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ORIGINAL PAPER

CuI-catalyzed synthesis of 2-(*tert*-butyldisulfanyl) heterocycles from 2-mercaptoheterocycles and *tert*-butanesulfinamide

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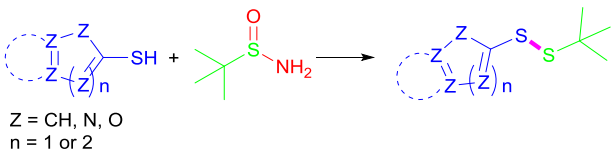
Abstract The valuable 2-(*tert*-butyldisulfanyl)heterocycles were effectively synthesized from 2-mercaptoheterocycles and *tert*-butanesulfinamide via unusual condensation. The reaction between 2-mercapto sulfur-containing heterocycles and *tert*-butanesulfinamide was performed under ligand-free CuI-catalyzed conditions. The synthetic processes described herein are simple, cost-efficient, and practical. Furthermore, a plausible mechanism is proposed for this transformation.

Graphical abstract



Keywords 2-(*tert*-Butyldisulfanyl)heterocycles · Copper catalysis · 2-Mercaptoheterocycles · *tert*-Butanesulfinamide · Condensation

Introduction

Disulfides are a class of valuable chemicals which can be used as antiviral agents in the treatment of AIDS [1], somatostatin agonists [2, 3], oxytocin analogs [4, 5], antitumor agents [6], and so on [7, 8]. Furthermore, disulfides are used as common organic reagents to construct new C–S bonds [9, 10].

Traditionally, disulfides are synthesized mainly through oxidation of thiols [11–13], reductive coupling of sulfonyl chlorides [14, 15] or sulfur chloride [16, 17], disulfides exchange [18, 19], or others [7, 20, 21]. Unsymmetrical disulfides are mainly synthesized via rhodium-catalyzed disulfide exchange. Efficient and green methodologies for the synthesis of unsymmetrical disulfides, especially with heterocyclic structures, are still strongly sought after [7].

As part of our ongoing research on reactions of *tert*-butanesulfinamide [22–25], the reaction of 2-mercaptobenzothiazole and *tert*-butanesulfinamide to yield *N*-(*tert*-butylsulfinyl)-2-aminobenzothiazole or 2-(*tert*-butylsulfinyl)thiobenzothiazole was explored. Nevertheless, the product was unexpectedly determined to be a 2-(*tert*-butyldisulfanyl)benzothiazole, based on ^{1}H, ^{13}C NMR, and mass spectra data.

The formation of 2-(*tert*-butyldisulfanyl)heterocycles was indeed verified via single crystal X-ray diffraction; the product **3a** was identified as 2-(*tert*-butyldisulfanyl)heterocycles, featuring an S–S single bond (Fig. 1).

In essence, an efficient method to synthesize unsymmetrical disulfides from commercially available thioheterocycles and *tert*-butanesulfinamide under mild conditions was revealed. To the best of our knowledge, *tert*-butanesulfinamide is firstly reported to act as oxidant and sulfur source rather than as nucleophiles and electrophiles in the reactions (Scheme 1) [26, 27].

Electronic supplementary material The online version of this article (doi:10.1007/s00706-015-1618-1) contains supplementary material, which is available to authorized users.

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Results and discussion

Typical Ullman conditions with K_2CO_3 as base and DMF as solvent were initially applied, obtaining a product with extremely low yield (Table 1, entry 1). Subsequently, a weak base (sodium acetate) was applied as additive, and 2-(*tert*-butyldisulfanyl)benzothiazole was obtained in much higher yield (entry 2). Solvents including DMA, DMSO, toluene, and 1,4-dioxane were also screened, but no better yield was obtained (entries 3–6 vs. 2). Changes of the copper source to CuBr, CuCl, Cu, and $Cu(OAc)_2$ were accompanied by poorer yields (entries 7–10 vs. 2). However, the use of Na_2SO_4 as an additive was observed to give an obvious increase of yield (entry 11). Surprisingly, magnesium sulfate dramatically increased the yield of 2-(*tert*-butyldisulfanyl)benzothiazole up to 96 % (entry 12). To increase temperature and to prolong reaction time are prove to be unnecessary (entries 13, 14 vs. 12). No addition of copper(I) iodide resulted in no product (entries 13 vs. 15).

