Simplified Preparation of Aliphatic Thioamides

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An improved procedure for preparing aliphatic thioamides, by the addition of hydrogen sulfide to nitriles at atmospheric pressure using amine catalysis, is presented. The ease of reaction was strongly dependent upon the solvent used, the chemical structure of the nitrile, and the nature and concentration of the amine catalyst.

ALTHOUGH some eight different procedures are known (*10*) for preparing thiocarboxamides, the approach most widely used has involved the base-catalyzed addition of hydrogen sulfide or thiols to nitriles. This reaction has been known for over a century (*10*), but it was not until fairly recently (*2*) that aromatic nitriles were shown to react readily with hydrogen sulfide in the presence of pyridine, forming good yields of the corresponding thioamides. Aliphatic nitriles, on the other hand, did not behave similarly, and (*10*) they "often react very slowly and give poor yields unless the reaction is carried out at elevated temperatures and pressures." The purpose of the present study was, therefore, to develop a simpler method for making aliphatic thioamides.

The use of certain organic amines as catalysts eliminated the need for an autoclave and afforded good yields of the desired thioamides at moderate temperatures and times of reaction. Some 26 aliphatic thioamides were thus prepared. Selected representative data on 15 of these are given in Table I; benzonitrile is included for comparison.

Several process parameters were studied briefly, with special emphasis on thioacetamide. A number of organic amines were established as effective catalysts for the reaction, including diethylamine, piperidine, pyrrolidine, tetramethylguanidine, diisopropylamine, diisobutylamine, 2,2′-iminodiethanol, dipropylamine, di-*sec*-butylamine and benzyltrimethylammonium hydroxide. Diethylamine was selected as the most promising because of its favorable boiling point (56° C.) and ease of recovery, and it consistently gave a good yield of thioamide of fair purity. On the other hand, some amines gave no thioamide under these conditions. These include triethylamine, 2,2′,2″-nitrilotriethanol, morpholine, and butylamine. These amines may be operative under other conditions or with other nitriles, however. For example, butylamine has been shown to catalyze the formation of dithiooxamide from cyanogen (*3*).

If the basic materials added to promote thioamide formation (*10*) function as true catalysts, a relatively small amount should suffice to promote complete conversion. However, catalyst requirements vary from none to a molar equivalent to the hydrogen sulfide used, depending upon the structure of the nitrile. Acetonitrile and its homologs (Table I) required the larger quantity of catalyst. 2,4-Dichlorophenoxyacetonitrile, on the other hand, gave a quantitative yield of excellent quality crude without the

Table I. Preparation of Thioamides

Nitrile	Moles[a] Diethylamine	Solvent[b]	Time,[c] Hours	Yield[d]	M.P., ° C. This Study[e]	M.P., ° C. Lit. (Ref.)
CH_3CN	1.2	Excess nitrile	3.5	62	111–3	115(*6*)
C_2H_5CN	1.1	Excess nitrile	3.5	19	40–3	42(*6*)
n-$C_{11}H_{23}CN$	1.3	DMF	3.7	29	76–9	82–3(*8*)
n-$C_{13}H_{27}CN$	1.1	DMF	3.7	33	73–8	87–8(*8*)
n-$C_{17}H_{35}CN$	1.1	DMF	5.2	50	96–7	96–7(*8*)
$NC(CH_2)_4CN$	1.1	DMF	3.3	63	174–5	170(*4*) 180(*9*)
Δ-CN	0.7	DMF	3.0	67[f]	114	. . .[g]
$(C_6H_5)_2CHCN$	1.0	DMF	0.5	90	146–9	153–4(*7*)
CH_3OCH_2CN	0.02	None	1.5	96	62–5	62–5(*1*)
2,4-$Cl_2C_6H_3OCH_2CN$	0	DMF	0.5	100	125–31[h]	. . .[i]
2,4-$Cl_2C_6H_3OCH_2CN$	1.0	DMF	0.5	88	134–6[h]	
2,4-$Cl_2C_6H_3OCH_2CN$	0.002	DMF	0.5	100	137–8[h]	
2,4-$Cl_2C_6H_3OCH_2CN$	0	DMSO	0.5	100	134–6[h]	
2,4,5-$Cl_3C_6H_2OCH_2CN$	0.7	DMF	0.5	85	212	. . .[j]
$Cl_5C_6OCH_2CN$	0.5	DMF	2.0	0	. . .	. . .
4-$O_2NC_6H_4OCH_2CN$	0.5	DMF	0.5	75	163–5	. . .[k]
3-$(F_3C)C_6H_4OCH_2CN$	0.4	DMF	0.5	67	136–7	. . .[l]
4-$ClC_6H_4SCH_2CN$	0.07	DMF	0.5	95	129–31	129–31(*5*)
C_6H_5CN	0.002	DMF	0.5	92	105–10	105–10(*2*)

