Minor Research project No: 6442/16(MRP/ UGC–SERO)

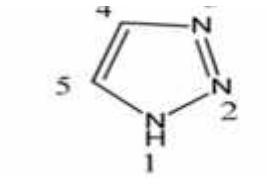
"Click and Cross-Coupling" Approach in One-Pot Synthesis of Fused 1,2,3-Triazoles.

Introduction:

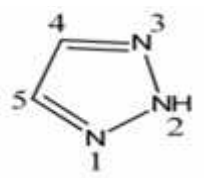
Cross-Coupling chemistry is one of the important areas for the construction of diversified moieties, in which two hydrocarbon fragments are coupled in the presence of metal catalyst.

Click chemistry includes extremely exothermic bond formations such as cycloaddition reactions, nucleophilic ring opening, addition reactions to carbon-carbon multiple bonds and non-aldol-type carbonyl reactions[1]. In recent times the formation of Carbon-Carbon and carbon-hetero atom bonds has been developed through intra and inters molecular cross-coupling reactions using various transition-metals. In this context, over the year's intra molecular version has been successfully explored for the synthesis of plentiful heterocyclic compounds that are of great biological, pharmaceutical and material interest.

1,2,3-Triazole is a five-membered basic aromatic heterocyclic ring with molecular formula $C_2H_3N_3$[2]. They are the building block for more complex chemical compounds, including pharmaceutical drugs such as mubritinib and tazobactam. There are two sets of isomers that differ in the relative positions of the three nitrogen atoms. Each of these has two tautomers that differ by which nitrogen has hydrogen bonded to it:



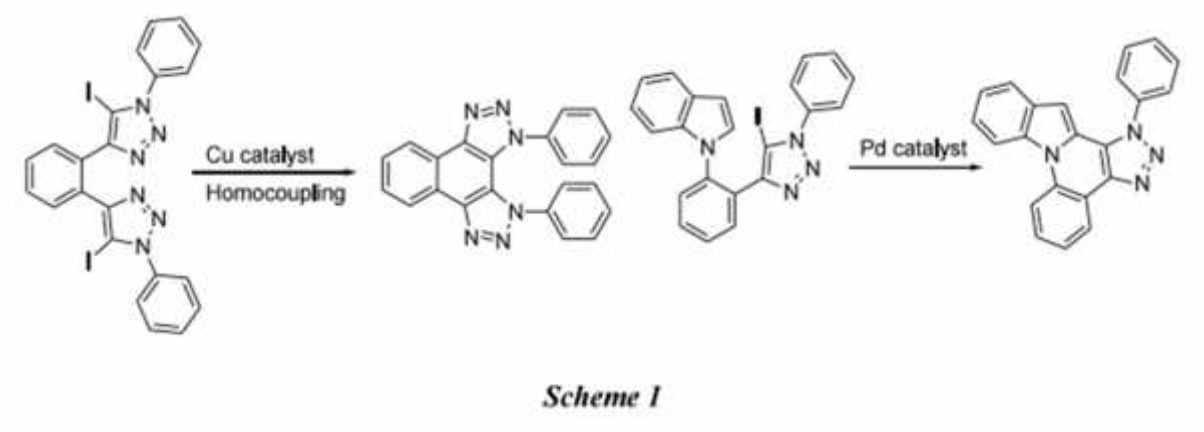
1*H*-1,2,3-triazole



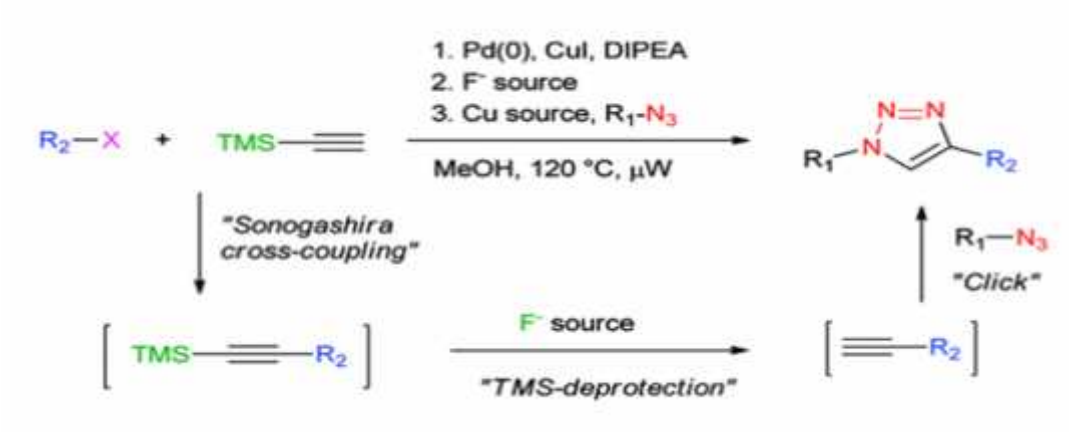
2*H*-1,2,3-triazole

It is a surprisingly stable structure compared to other organic compounds with three adjacent nitrogen atoms.

