Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

L -Proline-Promoted CuI-Catalyzed C-S Bond Formation between Aryl Iodides and Thiols

Hui Zhang [a] , Weiguo Cao [a b] & Dawei Ma [c]

[a] Department of Chemistry, Shanghai University, Shanghai, China

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai, China

[c] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai, China

Version of record first published: 25 Jul 2007.

To cite this article: Hui Zhang , Weiguo Cao & Dawei Ma (2007): L -Proline-Promoted CuI-Catalyzed C-S Bond Formation between Aryl Iodides and Thiols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:1, 25-35

To link to this article: http://dx.doi.org/10.1080/00397910600977533

Synthetic Communications®, 37: 25–35, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600977533

L-Proline-Promoted CuI-Catalyzed C-S Bond Formation between Aryl Iodides and Thiols

Hui Zhang
Department of Chemistry, Shanghai University, Shanghai, China

Weiguo Cao
Department of Chemistry, Shanghai University, Shanghai, China and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai, China

Dawei Ma
State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai, China

Abstract: An improved, mild procedure for the CuI-catalyzed coupling reactions of aryl iodides with aliphatic and aromatic thiols, using *L*-proline as the ligand, is reported. This procedure is noteworthy given its high generality and exceptional level of functional group toleration.

Keywords: aryl sulfide, *L*-proline, copper iodide, cross-coupling

INTRODUCTION

Methods for the formation of aryl–sulfur bonds are indispensable tools in synthetic chemistry. Their importance stems from the prevalence of aryl–sulfur bonds in many molecules that are of biological, pharmaceutical, and material interest.[1] However, only a few studies have been reported so far

Received in USA May 12, 2006
Address correspondence to Hui Zhang, Department of Chemistry, Shanghai University, Shanghai 200444, China. E-mail: yehao7171@163.com

for the formation of aryl–sulfur bonds using either Pd or Ni catalysts.[2,3] Alternatively, one can use Cu catalysts to mediate the C-S bond formation. This approach is attractive from an industrial perspective because Cu is much less expensive and toxic than Pd and Ni.[4]

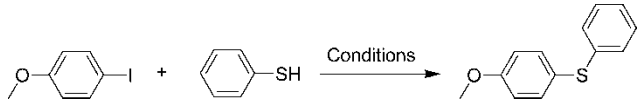
The traditional Cu-mediated coupling between thiols and aryl halides requires the use of copper salts in greater than stoichiometric amounts, polar solvents such as hexamethyl phosphoric acid triamide (HMPA), and high temperatures (around 200°C).[5] Recently, Bates et al. reported an improved protocol for the coupling between aryl iodides and thiols using 10 mol% CuI and 10 mol% neocuproine, with NaO^{t}Bu as the base, in toluene at 110°C.[6] Kong and Buchwald also reported an efficient Cu-catalyzed C-S coupling reaction between aryl iodides and thiols using 5 mol% CuI and 2 equivalents of $HOCH_2CH_2OH$ as ligand.[7] Wu and He then reported that microwave heating could enhance the CuI-catalyzed C-S couplings.[8] Naus et al. successfully utilized the CuI catalysts for the arylation of 1-thiosugars.[9]

Our recent results on amino acid–promoted CuI-catalyzed C-N and C-O coupling chemistry[10] suggest to us that by choosing a suitable amino acid as ligand, our catalytic system might be used for C-S couplings and would be tolerant of a wide variety of functional groups. At the same time, Deng et al. reported their protocol for the coupling reaction of aryl iodides with thiols, using 20 mol% *N*-methylglycine, 5 mol% CuI, and 2.5 equiv. KOH in dioxane at 100–120°C.[11] However, the scope of functional groups is somewhat limited by their use of a strong base and high temperature (>100°C). Thus, we describe our method as an improvement on their protocol. Under our mild conditions (20 mol% L-proline, 10 mol% CuI, 2 equiv. K_2CO_3 or K_3PO_4 as the mild base, in 1,2-dimethoxy ethane (DME) or DMF at 80°C), various functionalized aryl iodides coupled smoothly with thiols to give satisfying results.

