Copper-Catalyzed Synthesis of Sulfenamides Utilizing Diaryl Disulfides with Alkyl Amines

Nobukazu Taniguchi*

Department of Chemistry, Fukushima Medical University, Fukushima 960-1295, Japan
Fax +81(24)5471369; E-mail: taniguti@fmu.ac.jp

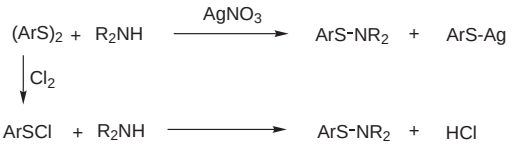
Received 18 April 2007

Abstract: The copper-catalyzed coupling of diaryl disulfides with alkyl amines can afford various sulfenamides in good yields. Furthermore, the present reaction is efficient and can be used for both of the aryl sulfide groups on disulfide.

Key words: sulfenamide, copper catalyst, diaryl disulfide, alkylamine

Sulfenamides, with a sulfur–nitrogen bond, have found widespread utilization as reagents or intermediates in organic synthesis.[1] For instance, these compounds are employed in oxidation of alcohol as a catalyst in the presence of *N*-chlorosuccinimide[2] or in an introduction of sulfur atom or nitrogen atom into an unsaturated carbon–carbon bond.[3]

As a general rule, to synthesize sulfenamide, a reaction of sulfenyl chloride with amine[4] or a coupling of disulfide with amine by silver nitrate[5] has been developed to date (Scheme 1).[6] Regrettably, these reactions require employments of toxic chlorine gas in order to prepare for sulfenyl chloride or a stoichiometric silver salt. Therefore, the development of a transition-metal-catalyzed procedure has been desired.

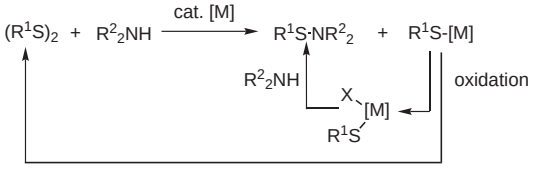


Scheme 1 Synthesis of sulfenaimides

To accelerate the metal-catalyzed coupling of disulfide with amine, oxidation of a generated metal–monosulfide complex as an intermediate is necessary (Scheme 2).[7]

As an approach to solve this problem, we researched conditions whereby disulfide or R^1S–[M]X was formed by oxidation of R^1S–[M][8] and found that a copper-catalyzed reaction can be carried out in air. In this paper, we wish to describe the methodology of the copper-catalyzed synthesis of sulfenamides using disulfides with alkylamines.

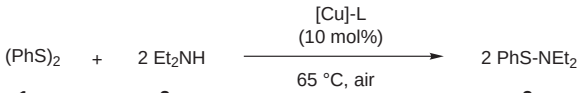
Initially, to optimize the reaction conditions, various solvents were examined (Table 1). When the reaction of



Scheme 2 Strategy of metal-catalyzed synthesis of sulfenamides from disulfides with amines

diphenyl disulfide **1** with diethylamine **2a** in the presence of CuI–TMEDA (1:1, 10 mol%) was performed in toluene (0.3 mL) at 65 °C, disulfide **1** was transformed to the corresponding sulfenamide **3a** in 55% yield (67% conversion of **1**) with recovery of **1** (Table 1, entry 1).[9] Fortunately, when other solvents such as DMF or DMSO were employed, the yield of **3a** increased to 73% and 74% (98% and 100% conversion of **1**), respectively (Table 1, entries 3 and 4). However, the conditions at 100 °C decreased the yield to 65% (Table 1, entry 5).

Table 1 Copper-Catalyzed Coupling of Bis(4-tolyl) Disulfide with Diethylamine



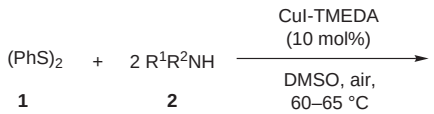
1 **2a** **3a**

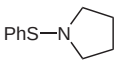
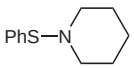
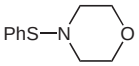
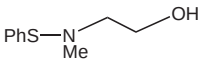
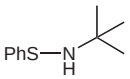
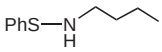
Entry	[Cu]	L	Solvent	Conv. of **1** (%)[a]	Yield of **3a** (%)[b]
1	CuI	TMEDA	PhMe	67	55
2			Dioxane	71	58
3			DMF	98	73
4			DMSO	100	74
5[c]				74	65
6		bpy		95	69
7		Ph_3P		95	71
8	CuCl	TMEDA		94	69
9	CuBr			98	72
10	$CuCl_2$			94	70

[a] Determined by ^1H NMR.
[b] Isolated yields after distillation.
[c] This reaction was carried out at 100 °C.

