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Mild Method for the Conversion of Amides to Thioamides

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Abstract: Aqueous ammonium sulfide was found to be an ideal substitute for hydrogen sulfide for the thiolysis of activated amides. High yields of the corresponding thioamides were obtained for a broad range of substrates, using two different procedures that are both operationally simple and inexpensive, as well as amenable to large-scale preparation. Preliminary results indicate that aqueous ammonium sulfide may also replace hydrogen sulfide in the synthesis of thionoesters from amides.

Heterocycles containing both nitrogen and sulfur within their backbones are found in all areas of chemistry, and over the past several years, there have been many synthetic strategies aimed at their preparation from simple and readily available precursors. One such strategy that has been used on numerous occasions involves the use of thioamides as starting materials, where both atoms can be introduced within the heterocyclic system in a single step.[1] In view of their synthetic importance, many routes have been developed to gain access to thioamides from various sources.[2]

Not surprisingly, one of the most exploited routes to thioamides involves the thionation of their amide analogues.[3] These can be classified as either proceeding through direct treatment of the amide with the thionating reagent or by prior activation of the amide with an electrophilic reagent. Methods employing the former strategy include treatment of the amide with P_4S_{10}, either with or without additives,[4] use of diethylthiocarbamoyl chloride,[5] ethylaluminum sulfide,[6] or boron sulfide,[7] and use of Lawesson's reagent.[8] A polymer-supported thionating reagent prepared from a commercially available diamine resin and ethyl dichlorothiophosphate has also recently been disclosed,[9] along with procedures involving microwave irradiation.[10] Methods that proceed through prior activation of the amide include combinations of oxalyl chloride or phosphorus oxychloride with benzyltriethylammonium tetrathiomolybdate,[11] phosphorus oxychloride with hexamethyldisilathiane,[12] and trialkyloxonium tetrafluoroborates with sodium hydrosulfide.[13]

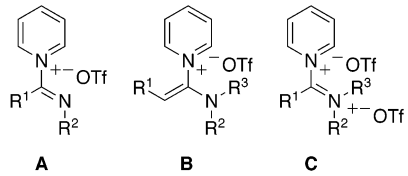

FIGURE 1. Pyridinium salts generated from the treatment of amides with Pyr and Tf_2O.

Over the past several years, our research group has enjoyed continued success in the area of amide activation by using trifluoromethanesulfonic (triflic) anhydride in the presence of pyridine. A wide variety of functional group interconversions starting from amides were rendered efficient by addition of the appropriate heteronucleophile.[14] The effectiveness of these reactions stems from the highly electrophilic nature of pyridinium salts **A**−**C**, formed from secondary and tertiary amides during the activation process (Figure 1).[15] In our initial procedure for the conversion of amides to thioamides, we relied on the use of hydrogen sulfide (H_2S) to effect the thiolysis of the pyridinium salts.[16] However, the inability to deliver a controlled amount of thionating reagent, combined with the requirement of using specialized equipment, prompted us to find a safer, cheaper, and more convenient alternative to effect this transformation.

Initially, we focused on the use of anhydrous sodium hydrosulfide (NaSH) and found that the addition of an excess of this reagent to the activated amides produced the desired thioamides in good yields.[17] Unfortunately, these reactions proceeded most efficiently with NaSH prepared by reacting hydrogen sulfide with sodium ethoxide in ethanol,[18] since the commercial material was found to be inadequate for our purposes. In addition, the

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(1) For a recent review on the synthesis of heterocycles from thioamides, see: Jagodzinski, T. S. *Chem. Rev.* **2003**, *103*, 197.

(2) For reviews on the preparation of thioamides, see: (a) Schaumann, E. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6; Chapter 2.4, pp 419−434. (b) Bauer, W.; Kühlein, K. In *Methoden Org. Chem.* **1985**, *E5*, 1218. (c) Walter, W.; Bode, K.-D. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 447. (d) Hurd, R. N.; De La Mater, G. *Chem. Rev.* **1961**, *61*, 45. (e) see also ref 3 and 8.

(3) For a review on thionation methods, see: Brillon, D. *Sulfur Rep.* **1992**, *12*, 297.