RESULTS AND DISCUSSION

In the first stage of the study, 4-methoxy-1-iodobenzene and thiophenol were used as the prototypical substrate combination for preliminary optimization of the reaction conditions (Table 1). Copper(I) complexes generally gave superior results compared to copper(II) sources in terms of conversion and yield of the desired product. A variety of these were efficient, but we chose to focus on the use of CuI because of its stability in air. Among different solvents, we found that DME was the solvent of the choice (Table 1, entry 2). Both K_2CO_3 and K_3PO_4 were found to be effective bases for this coupling reaction, but K_2CO_3 was better because of its higher yield of the product. Compared to *N,N*-dimethylglycine, L-proline was the better ligand (Table 1, entries 5, 6). Also, by lifting the temperature from 70°C to 80°C and increasing the reaction time to 40 h, almost all the starting material was converted into the desired product (Table 1, entry 8).

Table 1. CuI-catalyzed coupling reaction of thiophenol and 4-methoxy-1-iodobenzene under various conditions[a]



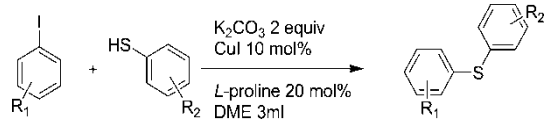
Entry	Solvent	Base	Ligand	T (°C)	Time (h)	Yield (%)[b]
1	DMF	K_2CO_3	*L*-proline	70	24	48
2	DME	K_2CO_3	*L*-proline	70	24	67
3	Dioxane	K_2CO_3	*L*-proline	70	24	40
4	Isopropanol	K_2CO_3	*L*-proline	70	24	57
5	DME	K_3PO_4	*L*-proline	70	24	55
6	DME	K_3PO_4	*N,N*-dimethylglycine	70	24	28
7	DME	Cs_2CO_3	*L*-proline	70	24	15
8	DME	K_2CO_3	*L*-proline	80	40	99

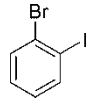
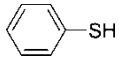
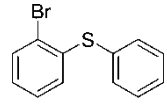
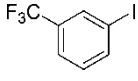
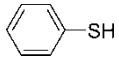
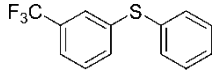
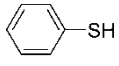
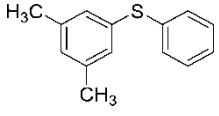
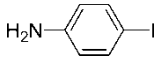
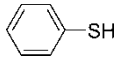
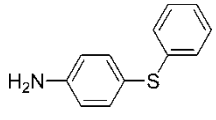
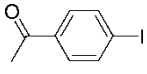
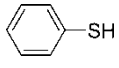
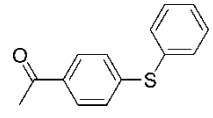
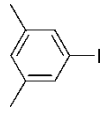
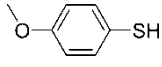
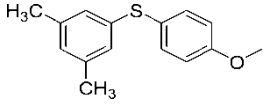
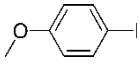
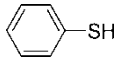
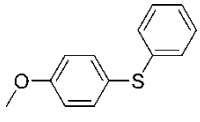
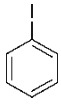
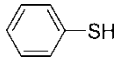
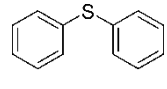
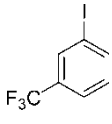
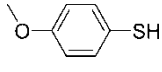
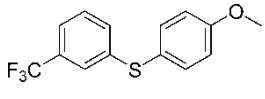
[a]General conditions: CuI 10 mol%, 20 mol% ligand, 3 ml solvent, 2 mmol aryl iodide, 1.2 equiv. PhSH, 2 equiv. base, under high purity nitrogen.
[b]Isolated yield.

