THE PREPARTION OF NITRILES

DAVID T. MOWRY

Central Research Laboratories, Monsanto Chemical Company, Dayton, Ohio

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I. Introduction

A. Historical background

Hydrogen cyanide was first prepared in 1782 by Scheele (511), who was later killed while attempting to isolate the anhydrous material. In 1811 Gay-Lussac (213) succeeded in preparing the pure acid and established its constitution. The first syntheses of nitriles were reported by Wöhler and Liebig, who prepared benzoyl cyanide and benzonitrile in 1832 (609), and by Pelouze who obtained propionitrile in 1834 (455).

Nearly a century followed before the volume of research in nitrile chemistry reached sizable proportions. It is true that many significant contributions to this field were made during this interval, but investigators were probably understandably reluctant to devote major efforts to such researches because of the hazards of toxicity. A more significant factor may have been the availability and price of the inorganic cyanide raw materials. The latter deterrent was effectively removed by increased attention to the nitrogen fixation problem during the first World War.

As a result, the fifteen-year period from 1920 to 1935 showed a fourfold increase in the average number of annual papers on nitrile chemistry. Subsequently, research in this field has continued at an ever-increasing tempo. The past decade, moreover, has witnessed the transition of organic nitriles from a position of laboratory curiosities to that of large-tonnage chemicals of commerce. Of the score or more that have become commercially available in the past ten years one might cite acrylonitrile (plastics, synthetic rubber, synthetic fibers), phthalonitrile (dyestuffs), adiponitrile (synthetic fibers), acetone cyanohydrin (plastics), or trichloroacetonitrile (fumigant) as examples of compounds which have reached large-volume production. Numerous others have found application in the fields of synthetic resins, war gases, insecticides, specialty solvents, and especially as intermediates for the chemical synthesis of pharmaceuticals, dyestuffs, vitamins, and plastics.

B. NATURAL OCCURRENCE

Nitriles do not occur in high concentration in nature, but their presence has been detected in minor amounts in a large number of plants. They are most commonly present as various glycosides of mandelonitrile, although glycosides of the cyanohydrins of other aldehydes and ketones (such as acetone) have been reported. Amygdalin, which is hydrolyzed to gentiobiose and *d*-mandelonitrile, is probably the best known example of this type. Concentrations of hydrogen cyanide run as high as 1 per cent of the dry weight of *Pangium edule* leaves. Rosenthaler states that lesser amounts are found in the stem, roots, flowers, leaves, fruit, and seeds of 360 varieties of 150 species of 41 cyanogenetic plant families of trees, flowers, ferns, legumes, mushrooms, etc. (495). They are generally not found in plants containing alkaloids or terpenes. The biochemical formation of the cyanophoric glycosides may be partially explained by Parrod's demonstration (451) that certain reducing sugars can be oxidized in the presence of ammonia and atmospheric oxygen to urea and hydrogen cyanide.

Phenylacetonitrile and β-phenylpropionitrile have been isolated from certain essential oils (272, 501), while acetonitrile has been isolated from coal tar and gas tar (575). Propionitrile, butyronitrile, valeronitrile, and some higher homologues have been identified as components of bone oil (588).

Because of the low concentrations involved, the extraction of nitriles from natural sources does not constitute a convenient method of preparation.

C. SCOPE OF REVIEW

The present survey is limited to a discussion of the esters of hydrogen cyanide. Other derivatives of cyanogen, such as the cyanates, isocyanides, thiocyanates,

and cyanamides, are beyond the scope of this review. Hydrogen cyanide itself and the cyanogen halides will be considered only insofar as they enter into or illustrate the synthesis of the higher nitriles.

First to be discussed are the methods of synthesis in which the cyano group is introduced directly into an organic compound, with the formation of a new carbon skeleton. Consideration will then be given to indirect methods in which the nitrogen is introduced and the carbon–nitrogen triple bond is formed. Finally, a very abbreviated statement dealing with the toxicity of the nitriles is presented, since these properties should be considered by those engaging in preparative work. A monograph has recently appeared which gives an extensive review of the chemical reactions of organic cyanogen compounds (402a).

D. NOMENCLATURE

Fehling is credited with coining the term "nitrile" in 1844 (12a). At least eight systems of nomenclature for these compounds have been employed. These are illustrated by the following names for $CH_3CH_2CH_2CN$: (*a*) butyronitrile, (*b*) propyl cyanide, (*c*) cyanopropane, (*d*) propanenitrile, (*e*) butanenitrile, (*f*) butanonitrile, (*g*) propane carbonitrile, and (*h*) nitrilobutane. System d, in which the term "nitrile" was considered as a replacement of a hydrogen atom, was used for certain structures by *Chemical Abstracts* before 1936. This has been abandoned in favor of system e, in which "nitrile" is considered to be replacing a methyl group, and system g, in which "carbonitrile" replaces a carboxylic acid substituent. These usages conform to the recommendations of the Geneva Congress of 1892 (Rule 39) and of the International Union of Chemistry at Liége in 1930 (Rule 32). The prefix "nitrilo" (system h) refers to the $N\equiv$ radical and is seldom encountered. Modern usage favors the nomenclature derived from the common name (system a) rather than the Geneva name (system f) of the analogous acid. Where necessary in a polyfunctional compound, the prefix cyano (system c) is used. The once popular system (system b) of naming nitriles as esters of hydrocyanic acid is being slowly abandoned.

