Copper-DMEDA Catalyzed Carbon-Sulfur Bond Formation for the Derivatization of 5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazole-2-thiol

Hassan Adrees, Zahra Begum, Haseen Ahmad, Rifhat Bibi, Sania Batool and Abbas Hassan*
Department of Chemistry, Quaid-i-Azam University, Islamabad 45320 Pakistan.
ahassan@qau.edu.pk*

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Summary: Sulfide linkage plays an important role not only in synthetic chemistry but also has vast applications in drug discovery as a pharmacologically active moiety. Transition metal-catalyzed thiolation is a challenging task as sulfur has a high affinity to bind with transition metal catalysts resulting in catalyst poisoning. Catalyst poisoning results in the inhibition of the reactivity and utility of the reactions. In the current work, a simple and facile method is developed to carry out *S*-arylation using hetero-aryl thiols and substituted aryl iodides. The reaction conditions were optimized using varied combinations of transition metal catalysts and ligands. The different copper sources included CuCl, CuI, and $Cu(OAc)_2$ different bidentate nitrogen-based ligands including bipyridine, di-*tert*-butylbipyridine, DMEDA, and sarcosine. The optimized condition consists of CuI as the catalyst and DMEDA as a ligand. The reaction was found to be optimum for a range of aryl iodides in the presence highly basic oxadiazole ring. The coupled products were isolated in excellent yields and show excellent functional group tolerance bearing $-NO_2$, -Cl, $-OCF_3$ groups.

Keywords: Copper catalysis, Carbon-sulfur (C-S) bond formation, Oxadiazole, Thioether, Heterocyclic derivatives

Introduction

The thioether linkages are prevalent in chemical biology, organic synthesis, materials chemistry as well as pharmaceutical compounds. [1] Heterocyclic compounds having a carbon-to-sulfur (C-S) linkage have an important place in medicinal chemistry due to their diverse biological applications. [2, 3] For instance, neflamapimode **1a** is a selective inhibitor of the p38 MAPKα enzyme used to treat neurodegenerative diseases, especially Alzheimer's disease. [4] Nelfinavir **1b** is a phenyl thioether, used against the human immune deficiency virus. [5] Promazine belongs to an active class of antipsychotics that are used for the treatment of neurosis and schizophrenia. [6] Diltiazem **1c** is used to treat high blood pressure and angina caused due to blockage of coronary artery spasm by calcium channels. [7] Probucol **1e** prevents the progression of atherosclerosis and employed for the treatment of hypercholesterolemia. [8] Ranitidine **1d** is used to cure stomach ulcers and erosive esophagitis. [9].

Similarly, 1,3,4-oxadiazole derivatives are important structural moieties found in numerous biologically active compounds that constitute an immensely attractive field of the pharmacological industry. [10] 1,3,4-Oxadiazole drugs possess various biological activities, for example, raltegravir **1e** is an anti-HIV [11, 12] and anti-SARS-COV-2 agent. [13] Similarly, zibotentan **1f** is an oxadiazole sulfone-based derivative that has anticancer properties. [14] The importance of oxadiazole can be further extended using late-stage derivatization and modification of distinct functional groups. One of the strategies for late-stage synthetic modification is transition metal-catalyzed transformation. The copper-mediated C_{Sp2}-X bond formation using the C-S coupling reaction of a thiol and aryl halide can be envisaged as an efficient and economical protocol. This can lead to the synthesis of more biologically active compounds.

The classical Ullmann reaction type reaction employs copper catalyst and has served the chemical sciences for more than a century. [15] However, the necessity of harsh reaction conditions including elevated temperature, stoichiometric use of copper, strong bases, and extended reaction time have limited the utility of its application. [16] The reaction often suffers from moderate yields, which also has limited its utility for a large-scale application. [17, 18] Transition-metal mediated C-S bond formation has made giant strides in synthetic organic chemistry for the synthesis of thioethers and their derivatives. [19] The C-S cross-coupling has been studied in detail using different transition metal catalysis, [20-22] including palladium, [23, 24] nickel, [25] copper, [26] gold, [27] rhodium, [28] ruthenium, [29] iron, [30] cobalt, [31] with the help of photocatalysis [32] and without the use of transition metals. [33] The different approaches have been modified for better substrate scopes, functional group tolerance, and higher reactivities.

*To whom all correspondence should be addressed.

