Copper Catalyzed Synthesis of Five and Six Membered Nitrogen Containing Heterocycles

A dissertation submitted in partial fulfillment for the degree of

Doctor of Philosophy

Submitted by

Anupal Gogoi

Roll No. 10612240

Department of Chemistry

Indian Institute of Technology Guwahati

January, 2016

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IN THE MEMORY OF MY FATHER

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Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the guidance of Professor Bhisma K. Patel.

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

January, 2016.
IIT Guwahati

Anupal Gogoi

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Department of Chemistry

CERTIFICATE

This is to certify that Anupal Gogoi has been working under my supervision since December, 2010 as a regular registered Ph. D. student. His thesis entitled **"Copper Catalyzed Synthesis of Five and Six Membered Nitrogen Containing Heterocycles"** is an authentic record of the results obtained from the research work done in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding his thesis to submit for the Ph. D. (Science) degree from this institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

January, 2016.

Prof. Bhisma K. Patel
(Thesis Supervisor)
Department of Chemistry
IIT Guwahati

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Still many names are missing whose contribution and help is worth mentioning.

Anupal Gogoi

SYNOPSIS

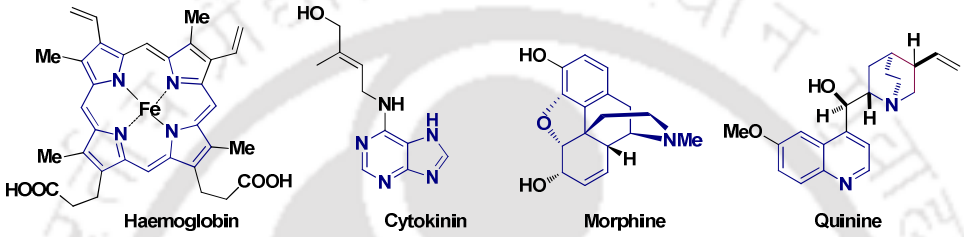
The contents of this thesis have been divided into five chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis describes the importance of various nitrogen heterocyclic scaffolds and different copper catalyzed strategies for their synthesis. All the other chapters deals with copper catalyzed C–C, C–N and C–O bond forming reactions leading to nitrogenous heterocycles. Chapter II A demonstrates a copper catalyzed method for the synthesis of 3-aroylindoles via sp^3 C–H bond functionalization of *o*-alknylated amine through C–C and C–O bond formation. Chapter II B describes a metal free cascade synthesis of 3-aroylindoles from *o*-alkynyl amine precursors via sp^3 C–H bond functionalization. Chapter III illustrates a Cu catalyzed route to indoloquinoxaline-6-ones starting from *o*-indolyl-*N*,*N*-dimethylarylamines through an intramolecular oxidative coupling pathway. Chapter IV portrays the synthesis of 3-methyleneisoindolin-1-ones from aryl alkynyl acids and 2-halobenzamides which proceeds via decarboxylative cross-coupling / *5-exo-dig* heteroannulation process. Chapter V describes a protocol for copper catalyzed syntheses of 4,5-disubstituted-1,2,4-triazole-3-thiones and 4,5-disubstituted-1,2,4-triazoles from *N*-arylidenearylthiosemicarbazides via an intramolecular C–N bond formation at the imine C–H bond followed by a desulfurization. Except chapter I, all other chapters comprise of seven subsections which include introduction, literature reports, present work, experimental section, references, spectral data and some selected spectra.

CHAPTER I. An Overview of Copper Catalyzed Synthesis of *N*-Hetrerocycles

This chapter provides a brief introduction of heterocyclic compounds, the importance nitrogen heterocycles and various copper catalyzed strategies adopted for the synthesis of nitrogen heterocycles.

Heterocycles constitute the largest classical division of organic compounds encompassing more than half of the known organic compounds. Among the various

heterocyclic moieties, nitrogen-containing heterocycles being the most significant heterocycles, occurs in many naturally occurring substances and pharmaceuticals and are essential for life. Nitrogen containing heterocycles also find applications in agrochemicals, dyestuffs, fluorescent sensors, brightening agents, information storage, analytical reagents, plastics, polymer industries and material sciences. They are also used as synthetic intermediates, protecting groups, chiral auxiliaries and metal ligands during various organic transformations.



Scheme I.1. *Examples of some biologically acitive N-heterocycles*

Copper salts have been extensively used in organic synthesis because of their low cost, less toxicity and excellent tolerance to different functional groups. A great number of Cu based C–C and C–X (X = N, O, S etc.) bond forming transformations have been developed over the past few decades. Consequently, numerous practical and efficient Cu-catalyzed protocols for the synthesis of *N*-heterocyclic scaffolds have also been emerged out. The Cu-catalyzed strategies can be classified mainly into four categories *viz.* (i) C–H bond functionalizations; (ii) *N*-arylation and *N*-vinylation reactions; (iii) tandem / domino reactions and (iv) cycloaddition reactions.

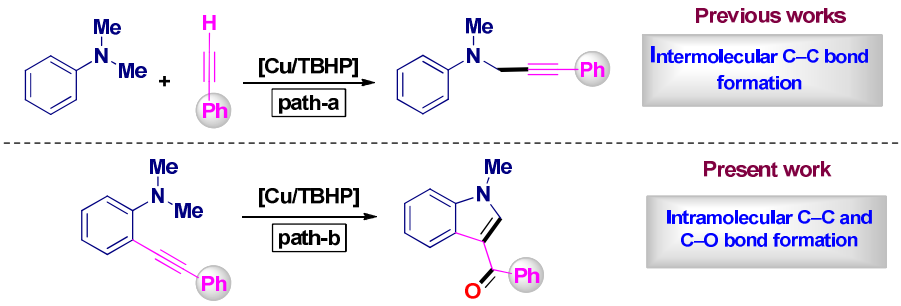
CHAPTER II A. A Copper Catalyzed Synthesis of 3-Aroylindoles via a sp^3 C–H Bond Activation Followed by C–C and C–O Bond Formation

This chapter demonstrates an efficient Cu(I) catalyzed protocol for the direct synthesis of 3-aroylindoles that proceeds via the sp^3 C–H bond functionalization α to the nitrogen atom of an *o*-alknylated amine with concomitant formation of C–C and C–O bonds.

Tertiary amines possessing alkyl groups are useful precursors for the sp^3 C–H bond functionalizations α to the nitrogen atom. These functionalizations in most cases have been stimulated by various transition metal salts in combination with organic peroxides through a single electron transfer process. However a review of literature reveal that these functionalizations occurred via an intermolecular attack of various C, N or O nucleophiles at the iminium ion generated *in situ*. Following these reports, we reasoned that if the nucleophile attacks intra-molecularly, they could be useful towards the synthesis of nitrogeneous heterocycles.

Among various nitrogenous heterocyclic scaffolds, the indolyl moiety, particularly the 3-acylindole has immense importance because of its relevance in natural products and pharmaceutical entities. Apart from their bioactive nature they also serve as useful precursors to various other indole based compounds through easy functional group transformations of its carbonyl group.

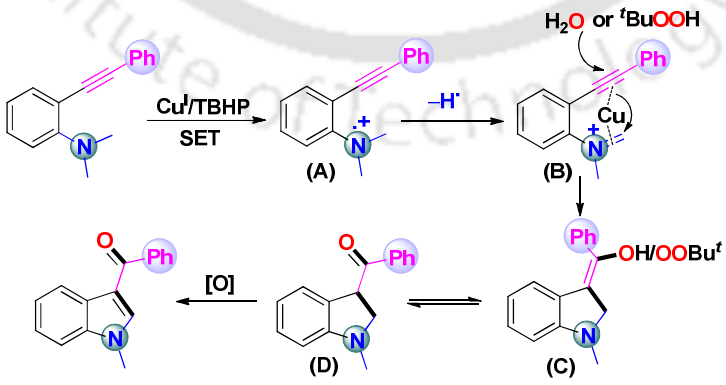
A myriad of applications of 3-aroylindoles led to the development of various synthetic protocols for their synthesis. Traditional routes to 3-acylindoles include Friedel–Crafts acylations, Vilsmeier–Haack acylations and the reactions of indole salts with acyl chlorides. Various limitations associated with these traditional methods led to the development various transition metal catalyzed approaches for their synthesis most of which based on C–H activation strategy. Transition metal catalyzed methodologies can be broadly categorized in two parts: (i) coupling of preformed indoles with different aroylating sources and (ii) synthesis from non-indole core starting materials. However, all the C–H functionalization routes reported so far for the synthesis of 3-aroylindoles involves sp^2 C–H bond functionalizations. Herein, we have developed a copper based sp^3 C–H bond functionalization strategy to construct 3-aroylindoles using *o*-alknylated-*N*,*N*–dimethyl amines as the precursor, where the alkynyl group is expected to function as the internal nucleophile towards an intramolecular attack onto the iminium carbon (path-b, Scheme II.A.1).



Scheme II.A.1. *Copper catalyzed oxidative Mannich reaction of tertiary amines with alkynes*

Various reaction parameters such as catalysts, oxidants, solvents and temperature were screened to achieve the most suitable conditions for this transformation. After a series of experimentation the optimized reaction conditions arrived was CuBr (10 mol%), aq TBHP (70 %) (3 equiv) at 80 ^{o}C in DMSO solvent and all other reactions were carried out adopting this condition. This methodology was found to be compatible to a variety of 2-alkynyl-*N*,*N*-dimethyl aniline derivatives providing their corresponding 3-aroylindoles in good yields. Irrespective of the nature of the substituents on the aryl ring of the alkynyl part, their corresponding 3-aroylindoles could be obtained in good yields. However, significant drops in the yields were observed for substrates possessing a moderately electron-withdrawing group on the aryl ring derived from the aniline part.

Based on literature reports, observations of the control reactions and yield of the products obtained from substituted substrates, a mechanism has been proposed for this transformation.



Scheme II.A.2. *Plausible mechanism for Cu(I) catalyzed formation of 3-aroylindoles*

In conclusion, we have developed an elegant method for the synthesis of 3-aroylindoles through a copper catalyzed oxidative process involving *o*-alkynylated *N*,*N*-dimethylamines in the presence of aqueous TBHP as the oxidant. This protocol simultaneously installs C–C and C–O bonds through an intramolecular oxidative path in the construction of 3-aroylindoles. Besides being a one pot and atom economical, judging the practical utility makes the present method the best alternative synthesis for 3-aroylindoles.

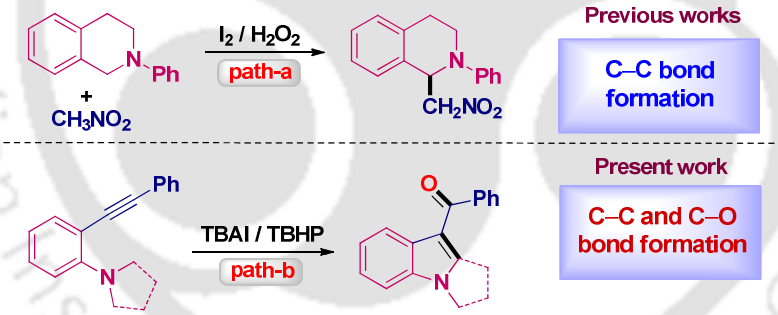
CHAPTER II B. A Metal Free Domino Synthesis of 3-Aroylindoles via Two sp^3 C-H Activation

This chapter illustrates a metal free protocol for the synthesis of 3-aroylindoles involving sp^3 C–H bond functionalization of *o*-alkynyl-*N,N*-dialkylamines with simultaneous C–C and C–O bond formation.

In modern organic synthesis, C–H functionalization strategies have brought about atom and step-economy by streamlining various arduous synthetic processes. However, in this forum, much of the attention has been focused on functionalizations of sp and sp^2 C–H bonds. In contrast high pK_a's (>30–35) as well as large bond dissociation energies (>104 kcal/mole) of various sp^3 C–H bonds make their selective activation a formidable challenge. The solutions to these challenges, led to the evolution of various sp^3 C–H activation strategies, one of them being the cross dehydrogenative coupling (CDC). In most cases, functionalizations of sp^3 C–H bonds α to heteroatoms are attained by CDC strategy using transition metal catalysts. The heteroatoms present in precursors are invariably *N*- or *O*- that generate an iminium or an oxonium ion intermediate *in situ* which are amenable for the construction of C–C or C–heteroatom bonds by an inter- or an intramolecular nucleophilic attack. For precursors like tertiary amines, a variety of transition metal catalysts in combination with organic peroxides are conducive for the formation of reactive intermediates. Noteworthy, an intramolecular nucleophilic attack at these iminium ions can generate various nitrogen containing heterocycles.

Although transition metal catalyzed processes are advantageous but are invariably associated with high cost and difficulties in removal of residual metals from the final

product which limits their utility in pharmaceutical industries. To overcome these disadvantages associated with metal catalysts, recently, photo-catalysts and molecular iodine or iodide compounds in combination with external oxidant has been employed for the functionalizations of sp^3 C–H bonds of *N,N*-dialkylamines. However, the use of designer ligand or metal which is essential for photocalytic methods make them more expensive when applied to a large scale reaction. Thus, molecular iodine or iodide catalyzed strategies are more advantageous. A molecular iodine-catalyzed cross-dehydrogenative coupling (CDC) reaction between tetrahydroisoquinoline and a carbon nucleophile such as nitromethane using hydrogen peroxide as the terminal oxidant was reported by Itoh and co-workers (path-a, Scheme II.B.1). The same has been achieved with TBAI as the catalyst although the yield of the desired product was low. Following this, we envisaged that instead of using metal catalysts, the intramolecular domino transformation of 2-alkynyl-*N,N*-dialkylamines to 3-aroyl indoles could be realized under a metal free condition. A trial reaction performed with using TBAI as the catalyst in the presence of peroxide generates 3-aroylindoles confirming our assumption.

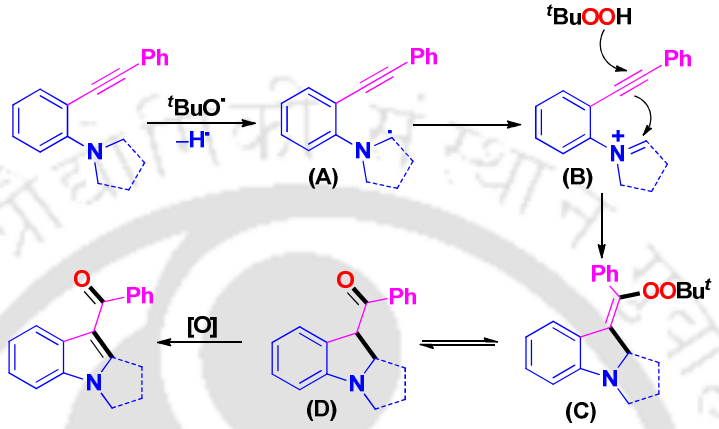


Scheme II.B.1. *Metal free sp^3 C–H bond functionalization of tertiary amines*

Reaction parameters such as catalysts, oxidants and solvents were varied to attain best possible yield of the desired product and the use of catalyst TBAI (20 mol%), aqueous TBHP (5 equiv) in DMSO at 80 ^oC were found to be the ideal conditions for this transformation. A series of 3-aroylindoles were synthesized in moderate to excellent yields from their aminoalkyne precursors adopting this condition. Excellent yields were obtained when both the rings contain electron-donating groups. However, the presence of a moderately electron-withdrawing group in the aryl ring bearing the tertiary amine group

resulted in comparatively lesser yields regardless of the nature of the substituents on the other ring.

Based on experimental findings of the labeling experiment and literature reports a mechanism has been proposed for this transformation (Scheme II.B.2).



Scheme II.B.2. *Proposed mechanism for TBAI catalyzed formation of 3-aroylindoles*

In conclusion, we have developed a metal free method for the synthesis of 3-aroylindoles from *o*-alkynyl-*N*,*N*-dialkylamine through a TBAI catalyzed intramolecular oxidative coupling pathway in presence of oxidant TBHP. The use of inexpensive and environmentally benign catalytic system and relatively lower reaction time and temperature make the present protocol practically more applicable.

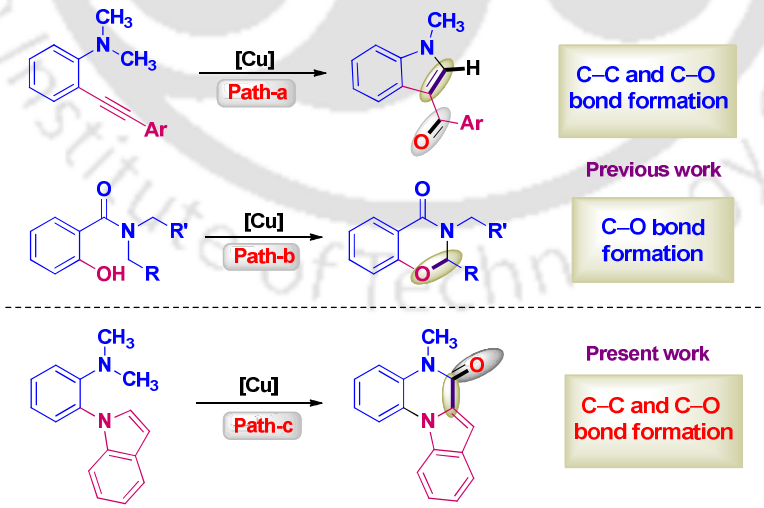
CHAPTER III. Copper (II) Catalyzed Synthesis of Indoloquinoxalin-6-ones via Oxidative Mannich Reaction

This chapter describes a unique copper catalyzed sp^3 C–H bond functionalization protocol for the synthesis of indoloquinoxalin-6-ones staring from 2-indolyl-*N*,*N*-dimethylamines.

The classical Mannich reaction leading to the synthesis of substituted β-amino carbonyl compounds comprised of two steps: *viz.* formation of an imine or an iminium ion obtained by the condensation of an amine with formaldehyde followed by the nucleophilic attack of an enolizable aldehyde or a ketone at the reactive carbon end of the imine or iminium ion. Appropriate redox active transition metal in conjunction with a suitable

oxidant can oxidize *N*,*N*-dialkylanilines to its corresponding iminium ion, which on trapping with a nucleophile will install the desired functionality at the carbon atom adjacent to nitrogen. This oxidative Mannich concept forms the basis of transition metal catalyzed inert sp^3 C–H functionalizations α to nitrogen atom in *N*,*N*-dialkylanilines. The *in situ* generated iminium carbon can be attacked either inter-molecularly or intra-molecularly with a suitable nucleophile. The intermolecular cross coupling with tertiary amines has undergone significant advances while the intra-molecular versions remain virtually unattended.

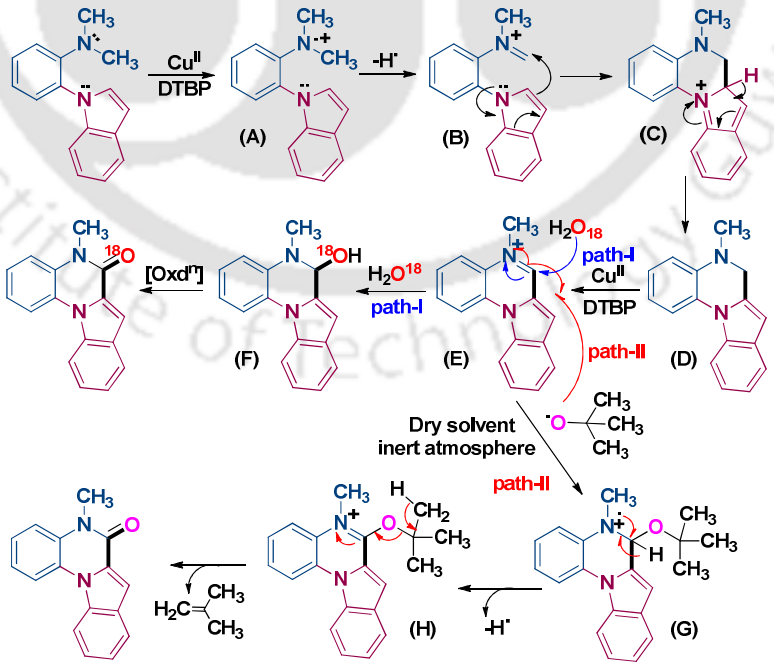
The concept of this intra-molecular oxidative Mannnich reaction has been utilized by us and other group to generate nitrogenous heterocycles under Cu-catalyzed conditions (path-a and b, Scheme III.1). However, the gate is still opened for other nucleophilic counterparts. Following this, we anticipated that if a nucleophilic heterocyclic moiety such as indole is installed at the *ortho* position of *N*,*N*-dialkylanilines, it may lead to similar results through C–C bond formation. A trial reaction attempted to examine the feasibility of this envisaged intramolecular CDC reaction, provided indolo[1,2-*a*]quinoxalin-6-one as the product which formed via the expected intramolecular $C(sp^2)$ –$C(sp^3)$ bond formation along with the installation of a carbonyl functionality at the expense of the remaining two sp^3 C–H's (path-c, Scheme III.1).



Scheme III.1. *Copper catalyzed intramolecular oxiadtaive cyclization of tertiary amines*

After screening the reaction with various reaction parameters such as catalysts, oxidants, solvents and temperatures, it was found that the use of $Cu(OAc)_2$ (10 mol%), DTBP (6 equiv) in DMSO solvent at 120 ^oC was the optimal conditions for this reaction. The above optimized conditions were then executed to a variety of 2-indolyl-*N*,*N*-dimethylamines to explore the substrate scope of the protocol. All substituted 2-indolyl-*N*,*N*-dimethylamines gave their corresponding indoloquinoxalin-6-one derivatives in moderate yields irrespective of the nature of substituents. However, the yields were marginally better and times taken were shorter for substrates possessing electron-donating groups on one or both the aryl rings than for substrates containing electron-withdrawing groups. The scope of the methodology has been extended to other heterocyclic systems such as pyrrole, imidazole and benzimidazoles, all gave their respective quinoxalinones in moderate yields.

Various control experiments were performed to find out the nature of the mechanism and origin of the oxygen source. On the basis of the results obtained from these control experiments as well as the literature reports, a plausible mechanism has been proposed for this transformation that comprises of two paths (Scheme III.2); both the mechanisms (path-I and path-II) are operating in tandem. The mechanism with other heterocycles is expected to follow the same pathway.



Scheme III.2. *Plausible mechanism for the formation of indoloquinoxalin-6-one*

In conclusion, we have developed a Cu catalyzed method for the synthesis of indoloquinoxaline-6-ones starting from *o*-indolyl-*N*,*N*-dimethylarylamines through an intramolecular oxidative coupling pathway. The process involves a formal three sp^3 C–H bonds and one sp^2 C–H bond cleavages with a concomitant installation of C–C and C–O bonds leading to the formation of indoloquinoxalin-6-ones. The use of cheaper catalytic system and extension of the methodology to other heterocyclic systems establishes practical applicability of the present protocol.

CHAPTER IV. A Cu-catalyzed Synthesis of Substituted 3-Methyleneisoindolin-1-one

This chapter illustrates a Cu(I)-catalyzed synthesis of substituted 3-methyleneisoindolin-1-ones involving decarboxylative cross-coupling of aryl alkynyl acids with 2-halobenzamides followed by *5-exo-dig* heteroannulation.

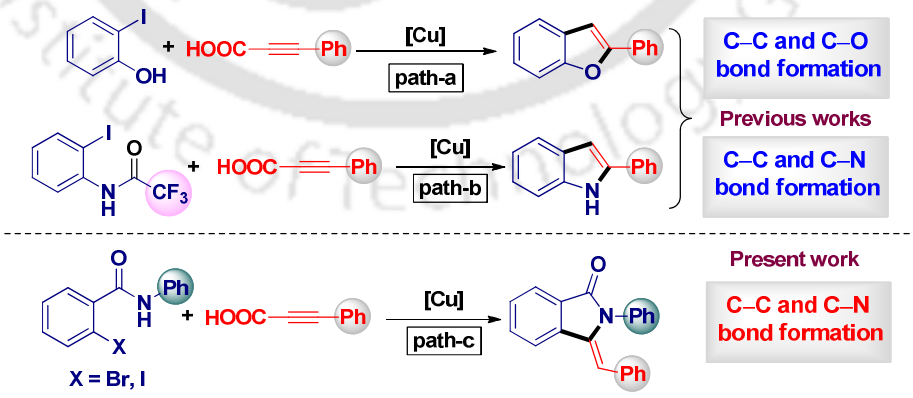
Substituted 3-methyleneisoindolin-1-ones are medicinally important heterocyclic scaffold prevalent in many natural products and pharmaceuticals. Apart from their significant biological profile they also find applications in material chemistry. Due to the myriad of applications of this important motif there has been development of numerous synthetic protocols for their synthesis. The traditional methods for the synthesis of 3-methyleneisoindolin-1-one include Horner-Wadsworth-Emmons type of condensation, addition / dehydration of phthalimides, 5-*exo-dig* cyclization of preformed 2-alkynylbenzamides and base triggered addition to benzonitriles. However, they are associated with poor regioselectivity in case of unsymmetrical substrates or require number of additional synthetic steps. These shortcomings stimulated the emergence of various transition metal catalyzed protocols for their synthesis.

In modern synthetic organic chemistry, transition metal catalyzed decarboxylative cross-coupling reactions using carboxylic acids have received much attention because of their ready availability and easy handling. In general, such reactions proceed via the *in situ* generation of organometallic species along with the extrusion of CO_2 as the side product. This reactive organometallic intermediate then couples with appropriate counterparts providing alternative routes to C–C or C–heteroatom bonds. Alkynyl carboxylic acids, being a member of carboxylic acids, are potential candidates for cross–coupling reactions

installing an alkynyl group into the substrates and numerous C–C and C–X (X = N, P and S) bond forming reactions has been achieved using transition metal catalysts such as palladium, copper, nickel, silver etc.

Not merely restricted to the synthesis of internal alkynes, the above strategy has much more to offer by manipulation of the alkynyl group. One way to achieve this is to activate the *in situ* generated alkynyl group with a soft metal followed by an intramolecular nucleophilic attack resulting into a heterocycle. This strategy has been demonstrated by Xue group and Muthusubramanian group for the synthesis of benzofuran derivatives and 2-arylindoles respectively which proceeds via a copper catalyzed decarboxylative cross–coupling of alkynyl carboxylic acids followed by heteroannulation. Taking cues from these reports, we envisaged that coupling of 2-halo benzamide with an alkynyl acid under an appropriate condition may result either 3-methylene-isoindolin-1-one via a 5-*exo-dig* cyclization or substituted isoquinolin-1-one via a 6-*endo-dig* cyclization. In an attempt to perform the above mentioned reaction under copper catalyzed condition resulted in a selective formation of 5-*exo-dig* product, 3-methylene-isoindolin-1-one, thus ruling out the other possibility *viz.* 6-*endo-dig* cyclization.

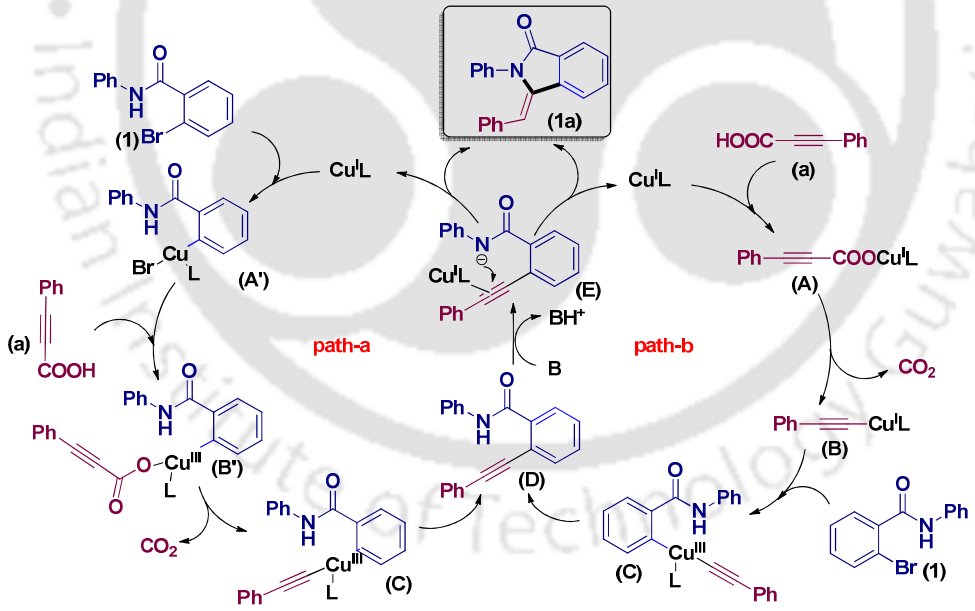
Various optimization reactions were carried out using different catalysts, ligands, bases and solvents in order to attain a suitable reaction condition and the use of CuI (10 mol %), 1,10-phen (10 mol %), Cs_2CO_3 (1.5 equiv) in DMSO solvent at 120 ^oC was found to be the most productive condition for this transformation.



Scheme IV.1. *Copper catalyzed strategies of decarboxylative cross-coupling with concomitant heterocyclization*

A variety of substituted 3–arylmethylene isoindolin-1-ones has been synthesized adopting this optimal reaction conditions. 2-bromobenzamides possessing electron-withdrawing groups provided marginally better yields of the products than for substrates possessing electron-donating groups. No significant electronic effect of substituents present in aryl propiolic acids could be ascertained; all provided their corresponding 3–methylene isoindolin-1-ones in moderate to good yields. The reaction when carried out with 2-iodo benzamides proceeded smoothly in absence of a ligand without effecting the product yields and reaction times. The reaction with an aliphatic alkynyl acid failed to give the desired product, instead hydroxylation *ortho* to amide moiety was observed.

Based on literature reports two alternative mechanisms were proposed for this transformation (Scheme IV.2). First mechanism shows oxidative addition of Cu(I) with 2-halobenzamide as the initial step (Path a, Scheme IV.2), while other mechanism shows generation of a Cu-alkynylide species via decarboxylation as the primary step (Path b, Scheme IV.2).



Scheme IV.2. *Plausible mechanism for the formation of 3-methyleneisoindolin-1-one*

In conclusion, we have developed a Cu(I)-catalyzed synthesis of substituted 3-methyleneisoindolin-1-ones involving decarboxylative cross-coupling of 2-

halobenzamides with aryl alkynyl acids followed by *5-exo-dig* heteroannulation. In this transformation alkynyl acids have been utilized to generate alkyne intermediate for the synthesis of this important heterocycle scaffold. While reactions of 2-iodo benzamides proceeded without ligand, for 2-bromo substrates the assistance of a ligand is essential.

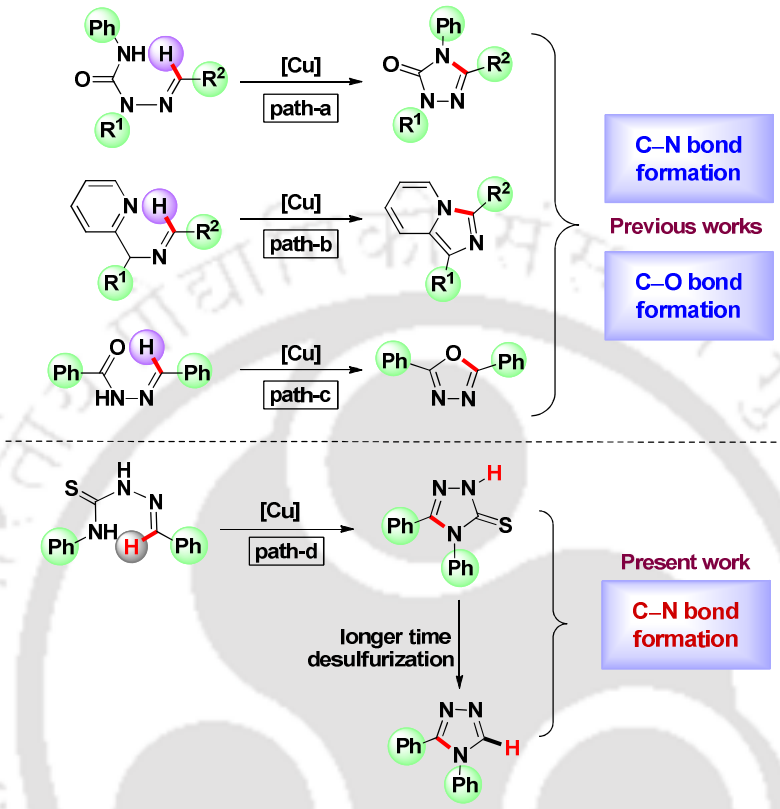
CHAPTER V. Synthesis of 1,2,4-Triazoles via Oxidative Heterocyclization: Selective C–N Bond Over C–S Bond Formation

This chapter deals with a copper catalyzed method for the synthesis of 4,5-disubstituted-1,2,4-triazole-3-thiones and 4,5-disubstituted 1,2,4-triazoles involving imine C–H bond functionalization of *N*-arylidenearylthiosemicarbazides.

Mercapto and thione derivatives of 1,2,4-triazoles are known to exhibit a variety of biological activities such as antibacterial, antifungal, antitumor, anti-inflammatory, antiviral, antitubercular, anticonvulsant and antidepressant activities. Applications of this scaffold have led to the development of various strategies for their synthesis. The common routes to 1,2,4-triazole-3-thiones include: (i) alkaline ring closure of acylthiosemicarbazides, (ii) reaction of acid hydrazides with carbon disulfide and hydrazine hydrate and (iii) thionation of 1,2,4-triazole-3-ones.

Functionalizations of ubiquitous and unreactive C–H bonds are more advantageous in terms of atom and step economy because of the non-requirement of substrate pre-functionalization. Although transition metal catalyzed sp^2 C–H bond functionalization of arenes and heteroarenes are well scrutinized, in contrast the functionalization of imine C(sp^2)–H bond are relatively scarce. Pertinent to imine C(sp^2)–H functionalizations, Cu-catalyzed C–N bond formations has been reported by various groups (path-a and b, Scheme V.1). Recently, our group achieved an oxidative C–O bond formation involving an amidic carbonyl and an imine C–H bond in *N*-arylidenearoylhydrazide (path-c, Scheme V.1). Here, we have developed a copper(II) catalyzed route to 1,2,4-triazole-3-thiones via selective C–N bond formation at the imine C–H bond of *N*-arylidenearylthiosemicarbazides (path-d, Scheme V.1). Upon prolonging the reaction time,

1,2,4-triazole-3-thiones desulfurizes to produce another class of heterocycles *viz.* 1,2,4-triazoles.

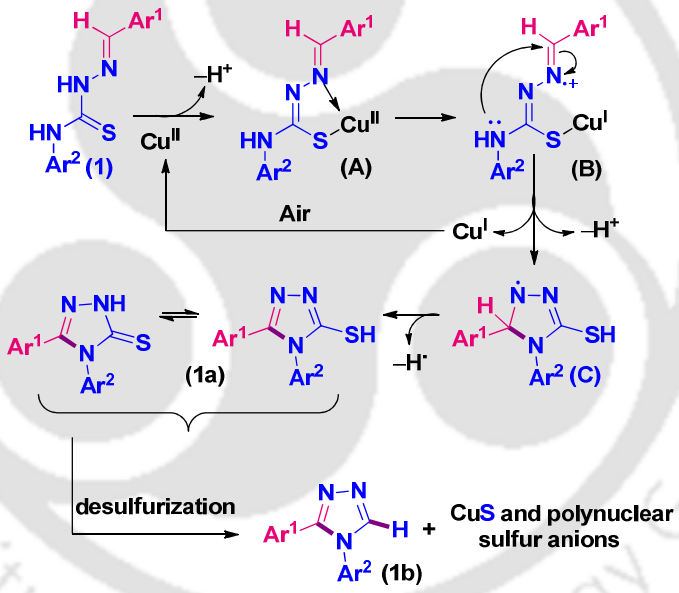


Scheme V.1. *Copper catalyzed heterocyclization via imine C–H bond functionalizations*

Rigorous optimizations were carried out to establish the appropriate reaction conditions and the use of $CuBr_2$ (30 mol %) in DMSO solvent at 80 ^{o}C was found to be optimal condition for this transformation. After figuring out the best optimum condition, this strategy has been applied to a set of *N*-arylidenearylthiosemicarbazides having electron-neutral, electron-donating and electron-withdrawing groups on one or both the aryl rings, all provided their corresponding 1,2,4-triazole-3-thiones in moderate to good yields. Although, no correlation between electronic effects of substituents and yields of products were observed, however, the time taken for the completion of reaction was shorter for substrates possessing electron-donating groups on either one or both the aryl rings than for substrates bearing one or two electron-withdrawing groups. The same series of *N*-arylidenearylthiosemicarbazides when kept for longer reaction time, underwent facile

transformation to their respective 1,2,4-triazoles through desulfurization of 1,2,4-triazole-3-thiones. A complete change in the reactivity pattern was observed when any one of the aryl rings (derived from either aldehyde or thiosemicarbazide) in *N*-arylidenearylthiosemicarbazides is *ortho*-disubstituted giving thiodiazole as the major or an exclusive product.

Based on literature reports on similar copper catalyzed oxidative heterocyclization a plausible mechanism for the formation of thione has been proposed (Scheme V.2). Although the mechanism of final desulfurization process could not be understand properly the involvement of Cu salt in the desulfurization step has been confirmed through isolation and characterization of CuS or an array of polynuclear sulfur anions. The source of hydrogen was established by various deuterium experiments.



Scheme V.2. *Proposed mechanism for the formation of 1,2,4-triazoles*

In conclusion, we developed an efficient Cu(II) catalyzed strategy for the synthesis of two important class of heterocycles *viz*. 4,5-disubstituted 1,2,4-triazole-3-thiones and 4,5-disubstituted 1,2,4-triazoles from arylidenearylthiosemicarbazides by simply tuning the reaction time. The thiophilic Cu assist the desulfurization of thiones with concomitant formation of CuS or an array of polynuclear sulfur anions which has been analyzed and confirmed by SEM and EDS analysis.

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Chapter I

An Overview of Copper Catalyzed Synthesis of N–Heterocycles

CHAPTER I

I. An Overview of Copper Catalyzed Synthesis of *N*–Heterocycles

I.1. Introduction to heterocyclic chemistry

Cyclic organic compound containing all carbon atoms in ring formation is referred to as **carbocyclic compound**. If at least one atom other than carbon forms a part of the ring then it is designated as a **heterocyclic compound** and the atom other than carbon is termed as **heteroatoms.** Nitrogen, oxygen and sulfur are the most common heteroatoms but heterocyclic rings containing other hetero atoms such as phosphorous, arsenic, antimony, silicon, tellurium, selenium, boron, germanium etc. are also widely known.[1]

Heterocyclic compounds can be classified into two categories:

1. **Aliphatic heterocyclic compounds**. Aliphatic heterocyclics are the cyclic analogues of amines, ethers, thioethers, amides, etc. Their properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4-membered) and common (5 to 7 membered) ring systems.
2. **Aromatic heterocyclic compound**. Aromatic heterocyclic compounds are those which have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties. Furthermore, these compounds also obey the general rule of aromaticity proposed by Hückel.

Heterocycles constitute the largest classical division of organic compounds encompassing more than half of the known organic compounds. Heterocycles make up an exceedingly important class of compounds because they are widely distributed in natural products, pharmaceuticals and agrochemicals. Apart from that various additives and modifiers used in cosmetic, reprography, information storage, plastics etc are heterocyclic in nature. Heterocyclic compounds are also used as anti-corrosive agents, photostabilizers, dyestuff, copolymer, photographic developers, fluorescent whitners, sensitizers, booster

agent, anti-oxidant in rubber and flavouring agent.[1,2] Such a wide range of applications of heterocycles stimulated the development of various new methods and the strategic development of known methods for the synthesis of heterocyclic compounds over several decades.

I.2. Importance of nitrogen-containing heterocycles

Among various heterocyclic moieties, nitrogen-containing heterocycles are the most important class of heterocycles, present in many naturally occurring compounds and is essential for life. Pyrimidine (cytosine, thymine and uracil) and purine (adenine and guanine) derivatives are respectively two and four nitrogen containg *N*-heterocycles found in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA participate in the encoding of genetic information and also pass information to RNA that control sequence of amino acids during protein synthesis. Vitamins in the group B, coenzyme precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, essential amino acids *viz*. proline, histidine and tryptophan, photosynthesizing pigment chlorophyll, the oxygen transporting material haemoglobin, the hormones kinetin, heteroauxin, cytokinins, neurotransmitter serotonin, histamine are some representative examples of nitrogen-containing heterocyclic compounds.[1]

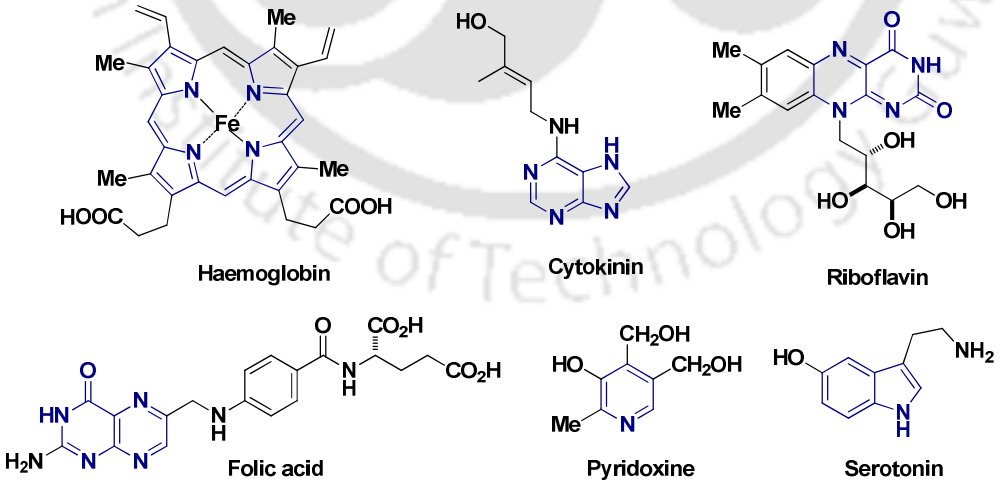


Figure I.2.1. *Examples of some naturally occurring N-heterocycles*

Nitrogeneous heterocycles, both natural and synthetic, are widely exists in pharmaceuticals. *N*-heterocyclic compounds promote salt formation which is helpful to improve their oral absorption and bioavailability[3] thereby making them privileged in numerous therapeutics. *N*-heterocycles exhibit a variety of biological activities such as anti-malarial, antipyretic, analgesic, antiulcer, cardiovascular, antibacterial, antifungal, anti-hypertensive, antithelimitic, anti-convulsant, anti-cancer, anti-diabetic, anti-tubercular and anti-inflammatory activities.[1,4]

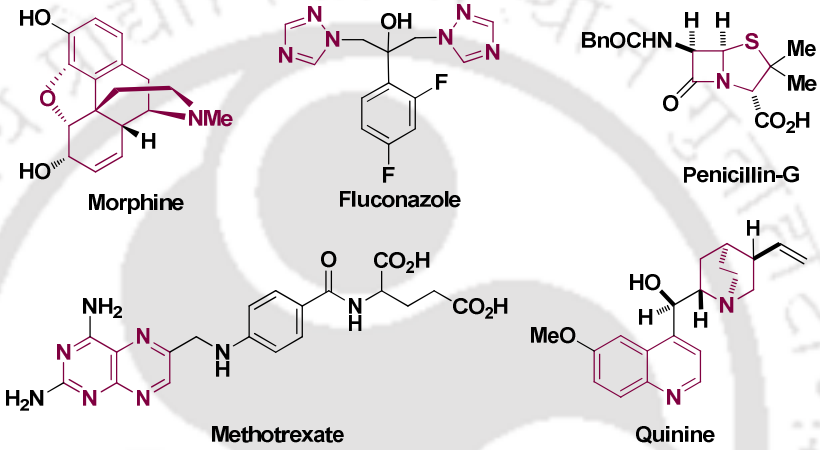


Figure I.2.1*. Examples of N-heterocyclic phramaceuticals*

Numerous *N*-heterocycles are used in the field of agriculture in the form of insecticides, fungicides, herbicides etc. *N*-heterocycles also find applications in dyestuffs, fluorescent sensors, brightening agents, information storage, analytical reagents, plastics and polymer industries. They are also extensively employed in the area of material sciences and used as synthetic intermediates, protecting groups, chiral auxiliaries and metal ligands during various organic transformations.[1,5]

I.3. Introduction to Cu catalysis

Among various transition metals, copper salts have been widely used in organic synthesis because of their low cost, less toxicity and excellent tolerance to different functional groups. Copper salts have been utilized as catalytic cross-coupling agents, Lewis acids as well as oxidizing agents.[6]

Copper can exist in four different oxidation states (Cu^0, Cu^I, Cu^{II} and Cu^{III}) and can exhibit in required oxidation states in different reaction conditions thereby making the mechanistic aspect of Cu-catalyzed reaction quite exciting. The transformations catalyzed by copper are thought to occur by a one-electron process, or a two-electron process or a combination of one- and two-electron processes.

Advantages associated with the copper slats stimulated the emergence of various copper-facilitated organic transformations in the last few decades. Accordingly, a great number of new, practical and efficient Cu-catalyzed protocols have also been developed for the synthesis of numerous heterocyclic scaffolds.[7]

I.3.1. Applications of ligands in copper catalysis

The efficiency of some copper mediated strategies have been enhanced by the addition of an external ligand in the reaction medium. This will lead to the generation of a copper complex in the medium which is actually responsible for the catalytic activity. Ligand-assisted Cu-catalyzed reactions are superior in terms of functional group tolerance, catalyst loading, milder reaction conditions, enhanced chemoselectivity and enantioselectivity. A ligand enhances the catalytic activity by (a) increasing the solubility of the metal in the medium by forming complex and (b) inhibiting the aggregation of metal salts.[7e-j,8] Some of the most commonly used ligands in Cu-mediated reactions are enlisted below.

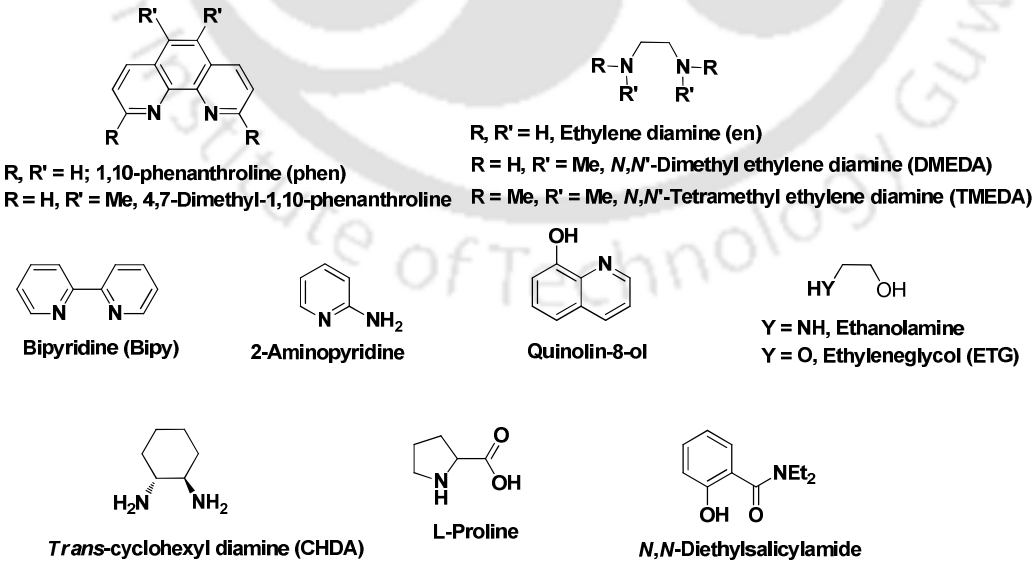


***Figure I.3.1**. Commonly used ligands in Cu catalysis*

I.4. Cu catalyzed synthesis of *N*-heterocycles

Cu-catalyzed protocols that lead to the synthesis of *N*-heterocyclic scaffolds involve the formation of either a C–C bond or a C–N bond or combination of both. Various Cu-catalyzed strategies can be broadly classified mainly into four categories *viz.* (i) C–H bond functionalizations; (ii) *N*-arylation and *N*-vinylation reactions; (iii) tandem / domino reactions and (iv) cycloaddition reactions.

I.4.1. C–H Bond functionalization

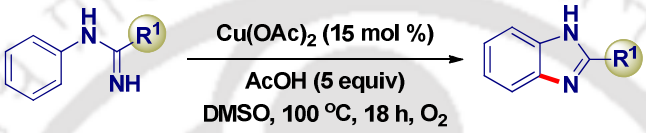
Transition-metal catalyzed C–H functionalization strategy has been successfully applied to the construction of complex heterocyclic moieties and therefore many convenient and efficient procedures have been developed in the last few years.[9] As an obvious consequence, various Cu-based C–H functionalization protocols for the synthesis of *N*-heterocycles have also emerged lately.[10,12] C–H functionalization methodologies for the construction of *N*-heterocycles can be categorized as (a) C–H amination and (b) C–C bond formation reaction.

I.4.1.1. C–H Amination reactions

C–H Aminations involve the conversion of a C–H bond to C–N bond via the nucleophilic addition of an amine group to a C–H bond. This C–H amination reaction has achieved remarkable progress over the past decade under various transition metal catalyzed conditions.[11,12] Consequently, numerous protocols for the synthesis of different *N*-heterocycles have emerged adopting this strategy. These C–H amination protocols are advantageous because they involve readily available starting materials, highly efficient, atom economic and practical applicability. Cu catalyzed C–H amination reactions leading to *N*-heterocycles usually involve functionalization of a sp^2 C–H bond. However, there are instances where more inert sp^3 C–H bond has also been functionalized.

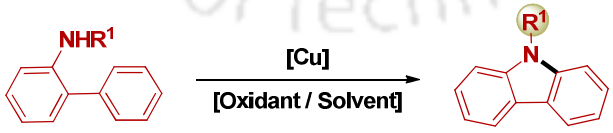
I.4.1.1.1. Representative examples of C–H amination reactions

First example of Cu catalyzed C–H amination leading to the synthesis of *N*-heterocycles was reported by Brasche and Buchwald in 2008 which involves a sp^2 C–H bond functionalization.[12a] The method describes the synthesis of benzimidazoles from amidines via an intramolecular coupling pathway in presence of copper acetate and oxidant molecular oxygen. The method provided good to excellent yields of the products and tolerates a wide range of functional groups (Scheme I.4.1.1.1.1).



Scheme I.4.1.1.1.1. *Cu catalyzed synthesis of benzimidazoles*

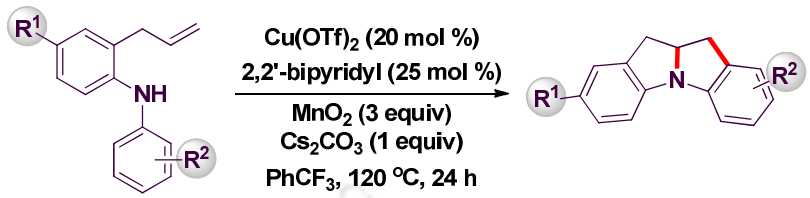
Chang group demonstrated a new synthetic route for the synthesis of carbazoles from *N*-substituted amidobiphenyls under copper-catalyzed or metal free conditions using hypervalent iodine (III) compound, diacetoxyiodobenzene (DIB) as the oxidant.[12b] Although the reaction proceeded in the absence of catalyst i.e. oxidant alone to provide carbazole products, combined use of copper(II) triflate and the iodine(III) species significantly improves the reaction efficiency and yields. The reaction is expected to follow a free radical pathway. A similar Cu-catalyzed picolinamide directed C–H amination reaction was reported by Hirano, Miura and co-workers to achieve carbazole derivatives using less expensive and abundant MnO_2 as the oxidant under microwave irradiation (Scheme I.4.1.1.1.2).[12c]



Scheme I.4.1.1.1.2. *Cu-catalyzed C–H amination leading to N-substituted carbazoles*

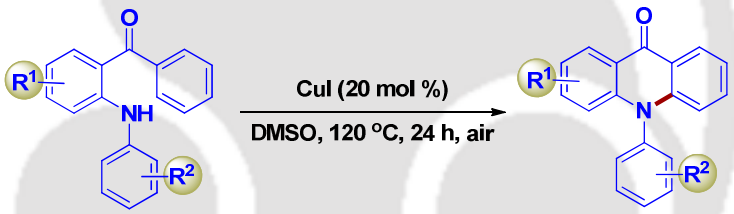
Sherman and Chemlar reported the synthesis of 10a,11-dihydro-10*H*-indolo[1,2-*a*] indoles through an intramolecular copper-catalyzed carboamination reaction of *N*-aryl-2-

allyl anilines.[12d] In this methodology 2,2′-bipyridyne was used as the ligand and MnO_2 as the oxidant along with $Cu(OTf)_2$ (Scheme I.4.1.1.1.3).



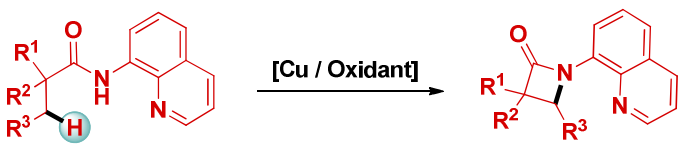
Scheme I.4.1.1.1.3. *Cu-catalyzed carboamination reaction leading to 10a,11-dihydro-10H-indolo[1,2-a] indoles*

Zhou, Deng and co-workers developed a Cu-catalyzed approach for the synthesis of *N*-aryl acridones via a sp^2 C–H bond functionalization of aryl(2-aminoaryl)methanones.[12e] In this intramolecular C–H amination reaction air was used as the oxidant under neutral conditions and the method afforded good yields of the products (Scheme I.4.1.1.1.4).



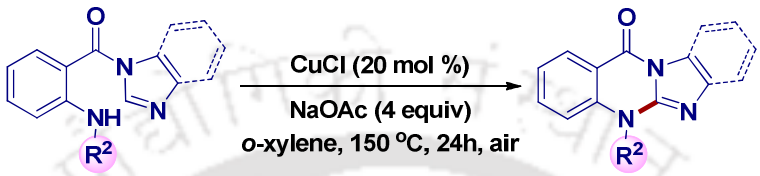
Scheme I.4.1.1.1.4. *Cu-catalyzed synthesis of N-aryl acridones*

Kanai *et al.* described a copper-catalyzed sp^3 C–H bond functionalization process for the synthesis of four membered *N*-heterocycles, *β*-lactams via a site-selective intramolecular amidation of *N*-(quinolin-8-yl)pivalamides where 8-aminoquinolinyl group served as the directing group.[12f] The reaction proceeded at a terminal methyl group as well as at the internal benzylic position of an alkyl chain. The same intramolecular dehydrogenative amidation reaction was achieved simultaneously by Ge group using CuCl as the catalyst and duroquinone as the oxidant (Scheme I.4.1.1.1.5).[12g]



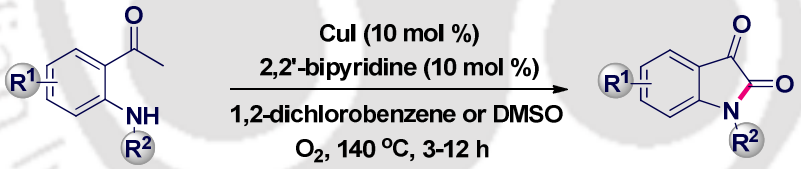
Scheme I.4.1.1.1.5. *Cu-catalyzed intramolecular sp^3 C–H bond amidation*

Qiao group achieved an intramolecular aerobic oxidative reaction of (1*H*-imidazol-1-yl)[2(alkylamino)phenyl]methanones and (1*H*-benzimidazol-1-yl)[2(alkylamino)phenyl]methanones using CuCl as the catalyst and air as the oxidant providing substituted imidazo/benzimidazo[2,1-*b*]quinazolinones in moderate to good yields (Scheme I.4.1.1.1.6).[12h]



Scheme I.4.1.1.1.6. *Cu-catalyzed route to 5-substituted Imidazo/benzimidazo[2,1-b]quinazolinones*

Cheng and co-workers developed a Cu(I)-catalyzed intramolecular aerobic oxidative C–H amination for the synthesis of isatins from 2-aminoacetophenones. 2,2′-bipyridine was used as the ligand along with the copper salt and the method provided various *N*-alkyl or aryl substituted isatins in good to excellent yields (Scheme I.4.1.1.1.7).[12i]



Scheme I.4.1.1.1.7. *Cu-catalyzed intramolecular sp^3 C–H bond amination*

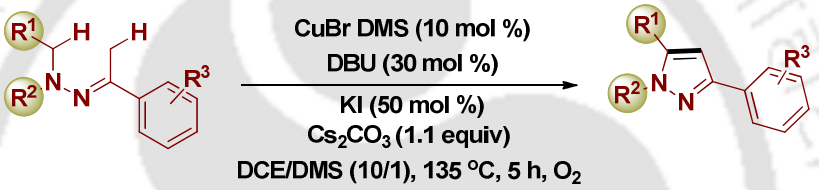
I.4.1.2. Carbon–Carbon bond forming reactions

C–C bond forming reaction being an important tool in organic synthesis, its scope has been extrapolated towards the synthesis of various heterocyclic moieties.[10a,13] Numerous Cu-catalyzed C–C bond forming strategies involving C–H functionalization for the synthesis of *N*-heterocycles have been developed in the past few years.[14,15,16] These C–C bond forming processes involve either one or two C–H bonds or a C–H bond and a C–X

bond during the construction of *N*-heterocyclic scaffold and involve functionalizations of all kinds of C–H (C_{sp3}–H, C_{sp2}–H and C_{sp}–H) bonds.