The reaction of 2-mercapto sulfur-containing heterocycles and *tert*-butanesulfinamide were then examined under the optimized conditions (Table 2). One equivalent of *tert*-butanesulfinamide was enough, and excess substrate was not necessary (entries 2 vs. 1). However, benzo[*d*]oxazole-

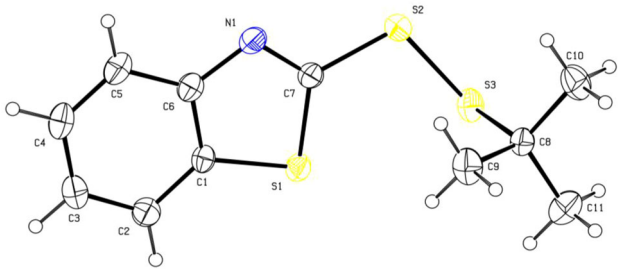
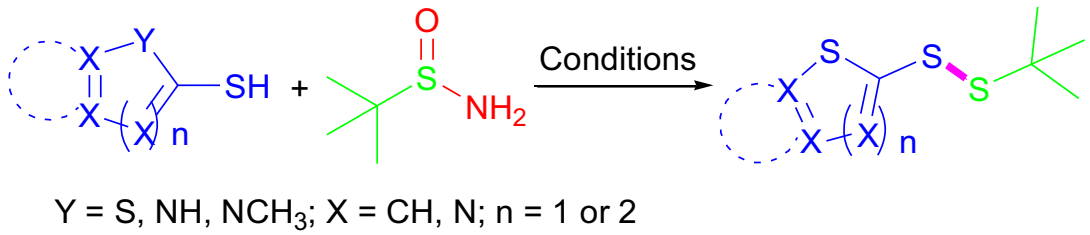


Fig. 1 Single crystal diagram of compound **3a**

Scheme 1



Y = S, NH, NCH_3; X = CH, N; n = 1 or 2

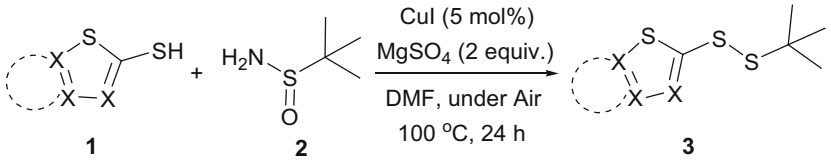
Table 1 Optimization of reaction conditions of 2-mercaptobenzothiazole and *tert*-butanesulfinamide

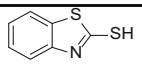
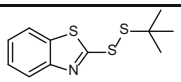
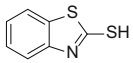
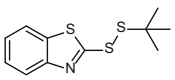
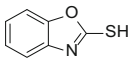
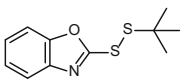
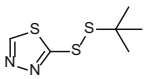
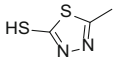
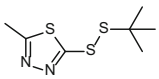
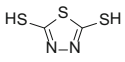
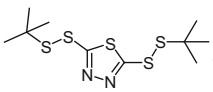
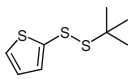
Entry	Catalyst	Additive	Solvent	*T*/°C	*T*/h	Yield/%[a]
1	CuI	K_2CO_3	DMF	100	24	<10
2	CuI	NaOAc	DMF	100	24	54
3	CuI	NaOAc	DMA	100	24	50
4	CuI	NaOAc	DMSO	100	24	34
5	CuI	NaOAc	Toluene	100	24	36
6	CuI	NaOAc	Dioxane	100	24	37
7	CuBr	NaOAc	DMF	100	24	41
8	CuCl	NaOAc	DMF	100	24	32
9	Cu	NaOAc	DMF	100	24	33
10	$Cu(OAc)_2$	NaOAc	DMF	100	24	38
11	CuI	Na_2SO_4	DMF	100	24	57
12	CuI	$MgSO_4$	DMF	100	24	96
13	CuI	$MgSO_4$	DMF	110	24	96
14	CuI	$MgSO_4$	DMF	100	48	96
15	–	$MgSO_4$	DMF	100	48	0

Reaction conditions: CuI (0.05 mmol), additive (2.0 mmol), 2-mercaptobenzothiazole (1.0 mmol), *tert*-butanesulfinamide (1.0 mmol), 4 cm^3 solvent, under air

[a] Isolated yield

Table 2 Reactions of 2-mercaptoheterocycles and *tert*-butanesulfinamide



Entry	2-Mercapto-heterocycle	Product		Yield /%[a]
1			**3a**	96
2[b]			**3a**	96
3			**3b**	51
4			**3c**	78
5			**3d**	91
6			**3e**	92
7			**3f**	89