SYNLETT 2007, No. 12, pp 1917–1920
Advanced online publication: 27.06.2007
DOI: 10.1055/s-2007-984539; Art ID: U03507ST

Table 2 Copper-Catalyzed Coupling of Diphenyl Disulfide with Various Amines



Entry	**3**		Time (h)	Conv. of **1** (%)[c]	Yield of **3** (%)[d]
1	PhS–N(Et)$_2$	A[a]	18	100	74
2	PhS–N(*i*-Pr)$_2$	A[a]	24	95	74
3		A[a]	18	100	80
4		A[a]	18	100	88
5		A[a]	18	100	82
6		A[a]	18	95	71
7		B[b]	18	90	74
8		B[b]	24	82	77
9	PhS–NHPh	B[b]	18	0	–

[a] Conditions A: The mixture of **1** (0.5 mmol), **2** (1.05 mmol), and CuI–TMEDA (1:1, 10 mol%) in DMSO (0.3 mL) was treated at 65 °C.
[b] Conditions B: NH_4PF_6 (10 mol%) was also added, and the reaction was carried out in DMSO (0.8 mL) at 60 °C.
[c] Determined by ^{1}H NMR.
[d] Isolated yields after distillation.

Other ligands (bpy and PPh_3) or other copper catalysts (CuCl, CuBr and $CuCl_2$) could give excellent results (Table 2, entries 6–10).

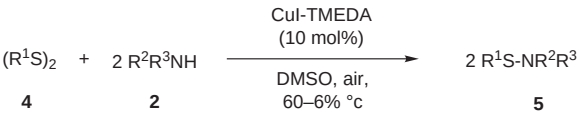
The coupling of diphenyl disulfide **1** with different alkylamines **2** was then investigated. As shown in Table 2, when a mixture of diphenyl disulfide **1** with secondary alkyl amines **2** were treated by CuI–TMEDA (1:1, 10 mol%) in DMSO (0.3 mL) at 65 °C, expected sulfenamides were obtained in good yields (Table 2, entries 1–6).[11]

On the other hand, in the reaction of primary alkyl amines, the addition of NH_4PF_6 (10 mol%) and the use of DMSO (0.8 mL) at 60 °C were required so as to obtain the good results (Table 2, entries 7 and 8). Unfortunately, aniline could not be converted into the corresponding product and starting materials were recovered (Table 2, entry 9).

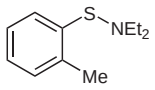
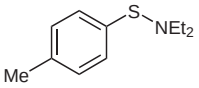
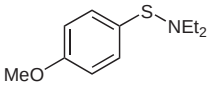
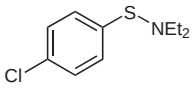
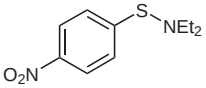
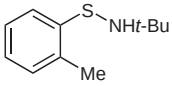
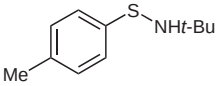
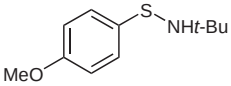
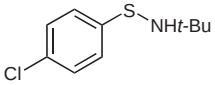
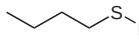
Thus, the copper-catalyzed preparation of sulfenamides using disulfides could take advantage of both primary and secondary alkyl amines.