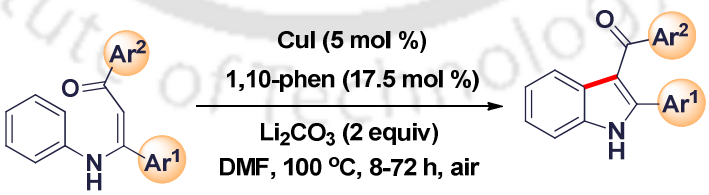
I.4.1.2.1. Representative examples of C–C bond forming reactions involving one or two C–H bond functionalizations

Ge and co-workers developed an efficient copper catalyzed aerobic intramolcular cross-dehydrogenative coupling of *N*,*N*-disubstituted hydrazones leading to the synthesis of pyrazole derivatives. The reaction involves functionalizations of two sp^3 C–H bonds and provides an environmentally friendly and atom-efficient approach to access pyrazole derivatives in good yields (Scheme I.4.1.2.1.1).[15a]



Scheme I.4.1.2.1.1. *Cu-catalyzed sp^3 C–H bond functionalization leading to pyrazoles*

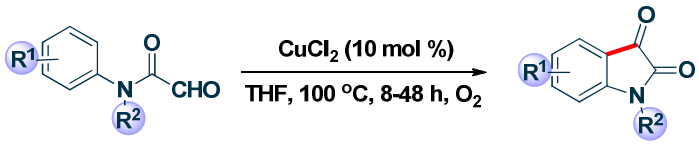
A novel copper catalyzed approach for the construction of multi-substitued indoles starting from readily available *N*-aryl enaminones was reported by Cacchi *el al*. This CuI / 1,10-phenanthroline catalyzed aerobic intramolecular cyclization reaction involves functionalization of an aryl C_{sp2}–H and an alkenyl C_{sp2}–H bond and compatible to a wide variety of substituents (Scheme I.4.1.2.1.2).[15b]



Scheme I.4.1.2.1.2. *Cu-catalyzed synthesis of multisubstituted indoles*

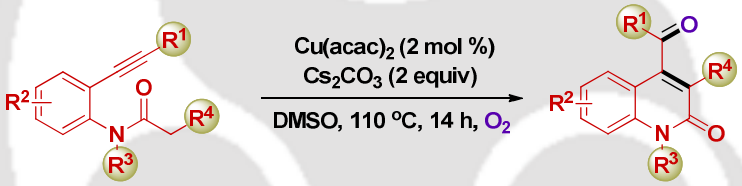
Li group described a copper catalyzed synthesis of indoline-2,3-diones via an aryl C_{sp2}–H and a formyl C_{sp2}–H bond functionalizations of fomyl-*N*-arylformamides. This

intramolecular C–H oxidation protocol employed O_2 as terminal oxidant and provided moderate to good yields of the products (Scheme I.4.1.2.1.3).[15c]



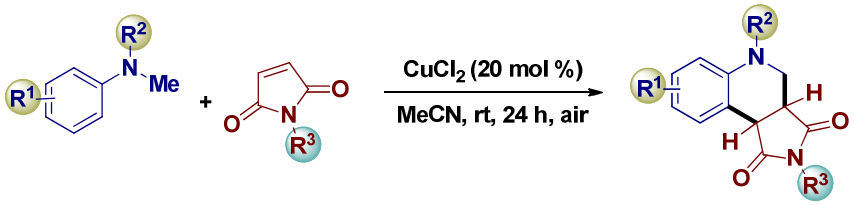
Scheme I.4.1.2.1.3. *Cu-catalyzed intramolecular C–H oxidation / acylation of fomyl-N-arylformamides*

Li and co-workers reported a Cu(II)-catalyzed route to quinolinones via a sp^3 C–H bond functionalization of *N*-(2-ethynylaryl)acetamides in an oxygen atmosphere. Atmospheric molecular oxygen was established to the source of the oxygen atom of the newly formed carbonyl group in this intramolecular carbocyclization / ketonization reaction (Scheme I.4.1.2.1.4).[15d]



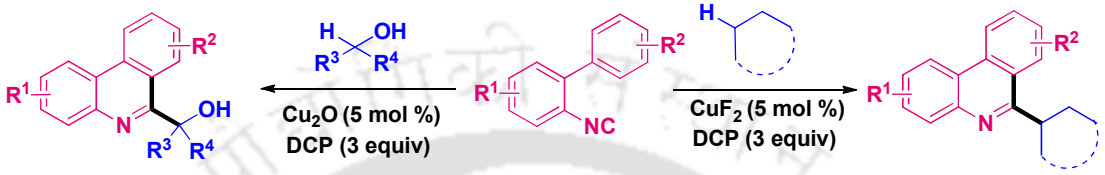
Scheme I.4.1.2.1.4. *Cu-catalyzed intramolecular oxidative carbocyclization / ketonization of N-(2-ethynylaryl)acetamides*

Miura and Hirano group demonstrated an efficient oxidative cyclization of *N*-methylanilines with electron-deficient olefins under a copper / O_2 catalytic condition. This intermolecular oxidative cyclized tetrahydroquinoline synthesis involves an aryl C_{sp2}–H and an alkyl C_{sp3}–H bond functionalization and are successful with alkenes such as maleimides and benzylidene malononitriles (Scheme I.4.1.2.1.5).[15e]



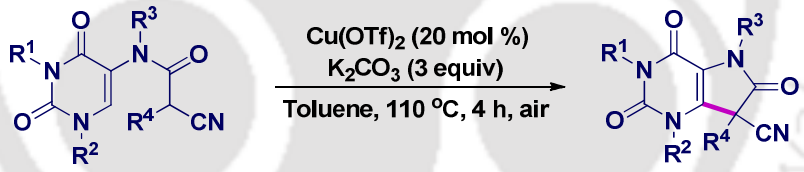
Scheme I.4.1.2.1.5. *Cu-catalyzed aryl C_{sp2}–H and C_{sp3}–H double bond functionalization leading to tetrahydroquinolinones*

An efficient Cu-catalyzed approach for the construction of 6-alkyl phenanthridines through a cascade alkylarylation reaction of 2-isocyanobiphenyls with simple alkanes and alcohols was developed by Liu and Huang group independently. This dual C(sp^3)–H / C(sp^2)–H functionalization process is expected to follow a free radical pathway (Scheme I.4.1.2.1.6).[15f,g]



Scheme I.4.1.2.1.6. *Cu-catalyzed synthesis of phenanthridine derivatives*

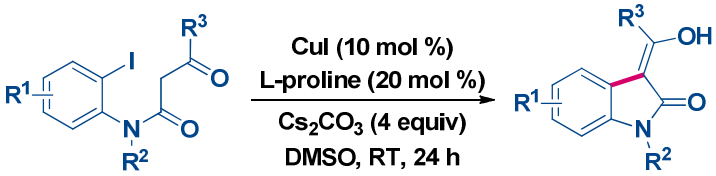
Roy, Mazumdar and co-workers reported a Cu-catalyzed intramolecular cross dehydrogenative coupling reaction to accomplish pyrrolo-pyrimidine derivatives. This intramolecular aerobic reaction is associated with functionalization of a heteroaromatic C(sp^2)–H and a C(sp^3)–H bond (Scheme I.4.1.2.1.7).[15h,i]



Scheme I.4.1.2.1.7. *Cu-catalyzed synthesis of pyrrolopyrimidines*

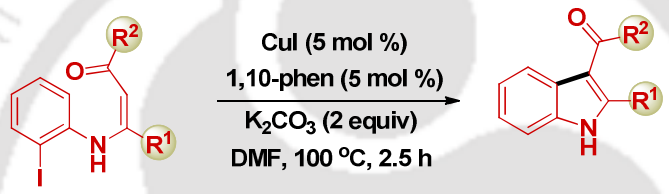
I.4.1.2.2. Representative examples of C–C bond forming reactions involving one C–H bond and one C–X bond

A CuI / L-proline-catalyzed mild and efficient approach for the preparation of 3-acyloxyindoles involving intramolecular C–H arylation strategy strating from *β*-keto 2-iodoanilides was described by Ma and Lu. Both acetoacetylated substrates and aryl carbonyl acetylated substrates were achieved in good yields and the electronic effects of the substituents on the aromatic rings were found to have little influence on the product yields (Scheme I.4.1.2.2.1).[16a]



Scheme I.4.1.2.2.1. *Cu-catalyzed intramolecular sp^3 C–H bond arylation of β-keto amides*

Cacchi and co-workers developed a CuI / 1,10-phenanthroline catalyzed cyclization of *N*-(2-iodoaryl)enaminones for the construction of 3-aroylindoles. The reaction involves aryaltion of an alkenyl sp^2 C–H bond and tolerates a variety of useful functionalities including ether, keto, cyano, bromo, and chloro substituents (Scheme I.4.1.2.2.2).[16b]



Scheme I.4.1.2.2.2. *Cu-catalyzed intramolecular sp^2 C–H bond arylation*

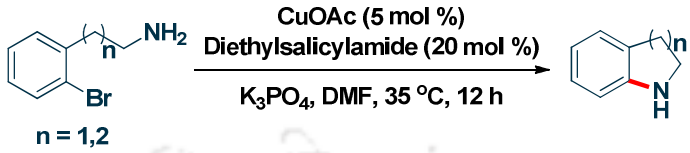
I.4.2. Intramolecular *N*-arylation and *N*-vinylation reactions

The application of copper catalysis to *N*-arylation and *N*-vinylation reactions has recently emerged as a powerful tool in synthetic organic chemistry for assembling various molecules including natural products.[7a-c,17] Not surprisingly, this Cu-catalyzed synthetic approach has been applied for the construction of various saturated and unsaturated *N*-heterocycles. [18,19] Although C–H amination also falls under the heading of *N*-arylation / alkylation reaction it is not included here as it is discussed in C–H functionalization section; this section only includes those reactions involving a C–X bond and a N–H bond.

I.4.2.1. Representative examples of intramolecular *N*-arylation and *N*-vinylation reactions

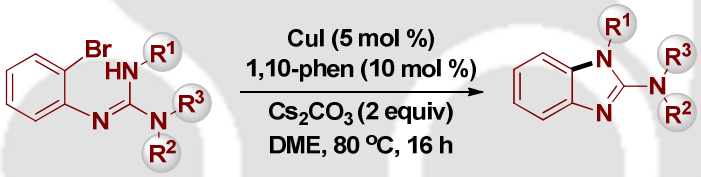
Buchwald *et al.* developed an efficient Cu-catalyzed intramolecular *N*-aryaltion of aryl halides and primary amines for the synthesis of five and six membered *N*-heterocycles. The

addition of diethylsalicylamide as a ligand was important to the success of this reaction. The ligand helps by preventing multiple substrate ligation and also increase the oxidation potential of Cu(I) complex (Scheme I.4.2.1.1).[19a]



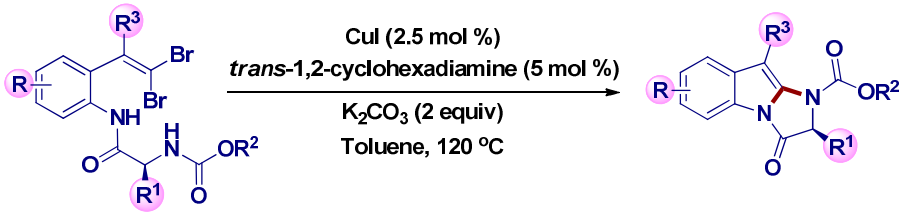
Scheme I.4.2.1.1. *Cu-catalyzed intramolecular N-arylation of primary amines*

Batey group demonstrated a Cu-catalyzed approach for the construction of 2-aminobenzimidazoles via an intramolecular C–N bond formation between an aryl halide and a guanidine moiety using both palladium and copper catalysts. In this transformation, the use of inexpensive copper salts such as CuI was found to be superior to palladium salts both in terms of yields and selectivities (Scheme I.4.2.1.2).[19b]



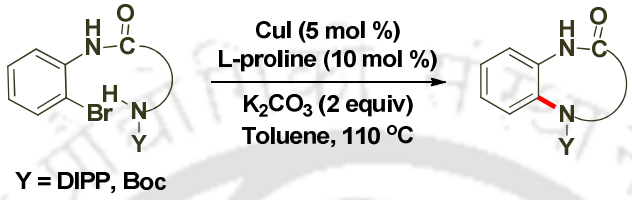
Scheme I.4.2.1.2. *Synthesis of 2-aminobanzimidazoles by intramolecular C–N coupling*

Lautens and co-workers realized a copper catalyzed approach to accomplish substituted imidazoindolones starting from readily accessible chiral 2-(gem-dibromovinyl)anilines. This intramolecular amidation reaction proceeds under the catalysis of CuI / *trans*-1,2-cyclohexadiamine which involves a double *N*-vinyaltion process (Scheme I.4.2.1.3).[19c]



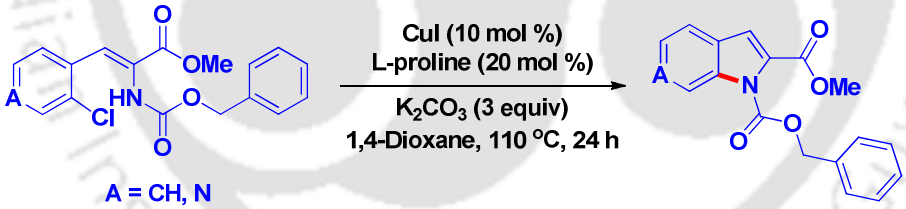
Scheme I.4.2.1.3. *Intramolecular Cu-catalyzed double amidation reaction*

An efficient copper-catalyzed intramolecular *N*-arylation of phosphoramidates and carbamates for the construction of medium- and large-sized nitrogen heterocycles was developed by Fu *et al*. Introduction of the phosphoryl group or a *tert*-butoxycarbonyl at the *N*-termini can improve the intramolecular cyclization under copper catalysis and these two groups can easily be removed under the mild conditions (Scheme I.4.2.1.4).[19d]



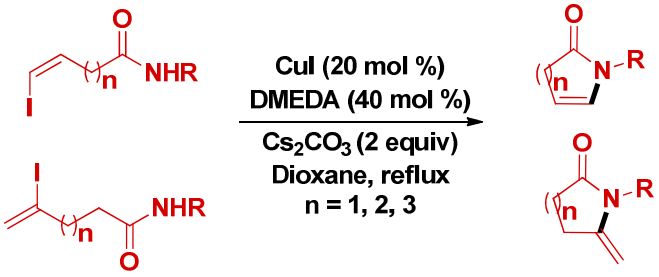
Scheme I.4.2.1.4. *Synthetic route of medium and large sized N-heterocycles via intramolecular Ullmann condensation*

Cusack *et al.* reported a new mild and efficient method for the conversion of ene-carbamates into their corresponding indole- or pyrrolo[2,3-*c*]pyridine-2-carboxylates through an intramolecular C–N bond forming reaction using CuI / L-proline catalytic system (Scheme I.4.2.1.5).[19e]



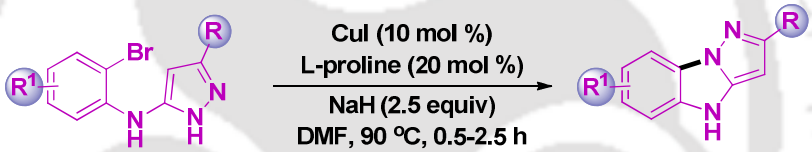
Scheme I.4.2.1.5. *Synthesis of indole- or pyrrolo[2,3-c]pyridine-2-carboxylates via intramolecular C–N bond formation*

Li group described an intramolecular vinylation of iodoenamides with CuI as the catalyst and *N,N′*-dimethylethylenediamine as the ligand to furnish a variety of five-, six-, and seven-membered *N*-vinylic lactams (Scheme I.4.2.1.6).[19f] *N*-Tosyl-3-halo-3-butenylamines when treated under the same reaction condition underwent similar *N*-vinylation reaction to afford 2-alkylideneazetidines which could be easily converted to their corresponding *β*-lactams by oxidation with ozone.[19g]



Scheme I.4.2.1.6. *Cu-catalyzed intramolecular N-vinylation of amides*

Ila and co-workers developed a novel Cu-catalyzed intramolecular cyclization of 5-(2-bromoanilino)-pyrazole precursors via intramolecular C–N bond formation to accomplish pyrazolo[1,5-*a*]benzimidazoles. The method is compatible with a range of electron-donating and -withdrawing substituents on the two aryl groups providing good yields of their respective products (Scheme I.4.2.1.7).[19h]



Scheme I.4.2.1.7. *Cu-catalyzed intramolecular C–N bond formation*

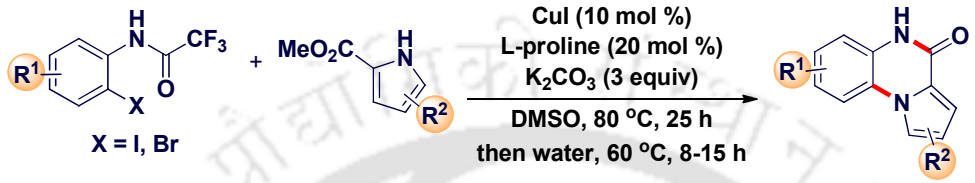
I.4.3. Tandem / domino reactions

An emerging area in the application of Cu-catalysis is the "tandem reactions" in which Cu assisted the formation of one or more C–X (X= C, N, O, S) bonds. In these reactions, the insertion of Cu to unsaturated C–halo or C–H bonds led to the formation of new C–X bonds. This strategy has been successfully applied for the synthesis of numerous heterocylic scaffolds and has been regarded as one of the major strategies for assembling *N*-heterocycles.[20,21]

I.4.3.1. Representative examples of tandem / domino reactions

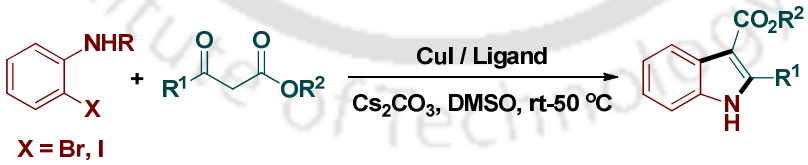
Ma group demonstrated an efficient CuI / L-proline assisted coupling of 2-halotrifluoroacetanilides with pyrrole-2-carboxylates to furnish pyrrolo[1,2-*a*]quinoxalines.

The whole reaction process involved a one-pot C–N coupling, hydrolysis and intramolecular condensation process to assemble pyrrolo[1,2-*a*]quinoxalines. Indole-2-carboxylate esters were compatible with this process, giving the corresponding fused tetracyclic compounds, while imidazole-2-carboxylate esters gave low yields of the desired coupling products (Scheme I.4.3.1.1).[21a]



Scheme I.4.3.1.1. *Cu-catalyzed C–N coupling / hydrolysis / condensation process leading to pyrrolo[1,2-a]quinoxalines*

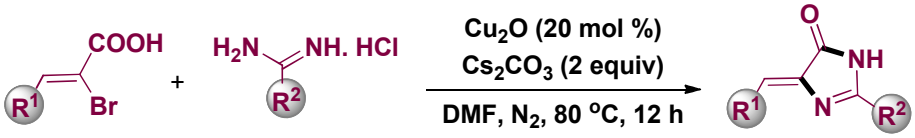
A tandem reaction between 2-iodoaniline and β-ketoester leading to 2,3-disubstituted indole derivatives was described by Tanimori and co-workers using CuI as catalyst and BINOL as ligand.[21b] The reaction proceeds under mild conditions producing moderate to good yields of the products. Almost at the same time, Ma group reported a similar strategy to assemble 2,3-disubstituted indoles based on a CuI / L-proline-catalyzed coupling of 2-halotrifluoroacetanilides with *β*-ketoesters and amides followed by acidic hydrolysis.[21c] However, conduction of the same reaction in anhydrous DMSO under otherwise identical condition resulted in the production of 2-trifluoromethyl substituted indoles as described by the same group (Scheme I.4.3.1.2).[21d]



Scheme I.4.3.1.2. *Cu-catalyzed tandem route to 2,3-disubstituted indole derivatives*

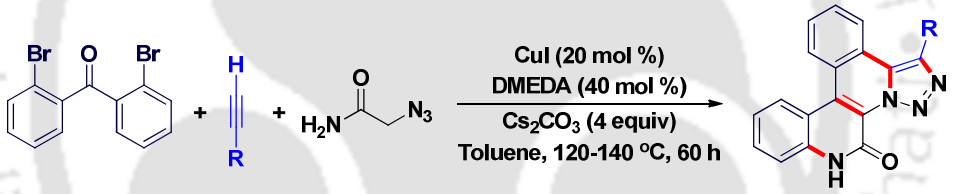
Fu *et al.* reported a simple and efficient copper catalyzed approach for the synthesis of 2,4-disubstituted imidazolones starting from readily available 2-bromo-3-alkylacrylic acids and amidines. The reaction involves intermolecular *N*-vinylation followed by condensation

to achieve the corresponding imidazolone derivatives in moderate to good yields without the addition of any ligand or additive under mild conditions (Scheme I.4.3.1.3).[21e]



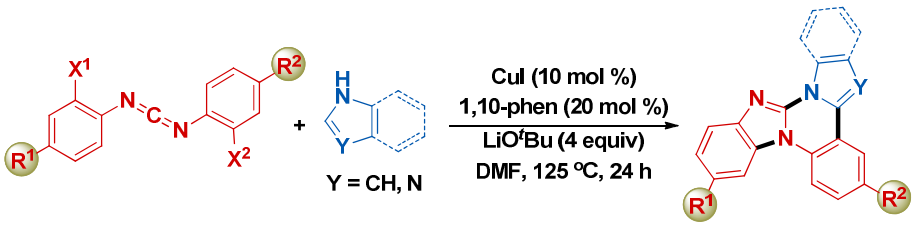
Scheme I.4.3.1.3. *Cu-catalyzed approach for synthesis of 2,4-disubstituted imidazolones*

Qian and co-workers developed a copper catalyzed three component reaction of bis(2-bromophenyl)methanone, terminal alkynes and 2-azidoacetamides leading to the synthesis of *N*-polyheterocycles.[21f] The reaction proceeds via a Cu-catalyzed domino cycloaddition / C–N coupling / cyclization / C–H arylation pathway. This cascade protocol resulted in the formation of three new rings and five new bonds (two C–C and three C–N bonds) during the course of the reaction (Scheme I.4.3.1.4).



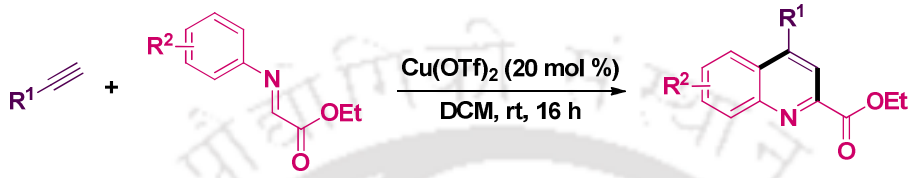
Scheme I.4.3.1.4. *Cu-catalyzed synthesis of N-polyheterocycles*

An efficient and versatile method for the construction of polycyclic benzimidazole derivatives starting from bis(*o*-haloaryl)-carbodiimides and azoles was demonstrated by Lv group.[21g] The reaction involves Cu-mediated domino addition / C–N coupling / sp^2 C–H arylation process to give polycyclic benzimidazoles in moderate to good yields (Scheme I.4.3.1.5).



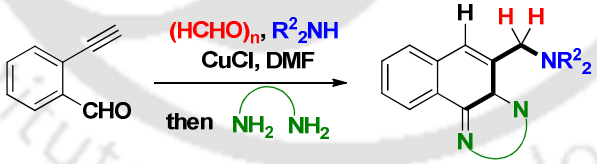
Scheme I.4.3.1.5. *Cu-catalyzed domino approach to polycyclic benzimidazole*

Liu *et al.* achieved a simple and convenient copper-catalyzed route for the synthesis of quinoline-2-carboxylate derivatives at room temperature starting from *N*-aryl-α-iminoethyl glyoxalates. The method involves sequential intermolecular addition of alkynes onto imines with subsequent intramolecular ring closure by arylation and tolerates a variety of useful functional groups (Scheme I.4.3.1.6).[21h]



Scheme I.4.3.1.6. *Cu-catalyzed tandem synthesis of quinoline-2-carboxylates*

A novel copper-catalyzed synthesis of 3-(aminomethyl) isoquinoline-fused polycyclic compounds through a four-component coupling and cascade cyclization strategy was described by Fujii, Ohno and co-workers. The reaction is associated with a Mannich-type reaction of 2-ethynylbenzaldehyde with paraformaldehyde and a secondary amine followed by treatment with a diamine component which gave tricyclic isoquinolines through cascade cyclization and oxidation process. This reaction resulted in the formation of one carbon-carbon and four carbon-nitrogen bonds in an atom-economical manner and produces fused isoquinolines of various ring sizes (Scheme I.4.3.1.7).[21i]



Scheme I.4.3.1.7. *Cu-catalyzed four component domino reactions*

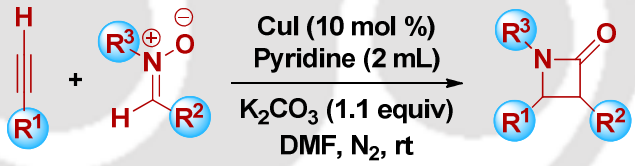
I.4.4. Cycloaddition reactions

Intermolecular cycloaddition reaction is another important method of achieving a variety of carbo- and heterocycles from simpler precursors.[22] Among cycloaddition reactions, the 1,3-dipolar cycloaddition has been established as a reliable and powerful tool for the synthesis of heterocyclic compounds from simple starting materials.[23] Use of a

transition metal catalyst such as copper instead of conventional conditions provides opportunities of performing the reaction under milder conditions by modifying the reactivity of the moiety through complexation. It also helps to overcome the poor regioselectivity observed in some of the corresponding thermal cycloadditions, as well as provide interesting new opportunities for asymmetric catalysis. A Cu-catalyzed 1,3-dipolar cycloaddition reactions disclose an alternative pathway to accomplish many interesting *N*-heyerocycles in an atom economical manner and more importantly provides some structural motifs in highly enantioenriched form.[24]

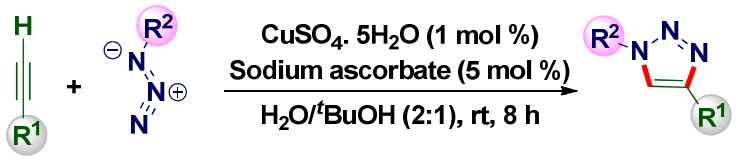
I.4.4.1. Representative examples of cycloaddition reactions

Miura group reported the first Cu-catalyzed [3+2] cycloaddition reaction for the synthesis of *N*-heterocycles which involves the reaction of terminal acetylenes with *C,N*-diarylnitrones to give *β*-lactam derivatives. The reaction is believed to occur via the formation of a copper acetylide dipolarophile intermediate which subsequently undergoes addition to the 1,3-dipole nitrone. Asymmetric induction was also observed during the reaction when chiral bisoxazoline type of ligands was used along with the copper salt (CuI) (Scheme I.4.4.1.1).[25a]



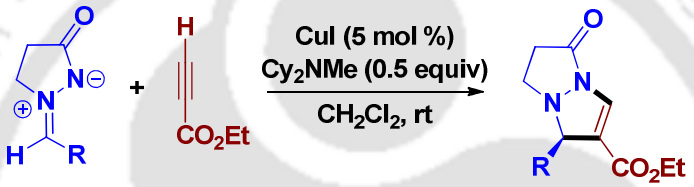
Scheme I.4.4.1.1. *Cu-catalyzed synthesis of β-lactams via [3+2] cycloaddition*

A copper(II) catalyzed [3+2] cycloaddition of terminal alkynes and azides leading to 1,2,3-triazoles was developed by Sharpless *et al* in 2002.[25b] A solid supported Cu(I) catalyzed method was reported by Meldal group in the same year.[25c] These newly emerged Cu catalyzed variants proceeds under a mild reaction condition, ecofriendly and high regio- and chemo-selectivity to the thermal uncatalyzed versions (Scheme I.4.4.1.2). Owing to the importance of 1,2,3-triazole moiety, extensive progress on this reaction has been achieved thereafter by varying various reaction parameters such as Cu salts, reaction medium, ligands etc.



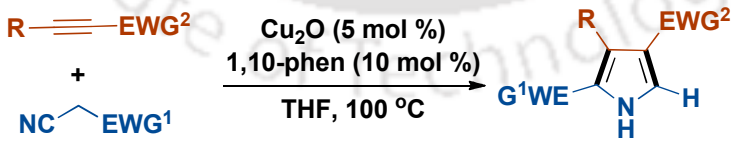
Scheme I.4.4.1.2. *Cu-catalyzed [3+2] cycloaddition of terminal alkynes and azides*

Shintani and Fu demonstrated a new copper-catalyzed 1,3-dipolar cycloaddition of an azomethine imine to an alkyne.[25d] A very good level of enentiomeric excess was obtained during the coupling of a wide range of azomethine imines and alkynes when phosphaferrocene-oxazoline was employed as a chiral bidentate ligand (Scheme I.4.4.1.3).



Scheme I.4.4.1.3. *1,3-Dipolar cycloaddition of azomethine imine to alkyne*

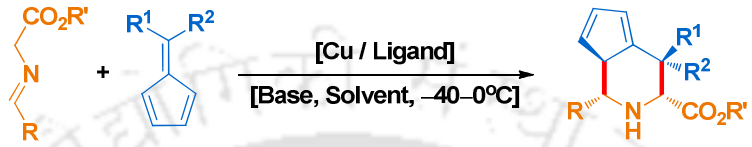
Yamamoto and co-workers described a copper-catalyzed [3+2] cycloaddition reaction of isocyanides with electron-deficient alkynes to give 2,4-di-EWG-substituted pyrroles. This heteroaromatization reaction involves α-cuprioisocyanide type of intermediate formed via the interaction of Cu_2O with isocyanide which is then reacted with electron deficient alkyne to produce 2,4-di-EWG-substituted pyrroles regioselectively (Scheme I.4.4.1.4).[25e]



Scheme I.4.4.1.4. *Synthesis of pyrroles via copper catalyzed condensation of isocyanides and alkynes*

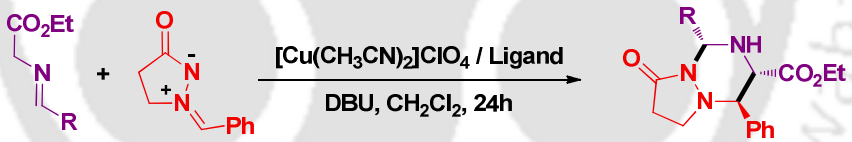
A novel Cu-catalyzed asymmetric [6+3] cycloaddition of azomethine ylides with readily available fulvenes under mild reaction conditions was developed independently by

Waldmann[25f,g] and Wang[25h] group simultaneously. The resultant four stereocenter containing piperidine derivatives are obtained with high regio- and enantioselectivity (Scheme I.4.4.1.5). Waldmann, Antonchick and co-workers combined this enantioselective [6+3] cycloaddition with a [4+2] cycloaddition in one pot to yield complex annulated piperidine derivatives with eight stereocenters.



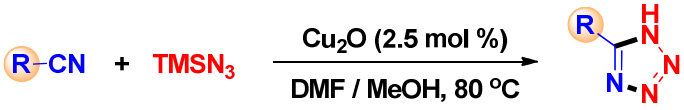
Scheme I.4.4.1.5. *Copper catalyzed [6+3] cycloaddition of azomethine ylides with fulvenes*

Guo, Hu and co-workers described a copper-catalyzed synthesis of optically active hexahydro-8*H*-pyrazolo[1,2-*a*][1,2,4]triazin-8-one derivatives via a [3+3] cycloaddition of azomethine ylides with azomethine imines. The reaction proceeds in the presence of a chiral ferrocenyl P, N ligands and provided the desired products with a high degree of diastereo- and enantio-selectivity (Scheme I.4.4.1.6).[25i]



Scheme I.4.4.1.6. *Copper catalyzed [3+3] cycloaddition of azomethine ylides with azomethine imines*

A Cu_2O catalyzed [3+2] cycloaddition reaction for the construction of 5-substituted 1*H*-tetrazoles was reported by Yamamoto group starting from nitriles and trimethylsilyl azides. The reaction proceeds without the assistance of a ligand or base or any additives and probably occurs through the *in situ* formation of a copper azide species, followed by a successive [3+2] cycloaddition with the nitriles (Scheme I.4.4.1.7).[25j]

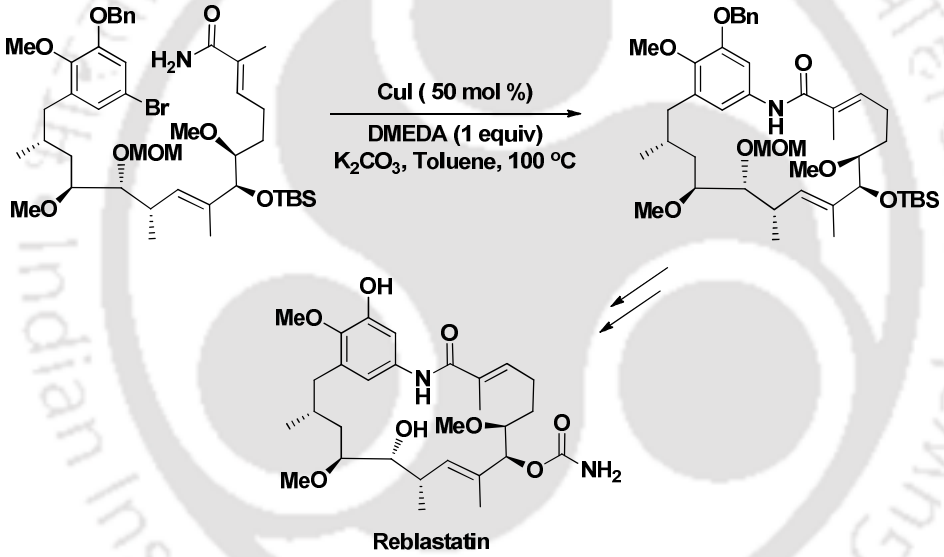


Scheme I.4.4.1.7. *Copper catalyzed synthesis of tetrazoles via [3+2] cycloaddition*

I.5. Applications of Cu-catalysis in total synthesis

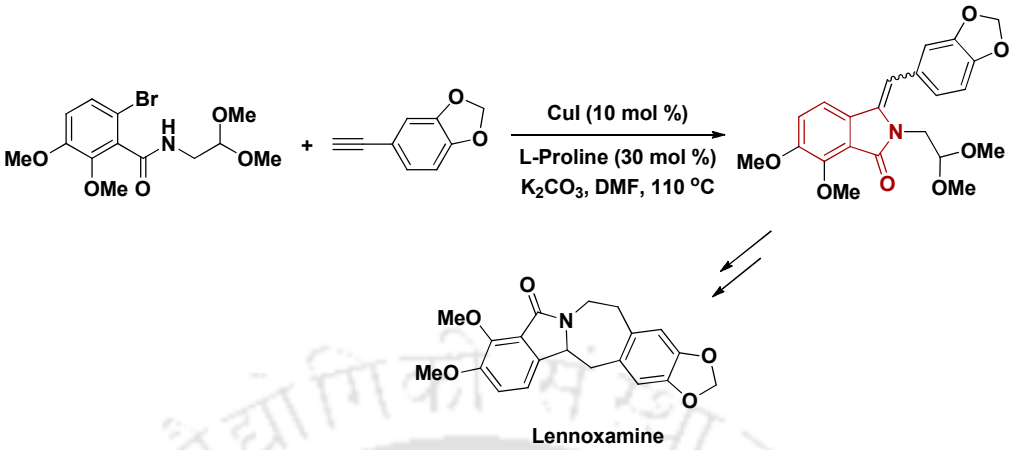
Cu-catalyzed strategies applied for the construction of *N*-heterocyclic compounds are not merely restricted to simple molecules but has been extrapolated to the total synthesis of various natural and non-natural products.[26] Two examples where Cu-catalyzed *N*-heterocycle synthesis acts as a key step during the total synthesis are described below.

Reblastatin, which is isolated from *Streptomyces hygroscopicus* is known to exhibit antitumor activity against human histiocytic lymphoma. Panek group demonstrated a total synthesis of Reblastatin which involves Cu-catalyzed *N*-arylation strategy as a key step leading to macrocyclic *N*-heterocycle synthesis (Scheme I.5.1).[26c]



Scheme I.5.1. *Total synthesis of Reblastatin*

Lennoxamine belongs to the isoindolobenzazepine alkaloid family and was extracted from the Chilean plant *Berberis darwinii*. A total synthesis of lennoxamine was reported by Ma and co-workers in which a Cu-catalyzed domino synthesis leading to isoindoline (*N*-heterocycle) core was accounted as an important step (Scheme I.5.2).[26d]



Scheme I.5.2. *Total synthesis of Lennoxamine*

I.5. References

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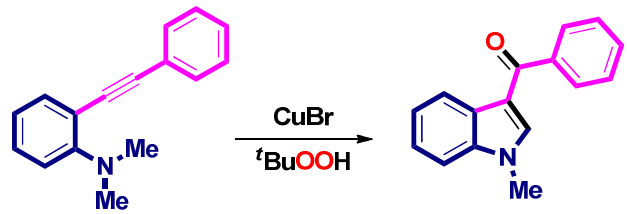
Chapter II A

A Copper Catalyzed Synthesis of 3-Aroylindoles via a sp^3 C–H Bond Activation Followed by C–C and C–O Bond Formation



- two C–H bond cleavage
- intramolecular C–C and C–O bond formation

Abstract: *An efficient Cu(I)-catalyzed synthesis of 3-aroylindoles has been achieved from o-alkynylated N,N-dimethylamines via a sp^3 C–H bond activation α to the nitrogen atom followed by an intramolecular nucleophilic attack with the alkyne using an aqueous solution of tert-butyl hydroperoxide (TBHP) as the oxidant. In this tandem catalytic synthesis of 3-aroylindoles both C–C and C–O bonds are installed at the expense of two sp^3 C–H bond cleavages.*

CHAPTER II A

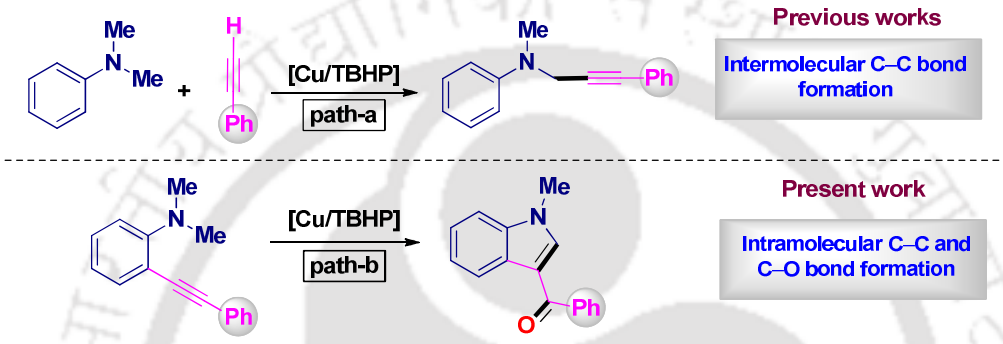
II.A. A Copper Catalyzed Synthesis of 3-Aroylindoles via a sp^3 C–H Bond Activation Followed by C–C and C–O Bond Formation

II.A.1. Introduction

C–H Bond functionalization processes have provided a great impetus to modern organic synthesis. Such functionalizations have led to the possibility of molecular diversities through the constructions of either C–C or C–X (X = hetero atoms) bonds via the cleavage of ubiquitous C–H bonds.[1] The two strategies usually followed are directing group assisted C–H bond functionalization[2] and the cross dehydrogenative coupling (CDC).[3] However, in recent times, the cross dehydrogenative coupling (CDC) strategy has had an upsurge because it is step and atom economic. The CDC approach has mostly been applied towards C–C bond forming reactions which are important in creating several significant building blocks.

Tertiary amines possessing alkyl groups are useful precursors for the sp^3 C–H bond functionalizations α to the nitrogen atom.[3b,3d,3e,3h,4] These functionalizations in most cases have been stimulated by various transition metal salts in combination with organic peroxides through a single electron transfer process.[4] However a review of the literature reveal that these functionalizations occurred via an intermolecular attack of various C, N or O nucleophiles at the iminium ion generated *in situ*. Following these reports, we reasoned that if the nucleophile attacks intramolecularly, they could be useful towards the synthesis of nitrogeneous heterocycles. *N,N*-Dialkylamines are known to undergo intermolecular cross dehydrogenative coupling (CDC) with terminal alkynes under Cu catalyzed condition producing propargylic amines through nucleophilic attack at the iminium ion generated from *N,N*-dialkylamines (path-a, Scheme II.A.1.1).[5] If the same alkynyl moiety is anchored at the *ortho* position of the tertiary amine, upon treatment to similar condition it may attack intramolecularly onto the iminium ion generated *in situ* leading to either a

five membered ring or a six membered ring. A trial reaction pursued to attain the intramolecular coupling of *o*-alknylated-*N*,*N*-dimethyl amine in the presence of a copper catalyst and a radical initiator resulted in the formation of 3-aroylindole via an intramolecular attack of the alkynyl carbon onto the iminium carbon and simultaneous oxidation of the other alkynyl carbon atom to a carbonyl functionality (path-b, Scheme II.A.1.1).



Scheme II.A.1.1. *Copper catalyzed oxidative coupling of tertiary amines*

II.A.2. Strategies for the synthesis of 3-aroylindoles

Among various nitrogenous heterocyclic scaffolds, the indolyl moiety, particularly the 3-acylindole has immense importance because of its relevance in natural products and pharmaceutical entities.[6] Many compounds having 3-acylindole as the core unit are reported to exhibit biological activities such as antidiabetic, anti-inflammatory, anticancer, inhibitor of HIV-1 integrase etc.[7] Apart from their bioactive nature they also serve as useful precursors to various other indole based compounds through easy functional group transformations of its carbonyl group.[8]

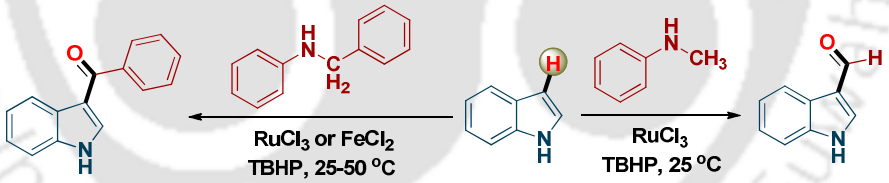
A myriad of applications of 3-aroylindoles led to the development of various protocols for their synthesis. Traditional routes to 3-acylindoles include Friedel–Crafts acylations,[9] Vilsmeier–Haack acylations,[10] and the reactions of indole salts with acyl chlorides.[11] Friedel-Crafts acylations require stoichiometric metal salts as Lewis acid promoters and strict exclusion of moisture. Use of stoichiometric amount of Lewis acid makes the

procedure environmentally unfriendly owing to the production of large quantities of salt waste. Vilsmeier-Haack acylations use equivalent amount of hazardous $POCl_3$, and suffer from lack of the amides used as carbonyl sources. The reactions of indole salts with acyl chlorides cannot tolerate the functional group sensitive to strong nucleophiles because Grignard reagents are used in these reactions. These limitations associated with the traditional methods led to the development of various transition metal catalyzed approaches for their synthesis most of which are based on C–H activation strategy. Transition metal catalyzed methodologies can be broadly categorized in two parts: (i) coupling of preformed indoles with different aroylating sources and (ii) synthesis from non-indole starting materials.

(i) Coupling of preformed indoles with aroylating sources

(a) Aniline as aroyl source

Su group developed a convenient and general method for formylation and aroylation of free (N–H) indoles via Ru- or Fe-catalyzed oxidative coupling of indoles with aniline derivatives (Scheme II.A.2.1).[12a] Formylation of indoles was also reported using *N*-methylaniline under metal free conditions.[12b]

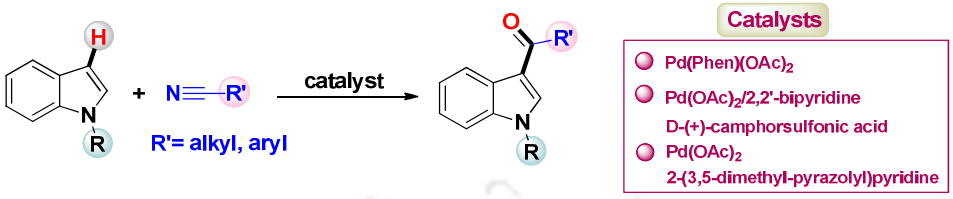


Scheme II.A.2.1. *Synthesis of 3-aroylindoles using N-benzylanilines as aroyl surrogate*

(b) Nitrile as an aroyl source

Nitriles under Pd catalyzed condition form ketimine intermediates through carbopalladation which on subsequent hydrolysis produces aryl ketones. This strategy project nitriles to be a promising aroyl source under Pd catalyzed condition and this methodology has attracted much attention from the Larock group,[13] the Lu group,[14] and others in recent years.[15] Song group developed a highly selective and operationally simple approach to 3-acylindoles following the aforementioned strategy which is applicable to both *N*-protected and unprotected indoles.[16a] Two similar Pd-catalyzed protocols have been

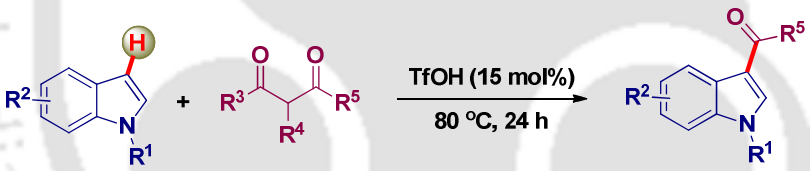
reported by Wang group and Sarkar group independently using appropriate ligands and additives (Scheme II.A.2.2).[16b,c]



Scheme II.A.2.2. *Synthesis of 3-aroylindoles using nitriles as aroyl surrogate*

(c) 1,3-Diketone as aroyl source

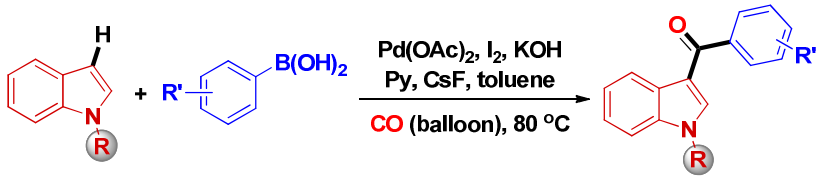
Li and co-workers demonstrated a novel solvent free triflic acid catalyzed synthesis of 3-acylindoles using 1,3-diones as acylating reagents. The reaction advances via C–C bond cleavage of 1,3-diketone accompanied by heterocyclic C–H bond functionalization to form new C–C bonds and is a greener and cheaper alternative route to 3-acylindoles (Scheme II.A.2.3).[17]



Scheme II.A.2.3. *Acid catalyzed C3-aroylation of indoles with 1,3-diones*

(d) Carbonylative coupling of indoles

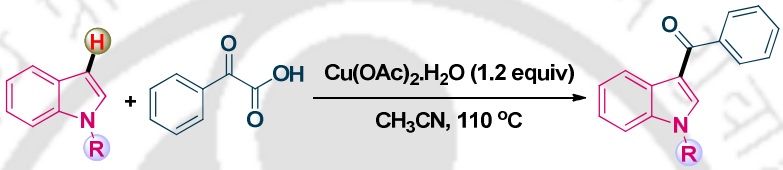
Guan group has recently developed a facile and efficient Pd-catalyzed carbonylation of indoles with CO and aromatic boronic acids for the synthesis of indol-3-yl aryl ketones. The reaction tolerates a wide range of functional groups and provided 3-aroyl indoles in high yields under mild conditions (Scheme II.A.2.4).[18]



Scheme II.A.2.4. *Synthesis of 3-aroylindoles from arylboronic acids*

(e) α-Oxoacid as aroyl source

α-Oxoacids are susceptible to undergo decarboxylation under oxidative conditions for which they are employed as aroyl sources in various transition metal catalyzed ketone synthesis. Wang *et al* reported a Cu-promoted decarboxylative direct C(3)–H acylation of *N*-substituted indoles with α-oxocarboxylic acids (Scheme II.A.2.5).[19a] Two analogous decarboxylative C3-acylation methodologies of free (N–H) indoles with α-oxocarboxylic acids were described by Zhang group and Wang group under Cu/Ag_2CO_3 and Pd catalyzed conditions respectively.[19b,c]

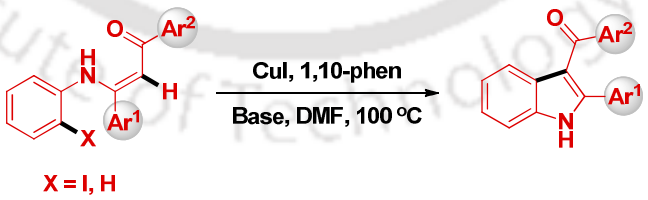


Scheme II.A.2.5. *Synthesis of 3-aroylindoles from α-oxoacids*

(ii) From non-indole starting materials

(a) From *N*-aryl enaminones

Cacchi group reported an efficient copper-catalyzed approach for the construction of multi-substituted 3-aroylindoles utilizing readily available *N*-aryl enaminone as the starting material (Scheme II.A.2.6).[20a] An analogous Cu-catalyzed C–C bond forming reaction leading to 3-aroylindoles was developed by the same group starting from *N*-(2-iodoaryl)-enaminones.[20b]

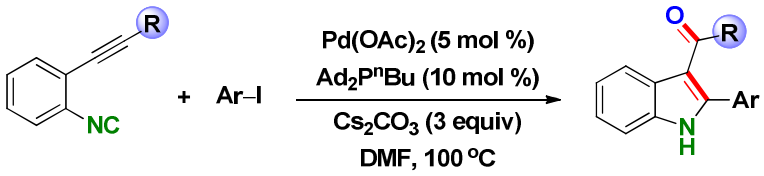


Scheme II.A.2.6. *Synthesis of 3-aroylindoles from N-aryl enaminones*

(b) From *o*-alkynylated isocyanides and aryl halide

A palladium-catalyzed protocol for the synthesis of 3-acyl-2-arylindole derivatives has been developed by Takemoto *et al* via a Pd mediated isocyanide insertion followed by

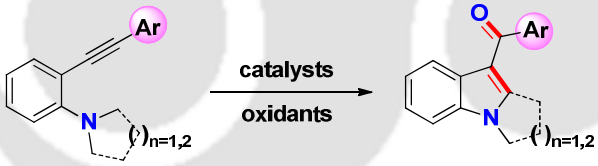
oxypalladation of alkyne.[21] Imidoylpalladium generated by isocyanide insertion is thought to be a key intermediate in this reaction (Scheme II.A.2.7).



Scheme II.A.2.7. *Synthesis of 3-aroylindoles from o-alkynylisocyanides and aryl iodides*

(c) From *o*-alkynylated-*N*,*N*-dialkylamines:

o-Alkynylated-*N*,*N*-dialkylamines has been realized to be a promising starting material for the synthesis of 3-aroylindoles through the sp^3 C–H functionalization of amines α to nitrogen atom under oxidative conditions. A Pd–Cu co-catalyzed oxidative intramolecular Mannich type reaction for the formation of 3-acylindoles has been reported by Liang group using *o*-alkynylated-*N*,*N*-dialkylamines in which *tert*-butyl hydroperoxide serve as an oxidant.[22a] Zhou *et al* developed a photocatalytic pathway for their synthesis by adopting the same strategy (Scheme II.A.2.8).[22b]

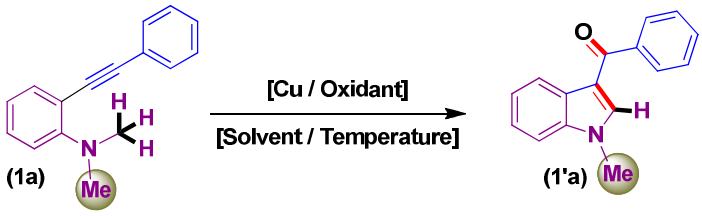


Scheme II.A.2.8. *Synthesis of 3-aroylindoles from o-alkynyl-N,N-dialkylamines*

II.A.3. Present work

The strategies leading to 3-aroylindoles based on intra-molecular coupling strategy from non-indole core staring materials are relatively less compared to indole based methodologies. Here, we have developed a Cu(I) catalyzed elegant protocol for the direct synthesis of 3-aroylindoles that proceeds via the sp^3 C–H bond functionalization α to the nitrogen atom of an *o*-alkynylated amine with concomitant formation of C–C and C–O bonds.

Table II.A.3.1. *Screening of reaction conditions*[a,b]



Entry	Catalyst (mol %)	Solvent	Oxidant (equiv)	Temp (^{o}C)	Yield (%)[b]
1	CuBr (10)	Toluene	TBHP[c] (1)	80	45
2	CuBr (10)	Toluene	TBHP[d] (1)	80	55
3	CuBr (10)	Toluene	TBHP[d] (2)	80	62
4	CuBr (10)	Toluene	TBHP[d] (3)	80	70
5	$CuBr_2$ (10)	Toluene	TBHP[d] (3)	80	58
6	CuCl (10)	Toluene	TBHP[d] (3)	80	55
7	CuI (10)	Toluene	TBHP[d] (3)	80	68
8	$Cu(OAc)_2$ (10)	Toluene	TBHP[d] (3)	80	40
9	$CuCl_2$ (10)	Toluene	TBHP[d] (3)	80	25
10	CuBr (5)	Toluene	TBHP[d] (3)	80	52
11	**CuBr (10)**	**DMSO**	**TBHP[d] (3)**	**80**	**77**
12	CuBr (10)	*o*–xylene	TBHP[d] (3)	80	66
13	CuBr (10)	dioxane	TBHP[d] (3)	80	62
14	CuBr (10)	DMF	TBHP (3)	80	25
15	CuBr (10)	THF	TBHP[d] (3)	80	10
16	CuBr (10)	DMSO	TBHP[d] (3)	100	60
17	CuBr (10)	DMSO	TBHP[d] (3)	60	43
18	Nil	DMSO	TBHP[d] (3)	80	0
19	CuBr (10)	DMSO	Nil	80	0
20	$Pd(OAc)_2$ (10)	DMSO	TBHP[d] (3)	80	35
21	$CoCl_2$ (10)	DMSO	TBHP[d] (3)	80	50
22	$FeCl_3$ (10)	DMSO	TBHP[d] (3)	80	45

[a]Reaction conditions: *o*-alkynyl-*N*,*N*-dimethylamine (**1a**), (0.25 mmol), time 2 h. [b]Isolated yield. [c]Decane solution (5–6 M). [d]70% aqueous solution.

