perature in 0.001N hydrochloric acid, solution was slow and required many days for completion. A more rapid method for the preparation of solutions of known dye concentration was to moisten the weighed sample of dye with concentrated hydrochloric acid and then dilute with water.

To start the decomposition reaction 25 ml. of dye solution was mixed with an equal volume of 0.5M sodium bicarbonate solution in a 30° thermostat. Experiments on the two dyes were carried out side by side in the same thermostat at the same time except that one was commenced 5 min. after the other to permit time for manipulation while maintaining identical periods for reaction. At measured times 5-ml. samples of the dye reaction solutions were pipeted into 10 ml. volumetric flasks containing 2 ml. of 1N hydrochloric acid. Acidification arrested the decomposition while leaving the color of the blue dye unaffected for colorimetric determination after the solution had been diluted to 10 ml. with water.

The rate of decomposition of the blue dye produced by photolysis of rhodamine B cyanide was the same as that of authentic cornflower blue. The reaction was of first order over most of its course. The rate constant was 6 × 10^{-5} at 30°.

On the basis of these comparative tests, the blue dye formed by photolysis of rhodamine B cyanide was identified as cornflower blue with the structure (VII).

The yield of dyes obtained in the photolysis carried out as described above from 0.6 g. of perhaps 90% rhodamine B cyanide sodium salt (III) was determined colorimetrically as 50 mg. of rhodamine B as base and 160 mg. of cornflower blue as thiocyanate. A little less than half of this amount of dye was precipitated from the photolysis solution by potassium thiocyanate. Other products of photolysis were not identified.

Acknowledgment. It is a pleasure to express gratitude to Dr. Eugene Lorand for some of the apparatus used in this work.

WASHINGTON 22, D. C.

[CONTRIBUTION FROM STAMFORD LABORATORIES, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Base-Catalyzed Reaction of Nitriles with Alcohols. A Convenient Route to Imidates and Amidine Salts

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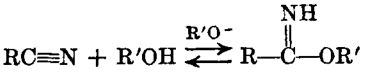
The base-catalyzed reaction of nitriles with alcohols to form imidates has been established as an attractive synthetic method which is useful for a wide variety of electronegatively substituted aliphatic and aromatic nitriles. This reaction is used as the basis for a convenient procedure for the preparation of amidine salts.

Recent developments in the chemistry of alkyl imidates in our Laboratory have led us to evaluate the alternative methods for their preparation. This paper deals with the base-catalyzed addition of alcohols to nitriles,



$$RC{\equiv}N + R'OH \underset{}{\overset{R'O^-}{\rightleftharpoons}} R{-}\overset{\overset{\displaystyle NH}{\|}}{C}{-}OR'$$

The reaction was discovered by Nef in 1895 in his work with cyanogen.[1] Shortly thereafter in papers by his students, easy base-catalyzed formation of imidates from substituted malonitriles was reported.[2] The general reaction was studied in considerable detail by Stieglitz[3] and Acree[4] and their collaborators in the course of work on the nature of homogeneous catalysis. Marshall and Acree[4a] in particular determined the position of equilibrium in the reaction of several nitriles with ethanol in the presence of sodium ethoxide at 25°. Their studies established that the reaction was alkoxide-catalyzed and that imidate formation was promoted by the presence of electron-attracting groups in the nitrile. Moreover, this work demonstrated that the equilibrium constants for the reactions of several common nitriles were sufficiently large to be useful.[5] Despite these promising early results, virtually no further use had been made of this reaction until the present work was undertaken.[6-8] We have now extended somewhat the

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(1) J. U. Nef, *Ann.*, **287**, 265 (1895), reported the reaction of cyanogen with an aqueous ethanol solution of potassium cyanide to give ethyl 1-cyanoformimidate and diethyl oxalimidate. H. M. Woodburn, A. B. Whitehouse, and B. G. Pautler, *J. Org. Chem.*, **24**, 210 (1959), have recently extended this reaction to other alcohols.

(2) (a) B. C. Hesse, *Am. Chem. J.*, **18**, 723 (1896). (b) J. C. Hessler, *Am. Chem. J.*, **22**, 169 (1899).

(3) (a) J. Stieglitz and H. I. Schlesinger, *Am. Chem. J.*, **39**, 738 (1908). (b) R. H. McKee, *Am. Chem. J.*, **26**, 209 (1901); **36**, 208 (1906); **42**, 1 (1909).

(4) (a) E. K. Marshall, Jr., and S. F. Acree, *Am. Chem. J.*, **49**, 127 (1913). (b) E. K. Marshall, Jr., J. P. Harrison, and S. F. Acree, *Am. Chem. J.*, **49**, 369 (1913).

(5) It has been pointed out by N. S. Bayliss, R. L. Heppolette, L. H. Little, and J. Miller, *J. Am. Chem. Soc.*, **78**, 1978 (1956), that the data of Marshall and Acree are inaccurate because of the analytical method employed although the general conclusions remain valid. Bayliss, *et al.* proposed improvements in technique which are essentially those used in the present work.