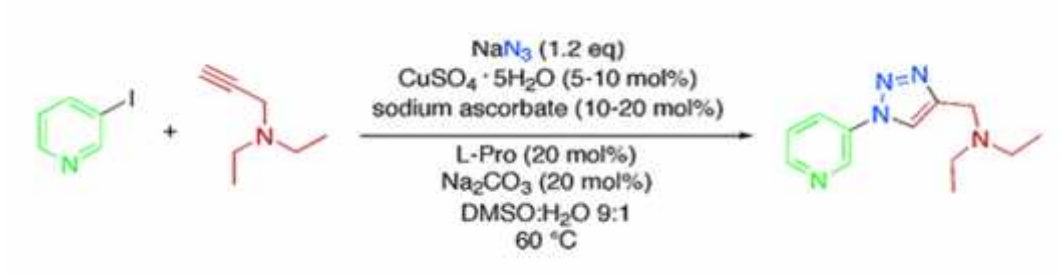
1,2,3-Triazoles are main class of heterocycles because of their extensive range of biological properties such as antimicrobial[3] , anticancer[4], anitubercular[5] , anti-HIV[6] , antimalarial[7] , antibacterial[8] , antifungal[9], antiviral[10] , antidiabetic11, antiallergic[12] behavior. These triazoles are used as synthons for the fused 1,2,3 triazoles that baren of high synthetic demand. To illustrate some examples for preparation of fused 1,2,3-Triazoles are shown in schemes-1,2,3[13,14].



Scheme 1



Scheme 2



Scheme 3

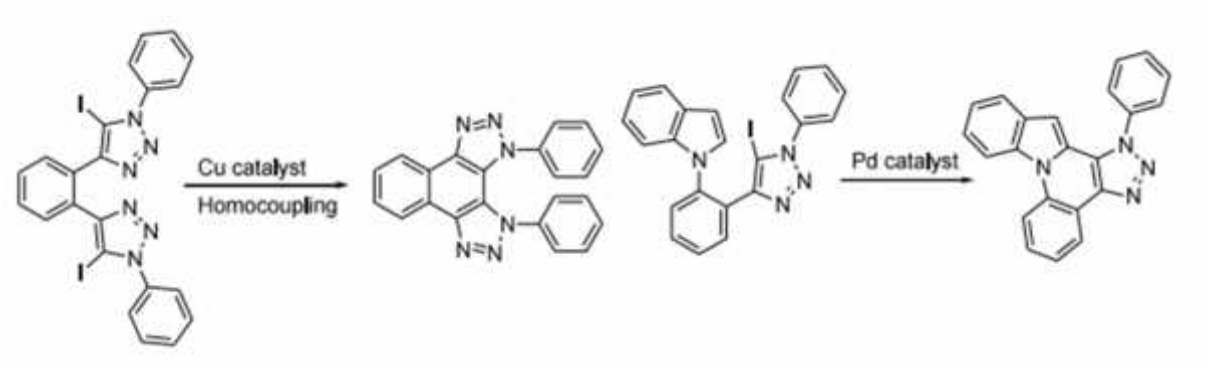
Hence, I would like to pursue the formation of fused 1,2,3-Triazoles from the appropriate starting precursors through Click and Cross-Coupling approach in one pot synthesis.

Present Research related to Research Plan

Cross-Coupling chemistry is one of the important areas for the construction of diversified moieties, in which two hydrocarbon fragments are coupled in the presence of metal catalyst. In recent times the formation of Carbon-Carbon and carbon-hetero atom bonds has been developed through intra and inters molecular cross-coupling reactions using various transition-metals. In this context, over the year's intra molecular version has been successfully explored for the synthesis of plentiful heterocyclic compounds that are of great biological, pharmaceutical and material interest. In this connection, in continuation I would like to peruse the formation of fused 1,2,3-Triazoles from the appropriate starting precursors through intra molecular cross-coupling reaction

Purpose of Proposed work

1,2,3-Triazoles are important nitrogen heterocyclic compounds, which have a broad range of many industrial applications such as dyes, agrochemicals and biologically active agents. Many methods for the synthesis of Triazoles have appeared during the past few years. These triazoles are used as synthons for the fused 1,2,3-Triazoles, that are of high synthetic demand. To illustrate, some examples for preparation of fused 1,2,3-Triazoles are shown in Scheme 4.