Optimization of reaction conditions. To check the feasibility of the intended intramolecular coupling of *o*-alkynylated-*N*,*N*-dimethyl amines an initial reaction was carried out by treating (**1a**) with CuBr (10 mol %) as the catalyst and TBHP (5-6 M in decane) (1 equiv) as the oxidant in toluene solvent at 80 ^{o}C, which yielded 3-aroylindole (**1′a**) in 45% isolated yield (entry 1, Table II.A.3.1). Interestingly, the use of an aqueous TBHP (70% wt in water) instead of TBHP in decane, gave a superior yield of 55% (entry 2, Table II.A.3.1). Further, increasing the amount of TBHP to 2 equiv and 3 equiv improved the yield to 62% and 70% respectively (entries 3–4, Table II.A.3.1). Copper(I)

bromide was found to be superior to the other Cu (I and II) salts such as CuCl, CuI, $Cu(OAc)_2$, $CuCl_2$ and $CuBr_2$ employed (entries 5–9, Table II.A.3.1). Decreasing the catalyst loading to 5 mol %, significantly lowered the product yield (52%) (entry 10, Table II.A.3.1). Further, when the reaction was carried out in DMSO solvent instead of toluene, an improved yield of 77% was obtained (entry 11, Table II.A.3.1). The reaction in other solvents such as *o*-xylene, 1,4-dioxane, DMF and THF did not give any satisfactory yields compared to DMSO (entries 12–15, Table II.A.3.1). Both increase (100 ^oC) and decrease (60 ^oC) in the reaction temperature had an adverse effect on the product yields (entries 16–17, Table II.A.3.1). The control experiments carried out with either the copper salt or TBHP alone did not give any trace of product (entries 18–19, Table II.A.3.1). The use of other catalyst such as $Pd(OAc)_2$, $CoCl_2$ and $FeCl_3$ in combination with aq TBHP gave inferior yields compared to CuBr (entries 20–22, Table Table II.A.3.1). Thus, CuBr (10 mol %), aq. TBHP (70%) (3 equiv) at 80 ^oC in DMSO solvent was found to be the most suitable condition for this transformation and all other reactions were carried out adopting this condition.

Substrate scope for 3-aroylindoles. The scope of this unique intramolecular strategy was next explored towards the synthesis of various 3-aroylated indoles from their respective *o*-alkynylated *N*,*N*-dimethylamines under the optimized reaction conditions. As shown in Scheme II.A.3.1, a variety of 2-alkynyl-*N*,*N*-dimethyl anilines could be transformed to their corresponding 3-aroylindoles. Initially, the effects of various substituents on the aryl ring (R^2) were examined. Irrespective of the nature of the substituents such as *p*-Me (**1b**), *p*-^{t}Bu (**1c**), and *p*-NO_2 (**1d**) all provided their corresponding 3-aroylindoles (**1′b**), (**1′c**), and (**1′d**) with yields ranging from 73–80% (Scheme II.A.3.1). The structure of the 3-aroylindole (**1′b**) has been unequivocally confirmed by X-ray crystallography (Figure II.A.3.1).

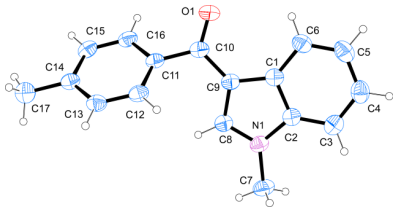
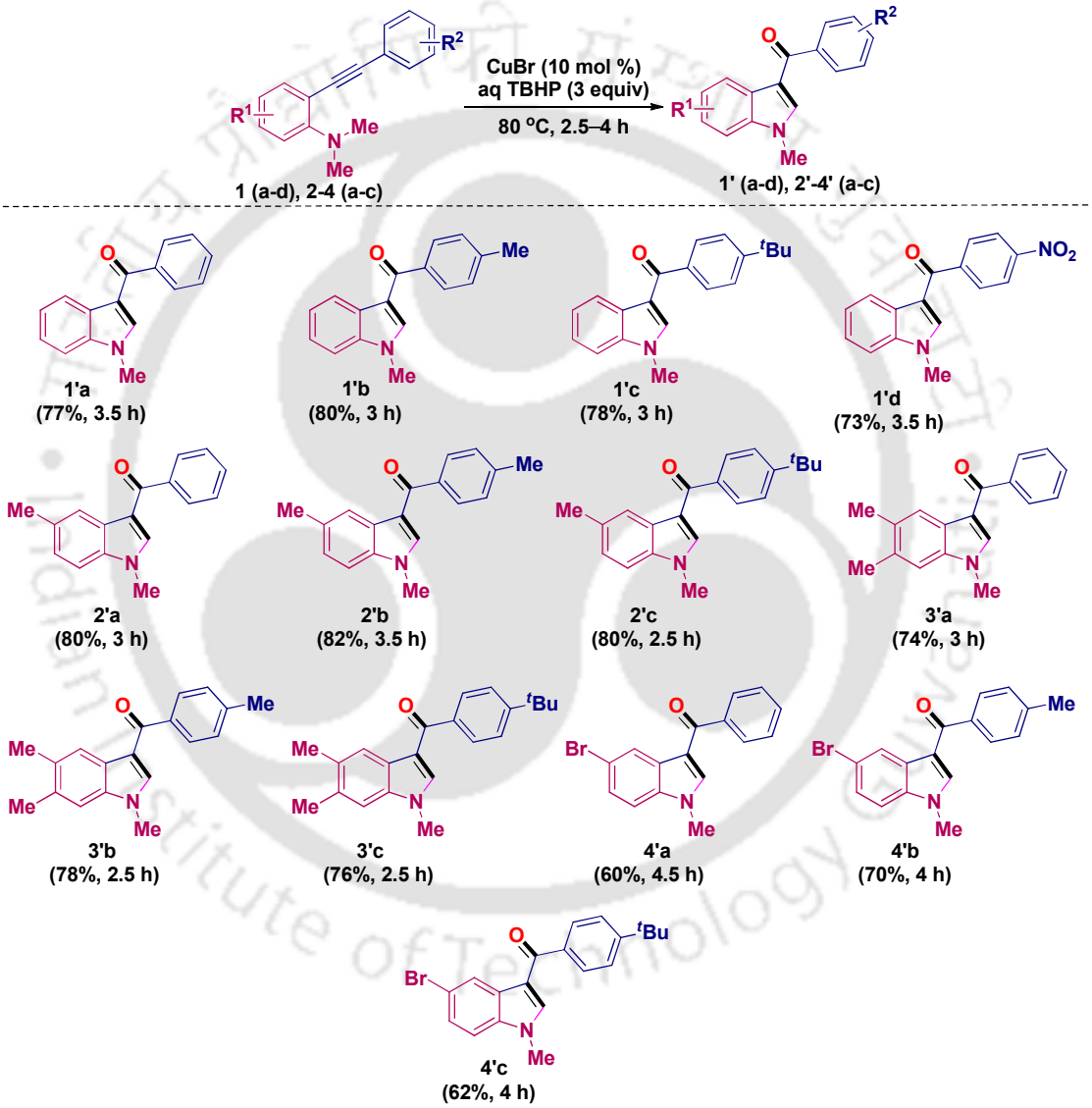


Figure II.A.3.1. *ORTEP view of* ***(1′b)***

When the *N*,*N*-dimethyl substituted aryl ring (R^1) of 2-alkynyl-*N*,*N*-dimethyl aniline is substituted with an electron donating group such as *p*-Me and the other aryl moiety (R^2) without a substituent (**2a**) and with substituents such as *p*-Me (**2b**) and *p*-^{t}Bu (**2c**) all yielded their 3-aroylated products (**2′a**), (**2′b**) and (**2′c**) respectively in excellent yields.

Scheme II.A.3.1. *Substrate scope for 3-aroylindoles*[a,b]

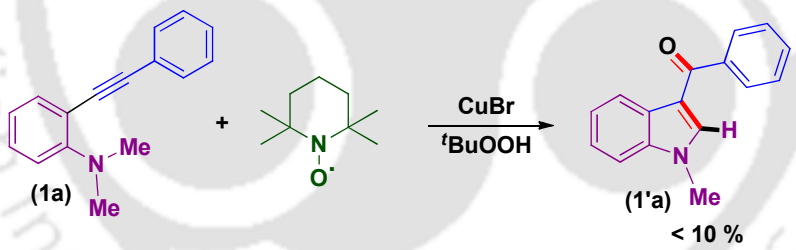


[a]Reaction conditions: *o*-alkynyl-*N*,*N*-dimethylamines **1** (**a-d**), **2-4** (**a-c**) (0.5 mmol), CuBr (0.05 mmol), 70% aqueous TBHP (1.5 mmol) in DMSO (2 mL) at 80 °C. [b]Isolated yield.

Similarly, when the *N*,*N*-dimethyl substituted aryl ring (R^1) of 2-alkynyl-*N*,*N*-dimethyl aniline is substituted with 3,4-dimethyl group and the other aryl moiety (R^2) without a

substituent (**3a**) and with substituents such as *p*-Me (**3b**) and *p*-^{t}Bu (**3c**) all gave their expected aroylated products (**3′a**), (**3′b**) and (**3′c**) respectively but in a slightly lesser yields (Scheme II.A.3.1). However, a significant drop in the yields were observed for substrates possessing a moderately electron withdrawing group such as *p*-Br as has been demonstrated with substrates (**4a**), (**4b**) and (**4c**) all giving their expected products (**4′a**), (**4′b**) and (**4′c**) in the yields ranging from 60–70% as shown in Scheme II.A.3.1.

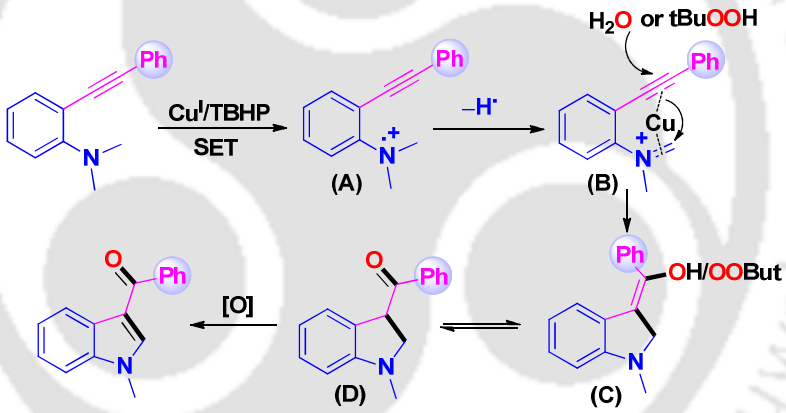
Mechanistic studies. To investigate the nature of the mechanism, when a standard reaction was carried out in the presence of radical scavenger TEMPO (3 equiv), the reaction gave many other side products and only a trace of the desired product (<10%), indicating the possibility a radical mechanism (Scheme II.A.3.2). As a further support to the radical path of the mechanism, a reaction was carried out with CuBr alone without the use of aq TBHP. The reaction failed to give any traces of the desired product and the starting material was recovered completely. These control experiments suggest that Cu(I) alone is not sufficient to form the iminium cation and the radical initiator TBHP is essential for this transformation.



Scheme II.A.3.2. *Reaction in presence of radical scavenger TEMPO*

Based on literature reports,[4,23] observations of the control reactions and yields of the products obtained from substituted substrates, a probable mechanism is proposed for this transformation as depicted in Scheme II.A.3.3. Copper salt in combination with peroxide serve as a single electron oxidant.[22a] This active oxidant accepts an electron from the nitrogen atom forming an aminyl radical cation species (**A**) (Scheme II.A.3.3). Abstraction of a proton radical α to the nitrogen atom gives an iminium intermediate (**B**). The intramolecular attack of the alkynyl group onto the iminium carbon in the intermediate (**B**)

results in C–C bond formation with concurrent formation of C–O bond by the attack of either water or TBHP onto the alkynyl moiety to give intermediate (**C**). Ketonization of the intermediate (**C**) provides 3-aroylindoline (**D**) which undergoes further oxidation to give 3-aroylindole (**1′a**) (Scheme II.A.3.3). Although Liang *et al* have proposed the nucleophilic attack of TBHP to the alkyne intermediate (**B**) but in our case the attack of water as the nucleophile cannot be completely ruled out since the reaction proceeds better with aqueous TBHP. The proposed mechanism (Scheme II.A.3.3) is supported from the fact that substrates containing electron withdrawing group such as bromo (**4a**, **4b** and **4c**) in the *N*,*N*–dimethyl substituted aryl ring (R^1) gave poor yields because of the instability of the aminyl radical cation (**A**). Further, when both the rings are substituted with electron donating groups as in the case of **2a**, **2b** and **2c** the product yields were found to be better which is partly because of the enhanced stability of the intermediate (**B**).



Scheme II.A.3.3. *Plausible mechanism for Cu(I) catalyzed formation of 3-aroylindoles*

In conclusion, we have developed an elegant method for the synthesis of 3-aroylindoles through a copper catalyzed oxidative process involving *o*-alkynylated *N*,*N*-dimethylamines in the presence of aqueous TBHP as the oxidant. This protocol simultaneously installs C–C and C–O bonds through an intramolecular oxidative path in the construction of 3-aroylindoles. This method uses inexpensive Cu catalyst without the requirement of any co-catalyst and additives and proceeds at a relatively lower temperature. Besides being a one pot and atom economical process, judging the practical utility makes the present method the best alternative synthesis for 3-aroylindoles.

II.A.4. Experimental section

II.A.4.1. General information. All the reagents were commercial grade and used without purification. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60−120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. The starting materials 2-alkynyl-*N*,*N*-dimethylamines were synthesized by adopting reported procedures.[24]

II.A.4.2. General procedure for the synthesis of (1-Methyl-1*H*-indol-3-yl)(phenyl)methanone (1′a): To a solution of *N*,*N*-dimethyl-2-(phenylethynyl) aniline (**1a**) (110.65 mg, 0.5 mmol) in DMSO (2 mL) was added CuBr (7.17 mg, 0.05 mmol), followed by TBHP 70% wt in water (215 µl, 1.5 mmol) and the resultant mixture was put into a preheated oil bath (80 ^{o}C) for 3.5 h. The resultant reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (9:1 hexane / ethyl acetate to give (1-methyl-1*H*-indol-3-yl)(phenyl)methanone (**1′a**) (90.58 mg, 77% yield).

The identity and purity of the product were confirmed by spectroscopic analysis. The same procedure was also followed for the synthesis of other 3-aroylindoles.

II.A.4.3. Crystallographic description of (1-Methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (1′b): $C_{17}H_{15}NO$, crystal dimensions 0.41 x 0.35 x 0.26 mm, M_r = 249.30, Monoclinic, space group P21/n, a =11.1536(9), b = 7.2700(6), c = 16.7473(14) Å, α = 90 °, β = 101.080(3) °, γ = 90 °, V = 1332.67(19) Å^3, Z = 4, ρ_{calcd} = 1.242 mg/m^3, μ = 0.077 mm^{-1}, F(000) = 528.0, reflection collected / unique = 3304 / 1785, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0493, wR_2 = 0.1117, R indices (all data): R_1 = 0.0872, wR_2 = 0.1201, goodness of fit = 0.997. CCDC reference number 917715.

II.A.5. References

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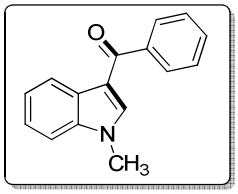
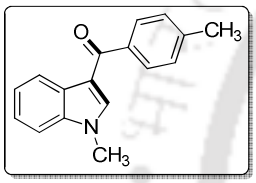
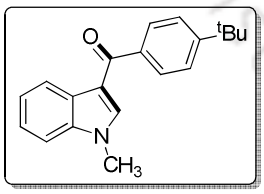
II.A.6. Spectral data



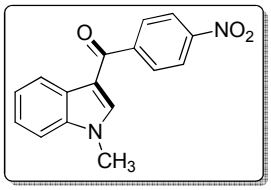
1-Methyl-1*H*-indol-3-yl)(phenyl)methanone (1′a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 7.31–7.38 (m, 3H), 7.44–7.53 (m, 3H), 7.78–7.81 (m, 2H), 8.40–8.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 33.7, 109.8, 115.8, 122.9, 123.8, 127.4, 128.5, 128.9, 131.3,132.4, 137.7, 138.1, 141.1, 191.1; IR (KBr): 2923, 2851, 1621, 1575, 1524, 1465, 1368, 1233, 1155, 1124, 1070, 872, 746, 716 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{13}NO$ (MH^+) 236.1070; found 236.1065.



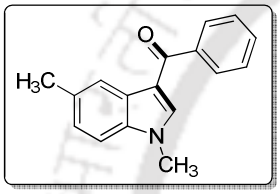
(1-Methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (1′b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 3.83 (s, 3H), 7.27 (d, J = 7.6 Hz, 2H), 7.31–7.35 (m, 3H), 7.52 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 8.38–8.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 33.7, 109.8, 115.9, 122.8, 122.9, 123.7, 127.4, 129.0, 129.1, 137.7, 137.8, 138.3, 141.7, 190.9; IR (KBr): 2925, 2851, 1731, 1619, 1523, 1465, 1369, 1230, 1123, 1070, 875, 771, 776 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}NO$ (MH^+) 250.1226; found 250.1224.



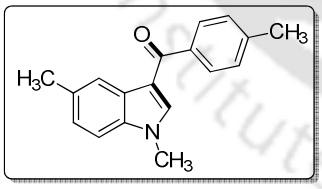
(4-*Tert*-butylphenyl)(1-methyl-1*H*-indol-3-yl)methanone (1′c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 9H), 3.84 (s, 3H), 7.32–7.36 (m, 3H), 7.48 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 8.41–8.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 29.9, 31.4, 35.1, 109.8, 115.9, 122.8, 123.0, 123.8, 125.4, 127.5, 128.9, 137.7, 138.0, 138.3, 154.8, 190.9; IR (KBr): 2963, 1689, 1612, 1524, 1464, 1367, 1268, 1235, 1185, 1125, 881, 745, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{21}NO$ (MH^+) 292.1696; found 292.1699.



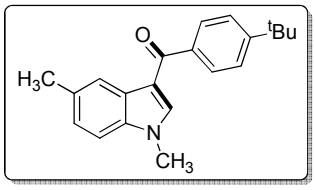
(1-Methyl-1*H*-indol-3-yl) (4-nitrophenyl) methanone (1′d): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.87 (s, 3H), 7.35–7.40 (m, 3H), 7.49 (s, 1H), 7.91–7.93 (m, 2H), 8.30–8.32 (m, 2H), 8.38–8.40 (m, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 33.7, 109.9, 115.3, 122.6, 123.3, 123.6, 124.2, 126.8, 126.9, 127.6, 128.5, 129.4, 137.7, 138.1, 146.3, 149.1, 188.4; IR (KBr): 2915, 2853, 1734, 1592, 1381, 1244, 1172, 1076, 982, 832, 742, 716 cm^{-1}; Anal. calcd for $C_{16}H_{12}N_2O_3$: C 68.56, H 4.32, N 9.99; found C 68.52, H 4.25, N 9.90.



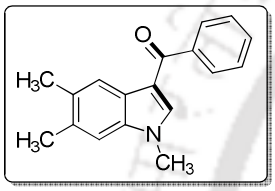
(1,5-Dimethyl-1*H*-indol-3-yl)(phenyl)methanone (2′a): ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.51 (s, 3H), 3.81 (s, 3H), 7.18 (d, J = 8.4 Hz, 1H), 7.24–7.27 (m, 1H), 7.45–7.49 (m, 3H), 7.53 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 8.257–8.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 21.7, 33.6, 109.4, 115.2, 122.5, 125.3, 127.5, 128.3, 128.7, 131.0, 132.5, 136.1, 138.2, 141.2, 190.9; IR (KBr): 2924, 2852, 1627, 1522, 1361, 1268, 1237, 1117, 741 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}NO$ (MH^+) 250.1226; found 250.1221.



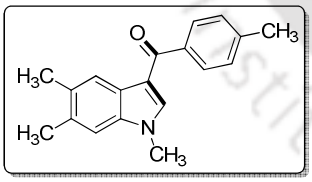
(1,5-Dimethyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (2′b): ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 2.44 (s, 3H), 2.51 (s, 3H), 3.81 (s, 3H), 7.17 (d, J = 8.4 Hz, 1H), 7.26–7.29 (m, 3H), 7.48 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 8.24–8.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.5, 21.6, 33.5, 109.4, 115.2, 122.4, 125.1, 127.6, 128.9, 129.0, 132.3, 136.0, 137.9, 138.3, 141.5, 190.8; IR (KBr): 3027, 2921, 1618, 1523, 1484, 1458, 1237, 1141, 1119, 1064, 845, 787, 738 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO$ (MH^+) 264.1383; found 264.1381.



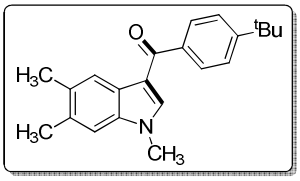
(4-*Tert*-butylphenyl)(1,5-Dimethyl-1*H*-indol-3-yl) methanone (2′c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 9H), 2.51(s, 3H), 3.81 (s, 3H), 7.17 (d, J = 9.6 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.48–7.51 (m, 3H), 7.76 (d, J = 8.4 Hz, 2H), 8.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 31.4, 33.6, 35.1, 109.4, 115.3, 122.6, 125.2, 125.3, 127.6, 128.7, 132.4, 136.1, 138.1, 138.4, 154.5, 190.8; IR (KBr): 2961, 2852, 1621, 1524, 1461, 1363, 1237, 1190, 1144, 1106, 1064, 848, 831, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{23}NO$ (MH^+) 306.1852; found 306.1862.



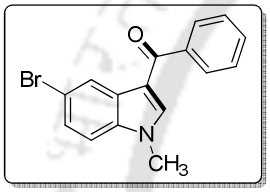
(1,5,6-Trimethy-l*H*-indol-3-yl)(phenyl)methanone (3′a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 2.40 (s, 3H), 3.78 (s, 3H), 7.12 (s, 1H), 7.40 (s, 1H), 7.43–7.51 (m, 3H), 7.77–7.79 (m, 2H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3, 20.8, 33.6, 110.1, 115.3, 122.9, 125.6, 128.3, 128.8, 131.0, 131.9, 133.0, 136.7, 137.6, 141.3, 191.0; IR (KBr): 2928, 2851, 1624, 1523, 1465, 1363, 1262, 1240, 1119, 1064, 982, 842, 739, 716 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO$ (MH^+) 264.1383; found 264.1376.



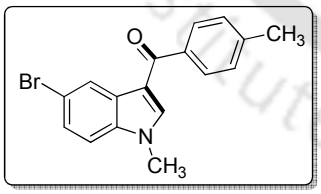
(1,5,6-Trimethy-l*H*-indol-3-yl)(*p*-tolyl)methanone (3′b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 3.80 (s, 3H), 7.14 (s, 1H), 7.27 (d, J = 10 Hz, 2H), 7.43 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.2, 20.7, 21.6, 33.5, 110.0, 115.2, 122.7, 125.5, 128.8, 128.9, 131.6, 132.8, 136.5, 137.3, 138.4, 141.3, 190.7; IR (KBr): 2923, 2857, 1618, 1525, 1470, 1363, 1256, 1240, 1177, 1116, 982, 836, 768 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{19}NO$ (MH^+) 278.1539; found 278.1530.



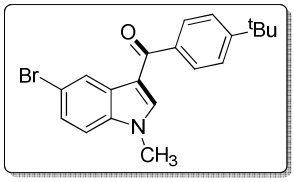
(4-*Tert*-butylphenyl)(1,5,6-trimethyl-1*H*-indol-3-yl) methanone (3′c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 9H), 2.41 (s, 3H), 2.42 (s, 3H), 3.79 (s, 3H), 7.14 (s, 1H), 7.45 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.2, 20.8, 31.3, 33.5, 34.9, 110.0, 115.1, 122.8, 125.2, 125.5, 128.6, 131.6, 132.8, 136.5, 137.4, 138.4, 154.4, 190.7; IR (KBr): 2962, 2847, 1620, 1519, 1462, 1356, 1252, 1235, 1170, 1112, 978, 834, 765 cm^{-1}; Anal. calcd for $C_{22}H_{25}NO$: C 82.72, H 7.89, N 4.38; found C 82.65, H 7.95, N 4.30.



(5-Bromo-1-methyl-1*H*-indol-3-yl)(phenyl)methanone (4′a): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.45–7.50 (m, 3H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 8.58 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 33.9, 111.3, 115.2, 116.6, 125.4, 126.8, 128.5, 128.7, 128.9, 131.5, 136.4, 138.6, 140.7, 190.6; IR (KBr): 3055, 2928, 1612, 1575, 1527, 1470, 1446, 1365, 1235, 1190, 1079, 1023, 803, 717, 699, 670 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}BrNO$ (MH^+) 314.0175; found 314.0179.



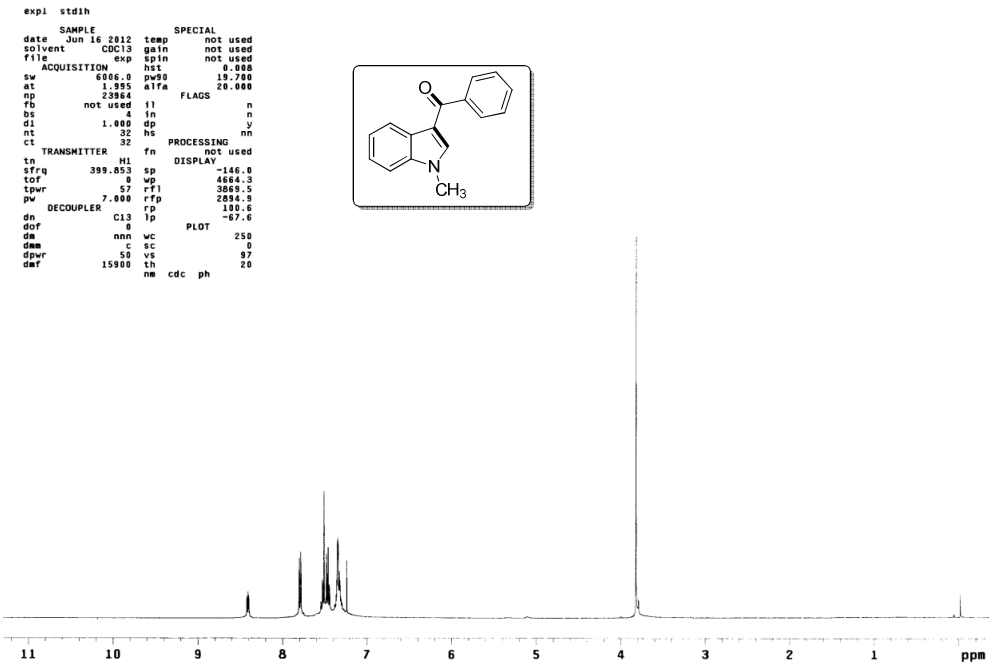
(5-Bromo-1-methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (4′b): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 3.81 (s, 3H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.40–7.43 (m, 1H), 7.50 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 8.57 (d, *J* = 1.6Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.6, 33.8, 111.2, 115.1, 116.3, 125.3, 126.5, 128.8, 129.1, 129.4, 136.2, 137.8, 138.3, 141.9, 190.3; IR (KBr): 2924, 2857, 1616, 1602, 1523, 1470, 1446, 1365, 1235, 1179, 1079, 1034, 883, 806, 763, 740 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}BrNO$ (MH^+) 328.0332; found 328.0338.



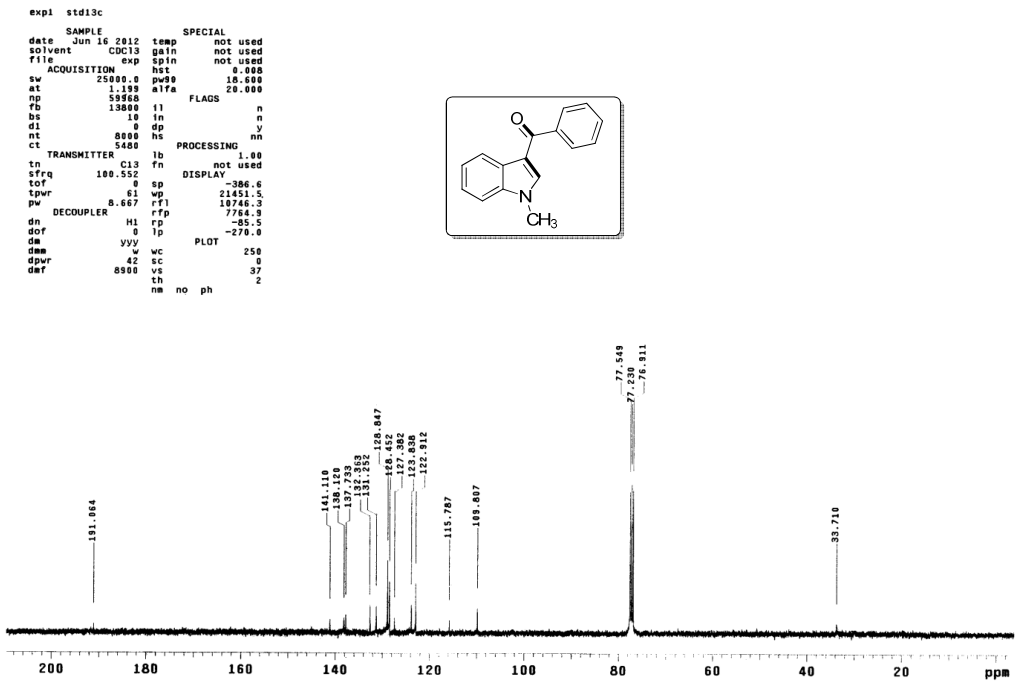
(4-*Tert*-butylphenyl)(5-bromo-1-methyl-1*H*-indol-3-yl) methanone (4′c): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 9H), 3.81 (s, 3H), 7.21 (d, J = 8.4 Hz, 1H), 7.40–7.43 (m, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.53 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 8.59 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.4, 33.9, 35.2, 111.2, 115.3, 116.6, 125.5, 126.7, 128.6, 128.8, 130.3, 133.8, 136.4, 137.9, 138.5, 155.1, 190.5; IR (KBr): 2961, 2853, 1626, 1524, 1463, 1364, 1267, 1235, 1105, 886, 798, 741, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{20}BrNO$ (MH^+) 370.0801; found 370.0809.

II.A.7. Spectra

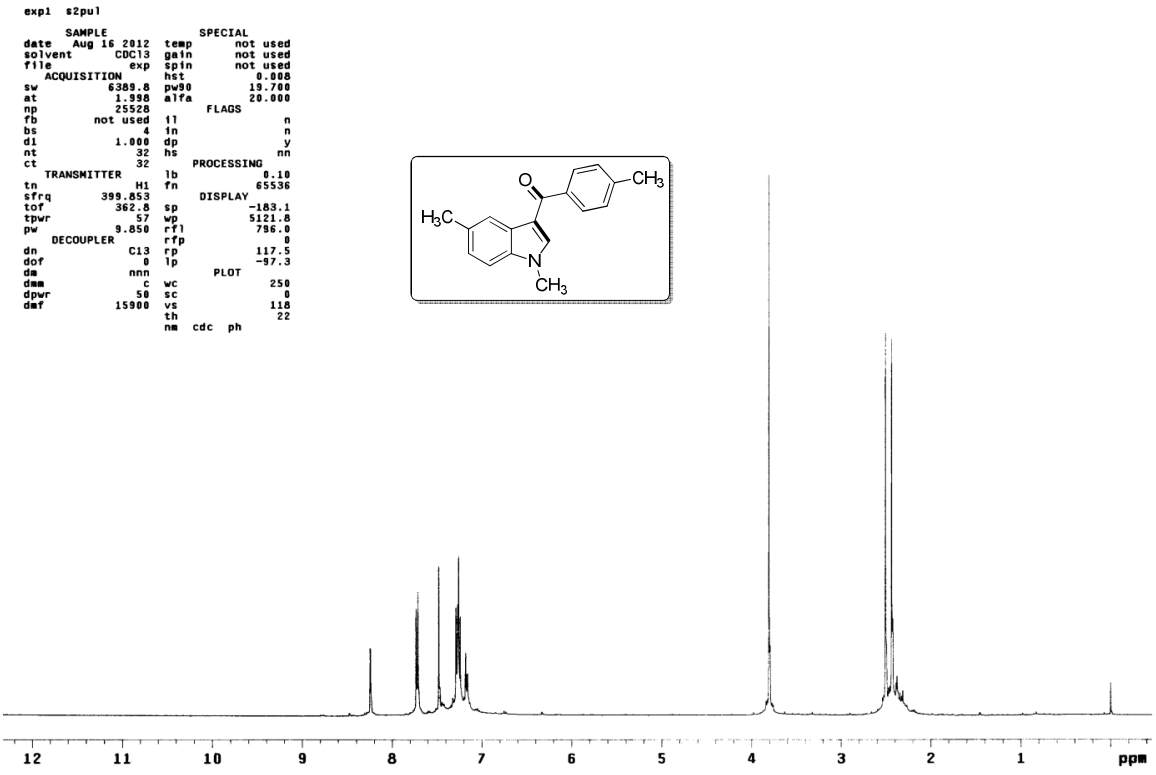
(1-Methyl-1*H*-indol-3-yl)(phenyl)methanone (1′a): ^{1}H NMR (400 MHz, $CDCl_3$)



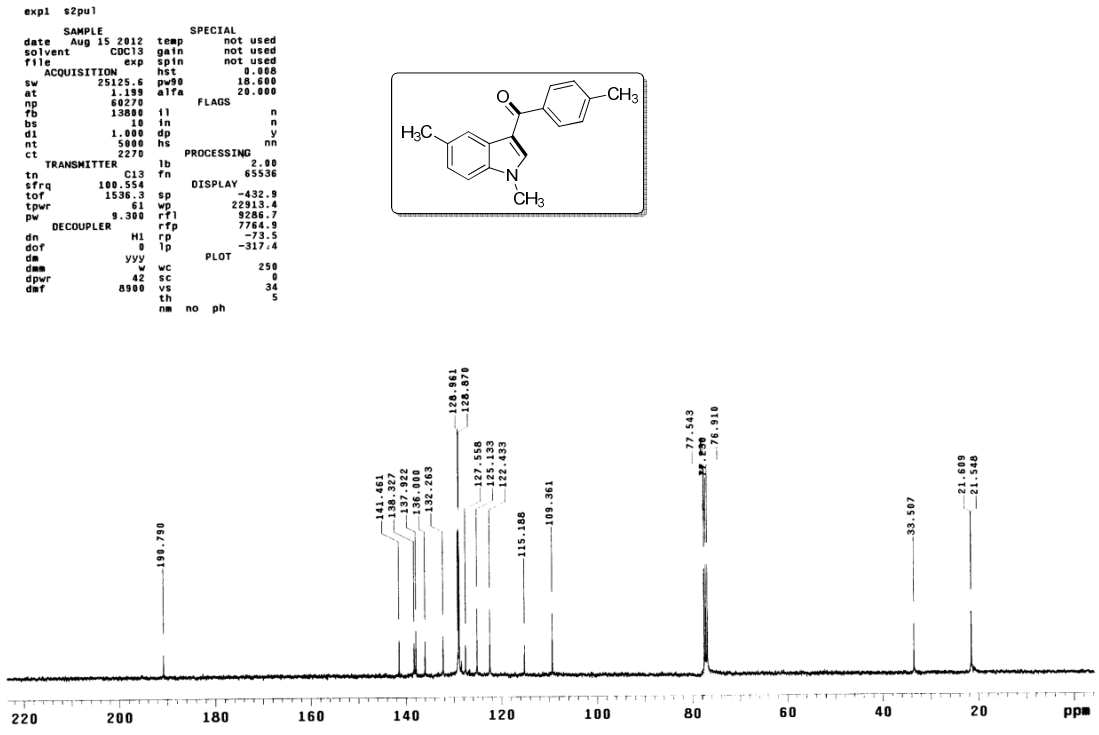
(1-Methyl-1*H*-indol-3-yl)(phenyl)methanone (1′a): ^{13}C NMR (100 MHz, $CDCl_3$)



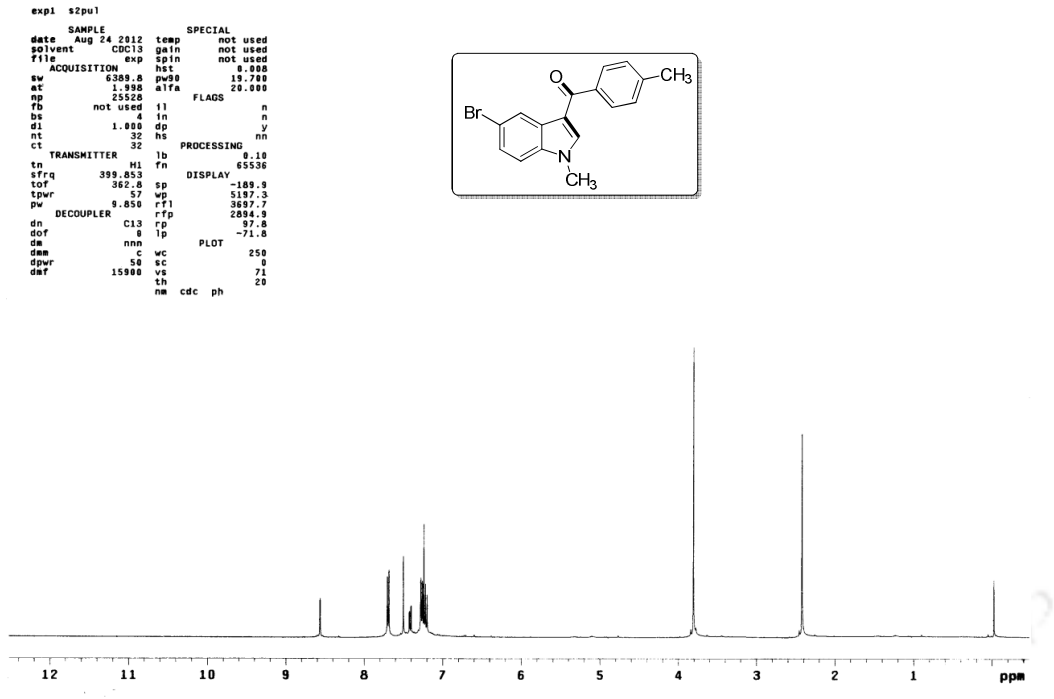
(1,5-Dimethyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (2′b): ^{1}H NMR (400 MHz, $CDCl_3$)



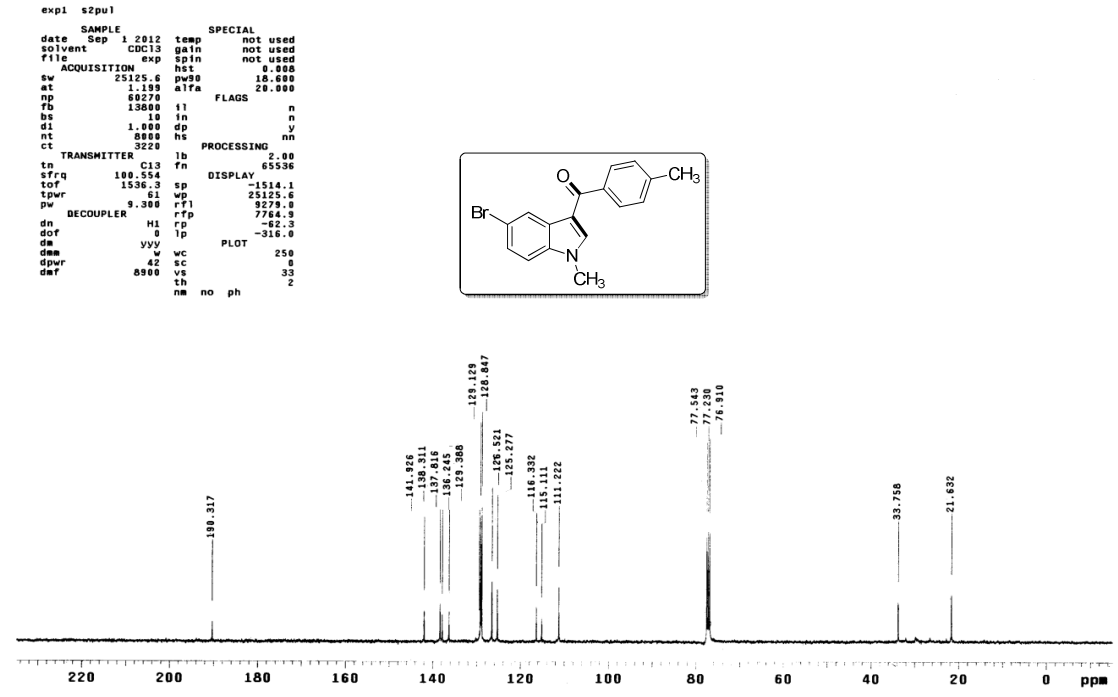
(1,5-Dimethyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (2′b): ^{13}C NMR (100 MHz, $CDCl_3$)



(5-Bromo-1-methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (4′b): ^{1}H NMR (400 MHz, $CDCl_3$)

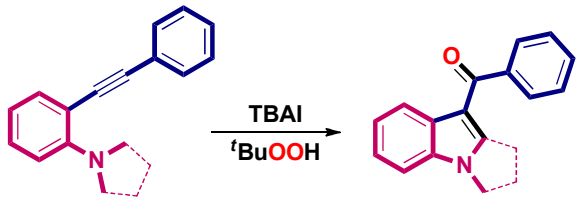


(5-Bromo-1-methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (4′b): ^{13}C NMR (100 MHz, $CDCl_3$)



Chapter II B

A Metal Free Domino Synthesis of 3-Aroylindoles via Two sp^3 C–H Activation



- two C–H bond cleavage
- intramolecular C–C and bond C–O bond formation
- inexpensive, environmentally benign catalyst

Abstract: *A metal free synthesis of 3-aroylindoles involving two sp^3 C–H activation has been achieved starting from o-alkynyl-N,N-dialkylamines using catalyst TBAI and oxidant TBHP.*

CHAPTER II B

II.B. A Metal Free Domino Synthesis of 3-Aroylindoles via Two sp^3 C–H Activation

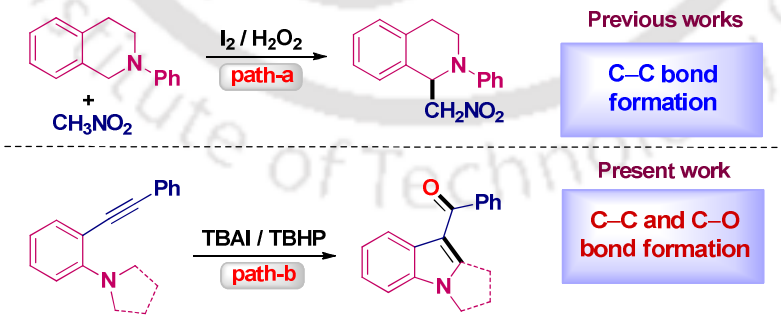
II.B.1. Introduction

In modern organic synthesis, C–H functionalization strategies have brought about atom and step-economy by streamlining various arduous synthetic processes.[1] However, in this forum, much of the attention has been focused on functionalizations of sp and sp^2 C–H bonds.[2] In contrast high pK_a's (>30–35) as well as large bond dissociation energies (>104 kcal/mole) of various sp^3 C–H bonds make their selective activation a formidable challenge. The solutions to these challenges, led to the evolution of various sp^3 C–H activation strategies, one of them being the cross dehydrogenative coupling (CDC). In most cases, functionalizations of sp^3 C–H bonds α to heteroatoms are attained by CDC strategy using transition metal catalysts.[3] The heteroatoms present in precursors are invariably *N*- or *O*- that generate iminium or oxonium ion intermediates *in situ*.[3,4] These reactive intermediates are formed by a single electron transfer from the heteroatoms to the metal centre that forms a radical cation. This is then followed by a loss of hydrogen radical from the adjacent carbon generating either an iminium or an oxonium ion which is amenable for the construction of C–C or C–heteroatom bonds via an inter- or an intramolecular nucleophilic attack. For precursors like tertiary amines, a variety of transition metal catalysts in combination with organic peroxides are conducive for the formation of reactive intermediates.[3,4a-c] Noteworthy, an intramolecular nucleophilic attack at these iminium ions can generate various nitrogen containing heterocycles.[4a,5]

Although transition metal catalyzed processes are advantageous but are invariably associated with high cost and difficulties in removal of residual metals from the final product which limits their utility in pharmaceutical industries. Further, for a copper catalyzed reaction often a doubt arises whether it is the real catalyst or a co-catalyst for the

traces of Pd present in commercial grade Cu salts. There are instances where the metal impurities present even in traces in commercial grade salts act as the actual catalyst.[6]

To overcome some of the disadvantages associated with metal catalysts recently photo-catalysts[7] and molecular iodine or iodide compounds[8] in combination with an external oxidant has been employed for the functionalizations of various C–H bonds. These greener catalytic approaches has also been employed for the functionalizations of sp^3 C–H bonds of *N,N*-dialkylamines.[7e-j,8a-e] The use of designer ligands and at times metals are unavoidable in any photo-catalytic process, thereby making the overall method expensive when applied to large scale reactions. Thus, molecular iodine or iodide catalyzed strategies are more advantageous. A molecular iodine-catalyzed cross-dehydrogenative coupling (CDC) reaction between tetrahydroisoquinoline and a carbon nucleophile such as nitromethane using hydrogen peroxide as the terminal oxidant was reported by Itoh and co-workers (path-a, Scheme II.B.1.1).[8c] The same has been achieved with TBAI as the catalyst although the yield of the products were low. Following this, we envisaged that instead of using metal catalysts, an intra-molecular domino transformation of 2-alkynyl-*N,N*-dialkylamines to 3-aroyl indoles could be realized under a metal free condition (path-b, Scheme II.B.1.1). It may be mentioned here that this intra-molecular oxidative Mannich concept i.e. the generation of iminium ion *in situ* followed by an intra-molecular nucleophilic addition to it, has been rarely realized in literature under metal free conditions.[9]



Scheme II.B.1.1. *Metal free sp3 C–H bond functionalization of tertiary amines*

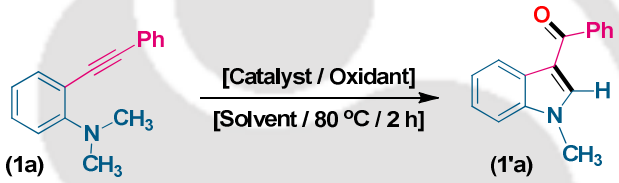
II.B.2. Strategies for the synthesis of 3-aroylindoles

Strategies are same as described in chapter II.A, section II.A.2.

II.B.3. Present work

Although a number of transition metal catalyzed inter- and intra-molecular routes to 3-aroylindoles have been developed, a metal free method involving sp^3 C–H bond functionalization is not reported so far. Herein, we have reported a metal free protocol for the synthesis of 3-aroylindoles involving sp^3 C–H bond functionalization of *o*-alkynyl-*N,N*-dialkylamines with simultaneous C–C and C–O bond formation.

Table II.B.3.1. *Screening of reaction conditions*[a,b]



Entry	Catalyst (mol%)	Oxidant (equiv)	Solvent	Yield %[b]
1	TBAI (20)	TBHP[c] (3)	DMSO	52
2	TBAI (20)	TBHP[c] (4)	DMSO	59
3	**TBAI (20)**	**TBHP[c] (5)**	**DMSO**	**74**
4	KI (20)	TBHP[c] (5)	DMSO	64
5	I_2 (20)	TBHP[c] (5)	DMSO	49
6	TBAB (20))	TBHP[c] (5)	DMSO	58
7	TBAI (20)	TBHP[d] (5)	DMSO	69
8	TBAI (20)	DTBP (5)	DMSO	<5
9	TBAI (20)	H_2O_2[e] (5)	DMSO	22
10	TBAI (20)	TBHP[c] (5)	DMF	62
11	TBAI (20)	TBHP[c] (5)	Toluene	46
12	TBAI (20)	TBHP[c] (5)	1,4-Dioxane	54
13	TBAI (20)	TBHP[c] (5)	DCE	37
14	TBAI (15)	TBHP[c] (5)	DMSO	56
15	TBAI (20)	Nil	DMSO	0
16	Nil	TBHP[c] (5)	TBHP[c] (5)	0

[a]Reaction conditions: *N,N*-dimethyl-2-(phenylethynyl) aniline (**1a**) (0.25 mmol), time 2 h, temperature 80 °C. [b]Isolated yield. [c]70% aqueous solution. [d]Decane solution (5–6 M). [e]50% aqueous solution.

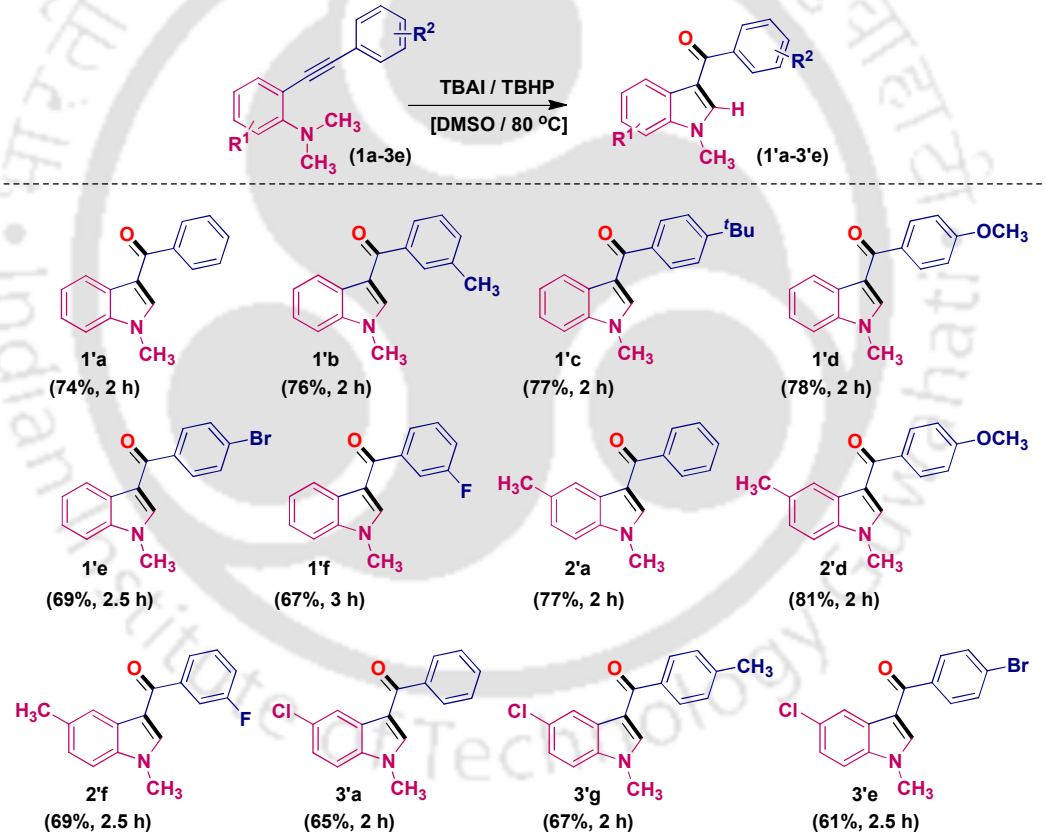
Optimization of reaction conditions. To check whether the envisaged metal free intramolecular coupling strategy works or not an initial reaction was commenced by

treating *N*,*N*-dimethyl-2-(2-phenylethynyl)benzenamine (**1a**) (1 equiv) with TBAI (20 mol%) and 70% aq. TBHP (3 equiv) at 80 ^{o}C. To our delight aroylindole (**1′a**) was isolated in 52% yield (entry 1, Table II.B.3.1). Encouraged by this metal-free cascade synthesis of 3-aroylindole, other reaction parameters such as catalysts, oxidants and solvents were varied to attain best possible yield. Increasing the amount of TBHP from 3 equiv. to 4 and 5 equiv. resulted in an improved yield of 59% and 74% respectively (entries 2–3, Table II.B.3.1). Instead of TBAI, the use of other halogen analogues such as KI, I_2, and tetrabutylammonium bromide (TBAB) were found to be less effective (entries 4–6, Table II.B.3.1). A decane solution of TBHP (5–6 M) (5 equiv) in lieu of its aqueous solution (70%) gave a comparable yield of 69%, however, other peroxides such as di-*tert*-butyl peroxide (DTBP) or aq. H_2O_2 (50%) failed to give satisfactory yield of the product (entries 7–9, Table II.B.3.1). Further, the use of other solvents such as DMF (62%), toluene (46%), 1,4-dioxane (54%), DCE (37%) were found to be less productive than DMSO (entries 10–13, Table II.B.3.1). The yield dropped to 56% when the catalyst loading was reduced to 15 mol% (entry 14, Table II.B.3.1). Neither TBAI nor TBHP alone were capable of triggering this domino transformation, suggesting an essential requirement of their combination (entries 15–16, Table II.B.3.1). Thus, catalyst TBAI (20 mol%), aqueous TBHP (5 equiv) in DMSO at 80 ^{o}C were found to be the ideal conditions for this transformation (entry 3, Table II.B.3.1).

Substrate scope for 3-aroylindoles. After achieving the optimized conditions, this methodology was applied to different *o*-alkynyl-*N*,*N*-dialkylamines to afford their respective 3-aroylindoles. As shown in Scheme II.B.3.1 and II.B.3.2, a series of aroylindoles could be obtained in moderate to excellent yields from their aminoalkyne precursors. At first, effects of substituents on the aryl ring of the alkynes were examined. The electron-donating substituents *viz*. *m*-Me (**1b**), *p*-^{t}Bu (**1c**) and *p*-OMe (**1d**) when present in the aryl ring of the alkyne had a positive impact on the products (**1′b–1′d**) yields (in the range of 76–78%) (Scheme II.B.3.1). However, when the aryl ring contains electron-withdrawing groups such as *p*-Br (**1e**) and *m*-F (**1f**), the reactions proceeded sluggishly to afford their corresponding aroylindoles (**1′e**) and (**1′f**) in slightly lesser yields (in the range 67–69%) (Scheme II.B.3.1). When the amine bearing aryl ring of the *o*-

alkynylamines are substituted with weakly electron-donating groups such as *p*-Me and the other aryl ring being unsubtituted (**2a**) or substituted with an electron-withdrawing group (**2f**), good yields of the products were achieved. An excellent yield of 81% was obtained when both the rings contain electron-donating groups as found for substrate (**2′d**) (Scheme II.B.3.1). A moderately electron-withdrawing group such as *p*-Cl present in the aryl ring bearing the tertiary amine group resulted in comparatively lesser yields regardless of the nature of the substituents on the other ring as exemplified for (**3′a**), (**3′g**) and (**3′e**) (Scheme II.B.3.1).

Scheme II.B.3.1. *Substrate scope for 3-aroylindoles*[a,b]



[a]Reaction conditions: *o*-alkynyl-*N*,*N*-dialkylamine (**1a-3e**) (0.25 mmol), TBAI (0.05 mmol), TBHP (1.25 mmol) DMSO (1 mL) at 80 °C. [b]Isolated yields.

