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).

DURHAM, N.C.

[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)

TABLE I

β-KETOAMIDES FROM CORRESPONDING β-KETONITRILES BY BORON FLUORIDE OR POLYPHOSPHORIC ACID (PPA)

β-Ketoamide	BF$_3$ method		PPA method		Lit.
	Yield, %	M.p., °C.	Yield, %	M.p., °C.	M.p., °C.
Benzoylaceto	77	110–111	87	109–111[a]	112–113[b]
m-Chlorobenzoylaceto	79	135–137	..	......	......
α-Propionylpropio	30[c]	83–84[d]	34	80–81[d]	82[e]
α-Benzoylpropio	72	150–152[f]	71	146–149[g]	145–146[h]; 153[b]
α-Benzoyl-*n*-valero	72[i]	154.5–156.5	82	155–157[f]	157–158[h]
α-*m*-Chlorobenzoyl-*n*-valero	83	136.5–137.5[j]	..	......	......
α-Acetyl-α-tolu	87	124–126	58	122–125	129–130[k]
α-Propionyl-α-tolu	80[l]	116–117.5	79	115–117	114–116[m]
α-Benzoyl-α-tolu	85[i]	171.5–173.5	69	172–174[j,n]	172–173[o]; 178[p]

[a] Reaction mixture was heated one hour at 115° instead of on steam-bath. [b] Reference 10. [c] The yield of crude product, m.p. 72–75°, was 63%. [d] Recrystallized once from ether. [e] C. Pingel, *Ann.*, 245, 87 (1888). [f] Recrystallized once from water. [g] Recrystallized once from methanol. [h] Reference 12. [i] The precipitated boron difluoride complex was decomposed with 50% ethanolic sodium acetate. [j] Recrystallized once from methanol–water. [k] Reference 9. [l] The precipitated boron difluoride complex was decomposed with aqueous sodium acetate. [m] Reference 8. [n] Reaction mixture was heated 20 minutes at 120° after heating on the steam-bath. [o] Reference 7. [p] E. Atkinson, H. Ingham and J. Thorpe, *J. Chem. Soc.*, 91, 593 (1907).

In the present investigation certain β-ketonitriles were converted to the corresponding β-ketoamides by adaptations of these methods. For example, benzoyl- and *m*-chlorobenzoylacetonitriles were converted to β-ketoamides of type I[4] in yields of 77–87%. The β-ketonitriles were prepared readily through the acylation of acetonitrile with the appropriate methyl ester by means of sodium amide.[5] The over-all reaction may be represented by equation 1.

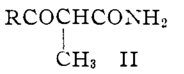
$$\mathrm{CH_3CN} \xrightarrow[\text{2, } \mathrm{RCOOCH_3}]{\text{1, } \mathrm{NaNH_2}} \mathrm{RCOCH_2CN}$$

$$\xrightarrow[\text{or PPA}]{\mathrm{BF_3(CH_3COOH)}} \underset{\mathrm{I}}{\mathrm{RCOCH_2CONH_2}} \quad (1)$$

$$\mathrm{R} = \mathrm{C_6H_5},\ m\text{-}\mathrm{ClC_6H_4}$$

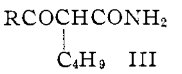
The boron fluoride method involved the rapid saturation of a mixture of the β-ketonitrile and aqueous acetic acid with the reagent, under which conditions the temperature rose spontaneously to 120–140°. The reaction was complete within a short time (10–20 minutes). The polyphosphoric acid method consisted generally in heating the β-ketonitriles with the reagent at the steam-bath temperature for 30 minutes.

In Table I are summarized the yields of β-ketoamides synthesized from β-ketonitriles by these two methods. Besides β-ketoamides of type I, the β-ketoamides prepared include those of types II, III and IV.



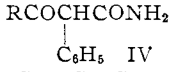
$$\begin{array}{l}\mathrm{RCOCHCONH_2}\\ \quad\ \ |\\ \quad\ \mathrm{CH_3}\quad \mathrm{II}\end{array}$$

R = CH_3CH_2, C_6H_5



$$\begin{array}{l}\mathrm{RCOCHCONH_2}\\ \quad\ \ |\\ \quad\ \mathrm{C_4H_9}\quad \mathrm{III}\end{array}$$

R = C_6H_5, *m*-ClC_6H_4



$$\begin{array}{l}\mathrm{RCOCHCONH_2}\\ \quad\ \ |\\ \quad\ \mathrm{C_6H_5}\quad \mathrm{IV}\end{array}$$

R = CH_3, CH_3CH_2, C_6H_5

It can be seen from Table I that both the boron fluoride and polyphosphoric acid methods generally gave good yields of β-ketoamides. The former method usually produced purer products and is probably more convenient to employ.[6]