Scheme 4

Experimental:

Materials:

Chemicals used:

All the chemicals which are used are used in the typical procedure are procured from Merc quality of LR grade.

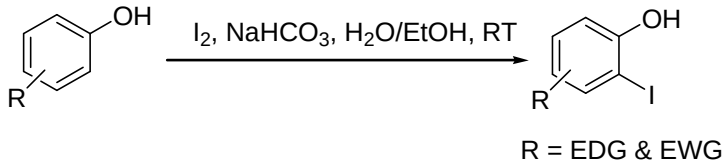
Glass ware used:

All the glass ware are used in the typical procedure to synthesis the products are procured from Borosil glasses.

Methods: <u>A typical procedure for Click and Cross-Coupling one pot synthesis of fused 1,2 3-triazoles:</u>

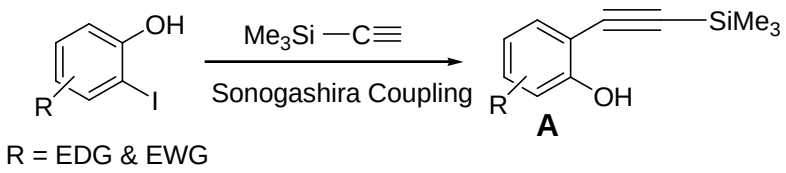
Step 1: Different substituted Iodo Phenols were prepared from their respective Phenols using the following reaction conditions (Scheme 1). To a Solution of $NaHCO_3$ in water, phenol was added slowly at room temperature. The reaction was stirred for 15 min at room temperature. To that, Iodine was added slowly at 0 °C and the whole reaction mixture stirred at 0 °C for 2 h. The progress of the reaction was checked using TLC. After completion of the reaction the reaction mixture was washed with EtOAc (10 ml *3) and H_2O (5 ml*3), and organic layer was separated and it was concentrated Using rotary evaporator. The crude reaction mixture was purified by column chromotography using 60-120 mesh silicagel to afford the target product.

The below process is very neat, efficient and greenery process. Here Iodine act as iodinating reagent for iodination and sodium bicarbonate act as a base for removing the proton and to proceed the reaction. All polar solvents like water, MeOH, EtOH etc. good for this reaction.



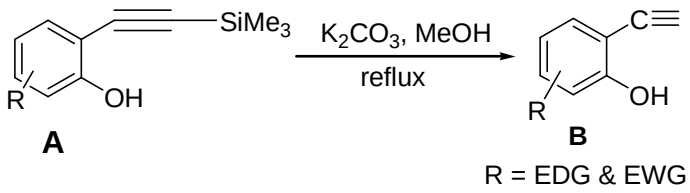
Scheme 5

Step 2: Substituted trimethylsilylethynyl benzenamines were synthesized from the various substituted 2-iodoanilines using the below reaction conditions (Scheme 2). Substituted 2-iodo anilines react with trimethylsilyl acetylene using sonagashira coupling reaction conditions. This reaction is also very efficient and neat. It precedes under mild reaction conditions.



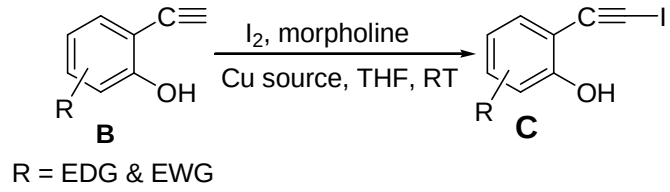
Scheme 6

Step 3: Substituted trimethylsilylethynyl benzenamine procide their respective desilylation products i.e. substituted amino phenyl acetylenes (Scheme 3). Desilylation can be occurred using inorganic bases like K_2CO_3, Cs_2CO_3 and KOH etc. in the presence of polar solvents like MeOH, EtOH, Acetone and water under reflux reaction conditions. Both electron donating and electron withdrawing substituted ortho amino phenyl acetylenes will be constructed.



