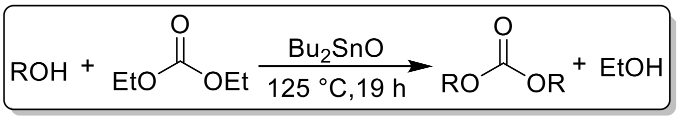
Scheme 5A.6

Debecker and co-workers synthesized unsymmetrical organic carbonates by the carboxymethylation of alcohols with dimethyl carbonate in presence of highly active sodium aluminate ($NaAlO_2$) at 90 °C for 8 to 24 hours (Scheme 5A.7).[17]



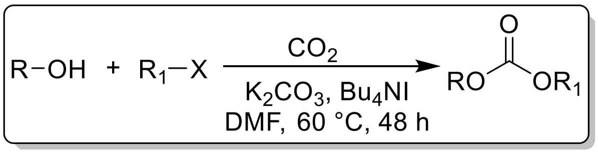
Scheme 5A.7

Kenar and co-workers synthesized organic carbonates of mid-, long-chain and Guerbet alcohols through a carbonate interchange reaction of diethyl carbonate with corresponding alcohols in presence of *n*-dibutyltin oxide catalyst at 125 °C for 19 hours (Scheme 5A.8).[30]



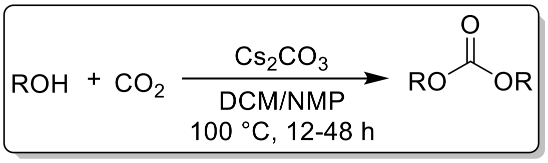
Scheme 5A.8

Shen et al. reported a simple method for the synthesis of mixed organic carbonates through the three-component coupling reaction of corresponding alkyl halides, alcohols under CO_2 in presence of K_2CO_3 and tetrabutylammonium iodide at 60 °C (Scheme 5A.9). [31]



Scheme 5A.9

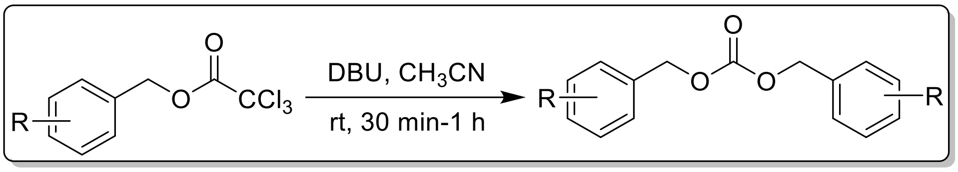
Saito and co-workers synthesized dialkyl carbonates from one pot reaction of alcohols and Cs_2CO_3 under 1 atmospheric pressure of CO_2 at 100 °C in dichloromethane for 12 to 48 hours (Scheme 5A.10).[32]



Scheme 5A.10

5A.2. Present work

We have developed a new method for synthesising alkyl carbonates that doesn't require high temperatures, specialised equipment and harsh chemicals. In this method, we have used ambient temperatures and very low quantity of inorganic carbonate *i.e.* Cs_2CO_3 to produce high yields. Alcohols, alkyl halides, and acetals are employed as starting ingredients in traditional alkyl carbonate synthesis techniques. However, we are the first to use alkyl trichloroester as a starting material for the synthesis of dialkyl carbonates in a simple and effective manner (Scheme 5A.11).

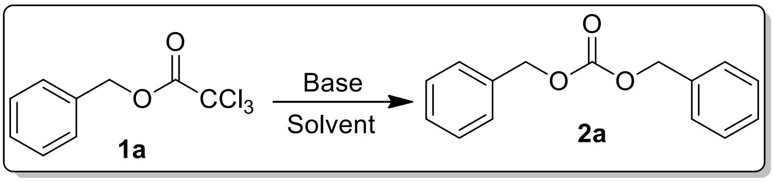


Scheme 5A.11

By applying the proposed approach, we have synthesised a variety of substituted alkyl carbonates with excellent yields.

5A.3. Results and discussion

Table 5A.1. Optimisation of Reaction conditions[a]



S.No	Base	Solvent	Base equivalents	Time (h)	Yield[b] (%)
1	Na_2CO_3	DMF	0.5	3	64
2	$NaHCO_3$	DMF	0.5	15	39
3	K_2CO_3	DMF	0.5	2.5	71
4	$KHCO_3$	DMF	0.5	5	58
5	Cs_2CO_3	DMF	0.5	0.5	80
6	NaOH	DMF	0.5	12	0
7	DBU	DMF	0.5	0.5	88
8	Et_3N	DMF	0.5	2	60
9	DABCO	DMF	0.5	2	75

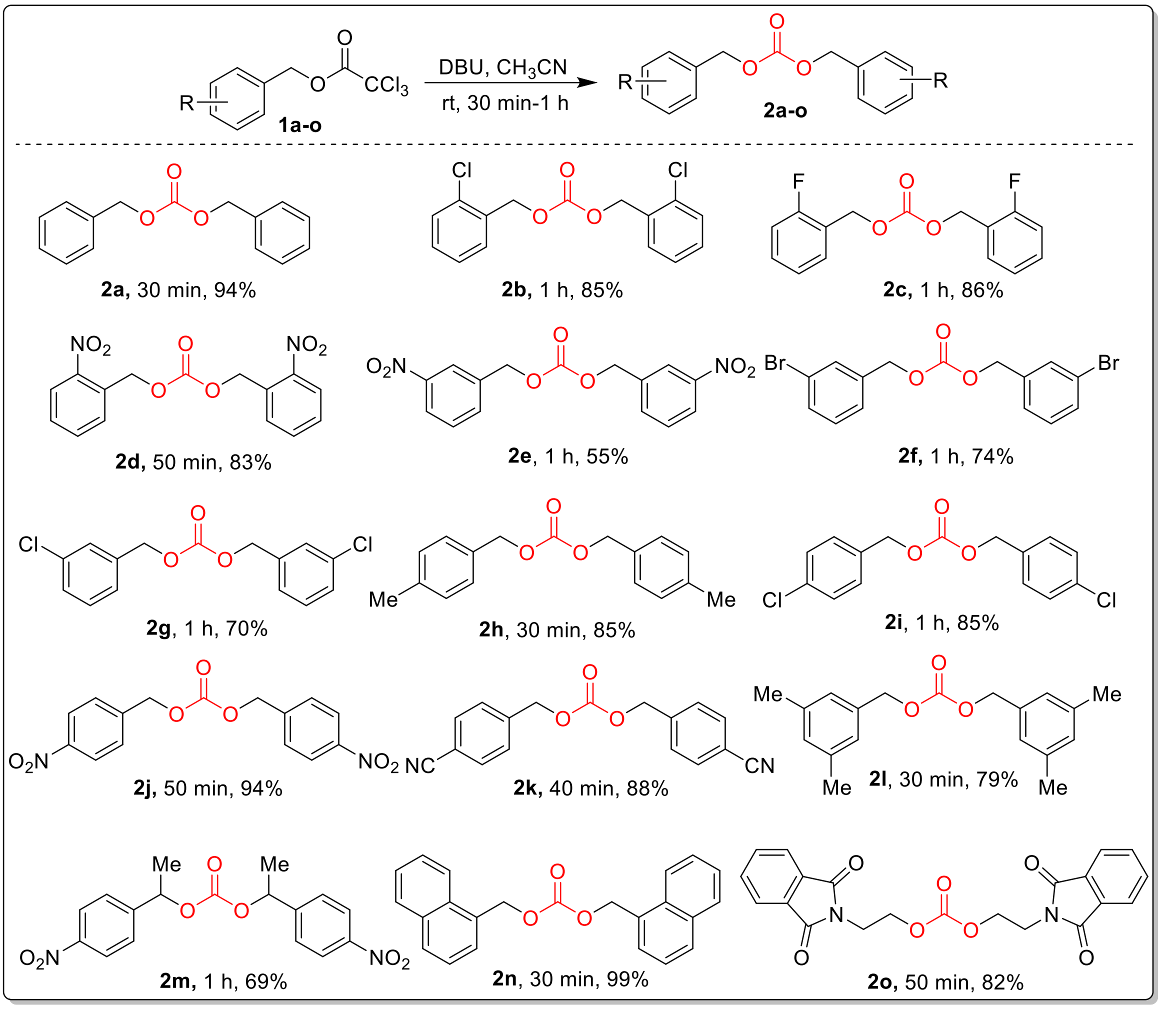
10	DBU	DMSO	0.5	2	65
11	DBU	DCM	0.5	12	50
12	DBU	EtOH	0.5	1	0
13	DBU	CH_3CN	0.5	0.5	95
14	DBU	CH_3CN	0.2	0.5	95
15	**DBU**	**CH_3CN**	**0.1**	**0.5**	**95**
16	DBU	CH_3CN	0.05	1	92
17	DBU	CH_3CN	0.02	1.5	90

[a]Reaction conditions: benzyl trichloroester **1a** (1.0 mmol), base (0.1 equiv.) in solvent (1.0 mL) at room temperature. [b]Yields are of isolated pure products.

Optimisation of synthesis of alkyl carbonates from alkyl trichloroesters is summarized in Table 5A.1. Benzyl 2,2,2-trichloroacetate **1a** was taken as model substrate for the optimization of reaction conditions. Initially for one equivalent of **1a** 0.5 equiv. of Na_2CO_3 was taken. After stirring at room temperature in DMF solvent it gave benzyl carbonate with 64% of yield (Table 5A.1, entry 1). To improve the desired product yield, we have proceeded reactions using different inorganic bases such as $NaHCO_3$, K_2CO_3, $KHCO_3$, Cs_2CO_3, NaOH and organic bases such as DBU, Et_3N and DABCO (Table 5A.1, entries 2-9). By comparing all the reaction yields we have observed that DBU was given 88% of yield (Table 5A.1, entry 5) in 30 minutes.

To know the effect of solvents on the reaction yield, we have screened the reaction using different solvents like DMSO, DCM, EtOH and CH_3CN (Table 5A.1, entries 10-13). Among all the solvents CH_3CN was acts as a good solvent for this reaction. These results prompted us to investigate the reaction condition by decreasing the equivalents of DBU (Table 5A.1, entries 7, 14-17). From these optimizations, we concluded that 0.1 equivalents of DBU was sufficient amount to afford the product with good yield. Therefore the optimized conditions are 1.0 mmol of benzyl trichloroester **1a**, 0.1 equivalents of DBU in 1.0 mL of CH_3CN solvent at room temperature as shown in (Table 5A.1, entry 15).

Table 5A.2. Synthesis of Dialkyl Carbonate Derivatives[a,b]



2a, 30 min, 94%
2b, 1 h, 85%
2c, 1 h, 86%
2d, 50 min, 83%
2e, 1 h, 55%
2f, 1 h, 74%
2g, 1 h, 70%
2h, 30 min, 85%
2i, 1 h, 85%
2j, 50 min, 94%
2k, 40 min, 88%
2l, 30 min, 79%
2m, 1 h, 69%
2n, 30 min, 99%
2o, 50 min, 82%

[a]Reaction conditions: Trichloroester **1a-o** (1.0 mmol), DBU (0.1 equiv.) in CH_3CN(1.0 mL) at room temperature. [b]Yields are of isolated pure products.

To evaluate the generality of this protocol and scope of the reaction a number of different benzyl trichloroesters comprising halogens (Table 5A.2, **2b-c, 2f-g, 2i**), electron withdrawing (Table 5A.2, **2d-e, 2j-k**), electron donating (Table 5A.2, **2h**), disubstituted (Table 5A.2, **2l**), secondary trichloroester (Table 5A.2, **2m**), bulky trichloroesters (Table 5A.2, **2n-o**) afforded the corresponding carbonates (Table 5A.2, **2a-o**). Notably, –Me substitution on benzyl trichloroester increased the reaction rate than other substitutions to furnish the desired carbonates (Table 5A.2, **2h, 2l**) with good yield.

We have found little effect on reaction yields because of different substitutions at *ortho* and *para* position of benzyl trichloroester (Table 5A.2, **2b-d, 2h-k**). The benzyl trichloroester substituted with -NO_2, at *meta* position was given less yield as compare to benzyl trichloroester substituted with -Br, -Cl at *meta* position (Table 5A.2, **2e-g**).

Interestingly, secondary trichloroester (Table 5A.2, **2m**) also underwent reaction smoothly to produce corresponding carbonate. Furthermore, naphthalen-1-ylmethyl 2,2,2-trichloroacetate (Table 5A.2, **2n**) and 2-(1,3-dioxoisoindolin-2-yl)ethyl 2,2,2-trichloroacetate (Table 5A.2, **2o**) easily underwent reaction and gave desired alkyl carbonate with excellent yields.

5A.4. Conclusions

In this chapter we have used trichloroester as a new precursor and developed simple methodology to synthesize the dialkyl carbonates. This method tolerates wide range of substrates including halogen, electron withdrawing, electron donating, and other substitutions on benzyl trichloroester. Using this protocol, we have synthesized 15 compounds in 69-99% of yield.

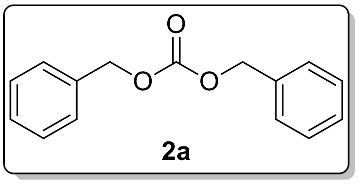
4B.5. Experimental Section

General Information. Alkyl trichloroesters were prepared using our reported method. Organic, inorganic bases were purchased from a commercial source and used as received. Reactions were conducted in round bottom flasks. Thin layer chromatography was performed on 200 μm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. ^{1}H NMR spectra were obtained at 400 MHz in $CDCl_3$ and were referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ and were referenced to the solvent resonance. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) were in hertz (Hz). Standard abbreviations were used to designate resonance multiplicities. Melting points were determined with a melting point apparatus and are uncorrected.

General procedure for the one-pot synthesis of dialkyl carbonates (2a-o). Alkyl trichloroester **1a-o** (1.0 mmol) was taken in an oven dried round bottom flask. To this flask Cs_2CO_3 (0.1 equiv), 1mL of DMF were added and stirred at room temperature. After completion of reaction (monitored by TLC) the organic layer was extracted with ethylacetate (3 x 20 mL). The extracted organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to obtain the crude product, which was further purified by silica gel column chromatography using ethylacetate and *n*-hexanes as eluent.

5A.6. Spectral data

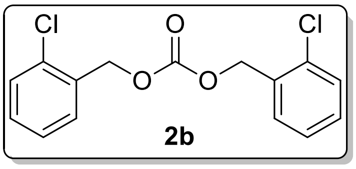
Dibenzyl carbonate (2a)[33]



2a

Colourless liquid (94%); FT-IR (KBr, cm^{-1}) 3066, 3034, 2958, 1746, 1498, 1455, 1392, 1264, 948, 910, 748, 696; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 (m, 10H), 5.07 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.1, 135.2, 128.6, 128.6, 128.4, 69.8.

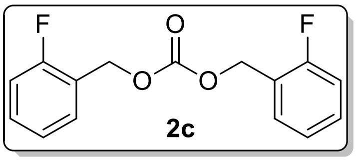
Bis(2-chlorobenzyl) carbonate (2b)[32]



2b

Colourless liquid (86%); FT-IR (KBr, cm^{-1}) 3070, 2931, 2856, 1749, 1259, 1057, 961, 931, 787,753; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25–7.19 (m, 4H), 7.12–7.08 (m, 4H), 5.12 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.1, 128.9, 128.2, 125.1, 125.1, 124.9, 122.2, 62.3.

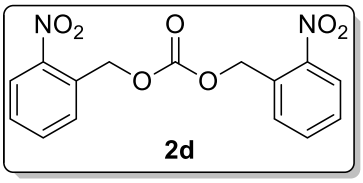
Bis(2-flourobenzyl) carbonate (2c)



2c

Colourless liquid (85%); FT-IR (KBr, cm^{-1}) 3033, 2983, 2933, 1744, 1258, 1057, 992, 860, 760, 698; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28 (dd, *J* = 8.0, 5.6 Hz, 4H), 6.96 (t, *J* = 8.4 Hz, 4H), 5.04 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.4, 156.9, 150.2, 126.3, 126.2, 125.8, 125.7, 110.9, 110.7, 64.3.

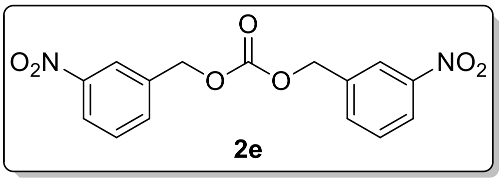
Bis(2-nitrobenzyl) carbonate (2d)



2d

White solid (83%); FT-IR (KBr, cm^{-1}) 3036, 2953, 2849, 1754, 1577, 1441, 1390, 1369, 1281, 1247, 971, 859, 794, 727, 676; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16 (d, *J* = 8.0 Hz, 2H), 7.75–7.64 (m, 4H), 7.53 (t, *J* = 6.4 Hz, 2H), 5.64 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.4, 147.3, 134.1, 131.5, 129.1, 128.8, 125.2, 66.6.

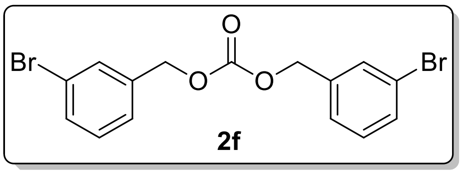
Bis(3-nitrobenzyl) carbonate (2e)



2e

White solid (55%); FT-IR (KBr, cm^{-1}) 3035, 2856, 2345, 1749, 1526, 1392, 1350, 1263, 1089, 947, 891, 799, 785, 736, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 2H), 8.22 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 8.0 Hz, 2H), 5.28 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 143.6, 138.7, 127.9, 124.6, 117.5, 116.7, 72.0.

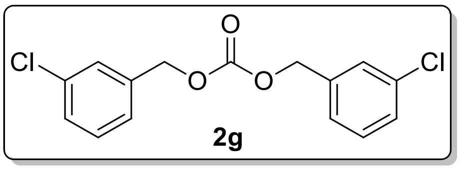
Bis(3-bromobenzyl) carbonate (2f)



2f

Colourless liquid (74%); FT-IR (KBr, cm^{-1}) 3025, 2956, 1745, 1568, 1440, 1376, 1262, 1068, 941, 892, 799, 785, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, J = 1.5 Hz, 2H), 7.42–7.37 (m, 2H), 7.25–7.20 (m, 2H), 7.18–7.14 (m, 2H), 5.06 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 137.3, 131.7, 131.2, 130.2, 126.8, 122.7, 77.4, 77.2, 77.0, 76.7, 68.8.

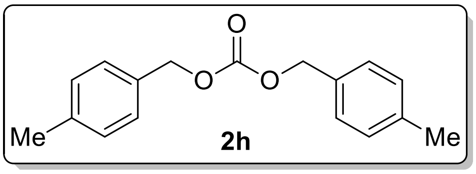
Bis(3-chlorobenzyl) carbonate (2g)



2g

Colourless liquid (70%); FT-IR (KBr, cm^{-1}) 2949, 1747, 1574, 1472, 1377, 1263, 1077, 941, 894, 788, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 2H), 7.29 (d, J = 6.0 Hz, 4H), 7.25 (t, J = 6.4 Hz, 2H), 5.14 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 137.0, 134.6, 130.0, 128.8, 128.3, 126.3, 68.9.

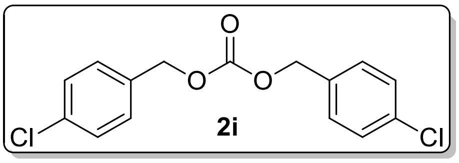
Bis(4-methylbenzyl) carbonate (2h)[34]



2h

Colourless liquid (85%); FT-IR (KBr, cm^{-1}) 2963, 2923, 2854, 1746, 1517, 1454, 1381, 1260, 943, 902, 808, 788, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.0 Hz, 4H), 7.09 (d, J = 8.0 Hz, 4H), 5.05 (s, 4H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.4, 132.3, 129.3, 128.5, 69.6, 21.2.

