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Copper oxide nanoparticles catalyzed synthesis of aryl sulfides via cascade reaction of aryl halides with thiourea

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ABSTRACT

Recyclable copper oxide nanoparticles catalyzed simple and highly efficient protocol for the synthesis of symmetrical aryl sulfides was developed by the cross-coupling of aromatic halides with inexpensive and commercially available thiourea which was used as an effective sulfur surrogate. The present cross-coupling protocol of thiourea, via cascade reaction with various substituted aryl halides, producing desired aryl sulfides, has an added advantage of avoiding foul-smelling thiols.

During the last few decades, aryl sulfides and their derivatives are found in numerous biological, pharmaceutical, and material science applications.[1] The classical methods for the synthesis of aryl sulfides require harsh reaction conditions, such as strong bases and elevated temperatures. Also the reduction of sulfones or sulfoxides involves strong reducing agents, such as DIBAL-H or $LiAlH_4$.[2] To overcome these difficulties, transition metal catalyzed coupling systems utilizing palladium,[3] nickel,[4] copper,[5] iron,[6] indium,[7] lanthanum,[8] and cobalt[9] have been developed. Even though several methodologies have been designed for the synthesis of aryl sulfides, most of these reactions include the coupling between thiols and an aryl halide. The direct use of volatile, hazardous, and foul-smelling thiols is still the main drawback, which leads to unavoidable environmental and safety problems. Hence it is desirable to find novel alternate catalytic protocols specially designed to avoid volatile and foul-smelling thiols to access such highly useful targets like aryl sulfides. Recently Zhou and co-workers reported an efficient C–S bond formation between potassium thiocyanate and aryl halides by a copper catalyst in water by using ligands.[10]

Recently, heterogeneous catalysts have attracted the attention of researchers due to their economic and industrial significance and published reports indicate that they scored over homogeneous catalysts. Among these, nanoscale heterogeneous catalysts are highly preferred as they offer high surface area and low-coordinated sites, which are responsible for the higher catalytic activity,[11] having the advantage of easy product purification and reusability of the catalyst.

In continuation of our interest in the field of cross-coupling reactions,[12] we report herein CuO nanoparticles catalyzed cascade reactions of thiourea and aryl halides forming symmetrical diphenyl sulfides under ligand-free conditions. However, to the best of our knowledge, this is the first report on the synthesis of symmetrical diaryl sulfides in the absence of any ligand or co-metal catalyst.

Initially, iodobenzene and thiourea were chosen as the model substrates to optimize the reaction conditions, such as various copper sources, catalysts, bases, solvents, and temperature under nitrogen atmosphere (Table 1, Scheme 1). First, several copper catalysts were screened and CuO nanoparticles were proven to be preeminent for this tandem reaction (Table 1, entry 2). The effect of solvents was also investigated and it was observed that the desired product was not obtained in the solvents toluene and THF (Table 1, entries 7 and 12). However, the reaction was highly effective with polar aprotic solvents such as DMSO and DMF (Table 1, entries 2, 8). Among various bases screened (e.g., KOH, Cs_2CO_3, Na_2CO_3, NaOH), Cs_2CO_3 was most effective in DMSO solvent (Table 1, entry 2). The control experiment confirmed that the reaction did not occur in the absence of the catalyst (Table 1, entry 10) as well as the base (Table 1, entry 11). The reaction when conducted at room temperature and 50 °C, the yields observed were very low (Table 1, entries 5 and 6). The ideal temperature for the reaction was found to be 110 °C.

While expanding the scope of the reaction, the cross-coupling of various substituted thioureas with different aryl halides was also

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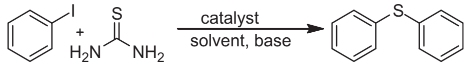
Table 1
Screening of copper-catalyzed synthesis of aryl sulfides[a]