Thus, the optimized reaction conditions were 10 mol% CuI, 2 equiv. K_2CO_3, and 20 mol% *L*-proline in dry DME at 80°C under high-purity nitrogen. In the first part of this study, these reaction conditions were applied to the coupling of various functionalized aryl iodides and thiophenol counterparts (Table 2). As can be seen, the reaction proceeds well with aryl iodides carrying either electron-donating (e.g., OCH_3) or electron-withdrawing groups (e.g., CF_3). The yields are mostly excellent. However, the bromo group in *o*-bromoiodobenzene does not show any significant coupling (Table 2, entry1); therefore, the present condition is not sufficient for the C-S coupling reactions using aryl bromides as reactants. Morever, when this procedure was applied to the coupling reactions of aryl iodides with alkyl thiols, the coupling products were obtained in low yields (Table 2, entry 11).

Because alkyl thiol is generally less ionized than arenethiol under the same basic condition, and the degree of ionization of the nucleophile in solvent plays an important role in this type of coupling reaction,[10,12] we choose the stronger base K_3PO_4 and the polar solvent DMF to replace K_2CO_3 and DME in the procedure. To our delight, aryl iodides could be coupled successfully with alkyl thiols in good yield under this improved condition (Table 3). This second portion of our work involved the application of our protocol to the combination of *ortho*-substituted aryl and of heteroaryl iodide substrates (Table 3, entries 6, 7). As can be seen from the result in entry 5, an alkanethiol with an electron-drawing ester group can only be coupled in moderate yield. This demonstrates that the protocol is not applied well with electron-deficient thiols.

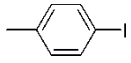
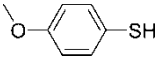
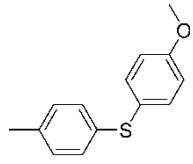
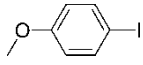
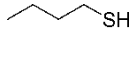
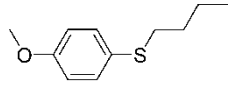
Table 2. CuI-catalyzed carbon-sulfur bond formation of arenethiols[a]



Entry	Aryl iodides	ArSH	Products	Yield (%)[b]
1				92
2				96
3				92
4				98
5				94
6				85
7				99
8				92
9				98

(*continued*)

Table 2. Continued

Entry	Aryl iodides	ArSH	Products	Yield (%)[b]
10				80
11				33

[a]Reaction conditions: ArI 2 mmol, ArSH 1.2 equiv., CuI 10 mol%, K_2CO_3 2 equiv., *L*-proline 20 mol%, in DME at 80°C under high purity nitrogen.
[b]Isolated yield.

CONCLUSION

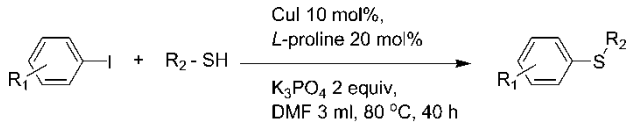
An improved mild procedure has been found for the CuI-catalyzed coupling reactions of aryl iodides with aliphatic and aromatic thiols with amino acid as the ligand. This method is particularly noteworthy given its high generality, exceptional level of functional group toleration, and satisfying yield of the coupling product.

