

Ionization of an α Hydrogen of Acetonitrile by *n*-Butyllithium and Alkali Amides. Condensations with Ketones and Aldehydes to Form β -Hydroxynitriles^{1a}

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Acetonitrile was found to undergo mainly ionization of an α hydrogen with *n*-butyllithium in tetrahydrofuran-hexane, rather than an addition reaction involving the cyanide group. The former course of reaction was evidenced by an addition reaction of the resulting lithioacetonitrile with benzophenone to form 3-hydroxy-3,3-diphenylpropanenitrile in 89% yield. Similarly, an α hydrogen of acetonitrile was ionized by sodium amide, lithium amide, and potassium amide in liquid ammonia and the resulting alkali acetonitrile was condensed with benzophenone to give this β -hydroxynitrile in yields of 93, 85, and 69%, respectively. The *n*-butyllithium method was extended to several other ketones and to benzaldehyde. These results illustrate convenient methods for the synthesis of such β -hydroxynitriles, which can be dehydrated with acid to form the corresponding unsaturated nitriles.

Ionization of an α hydrogen of acetonitrile in liquid ammonia by means of sodium amide has been demonstrated by alkylation² and benzoylation³ of the resulting sodionitrile. However, such an ionization by *n*-butyllithium appears not to have been realized previously. On the contrary, attack at the cyanide group of this nitrile by the related *n*-amyllithium has been reported, as evidenced by formation of methyl *n*-amyl ketone in 21–25% yield.⁴

We have found that alkali acetonitriles suitable for condensations with ketones and aldehydes can be prepared, not only by alkali amides in liquid ammonia, but also by *n*-butyllithium in tetrahydrofuran (THF)-hexane; this was demonstrated by condensations with benzophenone to afford β -hydroxynitrile 1 in good yields (Scheme I, Table I).

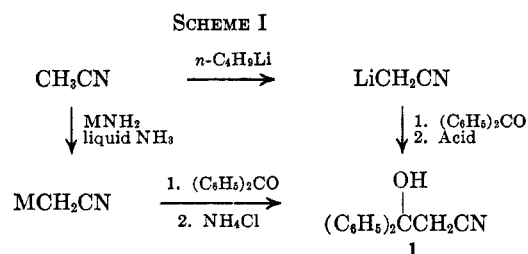


Table I shows that the yield of β -hydroxynitrile 1 with *n*-butyllithium was 89% when the ionization and condensation were both effected at -80° . However, the yield of 1 was only 70 and 16% when the ionization was effected at room temperature and at reflux, respectively, before the condensations were performed at 0° .

On the other hand, when acetonitrile and *n*-butyllithium in THF-hexane were refluxed for 1 hr in the absence of benzophenone, hydrolysis of the reaction mixture afforded in low yield a mixture of six products (by vpc) whose infrared spectrum contained bands due to N—H, C=N, C=O, and/or C=N—. Surpris-

TABLE I
CONDENSATIONS OF ACETONITRILE WITH BENZOPHENONE
BY MEANS OF *n*-BUTYLLITHIUM AND ALKALI AMIDES TO
FORM β -HYDROXYNITRILE 1

Reagent	Solvent	Temp, $^\circ\text{C}$	Ionization time, min	Condensation time, min	Yield, %
<i>n</i> -C ₄ H ₉ Li	THF-hexane	-80	60	10	89
<i>n</i> -C ₄ H ₉ Li	THF-hexane	25	60	10 ^a	70
<i>n</i> -C ₄ H ₉ Li	THF-hexane	64	60	10 ^a	16
NaNH ₂ ^b	NH ₃	-33	30	5	93
LiNH ₂ ^b	NH ₃	-33	60	5	85
KNH ₂ ^b	NH ₃	-33	15	5	69

^a The reaction was cooled to 0° and benzophenone was then added. ^b A 10% excess of alkali amide was employed.