The present methods of converting β-ketonitriles to β-ketoamides appear superior to those described previously employing concentrated sulfuric acid[7] or ethanolic[8] or aqueous[9] hydrogen chloride with which generally no yields have been reported. Also the present methods are considered superior to other known methods, one of which involves the ammonolysis of the respective β-ketoesters.[10] Although benzoylacetamide has been obtained in good yield by the ammonolysis of ethyl benzoylacetate, the reaction required several days.[11] Moreover, most other β-ketoesters that would be required for the preparation of the β-ketoamides listed in Table I are not readily available. In fact, some of them have been obtained from the β-ketonitriles.[12]

It should be pointed out that the reaction of β-ketonitriles with boron trifluoride in aqueous acetic acid produces a boron difluoride complex of the β-ketoamide from which the β-ketoamide is subsequently liberated by means of hot sodium acetate solution. One of these complexes, that of benzoylacetamide, was isolated from the reaction mixture in the conversion of benzoylacetonitrile to the amide. This complex, which gave a good analysis, also was obtained by treating benzoylacetamide with boron fluoride in ethylene chloride. In this experiment some etching of the glass container was observed indicating the evolution of hydrogen fluoride. By analogy with β-diketones, which produce similar boron difluoride complexes,[13] the reaction of boron trifluoride with benzoylacet-

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[4] H. R. Snyder and C. T. Elston (ref. 3) prepared one β-ketoamide of type I (R = 2,4-dimethylphenyl) by means of polyphosphoric acid.

[5] C. J. Eby and C. R. Hauser, *ibid.*, **79**, 723 (1957).

[6] Whereas the boron fluoride–acetic acid reaction mixture is readily neutralized with sodium hydroxide to form sodium acetate, the neutralization of polyphosphoric acid with sodium bicarbonate is troublesome. Also, the latter acid is somewhat difficult to handle.

(7) See, for example, R. Walther and P. G. Schickler, *J. prakt. Chem.*, [2] **55**, 305 (1897).

(8) See, for example, O. Dimroth and H. Feuchter, *Ber.*, **36**, 2238 (1903).

(9) O. Hromatka, *ibid.*, **75B**, 814 (1942).

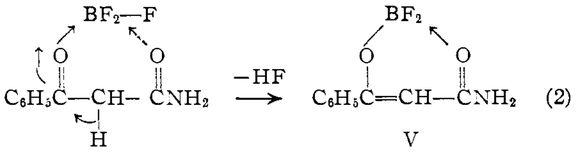
(10) J. T. Abrams and F. S. Kipping, *J. Chem. Soc.*, 1988 (1934).

(11) We obtained a 60% yield of benzoylacetamide from ethyl benzoylacetate and concentrated ammonium hydroxide on allowing the reaction mixture to stand at room temperature with occasional swirling for six days. The earlier workers (ref. 10) reported an 81% yield under similar conditions.

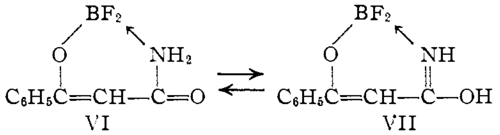
(12) J. B. Dorsch and S. M. McElvain, THIS JOURNAL, **54**, 2960 (1932).

(13) F. G. Young, F. C. Frostick, J. J. Sanderson and C. R. Hauser, *ibid.*, **72**, 3635 (1950); C. R. Hauser, F. C. Frostick and E. H. Man, *ibid.*, **74**, 3232 (1952).

amide may be represented by equation 2 in which the loss of hydrogen fluoride would give boron difluoride complex V.



Two other possible cyclic structures in which the nitrogen atom is part of the ring, would be tautomers VI and VII. Several resonance forms of each of these structures are possible.



It is of interest that, in contrast to benzoylacetamide, benzoylacetonitrile failed to form a boron difluoride complex on treatment with boron trifluoride in ethylene chloride, and the β-ketonitrile was largely recovered. Apparently the formation of the boron difluoride complex of a β-ketonitrile is prevented for steric reasons.

Experimental[14]

Conversion of β-Ketonitriles to β-Ketoamides.—These reactions were effected by boron fluoride in aqueous acetic acid or by polyphosphoric acid (PPA) as described below. The yields of products and the melting points on which the yields are based are given in Table I. Samples of the products generally were recrystallized until the melting points agree with those given in the literature.

(A) **BF_3 Method.**—A solution of 3.0 g. of the β-ketonitrile in 30 ml. of acetic acid and 4 ml. of water was saturated with gaseous boron fluoride until white fumes were evolved (10–15 minutes). The temperature rose to 120–140°.[15] After being cooled somewhat, the mixture was carefully neutralized with 6 *N* sodium hydroxide (to form sodium acetate) and then refluxed 30–60 minutes to break up the boron difluoride complex of the β-ketoamide. Some foaming occurred during the first 5–15 minutes of the reflux period. After being filtered rapidly with suction, the hot solution was cooled in ice-water. The resulting white precipitate of the β-ketoamide was either collected on a funnel with suction or taken up in three 100-ml. portions of equal parts of ethyl acetate and ether.[16] The extracts were washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed to give the β-ketoamide.