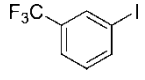
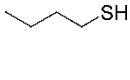
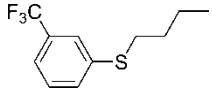
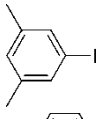
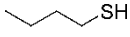
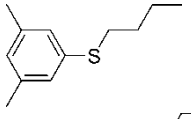
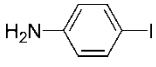
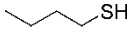
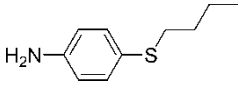
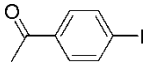
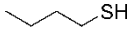
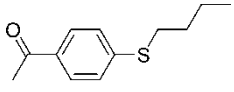
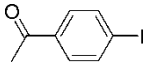
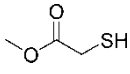
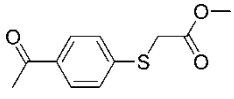
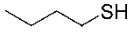
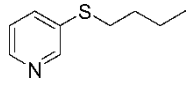
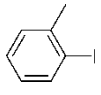
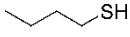
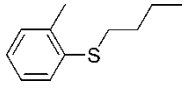
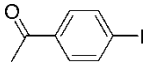
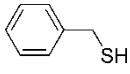
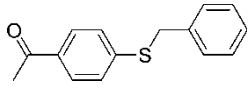
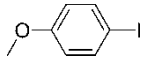
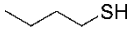
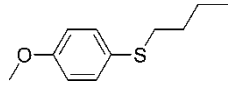
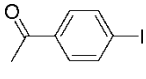
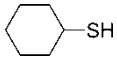
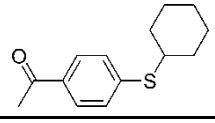
EXPERIMENTAL

General Considerations

All reactions were carried out in resealable tubes and run under an atmosphere of high-purity nitrogen. DME and DMF were freshly distilled from CaH_2. K_3PO_4 was purchased from Fluka and used without further purification. It is important that the base is powdered and free flowing, and the same is true for K_2CO_3. Aryl iodides, amino acids, and thiols were purchased from commercial sources and used without further purification. Copper(I) iodide was used after washing with THF. Flash-column chromatography was performed using silica gel H (10–40 μ). ^{1}H NMR and ^{13}C NMR was recorded on a 400-MHz instrument with chemical shifts reported relative to TMS. New compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrum (MS), and high resolution mass spectrum (HRMS). Compounds described in the literature were characterized by comparing their ^{1}H NMR to the previously reported data. All yields reported represent an average of at least two independent runs; the purity of the products was confirmed by ^{1}H NMR.

Table 3. CuI-catalyzed carbon–sulfur bond formation of alkylthiols[a]



Entry	Aryl iodides	R_2SH	Product	Yield (%)[b]
1				99
2				98
3				97
4				99
5				40
6				89
7				98
8				83
9				95
10				99

[a]Reaction conditions: ArI 2 mmol, R_2SH 1.2 equiv., CuI 10 mol%, K_3PO_4 2 equiv., *L*-proline 20 mol%, in DMF at 80°C under high purity nitrogen.
[b]Isolated yield.

General Procedure for the Coupling Reaction of Aryl Iodides with Thiols Catalyzed by CuI and L-proline

A screw-capped tube was charged with 10 mol% CuI, 20 mol% amino acid, 2 equiv. K_2CO_3 for arenethiol or K_3PO_4 for alkylthiol, 2 mmol aryl iodide (if solid), and 1.1 equiv thiol (if solid); evacuated; and backfilled with high-purity nitrogen (three cycles). Thiol (1.1 equiv.) (if liquid), 3 ml of DME for arenethiol or DMF for alkylthiol, and 2 mmol of aryl iodide (if liquid) were added by syringe at room temperature under nitrogen. The sealed tube was put into the oil bath, which was preheated to 80°C, and the reaction mixture was stirred at the same temperature for 40 h. The cooled mixture was partitioned between 10 ml of sat. NaCl aq. and 20 ml of EtOAc. The organic layer was separated, and the aqueous layer was extracted with 10 ml EtOAc each time until thin-layer chromatography (TLC) showed no trace of the product left in the aqueous layer. The combined organic layers were concentrated. Purification of the residue by flash chromatography on silica gel (3×15 cm, petroleum ether/ethyl acetate) gave the desired product.

Data

(2-Bromo-phenyl)-phenyl sulfide (Table 2, entry 1). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.57 (m, 1H), 7.34–7.47 (m, 5H), 7.12–7.16 (m, 1H), 7.01–7.05 (m, 1H), 6.91–6.94 (m, 1H); MS (EI) m/z 264 (M^+) (69), 266 [$(M + 2)^+$] (69), 265, 186, 185, 184, 152, 92.