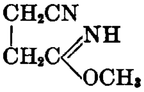
(6) Several instances have been reported of the unexpected occurrence of base-catalyzed addition of an alcohol to a nitrile group in the course of other work. (a) K. W. Breukink, *et al.*, *Rec. trav. chim.*, **76**, 401 (1957); (b) H. Bretschneider and G. Sporidi, *Monatsh.*, **85**, 1119 (1954); (c) R. L. Heppolette, J. Miller, and V. A. Williams, *J. Am. Chem. Soc.*, **78**, 1975 (1956); (d) K. Gundermann and H. Rose, *Chem. Ber.*, **92**, 1081 (1959); (e) T. Cuvigny, *Bull. soc. chim.*, **24**, 655 (1957); (f) J. Miller, *J. Am. Chem. Soc.*, **76**, 448 (1954); (g) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1012 (1945).

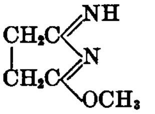
basic quantitative studies of Marshall and Acree to include consideration of certain preparatively important factors and have studied a broader range of nitriles including several of special significance in our concurrent work. Our results reaffirm that many electronegatively substituted aliphatic and aromatic nitriles may be converted to imidates extremely easily in useful yield by base-catalyzed reaction with a lower alcohol. This paper includes illustrations of the practical use of the process for the preparation of a number of interesting imidates and amidine salts.

The equilibrium conversion of nitrile to imidate in methanol at 25° in the presence of a catalytic amount of sodium methoxide[9] was determined for a wide variety of nitriles. The results obtained in those cases where a reaction could be detected are presented in Table I.

Although most of the data are self-explanatory, a few unusual results are discussed below.

(a) The equilibrium mixture obtained with succinonitrile appeared to contain approximately equivalent amounts of methyl 3-cyanopropionimidate (I) and the cyclic structure (II), possibly in

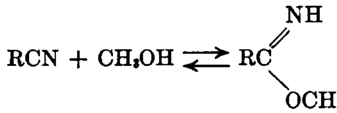

I


II

equilibrium with each other. Acid hydrolysis of the reaction mixture in the course of measuring the extent of imidate formation produced an approximately equimolar mixture of a weak and a strong base. These are presumed to be ammonia from I and 3-carbomethoxypropionamidine from II.[13]

TABLE I

BASE-CATALYZED CONVERSION OF NITRILES TO METHYL IMIDATES[a]


$$RCN + CH_3OH \rightleftharpoons RC(=NH)OCH_3$$

Nitrile[b,c]	Time, hr.[d]	Conversion to Imidate, %
NC—C(CH$_3$)$_2$C(CH$_3$)$_2$—CN[e]	22	1[f]
NC—(CH$_2$)$_4$—CN	24	1.5[f]
CH$_3$CN	2	2
C$_6$H$_5$CH$_2$CN	24	12
(C$_2$H$_5$)$_2$NCH$_2$CN	48	22
NC—CH$_2$CH$_2$—CN	24	69[g]
C$_4$H$_9$OCH$_2$OCH(CH$_3$)—CN[h]	96	86
[(C$_2$H$_5$)$_3$NCH$_2$CN]$^+$Cl$^-$[i,j]	48	76
(CH$_3$)$_3$COCH$_2$CN[k]	30	91
CH$_2$=CClCN[l]	24	90[m]
CH$_3$CHClCN	0.5	91[m]
CH$_2$ClCN	0.5	93[m]
(C$_2$H$_5$O)$_2$CHCN[n]	1	95
p-CH$_3$OC$_6$H$_4$CN	96	15
C$_6$H$_5$CN	20	20
p-ClC$_6$H$_4$CN	48	45
p-NO$_2$C$_6$H$_4$CN[o]	8	83
m-NO$_2$C$_6$H$_4$CN	4	86
p-C$_6$H$_4$(CN)$_2$[p]	7	108[g]
3-C$_5$H$_4$N—CN	24	71
2-C$_5$H$_4$N—CN	2	97
(CH$_3$)$_2$N—CN	24	100[q]
(C$_2$H$_5$)$_2$N—CN	144	100[q]

[a] At 25°. [b] Nitrile is 1.0*M* except as noted; methanol is 21*M* to 24*M*. [c] Concentration of sodium methoxide catalyst is 0.1*M* except as noted. [d] At least 95% of maximum imidate concentration was reached in the time given. [e] Nitrile, 0.38*M*; sodium methoxide, 0.042*M*. [f] Conversion per nitrile group. [g] Conversion assuming one reactive nitrile group. See text. [h] See footnote 10. [i] See footnote 11. [j] Nitrile, 0.61*M*; the the catalyst was 0.10*M* potassium cyanide. [k] Prepared as described by W. F. Gresham, U. S. Patent 2,425,615 (1947). [l] See footnote 12. [m] These values are probably low because of loss of alkoxide through interaction with the reactive chloride. Compare reference 4a. [n] J. G. Erickson, *J. Am. Chem. Soc.*, **73**, 1338 (1951). [o] Nitrile, 0.95*M*; sodium methoxide, 0.050*M*. The nitrile dissolved completely in six hours. [p] Nitrile, 0.40*M*; sodium methoxide, 0.10*M*. The final solution was saturated with terephthalonitrile which was present in excess. [q] This reactivity of dialkylcyanamides was first reported by R. H. McKee.[3b]

(b) The equilibrium conversion of 108% for terephthalonitrile is consistent for approximately 70–80% conversion to the monoimidate due to the strong activation of a *p*-cyano substituent in ben-

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(7) R. O. Norris, U. S. Patent **2,569,425** (1951), has disclosed the use of sodium cyanide in 2-methoxyethanol for the preparation of imidates from the 2-chloropropio- and 2-chlorobutyronitriles. These reagents were chosen to give a weakly basic reaction medium.