ingly, even when acetonitrile was refluxed for 1 hr with 3 equiv of *n*-butyllithium, no methyl *n*-butyl ketone could be isolated either neat or as its 2,4-dinitrophenylhydrazone derivative.⁵ That lower yields of β -hydroxynitrile 1 were obtained at higher temperatures in the above reactions of acetonitrile may be attributed to such side reactions as abstraction of a hydrogen from solvent THF by lithioacetonitrile, especially at higher temperatures, to regenerate acetonitrile,⁶ or to self-condensation affording various imino- or ketonitriles.⁷

Table I further shows that the yields of β -hydroxynitrile 1 with sodium amide, lithium amide, and potassium amide in liquid ammonia were 93, 85, and 69%, respectively. In each case, a 10 mol % excess of alkali amide was employed, and the reaction mixture obtained after addition of benzophenone was inversely neutralized;⁸ such conditions are known to minimize reversions of salts like (C₆H₅)₂C(OLi)CH₂CN to starting materials.⁹ The lower yield with the potassium salt than with the sodium or lithium salt (see Table I) appears ascribable partly to some reversion, since certain related potassium salts are known to undergo reversion more readily.⁹

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research at the University of Missouri, and to the Army Research Office (Durham, N. C.,) for partial support at Duke University; (b) University of Missouri; (c) Duke University.

(2) F. W. Bergstrom and R. Agostinho, *J. Amer. Chem. Soc.*, **67**, 2152 (1945).

(3) C. R. Hauser and L. J. Eby, *ibid.*, **79**, 728 (1957).

(4) G. Sumrell, *J. Org. Chem.*, **19**, 817 (1954).

(5) Interestingly, treatment of acetonitrile in THF at -80° with 3 equiv of *n*-butyllithium in hexane may have afforded trillithioacetonitrile, Li₃CCN, since addition of 3 equiv of benzyl chloride gave tribenzylacetonitrile in low yield; see E. M. Kaiser and C. R. Hauser, *J. Amer. Chem. Soc.*, **88**, 2348 (1966). The reaction was not investigated further.

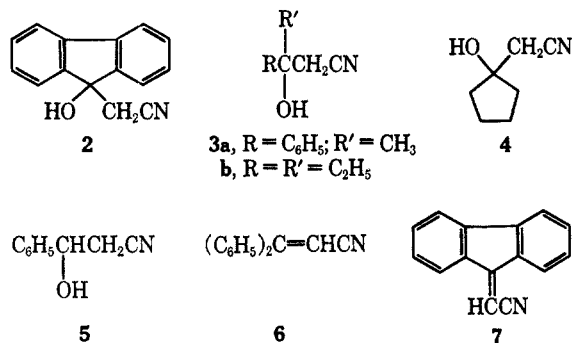
(6) See H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 1165 (1957).

(7) See C. R. Hauser and W. J. Humphlett, *ibid.*, **15**, 359 (1950).

(8) This method of neutralization involves pouring the reaction mixture into an excess of ammonium chloride in ammonia.

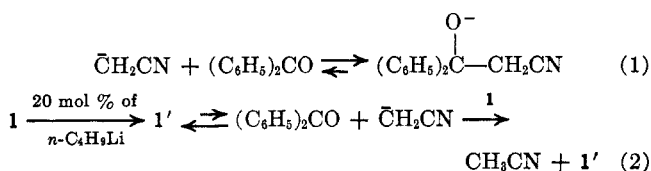
(9) See E. M. Kaiser and C. R. Hauser, *ibid.*, **31**, 3316 (1966).

The *n*-butyllithium method was extended to fluorenone, acetophenone, 3-pentanone, cyclohexanone, and benzaldehyde to form β -hydroxynitriles 2-5, respectively. Two of the β -hydroxynitriles (1 and 2) were dehydrated by means of 85% phosphoric acid to form unsaturated nitriles 6 and 7, respectively. Good to excellent yields (47-89%) were obtained for the condensation products and for the unsaturated nitriles. The structures of the products were supported by analyses and absorption spectra.



