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Biaryl thioether synthesis via CuI catalyzed dominothiolation of aryl halides in the presence of DMAP as ligand

Subhasish Roy, Prodeep Phukan *

Department of Chemistry, Gauhati University, Guwahati 781014, Assam, India

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ABSTRACT

An improved protocol has been developed for the synthesis of symmetrical biaryl sulfides via a dominothiolation reaction using CuI as catalyst in the presence of DMAP as ligand. The coupling reaction of aryl halides was carried out in the presence of 5 mol % of CuI and 20 mol % of DMAP using thiourea as sulfur transfer agent. High yields of corresponding product were obtained by carrying out the reaction in DMSO at 120 °C.

Selective construction of carbon-sulfur bond is an important tool in organic synthesis, because of wide applicability of organosulfur compounds in different branches of science.[1–3] Compounds having biarylthioether functionality are important intermediates for the synthesis of biologically and pharmaceutically important molecules.[4] Aryl sulfide moieties also found applications in the treatment of diseases such as Alzheimer's, Parkinson's, and HIV infections.[5] In general, transition metal catalyzed cross-coupling reaction provides an efficient pathway for the formation of C–S bonds.[6,7] Migita and co-workers reported for the first time, $Pd(PPh_3)_4$ catalyzed carbon–sulfur bond forming reaction between aryl halide and thiol.[6] Recently use of transition metals such as copper,[8] palladium,[9] indium,[10] nickel,[11] iron,[12] cobalt,[13] and lanthanum,[14] gained popularity in the coupling between aryl halide and thiophenol. Xu et al. reported C–S bond forming reaction between aryl boronic acid and thiophenol catalyzed by $CuSO_4$.[15] Because of the high volatility and toxicity of thiophenol, such reactions pose threats to the surroundings. Moreover, thiophenols get easily oxidized to their stable disulfides which are the major byproducts in most of the C–S cross-coupling reactions. Due to the difficulties of handling thiophenol and their derivatives, C–S coupling reaction is less extensively studied compared to C–N and C–O coupling. To overcome the above problems various sulfur transferring reagents such as disulfides, thiolates, metal sulfides, and CS_2 have been applied instead of thiophenol to form biarylthioethers.[16,11a] On the contrary, thiourea is a cheap, safe and effective sulfur transfer agent.[17] In the year 2010, Punniyamurthy reported an intramolecular sulfur transfer reaction using 1-(2-iodophenyl)thiourea in the presence of $CuSO_4{\cdot}5H_2O$ as catalyst.[18a] Later, a similar protocol was also developed by Patel and his coworkers using CuI as catalyst.[18b] Nageswar demonstrated the use of thiourea as sulfur source for the synthesis of biarylthioether in the presence of a catalytic amount of CuO nanoparticle.[19] The use of $Pd_2(dba)_3$/combination with Triphos as ligand for dominothiolation reaction of aryl halide has also been reported for the synthesis of biarylthioether.[20] The use of KSCN as sulfur transfer agent for $CuCl_2{\cdot}H_2O$ catalyzed C–S bond forming reaction of aryl halide was reported by Zhou.[21] However, this methodology takes long reaction time (48 h) to produce the desired biaryl sulfide product. In general, it has been observed that catalytic activity of a metal salt can be tuned by the addition of an appropriate ligand.[22] In the recent past, various ligands have been introduced to enhance the activity of metal catalysts for promoting various cross-coupling reactions.[23] However, most of the ligands are expensive and some of these are moisture sensitive. So, development of a cheap, commercially available, stable, and efficient ligand for promoting metal catalyzed cross-coupling reaction is of paramount interest.

Catalytic activity of DMAP has been well explored in organic synthesis.[24] However, there are a very few reports on the use of DMAP as a ligand for metal catalyzed cross-coupling reaction. Pd catalysts along with DMAP ligand have been found to catalyze Heck reaction and Barbier type allylation reaction quite

* Corresponding author. Tel.: +91 361 2570535; fax: +91 361 2570133.
E-mail address: pphukan@yahoo.com (P. Phukan).

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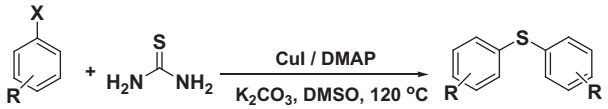
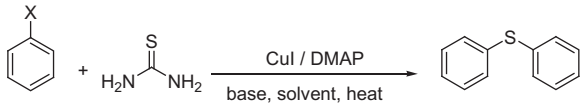


R = -H, 4-Me, 3-Me, 4-MeO, 3-NO_2, 2-NO_2, 4-NO_2, 4-NMe_2

X = Br, I

Scheme 1. CuI/DMAP catalyzed dominothiolation reaction of aryl halide.

