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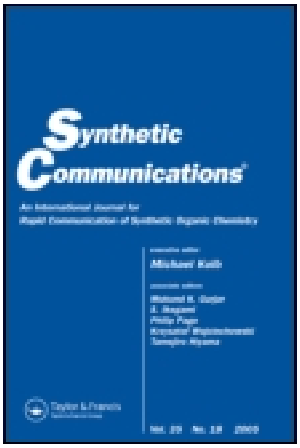

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Facile Preparation of Aryl Sulfides Catalyzed by PEG400 and Nickel without Solvent

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Facile Preparation of Aryl Sulfides Catalyzed by PEG400 and Nickel without Solvent

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Abstract: A variety of aryl sulfides were synthesized by aryl bromides with thiols, with PEG400 and nickel as catalysts under basic conditions in the absence of solvents. This article reported an easy and convenient method for formation of aryl-sulfur bonds.

Keywords: Aryl bromides, aryl sulfides, nickel bromide, PEG400, solventless, zinc

INTRODUCTION

Aryl sulfides have been widely used as intermediates in synthetic chemistry and as products in the pharmaceutical industry,[1,2] which have attracted continued interest. Many methods have been developed profitably for their synthesis. One traditional method for the preparation of aryl sulfides was reduction of aryl sulfones or aryl sulfoxides,[3] which usually required strong reducing agents, costly catalysts such as neocuproine,[4] $Pd(PPh_3)_4$,[5] DiPPF,[6] and $[Bmim]PF_6$.[7] The Sandmeyer reaction was another method for the preparation of aryl sulfides by diazonium salts of aromatic amino with thiols;[8] however, the troublesome procedures and undesirable yields have been found. Recently, metal-catalyzed preparation of aryl sulfides by the thiols with aryl halides, using a copper or

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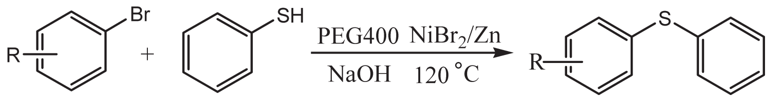


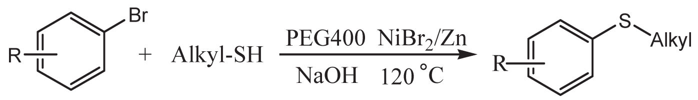
Scheme 1.

palladium catalyst under basic conditions, had been reported.[9,10] Traditional copper-mediated reactions suffered from drawbacks such as high reaction temperatures, the use of copper salts in greater than stoichiometric amounts, sensitivity to functional groups on the aryl halides, and irreproducibility.[11]

The reaction of thiols with alkyl halides was a common method for the preparation of aryl sulfides. The advantages of this reaction were mild conditions and higher yields. Most of reactions were carried out in organic solvents. Developing green chemical reactions is one of the most important purposes of organic synthesis at present. Organic synthesis in the absence of solvent was of greatly applied value and expansive prospects.[12,13] In this regard, PEG400 had been used as phase-transfer catalyst (PTC) and applied readily available reagents, which could be easily put into industrial production.

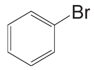
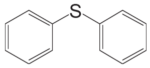
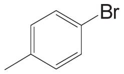
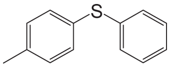
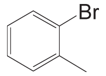
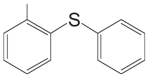
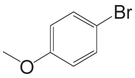
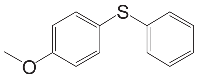
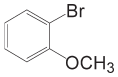
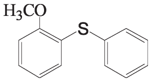
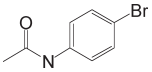
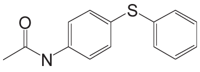
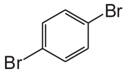
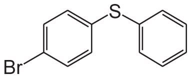
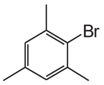
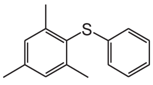
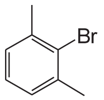
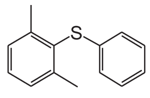
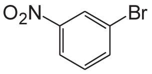
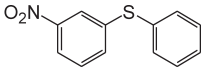
Polyethylene glycols (PEGs) could be regarded as the acyclic crown-ether and have been widely used as PTCs in many organic reactions because of their stability, low cost, low toxicity, and easy availability.[14,15] It had been proved that PEG incorporating seven to nine units was more effective in catalyzing the reactions in which Na^+ salts participated. In particular, because of the liquid property, perfect solubility in water, and the participation of two hydroxy groups during the destructing crystal lattice of the solids, PEG400 was more suitable for liquid–liquid or solid–liquid phase solvent-free organic reactions. The sulfur anions could easily enter the liquid phase and become a strong nucleophilic reagent that could promptly undergo nucleophilic substitution.

