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Cu-Catalyzed One-Pot Synthesis of Unsymmetrical Diaryl Thioethers by Coupling of Aryl Halides Using a Thiol Precursor†

D. J. C. Prasad and Govindasamy Sekar*

Department of Chemistry, Indian Institute of Technology Madras, Chennai, Tamil Nadu-600 036, India

gsekar@iitm.ac.in

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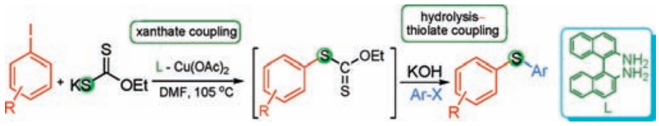
ABSTRACT



An efficient Cu-catalyzed one-pot approach for the synthesis of unsymmetrical diaryl thioethers using potassium ethyl xanthogenate as a thiol surrogate is developed. This new protocol avoids usage of intricate thiols and makes use of its easily available xanthate as a precursor, and thiol will be generated *in situ* to prepare the diaryl thioethers through a Cu-catalyzed double arylation. This strategy was further successfully utilized for the synthesis of symmetrical diaryl thioethers, aryl alkyl thioethers, and benzothiazoles.

Sulfur-containing organic molecules are a very important motif; particularly, aryl sulfides and their derivatives are imperative molecules having biological, pharmaceutical, and material interest (Figure 1).[1,2] The traditional methods for the synthesis of aryl sulfides involve condensation of arenethiols with aryl halides,[3] base-mediated nucleophilic substitution of activated aryl halides with thiols,[4] and treatment of aryl lithium or Grignard reagents with sulfurated electrophiles.[5] However, these methods often require harsh reaction conditions which are not suitable for molecules containing sensitive functional groups.[6] The development of transition-metal-catalyzed coupling of thiols with aryl halides has overcome these difficulties to a great extent. A number of methods have been developed for the synthesis of aryl sulfides using Pd,[7] Cu,[8] Fe,[9] and other metal

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† This paper is dedicated to Prof. M. Periasamy.

(1) (a) Jones, D. N. In *Comprehensive Organic Chemistry*; Barton, D. H.; Ollis, D. W., Eds.; Pergamon: New York, 1979; Vol. 3. (b) Rayner, C. M. *Contemp. Org. Synth.* **1996**, *3*, 499. (c) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (e) Marcincal-Lefebvre, A.; Gesquiere, J. C.; Lemer, C. *J. Med. Chem.* **1981**, *24*, 889. (f) Liu, G.; Link, J. T.; Pei, Z.; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K. C.; Okasinski, G. F.; Von Geldern, T. W.; Ormes, M.; Fowler, K.; Gallatin, M. *J. Med. Chem.* **2000**, *43*, 4025. (g) Aiello, S.; Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. *J. Med. Chem.* **2008**, *51*, 5135. (h) Dumas, J.; Brittelli, D.; Chen, J.; Dixon, B.; Hatoum-Mokdad, H.; Konig, G.; Sibley, R.; Witowsky, J.; Wong, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2531. (i) Moracci, F. M.; Liberatore, F.; Micheletti, F.; Liso, G.; Cardellini, M. *J. Med. Chem.* **1974**, *17*, 463.

(2) (a) Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbenhusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979. (b) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Okasinski, G. F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202. (c) Martino, G. D.; Edler, M. C.; Regina, G. L.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947.

(3) Bierbeek, A. V.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 6283.

(4) Campbell, J. R. *J. Org. Chem.* **1964**, *29*, 1830.

(5) Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004**, *69*, 3236.

(6) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(7) For selected Pd-catalyzed S-arylation of thiols, see: (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (b) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397. (c) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (d) Fernandez-Rodroeguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (e) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (f) Fernandez-Rodroeguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem.—Eur. J.* **2006**, *12*, 7782. (g) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069.