The *n*-butyllithium method could probably be extended still further to other ketones or aldehydes, and the alkali amide method would presumably also be quite general. β -Hydroxynitriles 1 and 5 have previously been reported but the reaction conditions, physical properties, structural proofs, and yields were not given.¹⁰ Also, ethylene cyanohydrin has been prepared from acetonitrile and formaldehyde by means of strong bases such as sodionaphthalene but the yield was only 1-8%.¹¹

The success of the addition reaction of the acetonitrile carbanion with a ketone or aldehyde appears ascribable to the formation of a weaker base, which would be an alkoxide type anion, for example, 1' (eq 1),¹² since the neutral β -hydroxynitrile 1 underwent cleavage to regenerate the starting ketone and nitrile on treatment with only a catalytic amount of *n*-butyllithium (eq 2). In this cleavage, neutral 1 functions as an acid that neutralizes the acetonitrile carbanion and forms more 1' which undergoes further cleavage.



In contrast to alkali acetonitriles, alkali phenylacetonitriles have been observed¹³ not to add satisfactorily to benzophenone; this seems attributable both to the more weakly basic nature of the phenylacetonitrile carbanion and to a steric factor arising through relief of strain in the cleavage of the anion of the adduct. However, magnesium and aluminum halide derivatives of phenylacetonitrile underwent addition to benzophenone; in these reactions, the coordinating capacities

(10) H. Lettre', G. Meiners, and H. Wichmann, *Naturwissenschaften*, **33**, 157 (1946).

(11) Y. Ogata, Y. Izawa, and Y. Osumi, *Bull. Chem. Soc. Jap.*, **37**, 74 (1964).

(12) Since the $\text{p}K_a$ of tertiary alcohols is near 19 and that of acetonitrile is 25, the alkoxide ion 1' should be a much weaker base than the acetonitrile carbanion; see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapter 1.

(13) E. M. Kaiser and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 4566 (1967).

of the metallic cations were presumed to play an important role.¹³

Experimental Section¹⁴

Condensations of Acetonitrile and Carbonyl Compounds Effected by *n*-Butyllithium. A. Benzophenone.—To a stirred solution of 34.5 ml (0.055 mol) of 1.6 *M* *n*-butyllithium in hexane,¹⁵ at -80° under nitrogen, was rapidly added 34.5 ml of anhydrous THF, followed immediately by a solution of 2.05 g (0.05 mol) of acetonitrile in 50 ml of THF added during 7 min. After stirring for 1 hr at -80° , the resulting white suspension was treated during 5 min with a solution of 9.1 g (0.05 mol) of benzophenone in 50 ml of THF. The cold bath was removed and the now pale yellow solution was stirred for 10 min before it was poured into ice-water-hydrochloric acid. The layers were separated and the aqueous layer was extracted with three 50-ml portions of ethyl ether. After the solvent was dried and stripped, the residual crude product was recrystallized from ethanol to afford 9.88 g (89%) of 3-hydroxy-3,3-diphenylpropanenitrile (1): mp $141.5-143^\circ$; ir (Nujol), 3400 (OH), 2290 (C \equiv N), 1380 and 1175 (OH and CO); nmr (CDCl₃), δ 7.38 (s, 10, ArH), 3.25 (s, 2, CH₂CN), 2.82 (s, 1, OH).

Anal. Calcd for C₁₅H₁₃NO: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.72; H, 5.82; N, 6.33.

In a similar run, the *n*-butyllithium,¹⁵ THF, and acetonitrile were mixed at room temperature. After stirring for 1 hr, the resulting solution was cooled to 0° then treated during 5 min with a solution of the ketone. Inverse neutralization and work-up as above afforded 7.8 g (70%) of 1, mp and mmp $141-143^\circ$; in addition, 2.7 g (15%) of benzophenone was recovered as its 2,4-dinitrophenylhydrazone, mp and mmp $239-240^\circ$.