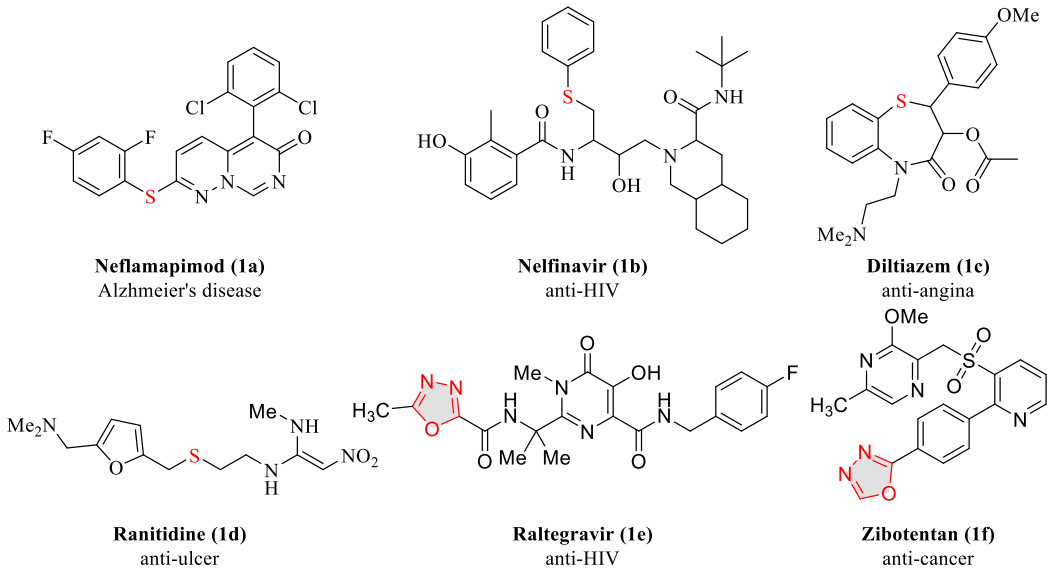


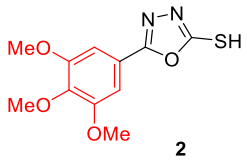
Fig. 1: Biological and Pharmacological active aryl thioethers and oxadiazole derivatives.

There is always remain a quest for new and improved reaction methodologies to facilitate chemical transformation under milder conditions. [3, 34] In accordance with our previous efforts in synthetic approaches, [35-39] herein, we investigate the copper-DMEDA catalyzed C-S coupling of oxadiazolethiol, specifically, 5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole-2-thiol **2** and diverse aryl iodides. The copper-DMEDA catalytic system has been developed by the Buchwald research group and found generally applicable for a variety of situations. [40] The reaction conditions have been thoroughly investigated and studied mechanistically. [41-44]. The same catalytic system was found superior in our application. The reaction conditions have been optimized using different copper sources and ligand screening. The optimized conditions were employed for the synthesis of diverse derivatives using different aryl iodides.

Experimental

Reaction progress was monitored with TLC using the pre-coated silica gel 60 F_{254}. Purification was carried out using Flash column chromatography over silica gel (particle size 200-300 mesh). Mass spectrometric (HRMS) experiments were carried out on Finnigan MAT-311A (Germany) using electron spray ionization techniques and reported as $[M+H]^+$. NMR analyses for the final products were recorded at Bruker NMR spectrometer (300 MHz for proton and 75 MHz for carbon) in deuterated solvents using TMS as an internal reference. The chemical shifts (δ) are reported in ppm and the coupling constants (*J*) values are reported in Hertz unit (Hz).

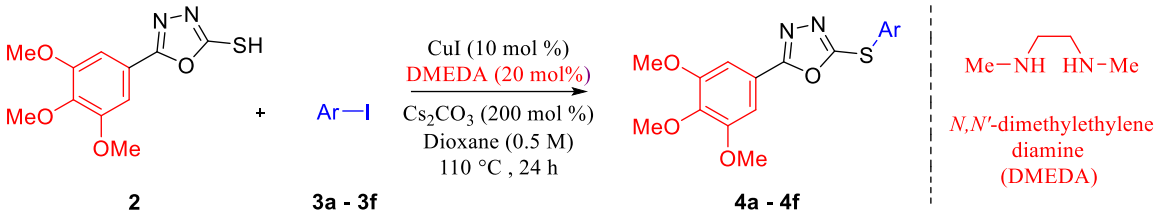
Procedure for the Synthesis of Substrate thiol **(2)**