II. Preparation by Metathesis (Alkylation of Cyanides)

The simple metathetical reaction involving direct esterification of an alcohol with hydrocyanic acid has only recently been demonstrated with certainty. Such reactions had been reported to take place in the vapor phase over dehydration catalysts such as alumina or thoria at about 300°C. (433). However, the actual reagent in these cases may have been either the olefin or the ether derived from the alcohol. Both of these derivatives are known to react with hydrogen cyanide (see pages 222, 244). Recent reports from Germany indicate that 2-butene-1,4-diol will react with hydrogen cyanide in the liquid phase at 60–80°C. The catalyst consists of ammoniacal cuprous chloride dissolved in dilute hydrochloric acid.

$$HOCH_2CH{=}CHCH_2OH + 2HCN \xrightarrow[\text{(70 per cent yield)}]{Cu_2Cl_2\cdot NH_4Cl} CNCH_2CH{=}CHCH_2CN + 2H_2O$$

Other reactive alcohols, such as allyl alcohol and benzyl alcohol, react similarly (530a). However, the principal methods of esterification have all been indirect ones, usually involving the reaction of a mineral acid ester of the alcohol with a salt of hydrocyanic acid.

A. ALKYL SULFATES AND METAL CYANIDES (PELOUZE SYNTHESIS)

Propionitrile, the first aliphatic nitrile to be described in the literature, was prepared by Pelouze in 1834 by the reaction of potassium ethyl sulfate and potassium cyanide (455). Ethyl sulfate gives similar results (583).

$$(C_2H_5)_2SO_4 + KCN \rightarrow C_2H_5CN + C_2H_5OSO_3K$$

Although the reaction was extended to the preparation of phenylacetonitrile (30), its chief application seems to have been the preparation of the lower aliphatic nitriles. It still is one of the most convenient laboratory methods for the preparation of acetonitrile and propionitrile. Methyl sulfate reacts at room temperature, while ethyl sulfate requires external heating. Yields calculated on the basis of the above equation are reported to be quantitative. This is not strictly true, since alkyl (methyl to isoamyl) potassium sulfates have been shown to react at somewhat higher temperatures with a second mole of potassium cyanide in 15–90 per cent yields (19, 580).

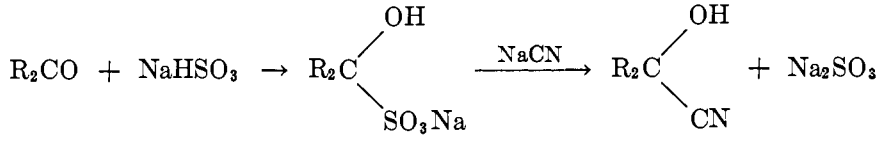
$$ROSO_3K + KCN \rightarrow RCN + K_2SO_4$$

By selection of a suitable temperature cycle the utilization of both alkyl groups may be effected in high yield (583).

The nitrile may be contaminated with as much as 10 per cent of the isocyanide, a result which seems to be caused partly by the presence of water. Sodium cyanide is stated to cause more hydrolysis of the nitrile group than potassium cyanide. This may be avoided by the use of an non-aqueous diluent such as xylene or tetralin which boils at a temperature greater than 130°C. (470).

Alkyl arylsulfonates react similarly with equimolar quantities of potassium cyanide to give aliphatic nitriles (191). The methyl ester is converted in higher yield than the ethyl ester (489). However, high yields are again obtained in the case of the higher aliphatic esters, and cetyl *p*-tolylsulfonate is converted to margaric nitrile in 86 per cent yield (524). Alkyl esters of methanesulfonic acid in some cases give better yields of alkyl cyanides than are obtained from the esters of *p*-toluenesulfonic acid (622). However, the secondary butyl ester gave largely 2-butene instead of α-methylbutyronitrile.

The bisulfite modification in the preparation of cyanohydrins of aldehydes and ketones is a special case in which a sodium sulfonate group is smoothly replaced by the cyanide ion (see page 231).



The use of phosphoric acid esters instead of the sulfates has apparently received scant attention. Williamson described the reaction of aryl phosphates with potassium cyanide in 1854 (601). This synthesis of aromatic nitriles, which gives 15–20 per cent yields, was extended by Heim (254) and Kreysler (331). Triethyl phosphate is stated to give propionitrile when heated with sodium cyanide (470).

B. ARYL SULFONATES AND METAL CYANIDES

The classic synthesis of benzonitrile by the fusion of the alkali metal salts of benzenesulfonic acid with potassium cyanide was discovered by Merz in 1868 (393). Further study of the reaction (394) revealed that a good yield of β-naphthonitrile was obtained from sodium β-naphthalenesulfonate by treatment with an excess of sodium cyanide. Naphthalene, water, hydrogen sulfide, ammonium carbonate, and ammonium cyanide were identified among the by-products. Increasing the mole ratio of sodium cyanide to sulfonate above 2:1 does not better the yield. The potassium salts give slightly better yields, while the calcium salts are inferior. α-Naphthonitrile is obtained in 50 per cent yield by the action of sodium cyanide (593).