When the latter reaction was repeated by refluxing the *n*-butyllithium¹⁵ and acetonitrile in THF-hexane for 1 hr before adding the ketone at 0° , 1.8 g (16%) of 1, mp and mmp $141-143^\circ$, and 9.1 g (50%) of benzophenone (as its 2,4-DNP), mp and mmp $239-240^\circ$, were recovered.

B. Fluorenone.—This reaction was accomplished essentially as described above for benzophenone at -80° using 9.0 g (0.05 mole) of fluorenone. Upon work-up, the resulting crude oil was chromatographed on Woelm neutral alumina grade I using 95% ethanol as the solvent. Recrystallization of the crude product from 90-120° ligroin-acetone afforded 5.17 g (47%) of 9-cyanomethyl-9-hydroxyfluorene 2: mp $97.5-98.5^\circ$; ir (melt), 3450 (OH), 2290 (C \equiv N), 1405 and 1160 (OH and CO).

Anal. Calcd for C₁₅H₁₁NO: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.27; H, 4.99; N, 6.26.

C. Acetophenone.—Using the above procedure, 6.0 g (0.05 mol) of acetophenone gave 5.66 g (70%) of 3-hydroxy-3-phenylbutanenitrile (3a), bp $149-150^\circ$ (4 mm). A small amount (0.95 g, 16%) of acetophenone was recovered: bp $70-71^\circ$ (4 mm); ir (neat), 3380 (OH), 2240 (C \equiv N), 1365 and 1145 (OH and CO); nmr (CDCl₃), δ 7.3 (m, 5, ArH), 3.44 (s, 1, OH), 2.65 (s, 2, CH₂CN), 1.6 (s, 3, CH₃).

Anal. Calcd for C₁₀H₁₁NO: C, 74.53; H, 6.82; N, 8.69. Found: C, 74.45; H, 6.76; N, 8.40.

D. 3-Pentanone.—As above, 4.3 g (0.05 mol) of 3-pentanone gave 4.3 g (68%) of 3-hydroxy-3-ethylpentanenitrile (3b): bp $63-64^\circ$ (2 mm); ir (neat), 3380 (OH), 2225 (C \equiv N), 1410 and 1140 (OH and CO); nmr (neat), δ 3.45 (s, 1, OH), 2.45 (s, 2, CH₂CN), 1.54 (q, 4, -CH₂CH₃), 0.82 (t, 6, -CH₂CH₃).

Anal. Calcd for C₇H₁₃NO: C, 66.14; H, 10.23; N, 11.02. Found: C, 66.08; H, 10.38; N, 11.00.

E. Cyclopentanone.—Similarly, 4.2 g (0.05 mol) of cyclopentanone afforded 3.8 g (61%) of 1-cyanomethyl-1-hydroxycyclopentane (4): bp $102-103^\circ$ (4 mm); ir (neat), 3395 (OH), 2250 (C \equiv N), 1400 and 1180 (OH and CO); nmr (neat), δ 3.7 (s, 1, OH), 2.59 (s, 2, CH₂CN), 1.63 (s, 8, ring H).

Anal. Calcd for C₇H₁₁NO: C, 67.20; H, 8.80; N, 11.20. Found: C, 67.05; H, 9.08; N, 10.94.

(14) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 either neat or as Nujol mulls. Nmr spectra were obtained with a Varian Associates A-60 spectrometer using neat liquids or deuteriochloroform solvent and tetramethylsilane as the internal standard. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Drying of ethereal extracts was accomplished by calcium sulfate.

(15) Supplied by the Foote Mineral Co., Exton, Pa.