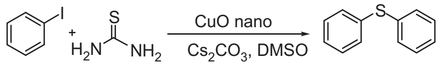
Entry	Copper source	Base	Solvent	Temp (°C)	Yield[b] (%)
1	Nano CuO	KOH	DMSO	110	20
2	Nano CuO	Cs_2CO_3	DMSO	110	97
3	Nano CuO	Na_2CO_3	DMSO	110	61
4	Nano CuO	NaOH	DMSO	110	Trace
5	Nano CuO	Cs_2CO_3	DMSO	50	49
6	Nano CuO	Cs_2CO_3	DMSO	rt	26
7	Nano CuO	Cs_2CO_3	Toluene	110	0
8	Nano CuO	Cs_2CO_3	DMF	110	68
9	Nano CuO	KOH	Toluene	110	0
10	--	KOH	DMSO	110	0[c]
11	Nano CuO	--	DMSO	110	0[d]
12	Nano CuO	Cs_2CO_3	THF	110	0
13	CuO	Cs_2CO_3	DMSO	110	60
14	Cu_2O	Cs_2CO_3	DMSO	110	67

[a] Reaction conditions: iodo benzene (2.0 mmol), thiourea (1.2 mmol), catalyst (5.0 mol %), base (2.0 equiv), solvent (2.0 mL), 15 h.

[b] Isolated yield.

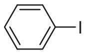
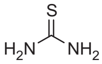
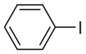
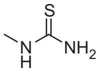
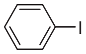
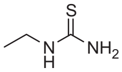
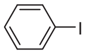
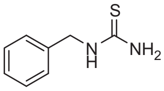
[c] In the absence of catalyst.

[d] In the absence of base.



Scheme 1. CuO nanoparticles catalyzed synthesis of aryl sulfides.

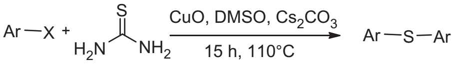
Table 2
Effect of different substituted thiourea on the synthesis of aryl sulfides[a]

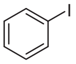
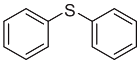
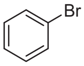
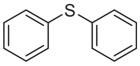
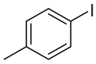
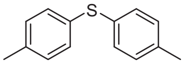
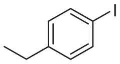
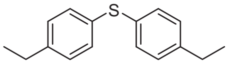
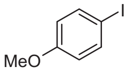
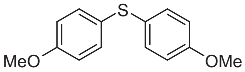
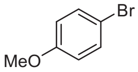
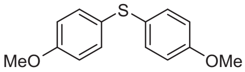
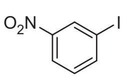
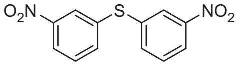
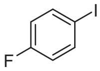
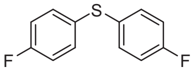
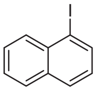
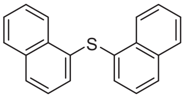
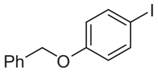
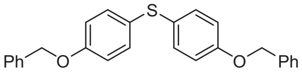
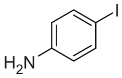
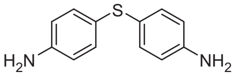
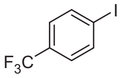
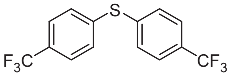
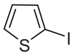
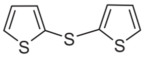
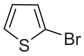
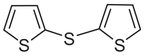
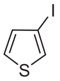
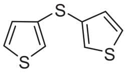
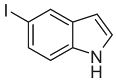
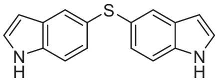
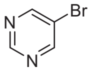
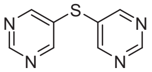
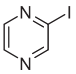
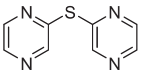
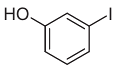
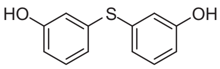
Entry	Aryl halide	Thioureas	Yield[b] (%)
1			97
2			93
3			89
4			86
5			86
6			81
7			81
8			75

[a] Reaction conditions: iodo benzene (2.0 mmol), thioureas (1.2 mmol), nano CuO (5.0 mol %), Cs_2CO_3 (2.0 equiv), DMSO (2.0 mL), 110 °C, 15 h.

[b] Isolated yield.

