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One-pot synthesis of aryl alkyl thioethers and diaryl disulfides using carbon disulfide as a sulfur surrogate in the presence of diethylamine catalyzed by copper(I) iodide in polyethylene glycol (PEG200)

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ABSTRACT

A copper catalyzed one-pot protocol for the preparation of aryl alkyl thioethers and diaryl disulfides using carbon disulfide as the sulfur source and diethylamine in polyethylene glycol (PEG200) is described.

Aryl alkyl thioether moieties are found in many pharmaceutically and biologically active compounds. Numerous examples of drugs applied for diabetes, Alzheimer's and Parkinson's diseases, inflammatory and immune diseases have aryl sulfide moieties in their structures.[1] Thus protocols leading to C–S bond generation, which are practical, cheap, and efficient have attracted a great deal of attention.[2] Cross-coupling reactions catalyzed by transition metal catalysts are a tactic for C–S bond generation.[3] The preparation of thioethers by the reaction of thiols with aryl halides catalyzed by transition metals such as palladium,[4] nickel,[5] cobalt,[6] copper,[7] indium,[8] iron,[9] and manganese salts[10] have been reported. Some of these studies have led to new and efficient methods, but the majority of the reported reactions are conducted in harmful organic solvents. Disposal of organic solvents is a major problem for the chemical industry. Furthermore, organic solvents are expensive, toxic, and flammable. In contrast, polyethylene glycols (PEGs) and their derivatives have negligible vapor pressures and are recognized to be inexpensive, thermally stable, recoverable, non-toxic compounds which are suitable media for environmentally friendly and safe chemical reactions.[11] We have reported previously the one-pot odorless C–S bond formation via Michael addition using thiourea and alkyl bromides in water,[12] in aqueous polyethylene glycol or in ionic liquids.[13] We have also applied this protocol for the odorless thioarylation of alkyl bromides with aryl halides in the presence of copper(I) iodide in wet PEG200.[14]

Moreover, after this report, some other sulfur surrogates such as thioacetamide,[15] thiourea,[16] potassium thiocyanate,[17] thioacetate,[18] potassium ethyl xanthogenate,[19] sodium hydrosulfide,[20] and elemental sulfur[21] were used for the conversion of aryl compounds (mostly halides) into aryl thioethers by catalysis with Pd or Cu.

The study of cross-coupling reactions of phenols due to their nature as electrophilic coupling partners is a challenging topic.[22] Most of the studied phenolic derivatives in carbon–sulfur bond formation reactions are triflates. Regardless of the exceptional reactivities of these compounds, triflates are materials with limited stability.[23] Therefore, other phenolic esters such as tosylates may be better precursors for electrophilic coupling reactions. Recently, a Letter in which a copper-catalyzed synthesis of diaryl thioethers by the reaction of aryl iodides with carbon disulfide in the presence of DBU was published.[24] This publication prompted us to report our preliminary findings in this area.

Herein, we report a one-pot synthesis of aryl alkyl thioethers and diaryl disulfides using carbon disulfide as a sulfur substitute in the presence of diethylamine catalyzed by copper(I) iodide in polyethylene glycol (PEG200) as an eco-friendly solvent. Aryl

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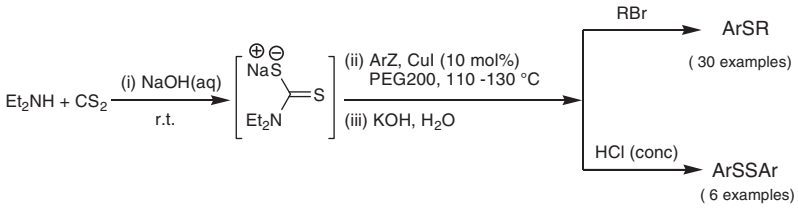


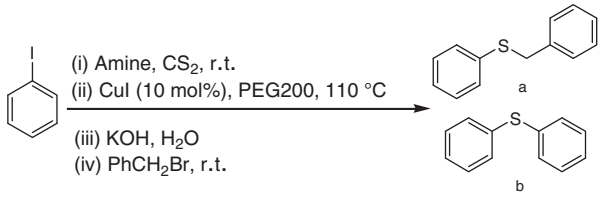
Scheme 1. Reagents and conditions: Z = I, Br or OTs Ar = phenyl, 4-methylphenyl, 4-methoxyphenyl, naphthalen-1-yl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, R = benzyl, *n*-butyl, cyclohexyl.