Bis(4-chlorobenzyl) carbonate (2i)[32]

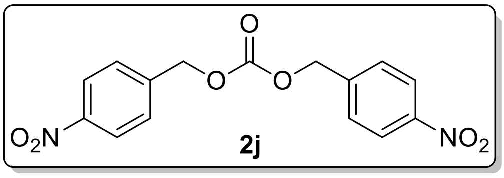


2i

Colourless liquid (75%); FT-IR (KBr, cm^{-1}) 2959, 2856, 1747, 1574, 1264, 1070, 942, 895, 796, 683;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 8H), 5.12 (s, 4H); ^{13}C NMR (100 MHz, CDCl3) δ 154.9, 134.6, 133.6, 129.8, 128.9, 69.0.

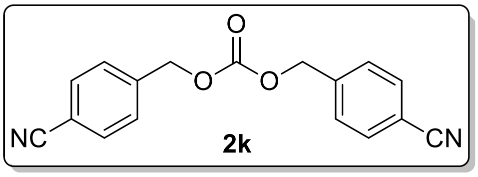
Bis(4-nitrobenzyl) carbonate (2j)[35]



2j

Pale yellow solid (94%); FT-IR (KBr, cm^{-1}) 3115, 3082, 1746, 1607, 1519, 1123, 942, 847, 804, 786, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 4H), 7.48 (d, *J* = 8.4 Hz, 4H), 5.21 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 148.0, 142.0, 128.5, 123.9, 68.4.

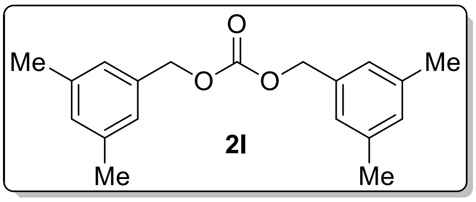
Bis(4-cyanobenzyl) carbonate (2k)



2k

White solid (88%); FT-IR (KBr, cm^{-1}) 3033, 2956, 2232, 1746, 1513, 1461, 1398, 1449, 1274, 958, 925, 819, 598; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 4H), 7.49 (d, *J* = 8.0 Hz, 4H), 5.23 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 140.1, 132.5, 128.4, 118.4, 112.6, 68.7.

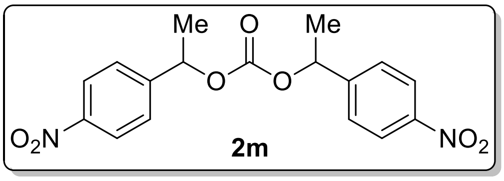
Bis(3,5-dimethylbenzyl) carbonate (2l)



2l

White solid (79%); FT-IR (KBr, cm^{-1}) 2983, 2925, 2854, 1747, 1517, 1454, 1381, 1260, 943, 902, 808, 788, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 4H), 6.86 (s, 2H), 5.01 (s, 4H), 2.21 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.2, 135.1, 130.2, 126.1, 69.8, 21.2.

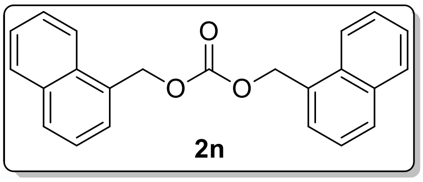
Bis(1-(4-nitrophenyl)ethyl) carbonate (2m)



2m

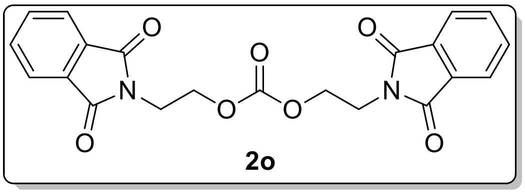
White solid (69%); FT-IR (KBr, cm^{-1}) 1946, 1751, 1606, 1519, 1349, 1265, 1063, 995, 863, 789, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 4H), 7.54 (d, *J* = 8.8 Hz, 4H), 5.73 (q, *J* = 6.4 Hz, 2H), 1.58 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 148.1, 147.7, 126.8, 124.0, 75.6 22.3.

Bis(naphthalen-2-ylmethyl) carbonate (2n)


2n

White solid (99%); FT-IR (KBr, cm^{-1}) 2370, 2349, 1747, 1717, 1279, 1256, 940, 912, 803, 794, 781, 768; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.88 (t, *J* = 8.0 Hz, 4H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.53 (dd, *J* = 13.8, 6.4 Hz, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 5.67 (s, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.2, 133.7, 131.6, 130.7, 129.6, 128.7, 127.8, 126.7, 126.0, 125.2, 123.5, 68.1.

Bis((1,3-dioxoisoindolin-2-yl)methyl) carbonate (2o)


2o

White solid (82%); FT-IR (KBr, cm^{-1}) 3418, 1745, 1650, 1307, 1047,996, 767, 543; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.90–7.80 (m, 8H), 4.24 (t, *J* = 4.8 Hz, 4H), 3.83 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, CDCl$_3$+DMSO-*d*$_6$) δ 168.0, 154.6, 134.1, 131.9, 123.4, 77.4, 65.0, 36.7, 29.6.

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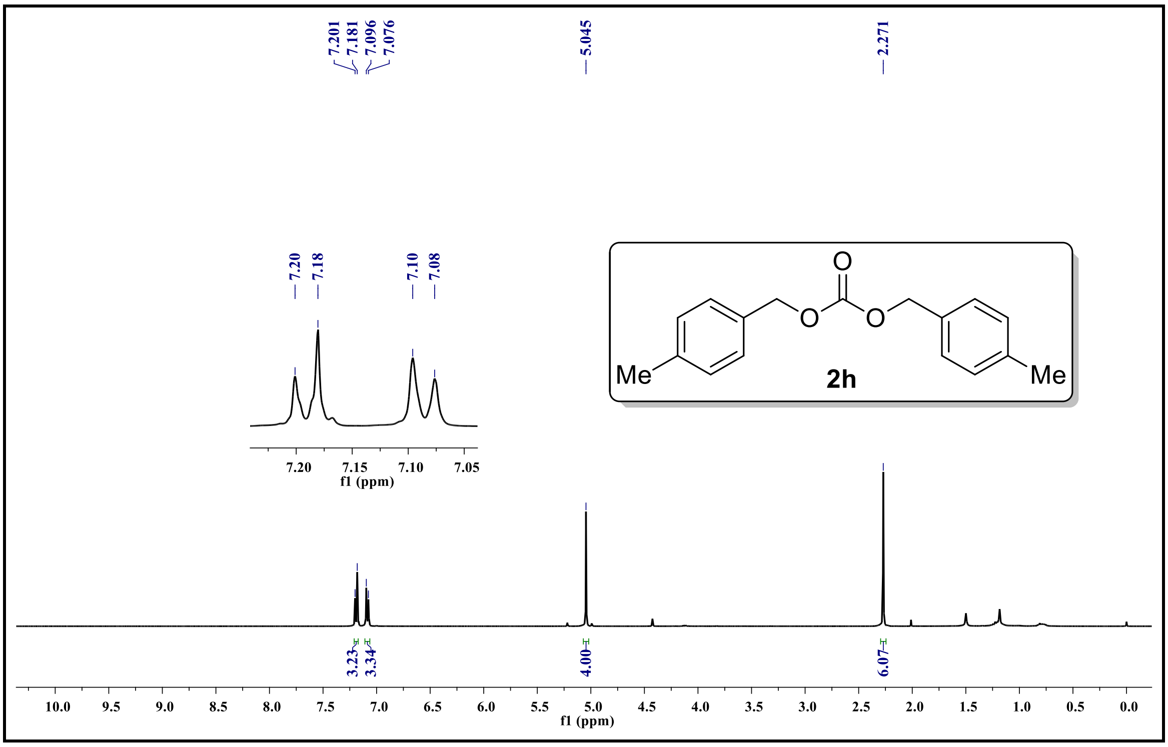
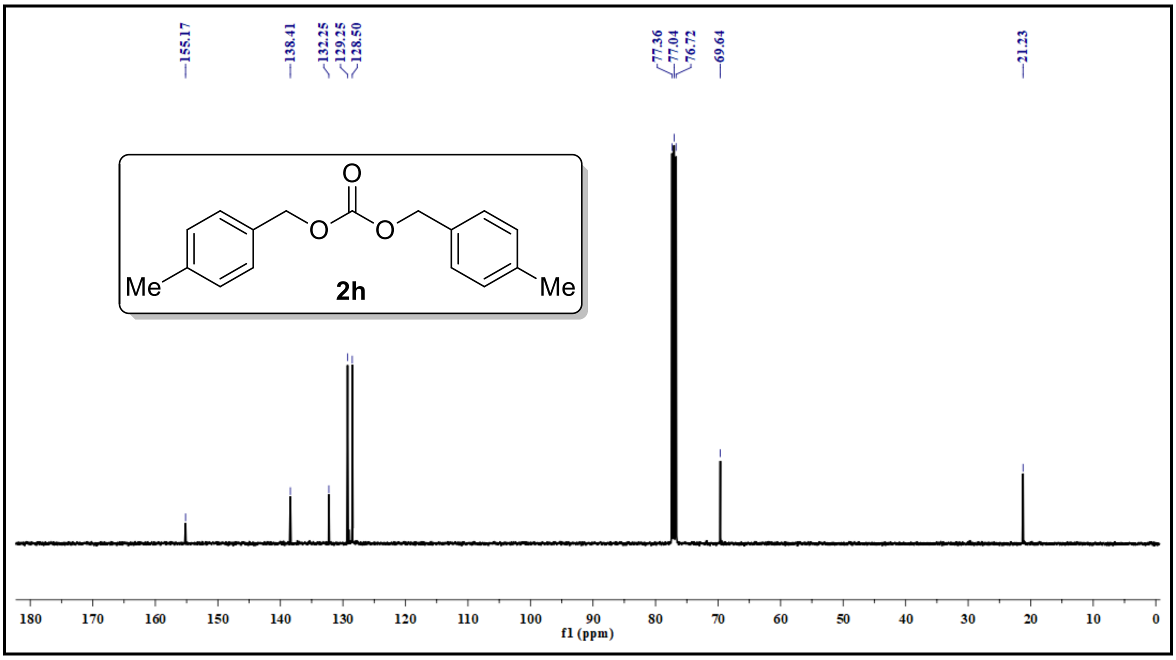
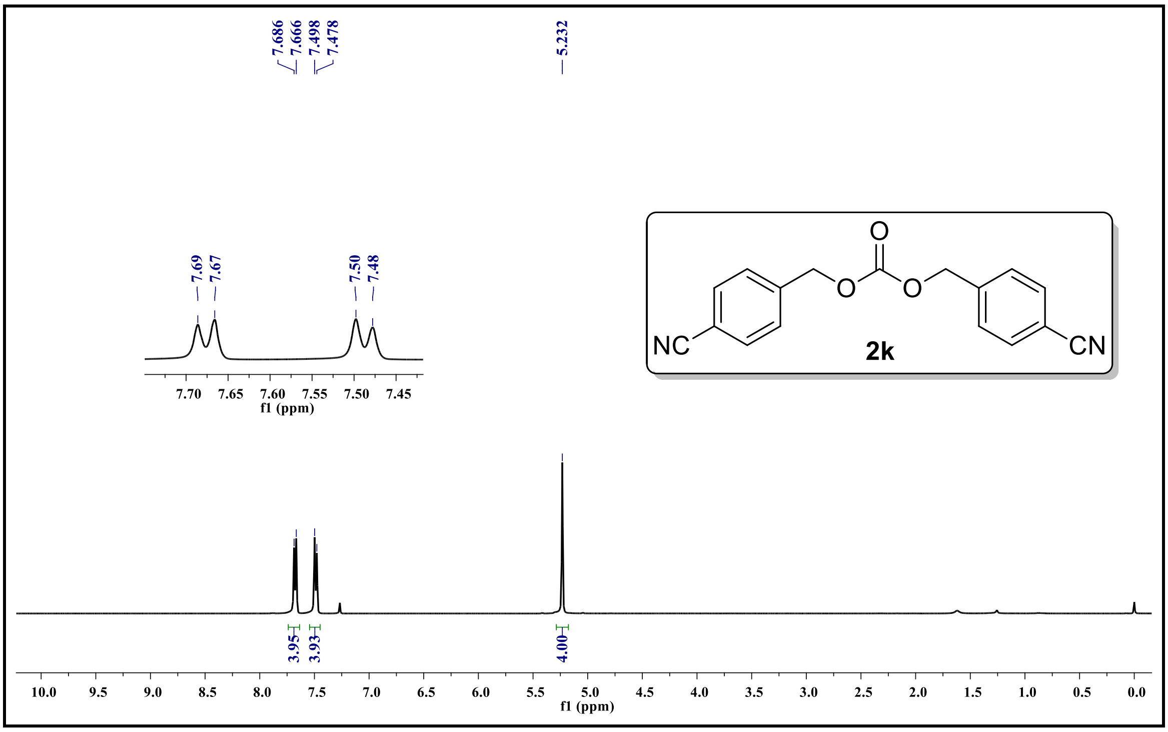
5A.8. Selected NMR (^{1}H and ^{13}C) Spectra