In continuation of our research on the use of PEGs as PTCs in organic synthesis without solvent,[16–18] we herein report a facile method for the preparation of aryl sulfides by the reaction of aryl bromides with thiols catalyzed by PEG400, nickel bromide, and zinc under basic conditions in the absence of solvents. The reactions are shown in Schemes 1 and 2. The experimental results are listed in Tables 1 and 2.



Scheme 2.

Table 1. Reactions of aryl bromides with thiophenol

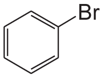
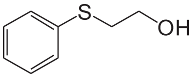
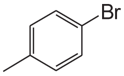
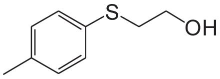
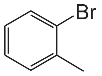
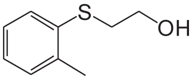
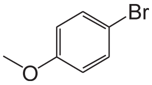
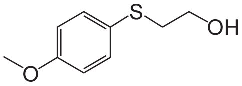
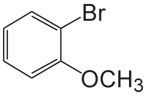
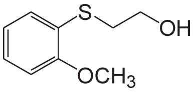
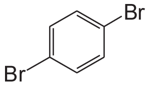
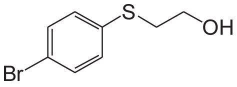
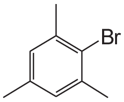
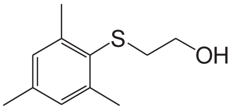
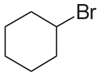
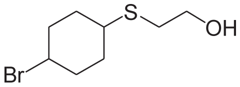
Entry	Aryl bromides	Product	Time (h)	Yield (%)
1			12	82
2			10	85
3			10	86
4			8	87
5			9	85
6			12	82
7[a]			11	79
8			8	90
9			10	84
10			14	46

[a] It may be reacted with double thiols to form p-bis(phenylthio)benzene.

RESULTS AND DISCUSSION

Taking the reaction of phenyl bromide and thiophenol as an example, a yield as low as 57% was obtained after the reaction was performed over 12 h without the presence of PEG400. However, when 4% mol PEG400 was added, the reaction time was greatly shortened and the yield was 90%. The amount of 4% mol of PEG400 was adequate to catalyze the reaction effectively. The more PEG400 employed, the more products would be lost during the course of washing with water.

Table 2. Reactions of aryl bromides with readily available alkyl thiols

Entry	Aryl bromides	Alkyl thiols	Product	Time (h)	Yield (%)
1		HSC_2H_4OH		12	80
2		HSC_2H_4OH		10	82
3		HSC_2H_4OH		10	81
4		HSC_2H_4OH		8	85
5		HSC_2H_4OH		10	74
6[a]		HSC_2H_4OH		10	77
7		HSC_2H_4OH		8	89
8		HSC_2H_4OH		12	68

[a] It may be reacted with double thiols to form p-bis(phenylthio)benzene.

