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Thiol as a Synthon for Preparing Thiocarbonyl: Aerobic Oxidation of Thiols for the Synthesis of Thioamides

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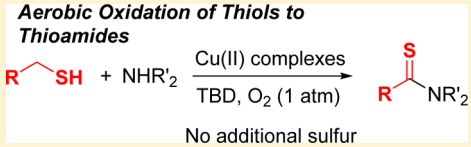
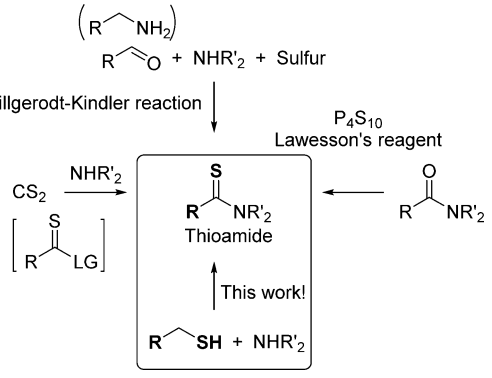
Supporting Information

ABSTRACT: It is a constant challenge to develop an environmentally friendly, atom-economical, and step-economical method for the preparation of thioamides. Herein, we describe an oxidation method that affords the direct conversion of thiols to thioamides without the use of exogenous sulfur reagents. This is the first instance of a successful utilization of thiols as a synthon for the preparation of thioamides under economical conditions.



The thioamide functional group is commonly found in biologically active compounds and antithyroid drugs.[1] It is also used as a synthetic precursor for a variety of important thio-heterocycles and in industrial applications as vulcanization agents and grease additives.[2] Various synthetic methods for thioamides have been subsequently reported; some of them are (1) reactions of carbon disulfide (CS_2) with nucleophiles, (2) Willgerodt–Kindler reactions using sulfur, and (3) thionation of amides using P_4S_{10} and Lawesson's reagent (Scheme 1).[3,4]

Scheme 1. Synthesis of Thioamides



The reaction of CS_2 with Grignard reagents has been reported as a classical method to form thioamides; however, it required additional modification of the dithiocarboxylic acid to form thioamides such as the formation of reactive thiocarbonyl benzotriazole intermediates.[4c] In addition, the volatility and toxicity of CS_2 were also addressed during the experiments. The Willgerodt–Kindler reaction using sulfur allows the direct formation of thioamides from aldehydes and amines. Unfortunately, it did not receive much attention for a long time due to the harsh reaction conditions required, but recent variations in the Willgerodt–Kindler reaction conditions such as the use of microwave irradiation, the use of water as a solvent, and the introduction of different aldehyde precursors made Willgerodt–Kindler-type reactions more useful for thioamide synthesis.[3b,4a,b,f,h,i,m] Finally, the use of thionation reagents to convert amides to thioamides is very selective, efficient, and general; nonetheless, the use of excessive amounts of sulfur transfer agents is not considered an atom-economical and environmentally friendly method.

While our research group was investigating the oxidative transformation of alcohols and aldehydes, we found that the direct conversion of thiols to thiocarbonyl derivatives had never been reported previously.[5] Although a few articles proposed the formation of a thiocarbonyl intermediate in the reaction of disulfides,[6] the direct formation of thiocarbonyl compounds from thiols has never been reported under aerobic conditions.[7] In this communication, we are pleased to report the use of thiols as a thiocarbonyl precursor for the synthesis of thioamides under aerobic conditions (Scheme 1). This is the first instance of a successful conversion of thiols to thiocarbonyls using oxygen as an oxidant. Even in the absence of metal complexes, thioamides were formed from thiols under aerobic oxidation conditions in reasonable yields.

