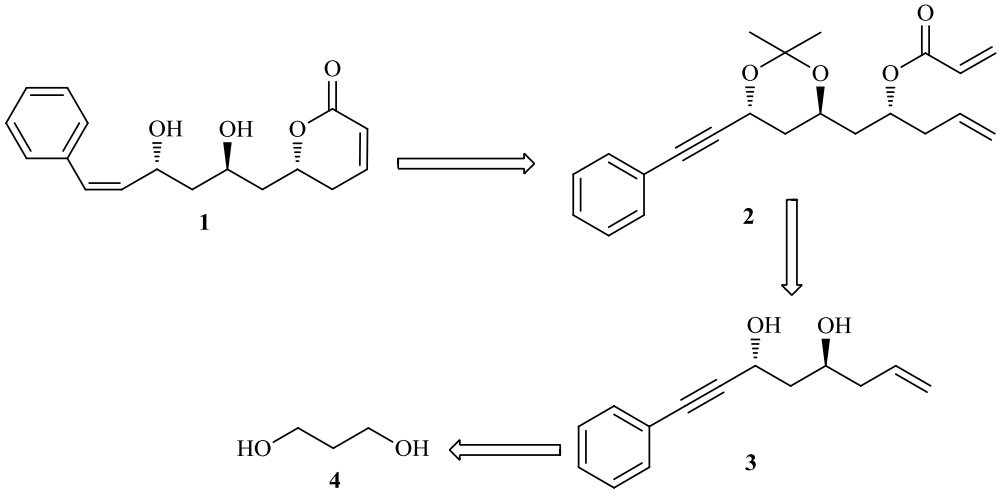
# SYNOPSIS

The thesis entitled "**The first stereoselective total synthesis of (*Z*)-Cryptomoscatone D2 and Cu-catalyzed distinct approaches for alkenylation, alkynylation of heteroarenes along with development of new synthetic methodologies**" has been divided into three chapters.

**CHAPTER I: The first stereoselective total synthesis of (*Z*)-Cryptomoscatone D2.**

The α, β- unsaturated δ-lactones (γ-pyrone derivatives) have frequently been isolated from various natural sources. They are known to possess different interesting biological properties including cytotoxic, antiviral and antibacterial activities. (*Z*)-Cryptomoscatone D2 (**1**), a novel compound of this group, was isolated from *Cryptocarya concinna*, a tree of the laurel family. The compound contains an α, β- unsaturated δ-lactone ring along with two hydroxyl groups having opposite stereostructure and an olefinic system with (*Z*)-configuration. The bioactivity of this compound was studied and it was identified as a $G_2$ checkpoint inhibitor while examining in human breast carcinoma MCF-7 cells. However, to our knowledge, the synthesis of this compound has not yet been reported.

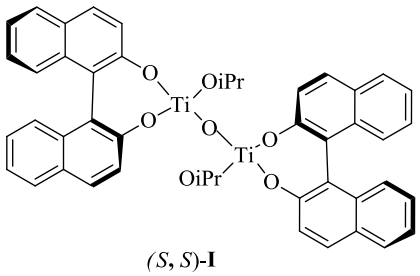
The retrosynthetic analysis (**Scheme 1**) revealed that the compound **1** can be prepared from the ester **2** which in turn can be synthesized from the unsaturated diol **3** generated from propane-1, 3-diol (**4**).



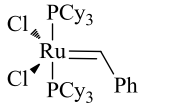

**Scheme 1**

The synthesis of (*Z*)-Cryptomoscatone D2 (**1**) was initiated (**Scheme 2**) by protecting one of the hydroxyl groups of propane-1, 3-diol (**4**) as the benzyl ether by treatment with

