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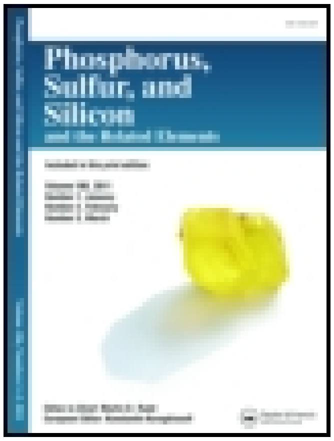

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Ligand-Free Copper-Catalyzed Synthesis of Unsymmetrical Thioethers by Coupling Aryl or alkyl Halides Using a Acetyl Thiourea Precursor in Wet Polyethylene Glyol (PEG 400)

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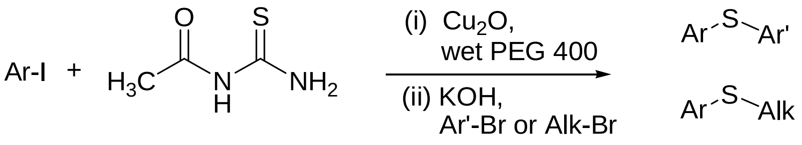
Abstract Unsymmetrical diaryl or aryl alkyl thioethers can be prepared in good to excellent yields by coupling the appropriate aryl iodides and aryl or alkyl bromines using acetyl thiourea as a thiol precursor, Cu_2O as a catalyst, KOH as a base and PEG 400-H_2O as a solvent under ligand-free conditions.



Key words Unsymmetrical thioether, copper, acetyl thiourea, PEG, cross-coupling, catalysis

INTRODUCTION

Unsymmetrical thioethers are important synthetic intermediates often found in biologically and pharmaceutically active molecules, and polymeric materials.[1] The traditional methods for the synthesis of unsymmetrical thioethers often require harsh reaction conditions such as Grignard reagents and elevated temperature,[2] and are not suitable for molecules containing sensitive functional groups. To overcome these drawbacks, palladium-,[3-5] nickel-,[6-7] copper-,[8-11] cobalt-,[12] indium-,[13-14] and iron-based[15-16] catalytic systems have been explored. These transition-metal-catalyzed coupling of thiols with alkyl halides or aryl halides have overcome these difficulties to a great extent. But, which methods have many disadvantages, like volatile, foul-smelling and less available of arenethiols, which drawbacks make these methods are less adoptable for the sustainable synthesis of various thioethers. Recently, efficient and odourless preparative methods of unsymmetrical thioethers have been achieved by the replacement of thiols with thiol precursors such as thiourea,[17] thiolyanate,[18] ethyl xanthagenate,[19, 20] thioacetamide[21] and thioacetate[22]. However, until now, new environmentally friendly methods for preparation of unsymmetrical thioethers are still rarely reported.

The use of polyethylene glycols (PEGs) as a solvent in organic reactions has attracted much attention due to the inexpensive, thermally stable, non-toxic, negligible vapor pressure and environmentally benign media for chemical reactions. In addition, ligand-free methods have been studied due to their advantages, such as high atom efficiency, simplified isolation of the product, and easy recovery of the catalysts. Herein, we report a new protocol for the synthesis of unsymmetrical thioethers by coupling the appropriate aryl iodides and aryl or alkyl bromines using acetyl thiourea as a thiol precursor, Cu_2O as a catalyst, KOH as a base and PEG 400-H_2O as a solvent under ligand-free conditions.

RESULTS AND DISCUSSION

We initiated our study by reacting iodobenzene (1 mmol) with acetyl thiourea (1 mmol) in the presence of 20 mol% Cu_2O, and PEG 400 (4 mL) at 105℃. After 24h, KOH (3 mmol) and *p*-bromoanisole (0.8 mmol) were added to the reaction mixture and the resulting mixture was heated further for 24h. The reaction proceeded well and the desired product (4-methoxyphenyl) (phenyl) sulfane was isolated in 46% yield.

In order to optimize the reaction conditions, several catalysts, solvents, and bases were screened in above model reaction, the results summarized in Table 1. Using PEG 400 as a solvent and KOH as a base, different copper catalysts were examined. The results shown that the reactions catalyzed by copper compounds in various oxidation states were carried out smoothly, and the desired products were obtained in moderate yields (Table 1, entries 1-4). In the absence of a copper catalyst, no desired product was isolated (Table 1, entry 5). This has proven that the presence of a copper catalyst was crucial for the reaction. Next, solvents were screened by using Cu_2O as a catalyst. Results show that PEG 400 was the best choice (Table 1, entry 1). Using H_2O

and aqueous solution of β-cyclodextrin as solvents, no desired product was formed (Table 1, 6 and 7). Seker et al. reported that glycol or 1,4-diol compound can serve as ligands in the Cu-catalyzed synthesis of thioethers[20]. It can be speculated that PEG was likely to serve as a ligand in the reaction. Surprisingly, when H_2O was added to PEG 400, the reaction was dramatically improved to give the coupling product in 81% yield (Table 1, entry 8). Reducing the amount of H_2O in PEG 400, the product yield decreased, however, increasing the water content in PEG 400, the yield of product did not change (Table 1, entries 9 and 10). Presumably, when H_2O was introduced into the reaction mixture, hydrolysis of the reaction intermediate may occur[21]. In addition, in the screening of the bases, the best yield was given by KOH (Table 1, entry 8).