[a] Per 1.0 mole of hydrogen sulfide. [b] DMF = dimethylformamide; DMSO = dimethyl sulfoxide. [c] Comprises 0.5 hour or less addition time, the remainder being the time of digestion. Reaction temp. 50° to 65° C. in all cases. [d] Mole per cent yield of fair quality crude product based on nitrile used. [e] Uncorrected m.p. of purified sample. [f] Purified yield given. [g] Anal. calcd. for C_4H_7NS: C, 47.5; H, 6.9; Found: C, 47.2; H, 6.9. [h] M.p. of crude product. [i] Anal. calcd. for $C_8H_7Cl_2NOS$: C, 40.6; H, 3.0; Found: C, 40.7; H, 2.9. [j] Anal. calcd. for $C_8H_6Cl_3NOS$: C, 35.4; H, 2.2; Found: C, 35.4; H, 2.4. [k] Anal. calcd. for $C_8H_8N_2O_3S$: C, 43.6; H, 3.8; Found: C, 43.3; H, 4.0. [l] Anal. calcd. for $C_9H_8F_3NOS$: C, 46.0, H, 3.4; S, 13.6; Found: C, 46.3; H, 3.3; S, 13.6.

catalyst. The best results, as indicated by melting point, however, were obtained by using a small quantity of catalyst.

A reaction solvent usually appears necessary even when the nitrile is a liquid. In appropriate cases, this can be excess nitrile (Table I). Dimethylformamide (DMF) gave excellent results and was generally employed. In one case, dimethyl sulfoxide (DMSO) gave a crude product of even higher melting point than DMF, and therefore, may be at least equally useful. Attempts to use other solvents—namely, toluene, dioxane, water, acetone, or absolute ethanol—were unsuccessful, since no thioamide formation was noted, even with the highly reactive 2,4-dichlorophenoxyacetonitrile. Methoxyacetonitrile exceptionally gave an excellent yield without the use of a solvent. DMF and DMSO are both water-miscible, which permits isolation of the usually water-insoluble thioamides by simply adding the reaction mixture to excess water.

Prompt workup of the reaction mixture was required to obtain a good yield of high quality product. Prolonged heating should also be avoided.

Chemical structure evidently has an important influence on thioamide formation. The compounds of structure $ROCH_2CN$ (Table I) all have lower requirements of catalyst and reaction time while, at the same time, giving higher yields or purer products than acetonitrile and its homologs. The electron-donating character of the oxygen atom in comparison with that of an alkyl group may account for this observed difference in reactivity. Pentachlorophenoxyacetonitrile gave no thioamide, in contrast to the dichloro- and trichloro- analogs, which reacted in excellent yield. The pentachloro compound may be too sterically hindered for interaction with the basis catalyst.

EXPERIMENTAL

The following examples are typical of the procedures used.

Thioacetamide. Into a mixture of diethylamine (153.6 grams, 2.1 moles) and acetonitrile (287.4 grams, 7.0 moles) was bubbled hydrogen sulfide (71.4 grams, 2.1 moles) for 30 minutes while the reaction mixture was maintained at 50° C. by external cooling with an ice bath. The reaction mixture was then held at 55° to 60° C. for 3 hours. After prompt removal of the amine and excess acetonitrile by distillation to a pot temperature of 85° C. at 20-mm. vacuum, the residue was triturated thrice with methylene chloride. Thioacetamide was obtained as a gray solid, m.p. 111-13° C., in 62% yield (94 grams).

2,4 - Dichlorophenoxyacetamide. 2,4 - Dichlorophenoxyacetonitrile (30.4 grams, 0.15 mole) was dissolved in 150 ml. of DMF, and the solution was heated to 55° C. in a laboratory reaction flask. Diethylamine (0.2 gram, 0.0003 mole) was added, followed by the introduction of hydrogen sulfide (6.8 grams, 0.2 mole) over 10 minutes with maintenance of the reaction temperature at 55° to 60° C. by external cooling. The mixture was held with stirring at 55° to 60° C. for 30 minutes, after which it was poured with stirring into 900 ml. of cold water. The solid product was filtered and air dried to constant weight. The yield was 35.5 grams (quantitative) m.p. 137-8° C.

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CORRECTION

In the article "Solubility Isotherms in the System Sodium Oxide–Boric Acid–Water. Revised Solubility–Temperature Curves of Boric Acid, Borax, Sodium Pentaborate, and Sodium Metaborate" by Nelson P. Nies and Richard W. Hulbert [J. CHEM. ENG. DATA **12**, 303 (1967)] the following corrections should be noted.

ERRATA

Page 303, column 1, after line 3 from bottom: insert "except in alkaline solutions near the metaborate composition."

Page 304, column 1, line 31 of Experimental Section: After "by" insert "addition of mannitol and".

Page 306, column 1, line 3 from bottom; page 307, column 2, lines 3 and 4, and line 8 from bottom; and page 310, column 2, lines 18, 21 and 29 from bottom: "2 to 9" and "(2 to 9)" should read "(2:9)".

Page 307, Table II, line 3 from bottom: "Na_2O-B_2O_3" should read "Na_2O/B_2O_3".

Page 310, column 2, line 14 from bottom: "(2 to 5.1)" should read "(2:5.1)".

Page 312, column 2, line 29: "*10, 16, 18*" should read "*10, 16–18*".

Page 313, Ref. 17: Add: Gale, W.A., "Boron Metallo-Boron Compounds and Boranes," R.M. Adams, Ed., p. 40, Interscience, New York, 1964.

Editor's Note: Normal editorial policy involves the use of the word "to" in connection with "ratio," but to avoid any misunderstanding, we have included in the errata the usage desired by the authors.
