[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

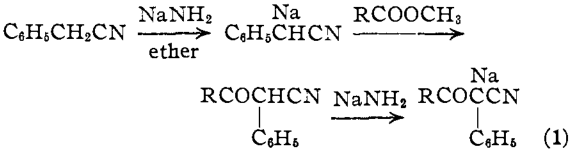
Acylations of Nitriles with Esters by Sodium Amide in Liquid Ammonia to Form β-Ketonitriles. Consideration of Amidine Formation[1]

BY CHARLES J. EBY[2] AND CHARLES R. HAUSER

RECEIVED JULY 23, 1956

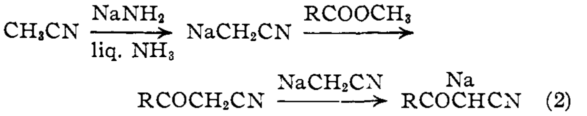
A general method was developed for acylating nitriles with esters by means of sodium amide in liquid ammonia to form β-ketonitriles. Two equivalents each of the nitrile and reagent were employed to one of the ester on which the yield was based. This method is particularly useful for acylating acetonitrile and its higher straight chain aliphatic homologs. It is compared with an earlier sodium amide method, in which the yield is based on the nitrile, and also with sodium alkoxide methods. Amidine formation is considered, especially with isobutyronitrile which exhibited mainly this type of reaction.

In a previous investigation[3] a method was developed for acylating nitriles with esters to form β-ketonitriles employing two molecular equivalents of sodium amide in ether to one of the nitrile and two of the ester. The method may be illustrated with phenylacetonitrile with which yields of 60–68% based on the nitrile were obtained (equation 1)



$$C_6H_5CH_2CN \xrightarrow[\text{ether}]{NaNH_2} C_6H_5\overset{Na}{C}HCN \xrightarrow{RCOOCH_3} RCO\underset{C_6H_5}{\underset{|}{C}}HCN \xrightarrow{NaNH_2} RCO\overset{Na}{\underset{\underset{C_6H_5}{|}}{C}}CN \quad (1)$$

In the present investigation another sodium amide method for acylating nitriles was developed involving two equivalents each of the reagent and nitrile to one of the ester, the yield being based on the ester. The method may be illustrated with acetonitrile (equation 2).



$$CH_3CN \xrightarrow[\text{liq. } NH_3]{NaNH_2} NaCH_2CN \xrightarrow{RCOOCH_3} RCOCH_2CN \xrightarrow{NaCH_2CN} RCO\overset{Na}{C}HCN \quad (2)$$

The reaction was carried out by adding the nitrile in ether to sodium amide in liquid ammonia,[4] followed after five minutes by the rapid addition of the ester in ether.[5] The reaction mixture was generally worked up after one hour.[6] The results are summarized in Table I.

It can be seen from Table I that the yields of the β-ketonitriles were good to excellent (54–94%).[7] Most of these products readily were obtained quite clean. For example, the melting point of *m*-chlorobenzoylacetonitrile was not raised by recrystallization, and the refractive index of α-benzoyl-*n*-valeronitrile was not changed much (only 0.0009) by distillation. However, the β-ketonitrile from the acetylation of propionitrile was evidently contaminated with the self-condensation product of the ester. α-Nicotinylpropionitrile decomposed on standing, but a derivative of it (a 2-pyridone) gave a satisfactory analysis as described in another paper.[8] Propionylacetonitrile polymerized readily.

Although the present method appears to produce better yields than the earlier one, the two methods complement one another when the yields are to be based on the ester and nitrile, respectively.[9] The present method is preferable for acylations of acetonitrile, which is relatively inexpensive,[10] and for certain acylations of higher aliphatic nitriles and phenylacetonitrile (see note 18). However, the earlier method usually would be chosen for acylations of phenylacetonitrile or certain other nitriles with relatively expensive esters.

In general, sodium amide is considered superior to sodium ethoxide[11] or sodium methoxide[12] since it produces better yields and allows the reaction to be completed in less time.