Therefore, our optimal reaction conditions were as follows: 10 mol% Cu_2O as the catalyst, aryl iodides (1 mmol) and Ar'-Br or Alk-Br (0.8 mmol) as the arylation reagents, and acetyl thiourea as the sulfur source (1 mmol), PEG 400-H_2O (10:1 ratio) as the solvent, and KOH as the base at 105°C.

Having identified the best reaction conditions, we next examined the scope of the coupling of acetyl thiourea with various aryl or alkyl halides (Table 2). The results shown that the electronic property of different substituent on the aryl rings have little effect on this coupling reaction, and aryl halides bearing both electron-withdrawing groups and electron-donating groups worked well, products were obtained in 77-83% yields (Table 1, entries 1-5 and 8-9).

Aryl iodides carrying an *ortho* substituent were also found to readily participate in the reaction. For instance, 2-iodotoluene and 2-iodonitrobenzene gave isolated yield of 76% and 77% respectively (Table 2, entries 6 and 7). Heteroaryl sulfides were also obtained with satisfactory yields (Table 2, entries 10-11). Replace aryl bromides with alkyl bromides in the second iteration could obtain excellent yields (Table 2, entries 12-15).

Based on the literatures[21, 23], we have also proposed a general pathway for the reaction as presented in Scheme 1.

In summary, we have introduced an efficient, versatile and odourless protocol for the preparation of unsymmetrical thioethers by coupling the appropriate aryl iodides and aryl or alkyl bromines using acetyl thiourea as a thiol precursor, Cu_2O as a catalyst in wet polyethylene glycol (PEG 400) without the use of any external ligands. Various diaryl thioethers and aryl alkyl thioethers were obtained in good to excellent yields. Further applications to the synthesis of biologically molecules are in progress.

EXPERIMENTAL

^{1}H and ^{13}C spectra were recorded in $CDCl_3$ on a 300 MHz instrument at 300 MHz (^{1}H) and 75 MHz (^{13}C) with TMS as internal standard.

General Procedure for Preparation of Thioether

Cu_2O (10 mol %), aryl iodide (1 mmol), acethyl thiourea (118 mg, 1 mmol) were placed in a small round-bottomed flask. PEG 400 (4 mL) and H_2O (0.4 mL) were then added together. The mixture was stirred for 24h at 105℃ under a nitrogen atmosphere. Then KOH (159 mg, 3mmol) and Ar’-Br or Alk-Br (0.8 mmol) were added and the reaction mixture was stirred for 24h. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into 10 mL of saturated sodium chloride aqueous solution and extracted with ethyl acetate (2×5 mL), dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography afforded the desired products. The Supplemental Materials contains characterization data of the known products from Table 2.

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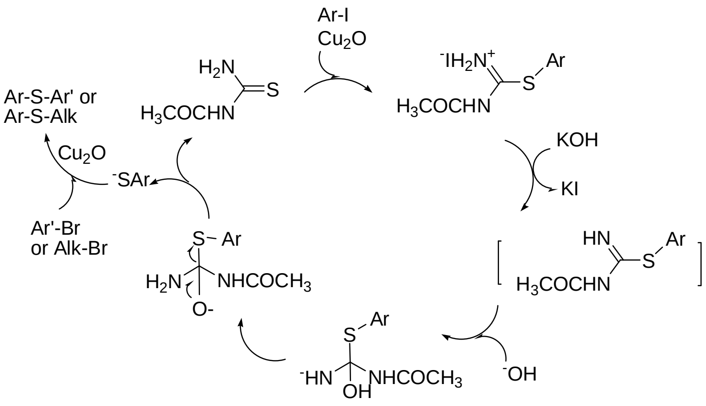
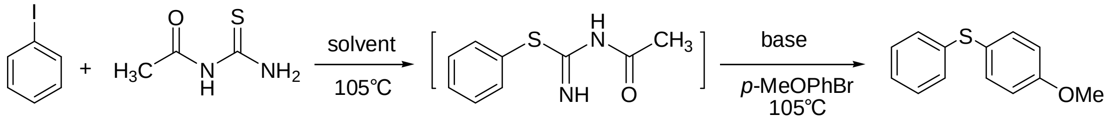