10.1021/ol103041s

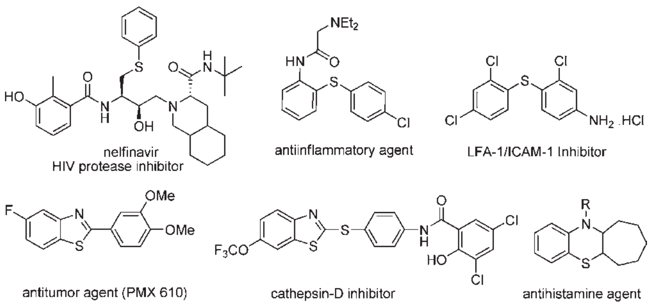


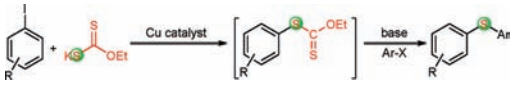
Figure 1. Some of the sulfur-containing biologically important molecules.

catalysts.[10] But, these metal-catalyzed reactions require readily oxidizable, foul-smelling, expensive, and less available arenethiols. In addition, there are only a very few methods available in the literature for preparation of aromatic thiols.[11]

Recently, Hartwig reported the $Pd(OAc)_2$-CyPF-^{t}Bu complex as a catalyst for the synthesis of diaryl thioethers from TIPS-SH and two different aryl halides, which is a striking improvement over the current methods.[12] Firouzbadi et al. used thiourea as a thiol precursor for the one-pot synthesis of aryl alkyl thioethers using copper as a catalyst.[13] However, this protocol works only for alkyl aryl thioether synthesis, as this method generates only alkyl thiolates.

As part of our continuous effort toward copper-catalyzed $C_{(aryl)}$–heteroatom bond formation and its application in important heterocycle synthesis,[14] herein, for the first time, we report a new one-pot synthesis of unsymmetrical diaryl thioethers from two different aryl halides and potassium ethyl xanthogenate as a thiol precursor.[15] In this one-pot synthesis, initially a copper-catalyzed $C_{(aryl)}$–S bond forming coupling reaction takes place between an aryl halide and potassium ethyl xanthogenate. Next, aryl xanthate hydrolysis takes place yielding an arene thiolate, which in turn undergoes a second $C_{(aryl)}$–S coupling reaction with another aryl halide to produce diaryl thioethers (Scheme 1).

Scheme 1. One-Pot Synthesis of Unsymmetrical Aryl Thioethers from Two Aryl Halides and Xanthate



We started our studies by reacting *p*-iodoanisole **1** with potassium ethyl xanthogenate **2** in the presence of 20 mol % CuI and 20 mol % ethylene glycol **L1** as a ligand at 105 °C. After 28 h, KOH and PhI were added to the reaction mixture and the resulting mixture was further heated for 20 h which afforded 46% of an unsymmetric diaryl thioether, (4-methoxyphenyl)(phenyl)sulfane **5**. In this reaction, first, there is a copper-catalyzed Ullmann type $C_{(aryl)}$–S bond formation between *p*-iodoanisole **1** and potassium ethyl xanthogenate **2** (xanthate coupling) to give *O*-ethyl *S*-4-methoxyphenyl carbonodithioate **3**.[16] Then, this carbonodithioate **3** was hydrolyzed by KOH to give corresponding thiolate **4**, and this *in situ* generated thiolate reacted with iodobenzene in the presence of the same copper catalyst to form a second $C_{(aryl)}$–S bond (thiolate coupling) to give the product unsymmetrical diaryl thioether **5** (Scheme 2).

It is very important to mention that this new one-pot protocol avoids usage of the above-mentioned intricate thiols and makes use of easily available xanthate **2** as a precursor which is doubly arylated through Cu-catalyzed $C_{(aryl)}$–S bond forming coupling reactions to give the diaryl thioether.