(8) F. Cramer, K. Pawelzik, and H. Baldauf, *Chem. Ber.*, **91**, 1049 (1958), have prepared a variety of trichloroacetimidates by base-catalyzed addition of alcohols to trichloroacetonitrile. W. Steinkopf, *Ber.*, **40**, 1643 (1907); **53B**, 1149 (1920), had obtained methyl trichloroacetimidate by reaction of trichloroacetonitrile with methanol in what must have been a base-catalyzed reaction. See also J. Houben and H. Kauffmann, *Ber.*, **46**, 2831 (1913).

(9) Both Marshall and Acree[4a] and Bayliss, *et al.*[3] chose to use equivalent or greater amounts of sodium alkoxide in nearly all of their work, although fully recognizing the catalytic nature of its action. We have instead used 10 mole % of catalyst based on the nitrile in most of our experiments.

(10) The nitrile was prepared by reaction of dibutylformal with lactonitrile essentially as described for similar compounds by D. J. Loder and W. M. Bruner, U. S. Patent **2,398,757** (1946); b.p. 119° at 50 mm., n_D^{25} 1.4082. Mass spectroscopy and vapor phase chromatography show that this material was approximately 88% pure with dibutylformal as the major impurity. The conversion observed has been corrected on this basis and is less exact than other data given.

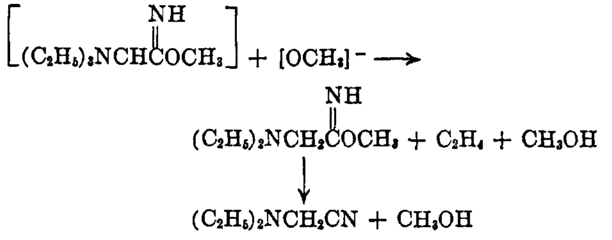
(11) (Cyanomethyl)triethylammonium chloride was prepared in 83% yield by reaction of chloroacetonitrile with a small excess of triethylamine at room temperature. The salt was recrystallized from acetone containing a little methanol, m.p. 190–191°. *Anal.* Calcd. for C$_8$H$_{17}$N$_2$Cl: 20.1. Found: Cl, 19.9.

(12) The reaction product is presumably methyl 2-chloro-3-methoxypropionimidate. See reference 6d.

(13) S. M. McElvain and J. P. Schroeder, *J. Am. Chem. Soc.*, **71**, 40 (1949), postulated the formation of the hydrochloride of II when dimethyl succinimidate dihydrochloride was treated with aqueous bicarbonate. Subsequent hydrolysis led to 3-carbomethoxypropionamidine hydrochloride.

zonitrile plus 30–40% diimidate due to the moderate activation of a *p*-carboximidate group.

(c) The conversion shown for cyanomethyltriethylammonium chloride was obtained with potassium cyanide as catalyst. When the more basic sodium methoxide was used, the indicated maximum conversion (73%) was reached in ninety minutes. Within a few hours, however, the apparent conversion dropped to 61%. This is consistent with the proposition that the alkoxide is destroyed with an equivalent amount of the imidate by the Hofmann degradation,



$$\left[(C_2H_5)_3NCH\overset{\overset{NH}{\|}}{C}OCH_3\right] + [OCH_3]^- \longrightarrow (C_2H_5)_2NCH_2\overset{\overset{NH}{\|}}{C}OCH_3 + C_2H_4 + CH_3OH \\ \downarrow \\ (C_2H_5)_2NCH_2CN + CH_3OH$$

In an effort to correlate the observed data with the polar effects of substituents in more quantitative fashion, we have attempted to apply the Hammett equation.[14]

Figure 1 shows a plot of the data for the aromatic nitriles in the form of log K *vs.* σ.[15] For reasons which follow, the correlation line is drawn on the basis of only the data for benzonitrile, *p*-chlorobenzonitrile, and *m*-nitrobenzonitrile and is well defined by these points. In our opinion, this correlation will adequately predict the reactivity of most common substituted benzonitriles. It is obvious that the data for *m*- and *p*-nitrobenzonitrile do not stand in proper relation to each other in view of the σ constants for these substituents. Moreover, the same defect can be seen in the data of Marshall and Acree.[4a] A corresponding large deviation from the correlation line is seen for the *p*-nitro group. It is probable that part of the discrepancy is due to loss of alkoxide through displacement of the nitro group in *p*-nitrobenzonitrile.[16] The *p*-methoxybenzonitrile produced would be chiefly present as such. This explanation is only partly supported by data showing progressive small reduction of the apparent equilibrium conversion as the alkoxide catalyst is increased. Use of the data for *p*-methoxybenzonitrile and for the cyanopyridines to define the correlation line might be advocated, but this has not been done in view of the lower confidence in the appropriate σ constants.[17–19]