Scheme 7

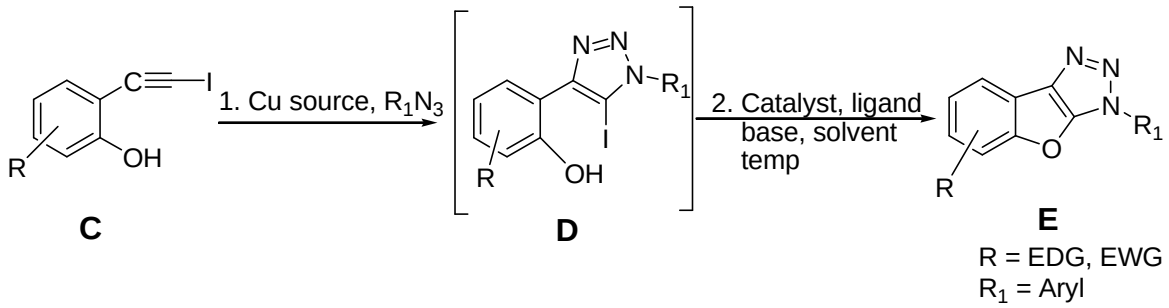
Step 4: Various substituted 1-Iodo-(2-aminophenyl acetylenes) were prepared by using the following reaction conditions (Scheme 4). Here, Iodine (1.2 eq) can act as a iodinating reagent and marpholine treated as a ligand for this reaction. All the reactions will be occurred using Cu source (20 mo %) in the presence of THF at room temperature.



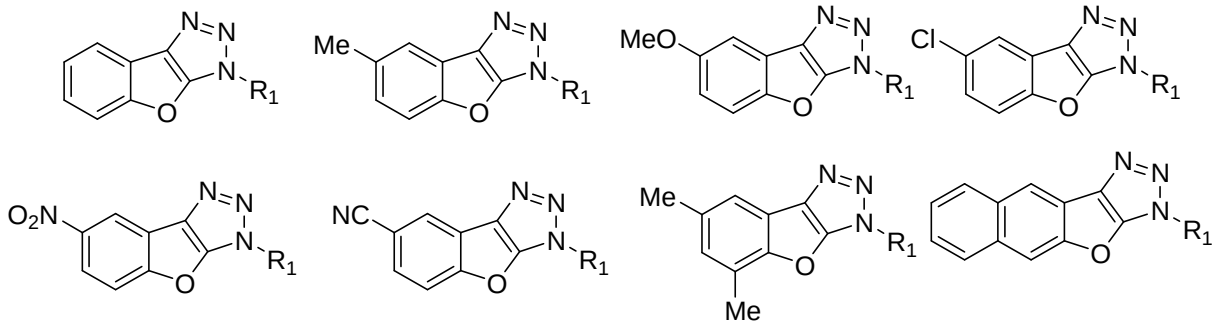
Scheme 8

Compound **C,** together with azides(1.1 eq) in one pot reaction will be studied for the synthesis of our target compounds fused 1, 2, 3-triazoles. In this reaction, the starting material compound **C** reacts with substituted azides using cheap and readily available copper source (20 mol%) in the presence of solvent under moderate temperature to afford the intermediate **D**, that will give target product fused 1,2,3-tetrazoles *via C-N* cross-coupling reaction in the presence of solvent DMSO (1 eq) at temperature 110 ^{o}C using catalyst Palladium Chloride.

In this connection, the effect of various copper sources, ligands, bases, solvents and different temperatures will be systematically pursued to lead the system.



The above said copper-sources, solvents, bases and ligands will be checked at various temperatures for the above reaction. After finishing the optimization for the synthesis of fused 1, 2, 3-triazoles the following substrate scope will be explored.



Results and Discussion:

We started our studies on Click and Cross-Coupling one pot synthesis of fused 1,2 3-triazoles with substituted phenols along with various cu sourced catalysts like copper sulphate, copper acetate and cupper iodide, Cuprous Bromide, Cuprous Oxide at 80-130 °C. Out of all these copper catalysts, copper iodide as a catalyst at 110 °C worked better in terms of yield **(Table 1).**

The reaction took place in four steps and the desired product in excellent yield 93% by using palladium Chloride as a catalyst at 110 °C in a solvent DMSO **(Table 2)**. The influence of electronic effects in this reaction have been studies by taking substituted phenols with both electron releasing and withdrawing groups. Better yields are obtained with phenols containing electron releasing groups and low yields are obtained with phenols containing electron withdrawing groups **(Table 3)**.