Reaction conditions: CuI (0.05 mmol), $MgSO_4$ (2.0 mmol), 2-mercaptoheterocyle (1.0 mmol), *tert*-butanesulfinamide (1.0 mmol), 4 cm^3 DMF, 100 °C, 24 h, under air, unless otherwise noted

[a] Isolated yield

[b] *tert*-Butanesulfinamide (1.5 mmol)

2-thiol afforded a lower yield of 51 % (entry 3), perhaps benzoxazole cycle has higher aromaticity. For 2-mercapto-1,3,4-thiadiazole, good yield was obtained (entry 4). It can be assumed that an electron-donating methyl on 2-mercapto-1,3,4-thiadiazole benefits this reaction (entry 5). Interestingly, both the two mercapto groups in 1,3,4-thiadiazole-2,5-dithiol reacted with *tert*-butanesulfinamide (entry 6). In addition, 2-mercaptoazoles, thiophene-2-thiol reacted with *tert*-butanesulfinamide to produce 2-(*tert*-butyldisulfanyl)thiophene in 89 % yield as well (entry 7).

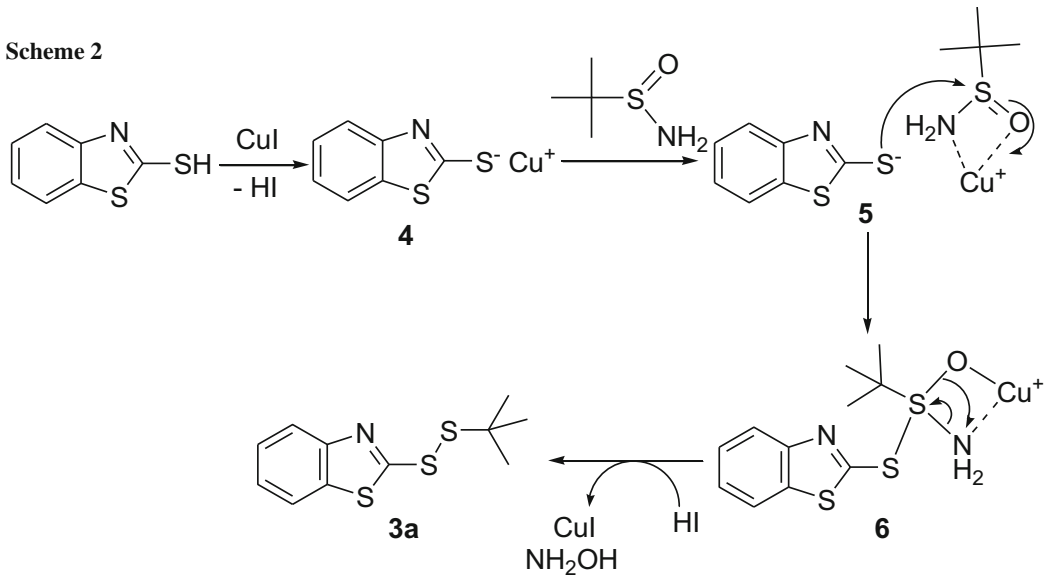
A plausible mechanism for condensation of 2-mercaptobenzothiazole and *tert*-butanesulfinamide to synthesize 2-(*tert*-butyldisulfanyl)heterocycles (Scheme 2) is, therefore, proposed. Under the reaction conditions, interaction of CuI and 2-mercaptobenzothioazole produces a cuprous salt of 2-mercaptobenzothioazole (**4**) and releases hydrogen iodide. The cuprous salt and *tert*-butanesulfinamide perform coordination transfer and nucleophilic attack (**5**). And then a complex **6** is formed. The complex **6** is not stable, and reductive elimination of complex **6** affords the final product **3a**, and releases hydroxylamine and CuI [28, 29].

In conclusion, a novel synthetic method of 2-(*tert*-butyldisulfanyl)heterocycles has been developed. CuI-catalyzed condensation of 2-mercapto sulfur-containing heterocycles and *tert*-butanesulfinamide afforded 2-(*tert*-butyldisulfanyl)heterocycles. This protocol is simple, cost-efficient, and practical.