Table 3
C–S cross-coupling of aryl halides with thiourea[a]



Entry	Aryl halide	Product	Yield[b] (%)
1			97
2			70[c]
3			93
4			91
5			96
6			73[c]
7			87
8			89
9			88
10			90
11			85
12			82
13			83
14			59[c]
15			79
16			75
17			60[c]
18			78
19			79

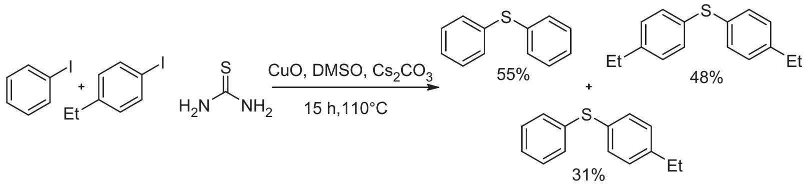
[a] Reaction conditions: aryl halides (2.0 mmol), thiourea (1.2 mmol), nano CuO (5.0 mol %), Cs_2CO_3 (2.0 equiv), DMSO (2.0 mL), 110 °C, 15 h, under a nitrogen atmosphere.

[b] Isolated yield.

[c] After 24 h.

investigated under optimized conditions (Table 2), providing the corresponding diaryl sulfides in excellent yields. Among these, thiourea appeared to be the best choice because of commercial availability and economic affordability for the synthesis of aryl sulfides (Table 2, entry 1).

In general, all the reactions were very clean, and the diaryl sulfides were obtained in high yields (Table 3).[13] This protocol efficiently cross coupled iodobenzenes having electron donating groups (e.g., Me, Et, and OMe) with thiourea to produce the corre-



Scheme 2. CuO nanoparticles catalyzed synthesis of aryl unsymmetrical and symmetrical sulfides.

Table 4
Recycling of CuO nanoparticles

Recycles	Yield (%)	Catalyst recovery[a] (%)
1	97	96
2	95	93
3	91	91
4	89	88

[a] Reaction conditions: aryl halides (2.0 mmol), thiourea (1.2 mmol), nano CuO (5.0 mol %), Cs_2CO_3 (2.0 equiv), DMSO (2.0 mL), 110 °C, 15 h, under a nitrogen atmosphere.

sponding aryl sulfides in excellent yields (Table 3, entries 3–5), whereas in the presence of electron withdrawing group (NO_2) a slight decrease in the yield of the diaryl sulfide (Table 3, entry 7) was observed. In the case of aryl iodide with a free amino group the reaction proceeded without the need of a protecting group and the desired product was obtained in good yields (Table 3, entry 11). It was observed that iodobenzene was more reactive. Consequently, cross-coupling reactions with fluoro substituted aryl iodides exhibited an interesting chemo selectivity proceeding exclusively at the iodo group (Table 3, entry 8). Utilizing optimized conditions, the coupling process was investigated with several hetero aromatic iodides resulting in the corresponding diaryl sulfides in impressive yields (Table 3, entries 13, 15, 16, and 18). In the case of the reaction of aryl bromides and hetero aromatic bromides with thiourea the process required longer reaction time to obtain reasonable yield of diaryl sulfides (Table 3, entries 2, 6, 14, and 17).

This protocol was also applied for the cross-coupling reaction between two different aryl halides by using iodobenzene and 4-ethyliodobenzene and the corresponding symmetric products were obtained in high yields when compared to unsymmetrical sulfide (Scheme 2).

After each cycle, the reaction mixture was allowed to cool, and the catalyst was recovered by simple centrifugation, washing with ethyl acetate, acetone and then drying in vacuo. The recovered CuO was used directly in the next cycle. The catalyst was found to be recyclable without the loss of catalytic activity up to four cycles (Table 4).

In conclusion, we have developed a recyclable CuO nanoparticles catalyzed synthesis of symmetrical diaryl sulfides under ligand-free conditions in the absence of any additive. The reaction employs a very simple catalyst system, having functional group tolerance, and resulting in good to excellent yields. The advantages of the novel and facile protocol are precluding volatile, foul smelling, and toxic thiols as well as utilizing economically affordable, recyclable and air stable catalyst under ligand-free conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.070.