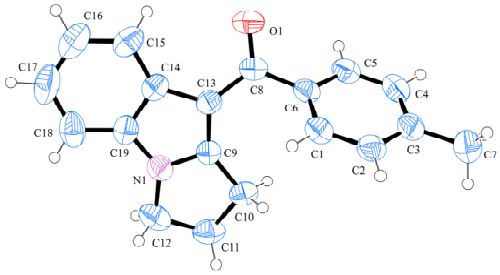
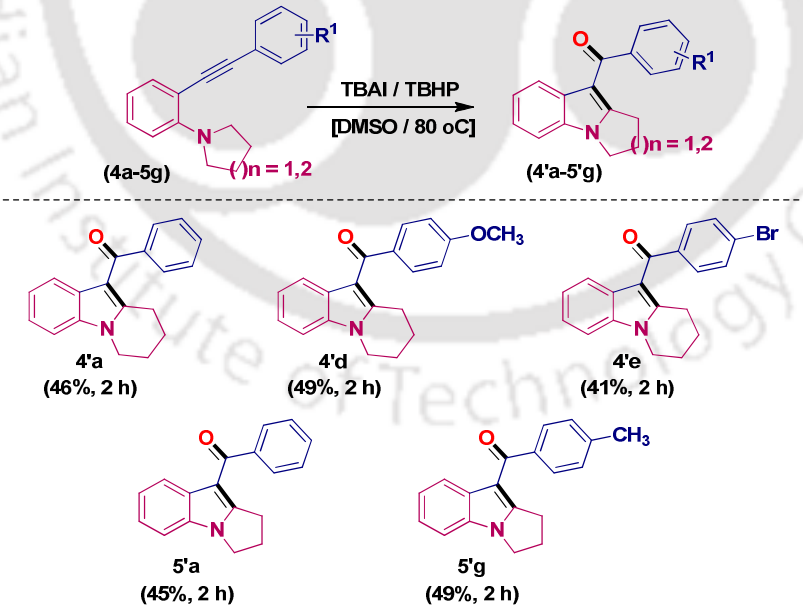


***Figure II.B.3.1**. ORTEP view of (**5′g**)*

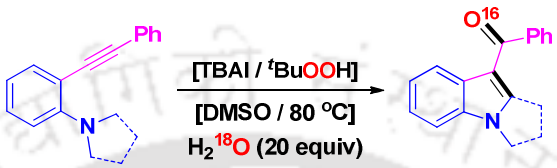
The scope of this methodology was next extended to annular tertiary amines. The *o*-alkynyl amines precursors with a six- or a five-membered ring provided their corresponding aroylindoles under the optimized reaction condition as has been demonstrated by the synthesis of (**4′a**), (**4′d**), (**4′e**) (**5′a**) and (**5′g**) (Scheme II.B.3.2). However, the yields were moderate which may be due to the ring strain associated with the resulting fused aroylindoles. The structure of the aroylindole (**5′g**) was confirmed by X-ray crystallography (Figure II.B.3.1).

***Scheme II.B.3.2.** Substrate scope for 3-aroylindoles*[a,b]



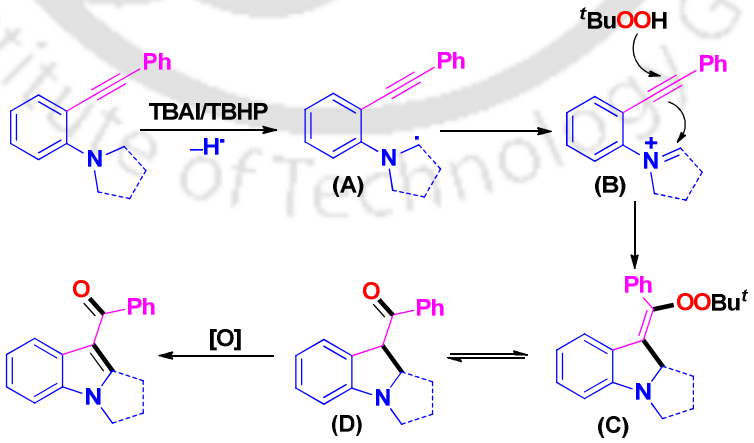
[a]Reaction conditions: *o*-alkynyl-*N*,*N*-dialkylamine (**4a-5g**) (0.25 mmol), TBAI (0.05 mmol), TBHP (1.25 mmol) DMSO (1 mL) at 80 °C. [b]Isolated yields.

Mechanistic investigations. To find out the origin of oxygen in 3-aroylindole a reaction of substrate (**1a**) was carried out in the presence of 20 equivalent of labeled water ($H_2{}^{18}O$) under otherwise identical conditions. The reaction afforded aroylindole (**1′a**) without any ^{18}O incorporation thereby ruling out water and leaving TBHP as the only possible source of oxygen.



Scheme II.B.3.3. *Labeling experiment with ^{18}O labeled water*

Based on literature reports[12a,n,o] and experimental findings of control reaction, a plausible mechanism has been proposed for this transformation (Scheme II.B.3.4). A radical species (A) is first generated from *o*-alkynyl-*N*,*N*-dialkylamine via a hydrogen radical abstraction from the carbon atom adjacent to the nitrogen atom which then further oxidizes to produce an iminium ion intermediate (**B**). The intermediate (**B**) then undergoes annulation by an intramolecular nucleophilic attack of the alkynyl group at the iminium carbon with simultaneous attack of TBHP at the alkenyl carbon to give intermediate species (**C**).[5,6] Ketonization of (**C**) provides 3-aroylindoline (**D**) which is finally oxidized/aromatized to its 3-aroylindole (Scheme II.B.3.4).



Scheme II.B.3.4. *Proposed mechanism for TBAI catalyzed formation of 3-aroylindoles*

In conclusion, we have developed a metal free method for the synthesis of 3-aroylindoles from *o*-alkynyl-*N*,*N*-dialkylamine through a TBAI catalyzed intramolecular oxidative coupling pathway in presence of oxidant TBHP. This protocol simultaneously installs C–C and C–O bonds at the expense of two sp^3 C–H bonds. The use of inexpensive and environmentally benign catalytic system and relatively lower reaction time and temperature make the present protocol practically more applicable.

II.B.4. Experimental section

II.B.4.1. General information. All the reagents were commercial grade and used without purification. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (600 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (150 MHz). HRMS spectra were recorded using ESI mode. IR spectra were recorded in KBr or neat. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. The starting materials 2-alkynyl-*N*,*N*-dimethylamines were synthesized by adopting reported procedures.[10]

II.B.4.2. General procedure for the synthesis of (1-methyl-1*H*-indol-3-yl)(phenyl)methanone (1′a). To a solution of *N*,*N*-dimethyl-2-(phenylethynyl) aniline (**1a**) (55.28 mg, 0.25 mmol) in DMSO (1 mL) was added TBAI (18.47 mg, 0.05 mmol),

followed by TBHP 70% wt. in water (180 µl, 1.25 mmol) and the resultant mixture was put into a preheated oil bath (80 ^{o}C) for 2 h. The resultant reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (9:1 hexane / ethyl acetate to give (1-methyl-1*H*-indol-3-yl)(phenyl)methanone (**1′a**) (43.53 mg, 74% yield). The identity and purity of the product were confirmed by spectroscopic analysis. The same procedure was also followed for the synthesis of other 3-aroylindoles.

II.B.4.3. Crystallographic description of (2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)(*p*-tolyl)methanone (5′g): $C_{19}H_{17}NO$, crystal dimensions 0.41 x 0.35 x 0.28 mm, M_r = 275.34, Triclinic, space group P-1, a = 7.5607(4), b = 9.6755(6), c = 11.352(1) Å, α = 107.554(5) ^{o}, β = 102.789(5) ^{o}, γ = 103.850(4) ^{o}, V = 729.07(10) Å^3, Z = 2, ρ_{calcd} = 1.254 mg/m^3, μ = 0.077 mm^{-1}, F(000) = 292.0, reflection collected / unique = 3682 / 2529, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0487, wR_2 = 0.1733, R indices (all data): R_1 = 0.0634, wR_2 = 0.1981, goodness of fit = 0.932. CCDC reference number 1006843.

II.B.5. References

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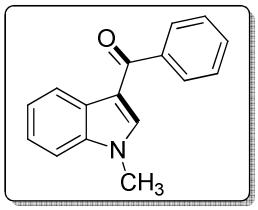
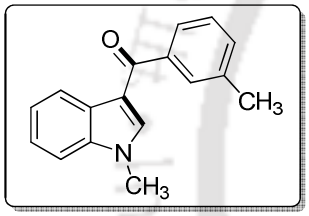
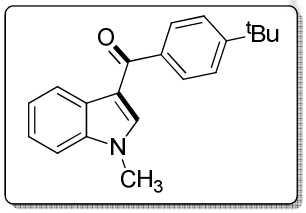
II.B.6. Spectral data



(1-Methyl-1*H*-indol-3-yl)(phenyl)methanone (1′a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.79 (s, 3H), 7.32–7.33 (m, 3H), 7.46 (t, J = 7.2 Hz, 2H), 7.48 (s, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.79 (d, J = 7.2 Hz, 2H), 8.41–8.43 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 33.7, 109.8, 115.7, 122.8, 122.9, 123.8, 127.4, 128.4, 128.8, 131.2, 137.7, 138.1, 141.1, 191.0; IR (KBr): 2923, 2851, 1621, 1575, 1524, 1465, 1368, 1233, 1155, 1124, 1070, 872, 746, 716 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{13}NO$ (MH^+) 236.1070; found 236.1077.

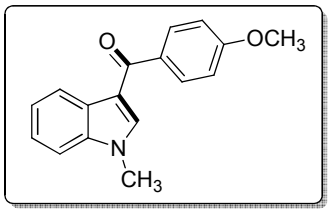


(1-Methyl-1*H*-indol-3-yl)(*m*-tolyl)methanone (1′b): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 3.83 (s, 3H), 7.32–7.36 (m, 5H), 7.51 (s, 1H), 7.57–7.59 (m, 1H), 7.61 (s, 1H), 8.40–8.41 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 33.7, 109.8, 116.0, 122.9, 123.0, 123.8, 126.1, 127.4, 128.2, 129.4, 132.0, 137.8, 138.0, 138.3, 141.2, 191.3; IR (KBr): 2950, 2924, 2857, 1617, 1587, 1521, 1465, 1367, 1268, 1241, 1202, 1120, 1070, 751 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}NO$ (MH^+) 250.1226; found 250.1232.

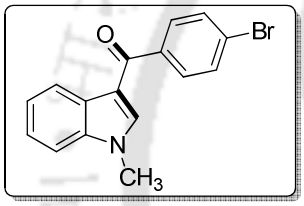


(4-(*tert*-Butyl)phenyl)(1-methyl-1*H*-indol-3-yl)methanone (1′c): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 9H), 3.82 (s, 3H), 7.32–7.35 (m, 3H), 7.48 (d, J = 8.4 Hz, 2H), 7.55 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 8.42–8.44 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 31.5, 33.7, 35.2, 109.7, 115.9, 122.8, 123.0, 123.8, 125.4, 127.5, 128.9, 137.7, 137.9, 138.4, 154.8, 190.8; IR (KBr): 2963, 1689, 1612, 1524, 1464, 1367, 1268, 1235, 1185, 1125, 881, 745, 709 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{21}NO$ (MH^+)

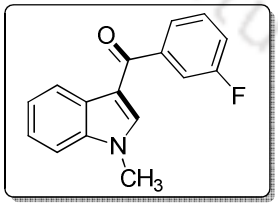
292.1696; found 292.1693.



(4-Methoxyphenyl)(1-methyl-1*H*-indol-3-yl)methanone (1′d): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.80 (s, 3H), 3.85 (s, 3H), 6.95 (d, J = 8.4 Hz, 2H), 7.29–7.34 (m, 3H), 7.50 (s, 1H), 7.81 (d, J = 9.0 Hz, 2H), 8.35–8.37 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 33.6, 55.6, 109.7, 113.7, 115.8, 122.6, 122.8, 123.6, 127.5, 131.0, 133.6, 137.3, 137.6, 162.3, 189.9; IR (KBr): 3042, 2917, 1614, 1599, 1567, 1528, 1505, 1461, 1371, 1252, 1234, 1169, 1151, 1122, 1023, 878, 845, 748 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}NO_2$ (MH^+) 266.1176; found 266.1172.

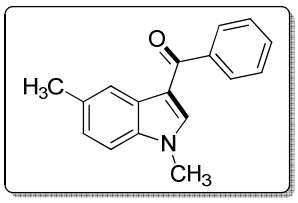


(4-Bromophenyl)(1-methyl-1*H*-indol-3-yl)methanone (1′e): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.79 (s, 3H), 7.31–7.33 (m, 3H), 7.45 (s, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 8.36–8.38 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 33.7, 109.9, 115.4, 122.7, 123.0, 123.9, 125.8, 127.2, 130.4, 131.6, 137.7, 137.9, 139.7, 189.6; IR (KBr): 3081, 2925, 1624, 1582, 1520, 1459, 1395, 1370, 1266, 1233, 1155, 1125, 1070, 1034, 1003, 877, 840, 772, 751 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}BrNO$ (MH^+) 314.0175; found 314.0184.

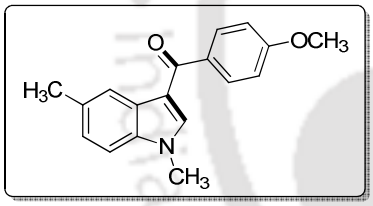


(3-Fluorophenyl)(1-methyl-1*H*-indol-3-yl)methanone (1′f): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.85 (s, 3H), 7.23–7.26 (m, 1H), 7.34–7.38 (m, 3H), 7.43–7.47 (m, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.52 (s, 1H), 7.59 (d, J = 7.2 Hz, 1H), 8.40–8.42 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 33.8, 109.9, 115.5, 115.7, 115.8, 118.1, 118.2, 122.9, 123.1, 124.1, 124.5, 127.3, 130.1, 130.2, 137.8, 138.1, 143.17, 143.21, 161.9, 163.6, 189.3; IR (KBr): 3050, 2923, 1621, 1578, 1522, 1468, 1426, 1395, 1369, 1266, 1244,

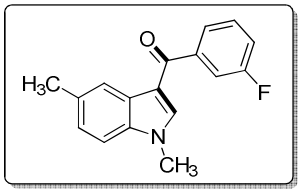
1024, 1152, 1126, 1113, 1080, 833, 828, 769, 753 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}FNO$ (MH^+) 254.0976; found 254.0980.



(1,5-Dimethyl-1*H*-indol-3-yl)(phenyl)methanone (2′a): ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.50 (s, 3H), 3.77 (s, 3H), 7.16 (d, J = 8.4 Hz, 1H), 7.23 (t, J = 6.6 Hz, 1H), 7.43–7.47 (m, 3H), 7.51 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 7.2 Hz, 2H), 8.26 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.7, 33.7, 109.4, 115.3, 122.6, 125.3, 127.6, 128.4, 128.8, 131.1, 132.6, 136.1, 138.2, 141.2, 191.0; IR (KBr): 3058, 2918, 1623, 1574, 1484, 1459, 1387, 1364, 1269, 1237, 1146, 1120, 1068, 1021, 907, 837, 795, 758, 718 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}NO$ (MH^+) 250.1226; found 250.1222.

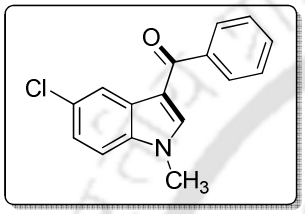


(1,5-Dimethyl-1*H*-indol-3-yl)(4-methoxyphenyl) methanone (2′d): ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.50 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 6.98 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.25–7.26 (m, 1H), 7.49 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 8.21 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.8, 33.7, 55.6, 109.4, 113.7, 115.5, 122.6, 125.3, 127.8, 131.0, 132.4, 133.9, 136.1, 137.4, 162.3, 190.0; IR (KBr): 2956, 2923, 1614, 1596, 1523, 1508, 1451, 1363, 1304, 1254, 1163, 1116, 1060, 1021, 910, 844, 775 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{17}NO_2$ (MH^+) 280.1332; found 280.1335.

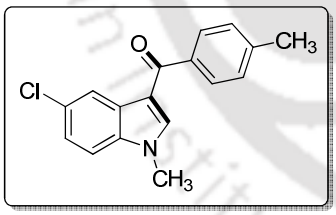


(1,5-Dimethyl-1*H*-indol-3-yl)(3-fluorophenyl)methanone (2′f): ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.52 (s, 3H), 3.82 (s, 3H),7.19 (d, J = 9.0 Hz, 1H), 7.22–7.25 (m, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.43–7.46 (m, 1H), 7.47 (s, 1H), 7.48–7.50 (m, 1H), 7.58 (d, J = 7.8 Hz, 1H), 8.25 (s, 1H);

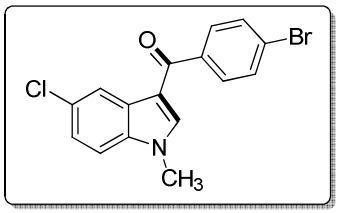
^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.7, 33.8, 109.6, 115.0, 115.6, 115.8, 118.0, 118.1, 122.6, 124.5, 125.6, 127.5, 130.09, 130.14, 132.9, 136.2, 138.2, 143.3, 143.4, 161.9, 163.6, 189.3; IR (KBr): 2922, 1624, 1581, 1523, 1482, 1452, 1428, 1364, 1269, 1244, 1206, 1149, 1116, 1065, 1032, 941, 893, 809, 792, 765, 739 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}FNO$ (MH^+) 268.1132; found 268.1137.



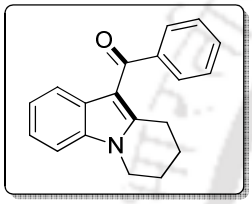
(5-Chloro-1-methyl-1*H*-indol-3-yl)(phenyl)methanone (3′a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 7.24–7.28 (m, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.51 (s, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.78 (d, J = 7.2 Hz, 2H), 8.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 33.9, 110.9, 115.3, 122.4, 124.2, 128.4, 128.5, 128.8, 128.9, 131.5, 136.1, 138.8, 140.7, 190.7; IR (KBr): 3050, 2928, 1610, 1598, 1575, 1528, 1470, 1449, 1362, 1235, 1179, 1082, 1023, 891, 812, 717, 698 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}ClNO$ (MH^+) 270.0680; found 270.0678.



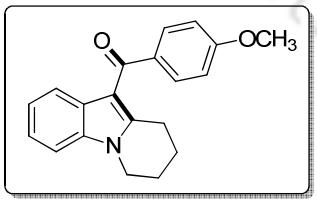
(5-Chloro-1-methyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (3′g): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 3.82 (s, 3H), 7.25–7.28 (m, 4H), 7.52 (s, 1H), 7.70 (d, J = 6.6 Hz, 2H), 8.41 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.7, 33.9, 110.8, 115.4, 122.4, 124.1, 128.4, 128.8, 128.9, 129.2, 136.0, 137.9, 138.5, 142.0, 190.4; IR (KBr): 3056, 2917, 1614, 1601, 1566, 1525, 1471, 1448, 1368, 1236, 1182, 1144, 1131, 1082, 1034, 892, 873, 838, 787, 763, 740, 702 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}ClNO$ (MH^+) 284.0837; found 284.0841.



(4-Bromophenyl)(5-chloro-1-methyl-1*H*-indol-3-yl)methanone (3′e): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.84 (s, 3H), 7.26–7.30 (m, 2H), 7.49 (s, 1H), 7.61 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 8.39 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 34.0, 110.9, 115.1, 122.4, 124.4, 126.2, 128.3, 129.2, 130.4, 131.8, 136.2, 138.5, 139.4, 189.3; IR (KBr): 3056, 2924, 1605, 1586, 1525, 1470, 1364, 1234, 1085, 1033, 1010, 892, 842, 811, 765, 741 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}BrClNO$ (MH^+) 347.9785; found 347.9782.

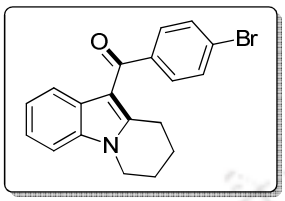


Phenyl(6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)methanone (4′a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.87–1.92 (m, 2H), 2.09–2.13 (m, 2H), 3.15(t, J = 6.6 Hz, 2H), 4.11 (t, J = 6.6 Hz, 2H), 7.07 (t, J = 6.6 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.28–7.30 (m, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.71 (d, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.4, 22.7, 25.4, 42.8, 109.2, 112.3, 121.1, 121.9, 122.1, 127.2, 128.4, 128.8, 131.2, 136.3, 142.1, 146.5, 192.6; IR (KBr): 3055, 2928, 1617, 1511, 1487, 1472, 1456, 1437, 1419, 1374, 1315, 1225, 1160, 1057, 929, 880, 740, 731 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}NO$ (MH^+) 276.1383; found 276.1385.

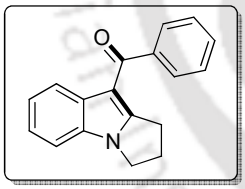


(4-Methoxyphenyl)(6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)methanone (4′d): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.87–1.91 (m, 2H), 2.09–2.13 (m, 2H), 3.16 (t, J = 6.6 Hz, 2H), 3.87 (s, 3H), 4.10 (t, J = 6.6 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 7.08 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.5, 22.8, 25.3, 42.7, 55.6, 109.2, 112.4, 113.5, 121.1, 121.7, 121.8, 127.3, 131.4, 134.4, 136.2, 145.7, 162.5,

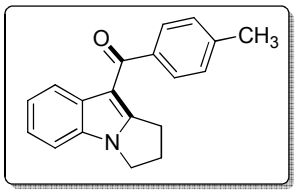
191.5; IR (KBr): 2926, 1601, 1510, 1557, 1422, 1373, 1318, 1252, 1230, 1161, 1059, 933, 928, 884, 840, 779, 746 cm^{-1}; HRMS (ESI): calcd. for $C_{20}H_{19}NO_2$ (MH^+) 306.1489; found 306.1493.



(4-Bromophenyl)(6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)methanone (4′e): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.91–1.95 (m, 2H), 2.12–2.16 (m, 2H), 3.18 (t, J = 6.6 Hz, 2H), 4.13 (t, J = 6.0 Hz, 2H), 7.10 (t, J = 7.8 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 4.2 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.60 (q, J = 8.4 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.3, 22.7, 25.5, 42.8, 109.3, 112.0, 121.0, 122.1, 122.3, 125.9, 127.0, 130.6, 131.7, 136.4, 140.8, 146.9, 191.2; IR (KBr): 2934, 1614, 1587, 1505, 1491, 1455, 1413, 1392, 1361, 1320, 1272, 1221, 1162, 1069, 1011, 929, 884, 836, 769, 746, 735 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{16}BrNO$ (MH^+) 354.0488; found 354.0485.



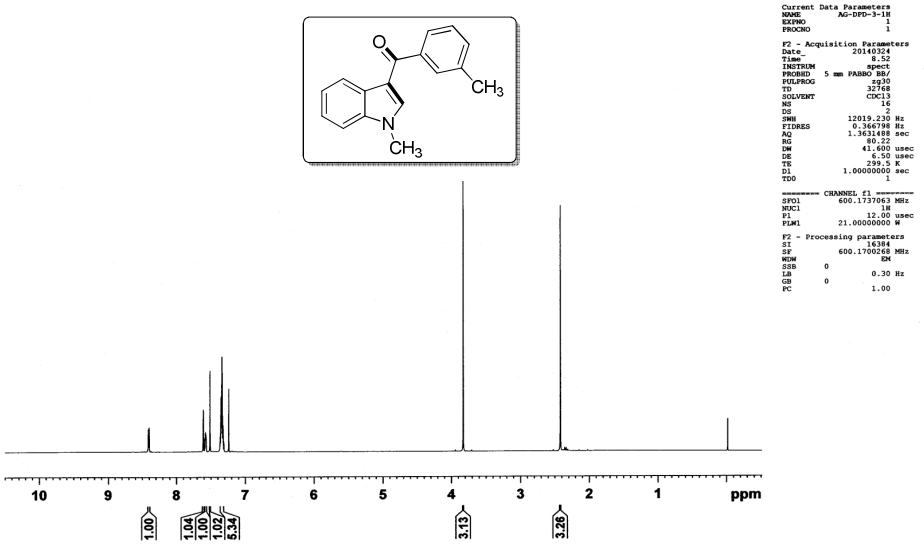
(2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)(phenyl)methanone (5′a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.56 (quin, J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 4.12 (t, J = 7.2 Hz, 2H), 7.21–7.25 (m, 2H), 7.26–7.28 (m, 1H), 7.44–7.47 (m, 2H), 7.50–7.53 (m, 1H), 7.68–7.69 (m, 2H), 8.03–8.05 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 26.9, 27.1, 44.6, 109.5, 109.9, 122.4, 122.5, 128.1, 128.3, 130.8, 131.5, 133.3, 142.0, 153.6, 191.9; IR (KBr): 3049, 2928, 1608, 1570, 1508, 1451, 1437, 1420, 1384, 1304, 1215, 1043, 1009, 960, 927, 841, 746 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}NO$ (MH^+) 262.1226; found 262.1221.



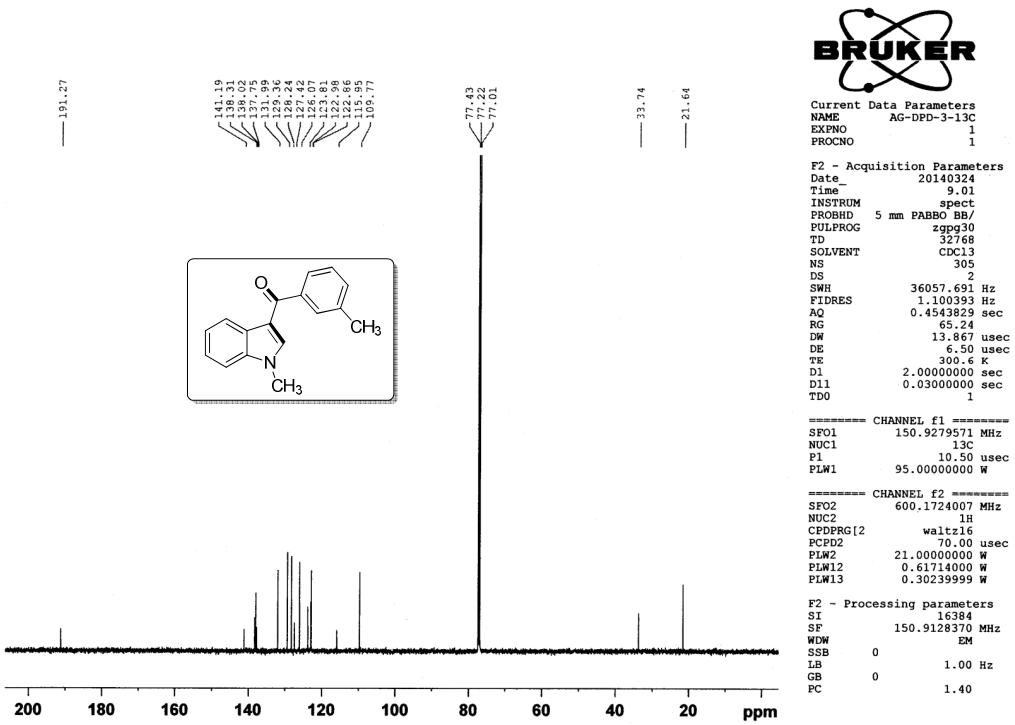
(2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)(*p*-tolyl)methanone (5′g): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 2.54 (quin, J = 7.2 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 4.10 (t, J = 7.2 Hz, 2H), 7.20–7.23 (m, 2H), 7.24–7.26 (m, 3H), 7.61 (d, J = 7.8 Hz, 2H), 8.03–8.04 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ(ppm) 21.7, 27.0, 27.2, 44.6, 109.6, 109.9, 122.2, 122.35, 122.42, 128.5, 129.0, 131.5, 133.2, 139.1, 141.3, 153.3, 191.8; IR (KBr): 3049, 2983, 1614, 1602, 1570, 1520, 1464, 1448, 1437, 1419, 1382, 1305, 1220, 1205, 1137, 1043, 1010, 962, 828, 771, 745 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}NO$ (MH^+) 276.1383; found 276.1389.

II.B.7. Spectra

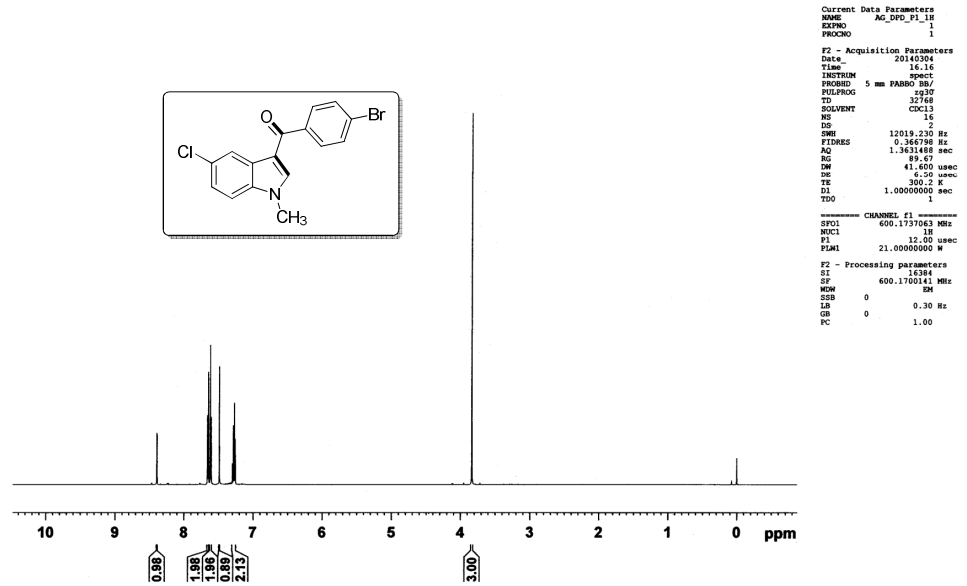
(1-Methyl-1*H*-indol-3-yl)(*m*-tolyl)methanone (1′b): ^{1}H NMR (600 MHz, $CDCl_3$)



(1-Methyl-1*H*-indol-3-yl)(*m*-tolyl)methanone (1′b): ^{13}C NMR (150 MHz, $CDCl_3$)



(4-Bromophenyl)(5-chloro-1-methyl-1*H*-indol-3-yl)methanone (3′e): ^{1}H NMR (600 MHz, $CDCl_3$)



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PROCNO 1

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

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NUC1 1H
P1 12.00 usec
PLW1 21.00000000 W

F2 - Processing parameters
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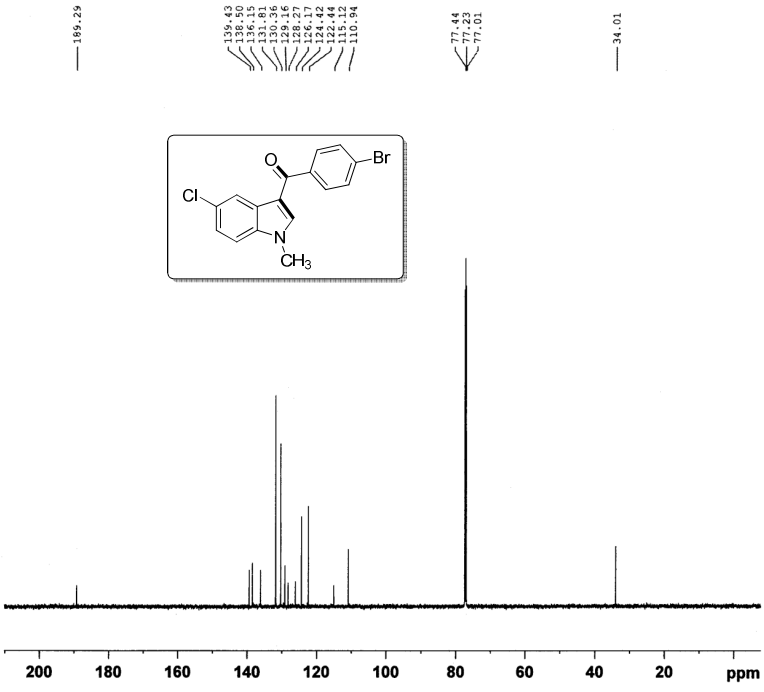
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

(4-Bromophenyl)(5-chloro-1-methyl-1*H*-indol-3-yl)methanone (3′e): ^{13}C NMR (150 MHz, $CDCl_3$)



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PROCNO 1

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FIDRES 1.100393 Hz
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RG 65.24
DW 13.867 usec
DE 6.50 usec
TE 300.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

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P1 10.50 usec
PLW1 95.00000000 W

======== CHANNEL f2 ========
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PCPD2 70.00 usec
PLW2 21.00000000 W
PLW12 0.61714000 W
PLW13 0.30239999 W

F2 - Processing parameters
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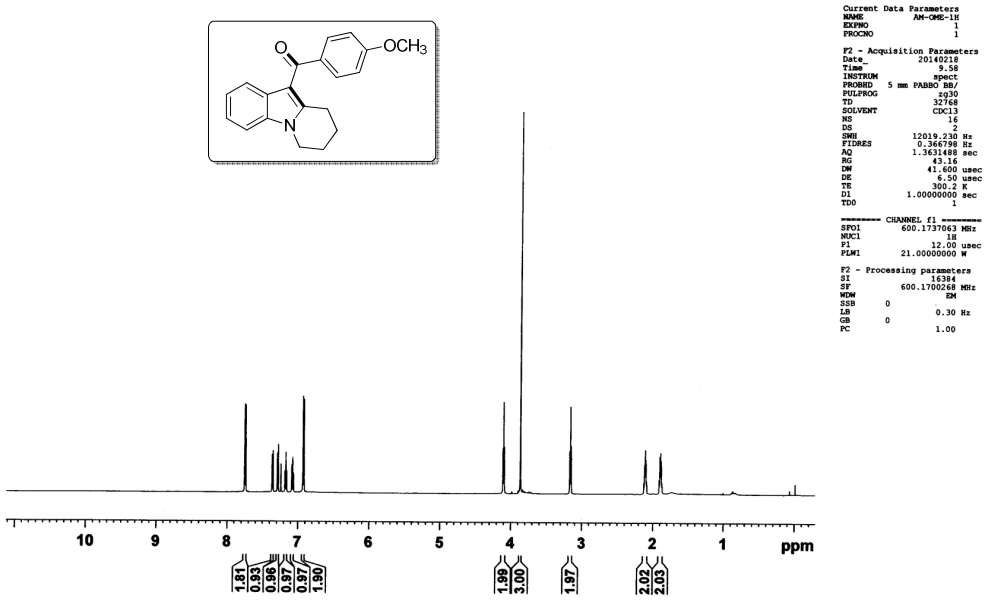
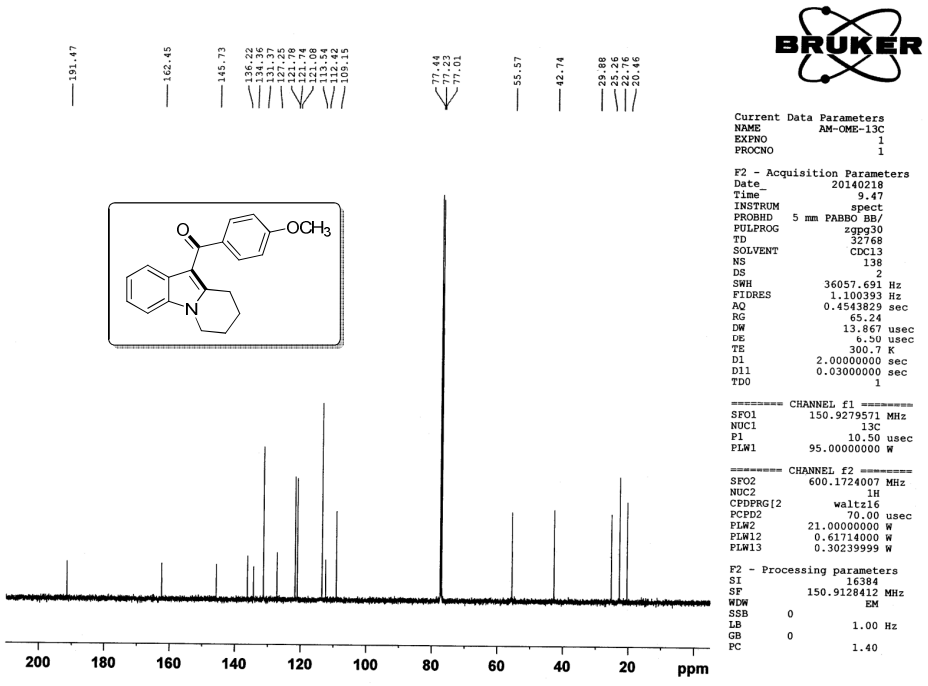
SF 150.9128369 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

(4-Methoxyphenyl)(6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)methanone (4′d): ^{1}H NMR (600 MHz, $CDCl_3$)

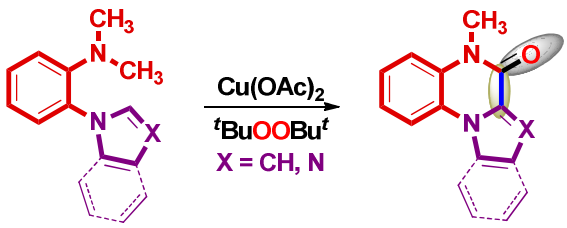


(4-Methoxyphenyl)(6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)methanone (4′d): ^{13}C NMR (150 MHz, $CDCl_3$)



Chapter III

Copper (II) Catalyzed Synthesis of Indoloquinoxalin-6-ones via Oxidative Mannich Reaction



- three sp^3 C-H bonds and one sp^2 C-H bond cleavages
- intramolecular C–C and bond C–O bond formation

Abstract: *A Cu catalyzed synthesis of indoloquinoxalin-6-ones has been developed starting from o-indolyl-N,N-dialkylamines via sp^3 C–H bond oxidation α to nitrogen atom using di-tert-butyl peroxide (DTBP) as the oxidant. Besides indoles, other heterocycles such as pyrrole, imidazole and benzimidazole have been successfully used which gave their respective fused quinoxalin-6-one derivatives. In this process one of the methyl group is transformed into a carbonyl functionality.*

CHAPTER III

III. Copper (II) Catalyzed Synthesis of Indoloquinoxalin-6-ones via Oxidative Mannich Reaction

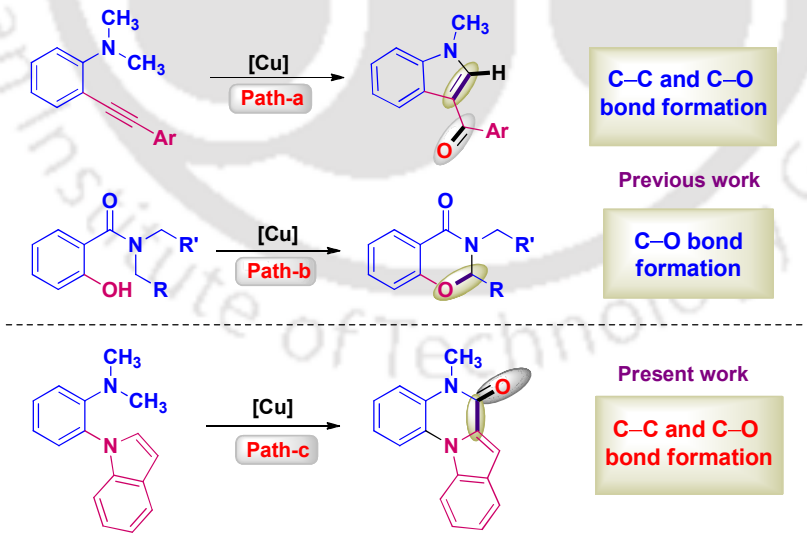
III.1. Introduction

The classical Mannich reaction leading to the synthesis of substituted β-amino carbonyl compounds involve three components *viz.* an enolizable aldehyde (or a ketone), an amine (1^o or 2^o) and formaldehyde. This important C–C bond forming process is comprised of two steps: *viz.* formation of an imine or iminium ion obtained by the condensation of an amine with formaldehyde followed by the nucleophilic attack of an enolizable aldehyde or a ketone at the reactive carbon end of the imine or iminium ion.[1] In a more generalized view, the imine or iminium ion generated via any alternative ways upon interception with a suitable nucleophile is likely to provide similar results.

Appropriate redox active transition metal in conjunction with a suitable oxidant can oxidize *N*,*N*-dialkylanilines to its corresponding iminium ion, which on trapping with a nucleophile will install the desired functionality at the carbon atom adjacent to nitrogen.[2] This oxidative Mannich concept forms the basis of transition metal catalyzed inert sp^3 C–H functionalizations α to nitrogen atom in *N*,*N*-dialkylanilines.[2] The *in situ* generated iminium carbon can be attacked either inter-molecularly or intra-molecularly with a suitable nucleophile. The inter-molecular cross coupling with tertiary amines has undergone significant advances encompassing a wide range of nucleophiles;[2,3] albeit the intra-molecular versions remain virtually unattended.[1f,4]

Few examples relevant to this oxidative intra-molecular cross-coupling strategy are, (i) oxidative $C(sp^3)$–$C(sp^3)$ bond formation leading to fused tetrahydroquinolines starting from dihydroisoquinolinyl phenyl ethanone derivatives under 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[4a] Ir- and trialkylammonium salt catalyzed conditions;[4b,c] (ii) oxidative cyclization of *o*-alkynyl-*N*,*N*-dimethylamines to 3-aroylindoles using Pd,[4d] tetrabutylammonium iodide[4e] and a photocatalyst;[4f] and (iii) Visible light-induced Ru-catalyzed intramolecular cyclization reactions of diamines.[4g]

The motivation of exploring the intra-molecular oxidative Mannich reaction led to our recent report on Cu catalyzed synthesis of 3-aroylindoles from 2-alkynyl-*N*,*N*-dialkylamines in which the alkynyl group serves as an internal nucleophile (path-a, Scheme III.1.1).[4g] A Cu catalyzed strategy for the synthesis of oxazinone derivatives from salicylamides was demonstrated by Maiti group which proceeds via a C(sp3)–O bond forming pathway (path-b, Scheme III.1.1).[4h] However, the gate is opened for other such internal nucleophiles, which may behave similar to alkynyl or hydroxyl group. Indolyl moiety is known to act as the coupling partner in inter-molecular CDC reactions, whereby it forms a C(sp^2)–C(sp^3) bond by C3 attack at the iminium ion generated from *N*,*N*-dialkylamines.[5] If the same indolyl moiety is anchored at the *ortho* position of *N*,*N*-dialkylanilines, the stereochemical orientation will inhibit the C3 attack but a *6-endo-dig* cyclization reaction can be anticipated via the C2 attack. A trial reaction attempted to examine the feasibility of this envisaged intra-molecular CDC reaction, provided indolo[1,2-*a*]quinoxalin-6-one as the product which formed via the expected intra-molecular C(sp^2) –C(sp^3) bond formation along with the installation of a carbonyl functionality at the expense of the remaining two sp^3 C–H's (path-c, Scheme III.1.1).



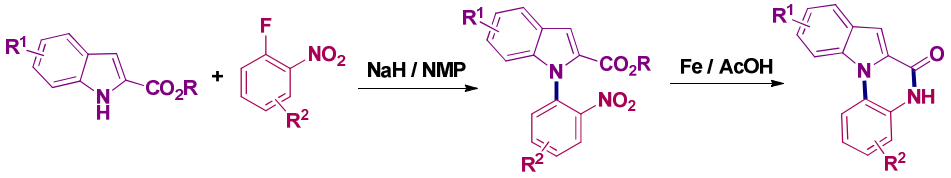
Scheme III.1.1. *Copper catalyzed intramolecular oxidataive cyclization of tertiary amines*

III.2. Strategies for indoloquinoxalin-6-ones

The indolo or pyrrolo fused quinoxalinone moiety is found in compounds displaying a variety of medicinal properties, such as anticancer, anxiolytic, antimicrobial, analgesic, antiallergic, antipsychotic, anti-HIV and antitumor activities.[6] Moreover, these compounds serve as key intermediates for the assembly of several heterocycles that display a wide range of biological activities.[7] The conventional route for the synthesis of pyrrolo- and indolo-[1,2-*a*]quinoxalinones comprise of three steps; *N*-arylation of pyrrole or indole with 2-nitroaryl derivatives, followed by reduction of the nitro group and cyclization to form the oxo-piperazine ring.[7] However, this pathway employs activated substrates, hazardous reagents such as phosgene or harsh reaction conditions. These limitations associated with the traditional methods led to the development of new and greener approaches for their synthesis which are enlisted below.

(i) Two step reaction of indole-2-carboxylates with 2-fluoronitrobenzenes

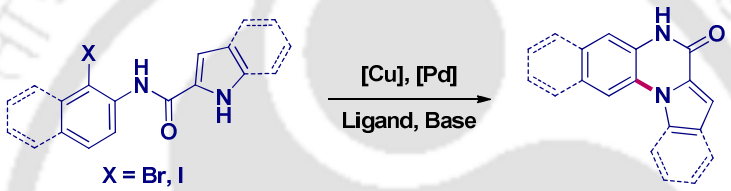
Russell group developed a two step reaction of indole-2-carboxylates with 2-fluoronitrobenzenes to furnish indoloquinoxalin-6-ones.[8a] In the first step, indole-2-carboxylates reacted with 2-fluoronitrobenzenes in l-methyl-2-pyrrolidinone (NMP) containing NaH to afford 1-(2-nitrophenyl)indole-2-carboxlyates. These compounds when reduced with iron in glacial acetic acid provided the indolo[l,2-*a*]quinoxalin-6(5*H*)-ones in fair to excellent yields (Scheme III.2.1). Guillion group described a similar strategy with the use of cesium carbonate and DMF for the initial coupling of indole-2-carboxylates with 2-fluoronitrobenzenes instead of NaH and NMP.[8b] An analogous coupling/reduction/condensation method using CuO, K_2CO_3 and Raney Ni was reported by Joseph and Basanagoudar.[8c] Although these strategies are much more similar to the conventional route, they avoid the use of hazardous carbonyl source materials such as phosgene or oxalyl chloride.



Scheme III.2.1. *Two step synthesis of indolo[l,2-a]quinoxalin-6-ones*

(ii) Intramolecular *N*-arylation of indole carboxamides

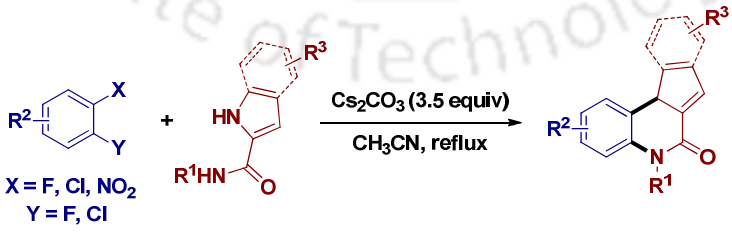
Martin group reported a Cu-catalyzed synthesis of indoloquinoxalinone derivatives involving an intramolecular *N*-arylation of indole carboxamides linked with a pendant haloarene.[9a] The method is equally successful with pyrrole carboxamide derivatives. The reaction when carried out under microwave irradiation increases the yields and decreases the reaction time significantly. A similar Pd catalyzed synthesis of pyrrolo- and indoloquinoxalinones was demonstrated by Beccalli *et al* from pyrrole-2-carboxamides or indole-2-carboxamides bearing a suitable *o*-halo substituted aryl- or heteroaryl group at the amide nitrogen (Scheme III.2.2).[9b]



Scheme III.2.2. *Intramoleular N-arylation of indole carboxamides*

(iii) Base triggered double *N*-arylation

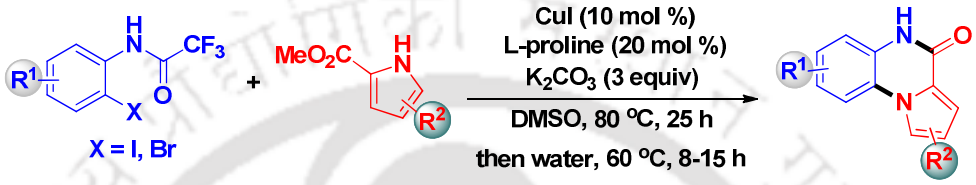
A transition metal free and a base mediated synthesis of pyrrolo[1,2-*a*]quinoxalines from pyrrole-2-carboxamides and 1,2-dihaloarenes / 1-fluoro-2-nitrobenzenes was described by Ma and co-workers under mild conditions providing good to excellent yields. Indole-2-carboxamides were also compatible with this approach, giving indolo[1,2-*a*]quinoxalinones in high yields (Scheme III.2.3).[10]



Scheme III.2.3. *Base mediated coupling of 1,2-dihalobenzenes or 2-halonitroarenes with pyrrole-2-carboxamides*

(iv) One pot coupling / hydrolysis / condensation strategy

Ma group demonstrated a CuI / L-proline catalyzed one-pot coupling / hydrolysis / intramolecular condensation process to assemble pyrrolo[1,2-*a*]quinoxalines from pyrrole-2-carboxylate esters and 2-halotrifluoroacetanilides. The method is equally successful to indole-2-carboxylate esters as well, providing the corresponding fused tetracyclic compounds (Scheme III.2.4).[11]



Scheme III.2.4. *Coupling / hydrolysis / condensation approach to pyrrolo[1,2-a]quinoxalines*

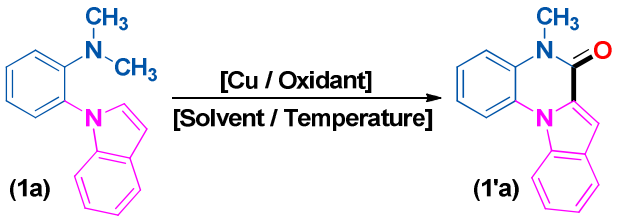
III.3. Present work

Although a significant number of coupling strategies have been developed for the synthesis of indolo[1,2-*a*]quinoxalin-6-ones, however, not a single route is known till date which is based on C–H functionalization strategy. Herein, we report a C–H functionalization protocol for the synthesis of indoloquinoxalin-6-ones staring from 2-indolyl-*N*,*N*-dimethylamines.

Optimization of reaction conditions. As mentioned above our initial intention was to achieve C–C bond formation from 2-indolyl-*N*,*N*-dimethylamine via an iminium ion generation followed by *6-endo-dig* cyclization. To check the viability of this intramolecular coupling reaction, 2-indolyl-*N*,*N*-dimethylamine (**1a**) was treated with CuBr (10 mol %) and aqueous TBHP (70%) (3 equiv) in DMSO at 80 °C. Interestingly, the reaction resulted in the formation of indolo[1,2-*a*]quinoxalin-6-one (**1′a**) in 19% yield (entry 1, Table III.3.1) via the expected intramolecular C–C bond formation along with multitudes of other products. This process is accompanied by concomitant installation of a carbonyl functionality at the expense of the remaining two sp^3 C–H's. In a quest to arrive at the most suitable reaction condition for this transformation, various reaction parameters

such as catalysts, oxidants, solvents and temperatures were scrutinized and the experimental findings are summarized in Table III.3.1. Various Cu(I) [CuBr, CuCl, Cu_2O] and Cu(II) salts [$Cu(OAc)_2$, $CuBr_2$, $CuCl_2$, $Cu(OTf)_2$] tested (entries 1–7, Table III.3.1) revealed $Cu(OAc)_2$ to be the most effective catalyst (entry 6, Table III.3.1). Changing the oxidant from aqueous TBHP to decane TBHP (3 equiv) resulted in an inferior yield (15%) of the product (entry 8, Table III.3.1). No doubt the use of TBHP at 80 ^oC gave the expected product (**1′a**) with the disappearance of starting material (**1a**) but is also associated with the formation of mono-demethylation of the starting material and a demethylated cyclized product, posing difficulties in separating the individual components. The use of DTBP as the oxidant slightly increased the product yield, while other oxidant such as H_2O_2 was almost inactive in bringing about the desired transformation (entries 9–10, Table III.3.1). Although the reaction was slower and the starting material remain unreacted at 80 ^oC even after 20 h but formation of above demethylated side products were not observed when DTBP was used as the oxidant. Increasing the reaction temperature to 100 ^oC and 120 ^oC resulted in an increased yield of the product 33% and 36% respectively (entries 11–12, Table III.3.1). The reaction produced better yields (46% and 52%) upon increasing the oxidant quantity to 5 and 6 equivalents respectively (entries 13–14, Table III.3.1). Thus, DTBP was overall found to be advantageous compared to commonly used oxidant (TBHP) for this transformation. Finally, various other polar (DMF, acetonitrile) and non-polar solvents (toluene, dioxane) were checked for this transformation (entries 15–18, Table III.3.1). Apart from toluene which produced comparable yield to DMSO, other solvents were found to have no positive effects on the reaction. In the absence of copper salt the reaction produce only a trace amount of the desired product (<5 %) suggesting its essential requirement for this transformation (entry 19, Table III.3.1). The addition of copper salt increases the rate of formation of the iminium ion thereby increasing the product yield. Thus, $Cu(OAc)_2$ (10 mol %), DTBP (6 equiv) in DMSO solvent at 120 ^oC was found to be the optimal condition and subsequent explorations to extend the scope of this transformation were performed adopting this.

Table III.3.1. *Screening of reaction conditions*[a,b]

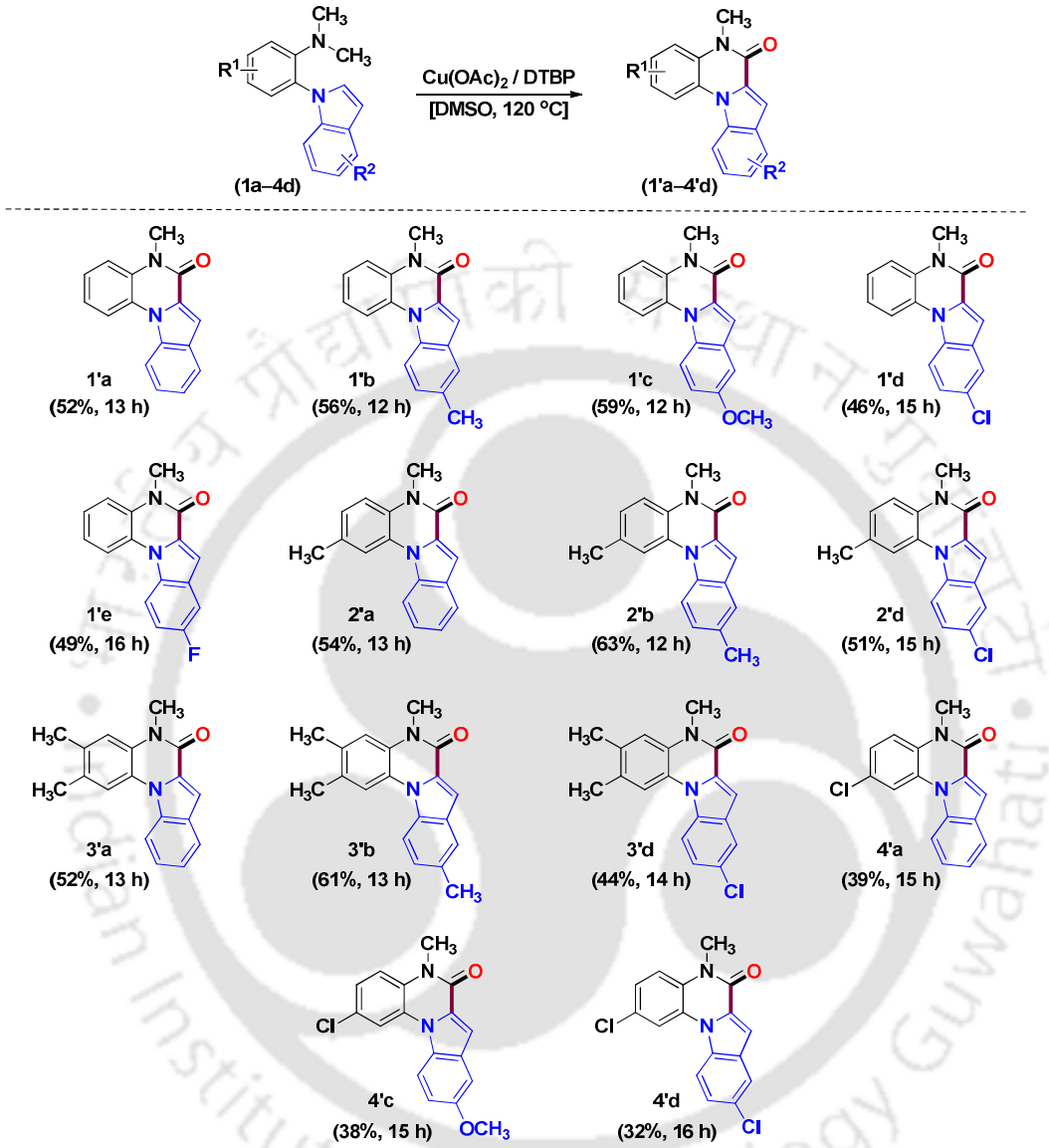


Entry	Catalyst (mol %)	Oxidant (equiv)	Temp. (°C)	Solvent	Yield (%)[b]
1	CuBr (10)	TBHP[c] (3)	80	DMSO	19
2	CuCl (10)	TBHP[c] (3)	80	DMSO	16
3	Cu_2O	TBHP[c] (3)	80	DMSO	21
4	$CuBr_2$ (10)	TBHP[c] (3)	80	DMSO	12
5	$CuCl_2$ (10)	TBHP[c] (3)	80	DMSO	10
6	$Cu(OAc)_2$ (10)	TBHP[c] (3)	80	DMSO	24
7	$Cu(OTf)_2$ (10)	TBHP[c] (3)	80	DMSO	18
8	$Cu(OAc)_2$ (10)	TBHP[d] (3)	80	DMSO	15
9	$Cu(OAc)_2$ (10)	DTBP (3)	80	DMSO	29
10	$Cu(OAc)_2$ (10)	H_2O_2[e] (3)	80	DMSO	8
11	$Cu(OAc)_2$ (10)	DTBP (3)	100	DMSO	33
12	$Cu(OAc)_2$ (10)	DTBP (3)	120	DMSO	36
13	$Cu(OAc)_2$ (10)	DTBP (5)	120	DMSO	46
14	**$Cu(OAc)_2$ (10)**	**DTBP (6)**	**120**	**DMSO**	**52**
15	$Cu(OAc)_2$ (10)	DTBP (6)	120	DMF	21
16	$Cu(OAc)_2$ (10)	DTBP (6)	120	CH_3CN	16
17	$Cu(OAc)_2$ (10)	DTBP (6)	120	Toluene	47
18	$Cu(OAc)_2$ (10)	DTBP (6)	120	Dioxane	12
19	-	DTBP (6)	120	DMSO	<5

[a]Reaction conditions: *N*,*N*-dimethyl-2-(indolyl) aniline (**1a**) (0.25 mmol), time 13 h. [b]Isolated yield. [c]70% aqueous solution. [d]Decane solution (5–6 M). [e]50% aqueous solution.

