[Contribution from the Rohm & Haas Co.]

Nitrile Groups. III. The Preparation of N-Substituted Formamides and Thioformamides from Hydrogen Cyanide[1]

PETER L. DE BENNEVILLE, JAMES S. STRONG, AND VINCENT T. ELKIND

Received February 27, 1956

The reaction of hydrogen cyanide with some primary and secondary amines in water gave N-substituted formamides. Acetone cyanohydrin refluxed with N-methylethanolamine in water gave N-methyl-N-β-hydroxyethylformamide. The reaction of hydrogen cyanide with equivalent amounts of an amine and hydrogen sulfide afforded a completely general method for the preparation of N-substituted thioformamides.

Addition of a reagent to the nitrile group of hydrogen cyanide may be expected to be more favorable than its addition to the nitrile group of a simple aliphatic nitrile. Hydrogen cyanide furnishes a proton-rich environment, steric effects are minimum, and the positive character of the nitrile carbon atom should be greater than with the nitriles.

In an actual instance, aqueous amines react with only activated nitriles,[1] and they react easily with hydrogen cyanide. Erickson[2] has shown that when anhydrous amines were mixed with anhydrous hydrogen cyanide at room temperature, N-substituted formamidines were formed. Subsequent hydrolysis of the reaction mixture gave the N-substituted formamide. The reaction of aqueous amines with hydrogen cyanide may be presumed to follow the same course differing essentially only in rate of reaction, which is enhanced in aqueous medium. In Table I are listed the times, *t*, required for 50% of the cyanide ion to be used up in the reaction of dimethylamine with hydrogen cyanide in methanol, water, and water-methanol solutions, at two different temperatures.

TABLE I

CYANIDE ION DISAPPEARANCE
$(CH_3)_2NH + HCN$

$(CH_3)_2$-NH, moles	HCN, moles	H_2O, moles	CH_3OH, moles	Temp., °C.	*t*, hrs.
1.5	1.5	6.2	—	30	6
1.5	1.5	6.2	—	50	1
2.0	1.5	3.0	3.7	50	0.5
1.8	1.5	—	2.5	30	15

Data are given in Table II for the preparation of a number of N-substituted formamides by the reaction of amines with hydrogen cyanide in water. The reaction is fairly general, but the hindered primary amine, *tert*-butylamine gave only polymer with 73% recovery of amine. Both aminolysis and hydrolysis were apparently too slow,[3] and polymerization of HCN was the dominant reaction. Aniline and methylaniline also failed to react.

In the conversion of N-methylaminoethanol to N-methyl-N-β-hydroxyethylformamide, acetone cyanohydrin was used as a source of hydrogen cyanide. Equilibria established under the conditions of reaction are displaced toward the stable end product, the formamide. A related behavior of acetone cyanohydrin under alkaline conditions has recently been published.[4]

The complications found by Erickson for the case of morpholine did not interfere when the reaction was carried out in water. It is probable that the higher rate of aminolysis in water excluded the other reactions which resulted when no solvent was present. As a relatively weaker base, morpholine has not always followed the pattern of its companion secondary heterocyclic amine, piperidine.[1]

The substitution of hydrogen sulfide for water in the reaction afforded an easy general method for the preparation of thioformamides (Table III). Reaction was qualitatively more rapid than the corresponding preparation of formamides, and was accompanied by a rise in temperature. A small yield was obtained even with aniline; the yield in this case was increased by the addition of ammonia. The primary *tert*-alkylamines, *tert*-butylamine and 1,1,3,3-tetramethylbutylamine gave fair yields of thioformamides by this method. This is the only case where these amines have given aminolysis in reaction at nitrile groups.[3]

EXPERIMENTAL

The following procedure is typical of the preparation of formamides. The reaction can also be carried out conveniently in water alone. The long standing period and reflux period are probably unnecessary; dimethylformamide has been prepared in 83% yield in a system so arranged as to maintain a slight back-pressure (1.5–2 in. of Hg) by heating at 50–75° for about three hours. Boiling points and melting

---

[1] Given at the Delaware Valley Regional Meeting of the American Chemical Society, February 16, 1956. For the previous paper in this series, see Hurwitz, Exner, and de Benneville, *J. Am. Chem. Soc.*, **77**, 3251 (1955).

[2] Erickson, *J. Org. Chem.*, **20**, 1569 (1955); U. S. patent 2,615,023 (1952); *Chem. Abstr.*, **47**, 9349 (1953).

[3] In previous work with the primary *tert*-alkylamines,[1] they have promoted hydrolysis rather than aminolysis.

[4] Nazarov and Zavyalov, *Zhur. Obschei Khim.*, **24**, 466 (1954); *Chem. Abstr.*, **49**, 6139 (1955).

TABLE II

FORMAMIDES, $HCONR^1R^2$

R^1R^2N—	Mol Ratio Amine:HCN:-H_2O	B.p., °C.	Mm.	Yield, %	n_D^{20}	N Calc'd	N Found
$(CH_3)_2N$—	1.3:1:2.6	151–152[a]	atm.	86	1.4313[a]	19.2	18.9
n-C_4H_9NH—	1.05:1:2	117–118	11[b]	60	1.4386[c]	13.9	13.7
$\underbrace{CH_2CH_2OCH_2CH_2}_{N-}$	1.2:1:2	236–237[b]	atm.	49	1.4845[c]	12.2	12.1
$\underbrace{CH_2CH_2CH_2CH_2CH_2}_{N-}$	2:1:2	221–222[d]	atm.	51	1.4817[c]	12.4	12.2
$CH_3NCH_2CH_2OH$	[e]	160–167	15	41	1.4715	13.6	13.6
$CH_3NCH_2CH_2NCH_3$	1:1:6.4	104–108	10	32	1.4666	24.1[f]	23.8
		165–185	10[g]	27	m.p. 81–82°	19.4[g]	19.7