(3-Triflurometh-phenyl)-phenyl sulfide (Table 2, entry 2). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.26–7.50 (m, 8H); MS (EI) m/z 254 (M^+), 255, 185, 184, 84, 77, 51.

(3,5-Dimethyl-phenyl)-phenyl sulfide (Table 2, entry 3). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.30 (m, 5H), 6.98 (s, 2H), 6.84 (d, $J = 0.9$ Hz, 1H), 2.22 (s, 6H); MS (EI) m/z 214 (M^+), 215, 199, 198, 184, 165, 77, 51.

(4-Amino-phenyl)-phenyl sulfide (Table 2, entry 4). Pale yellow solid. Mp: 94–96°C. (lit.[13] mp: 95.8°C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.32 (m, 7H), 6.65–6.69 (m, 2H), 3.80 (br s, 2H); MS (ESI) m/z 202 $(M + H)^+$.

1-(4-Phenylsulfanyl-phenyl)-ethanone (Table 2, entry 5). Yellow solid. Mp: 67–69°C. (lit.[14] mp: 65.8–66.5°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.83 (m, 2H), 7.48–7.51 (m, 2H), 7.39–7.42 (m, 3H), 7.20–7.22 (m, 2H), 2.55 (s, 3H); MS (EI) m/z 228 (M^+), 229, 214, 213, 185, 184, 152, 43.

1-Methoxy-4-(3,5-dimethylphenylsulfanyl)-benzene (Table 2, entry 6). Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.39 (m, 2H), 6.85–6.88 (m, 2H), 6.81 (s, 2H), 6.77 (s, 1H), 3.80 (s, 3H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 159.7, 138.7, 137.9, 135.1, 128.0, 126.3, 124.9, 115.0, 55.4, 21.3; MS (EI) m/z 244 (M^+), 245, 229, 186, 86, 84, 77, 47; HRMS (ESI) for $C_{15}H_{17}OS$ [$(M+H)^+$] found 245.0995, requires 245.0983.

1-Methoxy-4-phenylsulfanyl-benzene (Table 2, entry 7). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, $J = 8.7$ Hz, 2H), 7.10–7.24 (m, 5H), 6.89 (d, $J = 8.7$ Hz, 2H), 3.81 (s, 3H); MS (EI) m/z 216 (M^+), 217, 201, 171, 129, 77, 51, 45.

Diphenylsulfide (Table 2, entry 8). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.35 (m, 4H), 7.26–7.29 (m, 4H), 7.21–7.25 (m, 2H); MS (EI) m/z 186 (M^+), 185, 154, 109, 77, 65, 51, 39.

1-Methoxy-4-(3-trifluromethylphenylsulfanyl)-benzene (Table 2, entry 9). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, $J = 8.7$ Hz, 2H), 7.23–7.37 (m, 4H), 6.93 (d, $J = 8.7$ Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 141.0, 136.3, 131.5, 131.2, 130.4, 129.3, 123.91, 123.87, 122.40, 122.23, 122.19, 115.4, 55.5; MS (EI) m/z 284 (M^+), 286, 285, 270, 269, 241, 172, 171; HRMS (EI) for $C_{14}H_{11}F_3OS$ [$(M+H)^+$] found 284.0490, requires 284.0483.

1-Methoxy-4-*p*-tolylsulfanyl-benzene (Table 2, entry 10). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, $J = 9.1$ Hz, 2H), 7.12 (d, $J = 8.2$ Hz, 2H), 7.04 (d, $J = 8.2$ Hz, 2H), 6.85 (d, $J = 9.1$ Hz, 2H), 3.78 (s, 3H), 2.28 (s, 3H); MS (EI) m/z 230 (M^+), 231, 232, 216, 215, 200, 172, 171.

Butylsulfanyl-3-trifluoromethyl-benzene (Table 3, entry 1). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.24–7.46 (m, 3H), 2.95 (t, $J = 7.3$ Hz, 2H), 1.61–1.68 (m, 2H), 1.41–1.51 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H); MS (EI) m/z 234 (M^+), 235, 191, 178, 57, 45, 41, 39.