Experimental

The chemicals were purchased from Aldrich, Adamas, Aladdin, Alfa Aesar, and Kelong Chemical Companies, and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using commercial silica gel plates (GF254). Purification of the synthesized compounds was carried out by flash column

Scheme 2



chromatography with silica gel (300–400 mesh). Melting points were determined on an X-4 melting-point apparatus with microscope. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or -400 spectrometer (300 or 400 MHz for ^{1}H NMR, and 75 or 101 MHz for ^{13}C NMR, respectively). Chemical shifts (δ) were reported in ppm referenced to an internal tetramethylsilane standard or the deuterated solvent DMSO-d_6 or $CDCl_3$. Coupling constants J were reported in Hertz (Hz). High-resolution mass spectra (HR-MS) were obtained with micrOTOF-Q II (Bruker Daltonics). All IR spectra were taken on a Bruker Tensor-27 infrared spectrometer with an OPUS workstation.

Typical procedure for CuI-catalyzed amination of 2-mercaptothiazole analogs 3a–3f

2-Mercaptobenzothiazole (167 mg, 1.0 mmol, 1.0 equiv.) and 121 mg *tert*-butanesulfinamide (1.0 mmol, 1.0 equiv.) were added into a clean oven-dried test tube equipped with a stirring bar, then 10 mg CuI (0.05 mmol, 5 mol %) and 2.0 equiv. of anhydrous $MgSO_4$ were added to the mixture, seal the tube, and then 4 cm^3 of DMF was injected in the tube by syringe. The mixture stirred in an oil bath heated at 100 °C for 24 h. After cooled to room temperature, 4 cm^3 water was injected into the mixture and extracted the mixture with ethyl acetate (15 cm^3 × 3); the organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **3a**.

2-(tert-Butyldisulfanyl)benzothiazole **(3a)**
Yield 96 %; light yellow solid; m.p.: 78–80 °C (Ref. [30] 82 °C).

2-(2-tert-Butyldisulfanyl)benzo[d]oxazole
(**3b**, $C_{11}H_{13}NOS_2$)
Yield 51 %; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 1H), 7.51-7.43 (m, 1H), 7.29 (dd, J = 6.7, 4.5 Hz, 2H), 1.65 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.80, 151.21, 141.93, 124.56 (J = 8.25 Hz), 124.20 (J = 6.75 Hz), 119.18 (J = 24.0 Hz), 110.04 (J = 22.5 Hz), 49.65, 30.91 ppm; IR (KBr): $\bar{\nu}$ = 3416, 3236, 2926, 2032, 1620, 1385, 1099, 991, 869, 621, 480 cm^{-1}; HRMS: *m/z* calcd for $C_{11}H_{14}NOS_2$ ($[M + H]^+$) 240.0511, found 240.0481.

5-(tert-Butyldisulfanyl)-1,3,4-thiadiazole
(**3c**, $C_6H_{10}N_2S_3$)
Yield 78 %; yellow solid; m.p.: 66–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.01 (s, 1H), 1.36 (s, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.87, 152.64, 50.74, 29.74 ppm; IR (KBr): $\bar{\nu}$ = 3929, 3415, 3236, 2378, 2029, 1618, 1385, 1089, 990, 847, 704, 621, 480 cm^{-1}; HRMS: *m/z* calcd for $C_6H_{11}N_2S_3$ ($[M + H]^+$) 207.0079, found 207.0058.

2-(tert-Butyldisulfanyl)-5-methyl-1,3,4-thiadiazole **(3d)**
Yield 91 %; yellow solid; m.p.: 70–72 °C (Ref. [31]: 55 °C).

2,5-Bis(2-tert-butyldisulfanyl)-1,3,4-thiadiazole **(3e)**
Yield 92 %; yellow solid; m.p.: 69–71 °C (Ref. [31]: 63 °C).

2-(tert-Butyldisulfanyl)thiophene (**3f**, $C_8H_{12}S_3$)
Yield 89 %; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$ (dd, $J = 5.3$, 1.1 Hz, 1H), 7.21 (dd, $J = 3.5$, 1.1 Hz, 1H), 6.93 (dd, $J = 5.2$, 3.6 Hz, 1H), 1.37 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 136.89$, 132.51, 129.42, 127.38 ($J = 12$ Hz), 48.98, 30.52 ppm; IR (KBr): $\bar{\nu} = 3927$, 3415, 3236, 2960, 2894, 2858, 2033, 1620, 1454, 1401, 1363, 1216, 1162, 1086, 988, 871, 846, 702, 621, 482 cm^{-1}; HRMS: *m/z* calcd for $C_8H_{13}S_3$ ($[M + H]^+$) 205.0174, found 205.0187.

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