Consideration of Amidine Formation.—Nitriles having α-hydrogen may be attacked by sodium amide not only at the α-hydrogen to form the sodionitrile, but also at the nitrile group to produce the sodium salts of the corresponding amidines. Although acetonitrile and its higher aliphatic homologs having two α-hydrogens have been reported to exhibit the latter type of reaction,[13,14] they must undergo mainly the former type since their acylations have been realized in high yields as described above. Similarly, their alkylations have been successful.[4,15]

However, nitriles having only one α-hydrogen, for example diethylacetonitrile, have been shown to react with sodium amide in benzene[14,15] to form amidines in good yields. Such nitriles have also been alkylated, but special conditions (involving

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[1] Supported in part by Office Ordnance Research, U. S. Army.

[2] Monsanto Chemical Co. Fellow, 1954–1955.

[3] R. Levine and C. R. Hauser, THIS JOURNAL, **68**, 760 (1946).

[4] F. W. Bergstrom and R. Agostinho *ibid.*, **67**, 2152 (1945)) effected the benzoylation of acetonitrile with ethyl benzoate by sodium amide in liquid ammonia, but they employed equivalents of the three reactants and obtained only a 34% yield of benzoylacetonitrile.

[5] On increasing the addition time of the ester from 5 to 40 minutes the yield in the benzoylation of acetonitrile was decreased from 94 to 71%. Similarly, on increasing the addition time from 5 to 30 minutes, the yields in the benzoylation and propionylation of propionitrile were decreased from 93 to 55% and from 78 to 52%, respectively.

[6] An equally good yield (93%) was obtained in the benzoylation of propionitrile on working up the reaction mixture after ten minutes.

[7] An attempt to acylate acetonitrile with methyl *p*-nitrobenzoate produced tar. A similar observation has been reported with acetophenone and this ester; W. Bradley and R. Robinson, *J. Chem. Soc.*, **129**, 2364 (1926).

[8] C. R. Hauser and C. J. Eby, THIS JOURNAL, **79**, 728 (1957).

[9] Two analogous methods for acylating ketones have been developed in which the yields of β-diketones are based on the ketone and ester, respectively; see C. R. Hauser, F. W. Swamer and J. T. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1954, Vol. VIII, Chapter 3, p. 114.

[10] We are indebted to the Carbide and Carbon Chemicals Co. for a generous sample of acetonitrile.

[11] J. B. Dorsch and S. M. McElvain, THIS JOURNAL, **54**, 2960 (1932).

[12] R. Long, *ibid.*, **69**, 990 (1947).

[13] E. F. Cornell, *ibid.*, **50**, 3311 (1928). This worker employed sodium amide in liquid ammonia, but the details were not given.

[14] G. Newbery and W. Webster, *J. Chem. Soc.*, 738 (1947). These workers showed that the yields of amidine at least in benzene were only 10% or less.

[15] K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1932).

TABLE I

$$RCOOCH_3 + R'CH_2CN \xrightarrow[liq.\ NH_3]{NaNH_2} RCOCHR'CN$$

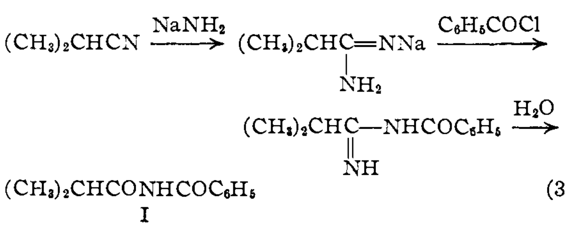
R	R'	Yield, %	M.p., °C.	B.p., °C. °C	B.p., °C. Mm.	Lit. M.p. or B.p., °C. (mm.)
C_2H_5	H	75[a]		97–98	12	109–110(20)[b]
C_6H_5	H	94	81–82[c]			80–81[d]
m-ClC_6H_4	H	84	79.5–80.5			81[e]
p-$CH_3OC_6H_4$	H	84	131–132.5[f]			129–130[g]
CH_3[h]	CH_3	63		89–90.5	30	91(31)[i]
C_2H_5	CH_3	78		90–92	20	193.5(760)[j]
C_6H_5	CH_3	93		128–130	3.1	128–130(3)[d]
C_5H_4N[k]	CH_3	54		126–127	0.75[l]	
C_6H_5	n-C_3H_7	78		149–149.5	4	139–140(3)[d]
m-ClC_6H_4	n-C_3H_7	70[m]		162–163	3	
CH_3[h]	C_6H_5	70[n]	87–89[f]			89–90[b]
C_2H_5	C_6H_5	74	70.5–72			71–72.5[b]
C_6H_5	C_6H_5	70	94–95[f]			89–90[b]