To increase the efficiency of the one-pot synthesis of diaryl thioethers, several ligands (**L2**–**L11**) were screened with CuI, and the results are summarized in Figure 2. A maximum yield of 72% thioether **5** was obtained in a shorter reaction time when we replaced the ligand **L1** with BINAM **L6**. Then the reaction was carried out with different copper salts to find out the efficient copper catalyst for this one-pot synthesis where the BINAM-$Cu(OAc)_2$ complex as a catalyst provided a maximum of 94% isolated yield for the diaryl thioether **5** (Table 1, entry 6). In this reaction, 82% of the ligand BINAM was recovered after the reaction which can be reused. Solvent study shows that nonpolar solvents such as toluene and xylene failed to provide any product, which may be due to the poor solubility of xanthate in nonpolar solvents (entries 12 and 13). DMF as a solvent gave the best result. Though a wide range of bases promoted the one-pot reaction, KOH turned out to be the most efficient

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(8) For selected copper-catalyzed S-arylation of thiols, see: (a) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (c) Chen, Y.-J.; Chen, H. H. *Org. Lett.* **2006**, *8*, 5609. (d) Rout, L.; Sen, T, K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583. (e) Lv, X .; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (f) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.—Eur. J.* **2007**, *13*, 5100. (g) Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199. (h) Sperotto, E.; Klink, G. P. M. V.; de Vries, J. G.; Koten, G. V. *J. Org. Chem.* **2008**, *73*, 5625.

(9) (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (b) Wu, J. R.; Lin, C. H.; Lee, C. F. *Chem. Commun.* **2009**, 4450.

(10) (a) Wong, Y. C.; Jayanth, T. T.; Cheng, C. H. *Org. Lett.* **2006**, *8*, 5613. (b) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697.

(11) (a) Sawada, N.; Itoh, T.; Yasuda, N. *Tetrahedron Lett.* **2006**, *47*, 6595. (b) Lloyd-Jones, G. C.; Moseley, J. D.; Renny, J. S. *Synthesis* **2008**, 661. (c) Jiang, Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett.* **2009**, *11*, 5250.

(12) Fernandez-Rodroeguez, M. A.; Hartwig, J. F. *Chem.—Eur. J.* **2010**, *16*, 2355.

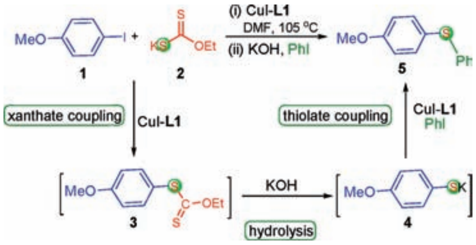
(13) Firouzabadi, H.; Iranpoor, N.; Gholinejad, M. *Adv. Synth. Catal.* **2010**, *352*, 119.

(14) (a) Naidu, A. B.; Jaseer, E. A.; Sekar, G. *J. Org. Chem.* **2009**, *74*, 3675. (b) Rao, R. K.; Naidu, A. B.; Sekar, G. *Org. Lett.* **2009**, *11*, 1923. (c) Prasad, D. J. C.; Sekar, G. *Org. Biomol. Chem.* **2009**, *7*, 5091. (d) Prasad, D. J. C.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 1411. (e) Prasad, D. J. C.; Sekar, G. *Synthesis* **2010**, 79. (f) Thakur, K. G.; Jaseer, E. A.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 2865. (g) Jaseer, E. A.; Prasad, D. J. C.; Dandapat, A.; Sekar, G. *Tetrahedron Lett.* **2010**, *51*, 5009.

(15) To the best of our knowledge, this is the first report for the use of potassium ethyl xanthogenate as a thiol surrogate in metal-catalyzed arylations, which is a cheaper and comercially available reagent.

(16) *O*-Ethyl S-4-methoxyphenyl carbonodithioate **3** was isolated with good yield.