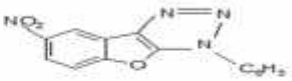
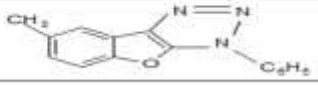
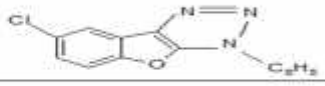
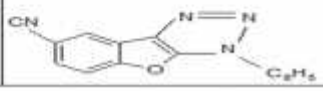
Table 1. Copper source Catalyst optimization

Entry	Copper catalyst	Yields(%)
1	Copper sulphate	75
2	Cupric Acetate	78
3	Cuprous Bromide	82
4	Cuprous Iodide	91
5	Cuprous Oxide	73

Table 2. Solvent optimization

Entry	Solvent	Yields(%)
1	Tetra hydro Furan	89
2	Triphenyl Phosphine	83
3	Triethonal amine	75
4	Dimethyl Sulphoxide	97
5	Toluene	78

Table 3. Study of substrate scope

Entry no	Substrate	Product	Yield(%)[a]
1			83
2			90
3			93
4			95
5			76

[a] yields refer to the isolated yield of purified product from the recrystallization. The product was identified from the isolated with the authenticated product.

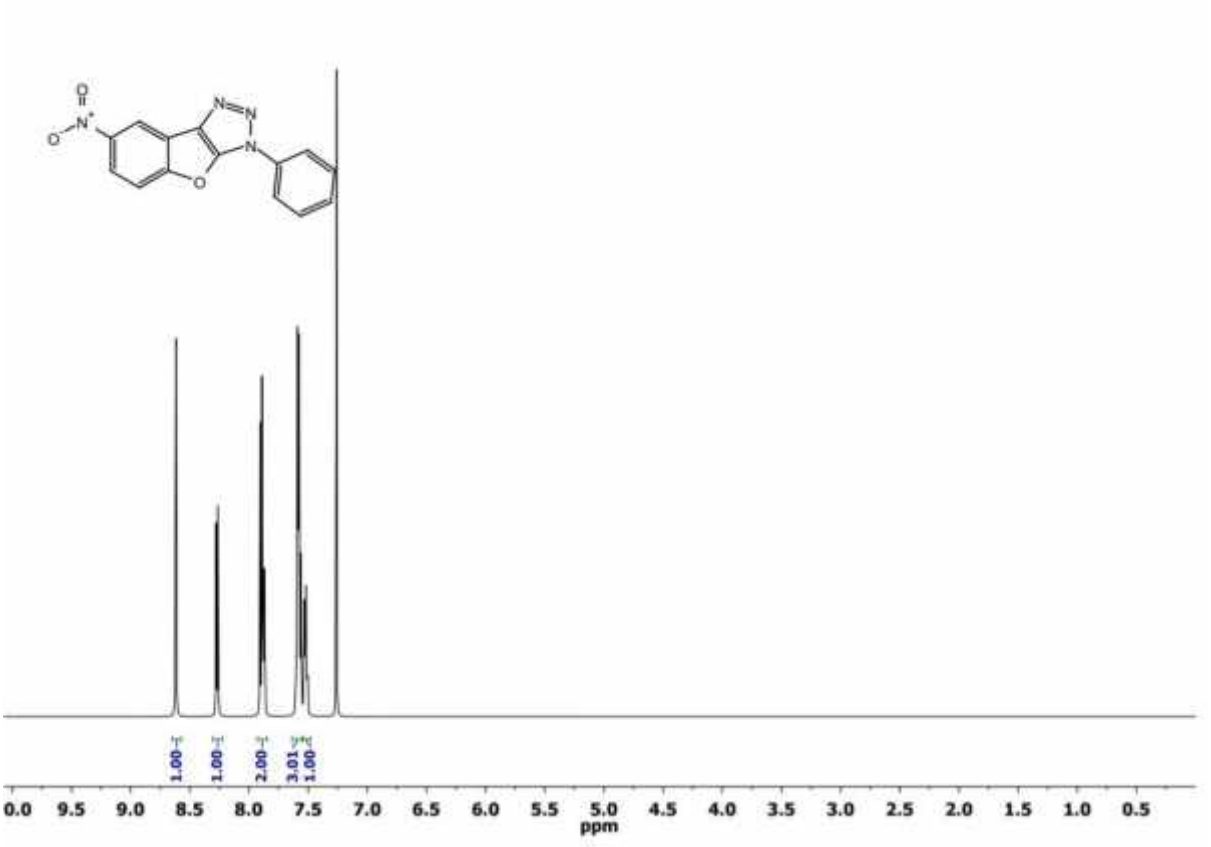
Conclusions

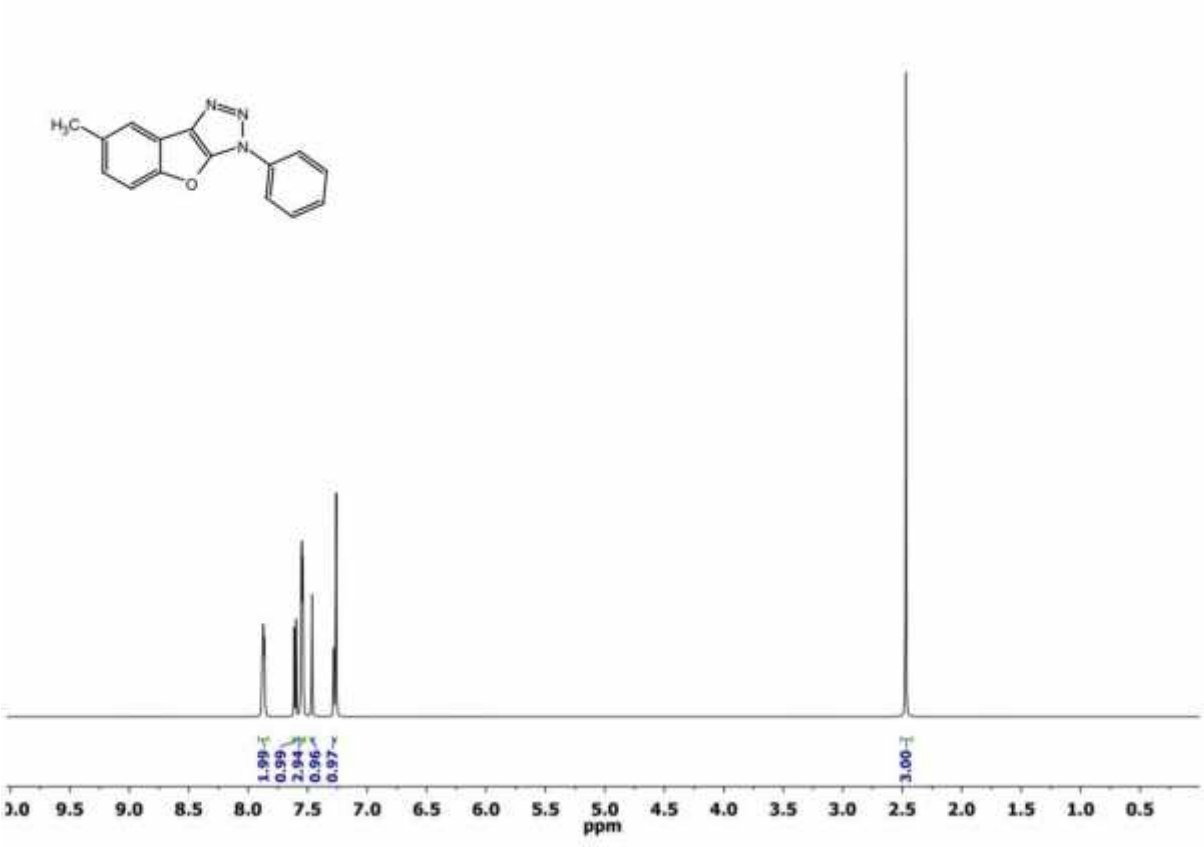
The summary of the present work is that we have developed a newer methodology for the click and cross coupling one pot synthesis of fused 1,2 3-triazoles from substituted phenols