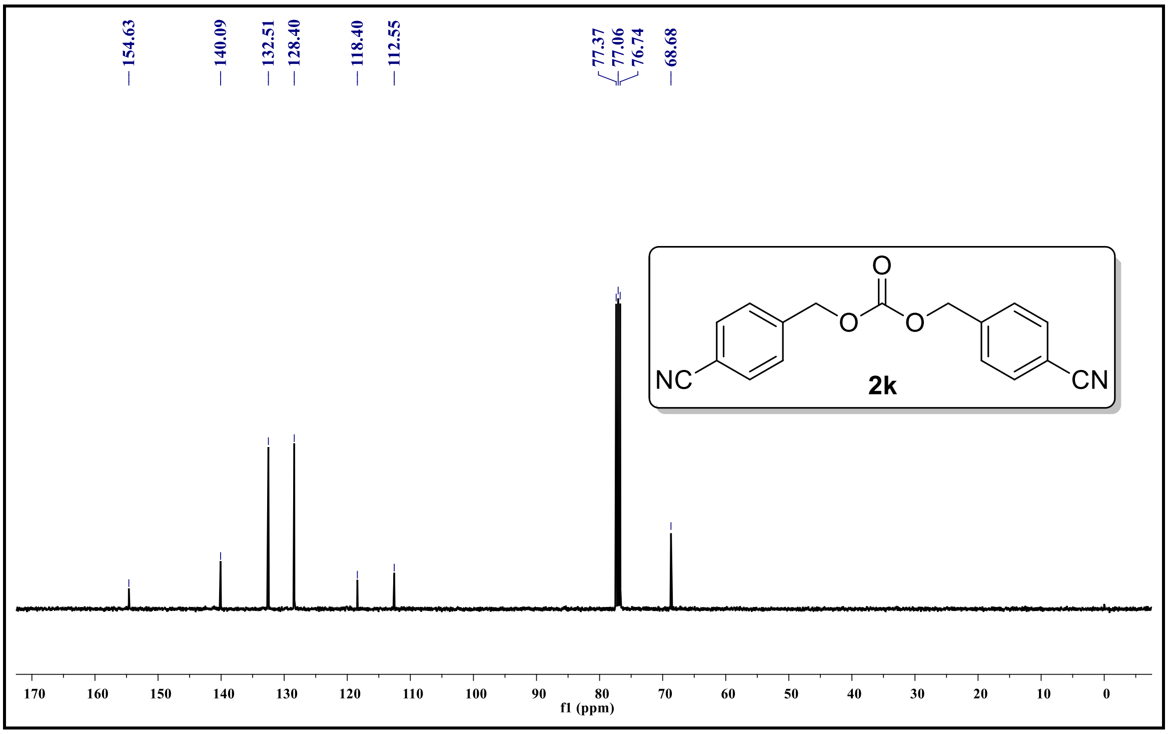
^{1}H NMR spectrum of compound **2h**



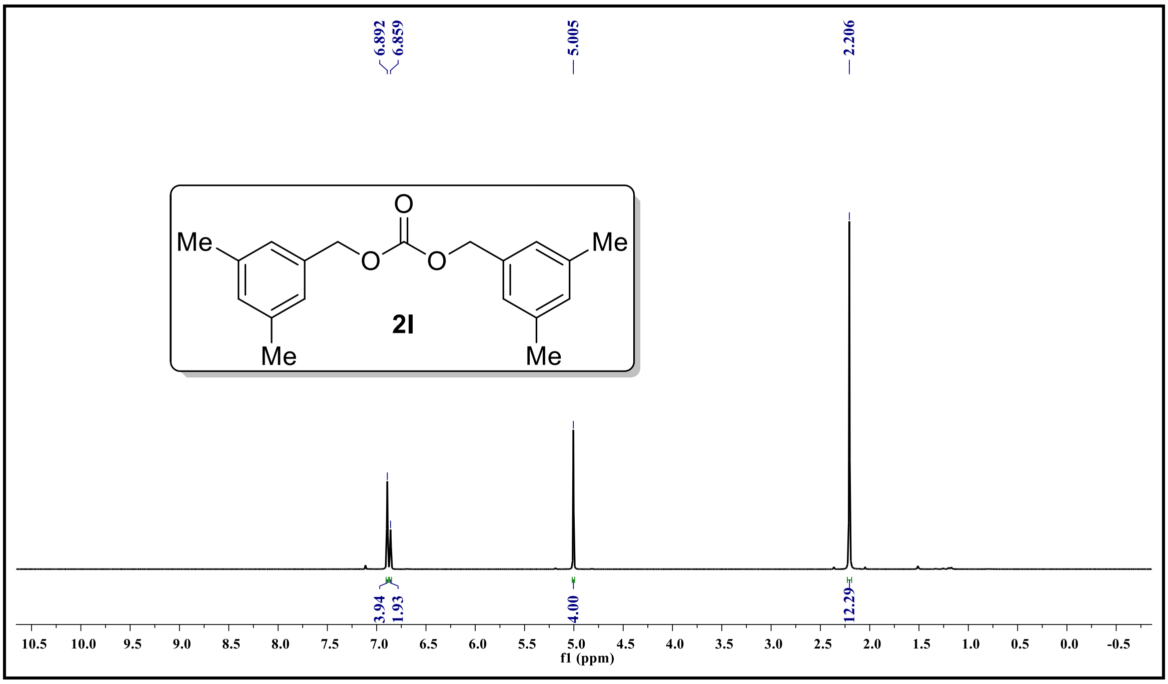
^{13}C NMR spectrum of compound **2h**



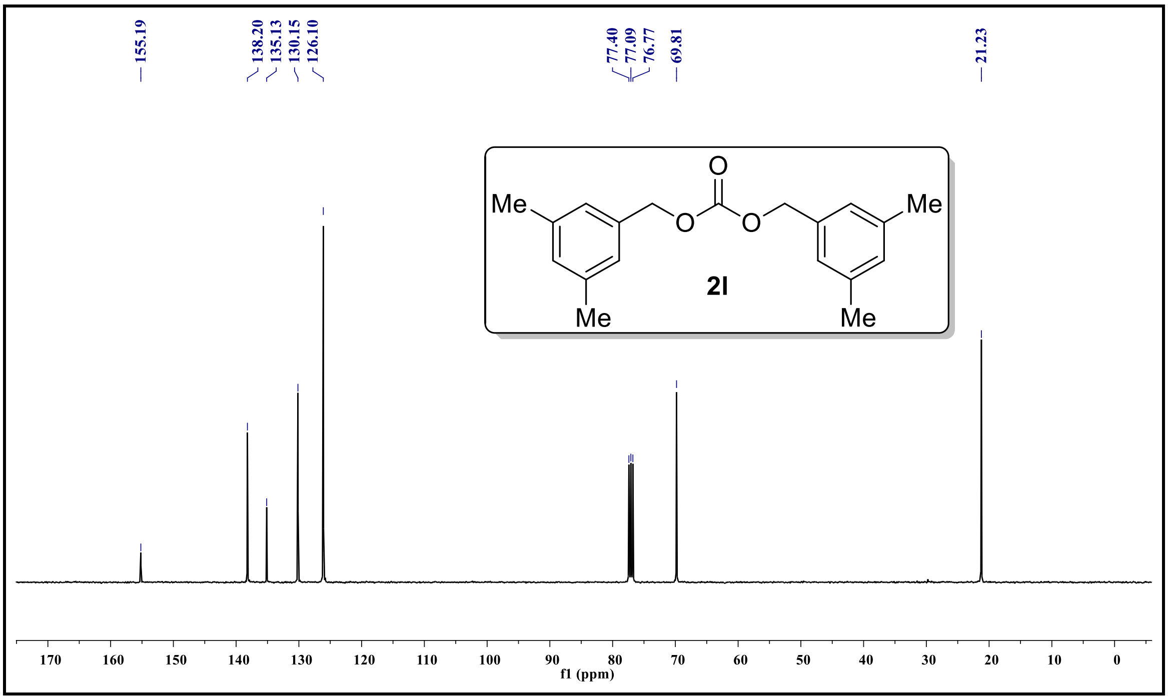
^{1}H NMR spectrum of compound **2k**



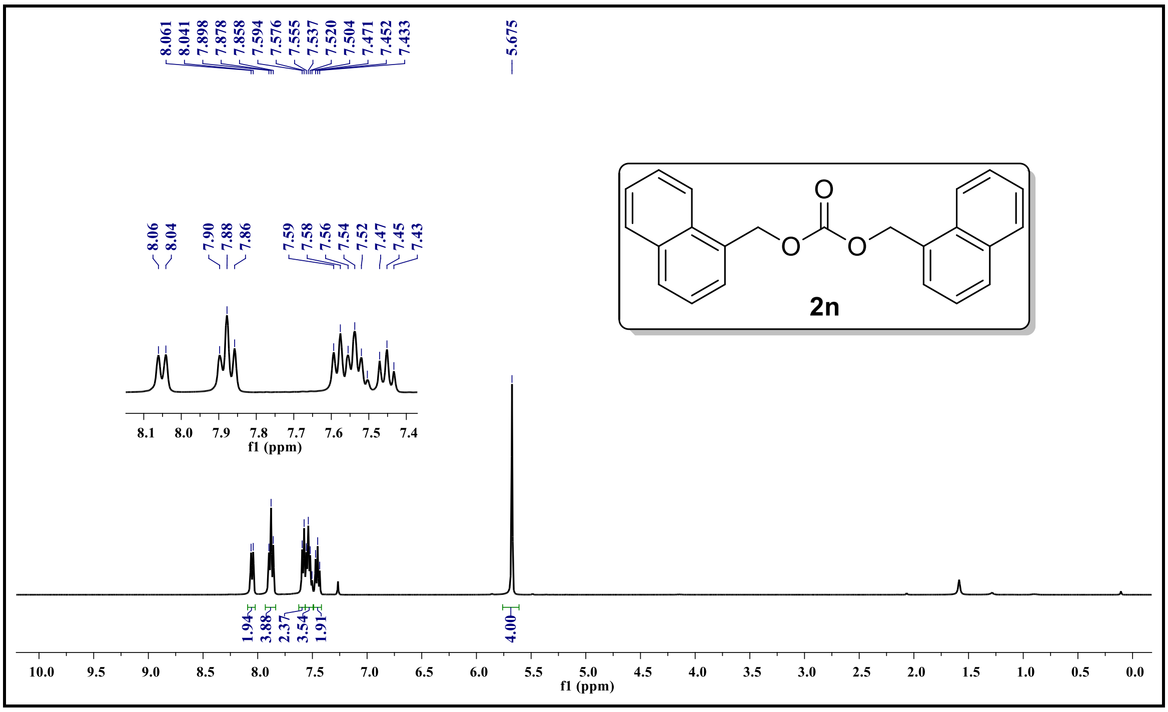
^{13}C NMR spectrum of compound **2k**



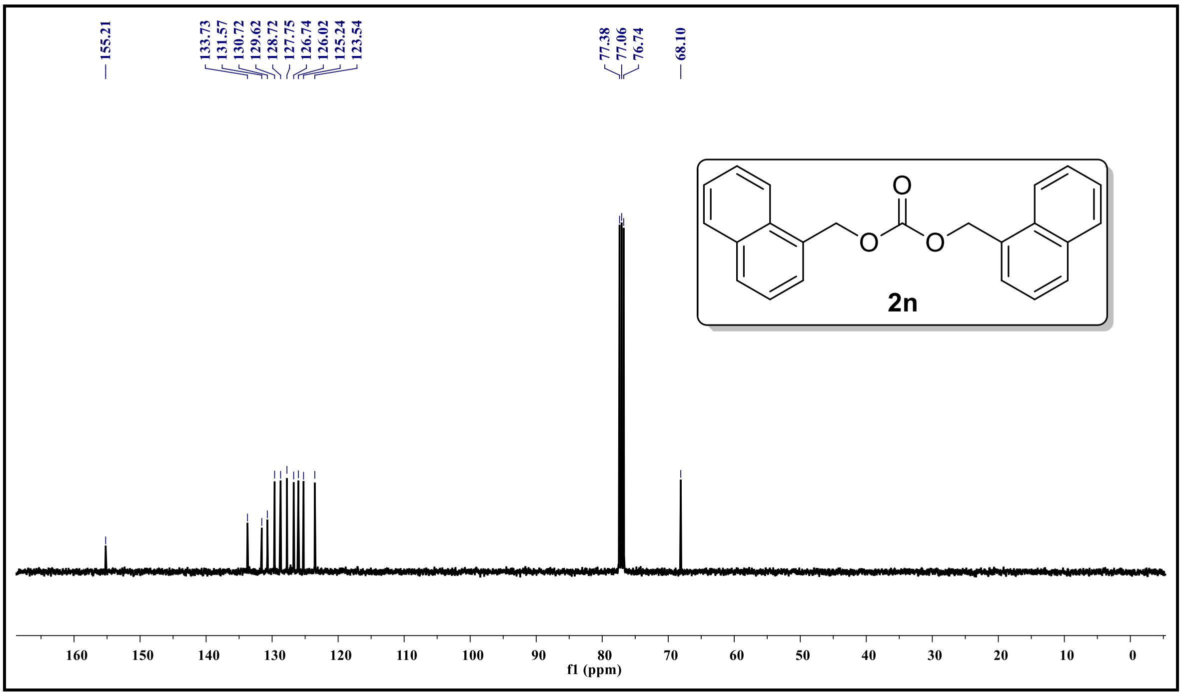
^{1}H NMR spectrum of compound **2l**



^{13}C NMR spectrum of compound **2l**



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



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

CHAPTER V (PART-B)

2,2,2-Trichloroacetates: Versatile Substrates for the Nucleophilic Substitution Reactions and Its Applications in Organic Synthesis

5B.1. Introduction

Organic Iodides

Halogen containing organic compounds are versatile and very useful intermediates in organic synthesis.[1] They play a pivotal role in the synthesis of pharmaceuticals and fine chemicals to treat diseases like diabetes,[2] HIV,[3] cancer,[4] and arthritis.[5] Organic iodides undergo lithiation to introduce electrophiles through a halogen-lithium exchange reaction and also reacts with nucleophiles such as alkoxides, amines to afford corresponding substituted products.[6] Alkyl iodides widely used as intermediates in carbon-carbon coupling,[7,8] rearrangement,[9] elimination[10,11] reactions. Even though alkyl iodides are less stable and more expensive than other halides these are more reactive and in few cases only alkyl iodides are reactive halides.[12]

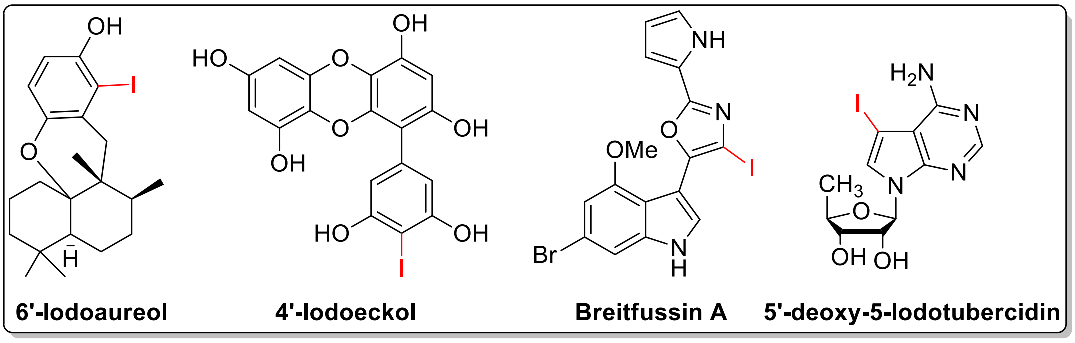


Figure 5B. 1. Some examples of natural products with iodine functionality.

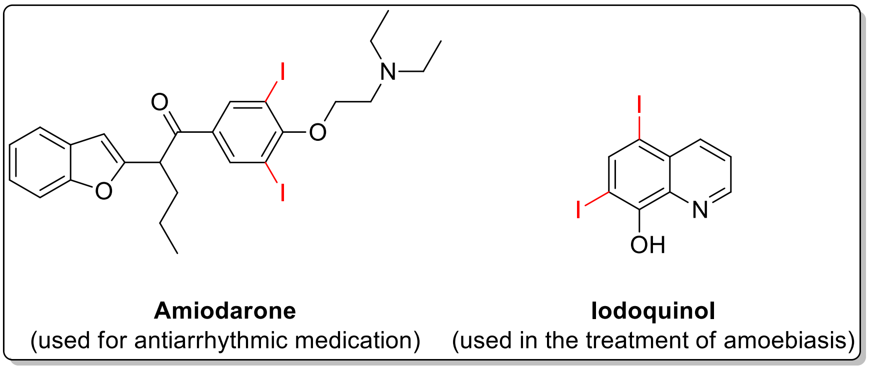


Figure 5B. 2. Examples of drugs with iodine functionality.

Numerous methods for the synthesis of organic iodides have been documented in the literature. In the majority of the reports, iodides were synthesised from alcohols.[13,14] But they have a number of drawbacks such as drastic conditions, presence of hazardous vapours,[15] use of excess reagents,[16] high temperatures,[17] tedious work-up procedures,[18] long reaction times,[19] and low yields. To overcome these challenges, novel and more straightforward procedures for the mild and efficient synthesis of alkyl iodides are desperately needed.

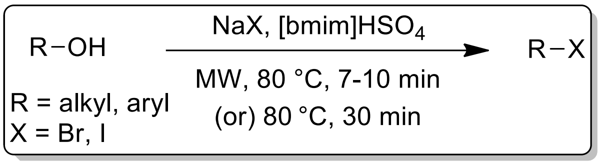
Organic Azides

Organic azides[20] are versatile intermediates in the synthetic organic chemistry. Azido functional group of organic azide reacts with both electrophiles as well as nucleophiles and also used as a precursor for the synthesis of nitrene intermediates, primary amines[21] and heterocycles such as triazoles and tetrazoles.[22,23] Azides are heat or shock sensitive and will decompose on exposure to UV light.[24,25] Nevertheless, organic azides are most important chemicals[26,27] as energy-rich materials,[28] pharmaceuticals,[29] pesticides.[30] Azido nucleoside derivatives used as anti-HBV agents,[31] used in the treatment of AIDS[32] and also their bioconjugation *via* Staudinger ligation.[33]

A variety of direct and indirect methods were reported in the literature. In most of the synthetic methods organic azides were synthesized directly from reaction of alkyl halide with inorganic azides. Among all the reports Mitsunobu displacement [34] is a versatile method, in which highly toxic hydrazoic acid (HN_3) is used as an azide source. Most of the methods have drawbacks such as high temperatures, complex synthetic procedures,[35] long reaction times,[36] low yields[35] and usage of halogenated solvents.[37] Therefore search for mild and efficient methods that could use less toxic chemicals for the chemoselective azidation is worthwhile.

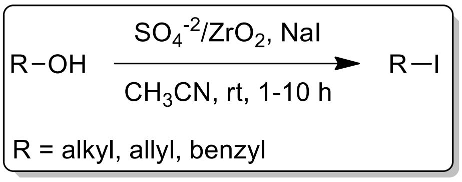
5B.1.1. Different synthetic approaches for the synthesis of alkyl iodide derivatives

Singh and co-workers reported the halogenation of alcohols using sodium halide and efficient reusable catalyst 1-butyl-3-methylimidazolium hydrogen sulphate [bmim]HSO_4 under microwave irradiation (MW) as well as thermal heating at 80 °C (Scheme 5B.1).[38]



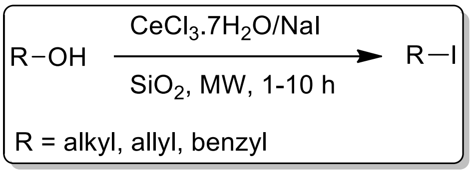
Scheme 5B.1

Jayaram and co-workers used SO_4^{-2}/ZrO_2 catalyst and NaI for the efficient synthesis of alkyl, allyl, benzyl iodides from their corresponding alcohols in CH_3CN at room temperature (Scheme 5B.2).[39]



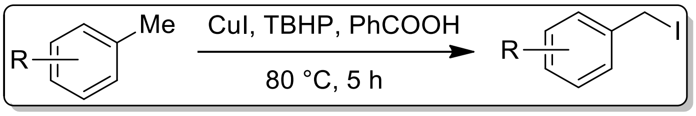
Scheme 5B.2

Hosseinzadeh and co-workers developed a simple and new methodology for the synthesis of organic iodides (primary, secondary, allylic and benzylic iodides) using a very cheap, nontoxic, and water tolerant $CeCl_3{\cdot}7H_2O$/NaI over SiO_2 from corresponding alcohols under a domestic microwave oven irradiation for 1 to 10 hours (Scheme 5B.3).[40]



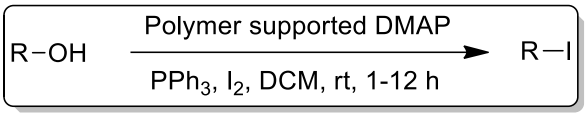
Scheme 5B.3

Xiong and co-workers reported the effective and new method for the synthesis of benzyl halides through direct halogenation of sp^3 C–H bond using *in situ* generated *t*-butyl hypoiodite, which is produced by the reaction of CuI, *t*-butyl hydroperoxide (TBHP) with benzoic acid at 80 °C (Scheme 5B.4).[41]



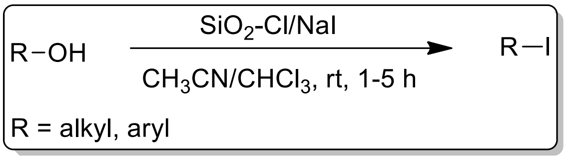
Scheme 5B.4

Rokhum and co-workers demonstrated a simple and chemoselective method for the iodination of alcohols by using reaction of triphenylphosphine (PPh_3), iodine (I_2) in presence of a catalytic amount of reusable polymer supported 4-(Dimethylamino)pyridine (DMAP) at room temperature (Scheme 5B.5).[42]



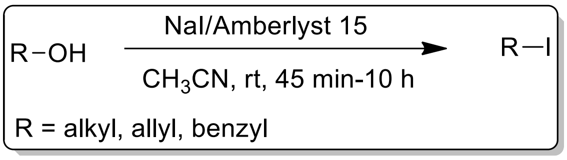
Scheme 5B.5

Karimi et al. used silica chloride (SiO_2-Cl) to convert alcohols into corresponding chlorides in $CHCl_3$ at room temperature as well as SiO_2-Cl/NaI for the conversion of alcohols into iodides in a mixture of $CH_3CN/CHCl_3$ solvent at room temperature (Scheme 5B.6).[43]



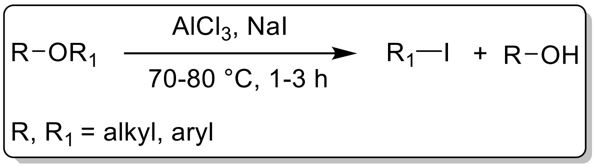
Scheme 5B.6

Tajbakhsh and co-workers used NaI/Amberlyst 15 for the mild and efficient conversion of alcohols (primary, secondary, benzylic and allylic alcohols) into iodides in acetonitrile solvent at room temperature (Scheme 5B.7).[44]



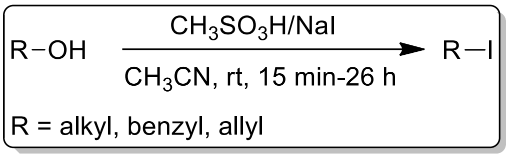
Scheme 5B.7

Asghari et al. reported the dealkylation of alkyl and aryl ether using $AlCl_3$-NaI. In this report they have synthesized alkyl or aryl iodides by grinding the mixture of alkyl or aryl ether, $AlCl_3$ and NaI without solvent in a agate mortor at 70-80 °C for 1-3 hours (Scheme 5B.8).[45]



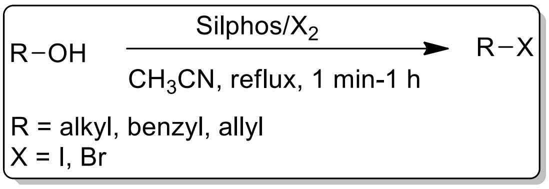
Scheme 5B.8

Kamal and co-workers developed a method for the synthesis of alkyl, allyl and benzyl iodides by using methanesulphonic acid and sodium iodide at room temperature (Scheme 5B.9).[46]



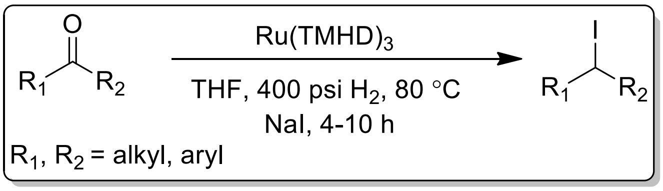
Scheme 5B.9

Iranpoor and co-workers reported a new method for the synthesis of alkyl iodides and bromides by using a cheap, easily prepared and new heterogeneous reagent, Silicaphosphine (Silphos), $[P(Cl)_{3-n}(SiO_2)_n]$ which is a new source of filterable phosphine. In this report iodides and bromides were synthesized by refluxing alcohols and molecular iodine or bromine in CH_3CN solvent (Scheme 5B.10).[47]



Scheme 5B.10

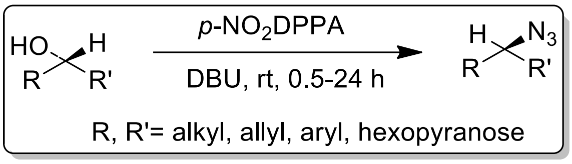
Bhor et al. reported the use of O-containing metal complex, $Ru(TMHD)_3$ for the synthesis of alkyl iodides and cyanides from corresponding aldehydes and ketones. In this report they followed sequential one-pot method so first $Ru(TMHD)_3$ complex actively hydrogenated the aldehydes or ketones into alcohols then addition of sodium iodide or copper cyanide leads to form their respective iodides and nitriles (Scheme 5B.11).[48]



Scheme 5B.11

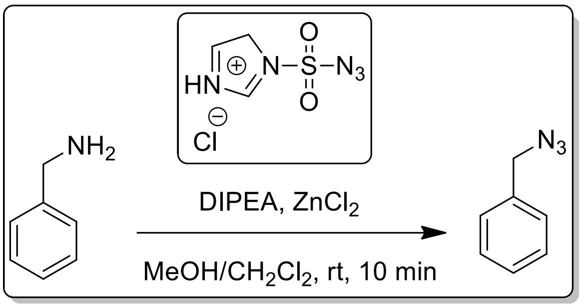
5B.1.2. Different synthetic approaches for the synthesis of alkyl azide derivatives

Shioiri and co-workers reported the stereoselective synthesis of alkyl azides and glycosyl azides from corresponding alcohols and hexopyranoses by one pot azidation method using bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA) and DBU (Scheme 5B.12).[49]



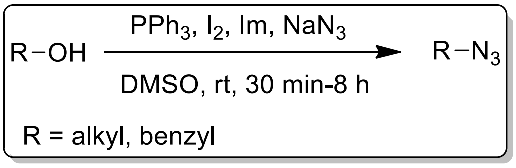
Scheme 5B.12

Rutjes and co-workers used continuous flow setup for small scale synthesis of benzyl azide using diazotransfer reagent, imidazole-1-sulfonyl azide hydrochloride and benzyl amine at room temperature. Also, they have successfully scaled up the azidation reaction up to gram scale (Scheme 5B.13).[50]