Witt showed that the less toxic potassium ferrocyanide gave somewhat better results (606). In general, the yields of purified aromatic nitriles vary from traces to 60 to 80 per cent depending on the structure of the reacting compound. Dry reagents, intimate mixing, and uniform heating of the reaction mass to high temperatures appear desirable. The use of about 70 per cent sand in the reaction mixture is claimed to increase yields by modifying the exothermic reaction (248), while the introduction of a quantity of iron filings is recommended to aid the distribution of heat (581). A smoother reaction and increased yields are also obtained by heating the reagents in an inert diluent such as a mineral oil having a boiling range of 310–400°C. (467). The reaction is commonly effected under vacuum or in the presence of a stream of inert gas, such as carbon dioxide, to facilitate the rapid removal of product from the reaction zone.

A number of dicyano derivatives of benzene, biphenyl, naphthalene, and higher condensed-ring systems have been prepared from the corresponding disulfonates. Yields are usually low (less than 20 per cent) and the product is contaminated with mononitrile. Phthalonitriles and naphthalonitriles have also been obtained from halobenzene- or halonaphthalene-sulfonic acids (144, 398, 436). Sodium 1,3,5-benzenetrisulfonate when fused with potassium cyanide is reported to give a small yield of trimesonitrile (288).

Whereas only traces of isophthalonitrile are obtained by this method (398), terephthalonitrile is obtained in yields of about 20 per cent (436). These observations suggest an activation of the sulfonic acid or halogen group by the cyano group if the two radicals are separated by an even number of carbon atoms. This tendency has been confirmed by Bradbrook and Linstead, who undertook the synthesis of ten different dicyanonaphthalenes by fusion of the appropriate sodium cyanonaphthalenesulfonate with potassium ferrocyanide (64). Thus, under comparable conditions, 1-naphthonitrile-2-sulfonate, -4-sulfonate, -5-sulfon-

ate, and -7-sulfonate were converted to the naphthalonitriles in 31–75 per cent yields, while the corresponding 3-sulfonate, 6-sulfonate, and 8-sulfonate gave yields of only 9–18 per cent. Confirmatory results were obtained with the 2-naphthonitrile derivatives, the 1-sulfonate and 6-sulfonate being converted in 84 and 42 per cent yields, respectively, while the 7-sulfonate gave only 8 per cent of the corresponding dinitrile. The effect is especially pronounced when the cyano group is in the same ring as the sulfonic acid group. This interesting activation is apparently not entirely explainable by the principles of resonance or vinology, since an analogous situation is found in the aliphatic series where no aromatic nuclei or double bonds exist (see page 197). A further conclusion is that there is no appreciable difference in yields or ease of reaction between α- or β-positions of the naphthalene ring.

Substituents such as alkyl, amino, or keto groups (336) appear to be unchanged by fusion with the alkali cyanide or ferrocyanide reagent. The reaction is successful with sulfonates of heterocyclic amines such as quinoline and pyridine. Sodium pyridine-3-sulfonate has been converted to nicotinonitrile in 46 per cent yield by this method (374), which forms the basis of a commercial synthesis of nicotinic acid and its amide (467). α-Cyanothiophene may also be prepared by means of this synthesis (160).

Certain unexpected side-reactions have been reported. Thus, potassium acenaphthene-3-sulfonate and potassium ferrocyanide give acenaphthylene as the main product (443). King and Wright have shown that migrations of the nitrile group from the β- to the α-position of the naphthalene nucleus sometimes occur in this synthesis (311). When sodium 2-naphthonitrile-7-sulfonate or the 2,7-naphthalenedisulfonate is treated with potassium cyanide, some 1,7-dicyanonaphthalene is obtained together with the 2,7-derivative. Similarly, 2-naphthonitrile-6-sulfonate gives a certain amount of 2,5-dicyanonaphthalene, together with the expected product.

The reaction of arylsulfonic acid salts with metal cyanides has been discussed at some length by Suter (553a).

C. HALIDES AND METAL CYANIDES

1. Aliphatic halides

The reaction of an organic halide and a metallic cyanide was first investigated in 1832 by Wöhler and Liebig (609), who obtained benzoyl cyanide by distillation of benzoyl chloride over mercuric cyanide. Conversion of alkyl halides to the nitriles by the use of the cyanides of alkali metals was accomplished by Williamson in 1854 (600) and the action of the heavy metal cyanides was studied by Gautier (209).

The reaction is commonly conducted in a boiling aqueous alcoholic solution of such concentration that both the halide and the alkali cyanide are dissolved. When insoluble metal cyanides such as copper cyanide are used, a non-aqueous system is preferred, frequently without solvent.

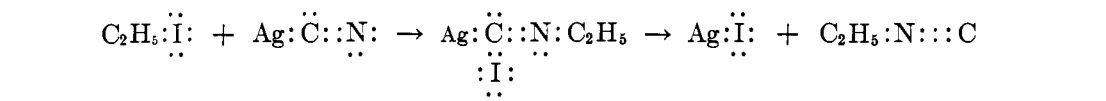
The reaction is almost always accompanied by the production of a certain

amount of the isomeric isocyanide. The ratio of isocyanide to nitrile depends largely on the nature of the metal cyanide employed. Guillemard (231), in an extensive study of different metal cyanides, showed that the heavier metal cyanides such as those of silver gave isocyanides exclusively, while with other metals the following percentages of isocyanide were in the mixture resulting from the reaction with ethyl iodide: cuprous copper, 56 per cent; cadmium, 11 per cent; nickel, 8 per cent; zinc, 2.6 per cent. Sodium and potassium cyanides gave only minor amounts of isocyanides. The temperature of reaction was also found to play an important rôle in the amount of isocyanide produced. All of the metallic cyanides gave normal nitriles if the reaction were conducted above 150°C. Lower temperatures favored isocyanide formation. The thermal effect was substantiated by studies of the isomerization of isocyanides in the absence of metallic cyanides. These findings led Guillemard to the hypothesis that the reaction always led primarily to the isocyanide, which underwent rearrangement in certain cases.