2

A slightly modified reported method was utilized for the synthesis of oxadiazole-2-thiol. [45] The 3,4,5-trimethoxybenzohydrazide **1**, (2 g, 8.84 mmol, 100 mol%) was refluxed in ethanol (90 mL, 0.1 M) with potassium hydroxide (4.95 g, 8.84 mmol, 100 mol%) and CS_2 (1 mL, 17.68 mmol, 220 mol %). The resulting mixture was refluxed for 18 h. The progress of reaction progress was monitored by TLC, and upon completion of the reaction, the reaction mixture was concentrated *in vacuo* and acidified with 1 M HCl in an ice bath. As a result, the crude product was obtained as precipitate, collected by filtration, and recrystallized from absolute ethanol to get corresponding compound **2** in 88% yield (2.1 g). The NMR data were in accordance with the literature. [45]

General Procedure for Arylation of 5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole-2-thiol

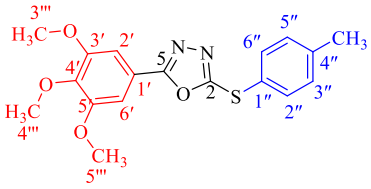


2 **3a - 3f** **4a - 4f**

Scheme 1. Arylation of aryl iodides using CuI-DMEDA catalytic system

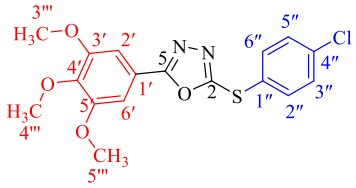
Iodobenzene (**3a**-**3f**) (0.55 mmol, 110 mol %) and substrate **2** (134.0 mg, 0.5 mmol, 100 mol %,) were mixed in a dry sealed tube (13 x 100 mm) with Cs_2CO_3 (325.8 mg, 200 mol %), CuI (9.5 mg, 0.05 mmol, 10 mol %) as catalyst and *N,N'*-dimethylethylenediamine (11 µL, 0.1 mmol, 20 mol%) as a ligand. Nitrogen gas was purged after the addition of dioxane (1 mL, 0.5 M). After nitrogen purge for 1 min, the reaction mixture was tightly sealed and then heated at 110 °C in an oil bath on stirring for 24 h. The reaction mixture was transferred to a flask and silica gel was added. The slurry was subjected to a flash column and the pure coupled product was obtained using *n*-hexane and ethyl acetate in 95:5 ratio as a mobile phase. The synthesized coupled products were solid ranging from white to yellow and brown in color.

Synthesis of 2-(p-Tolylthio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **(4a)**



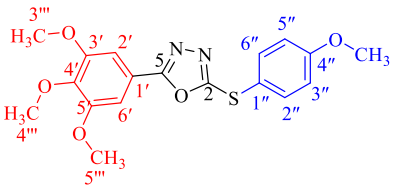
Yield: 82 %, yellow, m.p. = 126-128 (°C), R_f =0.2 (*n*-Hexane: Ethyl acetate 9:1). ^{1}H NMR: 7.61 (*d*, ^3J = 7.2 Hz, 2H, H-3”, 5”), 7.32 (*d*, ^3J = 7.2 Hz, 2H, H-2”, 6”), 7.22 (*s*, 2H, H-2’, 6’), 3.91 (*s*, 6H, 3’’’, 5’’’), 3.81 (*s*, 3H, H-4’’’), 2.38 (*s*, 3H, H-4’’’), 2.38 (*s*, 3H, H-4””). ^{13}C NMR: 166.0, 162.3, 153.9, 141.4, 140.2, 133.3, 130.4, 123.7, 118.6, 103.9, 59.8, 55.7, 20.3. HRMS: for $C_{18}H_{19}N_2O_4S^+$, 359.1060; found, 359.1065. GC-MS: (EI, m/z): 358 (M^+), 272, 193, 171, 150, 123, 91, 65.