On the basis of the above-described result, we also investigated the coupling of various diaryl disulfides with diethylamine or *tert*-butylamine. As expected, the corresponding products could be obtained in excellent yields

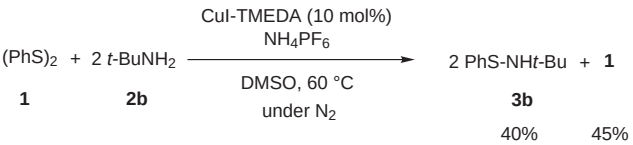
Table 3 Copper-Catalyzed Coupling of Various Diaryl Disulfides with Amine



R^2R^3NH = Et_2NH **2a**
t-$BuNH_2$ **2b**

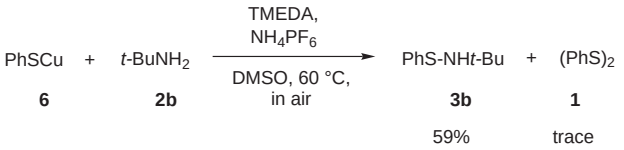
Entry	**5**		Time (h)	Conv. of **4** (%)[c]	Yield of **5** (%)[d]
1		A[a]	18	100	87
2		A[a]	18	100	73
3		A[a]	18	100	67
4		A[a]	24	100	70
5		A[a]	22	100	64
6		B[b]	24	100	60
7		B[b]	24	100	68
8		B[b]	24	100	71
9		B[b]	36	100	51
10		A[a]	48	5	–

[a] Conditions A: The mixture of **4** (0.5 mmol), **2** (1.05 mmol), CuI–TMEDA (1:1, 10 mol%) in DMSO (0.3 mL) was treated at 65 °C.
[b] Conditions B: NH_4PF_6 (10 mol%) was also added, and the reaction was carried out in DMSO (0.8 mL) at 60 °C.
[c] Determined by ^{1}H NMR.
[d] Isolated yields after distillation.



Scheme 3 Reaction of $(PhS)_2$ with *t*-$BuNH_2$ in the absence of oxygen

(Table 3, entries 1–9). However, when bis(*n*-butyl) disulfide was employed, the reactivity was significantly decreased (Table 3, entry 10).



Scheme 4 Reaction of PhSCu with *t*-$BuNH_2$

To clarify the reaction pathway for this sulfenamide synthesis, we next performed some experiments. When the reaction of diphenyl disulfide with *tert*-butylamine was carried out in the absence of oxygen, sulfenamide **3b** was obtained in only 40% yield and disulfide **1** was recovered in 45% yield (Scheme 3).

Moreover, the reactivity of PhSCu considered as an intermediate was also examined. The reaction with *tert*-butylamine gave sulfenamide **3b** in 59% yield (Scheme 4).[10]

Consequently, the coupling of disulfide with amine requires oxygen, and it seems that the copper catalyst works as a Lewis acid or co-oxidant in air.

From these results, a plausible reaction mechanism is considered as follows (Figure 1). After a reaction of R_2N–Cu(I)L_n **8** with disulfide, the corresponding PhS–NR_2 **3** and PhS–Cu(I)L_n **6** are obtained. Sequentially, herein produced **6** gives disulfide **1** or PhS–Cu(II)IL_n **9** via the oxidation. Finally, after the intermediate **10** is formed from **9**, it affords the corresponding sulfenamide by the oxidation.

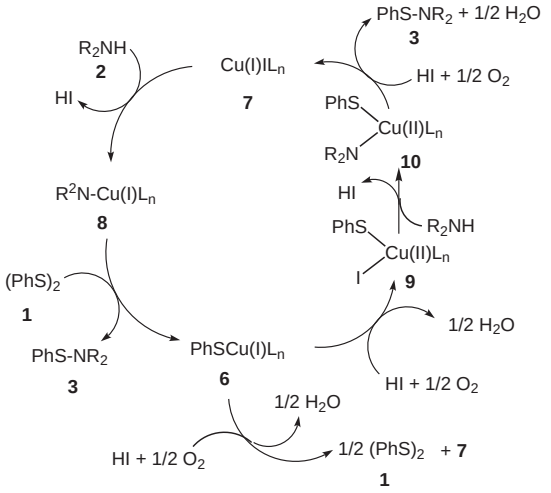


Figure 1 Plausible reaction mechanism

Further investigations on the exact details of the reaction mechanism are now in progress.

In conclusion, we could achieve the copper-catalyzed synthesis of sulfenamides having sulfur–nitrogen bond using diaryl disulfides with alkyl amines.

Acknowledgment

This work was supported by Meiji Seika Co. Ltd.

