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Copper-Catalyzed Formation of Sulfur–Nitrogen Bonds by Dehydrocoupling of Thiols with Amines

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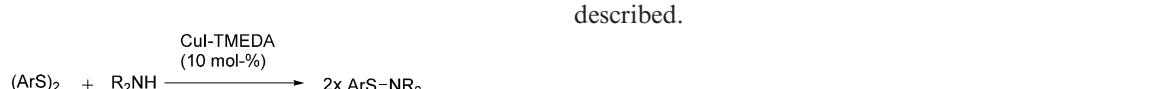
Keywords: Sulfur / Sulfenamides / Dehydrocoupling reactions / Copper / Palladium / Amines

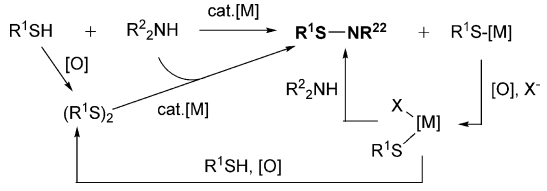
Copper-catalyzed formation of sulfur–nitrogen bonds can be performed by a dehydrocoupling of aryl thiols with amines. Sulfenamides or sulfonamides can be produced by the use of a copper catalyst in air or under oxygen atmosphere. Furthermore, a reaction involving the combination of a palladium catalyst and a copper catalyst selectively afforded sulfinamides.

Introduction

Transition-metal-catalyzed syntheses of organosulfur compounds with sulfur–nitrogen bonds are important procedures,[1] and the herein obtained derivatives have found wide utilization as intermediates[2] or reagents in organic synthesis.[3] Application of these compounds are also expected in material science.[4] However, the formation of sulfur–nitrogen bonds have usually been carried out by classic procedures.[5,6] For instance, sulfenamides are produced from sulfenyl chlorides with amines.[1] This is an inefficient method because for the synthesis of sulfenyl chlorides, it is necessary to employ disulfide with chlorine or *N*-chlorosuccinimide. Therefore, the development of a convenient and useful synthetic method that uses thiols is desired. It was previously reported that sulfenamides from disulfides can be obtained with a copper catalyst (Scheme 1).[7] However, the developed method cannot control the dehydrocoupling of thiols with amines. Furthermore, catalytic coupling of thiols with amines has not been developed to date. To achieve this, it was envisaged to carry out the reaction by using a transition-metal catalyst. Generally, regulation of the present reaction is very difficult owing to formation of disulfides as homocoupling products and/or of an inactive metal-thiolate complex. As a natural result, direct synthesis of sulfenamides by using thiols has not been explored so far. To construct these sulfur–nitrogen bonds, generation of disulfides by oxidation of thiols or of thiolate-copper complexes considered as intermediates is required (Scheme 2).[8]



Scheme 1. Copper-catalyzed coupling of disulfides with amines.



Scheme 2. Strategy for metal-catalyzed synthesis of sulfenamides by using thiols.

To solve these problems, numerous methods involving combinations of copper catalysts with amine ligands were researched under oxidative conditions, and it was found that copper-catalyzed coupling of thiols with amines was successful. In this paper, the synthetic methodology for the preparation of sulfenamides, sulfinamides and sulfonamides from thiols and amines with the use of a copper catalyst is described.

Results and Discussion

Initially, a large variety of Cu catalysts and ligands (Table 1) were examined. In the reaction of 4-MeC_6H_4SH (**1a**) with *tert*-butylamine (**2a**), when no ligands were added, *N*-(4-methylphenylthio)-*N*-(*tert*-butyl)amine **3aa** was obtained in only 43% yield (Entry 1). Systematically, the effect of amine ligands was investigated. The use of TMEDA resulted in 48% yield (Entry 2); however, the system CuI-bpy (1:1, 5 mol-%) afforded sulfenamides **3aa** in 90% yield without the formation of disulfide (Entry 3). On the contrary, other solvents such as DMF or toluene could not

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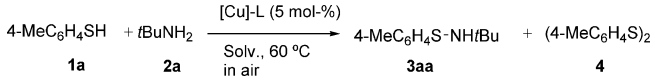
promote the reaction satisfactorily (Entries 4 and 5). When other copper salts [$Cu^{I}Br$, $Cu^{II}Cl_2$, $Cu^{II}(OAc)_2$] were used, the yield decreased slightly (Entries 6–8).