Butylsulfanyl-3,5-dimethyl-benzene (Table 3, entry 2). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 6.79 (s, 1H), 2.90 (t, $J = 7.3$ Hz, 3H), 2.28 (s, 6H), 1.59–1.65 (m, 2H), 1.42–1.48 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H); MS (EI) m/z 194 (M^+), 196, 195, 151, 138, 105, 91, 41.

4-Butylsulfanyl-aniline (Table 3, entry 3). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.23 (m, 2H), 6.60–6.62 (m, 2H), 3.68 (br s, 2H), 2.76 (t, $J = 7.3$ Hz, 2H), 1.51–1.58 (m, 2H), 1.37–1.43 (m, 2H), 0.88 (t, $J = 7.3$ Hz, 3H); MS (EI) m/z 181 (M^+), 183, 182, 138, 125, 124, 94, 80.

1-(4-Butylsulfanyl-phenyl)-ethanone (Table 3, entry 4). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.7$ Hz, 2H), 7.30 (d, $J = 8.7$ Hz, 2H), 2.99 (t, $J = 7.3$ Hz, 2H), 2.57 (s, 3H), 1.65–1.71 (m, 2H), 1.45–1.51 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H); MS (EI) m/z 208 (M^+), 209, 193, 152, 137, 109, 43, 41.

(4-Acetyl-phenylsulfanyl)-acetic acid methyl ester (Table 3, entry 5). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 8.3$ Hz, 2H), 3.75 (s, 5H), 2.59 (s, 3H); MS (EI) m/z 224 (M^+), 225, 210, 209, 165, 123, 45, 43.

3-Butylsulfanyl-pyridine (Table 3, entry 6). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.41 (br s, 1H), 7.62–7.64 (m, 1H), 7.19–7.22 (m, 1H), 2.93 (t, $J = 7.3$ Hz, 2H), 1.59–1.69 (m, 2H), 1.40–1.50 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H); MS (EI) m/z 167 (M^+), 168, 124, 111, 78, 67, 57, 41.

Butyl-o-tolyl sulfide (Table 3, entry 7). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, $J = 7.3$ Hz, 1H), 7.12–7.16 (m, 2H), 7.04–7.08 (m, 1H), 2.89 (t, $J = 7.3$ Hz, 2H), 2.36 (s, 3H), 1.61–1.69 (m, 2H), 1.43–1.49 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H); MS (EI) m/z 180 (M^+), 137, 124, 123, 91, 57, 45, 41.

1-(4-Benzylsulfanyl-phenyl)-ethanone (Table 3, entry 8). White solid. Mp: 113–115°C. (lit.[15] 113.9–115.3°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, $J = 8.7$ Hz, 2H), 7.26–7.38 (m, 7H), 4.22 (s, 2H), 2.56 (s, 3H); MS (EI) m/z 242 (M^+), 243, 108, 92, 91, 65, 45, 43.

1-Butylsulfanyl-4-methoxy-benzene (Table 3, entry 9). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 3.79 (s, 3H), 2.82 (t, $J = 7.3$ Hz, 2H), 1.53–1.58 (m, 2H), 1.39–1.44 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H); MS (EI) m/z 196 (M^+), 197, 153, 140, 139, 125, 57, 41.

1-(4-Cyclohexylmercapto-phenyl)-ethanone (Table 3, entry 10). Pale yellow crystals. Mp: 66–68°C. (lit.[16] mp: 67.5–68°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 2H), 3.28–3.33 (m, 1H), 2.56 (s, 3H), 2.02–2.05 (m, 2H), 1.78–1.82 (m, 2H), 1.25–1.45 (m, 6H); MS (ESI) m/z 235 (M^+).

ACKNOWLEDGMENT

We thank the foundation of Shanghai Municipal Commission of Education for financial support under Grant no. 05AX12.