Gautier (204) and Hartley (246) have observed that methyl iodide forms molecular complexes with one or two moles of silver cyanide but not with alkali cyanides. Decomposition of these complexes led to the isocyanide. It has been suggested that sodium cyanide is ionic in nature and reacts with ethyl iodide by an ionic mechanism.

$$C_2H_5I + CN^- \rightarrow C_2H_5CN + I^-$$

However, silver cyanide and cuprous cyanide have essentially covalent bonds and the reaction proceeds through the formation of an intermediate complex (454).



This view was recently substantiated by Gallais (206), who concluded from studies of the ultraviolet absorption spectra that the basic difference between sodium cyanide and silver cyanide was that the former was a simple salt while the latter existed as a covalent complex, $Ag[Ag(CN)_2]$. It appears that Guillemard's hypothesis of primary isocyanide formation does not account for all of the facts and contributes very little to an understanding of the different reaction mechanisms.

Ogg (441) has calculated from available data the heat of reaction and experimental activation energies of the reaction of methyl halides with the cyanide ion in aqueous solution. Data for a few other exchange reactions are included in table 1 for comparison.

Purification of the nitriles produced in these reactions is facilitated by the fact that isocyanides are rapidly hydrolyzed to formic acid and the amine by treatment with cold dilute acids (231). Hence washing the product with hydrochloric acid usually suffices to remove isocyanide impurities, the presence of which is easily detected by their characteristic offensive odor.

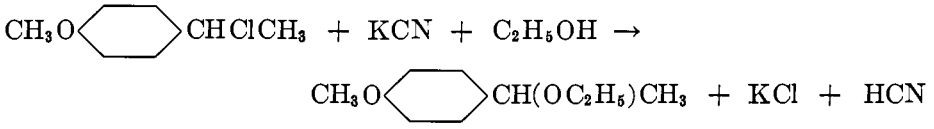
In addition to isocyanide formation, other side-reactions often occur in the reaction of organic halides with alkali cyanides in aqueous alcohol. A certain amount of hydrolysis of the product usually occurs under the basic conditions which obtain. In a large number of cases the hydrolysis is deliberately promoted by long heating at high temperatures to obtain the acids directly. The classic syntheses of tricarballylic acid from 1,2,3-tribromopropane (525), fumaric acid from 1,2-diiodoethylene (308), and citric acid from the cyanohydrin of *sym*-dichloroacetone (229) are illustrative of this technique. The nitrile is also frequently contaminated by the alcohols or ethers resulting from hydrolysis or alcoholysis of the halide reagent by the solvent under the influence of the basic alkali cyanide. In the case of the reaction of *p*-(α-chloroethyl)anisole with

TABLE 1

Heat of reaction of methyl halides with cyanide ion

REACTION	HEAT OF REACTION	ACTIVATION ENERGY
	kg.-cal./mole	*kg.-cal./mole*
$CH_3Cl + CN^-$	+19.8	22
$CH_3Br + CN^-$	+18.2	22
$CH_3I + CN^-$	+19.4	22
$CH_3Cl + OH^-$	+18.0	23
$CH_3Cl + C_2H_5O^-$	+17.1	21
$CH_3Cl + C_6H_5O^-$	+13.4	19.5
$CH_3Cl + CH_3COO^-$	+10.2	22.3
$CH_3Cl + SH^-$	+19.7	28

alcoholic potassium cyanide a nearly quantitative yield of the ethyl ether resulted and none of the expected nitrile was obtained (468).



Of the *alkyl halides*, the iodides react most readily. The bromides and chlorides react quite readily, while the fluorides appear to be inert. The yield and rate of the reaction of an alkyl chloride with an alkali cyanide may be improved by the addition of an alkali iodide as a promotor (248).

The reaction of normal alkyl iodides with potassium cyanide has served for the progressive synthesis of higher homologues by the following scheme:

$$RCOOR \rightarrow RCH_2OH \rightarrow RCH_2I \rightarrow RCH_2CN \rightarrow RCOOH$$

By this method, Levene and Taylor have synthesized progressively the nitriles containing from nineteen to twenty-six carbon atoms (359).

Variation in the structure of the alkyl group affords a great difference in reactivity. Thus, primary halides usually react readily, while secondary and

tertiary halides usually give dehydrohalogenation products with liberation of hydrogen cyanide from the alkali cyanide. Hass and Marshall found that *n*-amyl chloride reacted with sodium cyanide in 70 per cent conversion and about 95 per cent yield. Secondary amyl chloride, on the other hand, gave about 30 per cent yields and tertiary amyl chloride gave only the olefin (248). This difficulty may sometimes be obviated by using a non-basic metallic cyanide. In general, alicyclic halides also give olefins, although the conversion of cyclopentyl bromide to the nitrile has been accomplished with sodium cyanide in 27 per cent yield (491).