Table 1. Investigation of suitable conditions for the synthesis of sulfenamides.

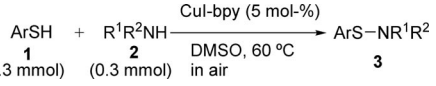


Entry	[Cu]	L	Solvent	**3aa**/**4**[a]	**3** [%][b]
1	CuI	none	DMSO	50:50	43
2		TMEDA	DMSO	50:50	48
3		bpy	DMSO	100:0	90
4		bpy	DMF	28:72[c]	21
5		bpy	$PhCH_3$	0:100[c]	0
6	CuBr	bpy	DMSO	83:17	73
7	$CuCl_2$	bpy	DMSO	83:17	78
8	$Cu(OAc)_2$	bpy	DMSO	77:23	72

[a] Determined by ^1H NMR spectroscopy. [b] Isolated yield after silica gel chromatography. [c] A trace of sulfinamide was also detected.

On the basis of the method described above, reactions of various thiols with different amines were carried out (Table 2). In most cases, expected sulfenamides **3** were produced in excellent yields, and it was clear that the reaction of thiophenol could employ various alkylamines (Entries 1–5).[9] Not only alkylamines but also arylamines were used in the procedure (Entries 6–8). The corresponding sulfenamides **3** were obtained in 40–55% yields. The yields of these reactions were slightly lower on account of oxidation of anilines.[10] Similarly, reactions of other aryl thiols with tBuNH$_2$ afforded satisfactory results (Entries 9–13). Regrettably, the use of 4-$O_2NC_6H_4SH$ or nBuSH did not promote the reaction (Entries 14–15).

Table 2. Copper-catalyzed coupling of thiols with amines.[a]

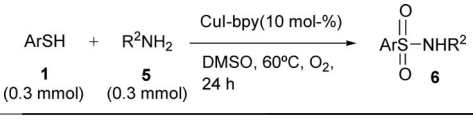


Entry	**1**	R^1R^2NH	Time [h]	**3** [%][b]
1	PhSH	Et_2NH	18	85
2		piperidine	18	87
3		tBuNH$_2$	18	88
4[c]		nBuNH$_2$	24	73
5[c]		iPrNH$_2$	18	82
6[c]		4-$MeC_6H_4NH_2$	18	55[d]
7[c]	4-MeC_6H_4SH	4-$ClC_6H_4NH_2$	36	40[d]
8[c]		PhNHMe	18	52[d]
9	2-MeC_6H_4SH	tBuNH$_2$	18	83
10	2-BrC_6H_4SH	tBuNH$_2$	18	74
11	4-MeC_6H_4SH	tBuNH$_2$	18	90
12	4-$MeOC_6H_4SH$	tBuNH$_2$	18	82
13	4-ClC_6H_4SH	tBuNH$_2$	18	83
14	4-$O_2NC_6H_4SH$	tBuNH$_2$	18	trace
15	nBuSH	tBuNH$_2$	18	trace

[a] The mixture of ArSH (0.3 mmol), R^1R^2NH (0.3 mmol), and CuI-bpy (1:1, 5 mol-%) in DMSO (0.2 mL) was treated at 60 °C in air. [b] Isolated yields after distillation. [c] 10 mol-% of CuI-bpy was used and 0.4 mL of DMSO was used. [d] Isolated yields after silica gel chromatography.

