CuBr-catalysed oxidative desulfurisation of thiobenzamides

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An efficient oxidative desulfurisation of thioamides by CuBr/TBHP is reported. Thioamides containing alkyl or aryl on the nitrogen undergo desulfurisation and give amides with good yields. Thioamides not containing substituent on the nitrogen undergo desulfurisation and give 1,2,4-thiadiazoles in moderate to good yields.

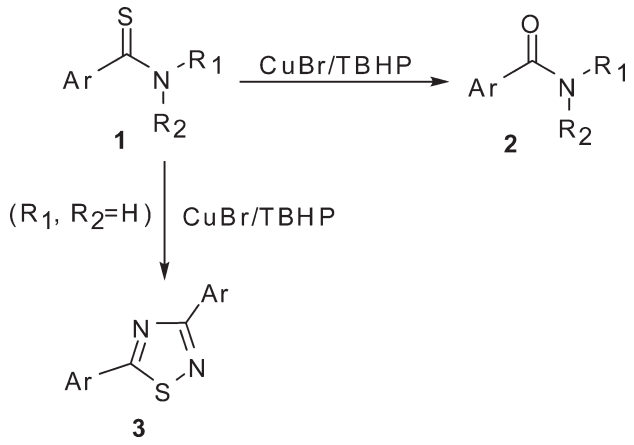
Keywords: CuBr, oxidative desulfurisation, thioamide

The conversion of thiocarbonyl compounds to their corresponding substrates has been extensively explored. According to the oxidants used, thioamides can undergo desulfurisation to generate amides,[1–8] thiadiazoles,[9–15] benzothiazoles,[16] *etc*.[17,18] For example, an effective system of $SOCl_2/H_2O_2$ has been used for the desulfurisation of thioamides to give amides.[1] Bose has reported the synthesis of benzothiazoles by intramolecular cyclisation of thioformanilides by DDQ[16]. In constrast, our group has found that DDQ mediates the oxidative dimerisation of thioamides which gives the different product, 1,2,4-thiadiazole.[15] The reported oxidants for the transformation of thioamides to amides or thiadiazoles are hydrogen peroxide,[1] oxygen,[2] *m*-chloroperbenzoic acid,[3] *tert*-butyl hypochlorite,[4] bromate or iodate solution,[5] bismuth nitrate,[6] hypervalent iodine,[9–11] dimethyl sulfoxide-electrophilic reagent,[12] polymer-supported diaryl selenoxide and telluroxide,[13] organotellurium,[14] *etc*. But some of these methods suffer from disadvantages such as the use of toxic or expensive reagents, difficult workup procedures. Therefore, the introduction of new methods and reagents for this transformation is still in demand.

Recently, the system of CuBr/TBHP (*tert*-butyl hydroperoxide) has been successfully applied in the oxidant reaction, especially in the cross-dehydrogenative-coupling reaction involving α-C–H bonds of nitrogen in amines.[19–27] With the interest of the conversion of thiocarbonyl compounds, herein, we report the system of CuBr/TBHP mediates an efficient oxidative desulfurisation of thiobenzamides to the corresponding products.

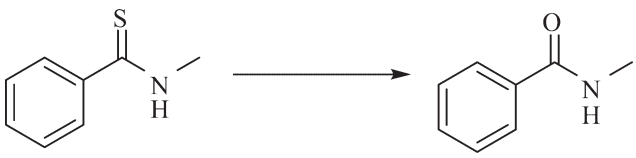
Results and discussion

To obtain the best reaction conditions, we selected the reaction of *N*-methylbenzothioamide with TBHP as a model. Initially, several catalysts (Table 1, entries 1–7) were screened. The reaction could proceed in all the catalysts tested and the product obtained was *N*-methylbenzamide. From Table 1, CuBr was chosen as the best catalyst. Then a series of solvents were examined (Table 1, entries 12–16). It was showed that the reaction gave the product with 89% yield when it was performed in $ClCH_2CH_2Cl$ (Table 1, entry 7).