Optimization results for thioamide formation from thiols are given in Table 1. Initially, the mixture of benzyl mercaptan (**1a**), morpholine (**1b**), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was subjected to aerobic conditions without the addition of metal complexes (Table 1, entry 1). The desired thioamide **1c** was obtained in 59% yield. To accelerate the oxidation process, we tested a variety of metal complexes with different loading percentages. With $CuCl_2$ loading percentages of 1, 2, 5, and 10 mol %, the yields for **1c** were 71, 82, 66, and 60%, respectively (entries 2–5). Under a nitrogen atmosphere, **1c** was obtained in 10% yield (entry 3). It can be seen that $CuCl_2$ loadings of 5 mol % or higher even retarded the formation of **1c**. Various copper and iron complexes were also tested with loadings of 2 mol %, and it was determined that $CuCl_2$ and $Cu(OTf)_2$ gave the most favorable yields for this

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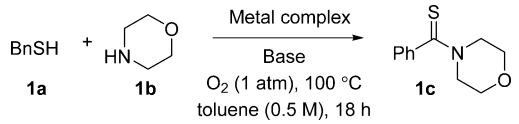
Table 1. Optimization of the Formation of Thioamide 1c



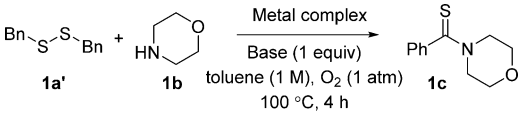
entry	metal complex (amt, mol %)	base (amt, equiv)	yield, %
1		TBD (1)	59
2	$CuCl_2$ (1)	TBD (1)	71
3	$CuCl_2$ (2)	TBD (1)	82 (10)[a]
4	$CuCl_2$ (5)	TBD (1)	66
5	$CuCl_2$ (10)	TBD (1)	60
6	CuCl (2)	TBD (1)	67
7	$CuBr_2$ (2)	TBD (1)	70
8	$Cu(OTf)_2$ (2)	TBD (1)	79
9	$FeCl_3 \cdot 6H_2O$ (2)	TBD (1)	70
10	$FeCl_2 \cdot 4H_2O$ (2)	TBD (1)	71
11	$CuCl_2$ (2)	DBU (1)	52

[a]Under a nitrogen atmosphere.

process (entries 6−10). In addition to TBD, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was utilized to afford **1c** in a lower yield (52%, entry 11).

Encouraged by our initial results, we decided to probe the reaction mechanism. On the basis of Ogata's publication of benzaldehyde formation from dibenzyl disulfide, we speculated that dibenzyl disulfide might be a key intermediate.[6] Under these oxidative conditions, the formation of a disulfide intermediate is not surprising.[7] The subsequent reaction of dibenzyl disulfide (**1a′**) with morpholine (**1b**) was conducted in the absence of metal complexes and in the presence of $CuCl_2$ (2 mol %). As shown in Table 2, **1c** was obtained with a yield of 54% without metal complexes, 73% with $CuCl_2$-TBD, and 44% with $CuCl_2$-DBU, which are comparable to the reaction yields of **1a**.

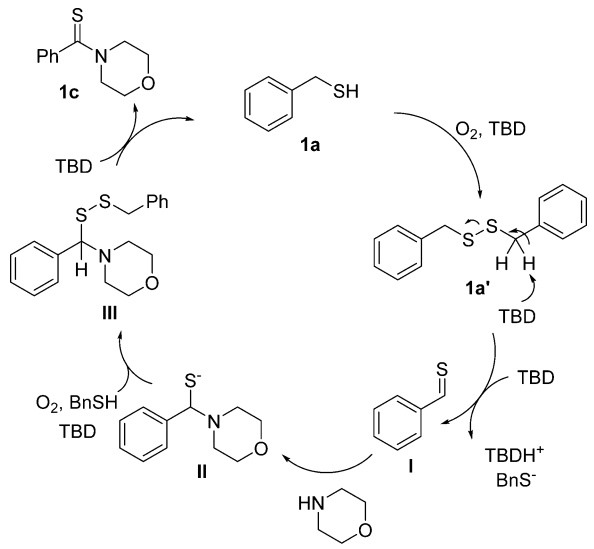
Table 2. Formation of Thioamide 1c from Dibenzyl Disulfide 1a′



entry	metal complex (amt, mol %)	base	yield, %
1		TBD	54
2	$CuCl_2$ (2)	TBD	73
3	$CuCl_2$ (2)	DBU	44