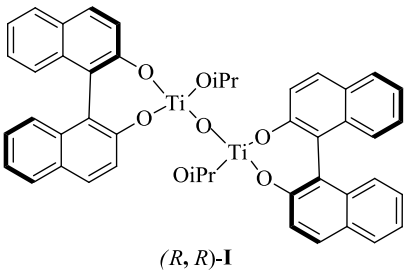
BnBr using NaH and TBAI to form the compound **5**. The compound **5** was oxidized with PCC to the corresponding aldehyde which underwent Maruoka asymmetric allylation employing (*S*)-Binol titanium complex, (*S, S*)-**I** and allyl tributyl stannane to produce the chiral homoallylic alcohol **6** (ee 96%). The hydroxyl group of this alcohol **6** was protected as the TBDPS ether by treatment with TBDPS-Cl and imidazole to form **7** which was subsequently treated with Li in naphthalene to generate the primary alcohol **8**. The alcohol **8** was then oxidized with IBX to the corresponding aldehyde which was reacted with phenyl acetylene using *n*-BuLi to afford the diastereoisomeric propargylic alcohols **9** (major) and **10** (minor) (with diastereoisomeric ratio 70:30). Both the compounds were separated by column chromatography. The minor alcohol **10** was subsequently converted into **9** under Mitsunobu conditions by reaction with *p*-nitro benzoic acid, TPP and DIAD followed by treatment with methonolic $K_2CO_3$. Next, the deprotection of TBDPS ether group of **9** with TBAF yielded the required diol **3** which on treatment with DMP and PPTS afforded the acetonide **11**. The 1, 3-*anti* relationship in **11** was realized by analysis of its $^{13}C$ NMR spectrum which showed that the methyl carbons resonated at δ 24.8 and the acetonide carbon at δ 100.3. Compound **11** was treated with $OsO_4$ and NMO in aqueous acetone and subsequently the resulting diol was treated with $NaIO_4$ to form an aldehyde which was again subjected to Maruoka asymmetric allylation using (*R*)- Binol titanium complex, (*R, R*)-**I** to form the homoallyl alcohol **12**. The alcohol **12** was converted into the acryloyl ester **2** which underwent the ring closing metathesis using Grubbs' 1$^{st}$ generation catalyst to form the α, β-unsaturated lactone **13**. The deprotection of the acetonide group (4*N* HCl, MeOH) of **13** furnished the diol **14**. Finally the hydrogenation of the later on employing Lindlar's catalyst yielded the target molecule, (*Z*)-Cryptomoscatone D2 (**1**) whose optical and spectral properties were found to be identical to those of the natural product.