F. **Benzaldehyde**.—Finally, 5.3 g (0.05 mol) of benzaldehyde gave 5.7 g (78%) of 3-hydroxy-3-phenylpropanenitrile (5): bp 154–155° (1 mm); ir (neat), 3395 (OH), 2275 (C≡N), 1315 and 1095 (OH and CO); nmr (neat), δ 6.9 (s, 5, ArH), 4.38 (m, 2, CHOH), 2.12 (d, 2, CH₂CN).

Anal. Calcd for C₉H₉NO: C, 73.55; H, 6.11. Found: C, 73.50; H, 6.19.

Condensation of Acetonitrile and Benzophenone by Alkali Amides in Ammonia. A. **Sodium Amide**.—To a stirred suspension of 0.055 mol of sodium amide in 300 ml of commercial anhydrous liquid ammonia¹⁶ [prepared from 1.27 g (0.055 g-atom) of sodium metal] was added during 5 min a solution of 2.05 g (0.05 mol) of acetonitrile in 50 ml of ether. After 30 min, the black solution was treated during 5 min with a solution of 9.1 g (0.05 mol) of benzophenone in 50 ml of ether. After 5 min, the now blue-black solution was poured into a magnetically stirred suspension of 20 g of ammonium chloride in 200 ml of ammonia. The ammonia was allowed to evaporate and the solid residue was hydrolyzed by the addition of 100 ml of 3 N hydrochloric acid. Work-up as in part A above afforded 10.3 g (93%) of β -hydroxynitrile 1, mp and mmp 141–142°.

B. **Lithium Amide**.—This reaction was effected essentially as described for sodium amide above except that the amide ion was prepared from 0.385 g (0.055 g-atom) of lithium metal. In addition, the solution derived from acetonitrile and lithium amide was stirred for 1 hr before the ketone was added. Work-up gave 9.42 g (85%) of product 1, mp and mmp 141–142°.

C. **Potassium Amide**.—This reaction was performed as in

(16) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

parts A and B using 2.15 g (0.055 g-atom) of potassium metal to form the amide ion; the ionization time before the addition of the ketone was 15 min. Work-up afforded 7.6 g (69%) of 1, mp and mmp 141–142°.

Dehydration of β -Hydroxynitrile 1 to Afford Unsaturated Nitrile 6.— β -Hydroxynitrile 1 (3.0 g, 0.0134 mol) was suspended in 80 ml of 85% phosphoric acid; the magnetically stirred mixture was brought to reflux for 15 min; and all of the solid dissolved or oiled. The mixture was then poured into ice water and the product was extracted by three 50-ml portions of ether. After the crude product was dried and concentrated, distillation gave 1.8 g (65%) of 1-cyano-2,2-diphenylethene (6): bp 172–173° (5 mm); ir (neat), 2205 (C≡N), 832 (C=C); nmr (CDCl₃), δ 7.4 (m, 10, ArH), 5.7 (s, 1, =CHCN).

Anal. Calcd for C₁₅H₁₁N: C, 87.80; H, 5.36; N, 6.82. Found: C, 87.77; H, 5.49; N, 6.78.

Dehydration of β -Hydroxynitrile 2 to Afford Unsaturated Nitrile 7.—This dehydration was effected as described above except that 1.5 g of 2 and 40 ml of 85% phosphoric acid were employed. Work-up as above and subsequent recrystallization from methanol afforded 0.9 g (55%) of 1-cyano-2-fluorenylethene (7): mp 109–111°; ir (Nujol), 2190 (C≡N), 835 (C=C); nmr (CDCl₃), δ 7.48 (m, 8, ArH), 6.02 (s, 1, =CHCN).

Anal. Calcd for C₁₆H₉N: C, 88.67; H, 4.43. Found: C, 88.54; H, 4.60.

Registry No.—1, 3531-23-5; 2, 17190-25-9; 3a, 14368-31-1; 3b, 17190-27-1; 4, 14368-37-7; 5, 17190-29-3; 6, 3531-24-6; 7, 4425-74-5; acetonitrile, 75-05-8; *n*-butyllithium, 109-72-8.