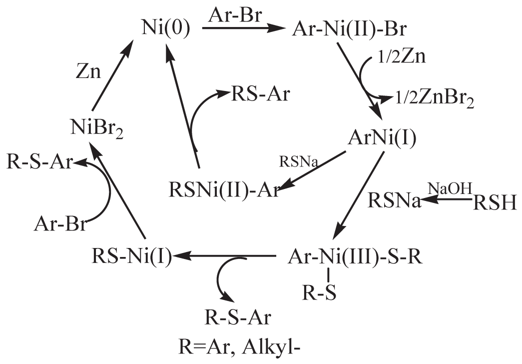
Because the reaction should proceed under basic conditions, we compared different kinds of bases, such as anhydrous K_2CO_3, NaOH, Et_3N, and CaO. Our initial choice of base was anhydrous K_2CO_3 because K_2CO_3 was found to be an effective base for this coupling reaction, but 2 equiv were needed; the use of other bases such as CaO or Et_3N gave somewhat lower yields. NaOH can also give excellent yields, and the amount was reduced to 1.2 equiv. NaOH is a more suitable base.

To shorten the reaction time, the reactions of thiophenol and aryl bromides were heated at 110–120 °C. As shown as in Table 1, longer reaction periods were needed in the reactions of 4-acetamide bromobenzene (entry **6**) because of $\pi-\pi$ conjugation of the carbonyl group with the benzene ring and the steric effect of the benzene ring. It is the same reason that the coupling of aryl bromides with electron-donating groups such as -CH_3 and -OCH_3 in the aromatic ring and thiophenol could be carried out in a relatively shorter time than with electron-withdrawing groups such as -Br and-NO_2. In particular, for entry **10**, the yield was very low because -NO_2 is a strong electron-withdrawing group; another reason is that the reduction of the nitro group with thiol will take place competitively.

Based on the results listed in Table 2, the coupling of aryl bromides with some readily available alkanethiols could take place in these reaction conditions. Moreover, 1,3,5-trimethyl-bromobenzene could be carried out in excellent yield (entry **7** in Table 2).

This catalytic process requires a nickel salt and zinc, and it is clear that neither $NiBr_2$ nor zinc itself had the ability to insert into Ar-Br.[19] In contrast, Ni(0) can insert into these bonds. The facts show that in the thiolation of aryl bromide, at the first step, an Ni(0) species is formed by the reduction by zinc. At the next step, this Ni(0) species inserts into Ar–Br bonds, and Ar–Ni(II)–Br is produced. It is worth noting that Ar–Ni(II)–Br alone cannot transform Ar–Br to ArSR. Actually, Ar–Ni(II)–Br is unavailable for the synthesis of ArSR. However, the zinc was added as the reductive reagent. Given these results, it is presumed that ArNi(I) is an activating species for the thiolation. Hence, it is anticipated that the nickel-catalyzed thiolation of aryl bromide is accelerated by ArNi(I). From these results, the reaction mechanism is considered as follows (Scheme 3).

In summary, we have developed a convenient and efficient method for preparing aryl sulfides by the reaction of aryl bromides with thiols catalyzed by PEG400, nickel bromide, and zinc without solvent, which offered carbon–sulfur bond formation for both aromatic and alkanethiols under mild conditions. The advantages of this procedure are higher yield, operational simplicity, low cost, and less pollution to environment. We assume that the method is suitable to be put into industrial application.



Scheme 3.

EXPERIMENTAL

Thin layer chromatography (TLC) was GF_{254} with petroleum ether/ethyl acetate (10/1) as eluent. Aryl bromides, thiophenols, alkyl thiols, and PEG400 were commercially available and used without further purification. ^{1}H NMR spectra were obtained on a Brucker Avance (400-MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr).

Typical Procedure for the Preparation of 4-Methoxyphenyl Phenyl Sulfide (Entry 4, Table 1)

Thiophenol (11 ml, 0.1 mol) was added to a mixture of nickel bromide (2.2 g, 0.01 mol), zinc (1 g, 0.015 mol), NaOH (4.8 g, 0.12 mol), and PEG400 (1.6 g, 0.004 mol), and the mixture was stirred in a 50-mL three-necked, round-bottomed flask equipped with a magnetic stirrer for 1 h at 80 °C. Then 4-methoxy bromobenzene (13 ml, 0.1 mol) was added, and the mixture was vigorously stirred at 120 °C. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was washed three times with 50 ml of water. The organic phase was separated and dried over magnesium sulfate. Then 18 g of the title compound as a colorless oil was collected. ^{1}H NMR ($CDCl_3$): δ: 3.82 (s, 3H, CH_3), 6.90 (d, $J = 8.8$ Hz, 2H), 7.1–7.3 (m, 5H, ArH), 7.42 (d, $J = 8.8$ Hz, 2H); IR (KBr, cm^{-1}) v: 3058, 3004, 2941, 2834, 1592, 1492, 1287, 1243, 1171.