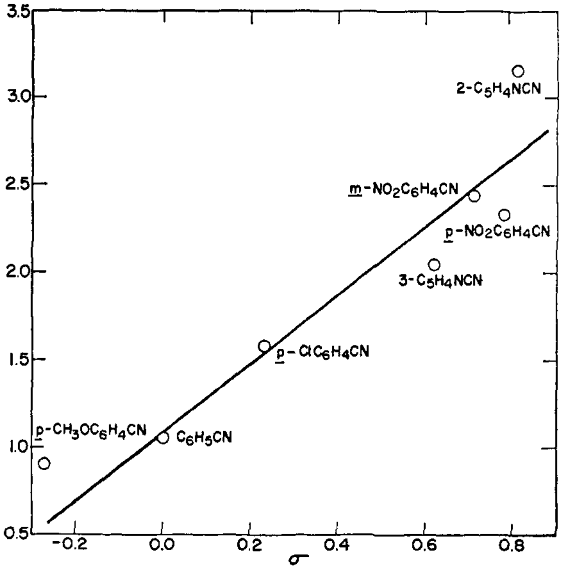


Fig. 1. Base-catalyzed conversion of nitriles to methyl imidates

We have not attempted to use Taft's σ^* correlation[20] with the data on aliphatic nitriles because the selection of compounds studied does not seem appropriate. The underlying dependence on inductive effects is evident, however, and the response to electron-attracting substituents appears to be strong.

The data in Table I confirm the conclusion from the early work of Marshall and Acree that imidate formation is promoted by electronegative substituents in the nitrile. It is particularly significant that this effect is large and results in high conversions with a very large number of interesting nitriles. On the other hand, in addition to the inadequate conversions obtained with benzonitrile and the simple aliphatic nitriles, no reaction was observed with nitriles having: (a) a strongly acidic α-hydrogen atom (ethyl cyanoacetate, etc.), (b) highly alkali-sensitive substituents (2-acetoxy-

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[14] L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 184.

[15] The equilibrium constants are calculated from the conversion data by the approximation: $K = [RC(NH)OCH_3]/21.5[RCN]$, where 21.5 is taken as the average original molar concentration of methanol for the series of nitriles in question, and the decrease in this value with reaction is ignored. The values of σ are taken from H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

[16] W. Reinders and W. E. Ringer, *Rec. trav. chim.*, **18**, 327 (1899). P. K. Lulofs, *Rec. trav. chim.*, **20**, 321 (1901). The *p*-nitro group in the imidate would probably be stable to alkoxide.

[17] H. H. Jaffé, *Chem. Revs.*, **53**, 230 (1953). The data for the *p*-methoxy group diverges widely from a Hammett correlation of the equilibrium constants for the related formation of cyanohydrins from substituted benzaldehydes; J. W. Baker, G. F. C. Barrett, and W. T. Tweed, *J. Chem. Soc.*, 2831 (1952); J. W. Baker and H. B. Hopkins, *J. Chem. Soc.*, 1089 (1949). However, the divergence is in the opposite sense to that found in the present work.

[18] H. H. Jaffé, *Chem. Revs.*, **53**, 245 (1953); *J. Chem. Phys.*, 20, 1554 (1952).

[19] Although the data of Marshall and Acree[4a] is inaccurate for reasons pointed out by Bayliss, *et al.*[5] and the conversions reported are appreciably lower than those indicated by the present work, nevertheless, the early data is consistent within itself and a Hammett correlation based on derived equilibrium constants gives a very satisfactory straight line (six points) except for the discordant *p*-nitro substituent.

[20] R. W. Taft, Jr., *J. Am. Chem. Soc.*, **75**, 4231 (1953).

propionitrile, 2,3-dichloropropionitrile), (c) electropositive substituents (*p*-aminobenzonitrile), and (d) bulky blocking groups (2-carbethoxy-2-ethylbutyronitrile).

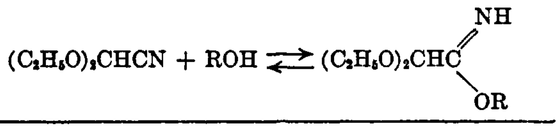
It was of interest to consider the practical effect of the reaction temperature upon the equilibrium constant. Although thermodynamic considerations suggest that imidate formation is exothermic and therefore, would be inhibited at higher temperatures, it was possible that in some cases greater nitrile solubility would be a more important practical factor. It was found that with *p*-nitrobenzonitrile, the equilibrium conversion of 80% at 25° at $0.94M$ total concentration was depressed to about 50% at 65°. Similarly with terephthalonitrile at $0.38M$ total concentration the conversion was 108% at 25° and 63% at 65°. Despite this effect, preparation of methyl *p*-nitrobenzimidate was more efficient at 65° as a result of solubility relationships.

Some experiments were tried in which better solvents were used with methanol to improve the results with difficultly soluble nitriles. However, in all such cases the high solubility was ineffective because of reduced equilibrium conversion. Rather surprisingly, this was also true with 2-methoxyethanol[7] as the additional solvent.

A series of experiments in which 2,2-diethoxyacetonitrile was used as a standard reagent was carried out to show the effects of varying the alcohol. The results, summarized in Table II, were somewhat surprising in showing only a small decrease in conversion and reaction rate with primary alcohols of increasing molecular weight up through C_4. Even isopropyl alcohol gave a useful reaction. It is noteworthy that in this series the concentration of the alcohol reactant varied from about $22M$ in the case of methanol to $11M$ with butanol. Included in Table II are results with methanol containing 1% and 3% water which demonstrate good tolerance for moisture which might be present in technical reagents. It was also demonstrated that *p*-nitrobenzonitrile gives essentially the same degree of reaction with ethanol as with methanol.