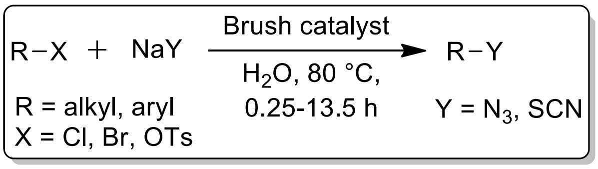
Scheme 5B.13

Rokhum et al. synthesized alkyl and benzyl azides by stirring grinded mixture of alcohol, triphenylphosphine (PPh_3), iodine (I_2), imidazole (Im) and solution of sodium azide (NaN_3) in DMSO at room temperature (Scheme 5B.14).[51]



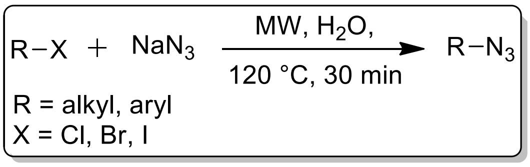
Scheme 5B.14

Wei and co-workers reported the synthesis of alkyl azides and thiocyanates from alkyl halides and tosylates with sodium azide or sodium thiocyanate (NaSCN) *via* on-water nucleophilic substitutions using efficient and reusable dilayer brush bearing *n*-octyl group catalyst at 80 °C (Scheme 5B.15).[52]



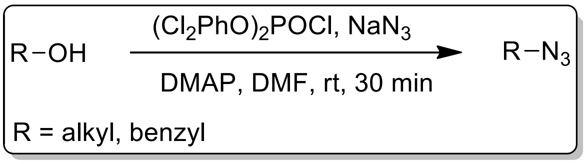
Scheme 5B.15

Varma and co-workers synthesized alkyl azides by microwave promoted reaction of alkyl halides and sodium azide at MW power 70-100 W at 120 °C for 30 min in aqueous media (Scheme 5B.16).[53]



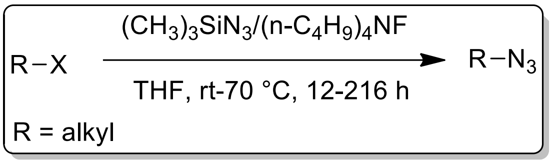
Scheme 5B.16

Hu and co-workers synthesized alkyl azides by one pot reaction of alcohols, bis(2,4-dichlorophenyl) phosphate, (dimethylamino)pyridine (DMAP) and sodium azide in DMF at room temperature. In this report phosphorylpyridinium azide is acted as activating agent under this condition (Scheme 5B.17).[54]



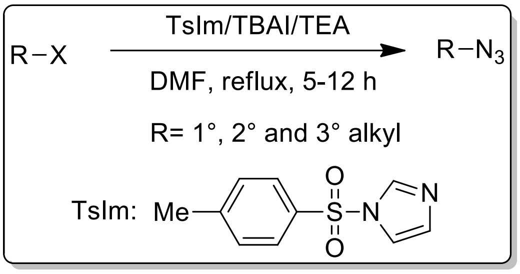
Scheme 5B.17

Takaya and co-workers used tetra butyl ammonium fluoride for the fluoride ion induced S_N2 reaction of alkyl halides, phosphates or tosylates with trimethylsilyl azide in THF to produce variety of primary and secondary alkyl azides (Scheme 5B.18).[55]



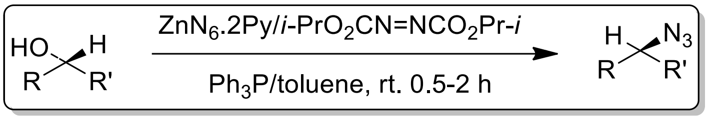
Scheme 5B.18

Behrouz et al. reported the synthesis of alkyl azides by refluxing a mixture of alcohol, *N*-(*p*-toluenesulfonyl)imidazole (TsIm), NaN_3, triethylamine (TEA) and tetra-*n* butylammonium iodide (TBAI) in DMF (Scheme 5B.19).[56]



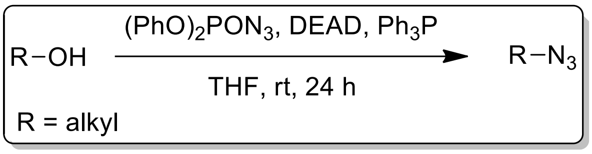
Scheme 5B.19

Rollin and co-workers reported Mitsunobu-type substitution for the conversion of alcohols into azides. In this report alcohols react with zinc azide/bis-pyridine complex in presence of diisopropyl azodicarboxylate/triphenylphosphine couple at room temperature to yield corresponding azides (Scheme 5B.20).[57]



Scheme 5B.20

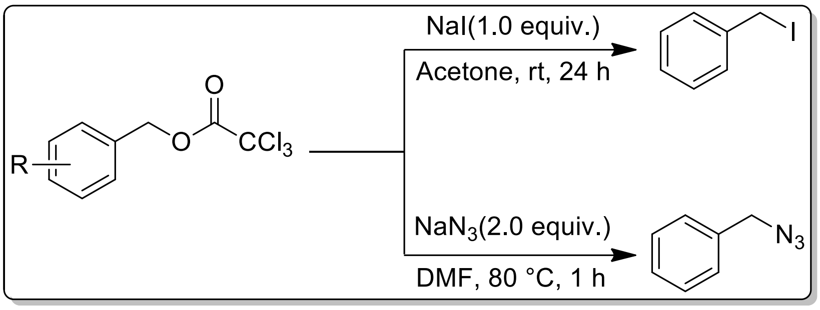
Bose and co-workers used stable and distillable, diphenylphosphoryl azide for the conversion of alcohols into corresponding azides. In this method to the mixture of equimolar alcohol, triphenylphosphine and diethylazodicarboxylate (DEAD) in tetrahydrofuran (THF) added diphenylphosphoryl azide solution and continued stirring at room temperature for 24 hours to produce alkyl azides (Scheme 5B.21).[58]



Scheme 5B.21

5B.2. Present work

We established easy and simple methodologies for the syntheses of both alkyl iodides and alkyl azides, without employing harmful compounds, halogenated solvents, complex synthetic techniques and high temperatures. Traditionally, alcohols have been employed as starting materials for the synthesis of alkyl iodides and azides. But in this chapter, we have used alkyl trichloroesters as precursors for the efficient synthesis of alkyl iodides and azides.

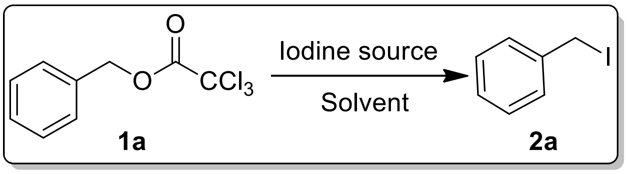


Scheme 5B.22

By applying above protocol for various alkyl trichloroesters we have synthesized a library of alkyl iodides and alkyl azides with good yields.

5B.3. Results and discussion

Table 5B.1. Optimization of reaction conditions of synthesis of benzyl iodides from benzyl trichloroesters^{a}

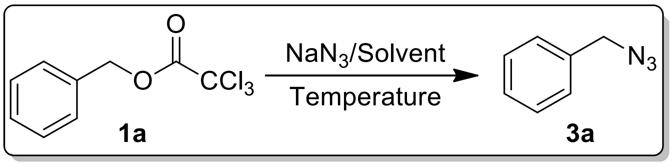


S.No	Iodine Source	Solvent	Time	Yield[b] (%)
1	**NaI**	**Acetone**	**24 h**	**70**
2	KI	Acetone	24 h	62
3	NaI	DMF	24 h	59
4	NaI	DMSO	24 h	60
5	NaI	MeOH	24 h	0
6	NaI	CH_3CN	24 h	35

[a]Reaction conditions: benzyl trichloroester **1a** (1.0 mmol), Iodine source (1.0 equiv.) in solvent(1.0 mL) at room temperature. [b]Yields are of isolated pure products.

Optimization of synthesis of benzyl iodides from benzyl trichloroesters were summarized in the Table 5B.1. In this optimization reaction benzyl,2,2,2-trichloroacetate **1a** was taken as model substrate. Initially sodium iodide (NaI) was taken as iodine source and reaction was carried out in acetone solvent to afford 70% of benzyl iodide (Table 5B.1, entry 1). To know the effect of iodine source on product yield, we have used potassium iodide (KI) but it gave lesser yield than sodium iodide (Table 5B.1, entry 2). To improve the product yield, we have conducted reactions in different polar solvents such as DMF, DMSO, MeOH and CH_3CN (Table 5B.1, entries 3-6). Among all the solvents reaction was underwent smoothly in acetone with good yield of product.

Table 5B.2. Optimization of reaction conditions of synthesis of benzyl azides from benzyl trichloroesters[a]

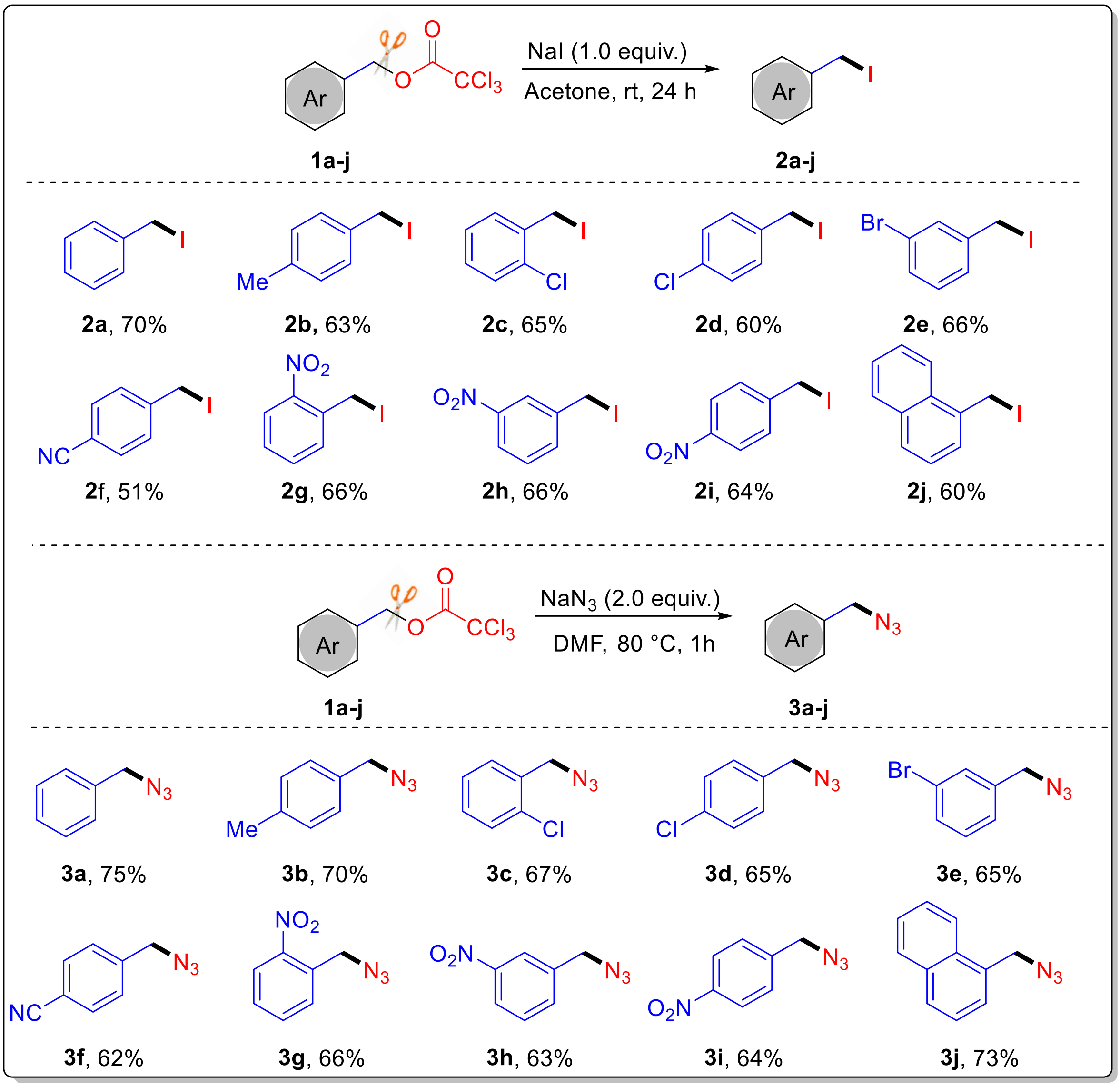


S.No	**Solvent**	**Temp (°C)**	**Time**	**Yield[b] (%)**
1	DMF	rt	24 h	0
2	DMF	40	14 h	35
3	DMF	60	6 h	53
4	**DMF**	**80**	**1 h**	**85**
5	DMSO	80	2 h	68
6	CH_3CN	80	5 h	60
7	Acetone	80	12 h	0
8	H_2O	80	12 h	0

[a]Reaction conditions: benzyl trichloroester **1a** (1.0 mmol), NaN_3 (2.0 equiv.) in solvent (1.0 mL) at different temperatures. [b]Yields are of isolated pure products.

The results of optimization of benzyl azides were shown in the Table 5B.2. Benzyl 2,2,2-trichloroacetate **1a** was taken as model substrate for this reaction. Initially, benzyl 2,2,2-trichloroacetate and sodium azide (2.0 equiv.) were stirred in DMF at room temperature for 24 h but no product was observed (Table 5B.2, entry 1). To know the effect of temperature on the reaction, we have conducted this reaction at different temperatures such as 40 °C, 60 °C and 80 °C (Table 5B.2, entries 2-4). From this experiments, we have observed that decrement in the reaction time as well as increment in the product yield and the reaction at 80 °C gave 85% of yield of the product in 1 h (Table 5B.2, entry 4). Finally, to improve the product yield we have screened the reaction in different solvents like DMSO, CH_3CN, Acetone and water (Table 5B.2, entries 5-8). The reactions in presence of DMSO, CH_3CN solvents gave moderate to good yield of product (Table 5B.2, entries 5-6) whereas acetone and water did not give any product (Table 5B.2, entries 7-8). Therefore among all the conditions, reaction in DMF solvent at 80 °C is the suitable condition for the synthesis of benzyl azides from benzyl trichloroacetates.

Table 5B.3. Synthesis of benzyl Iodide and Azide Derivatives^{a,b,c}



[a]Reaction conditions: Trichloroesters **1a-j** (1.0 mmol), NaI (1.0 equiv.) in acetone (1.0 mL) at room temperature. [b]Reaction conditions: Trichloroesters **1a-j** (1.0 mmol), NaN_3 (2.0 equiv.) in DMF (1.0 mL) at 80 °C. [c]Yields are of isolated pure products.

To examine the generality and scope of alkyl iodide synthetic method, different benzyl trichloroesters containing halogens (Table 5B.3, **1c-e**), electron donating (Table 5B.3, **1b**), electron withdrawing (Table 5B.3, **1f-i**) and naphthyl substituted (Table 5B.3, **1j**) trichloroesters were taken to afford the corresponding iodides (Table 5B.3, **2a-2j**). Benzyl trichloroacetate with -Me substitution undergo reaction easily to form corresponding benzyl iodide with good reaction yield (Table 5B.3, **2b**). Halogen substitutions on *ortho*, *meta*, *para* positions of benzyl trichloroester have shown little effect on reaction yields (Table 5B.3, **2c-e**). Notably, electron withdrawing groups such as -CN, $-NO_2$ substitution on benzyl trichloroester produced the corresponding iodides with good yields (Table 5B.3, **2f-i**). Furthermore, naphthalen-1-ylmethyl 2,2,2-trichloroacetate underwent reaction smoothly to give desired alkyl iodides with good yield (Table 5B.3, **2j**).

To investigate the scope and generality of the alkyl azide synthetic method various *ortho*, *meta*, *para* substituted benzyl trichloroesters (Table 5B.3, **1a-i**) and naphthalen-1-ylmethyl 2,2,2-trichloroacetate (Table 5B.3, **1j**) were reacted with sodium azide to form corresponding azides with a less difference in the reaction yields (Table 5B.3, **3a-j**).

5B.4. Conclusions

In this chapter we have used less toxic chemicals, simple synthetic procedures and alkyl trichloroester as new precursor to synthesize various substituted alkyl iodides and azides. This protocol tolerates various substitutions (halogens, EDG and EWG) on benzyl trichloroester. We have synthesized 20 compounds with 60–75 % of yield using wide range of alkyl trichloroesters.

5B.5. Experimental Section

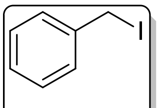
General Information. Alkyl trichloroesters were prepared using our reported method. NaI, KI and NaN_3 were purchased from a commercial source and used as received. Reactions were conducted in round bottom flasks. Thin layer chromatography was performed on 200 µm aluminium-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. ^1H NMR spectra were obtained at 400 MHz in $CDCl_3$ and were referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ and were referenced to the solvent resonance. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) were in hertz (Hz). Standard abbreviations were used to designate resonance multiplicities. Melting points were determined with a melting point apparatus and are uncorrected.

General procedure for the synthesis of alkyl iodides (2a-j). A dried round bottom flask was charged with alkyl trichloroester **1a-j** (1 mmol) and NaI (1.0 equiv.) in acetone and stirred at room temperature for 24 h. After completion (monitored by TLC), acetone was evaporated to give a residue that was extracted with water and ethylacetate (3 x 20 mL). The extracted organic layers were dried over Na_2SO_4 and evaporated under reduced pressure and purified by silica gel column chromatography using hexanes and ethylacetate as eluent.

General procedure for the synthesis of alkyl azides (3a-j). Alkyl trichloroester **1a-j** (1 mmol) and NaN_3 (2.0 equiv.), DMF (1.0 mL) were added to an oven dried round bottom flask and stirred for 1 h at 80 °C. The progress of reaction was monitored by TLC. After completion of reaction, organic layer was extracted with water and ethylacetate (3 x 20 mL). After drying over Na_2SO_4, the extracted organic layers were evaporated under reduced pressure and purified by silica gel column chromatography using *n*-hexanes and ethylacetate as eluent.

5B.6. Spectral data

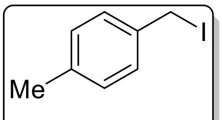
(Iodomethyl)benzene (2a)[59]



2a

Colourless liquid (70%); FT-IR (neat, cm^{-1}) 3024, 2934, 1710, 1612, 1158, 1045, 845, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.25–7.20 (m, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 128.9 128.8, 127.9, 5.8.

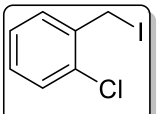
1-(Iodomethyl)-4-methylbenzene (2b)[60]



2b

Pale yellow solid (63%); FT-IR (KBr, cm^{-1}) 3044, 3001, 2923, 2854, 1711, 1612, 1512, 1446, 1157, 1045, 804; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 4.40 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.3, 129.6, 128.7, 21.3, 6.2.

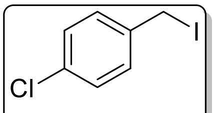
1-Chloro-2-(iodomethyl)benzene (2c)[61]



2c

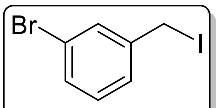
Colourless liquid (65%); FT-IR (neat, cm^{-1}) 2923, 1918, 1571, 1429, 1051, 829, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 4.4 Hz, 3H), 7.23 (dq, J = 8.8, 4.2 Hz, 1H), 4.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 131.4, 128.2, 127.8, 127.4, 127.0, 124.9, 0.0.

1-Chloro-4-(iodomethyl)benzene (2d)[59]


2d

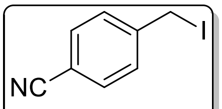
Pale yellow solid (60%); FT-IR (KBr, cm^{-1}) 2954, 2924, 2854, 1902, 1592, 1487, 1212, 1152, 1012, 547, 459; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31–7.28 (m, 4H), 4.44 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.9, 133.6, 130.1, 129.1, 4.3.

1-Bromo-3-(iodomethyl)benzene (2e)[62]


2e

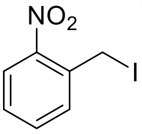
Pale yellow solid (66%); FT-IR (KBr, cm^{-1}) 2923, 1876, 1585, 1211, 876, 685, 666 ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 4.38 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 136.8, 133.9, 130.6, 130.2, 129.5, 127.4, 2.4.