(4) (a) Hartke, K.; Gerber, H.-D. *J. Prakt. Chem.* **1996**, *338*, 763. (b) Use of ultrasound, see: Raucher, S.; Klein, P. *J. Org. Chem.* **1981**, *46*, 3558. (c) Use of $NaHCO_3$, see: Scheeren, J. W.; Ooms, P. H. J.; Nivard, R. J. F. *Synthesis* **1973**, 149. (d) Use of Na_2CO_3, see: Brillon, D. *Synth. Commun.* **1990**, *20*, 3085. (e) Use of RLi, see: Goel, O. P.; Krolls, U. *Synthesis* **1987**, 162. (f) Use of $(TMS)_2O$, see: Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461.

(5) Ogata, M.; Matsumoto, H. *Heterocycles* **1978**, *11*, 139.

(6) Hirabayashi, T.; Inoue, K.; Yokota, K. *J. Organomet. Chem.* **1975**, *92*, 139.

(7) (a) Steliou, K.; Mrani, M. *J. Am. Chem. Soc.* **1982**, *104*, 3104. (b) Wojtkowski, P. W.; Dolfini, J. E.; Kocy, O.; Cimarusti, C. M. *J. Am. Chem. Soc.* **1975**, *97*, 5628.

(8) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

(9) Ley, S. V.; Leach, A. G.; Storer, R. I. *J. Chem. Soc., Perkin Trans. 1* **2001**, 358.

(10) Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697.

(11) Ilankumaran, P.; Ramesha, A. R.; Chandrasekaran, S. *Tetrahedron Lett.* **1995**, *36*, 8311.

(12) Smith, D. C.; Lee, S. W.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 348.

(13) Bodine, J. J.; Kaloustian, M. *Synth. Commun.* **1982**, *12*, 787.

(14) (a) Amidines, see: Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677. (b) Thiazolines, see: Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908. (c) Esters, see: Charette, A. B.; Chua, P. *Synlett* **1998**, 163. (d) Cyclic Ortho esters, see: Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499.

(15) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694.

(16) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1998**, *39*, 245.

(17) For instance, thioamides **2c** (80%), **2d** (63%), **2f** (94%), and **5b** (90%) were obtained after adding NaSH (3.0 equiv) to the activated amides at 0 °C.

(18) Kleinberg, J. *Inorg. Synth.* **1963**, *7*, 128.

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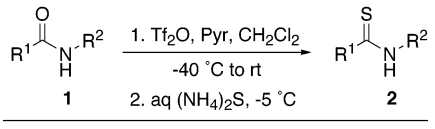
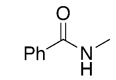
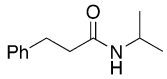
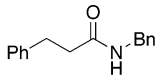
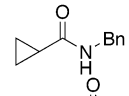
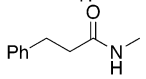
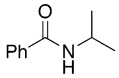
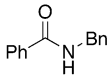
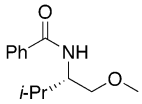
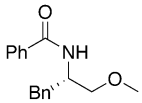
TABLE 1. Synthesis of Secondary Thioamides



1 **2**

Entry	Substrate	Product	Yield (%)[a]
1		**2a**	37 (A)[b]
2			91 (B)
3		**2b**	33 (A)
4			62 (B)
5		**2c**	42 (A)
6			83 (B)
7		**2d**	35 (A)
8			75 (B)
9		**2e**	41 (A)
10			80 (B)
11		**2f**	89 (A)[c]
12		**2g**	90 (A)
13			88 (A)[d]
14		**2h**	82 (A)
15		**2i**	86 (A)

[a] The letter in parentheses refers to the method of addition of $(NH_4)_2S$. Method A: addition of ammonium sulfide to the reaction mixture. Method B: slow addition of reaction mixture to ammonium sulfide. [b] 3 was also isolated (53%). [c] Addition done at −15 °C. [d] Performed on a 5 mmol scale with commercial reagents.

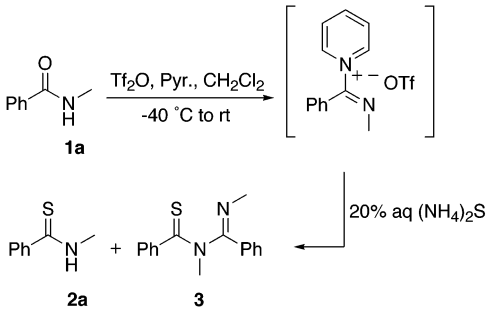
high cost associated with this reagent convinced us to search for a more affordable alternative.