Synthesis of 2-((4-Chlorophenyl)thio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **(4b)**



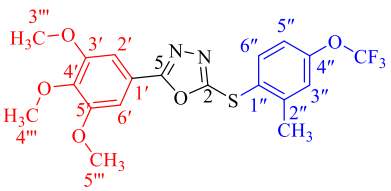
Yield: 88 %, light yellow, m.p. = 127-128 °C, R_f =0.2 (*n*-Hexane: Ethyl acetate 9:1). ^{1}H NMR: 7.75 (*d*, ^3J = 7.3 Hz ,2H, H-3”, 5”), 7.55 (*d*, ^3J = 7.3 Hz, 2H, H-2”, 6”), 7.24 (*s*, 2H, H-2’, 6’), 3.91 (*s*, 6H, 3’’’, 5’’’), 3.81 (*s*, 3H, H-4’’’). ^{13}C NMR: 166.3, 161.5, 154, 141.6, 135.4, 134.5, 129.8, 126.5, 118.5, 104, 59.8, 55.8. HRMS: for $C_{17}H_{16}ClN_2O_4S^+$, 379.0514; found, 379.0516. GC-MS: (EI, m/z): 378, 193, 143, 108, 75, 50.

Synthesis of 2-((4-methoxyphenyl)thio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **(4c)**



Yield: 84 %, white solid, m.p. = 120-121 °C, R_f =0.2 (*n*-Hexane: Ethyl acetate 9:1). ^{1}H NMR: 7.68 (*d*, ^3J = 7.1 Hz, 2H, H-3”, 5”), 7.21 (*d*, ^3J = 7.1 Hz, 2H, H-2”, 6”), 7.07 (*s*, 2H, H-2’, 6’), 3.90 (*s*, 6H, 3’’’, 5’’’), 3.86 (*s*, 3H, H-4’’’), 3.80 (*s*, 3H, H-4””), ^{13}C NMR: 165.8, 163.0, 161.4, 153.9, 141.4, 136.0, 118.6, 116.8, 115.3, 103.9, 59.8, 55.7, 55.0. HRMS: for $C_{18}H_{19}N_2O_5S^+$, 375.1009; found, 375.1013. GC-MS: (EI, m/z): 374, 193, 139, 95, 64.

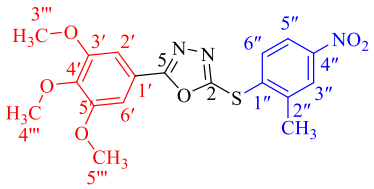
Synthesis of 2-((2-methyl-4-(trifluoromethoxy)phenyl)thio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **(4d)**



Yield: 80 %, white, m.p. = 161-162 °C, R_f =0.2 (*n*-Hexane: Ethyl acetate 9:1). ^{1}H NMR: 7.86 (*d*, ^3J = 7.2 Hz, 1H, H- 6”), 7.23-7.45 (*m*, 4H, H-2’, 6’, 3”, 5”), 3.91 (*s*, 6H, 3’’’, 5’’’), 3.81 (*s*, 3H, H-4’’’), 2.64

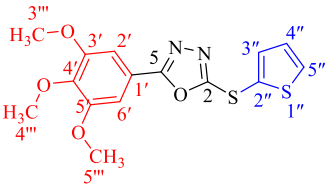
(s, 3H, H-4''''). ^{13}C NMR: 166.1, 161.4, 154, 144.5, 136.9, 131.1, 128.7, 125.6, 125.5, 123.2, 122.1, 119.4, 118.7, 118.5, 115.3, 103.9, 59.86, 55.74, 20.1. HRMS: for $C_{19}H_{18}F_3N_2O_5S^+$, 443.0883; found, 443.0887. GC-MS: (EI, m/z): 442, 193, 150, 120,93,69, 50.

Synthesis of 2-((2-methyl-4-nitrophenyl)thio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **(4e)**



Yield: 83 %, light Red, m.p. = 158-160 °C, R_f =0.2 (*n*-Hexane: Ethyl acetate 9:1). ^{1}H NMR: 8.18 (*d*, 1H, ^4J = 1.2 Hz, H-3"), 8.07 (*dd*, ^3J = 7.2 Hz , ^4J = 1.2 Hz, 1H, H-5"), 7.72 (*d*, ^3J = 7.2 Hz, 1H, H-6"), 7.24 (*s*, 2H, H-2', 6'), 3.93 (*s*, 6H, 3''', 5'''), 3.86 (*s*, 3H, H-4'''), 2.62 (s, 3H, H-4''''). ^{13}C NMR: 166.9, 160.0, 153.7, 148.1, 141.4, 135.7, 133.3, 130.9, 125.5, 121.93, 118.1, 104.1, 61.0, 56.4, 20.8. HRMS: for $C_{18}H_{18}N_3O_6S^+$, 404.0911; found, 404.0915. GC-MS: (EI, m/z): 403, 271, 246, 193, 121, 94.