TABLE II

REACTION OF 2,2-DIETHOXYACETONITRILE WITH ALCOHOLS



$$(C_2H_5O)_2CHCN + ROH \rightleftarrows (C_2H_5O)_2CH\overset{NH}{\underset{OR}{C}}$$

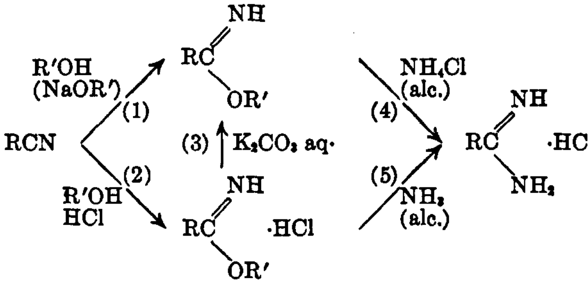
R	Equilibrium Conversion, %[a]
CH_3	95
CH_3[b]	95
CH_3[c]	91
C_2H_5	89
$CH_3CH_2CH_2$	82
$CH_3(CH_2)_3$	78
$(CH_3)_2CHCH_2$	78
$(CH_3)_2CH$	63

[a] Nitrile concentration is $1.0M$ in the alcohol; alkoxide, $0.10M$. All reactions reached equilibrium in 50–80 minutes. [b] Methanol containing 1% water. [c] Methanol containing 3% water.

We have not considered it important to make a detailed study of the reaction kinetics. The mechanism is presumably quite analogous to the classic cyanohydrin formation studied by Lapworth and Manske.[21] However, rate data obtained in experiments with 2,2-diethoxyacetonitrile in methanol have confirmed the expected pseudo-unimolecular character of the reaction and the linear dependence of the specific reaction rate on the catalyst concentration.

The simplicity of the base-catalyzed conversion of nitriles to imidates makes the process highly attractive as a preparative method. It can probably be considered useful in any case where the conversion is greater than 50%. In our work we have often found that the unchanged nitrile is not detrimental in subsequent synthetic steps and usually can be recovered. Although many common aromatic and all unsubstituted aliphatic nitriles are considered inoperative, the large group of substituted aliphatic types which seem to react very well include many of the most interesting and useful compounds. It is important to appreciate that those nitriles which are unsuited for the base-catalyzed reaction usually give excellent results in the Pinner synthesis.[22] Conversely, the nitriles which are most reactive in the base-catalyzed process often give unstable imidate hydrochlorides.[23] Thus, the two processes complement each other very agreeably.

For the large group of imidates which may be prepared by either the base-catalyzed reaction (1) or the Pinner synthesis (2) several considerations may recommend the former procedure. When the imidate base is desired the direct route (1) is obviously more attractive than the alternative, (2) plus (3). Since imidates may be very efficiently converted to amidine salts by reaction with various ammonium salts,[24] reaction (4) offers a very useful alternative to the more conventional amidine synthesis (5). The sequence (1) and (4) is especially



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[21] A. Lapworth and R. H. F. Manske, *J. Chem. Soc.*, 2533 (1928).

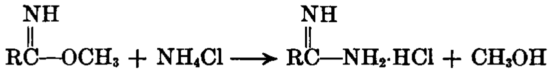
[22] A. Pinner, *Die Imidoäther und ihre Derivate*, Robert Oppenheim (Gustav Schmidt), Berlin, Germany, 1892.

[23] Cramer, *et al.*, reference 8, have made good use of this distinction in their indirect esterification of phosphorus acids by means of trichloroacetimidates.

[24] A. Knorr, *Ber.*, 50, 229 (1917).

TABLE III

PREPARATION OF AMIDINE HYDROCHLORIDES



$$RC(=NH)-OCH_3 + NH_4Cl \longrightarrow RC(=NH)-NH_2\cdot HCl + CH_3OH$$

R	Molar Concn. Original Nitrile[a]	Molar Concn. NaOCH$_3$ Catalyst[a]	Yield, %[b]	M.P.	Chlorine, % Calcd.	Found
CH_2Cl—	2.5	0.07	96	95–99[c]	27.5	28.25
CH_3CHCl—	3.1	0.20	73	130–131	[d]	
$(CH_3)_3COCH_2$—	1.00	0.10	78	157–159	21.3	21.5
m-$NO_2C_6H_4$—	1.00	0.10	80	250–252[e]	17.6	17.6
p-$NO_2C_6H_4$—	0.95	0.050	78	285–287[f]	17.6	18.2
3-C_5H_4N—	1.00	0.10	65	192–194[g]		
2-C_5H_4N—	1.00	0.10	95	149–151	22.5	22.8

[a] Data for the methyl imidate preparation. [b] Based on original nitrile. [c] Crude product. W. Klarer and E. Urech, *Helv. Chim. Acta*, **27**, 1762 (1944), give m.p. 104–106°. [d] *Anal.* Calcd. for $C_3H_8N_2Cl_2$: C, 25.19; H, 5.64; N, 19.59. Found: C, 25.20; H, 5.65; N, 19.29. [e] J. Tafel and C. Enoch, *Ber.*, **23**, 1552 (1890), give m.p. 240°. [f] A. Pinner and F. Gradenwitz, *Ann.*, **298**, 49 (1897) report no m.p. [g] H. J. Barber and R. Slack, *J. Am. Chem. Soc.*, **66**, 1607 (1944), give m.p. 190°.

advantageous with nitriles which are unstable to alcoholic hydrogen chloride[25] and in cases where the imidates may give side reactions in alcoholic ammonia.[26] Several examples are given in the Experimental Section to illustrate the practical use of the base-catalyzed reaction for the synthesis of imidates. Also described is the procedure used to prepare amidine salts from methanolic imidate solutions. Table III summarizes a number of such amidine hydrochloride preparations. Finally, an example is given to illustrate the conversion of a nitrile to an ester by hydrolysis of an intermediate imidate.