Scheme 1

Table 1 Optimisation of the reaction conditions[a]



1a **2a**

Entry	Catalyst	Solvent[b]	Yield/%[c]
1	CuCl	$ClCH_2CH_2Cl$	77
2	CuI	$ClCH_2CH_2Cl$	62
3	$CuCl_2$	$ClCH_2CH_2Cl$	79
4	$CuBr_2$	$ClCH_2CH_2Cl$	80
5	$FeCl_2$	$ClCH_2CH_2Cl$	87
6	$FeCl_3$	$ClCH_2CH_2Cl$	74
7	CuBr	$ClCH_2CH_2Cl$	89
8	CuBr[d]	$ClCH_2CH_2Cl$	84
9	CuBr[e]	$ClCH_2CH_2Cl$	89
10	CuBr	$ClCH_2CH_2Cl$	77[f]
11	CuBr	$ClCH_2CH_2Cl$	82[g]
12	CuBr	CH_2Cl_2	82[h]
13	CuBr	CH_3NO_2	76
14	CuBr	1,4-Dioxane	83
15	CuBr	H_2O	44
16	CuBr	Toluene	64

[a] Reactions were carried out on a 0.5 mmol scale at 50 °C, TBHP (0.7 mol equiv., 70% in water), 10 mol% catalyst. [b] 1 mL. [c] Isolation yields. [d] 5 mol%. [e] 15 mol%. [f] r.t. [g] 60 °C. [h] 40 °C.

With the optimised reaction conditions established, various thiobenzamides were subjected to the oxidative desulfurisation (Table 2). All the thioamides containing alkyl or aryl on the nitrogen could proceed and the corresponding amides were obtained in 70–95% yields (Table 2, entries 1–11). No product was given when *N*-methyl-2-phenylethanethioamide was tried in the reaction (Table 2, entry 12).

We then investigated the thiobenzamides which do not contain substituent on the nitrogen (Table 3). Under the same reaction conditions, the thioamides underwent oxidative desulfurisation to give different products, 3,5-disubstituted-1,2,4-thiadiazoles. All the thioamides bearing an electron-donating or electron-withdrawing group on the aromatic ring could react and 63–90% yields were obtained. Obvious electronic effect of the substituent on the aromatic ring was observed.

In summary, we have developed an efficient oxidative desulfurisation of thiobenzamides by CuBr/TBHP. A series of benzamides and 3,5-disubstituted 1,2,4-thiadiazoles are synthesised concisely. It is a valuable addition to the existing methods available for the oxidative desulfurisation of thiobenzamides.

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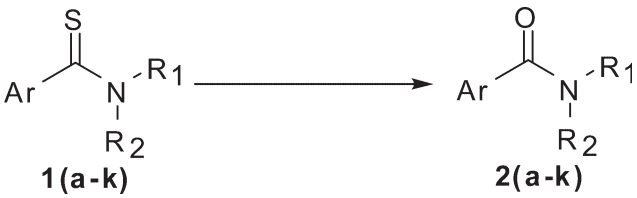
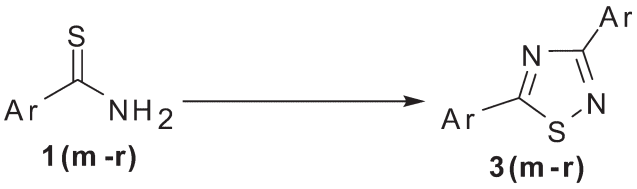
Table 2 Oxidative desulfurisation of thiobenzamides to benzamides[a]



Entry	Ar, R^1, R^2	Yield/%[b]
1	Ph, CH_3, H (**1a**)	89 (**2a**)
2	4-MeC_6H_4, CH_3, H (**1b**)	78 (**2b**)
3	4-BrC_6H_4, CH_3, H (**1c**)	79 (**2c**)
4	Ph, CH_3, CH_3 (**1d**)	71 (**2d**)
5	Ph, $CH(CH_3)_2$, H (**1e**)	91 (**2e**)
6	Ph, C_6H_{11}, H (**1f**)	79 (**2f**)
7	Ph, Ph, H (**1g**)	84 (**2g**)
8	Ph, 4-MeC_6H_4, H (**1h**)	96 (**2h**)
9	Ph, 4-ClC_6H_4, H (**1i**)	86 (**2i**)
10	4-MeC_6H_4, Ph, H (**1j**)	85 (**2j**)
11	4-ClC_6H_4, Ph, H (**1k**)	70 (**2k**)
12	$C_6H_5CH_2$, CH_3, H (**1l**)	Null

[a] Reactions were carried out on a 0.5 mmol scale at 50 °C, TBHP (0.7 mmol, 70% in water), 10 mol% catalyst for 3h.
[b] Isolation yields.