Scheme 1 Possible mechanism

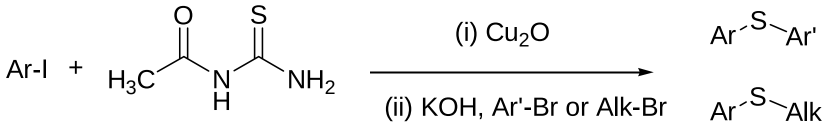
Table 1 Optimization of Catalysts, Solvents and Based for Synthesis of Thioethers[a]

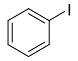
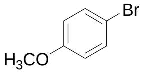
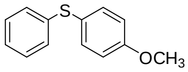
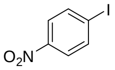
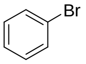
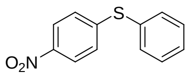
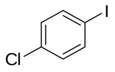
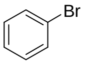
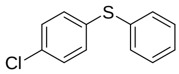
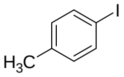
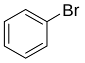
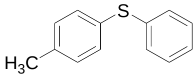
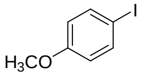
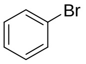
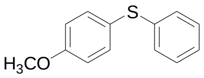
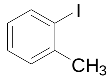
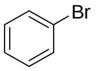
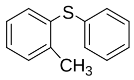
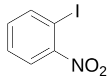
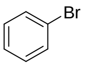
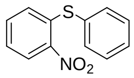
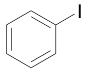
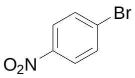
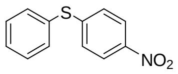
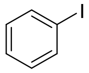
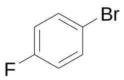
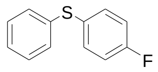
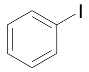
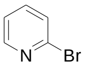
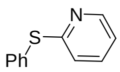
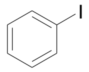
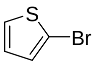
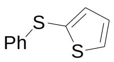
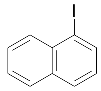
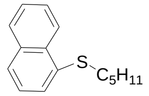
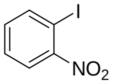
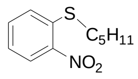


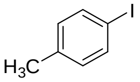
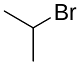
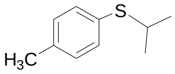
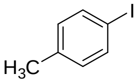
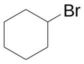
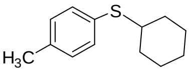
entry	catalyst	solvent	base	Yield (%)[b]
1	Cu_2O	PEG 400	KOH	46
2	CuI	PEG 400	KOH	43
3	CuO	PEG 400	KOH	45
4	$Cu(OAc)_2$	PEG 400	KOH	42
5	-	PEG 400	KOH	0
6	Cu_2O	H_2O	KOH	0
7	Cu_2O	Aqueous solution of β-cyclodextrin	KOH	0
8	Cu_2O	PEG 400-H_2O (20 : 1 ratio)	KOH	81
9	Cu_2O	PEG 400-H_2O (25 : 1 ratio)	KOH	72
10	Cu_2O	PEG 400-H_2O (10 : 1 ratio)	KOH	81
11	Cu_2O	PEG 400-H_2O (10 : 1 ratio)	K_3PO_3	78
12	Cu_2O	PEG 400-H_2O (10 : 1 ratio)	Na_2CO_3	62
13	Cu_2O	PEG 400-H_2O (10 : 1 ratio)	K_2CO_3	70

[a] Reaction conditions: iodobenzene (1 mmol), catalyst (10 mol%), solvent (4 mL), base (3 mL), *p*-MeOPhBr (0.8 mmol), acethyl thiourea (1 mmol), 105□; [b] Isolated yield.

Table 2 Copper Catalyzed Synthesis of Thioethers with Acetyl Thiourea and Various Aryl or Alkyl Halides [a]



entry	Ar-I	Ar'-Br or Alk-Br	product	yield (%)[b]	ref.[c]
1				81	22
2				79	19
3				77	19
4				83	19
5				80	19
6				76	24
7				77	24
8				83	24
9				80	24
10				80	19
11				73	19
12		$C_5H_{11}Br$		88	19
13		$C_5H_{11}Br$		82	24

14				80	24
15				84	24

[a] Reaction conditions: aryl iodide (1 mmol), Cu_2O (10 mol%), PEG 400-H_2O (10:1 ratio, 4 mL), KOH (3 mmoL), Ar'-Br or Alk-Br (0.8 mmol), acethyl thiourea (1 mmol), 105□; [b] Isolated yield; [c]References of product characteristics.