EXPERIMENTAL[27]

Studies of the nitrile-imidate equilibrium. In general, 0.100 mole of the purified nitrile was mixed with anhydrous methanol,[28] 0.010 mole of sodium methoxide was added and the solution was diluted to 100 ml. at 25°. Aliquots were withdrawn at intervals, added to a mixture of excess 0.100*N* hydrochloric acid and methanol and, after 30–45 min., were back-titrated potentiometrically or to the methyl orange endpoint. It was assumed that the catalyst was stable, and the amount used was subtracted from the total base found to obtain the imidate content. The assumption of catalyst stability was substantiated in all but a few cases by the final constant maximum titer. The data obtained were reproducible to ±1%.[29] Occasionally other catalyst concentrations were used or the methoxide was replaced by potassium cyanide, and sometimes the nitrile was limited to lower concentration by solubility or availability. Some nitriles were largely undissolved at the start of the reaction but went into solution as the reaction progressed.

In general we did not attempt to determine the reaction rate. In most cases substantial conversion occurred within 30 min. and the reaction was close to equilibrium in less than 24 hr. In all cases, the reactions were continued until no further increase in imidate was detectable. In Table I are summarized the results of comparative reactions under the standard conditions for those nitriles with which a reaction could be detected. Several nitriles gave no apparent imidate under the standard conditions: 3-ethoxypropionitrile, ethyl cyanoacetate, 2-carbethoxy-2-ethylbutyronitrile, 2,3-dichloroacrylonitrile, 2,3-dichloropropionitrile, 2,2,3-trichloropropionitrile, 2-acetoxypropionitrile, benzoylacetonitrile, diethyl cyanomethanephosphonate, *p*-aminobenzonitrile, *p*-acetamidobenzonitrile, *o*-tolunitrile, *o*-chlorobenzonitrile, and 1-naphthonitrile.

Titration of acid-hydrolyzed aliquots from the succinonitrile reaction solution was carried out potentiometrically. Two well defined endpoints were observed, at about *p*H 7 and *p*H 3.5. After correction of the titer for the catalyst present, the two product bases were seen to be present in about equivalent amounts. The total amount of base had increased slightly at 50 hr. over the 24-hr. observation, but the ratio of products was essentially unchanged.

Potentiometric titration of the hydrolyzed cyanopyridine reaction solutions showed that a sharp endpoint was obtained at *p*H 4.5–7.0 without interference from the feebly basic pyridine structure.

Additional experiments were carried out with *p*-nitrobenzonitrile at different catalyst concentrations in an effort to assess the importance of the displacement of the *p*-nitro group by the alkoxide ion.[16] At 25° and 0.95*M* nominal concentration the following equilibrium conversions were obtained: 0.050*M* sodium methoxide, 83%; 0.10*M* sodium methoxide, 81%; 0.20*M* sodium methoxide, 78%.

Effect of temperature. In 7 hr. at 25°, 100 cc. of methanol containing 0.010 mole of sodium methoxide dissolved 5.10 g. (0.040 mole) of terephthalonitrile (excess present). Titration showed the presence of 0.042 mole of imidate at that time. This figure increased slightly to 0.043 mole after 3 days. Thus, conversion was 108% based on one nitrile group per molecule. When the reaction mixture was subsequently heated at 65° for 3 hr. the imidate content dropped to 0.025 mole; conversion 62.5%.

In a similar experiment it was shown that the equilibrium conversion to imidate in a nominally 0.94*M* solution of *p*-nitrobenzonitrile decreased from 80% to 50% on heating from 25° to 65°. When the heated solution was subsequently stored for 18 hr. at 25° the conversion rose again to 73%.[30]

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[25] 2-*t*-Butoxypropionitrile and 2-(butoxymethoxy)-propionitrile give ethyl lactimidate in the Pinner reaction.

[26] For example: ethyl 1-carbethoxyformimidate, methyl 2-chloroacetimidate.

[27] Melting points were determined by the capillary method and are uncorrected. Microanalyses were carried out in these laboratories under Dr. J. A. Kuck or by the Galbraith Microanalytical Laboratories.

[28] Fisher Scientific Company's "Spectranalyzed®" grade.

[29] This procedure is quite similar to that used by Bayliss, *et al.*, reference 5. Hydrolysis in the dilute acid produces ammonium ion in all cases and eliminates the problems due to variable imidate basicity. Bayliss' data for *m*-nitrobenzonitrile is in satisfactory agreement with our results.

[30] Reference 16 indicates the catalyst would react with the *p*-nitro group to a considerable extent.

The expected higher conversion at temperatures below 25° was observed with a 1.0M solution of p-chlorobenzonitrile in methanol. The equilibrium conversion increased from 45% at 25° to 55% at 10° (held for 24 hr.) and dropped again to the original value on warming to 25°.

