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## Preparation of Primary Thioamides From Nitriles Using Sodium Hydrogen Sulfide and Diethylamine Hydrochloride

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**Abstract:** Primary thioamides are prepared in moderate to excellent yields by treating nitriles with sodium hydrogen sulfide and diethylamine hydrochloride in an appropriate solvent with mild heating.

Keywords: Diethylamine hydrochloride, nitrile, sodium hydrogen sulfide, thioamide

Primary thioamides are an important class of molecules, which have found wide use within the synthetic organic chemistry community. In particular they are useful intermediates in the preparation of sulfur-containing heterocycles such as thiazoles.<sup>[1]</sup> Consequently there is a wide body of literature regarding the production of primary thioamides, which vary in the precursors and the reagents employed.<sup>[2]</sup> The most common substrate employed is a nitrile. Examples of reagents are phosphorus decasulfide and sodium sulfide,<sup>[3]</sup> thioacetic acid,<sup>[4]</sup> O,O-dialkyl dithiophosphates,<sup>[5,6]</sup> diphenylphosphinodithioic acid,<sup>[7]</sup> ammonium sulfide,<sup>[8]</sup> and sodium trimethylsilanethio-late.<sup>[9,10]</sup> The most common method involves the addition of hydrogen sulfide to a nitrile.<sup>[11]</sup> A base, either organic or inorganic, is usually employed in either catalytic or stoichiometric quantity. Although effective

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for the conversion of most aromatic nitriles, this method is not very efficient for the conversion of nonactivated aliphatic nitriles. It had been reported that a combination of a secondary amine and a polar aprotic solvent such as N,Ndimethyl formamide (DMF) was an effective medium for the conversion of aliphatic nitriles to thioamides using hydrogen sulfide.<sup>[12]</sup> This method, although reasonably effective, suffers from several drawbacks. The use of the toxic and obnoxious (stench) hydrogen sulfide is required, and the stoichiometry of this gaseous reagent is difficult to control. In addition the isolation of low-molecular-weight or water-soluble thioamides from the DMF on workup can be problematic.

We report herein a variation on this method, which utilizes a mixture of the solid reagents sodium hydrogen sulfide hydrate and diethyl amine hydrochloride in either DMF or a mixture of 1,4-dioxane and water as solvent (Scheme 1). The need for gaseous hydrogen sulfide is eliminated and accurate control of reagent stoichiometry is readily achieved. For thioamides with some aqueous solubility the use of the water/1,4-dioxane solvent system simplifies product isolation, which can be carried out via exhaustive extraction with ethyl acetate. Aromatic and activated nitriles are rapidly converted in high yield. Nonactivated aliphatic nitriles are converted more slowly, and an excess of reagents is required to help drive the reaction toward completion, especially with hindered nitriles such as t-butyl nitrile (Table 1).

## **GENERAL REACTION PROCEDURE**

Nitrile (75 mmol), water (40 mL), 1,4-dioxane (40 mL), sodium hydrogen sulfide hydrate (225 mmol; caution, toxic!), and diethyl amine hydrochloride (225 mmol) (6 eq. of reagents used for t-butyl nitrile) were added to a threenecked, round-bottomed flask equipped with a thermometer, a magnetic stirrer, and nitrogen inlet. The solution was then heated to  $55^{\circ}$ C until GC, LC/MS, or TLC showed that conversion was maximal (in the case of aliphatic nitriles conversion was not always complete). The reaction was allowed to cool, water (200 mL) was added, and the product was either isolated by filtration or extracted with ethyl acetate (6 × 75 mL). The combined extracts were dried over magnesium sulfate, and the solvent was evaporated. The product was characterized by <sup>1</sup>H NMR and <sup>13</sup>C NMR. In most cases the product was of sufficient purity to use directly. If required



Scheme 1.

Entry	Nitrile	Solvent	Time (h)	Yield (%)
1	<sup>n</sup> C <sub>11</sub> H <sub>22</sub> CN	DMF	72	58 <sup><i>a</i></sup>
2	C <sub>2</sub> H <sub>5</sub> CN	Dioxane/water	48	76
3		Dioxane/water	42	97
4	MeO C <sub>ŠN</sub>	Dioxane/water	3	85
6	HOCEN	Dioxane/water	96	56 <sup><i>a</i></sup>
7	C <sup>EN</sup>	Dioxane/water	6	98
8	O C <sup>EN</sup>	Dioxane/water	6	98
9	of the case	Dioxane/water	6	91
10	¥ <sup>C≦N</sup>	DMF	48	50

Table 1. Conversion of nitriles to thioamides

<sup>a</sup>Yield following purification.

the product could be purified either using flash chromatography or recrystallization.

Samples of thioamides prepared in Table 1 were analyzed as follows.

- 1. Mp 86.5°C (ethanol); lit.<sup>[13]</sup> 82–83°C. Microanalysis: Found C, 66.11; H, 11.77; N, 6.35. C<sub>12</sub>H<sub>25</sub>NS requires C, 66.91; H, 11.70; N, 6.50. 2. Mp 40.6°C (hexane/ether); lit.<sup>[12]</sup> 40–43°C. Microanalysis: Found C,
- 40.52; H, 8.05; N, 15.55. C<sub>3</sub>H<sub>7</sub>NS requires C, 40.41; H, 7.91; N, 15.71. 3. Mp 131.0°C (ether); lit.<sup>[12]</sup> 114°C. Microanalysis: Found C, 47.17; H,
- 6.84; N, 13.64. C<sub>3</sub>H<sub>7</sub>NS requires C, 47.49; H, 6.97; N, 13.84.
- Mp 64.4°C (ether); lit.<sup>[12]</sup> 62–65°C. Microanalysis: Found C, 34.21; H, 4. 6.66; N, 13.11. C<sub>3</sub>H<sub>7</sub>NOS requires C, 34.27; H, 6.71; N, 13.32.
- 5. Mp 96.9°C (ethanol); lit.<sup>[7]</sup> 96.5–97.5°C. Microanalysis: Found C, 63.14; H, 6.00; N, 9.13. C<sub>8</sub>H<sub>9</sub>NS requires C, 63.54; H, 6.00; N, 9.26.

- Mp 124.9°C (ethanol/water). Microanalysis: Found C, 59.72; H, 5.96; N, 7.67. C<sub>9</sub>H<sub>11</sub>NOS requires C, 59.64; H, 6.12; N, 7.73.
- Mp 118.3°C (ethanol); lit.<sup>[7]</sup> 115.5–116.5. Microanalysis: Found C, 61.25; H, 5.06; N, 10.12. C<sub>7</sub>H<sub>7</sub>NS requires C, 61.28; H, 5.14; N, 10.21.
- Mp 221.9°C, (ethanol); lit.<sup>[14]</sup> 230–231°C. Microanalysis: Found C, 55.51; H, 5.11; N, 14.17. C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>OS requires C, 55.65; H, 5.19; N, 14.42.
- Mp 191.7°C (ethanol); lit.<sup>[15]</sup> 189–191°C. Microanalysis: Found C, 55.05; H, 4.40; N, 7.05. C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub>S requires C, 55.37; H, 4.65; N, 7.17.
- Mp 116.9°C (ethanol/water); lit.<sup>[16]</sup> 116–119°C. Microanalysis: Found C, 51.20; H, 9.50; N, 11.87. C<sub>5</sub>H<sub>11</sub>NS requires C, 51.24; H, 9.46; N, 11.95.

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