Compounds of the neopentyl halide type are remarkably inactive. Franke was unable to obtain nitriles by the action of potassium cyanide on 2,2-dialkyl-1,3-dibromopropanes (194), while neopentyl chloride was recovered unchanged after contact with cuprous cyanide at 90°C. for 200 hr. (592).

The conversion of *dihalides* to nitriles is influenced by the fact that a cyano substituent apparently activates a halogen removed from it by an even number of carbon atoms, and slightly inhibits the halogen atoms separated from it by an odd number of carbon atoms. Thus, the first cyano group to enter a molecule influences the ease with which the second halogen atom is replaced. Attempts to convert methylene halides or chloroacetonitrile to malononitrile have been unsuccessful (419), although ethylidene bromide has been partially converted to succinic acid probably through the successive steps of metathesis, dehydrobromination, addition of hydrogen cyanide, and hydrolysis.

$$CH_3CHBr_2 \xrightarrow{KCN} [CH_3CHBrCN] \xrightarrow{-HBr}$$

$$[CH_2{=}CHCN] \xrightarrow{+HCN} [CNCH_2CH_2CN] \rightarrow \begin{matrix} CH_2COOH \\ | \\ CH_2COOH \end{matrix}$$

Ethylene dibromide, however, is smoothly converted to succinonitrile by sodium cyanide in refluxing aqueous ethanol (177), but β-bromopropionitrile cannot be isolated when a deficiency of sodium cyanide is used (419). Although ethylene dichloride will not react in this solvent even at 180°C. under pressure, β-chloropropionitrile is rapidly converted in excellent yields to succinonitrile at 40°C. (419). A two-step dehydrohalogenation–hydrogen cyanide addition mechanism could be advanced to explain the high reactivity of β-chloropropionitrile. However, this mechanism cannot account for the behavior of the isomeric xylylene dibromides described in the following paragraph. The conversion of 1-chloro-3-bromopropane to γ-chlorobutyronitrile (6) illustrates the difference in reactivity of different halogens, while the absence of appreciable quantities of glutaronitrile gives further evidence of the inhibiting action of a cyano group in the 3-position. Similarly, the only product isolated from the reaction of sodium cyanide and 1,3-dichloro-2-propanol was 3-chloro-2-hydroxybutyronitrile (69). However, an increased reaction time and an excess of potassium cyanide did permit the formation of an 11 per cent yield of β-methylglutaronitrile from 1,3-dichloro-2-methylpropane, although the main product was the chloronitrile (123). Tetramethylene chloride or bromide, on the other hand, is smoothly converted to adiponitrile

in very high yield (515), and this synthesis is reported to have been adopted in commercial production in Germany in recent years (151).

The alternating activation of halides by the cyano group is apparently transmitted through aromatic rings. Thus, two groups of investigators showed that *o*- and *p*-xylylene dibromides are converted only to dinitriles. No bromonitrile could be detected in the products, even when a deficiency of potassium cyanide was employed. On the other hand, the use of an excess of potassium cyanide failed to convert the meta isomer to the dinitrile, although the bromonitrile was obtained in 90 per cent yield (220, 605). 1,2,4-Tris(chloromethyl)benzene has been similarly converted to the trinitrile (340).

The tendency toward inhibition appears to diminish as the intervening chain length increases. α,ω-Dinitriles from seven to thirty-four carbon atoms in length have been smoothly synthesized in high yields from potassium cyanide and the dibromides (71, 74, 112, 623).

Haloalcohols are converted in aqueous or alcoholic solution to hydroxynitriles. Ethylene chlorohydrin, for example, reacts smoothly at moderate temperatures to give 85–95 per cent yields of ethylene cyanohydrin (33). This reaction was for many years the basis of the commercial synthesis of this intermediate for acrylonitrile. Other olefin chlorohydrins react similarly (180, 317). Dewael made the interesting observation that 2-chloropropanol was converted in 60 per cent yield by alcoholic potassium cyanide to β-hydroxybutyronitrile instead of the expected β-hydroxyisobutyronitrile (158). He concluded that the reaction proceeded by dehydrohalogenation to propylene oxide and that this intermediate then added hydrogen cyanide in the normal fashion.

$$CH_3CHClCH_2OH \xrightarrow{KCN} \left[\begin{array}{c} O \\ / \quad \backslash \\ CH_3CH\text{—}\!\!-CH_2 \end{array}\right] \xrightarrow{HCN} CH_3CHOHCH_2CN$$

Since reactions similar to those hypothesized are known to take place under conditions obtaining in the experiment, it is reasonable to suspect that this mechanism may be operative in the reaction of all olefin chlorohydrins with alkali cyanides. Derivatives of chloroalcohols such as ethers (449, 462), thioethers (121), and esters (419) usually react normally. Similar behavior is exhibited by amidoalkyl chlorides (72) and aminoalkyl chlorides (121). An unexpected by-product was observed in the case of the reaction of bis(β-chloroethyl) sulfide (mustard gas) and potassium cyanide (43).

$$\begin{array}{l} CH_2CH_2Cl \\ S \\ CH_2CH_2Cl \end{array} \xrightarrow{KCN} \begin{array}{l} CH_2CH_2CN \\ S \\ CH_2CH_2CN \end{array} + \begin{array}{l} CH_2SCH_2CH_2CN \\ | \\ CH_2SCH_2CH_2CN \end{array}$$

Its formation was explained by a side-reaction of the intermediate chloronitrile, through a sulfonium salt mechanism.