[a] Brühl, *Z. Physik. Chem.*, 22, 389 (1897) reports b.p. 155°, $n_D^{22.4}$ 1.4294. [b] Blicke and Li, *J. Am. Chem. Soc.*, **74**, 3933 (1953) report b.p. 122–123° (16 mm.) for N-*n*-butylformamide; b.p. 229–232° (745 mm.) for N-formylmorpholine. [c] n_D at 25°. [d] Staple and Wagner, *J. Org. Chem.*, **14**, 572 (1949) report b.p. 218–220°. [e] From acetone cyanohydrin (see experimental). [f] Calc'd for N-β-(methylamino)ethyl-N-methylformamide. [g] Calc'd for N,N'-dimethyl-N,N'-ethylene-bis-formamide.

TABLE III

THIOFORMAMIDES, $HCSNR^1R^2$

R^1R^2N	B.p., °C.	Mm.	Yield, %	N Calc'd	N Found
$(CH_3)_2N$	105–108	13[a]	84	15.7	15.6[a]
n-C_4H_9NH	160–172	25	85	12.0	12.2
tert-C_4H_9NH	m.p. 124–125		45	12.0	11.8[b]
tert-$C_8H_{17}NH$[c]	m.p. 58–60		36	8.1	8.2[c]
C_6H_5NH	m.p. 137–139[d]		26	—	—
C_6H_{11}(cyclo)NH	124–126°/0.8		73	9.8	10.1
$NH(CH_2)_6NH$	m.p. 118–120		29	13.7	13.7[e]

[a] Willstätter and Wirth, *Ber.*, **42**, 1920 (1909) report b.p. 97° (12 mm.); S, Found 36.2; Calc'd 36.0. [b] S, Found 27.5; Calc'd 27.4. [c] 1,1,3,3-Tetramethylbutylamine. S, Found 18.9; Calc'd 18.4. [d] Reissert, *Ber.*, **37**, 3714 (1904) reports m.p. 138°. The yield was substantially aided by adding ammonia to increase the basicity. [e] Calculated for N,N'-hexamethylene bis-thioformamide. S, Found 31.2; Calc'd 31.4.

points are uncorrected. Analyses were carried out under the direction of Mr. T. P. Callan.

N,N-Dimethylformamide. Anhydrous dimethylamine (179 g., 4 moles) was passed into a mixture of methanol (300 ml.) and water (108 g., 6 moles). Anhydrous hydrogen cyanide (81 g., 3 moles) was added at 3–7° over a period of one-half hour. The mixture was allowed to stand at room temperature overnight, and then was heated at reflux (71°) for eight hours. Then it was distilled through a 12-in. Vigreux column to yield 181 g. of dimethylformamide boiling at 151–152°. Careful redistillation of fore-runs gave 5 g. more for a total of 186 g. (85%).

Study of CN^- disappearance. The appropriate solutions were prepared at 0°, and the temperature then was rapidly raised to the indicated one. Aliquots were removed periodically and were titrated for cyanide ion with 0.1 *N* silver nitrate.

Formamides from N,N'-dimethylethylenediamine. N,N'-Dimethylethylenediamine (88 g., 1.0 mole), water (115 g., 6.4 moles), and hydrogen cyanide (27 g., 1.0 mole) were combined at room temperature and allowed to stand one week. The mixture was heated at 104° for five hours under reflux. On distillation there were obtained after fore-runs, fractions boiling at 99–108° at 10 mm. (37 g., 32% as monoformamide) and 168–185° at 10 mm. (19.5 g., 27% as bisformamide). The first fraction was redistilled to give 29 g. of pure N-methyl-N-β-(methylamino)ethylformamide. The second fraction crystallized to a solid melting at 81–82°.

N-Methyl-N-β-hydroxyethylformamide. β-N-Methylaminoethanol (150 g., 2.0 moles), acetone cyanohydrin (128 g., 1.5 moles), and water (200 g., 11 moles) were heated at reflux (80–90°) for seven hours. The reaction mixture then was distilled from a Claisen flask to yield 76 g., boiling at 160–175° (15 mm.). This liquid was redistilled to give 62.5 g. (40.5%) boiling at 160–167° (15 mm.).

Thioformamides. The following procedure is typical for solid thioformamides. Liquids were distilled *in vacuo* directly from the residue after removal of solvent.

N-tert-Butylthioformamide. Hydrogen sulfide (117 g., 3.4 moles) was passed into a solution of *tert*-butylamine (219 g., 3 moles) in anhydrous methanol (300 ml.) with cooling. Hydrogen cyanide (81 g., 3 moles) then was added and the ice-bath was removed. The temperature rose and was maintained by occasional cooling at about 40°. After standing overnight, the reaction mixture was poured into 1500 ml. of water, and the crystalline product was removed by filtration and washed with water. After drying *in vacuo*, there was obtained 157 g. (45%) of N-*tert*-butylthioformamide, melting at 124–125°.

Thioformanilide. To a solution of aniline (93 g., 1 mole) in 250 ml. of dry methanol at 10° was added ammonia (28 g., 1.65 moles), hydrogen sulfide (52.5 g., 1.55 moles), and hydrogen cyanide (27 g., 1 mole) in that order. After the mixture was stirred overnight, it was poured into 2000 ml. of water and the solid was recovered by filtration. After recrystallization from ethanol, the product (36 g., 25%) melted at 137–139°. Only a trace amount (0.25%) was obtained when the ammonia was omitted.

PHILADELPHIA 37, PENNA.