REFERENCES

1. (a) Liu, L.; Stelmach, J. E.; Natarajan, S. R.; Chen, M.-H.; Singh, S. B.; Schwartz, C. D.; Fitzgerald, C. E.; O'Keefe, S. J.; Zaller, D. M.; Schmata, D. M.; Doherty, J. B. SAR of 3,4-Dihydropyrido[3,2-*d*]pyrimidone p38 inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3979–3982; (b) Arguello, J. E.; Schmidt, L. C.; Penenory, A. B. "One-pot" two-step synthesis of aryl sulfur compounds by photoinduced reactions of thiourea anion with aryl halides. *Org. Lett.* **2003**, *5*, 4133–4136; (c) Zhang, X.-M.; Ma, M.; Wang, J.-B. Catalytic asymmetric [2,3]-sigmatropic rearrangement of sulfur ylides generated from carbenoids and allenic 2-methylphenyl sulfide. *Chin. J. Chem.* **2003**, *21*, 878–882; (d) Yao, H.; Richardson, D. E. Bicarbonate surfoxidants: Micellar oxidations of aryl sulfides with bicarbonate-activated hydrogen peroxide. *J. Am. Chem. Soc.* **2003**, *125*, 6211–6221; (e) Savarin, C.; Srogl, J.; Liebeskind, L. S. A mild, nonbasic synthesis of thioethers: The copper-catalyzed coupling of boronic acids with *N*-thio(alkyl, aryl, heteroaryl)imides. *Org. Lett.* **2002**, *4*, 4309–4312; (f) Nose, M.; Suzuki, H. Convient one-pot procedure for converting aryl sulfides to nitroaryl sulfones. *Synthesis* **2002**, 1065–1071; (g) 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. Discovery of novel *p*-arylthio cinnamides as antagonists of leukocyte function-associated antigen-1/intracellular adhesion molecule-1 interaction, 1: Identification of an additional binding pocket based on an anilino diaryl sulfide lead. *J. Med. Chem.* **2000**, *43*, 4025–4040.
2. Kondo, T.; Mitsudo, T. Metal-catalyzed carbon–sulfur bond formation. *Chem. Rev.* **2000**, *100*, 3205–3220.
3. (a) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. A general and long-lived catalyst for the palladium-catalyzed coupling of aryl halides with thiols. *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181, ASAP article; (b) Itoh, T.; Mase, T. A general palladium-catalyzed coupling of aryl bromides/triflates and thiols. *Org. Lett.* **2004**, *6*, 4587–4590; (c) Murata, M.; Buchwald, S. L. A general and efficient method for the palladium-catalyzed cross-coupling of thiols and secondary phosphines. *Tetrahedron* **2004**, *60*, 7397–7403; (d) Moreau, X.; Campagne, J.-M. Palladium catalyzed thiol cross-coupling of cysteine derivatives with aryl and alkenyl halides. *J. Organomet. Chem.* **2003**, *687*, 322; (e) Wolf, C.; Lerebours, R. Use of highly active palladium-phosphinous acid catalysts in Stille, Heck, amination, and thiation reactions of chloroquinolines. *J. Org. Chem.* **2003**, *68*, 7077; (f) Baskin, J. M.; Wang, Z. An efficient copper catalyst for the formation of sulfones from sulfinic acid salts and aryl iodides. *Org. Lett.* **2002**, *4*, 4423; (g) Li, G. Highly active, air-stable palladium catalysts for the C-C and C-S bond-forming reactions of vinyl and aryl chlorides: Use of commercially available [(t-Bu)(2)P(OH)](2)PdCl(2), [(t-Bu)(2)P(OH)PdCl(2)](2), and [[(t-Bu)(2)PO. . .H. . .OP(t-Bu)(2)]PdCl] (2) as catalysts. *J. Org. Chem.* **2002**, *67*, 3643; (h) Schopfer, U.; Schlapbach, A. A general palladium-catalyzed synthesis of aromatic and heteroaromatic thioethers. *Tetrahedron* **2001**, *57*, 3069.
4. (a) Kunz, K.; Scholz, U.; Ganzer, D. Renaissance of Ullmann and Goldberg reactions—progress in copper catalyzed C-N-, C-O- and C-S-coupling. *Synlett* **2003**, 2428–2439; (b) Ley, S. V.; Thomas, A. W. Morden synthetic methods for copper-mediated C (aryl)-O, C (aryl)-N, and C(aryl)-S bond formation. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; (c) Deng, W.; Liu, L.; Guo, Q.-X. Recent