4-(Iodomethyl)benzonitrile (2f)[63]


2f

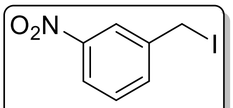
Pale yellow solid (51%); FT-IR (KBr, cm^{-1}) 2924, 2223, 1931, 1602, 1409, 1157, 1078, 842, 827, 573, 530; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 4.43 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.7, 132.6, 129.5, 118.5, 111.6, 2.8.

1-(Iodomethyl)-2-nitrobenzene (2g)[64]


2g

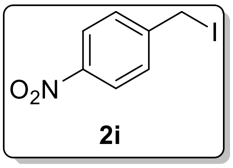
Pale yellow solid (66%); FT-IR (KBr, cm^{-1}) 2924, 1604, 1516, 1305, 1101, 791, 746, 694; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.54 (d, J = 6.4 Hz, 1H), 7.51–7.43 (m, 1H), 4.81 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.5, 135.1, 134.0, 132.4, 129.2, 125.9, 0.0.

1-(Iodomethyl)-3-nitrobenzene (2h)[42]


2h

Pale yellow solid (66%); FT-IR (KBr, cm^{-1}) 3061, 3040, 1524, 1352, 1312, 1164, 807, 736, 686; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.23 (s, 1H), 8.11–8.09 (m, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.1, 139.2, 132.5, 127.7, 121.3, 120.5, 0.0.

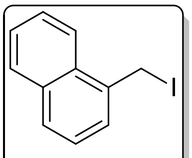
1-(Iodomethyl)-4-nitrobenzene (2i)[42]



2i

Pale yellow solid (64%); FT-IR (KBr, cm^{-1}) 2930, 1604, 1594, 1517, 1342, 1157, 854, 797, 693, 559; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.7, 127.5, 122.0, 0.0.

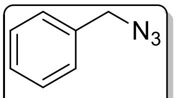
1-(Iodomethyl)naphthalene (2j)[65]



2j

White solid (60%); FT-IR (KBr, cm^{-1}) 3042, 2974, 2923, 2854, 1709, 1692, 1685, 1593, 1363, 1040, 784, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 4.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 134.2, 130.8, 129.2, 128.8, 126.7, 126.4, 126.2, 125.7, 124.0, 4.0.

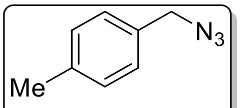
(Azidomethyl)benzene (3a)[56]



3a

Colourless liquid (75%); FT-IR (neat, cm^{-1}) 3050, 2936, 2105, 1473, 1252, 1054, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 4.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 128.9, 128.4, 128.3, 54.8.

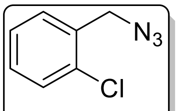
1-(Azidomethyl)-4-methylbenzene (3b)



3b

White solid (70%); FT-IR (KBr, cm^{-1}) 3025, 2925, 2857, 2098, 1516, 1256, 803,754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.20 (m, 4H), 4.32 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 132.3, 129.5, 128.3, 54.7, 21.2.

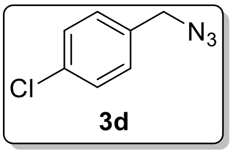
1-(Azidomethyl)-2-chlorobenzene (3c)



3c

Colourless liquid (67%); FT-IR (neat, cm^{-1}) 3052, 2932, 2101, 1474, 1262, 1054, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.40 (m, 2H), 7.36–7.30 (m, 2H), 4.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 133.3, 130.0, 129.8, 129.7, 127.2, 52.3.

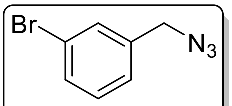
1-(Azidomethyl)-4-chlorobenzene (3d)



3d

White solid (65%); FT-IR (KBr, cm^{-1}) 3022, 2926, 2099, 1492, 1250, 1091, 838, 798; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.38 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.3, 133.9, 129.5, 129.1, 54.1.

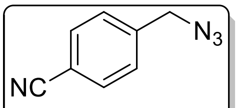
1-(Azidomethyl)-3-bromobenzene (3e)



3e

Colourless liquid (65%); FT-IR (neat, cm^{-1}) 3028, 2926, 2099, 1571, 1256, 1071, 880, 778, 712; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43–7.36 (m, 2H), 7.26–7.13 (m, 2H), 4.25 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.7, 131.4, 131.1, 130.4, 126.7, 122.9, 54.1.

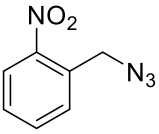
4-(Azidomethyl)benzonitrile (3f)



3f

White solid (62%); FT-IR (KBr, cm^{-1}) 3030, 2931, 2848, 2230, 2103, 1610, 1291, 848, 816; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 4.44 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.8, 132.7, 128.5, 118.5, 112.2, 54.1.

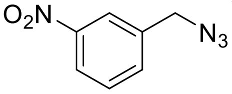
1-(Azidomethyl)-2-nitrobenzene (3g)[56]



3g

Colourless liquid (66%); FT-IR (neat, cm^{-1}) 3033, 2927, 2855, 2104, 1527, 1350, 1293, 788, 729; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (d, J = 8.4 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 6.4 Hz, 1H), 7.54 – 7.45 (m, 1H), 4.40 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.0, 135.2, 134.1, 132.5, 129.2, 125.8, 54.1.

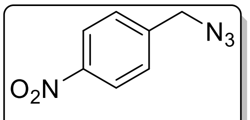
1-(Azidomethyl)-3-nitrobenzene (3h)



3h

Pale yellow solid (63%); FT-IR (KBr, cm^{-1}) 3023, 2927, 2105, 1578, 1254, 1071, 838, 788; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.4 (s, 1H), 8.21–8.11 (m, 1H), 7.80 (d, J =7.6 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 4.35 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.5, 136.2, 132.5, 128.3, 123.1, 54.3

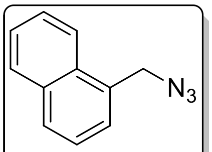
1-(Azidomethyl)-4-nitrobenzene (3i)[56]



3i

Pale yellow solid (63%); FT-IR (KBr, cm^{-1}) 3025, 2920, 2850, 2103, 1560, 1356, 1296, 784, 715; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 4.28 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.6, 143.7, 128.5, 123.1, 55.0.

1-(Azidomethyl)naphthalene (3j)



3j

White solid (73%); FT-IR (KBr, cm^{-1}) 3057, 2936, 2098, 1252, 791, 776; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, J = 8.2 Hz, 1H), 7.95–7.84 (m, 2H), 7.63–7.52 (m, 2H), 7.52–7.44 (m, 2H), 4.78 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 133.9, 131.4, 131.0, 129.5, 128.9, 127.3, 126.8, 126.2, 125.3, 123.5, 53.1.

5B.7. References

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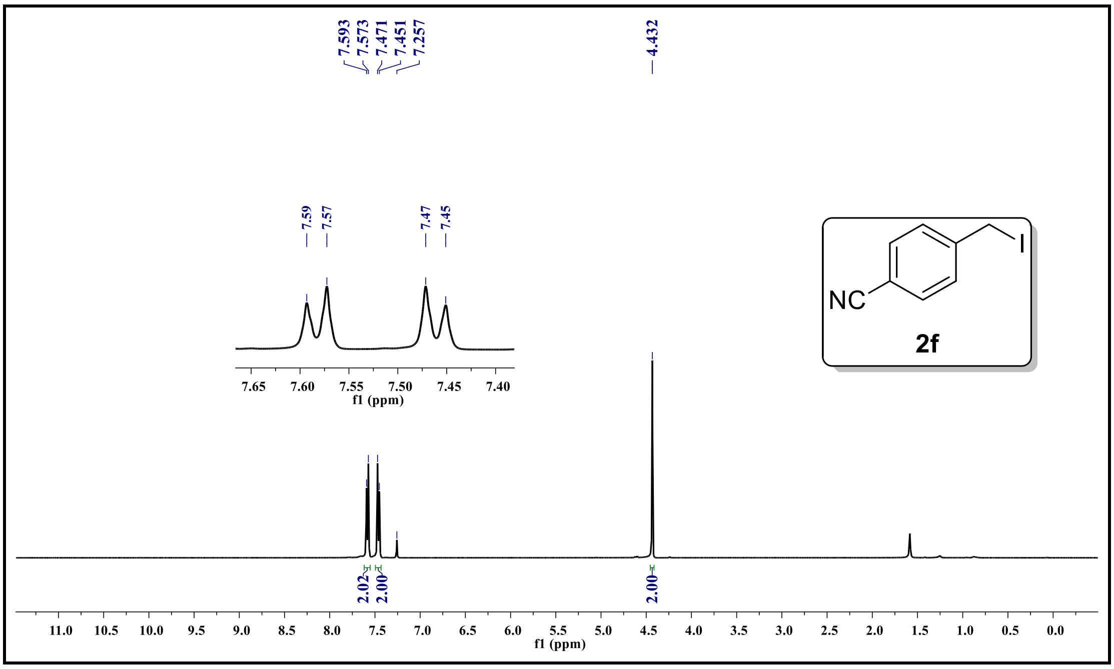
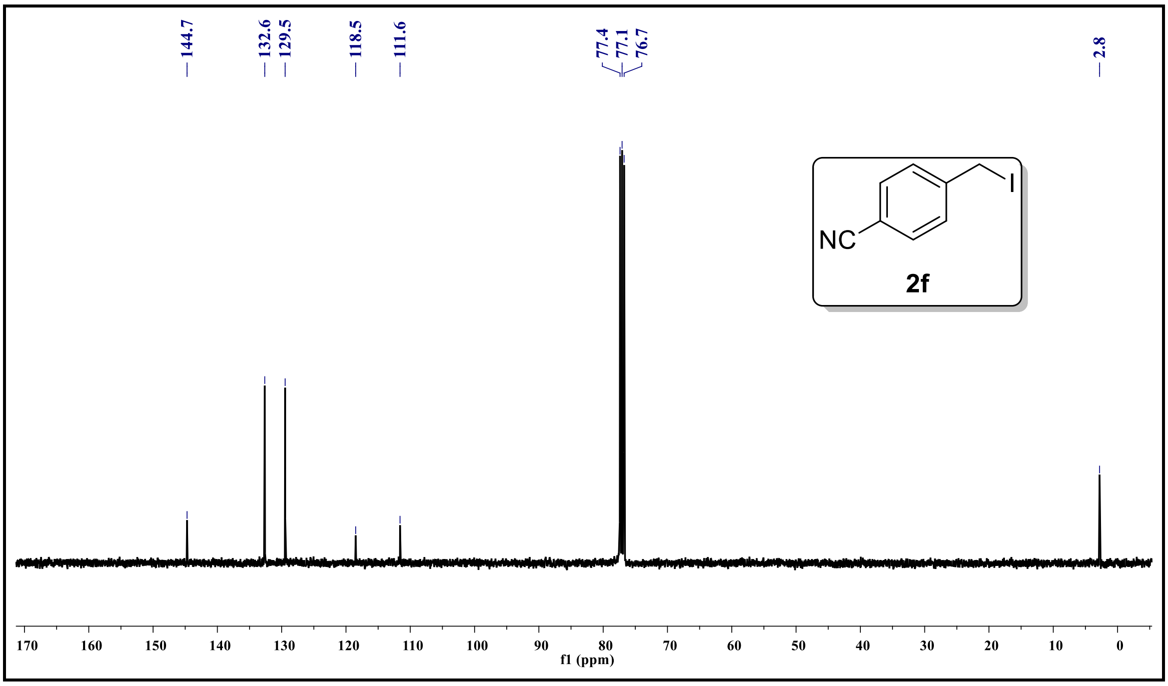
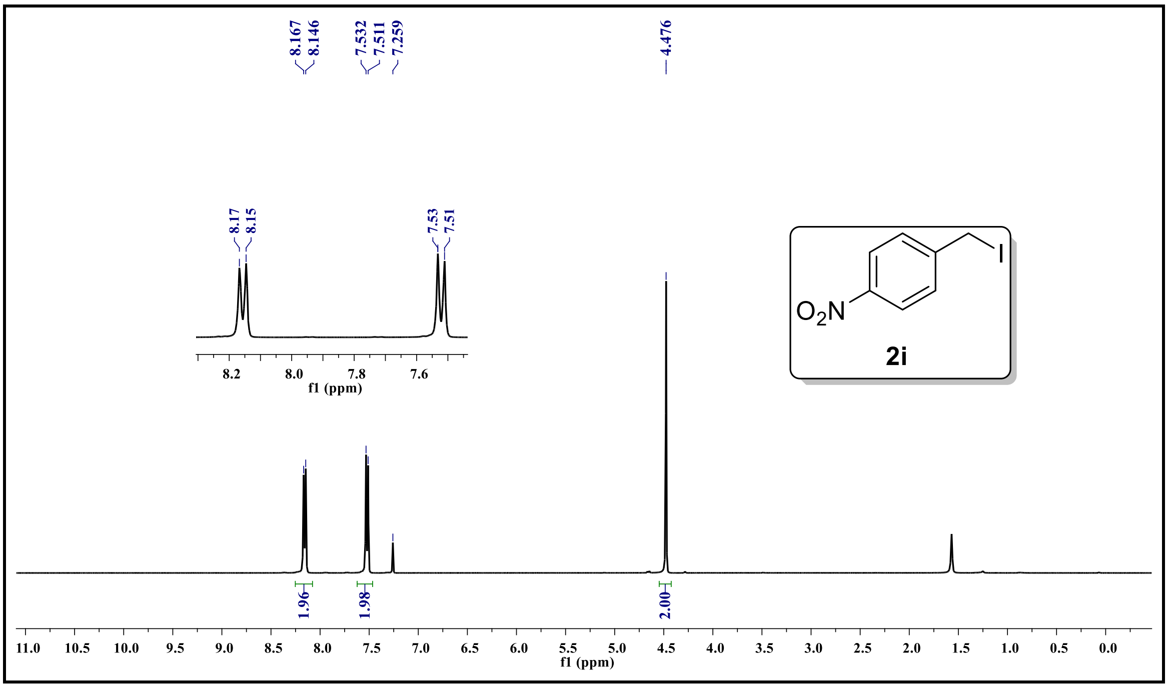
5B.8. Selected NMR (^{1}H and ^{13}C) Spectra