On the basis of the results in Tables 1 and 2, we propose a plausible mechanism (Scheme 2). In the beginning, **1a** undergoes dimerization to form **1a′** under aerobic conditions.[7] The deprotonation of disulfide **1a′** affords thiobenzaldehyde **I**, which reacts with morpholine to form **II**. Analogous to the formation of **1a′** under aerobic conditions, **III** was formed by oxygen from **II** and **1a**. Intermediate **III** then underwent deprotonation by TBD to afford thioamide **1c** and **1a**.[8] Because **1c** was formed in the absence of metal complexes in 59% yield, the proposed mechanism does not incorporate any copper complexes. Copper complexes are presumed to accelerate the oxidative process to form the disulfide intermediates **1a′** and **III**.

Scheme 2. Plausible Reaction Mechanism for the Formation of Thioamide 1c



The substrate scope of the reaction was investigated further by using diverse benzyl mercaptan derivatives and amines (Table 3). The chloro-substituted benzyl mercaptan **2a** reacted with morpholine to form thioamide **2c** in 78% yield (entry 1). The fluoro-substituted benzyl mercaptan **3a** was converted to the corresponding amide **3c** in 61% yield (entry 2). Formation of the thioamide using electron-rich thiols (**4a** and **5a**) and morpholine occurred smoothly to form **4c** and **5c** in 78 and 74% yields, respectively (entries 3 and 4). In addition to the reactiona of various thiols, a variety of amines were also tested under these reaction conditions. The reactions of six-membered heterocyclic amines **2b** and **3b** with benzyl mercaptan (**1a**) afforded **6c** and **7c** in 66% and 83% yields, respectively (entries 5 and 6). The five-membered heterocyclic amine pyrrolidine (**4b**) participated in the reaction to form **8c** in 86% yield (entry 7). Acyclic *sec*-amines **5b** and **6b** afforded the desired products **9c** and **10c** in 47 and 64% yields, respectively, which are comparable to those obtained using cyclic amines (entries 8 and 9). In comparison to the case for *sec*-amines, the reaction of a primary amine, benzyl amine **7b**, formed the desired product **11c** in a lower yield (20%, entry 10). Finally, 1,2,3,4-tetrahydroisoquinoline (**8b**) formed the desired product **12c**, in 70% yield (entry 11).

In conclusion, we have reported aerobic oxidation conditions for the synthesis of thioamides from thiols without the use of additional sulfur compounds. A diverse range of benzyl mercaptan derivatives reacted with morpholine to form various thioamides in good yields. The amine nucleophiles, which include aliphatic *sec*-amines, benzylic primary and *sec*-amines, and tetrahydroisoquinoline, all participated in the reaction to give good yields. A possible mechanism for the formation of thioamides was also proposed. Overall, thiocarbonyl compounds could be prepared directly from thiols; this process is not considered a general oxidation process of thiols, unlike alcohol oxidation. This methodology could potentially provide a platform for the synthesis of a variety of thiocarbonyl and thioamide derivatives under atom-economical and step-economical conditions.