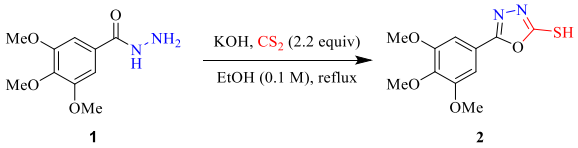
Synthesis of 2-(thiophen-2-ylthio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **(4f)**



Yield: 77 %, brown solid, m.p. = 150-153 (°C) , R_f =0.3 (*n*-Hexane: Ethyl acetate 9:1). ^{1}H NMR: 7.20 (*s*, 2H, H-2', 6'), 7.14 (*dd* ,1H, H-4'', ^3J = 3.9, ^3J =5.4 Hz), 7.62 (*dd*, 1H, H-5'' ,^4J = 1.2, ^3J =5.4 H), 7.51 (*dd*, 1H, H-3'', ^4J = 1.2, ^3J =3.6 Hz), 3.93 (*s*, 6H, 3''',5'''), 3.92 (*s*, 3H, H-4'''). ^{13}C NMR: 166.2, 162.4, 153.6, 141.2, 137.8, 133.2, 128.1, 122, 118.4, 104, 61, 56.3. HRMS: for $C_{15}H_{15}N_2O_4S_2^+$, 351.0468; found, 351.0473. GC-MS: (EI, m/z): 350, 235, 193, 135, 115, 71, 50.

Result and Discussion

Synthesis of substrate **2** was executed following a reported procedure. [45] the 3,4,5-trimethoxybenzohydrazide **1**, was refluxed in the presence of carbon disulfide and potassium hydroxide resulting in potassium dithiocarbazate salt and upon cyclization, oxadiazole is formed. The product crystallized from the reaction mixture. The crude product required purification for the next step and was recrystallized from absolute ethanol. The product compound **2** was isolated in 88% yield.

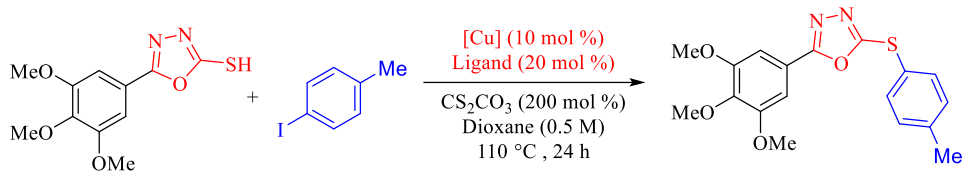


1 **2**

Scheme 2. Synthesis of substrate **2**.

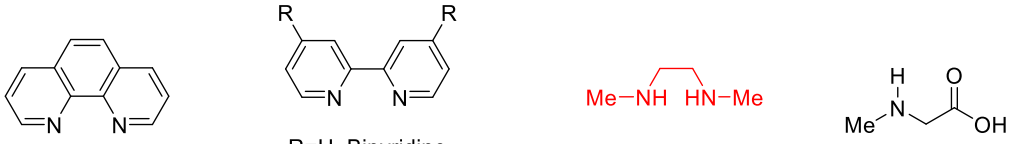
Initially, the coupling reaction was carried out with substrate **2** and 4-iodotoulene **3a** in the presence of cuprous chloride catalyst and with 1,10-phenanthroline as a ligand in dioxane as a solvent. The reaction was carried out at 110 °C. The corresponding *S*-arylation was obtained in low yield. The reaction was performed by changing various catalysts and ligands as shown in table 1. Under the above-mentioned conditions reaction was performed with various Cu(I) and Cu(II) catalyst sources such as cuprous chloride, cupric acetate, and 1,10-phenanthroline as a ligand. The corresponding coupled product **4a** was obtained in 74% by using CuI and 1,10-phenanthroline as a catalytic system. The reaction was further studied using CuI as the copper source and different bidentate nitrogen-based ligands including bipyridine, di-*tert*-butylbipyridine, DMEDA, and sarcosine. In the above-mentioned catalytic system, the maximum yield was obtained with CuI and DMEDA in 82% isolated yield (Table 1, entries 4-7). The 2,2`-bipyridine was found less effective ligand than phenanthrene and resulted in a 36% yield. This can be attributed to the flexible nature of the bipyridine ligand. The ligand 4,4 -di-tert-butyl-2,2 -bipyridyl (dtbbpy) on the other hand is electron-rich and the steric makes it a somewhat organized ligand. The dtbbpy resulted in a yield comparable to the phenanthrene. Finally, sarcosine was utilized, which is basically *N*-methylglycine and has been an effective ligand for C-N cross-coupling. [46, 47] However, in our case, it resulted in only 28% yield (Table 1, entry 7). The reaction was further optimized by changing the base and temperature, however, there was not any improvement in yields. The same was found in the case of solvents changing from dioxane to THF, toluene, and dichloroethane.