While screening for a better thionating reagent, we were curious to see if a 20 wt % aqueous solution of ammonium sulfide ($(NH_4)_2S$) could be a viable substitute for either hydrogen sulfide or sodium hydrosulfide. At first, the idea may seem counterintuitive, since the water or ammonia present could also react with the activated amide to give either the starting material or an amidine, but we reasoned that the highly nucleophilic character of the sulfide ion may override their effect. Indeed, treatment of a nitrile with 20% aqueous ammonium sulfide was reported to give a high yield of the primary thioamide.[19]

As illustrated in Table 1, addition of 1.5 equiv of aqueous $(NH_4)_2S$ to the activated amides at −5 °C produced the desired secondary thioamides, albeit in modest yields (method A, see entries 1, 3, 5, 7, and 9). The addition of more aqueous $(NH_4)_2S$ (3.0 and 6.0 equiv) did not improve the conversions, nor did conducting the reaction at a higher temperature (20 °C) when using amide **1e** as a model substrate. In virtually every run

(19) (a) Spychala, J. *Tetrahedron* **2000**, *56*, 7981. (b) Spychala, J. *Synth. Commun.* **1997**, *27*, 3431.

SCHEME 1



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

using this amide, a less polar byproduct was formed along with the thioamide (determined by TLC analysis), but attempts to isolate the former by chromatography failed in every case. To gain further insight, we deemed it necessary to determine the nature of this product and decided to screen other amides. Gratifyingly, when amide **1a** was used, the byproduct proved to be stable and was easily purified by chromatography. Full spectral characterization of this compound clearly established that *N*,*N*′-dimethyl-*N*-thiobenzoylamidine (**3**) was formed over the course of the reaction, presumably according to the sequence outlined in Scheme 1.[20]

Since this product is formed by condensation of thioamide **2a** with the pyridinium salt, we reasoned that proceeding by slow addition (30−45 min) of the pyridinium salt into the aqueous $(NH_4)_2S$ solution (3.0 equiv) would obviate the formation of undesired **3** (method B). To our delight, the yields of thioamides increased dramatically, as can be seen by comparing entries 1−10 in Table 1 (methods A and B). The extent of dimerization appears to be very sensitive to steric interactions, and in the cases where both R^1 and R^2 are bulky, method A can be used (compare entries 1 and 9 with entries 11−13). Amides such as **1h** and **1i**, which we have recently reported as effective chiral auxiliaries for the diastereoselective synthesis of 2-substituted 1,2-dihydropyridines,[21] were also smoothly converted to their corresponding thioamides in high yields. The reaction can be performed on a more substantial amount of amide, and the solvent (dichloromethane) and reagents (pyridine, triflic anhydride) do not require extensive purification or drying prior to use (compare entries 12 and 13).[22] Due to the nature of the thionating reagent, crude reaction mixtures obtained after a simple filtration on a short pad of silica gel are devoid of any major impurities, which can be a serious drawback when other thionating reagents are used.

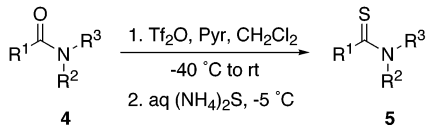
The method is also applicable for the synthesis of tertiary thioamides and thiolactams, as depicted in Table 2. Amides **4a**, **4b**, **4d** and **4e** reacted smoothly to give the corresponding thioamides in high yields according to method A, whereas amide **4c** required the slow addition of the reaction mixture to the aqueous $(NH_4)_2S$ solution and only gave a moderate yield of the thioamide.

(20) This compound has been previously reported, but no spectral characterization was available: Takikawa, Y.; Shimada, K.; Sato, K.; Sato, S.; Takizawa, S. *Bull. Chem. Soc. Jpn* **1985**, *58*, 995.

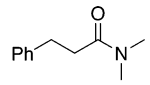
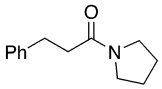
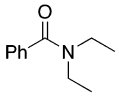
(21) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

(22) The reaction was also performed on a 25 mmol scale with amide **1g** according to method A (84%).