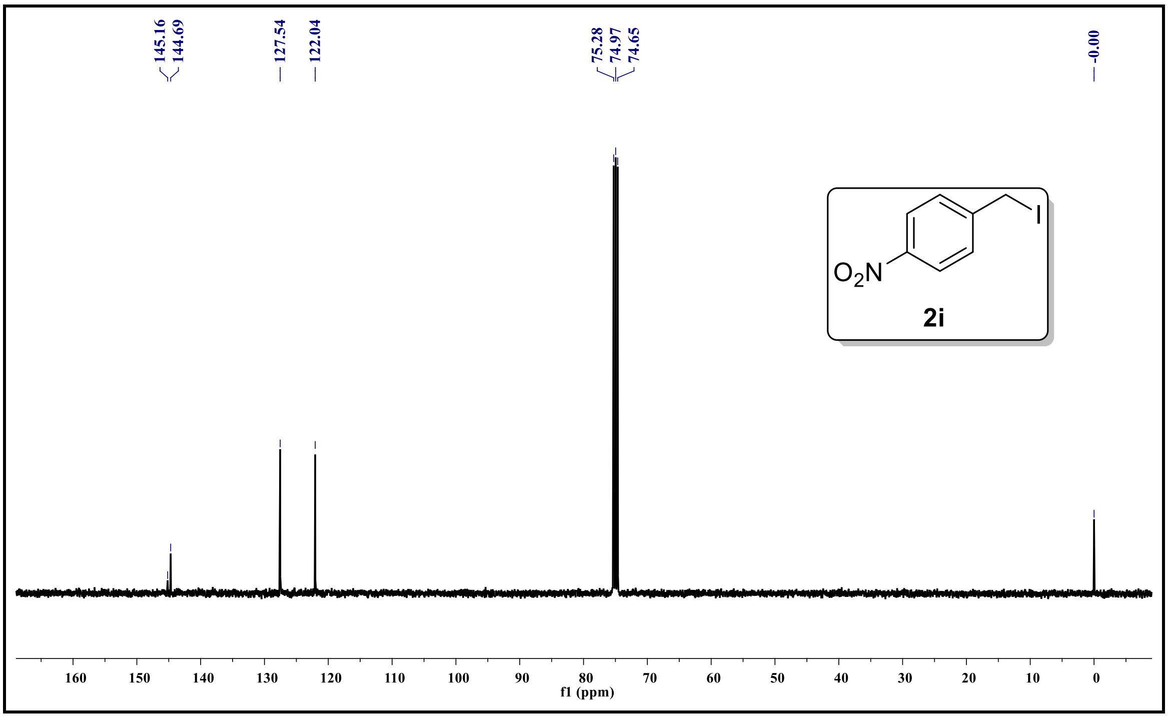
^{1}H NMR spectrum of compound **2f**



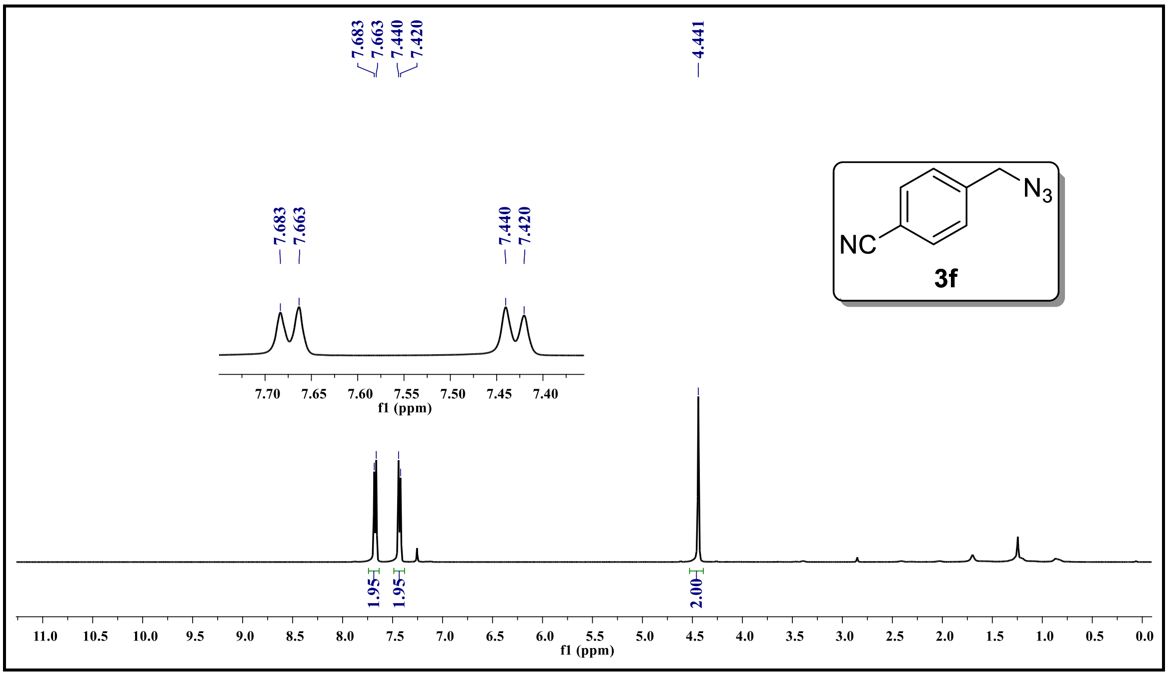
^{13}C NMR spectrum of compound **2f**



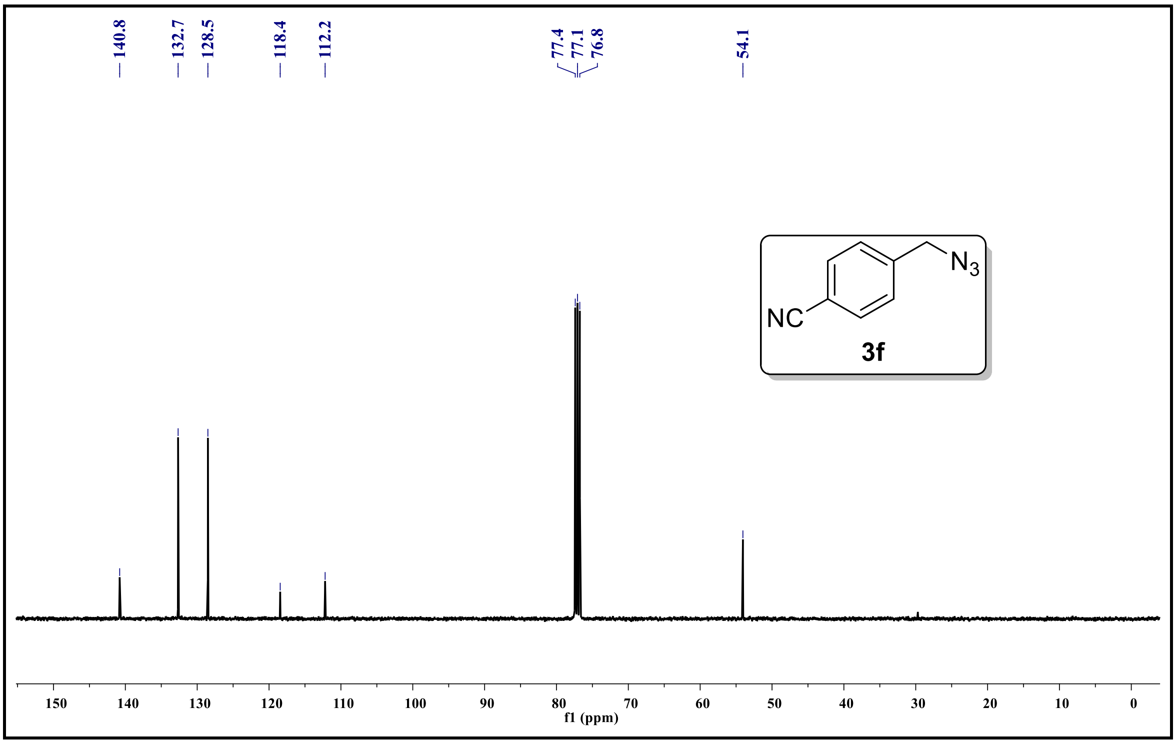
^{1}H NMR spectrum of compound **2i**



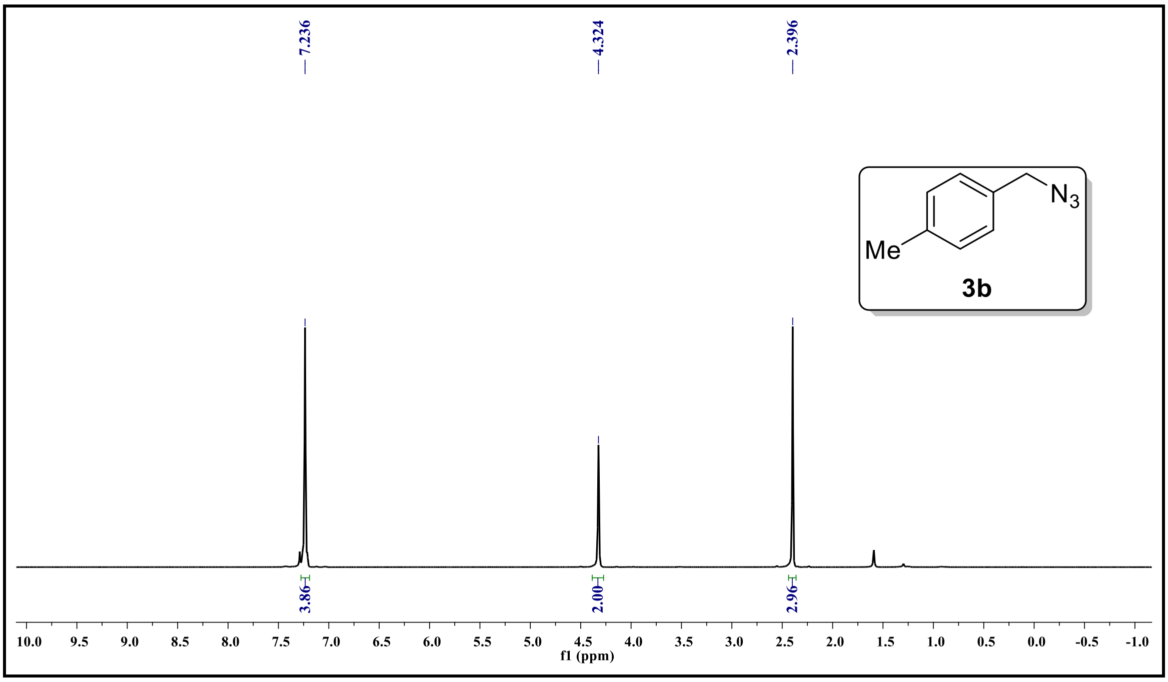
^{13}C NMR spectrum of compound **2i**



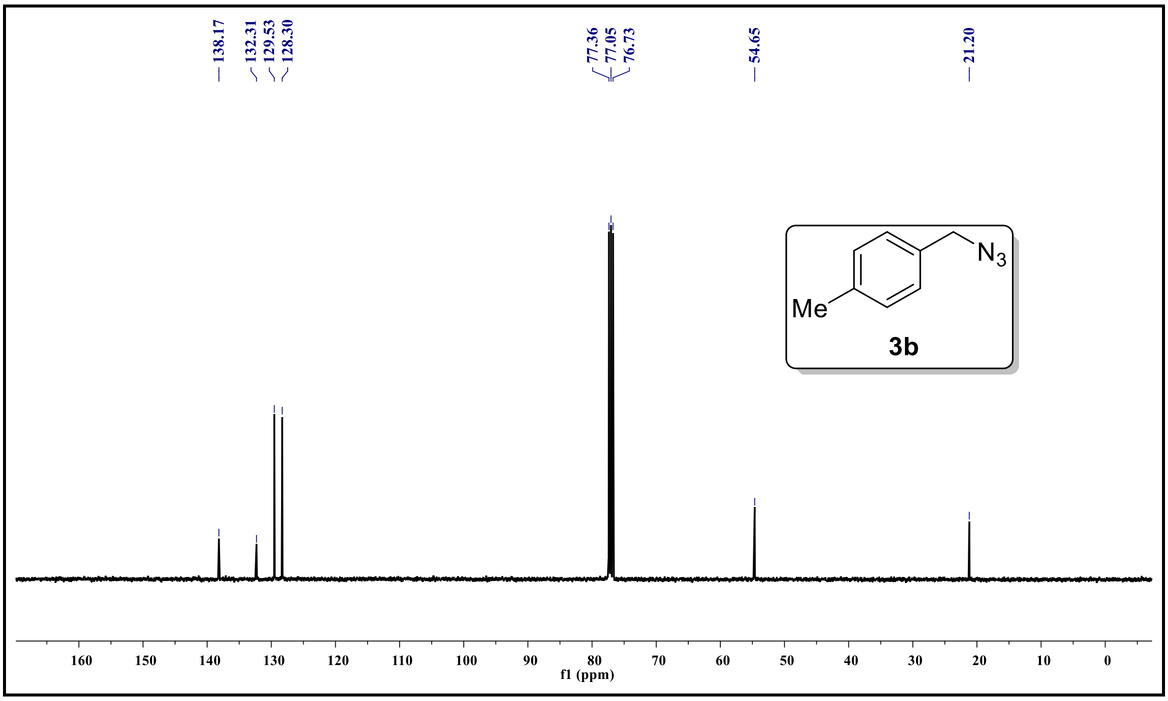
^{1}H NMR spectrum of compound **3f**



^{13}C NMR spectrum of compound **3f**



^{1}H NMR spectrum of compound **3b**



^{13}C NMR spectrum of compound **3b**

SUMMARY

New Methodologies for C−C and C−X (N, O & I) Bond Formation by Copper Nanoparticles and Trichloroacetonitrile

CHAPTER I

Introduction

The literature survey, objectives and prerequisites of the present study are presented in this chapter. Apart from this, a brief introduction to the synthesis of copper nanoparticles (CuNPs) by rongalite and other phytochemicals and their synthetic applications in various fields is discussed.[1-2] Trichloroacetonitrile with the chemical formula of CCl_3CN has been employed in versatile organic reactions, *viz.* the Overman rearrangement, preparation of benzylating or *t*-butylating agents, and glycosylation reactions.[3] Taking advantage of the strong electron-withdrawing character of the cyano group, trichloroacetonitrile serves as an alternative to carbon tetrachloride (CCl_4) in substitution reactions with triphenylphosphine.[4]

Moreover, the cyano group is able to delocalize a carbon radical at the α-position, which lowers the energy of activation to enhance the rate of the overall reaction.[5] Thus, it is expected that trichloroacetonitrile would react with the alcohols in presence of base to produce trichloroacetamidates which intern serve as an intermediate to give the desired products. The reactivity of trichloroacetamidates and its application will be discussed in this chapter.

The structures of the synthesized compounds were characterized by FTIR, NMR and Mass spectral methods. All these compounds described in the thesis were synthesized using conventional methods.

CHAPTER-II

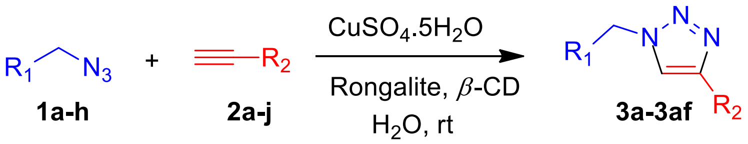
Part A

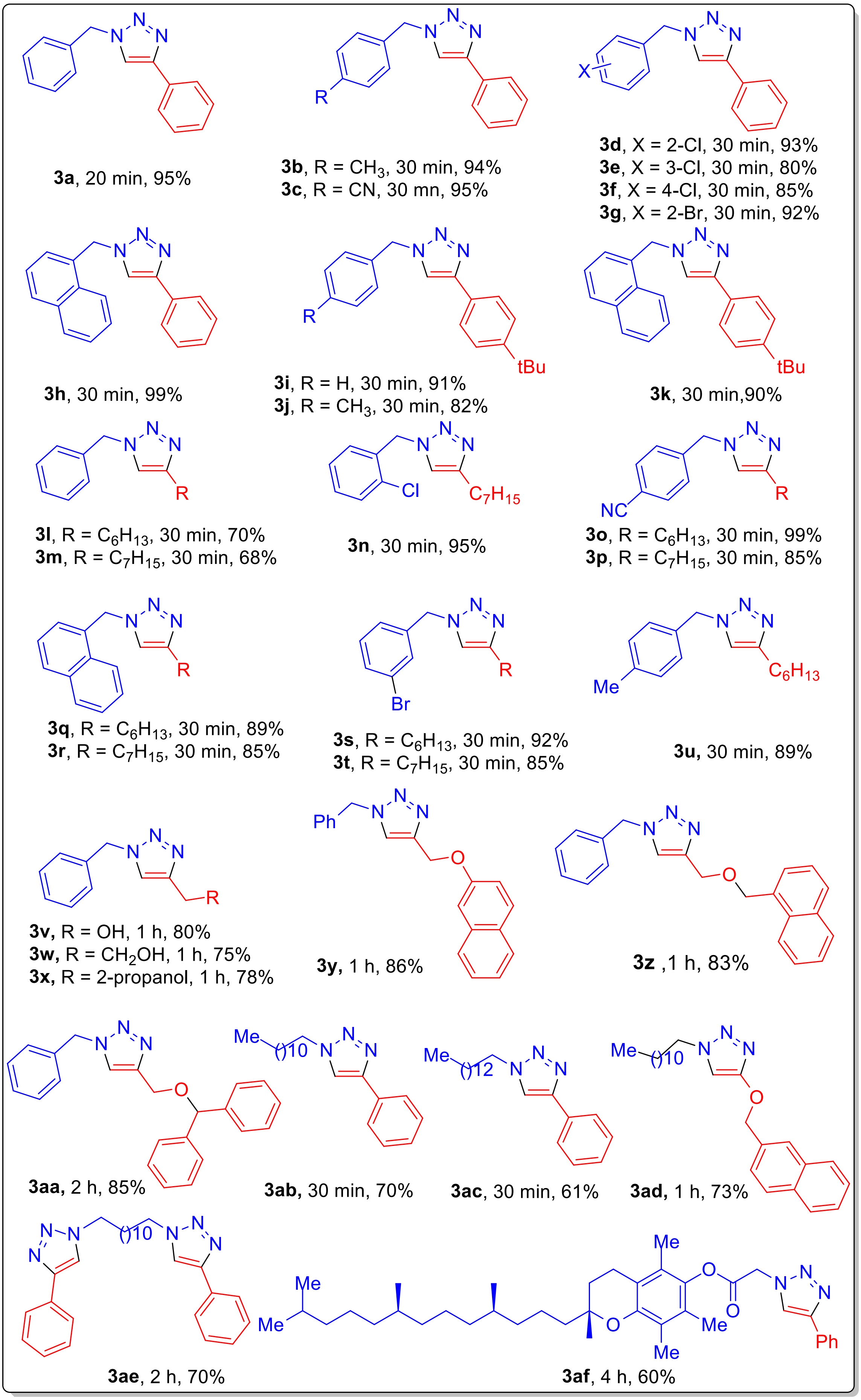
In Situ Generation of Copper Nanoparticles by Rongalite and Their Use as Catalyst for Click Chemistry in Water

The development of new catalytic methods toward the synthesis of chemical products forms a key to achieve chemical sustainability. To this end, metallic nanoparticles emerged as an alternative catalysts in the organic synthesis due to their high reactivity, high surface area, sustainability, easy recovery of the catalyst. There is a mounting evidence knowing increased interest to synthesize copper CuNPs in the field of synthetic chemistry and material chemistry due to their low cost compared to other metallic nanomaterials such as palladium, gold and silver. The main difficulty lies in their preparation and preservation as they are oxidized immediately when exposed to air and requires inert atmosphere and capping agents.[6-7] To avoid the use of toxic reducing agents, capping agents and special reaction setup is used to prepare CuNPs, we have developed green method which involve *in situ* generation of CuNPs by rongalite. This makes the process economical, nontoxic and environment friendly.

Recently, CuNPs catalyzed click chemistry has increased exponentially since the discovery of copper metal (stoichiometric ratio of turnings or powder) which can be a source of the catalytic species and this to ensure the green chemistry principles of reusability, efficiency and operational simplicity compared to their traditional methods. Triazole heterocyclic compounds have been paid special attention due to their potential applications as medicinal agents, agrochemicals, man-made materials, artificial acceptors, supramolecular ligands, biomimetic catalysts and so on. Considering their importance, herewith we have synthesized CuNPs *in situ* using rongalite as reducing agent at room temperature and used for click reaction in water.[8]

The optimized reaction conditions are as follows, in an oven dried round bottom flask, azide **1a-h** & **4a-f** (1.0 mmol) and alkyne **2a-j** (1.1 mmol) were added to a mixture of copper(II)sulfate pentahydrate (0.1 mmol), rongalite (0.5 mmol), and β-cyclodextrin (0.02 mmol) in H_2O (1.0 mL). The mixture was allowed to stir at room temperature to produce the desire products **3a-af** and **5a-5k** (Scheme 2A.1 and Scheme 2A.2).





3a, 20 min, 95%

3b, R = CH_3, 30 min, 94%
3c, R = CN, 30 mn, 95%

3d, X = 2-Cl, 30 min, 93%
3e, X = 3-Cl, 30 min, 80%
3f, X = 4-Cl, 30 min, 85%
3g, X = 2-Br, 30 min, 92%

3h, 30 min, 99%

3i, R = H, 30 min, 91%
3j, R = CH_3, 30 min, 82%

3k, 30 min,90%

3l, R = C_6H_{13}, 30 min, 70%
3m, R = C_7H_{15}, 30 min, 68%

3n, 30 min, 95%

3o, R = C_6H_{13}, 30 min, 99%
3p, R = C_7H_{15}, 30 min, 85%

3q, R = C_6H_{13}, 30 min, 89%
3r, R = C_7H_{15}, 30 min, 85%

3s, R = C_6H_{13}, 30 min, 92%
3t, R = C_7H_{15}, 30 min, 85%

3u, 30 min, 89%

3v, R = OH, 1 h, 80%
3w, R = CH_2OH, 1 h, 75%
3x, R = 2-propanol, 1 h, 78%

3y, 1 h, 86%

3z ,1 h, 83%

3aa, 2 h, 85%

3ab, 30 min, 70%

3ac, 30 min, 61%

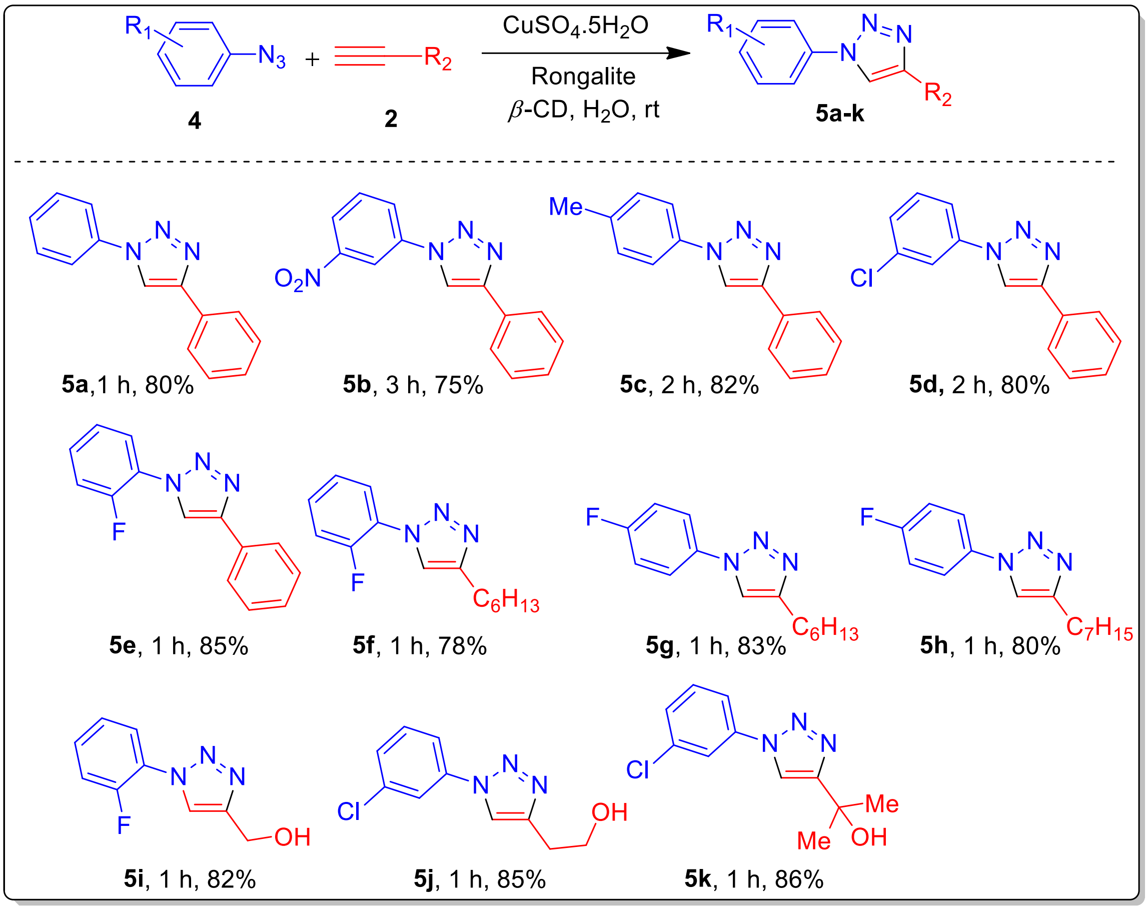
3ad, 1 h, 73%

3ae, 2 h, 70%

3af, 4 h, 60%

Scheme 2A.1. Click reaction of benzyl azides with various alkynes using *β*-Cyclodextrin (*β*-CD) and rongalite in water.

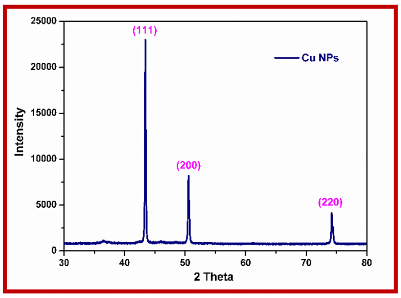
Similar procedure was applied for the synthesis of triazoles from aryl azides (scheme 2A.2).