Table-1: Reaction condition optimization for *S*-Arylation of compound **2**.

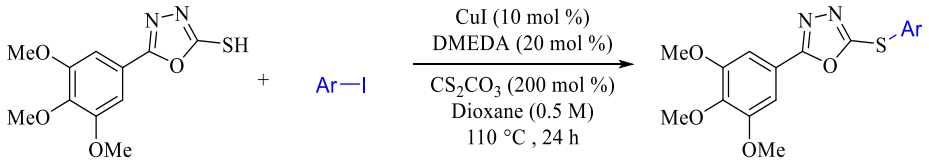


2 **3a** **4a**

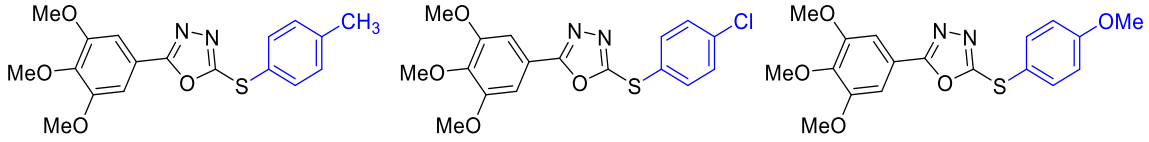
S. No.	Catalyst	Ligand	Yield (%)
1	CuCl	1,10-Phenanthroline	Trace
2	$Cu(OAc)_2$	1,10-Phenanthroline	Trace
3	CuI	1,10-Phenanthroline	74
4	CuI	Bipyridine	36
5	CuI	4,4'-Di-tert-butyl-2,2'-dipyridyl	62
6	CuI	*N,N'*-Dimethylethylenediamine	82
7	CuI	Sarcosine	28



Phenanthroline R=H, Bipyridine R=^{t}Bu, 4,4'-Di-tert-butyl-2,2'-dipyridyl *N, N*'-dimethylethylene diamine Sarcosine



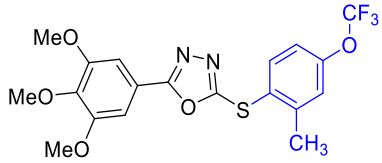
2 **3a - 3f** **4a - 4f**



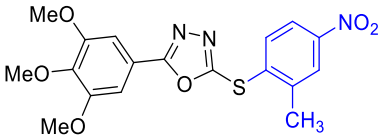
4a, 82 %

4b, 88 %

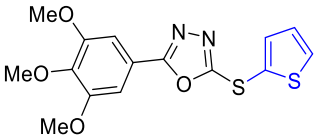
4c, 84 %



4d, 80 %



4e, 83 %



4f, 77 %

Scheme 3: C-S cross coupling reaction of 5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole-2-thiol with various iodo-benzenes.

After successful reaction optimization, the *S*-arylation was performed with various aryl iodides. In all cases, excellent yields were obtained using the thiol substrate 2 (Scheme 3). In the case of 4-chloroiodobenzene **3b**, the coupling product **4b** was isolated in 88% yield. The regioselectivity was confirmed by ^{13}C NMR spectroscopy, due to the absence of a downfield signal around ~90 ppm for the heavy atom effect of the iodide, which suggested the coupling at the iodide position. [48] The result was further confirmed by mass spectrometric analysis. When 4-iodoanisole was treated under the same condition, the coupled product **4c** was isolated in 84% yield. Disubstituted aryl iodide also resulted in products **4d** and **4e** in good yields. In the case of **4d** and **4e**, both aryl iodides having the *o*-methyl group have been tolerated well. In addition, **4d** has trifluoromethyl while **4e** has nitro- group that has no profound effect upon the reaction. Finally, a heteroaryl iodide, 2-iodothiophene also smoothly underwent the coupling reaction resulting in the product **4f** in 77% yield. Here, it is noteworthy that the sulfur of the thiophene may coordinate with the catalytic copper and the strong chelation can inhibit the catalytic cycle, however, the reaction conversion was excellent (Scheme3)