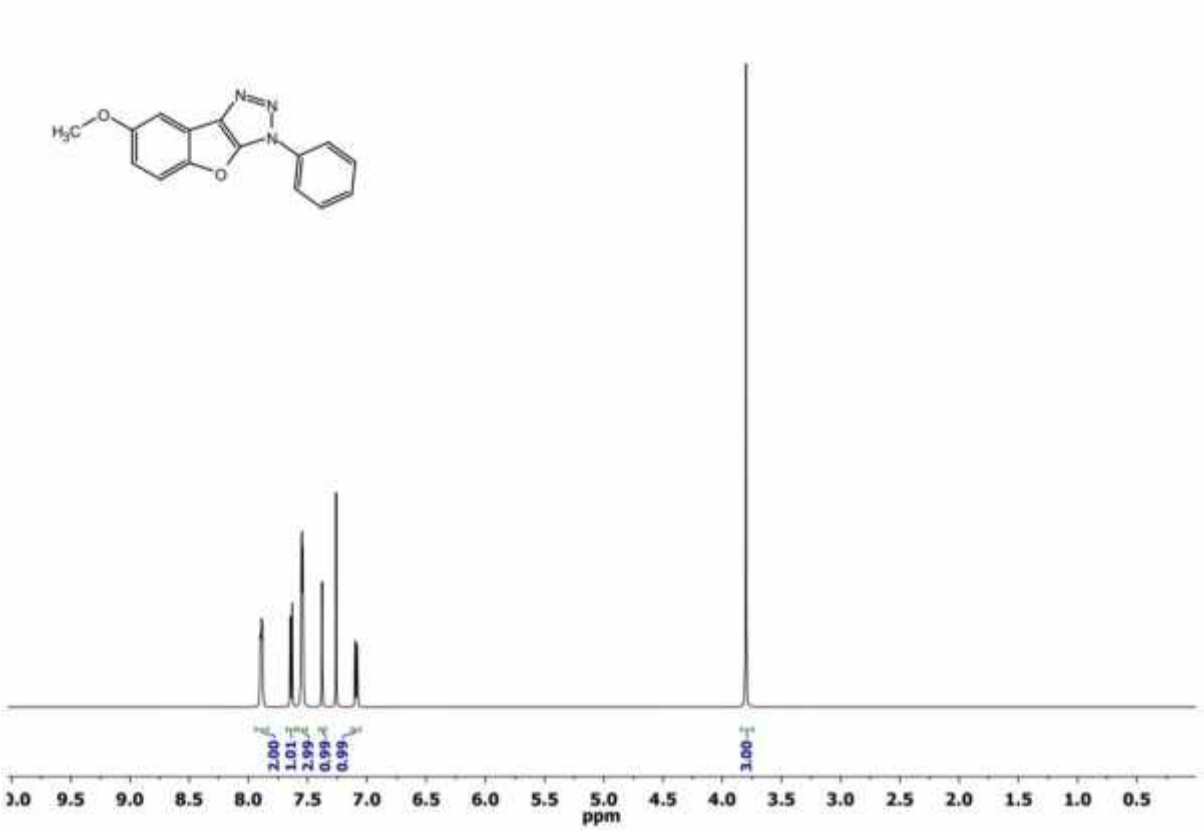
The present methodology has been significantly important for the following reasons

1) The catalysts used were copper iodide and palladium acetate which are cheap and abundant, 2) This methodology gives an appropriate route to synthesise 1,2,3-Triazoles which are important nitrogen heterocyclic compounds, which have a broad range of many industrial applications such as dyes, agrochemicals and biologically active agents.

Spectra obtained:




H3C
N
N
N
O
1.99
0.99
2.94
0.96
0.97
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