Substrate scope for indoloquinoxalin-6-ones. The above optimized conditions were then executed to a variety of 2-indolyl-*N*,*N*-dimethylamines to explore the substrate scope of the protocol. At first, the effects of various substituents on the indolyl ring (R^2) were examined keeping the aniline part fixed. Substitution on the aryl ring R^2 with electron-donating groups such as 5-Me (**1b**), 5-OMe (**1c**) and electron-withdrawing groups such as 5-Cl (**1d**), 5-F (**1e**) all afforded their corresponding indoloquinoxalin-6-ones (**1′b**-**1′e**) in the range of 46–59% yields (Scheme III.3.1). However, the yields were better and time taken were shorter for substrates possessing electron-donating groups **1′b** (56%) and **1′c** (59%) than for substrates possessing electron-withdrawing groups **1′d** (46%) and **1′e** (49%).

Scheme III.3.1. *Substrate scope for indoloquinoxalin-6-ones*[a,b]



[a]Reaction conditions: *o*-indolyl-*N*,*N*-dimethylamine (**1a-4d**) (0.25 mmol), $Cu(OAc)_2$ (0.025 mmol), DTBP (1.5 mmol) in DMSO (1 mL) at 120 °C. [b]Yield of isolated pure product.

The structure of (**1′b**) has been confirmed by X-ray crystallography (Figure III.3.1). When the amine bearing aryl ring (R^1) of 2-indolyl-*N*,*N*-dimethyl aniline is substituted with an electron-donating group such as 4-Me and the other aryl moiety (R^2) without a substituent (**2a**) and with substituents such as 5-Me (**2b**) and 5-Cl (**2d**) all yielded their indoloquinoxalin-6-ones in moderate yields (Scheme III.3.1). The yield improved when

both the rings contain electron-donating groups such as (4-Me) as was found in (**2′b**) (63%) than for substrates bearing electron-neutral (**2′a**) (54%) or electron-withdrawing group (**2′d**) (51%) in the aryl ring R^2. Similar reactivity trends were observed when the aryl ring R^1 is substituted with electron-donating group such as 3,4-di-Me and the substituents on the other aryl ring R^2 were varied from electron-neutral (**3a**), electron-donating (**3b**) and electron-withdrawing (**3d**). Substitution of the aryl ring R^1 with a moderately electron-withdrawing group such as 4-Cl resulted in comparatively lesser yields of the expected products irrespective of the nature of the substituents on the other ring as has been demonstrated with substrates (**4a**), (**4c**) and (**4d**) (Scheme III.3.1).

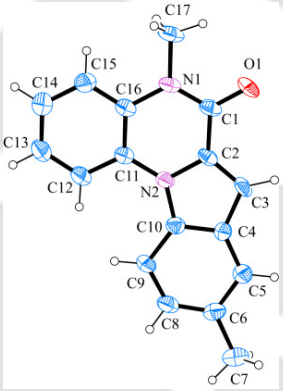
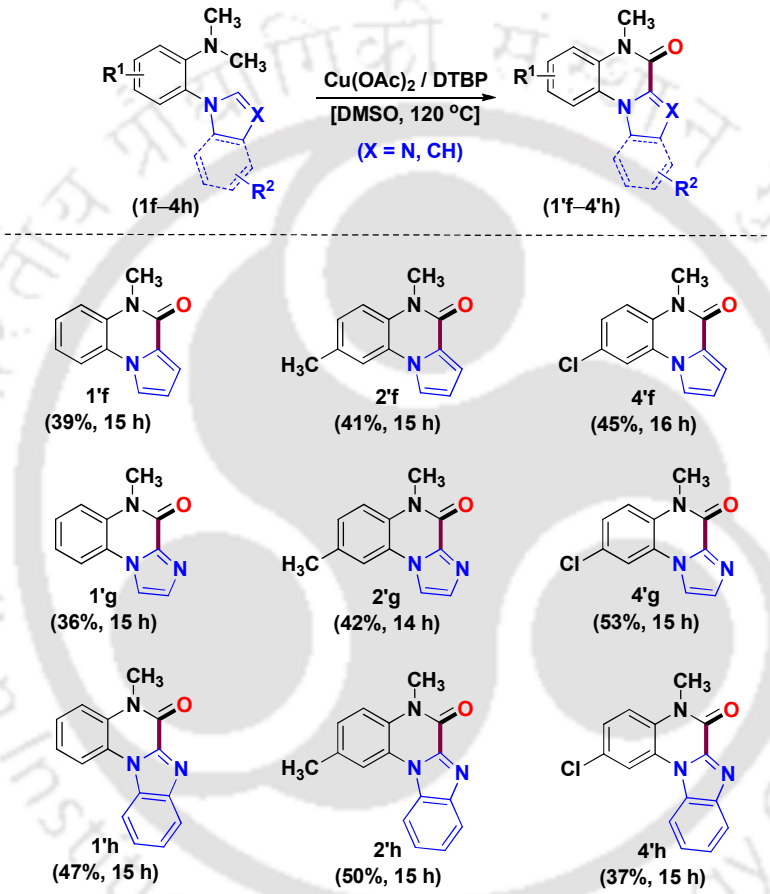


Figure III.3.1. *ORTEP view of (**1′b**)*

Electrophilic aromatic substitutions in indoles take place at C-3 position on the five membered ring. But as seen above, under a compelling intra-molecular process the electrophilic substitution took place at C-2 position on the nitrogen bearing heterocycle (Scheme III.3.1). On the other hand pyrrole, a reactive heterocycle undergo substitution at the C-2 position. Thus, an analogous fused pyrrole system should react giving their pyrrolo quinoxalin-6-ones. Fused pyrroles such as (**1f**), (**2f**) and (**4f**) when subjected to the present optimized reaction condition gave their respective pyrrolo quinoxalin-6-ones (**1′f**), (**2′f**) and (**4′f**) in modest yields (Scheme III.3.2). Another set of starting materials (**1g**), (**2g**) and (**4g**) bearing imidazole, a five membered di-nitrogen heterocycle, where the electrophilic substitution is favoured at the C-2 position were specifically designed. All underwent intra-molecular oxidative heterocylclization under the present reaction conditions giving

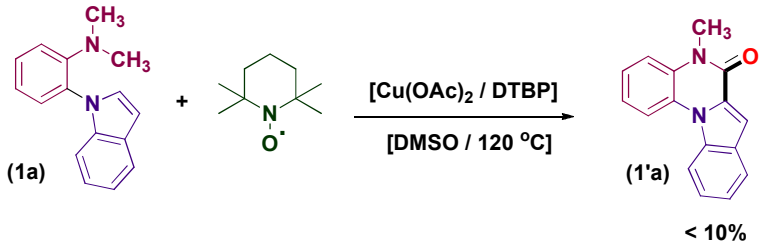
corresponding imidazolo quinoxalin-6-ones (**1′g**), (**2′g**) and (**4′g**) in moderate yields (Scheme III.3.2). The success of this oxidative Mannich reaction was finally applied to benzimidazole based precursors (**1h**), (**2h**) and (**4h**), all of which afforded their respective oxidative cyclized products (**1′h**), (**2′h**) and (**4′h**) in modest yields (Scheme III.3.2).

Scheme III.3.2. *Substrate scope for quinoxalin-6-ones*[a,b]



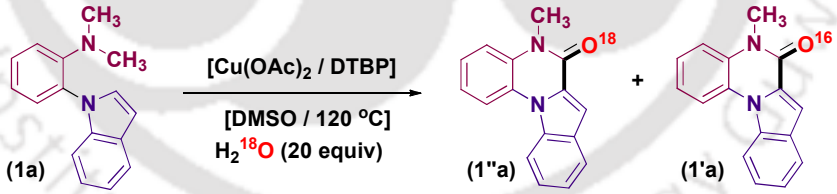
[a]Reaction conditions: *o*-indolyl-*N*,*N*-dimethylamine (**1f-4h**) (0.25 mmol), $Cu(OAc)_2$ (0.025 mmol), DTBP (1.5 mmol) in DMSO (1 mL) at 120 °C.
[b]Yield of isolated pure product.

Mechanistic investigations. To get an insight into the nature of mechanism, an experiment was carried out in the presence of a radical scavenger TEMPO (6 equiv) under otherwise identical conditions. Retardation in the expected product formation was observed along with the formation of a multitude of other side products indicating a radical nature of the mechanism.



Scheme III.3.3. *Reaction in presence of radical scavenger TEMPO*

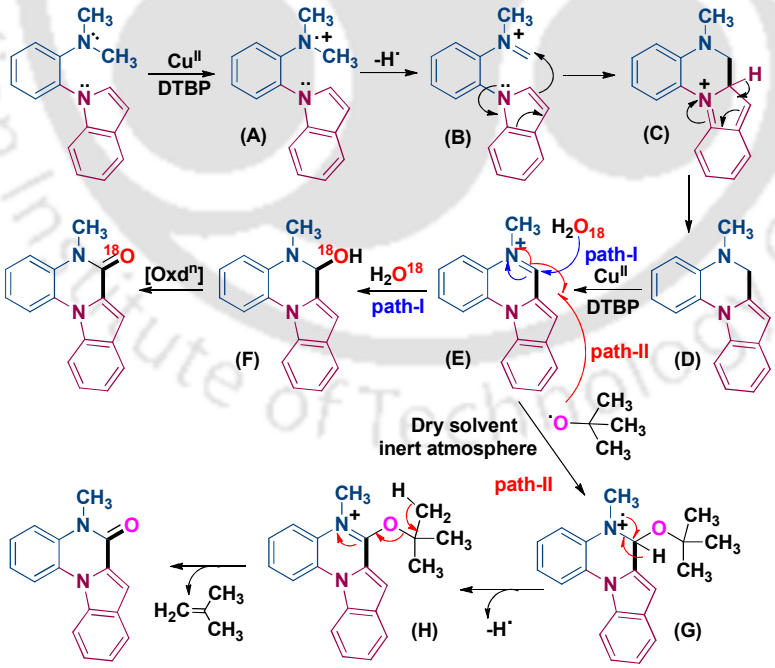
The reaction of substrate (**1a**) under an atmosphere of nitrogen afforded 5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (**1′a**) without effecting the yield. This suggests atmospheric oxygen not to be the source of carbonyl oxygen. In another experiment when substrate (**1a**) was treated in presence of 20 equivalents of $H_2{}^{18}O$ under otherwise identical condition, ^{18}O incorporated 5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (**1′′a**) was obtained as confirmed from HRMS analysis of the reaction mixture. This validates water to be the source of carbonyl oxygen which is often present in the commercial grade DMSO. This reaction when carried out in an anhydrous DMSO under a nitrogen atmosphere was also found to be equally effective. This suggests that in addition to water, perhaps a tertiary butyl radical obtained from DTBP via the homolytic cleavage may serve as the source of oxygen.



Scheme III.3.4. *Labeling experiment with ^{18}O labeled water*

Based on the experimental findings of the control experiments and literature reports,[2e-h,3a-c,4a,4f,11] two mechanistic pathways have been proposed for this transformation (Scheme III.3.5). An aminyl radical cation (**A**) is generated via a single electron transfer facilitated by Cu(II) in combination with peroxide. This aminyl radical cation (**A**) upon subsequent abstraction of a hydrogen radical α to the nitrogen produces an iminium ion intermediate (**B**). The intermediate (**B**) undergoes intramolecular cyclization via the nucleophilic attack

from the C2 position of indolyl ring producing intermediate (**C**). Rearomatization of intermediate (**C**) generates 5-methyl-5,6-dihydroindolo[1,2-*a*]quinoxaline (**D**). A similar iminium intermediate (**E**) is generated again via a single electron transfer/proton abstraction process. This is then followed by the nucleophilic attack of water at the iminium carbon to produce intermediate (**F**) which is finally oxidized to product (**1′a**) (path-I, Scheme III.3.5). In an alternative pathway, tertiary butyl radical obtained from DTBP attacks at the iminium ion intermediate (**E**) to generate intermediate (**G**) (path-II Scheme III.3.5). Loss of a hydrogen radical from (**G**) gives another iminium ion intermediate (**H**), which loses a molecule of isopropylene to give the expected product as shown in (path-II, Scheme III.3.5). Thus, both the mechanisms (path-I and path-II) are operating in tandem. Further, addition of external water (1, 2 and 3 equivalents) to the reaction medium under otherwise identical conditions did not improve the product yield. This indirectly supports the above dual mechanisms as there are sufficient nucleophiles (water and tertiary butyl radical) present in the medium. The mechanism with other heterocycles such as pyrrole, imidazole and benzimidazole is expected to follow the same pathway.



Scheme III.3.5. *Plausible mechanism for the formation of indoloquinoxalin-6-one*

In conclusion, we have developed a Cu catalyzed method for the synthesis of indoloquinoxaline-6-ones starting from *o*-indolyl-*N*,*N*-dimethylarylamines through an intramolecular oxidative coupling using DTBP as the oxidant. The process involves a formal three sp^3 C–H bonds and one sp^2 C–H bond cleavages with a concomitant installation of C–C and C–O bonds leading to the formation of indoloquinoxalin-6-ones. The use of cheaper catalytic system and extension of the methodology to other heterocyclic systems establishes practical applicability of the present protocol.

III.4. Experimental section

III.4.1. General information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with tetramethylsilane as the internal standard for ^{1}H NMR (600 MHz) $CDCl_3$ and DMSO-d_6 solvent as the internal standard for ^{13}C NMR (150 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using ESI mode. FT-IR spectra were recorded in KBr or neat. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

III.4.2. General procedure for the synthesis of 2-(1*H*-Indol-1-yl)-*N*,*N*-dimethylaniline (1a). A mixture of 1*H*-Indole (2 mmol), cuprous oxide (0.15 mol) and potassium hydroxide (3 mmol) is taken in 25 mL round bottom flask and charged with N_2 gas

(balloon). To this, DMSO (2 mL) and then 2-iodo-*N*,*N*-dimethylaniline (1 mmol) was added. The resultant mixture was then put into a preheated oil bath at 120 ^{o}C and stirred for 24 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and then passed through celeite. Water (5 mL) was added to the filtrate and organic layer was collected. The aqueous layer was extracted one more time with ethyl acetate (10 mL). Organic phase was dried over anhydrous Na_2SO_4 and concerntrated in vacuo. The crude product was purified by column chromatography over a column of silica gel (hexane : ethyl acetate = 50 : 1) to give 2-(1*H*-indol-1-yl)-*N*,*N*-dimethylaniline (**1a**) in 58% yield (137 mg).

However, the aforementioned method provides inferior yields for chloro derivatives (**4a**-**4g**) and they were synthesized by alternative method.[13]

III.4.3. General procedure for the synthesis of 5-Methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′a). To a solution of *N*,*N*-dimethyl-2-(indolyl) aniline (**1a**) (59.08 mg, 0.25 mmol) in DMSO (1 mL) was added $Cu(OAc)_2$ (4.54 mg, 0.025 mmol), followed by ditertiarybutyl peroxide (DTBP) (219 mg, 1.5 mmol) and the resultant mixture was put into a preheated oil bath (120 ^{o}C) for 13 h. The resultant reaction mixture was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate, decanted and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (9:1 hexane / ethyl acetate to give 5-Methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (**1′a**) (32.27 mg, 52% yield). The same procedure was also followed for intramolecular coupling of other 2-indolyl-*N*,*N*-dimethyl amine derivatives (**1b**–**4h**).

III.4.4. General procedure for the labelling experiment. *N*,*N*-Dimethyl-2-(indolyl) aniline (**1a**) (59.08 mg, 0.25 mmol) was taken in a 10 mL round bottom flask and DMSO (1 mL) was added to it. $Cu(OAc)_2$ (4.54 mg, 0.025 mmol), di-tertiarybutyl peroxide (DTBP) (219 mg, 1.5 mmol) and $H_2{}^{18}O$ water (100 mg, 5 mmol) was added to the reaction mixture and the resultant solution was put in a preheated oil bath at 120 ^{o}C for 13 h. After completion of the reaction, it was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). A small amount of the extract was passed through

a 0.2 μm filter paper and the filtrate was diluted with acetonitrile (HPLC grade) and with this diluted solution HRMS was recorded.

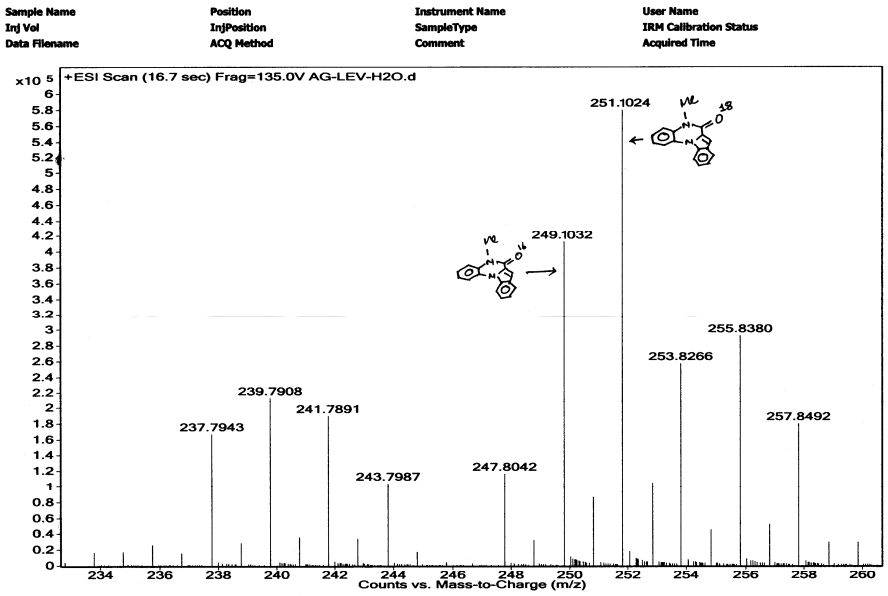


Figure III.4.4.1. *HRMS of ^{18}O labelled experiment*

III.4.5. Crystallographic description of 5,9-Dimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′b). $C_{17}H_{14}N_2O$, crystal dimensions 0.43 x 0.35 x 0.29mm, M_r = 262.30, Triclinic, space group P-1, a = 8.011(7), b = 8.942(7), c = 10.005(8) Å, α = 83.92(3)°, β = 76.19(3) °, γ = 67.20(3) °, V = 641.5(9) Å^3, Z = 2, ρ_{calcd} = 1.358 g/cm^3, μ = 0.086 mm^{-1}, F(000) = 276.0, reflection collected / unique = 2158 / 959, refinement method = full-matrix least-squares on F^2, final R indices [I > 2σ (I)]: R_1 = 0.0899, wR_2 = 0.1833, R indices (all data): R_1 = 0.1693, wR_2 = 0.2038, goodness of fit = 1.179. CCDC reference number 1429999.

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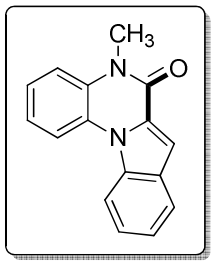
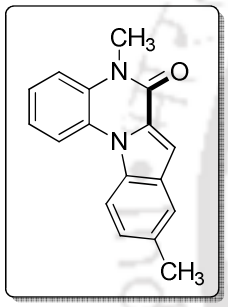
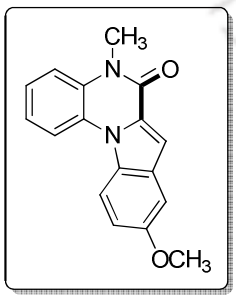
III.6. Spectral data



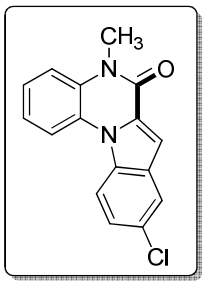
5-Methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′a): Brown solid; mp 151–153 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.67 (s, 3H), 7.27–7.36 (m, 4H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.28–8.29 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.1, 107.0, 114.4, 115.5, 115.7, 122.6, 123.36, 123.41, 124.3, 125.5, 126.8, 128.2, 129.4, 130.0, 134.4,156.8; IR (KBr): 2922, 2853, 1653, 1506, 1452, 1389, 1301, 1248, 1199, 1122, 1019, 812, 733 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{12}N_2O$ (MH^+) 249.1022; found 249.1029.



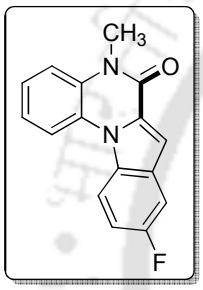
5,9-Dimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′b): Brown solid; mp 183–185 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.50(s, 3H), 3.66 (s, 3H), 7.24–7.31 (m, 4H), 7.45 (s, 1H), 7.61 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 29.1, 106.5, 114.0, 115.4, 115.7, 122.8, 123.4, 124.1, 126.9, 127.3, 128.2, 129.7, 129.9, 132.2, 132.8, 156.8; IR (KBr): 2919, 2853, 1656, 1602, 1506, 1466, 1390, 1300, 1249, 1197, 1127, 1043, 866, 789, 727 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ (MH^+) 263.1179; found 263.1170.



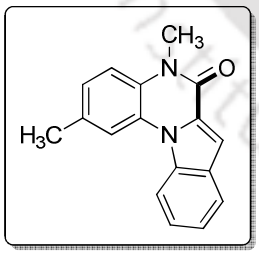
9-Methoxy-5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′c): Brown solid; mp 146–148 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.68 (s, 3H), 3.90 (s, 3H), 7.11 (d, *J* = 9.6 Hz, 1H), 7.20 (s, 1H), 7.27–7.30 (m, 2H), 7.31–7.33 (m, 1H), 7.45 (s, 1H), 8.07–8.09 (m, 1H), 8.20–8.22 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.1, 55.8, 103.3, 106.4, 115.15, 115.24, 115.7, 116.5, 123.4, 124.1, 126.7, 128.6, 129.6, 129.9, 130.3, 155.7, 156.6; IR (KBr): 2924, 2853, 1650, 1611, 1550, 1507, 1468, 1450, 1415, 1389, 1364, 1301, 1254, 1218, 1178, 1020, 857, 797, 732 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}N_2O_2$ (MH^+) 279.1128; found 279.1138.



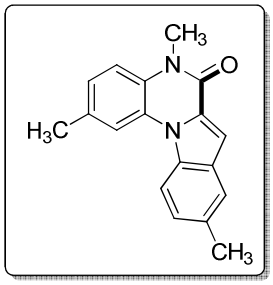
9-Chloro-5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′d): Light green solid; mp 178–180 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.67 (s, 3H), 7.29–7.34 (m, 3H), 7.37 (d, J = 9.0 Hz, 1H), 7.41 (s, 1H), 7.74 (d, J = 2.4 Hz, 1H) 8.07 (d, J = 9.0 Hz, 1H), 8.15–8.16 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.2, 106.2, 115.3, 115.4, 115.9, 122.4, 123.5, 124.7, 125.7, 126.3, 128.3, 129.3, 130.0, 130.3, 132.5, 156.3; IR (KBr): 2923, 2853, 1657, 1604, 1503, 1446, 1390, 1295, 1243, 1137, 1069, 862, 800, 734 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}ClN_2O$ (MH^+) 283.0633; found 283.0637.



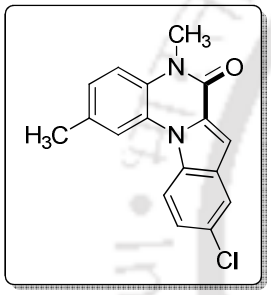
9-Fluoro-5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′e): Brown solid; mp 192–194 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.69 (s, 3H), 7.22 (t, J = 9.0 Hz, 1H), 7.30–7.36 (m, 3H), 7.45 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 8.14–8.16 (m, 1H), 8.21–8.22 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.2, 106.5, 106.6, 107.6, 107.8, 114.1, 114.3, 115.2, 115.3, 115.4, 115.9, 123.5, 124.6, 126.4, 129.6, 129.9, 130.06, 130.13, 131.0, 156.4, 158.0, 159.6; IR (KBr): 2924, 2853, 1658, 1618, 1505, 1466, 1445, 1392, 1301, 1252, 1206, 1171, 959, 848, 793, 733 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}FN_2O$ (MH^+) 267.0928; found 267.0939.



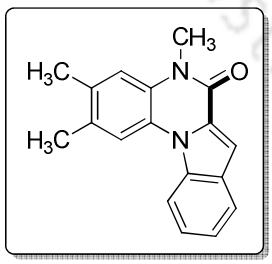
2,5-Dimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (2′a): Brown solid; mp 187–188 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.52 (s, 3H), 3.69 (s, 3H), 7.12 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.57 (s, 1H); 7.88 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H), 8.28 (d, J = 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 29.1, 106.9, 114.5, 115.6, 116.1, 122.5, 123.4, 124.9, 125.3, 126.7, 127.7, 128.4, 129.4, 133.3, 134.4, 156.7; IR (KBr): 2921, 2855, 1653, 1563, 1511, 1454, 1387, 1296, 1260, 1019, 808, 727 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ (MH^+) 263.1179; found 263.1185.



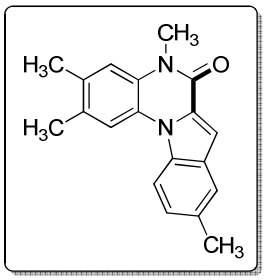
2,5,9-Trimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (2′b): Brown solid; mp 175–176 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 2.50 (s, 3H), 3.63 (s, 3H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.44 (s, 1H), 7.60 (s, 1H), 8.01 (s, 1H), 8.05 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.48, 21.54, 29.1, 106.4, 114.1, 115.6, 116.0, 122.8, 124.8, 126.8, 127.2, 127.7, 128.5, 129.8, 132.1, 132.8, 133.3, 156.8; IR (KBr): 2922, 2853, 1651, 1560, 1514, 1455, 1384, 1294, 1260, 1136, 1038, 864, 808, 723 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{16}N_2O$ (MH^+) 277.1335; found 277.1332.



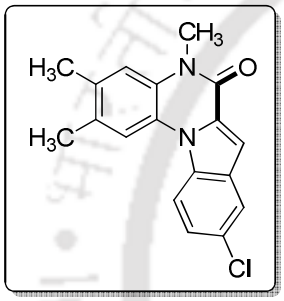
9-Chloro-2,5-dimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (2′d): Brown solid; mp 212–215 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.50 (s, 3H), 3.65 (s, 3H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.42 (s, 1H), 7.76 (s, 1H), 7.96 (s, 1H), 8.09 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 29.2, 106.0, 115.4, 115.8, 115.9, 122.4, 125.4, 125.5, 126.2, 127.7, 128.2, 129.5, 130.4, 132.5, 133.5, 156.2; IR (KBr): 2920, 2853, 1654, 1566, 1511, 1454, 1389, 1292, 1141, 1073, 903, 860, 809, 773, 741, 721 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}ClN_2O$ (MH^+) 297.0789; found 297.0782.



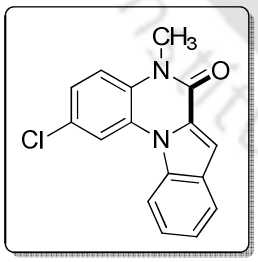
2,3,5-Trimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (3′a): Brown solid; mp 191–193 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 2.36 (s, 3H), 3.64 (s, 3H), 7.04 (s, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.53 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.02 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.8, 28.9, 106.2, 114.3, 116.3, 116.5, 122.2, 123.1, 124.4, 125.0, 127.5, 128.2, 129.2, 131.6, 132.6, 134.0, 156.5; IR (KBr): 2921, 2856, 1644, 1554, 1514, 1454, 1389, 1294, 1154, 1018, 835, 734 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{16}N_2O$ (MH^+) 277.1335; found 277.1327.



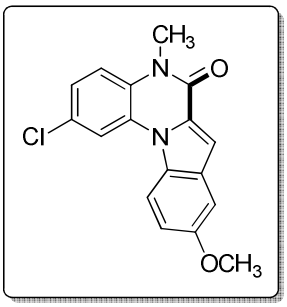
2,3,5,9-Tetramethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (3′b): Brown solid; mp 236–238 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 2.41 (s, 3H), 2.52 (s, 3H), 3.67 (s, 3H), 7.09 (s, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.46 (s, 1H), 7.64 (s, 1H), 8.05 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.9, 21.5, 29.1, 106.0, 114.1, 116.5, 116.8, 122.7, 124.8, 127.0, 127.8, 128.4, 129.7, 131.8, 131.9, 132.5, 132.7, 156.9; IR (KBr): 2920, 2853, 1647, 1552, 1516, 1454, 1386, 1327, 1295, 1252, 1013, 828, 778, 729 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{18}N_2O$ (MH^+) 291.1492; found 291.1498.



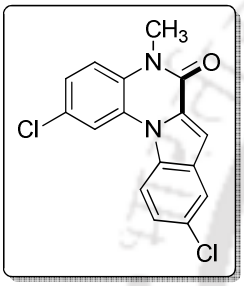
9-Chloro-2,3,5-trimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (3′d): Brown solid; mp 271–273 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 2.38 (s, 3H), 3.63 (s, 3H), 7.06 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.41(s, 1H), 7.77 (s, 1H), 7.89 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.9, 20.0, 29.1, 105.6, 115.3, 116.4, 116.9, 122.3, 124.2, 125.4, 127.8, 128.0, 129.4, 130.3, 132.0, 132.4, 133.2, 156.4; IR (KBr): 2922, 2853, 1665, 1648, 1557, 1516, 1455, 1390, 1294, 1150, 1071, 1014, 858, 775, 720 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}ClN_2O$ (MH^+) 311.0946; found 311.0956.



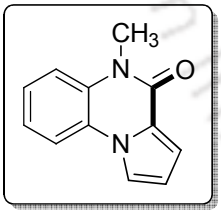
2-Chloro-5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (4′a): Light green solid; mp 240–242 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.67 (s, 3H), 7.26–7.28 (m, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.57 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.27 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.3, 107.9, 114.2, 115.7, 116.7, 123.1, 123.6, 124.1, 126.0, 127.5, 128.1, 128.9, 129.5, 134.4, 156.5; IR (KBr): 2922, 2850, 1657, 1601, 1504, 1454, 1387, 1285, 1254, 1099, 1016, 968, 815, 732 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{11}ClN_2O$ (MH^+) 283.0633; found 283.0621.



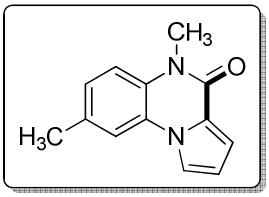
2-Chloro-9-methoxy-5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (4′c): White solid; mp 248–250 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.69 (s, 3H), 3.92 (s, 3H), 7.19 (d, J = 9.6 Hz, 1H), 7.25–7.27 (m, 3H), 7.50 (s, 1H), 8.08 (d, J = 9.6 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.2, 55.8, 103.5, 107.2, 115.0, 115.2, 116.6, 116.9, 123.8, 127.3, 128.4, 128.7, 128.8, 129.4, 130.5, 156.0, 156.2; IR (KBr): 2924, 2851, 1660, 1616, 1556, 1503, 1459, 1391, 1290, 1258, 1217, 1106, 1026, 823, 779, 728 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{13}ClN_2O_2$ (MH^+) 313.0738; found 313.0729.



2,9-Dichloro-5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (4′d): Brown solid; mp 180–182 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.67 (s, 3H), 7.26–7.30 (m, 2H), 7.44–7.47 (m, 2H), 7.81 (s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.4, 107.0, 115.1, 115.6, 116.9, 122.7, 124.5, 126.2, 127.0, 128.8, 129.1, 129.2, 130.5, 132.5, 156.0; IR (KBr): 2923, 2852, 1659, 1605, 1559, 1503, 1452, 1385, 1285, 1247, 1073, 1019, 867, 814, 729 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{10}Cl_2N_2O$ (MH^+) 317.0273; found 317.0270.

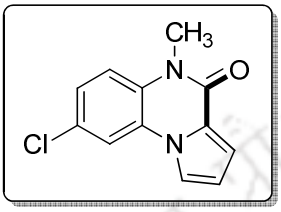


5-Methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (1′f): Brown solid; mp 117–118 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.64 (s, 3H), 6.64 (t, J = 9.0 Hz, 1H), 7.20–7.22 (m, 2H), 7.28–7.32 (m, 2H), 7.62 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 28.6, 112.8, 113.4, 114.6, 115.8, 116.1, 123.0, 123.5, 124.1, 125.7, 130.5, 155.7; IR (KBr): 3122, 2925, 2853, 1643, 1513, 1465, 1423, 1372, 1302, 1266, 1233, 1176, 1121, 1023, 741 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_{10}N_2O$ (MH^+) 199.0866; found 199.0869.

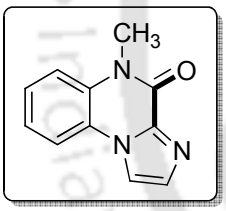


5,8-Dimethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (2′f): Brown solid; mp 122–124 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 3.63 (s, 3H), 6.63 (t, J = 3.0 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.17–7.20 (m, 2H), 7.46 (s, 1H), 7.61 (s, 1H); ^{13}C NMR (150

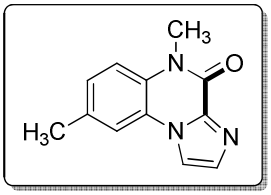
MHz, $CDCl_3$): δ (ppm) 21.1, 28.6, 112.7, 113.2, 115.0, 115.7, 116.0, 123.6, 124.0, 126.5, 128.3, 133.0, 155.7; IR (KBr): 3129, 2923, 2853, 1640, 1514, 1422, 1371, 1236, 1120, 1028, 874, 793, 725, 628 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{12}N_2O$ (MH^+) 213.1022; found 213.1036.



8-Chloro-5-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (4′f): Brown solid; mp 137–139 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 3.60 (s, 3H), 6.64 (t, *J* = 3.0 Hz, 1H), 7.16–7.19 (m, 2H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.52 (s, 1H), 7.56 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 28.7, 113.4, 113.9, 114.7, 116.4, 116.8, 123.3, 124.7, 125.5, 128.4, 129.1, 155.3; IR (KBr): 2923, 2852, 1654, 1508, 1464, 1427, 1368, 1120, 1027, 845, 812, 736, 626, 568 cm^{-1}; HRMS (ESI): calcd. for $C_{12}H_9ClN_2O$ (MH^+) 233.0476; found 233.0465.

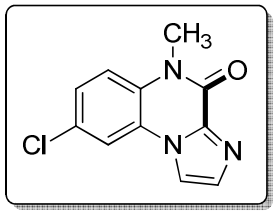


Methylimidazo[1,2-*a*]quinoxalin-4(5*H*)-one (1′g): Brown solid; mp 201–203 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 3.75 (s, 3H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.62 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ(ppm) 29.3, 114.0, 115.8, 116.1, 122.5, 123.6, 127.5, 130.5, 133.8, 136.6, 153.2; IR (KBr): 3122, 2923, 2854, 1662, 1516, 1462, 1402, 1341, 1301, 1253, 1175, 1123, 1031, 971, 752 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_9N_3O$ (MH^+) 200.0818; found 200.0829.

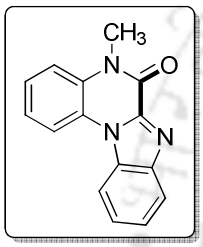


5,8-Dimethylimidazo[1,2-*a*]quinoxalin-4(5*H*)-one (2′g): White solid; mp 280–281 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 2.50 (s, 3H), 3.75 (s, 3H), 7.27–7.32 (m, 2H), 7.52 (s, 1H), 7.63 (s, 1H), 7.85 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 20.8, 29.6, 113.8, 115.8, 115.9, 122.0, 127.9, 128.1, 133.4, 133.7, 136.4, 152.9; IR (KBr): 3089, 2923, 2853, 1676, 1532, 1499, 1417, 1337, 1254, 1131, 1092, 1026, 996, 792, 651 cm^{-1}; HRMS (ESI): calcd. for

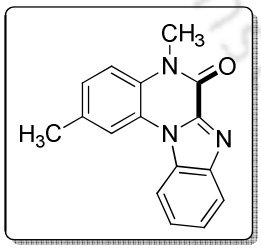
$C_{12}H_{11}N_3O$ (MH^+) 214.0975; found 214.0984.



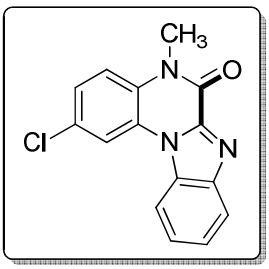
8-Chloro-5-methylimidazo[1,2-*a*]quinoxalin-4(5*H*)-one (4′g): Brown solid; mp 301–302 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.62 (s, 3H), 7.54–7.55 (m, 1H), 7.61–7.62 (m, 2H), 8.39 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.0, 116.0, 116.1, 117.9, 122.9, 126.7, 127.5, 128.9, 132.9, 135.7, 152.1; IR (KBr): 3133, 2922, 2852, 1676, 1522, 1501, 1467, 1437, 1398, 1333, 1251, 1135, 1095, 988, 801, 771, 650 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_8ClN_3O$ (MH^+) 234.0429; found 234.0435.



5-Methylbenzo[4,5]imidazo[1,2-*a*]quinoxalin-6(5*H*)-one (1′h): Brown solid; mp 129–131 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.77 (s, 3H), 7.35–7.39 (m, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.48–7.54 (m, 2H), 8.05 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.9, 114.1, 115.7, 116.1, 122.9, 124.0, 124.9, 125.3, 126.0, 126.2, 129.7, 131.3, 140.2, 144.2, 154.0; IR (KBr): 2923, 2854, 1665, 1529, 1458, 1392, 1348, 1257, 1101, 1021, 803, 740 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{11}N_3O$ (MH^+) 250.0975; found 250.0971.



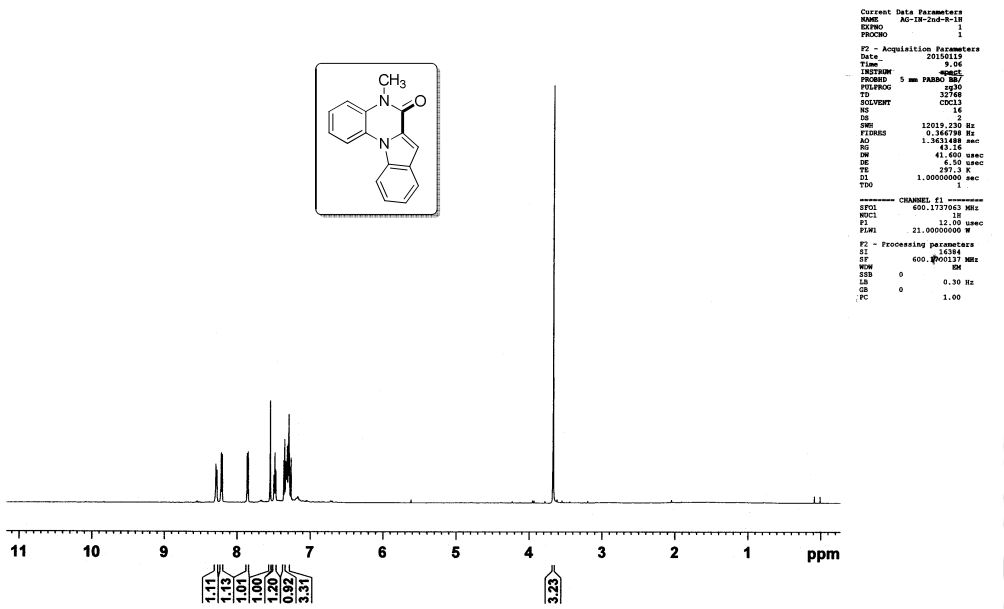
2,5-Dimethylbenzo[4,5]imidazo[1,2-*a*]quinoxalin-6(5*H*)-one (2′h): White solid; mp 264–266 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.46 (s, 3H), 3.72 (s, 3H), 7.16 (d J = 8.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.47–7.52 (m, 2H), 7.94 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 29.9, 114.1, 115.88, 115.90, 122.8, 124.7, 125.2, 125.9, 126.9, 127.4, 131.2, 134.1, 140.3, 144.2, 153.8; IR (KBr): 2921, 2851, 1668, 1532, 1457, 1391, 1349, 1263, 1137, 1014, 801, 730, 630, 574 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{13}N_3O$ (MH^+) 264.1131; found 264.1134.



2-Chloro-5-methylbenzo[4,5]imidazo[1,2-*a*]quinoxalin-6(5*H*)-one (4′h): White solid; mp 303−304 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.70 (s, 3H), 7.51−7.57 (m, 2H), 7.61 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 8.39 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 29.6, 114.8, 115.0, 117.9, 121.5, 124.9, 125.0, 125.6, 125.8, 127.9, 128.5, 130.5, 140.0, 143.3, 152.9; IR (KBr): 3101, 2922, 2852, 1676, 1529, 1454, 1394, 1345, 1295, 1254, 1137, 1042, 988, 820, 726 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{10}ClN_3O$ (MH^+) 284.0585; found 284.0574.

III.7. Spectra

5-Methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′a): ^{1}H NMR (600 MHz, $CDCl_3$)

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Current Data Parameters
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PROCNO              1

F2 - Acquisition Parameters
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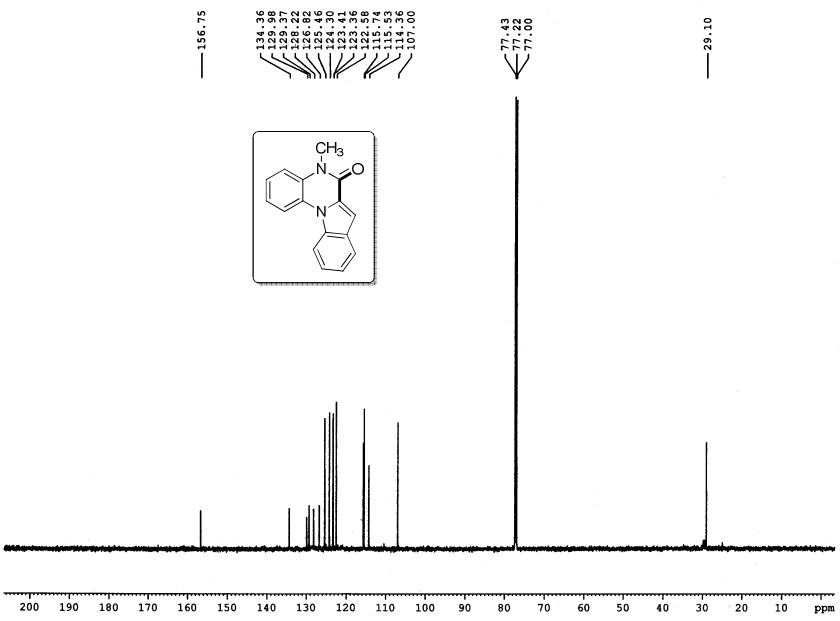
Time               9.06
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG          zg30
TD              32768
SOLVENT          CDCl3
NS                 16
DS                  2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ            1.3631488 sec
RG              43.16
DW             41.600 usec
DE              6.50 usec
TE             297.3 K
D1          1.00000000 sec
TD0                 1

======== CHANNEL f1 ========
SFO1       600.1737063 MHz
NUC1              1H
P1              12.00 usec
PLW1       21.00000000 W

F2 - Processing parameters
SI              16384
SF         600.1700137 MHz
WDW               EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```

5-Methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (1′a): ^{13}C NMR (150 MHz, $CDCl_3$)

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Current Data Parameters
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EXPNO               1
PROCNO              1

F2 - Acquisition Parameters
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Time               9.15
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG         zgpg30
TD              32768
SOLVENT          CDCl3
NS                300
DS                  2
SWH          36057.691 Hz
FIDRES        1.100393 Hz
AQ            0.4543829 sec
RG              65.24
DW             13.867 usec
DE              6.50 usec
TE             298.6 K
D1          2.00000000 sec
D11         0.03000000 sec
TD0                 1