References and Notes

(1) (a) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993. (b) Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.
(2) (a) Matsuo, J.-i.; Iida, D.; Tatani, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 223. (b) Matsuo, J.-i.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739.
(3) (a) Kuniyasu, H.; Kato, T.; Asano, S.; Ye, J.-H.; Ohmori, T.; Morita, M.; Hiraike, H.; Fujiwara, S.-i.; Terao, J.; Kurosawa, H.; Kambe, N. *Tetrahedron Lett.* **2006**, *47*, 1141. (b) Kondo, T.; Baba, A.; Nishi, Y.; Mitsudo, T.-a. *Tetrahedron Lett.* **2004**, *45*, 1469. (c) Zyk, N. V.; Beloglzkina, E. K.; Gazzaeva, R.; Tyurin, V. S.; Titanyuk, I. D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *155*, 33.
(4) (a) Miura, Y.; Asada, H.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1855. (b) Heimer, N. E.; Field, L. *J. Org. Chem.* **1970**, *35*, 3012.
(5) (a) Davis, F. A.; Friedman, A. J.; Kluger, E. W.; Skibo, E. B.; Fretz, E. R.; Milicia, A. P.; LeMasters, W. C.; Bentley, M. D.; Lacadie, J. A.; Douglass, I. B. *J. Org. Chem.* **1977**, *42*, 967. (b) Davis, F. A.; Slgeir, W. A. R.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809.
(6) Intramolecular S–N bond formation is also reported: (a) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *Org. Lett.* **2006**, *8*, 4811. (b) Jin, C. K.; Moon, J.-K.; Lee, W. S.; Nam, K. S. *Synlett* **2003**, 1967.
(7) Taniguchi, N. *J. Org. Chem.* **2004**, *69*, 915.
(8) (a) Taniguchi, N. *Synlett* **2006**, 1351. (b) Taniguchi, N. *J. Org. Chem.* **2007**, *72*, 1241. (c) Taniguchi, N. *J. Org. Chem.* **2006**, *71*, 7874.
(9) **Typical Procedure**
To a mixture of CuI (9.5 mg, 0.05 mmol), TMEDA (5.8 mg, 0.05 mmol), and DMSO (0.3 mL) were added $(PhS)_2$ (109.2 mg, 0.5 mmol) and Et_2NH (76.8 mg, 1.05 mmol), and the mixture was stirred at 65 °C for 18 h in air. After the residue was dissolved in Et_2O, the solution was washed with H_2O and sat. NaCl and dried over anhyd $MgSO_4$. The crude product was distilled (140 °C/30 Pa) to give *N*-(phenylthio)-*N*,*N*-diethylamine (134.8 mg, 74%).[5a]
***N*-(Phenylthio)-*N*,*N*-diethylamine**
IR (neat): 2970, 2847, 1582, 1475, 1438, 1374 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 4 H), 7.15–7.08 (m, 1 H), 3.00 (q, *J* = 7.1 Hz, 4 H), 1.18 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 141.2, 128.4, 125.3, 125.0, 52.1, 13.7. Anal. Calcd for $C_{10}H_{15}NS$: C, 66.25; H, 8.34; N, 7.73. Found: C, 65.92; H, 8.02; N, 7.80.
***N*-(Phenylthio)pyrrolidine**
IR (neat): 2967, 2845, 1582, 1475, 1438 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 4 H), 7.18–7.14 (m, 1 H), 3.13–3.09 (m, 4 H), 1.87–1.82 (m, 4 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 139.4, 128.6, 126.3, 125.9, 55.2, 25.6. Anal. Calcd for $C_{10}H_{13}NS$: C, 66.99; H, 7.31; N, 7.81. Found: C, 66.70; H, 7.24; N, 7.84.
***N*-(Phenylthio)-*N*-(methyl)aminoethanol**
IR (neat) 3391, 2940, 2880, 1582, 1476, 1438 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.40–7.23 (m, 5 H), 3.77 (t, *J* = 5.1 Hz, 2 H), 3.02 (t, *J* = 5.1 Hz, 2 H), 2.87 (s, 3 H), 2.00 (br, 1 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 136.3, 129.4, 128.8, 127.5, 60.8, 59.9, 47.3. Anal. Calcd for $C_9H_{13}NS$: C, 58.98; H, 7.15; N, 7.64. Found: C, 59.17; H, 7.11; N, 7.24.
***N*-(Phenylthio)-*N*-butylamine**
IR (neat): 3338, 2957, 2929, 1582, 1476, 1438 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 4 H), 7.15–7.10

(m, 1 H), 2.93 (q, *J* = 6.9 Hz, 2 H), 2.80 (br, 1 H), 1.56–1.50 (m, 2 H), 1.48–1.31 (m, 2 H), 0.90 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 141.9, 128.7, 125.2, 123.8, 51.9, 32.5, 20.0, 13.9. Anal. Calcd for $C_{10}H_{15}NS$: C, 66.25; H, 8.34; N, 7.73. Found: C, 66.46; H, 8.05; N, 7.70.