Use of inert solvents. Equilibrium conversions at 25° of p-nitrobenzonitrile (0.35M) to imidate were 13% in 90% benzene (10% methanol) and 15% in 80% dioxane. With terephthalonitrile in 50% nitrobenzene (0.13M) conversion was 19% and in 80% 2-methoxyethanol[31] (0.083M) was 26%. The unexpectedly low conversion in 50% nitrobenzene suggests an adverse effect.

Variation of the alcohol reactant. With 2,2-diethoxyacetonitrile used as a standard reagent, 1.0M solutions in several alcohols were prepared with the corresponding sodium alkoxides (0.10M) as catalysts for imidate formation. Equilibria were determined at 25° in the usual manner. Data were also obtained for methanol containing small amounts of water. The results are summarized in Table II.

Reaction of p-nitrobenzonitrile (1.0M) with anhydrous ethanol containing 0.010M sodium methoxide gave an equilibrium conversion of 78% imidate at 25°, only slightly less than that obtained in methanol.[32]

Reaction rate as a function of catalyst concentration. Solutions of 2,2-diethoxyacetonitrile in methanol were prepared (1.00M) in which sodium methoxide was present at several concentrations. The reaction rate at 25° was determined by periodic analysis of aliquots for imidate content. Pseudounimolecular specific reaction rate constants were derived from the experimental data using the relation, $k = \frac{x_e}{at} \ln (x_e/x_e - x)$, where a is the initial molar concentration of nitrile, x is the molar concentration of imidate at t minutes and x_e is the equilibrium value.[33] Plots of t/x_e versus $\log (x_e/x_e - x)$ gave satisfactory straight lines whose slopes gave the values below for k. Bimolecular rate constants (k') for the nitrile–methoxide ion reaction were obtained from the relation, $k' = k/[CH_3O^-]$.[34]

Molar Conc. Catalyst	k, Min.$^{-1}$	k', l. mole^{-1} min.$^{-1}$
0.10	0.098	0.98
0.071	0.071	0.99
0.050	0.048	0.96

Use of potassium cyanide as catalyst. Potassium cyanide in methanol at the normal catalyst level could be accurately titrated at the methyl orange endpoint.

p-Nitrobenzonitrile (10.0 g., 0.0676 mole) dissolved slowly in a 0.050M solution of potassium cyanide in anhydrous methanol at 25°. A clear solution was obtained after 120 hr. and titration at that time showed that conversion to the imidate was 78%. In an additional 24 hr. equilibrium was reached at 79% conversion, essentially equal to that obtained in the much faster reaction with sodium methoxide catalysis.

Cyanomethyltriethylammonium chloride reacted normally with methanol in the presence of potassium cyanide although methoxide had caused degradation.

Preparation of imidates, methyl 2-isopropoxyacetimidate. A solution of 15 g. (0.15 mole) of isopropoxyacetonitrile[35] and 0.5 g. (0.01 mole) of sodium methoxide in 50 cc. of methanol was allowed to stand overnight at room temperature. Titration of an aliquot indicated 81% conversion. The solution was saturated with carbon dioxide to destroy the catalyst and after 15 min. was filtered. The filtrate was distilled yielding 13.2 g., b.p. 32–37° at 2 mm., which was 89.5% imidate by titration; yield, 60%. The major part of the unconverted nitrile was recovered with some imidate as a forerun which could be recycled.

Methyl pyridine-2-carboximidate. A solution of 26.0 g. (0.25 mole) of 2-cyanopyridine and 1.35 g. (0.025 mole) of sodium methoxide in 225 cc. of methanol was allowed to stand overnight at room temperature. Acetic acid (1.5 cc., 0.025 mole) was then added and the solution was distilled. The material boiling at 118–122° at 28 mm. weighed 31.4 g. and was 97% imidate by titration. The yield was therefore 90% based on the nitrile used.

Methyl p-nitrobenzimidate. A mixture of 35 g. (0.25 mole) of p-nitrobenzonitrile and 100 cc. of methanol containing 1.0 g. of sodium methoxide was boiled under reflux 4 hr. To the hot solution was then added 1.5 g. of acetic acid to neutralize the catalyst. Chilling caused crystallization of 13.3 g. of unchanged nitrile which was separated. The mother liquor was diluted with 300 cc. of cold water and allowed to stand 1 hr. to complete crystallization of the crude imidate. The solid obtained weighed 21.7 g., m.p. *ca.* 75°. Titration showed this material was 77% methyl p-nitrobenzimidate; some methyl p-nitrobenzoate and p-nitrobenzamide were present as well as the nitrile. The yield of imidate was 63% based on unrecovered nitrile.

Ethyl 2-chloropropionimidate. 2-Chloropropionitrile (65.0 g., 0.73 mole) was dissolved in 200 cc. of absolute ethanol and 2.2 g. (0.040 mole) of sodium methoxide was added. The mixture was held at about 25° for 45 min. by gently cooling. Acetic acid (2.4 cc., 0.040 mole) was then added and the solution was distilled at reduced pressure. The fraction boiling at 70–75° at 60 mm. weighed 53 g. and was 95% imidate by titration; yield, 51%.

Preparation of amidine salts. Several amidine hydrochlorides have been prepared by reaction of a methanolic solution of an imidate prepared *in situ* with an amount of ammonium chloride equivalent to the total base present.[24] Usually the reaction mixture was merely stirred for a few hours until the salt dissolved, but heating may be employed to speed the process in most cases. The reaction time allowed varied from 1–24 hr. with excellent results in all cases. Probably the reaction is essentially complete when the salt has dissolved. The solvent methanol was evaporated to recover the amidine salt. The residue was extracted with ether or acetone to remove the residual nitrile and was finally extracted with a small quantity of water or recrystallized from a solvent which did not dissolve ammonium chloride. In rare cases the amidine salt crystallized directly from the reaction solution. Examples are summarized in Table III.

