[Contribution from the Department of Chemistry, Duke University]

CONVERSION OF NITRILES TO AMIDES AND ACIDS BY MEANS OF BORON FLUORIDE

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The hydrolysis of nitriles has previously been stopped at the intermediate amide stage by employing concentrated sulfuric acid (1), hydrogen peroxide with sodium hydroxide (2), or polyphosphoric acid (3).

We have accomplished this by means of boron fluoride in aqueous acetic acid with which various nitriles were converted exclusively to the corresponding amides (Table I). The method usually involved saturating a solution of the nitrile in aqueous acetic acid with boron fluoride under which conditions the temperature of the reaction mixture rose to 115–135° (Procedure A). Equally good results were obtained by heating the nitrile at 115–120° for ten minutes with a boron fluoride-acetic acid complex[2] to which had been added some water (Procedure B). In both procedures the reaction mixtures were subsequently decomposed with alkali.

We further found that by treatment with the boron fluoride-acetic acid complex[2] (anhydrous) certain of the nitriles were converted exclusively to amides but certain others produced mixtures of amides and acids (Table II).

It can be seen from Table I that the aqueous acetic acid reagent produced excellent yields of the amide, which, without recrystallization, usually melted within a degree or two of the recorded value. For example, phenylacetonitrile and benzonitrile were converted almost quantitatively to phenylacetamide and benzamide respectively. However, the method failed with mesitonitrile which was recovered unchanged. The recent polyphosphoric acid method (3) likewise failed with this nitrile.

It can be seen from Table II that the anhydrous reagent likewise produced high yields of the amide and no acid with phenylacetonitrile, diphenylacetonitrile, and *p*-nitrobenzonitrile, but the reaction products were not as clean as those obtained with the aqueous reagent (Table I). It can also be seen from Table II that the anhydrous reagent gave both the amide and the acid with *p*-chlorobenzonitrile, benzonitrile and *o*- and *p*-tolunitriles. Actually the acid was the main product with the last two nitriles.

It is of particular interest that even those nitriles which formed both the amide and acid with the anhydrous reagent yielded exclusively the amide with the aqueous acetic acid reagent (compare Tables I and II). The most striking

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[1] Allied Chemical and Dye Corporation Fellow, 1954–1955.

[2] A complex consisting of one molecule of boron fluoride to two molecules of acetic acid, obtained from the General Chemical Division, Allied Chemical and Dye Corporation, was employed. A similar complex, prepared in this laboratory by saturating purified acetic acid (distilled from acetic anhydride) with gaseous boron fluoride at 50–70°, was also used. The latter complex apparently contained slightly more boron fluoride than that obtained commercially.

TABLE I

AMIDES FROM NITRILES WITH BORON FLUORIDE IN AQUEOUS ACETIC ACID

Nitrile	Amide	Procedure	Yield,[a] %	M.P., °C.	Lit. M.P., °C.
Phenylacetonitrile	Phenylacetamide	A	97	154–156	156–157
Diphenylacetonitrile	Diphenylacetamide	A	97	168–169	167–168
p-Nitrobenzonitrile	*p*-Nitrobenzamide	A	94	198–200	201
p-Chlorobenzonitrile	*p*-Chlorobenzamide	B	97[b]	177–179	179
Benzonitrile	Benzamide	A	95[b]	126–128	128
o-Tolunitrile	*o*-Toluamide	A	87[c]	144–145	142
p-Tolunitrile	*p*-Toluamide	B	97[d]	155–156	158

[a] These yields are based on products having the melting points recorded. [b] Obtained even with one equivalent of water. [c] Recrystallized once from water. [d] When one equivalent of water was used, the yield of amide was only 48%, and an approximately equal yield of *p*-toluic acid was obtained.

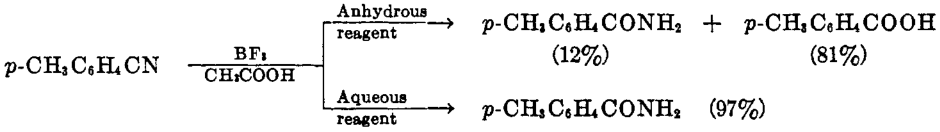
TABLE II

AMIDES AND ACIDS FROM NITRILES WITH BORON FLUORIDE IN ANHYDROUS ACETIC ACID

Nitrile	Yield,[a] %	Amide M.P., °C.	Lit. M.P., °C.	Yield,[a] %	Acid M.P., °C.	Lit. M.P., °C.
Phenylacetonitrile	95[b]	152–153	156–157	0		
Diphenylacetonitrile	88[b]	164–165	167–168	0		
p-Nitrobenzonitrile	93	197–199	201	0		
p-Chlorobenzonitrile	68	178–179	179	26	238–240	242
Benzonitrile	65	120–124	128	28[b]	122	122
o-Tolunitrile	12	136–138	142	68[b]	104–105	105
p-Tolunitrile	12[b]	156–157	158	81	176–178	178