***N*-(Phenylthio)-*N*-(*tert*-butyl)amine**[4a,5a]

IR (neat): 3327, 2969, 1582, 1476, 1361 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 7.6 Hz, 2 H), 7.26 (t, *J* = 7.6 Hz, 2 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 2.78 (br, 1 H), 1.17 (s, 9 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 144.4, 128.4, 124.4, 122.4, 54.7, 29.2. Anal. Calcd for $C_{10}H_{15}NS$: C, 66.25; H, 8.34; N, 7.73. Found: C, 65.98; H, 8.20; N, 7.54.

(10) ***N*-(2-Methylphenylthio)-*N*,*N*-diethylamine**

IR (neat): 2970, 2849, 1589, 1463, 1378 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.9 Hz, 1 H), 7.15 (t, *J* = 7.9 Hz, 1 H), 7.07–6.97 (m, 2 H), 3.05 (q, *J* = 7.0 Hz, 4 H), 2.20 (s, 3 H), 1.17 (t, *J* = 7.0 Hz, 6 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 141.2, 131.6, 129.7, 125.8, 124.0, 122.8, 52.1, 18.5, 13.5. Anal. Calcd for $C_{11}H_{17}NS$: C, 67.64; H, 8.77; N, 7.17. Found: C, 67.34; H, 8.71; N, 7.02.

***N*-(4-Methylphenylthio)-*N*,*N*-diethylamine**

IR (neat): 2970, 2830, 1597, 1489, 1374 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.9 Hz, 2 H), 7.10 (d, *J* = 7.9 Hz, 2 H), 2.93, (q, *J* = 7.0 Hz, 4 H), 2.32 (s, 3 H), 1.19 (t, *J* = 7.0 Hz, 6 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 136.0, 135.8, 129.3, 127.3, 51.9, 21.0, 13.7. Anal. Calcd for $C_{11}H_{17}NS$: C, 67.64; H, 8.77; N, 7.17. Found: C, 67.51; H, 8.79; N, 7.22.

***N*-(4-Methoxylphenylthio)-*N*,*N*-diethylamine**

IR (neat): 2971, 2835, 1590, 1492 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 3.80 (s, 3 H), 2.81 (q, *J* = 7.0 Hz, 4 H), 1.21 (t, *J* = 7.0 Hz, 6 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 159.5, 132.8, 126.9, 114.1, 55.3, 51.4, 13.7. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.47; H, 8.03; N, 6.42.

***N*-(2-Methylphenylthio)-*N*-(*tert*-butyl)amine**

IR (neat): 3322, 2969, 1589, 1463, 1361 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.9 Hz, 1 H), 7.18, (t, *J* = 7.9 Hz, 1 H), 7.05–6.95 (m, 2 H), 2.60 (br, 1 H), 2.23 (s, 3 H), 1.19 (s, 9 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 142.5, 131.5, 129.5, 125.9, 123.9, 122.4, 54.6, 29.2, 18.5. Anal. Calcd for $C_{11}H_{17}NS$: C, 67.64; H, 8.77; N, 7.17. Found: C, 67.54; H, 8.79; N, 6.97.

***N*-(4-Methylphenylthio)-*N*-(*tert*-butyl)amine**

IR (neat): 3325, 2969, 1598, 1490, 1361 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.2 Hz, 2 H), 7.08 (d, *J* = 8.2 Hz, 2 H), 2.80 (br, 1 H), 2.30 (s, 3 H), 1.17 (s, 9 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 140.8, 134.3, 129.2, 122.9, 54.8, 29.2, 20.9. Anal. Calcd for $C_{11}H_{17}NS$: C, 67.64; H, 8.77; N, 7.17. Found: C, 67.35; H, 8.71; N, 6.92.

(11) Adams, R.; Reifschneider, W.; Ferretti, A. *Org. Synth., Coll. Vol. V*; John Wiley & Sons: New York, **1973**, 107–110.