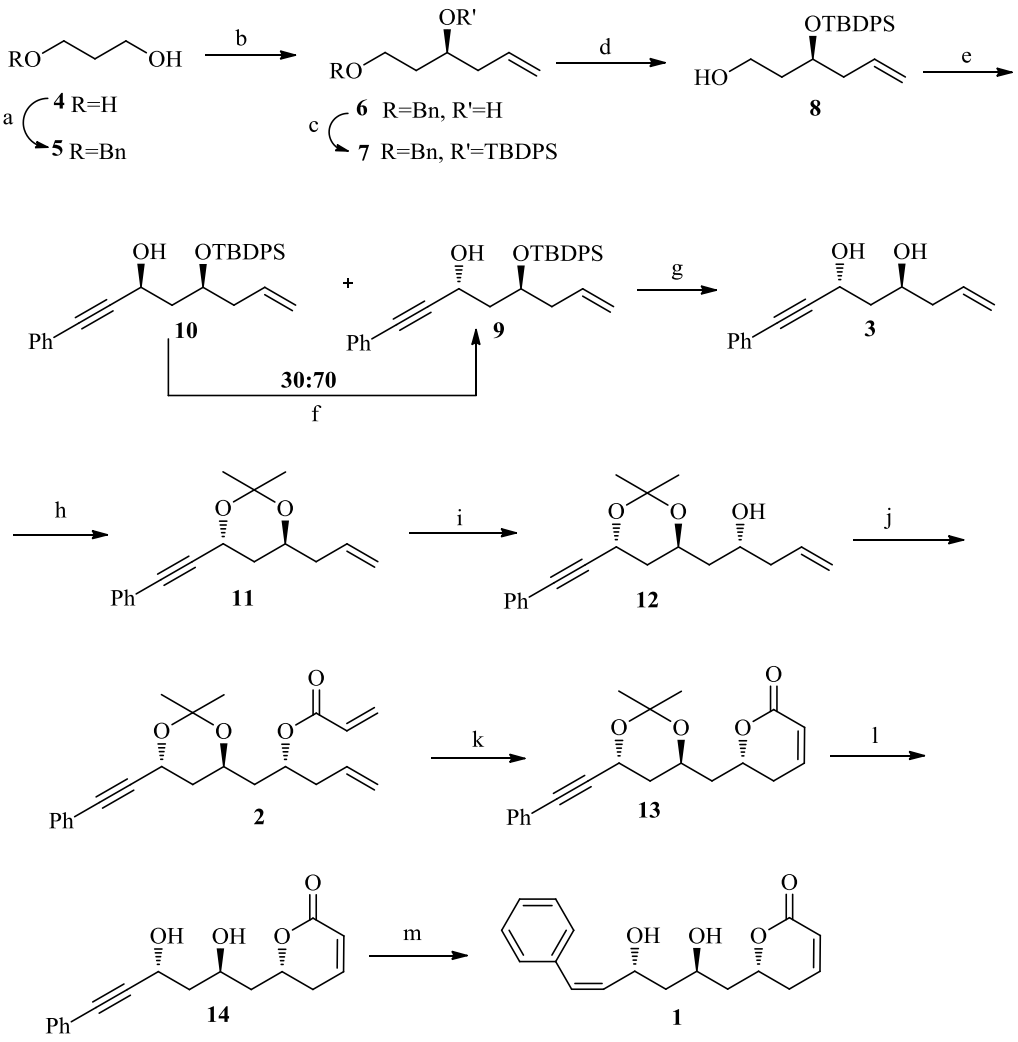

(*S, S*)-**I**




Grubbs' 1$^{st}$ generation catalyst




(*R, R*)-**I**




**Scheme 2.** Synthesis of (*Z*)-cryptomoscatone D2 (**1**). Reagents and conditions: a) BnBr, NaH, TBAI, THF. 0 $^{o}$C to rt, 2h, 87%; b) i) PCC, Celite, $CH_2Cl_2$, rt, 2 h; ii) (*S*, *S*)-**I** (10 mol%), allyltributyltin, 4A$^{o}$ MS, $CH_2Cl_2$, -20 $^{o}$C, 72 h, ee 96%, 85% (over two steps); c) TBDPSCl, imidazole, cat. DMAP, $CH_2Cl_2$, 0 $^{o}$C to rt, 4h, 88%; d) Li in naphthalene, -20 $^{o}$C, 3h, 91%; e) i) IBX, $CH_2Cl_2$/DMSO, 0 $^{o}$C to rt, 6h; ii) Phenyl acetylene, *n*-BuLi, anhyd.THF, -20 $^{o}$C, 3h, 84% (over two steps); f) i) 4-$NO_2$-PhCOOH, TPP, DIAD, anhyd. THF, 0 $^{o}$C to rt, 12 h (ii) $K_2CO_3$, MeOH, 1 h, 87% (over two steps); g) TBAF, dry THF, 0 $^{o}$C to rt, 4h, 95%; h) 2, 2-DMP, PPTS, $CH_2Cl_2$, 0 $^{o}$C, 30 min, 91%; i) i) $OsO_4$, NMO, acetone/$H_2O$, $NaIO_4$, 27 $^{o}$C, 4h; ii) (*R*, *R*)-**I** (10 mol%), allyltributyltin, 4A$^{o}$ MS, $CH_2Cl_2$, -20 $^{o}$C, 72h, 75% (over two steps); j) acryloyl chloride, $^{i}Pr_2NEt$, $CH_2Cl_2$, -78 $^{o}$C, 2h, 90%; k) Grubbs' 1$^{st}$ generation catalyst (10 mol%), $CH_2Cl_2$, reflux, 12h, 72%; l) 4*N* HCl, MeOH, 0 $^{o}$C, 30 min, 92%; m) Pd/$CaCO_3$, $H_2$, quinoline, EtOAc, rt, 6h, 90%.

In conclusion, we have developed the first stereoselective total synthesis of a natural bioactive lactone (*Z*)-Cryptomoscatone D2 starting from propane-1, 3-diol by utilizing the

Maruoka allylation, ring closing metathesis and selective reduction of the alkyne as the key steps.

**CHAPTER II: Copper catalyzed alkenylation, alkynylation of heteroarenes *via* C-H, N-H activation.**

This chapter further divided into two sections.

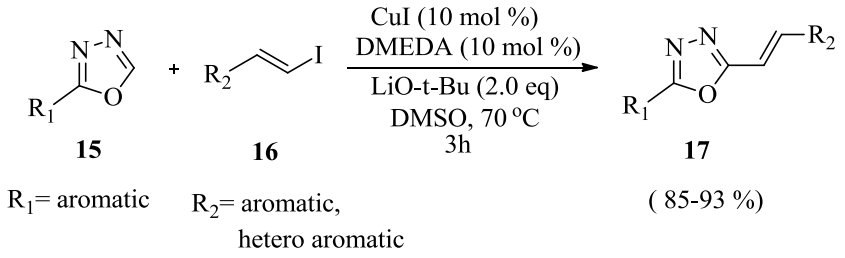
**SECTION-A: Copper catalyzed direct cross-coupling of 1, 3, 4-oxadiazoles with *trans*-β-halostyrenes and 1, 1-dibromo-1-alkenes.**

Oxadiazoles are an important class of five membered heterocyclic compounds with a broad range of biological activities. These five-member heterocycles are also useful intermediates in organic synthesis and widely employed as electron transporting and hole-blocking materials. Moreover, it is considered that the presence of toxophoric –N-C–O– linkage is responsible for their potent pharmacological activity. Further, 1, 3, 4-oxadiazole heterocyclic's are very good bioisosters of amide and ester functionalities with substantial improvement in biological activity by participating in hydrogen bonding interactions with different receptors. Thus the synthesis of oxadiazole derivatives is an useful task in pharmaceutical and material sciences.