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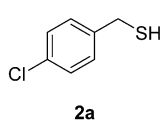
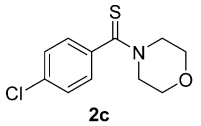
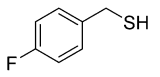
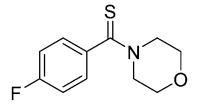
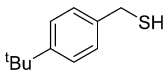
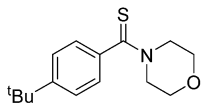
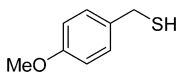
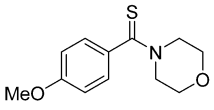
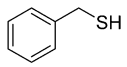
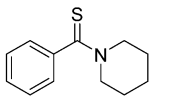
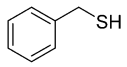
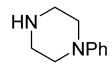
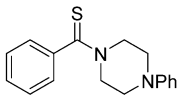
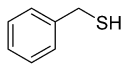
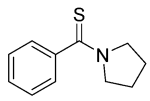
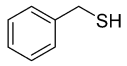
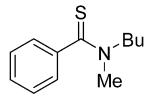
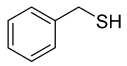
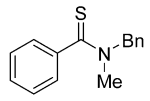
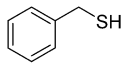
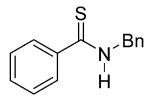
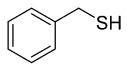
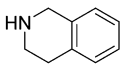
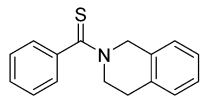
Table 3. Substrate Scope

Entry	Thiols	Amines	Products	Yield
1	 **2a**	 **1b**	 **2c**	78%
2	 **3a**	 **1b**	 **3c**	61%
3	 **4a**	 **1b**	 **4c**	78%
4	 **5a**	 **1b**	 **5c**	74%
5	 **1a**	 **2b**	 **6c**	66%
6	 **1a**	 **3b**	 **7c**	83%
7	 **1a**	 **4b**	 **8c**	86%
8	 **1a**	 **5b**	 **9c**	47%
9	 **1a**	 **6b**	 **10c**	64%
10	 **1a**	 **7b**	 **11c**	20%
11	 **1a**	 **8b**	 **12c**	70%

EXPERIMENTAL SECTION

General Considerations. Anhydrous solvents were transferred by an oven-dried syringe. Toluene was distilled prior to use. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a 400 MHz spectrometer. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). ^{13}C NMR spectra were recorded with a 100 MHz spectrometer. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) relative to the center of the triplet at 77.00 ppm for deuteriochloroform. High-resolution mass spectra were obtained with a magnetic sector−electric sector double-focusing mass analyzer. IR spectra were recorded with a FT-IR spectrometer. *Caution!* The experiments should be carried out in a well-ventilated hood because thiols have a very disagreeable smell.

General Procedure for the Reaction. Copper(II) chloride (1.3 mg, 0.01 mmol) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD; 69.6 mg, 0.5 mmol) was added to a solution of benzyl mercaptan (124.2 mg, 1.0 mmol) and morpholine (43.6 mg, 0.5 mmol) in toluene (0.5 M, 1 mL). A slow stream of O_2 was passed through this solution for 10 min. Then, the reaction mixture was stirred at 100 °C for 18 h under an O_2 atmosphere. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography by using 10% ether/90% hexane as an eluent to give morpholino(phenyl)methanethione (**1c**; 85.1 mg, 82%). In larger scale reactions, the yields of **1c** were 79 and 66% using 130.8 mg (1.5 mmol) and 218 mg (2.5 mmol) of morpholine, respectively.

Representative Procedure for the Reaction of Dibenzyl Disulfide with Morpholine. Copper(II) chloride (1.3 mg, 0.01 mmol) and 1,5,7-triazabicyclo[4.4.0] dec-5-ene (TBD; 69.6 mg, 0.5 mmol) was added to a solution of dibenzyl disulfide (123.2 mg, 0.5 mmol) and morpholine (43.6 mg, 0.5 mmol) in toluene (0.5 M, 1 mL). A slow stream of O_2 was passed through this solution for 10 min. Then, the reaction mixture was stirred at 100 °C for 4 h under an O_2 atomosphere. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography by using 10% ether/hexane as an eluent to give morpholino(phenyl)-methanethione (**1c**; 75.2 mg, 73%).

*Morpholino(phenyl)methanethione (**1c**).* Yield: 85.1 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.41 (t, 2H, J = 4.8 Hz), 3.86 (t, 2H, J = 4.8 Hz), 3.59 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 200.7, 142.3, 128.7, 128.4, 125.8, 66.8, 66.5, 52.6, 49.6. IR (neat, cm^{-1}): 2920, 2853, 1480, 1291, 1112. HRMS m/z (EI, [M]$^+$): $C_{11}H_{13}NOS$ calcd 207.0718, found 207.0719.