Synthesis of Four Methoxy-Substituted 1,8-Naphthalic Anhydrides and of the Three Monomethyl-1,8-naphthalic Anhydrides¹

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The 2-, 3-, and 4-methoxy-1,8-naphthalic anhydrides were synthesized by starting, respectively, with a Friedel-Crafts reaction on β -methoxynaphthalene, sulfonation of 1,8-naphthalic anhydride, and nitration of acenaphthene. 2,3-Dimethoxy-1,8-naphthalic anhydride was prepared in very low yield *via* the Friedel-Crafts reaction of diphenyloxalimide chloride with 2,3-dimethoxynaphthalene. The 2- and 4-methyl-1,8-naphthalic anhydrides were prepared, respectively, *via* the Friedel-Crafts reaction on β -methyl-naphthalene and bromination of acenaphthene. Synthesis of 3-methyl-1,8-naphthalic anhydride *via* Friedel-Crafts methylation of acenaphthene failed. Although ethylation of acenaphthene yields 4-ethylacenaphthene, methylation yields 5-methylacenaphthene. Successful synthesis of 3-methyl-1,8-naphthalic anhydride followed the discovery that diborane reduction of 3-bromo-1,8-naphthalic anhydride yields 5-bromo-2,1,3-*peri*-naphthopyran. After the bromine had been converted into methyl *via* the carboxylic acid, oxidation yielded the 3-methyl-1,8-naphthalic anhydride. Numerous attempts to synthesize 3,4-dimethoxy-1,8-naphthalic anhydride failed. In the nmr spectra of the anhydrides, resonance for the methyl hydrogens in both the methyl-substituted and methoxy-substituted anhydrides followed the same pattern, highest field for the 3 position and lowest field for the 2 position.

In determining the structure of trimethylherqueinone B, a derivative of the naturally occurring pigment herqueinone, a tetramethoxymonomethyl-1,8-naphthalic anhydride was isolated as a degradation product.² In order to allow location of the substituents in the naphthalene ring by spectroscopic methods, methoxy- and methyl-substituted 1,8-naphthalic anhydrides were required as reference compounds. The present report is concerned with synthesis of these compounds.

Although the monomethoxy-1,8-naphthalic anhydrides have been reported in the literature, each of the three has been characterized poorly or not at all. The 2-methoxy-1,8-naphthalic anhydride has been obtained by us in high yield by oxidation of 3-methoxyacenaphthenequinone; however, this intermediate was obtained

in relatively poor yield from a Friedel-Crafts reaction with β -methoxynaphthalene and diphenyloxalimide chloride. The best approach to the 3-methoxy-1,8-naphthalic anhydride³ proved to be sulfonation of the parent anhydride. Alkali fusion and methylation yielded the desired compound. The 4-methoxy isomer could not be obtained in significant yield, proceeding by way of the sulfonation of acenaphthene;⁴ however, nitration of acenaphthene proved to be a satisfactory approach. Reduction to the amine, high pressure hydrolysis to 5-acenaphthenol, methylation, and dichromate oxidation yielded the 4-methoxy-1,8-naphthalic anhydride.

In order to allow the desired deductions from spectra,

(1) This investigation was supported in part by a research grant (G 24347) from the National Science Foundation.

(2) J. Cason, J. S. Correia, R. B. Hutchison, and R. F. Porter, *Tetrahedron*, **18**, 839 (1962).

(3) A reaction using 3-methoxy-1,8-naphthalic anhydride has been reported by K. Dziewonski, W. Kohl, and W. Dymek, *Bull. Intern. Acad. Polon. Sci.*, 394 (1934); *Chem. Zentr.*, 2169 (1935I). No properties or method of synthesis are included in German or English abstracts.

(4) K. Dziewonski and T. Stolyhwo, *Ber.*, **57**, 1540 (1924).