The widespread applications of heteroarenes in medicinal chemistry and in materials science have driven the development of a plethora of new synthetic strategies to prepare appropriately substituted heterocyclic cores. Metal-catalyzed direct functionalization of C-H bonds of heteroarenes is great importance in recent organic synthesis to generate concisely the molecular complexity. In fact, the transformation of C-H to C-C bonds in the presence of a metal catalyst is a highly valuable preparative reaction because of its atom economy. Thus various arenes and heteroarenes have been subjected to direct arylation, alkenylation, and alkynylation using different catalytic systems. A wide range of metal catalysts including palladium, rhodium, or ruthenium have been exploited for these transformations. However, the use of copper catalysts remains quite rare, despite the clear advantages in their availability and cost-effectiveness.

Copper-mediated creation of an alkenyl-heteroaryl linkage between a $sp^2$-hybridized heteroaryl carbon of 1, 3, 4-oxadiazole and a $sp^2$-hybridized carbon of alkenyl halide using C-H bond activation has not yet been reported. Here we have observed that 1, 3, 4-

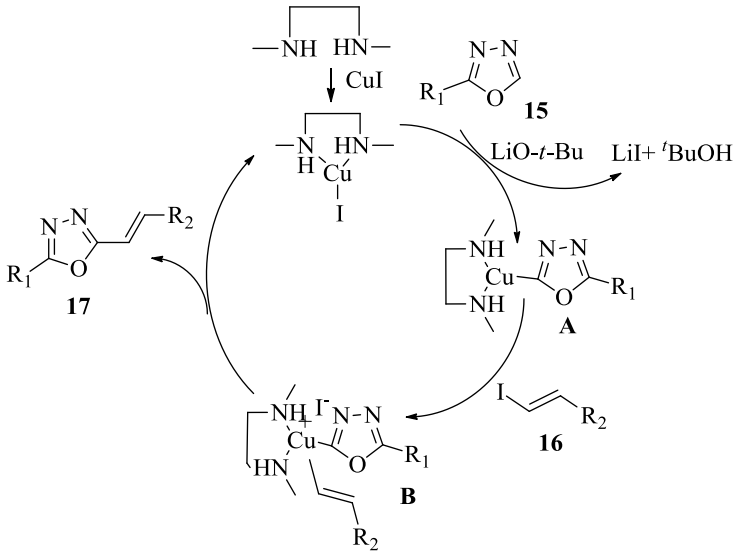
oxadiazoles underwent direct alkenylation with *trans*-β-iodostyrenes in the presence of CuI using a ligand, *N*, *N*'-dimethylethylene diamine (DMEDA) and LiO-*t*-Bu. (**Scheme 3**)




**Scheme 3**

The oxadiazoles (**15**) containing electron-donating as well as electron-withdrawing groups in the aromatic ring underwent the conversion smoothly. The *trans*-β-iodo olefins (**16**) having heteroaromatic moiety also afforded the desired alkenyl products (**17**) in high yields. For each conversion the reaction time was 3h. The structures of the products were established from their spectral (IR, $^{1}H$ and $^{13}C$ NMR and HRMS) data.

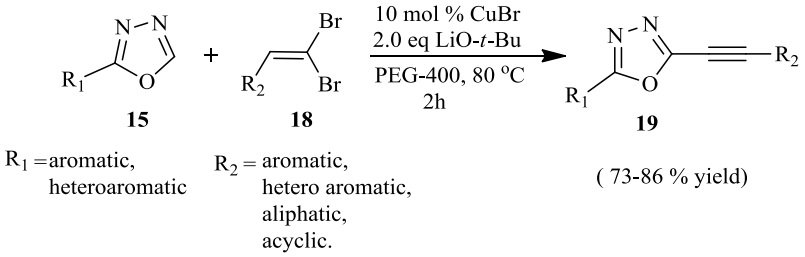
The plausible mechanism for this transformation is shown in **Scheme 4**. This mechanism involves the base assisted transmetallation of 1, 3, 4-oxadiazole to form (heteroaryl) Cu (I) intermediate **A.** Oxidative addition of *trans*-β-iodostyrene (**16**) to **A** to form the copper (III) complex **B** followed by reductive elimination leads to the formation of expected alkenylated product (**17**).




**Scheme 4. Plausible mechanism of alkenylation**

In conclusion, we have developed for the first time an efficient method for direct alkenylation of 1, 3, 4-oxadiazoles with *trans*-β-iodo olefinic system using a combination of CuI/DMEDA as a catalyst.