[a] These yields are based on products having the melting points recorded. [b] Recrystallized once from water.

example is that of *p*-tolunitrile for which the two courses of reaction are represented below. Even when the reagent contained more water than acetic acid, the amide was obtained exclusively. These results are in contrast to the well known fact that, with sulfuric acid, the presence of water generally favors the further hydrolysis of the amide to the carboxylic acid (1).

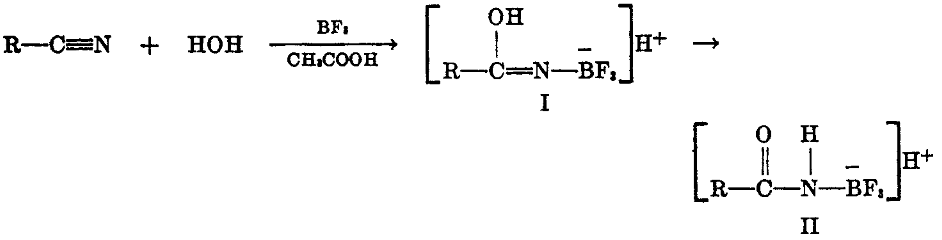


$$p\text{-}CH_3C_6H_4CN \xrightarrow[CH_3COOH]{BF_3} \left\{ \begin{array}{l} \xrightarrow{\text{Anhydrous reagent}} p\text{-}CH_3C_6H_4CONH_2\ (12\%) + p\text{-}CH_3C_6H_4COOH\ (81\%) \\ \xrightarrow{\text{Aqueous reagent}} p\text{-}CH_3C_6H_4CONH_2\ (97\%) \end{array} \right.$$

The minimum amount of water required to form exclusively the amide varied with the nitrile. With *p*-tolunitrile, two equivalents of water appeared to be required since one equivalent gave approximately as much acid as amide. This is probably true also with *o*-tolunitrile. However, with benzamide or *p*-chlorobenzamide, only one equivalent of water was required to give exclusively the amide.

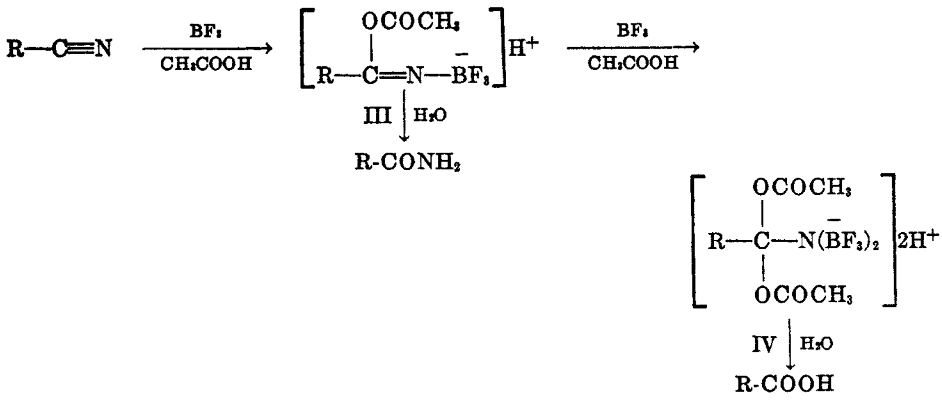
As mentioned above, *p*-nitrobenzonitrile, phenylacetonitrile, and diphenylacetonitrile gave exclusively the amide even with the anhydrous reagent. In general, at least three equivalents of water to one of the nitrile are recommended if exclusive amide formation is desired.