TABLE 2. Synthesis of Tertiary Thioamides and Thiolactams



4 **5**

Entry	Substrate	Product	Yield (%)[a]
1		**5a**	95 (A)
2		**5b**	90 (A)
3		**5c**	53 (B)
4		**5d**	85 (A)
5		**5e**	92 (A)

[a] The letter in parentheses refers to the method of addition of $(NH_4)_2S$. Method A: addition of ammonium sulfide to the reaction mixture. Method B: slow addition of reaction mixture to ammonium sulfide.

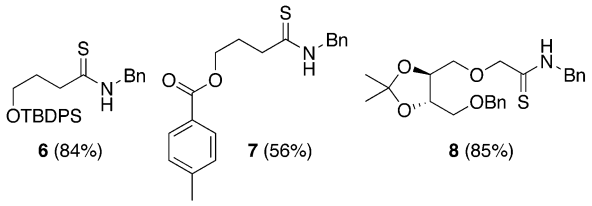
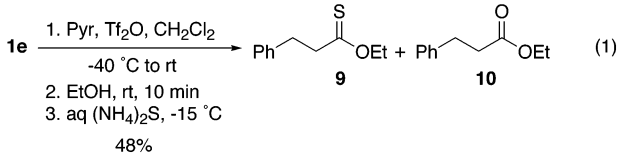


FIGURE 2. Functional/protecting group compatibility.

To further illustrate the generality of this approach, we decided to investigate the compatibility of the reaction conditions employed with some of the more common functional groups encountered in total synthesis. In our preliminary communication, we demonstrated that silyl ethers, benzyl ethers, acetonides, and esters were not affected over the course of the reaction, and we were relieved to see that the use of aqueous ammonium sulfide did not significantly affect the reaction either (see Figure 2). Indeed, yields were comparable to those obtained with H_2S for thioamides **6** and **8**, whereas a slight decrease was observed in the case of thioamide **7** bearing a benzoate protecting group.

Finally, preliminary results suggest that aqueous ammonium sulfide can replace hydrogen sulfide in the conversion of amides to thionoesters (see eq 1). Accordingly, after initial activation of amide **1e** with triflic anhydride and pyridine, sequential treatment with EtOH (1.5 equiv) and aqueous $(NH_4)_2S$ (1.5 equiv) gave thionoester **9** along with small amounts of ester **10** (6:1 ratio).



In conclusion, we have shown that aqueous ammonium sulfide is a suitable replacement for hydrogen sulfide for the conversion of amides into thioamides. The ability of delivering a controlled amount of this inexpensive and widely available reagent, without having to rely on any specialized equipment, are key features that any synthetic chemist will surely appreciate. The yields for a variety of thioamides were comparable with our previously reported procedure, and the conditions were shown to be tolerant of other functional groups as well. The use of aqueous $(NH_4)_2S$ was also extended to the synthesis of a thionoester, albeit in modest yield. Further improvements will be reported in due course.

Experimental Section

Method A. A solution of amide (1 mmol) and pyridine (240 μL, 3 mmol) in dichloromethane (5.0 mL) was cooled to −40 °C, and trifluoromethanesulfonic anhydride (200 μL, 1.2 mmol) was added along the inner side of the flask. The mixture was allowed to gradually warm to −5 °C over a period of 2 h and was then stirred for an additional 2 h at room temperature. The reaction was then cooled to −5 °C, and aqueous ammonium sulfide (510 μL of a 20 wt % solution, 1.5 mmol) was rapidly added. After ca. 2 h at −5 °C, the crude reaction mixture was filtered through a short pad of silica. Flash chromatography of the resulting residue with EtOAc/hexane afforded the corresponding thioamide.

Method B. A solution of amide (1 mmol) and pyridine (240 μL, 3 mmol) in dichloromethane (5.0 mL) was cooled to −40 °C, and trifluoromethanesulfonic anhydride (200 μL, 1.2 mmol) was added along the inner side of the flask. The mixture was allowed to gradually warm to −5 °C over a period of 2 h and stirred for an additional 2 h at room temperature. The resulting solution was then added dropwise to aqueous ammonium sulfide (1.02 mL of a 20 wt. % solution, 3.0 mmol) cooled to −5 °C over a 30−45 min period. After ca. 2 h at −5 °C, the crude reaction mixture was filtered through a short pad of silica. Flash chromatography of the resulting residue with EtOAc/hexane afforded the corresponding thioamide.

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Supporting Information Available: General information and characterization data for thioamides **2a**−**i**, **5a**−**c**, **6**−**8**, and amidine **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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