Our further studies on C-H activation of 1, 3, 4-oxadiazoles, we have observed that 1, 3, 4-oxadiazoles (**15**), when treated with 1, 1-dibromo-1-alkenes (**18**) using CuBr and LiO-*t*-Bu in polyethylene glycol (PEG-400) at 80 $^{o}$C, afforded the corresponding 2-alkynyl derivatives (**19**) in 2h (**Scheme 5**).

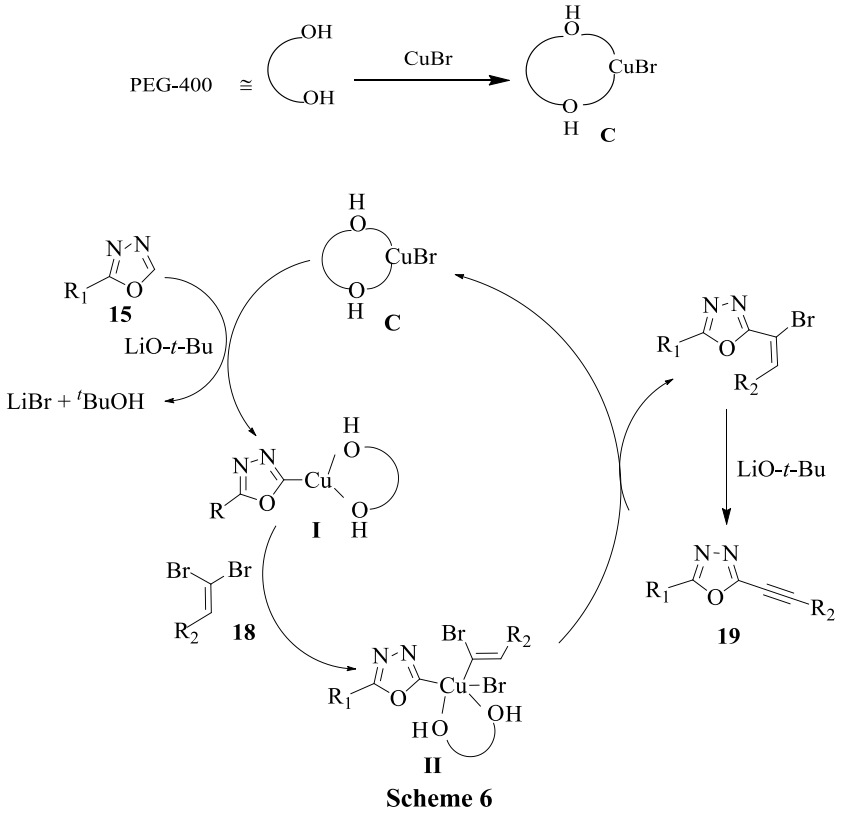



**Scheme 5**

The present copper-mediated direct cross-coupling reaction was carried out using various 2-aryl-1,3,4-oxadiazoles (**15**) and different 1,1-dibromo-1-alkenes (**18**). The aryl group of the oxadiazoles contained both aromatic and heteroaromatic moieties. The aromatic moiety possessed electron-donating as well as electron-withdrawing groups while the heteroaromatic moiety was consisted of oxygen and nitrogen heterocycles. The 1,1-dibromo-1-alkenes (**18**) also contained both aromatic and aliphatic groups. Thus the present conversion has versatile scope for the preparation of various alkynylated oxadiazole derivatives. The structures of the products were established from their spectral (IR, $^{1}$H and $^{13}$C NMR and HRMS) data.

Polyethylene glycol (PEG-400) has been used here as a reaction medium. In recent years chemists like to avoid volatile organic solvents, especially chlorinated solvents which create environmental problems. Polyethylene glycol (PEG-400) is an eco-friendly, biologically acceptable inexpensive water soluble polymeric compound. It is a green solvent system, less expensive, recyclable and miscible with different organic solvents. This solvent medium has successfully been utilized here for alkynylation of oxadiazoles.

With an understanding about the copper-catalyzed cross-coupling reactions a plausible mechanism of the present conversion is given below. The reaction medium, polyethylene glycol acts here as a ligand to form the species **C** (**Scheme 6**). The mechanism involves the (heteroaryl) Cu (I) intermediate **I** and the Cu (III) complex **II** to form the alkynylated product **19**.