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

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

F2 - Processing parameters
SI              16384
SF         150.9128424 MHz
WDW               EM
SSB       0
LB              1.00 Hz
GB        0
PC              1.40
```
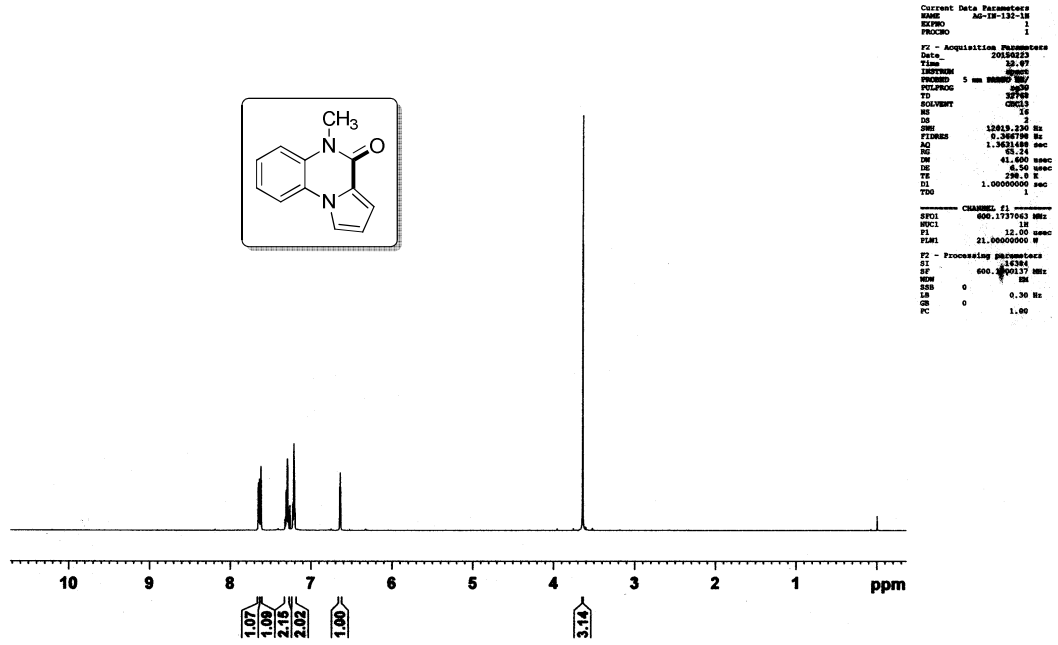
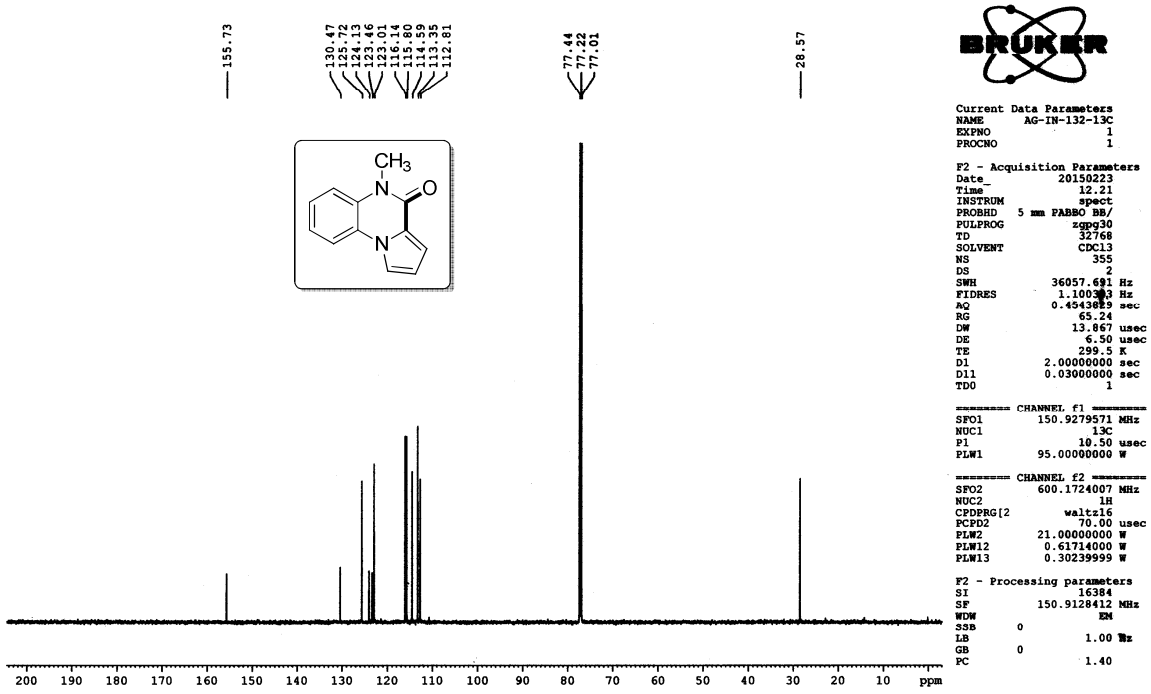

5-Methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (1′f): ^{1}H NMR (600 MHz, $CDCl_3$)

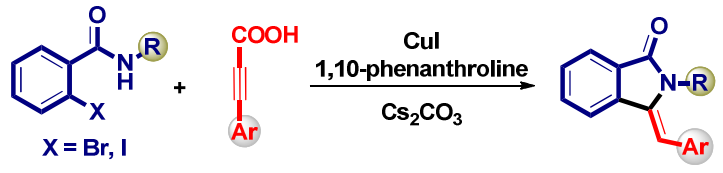


5-Methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (1′f): ^{13}C NMR (150 MHz, $CDCl_3$)



Chapter IV

A Cu-Catalyzed Synthesis of Substituted 3-Methyleneisoindolin-1-one



- C–C and C–N bond formation
- arylalkynyl acids as coupling partner

Abstract: *A Cu(I)-catalyzed synthesis of substituted 3-methyleneisoindolin-1-ones using alkynyl acids as alkyne source has been developed. The reaction involves decarboxylative cross-coupling of 2-halobenzamides with aryl alkynyl acids followed by 5-exo-dig heteroannulation. While reactions of 2-iodo benzamides proceeded without ligand, for 2-bromo substrates assistance of a ligand is essential.*

CHAPTER IV

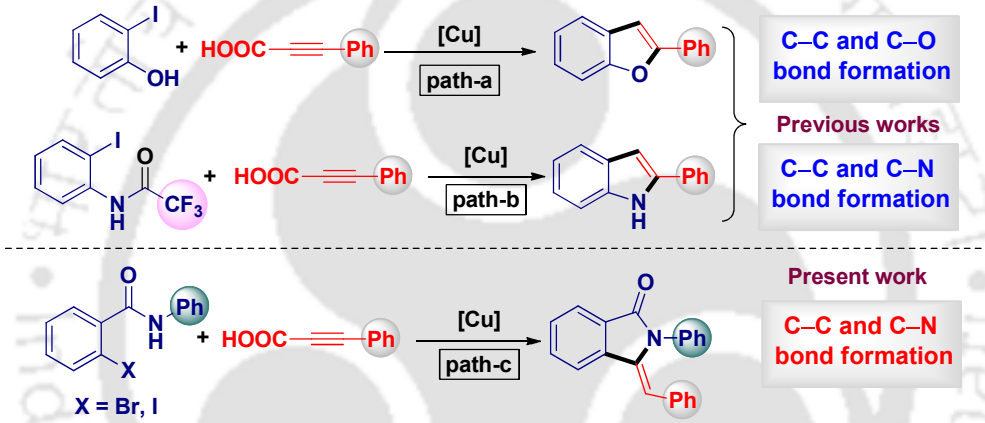
IV. A Cu-catalyzed Synthesis of Substituted 3-Methyleneisoindolin-1-one

IV.1. Introduction

In modern synthetic organic chemistry, transition metal catalyzed decarboxylative cross-coupling reactions using carboxylic acids have received much attention because of their ready availability and easy handling. In general, such reactions proceed via the *in situ* generation of organometallic species along with the extrusion of CO_2 as the side product. This reactive organometallic intermediate then couples with appropriate counterparts providing alternative routes to C–C or C–heteroatom bonds.[1] As one of the members of carboxylic acids, alkynyl carboxylic acids are potential candidates for cross–coupling reactions installing an alkynyl group into the substrates. Unlike aryl or vinyl carboxylic acids, decarboxylative coupling of alkynyl carboxylic acids can be initiated by a single catalytic system also though a few coupling reactions utilizes bimetallic as well as trimetallic catalytic systems.[1,2] The formation of C–C (sp^2–sp, sp–sp and sp^3–sp), C–N, C–P and C–S bonds with alkynyl acids has been achieved so far using transition metal catalysts such as palladium, copper, nickel, silver etc. Some of the lately reported examples of decarboxylative cross coupling of alkynyl carboxylic acids include: (i) coupling with aryl and alkyl halides under Cu and Pd catalyzed condition;[2a,3] (ii) coupling with terminal alkynes;[4] (iii) coupling with boronic acids;[5] (iv) Cu mediated coupling with secondary amines;[2d] (v) reaction with thiols;[2e] (vi) Cu-Pd-Ag catalyzed coupling with phosphites.[6]

Not merely restricted to the synthesis of internal alkynes, the above strategy has much more to offer by manipulation of the alkynyl group. One way to achieve this is to activate the *in situ* generated alkynyl group with a soft metal followed by an intramolecular nucleophilic attack resulting into a heterocycle. This strategy has been demonstrated by Xue group for the synthesis of benzofuran derivatives which proceeds via a copper catalyzed decarboxylative cross–coupling of alkynyl carboxylic acids with aryl halides followed by heteroannulation through the nucleophilic attack of the adjacent hydroxy

group.[2a] A copper mediated synthesis of 2-arylindoles has also been realized by Muthusubramanian *et al.* from 2-iodotrifluoroacetanilide and alkynyl acids following the same domino decarboxylative coupling and cyclization strategy.[7] Taking cues from these reports, we envisaged that coupling of 2-halo benzamide with an alkynyl acid under an appropriate condition may result either 3-methylene-isoindolin-1-one via a 5-*exo-dig* cyclization or substituted isoquinolin-1-one via a 6-*endo-dig* cyclization.[3] In an attempt to perform the above mentioned reaction under a copper catalyzed condition resulted in a selective formation of 5-*exo-dig* product, 3-methylene-isoindolin-1-one, thus ruling out the other possibility *viz.* 6-*endo-dig* cyclization.



Scheme IV.1.1. *Copper catalyzed strategies of decarboxylative cross-coupling with concomitant heterocyclization*

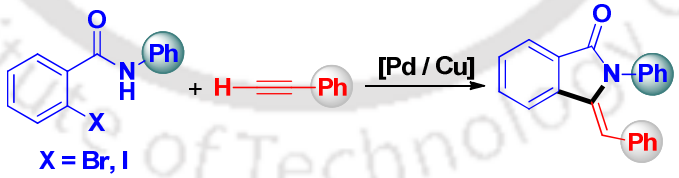
IV.2. Strategies for the synthesis of 3-methylene-isoindolin-1-ones

Substituted 3-methyleneisoindolin-1-ones are medicinally important heterocyclic scaffold prevalent in many natural products and pharmaceuticals.[8] Biological activities exhibited by isoindolin-1-ones include antihypertensive,[9] antipsychotic,[10] antiinfammatory,[11] anesthetic,[12] antiulcer,[13] vasodilatory,[14] antiviral,[15] and antileukemic[16] properties. Apart from their significant biological profile; they also find applications in material chemistry.[17] Due to the myriad of applications of this important motif there has been development of numerous synthetic protocols for their synthesis. The traditional methods for the synthesis of 3-methyleneisoindolin-1-one include Horner-Wadsworth-

Emmons type of condensation,[18] addition/dehydration of phthalimides,[19] 5-*exo-dig* cyclization of preformed 2-alkynylbenzamides[20] and base triggered addition to benzonitriles.[21] However, they are associated with poor regioselectivity in case of unsymmetrical substrates or require number of additional synthetic steps. These shortcomings stimulated the emergence of various transition metal catalyzed protocols for the synthesis of same and these are enlisted below.

(i) Sonagashira coupling-hydroamination of *ortho* halo benzamides with terminal alkynes

Kundu group developed a Pd(II)-Cu(I) catalyzed approach for the synthesis of (*Z*)-3-methyleneisoindolin-1-ones from 2-iodobenzamides and terminal alkynes in a regio- and stereoselective manner through Sonogashira coupling followed by *5-exo-dig* cyclization.[20d] Following the same strategy, Cuny *et al.* reported a microwave assisted Pd catalyzed (Cu-free) method for their synthesis.[22a] Two more greener approaches have been achieved by Naskar group and Sen group in an aqueous miceller medium and an aqueous medium respectively using Pd catalyst.[22b,c] Recently, Ma and co-workers demonstrated a palladium free copper(I) catalyzed method for the synthesis of (*Z*)-3-methyleneisoindolin-1-ones from 2-bromobenzamides and terminal alkynes.[22d] Two similar Cu only methodologies have been reported by Zeng *et al.* and Zhang *et al.*[22e,f] However, the production of diyne as a side product is the major drawback associated with all the above mentioned strategies, as a result an excess of alkyne is needed to be used during the reaction (Scheme IV.2.1).

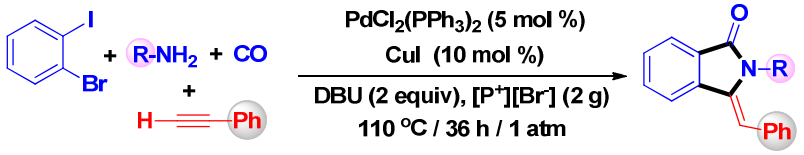


Scheme IV.2.1. *Synthesis of (Z)-3-methyleneisoindolin-1-ones by Sonogashira coupling followed by 5-exo-dig cyclization*

(ii) Sonagashira coupling-carbonylation-hydroamination of *ortho* di-halo arenes

Alper *et al.* reported a palladium catalyzed synthesis of substituted (*Z*)-3-methylene-isoindolin-1-one from dihaloarene, terminal alkyne, amine and carbon monoxide in

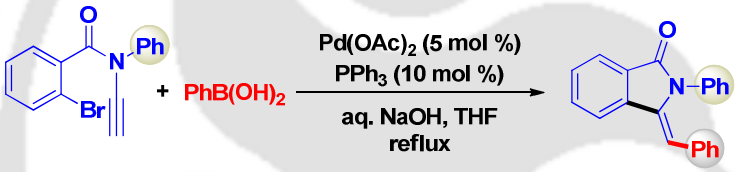
phosphonium salt ionic liquids. This protocol is based on a sequential use of Sonogashira coupling, carbonylation, and hydroamination process (Scheme IV.2.2).[23]



Scheme IV.2.2. *Synthesis of (Z)-3-methyleneisoindolin-1-ones via Sonogashira coupling / carbonylation / hydroamination*

(iii) Heck-Suzuki-Miyaura domino reactions involving ynamides

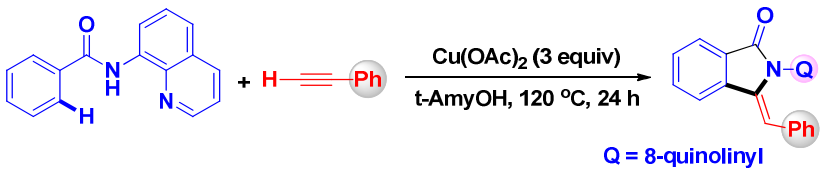
Cossy group demonstrated a palladium catalyzed Heck-Suzuki-Miyaura domino reactions of various ynamides and boronic acids for the synthesis of (*Z*)-3-(arylmethylene)isoindolin-1-ones in a stereoselective manner (Scheme IV.2.3).[24]



Scheme IV.2.3. *Synthesis of (Z)-3-methyleneisoindolin-1-ones by Heck-Suzuki-Miyaura domino reactions*

(iv) C–H Activation strategy

Apart from these cross-coupling strategies mentioned above, recently You *et al.* developed a Cu mediated approach to 3-methylene isoindolin-1-one that proceeds via tandem oxidative cross-coupling between C(sp^2)–H of unactivated arenes with C(sp)–H of terminal alkynes followed by an intramolecular annulation.[25] In this process, the oxidative coupling of alkyne to amide is assisted by 8-aminoquinoline group through a bidentate chelation (Scheme IV.2.4).

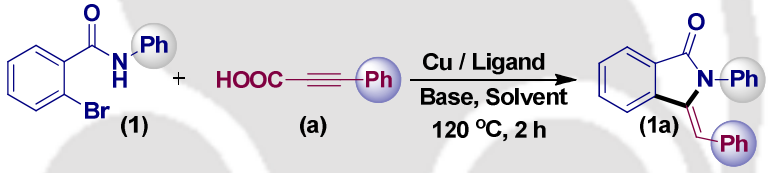


Scheme IV.2.4. *Synthesis of (Z)-3-methyleneisoindolin-1-ones following C–H activation strategy*

IV.3. Present work

The production of competing diyne byproduct (Scheme IV.2.1, Scheme IV.2.3 and Scheme IV.2.4) and the use of expensive and multi-stepped processes (Scheme III.2.2) are the major disadvantages associated with the aforementioned strategies. Although, alkynyl carboxylic acids are used as an alternative to terminal alkyne in many cross-coupling methodologies, their use for the construction of 3-methylene isoindolin-1-one is not reported in literature. The use of alkynyl carboxylic acids in lieu of terminal alkynes are advantageous because of their superior reactivity and ready availability.[26] Moreover, they are less susceptible to homocoupling; thereby suppressing the competing diyne byproduct in Sonogashira reaction.[27] Herein, we have reported a Cu(I)-catalyzed synthesis of substituted 3-methyleneisoindolin-1-ones involving decarboxylative cross-coupling aryl alkynyl acids with 2-halobenzamides followed by *5-exo-dig* heteroannulation.

Table IV.3.1. *Screening of reaction conditions*[a,b]



Entry	Catalyst (mol %)	Base (equiv)	Ligand (mol %)	Solvent	Yield (%)[b]
1	CuI (10)	Cs_2CO_3 (1.5)	-	DMF	32
2	CuI (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	DMF	59
3	CuBr (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	DMF	51
4	CuCl (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	DMF	43
5	$Cu(OAc)_2$ (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	DMF	38
6	$CuCl_2$ (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	DMF	40
7	$CuBr_2$(10)	Cs_2CO_3 (1.5)	1,10-phen (10)	DMF	49
8	CuI (10)	K_2CO_3(1.5)	1,10-phen (10)	DMF	53
9	CuI (10)	K_3PO_4(1.5)	1,10-phen (10)	DMF	41
10	CuI (10)	NEt_3 (1.5)	1,10-phen (10)	DMF	<5
11	CuI (10)	Cs_2CO_3 (1.5)	DEM (10)	DMF	35
12	CuI (10)	Cs_2CO_3 (1.5)	L-proline (10)	DMF	54
13	CuI (10)	Cs_2CO_3 (1.5)	TMEDA (10)	DMF	39
14	CuI (10)	Cs_2CO_3 (1.5)	DMEDA (10)	DMF	46
15	**CuI (10)**	**Cs_2CO_3 (1.5)**	**1,10-phen (10)**	**DMSO**	**69**
16	CuI (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	1,4-dioxane	42
17	CuI (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	NMP	49
18	CuI (10)	Cs_2CO_3 (1.5)	1,10-phen (10)	DCE	53

[a]Reaction conditions: 2-Bromobenzamide (**1**) (0.25 mmol), Phenyl propiolic acid (**a**) (0.3 mmol) at 120 °C, time 2 h.

Optimization of reaction conditions. As mentioned above, our initial intenton was to check the coupling of 2-halo benzamide with an alkynyl acid under copper catalyzed condition which may provide either 5-*exo-dig* cyclized product or 6-*endo-dig* cyclized product upon decarboxylative cross-coupling with concomitant heteroannulation. With this motif, an initial reaction was attempted by treating 2-bromobenzamide (**1**) with phenyl propiolic acid (**a**) (1.2 equiv) in the presence of CuI (10 mol %), Cs_2CO_3 (1.5 equiv) in DMF solvent at 120 ^oC. To our delight, the reaction resulted in a selective formation of *5-exo-dig* product, 3-phenylmethylene isoindolin-1-one (**1a**) in 32% yield (entry 1, Table IV.3.1). Encouraged by the initial success, further optimizations were carried out to attain an improved yield of the product (**1a**). Several reports revealed that for substrates undergoing metal catalyzed cross-coupling reactions involving bromo substituent, assistance of a ligand often facilitates the process.[28] Furthermore, an orthogonal selectivity has been demonstrated during a ligand assisted Cu-catalyzed reaction.[28f,i] A ligand functions by inhibiting the aggregation of the metal and improve the solubility of the catalyst/co-catalyst; thereby resulting in better catalytic activity of the metal. Taking cues from the aforementioned reports, when the coupling between 2-bromobenzamide (**1**) (1 equiv) and phenyl propiolic acid (**a**) (1.2 equiv) was performed in the presence of ligand 1,10-phenanthroline (10 mol %), CuI (10 mol %), Cs_2CO_3 (1.5 equiv) the product (**1a**) was obtained in an improved yield of 59% (entry 2, Table IV.3.1). During the catalyst screening CuI was found to be superior over all other Cu(I) and Cu(II) salts such as CuBr, CuCl, $Cu(OAc)_2$, $CuCl_2$, $CuBr_2$ tested (entries 3–7, Table IV.3.1). Replacement of base Cs_2CO_3 with other inorganic bases such as K_2CO_3, K_3PO_4 resulted in lower yields (entries 8–9, Table IV.3.1). The use of organic base like NEt_3 was found to be almost ineffective in bringing about the transformation (entry 10, Table IV.3.1). Other ligands such as diethylmalonate (DEM), L-proline, tetramethylethylenediamine (TMEDA), dimethylethylenediamine (DMEDA) tested were found to be inferior to 1,10-phenanthroline (entries 11–14, Table IV.3.1). Further, improvement in the yield (69%) was observed when the reaction was performed in DMSO instead of DMF (entry 15, Table IV.3.1). Other solvents such as 1,4-dioxane, 1,2-dichloroethane (DCE) and *N*-methyl-2-pyrrolidone (NMP) were found to be unsuitable for this transformation (entries 16–18, Table IV.3.1). Thus, CuI (10 mol %), 1,10-phen (10 mol %), Cs_2CO_3 (1.5 equiv) in DMSO

solvent at 120°C was found to be the optimal condition and rest of the reactions were performed under exactly identical conditions.

Substrate scope for 3-arylmethylene-isoindolin-1-ones. After establishing the optimized conditions, the substrate scope for this decarboxylation-heteroannulation methodology was explored. A variety of substituted 3–arylmethylene isoindolin-1-ones has been synthesized as shown in Scheme IV.3.1. At first, the effect of substituents present on the *N*-aryl ring of benzamide was examined by reacting them with phenyl propiolic acid (**a**). The *N*-aryl ring of amide bearing electron-donating groups such as 3-Me (**2**), 3,4-diMe (**3**), 4-OMe (**4**) yielded their respective products (**2a**), (**3a**) and (**4a**) in 62%, 78% and 66% respectively (Scheme IV.3.1). While benzamides derived from aryl amines possessing moderately electron-withdrawing groups such as 4-Cl (**5**), 4-Br (**6**), 4-F (**7**) provided their corresponding isoindolin-1-one (**5a**), (**6a**) and (7**a**) in 72%, 73% and 76% yields respectively (Scheme IV.3.1). A comparison between two sets of substrates one possessing electron-donating groups and other electron-withdrawing groups shows that yields are marginally better with the latter set with the lone exception being 3,4-diMe substrate (**3**). The structure of the product (**5a**) has been confirmed by X-ray crystallography (Figure IV.3.1).

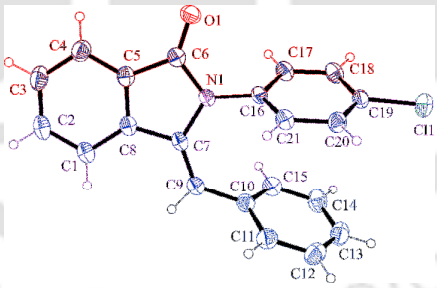
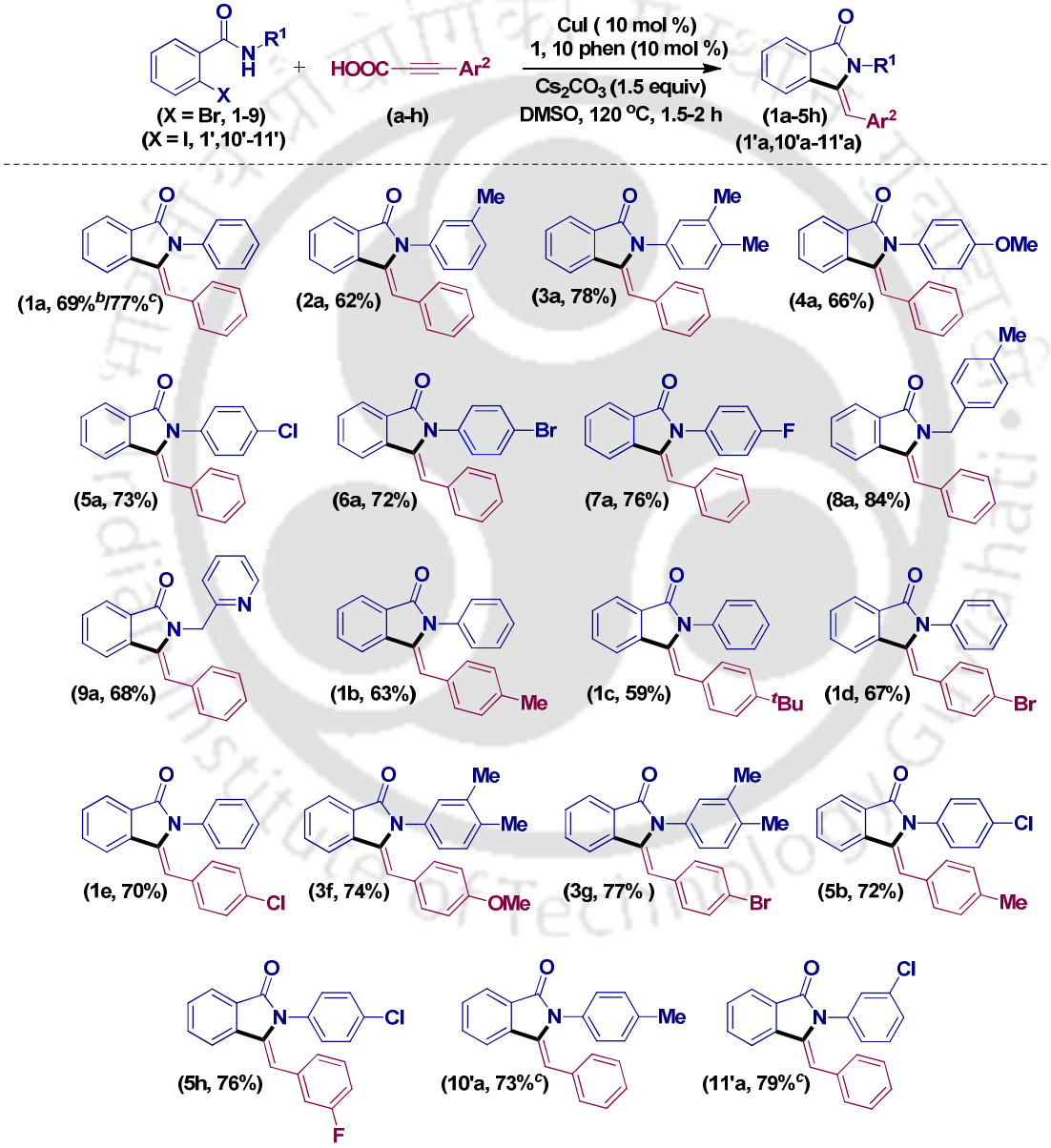


Figure IV.3.1. *ORTEP view of compound (**5a**)*

Instead of an aryl group when a benzyl substituent is attached to the *N*-atom of the benzamide (**8**), the product (**8a**) was obtained in good yield (84%). However, with analogous picolinamide (**9**) there was substantial drop in the yield (68%). The variation of substituents in aryl alkynyl acids were scrutinized by reacting them with benzamide (**1**). Aryl propiolic acids possessing electron-donating groups such as 4-Me (**b**), 4-^{t}Bu (**c**) and

electron-withdrawing groups such as 4-Br (**d**), 4-Cl (**e**) underwent facile reactions with (**1**) affording their respective products (**1b**), (**1c**), (**1d**) and (**1e**) in moderate yields as shown in (Scheme IV.3.1). From the trends in products yield it is evident that no significant electronic effect of substituents present in aryl propiolic acids could be ascertained.

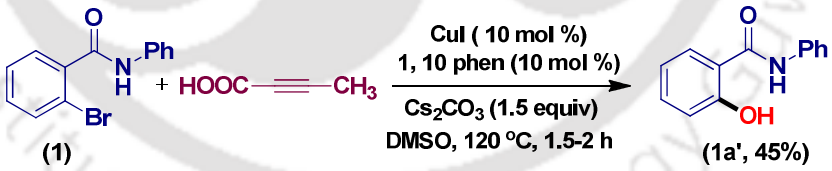
Scheme IV.3.1. *Substrate scope for 3-arylmethylene-isoindolin-1-ones*[a,d]



[a]Reaction conditions: 2-halobenzamide (**1-5**) (0.5 mmol), arylalkynyl acid (**a-h**) (0.6 mmol), CuI (10 mol %), 1,10-phen (10 mol %), Cs_2CO_3 (1.5 equiv), DMSO (2 mL) at 120 °C. [b]X = Br. [c]X = I. [d]Isolated yield.

An attempt was made to find out whether some combination of substituents present in *N*-aryl ring of the benzamides and aryl ring of alkynyl acids (based on their electronic effects) could be the most suitable for this transformation. With this motive two independent reactions were carried out with benzamide containing electron-donating 3,4-diMe group in the *N*-aryl ring (**3**) with aryl alkynyl acids bearing electron-donating 4-OMe group (**f**) and having electron withdrawing 4-Br group (**g**). Another set of reactions were performed with benzamide possessing electron withdrawing 4-Cl group (**5**) with aryl alkynyl acids bearing electron-donating group 4-Me (**b**) and having electron-withdrawing 3-F group (**h**). However, judging by the yield pattern of products (**3f**), (**3g**), (**5b**) and (**5h**) obtained from the aforementioned combinations, again no correlation between yields and substituent effect could be arrived (Scheme IV.3.1).

To check the efficacy of this transformation with aliphatic alkynyl acid a reaction was performed between 2-bromobenzamide (**1**) and 2-butynoic acid. The reaction failed to give the desired isoindolin-1-one product, instead hydroxylation *ortho* to amide (**1a′**) moiety was observed under the reaction condition (Scheme IV.3.2). Similar hydroxylation of *o*-haloanilides and *o*-halo benzamides has been observed during Cu catalyzed reaction in an aqueous medium.[29] Due to lesser reactivity of bromo group towards oxidative addition with aliphatic alkyne species the hydroxylation path is preferred and the possible hydroxyl source is from the water present in the commercial grade DMSO.

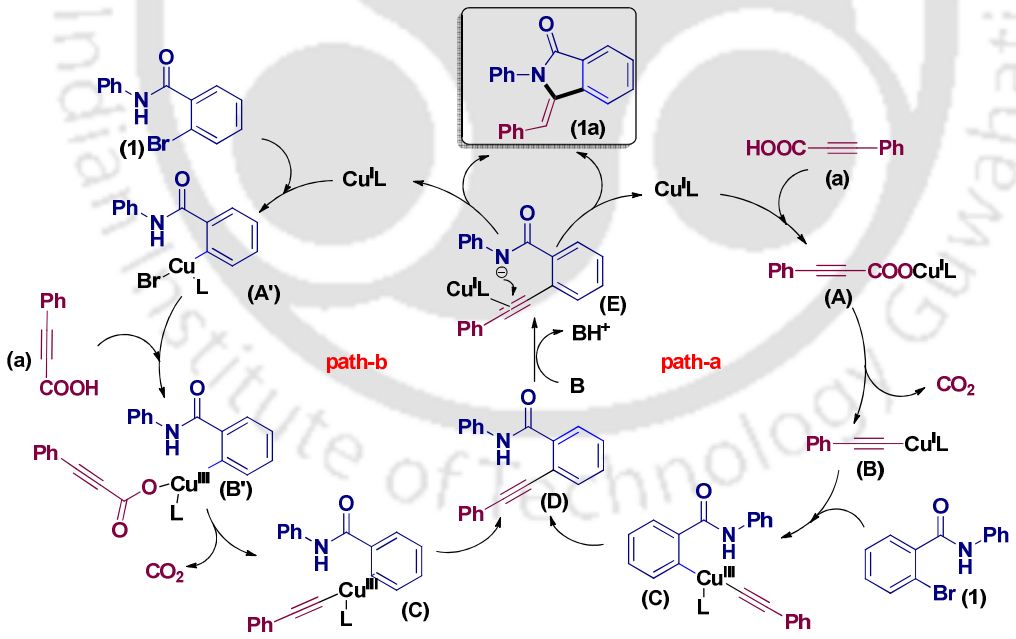


Scheme IV.3.2. *Competitive hydroxylation of 2-bromobenzamide*

After successful accomplishment of the present transformation with 2-bromo benzamides next we turned our attention towards more reactive 2-iodo benzamides. The reaction of 2-iodo benzamide (**1′**) with phenyl propiolic acid (**a**) under previous optimized conditions provided 3-phenylmethylene isoindolin-1-one (**1a**) in 77% isolated yield (Scheme IV.3.1). Interestingly, the same reaction when performed in the absence of ligand 1,10-phen, proceeded smoothly virtually unaffecting the yield and reaction time. This

illustrates the higher reactivity of C–I bond compared to C–Br bond towards decarboxylative C–C bond formation. Further, this ligand free condition was then applied for the reaction of 2-iodo benzamides (**2′**) and (**3′**) with phenyl propiolic acid (**a**) which provided their corresponding isoindolin-1-one products (**2′a**) and (**3′a**) in 73% and 79% yields respectively (Scheme IV.3.1). The trend in the yields obtained from 2-iodo precursors without the involvement of ligand was found to be identical to that of 2-bromo benzamides with assistance of ligand.

Mechanistic studies. Based on the literature reports,[2a,2d-e,4,30] two mechanistic pathways have been proposed for the formation of 3-phenylmethyleneisoindolin-1-one as outlined in Scheme IV.3.3. In the first mechanism (path-a, Scheme IV.3.3), Cu(I) initially binds with phenyl propiolic acid (**a**) to generate intermediate (**A**). This Cu(I) species via a decarboxylative path gives Cu-alkynylide species (**B**) which undergoes oxidative addition with 2-bromobenzamide (**1**) to produce Cu(III) intermediate (**C**). Reductive elimination of Cu from (**C**) gives the *ortho*-alkynylated product (**D**).



Scheme IV.3.3. *Plausible mechanism for the formation of 3-methyleneisoindolin-1-one*

Deprotonation of the amide N–H of the intermediate (**D**) and subsequent hydroamination[31] of C–C triple bond promoted by co-ordination of Cu(I) with the alkynyl group results in the formation of 3-phenylmethyleneisoindolin-1-one (**1a**) via the intermediacy of (**E**) along with regeneration of Cu(I) (path-a, Scheme IV.3.3).

However, in the alternative mechanism (path-b, Scheme IV.3.3) initial oxidative addition of Cu(I) with 2-halobenzamide occurs first to give intermediate (**A′**). Intermediate (**A′**) couples with phenylpropiolic acid (**a**) to give intermediate (**B′**). Loss of CO_2 from intermediate (**B′**) would give intermediate (**C**) which eventually lead to the formation of desired product (**1a**) as shown in (path-b, Scheme III.3.3).

In conclusion, we have developed a Cu(I)-catalyzed synthesis of substituted 3-methyleneisoindolin-1-ones involving decarboxylative cross-coupling of 2-halobenzamides with aryl alkynyl acids followed by *5-exo-dig* heteroannulation. In this transformation alkynyl acids have been utilized to generate alkyne intermediate for the synthesis of this important heterocyclic scaffold. While reactions of 2-iodo benzamides proceeded without ligand, for 2-bromo subtrates the assistance of a ligand is essential.

IV.4. Experimental section

IV.4.1. General information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H NMR (600 MHz) $CDCl_3$ solvent as the internal standard for ^{13}C NMR (150 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using ESI mode. FT-IR spectra were recorded in KBr or neat. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods

implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Alkynyl carboxylic acids were synthesized by using reported procedures.[7]

IV.4.2. General procedure for the synthesis of (*Z*)-3-Benzylidene-2-phenylisoindolin-1-one (1a). To a solution of 2-bromobenzamide (**1**) (138 mg, 0.5 mmol) in DMSO (2 mL) was added CuI (9.5 mg, 0.05 mmol), 1,10-phen (9 mg, 0.05 mmol), Cs_2CO_3 (245 mg, 0.75 mmol), phenyl propiolic acid (**a**) (87.6 mg, 0.6 mmol) and the resultant mixture was stirred in a preheated oil bath at 120 ^oC for 2 h. The reaction mixture was then cooled to room temperature, admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (19:1 hexane / ethyl acetate) to give (*Z*)-3-benzylidene-2-phenylisoindolin-1-one (**1a**) (102.5 mg, 69% yield). The same procedure was also followed for other derivatives also.

IV.4.3. Crystallographic description of (*Z*)-3-Benzylidene-2-(4-chlorophenyl)isoindolin-1-one (5a). $C_{21}H_{14}ClNO$, crystal dimensions 0.43 x 0.33 x 0.28 mm, M_r = 331.78, Triclinic, space group P-1, a = 7.6383(7), b = 9.0793(8), c = 12.1907(10) Å, α = 103.312(3) ^{o}, β = 93.496(3) ^{o}, γ = 96.408(3) ^{o}, V = 814.28(12) Å^3, Z = 2, ρ_{calcd} = 1.353 mg/m^3, μ = 0.241 mm^{-1}, $F(000)$ = 344.0, reflection collected / unique = 4062/ 2881, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0412, wR_2 = 0.1122, R indices (all data): R_1 = 0542, wR_2 = 0.1201, goodness of fit = 1.001. CCDC reference number 1024354.

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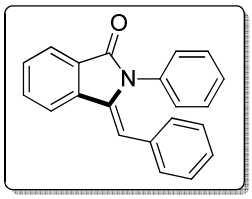
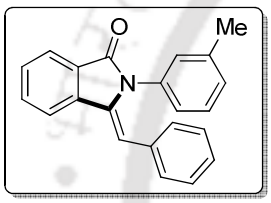
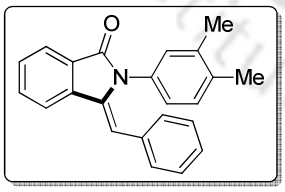
IV.6. Spectral data



(*Z*)-3-Benzylidene-2-phenylisoindolin-1-one (1a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.82 (s, 1H), 6.84 (d, J = 7.8 Hz, 2H), 6.90 (t, J = 7.8 Hz, 2H), 6.95 (t, J = 7.8 Hz, 1H), 7.03–7.09 (m, 5H), 7.54 (t, J = 7.8 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 107.8, 119.6, 124.1, 126.8, 126.9, 127.4, 128.0, 128.4, 129.3, 129.4, 132.6, 133.8, 134.6, 136.1, 138.9, 168.2; IR (KBr): 3029, 2922, 1705, 1647, 1494, 1469, 1388, 1297, 1123, 1069, 761, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}NO$ (MH^+) 298.1226; found 298.1232.

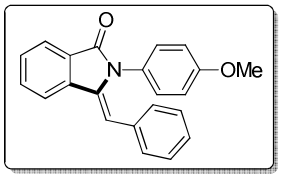


(*Z*)-3-Benzylidene-2-(*m*-tolyl)isoindolin-1-one (2a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.06 (s, 3H), 6.77 (s, 1H), 6.81 (s, 1H), 6.84 (d, J = 7.2 Hz, 3H), 6.91 (t, J = 7.2 Hz, 2H), 6.93–6.96 (m, 2H), 6.99 (t, J = 7.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.83, (d, J = 7.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 107.8, 119.5, 124.0, 124.6, 126.8, 127.3, 127.7, 128.1, 128.2, 128.3, 129.1, 129.4, 132.6, 134.0, 134.7, 135.8, 138.3, 138.8, 168.1; IR (KBr): 3048, 2921, 1707, 1631, 1489, 1449, 1402, 1351, 1300, 1184, 1120, 926, 798, 767, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{17}NO$ (MH^+) 312.1383; found 312.1391.

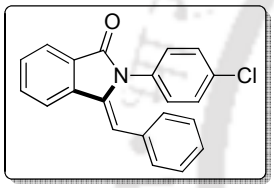


(*Z*)-3-Benzylidene-2-(3,4-dimethylphenyl)isoindolin-1-one (3a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.95 (s, 3H), 2.10 (s, 3H), 6.71 (s, 1H), 6.79 (s, 1H), 6.83–6.86 (m, 4H), 6.88 (t, J = 7.2 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.4, 19.5, 107.6, 119.5, 124.0, 124.9, 126.5, 127.1, 128.2, 128.8, 129.1, 129.3, 129.5, 132.4, 133.5, 134.0, 134.9, 135.4, 136.6, 138.8, 168.1; IR (KBr): 3018, 2966, 2918, 1710, 1634, 1606, 1500, 1468, 1446, 1394, 1341, 1302, 1184, 1112, 909, 811, 766, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{19}NO$ (MH^+) 326.1539; found

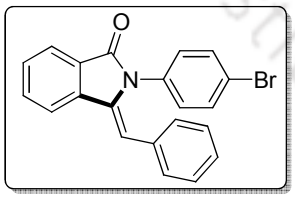
326.1536.



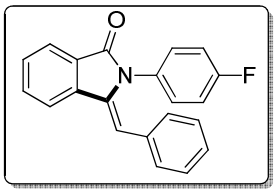
(*Z*)-3-Benzylidene-2-(4-methoxyphenyl)isoindolin-1-one (4a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.71 (s, 3H), 6.62 (d, *J* = 7.2 Hz, 2H), 6.82 (s, 1H), 6.87 (d, *J* = 7.2 Hz, 2H), 6.94–7.01 (m, 5H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.6, 107.6, 113.8, 119.5, 123.9, 126.6, 127.3, 128.0, 128.5, 128.9, 129.3, 132.5, 133.7, 134.8, 138.7, 158.5, 168.3; IR (KBr): 3014, 2929, 1714, 1640, 1607, 1511, 1467, 1445, 1391, 1298, 1248, 1123, 825, 766, 695 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{17}NO_2$ (MH^+) 328.1332; found 328.1339.



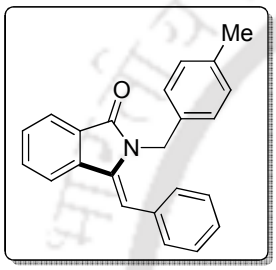
(*Z*)-3-Benzylidene-2-(4-chlorophenyl)isoindolin-1-one (5a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.83–6.85 (m, 3H), 6.95–6.99 (m, 4H), 7.01–7.04 (m, 3H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 108.0, 119.7, 124.2, 127.1, 127.6, 127.8, 128.5, 128.6, 129.4, 129.6, 132.6, 132.9, 133.6, 134.4, 134.6, 138.7, 168.0; IR (KBr): 3050, 3021, 2927, 1701, 1643, 1471, 1442, 1384, 1342, 1314, 1189, 1129, 1085, 1012, 820, 760, 725, 694 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{14}ClNO$ (MH^+) 332.0837; found 332.0832.



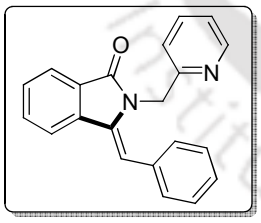
(*Z*)-3-Benzylidene-2-(4-bromophenyl)isoindolin-1-one (6a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.83–685 (m, 3H), 6.91–6.93 (m, 2H), 6.96 (t, *J* = 7.2 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.16–7.18 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 108.0, 119.7, 120.5, 124.2, 127.1, 127.6, 127.8, 128.9, 129.4, 129.6, 131.4, 132.9, 133.6, 134.4, 135.1, 138.7, 167.9; IR (KBr): 3051, 2923, 1710, 1638, 1487, 1394, 1342, 1302, 1183, 1122, 1066, 1007, 818, 762, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{14}BrNO$ (MH^+) 376.0332; found 376.0341.



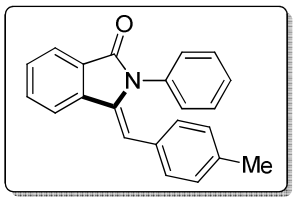
(*Z*)-3-Benzylidene-2-(4-fluorophenyl)isoindolin-1-one (7a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.74–6.77 (m, 2H), 6.83–685 (m, 3H), 6.95 (t, *J* = 7.8 Hz, 2H), 6.99–7.03 (m, 3H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 107.8, 115.2, 115.3, 119.6, 124.1, 127.0, 127.5, 127.9, 129.0, 129.1, 129.4, 129.5, 132.1, 132.8, 133.6, 134.7, 138.7, 160.6, 162.2, 168.2; IR (KBr): 3054, 1706, 1640, 1604, 1505, 1471, 1446, 1379, 1301, 1217, 1121, 828, 765, 694 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{14}FNO$ (MH^+) 316.1132; found 316.1135.



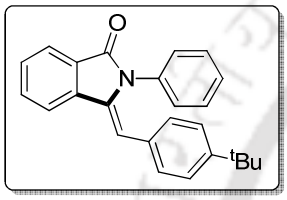
(*Z*)-3-Benzylidene-2-(4-methylbenzyl)isoindolin-1-one (8a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 3H), 4.94 (s, 2H), 6.48 (d, *J* = 7.8 Hz, 2H), 6.74 (s, 1H), 6.90 (d, *J* = 7.2 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.29–7.32 (m, 3H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.2, 44.8, 107.6, 119.6, 123.6, 126.6, 127.5, 128.1, 128.3, 128.8, 129.1, 129.9, 132.2, 134.0, 134.5, 134.8, 136.4, 138.7, 169.2; IR (KBr): 3049, 2920, 1706, 1655, 1620, 1471, 1429, 1395, 1343, 1288, 1108, 958, 786, 757, 695 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{19}NO$ (MH^+) 326.1539; found 326.1535.



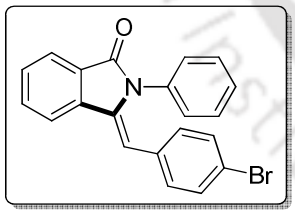
(*Z*)-3-Benzylidene-2-(pyridin-2-ylmethyl)isoindolin-1-one (9a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.98 (s, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.73 (s, 1H), 6.95 (d, *J* = 7.8 Hz, 2H), 6.98–7.00 (m, 1H), 7.12 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 47.0, 107.5, 119.7, 120.3, 121.7, 123.8, 127.6, 128.0, 128.4, 129.3, 129.4, 132.4, 134.3, 134.9, 136.3, 138.6, 149.3, 156.5, 169.1; IR (KBr): 3059, 3008, 2932, 1702, 1654, 1591, 1473, 1431, 1399, 1366, 1344, 1119, 984, 949, 753, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{16}N_2O$ (MH^+) 313.1335; found 313.1343.



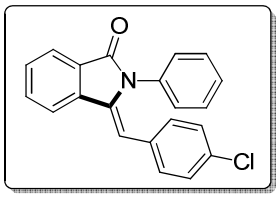
(*Z*)-3-(4-Methylbenzylidene)-2-phenylisoindolin-1-one (1b): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.17 (s, 3H), 6.71 (q, J = 4.2 Hz, 4H), 6.79 (s, 1H), 7.05–7.09 (m, 5H), 7.52 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 108.1, 119.5, 124.1, 126.8, 127.4, 127.9, 128.1, 128.4, 129.2, 129.3, 130.8, 132.6, 134.0, 136.2, 136.7, 139.0, 168.2; IR (KBr): 3034, 3023, 2920, 1706, 1647, 1495, 1468, 1386, 1339, 1299, 1183, 1122, 922, 827, 758, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{17}NO$ (MH^+) 312.1383; found 312.1389.



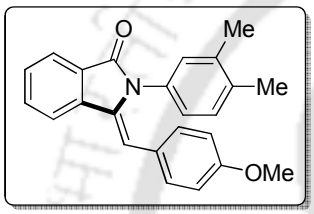
(*Z*)-3-(4-(*tert*-Butyl)benzylidene)-2-phenylisoindolin-1-one (1c): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.19 (s, 9H), 6.73 (d, J = 7.8 Hz, 2H), 6.83 (s, 1H), 6.89 (d, J = 7.8 Hz, 2H), 7.00–7.04 (m, 5H), 7.52 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 6.6 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 31.4, 34.6, 108.0, 119.5, 124.1, 124.3, 126.7, 127.5, 128.0, 128.2, 128.9, 129.25, 129.33, 130.8, 132.6, 134.4, 136.1, 138.9, 150.0, 168.1; IR (KBr): 3054, 2960, 1712, 1599, 1495, 1469, 1380, 1338, 1300, 1182, 1111, 1063, 1017, 844, 758, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{23}NO$ (MH^+) 354.1852; found 354.1849.



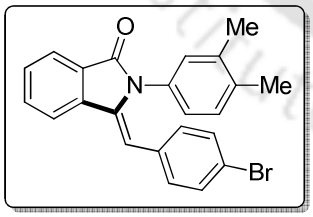
(*Z*)-3-(4-Bromobenzylidene)-2-phenylisoindolin-1-one (1d): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.69 (t, J = 4.2 Hz, 3H), 7.02 (d, J = 7.8 Hz, 2H), 7.04–7.06 (m, 2H), 7.10–7.12 (m, 3H), 7.54 (t, J = 7.8 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 106.2, 119.6, 120.9, 124.1, 127.2, 127.4, 127.9, 128.6, 129.6, 130.5, 130.7, 132.7, 135.1, 135.9, 138.6, 168.1; IR (KBr): 3055, 2923, 1708, 1638, 1593, 1486, 1391, 1300, 1181, 1123, 1070, 1007, 845, 810, 763, 694 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{14}BrNO$ (MH^+) 376.0322; found 376.0327.



(*Z*)-3-(4-Chlorobenzylidene)-2-phenylisoindolin-1-one (1e): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.72 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 2H), 7.05–7.06 (m, 2H), 7.10–7.13 (m, 3H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 106.2, 119.6, 124.2, 127.2, 127.5, 127.6, 128.0, 128.6, 129.6, 130.5, 132.3, 132.70, 132.74, 135.2, 136.0, 138.7, 168.1; IR (KBr): 3057, 2922, 1708, 1647, 1596, 1488, 1388, 1297, 1120, 1088, 905, 760, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{14}ClNO$ (MH^+) 332.0837; found 332.0833.

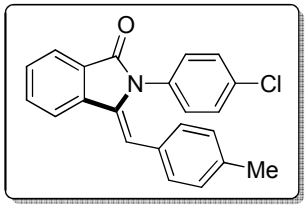


(*Z*)-2-(3,4-Dimethylphenyl)-3-(4-methoxybenzylidene)isoindolin-1-one (3f): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.99 (s, 3H), 2.13 (s, 3H), 3.68 (s, 3H), 6.43 (d, *J* = 9.0 Hz, 2H), 6.73–6.76 (m, 4H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.90 (t, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.5, 19.6, 55.4, 107.6, 114.2, 119.4, 124.0, 124.9, 126.5, 128.1, 128.8, 129.0, 129.5, 130.5, 130.9, 132.4, 133.7, 133.8, 135.3, 136.6, 139.0, 158.6, 168.2; IR (KBr): 2918, 1713, 1632, 1601, 1507, 1468, 1386, 1342, 1302, 1247, 1175, 1107, 1024, 910, 837, 759, 692 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{21}NO_2$ (MH^+) 356.1645; found 356.1656.

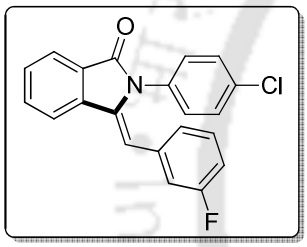


(*Z*)-3-(4-Bromobenzylidene)-2-(3,4-dimethylphenyl)isoindolin-1-one (3g): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.98 (s, 3H), 2.17 (s, 3H), 6.61 (s, 1H), 6.66–6.68 (m, 3H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.4, 19.5, 105.9, 119.5, 120.6, 124.0, 125.0, 128.1, 128.7, 129.5, 129.6, 130.1, 130.4, 132.5, 133.0, 133.2, 135.6, 136.0, 136.7, 138.4, 167.9; IR (KBr): 3027, 2919, 1705, 1647, 1500, 1484, 1385, 1309, 1184, 1114, 1070, 1010, 915, 818, 757, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{18}BrNO$

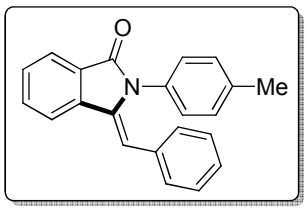
(MH^+) 404.0645; found 404.0652.



(*Z*)-2-(4-Chlorophenyl)-3-(4-methylbenzylidene)isoindolin-1-one (5b): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.22 (s, 3H), 6.72 (d, J = 7.8 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.81 (s, 1H), 6.98 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 108.3, 119.6, 124.1, 127.7, 128.3, 128.4, 128.6, 129.3, 129.4, 130.6, 132.5, 132.8, 133.9, 134.7, 137.2, 138.8, 168.0; IR (KBr): 3043, 2918, 1713, 1637, 1492, 1471, 1396, 1343, 1304, 1182, 1122, 1084, 912, 832, 759, 691 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{16}ClNO$ (MH^+) 346.0993; found 346.0985.