progress in copper-catalyzed cross-coupling reactions. *Chin. J. Org. Chem.* **2004**, *24*, 150.
5. Lindery, J. Copper assisted nucleophilic substitution of aryl halogen. *Tetrahedron* **1984**, *40*, 1433–1456.
6. Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. A general method for the formation of aryl–sulfur bonds using copper (I) catalysts. *Org. Lett.* **2002**, *4*, 2803–2806.
7. Kong, F. Y.; Buchwald, S. L. A general, efficient, and inexpensive catalyst system for the coupling of aryl iodides and thiols. *Org. Lett.* **2002**, *4*, 3517–3520.
8. Wu, Y.-J.; He, H. Copper-catalyzed cross-coupling of aryl halides and thiols using microwave heating. *Synlett* **2003**, 1789.
9. Naus, P.; Leseticky, L.; Smrcek, S.; Tislerova, I.; Sticha, M. Copper-assisted arylation of 1-thiosugars: Efficient route to triazene substituted arylthioglycosides. *Synlett* **2003**, 2117.
10. (a) Ma, D.; Cai, Q. *N,N*-Dimethyl glycine-promoted Ullmann coupling reaction of phenols and aryl halides. *Org. Lett.* **2003**, *5*, 3799–3802; (b) Ma, D.; Cai, Q.; Zhang, H. Mild method for Ullmann coupling reaction of amines and aryl halides. *Org. Lett.* **2003**, *5*, 2453–2455; (c) Ma, D.; Cai, Q. *L*-Proline promoted Ullmann-type coupling reactions of aryl iodides with indoles, pyrroles, imidazoles or pyrazoles. *Synlett* **2004**, 128–130; (d) Zhu, W.; Ma, D. Synthesis of aryl azides and vinyl azides via proline promoted CuI-catalyzed coupling reactions. *Chem. Commun.* **2004**, 888–889; (e) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. Preparation of N-aryl compounds by amino acid–promoted Ullmann-type coupling reactions. *Synthesis* **2005**, 496–499; (f) Zhang, H.; Cai, Q.; ;Ma, D. Amino acid promoted CuI-catalyzed C-N bond formation between aryl halides and amines or N-containing heterocycles. *J. Org. Chem.* **2005**, *70*, 5164–5173.
11. Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. CuI-catalyzed coupling reactions of aryl iodides and bromides with thiols promoted by amino acid ligands. *Synlett* **2004**, 1254–1258.
12. Bordwell, F. G. Equilibrium acidities in dimethyl sulfoxide solution. *Acc. Chem. Res.* **1988**, *21*, 456–463.
13. Hambly, A. N.; O'Grady, B. V. Hydrogen bonding in organic compounds, IX: Intramolecular reactions between the primary amino group and amino, nitro, sulfide, and sulfone groups in aromatic compounds. *Aust. J. Chem.* **1964**, *17*, 860–876.
14. Cutler, R. R.; Stenger, R. J.; Suter, C. M. New antibacterial agents: 2-Acylamino-1-(4-hydrocarbonyl sulfonylphenyl)-1,3-propanediols and related compounds. *J. Am. Chem. Soc.* **1952**, *74*, 5475–5481.
15. Franke, A.; Mattern, G.; Traber, W. Synthetic juvenile hormones, 1: The p-substituted methylcinnamic acid derivatives. *Helv. Chim. Acta* **1975**, *58*, 268–278.
16. Du Pont de Nemours. US patent 2763692, 1955.