A Mild, Convenient Preparation of *N,N*-Disubstituted Thioformamides From Secondary Amines

John E. Mills

McNeil Pharmaceutical, Spring House, Pennsylvania 19411, U.S.A.

A number of *N,N*-disubstituted thioformamides can be conveniently prepared in good yield by heating the corresponding secondary amine at about 110°C with commercially available dimethylthioformamide. The reaction is sensitive to steric and electronic factors as evidenced by the failure of *N*-methylcyclohexanamine and *N*-methylbenzeneamine to react. Solid thioformamides often crystallize directly from the reaction in analytically pure form.

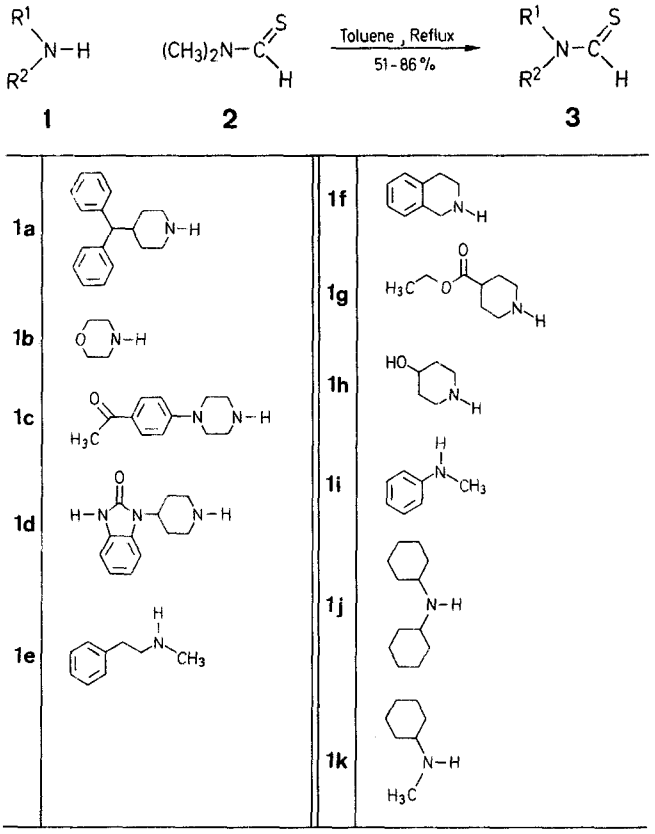
Thioformamides have been reported to be synthetically useful functional groups for a number of chemical transformations[1-9]. Included in these transformations are homologations[2], conversion to *N*-trifluoromethylamines[8], and condensations which can yield amidines[7], enamines[3], or more highly functionalized thioformamides[2]. Although a number of methods have been developed for the preparation of thioamides[1,10,11], many of those methods are not directly applicable for the preparation of thioformamides. Methods suitable for the preparation of thioformamides are the transformation of amides via imidoyl halides[12], Vilsmeier reagents[13], phosphorus pentasulfide[14], or boron trisulfide[15]. In the presence of hydrogen cyanide and hydrogen sulfide, amines have yielded substituted thioformamides[16]. Certain tertiary amines have been converted to thioformamides with

carbon disulfide at 100 °C at 10 atm[17]. Carbon disulfide has also been used to prepare dimethylthioformamide from dimethylformamide[17]. A general synthesis of thioformamides appears to be the reaction of amines with chloroform and hydrogen sulfide in the presence of sodium hydroxide[18]. Another general method for the preparation of disubstituted thioformamides appears to be the reaction of secondary amines with formamide in the presence of phosphorus pentasulfide[19]. Other methods have been developed using special reagents[20,21,22] or from formamide derivatives[23]. Without exception, all the methods developed to date suffer from the use of extremely toxic, unstable, or very odoriferous reagents, or from the use of reaction conditions not easily achieved in most organic chemistry laboratories.

We have found that a number of secondary amines (**1**) can be easily transformed into disubstituted thioformamides (**3**) simply by heating the amine with commercially available dimethylthioformamide (**2**) (Scheme **A**).

For nucleophilic amines, one equivalent of **2** in refluxing toluene converted > 95% of starting amine **1** to thioformamide **3** in 18 to 24 h. In many cases, the pure thioformamides were obtained directly from the reaction mixture by filtration. In those cases where the reaction was slow, good results could often be obtained by carrying out the transamination in neat **2** at 100 °C. In most cases, the rate of the reaction could be increased by passing an inert gas over the reaction to help expel dimethylamine from the reaction.