**Scheme 6**

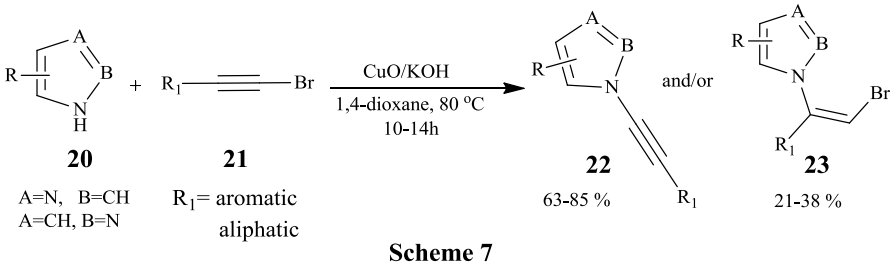
In conclusion we have developed copper-mediated green method for alkynylation of 1, 3, 4-oxadiazoles using PEG-400 as solvent medium. The costly Pd-based catalysts have been avoided here. The mild reaction conditions, operational simplicity, ligand and volatile solvent free conversion, application of a non-toxic and recyclable medium, high yields and rapid formation of the products are the notable advantages of the method.

**SECTION-B: Copper (II) oxide catalyzed ligand-free cross-coupling reaction of imidazoles and pyrazoles with bromoalkynes.**

Alkynes are building blocks in synthetic organic chemistry. Ynamines are those compounds which have direct linkage of amino nitrogen atom with an alkyne functional group. *N*-Alkynyl heteroarenes are valuable intermediates in organic synthesis as well as in

medicinal chemistry. They are also known to possess important biological and photoconductive properties.

Our studies on N-H activation of heteroarenes *viz.* imidazoles and pyrazoles, we have discovered that the treatment of heteroarenes (**20**) with bromoalkynes (**21**) in the presence of catalytic amount of CuO using KOH in 1, 4-dioxane afforded the corresponding *N*-alkynyl and/or *N*-bromoalkenyl heteroarenes at 80 $^{o}$C (**Scheme 7**).




**Scheme 7**

A series of *N*-alkynyl imidazoles were finally prepared following the method as standardized above (**Scheme 7**). Various substituted imidazoles including benzimidazoles were employed to prepare the products. Both aromatic and aliphatic bromoalkynes underwent the conversion smoothly. The conversion was complete within 10-14h and the *N*-alkynyl imidazoles were formed in high yields (67-85%).

Some of the imidazole derivatives also formed *N*-bromoalkenyl compound along with *N*-alkynyl product and some of them as the sole product. The olefinic double bond in all the *N*-bromoalkenyl products was in (*Z*)-configuration as the olefinic proton did not show any NOESY correlation with the protons of the imidazole core.

The above reaction was also successfully applied for C-N coupling of bromoalkynes with pyrazoles to produce a series of *N*-alkynyl pyrazoles. The structures of all the products were established from their spectral (IR, $^{1}$H and $^{13}$C NMR, ESIMS and HRMS) data.

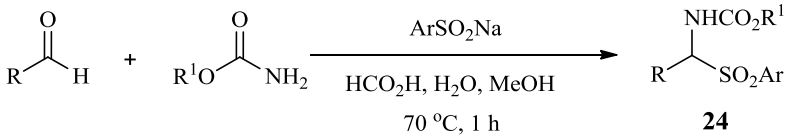
In conclusion, we have developed a simple and efficient coupling reaction of heteroarenes with bromoalkynes using Cu (II) oxide (as a catalyst) and KOH in 1, 4-dioxane to prepare *N*-alkynylated and/or *N*-bromoalkenylated heteroarenes under ligand-free conditions.

**CHAPTER III: Development of new synthetic methodologies.**

This chapter further divided into three sections.

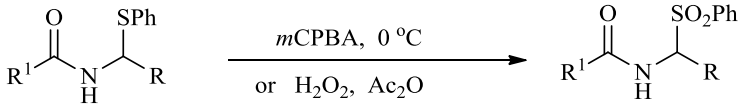
**SECTION-A: Introduction to α-amido sulfones.**

α-Amido sulfones **24** can be conveniently prepared by a three-component coupling involving an aldehyde, an amide or a carbamate and benzene/*p*-toluene sulfinic acid or its sodium salt. (**Scheme 8**)




**Scheme 8**

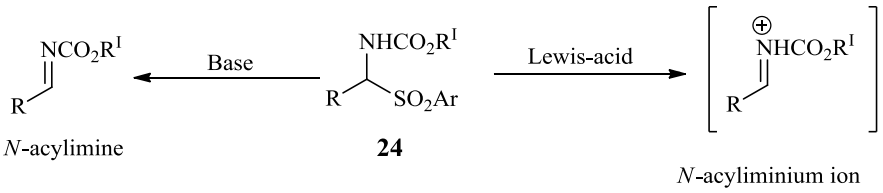
An alternative method was also developed by the oxidation of the corresponding sulfides using hydrogen peroxide or *m*CPBA. (**Scheme 9**)




**Scheme 9**

An important feature that associated with the chemistry of *α*-amido sulfones is their ease of preparation. In addition, most of these compounds are stable solids that precipitate from the reaction mixture and require little or no purification before use. They can be stored for prolonged times.