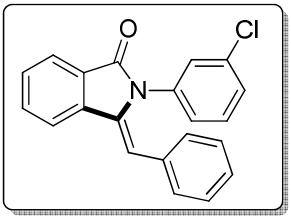


(*Z*)-2-(4-Chlorophenyl)-3-(3-fluorobenzylidene)isoindolin-1-one (5h): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.56 (d, J = 9.6 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 6.71–6.74 (m, 2H), 6.92 (q, J = 7.8 Hz, 1H), 6.99 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 106.2, 113.9, 114.0, 116.1, 116.3, 119.7, 124.2, 125.2, 127.8, 128.5, 128.6, 129.0, 129.1, 129.8, 132.9, 133.0, 134.5, 135.4, 135.8, 135.9, 138.4, 161.3, 162.9, 167.9; IR (KBr): 3056, 3023, 1703, 1645, 1580, 1488, 1388, 1313, 1127, 1088, 871, 819, 762, 697 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{13}ClFNO$ (MH^+) 350.0742; found 350.0735.

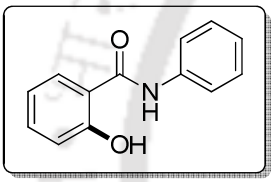


(*Z*)-3-Benzylidene-2-(*p*-tolyl)isoindolin-1-one (10′a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 6.79 (s, 1H), 6.83–6.94 (m, 8H), 6.96 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.65 (t, J = 6.6 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.2, 107.7, 119.6, 124.0, 126.6, 127.25, 127.34, 128.1, 129.0, 129.3, 129.4, 132.5, 133.5, 133.8, 134.8, 136.8, 138.9, 168.2; IR (KBr): 3044, 3021, 2920, 1707, 1641, 1512, 1469, 1389, 1341, 1301, 1186, 1126, 1073, 925, 809, 760, 692 cm^{-1}; HRMS

(ESI): calcd. for $C_{22}H_{17}NO$ (MH^+) 312.1383; found 312.1389.



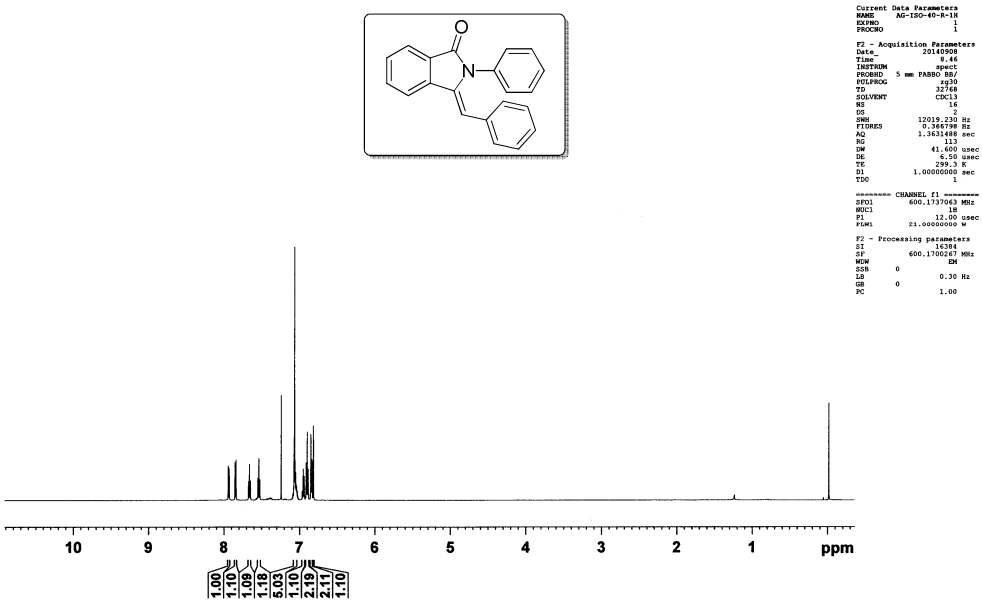
(*Z*)-3-Benzylidene-2-(3-chlorophenyl)isoindolin-1-one (11′a): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.85 (s, 1H), 6.87 (d, J = 7.8 Hz, 2H), 6.96–7.02 (m, 7H), 7.54 (t, J = 7.8 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 108.1, 119.7, 124.2, 125.6, 127.0, 127.2, 127.6, 127.8, 127.9, 129.1, 129.2, 129.6, 132.9, 133.6, 134.0, 134.3, 137.1, 138.7, 167.9; IR (KBr): 3070, 1706, 1632, 1588, 1473, 1401, 1350, 1298, 1183, 1126, 1072, 925, 905, 798, 767, 702, 690 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{14}ClNO$ (MH^+) 332.0837; found 332.0841.



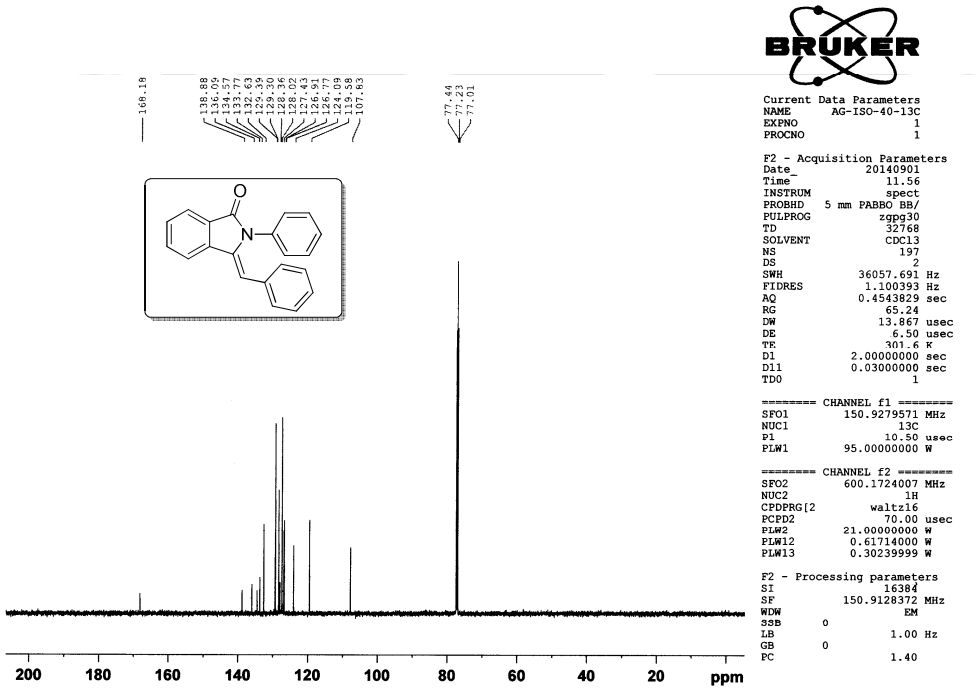
2-Hydroxy-*N*-phenylbenzamide (1a′): ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.92 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H), 7.55–7.59 (m, 3H), 8.08 (s, 1H), 12.01 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 114.8, 119.1, 119.2, 121.5, 125.6, 125.7, 129.4, 134.9, 136.8, 162.0, 168.6; IR (KBr): 3299, 2923, 1621, 1556, 1500, 1455, 1375, 1332, 1201, 1158, 894, 753 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{11}NO_2$ (MH^+) 214.0823; found 214.0863.

IV.7. Spectra

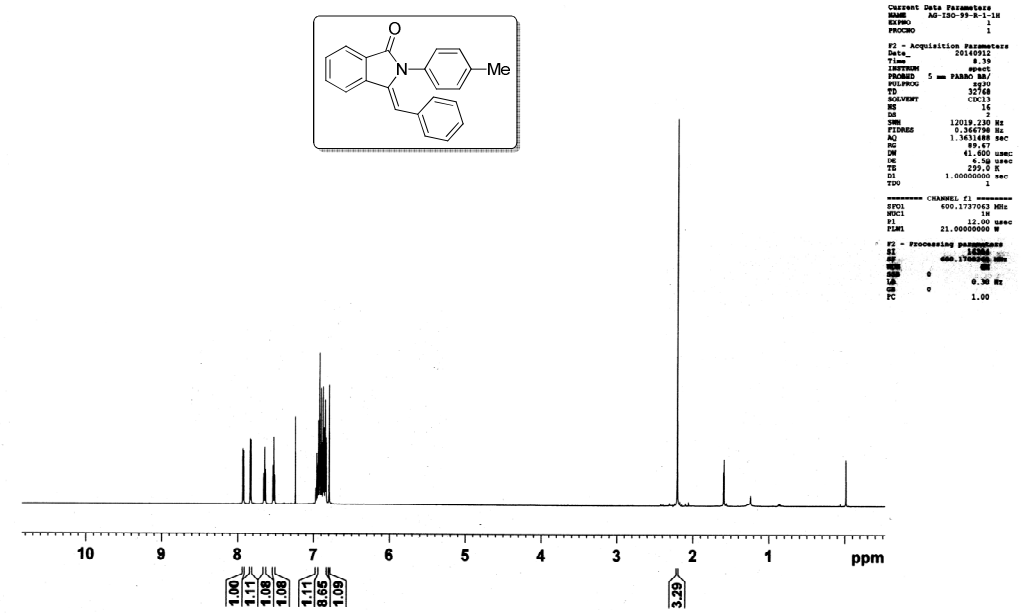
(*Z*)-3-Benzylidene-2-phenylisoindolin-1-one (1a): ^{1}H NMR (600 MHz, $CDCl_3$)



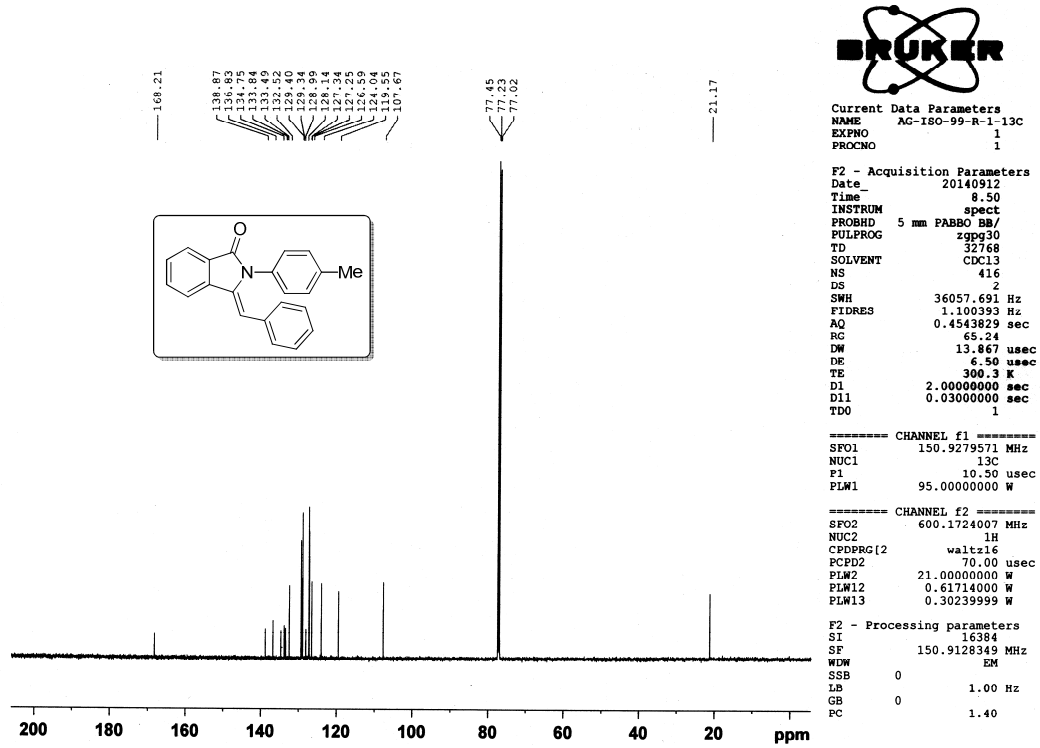
(*Z*)-3-Benzylidene-2-phenylisoindolin-1-one (1a): ^{13}C NMR (150 MHz, $CDCl_3$)



(*Z*)-3-Benzylidene-2-(*p*-tolyl)isoindolin-1-one (10′a): ^{1}H NMR (600 MHz, $CDCl_3$)



(*Z*)-3-Benzylidene-2-(*p*-tolyl)isoindolin-1-one (10′a): ^{13}C NMR (150 MHz, $CDCl_3$)



BRUKER

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PROCNO 1

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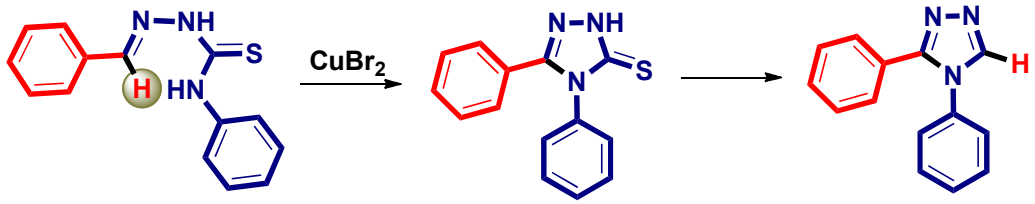
Chapter V

Synthesis of 1,2,4-Triazoles via Oxidative Heterocyclization: Selective C–N Bond Over C–S Bond Formation



Abstract: *The higher propensity of C–N over C–S bond forming ability was demonstrated, through formal C–H functionalization during the construction of 4,5-disubstituted 1,2,4-triazole-3-thiones from arylidenearylthiosemicarbazides catalyzed by Cu(II). However, streric factor imparted by the o-disubstituted substrates tend to change the reaction path giving thiodiazole as the major or an exclusive product. Upon prolonging the reaction time, the in situ generated thiones are transformed to 4,5-disubstituted 1,2,4-triazoles via a desulfurization process. Desulfurization of 1,2,4-triazole-3-thiones is assisted by thiophilic Cu to provide 1,2,4-triazoles with concomitant formation of CuS and polynuclear sulphur anions as confirmed from scanning electron microscope (SEM) and energy-dispersive X-ray spectroscopy (EDS) measurements.*

CHAPTER V

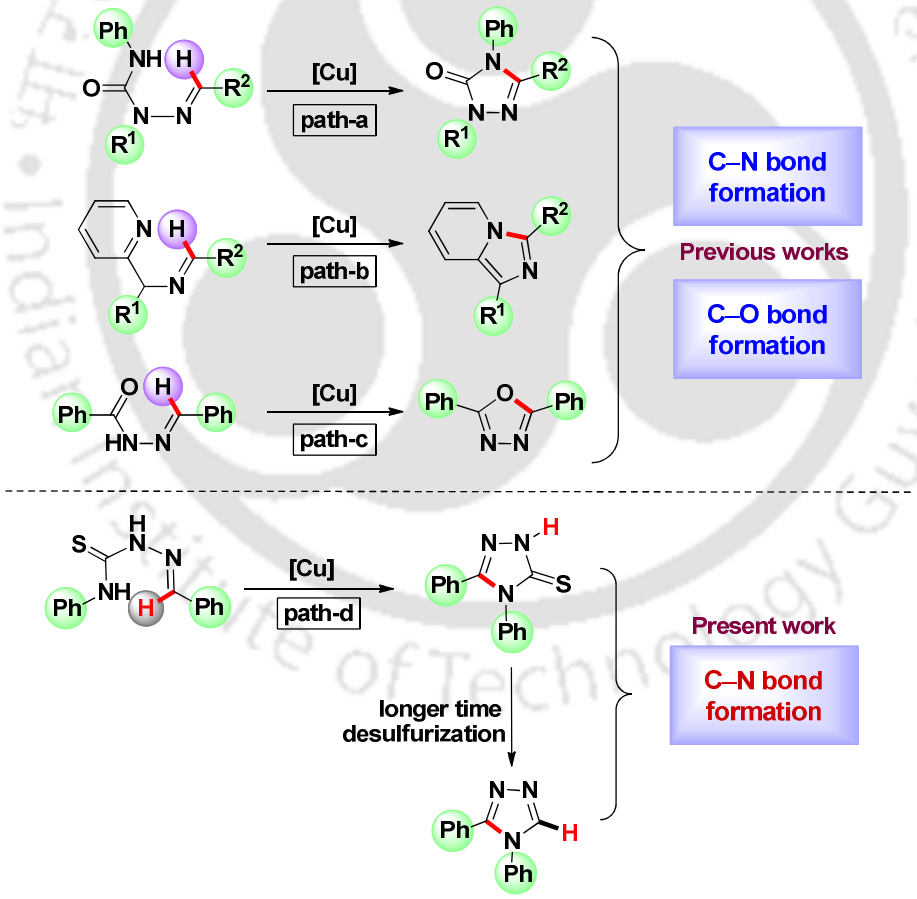
V. Synthesis of 1,2,4-Triazoles via Oxidative Heterocyclization: Selective C–N Bond Over C–S Bond Formation

V.1. Introduction

The non-requirement of substrate pre-functionalization leads to step and atom economy in transition metal catalyzed C–H bond functionalizations. Lately, the ubiquitous C–H bonds in organic compounds can be foreseen as quiescent synthetic equivalent of several useful functional groups. Because of the reduced number of steps in achieving the targeted synthesis these strategies are of paramount importance.[1] Of all C–H (sp, sp^2 and sp^3) bonds, the functionalizations of sp^2 C–H bonds of aromatics and hetero-aromatics have been well scrutinized.[2] However, analogous manipulation of imine sp^2 C–H bonds are relatively scarce. Some examples of late transition metal catalyzed imine C–H bond functionalizations are: (i) addition of 2-methylaza-arenes to imine catalyzed by Pd;[3a] (ii) benzonitrile addition to sulfenylamine catalyzed by Pd;[3b,c] (iii) oxidative coupling of arylimines with alkynes[3d] and 2-pyridyl[3e] using Rh and (iv) a Cu-catalyzed arylation of imine C–H bond in benzotriazepines.[3f] Besides, some of the substrates possessing imine functionality have been reported to undergo skeletal rearrangement[4a-c] or utilize the proximate effect of coordination to the metal centre which serves as a directing group toward sp^2 and sp^3 C–H bond activation.[4d-f]

Pertinent to imine C(sp^2)–H functionalizations, Noto group has demonstrated a copper catalyzed synthesis of 1,2,4-triazoles from benzaldehyde semicarbazones via an oxidative C–N bond formation at the imine C(sp^2)–H (path-a, Scheme V.1.1).[5] An analogous copper catalyzed oxidative C–N bond forming protocol was reported by Döring *et al.* and Zhu *et al.* indpendently for the synthesis of heterobicycles from various Schiff bases (path-b, Scheme V.1.1).[6] Recently, we have achieved an elegant method for the synthesis of 2,5-substituted 1,3,4-oxadiazole via oxidative C–O bond formation involving

an amidic carbonyl and an imine C–H bond in *N*-arylidenearoylhydrazide system (path-c, Scheme V.1.1).[7] Inspired by these developments on imine C(sp^2)–H bond functionalizations particularly using copper catalyst, we anticipated that a copper based strategy could be applied to imine C–H functionalization of arylidenearylthiosemicarbazide. If the C–H functionalization strategy works there exist two distinct possibilities *viz.* C–N bond or a C–S bond formation leading to the formation of either a 1,3,4-thiadiazole-2-amine or a 2,4-dihydro-3*H*-1,2,4-triazole-3-thione. In an attempt to perform the functionalization of arylidenearylthiosemicarbazide under copper catalyzed condition resulted in a selective formation of 1,2,4-triazole-3-thione as the sole product (path-d, Scheme V.1.1). Thus, out of the two possibilities, selective formation of C–N bond involving the thioamidic NH and an imine C–H bond is taking place.



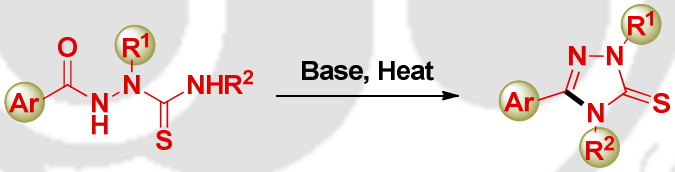
Scheme V.1.1. *Copper catalyzed heterocyclization via imine C–H bond functionalizations*

V.2. Strategies for 1,2,4-triazole-3-thiones

Mercapto and thione derivatives of 1,2,4-triazoles are known to exhibit a variety of biological activities such as antibacterial,[8a-e] antifungal,[8f-g] antitumor,[8h] anti-inflammatory,[8i] antiviral,[8j] antitubercular,[8k] anticonvulsant[8l] and antidepressant[8m] activities. Various applications of this scaffold has led to the development of various strategies for their synthesis which can be categorized as (i) cyclodehydration of acylthiosemicarbazides;[9] (ii) condensation of aroylisothiocyanates and hydrazines,[10] and (iii) thionation of 1,2,4-triazole-3-ones.[11]

(i) Cyclodehydration of acylthiosemicarbazides

Cyclodehydration of acylthiosemicarbazides under basic conditions is the most explored synthetic route for the synthesis of 1,2,4-triazole-3-thiones. This has been achieved with a variety of bases such as sodium hydroxide,[9a-c] potassium hydroxide,[9d] sodium carbonate,[9e] triethylamine,[9f] sodium hydrogenocarbonate[9g] etc. The use of microwave irradiation instead of conventional heating for the cyclization of acylthiosemicarbazide is also reported under solid supported condition which reduces the reaction time significantly (Scheme V.2.1).[9h]



Scheme V.2.1. *Base mediated cyclodehydration of acylthiosemicarbazides*

(ii) Condensation of aroylisothiocyanates and hydrazines

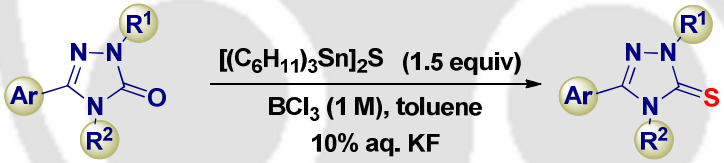
Hoggarth reported the synthesis of 1,2,4-triazole-3-thiones using benzoyl isothiocyanate which on reaction with an excess of hydrazine in an alcoholic solvent produced a mixture of triazole-3-thione and benzoylhydrazide.[10a] A slightly modified method was developed by Durant group later which avoids the use of excess hydrazine and the reaction is performed in benzene instead of alcohol. However, in the presence of a

strong nucleophile such as methylhydrazine a competing benzoylation reaction was also observed in this protocol (Scheme V.2.2).[10b]

Scheme V.2.2. *Condensation of aroylisothiocyanate with hydrazines*

(iii) Thionation of 1,2,4-triazol-3-ones

Kane demonstrated a synthetic route to 1,2,4-triazole-3-thiones via a thionation reaction using a combination of bis(tricyclohexylstannyl) sulphide and boron trichloride.[11] The method avoids the use of toxic alkyl hydarzines and provided moderate to good yields of the products. However, relatively high cost of bis(tricyclohexylstannyl) sulphide along with its high molecular weight restricted its utility to smaller scale reactions (Scheme V.2.3).

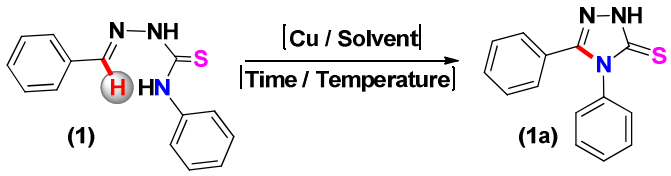


Scheme V.2.3. *Thionation of 1,2,4-triazol-3-ones*

V.3. Present work

Although a few methodologies for the synthesis of 1,2,4-triazole-3-thiones are reported in literature, till date, no catalytic approaches have been developed. Herein, we have reported a copper catalyzed method for the synthesis of 4,5-disubstituted-1,2,4-triazole-3-thiones involving imine C–H bond functionalization of *N*-arylidenearylthiosemicarbazides. However, when any one of the aryl ring of arylidenearylthiosemicarbazide moiety is *o*-disubstituted, the reactivity pattern changes completely giving thiodiazole as the major or an exclusive product.

Table V.3.1. *Screening of reaction conditions*[a,b]



Entry	Catalyst (mol %)	Solvent	Temp (^{o}C)	Time (h)	Yield[b] (%)
1	$Cu(OTf)_2$ (10)	DMSO	110	2	23
2	$Cu(OTf)_2$ (20)	DMSO	110	2	37
3	$Cu(OTf)_2$ (30)	DMSO	110	2	64
4	$Cu(OTf)_2$ (30)	DMSO	80	2	61
5	$Cu(ClO_4)_2.6H_2O$ (30)	DMSO	80	2	67
6	**$CuBr_2$ (30)**	**DMSO**	**80**	**0.75**	**69**
7	$CuSO_4.5H_2O$ (30)	DMSO	80	2	68
8	$CuCl_2$ (30)	DMSO	80	0.75	59
9	$Cu(OAc)_2$ (30)	DMSO	80	2	62
10	CuCl (30)	DMSO	80	2	60
11	CuBr (30)	DMSO	80	2	56
12	$CuBr_2$ (30)	DMF	80	0.75	0
13	$CuBr_2$ (30)	DMA	80	0.75	0
14	$CuBr_2$ (30)	Dioxane	80	0.75	0
15	$CuBr_2$ (30)	CH_3CN	80	0.75	15

[a]Reaction conditions: *N*-arylidenearylthiosemicarbazide (**1**) (0.25 mmol). [b]Isolated yields of pure product.

Optimization of reaction conditions. To check the efficacy of a copper catalyst towards the functionalization of imine C–H bond of arylidenearylthiosemicarbazide, an initial reaction was attempted by treating arylidenearylthiosemicarbazide (**1**) with 10 mol % of $Cu(OTf)_2$ in DMSO at 110 ^{o}C. The reaction after 2 h, provided a product in 23% yield (entry 1, Table V.3.1). The structure was revealed to be 4,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**1a**) upon spectroscopic analysis. However, under the aforesaid reaction conditions there was substantial decomposition of starting material giving multitudes of unidentifiable side products; thus further optimization was necessary. In pursuit to achieve an improved yield of thione (**1a**) from (**1**) various other reaction parameters such as catalyst quantity, salts of copper, solvents and reaction temperature were varied and the results are summarized in Table V.3.1. Increasing the $Cu(OTf)_2$ loading to 20 mol % and 30 mol % resulted in an improved yield of the product (**1a**) (entries 2–3, Table V.3.1). When the reaction was carried out at 80 ^{o}C instead of 110 ^{o}C,

no significant difference in yield was observed (entry 4, Table V.3.1). Among all other Cu(II)-salts [$Cu(ClO_4)_2.6H_2O$, $CuBr_2$, $CuSO_4.5H_2O$, $CuCl_2$, $Cu(OAc)_2$] and Cu(I) salts [CuCl and CuBr] tested, the use of $CuBr_2$ provided the best yield of (**1a**) (69%) in a shorter reaction time (entries 5−11, Table V.3.1). Although catalysts $Cu(ClO_4)_2.6H_2O$ and $CuSO_4.5H_2O$ were equally effective in bringing about the transformation, but the time taken for completion of the reactions were longer compared to the use of $CuBr_2$. Except for DMSO, all other polar solvents like DMF, DMA, acetonitrile and non-polar solvent like 1,4-dioxane were unsuitable for this reaction (entries 12−15, Table V.3.1). Addition of base to the reaction was not beneficial. When the reaction was carried out in the presence of a base Cs_2CO_3 (1 equiv) keeping all other parameters constant it gave poor yield of the desired product along with several other side products. No doubt at higher temperature (above 80 ^oC), triazole-thiones (Scheme V.3.1) are formed rapidly but are also transform *in situ* to triazoles (Scheme V.3.3). Thus higher temperature was not suitable for the formation of triazole-thiones (Scheme V.3.1). Thus, the use of $CuBr_2$ (30 mol %) in DMSO solvent at 80 ^oC was found to be the optimal conditions for this transformations and rest of the reactions were performed adopting these conditions.

Substrate scope for 1,2,4-triazole-3-thiones. After figuring out the best optimum condition, we next explored the scope of various substrates leading to the formation of thiones. First, *N*-arylidenearylthiosemicarbazides derived from various substituted arylaldehydes were subjected to the present reaction conditions to see the effects of substitution. When the Ar^1 ring is substituted with electron-donating groups such as 4-OCH_3 (**2**), 4-CH_3 (**3**) or electron-withdrawing groups such as 3-Br (**4**), 4-Cl (**5**), all provided their corresponding 1,2,4-triazole-3-thiones (**2a**–**5a**) in yields ranging from 67-74% (Scheme V.3.1). No particular correlation between the electronic nature of the substituents and the yields of products could be ascertained; except slightly longer reaction times required for substrates (**4**) and (**5**) possessing electron-withdrawing groups (Scheme V.3.1). When the aryl ring Ar^2 bears an electron-donating group such as 4-CH_3 and Ar^1 is unsubstituted as in (**6**), a moderate yield (67%) of the corresponding 1,2,4-triazole-3-thione (**6a**) was obtained. Various possible permutations and combinations of substituents in both the aryl (Ar^1 and Ar^2) rings of *N*-arylidenearylthiosemicarbazides were next investigated.

Keeping the Ar^2 (4-CH_3) part constant, when the substituents in the Ar^1 ring were varied with either electron-donating [4-CH_3 (**7**) and 3,4-di-OCH_3 (**8**)] or electron-withdrawing [4-Cl (**9**) and 4-F (**10**)] groups all underwent effective cyclization via the formation of C–N bond (Scheme V.3.1). With other combinations of electron-donating substituents in the aryl rings [4-CH_3 and 2-OCH_3 (**11**), 4-OBu and 4-^{n}Bu (**12**), 3,4-di-OCH_3 and 3,4-di-CH_3 (**13**)], moderate to good yields of their respective thiones (**11a–13a**) were obtained in shorter reaction times. An electron-withdrawing group (4-Br) in Ar^2 and an unsubstituted Ar^1 ring as in (**14**), provided good yield (74%) of the thione (**14a**). Keeping the substituent 4-Br in ring Ar^2 and varying the substituents in ring Ar^1 *viz.* 4-CH_3 (**15**), 4-OCH_3 (**16**), 4-Cl (**17**) and 4-Br (**18**), desired thiones (**15a–18a**) were obtained in the range of 61-79% yields (Scheme V.3.1). Replacing 4-Br with 4-Cl in the Ar^2, and the Ar^1 having 4-CH_3 (**19**) and 4-Cl (**20**) substituents, a similar pattern in yields and reaction times were observed as with aforementioned 4-Br substituted (in Ar^2 ring) substrates (**15–18**) (Scheme V.3.1). The structure of thione (**20a**) has been further confirmed by XRD analysis as shown in Figure V.3.1.

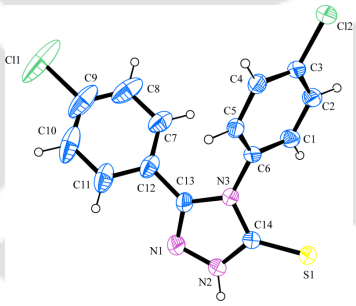
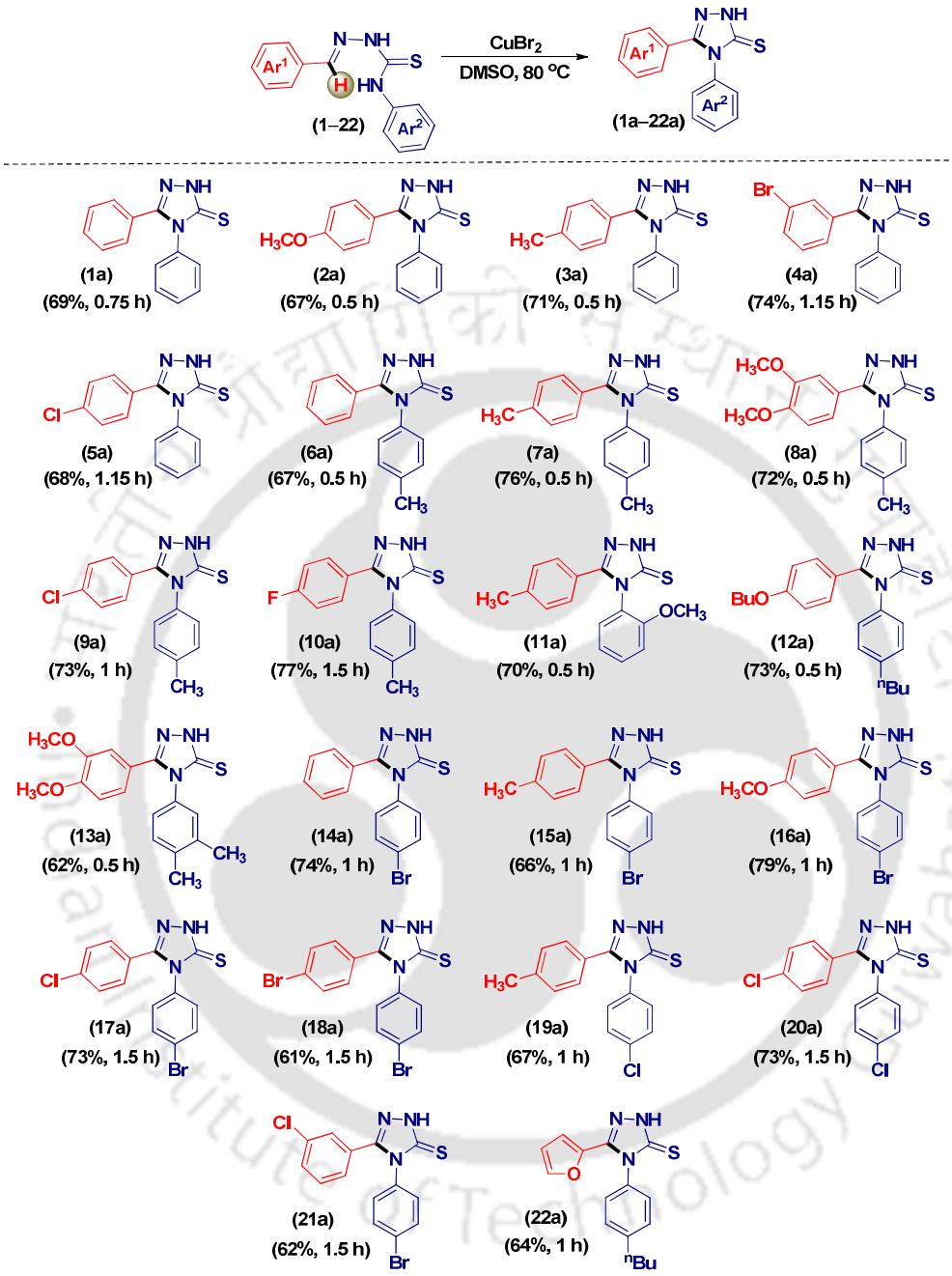


Figure V.3.1. *ORTEP view of* ***(20a)***

The synthetic utility of this transformation has been demonstrated by the synthesis of an anti-microbial compound (**21a**)[8e] in 62% yield (Scheme V.3.1) from its corresponding arylidenearylthiosemicarbazide (**21**). The reaction was also successful with *N*-arylidenethiosemicarbazide derived from a heterocyclic aldehyde, 2-furaldehyde (**22**), which gave a moderate yield (64%) of the corresponding thione (**22a**). Judging from the yield patterns in all the preceding set of substrates, it may be said that the electronic effects of substituents have no significant role in controlling the product yields.

Scheme V.3.1. *Substrate scope of 1,2,4-triazole-3-thiones*[a,b]

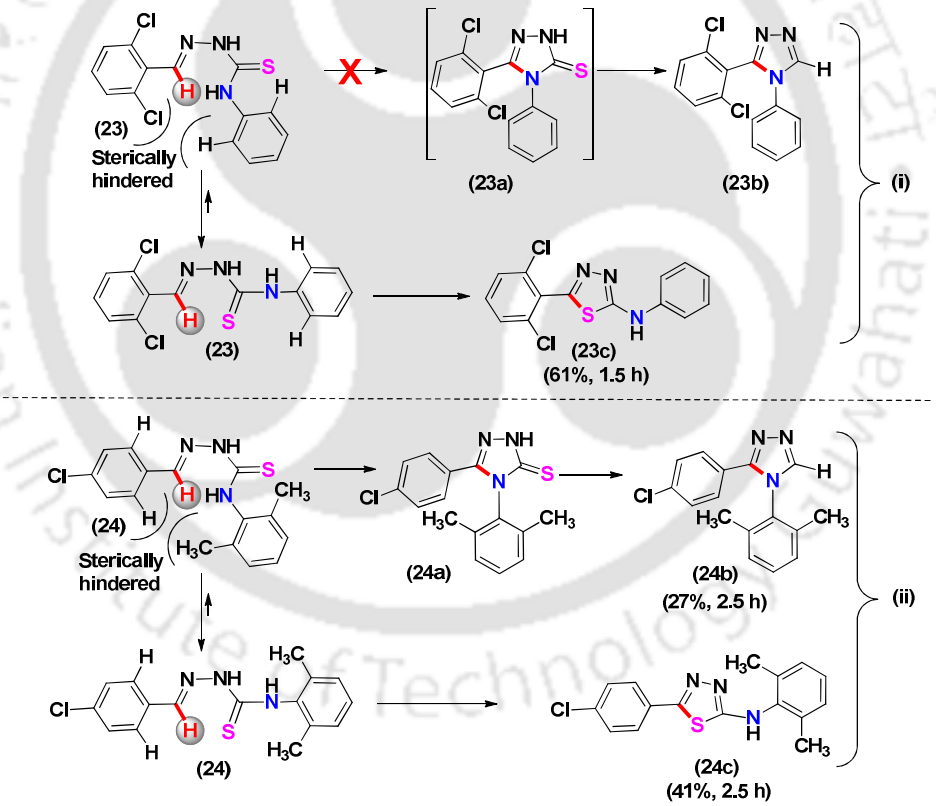


[a]Reaction conditions: *N*-arylidenearylthiosemicarbazide (**1-22**) (0.5 mmol), $CuBr_2$ (0.15 mmol), in DMSO (2 mL) at 80 °C. [b]Isolated yields of pure product.

A complete change in the reactivity pattern was observed when any one of the aryl rings (derived from either aldehyde or thiosemicarbazide) in arylidenearylthiosemicarbazides is *ortho*-disubstituted. Arylidenearylthiosemicarbazide

(**23**) derived from 2,6-dichlorobenzaldehyde gave exclusively 1,3,4-thiadiazole-2-amine (**23c**) and no traces of (**23a**) or (**23b**) (Scheme V.3.2 (i)). Here, probably due to the extreme steric reason imparted by both *o*-chloro groups (Scheme V.3.2(i)) the thiourea moiety in (**23**) adopted a *syn-syn* conformation as oppose to *syn-anti* conformation. This brings the sulphur atom to the proximity of imine C–H for oxidative cyclization (C–S bond formation) giving exclusively thiadiazole (**23c**). In yet another steric controlled reaction arylidenearylthiosemicarbazide (**24**) derived from 2,6-dimethylthiosemicarbazide gave 1,3,4-thiadiazole-2-amine (**24c**) along with 1,2,4-triazole (**24b**) in the ratio of (3:2) (Scheme V.3.2(ii)). Compound (**24b**) must have originated from its corresponding thione (**24a**) which however could not be isolated.

Scheme V.3.2. *Change in the reactivity pattern for sterically hindered substrates*[a]

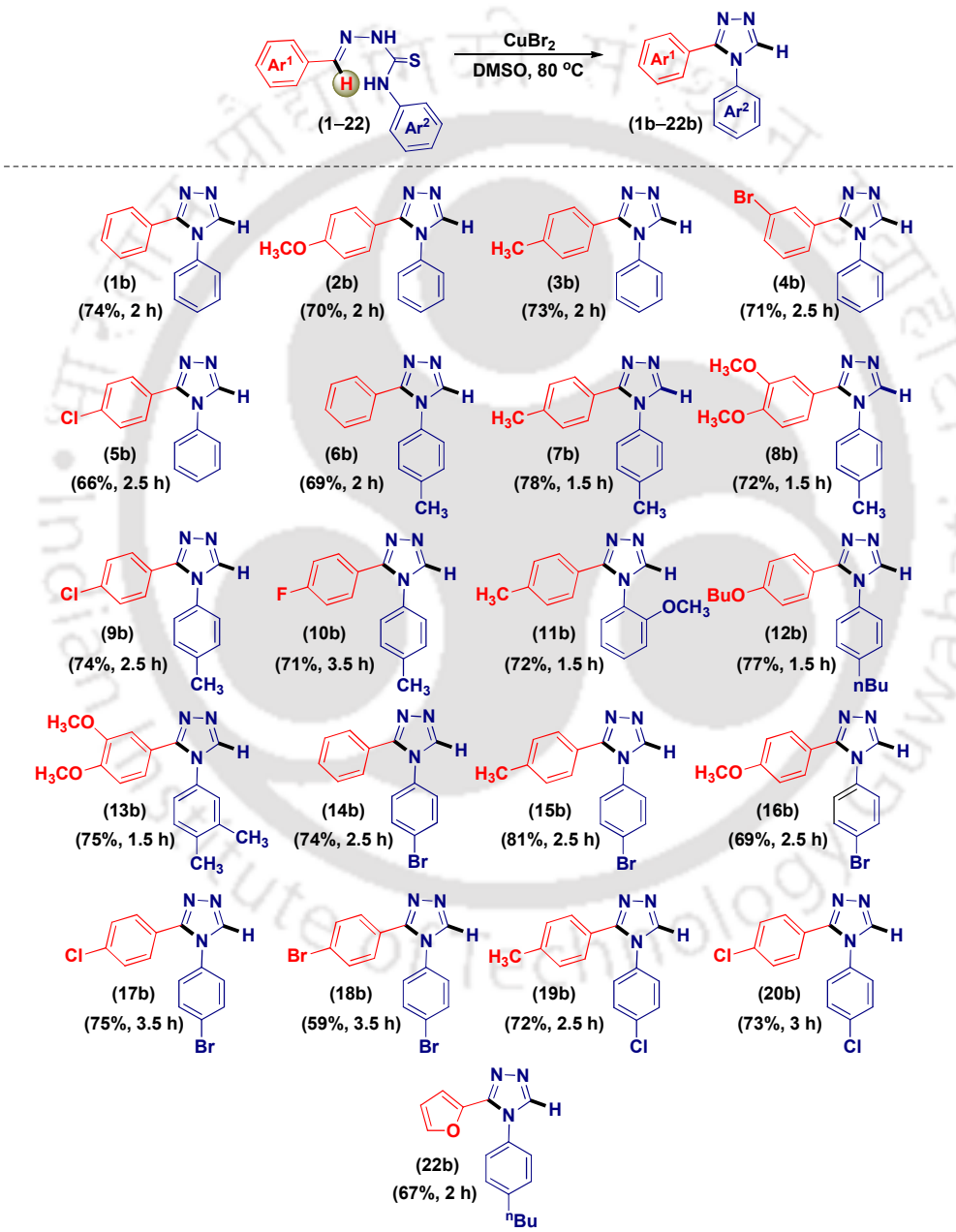


[a]Reaction conditions: *N*-arylidenearylthiosemicarbazide (**23-24**) (0.5 mmol), $CuBr_2$ (0.15 mmol), in DMSO (2 mL) at 80 °C.

It may be mentioned here that during the optimization process, when the reaction (Table V.3.1, entry 5) was prolonged, disappearance of the product (**1a**) and appearance of

a new product having lower R_f than (**1a**) was observed. This product upon isolation and usual characterization by spectroscopic technique was found to be 1,2,4-triazole (**1b**) (Scheme V.3.3) *i.e.* loss of a sulfur atom from the parent molecule. It is likely that the product (**1b**) might have formed via the desulfurization of (**1a**).

Scheme V.3.3. *Substrate scope of 1,2,4-triazoles*[a,b]



[a]Reaction conditions: *N*-arylidenearylthiosemicarbazide (**1-22**) (0.5 mmol), $CuBr_2$ (0.15 mmol), in DMSO (2 mL) at 80 °C. [b]Isolated yields of pure product.

To reconfirm the origin of the product (**1b**) when a preformed 4,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**1a**) was treated under the identical reaction conditions, 1,2,4-triazole (**1b**) was formed exclusively after 1.5 h, confirming our assumption. Thus, it was observed that by simply prolonging the reaction time, product (**1b**) was obtained exclusively.

The same thiosemicarbazides (**1–20**) and (**22**) which were used for the synthesis of thiones were now employed for the synthesis of a series of 4,5-diaryl-1,2,4-triazoles under the same reaction conditions but just by prolonging the reaction times. All the thiosemicarbazides underwent facile transformation to their respective triazoles (**1b–20b**) and (**22b**) via the loss of a sulphur atom from their intermediate thiones (Scheme V.3.3). Structure of the compound (**7b**) has been unequivocally confirmed by X-ray crystallography as shown in Figure V.3.2.

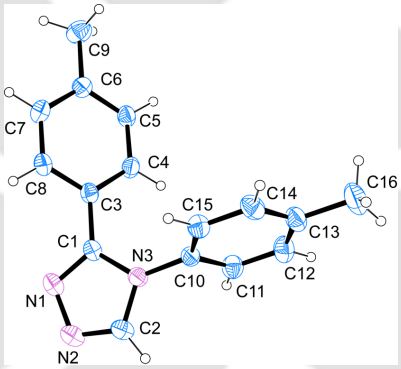
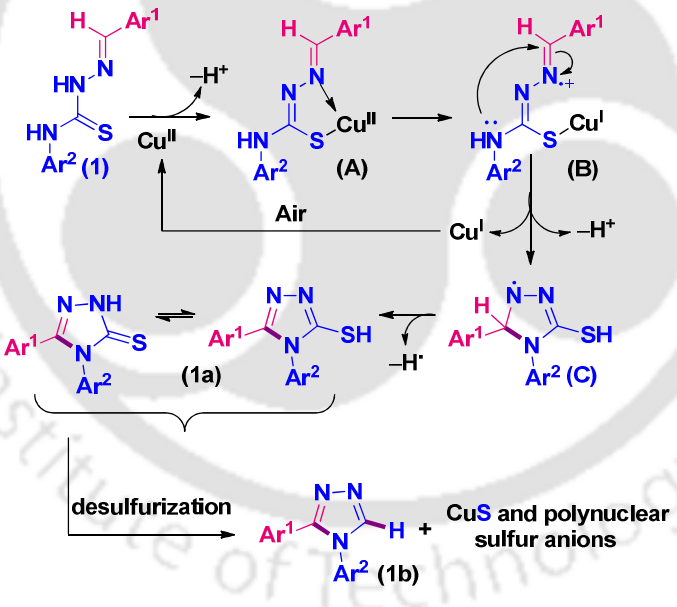


Figure V.3.2. *ORTEP view of (**7b**)*

Here again, no correlation between electronic effects of the substituents and yields of products were observed, but whatever little effect was seen it was similar to the one observed during the formaton of their respective thiones. However, the time taken for the completion of reaction was shorter for substrates possessing electron-donating groups on either one or both the aryl rings than for substrates bearing one or two electron-withdrawing groups. This observation is consistent with the formation of their intermediate thiones.

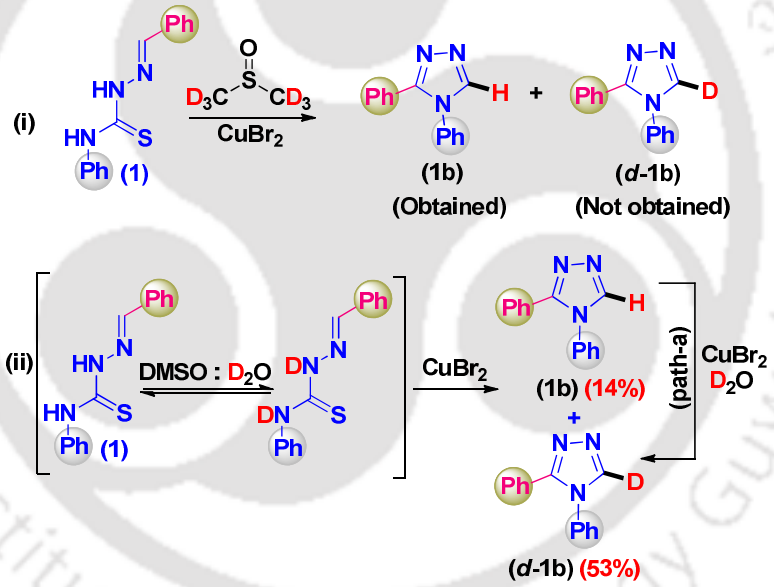
Mechanistic studies. A plausible mechanism for the formation of thione (**1a**) is proposed (Scheme V.3.4) which is in accordance with the earlier reports on copper catalyzed oxidative heterocyclization.[5,12] Copper(II) undergoes ligation with arylidenearylthiosemicarbazide (**1**) through its imine nitrogen and the soft sulfur atom to give a 5-membered complex (**A**). The co-ordinated Cu(II) is reduced to Cu(I) by a single electron transfer from the imine nitrogen resulting in the formation of a nitrogen centered radical cation (**B**) (Scheme V.3.4). The Cu(I) generated in the medium is oxidized back to Cu(II) for the next catalytic cycle by the atmospheric oxygen. This type of reduction and reoxidation has been confirmed by EPR and UV-Vis spectroscopic studies by others.[12b] The formation of a radical cation (**B**) facilitates the nucleophilic attack onto its imine carbon by the terminal thioamidic nitrogen resulting in a nitrogen centred radical (**C**). Loss of a hydrogen radical from (**C**) gives the thione (**1a**) (Scheme V.3.4). Similar cation radical and abstraction of H radical has been reported on analogous system using Cu(II).[13]



Scheme V.3.4. *Proposed reaction mechanism*

The exact pathway leading to the loss of sulphur to give 1,2,4-triazole (**1b**) is not clear at this moment. However, a similar desulfurization of (**1a**) under an oxidative condition *i.e.* in the presence of AcOH / hydrogen peroxide is reported.[14] To find out the origin of C-5 hydrogen in (**1b**), the reaction of substrate (**1**) was carried out in DMSO-d_6 under

otherwise identical conditions, no deuterium incorporated product (***d*-1b**) was observed (Scheme V.3.5 (i)). However, a deuterium incorporated product (***d*-1b**) along with a non deuterated product (**1b**) (Scheme V.3.5 (ii)) were obtained in the ratio of 4:1 when the reaction was performed in the presence of DMSO : D_2O (1:1, 1 mL). When the isolated product (**1b**) was subjected to the present reaction condition, but in the presence of D_2O, a deuterium exchanged product (***d*-1b**) at C5-H was observed (Scheme V.3.5, path-a). Thus the C-5 hydrogen is not originating from the solvent (DMSO) rather one of the proton (or deuterium, obtained by exchange of NH with D_2O) from nitrogen atom is transferred to C-5 position. Further the deuterated product (***d*-1b**) can be obtained from the non deuterated product (**1b**) in the presence of $CuBr_2$ and D_2O which keeps the medium (water present in commercial grade DMSO) also in the possible list of C-5 hydrogen source.



Scheme V.3.5. *Origin of C-5 hydrogen*

Formation of CuS in the reaction medium has been confirmed by solid state UV (Figure V.3.3).[15] If sulphur extrusion is by the formation of CuS alone, than a minimum of one equivalent of Cu salt is needed for the transformation of (**1a**) to (**1b**) (Scheme V.3.4), however, a complete transformation is taking place with just 30 mol % of the $CuBr_2$.

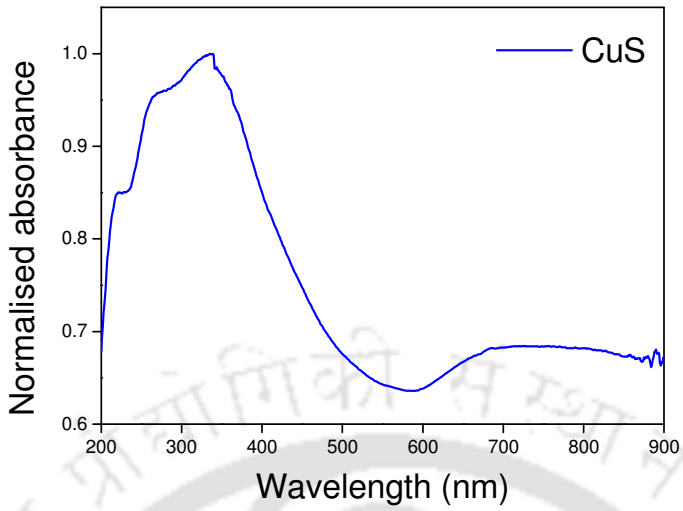


Figure V.3.3. *Solid state UV-Visible spectrum of isolated Cu salt*

In addition to the formation of CuS a range of polynuclear anions containing sulphur rings or chains are possible and such has been observed by us earlier and also reported in literature.[16] As can be seen from SEM the flake like structures (Figure V.3.4) resembles the formation of CuS / polysulfide which is also evident from the elemental composition from EDS analysis.

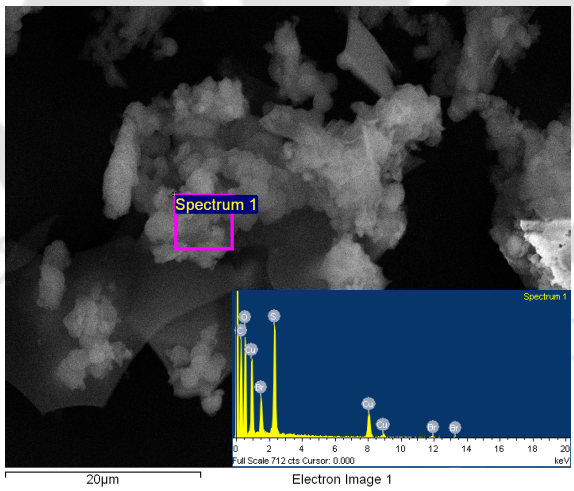


Figure V.3.4. *SEM and EDS analysis of the isolated Cu salt*

In conclusion, we developed an efficient Cu(II) catalyzed strategy for the synthesis of two important class of heterocycles *viz*. 4,5-disubstituted 1,2,4-triazole-3-thiones and 4,5-

disubstituted 1,2,4-triazoles from arylidenearylthiosemicarbazides by simply tuning the reaction time. Oxidative C–N bond over C–S formations afforded 4,5-disubstituted 1,2,4-triazole-3-thiones and their desulfurization give 4,5-disubstituted 1,2,4-triazoles. However, streric factor imparted due to the presence of *o*-disubstituted substrates in any of the aryl rings of arylidenearylthiosemicarbazides, the reactivity pattern changes giving thiodiazole as the major or an exclusive product. The thiophilic Cu assist the desulfurization of thiones with concomitant formation of CuS or an array of polynuclear sulfur anions which has been analyzed and confirmed by SEM and EDS analysis. The synthetic utility of this strategy has been successfully applied for the synthesis of an anti-microbial compound (**21a**).

V.4. Experimental section

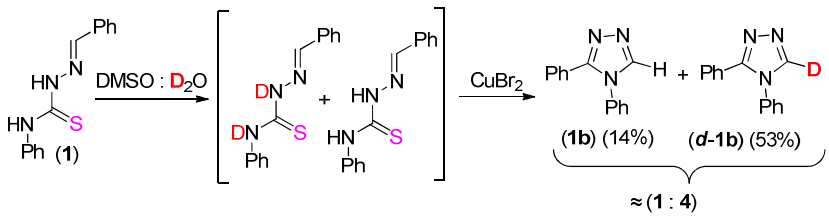
V.4.1. General information. All the reagents were commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm). NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with tetramethylsilane as the internal standard for ^{1}H NMR (600 MHz) and $CDCl_3$ and DMSO-d_6 solvent as the internal standard for ^{13}C NMR (150 MHz). Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. FT-IR spectra were recorded in KBr or neat. HRMS spectra were recorded using ESI mode. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. The arylidenearylthiosemicarbazides were

prepared by the condensation of one equivalent of *N*-phenylhydrazinecarbothioamide with 1.2 equivalents of arylaldehydes in etanolic medium under reflux condition for 2-6 h.

V.4.2. General procedure for the synthesis of 4,5-Diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (1a). To a solution of 1-benzylidene-4-phenylthiosemicarbazide (**1**) (127.67 mg, 0.5 mmol) in DMSO (2 mL) was added $CuBr_2$ (33.50 mg, 0.15 mmol) and the resultant solution was put into a preheated oil bath (80 ^oC) for 0.75 h. The reaction mixture was cooled to room temperature and admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (8:2 hexane / ethyl acetate) to give 4,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**1a**) (87.40 mg, 69 % yield). The same procedure was also followed for oxidative heterocyclization of other arylidenearylthiosemicarbazides (**2**–**22**).

V.4.3. Deuterium exchange experiment. 2-Benzylidene-*N*-phenylhydrazinecarbothioamide (**1**) (63.84 mg, 0.25 mmol) was taken in a 10 mL round bottom flask. To which was added DMSO (0.5 mL) and D_2O (0.5 mL) and the mixture was stirred at room temperature for 3 h. Then $CuBr_2$ (16.75 mg, 0.075 mmol) was added to it and the resultant reaction mixture was put into a preheated oil bath (80 ^oC) for 2 h. After completion of the reaction it was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (8:2 hexane / ethyl acetate) to give deuterated product (***d*-1b**) and non-deuterated product (**1b**). The ratio of deuterated product (***d*-1b**) and non-deuterated product (**1b**) was determined by ^1H NMR. The ratio of (***d*-1b**) : (**1b**) was found to be 4:1.

Calculation of ratio of deuterated vs non-deuterated product



The ratio of the deuterated product (***d*-1b**) and non-deuterated product (**1b**) was calculated on the basis of the integration ratio of the C-5 proton peak at 8.33 ppm.

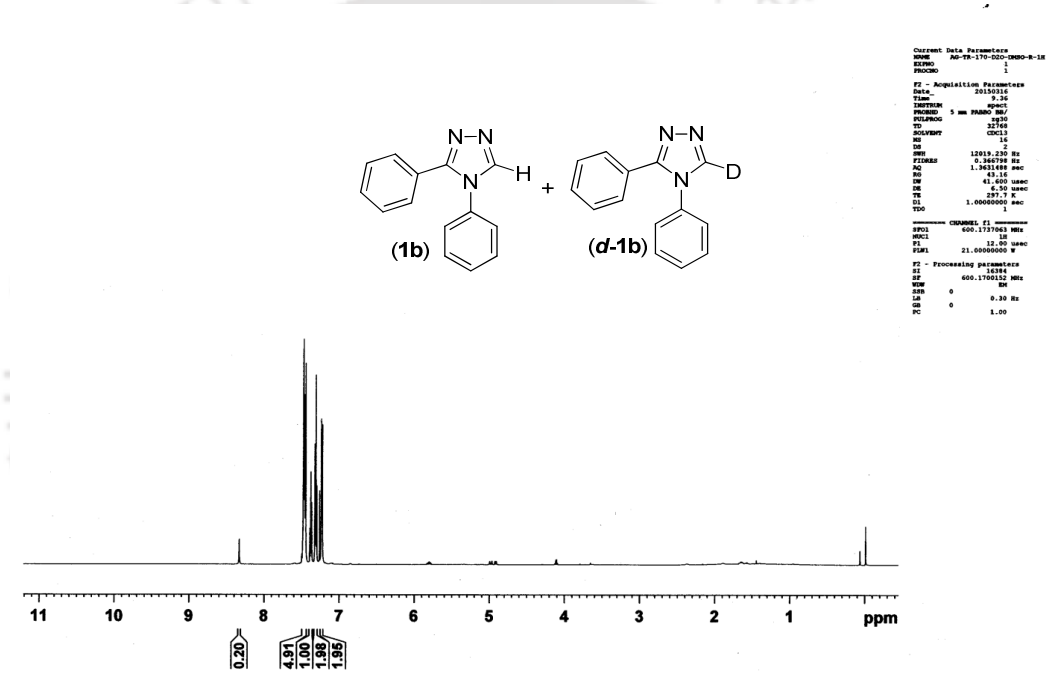
Calculation:

For an aromatic proton at 7.38 ppm, the integration value is 1.00.

Now for the integration value of the C-5 proton originating at 8.33 ppm is 0.20.

Upon correlation with the original spectra of (**1b**) the deuterium incorporated in the triazole product is 1 – 0.2 = 0.8.

Thus the ratio of the product (***d*-1b**) : (**1b**) = 0.8 : 0.2 = 4 : 1



V.4.4. Deuterium exchange experiment of (1b) to (*d*-1b). 3,4-Diphenyl-4*H*-1,2,4-triazole (**1b**) (55.25 mg, 0.25 mmol) was taken in a 10 mL round bottom flask and DMSO (0.5 mL) and D_2O (0.5 mL) was added to it. Then $CuBr_2$ (16.75 mg, 0.075 mmol) was added to the solution and the resultant reaction mixture was put into a preheated oil bath (80 ^oC) for 2 h. After which the reaction it was admixed with water (5 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with (8:2 hexane / ethyl acetate) to give deuterated product (***d*-1b**) and non-deuterated product (**1b**). The ratio of deuterated product (***d*-1b**) and non-

deuterated product (**1b**) was determined from the integration of their ^{1}H NMR. The ratio of (***d*-1b**): (**1b**) was found to be nearly 1:1.

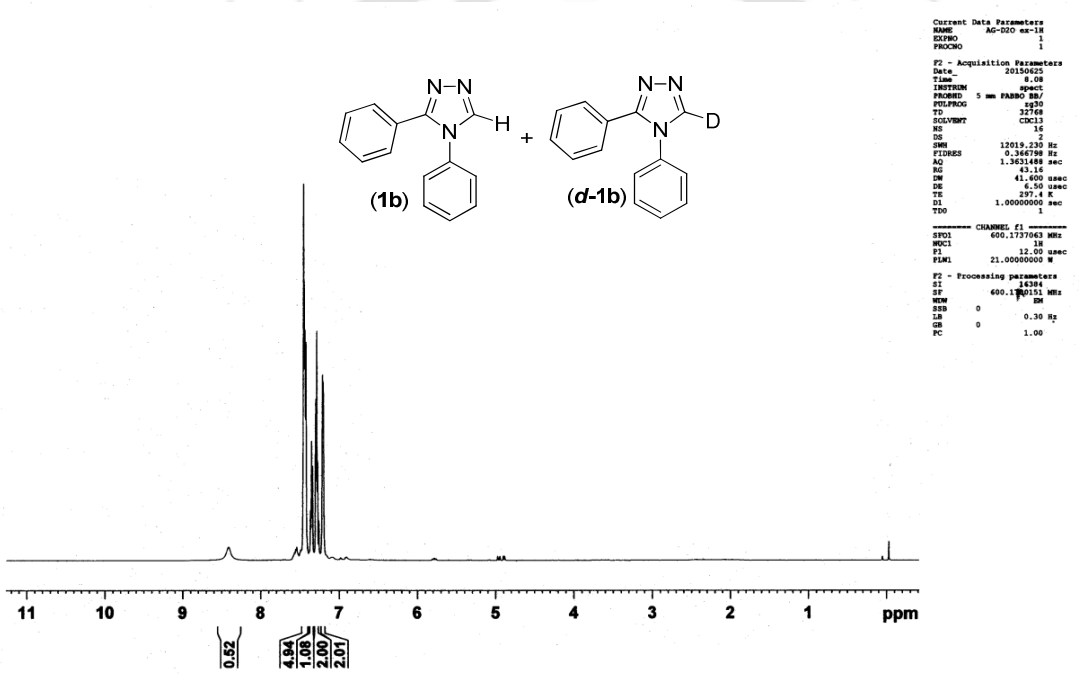
Calculation:

For an aromatic proton at 7.38 ppm, the integration value is 1.08.

Now for the integration value of the C-5 proton originating at 8.33 ppm is 0.52.

Upon correlation with the original spectra of (**1b**) the deuterium incorporated in the triazole product is 1 – 0.52 = 0.48.

Thus the ratio of the product (***d*-1b**) : (**1b**) = 0.48 : 0.52 = 1 : 1



V.4.5. Crystallographic description of 4,5-Bis(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (20a). $C_{14}H_9Cl_2N_3S$, crystal dimensions 0.41 x 0.35 x 0.25 mm, M_r = 322.20, Monoclinic, space group P21/c, a =6.2831(3), b = 11.0852(6), c = 21.1130(11) Å, α = 90 °, β = 92.069(3) °, γ = 90 °, V = 1469.55(13) Å^3, Z = 4, ρ_{calcd} = 1.456 g/cm^3, μ = 0.575 mm^{-1}, F(000) = 656.0, reflection collected / unique = 3689 / 2467, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0567, wR_2 = 0.1652, R indices (all data): R_1 = 0.0880, wR_2 = 0.1814, goodness of fit = 1.087. CCDC reference number 1055788.

V.4.6. Crystallographic description of 3,4-Di-*p*-tolyl-4*H*-1,2,4-triazole (7b). $C_{16}H_{15}N_3$, crystal dimensions 0.41 x 0.37 x 0.24 mm, M_r = 249.31, Monoclinic, space group P21/c, a =5.9017(2), b = 14.1916(4), c = 16.0475(4) Å, α = 90 °, β = 92.732(2) °, γ = 90 °, V = 1342.52(7) Å^3, Z = 4, ρ_{calcd} = 1.234 g/cm^3, μ = 0.075 mm^{-1}, $F(000)$ = 528.0, reflection collected / unique = 3295 / 2384, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0454, wR_2 = 0.1489, R indices (all data): R_1 = 0.0653, wR_2 = 0.1631, goodness of fit = 1.121. CCDC reference number 1054230.

V.5. References

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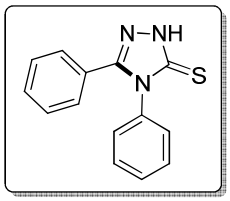
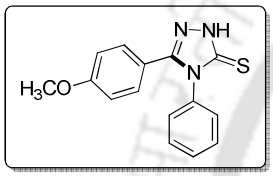
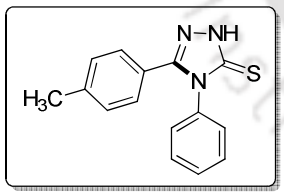
V.6. Spectral data



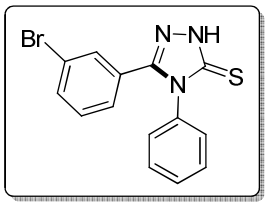
4,5-Diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (1a): White solid; mp 275–278 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.30–7.36 (m, 6H), 7.40 (t, J = 7.8 Hz, 1H), 7.48–7.49 (m, 3H), 14.14 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 125.8, 128.2, 128.5, 128.7, 129.3, 129.4, 130.3, 134.5, 150.5, 168.6; IR (KBr): 3436, 3103, 2927, 2746, 1546, 1506, 1445, 1402, 1335, 1275, 1243, 1077, 969, 770, 701, 690, 609 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}N_3S$ (MH^+) 254.0746; found 254.0753.



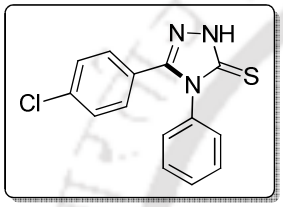
5-(4-Methoxyphenyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (2a): White solid; mp 270–272 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 3.72 (s, 3H), 6.88 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 9.0 Hz, 2H), 7.33–7.34 (m, 2H), 7.48–7.50 (m, 3H), 14.03 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 55.3, 114.0, 117.9, 128.7, 129.3, 129.4, 129.7, 134.7, 150.4, 160.6, 168.4; IR (KBr): 3434, 3093, 2929, 1612, 1516, 1426, 1391, 1330, 1255, 1179, 1025, 968, 838, 752, 694, 594 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}N_3OS$ (MH^+) 284.0852; found 284.0857.



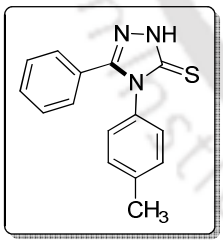
5-(4-Methylphenyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (3a): White solid; mp 261–263 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 7.08 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.31–7.32 (m, 2H), 7.49–7.51 (m, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 20.8, 122.9, 128.1, 128.7, 129.1, 129.3, 129.4, 134.6, 140.2, 150.6, 168.5; IR (KBr): 3081, 3010, 2921, 1514, 1497, 1420, 1329, 1278, 1240, 970, 822, 725, 696, 589 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}N_3S$ (MH^+) 268.0903; found 268.0915.



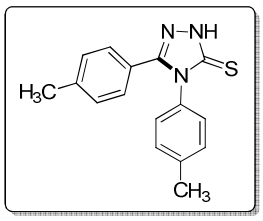