*(4-Chlorophenyl)(morpholino)methanethione (**2c**).* Yield: 95.0 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 2H, J = 8.4 Hz), 7.21 (d, 2H, J = 8.8 Hz), 4.38 (t, 2H, J = 4.4 Hz), 3.85 (t, 2H, J = 4.4 Hz), 3.59 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.0, 140.5, 134.6, 128.6, 127.2, 66.7, 66.5, 52.7, 49.7. IR (neat, cm^{-1}): 2949, 1474, 1289, 1114, 1033. HRMS m/z (EI, [M]$^+$): $C_{11}H_{12}ClNOS$ calcd 241.0328, found 241.0330.

*(4-Fluorophenyl)(morpholino)methanethione (**3c**).* Yield: 68.7 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, 2H, J = 8.4, 5.2 Hz), 7.05 (t, 2H, J = 8.8 Hz), 4.42 (t, 2H, J = 4.4 Hz), 3.88 (t, 2H, J = 4.4 Hz), 3.63 (d, 4H, J = 7.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.9, 164.1, 161.7, 138.7, 128.4, 128.3, 116.0, 115.7, 67.1, 67.0, 53.2, 50.3. IR (neat, cm^{-1}): 2983, 2920, 1601, 1485, 1292, 1228. HRMS m/z (EI, [M]$^+$): $C_{11}H_{12}FNOS$ calcd 225.0624, found 225.0623.

*(4-tert-Butylphenyl)(morpholino)methanethione (**4c**).* Yield: 102.6 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, 2H, J = 7.2 Hz), 7.22 (d, 2H, J = 7.6 Hz), 4.42 (s, 2H), 3.86 (s, 2H), 3.63 (s, 4H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 201.0, 152.1, 139.6, 125.9, 125.5, 67.1, 66.8, 52.9, 50.0, 35.1, 31.7. IR (neat, cm^{-1}): 2963, 2860, 1473, 1259, 1114. HRMS m/z (EI, [M]$^+$): $C_{15}H_{21}NOS$ calcd 263.1344, found 263.1345.

*(4-Methoxyphenyl)(morpholino)methanethione (**5c**).* Yield: 88.2 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, 2H, J = 8.4 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.40 (s, 2H), 3.86 (s, 2H), 3.81 (s, 3H), 3.65 (s, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 200.6, 159.9, 134.6, 127.8, 113.5, 66.7, 66.5, 55.5, 52.9, 50.1, 29.8. IR (neat, cm^{-1}): 2921, 2854, 1605, 1473, 1250, 1034. HRMS m/z (EI, [M]$^+$): $C_{12}H_{15}NO_2S$ calcd 237.0824, found 237.0824.

*Phenyl(piperidin-1-yl)methanethione (**6c**).* Yield: 68.2 mg, 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.35 (t, 2H, J = 5.6 Hz), 3.50 (t, 2H, J = 5.6 Hz), 1.77 (m, 4H), 1.56 (t, 2H, J = 5.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 198.9, 143.1, 128.1 (2C), 125.2, 53.2, 50.7, 27.0, 25.7, 24.3. IR (neat, cm^{-1}): 2939, 2856, 1479, 1444,

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1244. HRMS m/z (EI, $[M]^+$): $C_{12}H_{15}NS$ calcd 205.0925, found 205.0925.

*Phenyl(4-phenylpiperazin-1-yl)methanethione (**7c**).* Yield: 117.2 mg, 83%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 7H), 6.93 (m, 3H), 4.58 (t, 2H, J = 5.2 Hz), 3.75 (t, 2H, J = 5.2 Hz), 3.41 (t, 2H, J = 5.2 Hz), 3.17 (t, 2H, J = 5.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.2, 149.9, 142.4, 129.0, 128.5, 128.2, 125.6, 120.4, 116.3, 51.7, 49.8, 49.1, 48.8. IR (neat, cm^{-1}): 2916, 1599, 1494, 1229, 1023. HRMS m/z (EI, $[M]^+$): $C_{17}H_{18}N_2S$ calcd 282.1191, found 282.11935.