Attention was then focused on the direct formation of sulfonamides or sulfinamides from thiols with amines in one pot. As a general rule, these compounds are synthesized by reaction of sulfonyl chlorides with amines or by oxidation of sulfenamides, but strong oxidants are necessary.[11] Accordingly, a method that used the copper catalyst under mild conditions was investigated. Firstly, a copper-catalyzed preparation of sulfonamides was examined. To achieve this, it was necessary to study the system CuI-bpy (1:1, 10 mol-%) under an oxygen atmosphere (Table 3). Fortunately, when tBuNH$_2$ was employed as an amine, *N*-(phenylsulfonyl)-*N*-(*tert*-butyl)amine was obtained in 90% yield with trace amounts of sulfenamide and sulfinamide (Entry 1). The present method can take advantage of various aryl thiols (Entries 2–5). On the contrary, the use of other amines did not result in the corresponding sulfonamides, and the formation of complex mixtures was often observed (Entries 6–7).

Table 3. Synthesis of sulfonamides with the use of a copper catalyst.[a]



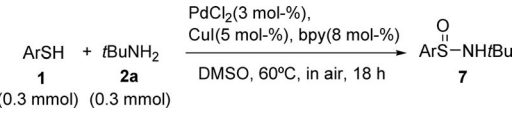
Entry	ArSH	R^2NH	**6** [%][b]
1[c]	PhSH	tBuNH$_2$	90
2[c]	4-MeC_6H_4SH	tBuNH$_2$	71
3[c]	4-$MeOC_6H_4SH$	tBuNH$_2$	70
4[c]	4-ClC_6H_4SH	tBuNH$_2$	45[d]
5[c]	2-MeC_6H_4SH	tBuNH$_2$	60
6	PhSH	Et_2NH	0[e]
7	4-MeC_6H_4SH	iPrNH$_2$	0

[a] The mixture of ArSH (0.3 mmol), R^1R^2NH (0.3 mmol), and CuI-bpy (1:1, 10 mol-%) in DMSO (0.2 mL) was treated at 60 °C under oxygen. [b] Isolated yields after silica gel chromatography. [c] Formation of trace amounts of sulfenamide and sulfinamide was also observed. [d] The disulfide of **1** was also obtained in 42% yield. [e] The sulfenamide was obtained in 80% yield.

The preparation of sulfinamides was then examined (Table 4). When a mixture of ArSH with *tert*-butylamine was treated with only the CuI-bpy catalyst, the desired sulfinamide was not selectivity produced.[12] Similarly, the palladium catalyst only also did not afford the corresponding sulfinamide (Entry 1). Noteworthy, the combination of $PdCl_2$ (3 mol-%) and CuI (5 mol-%) afforded *N*-(phenylsulfinyl)-*N*-(*tert*-butyl)amine in 68% yield with trace amounts of sulfenamide and disulfide (Entry 2). Various aryl thiols could also be used in the procedure (Entries 3–6).[13] The reaction with 2-MeC_6H_4SH required the use of 10 mol-% of $PdCl_2$ under an oxygen atmosphere owing to the slow oxidation of the sulfenamides (Entry 6). Furthermore, this procedure can also use disulfides (Entries 7–8).

In order to deduce the reaction mechanism, the reaction in the absence of oxygen was examined and the reactivity of $PhSCu^{I}$ (an intermediate) was considered. As shown in Scheme 3, when the reaction of thiophenol (**1b**) with tBuNH$_2$ (**2a**) was performed under nitrogen, the corre-

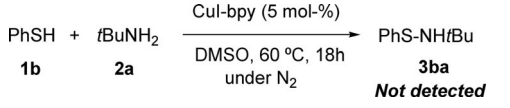
Table 4. Synthesis of sulfinamide by use of the combination of a copper and a palladium catalyst.[a]



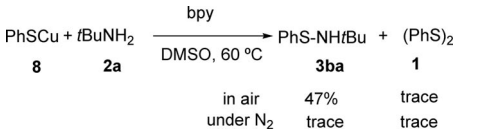
Entry	ArSH	**7** [%][b]	Sulfenamide	Disulfide [%][b]
1[c]	PhSH	0	0	72
2	PhSH	68	trace	trace
3	4-MeC_6H_4SH	75	trace	trace
4	4-$MeOC_6H_4SH$	65	trace	trace
5	4-ClC_6H_4SH	45	trace	50
6[d]	2-MeC_6H_4SH	74	trace	0
7[e]	$(PhS)_2$	62	trace	0
8[e]	$(4\text{-}MeC_6H_4S)_2$	60	trace	0