Scheme 2. Double Arylation of Sulfur Using Cu Catalyst



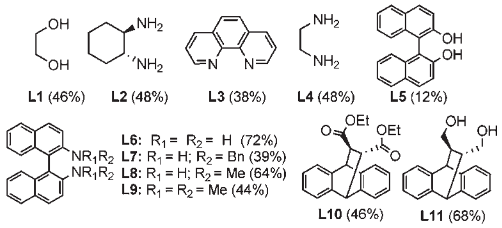
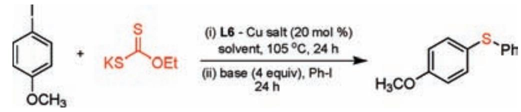


Figure 2. Ligands screened for the Cu-catalyzed one-pot synthesis of a diaryl thioether.

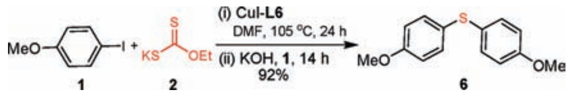
Table 1. Effect of Cu Salts, Solvents, and Bases on One-Pot Synthesis of Diaryl Thioether



entry	copper salt	solvent	base	yield (%)[a]
1	CuI	DMF	KOH	72
2	CuBr	DMF	KOH	56
3	CuCl	DMF	KOH	57
4	$Cu(OTf)_2$	DMF	KOH	78
5	$CuCl_2$	DMF	KOH	51
6	$Cu(OAc)_2$	DMF	KOH	94[b]
7	Cu_2O	DMF	KOH	42
8	$CuSO_4$	DMF	KOH	74
9	$Cu(OAc)_2$	DMSO	KOH	41
10	$Cu(OAc)_2$	dioxane	KOH	12[c]
11	$Cu(OAc)_2$	acetonitrile	KOH	32[c]
12	$Cu(OAc)_2$	toluene	KOH	00
13	$Cu(OAc)_2$	xylene	KOH	00
14	$Cu(OAc)_2$	DMF	NaOH	78
15	$Cu(OAc)_2$	DMF	NaO^tBu	56
16	$Cu(OAc)_2$	DMF	K_2CO_3	68
17	$Cu(OAc)_2$	DMF	Cs_2CO_3	84

[a] Isolated yield. [b] 82% Of the ligand BINAM was recovered after the reaction which can be reused. [c] Reaction was carried out at boiling point of the solvent.

Scheme 3. Synthesis of Cu-Catalyzed Symmetrical Diaryl Thioether



base. The reaction provided only 35% diaryl thioether **5** when only $Cu(OAc)_2$ was used as a catalyst without a ligand. Importantly, not even a trace amount of thioether formed when the reaction was carried out without **L6**-$Cu(OAc)_2$. Using this protocol, symmetrical diaryl thioether **6** could be obtained in excellent yield (Scheme 3). Since, the syntheses of unsymmetrical thioethers are more advantageous than symmetrical thioethers, we focused our interest on the synthesis of unsymmetrical thioethers.

To probe the scope of copper-catalyzed *in situ* generation of thiolates and its application in a one-pot synthesis of diaryl thioethers, the methodology was examined with several types of aryl iodides, and the results are summarized in Table 2. For this diaryl thioether synthesis, all types of aryl iodides, particularly, electron-releasing, electron-withdrawing, and sterically hindered *ortho*-substituted aryl iodides are well tolerated. The xanthate coupling is favored when substitution in an aryl iodide is more electron-withdrawing in nature (entries 10 vs 15, 17), but the thiolate coupling involves a slightly longer reaction time when the thiolate has an electron-withdrawing substituent (entries 10 vs 17). The thiolate coupling is faster when the second aryl iodide contains an electron-withdrawing group (entries 8 and 9). Sterically hindered *ortho*-substituted aryl iodides also gave good yields for this diaryl thioether synthesis. Importantly, 60% of the isolated yield was obtained even both of the aryl iodides are *ortho*-substituted (entry 12). Heteroatom-containing aryl iodides also provided very good results for the diaryl thioether synthesis (entries 5 and 13). In this one-pot process, the coupling reaction selectively takes place with the iodo group of *o*-bromoiodobenzene (entries 4 and 14). A wide range of functional groups including an amino group are well tolerated. Less reactive aryl bromides can be utilized for this diaryl thioether synthesis particularly when they have electron-withdrawing substituent's (entries 18–21). A heteroatom-containing aryl bromide also provided a 62% isolated yield for the corresponding diaryl sulfide.