H3C
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O
2.00
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9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
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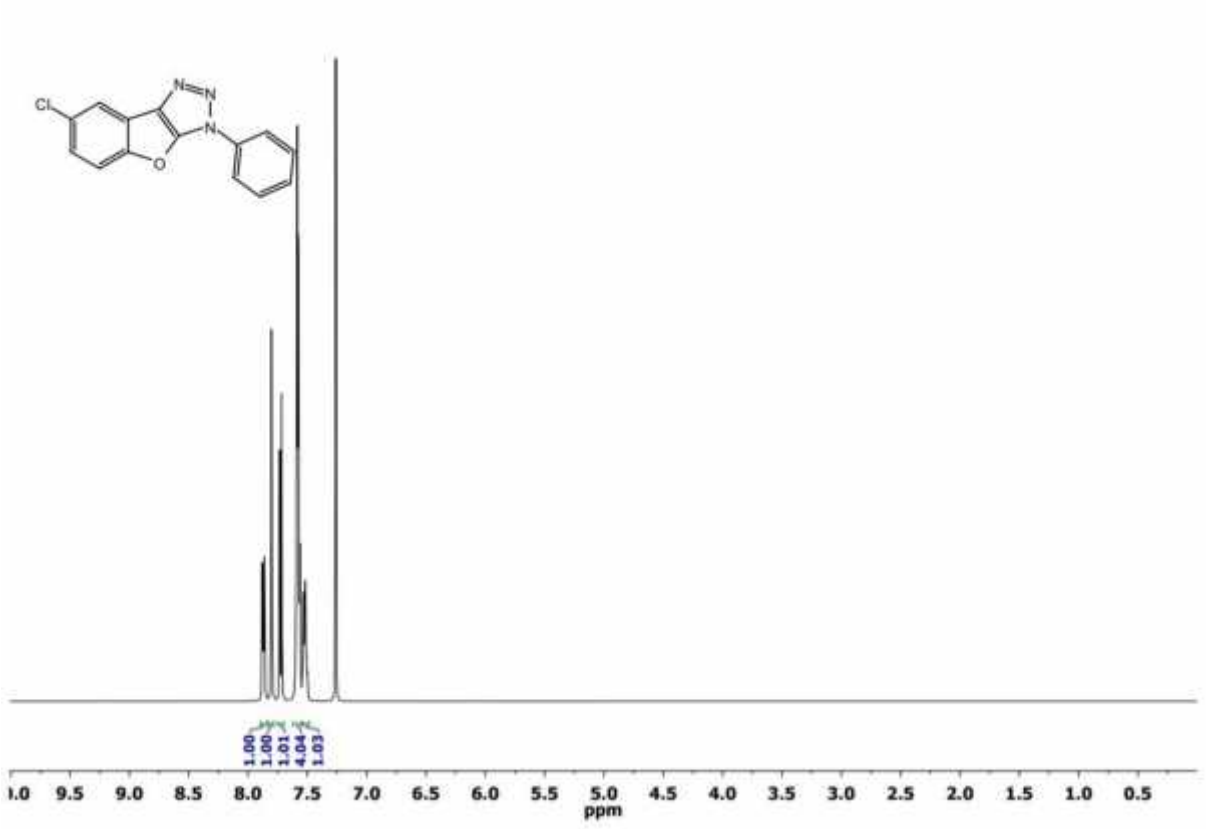
Cl
N
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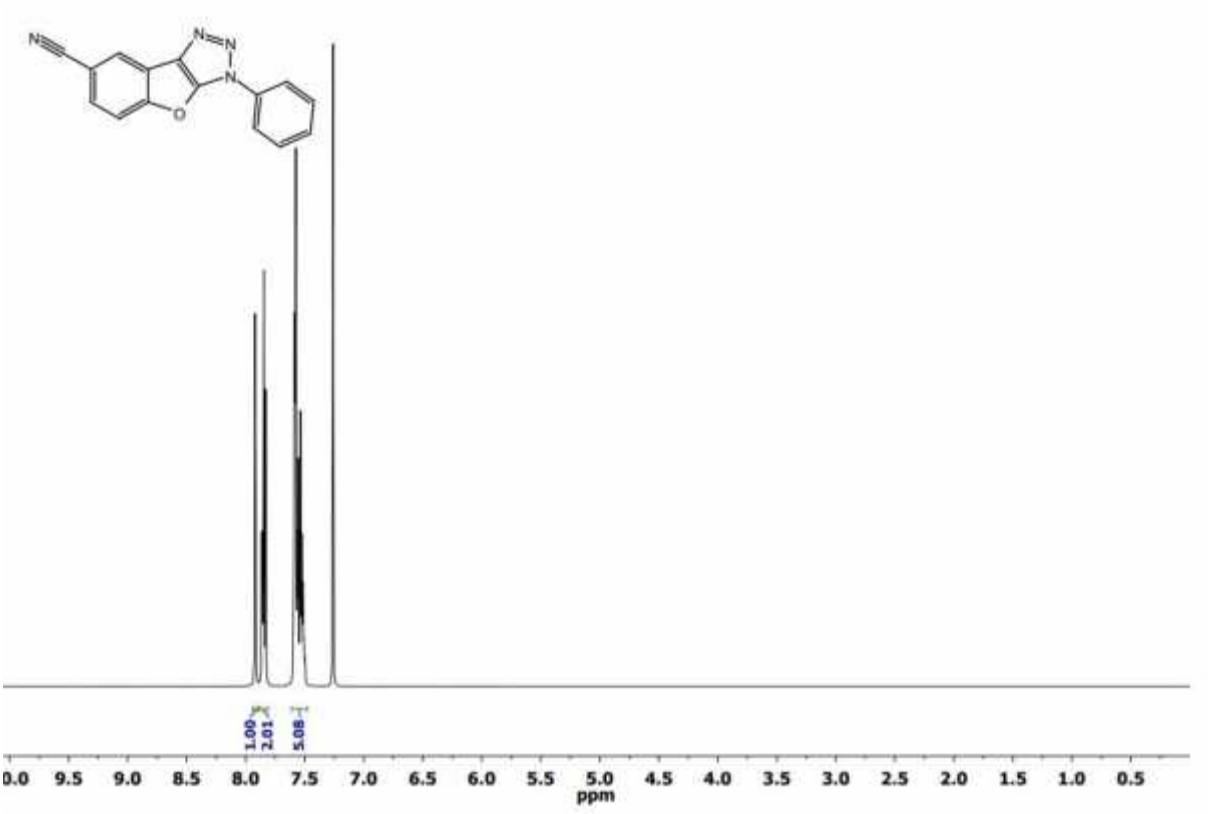
N
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2.0
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ppm

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