The generality of this method is shown by the wide variety of amines that undergo this reaction (Table). The reaction conditions are mild enough to accommodate a number of reactive functional groups. For example, secondary amines containing urea, amide, ester, or hydroxy groups yield the corresponding thioformamides under these conditions. Secondary amines do not condense with aryl alkyl ketones in competition with **2** as evidenced by the preparation of the thioformamide of keto-amine **1c**. Likewise, **2** is more reactive with secondary amines than secondary amines are with ethyl esters, as evidenced by the isolation of the desired thioformamide using amine **1g**.



Scheme A

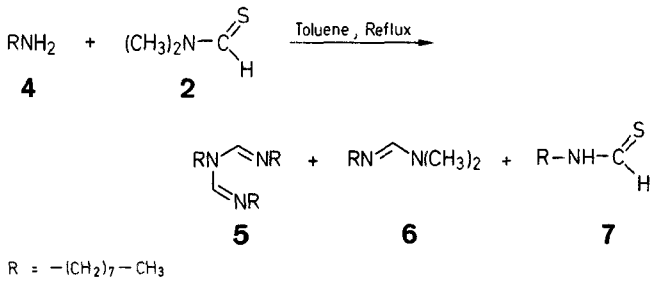
This method for the synthesis of thioformamides appears to be limited to secondary amines. For example, when 1-

Table. *N,N*-Disubstituted Thioformamides **3a–h** prepared

Substrate	Reaction Conditions Solvent/Equiv. of 2/Time	Product	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or Lit. Data	I.R. ($CHCl_3$) $\nu_{C=S}$, $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) $\delta_{CH=S}$ [ppm]	^{13}C-N.M.R. ($CDCl_3$) $\delta_{CH=S}$, $\delta_{CH=O}$ [ppm]
1a	toluene/1.5/24 h	**3a**	86	152–154°	152–154°[7]	–	–	–
1b	toluene/1.0/24 h	**3b**	69	67–68°	67.5°[23]	1503, 1442	9.15	186.9, –
1c	toluene/1.1/42 h	**3c**	65	163–168°	$C_{13}H_{16}N_2OS$ (232.3)	1504, 1673	9.36	186.9, 196.3
1d	toluene/1.6/42 h	**3d**	61	211–220°	$C_{13}H_{15}N_3OS$ (261.3)	1504, 1699	9.52	187.1, 155.1
1e	neat/1.05/18 h	**3e**	82	145–150°/0.75[b]	$C_{10}H_{13}NS$ (179.3)	1520, 1457	8.87, 9.03	188.2, 188.0
1f	toluene/1.0/18 h	**3f**	58	80–82°	$C_{10}H_{11}NS$ (177.3)	1494, 1456	9.41, 9.38	187.2, 186.7
1g	toluene/1.1/48 h	**3g**	87	155–158°/0.2[b]	$C_9H_{15}NO_2S$ (201.3)	1512, 1504, 1456, 1732	9.17	186.7, 173.3
1h	toluene/1.1/48 h	**3h**	79	170°/0.05[b]	$C_6H_{11}NOS$ (145.2)	1513, 1452	9.16	186.2
1i	toluene/1.1/48 h[c]		no reaction					
1j	xylene/5.0/100 h		no reaction					
1k	toluene/1.1/48 h		no reaction					

[a] Satisfactory microanalyses obtained: C ±0.39, H ±0.31, N ±0.46, S ±0.25.
[b] Distilled in a Kugelrohr apparatus.
[c] Potassium carbonate (0.024 eq) added.

octanamine was heated with **2**, analysis of the reaction mixture by gas liquid chromatography (G.L.C.) showed a mixture of several products. Analysis of the crude reaction mixture using G.L.C./mass spectroscopy revealed the formation of amidines **5** and **6**, as well as the desired thioformamide **7** (Scheme **B**).



Scheme **B**

Although these compounds were not isolated from the reaction mixture, their identities were verified by independent synthesis and G.L.C. analysis through coinjection. This result was not without precedent, since Pettit has reported the formation of *N',N'*-dimethyl-*N*-(1-naphthalenyl)-methanimidamide from the reaction of 1-naphthalenamine with **2**[24]. A number of other investigators have reported mixtures of products when other thioamides were reacted with primary amines[1].