α-Amido sulfones (**24**) furnish the corresponding *N*-acylimines and *N*-acyliminium ions *in situ* when treated with base and Lewis-acid respectively (**Scheme 10**).




**Scheme 10**

The resulting *N*-acylimines and *N*-acyliminium ions have been widely used in combination with hard metallic reagents, other non-stabilized carbanions, metal stabilized

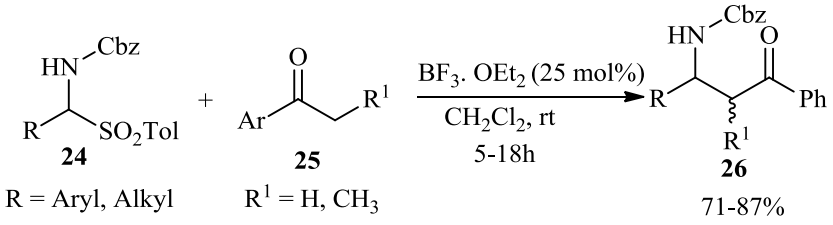
enolates and other nucleophiles to prepare a large array of amino derivatives. The products were obtained in both racemic and enantiopure form exploiting diastereo and enantioselective processes. The compounds produced were further transformed into useful synthetic intermediates and bioactive natural products. Some of the applications of *α*-amido sulfones in the synthesis of natural products were discussed in this section.

**SECTION-B: Synthesis of *N*-benzyloxycarbonyl β-amino ketones from α-amido sulfones.**

β-Amino carbonyl compounds exhibit significant biological activity and their skeleton is present in different medicinally important compounds. They are also valuable building blocks for the synthesis of pharmaceuticals and bioactive natural molecules. Paclitaxel, a prominent anticancer compound, contains a β-amino carbonyl function in its side chain, which is an important segment for its bioactivity. The general protocol for the synthesis of β-amino carbonyl compounds is the Mannich-type reaction of aldehydes, amines (or directly imines), and enolizable ketones or silyl enolates.

Because of their interesting biological properties, several methods have been developed. However, many of these methods have different drawbacks, such as the use of toxic reagents and expensive catalysts in excess, long reaction times, drastic conditions, and unsatisfactory yields.

Our goal was to develop a simple and efficient protocol for the synthesis of β-amino carbonyl compounds. We have discovered that the treatment of α-amido sulfones (**24**) with aromatic ketones (**25**) in the presence of catalytic amount of $BF_3.OEt_2$ afforded the corresponding protected β-amino ketones (**26**) at room temperature (**Scheme 11**).




**Scheme 11**

Various α-amido sulfones like aliphatic, acyclic, aromatic and heteroaromatic were successfully converted into corresponding β-amino ketones in good yields. Sulfones having both electron-withdrawing and electron-donating remained intact. The reaction

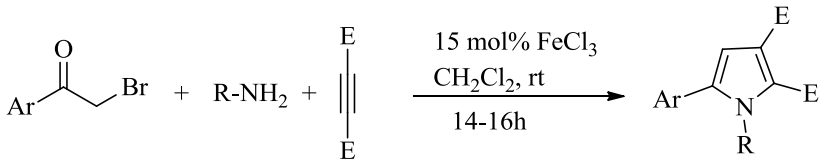
times required for the conversion was 5-10h. The reaction when carried out with propiophenone both *anti*- and *syn*- isomers were formed and they were carefully separated. The *anti*- and *syn*- isomers were characterized by comparision of their $^1$H NMR spectrum, in which the coupling constant between H-2 and H-3 for an *anti*- isomer is known to be 6-8 Hz while for a *syn*- isomer 3-5 Hz. The –NH- proton of an *anti*-isomer also resonates at an up-field (δ 5.0-5.5) compared to that of a *syn*- isomer (δ 6.5-7.0).The structures of all the products were settled from their spectral [IR, $^1$H and $^{13}$C NMR, ESIMS and HRMS)] data.

In conclusion, we have developed a simple, mild and efficient method for the synthesis of protected β-amino ketones at room temperature and in high yields by treatment of α-amido sulfones with aromatic ketones in the presence of $BF_3.OEt_2$ as a catalyst.