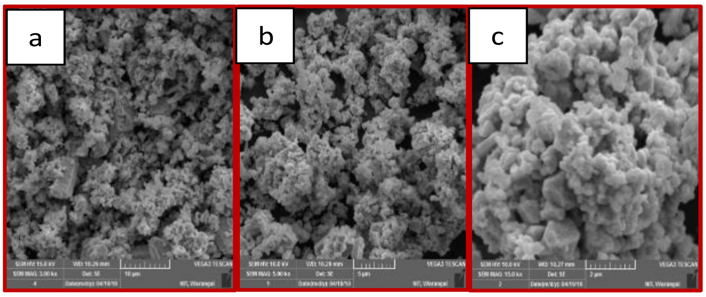


Scheme 2A.2. Click reaction of aryl azides with various alkynes using *β*-Cyclodextrin (*β*-CD) and rongalite in water.

We found in the literature that rongalite is capable of converting copper(II) chloride into nanoparticles such as Cu and Cu_2O at higher temperature (70-100 ^oC). These findings arose our interest to analyze the composition of copper complex to know the type of copper species present and responsible for click reaction. Further, we investigated the reaction mechanism of Click reaction catalyzed by Cu NPs. For this, Cu NPs were prepared and analyzed using Powder XRD and SEM.

Figure 1. XRD pattern and SEM images (in different magnifications a) 10 µm, b) 5 µm, c) 2 µm) of CuNPs synthesized in presence of *β*-cyclodextrin.





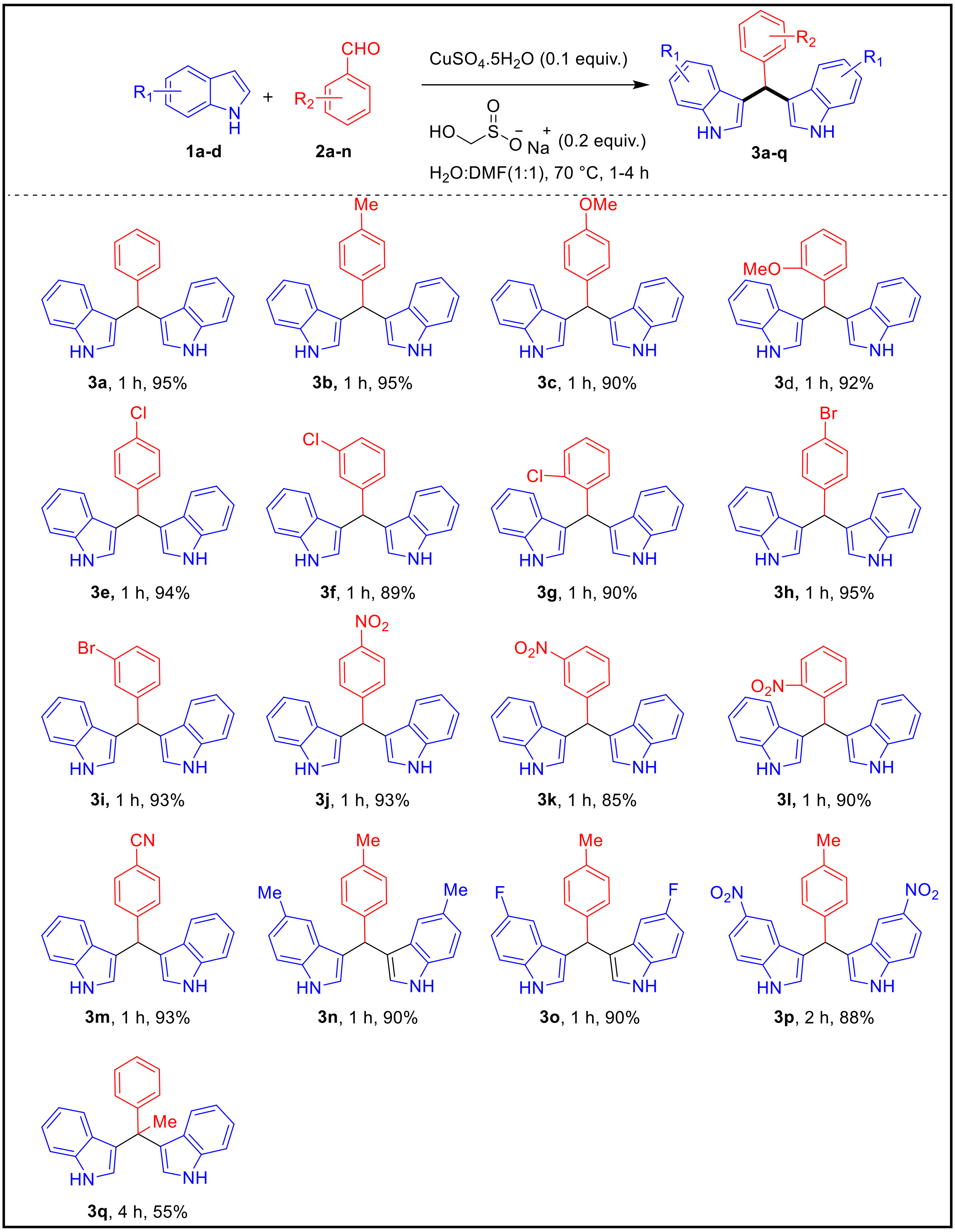
The PXRD patterns is indexed the presence of face centered cubic (f.c.c.) Cu (JCPDS, card no. 04-0836). The peaks at 43.36°, 50.48°, 74.35° belong to (111), (200), (220) planes of Cu nanoparticles. The average crystallite size was determined by using Scherrer's equation. The calculated average crystallite size of CuNPs is about to be 39 nm. SEM was carried out to know the morphological characteristics of formed Cu nanoparticles (Fig. 1). Image of Fig. 1 (**a, b, c**) is the group of SEM images which clearly shows the formation of 'Cu' nanoparticles with irregular shape and the formed nanoparticles are agglomerated.

CHAPTER II

Part B

Facile Synthesis of 3,3'-Bis(indolyl)methanes using *in situ* Generated Copper Nanoparticles by Rongalite

Bis(indolyl)methanes (BIMs) containing compounds possess wide variety of biological activities and therapeutic value *viz.* antibacterial, antifungal, cytotoxic, anti-inflammatory among others.[9] In addition, bis(indolyl)methane promote estrogen metabolism in both men and women and is expected to prevent from breast cancer. The synthetic bis(indolyl)methanes have been used not only as therapeutic agents but also as functional organic materials in the field of dyes and sensors.[10] Therefore, there is a great deal of interest in the synthesis of this class of compounds. These class of compounds are traditionally synthesized by the condensation of indoles with wide variety of aldehydes in the presence of both Lewis and Bronsted acid catalysts via electrophilic substitution. A plethora of homogeneous catalysis using Lewis acid catalysts have been reported for mediating this synthesis.[11] Even though processes involving homogeneous catalysis favours high product yield and efficiency, they have their limitations in the form of residual catalyst in the final products and catalyst recovery. This makes extension of these methods economically and environmentally unwarranted. In this regard, use of supported catalysts provides an alternative avenue through the benefits such as easy separation, recyclability and nontoxic nature.[12]



Scheme 2B.1. Synthesis of Bis(indolyl) methanes using *in situ* generated Cu nanoparticles.

In our continuous efforts towards development of efficient catalysis using copper nanoparticles, we have developed a new method for *in situ* preparation of CuNPs for BIMs synthesis (Scheme 2B.1).

The optimized reaction conditions are as follows, indole **1a-d** (2 mmol) and benzaldehyde **2a-n** (1 mmol) were added to the mixture of rongalite (0.2 equiv.), copper(II) sulfate (0.1 equiv.) in water. This reaction mixture was allowed to heat at 70 °C for 1-4 hours to get desired product **3a-q** (Scheme 2B.1).

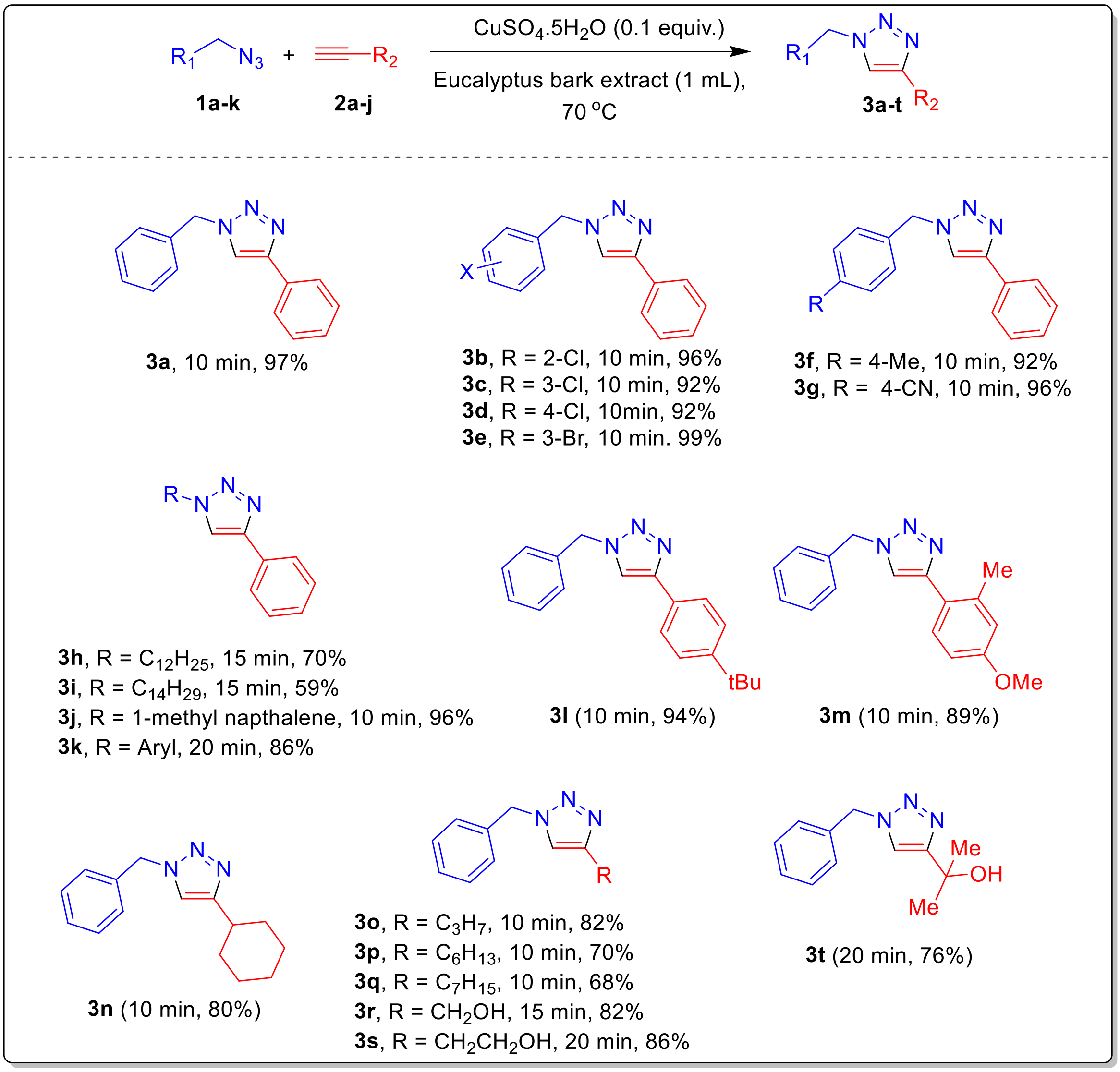
CHAPTER III

Phytochemicals Promoted Copper Catalyzed Azide Alkyne Cycloaddition Reactions in Water

Phytochemicals are ubiquitous in the plant-based diet available to humans.[13] Most of the plant extracts exhibit anticancer, antioxidant, antimicrobial, analgesic, and wound healing properties. Literature reports reveal that phytochemicals are safer and are largely more effective alternatives with less adverse effects. Apart from their biological activity, phytochemicals are also used as reducing agents to convert metal salts to the corresponding metal nanoparticles under environmentally benign conditions. Particularly, eucalyptus globulus plant extracts gained attention all over the world as it contains around 29 polyphenolic compounds which act as therapeutic agents, flavoured foods, perfumes, beverages. These polyphenolic compounds are also useful to prepare metal nanoparticles and reduction of graphene oxide to graphene.[14]

Considering the importance of eucalyptus bark extract, herewith we have developed a green protocol for the copper catalyzed azide alkyne cycloaddition (CuAAC) reactions in water using *in situ* generated copper nanoparticles by aqueous polyphenol extracts of eucalyptus bark and other phytochemical extracts.

The optimized reaction conditions are as follows, in an oven dried round bottom flask, azide **1a-k** (1.0 mmol) and alkyne **2a-j** (1.1 mmol) were added to the a mixture of copper(II)sulfate pentahydrate (0.1 equiv.), aqueous extracts of eucalyptus bark (1.0 mL). The mixture was allowed to stir at 70 °C to produce the desired products **3a-t** (Scheme 3.1).



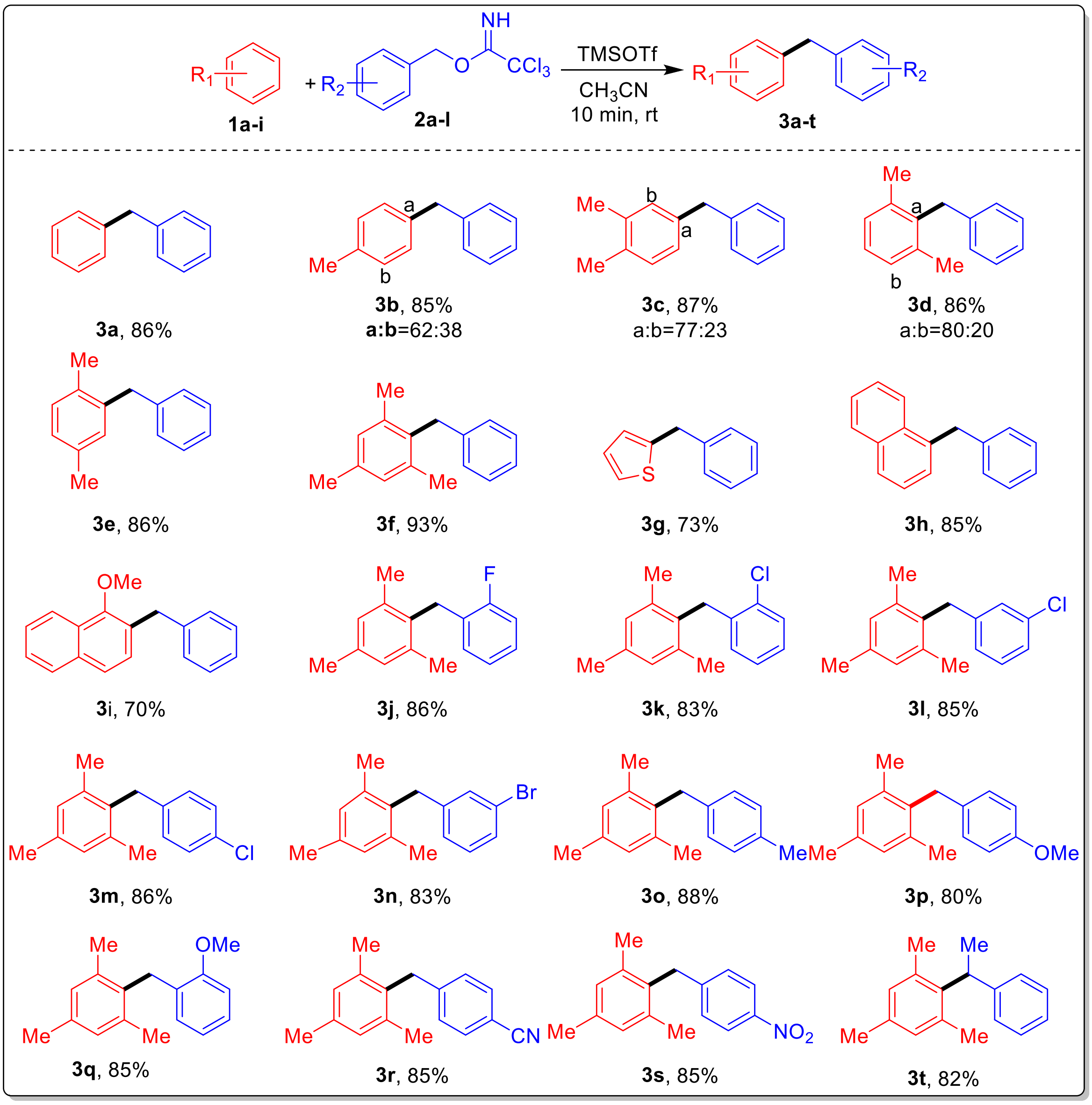
Scheme 3.1. Synthesis of triazoles using aqueous extracts of eucalyptus bark.

CHAPTER IV

Part A

Acid-Catalyzed Benzylation of Arenes with *O*-Benzyl Trichloroacetamidates: Synthesis of Diarylmethanes

Diarylmethane derivatives are fundamental building blocks in organic synthesis and their preparation is an important industrial goal. They are important precursors for preparing dyes and medicines, and they are also frequently used as subunits in supramolecular structures such as macrocycles, catenanes, and rotaxanes.[15] Traditionally, the diarylmethanes are synthesised from benzyl halides, benzyl alcohols and benzyl hydroxamates by Friedal-Craft reaction. Richard R. Schmidt *et al.* used *O*-Benzyl trichloroacetamidates having electron-withdrawing substituents as benzylating agent for arenes[16] and produced diarylmethanes at room temperature. Although, this reported method gave products in good yields but suffers from the longer reaction time and mandate electron withdrawing group on the benzylating agent. To overcome these problems, by changing solvent we are able to convert both electron donating and electron withdrawing groups substituted *O*-benzyl trichloroacetamidates into diarylmethanes at room temperature in very less time.



Scheme 4A.1. Synthesis of diarylmethanes using *O*-benzyl trichloroacetamidates.

The optimized reaction conditions are as follows, in an oven dried round bottom flask, arene **1a-i** (1.5 mmol) and benzyl trichloroacetamidate **2a-l** (1.0 mmol) were mixed in CH_3CN. To this mixture TMSOTf (0.1 equiv.) was added drop wise. Then the reaction mixture was allowed to stir at room temperature to produce the desired products **3a-t** (Scheme 4A.1).