The mechanism of formation of the amide with the aqueous acetic acid reagent presumably involves the addition of water to the boron fluoride coordination complex of the nitrile to form I which isomerizes to II. In a blank experiment with benzamide and the aqueous boron fluoride-acetic acid reagent, with which II would presumably be formed, the amide was recovered unchanged (96%). A similar mechanism has often been represented for the acid-catalyzed hydrolysis of nitriles to form the amide (1, 4) which is usually further hydrolyzed by the acid (hydrochloric or sulfuric) to the carboxylic acid.



$$R{-}C{\equiv}N \;+\; HOH \xrightarrow[CH_3COOH]{BF_3} \underset{\text{I}}{\left[\begin{array}{c} \quad OH \\ \quad | \\ R{-}C{=}N{-}\overset{-}{}BF_3 \end{array}\right]H^+} \rightarrow \underset{\text{II}}{\left[\begin{array}{c} \quad O \quad H \\ \quad \| \quad\; | \\ R{-}C{-}N{-}\overset{-}{}BF_3 \end{array}\right]H^+}$$

The conversion of the nitrile to the amide with the anhydrous reagent appears to involve the intermediate formation of complex III, and that of the nitrile to the acid, the intermediate formation of complex IV. The subsequent hydrolysis of these intermediates might be expected to yield the amide and acid respectively. Complex III would result from the addition of one molecule each of boron fluoride and acetic acid. This reaction would be analogous to the well known acid—catalyzed addition of ethanol to nitriles to form imino ethers (4). In contrast to complex I which apparently isomerized rapidly to the relatively stable complex II, complex III cannot isomerize, and therefore may undergo further addition of boron fluoride and acetic acid to form complex IV leading to the formation of the acid. The acid is not produced through the intermediate formation of the amide since, in a blank experiment with the anhydrous reagent, benzamide was



$$R{-}C{\equiv}N \xrightarrow[CH_3COOH]{BF_3} \left[\begin{array}{c} \quad OCOCH_3 \\ \quad | \\ R{-}C{=}N{-}\overset{-}{}BF_3 \end{array}\right]H^+ \xrightarrow[CH_3COOH]{BF_3} \left[\begin{array}{c} OCOCH_3 \\ | \\ R{-}C{-}\overset{-}{N}(BF_3)_2 \\ | \\ OCOCH_3 \end{array}\right]2H^+$$

$$\text{III} \xrightarrow{H_2O} R\text{-}CONH_2 \qquad \text{IV} \xrightarrow{H_2O} R\text{-}COOH$$

recovered unchanged. Neither does the acid appear to arise along with the amide from the subsequent hydrolysis of complex III involving a mode of hydrolysis different from that which produces the amide. Thus, the same relative yields of acid and amide were obtained when the reaction mixture from *p*-tolunitrile with the anhydrous reagent was added to alkali as when the alkali was added to the reaction mixture. Moreover, *p*-nitrobenzonitrile yielded exclusively the amide when the reaction mixture was worked up by either of these procedures.

That the amide arises from complex III and the acid from complex IV is supported by two observations with *p*-tolunitrile and the anhydrous reagent. First, the use of only one equivalent of boron fluoride produced mainly the amide (59%) and only a little of the acid (3%), whereas the use of two equivalents of boron fluoride gave relatively more of the acid (35%), and that of the usual four to five equivalents, still more of the acid (81%). Secondly, when the reaction (with excess of the reagent) was stopped after only one minute, the yield of amide was relatively greater (35%) and that of the acid correspondingly less (58%) than when the reaction was allowed to proceed for the usual ten minutes (see Table II).

Since relatively more of the acid was obtained as the *para* substituents of the benzonitriles were varied in the order, $NO_2 < Cl, H < CH_3$ (Table II), the controlling factor in the formation of the acid appears to be the extent of coordination of the second molecule of boron fluoride with the nitrogen of complex III. If the nucleophilic attack of the acetic acid on complex III were the controlling factor, the reverse order should be expected, unless complex III is the precursor for the acid, and complex IV, that for the amide which seems unlikely.

It should be mentioned that, because the coordination of a second molecule of boron fluoride with the nitrogen of complex III may introduce strain in complex IV, a proton might coordinate instead to form a complex analogous to IV, the subsequent hydrolysis of which should similarly produce the acid. In general, however, boron fluoride presumably undergoes coordination preferentially to a proton.

EXPERIMENTAL[3]

Amides from nitriles with boron fluoride in aqueous acetic acid. Table I. Procedure A. A solution of 3.0 g. of the nitrile and 0.8–4.0 g. (2–10 equivalents) of water in 20 ml. of acetic acid was saturated rapidly with gaseous boron fluoride (passed over the surface until copious white fumes were evolved), the temperature rising to 115–135°. In the reaction with *p*-nitrobenzonitrile complete solution did not occur until the mixture became hot. The cooled, stirred (mechanical stirrer) reaction mixture which was immersed in an ice-bath, was made alkaline by the slow addition of 6 *N* sodium hydroxide (about 130 ml.), and then was extracted with three 100-ml. portions of a mixture of equal volumes of ether and ethyl acetate. The scum which usually formed at the interface of the two layers was drawn off along with the aqueous alkaline layer. The combined ether-ethyl acetate extracts were dried over Drierite and the solvents were evaporated under reduced pressure to yield the amide. Filtration of the aqueous alkaline layer, followed by acidification, precipitated no carboxylic acid.