In other work we have obtained excellent yields of amidine thiocyanates, acetates, and bromides by using the appropriate ammonium salts with a variety of purified imidates in methanol or ethanol. It is clear that these salts could satisfactorily be substituted for the chloride used in the present investigation.

Preparation of methyl p-cyanobenzoate. A mixture of 10.0 g. (0.078 mole) of terephthalonitrile and 100 cc. of methanol containing 0.50 g. of sodium methoxide was boiled for 2.5 hr. The hot solution, containing methyl p-cyanobenzimidate in equilibrium with dinitrile and diimidate, was then decanted from undissolved terephthalonitrile (2.1 g.) into 150 cc. of ice water containing 12 cc. of 12N hydrochloric acid. The suspension obtained was allowed to stand overnight to

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[31] Norris' work[7] suggested that 2-methoxyethanol would be as useful as lower alcohols.

[32] The equilibrium conversion reported by Marshall and Acree[4a] was 62% at 0.25M concentration in ethanol at 25°.

[33] S. Glasstone, *The Elements of Physical Chemistry,* D. Van Nostrand Company, Inc., New York, N. Y., 1946, p. 601.

[34] F. O. Rice and H. C. Urey in *A Treatise on Physical Chemistry,* H. S. Taylor, ed., D. Van Nostrand Company, Inc., New York, N. Y., 1931. Chap. XIV, p. 959.

[35] R. A. Barnes and W. M. Budde, *J. Am. Chem. Soc.,* **68,** 2339 (1946).

complete hydrolysis of the imidate. The precipitated solids were then dried and extracted with ether. Thus, another 2.4 g. of insoluble terephthalonitrile was recovered (m.p. 215°). Evaporation of the ether solution gave 4.6 g. of methyl *p*-cyanobenzoate, m.p. 59–61° (lit.[36] m.p. 62°). The yield was 61% based on unrecovered terephthalonitrile. Dimethyl terephthalate (m.p. 140°) which was expected to arise from the diimidate present at equilibrium was not found, but could conceivably have been dissolved in the discarded aqueous methanol.

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[36] H. Rupe and K. Majewski, *Ber.*, **33**, 3405 (1900).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Pschorr Cyclizations in the Pyridine Series. The Synthesis of Benz[*f*]- and Benz[*h*]isoquinoline[1]

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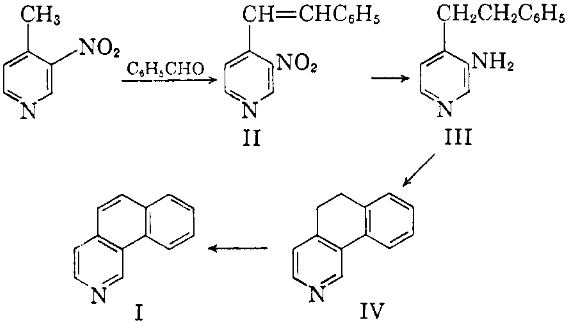
Convenient syntheses of the title compounds using the Pschorr cyclization are reported.

Dehydrogenation of diterpene alkaloids gives rise to alkylbenz[*h*]-isoquinolines[3–6] (3-azaphenanthrenes I), whose synthesis presents certain problems. Thus, several attempts to apply the Bischler-Napieralski reaction[7] to the cyclization of *N*-acyl-β-2-naphthylethylamines failed,[8] the only successful example being the conversion of a somewhat difficulty accessible oxime to 1-methylbenz[*h*] isoquinoline.[9] Koelsch and Lindquist[10] prepared I in 3% overall yield from 1,2-naphthalic anhydride, but their method does not appear to lend itself easily to the synthesis of substituted benz[*h*]isoquinolines. The Pictet-Spengler reaction[11] was successful in the two instances tried,[8,12] but again the synthesis of the requisite starting materials may be attended by difficulties.

For these reasons it was decided to study the preparation of I by the following route, which should, in theory, be adaptable to the synthesis of many different derivatives. 3-Nitro-4-picoline was prepared in good yield by a modification of the method of Baumgarten, Su, and Krieger[13] and condensed with benzaldehyde in 44% yield. II exhibited an infrared band at 785 cm.$^{-1}$ (*trans*-ethylenic double bond); the corresponding amine would therefore not have been suitable for the Pschorr cyclization.[14] Hence, II was catalytically reduced to III which smoothly underwent the Pschorr synthesis (40% yield). It was found that the so-called Gattermann copper[14] could be successfully replaced by commercially available copper powder and that the cyclization could also be effected by warming the diazonium solution on the steam bath without catalyst, although the yield was somewhat lower.



As elementary analysis did not distinguish satisfactorily between IV and a possible by-product, 4-(β-phenethyl)pyridine,[15] the latter was synthesized from 4-picoline-1-oxide by way of 4-styrylpyridine 1-oxide.[16] Its properties clearly differentiated it from IV. Finally, IV was dehydrogenated to I, which again was different from 4-styrylpyridine, the dehydrogenation product of V.

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[2] Abstracted from a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1960.

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