5-(3-Bromophenyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4a): Light yellow solid; mp 223–225 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.28–7.31 (m, 2H), 7.37–7.39 (m, 2H), 7.45 (s, 1H), 7.50–7.53 (m, 3H), 7.60–7.62 (m, 1H), 14.21 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 121.5, 127.2, 127.9, 128.7, 129.4, 129.5, 130.6, 130.8, 133.1, 134.3, 149.1, 168.7; IR (KBr): 3436, 3080, 2921, 1542, 1490, 1475, 1402, 1331, 1302, 1280, 1240, 975, 801, 715, 698, 618 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}BrN_3S$ (MH^+) 331.9852; found 331.9844.



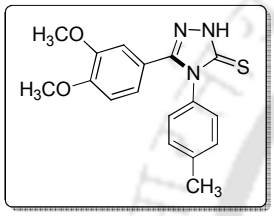
5-(4-Chlorophenyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (5a): White solid; mp 270–272 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.25 (d, J = 9.0 Hz, 2H), 7.28–7.30 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.46–7.48 (m, 3H), 14.12 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6 + $CDCl_3$): δ (ppm) 124.5, 128.5, 128.7, 129.4, 129.5, 129.8, 134.3, 135.5, 149.5, 168.8; IR (KBr): 3057, 2915, 1599, 1540, 1499, 1452, 1416, 1329, 1279, 1238, 1091, 1015, 970, 835, 744, 696 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}ClN_3S$ (MH^+) 288.0357; found 288.0353.



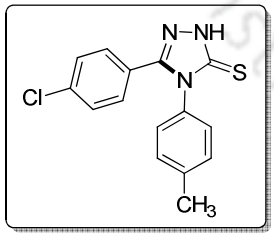
4-(4-Methylphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (6a): White solid; mp 219–221 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 7.17 (d, J = 8.4 Hz, 2H), 7.27–7.28 (m, 4H), 7.32 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 125.7, 128.1, 128.4, 128.8, 130.6, 130.8, 131.9, 140.2, 151.6, 169.6; IR (KBr): 3109, 3033, 2933, 1548, 1516, 1500, 1482, 1445, 1398, 1333, 1276, 1239, 968, 819, 771, 696, 603 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}N_3S$ (MH^+) 268.0903; found 268.0915.



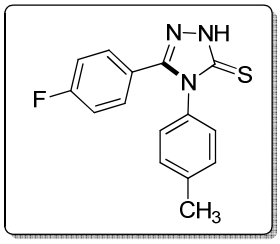
4,5-Bis(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (7a): White solid; mp 233–235 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 3H), 2.40 (s, 3H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 12.27 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.57, 21.59, 122.8, 128.2, 128.3, 129.6, 130.6, 132.1, 140.2, 141.2, 151.7, 169.6; IR (KBr): 3090, 2923, 1614, 1514, 1486, 1420, 1329, 1243, 1243, 1020, 969, 818, 717, 583 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{15}N_3S$ (MH^+) 282.1059; found 282.1055.



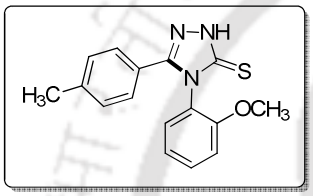
5-(3,4-Dimethoxyphenyl)-4-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (8a): Brown solid; mp 215–217 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.36 (s, 3H), 3.51 (s, 3H),3.72 (s, 3H), 6.82 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.90–6.92 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 14.01 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 20.7, 55.1, 55.5, 111.35, 111.41, 117.9, 121.1, 128.5, 129.8, 132.3, 139.0, 148.2, 150.3, 150.4, 168.6; IR (KBr): 3273, 2929, 1608, 1515, 1477, 1464, 1397, 1335, 1286, 1257, 1234, 1137, 1018, 821, 769, 715, 583 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{17}N_3O_2S$ (MH^+) 328.1114; found 328.1107.



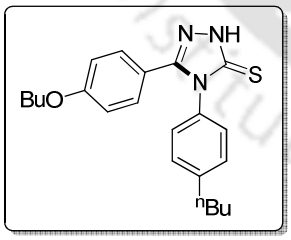
5-(4-Chlorophenyl)-4-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (9a): White solid; mp 223–226 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.33 (s, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.27-7.31 (m, 4H), 7.42 (d, *J* = 8.4 Hz, 2H), 14.12 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 20.7, 124.7, 128.3, 128.7, 129.8, 130.0, 131.7, 135.2, 139.0, 149.7, 168.8; IR (KBr): 3062, 3033, 2903, 1544, 1513, 1472, 1428, 1416, 1375, 1328, 1234, 1091, 1039, 1016, 832, 818, 745, 615 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}ClN_3S$ (MH^+) 302.0513; found 302.0516.



5-(4-Fluorophenyl)-4-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (10a): White solid; mp 222–224 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 3H), 6.98 (t, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.33–7.35 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 116.1 (d, *J* = 21.9 Hz), 121.9, 128.1, 130.6 (d, *J* = 8.7 Hz), 130.7, 131.7, 140.4, 150.7, 164.0 (d, *J* = 251.3 Hz), 169.4; IR (KBr): 3075, 2923, 1609, 1510, 1422, 1391, 1329, 1277, 1235, 1159, 971, 844, 816, 732, 718, 584 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}FN_3S$ (MH^+) 286.0809; found 286.0817.

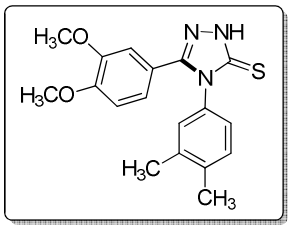


4-(2-Methoxyphenyl)-5-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (11a): White solid; mp 256–259 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.24 (s, 3H), 3.54 (s, 3H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.11–7.13 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 14.01 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 20.8, 55.8, 112.9, 120.9, 123.1, 123.3, 127.2, 129.1, 130.4, 131.3, 140.2, 151.1, 154.5, 168.8; IR (KBr): 3436, 3082, 2924, 1603, 1509, 1464, 1430, 1326, 1259, 1183, 1118, 1022, 824, 757, 593 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{15}N_3OS$ (MH^+) 298.1009; found 298.1001.

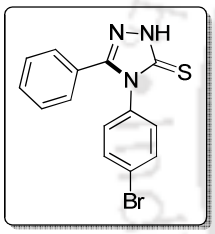


4-(4-Butylphenyl)-5-(4-butoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (12a): White solid; mp 200–202 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.95 (t, *J* = 7.2 Hz, 6H), 1.38 (q, *J* = 7.8 Hz, 2H), 1.45 (q, *J* = 7.2 Hz, 2H), 1.64 (quintet, *J* = 7.8 Hz, 2H), 1.73 (quintet, *J* = 7.2 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 3.92 (t, *J* = 6.6 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 7.20–7.24 (m, 4H), 7.29 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 13.9, 14.1, 19.3, 22.5, 31.3, 33.3, 35.5, 67.9, 114.7, 117.7, 128.2, 129.8, 129.9, 132.2, 144.9, 151.5, 161.0, 168.9; IR (KBr): 3436, 3086, 2927, 2867, 1608, 1513, 1397, 1329, 1253, 1178, 1029, 968, 835, 738, 593 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{27}N_3OS$ (MH^+)

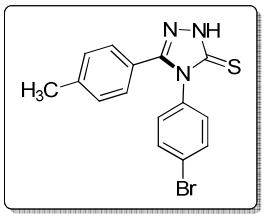
382.1948; found 382.1942.



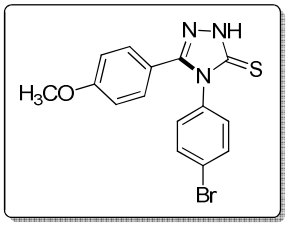
5-(3,4-Dimethoxyphenyl)-4-(3,4-dimethylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (13a): Light brown solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.28 (s, 3H), 2.32 (s, 3H), 3.65 (s, 3H), 3.86 (s, 3H), 6.74 (d, J = 8.4 Hz, 1H), 6.90–6.92 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 7.27–7.28 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.8, 20.0, 55.8, 56.1, 111.0, 118.1, 121.5, 125.8, 129.2, 131.0, 132.5, 138.7, 138.9, 148.9, 150.9, 151.3, 169.3; IR (KBr): 3442, 3081, 2923, 1607, 1516, 1460, 1399, 1342, 1258, 1229, 1142, 1023, 863, 823, 768, 716, 596 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{19}N_3O_2S$ (MH^+) 342.1271; found 342.1274.



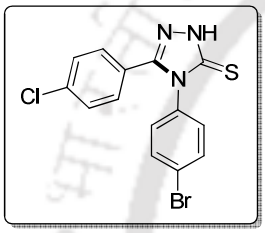
4-(4-Bromophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (14a): White solid; mp 204–206 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.32–7.38 (m, 6H), 7.43 (t, J = 7.2 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 14.17 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 122.6, 125.6, 128.4, 128.6, 130.4, 131.0, 132.3, 133.9, 150.4, 168.5; IR (KBr): 3078, 2925, 1616, 1547, 1491, 1396, 1329, 1278, 1235, 1021, 968, 825, 771, 695, 609 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}BrN_3S$ (MH^+) 331.9852; found 331.9857.



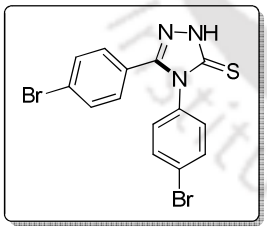
4-(4-Bromophenyl)-5-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (15a): White solid; mp 226–228 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.26 (s, 3H), 7.16–7.20 (m, 4H), 7.30 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.0 Hz, 2H), 14.13 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.0, 122.79, 122.84, 128.4, 129.4, 131.1, 132.5, 134.0, 140.6, 150.7, 168.5; IR (KBr): 3060, 2919, 1546, 1513, 1492, 1418, 1393, 1330, 1281, 1238, 1070, 969, 821, 766, 716, 651, 588 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}BrN_3S$ (MH^+) 346.0008; found 346.0019.



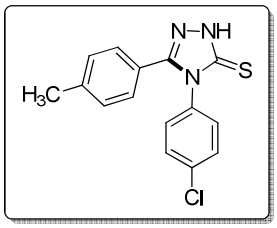
4-(4-Bromophenyl)-5-(4-methoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (16a): White solid; mp 233–235 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 3.73 (s, 3H), 6.92 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 14.10 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 55.3, 114.1, 117.7, 122.6, 129.9, 131.0, 132.3, 134.0, 150.3, 160.7, 168.2; IR (KBr): 3434, 3074, 2924, 1609, 1508, 1395, 1328, 1256, 1178, 1073, 1022, 968, 833, 591 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}BrN_3OS$ (MH^+) 361.9957; found 361.9962.



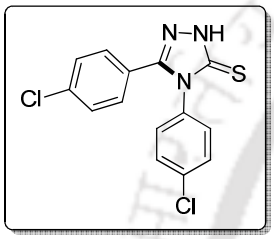
4-(4-Bromophenyl)-5-(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (17a): White solid; mp 272–275 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.32–7.36 (m, 4H), 7.47 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 14.22 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 122.7, 124.5, 128.8, 130.2, 130.9, 132.4, 133.6, 135.3, 149.5, 168.5; IR (KBr): 3436, 3062, 2920, 1604, 1489, 1425, 1369, 1324, 1255, 1091, 1011, 830, 731, 614, 550 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9BrClN_3S$ (MH^+) 365.9462; found 365.9450.



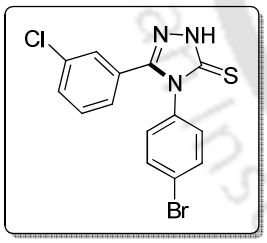
4,5-Bis(4-bromophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (18a): White solid; mp 266–269 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.26 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 14.21 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 122.7, 124.2, 124.9, 130.4, 130.9, 131.7, 132.4, 133.6, 149.6, 168.6; IR (KBr): 3437, 3061, 3024, 2922, 1597, 1543, 1492, 1413, 1328, 1232, 1069, 1024, 1010, 820, 735, 725, 613 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9Br_2N_3S$ (MH^+) 409.8957; found 409.8951.



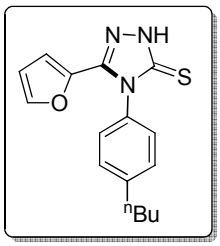
4-(4-Chlorophenyl)-5-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (19a): White solid; mp 226–228 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 7.12 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.6, 122.4, 128.4, 129.7, 129.8, 130.2, 133.1, 136.1, 141.5, 151.5, 169.3; IR (KBr): 3440, 3084, 2923, 1513, 1497, 1384, 1330, 1094, 969, 821, 721, 590 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}ClN_3S$ (MH^+) 302.0513; found 302.0502.



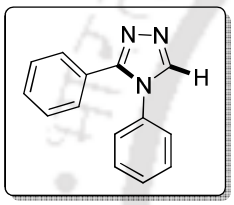
4,5-Bis(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (20a): Light brown solid; mp 223–226 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.29 (d, J = 8.4 Hz, 2H), 7.38–7.43 (m, 4H), 7.54 (d, J = 8.4 Hz, 2H), 14.12 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 124.5, 128.8, 129.4, 130.2, 130.6, 133.2, 134.1, 135.3, 149.6, 168.8; IR (KBr): 3437, 3064, 2919, 1604, 1496, 1414, 1326, 1276, 1238, 1094, 968, 837, 744 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9Cl_2N_3S$ (MH^+) 321.9967; found 321.9957.



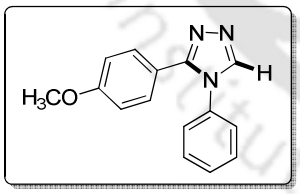
4-(4-Bromophenyl)-5-(3-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (21a): White solid; mp 228–230 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.23 (d, J = 7.8 Hz, 1H), 7.36–7.41 (m, 4H), 7.51 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 14.25 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 122.8, 127.1, 127.6, 128.2, 130.4, 130.6, 130.9, 132.4, 133.2, 133.6, 149.2, 168.6; IR (KBr): 3443, 3060, 2920, 1541, 1491, 1435, 1329, 1281, 1237, 1069, 980, 825, 783, 713, 614 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9BrClN_3S$ (MH^+) 365.9462; found 365.9471.



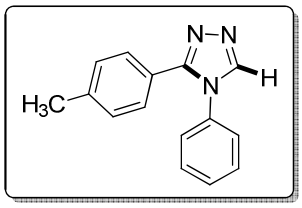
4-(4-Butylphenyl)-5-(furan-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (22a): Brown solid; mp 202–205 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.97 (t, J = 7.2 Hz, 3H), 1.38–1.44 (m, 2H), 1.68 (quintet, J = 7.8 Hz, 2H), 2.72 (t, J = 7.8 Hz, 2H), 5.90–5.91 (m, 1H), 6.32–6.33 (m, 1H), 7.26–7.27 (m, 2H), 7.37 (d, J = 7.8 Hz, 2H), 7.47 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.1, 22.6, 33.4, 35.6, 111.6, 113.1, 128.1, 130.0, 131.5, 140.2, 144.3, 144.9, 145.8, 169.0; IR (KBr): 3437, 3084, 2925, 2863, 2774, 1621, 1523, 1452, 1325, 1280, 1247, 1024, 977, 839, 752, 624 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{17}N_3OS$ (MH^+) 300.1165; found 300.1161.



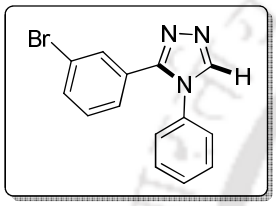
3,4-Diphenyl-4*H*-1,2,4-triazole (1b): White solid; mp 147–149 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.23–7.24 (m, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.44–7.49 (m, 5H), 8.32 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 125.8, 126.4, 128.6, 128.7, 129.5, 129.98, 130.04, 134.6, 144.9, 153.3; IR (KBr): 3111, 3053, 2921, 1721, 1598, 1555, 1507, 1468, 1389, 1214, 1072, 1017, 957, 770, 692, 568 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{11}N_3$ (MH^+) 222.1026; found 222.1032.



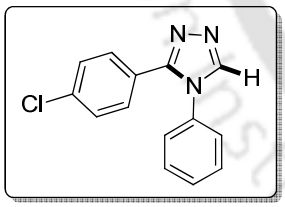
3-(4-Methoxyphenyl)-4-phenyl-4*H*-1,2,4-triazole (2b): White solid; mp 130–132 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 3.74 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.37–7.38 (m, 2H), 7.50–7.51 (m, 3H), 8.80 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 55.7, 114.5, 119.3, 126.6, 129.6, 130.2, 130.3, 135.2, 145.7, 152.6, 160.7; IR (KBr): 3115, 2927, 2850, 1613, 1502, 1469, 1379, 1254, 1209, 1174, 1024, 835, 769, 693, 563 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}N_3O$ (MH^+) 252.1131; found 252.1135.



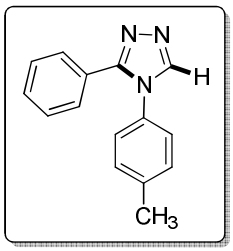
4-Phenyl-3-(*p*-tolyl)-4*H*-1,2,4-triazole (3b): Light yellow solid; mp 163–165 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H), 7.05 (d, J = 7.8 Hz, 2H), 7.17–7.18 (m, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.40–7.42 (m, 3H), 8.24 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 123.5, 125.8, 128.6, 129.3, 129.5, 130.0, 134.8, 140.1, 144.7, 153.3; IR (KBr): 3108, 2924, 1596, 1502, 1474, 1452, 1383, 1202, 1183, 1087, 1011, 954, 822, 769, 729, 695, 664 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}N_3$ (MH^+) 236.1182; found 236.1195.



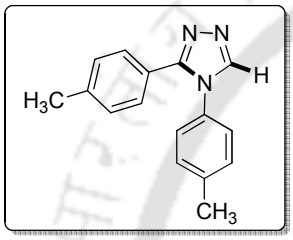
3-(3-Bromophenyl)-4-phenyl-4*H*-1,2,4-triazole (4b): Light brown solid; mp 150–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.17 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.2 Hz, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.49–7.54 (m, 4H), 7.70 (s, 1H), 8.34 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 122.8, 125.9, 127.1, 128.4, 129.9, 130.2, 130.3, 131.7, 133.1, 134.4, 145.1, 151.9; IR (KBr): 2923, 1636, 1597, 1502, 1445, 1379, 1202, 1071, 1018, 790, 767, 695, 683 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}BrN_3$ (MH^+) 300.0131; found 300.0139.



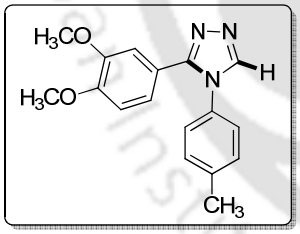
3-(4-Chlorophenyl)-4-phenyl-4*H*-1,2,4-triazole (5b): White solid; mp 165–168 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.24–7.26 (m, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.50–7.52 (m, 3H), 8.33 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 125.0, 125.9, 129.1, 129.9, 130.0, 130.3, 134.6, 136.4, 145.1, 152.4; IR (KBr): 3106, 2923, 2853, 1595, 1569, 1502, 1467, 1453, 1406, 1380, 1205, 1094, 1083, 1016, 956, 831, 773, 740, 728, 696, 664 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}ClN_3$ (MH^+) 256.0636; found 256.0631.



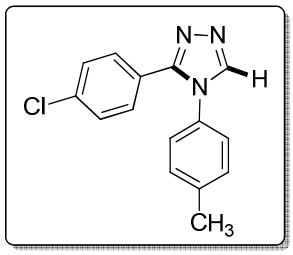
3-Phenyl-4-(*p*-tolyl)-4*H*-1,2,4-triazole (6b): White solid; mp 144–147 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 8.25 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 125.7, 126.6, 128.67, 128.72, 130.0, 130.7, 132.2, 139.8, 145.0, 153.3; IR (KBr): 3109, 3063, 2921, 1515, 1495, 1467, 1442, 1390, 1284, 1198, 1073, 1016, 822, 775, 716, 696, 664 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{13}N_3$ (MH^+) 236.1182; found 236.1175.



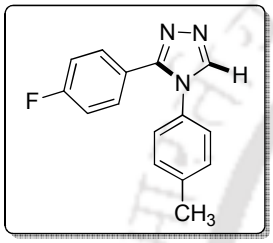
3,4-Di-*p*-tolyl-4*H*-1,2,4-triazole (7b): White solid; mp 192–194 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.30 (s, 3H), 2.39 (s, 3H), 7.07–7.09 (m, 4H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 8.23 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.1, 21.3, 123.6, 125.5, 128.4, 129.2, 130.4, 132.1, 139.6, 139.9, 144.8, 153.2; IR (KBr): 3116, 3033, 2920, 1612, 1517, 1474, 1385, 1206, 1037, 1008, 956, 731, 668 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{15}N_3$ (MH^+) 250.1339; found 250.1335.



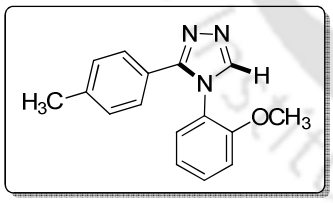
3-(3,4-Dimethoxyphenyl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole (8b): Light brown liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 3H), 3.68 (s, 3H), 3.80 (s, 3H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 3H), 7.22 (d, *J* = 7.8 Hz, 2H), 8.23 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 55.9, 56.0, 110.9, 111.7, 119.0, 121.5, 125.9, 130.6, 132.4, 139.8, 144.2, 148.9, 150.4, 153.6; IR (KBr): 3120, 2925, 1610, 1517, 1244, 1174, 1141, 1022, 871, 820, 767, 733, 669, 550 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{17}N_3O_2$ (MH^+) 296.1394; found 296.1390.



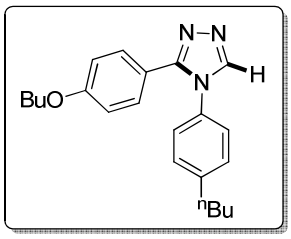
3-(4-Chlorophenyl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole (9b): Light brown solid; mp 163–166 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 7.08 (d, J = 8.4 Hz, 2H), 7.25–7.28 (m, 4H), 7.39 (d, J = 7.2 Hz, 2H), 8.27 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 125.0, 125.6, 128.9, 129.8, 130.7, 131.8, 136.1, 140.0, 145.1, 152.3; IR (KBr): 3108, 3035, 2920, 1602, 1569, 1516, 1463, 1407, 1384, 1318, 1207, 1095, 1015, 1008, 956, 859, 843, 817, 733, 669 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}ClN_3$ (MH^+) 270.0793; found 270.0799.



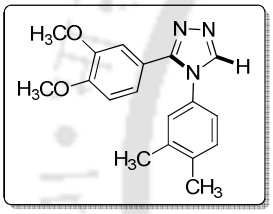
3-(4-Fluorophenyl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole (10b): White solid; mp 127–129 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H), 7.02 (t, J = 8.4 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.46–7.48 (m, 2H), 8.32 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.3, 115.9 (d, J = 21.8 Hz), 122.8, 125.6, 130.7 (d, J = 6.5 Hz), 132.0, 140.0, 145.5, 153.3, 163.7 (d, J = 249.3 Hz); IR (KBr): 3108, 3059, 2923, 1605, 1518, 1469, 1386, 1319, 1226, 1209, 1182, 1086, 1010, 852, 814, 736, 670, 627 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}FN_3$ (MH^+) 254.1088; found 254.1085.



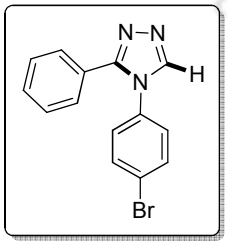
4-(2-Methoxyphenyl)-3-(*p*-tolyl)-4*H*-1,2,4-triazole (11b): Light yellow solid; mp 137–139 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 3H), 3.59 (s, 3H), 6.94–6.98 (m, 2H), 7.03 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 7.38–7.41 (m, 1H), 8.17 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.4, 55.7, 112.6, 121.1, 123.6, 124.2, 127.9, 128.1, 129.2, 131.2, 139.2, 145.2, 153.9, 154.1; IR (KBr): 3084, 3021, 2921, 1603, 1513, 1489, 1468, 1290, 1262, 1208, 1024, 822, 751, 739, 665, 529 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{15}N_3O$ (MH^+) 266.1288; found 266.1302.



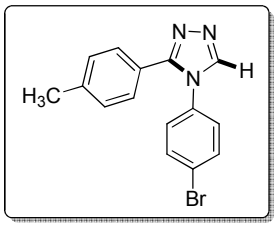
3-(4-Butoxyphenyl)-4-(4-butylphenyl)-4*H*-1,2,4-triazole (12b): Light brown solid; mp 59–61 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.85–0.91 (m, 6H), 1.30 (sextet, J = 7.8 Hz, 2H), 1.40 (sextet, J = 7.2 Hz, 2H), 1.55 (quintet, J = 7.2 Hz, 2H), 1.66 (quintet, J = 7.8 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 3.94 (t, J = 6.6 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.28–7.32 (m, 4H), 8.74 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 13.6, 13.7, 18.7, 21.7, 30.7, 32.9, 34.3, 67.3, 114.4, 118.8, 125.9, 129.5, 129.8, 132.3, 143.6, 145.3, 152.1, 159.7; IR (KBr): 2957, 2929, 2871, 1613, 1515, 1466, 1385, 1288, 1251, 1177, 1026, 836, 737, 568 cm^{-1}; HRMS (ESI): calcd. for $C_{22}H_{27}N_3O$ (MH^+) 350.2227; found 350.2239.



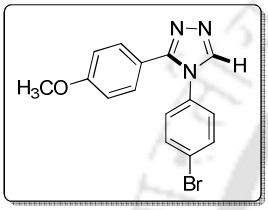
3-(3,4-Dimethoxyphenyl)-4-(3,4-dimethylphenyl)-4*H*-1,2,4-triazole (13b): Light brown gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.19 (s, 3H), 2.25 (s, 3H), 3.67 (s, 3H), 3.78 (s, 3H), 6.67 (d, J = 8.4 Hz, 1H), 6.81–6.83 (m, 1H), 6.89–6.90 (m, 1H), 6.97 (s, 1H), 7.12 (s, 1H), 7.15 (d, J = 7.8 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 19.6, 19.8, 55.8, 55.9, 110.9, 111.6, 118.9, 121.4, 123.4, 126.8, 130.9, 132.5, 138.4, 138.7, 145.0, 148.8, 150.3, 153.1; IR (KBr): 2928, 2848, 1609, 1498, 1259, 1141, 1023, 862, 819, 730, 659, 593 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{19}N_3O_2$ (MH^+) 310.1550; found 310.1542.



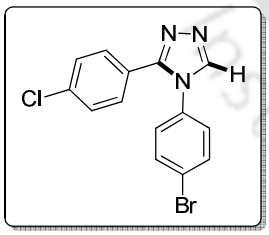
4-(4-Bromophenyl)-3-phenyl-4*H*-1,2,4-triazole (14b): White solid; mp 219–222 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.08 (d, J = 8.4 Hz, 2H), 7.27–7.30 (m, 2H), 7.34–7.39 (m, 3H), 7.54–7.56 (m, 2H), 8.26 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 123.6, 126.1, 127.3, 128.8, 128.9, 130.3, 133.3, 133.7, 145.0, 153.7; IR (KBr): 3126, 3065, 3034, 1551, 1497, 1468, 1388, 1240, 1200, 1067, 1014, 838, 818, 707, 687, 662 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{10}BrN_3$ (MH^+) 300.0131; found 300.0125.



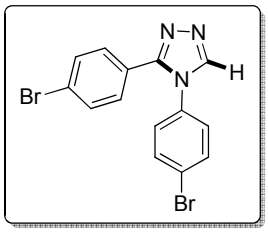
4-(4-Bromophenyl)-3-(*p*-tolyl)-4*H*-1,2,4-triazole (15b): White solid; mp 231–233 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 7.09 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 8.26 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 21.5, 119.4, 123.2, 123.5, 127.4, 128.7, 129.6, 133.3, 133.8, 140.5, 144.8, 153.4; IR (KBr): 3126, 3066, 3036, 2921, 1497, 1475, 1384, 1199, 1068, 1014, 985, 839, 818, 724, 663 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}BrN_3$ (MH^+) 314.0287; found 314.0281.



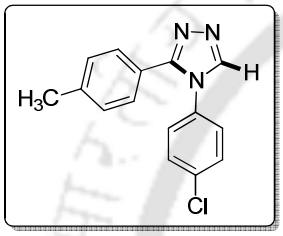
4-(4-Bromophenyl)-3-(4-methoxyphenyl)-4*H*-1,2,4-triazole (16b): Light brown solid; mp 169–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.76 (s, 3H), 6.81 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 8.24 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 55.5, 114.3, 118.4, 123.5, 127.4, 130.3, 133.3, 133.9, 144.4, 153.1, 161.1; IR (KBr): 3424, 3124, 3034, 2929, 1617, 1574, 1498, 1475, 1385, 1294, 1261, 1201, 1175, 1069, 1029, 830, 816, 662, 567 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}BrN_3O$ (MH^+) 330.0237; found 330.0249.



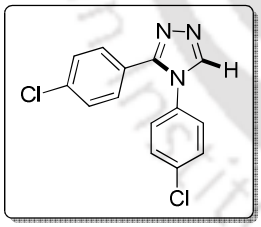
4-(4-Bromophenyl)-3-(4-chlorophenyl)-4*H*-1,2,4-triazole (17b): Light brown solid; mp 185–187 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.09 (d, 2H, J = 9.0 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 8.28 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 124.0, 124.6, 127.4, 129.0, 129.3 130.0, 133.6, 136.6, 144.4, 152.9; IR (KBr): 2927, 2863, 1723, 1494, 1280, 1197, 1068, 1012, 826, 662 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9BrClN_3$ (MH^+) 333.9741; found 333.9746.



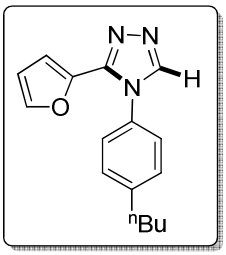
3,4-bis(4-Bromophenyl)-4*H*-1,2,4-triazole (18b): White solid; mp 242–244 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.09 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 8.29 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 124.0, 125.0, 125.1, 127.4, 130.2, 132.2, 133.5, 133.6, 144.9, 152.4; IR (KBr): 3121, 3034, 2920, 1599, 1567, 1495, 1459, 1405, 1380, 1199, 1067, 1013, 841, 821, 722, 664 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9Br_2N_3$ (MH^+) 377.9236; found 377.9246.



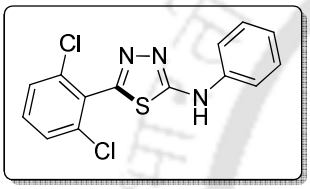
4-(4-Chlorophenyl)-3-(*p*-tolyl)-4*H*-1,2,4-triazole (19b): White solid; mp 194–196 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 2.30 (s, 3H), 7.21 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 7.41 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 8.84 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 21.3, 124.0, 128.4, 128.9, 129.7, 130.2, 133.9, 134.2, 140.0, 145.8, 152.7; IR (KBr): 3434, 3040, 2922, 1500, 1476, 1385, 1199, 1093, 1085, 1015, 840, 819, 726, 665, 568 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{12}ClN_3$ (MH^+) 270.0793; found 270.0780.



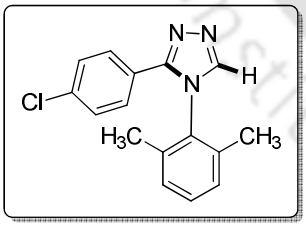
3,4-Bis-(4-chlorophenyl)-4*H*-1,2,4-triazole (20b): White solid; mp 165–167 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.15 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 9.0 Hz, 2H), 8.26 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 124.6, 127.1, 129.2, 130.0, 130.5, 132.9, 135.9, 136.6, 145.1, 152.9; IR (KBr): 3043, 2924, 1602, 1554, 1497, 1408, 1199, 1093, 1014, 833, 729, 565 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9Cl_2N_3$ (MH^+) 290.0246; found 290.0241.



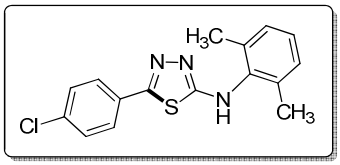
4-(4-Butylphenyl)-3-(furan-2-yl)-4*H*-1,2,4-triazole (22b): Brown gummy; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.91 (t, J = 7.2 Hz, 3H), 1.34 (sextet, J = 7.8 Hz, 2H), 1.61 (quintet, J = 7.2 Hz, 2H), 2.66 (t, J = 7.8 Hz, 2H), 6.34 (s, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.38 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 14.0, 22.4, 33.5, 35.4, 111.5, 112.0, 126.1, 129.8, 131.7, 142.6, 144.3, 145.4, 147.0, 153.4; IR (KBr): 2959, 2864, 2836, 1602, 1561, 1516, 1464, 1407, 1275, 1205, 1097, 1015, 904, 835, 668, 569 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{17}N_3O$ (MH^+) 268.1444; found 268.1452.



5-(2,6-dichlorophenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (23c): White solid; mp 228–230 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.02 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.64–7.69 (m, 4H), 10.63 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 117.6, 122.2, 128.2, 128.6, 129.1, 132.8, 135.3, 140.3, 150.6, 166.2; IR (KBr): 3439, 3245, 3061, 2923, 1602, 1571, 1501, 1455, 1430, 1190, 1109, 979, 789, 752, 693 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_9Cl_2N_3S$ (MH^+) 321.9967; found 321.9981.



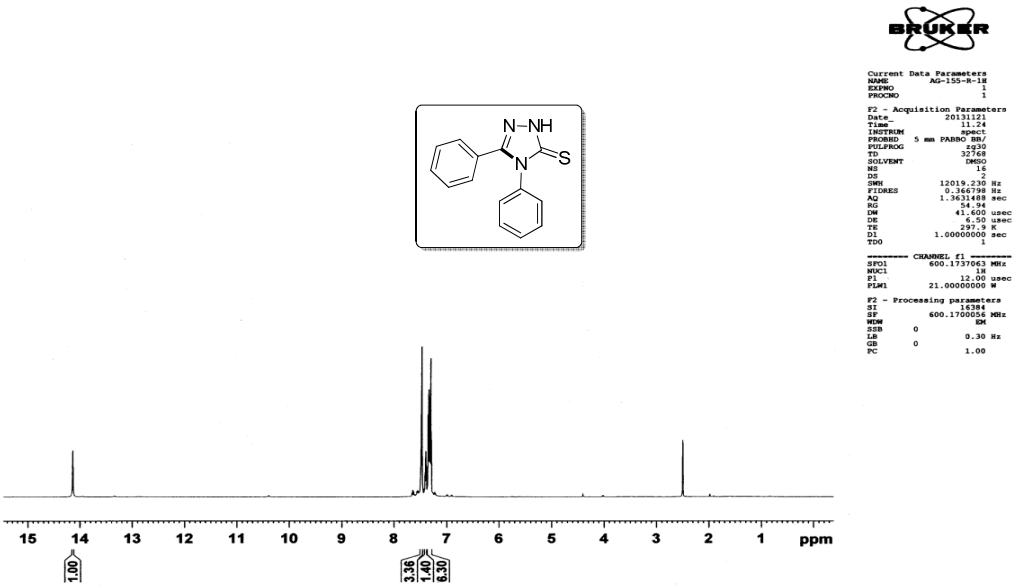
3-(4-chlorophenyl)-4-(2,6-dimethylphenyl)-4*H*-1,2,4-triazole (24b): White solid; mp 181–183 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 1.97 (s, 6H), 7.21 (d, J = 7.2 Hz, 2H), 7.27 (d, J = 6.6 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 17.9, 125.3, 128.2, 129.2, 129.3, 130.3, 132.9, 135.4, 136.3, 144.6, 151.8; IR (KBr): 3436, 3118, 3057, 2920, 2853, 1671, 1571, 1488, 1464, 1408, 1368, 1197, 1094, 1010, 983, 849, 816, 784, 731, 669 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}ClN_3$ (MH^+) 284.0949; found 284.0942.



5-(4-chlorophenyl)-*N*-(2,6-dimethylphenyl)-1,3,4-thiadiazol-2-amine (24c): White solid; mp 229–231 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 7.16–7.20 (m, 3H), 7.33 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 7.8 Hz, 2H), 9.53 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 18.4, 128.0, 128.3, 129.2, 129.25, 129.34, 129.7, 135.4, 136.6, 138.8, 156.5, 172.5; IR (KBr): 3436, 3157, 2920, 2852, 1596, 1555, 1505, 1467, 1427, 1262, 1212, 1089, 1014, 981, 832, 785, 642 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}ClN_3S$ (MH^+) 316.0670; found 316. 0682.

V.7. Spectra

4,5-Diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (1a): ^{1}H NMR (600 MHz, DMSO-d_6)

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PROCNO                  1

F2 - Acquisition Parameters
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PULPROG          zg30
TD              32768
SOLVENT          DMSO
NS                  16
DS                   2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ            1.3631488 sec
RG                54.94
DW               41.600 usec
DE                6.50 usec
TE              297.9 K
D1           1.00000000 sec
TD0                  1

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NUC1               1H
P1               12.00 usec
PLW1        21.00000000 W

F2 - Processing parameters
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SF          600.1700056 MHz
WDW               EM
SSB          0
LB                0.30 Hz
GB           0
PC                1.00
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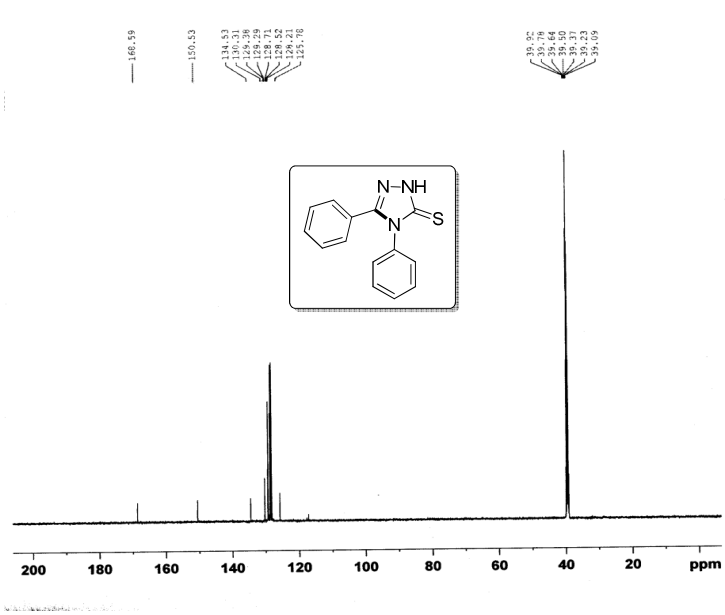
4,5-Diphenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (1a): ^{13}C NMR (150 MHz, DMSO-d_6)

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PROCNO                  1

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PULPROG         zgpg30
TD              32768
SOLVENT          DMSO
NS                 201
DS                   2
SWH          36057.691 Hz
FIDRES        1.100393 Hz
AQ            0.4543829 sec
RG                65.24
DW               13.867 usec
DE                6.50 usec
TE              298.4 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

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

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

F2 - Processing parameters
SI                16384
SF          150.9129408 MHz
WDW               EM
SSB          0
LB                1.00 Hz
GB           0
PC                1.40
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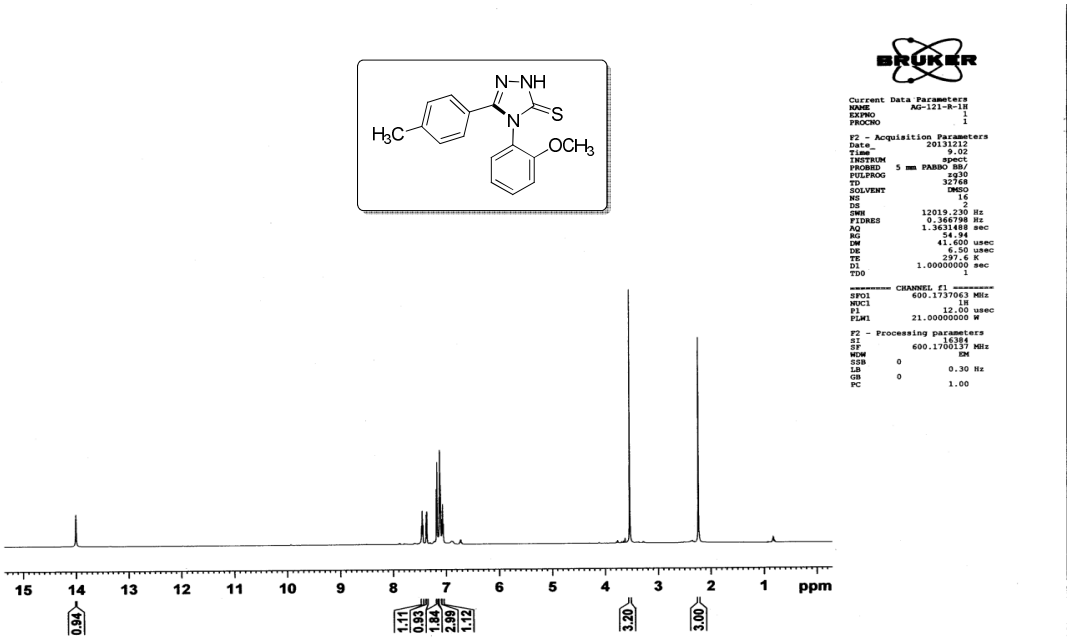
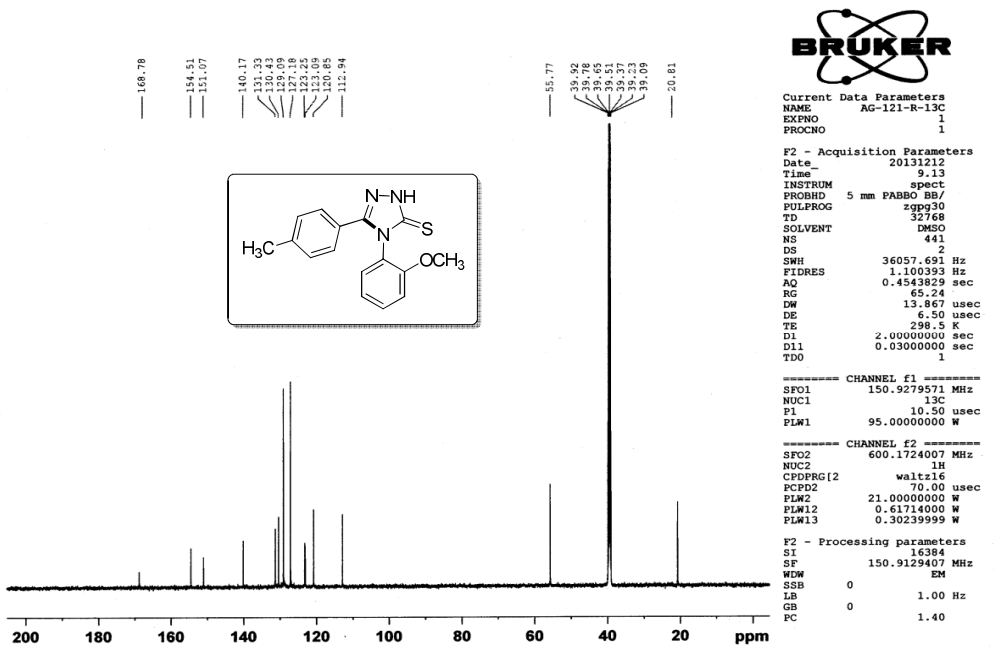
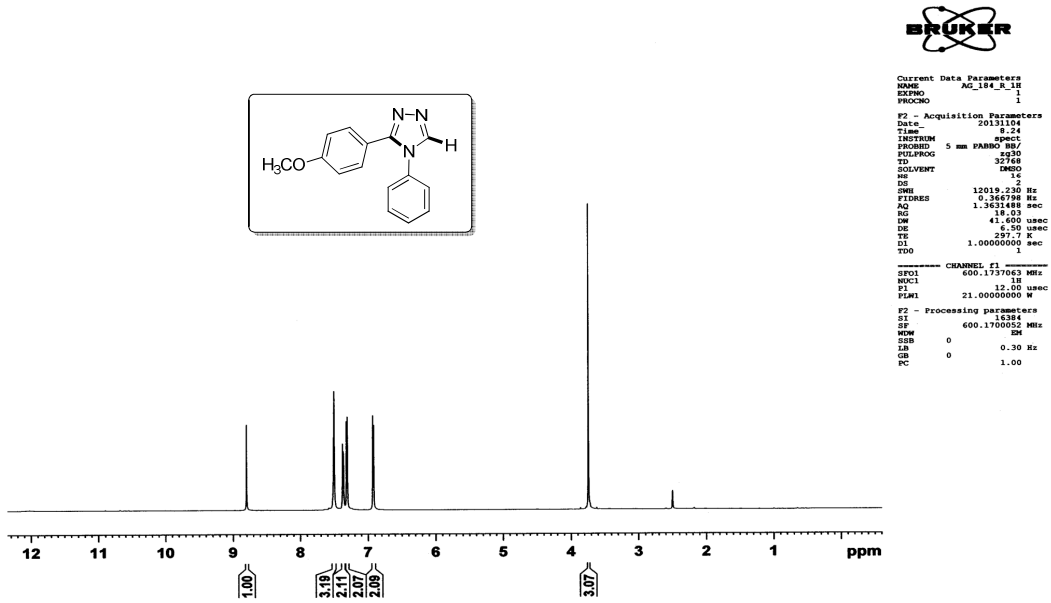
4-(2-Methoxyphenyl)-5-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (11a): ^{1}H NMR (600 MHz, $CDCl_3$)



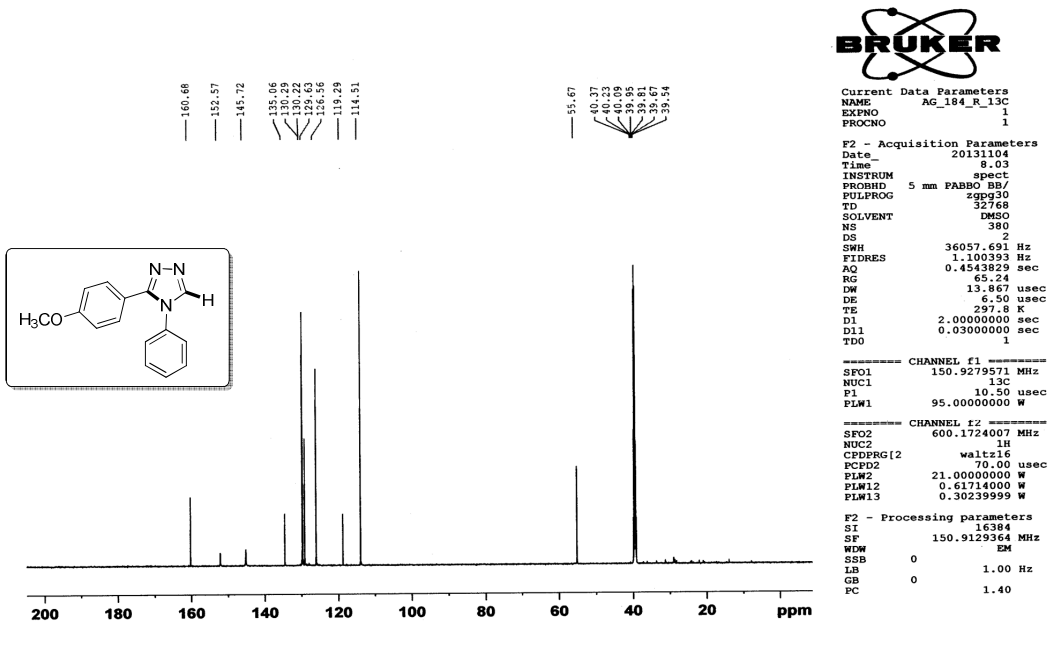
4-(2-Methoxyphenyl)-5-(4-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (11a): ^{13}C NMR (150 MHz, DMSO-d_6)



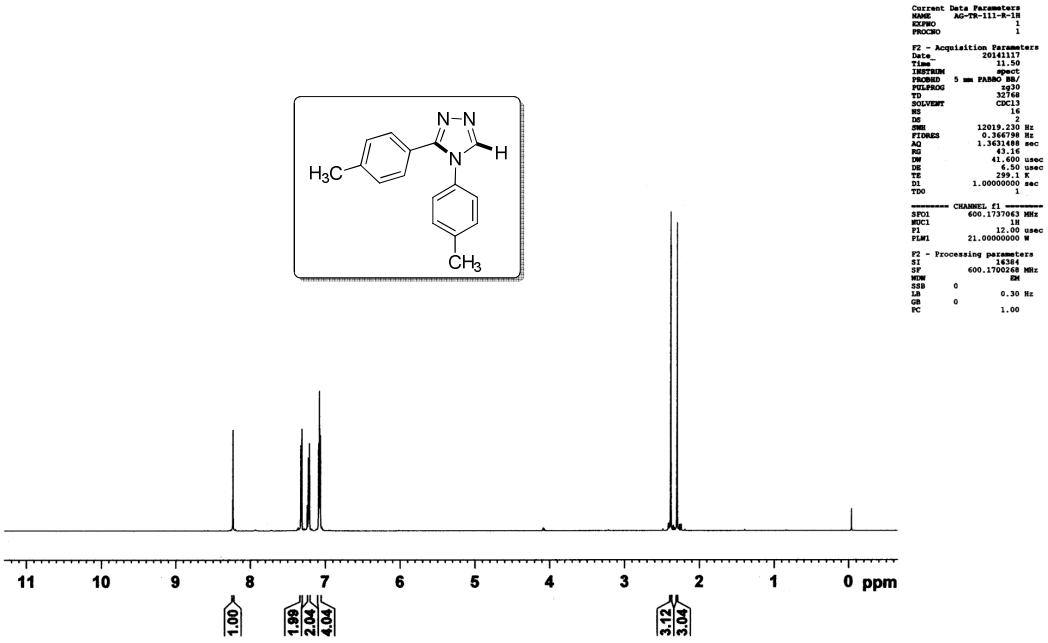
3-(4-Methoxyphenyl)-4-phenyl-4H-1,2,4-triazole (2b): ^{1}H NMR (600 MHz, DMSO-d_6)



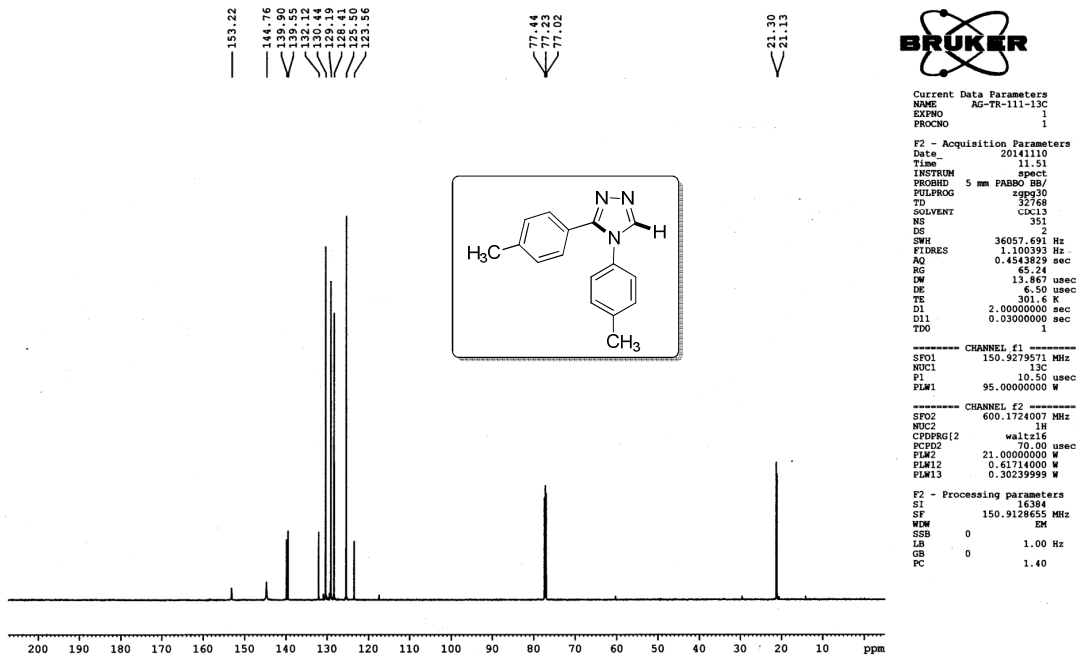
3-(4-Methoxyphenyl)-4-phenyl-4H-1,2,4-triazole (2b): ^{13}C NMR (150 MHz, DMSO-d_6)



3,4-Di-*p*-tolyl-4H-1,2,4-triazole (7b): ^{1}H NMR (600 MHz, $CDCl_3$)



3,4-Di-*p*-tolyl-4H-1,2,4-triazole (7b): ^{13}C NMR (150 MHz, $CDCl_3$)



PUBLICATIONS

1. "**Copper (II) catalyzed synthesis of indoloquinoxalin-6-ones via oxidative Mannich reaction**"

   Anupal Gogoi, Prasenjit Sau, Wajid Ali, Srimanta Guin, Bhisma K. Patel *Eur. J. Org. Chem.* **2016**, 1449.

2. "**Synthesis of 1,2,4-triazoles via oxidative heterocyclization: selective C–N bond over C–S bond formation**"

   Anupal Gogoi, Srimanta Guin, Suresh Rajamanickam, Saroj K. Rout, Bhisma K. Patel *J. Org. Chem.* **2015**, *80*, 9016.

3. **"A copper-catalyzed synthesis of substituted 3-methyleneisoindoli-1-one"**

   Anupal Gogoi, Srimanta Guin, Saroj K. Rout, Ganesh Majji, Bhisma K. Patel *RSC Adv.* **2014**, *4*, 59902.

4. "**Thioesterification of alkylbenzenes with thiols via copper-catalyzed cross-dehydrogenative coupling without directing group**"

   Wajid Ali, Srimanta Guin, Saroj K. Rout, Anupal Gogoi, Bhisma K. Patel *Adv. Synth. Catal.* **2014**, *356*, 3099.

5. "**A metal free domino synthesis of 3-aroylindoles via two sp^3 C–H activation**"

   Anupal Gogoi, Anju Modi, Srimanta Guin, Saroj K. Rout, Bhisma K. Patel *Chem. Commun.* **2014**, *50*, 10445.

6. "**A palladium(II)-catalyzed synthesis of α-ketoamides via chemoselective aroyl addition to cyanamides**"

   Srimanta Guin, Saroj K. Rout, Anupal Gogoi, Wajid Ali, Bhisma K. Patel *Adv. Synth. Catal.* **2014**, *356*, 2559.

7. "**Copper-catalyzed esterification of alkylbenzenes with cyclic ethers and cycloalkanes via C(sp^3)–H activation following cross-dehydrogenative coupling**"

   Srimanta Guin, Saroj K. Rout, Anupal Gogoi, Majji Ganesh, Bhisma K. Patel *Org. Lett.* **2014**, *16*, 3086.

8. "**Terminal aryl alkenes and alkynes as arylcarboxy surrogates toward *o*-benzoxylation of 2-phenylpyridine catalyzed by copper**"

Srimanta Guin, Saroj K. Rout, Wajid Ali, Anupal Gogoi, Bhisma K. Patel *Org. Lett.* **2014**, *16*, 1614.

9. "**Iodine-catalyzed oxidative cyclization of acylhydrazones to 2,5-substituted 1,3,4-oxadiazoles**"

   Majji Ganesh, Saroj K. Rout, Srimanta Guin, Anupal Gogoi, Bhisma K. Patel *RSC Adv.* **2014**, *4*, 5357.

10. **"CuO nanoparticle catalyzed synthesis of 2*H*-indazoles under ligand free conditions"**

    Nilufa Khatun, Anupal Gogoi, Pallabita Basu, Prasenjit Das, Bhisma K. Patel *RSC Adv.* **2014**, *4*, 4080.

11. "**A copper-catalyzed synthesis of 3-aroylindoles via a sp^3 C–H activation followed by C–C and C–O bond formation**"

    Anupal Gogoi, Srimanta Guin, Saroj K. Rout, Bhisma K. Patel *Org. Lett.* **2013**, *15*, 1802.

12. "**Directing group assisted copper-catalyzed chemoselective *O*-aroylation of phenols and enols using alkylbenzenes**"

    Saroj K. Rout, Srimanta Guin, Arghya Banerjee, Nilufa Khatun, Anupal Gogoi, Bhisma K. Patel *Org. Lett.* **2013**, *15*, 4106.

13. "**Easy access to benzylic esters directly from alkyl benzenes under metal-free conditions**"

    Majji Ganesh, Srimanta Guin, Anupal Gogoi, Saroj K. Rout, Bhisma K. Patel *Chem. Commun.* **2013**, *49*, 3301.

14. **"Cu (II) catalyzed chemoselective oxidative transformation of thiourea to thioaminoguanidine /2-aminobenzothiazole"**

    Santosh K. Sahoo, Nilufa Khatun, Anupal Gogoi, Bhisma K. Patel *RSC Adv.* **2013**, *3*, 438.

15. "**Desulfurization strategy in the construction of azoles possessing additional nitrogen, oxygen or sulfur using a copper(I) catalyst**"

    Srimanta Guin, Saroj K. Rout, Anupal Gogoi, Shyamapada Nandi, Krishna Kanta Ghara, Bhisma K. Patel *Adv. Synth. Catal.* **2012**, *354*, 2757.