*Phenyl(pyrrolidin-1-yl)methanethione (**8c**).* Yield: 82.2 mg, 86%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 5H), 3.93 (t, 2H, J = 7.2 Hz), 3.43 (t, 2H, J = 7.2 Hz), 2.04 (m, 2H), 1.93 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.7, 143.7, 128.5, 128.1, 125.4, 53.9, 53.5, 26.7, 24.8. IR (neat, cm^{-1}): 2972, 2873, 1469, 1449, 1267. HRMS m/z (EI, $[M]^+$): $C_{11}H_{13}NS$ calcd 191.0769, found 191.0765.

*N-Butyl-N-methylbenzothioamide (**9c**).* Yield: 49.2 mg, 47%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 5H), 4.10 (t, 1H, J = 7.6 Hz), 3.52 (d, 1.5H, J = 1.6 Hz), 3.42 (t, 1H, J = 7.6 Hz), 3.06 (d, 1.5H, J = 1.6 Hz), 1.80 (m, 1H), 1.55 (m, 1H), 1.44 (m, 1H), 1.12 (m, 1H), 1.00 (t, 1.5H, 7.2 Hz), 0.77 (t, 1.5H, 7.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.7, 200.2, 143.6, 143.3, 128.2, 128.1 (2C), 125.4, 125.2, 55.9, 54.6, 42.1, 40.9, 30.6, 28.0, 20.4, 19.9, 14.2, 13.8. IR (neat, cm^{-1}): 2960, 2933, 1505, 1401, 1287, 1145. HRMS m/z (EI, $[M]^+$): $C_{12}H_{17}NS$ calcd 207.1082, found 207.1080.

*N-Benzyl-N-methylbenzothioamide (**10c**).* Yield: 76.8 mg, 64%. ^1H NMR (400 MHz, $CDCl_3$) (two rotamers): δ 7.26 (m, 10H), 5.43 (s, 1H), 4.69 (s, 1H), 3.45 (s, 1.5H), 2.98 (s, 1.5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 201.7, 143.1, 143.0, 135.2, 135.0, 128.8, 128.7, 128.4, 128.3, 128.2 (2C), 127.8 (2C), 127.7, 126.8, 125.5, 125.3, 59.5, 57.4, 41.3, 41.1. IR (neat, cm^{-1}): 3028, 2927, 1499, 1397, 1291, 1214. HRMS m/z (EI, $[M]^+$): $C_{15}H_{15}NS$ calcd 241.0925, found 241.0921.

*N-Benzylbenzothioamide (**11c**).* Yield: 22.3 mg, 20%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (br, 1H), 7.73 (d, 2H, J = 7.6 Hz), 7. 40 (m, 8H), 4.97 (d, 2H, J = 5.2 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.7, 141.3, 136.0, 131.0, 128.9, 128.3, 128.2, 128.0, 126.6, 51.1. IR (neat, cm^{-1}): 3310, 3029, 2925, 1522, 1449, 1336. HRMS m/z (EI, $[M]^+$): $C_{14}H_{13}NS$ calcd 227.0769, found 227.0768.