[a] Crude yield; only part of product was distilled, the remainder polymerized. [b] Ref. 3. [c] Recrystallized once from ethyl ether. [d] Ref. 11. [e] E. von Meyer, *J. prakt. Chem.*, [2] **92**, 182 (1915). [f] Recrystallized once from methanol or methanol and water. [g] A. Sonn, *Ber.*, 51, 825 (1918). [h] Ethyl acetate used. [i] E. Mohr, *J. prakt. Chem.*, [2] **75**, 551 (1907). [j] See E. von Meyer, *ibid.*, [2] **38**, 339 (1888); M. Hanriot and L. Bouveault, *Bull. soc. chim. France*, [3] **1**, 176 (1879). [k] Ethyl nicotinate used. [l] $n^{25}D$ 1.5512. [m] The yield of crude product, b.p. 158–161° (2.8 mm.), $n^{25}D$ 1.5375, was 86%. [n] The yield of crude product, m.p. 82–85°, was 76%.

the addition of sodium amide to a mixture of the nitrile and alkyl halide[14,15]) appear to be required. Apparently some ionization of the α-hydrogen of these nitriles first occurs, but the reaction gradually reverses in favor of amidine formation.

In the present investigation treatment of isobutyronitrile with sodium amide in liquid ammonia followed by methyl benzoate (present conditions of acylation of nitriles having two α-hydrogens) produced mainly benzamide and recovered nitrile. Some amidine appeared also to have been formed and then decomposed to the nitrile during the distillation. Amidine as well as benzamide was isolated in another experiment when the conditions were altered slightly. The benzamide obtained in these experiments apparently arose from reaction of the ester with the amide ion which is present in equilibrium with the nitrile anion.

Isobutyronitrile produced mainly amidine upon treatment with sodium amide in liquid ammonia followed by replacement of the ammonia with ether. Thus, on adding benzoyl chloride to the resulting ether suspension and hydrolyzing the reaction mixture, the N-acylated amide I was obtained in 50% yield (equation 3).



$$(CH_3)_2CHCN \xrightarrow{NaNH_2} (CH_3)_2CH\underset{\substack{|\\ NH_2}}{C}{=}NNa \xrightarrow{C_6H_5COCl} (CH_3)_2CH\underset{\substack{\|\\ NH}}{C}{-}NHCOC_6H_5 \xrightarrow{H_2O} \underset{I}{(CH_3)_2CHCONHCOC_6H_5} \qquad (3)$$

The structure of product I was established by treatment with hydrochloric acid to give benzoic acid (87%) and with polyphosphoric acid (PPA) to give benzamide (60%) (equations 4a and 4b).

$$\underset{60\%}{C_6H_5CONH_2} \xleftarrow[PPA]{(4b)} \underset{I}{(CH_3)_2CHCONHCOC_6H_5} \xrightarrow[HCl]{(4a)} C_6H_5COOH,\ 87\%$$

Experimental[16]

The Acylation of Nitriles with Esters by Means of Sodium Amide in Liquid Ammonia.—A suspension of 0.5 mole of sodium amide[17] in 600 ml. of liquid ammonia was prepared in a 1-l. three-necked round-bottomed flask equipped with a sealed stirrer, a dropping funnel and a reflux condenser. To the stirred suspension was added during 5 minutes a solution of 0.5 mole of the nitrile in an equal volume of anhydrous ether. Propio-, valero- and phenylacetonitriles produced an immediate greenish color. After 5 minutes a solution of 0.25 mole of the ester in an equal volume of ether was added as rapidly as feasible (about 5 minutes) and stirring continued one hour. If the reaction mixture became thick, more ether was added to facilitate stirring. The ammonia was removed rapidly (about 10 minutes) on the steam-bath as ether was being added to keep the volume at approximately 500 ml. The reaction mixture was then cautiously poured with stirring onto 500 g. of crushed ice, which soon melted. The two layers were separated and, except where the nitrile was to be recovered, the ether layer was discarded.[18] The cold aqueous solution of the sodio-β-ketonitrile[19] was usually filtered with suction through Amend Hyflo Super-Cel (on a filter paper in a buchner funnel) to remove colored suspended material.[20] After washing the Super-Cel with ice-water, the filtrate and washings were combined and acidified with iced 6 *N* hydrochloric acid.[21] The liberated β-ketonitrile was either taken up in ether (three extractions), or collected on a funnel and recrystallized.[22] The ether solution was washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed, and the residue of β-ketonitrile recrystallized or distilled *in vacuo* through a 25-cm. Podbielniak-type column. When the solids were recrys-

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(16) Melting points and boiling points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(17) See C. R. Hauser, F. W. Swamer, J. T. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1954, Vol. VIII, Chapter 3, p. 122.