[a] The mixture of ArSH (0.3 mmol), *t*$BuNH_2$ (0.3 mmol), $PdCl_2$ (3 mol-%), CuI (5 mol-%), and bpy (8 mol-%) in DMSO (0.2 mL) was treated at 60 °C in air. [b] Isolated yields after silica gel chromatography. [c] CuI was not added. [d] This reaction was performed by using $PdCl_2$ (10 mol-%), CuI (5 mol-%), and bpy (15 mol-%) for 42 h under an oxygen atmosphere. [e] NH_4PF_6 (10 mol-%) was added under oxygen.

sponding sulfenamide **3ba** was not detected at all. On the other hand, the reaction of $PhSCu^{I}$ (**8**)[14] with *t*$BuNH_2$ (**2a**) produced **3ba** in 47% yield in air (Scheme 4). These results suggest that oxygen is necessary for the present procedure and that the oxidation of $PhSCu^{I}$ proceeds in air. Therefore, the reaction mechanism is proposed as follows (Figure 1). Cycle A: After $PhSCu^{I}$ is formed from PhSH with $Cu^{I}I$, the oxidation of $PhSCu^{I}$ gives $PhSCu^{II}(I)L_n$.[15] Consequently, reactions of $PhSCu^{II}(I)L_n$ with amines produce sulfenamides, and $Cu^{I}I$ regenerates in the presence of oxygen. Cycle B: After $(PhS)_2$ is produced by the oxidation of PhSH, sulfenamides are produced from disulfides with amines by a copper catalyst. Finally, $PhSCu^{II}(I)L_n$ is formed.[7] Furthermore, the reaction under oxygen affords sulfonamides by the oxidation of sulfenamides. On the contrary, in the synthesis of sulfinamides, it seems that the conversion of sulfenamides to sulfonamides is restrained by the addition of a palladium catalyst. Further investigations on the exact details of the mechanism are now in progress.



Scheme 3. The reaction of PhSH with an amine in the absence of oxygen.



Scheme 4. The reaction of PhSCu with an amine.

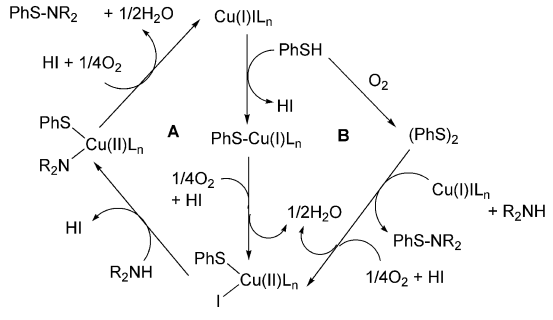


Figure 1. A plausible mechanism.

Conclusions

Copper-catalyzed sulfur–nitrogen bond formation was achieved by dehydrocoupling of thiols with amines. The present procedure can afford sulfenamides or sulfonamides in good yields. Addition of palladium can selectively produce sulfinamides.

Experimental Section

Copper-Catalyzed Synthesis of Sulfenamides: To a mixture of CuI (2.9 mg, 0.015 mmol), bpy (2.3 mg, 0.015 mmol), and DMSO (0.2 mL) were added PhSH (33.1 mg, 0.3 mmol) and *tert*-butylamine (33.4 mg, 0.33 mmol), and the mixture was stirred at 60 °C for 18 h in air. After the residue was dissolved in Et_2O, the solution was washed with H_2O and saturated sodium chloride and dried with anhydrous magnesium sulfate. The crude product was distilled (150 °C/30 Pa) to give *N*-(phenylthio)-*N*-(*tert*-butyl)amine (48.1 mg, 88%).[3f] ^{1}H NMR (270 MHz, $CDCl_3$, 24 °C): δ = 7.34 [d, ^3J(H,H) = 7.6 Hz, 2 H, Ar-H], 7.26 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, Ar-H), 7.05 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H, Ar-H), 2.78 (br., 1 H, NH), 1.17 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$, 24 °C): δ = 144.4 (C), 128.4 (CH), 124.4 (CH), 122.4 (CH), 54.7 (C), 29.2 (CH_3) ppm. IR (neat): $1/\lambda$ = 3327, 2969, 1582, 1476, 1361 cm^{-1}. $C_{10}H_{15}NS$ (181.30): C 66.25, H 8.34, N 7.73; found C 66.01, H 8.21, N 7.64.