*(3,4-Dihydroisoquinolin-2(1H)-yl)(phenyl)methanethione (**12c**).* Yield: 88.1 mg, 70%. ^1H NMR (400 MHz, $CDCl_3$) (two rotamers): δ 7.13 (m, 9H), 5.40 (s, 1H), 4.69 (s, 1H), 4.51 (t, 1H, J = 6.4 Hz), 3.79 (t, 1H, J = 6.4 Hz), 3.13 (t, 1H, J = 6.0 Hz), 2.90 (t, 1H, J = 6.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.1, 199.5, 142.9, 142.8, 134.6, 133.2, 132.1, 128.6, 128.5, 128.3, 128.2, 128.1, 127.3, 126.8, 126.7, 126.6, 126.4, 125.8, 125.5, 54.0, 52.2, 50.0, 48.5, 29.9, 28.2. IR (neat, cm^{-1}): 3024, 2927, 1444, 1291, 1219. HRMS m/z (EI, $[M]^+$): $C_{16}H_{15}NS$ calcd 253.0925, found 253.0927.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^1H NMR and ^{13}C NMR spectra for **1c**–**12c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Bertlett, P. A.; Spear, K. L.; Jacobsen, N. E. *Biochemistry* **1982**, *21*, 1608–1611. (b) Bond, M. D.; Holmquist, B.; Vallee, B. L. *J. Inorg. Biochem.* **1986**, *28*, 97–105. (c) Yu, K.-L.; Torri, A. F.; Luo, G.; Cianci, C.; Grant-Young, K.; Danetz, S.; Tiley, L.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3379–3382. (d) Wei, Q.-L.; Zhang, S.-S.; Gao, J.; Li, W.-h.; Xu, L.-Z.; Yu, Z.-G. *Bioorg. Med. Chem.* **2006**, *14*, 7146–7153. (e) Gannon, M. K., II; Holt, J.; Bennett, S. M.; Wetzel, B. R.; Loo, T. W.; Bartlett, M. C.; Clarke, D. M.; Sawada, G. A.; Higgins, J. W.; Tombline, G.; Raub, T. J.; Detty, M. R. *J. Med. Chem.* **2009**, *52*, 3328–3341. (f) Petersson, E. J.; Goldberg, J. M.; Wissner, R. F. *Phys. Chem. Chem. Phys.* **2014**, *16*, 6827–6837.

(2) For selected papers on reactions using thioamides, see: (a) Jagodziński, T. S. *Chem. Rev.* **2003**, *103*, 197–227 (review article). (b) Goossen, L. J.; Blanchot, M.; Salih, K. S. M.; Karch, R.; Andreas, R.-N. *Org. Lett.* **2008**, *10*, 4497–4499. (c) Iwata, M.; Yazaki, R.; Chen, I.-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554–5560. (d) Kawato, Y.; Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2011**, *67*, 6539–6546. (e) Yu, H.; Liu, X.; Ding, L.; Yang, Q.; Rong, B.; Gao, A.; Zhao, B.; Yang, H. *Tetrahedron Lett.* **2013**, *54*, 3060–3062. (f) Matsuzawa, A.; Opie, C. R.; Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2014**, *20*, 68–71. (g) Murai, T.; Mutoh, Y. *Chem. Lett.* **2012**, *41*, 2–8 (highlight review).

(3) For selected review articles on thioamide synthesis and the Willgerodt–Kindler reaction, see: (a) Hurd, R. N.; DeLaMater, G. *Chem. Rev.* **1961**, *61*, 45–86. (b) Priebbenow, D. L.; Bolm, C. *Chem. Soc. Rev.* **2013**, *42*, 7870–7880.