(18) Valeronitrile was recovered in 30% yield and phenylacetonitrile in 45–55% yields from the ether layer.

(19) Since sodioanisoylacetonitrile was insoluble, the mixture was acidified directly.

(20) Sodio-benzoyl- and sodio-*m*-chlorobenzoylacetonitriles partly precipitated during filtration, and considerable water was required to dissolve them.

(21) In the preparation of α-nicotinylpropionitrile, the solution was acidified with acetic acid and then neutralized with sodium carbonate.

(22) α-Acetyl-α-tolunitrile, *m*-chlorobenzoylacetonitrile and anisoylacetonitrile were collected in this latter manner.

tallized the addition of a few drops of 6 *N* hydrochloric acid to the solvent prevented coloring of the product.[23]

The results are summarized in Table I. The melting points or boiling points given in this table are for the products on which the yields are based. In general, the physical constants agreed with those in the literature or were raised to these values (in the case of the solids) by recrystallization.

Several of the products were redistilled *in vacuo* and refractive indices and analyses determined. α-Propionylpropionitrile previously was distilled only at atmospheric pressure (see Table I). Our product boiled at 76–77° (10 mm.), n^{25}D 1.4250.

Anal. Calcd. for C_6H_9ON: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.67; H, 7.96; N, 12.73.

α-Benzoyl-*n*-valeronitrile has been reported to boil at 139–140° (3 mm.).[11] Our product boiled at 149–149.5° (4 mm.) and at 152° (4.5 mm.), n^{25}D 1.5255.

Anal. Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.86; H, 6.92; N, 7.53.

α-Acetylpropionitrile, b.p. 90–90.5° (30 mm.), n^{25}D 1.4215, appeared to be contaminated with about 5% ethyl acetoacetate, b.p. 87.8° (29.3 mm.), n^{20}D 1.2194.[24]

Anal. Calcd. for C_5H_7ON: C, 61.84; H, 7.27; N, 14.42. Found: C, 60.74; H, 7.57; N, 13.92.

α-*m*-Chlorobenzoyl-*n*-valeronitrile, b.p. 162–163° (3 mm.), n^{25}D 1.5381, is reported here for the first time.

Anal. Calcd. for $C_{12}H_{12}ONCl$: C, 65.01; H, 5.46; N, 6.32. Found: C, 64.90; H, 5.59; N, 6.29.

Reactions of Isobutyronitrile.[25] (A) **With Sodium Amide and Methyl Benzoate.**—When 0.50 mole of sodium amide in liquid ammonia was treated with 34.5 g. (0.50 mole) of isobutyronitrile and 34 g. (0.25 mole) of methyl benzoate as in the general procedure, the green color disappeared after about half the ester was added, leaving a gray suspension. The reaction mixture was decomposed with ice-water as usual and the ether layer was separated and dried over magnesium sulfate. Removal of the solvent gave a residue which upon distillation at atmospheric pressure gave 17.0 g. (49%) of isobutyronitrile, b.p. 99–104°,[26] and 2.7 g. (8%) of methyl benzoate. The residue in the pot was recrystallized from benzene to give 10.7 g. (39%) of benzamide, m.p. and mixed m.p. 126–128°. Redistillation of the recovered nitrile gave 13.6 g. (40%), b.p. 102.5–104°, n^{25}D 1.3712.

When the reaction was repeated and the mixture stirred in ether for two days, there was isolated a 24% yield of isobutyramidine boiling at 105–107° (20 mm.) and on redistillation, at 93–94° (10 mm.), n^{25}D 1.4800.

Anal. Calcd. for $C_4H_{10}N_2$: C, 55.71; H, 11.70; N, 32.53. Found: C, 55.15; H, 11.82; N, 32.04.