**SECTION-C: Synthesis of polysubstituted pyrroles.**

Pyrroles are among the most important heterocyclic compounds as they are structural elements of various bioactive natural products and pharmaceutical agents. They are also valuable intermediates in organic synthesis. Some of the pyrrole derivatives are widely applied as organic conducting materials. Due to wide range of their applications, several methods have been developed.

We have observed that the treatment of phenacyl bromide (**27**) derivatives with amines (**28**) and dialkyl acetylene dicarboxylates (**29**) in the presence of catalytic amount of $FeCl_3$ produced the corresponding 1,2,3,5-substituted pyrroles (**30**) at room temperature (**Scheme 12**).




**27** **28** **29** **30**

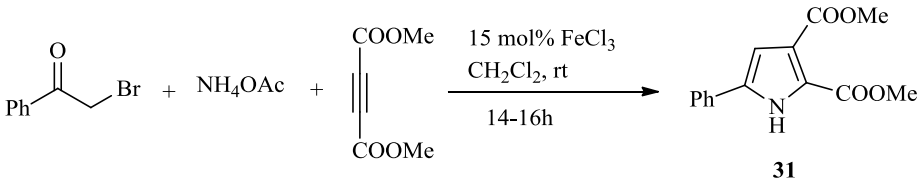
R = aryl, alkyl E = COOEt, COOMe 85-89 %

**Scheme 12**

Thus $FeCl_3$ was considered to be the catalyst of choice to prepare subsequently a series of substituted pyrroles. The reaction was complete within 14-16 h and the products were formed in high yields. Both aromatic and aliphatic amines underwent the conversion equally well. The derivatives of phenacyl bromide containing electron-withdrawing groups

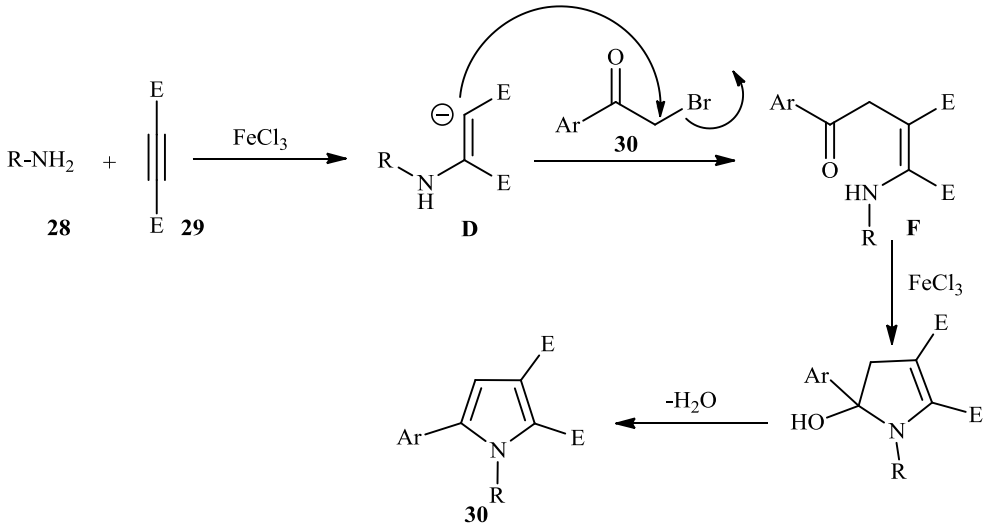
also afforded the products smoothly. The structures of the products were settled from their spectral (IR, $^{1}H$ and $^{13}C$ NMR and MS) and analytical data.

Similarly when phenacyl bromide was treated with $NH_4OAc$ and dimethyl acetylene dicarboxylate under the present reaction conditions the trisubstituted pyrrole **31** was formed in good yield (84%). (**Scheme 13**)




**Schme 13**

The structures of all the products were settled from their spectral (IR, $^{1}H$ and $^{13}C$ NMR and MS) and analytical data. The possible mechanism of the present conversion involves the initial reaction of the amine (**28**) with dialkyl acetylene dicarboxylate (**29**) in the presence of the catalyst to form the anion **D** which then attacks the phenacyl bromide (**27**) to produce the intermediate **F**. Subsequent cyclization of **F** followed by dehydration afforded the polysubstituted pyrrole **30** (**Scheme 14**). When the reaction was carried out separately with aniline and dimethyl acetylene dicarboxylate using $FeCl_3$ the alkene corresponding to the anion **D** (with *E*-configuration) was only obtained.




**Scheme 14**

In conclusion, we have demonstrated a new efficient method for an easy access to 1,2,3,5-tetrasubstituted and 2,3,5-trisubstituted pyrroles by treatment of phenacyl bromide or its derivatives, amines and dialkyl acetylene dicarboxylates using $FeCl_3$ as a catalyst.