If the halogen is attached to a carbon atom bound to an oxygen atom, as in α-chloroalkyl esters (85) or ethers, a pronounced activation is noted. In most of

these cases copper, mercury, or silver cyanides have been used because of the tendency of aqueous alkali cyanides to promote cleavage of the carbon–oxygen bond, while anhydrous alkali cyanides are usually unreactive. A large number of chloromethyl ethers have been converted to cyanomethyl ethers, notably by Henze and coworkers (8, 89, 212, 260, 533). The reaction is commonly effected in boiling benzene or ether and yields of 55–80 per cent are reported. The yields of higher α-cyanoalkyl ethers decrease with increasing chain length (364). For the reaction

$$\mathrm{ClCH_2CH_2O}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{C}}\mathrm{HR} \xrightarrow{\mathrm{Cu_2(CN)_2}} \mathrm{ClCH_2CH_2O}\underset{\underset{\mathrm{CN}}{|}}{\mathrm{C}}\mathrm{HR}$$

the yields of nitriles were as follows: R = H (50 per cent); R = CH_3 (41 per cent); R = C_2H_5 (38 per cent); R = C_3H_7 (35 per cent). The above reaction also illustrates the activating influence of the ether linkage on a halogen in the α-position. The second halogen, in the β-position, is not replaced, although bischloromethyl ethers are converted to dinitriles under similar conditions (8). A similar effect was noted in the following reaction, which was effected in 81 per cent yield by means of cuprous cyanide and in 65 per cent yield by means of mercurous cyanide (537):

$$\mathrm{ClCH_2}\underset{\underset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HOCH_2Cl} \longrightarrow \mathrm{ClCH_2}\underset{\underset{\mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HOCH_2CN}$$

α,β-Dibromoethyl alkyl ethers (25, 463) and α,β-dichloroethyl acetate (419) react with cuprous cyanide in 40–50 per cent yields.

$$\mathrm{CH_2BrCHBrOR} \xrightarrow{\mathrm{CuCN}} \mathrm{CH_2BrCH(CN)OR}$$

Potassium cyanide effects a similar reaction together with cleavage of the ether group, and β-chlorolactonitrile is obtained in 24 per cent yield (278, 419).

$$\mathrm{CH_2ClCHClOC_2H_5} \xrightarrow{\mathrm{KCN}} \mathrm{CH_2ClCHOHCN}$$

Similar activation is conferred upon a chlorine atom attached to a carbon adjacent to a nitrogen atom. In the following case, dehydrohalogenation accompanies the metathesis reaction (267).

$$\mathrm{C_6H_5CONHCHClCCl_3} \xrightarrow{\mathrm{KCN}} \mathrm{C_6H_5CONH}\underset{\underset{\mathrm{CN}}{|}}{\mathrm{C}}\mathrm{{=}CCl_2}$$

Unsaturated alkyl halides are affected by additional complicating factors in their reactions with metal cyanides. If the halide is of the vinyl type, its reactivity is greatly diminished. This difference is illustrated by the reactions of the following dichloroölefins in which the halogen attached to the olefinic carbon is not replaced (123, 128).

$$ClCH{=}C(CH_3)CH_2Cl \longrightarrow ClCH{=}C(CH_3)CH_2CN$$

$$CH_3C(Cl){=}CHCH_2Cl \longrightarrow CH_3C(Cl){=}CHCH_2CN$$

The use of bromides or iodides with cuprous cyanide at temperatures of 150–250°C. enables some α,β-unsaturated nitriles to be prepared. These conditions, which are reminiscent of those obtaining in the Rosenmund-von Braun aromatic nitrile synthesis (see pages 207–208) were used by Jennen (293) to prepare fumaronitrile from *sym*-diiodoethylene. The dibromo- and dichloro-ethylenes will not react below the decomposition temperature of the product. A trace of a tertiary amine acts as a promotor in this reaction and enables the yields to be raised from 30 to 75 per cent (268). Koelsch has applied this technique to the preparation of α,β,β-triphenylacrylonitrile and related compounds from the appropriate vinyl bromides (315).

Acetylenic halides on the other hand react readily with methanolic potassium cyanide, but the sole product is the cyanoether which results from addition of the alcohol to the intermediate nitrile (413).

$$C_5H_{11}C{\equiv}CCl + KCN \xrightarrow{CH_3OH} C_5H_{11}C(OCH_3){=}CHCN$$

No reaction takes place in dioxane solution, even if the bromo- or iodo-acetylene is used (373).