Representative NMR analysis 2-(thiophen-2-ylthio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **4f**

Synthesis of coupled product **4f** in a series of **(4a-4f)** was confirmed by ^{1}H-NMR spectroscopy, the appearance of singlet for three protons at 3.92 ppm represents *para* methoxy protons. Six *ortho* methoxy protons resonate as a singlet at 3.93 ppm. The proton at position 5 of the thiophene ring resonates as *dd* at 7.62 ppm. Similarly, the protons present at positions 3 and 4 of the thiophene ring appears as *dd* at 7.51 ppm and 7.14 ppm respectively. The singlet at 7.20 ppm corresponds to two *ortho* protons of the phenyl ring (Fig. 2).

Synthesis of compound **4f** was confirmed by ^{13}C-NMR spectroscopy. The signal at 56.3 ppm corresponds to two equivalent methoxy carbon. The signal at 61.0 ppm corresponds to the *para*-methoxy carbon. Carbon numbers 3 and 4 of the thiophene ring resonate at 118 ppm and 122 ppm respectively. While carbon-5 of the thiophene ring resonates at 133 ppm. *Ipso* carbon of the phenyl ring appears at 128 ppm, while the carbon of the phenyl ring at which the methoxy group is attached appears at 141.2 ppm (Fig. 2).

Mass spectrometry and fragmentation pattern for 2-(thiophen-2-ylthio)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **4f**

The purity of synthesized compound **4f** was further confirmed from the Gas chromatography. The appearance of the single peak which corresponds to the elution of a single product from the column at 19.9 min. The appearance of a molecular ion peak at m/z = 350 in the mass spectrum justifies the formation of compound **4f** as depicted in Fig. 3. The presence of a base peak at m/z = 193 corresponds to the most stable daughter fragment formed by loss of 157 mass unit from molecular ion. Similarly, a peak at m/z = 115 arises due to the detection of the thiophene-2-thiol cation. The appearance of the peak at m/z = 135 corresponds to the detection of 2,3-dimethoxy-cyclobutan-1-carbonitrile radical cation, which arises due to the loss of methoxy ethane, from daughter fragment at m/z = 193.

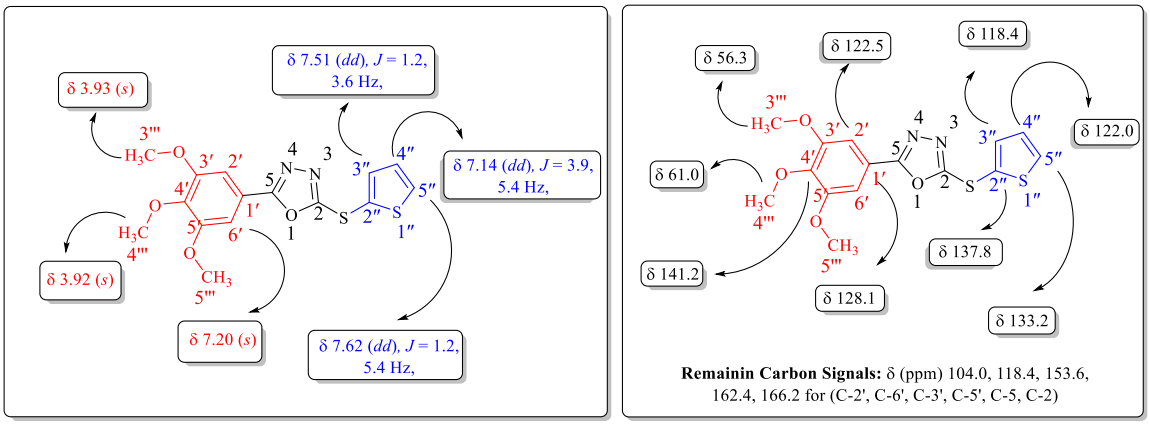


Fig. 2: Schematic representation of ^{1}H and ^{13}C-NMR analyses of compound **4f**.