Table 1
Optimization of the reaction conditions with respect to the effect of catalysts, solvents, and the temperature on the formation of phenyl benzyl thioether from iodobenzene and benzyl bromide

Entry	Catalyst	Solvent	Base	Temp (°C)	Yield (%)
1	CuI	DMF	KOH	90	50
2	CuI	PEG200	KOH	90	70
3	CuI	DMSO	KOH	90	50
4	**CuI**	**PEG200**	**KOH**	**110**	**90**
5	CuI	PEG200	K_2CO_3	110	70
6	$Cu(OAc)_2$	PEG200	KOH	110	60
7	$CuCl_2$	PEG200	KOH	110	70
8	CuCl	PEG200	KOH	110	75
9	$PdCl_2/PPh_3$	PEG200	KOH	110	NR
10	CuI	PEG200	NaOH	110	85

The bold letters represent the most effective reaction conditions.

Table 2
The effect of using different organic bases on the reaction of iodobenzene with benzyl bromide



Entry	Amine	Base	Time (h)	Yield[a] (%)	Yield[b] (%)
1	**Et_2NH**	**KOH**	**20**	**92**	**0**
2	DBU	—	15	35	45
3	DBU	KOH	15	55	40
4	DABCO	—	24	NR	NR
5	Piperidine	KOH	24	83	0

The bold letters represent the most effective reaction conditions.
[a] phenyl benzyl thioether.
[b] diphenyl thio ether.

iodides, bromides, and tosylates were reacted with alkyl bromides to produce the corresponding aryl alkyl thioethers in good to excellent yields. In addition, the generation of diaryl disulfides occurred in excellent yields using this method (Scheme 1).

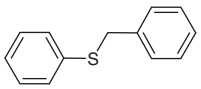
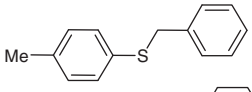
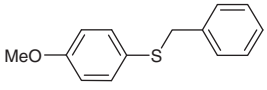
Optimization of the conditions was performed on the reaction of iodobenzene and benzyl bromide as a model system using different solvents, Cu and $PdCl_2/Ph_3P$ catalysts, inorganic bases, CS_2 and organic bases at two different temperatures (90 and 110 °C). The results showed that when PEG200 was used as the solvent, KOH as the inorganic base, CuI as the catalyst, and diethylamine as an organic base with heating at 110 °C, the desired phenyl benzyl thioether was isolated in an excellent yield (entry 4, Table 1). According to the results in Table 1, all the copper salts catalyzed the reaction but the most significant was CuI. Surprisingly, $PdCl_2/PPh_3$ did not show any catalytic activity in this reaction. Among the solvents, the most effective was PEG200 (entries 1–3, Table 1). The temperature also affected the yield of the desired product which ranged from 70% to 90% when the temperature was raised from 90 to 110 °C (entries 2 and 4, Table 1). The effect of organic bases on the reaction of iodobenzene with benzyl bromide showed that the nature of the organic base was important affecting both the pathway of the reaction and also the yield of the desired product (Table 2). Among the organic bases the most effective was diethylamine (Table 2).

When aryl iodides were reacted with alkyl bromides in PEG200, under the optimized conditions, the reactions proceeded well to produce the corresponding unsymmetrical thioethers in good to excellent yields[25] (Table 3).

Phenolic triflates are the most studied phenolic derivatives in carbon–sulfur bond formation reactions.[23] But other phenolic esters such as tosylates may be more suitable precursors to be studied for C–S bond formation reactions. Thus, we studied the reactions of phenolic tosylates under the optimized conditions at 130 °C. The reactions gave the corresponding aryl alkyl sulfides in 65–75% isolated yields (Table 4).

We have also studied the reaction of aryl bromides with alkyl bromides for the formation of aryl alkyl thioethers. These reactions

Table 3
Aryl alkyl C–S bond formation by means of the reaction of aryl iodides and alkyl bromides using CS_2 catalyzed by CuI in PEG200 at 110 °C

Entry	ArI	RBr	Product[25]	Time (h)	Yield (%)
1	**1a**	**2a**	 **5a**	20	92
2	**1b**	**2a**	 **5b**	22	90
3	**1c**	**2a**	 **5c**	22	90

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