In a similar manner a solution of 3.0 g. of *p*-tolunitrile in 8.0 g. (18 equivalents) of water

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[3] Melting points are uncorrected.

and 24 g. (16 equivalents) of acetic acid was saturated with boron fluoride to give a 94% yield of *p*-toluamide, m.p. 157–158°; reported m.p. 158° (5). No *p*-toluic acid was found.

Procedure B. A solution of 3.0 g. of the nitrile, 0.8–4.0 g. (2–10 equivalents) of water and 20 g. of the boron fluoride-acetic complex[3] was heated in an oil-bath at 115–120° for 10 minutes. (With *p*-nitrobenzonitrile solution was achieved only after the reaction mixture became hot). After cooling, the reaction mixture was decomposed with 100 ml. of 6 *N* sodium hydroxide and the amide was isolated by extraction with ether and ethyl acetate as described in Procedure *A*.

Amides and acids with boron fluoride in anhydrous acetic acid. Table II. A solution of 3.0 g. of the nitrile in 20 g. of the anhydrous boron fluoride-acetic acid complex[2] was heated in an oil-bath at 115–120° for 10 minutes. After cooling, 100 ml. of 6 *N* sodium hydroxide was added slowly with stirring, and the resulting mixture was shaken with a mixture of equal parts of ether and ethyl acetate. The organic layer was evaporated to give the amide, and the aqueous alkaline layer was filtered and acidified with 12 *M* hydrochloric acid to precipitate the carboxylic acid. The acid, if present, was collected on a funnel, washed with water, and sucked dry.

When the reaction with *p*-tolunitrile was repeated and the reaction mixture (after cooling) was added slowly with stirring to 100 ml. of iced 6 *N* sodium hydroxide, there was obtained a 12% yield of *p*-toluamide, m.p. 156–157°, reported m.p. 158° (5), and a 75% yield of *p*-toluic acid, m.p. 178–179°; reported m.p. 178° (5). When the reaction of *p*-nitrobenzonitrile was repeated and the reaction mixture similarly was added to alkali, *p*-nitrobenzamide, m.p. 196–198°, reported m.p. 201° (5) was obtained in 90% yield and no *p*-nitrobenzoic acid was found. These results are essentially the same as those obtained by the general procedure described above in which the alkali was added to the reaction mixture (see Table II).

Evidence for the formation of intermediate complexes III and IV. A. One minute reaction time. To 20 g. of the anhydrous boron fluoride acetic-acid complex,[2] which had been preheated to 115–120° in an oil-bath, there was added 3.0 g. of *p*-tolunitrile. The mixture was swirled in the bath for one minute and then was poured rapidly (10 seconds) into 100 ml. of iced 6 *N* sodium hydroxide. There was obtained a 35% yield of *p*-toluamide, m.p. 155–157°, and a 58% yield of *p*-toluic acid, m.p. 177–178°.

B. With one and two equivalents of boron fluoride. When the reaction of 3.0 g. of *p*-tolunitrile with 4.55 g. of the commercial boron fluoride-acetic acid complex[2] (containing one equivalent of boron fluoride) in 16 g. of acetic acid was carried out in the usual manner (heated at 115–120° for 10 minutes), there was obtained, in addition to some unreacted nitrile, a 59% yield of *p*-toluamide, m.p. 157–158°, and a 3% yield of *p*-toluic acid, m.p. 177–178°.

When the reaction of 3.0 g. of the nitrile with 9.1 g. of the commercial boron fluoride-acetic acid complex (containing two equivalents of boron fluoride) in 11 g. of acetic acid was similarly carried out, there was isolated a 56% yield of *p*-toluamide, m.p. 157–158°, and a 35% yield of *p*-toluic acid, m.p. 177–179°.

SUMMARY

1. A number of nitriles were found to be converted exclusively to the corresponding amides by boron fluoride in acetic acid in the presence of water. In the absence of water, certain of the nitriles produced some of the corresponding acids in addition to the amide.

2. The use of the aqueous acetic acid reagent furnishes a useful method for converting nitriles to amides in almost quantitative yields.

3. Mechanisms are suggested for the courses of reaction with the aqueous and anhydrous reagents.

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