Allylic halides are also very reactive but introduce complications caused by two types of isomerization, *viz.*, migration of the double bond and 1,3- or 1,5-anionotropic rearrangements. Early workers assumed that the reaction product of allyl bromide and potassium cyanide was allyl cyanide, but it was later shown that isomerization to crotononitrile had taken place (20, 448, 459). The reaction will not proceed in the absence of a trace of water even at 120°C. (459). In alcoholic solution, by-products formed include β-ethoxybutyronitrile (488) and methyl succinonitrile (457). These arise from the addition of alcohol and hydrogen cyanide to the reactive α,β-double bond under the alkaline conditions which obtain. The side-reactions caused by the basic reagent are avoided by the use of cuprous cyanide, and very high yields of the unisomerized product are obtained (79, 258). A trace of pyridine serves to eliminate the induction period which occurs when very pure reagents are used (431a). This technique has been applied to the preparation of numerous cyanides of the allyl type (154). Apparently rearrangements do not always take place with alcoholic alkali cyanides, since no shifting of the double bond was detected in the conversion of 3-chlorocyclopentene to the nitrile by potassium cyanide in aqueous alcoholic solution (146).

Dihalides of the allyl type, such as 1,4-dichloro-2-butene, react readily with potassium cyanide to give some of the normal product, dihydromuconononitrile, but

the principal product is 1-cyano-1,3-butadiene which arises through dehydrohalogenation of the intermediate chloronitrile (105, 235).

$$ClCH_2CH{=}CHCH_2Cl + 2KCN \rightarrow$$

$$CNCH_2CH{=}CHCH_2CN \quad (5\text{–}20 \text{ per cent})$$

$$+$$

$$CH_2{=}CH{-}CH{=}CHCN \quad (13\text{–}70 \text{ per cent})$$

Increased yields of the dinitrile are stated to be obtained if the reaction is run in the absence of air and in the presence of a solvent such as acetonitrile (335). Surprisingly, 1,4-dichloro-2-butyne is inert to the action of either potassium cyanide or cuprous cyanide (295).

1-Chloro-2,3-butadiene undergoes many metathetical reactions without undergoing rearrangements, but with potassium cyanide in methanol the isomerized product is obtained, together with some 5-methoxy-3-pentenonitrile arising from 1,4-addition of the solvent.

$$CH_2{=}C{=}CHCH_2Cl + KCN \xrightarrow{CH_3OH} CH_2{=}CHCH{=}CHCN$$

$$+$$

$$CH_3OCH_2CH{=}CHCH_2CN$$

No 2-cyano-1,3-butadiene, which would be expected to arise by 1,3-anionotropic rearrangement, was detected (127).

Lane, Fentress, and Sherwood observed that when 1-chloro-2-butene reacts with cuprous cyanide an allylic rearrangement takes place, so that the product is a mixture of 91.5 ± 0.5 per cent 1-cyano-2-butene and 8.5 ± 0.5 per cent 2-cyano-3-butene. The same ratio of product isomers is obtained if the starting materials are 90 per cent 2-chloro-3-butene and 10 per cent 1-chloro-2-butene or 80 per cent 2-bromo-3-butene and 20 per cent 1-bromo-2-butene. The reacting chlorides easily undergo the allylic rearrangement, but the equilibrium mixture consists of 74 per cent of the primary chloride and 26 per cent of the secondary chloride. The product nitriles do not rearrange under the conditions of the experiment. The authors conclude from the above data that the reaction proceeds through a mesomeric carbonium ion and is not a simple bimolecular substitution (349).

$$CH_3CH{=}CHCH_2X$$

$$+ \qquad \rightarrow X^- + [CH_3CH{\cdots}CH{\cdots}CH_2]^+ \xrightarrow{CN^-}$$

$$CH_3CHXCH{=}CH_2$$

$$CH_3CH{=}CHCN \quad (91.5 \text{ per cent})$$

$$+$$

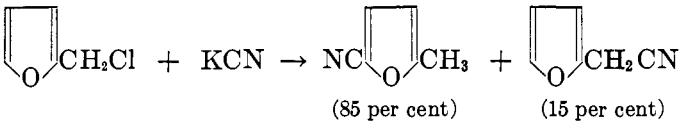
$$CH_3\underset{\displaystyle CN}{\underset{|}{C}}HCH{=}CH_2 \quad (8.5 \text{ per cent})$$

A similar rearrangement has been reported for the reaction of sorbyl chloride

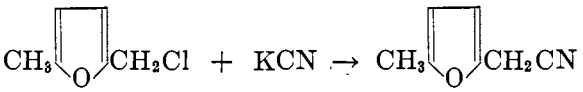
and potassium cyanide, but the anionotropic rearrangement here is of the 1,5-type (480).

$$CH_3CH{=}CHCH{=}CHCH_2Cl + KCN \rightarrow CH_3\underset{\displaystyle CN}{\underset{|}{C}}HCH{=}CHCH{=}CH_2$$

The reaction between furfuryl chloride and potassium cyanide was originally assumed to give furylacetonitrile. Runde, Scott, and Johnston (498, 523) and Reichstein (478) independently discovered that only a small amount of this product is obtained. The major product is 5-methylfuronitrile, the result of a 1,5-rearrangement.

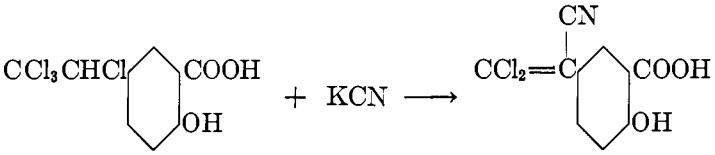


A similar rearrangement takes place with α-(1-chloroethyl)furan (482), but 5-methylfurfuryl chloride is converted without appreciable rearrangement (481, 523).