(4) For selected articles on the synthesis of thioamides, see: (a) Moghaddam, F. M.; Ghaffarzadeh, M. *Synth. Commun.* **2001**, *31*, 317–321. (b) Aghapoor, K.; Darabi, H. R.; Tabar-Heydar, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1183–1187. (c) Katritzky, A. R.; Witek, R. M.; Rodriguez-Garcia, V.; Mohapatra, P. P.; Rogers, J. W.; Cusido, J.; Abdel-Fattah, A. A. A.; Steel, P. J. *J. Org. Chem.* **2005**, *70*, 7866–7881. (d) Kaleta, Z.; Tárkányl, G.; Gömöry, Á.; Kálmán, F.; Nagy, T.; Soós, T. *Org. Lett.* **2006**, *8*, 1093–1095. (e) Kaleta, Z.; Makowski, B. T.; Soós, T.; Dembinski, R. *Org. Lett.* **2006**, *8*, 1625–1628. (f) Okamoto, K.; Yamamoto, T.; Kanbara, T. *Synlett* **2007**, 2687–2690. (g) Cho, D.; Ahn, J.; De Castro, K. A.; Ahn, H.; Rhee, H. *Tetrahedron* **2010**, *66*, 5583–5588. (h) Pathare, S. P.; Chaudhari, P. S.; Akamanchi, K. G. *Appl. Catal. A: Gen.* **2012**, *425–426*, 125–129. (i) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 4274–4277. (j) Nguyen, T. B.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2014**, *16*, 310–313. (k) Doszczak, L.; Rachon, J. *Chem. Commun.* **2000**, 2093–2094. (l) Qu, Y.; Li, Z.; Xiang, H.; Zhou, X. *Adv. Synth. Catal.* **2013**, *355*, 3141–3146. (m) Cuntreddi, T.; Vanjari, R.; Singh, K. N. *Tetrahedron* **2014**, *70*, 3887–3892.

(5) Ji, M.; Wang, X.; Lim, Y. N.; Kang, Y.-W.; Jang, H.-Y. *Eur. J. Org. Chem.* **2013**, 7881–7885.

(6) For the conversion of dibenzyl disulfide to benzaldehyde, see: (a) Ogata, Y.; Nakagawa, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1193–1194. (b) Tanimoto, S.; Nazawa, S.; Inoue, Y. *Bull. Inst. Chem. Res., Kyoto Univ.* **1990**, *68*, 193–198.

(7) For selected papers regarding disulfide formation, see: (a) Liu, K. T.; Tong, Y. C. *Synthesis* **1978**, 669–670. (b) Pryor, W. A.; Church, D. F.; Govindan, C. K.; Crank, G. *J. Org. Chem.* **1982**, *47*, 156–159. (c) Firouzabadi, H.; Iranpoor, N.; Parham, H. A. *Synth. Commun.* **1984**, 717–724. (d) McKilop, A.; Koyuncu, D. *Tetrahedron Lett.* **1990**, *31*, 5007–5010. (e) Evans, B. J.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1990**, *55*, 2337–2344. (f) Choi, J.; Yoon, N. M. *J. Org. Chem.* **1995**, *60*, 3266–3267. (g) Shaabani, A.; Lee, D. G. *Tetrahedron Lett.* **2001**, *42*, 5833–5836. (h) Ali, M. H.; McDermott, M. *Tetrahedron Lett.* **2002**, *43*, 6271–6273. (i) Hajipour, A. R.; Mallakpour, S. E.; Adibi, H. *J. Org. Chem.* **2002**, *67*, 8666–8668. (j) Khazaei, A.; Zolfigol, M. A.; Rostami, A. *Synthesis* **2004**, 2959–2961. (k) Silveira, C. C.; Mendes, S. R. *Tetrahedron Lett.* **2007**, *48*, 7469–7471. (l) Ruano, J. L. G.; Parra, A.; Alemán, J. *Green Chem.* **2008**, *10*, 706–711. (m) Singh, D.; Galetto, F. Z.; Soares, L. C.; Rodrigues, O. E. D.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, *67*, 2661–2665. (n) Dhakshinamoorthy, A.; Alvaro,

M.; Garcia, H. *Chem. Commun.* **2010**, *46*, 6476−6478. (o) Abaee, M. S.; Mojtahedi, M. M.; Navidipoor, S. *Synth. Commun.* **2011**, *41*, 170−176.
(8) (a) Carmack, M.; Behforouz, M.; Berchtold, G. A.; Berkowitz, S. M.; Wiesler, D.; Barone, R. *J. Heterocycl. Chem.* **1989**, *26*, 1305−1318. (b) Carmack, M. *J. Heterocycl. Chem.* **1989**, *26*, 1319−1323.

dx.doi.org/10.1021/jo501378v | *J. Org. Chem.* 2014, 79, 7256−7260