Copper-Catalyzed Synthesis of Sulfonamides: To a mixture of CuI (2.9 mg, 0.015 mmol), bpy (2.3 mg, 0.015 mmol), and DMSO (0.2 mL) were added PhSH (33.1 mg, 0.3 mmol) and *tert*-butylamine (33.4 mg, 0.33 mmol), and the mixture was stirred at 60 °C for 24 h under oxygen by using a balloon. After the residue was dissolved in Et_2O, the solution was washed with H_2O and saturated sodium chloride and dried with anhydrous magnesium sulfate. Chromatography on silica gel (80% Et_2O in hexane) gave *N*-(phenylsulfonyl)-*N*-(*tert*-butyl)amine (57.8 mg, 90%). ^{1}H NMR (270 MHz, $CDCl_3$, 24 °C): δ = 7.93–7.89 (m, 2 H, Ar-H), 7.54–7.45, (m, 3 H, Ar-H), 4.84 (br., 1 H, NH), 1.22 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$, 24 °C): δ = 143.4 (C), 132.1 (CH), 128.8 (CH), 126.9 (CH), 54.7 (C), 30.1 (CH_3) ppm. IR ($CHCl_3$): $1/\lambda$ = 3279, 2976, 1447, 1318, 1151 cm^{-1}. $C_{10}H_{15}NO_2S$ (213.30): C 56.31, H 7.09, N 6.57; found C 56.14, H 7.15, N 6.61.

Copper-Catalyzed Synthesis of Sulfinamides: To a mixture of CuI (2.9 mg, 0.015 mmol), $PdCl_2$ (1.6 mg, 0.009 mmol), bpy (3.7 mg, 0.024 mmol), and DMSO (0.2 mL) were added PhSH (33.1 mg, 0.3 mmol) and *tert*-butylamine (24.1 mg, 0.33 mmol), and the mixture was stirred at 60 °C for 18 h in air by using a balloon. After the residue was dissolved in Et_2O, the solution was washed with H_2O and saturated sodium chloride and dried with anhydrous magnesium sulfate. Chromatography on silica gel (60% Et_2O in hexane) gave *N*-(phenylsulfinyl)-*N*-(*tert*-butyl)amine (40.2 mg, 68%). ^{1}H NMR (270 MHz, $CDCl_3$, 24 °C): δ = 7.71–7.68 (m, 2 H, Ar-H),

7.50–7.46, (m, 3 H, Ar-H), 3.86 (br., 1 H, NH), 1.41 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$, 24 °C): δ = 146.6 (C), 130.6 (CH), 128.7 (CH), 125.6 (CH), 54.3 (C), 31.1 (CH_3) ppm. IR ($CHCl_3$): $1/\lambda$ = 2974, 1475, 1368, 1053 cm^{-1}. $C_{10}H_{15}NOS$ (197.30): C 60.88, H 7.66, N 7.10; found C 60.61, H 7.61, N 6.96.

Supporting Information (see footnote on the first page of this article): Analytical data for 23 compounds with the ^1H NMR spectra.

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[9] In the absence of a copper-catalyst, the reaction of secondary amines (diethylamine or piperidine) with PhSH in air produced the corresponding sulfenamide in 30–41% yield; however, the reaction with the primary amine did not afford the sulfenamide at all.

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[12] Coupling of thiophenol with *tert*-butylamine by using CuI-bpy (10 mol-%) under oxygen afforded a mixture of sulfenamide, sulfinamide, and sulfonamide.

[13] Alkyl thiols or other amines did not afford satisfactory results.

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