Steric and electronic factors appear to play important roles in this reaction. As shown in the Table, *N*-methylbenzeneamine failed to give thioformamide even in the presence of added catalytic base. Dicyclohexylamine failed to react even after 100 h at reflux in toluene with a large excess of **2**. *N*-Methylcyclohexanamine also failed to react with **2** under standard reaction conditions.

This synthetic method provides a mild, convenient process for the preparation of *N,N*-disubstituted thioformamides. In those cases where the product is a crystalline solid, workup often involves only filtration of the product from the reaction medium.

***N,N*-Disubstituted Thioformamides 3a–k; General Procedure:**
Amine **1** (15 mmol), toluene (30 ml), and thiodimethylformamide (**2**; 1.5 g, 17 mmol) are placed in a 100 ml round bottom flask and heated at reflux overnight. The reaction is monitored by G.L.C. until < 10% of the volatiles are starting amine. The mixture is cooled to room temperature and the solid isolated by filtration. If no solid crystallizes upon cooling, the solvent is removed under reduced pressure, and the residue is triturated with diethyl ether or ethyl acetate. In those cases where the product is a liquid, it is purified by column chromatography over silica gel (50 g) using dichloromethane as eluent. Analytical samples of liquids are prepared by distillation of the purified liquid using a Kugelrohr apparatus (Table).

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[1] Hurd, R.N., DeLaMater, G. *Chem. Rev.* **1961**, *61*, 45.
[2] Enders, D., Seebach, D. *Angew. Chem.* **1973**, *85*, 1104; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 1014.
[3] Ireland, R.E., Brown, Jr., F.R. *J. Org. Chem.* **1980**, *45*, 1868.
[4] Ho, T.-L., Wong, C.M. *Synth. Commun.* **1975**, *5*, 299.
[5] Hattori, K., Takido, T., Itabashi, K. *Nippon Kagaku Kaishi* **1979**, 101; *C.A.* **1979**, *90* 137380.
[6] Dingwall, J.G., Reid, D.H., Wade, K. *J. Chem. Soc. C* **1969**, 913.
[7] Scott, M.K., Jacoby, H.I., Mills, J.E., Bonfilio, A.C., Rasmussen, C.R. *J. Med. Chem.* **1983**, *26*, 535.
[8] Baasner, B., Petruck, G.M., Hagemann, H., Klauke, E. *Ger. Offen. DE* 3 044 216 (1982), Bayer AG; *C.A.* **1982**, *97*, 181932.
[9] Guenther, E., Kochmann, W., Pallas, M., Roethling, T. *Ger. Offen. (East)* 91645 (1973); *C.A.* **1973**, *78*, 71668r.
[10] See references 48–53 in: Walter, W., Bode, K.-D. *Angew. Chem.* **1966**, *18*, 517; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 447.
[11] Harpp, D.N., MacDonald, J.G. *Tetrahedron Lett.* **1983**, *24*, 4927.
[12] Eilingsfeld, H., Seefelder, M., Weidinger, H. *Chem. Ber.* **1963**, *96*, 2671.
[13] Helbert, M., Renou, J.P., Martin, M.L. *Tetrahedron* **1979**, *35*, 1087.
[14] Hofmann, A.W. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 340.
[15] Steliou, K., Mrani, M. *J. Am. Chem. Soc.* **1982**, *104*, 3104.
[16] de Benneville, P.L., Strong, J.L., Elkind, V.T. *J. Org. Chem.* **1956**, *21*, 772.
[17] Petermann, J., Plieninger, H. *Tetrahedron* **1975**, *31*, 1209.
[18] Walter, W., Maerten, G. *Justus Liebigs Ann. Chem.* **1963**, *669*, 66.
[19] Westphal, K., Andersag, H. *U.S. Patent* 2 265 212 (1942); *C.A.* **1942**, *36*, 1950.
[20] Perregaard, J., Thomsen, I., Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 321.
[21] Yde, B., Yousif, N.M., Pedersen, U., Thomsen, I., Lawesson, S.-O. *Tetrahedron* **1984**, *40*, 2047.
[22] Hirabayashi, T., Inoue, K., Yokota, K. *J. Organomet. Chem.* **1975**, *92*, 139.
[23] Kantlehner, W., Haug, E., Farkas, M. *Justus Liebigs Ann. Chem.* **1982**, 1582.
[24] Pettit, G.R., Garson, L.R. *Can. J. Chem.* **1965**, *43*, 2640.