Table 3 Oxidative desulfurisation of thioamides to 1,2,4-thiadiazoles[a]



Entry	Ar	Yield/%[b]
1	Ph, **1m**	79, **3m**
2	4-$CH_3OC_6H_4$, **1n**	90, **3n**
3	4-FC_6H_4, **1o**	56, **3o**
4	3-$CH_3C_6H_4$, **1p**	63, **3p**
5	3-ClC_6H_4, **1q**	78, **3q**
6	2-thienyl, **1r**	78, **3r**

[a] Reactions were carried out on a 0.5 mmol scale at r.t., TBHP (0.7 mmol, 70% in water), 10 mol% catalyst for 0.5h.
[b] Isolation yields.

Experimental

Column chromatography was carried out on silica gel (200–300 mesh). ^{1}H NMR spectra was recorded on Bruker AMX-500 MHz instrument and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). IR spectra were determined on a Brucker Tensor 27 spectrometer. Melting points were uncorrected. All reagents were weighed and handled in air at room temperature and all reactions were performed without exclusion of air or moisture.

*Amide (***2a**–**k***) or thiadiazole (***3m**–**r***); general procedure*

TBHP (0.7 mmol), CuBr (10 mol%) was added to a stirred suspension of thioamide (**1**, 0.5 mmol) in 1,2-dichloroethane (1 mL), at 50 °C or room temperature. The mixture was stirred for the time indicated in Tables 2 and 3. After completion of the reaction, 1,2-dichloroethane was removed under reduced pressure. The residue obtained was purified through silica gel using petroleum ether/ethyl acetate (10:1–2:1) as an eluent.

N-Methylbenzamide (**2a**): Solid, m.p. 77–78 °C (lit.[28] 75–77 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78–7.62 (m, 2H), 7.50–7.47 (m, 1H), 7.43–7.40 (m, 2H), 6.42 (bs, 1H), 3.00 (s, 3H) ppm. IR (KBr): 3328, 1638, 1578, 1553, 698 cm^{-1}.

N-Methyl-p-toluamide (**2b**): Solid, m.p. 145–146 °C (lit.[28] 143–145 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.30 (bs, 1H), 3.00 (s, 3H), 2.39 (s, 3H) ppm. IR (KBr): 3338, 1633, 1549, 1508, 1303, 835, 752 cm^{-1}.

4-Bromo-N-methylbenzamide (**2c**): Solid, m.p. 163–164 °C (lit.[29] 163–164 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65–7.63 (m, 2H), 7.58–7.55 (m, 2H), 6.28 (bs, 1H), 3.00 (s, 3H) ppm. IR (KBr): 3344, 2932, 1639, 1550, 1483, 1322, 839, 750 cm^{-1}.

N, N-Dimethylbenzamide (**2d**): Solid, m.p. 44–46 °C (lit.[30] 43–45 °C). ^{1}H NMR (500 MHz, $CDCl_3$):[31] δ 7.43–7.38 (m, 5H), 3.10 (s, 3H), 3.01 (s, 3H) ppm. IR (KBr): 3465, 2934, 1625, 1340, 1087, 736 cm^{-1}.

N-Isopropylbenzamide (**2e**): Solid, m.p. 98–100 °C (lit.[32] 99–100 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77–7.75 (m, 2H), 7.51–7.48 (m, 1H), 7.44–7.41 (m, 2H), 5.98 (bs, 1H), 4.35–4.26 (m, 1H), 1.28 (s, 3H), 1.27 (s, 3H) ppm. IR (KBr): 3299, 2972, 1632, 1535, 698 cm^{-1}.

N-Cyclohexylbenzamide (**2f**): Solid, m.p. 145–146 °C (lit.[1] 144 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77–7.75 (m, 2H), 7.51–7.48 (m, 1H), 7.44–7.41 (m, 2H), 6.02 (bs, 1H), 4.03–3.95 (m, 1H), 2.06–2.03 (m, 2H), 1.79–1.75 (m, 2H), 1.69–1.65 (m, 1H), 1.49–1.39 (m, 2H), 1.30–1.20 (m, 3H) ppm. IR (KBr): 3315, 2935, 2853, 1627, 1578, 1533, 1330, 693 cm^{-1}.