In some cases after saturation with boron fluoride, the reaction mixture was cooled and diluted with ice-water to precipitate the boron difluoride complex of the β-ketoamide. The precipitate was collected on a funnel with suction and refluxed 2 hours with 13.6 g. of sodium acetate trihydrate in water or 50% ethanol. A sufficient amount of solvent was employed to effect the solution of the complex at the reflux temperature. The β-ketoamide was then isolated in the usual manner.

Certain of the products obtained as described above were essentially pure while others required recrystallization from appropriate solvents to raise their melting points to the literature values (see Table I). *m*-Chlorobenzoylacetamide melted at 135–137° after one recrystallization from water, and at 137.5–139° (lustrous white plates) after two additional recrystallizations from water.

Anal. Calcd. for $C_9H_8O_2NCl$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.75; H, 4.08; N, 7.08.

α-*m*-Chlorobenzoyl-*n*-valeramide, after one recrystallization from methanol-water, melted at 136.5–137.5°.

Anal. Calcd. for $C_{12}H_{14}O_2NCl$: C, 60.12; H, 5.89; N, 5.84. Found: C, 60.16; H, 5.96; N, 5.75.

(B) **PPA Method.**—A mixture of 75–125 g. of polyphosphoric acid[17] and 0.025–0.05 mole of the β-ketonitrile was heated with stirring on the steam-bath for 30 minutes, and the warm solution then poured directly with stirring onto 200–300 g. of crushed ice. After stirring for 30 minutes, the precipitate of the β-ketoamide was collected on a funnel with suction, and the filtrate neutralized with solid sodium bicarbonate to precipitate more of the β-ketoamide. In certain cases no precipitate formed until the reaction mixture was neutralized. Even then some of the β-ketoamides failed to precipitate or only partially precipitated. In these cases the solution was saturated with sodium chloride and extracted with three 100-ml. portions of equal volumes of ethyl acetate and ether. After drying over magnesium sulfate, the solvents were removed leaving the solid β-ketoamides which generally were recrystallized from appropriate solvents (see Table I).

Isolation of Boron Difluoride Complex of Benzoylacetamide (V). A. Through Conversion of the β-Ketonitrile to the β-Ketoamide by the Boron Fluoride Method in Acetic Acid.—A solution of 1.5 g. of benzoylacetonitrile in 15 ml. of acetic acid and 2 ml. of water was saturated with boron fluoride as described above. The reaction mixture was cooled and diluted with ice-water to precipitate 1.65 g. (76%) of the boron difluoride complex of benzoylacetamide (V), m.p. 182–186°. After recrystallization from ether-petroleum ether, the complex melted at 186.5–188.5°.

Anal. Calcd. for $C_9H_8O_2NBF_2$: N, 6.64. Found: N, 6.62.

B. From Benzoylacetamide in Ethylene Chloride.—A solution of 0.9 g. of benzoylacetamide in 200 ml. of dry ethylene dichloride, cooled in an ice-bath, was saturated with gaseous boron trifluoride until copious white fumes were evolved, and then for 10 minutes longer. The solution became yellow and a yellow oil separated. The solution above the oil was decanted and the solvent removed under vacuum (water aspirator) leaving more yellow oil. The combined oils were placed in a vacuum desiccator overnight, becoming solid. The flask containing this solid was etched slightly. The solid was dissolved in ether, and petroleum ether added. The resulting oil was separated and triturated with petroleum ether to give 0.55 g. (47%) of complex V, m.p. 186.5–189.5°, which was not depressed on admixture with a sample of the complex produced in (A). Evaporation of the solvent from the mother liquor left more (0.55 g.) of complex V, m.p. 176–182°, total yield 95%.

Attempt to Prepare the Boron Difluoride Complex of Benzoylacetonitrile in Ethylene Chloride.—When a solution of 2.9 g. of benzoylacetonitrile in 25 ml. of dry ethylene dichloride was saturated with boron trifluoride and the reaction mixture worked up as described above for benzoylacetamide in procedure (B), only the β-ketonitrile was recovered. One recrystallization from ethyl ether gave 2.6 g. (90%) of the β-ketonitrile, m.p. 81–82°, which was not depressed on admixture with an authentic sample of the starting material.

DURHAM, NORTH CAROLINA

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[14] Melting points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

[15] In some cases complete solution of the β-ketonitrile was not attained until the reaction mixture became hot.

[16] With α-propionylpropionamide, the water was saturated with sodium chloride before extraction.

[17] We are indebted to the Victor Chemical Works, Chicago, Ill., for a generous sample of this reagent.