This new synthetic procedure was successfully utilized for the synthesis of an aryl alkyl thioether by coupling the appropriate aryl iodides and alkyl halides using xanthate **2** as a thiol precursor (Table 3). In this protocol, the overall reaction takes a much shorter time for the final product formation with 10 mol % catalyst, as the second C–S bond formation is a simple nucleophilic substitution.

After completion of the synthesis of various diaryl and aryl alkyl thioethers in a one-pot process through *in situ* generation of an aryl thiolate using xanthate **2** as a thiol precursor, this new methodology was successfully utilized in the synthesis of biologically important benzothiazoles[17]

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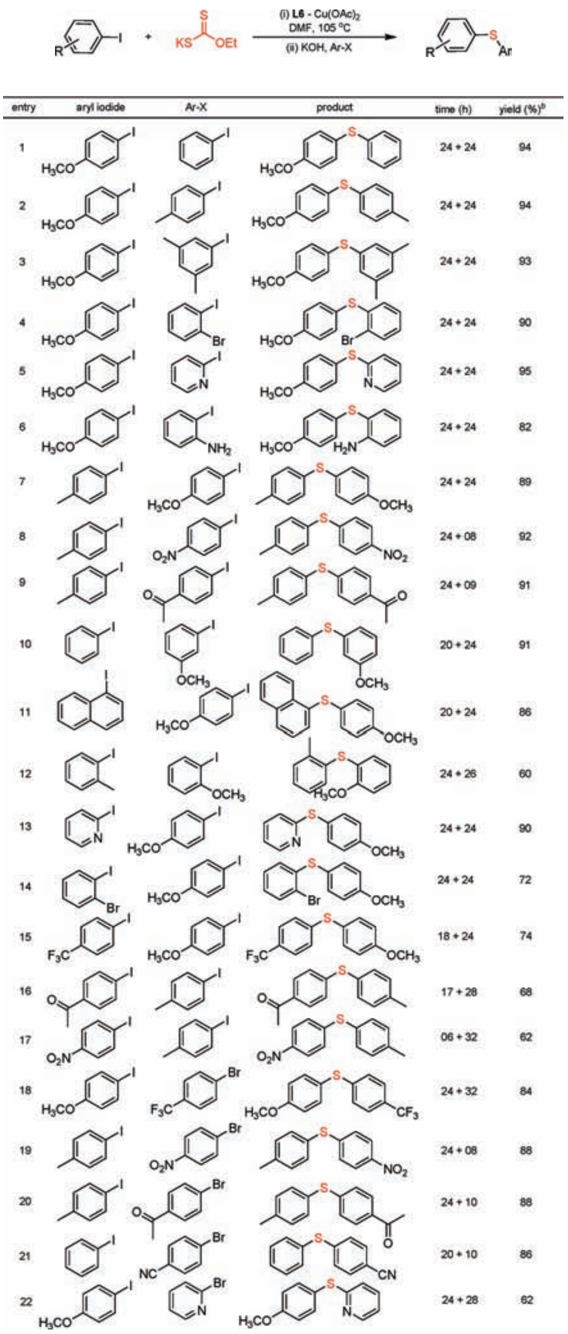
(17) (a) Itoh, T.; Mase, T. *Org. Lett.* **2007**, *9*, 3687. (b) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222.