Typical Procedure for the Preparation of Phenyl Alkyl Thioether (Entry 1, Table 2)

2-Mercapto-ethanol (7.1 ml, 0.1 mol), was added to a mixture of nickel bromide (2.2 g, 0.01 mol), zinc (1 g,0.015 mol), NaOH (4.8 g, 0.12 mol), and PEG400 (1.6 g, 0.004 mol), and the mixture was stirred in a 50-mL three-necked, round-bottomed flask equipped with a mechanical stirrer for 1 h at 80 °C. Then bromobenzene (10.47 ml, 0.1 mol) was added, and the mixture was vigorously stirred at 120 °C. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was washed three times with 50 ml of water. The organic phase was separated and dried over anhydrous magnesium sulfate. Then 12 g of phenyl alky thioether was collected. ^{1}H NMR ($CDCl_3$) δ 2.52 (s, H, OH), 3.08 (d, 2H, CH_2), 3.70 (d, 2H CH_2), 7.1–7.5 (m, 5H, ArH); IR (KBr, cm^{-1}) v: 3076, 3059, 3020, 3005, 2955, 2877, 1640, 1574, 1425, 1385, 1333, 1225, 1168, 1157, 1088, 935, 836, 821, 616.

Other Results

Compound **1** (Table 1). ^{1}H NMR ($CDCl_3$): δ: 7.0–7.2 (m, 10H, ArH); IR (KBr, cm^{-1}) ν: 3146, 3073, 3059, 3020, 3004, 1949, 1879, 1800, 1734, 1500, 1384, 1327, 1302, 1270, 1169, 1157, 1068, 1000, 955, 916, 908, 901, 838, 616, 457.

Compound **2** (Table 1). ^{1}H NMR ($CDCl_3$): δ: 2.35 (s 3H, CH_3), 6.86 (d, $J = 8.8$ Hz, 2H), 7.08 (d, $J = 8.8$ Hz, 2H), 7.06–7.20 (m, 5H, ArH).

Compound **6** (Table 1). ^{1}H NMR ($CDCl_3$): δ: 2.02 (s 3H, CH_3), 7.0–7.20 (m, 5H, ArH), 7.18 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 8.8$ Hz, 2H), 8.0 (brs 1H, NH).

Compound **8** (Table 1). ^{1}H NMR ($CDCl_3$): δ: 2.35 (s 3H, $3CH_3$), 6.47 (s 1H, 2CH), 7.0–7.20 (m, 5H, ArH).

Compound **9** (Table 1). ^{1}H NMR ($CDCl_3$): δ: 2.35 (s 3H, $2CH_3$), 6.67–6.76 (m, 3H, ArH), 7.0–7.2 (m, 5H, ArH).

Compound **2** (Table 2). ^{1}H NMR ($CDCl_3$): δ: 2.35 (s 3H, CH_3), 2.52 (s, H, OH), 3.06 (d, 2H, CH_2), 3.87 (d, 2H CH_2), 6.96–7.06 (m, 4H, ArH).

Compound **4** (Table 2). ^{1}H NMR ($CDCl_3$): δ: 2.52 (s, H, OH), 3.06 (d, 2H, CH_2), 3.87 (d, 2H CH_2), 3.82 (s 3H, CH_3), 6.67–7.07 (m, 4H, ArH).

Compound **8** (Table 2). ^{1}H NMR ($CDCl_3$): δ: 1.46–1.89 (m 2H, $5CH_2$), 2.48 (s 1H, CH), 2.50 (s, H, OH), 2.63 (d, 2H, CH_2), 3.90 (d, 2H CH_2).

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