N-Phenylbenzamide (**2g**): Solid, m.p. 161–162 °C (lit.[1] 161–163 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (bs, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H) ppm. IR (KBr): 3344, 2924, 1656, 1599, 1534, 1438, 751, 691 cm^{-1}.

N-(p-Tolyl)benzamide (**2h**): Solid, m.p. 158–159 °C (lit.[1] 158–159 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (bs,1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.55–7.53 (m, 3H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 2.35 (s, 3H) ppm. IR (KBr): 3310, 2924, 1648, 1510, 1320, 813, 695 cm^{-1}.

N-(4-Chlorophenyl)benzamide (**2i**): Solid, m.p. 196–197 °C (lit.[33] 192–194 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88–7.87 (m, 2H), 7.83 (bs, 1H), 7.63–7.61 (m, 2H), 7.60–7.57 (m, 1H), 7.53–7.50 (m, 2H), 7.36–7.35 (m, 2H) ppm. IR (KBr): 3350, 1655, 1519, 1493, 1399, 825, 719 cm^{-1}.

4-Methyl-*N*-phenylbenzamide (**2j**): Solid, m.p. 145–146 °C (lit.[33] 145–147 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (bs, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.39–7.36 (m, 2H), 7.29–7.27 (m, 2H), 7.17–7.14 (m, 1H), 2.43 (s, 3H) ppm. IR(KBr): 3449, 2924, 1650, 1524, 1439, 1321, 747, 689 cm^{-1}.

4-Chloro-N-phenylbenzamide (**2k**): Solid, m.p. 201–203 °C (lit.[33] 191–193 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.77 (bs, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J*=8.0 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H) ppm. IR(KBr): 3353, 2924, 1639, 1550, 1483, 1322, 839, 750 cm^{-1}.

3,5-Diphenyl-1,2,4-thiadiazole (**3m**): Solid, m.p. 89–90 °C (lit.[9] 91–91.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43–8.40 (m, 2H), 8.09–8.07 (m, 2H), 7.58–7.49 (m, 6H) ppm. IR (KBr): 1477, 1440, 1330, 760, 707, 682 cm^{-1}.

3,5-Bis(4-methoxyphenyl)-1,2,4-thiadiazole (**3n**): Solid, m.p. 140–141 °C (lit.[9] 139–139.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35–8.32 (m, 2H), 8.00–7.98(m, 2H), 7.03–7.00 (m, 4H), 3.90 (s, 6H) ppm. IR (KBr): 2937, 1608, 1476, 1252, 1168, 834, 747 cm^{-1}.

3,5-Bis(4-fluorophenyl)-1,2,4-thiadiazole (**3o**): Solid, m.p. 185–186 °C (lit.[34] 185–186 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40–8.37 (m, 2H), 8.07–8.04 (m, 2H), 7.25–7.17 (m, 4H) ppm. IR (KBr): 2925, 1599, 1475, 1233, 833, 744 cm^{-1}.

3,5-Bis(3-methylphenyl)-1,2,4-thiadiazole (**3p**): Solid, m.p. 56–57 °C (lit.[9] 55–57 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.90 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.44–7.39 (m, 2H), 7.37(d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 2.48 (s, 6H) ppm. IR (KBr): 2918, 1480, 1310, 800, 732 cm^{-1}.

3,5-Bis(3-chlorophenyl)-1,2,4-thiadiazole (**3q**): Solid, m.p.[35] 130–131 °C (lit. 128–128.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.29–8.27 (m, 1H), 8.08 (s, 1H), 7.91–7.90 (m, 1H), 7.55–7.53 (m, 1H), 7.50–7.44 (m, 3H) ppm. IR (KBr): 2925, 1467, 1304, 1004, 793, 731 cm^{-1}.

3,5-Bis(2-thiophene)-1,2,4-thiadiazole (**3r**): Solid, m.p. 92–94 °C (lit.[36] 84–86 °C). ^{1}H NMR (500 MHz, $CDCl_3$):[37] δ 7.95–7.94 (m, 1H), 7.71–7.70 (m, 1H), 7.60–7.59 (m, 1H), 7.48–7.47 (m, 1H), 7.19–7.15 (m, 2H) ppm. IR (KBr): 1540, 1465, 1414, 1312, 839, 709 cm^{-1}.

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Electronic Supplementary Information

Spectroscopic data for all products have been deposited in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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