Table 2. One-Pot Synthesis of Unsymmetrical Diaryl Sulfides from Two Aryl Halides and Xanthate As Thiol Precursor[a]

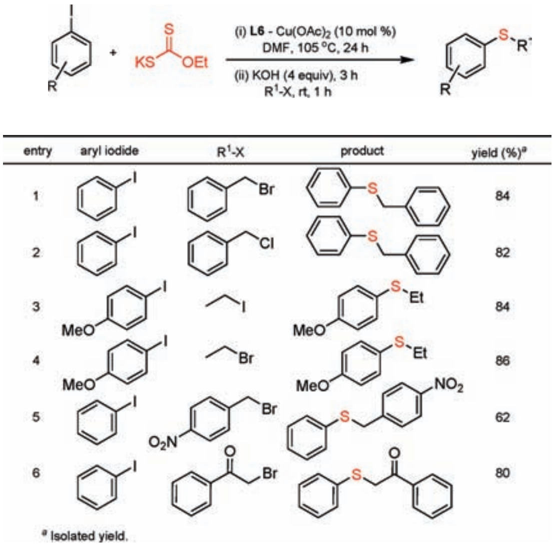


entry	time (h)	yield (%)[b]
1	24 + 24	94
2	24 + 24	94
3	24 + 24	93
4	24 + 24	90
5	24 + 24	95
6	24 + 24	82
7	24 + 24	89
8	24 + 08	92
9	24 + 09	91
10	20 + 24	91
11	20 + 24	86
12	24 + 26	60
13	24 + 24	90
14	24 + 24	72
15	18 + 24	74
16	17 + 28	68
17	06 + 32	62
18	24 + 32	84
19	24 + 08	88
20	24 + 10	88
21	20 + 10	86
22	24 + 28	62

[a] Reaction conditions: 0.75 mmol of aryl iodide, 0.75 mmol of potassium ethyl xanthogenate, 0.10 mmol of $Cu(OAc)_2$, 0.10 mmol of **L6**, 2.0 mmol of KOH, and 0.50 mmol of Ar−X at 105 °C in 3 mL of DMF. [b] Isolated yield.

from 2-iodoanilides and xanthate (Scheme 4). 2-(4-Methoxyphenyl)benzothiazole **7** was obtained from the copper-catalyzed one-pot reaction of *N*-(2-iodophenyl)-4-methoxybenzamide and potassium ethyl xanthogenate in the presence of 10 mol % of $Cu(OAc)_2$ at 80 °C in DMF in 15 h. It is very important to mention that benzothiazole **9** containing an aliphatic tertiary butyl group at the 2-position was also obtained in good yield.

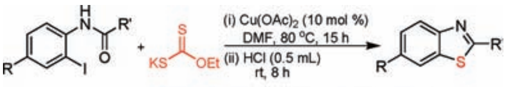
Table 3. Cu-Catalyzed One-Pot Synthesis of Aryl Alkyl Thioether Using Thiol Precursor



entry	yield (%)[a]
1	84
2	82
3	84
4	86
5	62
6	80

[a] Isolated yield.

Scheme 4. Cu-Catalyzed One-Pot Synthesis of Benzothiazoles Using Thiol Precursor



R = H; R' = -C_6H_4-*p*-OMe: **7** (75% yield)
R = CH_3; R' = -C_6H_5: **8** (77% yield)
R = H; R' = -^{t}Bu: **9** (72% yield)

In conclusion, we have developed a new Cu-catalyzed one-pot approach for the synthesis of diaryl thioethers using potassium ethyl xanthogenate as a thiol surrogate. In this methodology, limitedly available, foul-smelling, and unstable arene thiols are *in situ* generated from easily available aryl iodides and potassium ethyl xanthogenate through a $C_{(aryl)}{-}S$ bond forming coupling reaction. The readily formed aryl thiolate easily reacted with a second aryl halide to provide unsymmetrical diaryl thioethers through a second $C_{(aryl)}{-}S$ bond forming coupling reaction. This strategy was successfully utilized for the synthesis of symmetrical diaryl thioethers, aryl alkyl thioethers, and benzothiazoles. We are currently pursuing further application of this one-pot procedure for the synthesis of several classes of sulfur-containing biologically important molecules.

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Supporting Information Available. Experimental procedures, characterization data, ^1H NMR and ^{13}C NMR spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.