Table 1
CuI/DMAP catalyzed biarylsulfide synthesis from iodobenzene[a]



Entry	CuI (mol %)	Bases	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	0	K_2CO_3	DMSO	100	24	0
2	5	—	DMSO	100	24	0
3	5	K_2CO_3	DMSO	100	12	70
4	5	Cs_2CO_3	DMSO	100	16	52
5	5	K_3PO_4	DMSO	100	14	57
6	5	K_2CO_3	DMSO	120	10	80
7	5	K_2CO_3	DMSO	140	10	82
8	10	K_2CO_3	DMSO	120	10	83
9	20	K_2CO_3	DMSO	120	10	83
10	5	K_2CO_3	Dioxane	120	24	Trace
11	5	K_2CO_3	DMF	120	16	60

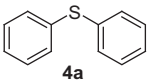
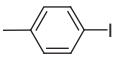
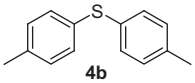
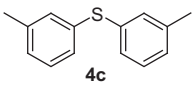
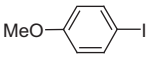
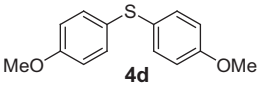
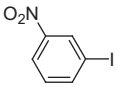
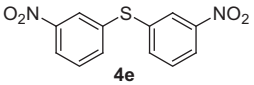
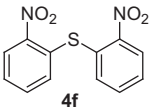
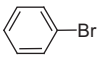
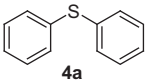
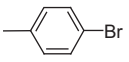
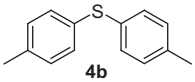
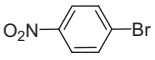
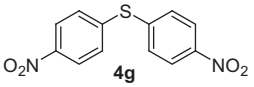
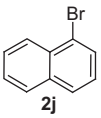
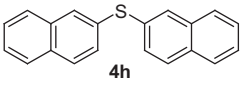
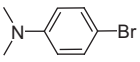
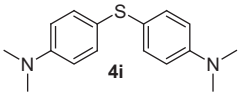
[a] Reaction condition: iodobenzene (2 mmol), thiourea (1.2 mmol), base (2 mmol), solvent (2 mL).
[b] Isolated yield.

effectively.[25] Navale and Bhat recently reported homo and hetero coupling of alkyne using CuI/DMAP catalytic system.[26] It has been observed that Cu-based catalytic systems are found to be very attractive because of their low cost and low toxicity. Literature review reveals several reports for various Cu-catalyzed cross-coupling reactions in the presence of suitable ligands.[27] In continuation of our study on CuI catalyzed reactions,[28] we wish to report herein a new catalytic route comprising of CuI and DMAP for dominothiolation to obtain biaryl sulfides (Scheme 1).

Initially, the reaction of iodobenzene was chosen as a model reaction to find out the optimum condition. In a typical reaction, iodobenzene (2 mmol), thiourea (1.2 mmol), and 2 mL of DMSO were added to a round bottom flask. To the stirred solution of the reaction mixture under nitrogen atmosphere were added CuI (5 mol %), DMAP (20 mol %), and K_2CO_3 (2 mmol). The reaction mixture was heated at 100 °C (bath temperature) in an oil bath. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was subjected to aqueous work-up and the crude product was purified by flash chromatography to yield the pure biarylthioether. Initial reaction without any catalyst failed to produce any product even after 24 h of reaction (Table 1, entry 1). Similarly, the reaction was unsuccessful in absence of base (Table 1, entry 2). Use of 5 mol % of CuI as catalyst in the presence of K_2CO_3 as base and DMSO as solvent at 100 °C gives 70% of the product yield in 12 h of reaction (Table 1, entry 3). Use of Cs_2CO_3 and K_3PO_4 as base produced only 52% and 57% of yield, respectively (Table 1, entries 4 and 5). When the temperature of the reaction was raised to 120 °C, improvement of the product yield (80%) as well as the reaction rate has been observed (Table 1, entry 6). Further increase in the reaction temperature did not affect the reaction appreciably. It was further observed that increasing the catalyst loading up to 10 mol % increases the product yield slightly (by 2%) under the same reaction condition. Further increase in the catalyst loading up to 20 mol % did not increase the product yield appreciably (Table 1, entries 8 and 9). The reaction has been tested with other solvents such as DMF and dioxane. While DMF gives 60% of yield (Table 1, entry 11), dioxane failed to give any product at all (Table 1, entry 10). Hence, the use of 2 mmol of aryl halide, 1.2 mmol of thiourea, 5 mol % of CuI, and 20 mol % of DMAP in DMSO at 120 °C has been found to be the optimum reaction condition for achieving the best yield of biaryl thioether.

After establishing the optimum reaction condition, the process was extended to a variety of aryl halides.[29] The results are presented in Table 2. It can be seen from Table 2 that both iodo and bromo substituted aryl halides could be transformed into corresponding product quite efficiently. As expected, the aryl iodides are more reactive than the aryl bromide counterpart.

Table 2
Allylation of aldehyde using $Pd(OAc)_2$ and DMAP[a]

Entry	Substrate	Product	Yield[b]
1	 **2a**	 **4a**	80
2	 **2b**	 **4b**	81
3	 **2c**	 **4c**	75
4	 **2d**	 **4d**	80
5	 **2e**	 **4e**	86
6	 **2f**	 **4f**	89
7	 **2g**	 **4a**	74
8	 **2h**	 **4b**	72
9	 **2i**	 **4g**	85
10	 **2j**	 **4h**	68
11	 **2k**	 **4i**	60

[a] Reaction condition: aryl halide (2 mmol), thiourea (1.2 mmol), CuI (5 mol %), DMAP (20 mol %), DMSO (2 mL), 120 °C, 12 h.
[b] Isolated yield.