References and notes

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13. *General procedure for the synthesis of aryl sulfides:*
To a stirred solution of aryl halides (2.0 mmol) and thiourea (1.2 equiv) in dry DMSO (2.0 mL) at rt was added nano CuO (5.0 mol %) followed by Cs_2CO_3 (2.0 equiv) and heated at 110 °C for 15 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool, and a 1:1 mixture of ethyl acetate/water (20 mL) was added. The combined organic extracts were dried with anhydrous Na_2SO_4. The solvent and volatiles were completely removed under vacuum to give the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to afford the corresponding coupling product in excellent yields.
Recycling of the catalyst:

after the reaction was complete, the reaction mixture was allowed to cool, and a 1:1 mixture of ethyl acetate/water (2.0 mL) was added and CuO was removed by centrifugation. After each cycle, the catalyst was recovered by simple centrifugation, washing with deionized water and ethyl acetate and then drying in vacuo. The recovered nano CuO was used directly in the next cycle.

Data of representative examples:

*Dip-tolylsulfane (*Table 3, *entry 3)*: yellow oil;^{1}H NMR (200 MHz, CDCl$_3$, TMS): δ = 7.21 (d, 4H, *J* = 8.0 Hz), 7.06 (d, 4H, *J* = 8.0 Hz), 2.32 (s, 6H); ^{13}C NMR (50 MHz, CDCl$_3$, TMS): δ = 136.7, 132.81, 131.0, 129.8, 96.1.

*Bis(4-ethylphenyl)sulfane (*Table 3, *entry 4)*: colorless oil; ^{1}HNMR (300 MHz, CDCl$_3$, TMS): δ = 7.21(d, 4H, *J* = 7.8 Hz), 7.07 (d, 4H, *J* = 7.8 Hz), 2.62–2.52 (m, 4H), 1.26 (t, 6H, *J* = 7.8 Hz);^{13}C NMR (75 MHz, CDCl$_3$, TMS): δ = 143.1, 132.7, 131.0, 128.6, 28.3, 15.4; mass (EI): *m*/*z* 242 [M]$^+$; Anal. calcd for: ($C_{16}H_{18}S$) C, 79.29; H, 7.49; S, 13.23; found: C,79.22; H,7.42; S,13.19.

Bis(3-nitrophenyl)sulfane (Table 3, *entry 7)*: pale yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ = 8.19–8.15 (m, 4H), 7.65 (d, 2H, *J* = 8.3 Hz), 7.55 (t, 2H, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, CDCl$_3$, TMS): δ = 148.8, 136.7, 130.7, 125.6, 122.7; mass (EI): *m*/*z* 276 [M]$^+$; Anal. calcd for: ($C_{12}H_8N_2O_4S$) C, 52.17; H, 2.92; S, 11.61; N, 10.14; found: C, 52.12; H, 2.86; S, 11.55; N, 10.9.

*4,4′-Thiodianiline (*Table 3, *entry 11)*: brown solid; mp 104–105 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ = 7.10 (d, 4H, *J* = 8.68 Hz), 6.52 (d, 4H, *J* = 8.68 Hz), 3.51 (br s, 4H); ^{13}C NMR (75 MHz, CDCl$_3$, TMS): δ = 145.5, 133.8, 132.6, 124.8, 115.6; mass (EI): *m*/*z* 216 [M]$^+$; Anal. calcd for: ($C_{12}H_{12}N_2S$) C, 66.63; H, 5.59; N, 12.95; S, 14.82; Found: C, 66.61; H, 5.58; N, 12.92; S, 14.81.

*Dithiophen-3-ylsulfane (*Table 3, *entry 15)*: yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ = 7.31–7.25 (m, 2H), 7.17–7.11(m, 2H), 6.96–6.94 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, TMS): δ = 129.6, 126.4, 124.7; mass (EI): *m*/*z* 197 [M]$^+$; Anal. calcd for: ($C_8H_6S_3$) C, 48.45; H, 3.05; S, 48.50; found: C,48.42; H,3.02; S,48.47.

Dipyrimidin-5-ylsulfane (Table 3, *entry 17)*: colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ = 9.15 (s, 2H), 8.74(s, 4H); ^{13}C NMR (75 MHz, CDCl$_3$, TMS): δ = 158.6, 157.7, 129.8; mass (EI): *m*/*z* 190 [M]$^+$; Anal. calcd for: ($C_8H_6N_4S$) C, 50.51; H, 3.18; N, 29.45; S, 16.86; found: C, 50.45; H, 3.13; N, 29.41; S, 16.81.