CHAPTER IV

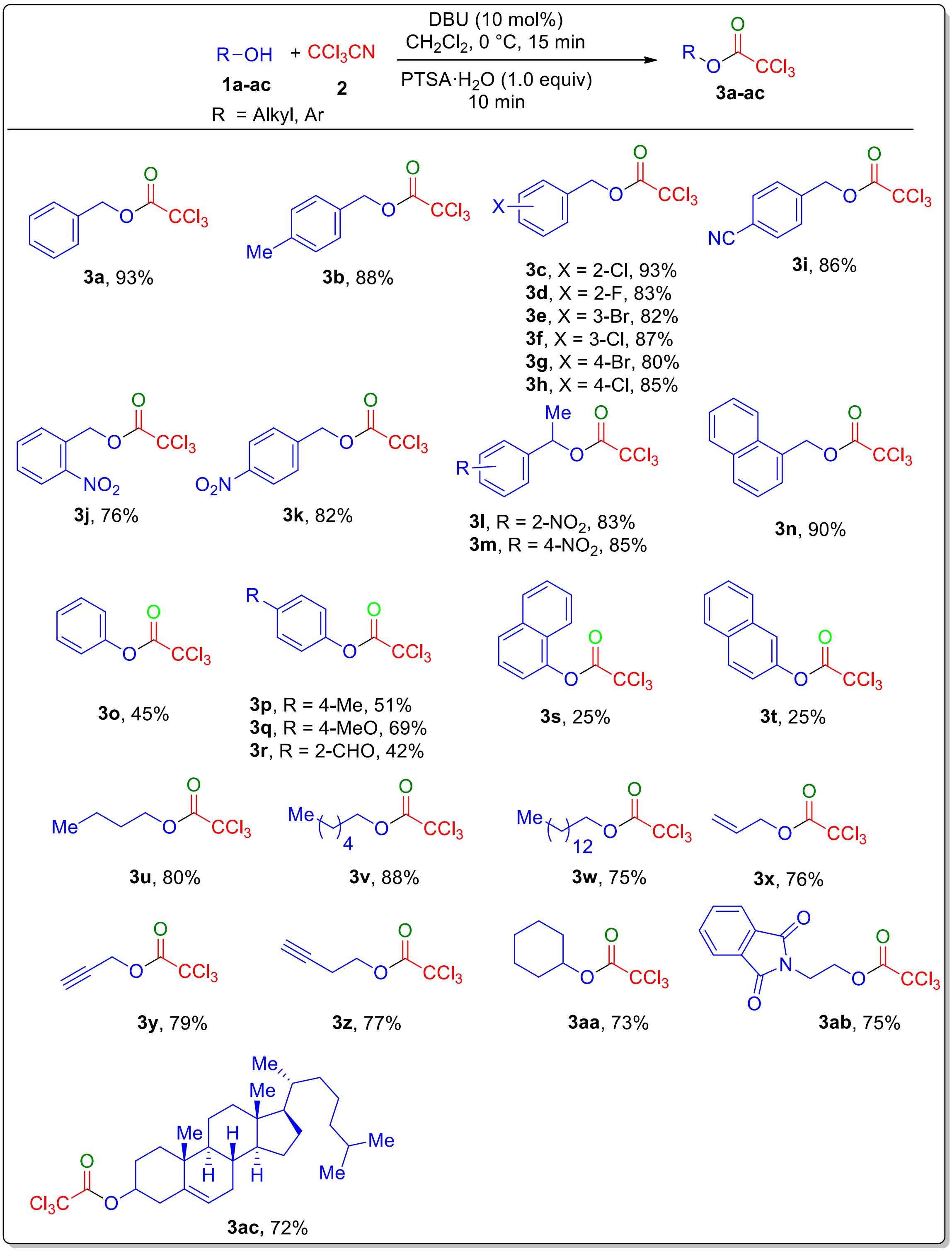
Part B

A Facile One-Pot Synthesis of 2,2,2-Trichloroacetates through Acid-Catalyzed Deimination

The halogens are ubiquitous and are found in many natural products and biologically active compounds as an integral part of them.[17] Among these halogenated compounds so formed, substitution with chlorine especially the one involving fully chlorinated trichloromethyl group (CCl_3) has piqued the interest of chemists world over due to its abundant presence in nature as well as it being in the repertoire of pharmaceuticals and agrochemicals.[18] Also, trichloromethyl group (CCl_3) plays a pivotal role in the biological activity of many molecules, such as larvicidal activity, to treat anxiety disorders and anti-Alzheimer's Salubrinal.[19-20]

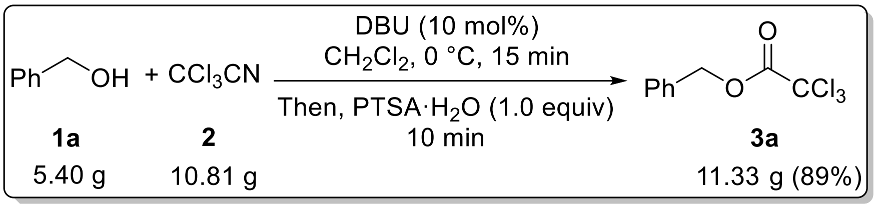
In order to simplify the synthesis, herein we report an efficient one-pot synthesis of trichloroacetates from trichloroacetonitrile with various alcohols under mild reaction conditions *via* trichloroacetamidate intermediate.

Optimized reaction conditions as are follows, alcohol **1a-ac** (1 mmol) and DBU (10 mol %) were stirred in dichloromethane for 5 minutes at 0 °C, then trichloroacetonitrile **2** (1.5 mmol) was added drop wise to the reaction mixture and allowed to stir until trichloroacetamidate was formed (monitored by TLC). Then, PTSA·H_2O (1.0 mmol) was added and allowed the reaction for appropriate reaction timings to produce the desired products **3a-ac** (Scheme 4B.1).



Scheme 4B.1. Synthesis of trichloroester derivatives.

Gram scale synthesis of trichloroesters:



This protocol is also applicable for gram scale synthesis of benzyl trichloroacetates from benzyl alcohols.

CHAPTER V

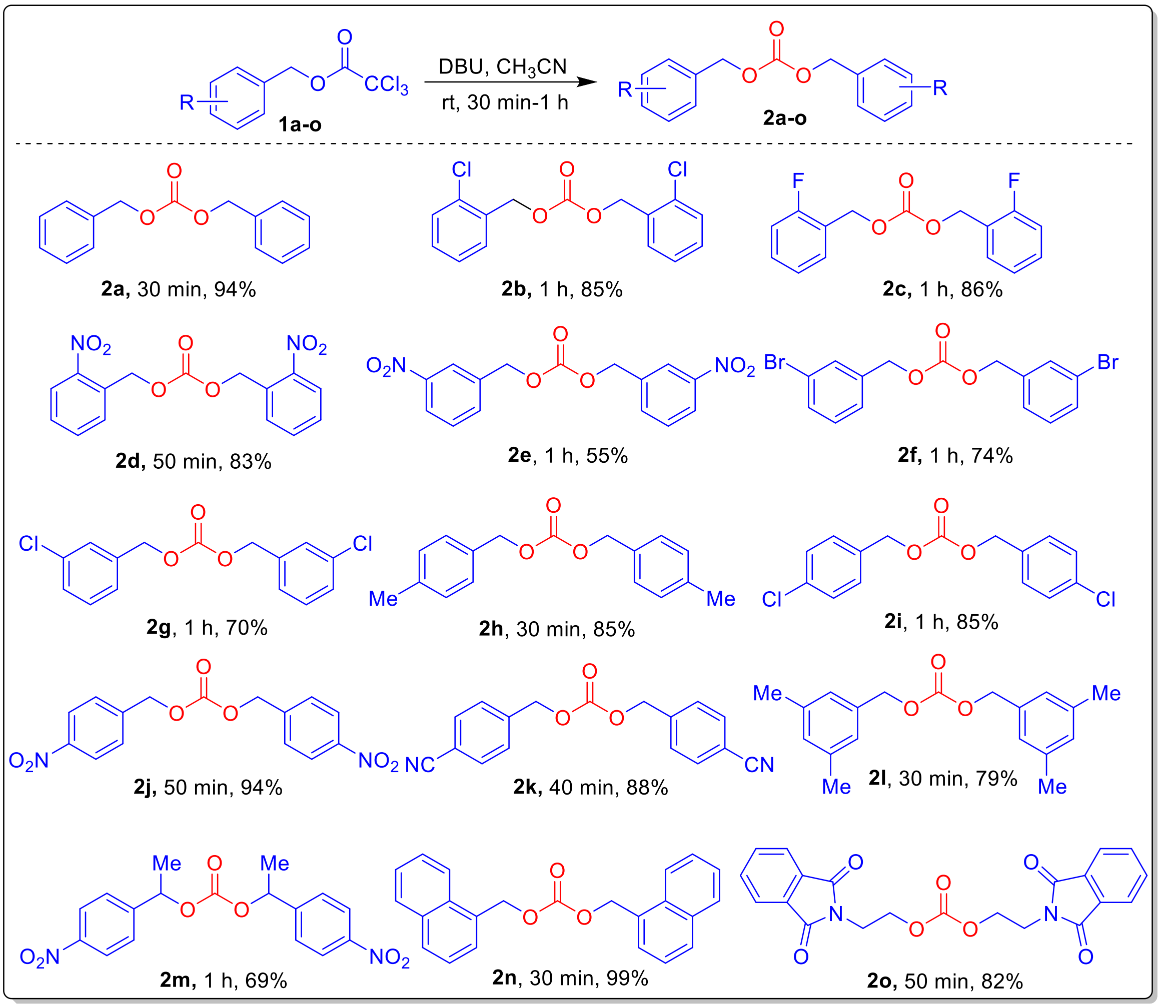
Part A

Base Promoted Synthesis of Dialkyl Carbonates From 2,2,2-Trichloroacetates

Dialkyl carbonates have been used for a variety of purposes, such as fuel additives, dyes, agrochemicals, and drugs for the treatment of lipidemia and depression. They can act as protecting groups of alcohols and phenols, [21] and are used as monomers for organic glasses and used as solvents in the manufacture of lithium batteries.[22] The toxic reagents,[23-24] such as phosgene, dimethyl sulphate, pyridine, carbon monoxide were used for the preparation of organic carbonates in conventional methods and are to be carried out at higher temperatures and pressures.

Thus, bearing in mind these drawbacks, it seems advisable to develop more convenient and environmentally benign catalytic systems for the synthesis of carbonated compounds.

Optimized reaction conditions as follows, benzyl trichloroester **1a-o** (1mmol), CS_2CO_3 (0.1 mmol) were added in DMF and allowed to stir at room temperature to produce desired dibenzyl carbonates **2a-o** (Scheme 5A.1).



Scheme 5A.1. Synthesis of symmetrical benzyl carbonates from trichloroesters.

CHAPTER V

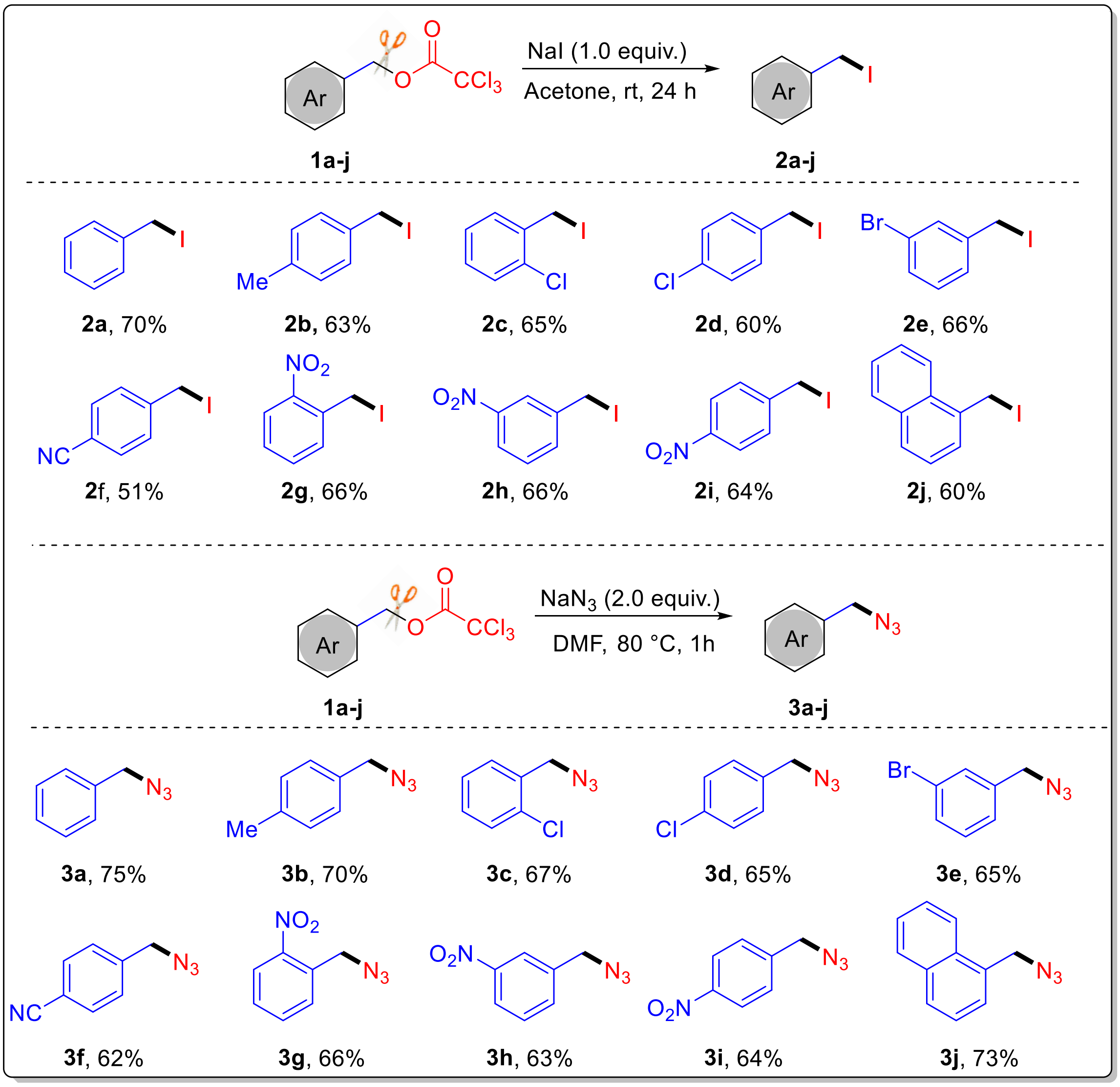
Part B

2,2,2-Trichloroacetates: Versatile Substrates for the Nucleophilic Substitution Reactions and Its Applications in Organic Synthesis

Alkyl iodides, are versatile building blocks in synthetic organic chemistry because of their outstanding reactivity in various reactions such as alkylation,[25] cross coupling,[26] reduction,[27] addition,[28] esterification,[29] and organometallic transformations.[30]

Similarly, Organic azides are useful intermediates for the synthesis of nitrogen-containing compounds. For example, organic azides are used as equivalents of primary amines and are employed in the Staudinger reaction. Photo induced nitrene formation of organic azides and 1,3-dipolar reaction of organic azides with terminal alkynes are widely used in the fields of biological and polymer chemistry.[31]

In conventional methods for the synthesis of both alkyl iodides and alkyl azides, they used alkyl chloride or alkyl bromides which are lachrymatory in nature as precursors. Herewith we used trichloroesters in place of alkyl halides to produce benzyl iodides and benzyl azides.



Scheme 5B.1. Synthesis benzyl iodides and benzyl azides from trichloroesters.

Optimized reaction conditions for the synthesis of benzyl iodides are as follows, benzyl trichloroester **1a-j** (1 mmol), NaI (1 mmol) were added in acetone and allowed to stir at room temperature to produce desired benzyl iodides **2a-j** (Scheme 5B.1).

Similarly, optimized reaction conditions for the synthesis of benzyl azides are as follows, benzyl trichloroester **1a-j** (1 mmol), NaN_3 (2 mmol) were added in DMF and allowed to stir at 80 °C to produce desired benzyl iodides **3a-j** (Scheme 5B.2).

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APPENDICES

List of Publications

Published

1. **Soumya Poshala**, Sanjeeva Thunga, Saikumar Manchala, and Hari Prasad Kokatla*. In Situ Generation of Copper Nanoparticles by Rongalite and Their Use as Catalyst for Click Chemistry in Water. *ChemistrySelect* 2018, *3*, 13759–13764.

2. **Soumya Poshala**, Sanjeeva Thunga, Sivaparwathi Golla, Vanaparthi Satheesh, Hari Prasad Kokatla*. A Facile One-Pot Synthesis of 2,2,2-Trichloroacetates Through Acid-Catalyzed Deimination and Its Applications. *ChemistrySelect* **2019**, *4*, 10466–10470.

3. Sanjeeva Thunga, **Soumya Poshala**, and Hari Prasad Kokatla*. Methyl 2-Nitrosobenzoate: A Simple Dehydrating Agent for the Synthesis of Nitriles from Aldoximes. *ChemistrySelect* **2018**, *3*, 4425–4429.

4. Sanjeeva Thunga, **Soumya Poshala**, Naveen Kumar Anugu, Ramaiah Konakanchi, Satheesh Vanaparthi and Hari Prasad Kokatla*. An efficient Pd(II)-(2-aminonicotinaldehyde) complex as complementary catalyst for the Suzuki-Miyaura coupling in water. *Tetrahedron Lett*. **2019**, *60*, 2046–2048.

5. Sivaparwathi Golla, **Soumya Poshala**, Ravinder Pawar, Hari Prasad Kokatla*. Rongalite-Promoted Metal-Free Aerobic ipso-Hydroxylation of Arylboronic Acids Under Sunlight: DFT Mechanistic Studies. *Tetrahedron Lett*. **2020**, *61*, 151539.

6. Sivaparwathi Golla, Swathi Jalagam, **Soumya Poshala**, Hari Prasad Kokatla*. Transition Metal-Free Functionalization of 2-Oxindoles *via* Sequential Aldol and Reductive Aldol Reactions Using Rongalite as C1 Reagent. *Org. Biomol. Chem*. **2022**, *20*, 4926–4932.

7. Naveen Kumar Anugu, Sanjeeva Thunga, **Soumya Poshala**, Hari Prasad Kokatla*. N-Oxide-Induced Ugi Reaction: A Rapid Access to Quinoline-C2-amino Amides via Deoxygenative C(sp2)-H Functionalization. *J. Org. Chem*. **2022**, *87*, 15, 10435–10440.

Manuscripts under preparation

1. Facile Synthesis of 3,3’-Bis(indolyl)methanes using in situ Generated Copper Nanoparticles by Rongalite.
   Soumya Poshala and Hari Prasad Kokatla.

2. Phytochemicals Promoted Copper Catalyzed Azide Alkyne Cycloaddition Reactions in Water.
   Soumya Poshala and Hari Prasad Kokatla.

3. Acid-Catalyzed Benzylation of Arenes with O-Benzyl Trichloroacetamidates: Synthesis of Diarylmethanes.
   Soumya Poshala and Hari Prasad Kokatla.

4. Base Promoted Synthesis of Dialkyl Carbonates From 2,2,2-Trichloroacetates.
   Soumya Poshala and Hari Prasad Kokatla.

5. 2,2,2-Trichloroacetates: Versatile Substrates for the Nucleophilic Substitution Reactions and Its Applications in Organic Synthesis.
   Soumya Poshala and Hari Prasad Kokatla.

Papers Presented In International And National Conferences

International

1. **International conference on "Advances in Chemical Sciences and Technologies-2019 (ACST-2019)"**organized by Department of chemistry, National Institute of Technology, Warangal during 23th-25th September 2019.

2. **International conference on "Advanced Functional Materials (ICFAM-2017)**" organized by department of chemistry, RGUKT, Basar during 18th-20th December 2017.

National

1. **TEQIP-III sponsored National conference on "Emerging Trends in Instrumental Methods of chemical Analysis (ETIMCA-2019)**" organized by Department of Chemistry, National Institute of Technology, Warangal during 30th-31st January 2019.
2. **National Symposium on "Materials in Healthcare (MIH-2018)**" organized by GITAM University, Hyderabad during 6th-8th September 2018.
3. **"National XIV J-NOST (J- National Organic Symposium Trust)"conference for research scholars** organized by CSIR-Indian Institute of Chemical Technology, Hyderabad during 28th November-1st December 2018.
4. **National Conference on "Recent Development in Chemical Sciences and Allied Technologies (RDCST-2017)**" organized by Department of chemistry, National Institute of Technology, Warangal during 29th-30th June 2017.
5. **National Conference on ''Frontiers in chemical sciences and technologies'' (FCST-2016)** during 28th-29th January 2016, organized by the Department of Chemistry, NIT Warangal. Telangana.
6. **UGC Sponsored National Seminar on "Recent Advances in Chemistry (RAC-2015)"** organized by Department of Chemistry, Kakatiya University, Warangal during 30th-31st March 2015.

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Mrs. Poshala Soumya was born in Gavicherla, Warangal Rural district of Telangana State, India. She has completed her secondary school education (Kakathiya High School) in Ramchandrapuram, Intermediate (Mahathi Junior College) in hanamkonda, and her B.Sc. from Aurora degree college affiliated to Kakathiya University in Hanamkonda. After completion of her M.Sc. (Organic Chemistry) from National Institute Technology Warangal, she has joined for the Ph.D., programme in July 2014 under the guidance of Dr. K. Hari Prasad (Associate Professor) Department of Chemistry, National Institute of Technology Warangal with the financial assistance from the NITW. She has published seven research articles in peer reviewed international journals and presented papers in four national/international conferences. Her research interest lies in the development of new methodologies for the synthesis of bio-active molecules by employing efficient and greener methodologies.