A sample (1.72 g.) of this product was treated with 10 ml. of water at room temperature for one day and the water then removed under vacuum. The residue was recrystallized from ether to give 1.35 g. (78%) of isobutyramide, m.p. 129–131°, reported m.p. 129–130°.[27]

(B) **With Sodium Amide and Benzoyl Chloride.**—A suspension of 0.5 mole of sodium amide was prepared in liquid ammonia and 34.5 g. (0.5 mole) of isobutyronitrile was added. An immediate green color was produced. After 10 minutes the liquid ammonia was replaced rapidly with dry ether by means of the steam-bath. The green color gradually disappeared leaving a gray flocculent precipitate. After the mixture was refluxed 20 minutes in ether and the system swept by a current of dry nitrogen, a solution of 70.25 g. (0.5 mole) of benzoyl chloride in an equal volume of dry ether was added as rapidly as possible (about 15 minutes). After standing overnight, the reaction mixture was poured onto 500 ml. of iced 1.1 *N* hydrochloric acid and extracted twice with ether. Distillation of the ether extract gave no isolatable material. The water layer, on standing overnight, precipitated white needles which after recrystallization from methanol–water gave 44.9 g. (50%) of N-isobutyrylbenzamide (I), m.p. 154–155.5°.

Anal. Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.35; H, 6.96; N, 7.18.

A sample (4.75 g.) of I was refluxed with 60 ml. of 6 *N* hydrochloric acid for 30 minutes to give on cooling 2.65 g. (87%) of benzoic acid, m.p. and mixed m.p. 121–122°. The mother liquor had an odor of isobutyric acid.

A sample (4.75 g.) of I with 75 g. of polyphosphoric acid was stirred on the steam-bath for 30 minutes, and then stirred for 30 minutes with ice. After neutralizing with sodium bicarbonate and recrystallizing the solid from water, there was obtained 1.8 g. (60%) of benzamide, m.p. and mixed m.p. 126.5–128.5°

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[23] See S. Cusmano, *Gazz. chim. ital.*, **78**, 764 (1948); *C. A.*, **43**, 5394i (1949).

[24] B. Prager and P. Jacobson, "Beilstein's Handbook of Organic Chemistry," Julius Springer, Berlin, 1921, Fourth Edition, Vol. III, p. 633.

[25] Isobutyronitrile, obtained from Eastman Kodak Co., was dried over magnesium sulfate and distilled, b.p. 102.5–103.5°, n^{25}D 1.3712; reported b.p. 103.85° (J. Timmermans and Y. Delcourt, *J. chim. phys.*, **31**, 85 (1934)), n^{25}D 1.3713 (*Org. Syntheses*, **25**, 61 (1945)). In spite of this purification the nitrile apparently contained a trace of impurity since it produced slight fuming over liquid ammonia. A sample of the nitrile that had been recovered after treatment with sodium amide in liquid ammonia had the same boiling point and refractive index but it produced no fuming over liquid ammonia.

[26] A vapor which was basic toward moist indicator paper was evolved during the distillation. Certain amidines decompose upon heating giving ammonia and the corresponding nitriles; see R. L. Shriner and F. W. Neumann, *Chem. Revs.*, **35**, 388 (1944).

[27] H. Meyer, *Monatsh.*, **27**, 43 (1906).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Conversion of β-Ketonitriles to β-Ketoamides by Boron Fluoride in Aqueous Acetic Acid and by Polyphosphoric Acid[1]

BY CHARLES R. HAUSER AND CHARLES J. EBY

RECEIVED JULY 23, 1956

A number of β-ketonitriles were converted in good yields to the corresponding β-ketoamides by boron fluoride and by polyphosphoric acid. Both of these methods are considered superior to other known methods. The boron trifluoride method produces boron difluoride complexes of the β-ketoamides. The boron difluoride complex of benzoylacetamide was isolated. Possible structures for this complex are suggested. Benzoylacetonitrile failed to form the corresponding boron difluoride complex.

It has been shown recently that ordinary nitriles such as benzonitrile may be converted in good yield to the corresponding amides by means of boron fluoride in aqueous acetic acid[2] or by polyphosphoric acid (PPA).[3]

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[1] Supported by the Office of Ordnance Research, U. S. Army.

[2] C. R. Hauser and D. S. Hoffenberg, *J. Org. Chem.*, **20**, 1448 (1955).

[3] H. R. Snyder and C. T. Elston, THIS JOURNAL, **76**, 3039 (1954)