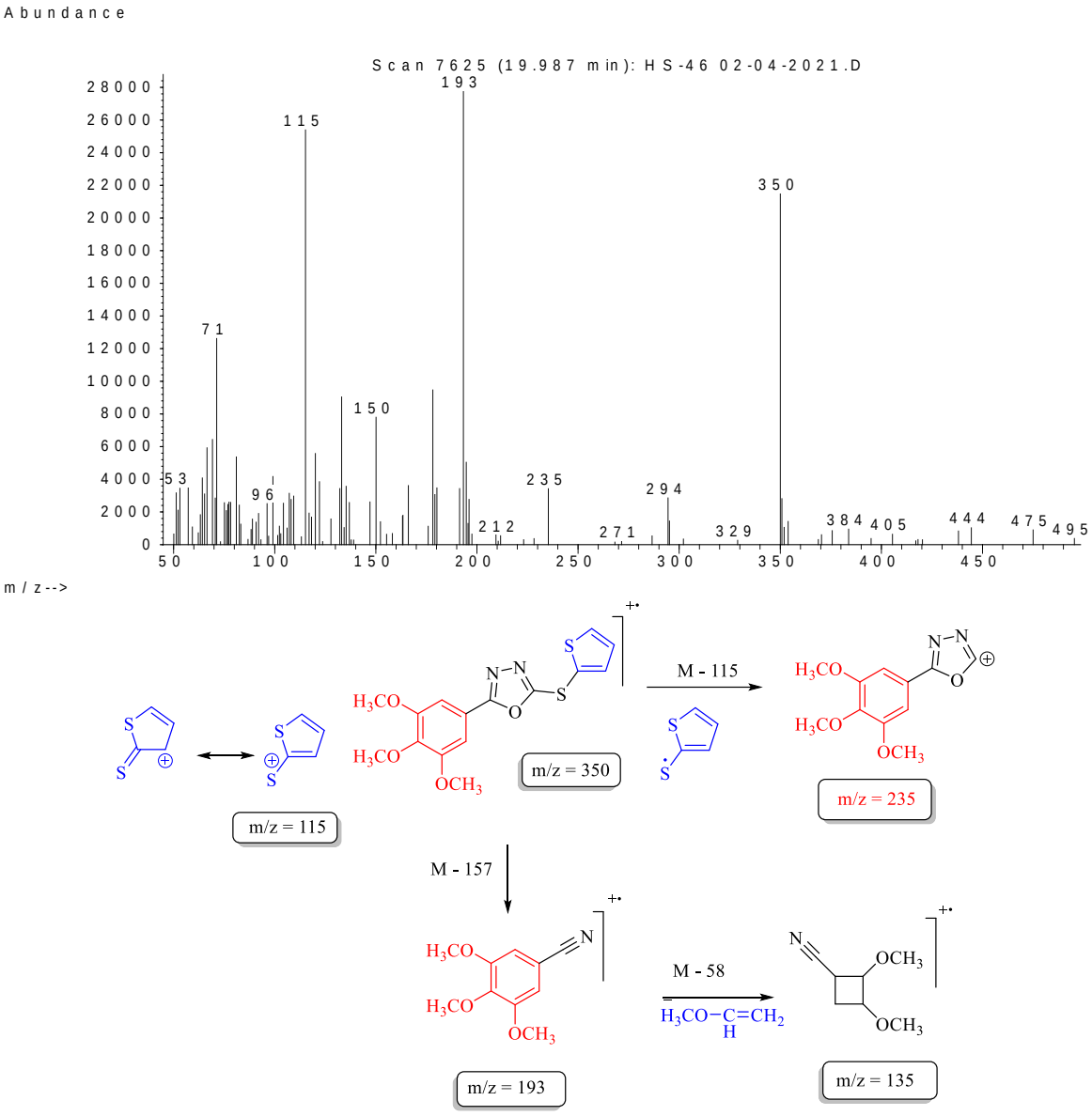


Fig. 3: Mass spectrum and fragmentation pattern of compound **4f** according to EI-MS**.**

Conclusion

The present synthetic investigation deals with the application of the proficient and versatile method for C-S bond formation involving copper as a catalyst. The synthetic approach is optimized using a diverse combination of copper sources and ligands. We have successfully investigated the combination of copper and ligand to produce the required target molecule in excellent yield using a diversity of substituted aryl halides leading to the synthesis of higher molecular architecture. The challenging aspect of the synthesis was the optimization of the reaction conditions. The reaction conditions was found to be copper iodide as catalyst and *N,N'*-dimethylethylenediamine as ligand in dioxane produced the coupling products in good yields for the C-S coupling product. The optimized conditions for the copper-catalyzed *S*-arylation resulted in excellent yield and functional group tolerance. The coupled compounds are of great interest because of their biological and medicinal potential in the pharmaceutical industry. Synthesis and purity of target compounds were ascertained by the use of analytical tools including GC-MS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

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