Benzyl chloride and thenyl chloride give only the normal products (387).

Halides of the benzyl type are converted very readily to arylacetonitriles in 80–90 per cent yields with alkali cyanides in water or aqueous alcohols at reflux (383, 419). α-Chloromethylnaphthalene gives similar results (122, 384). Carbethoxy (406) and phthalide (107) substituents on the aromatic nucleus were unaffected by the reagent. However, 5-(α,β,β,β-tetrachloroethyl)salicyclic acid underwent both metathesis and dehydrohalogenation (159).



The principal by-products are arylcarbinols, arylacetamides, and ethers which arise through reaction with the solvent. Side-reactions do not become very serious except in the case of especially reactive halogen atoms. Most of these cases involve alkylbenzyl or alkoxybenzyl halides or benzohydryl halides. The formation of ethers was eliminated in the case of 1-chloromethyl-2-methoxynaphthalene by reacting it with potassium cyanide in 66 per cent acetone solution at 30–35°C. (133). The use of cyanides of the heavy metals, such as mercuric cyanide in acetonitrile solution, gives similar results (607). Cuprous cyanide in pyridine (202) or phenylacetonitrile (263) solution has given good results. The reaction of *p*-methoxybenzyl chloride and cuprous cyanide, however, yields only tars reminiscent of the polymers obtained from benzyl chloride and acidic

metal chlorides. However, benzyl chloride itself is converted to phenylacetonitrile in 71 per cent yield under the same conditions (587).

Halides containing halogen alpha to a carboxyl group are also highly reactive toward alkali cyanides. Thus, sodium chloroacetate is transformed almost instantaneously to sodium cyanoacetate in cold aqueous solution. Conversion of methyl esters is conveniently accomplished with methanolic potassium cyanide (439). Although it was noted earlier that a halogen was relatively inactive if attached to an ethylenic carbon atom, this influence is counterbalanced by the presence of an α-carbethoxy group. For example, methyl α-chloroacrylate reacts readily with sodium cyanide to give methyl β-cyanoacrylate (137, 418).

$$CH_2{=}\underset{\displaystyle Cl}{\overset{|}{C}}COOCH_3 + NaCN \longrightarrow CNCH{=}CHCOOCH_3$$

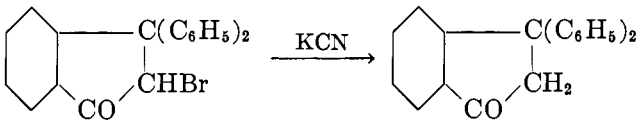
The fact that a rearrangement has taken place indicates that the mechanism must involve a 1,4-addition of hydrogen cyanide to the carbonyl–olefin conjugated system and removal of the chlorine by dehydrohalogenation. α-Chloroacrylonitrile reacts in a strictly analogous fashion, but esters of chloromaleic, chlorofumaric, and α-chlorocrotonic acids appear to be inert (108, 419).

Certain *halides containing halogen alpha to a carbonyl group* react normally. Thus, ethyl α-bromopropionate and alcoholic potassium cyanide are converted to ethyl α-cyanopropionate (547). Phenacyl halides and many of their nuclear-substituted derivatives appear to give the normal reaction (82, 469).

$$C_6H_5COCH_2X + KCN \longrightarrow C_6H_5COCH_2CN$$

α-Bromohydrindone (297) and α-bromopinacolone (596) are similarly converted to the β-ketonitriles.

In many cases, especially if the halide is secondary, dehydrohalogenation or reduction (with replacement of the halide by hydrogen) occurs. Thus, 2-bromo-3,3-diphenylhydrindone (204),



and benzalacetophenone dihalides (264, 427)

$$C_6H_5CO\,CHClCHClC_6H_5 \xrightarrow{KCN} C_6H_5CO\,CH_2CH(C_6H_5)CN$$

are smoothly converted to the reduced forms. In the latter case, reduction appears to be followed by dehydrohalogenation to benzalacetophenone, which can be isolated at low temperatures. Addition of hydrogen cyanide to the unsaturated ketone then proceeds in the normal fashion.

The action of alcoholic potassium cyanide on chloral and related compounds has been studied in detail by Chattaway and Irving (108). This reaction results in simultaneous reduction of one of the α-chlorine atoms and conversion of the aldehyde group to a carbethoxy group.

$$CCl_3CHO + KCN + C_2H_5OH \xrightarrow{(88\%\ \text{yield})} CHCl_2COOC_2H_5 + KCl + HCN$$

Use of other alcohols as solvents results in the formation of the corresponding esters. Dichloroacetaldehyde and monochloroacetaldehyde are similarly converted to esters of chloroacetic acid and acetic acid, respectively. Butyrochloral reacts similarly, but above 15°C. dehydrohalogenation also occurs.

$$CH_3CHClCCl_2CHO + KCN + C_2H_5OH \longrightarrow CH_3CHClCHClCOOC_2H_5$$

$$\xrightarrow{KCN} CH_3CH{=}CClCOOC_2H_5$$

The use of chloral diacetate gives analogous results, and the corresponding aldehyde ammonia derivatives are converted to the amides in 93 per cent yield.

$$CCl_3CH(OH)NH_2 + KCN \longrightarrow CHCl_2CONH_2$$

Chloral and potassium cyanide in aqueous solution lead to potassium dichloroacetate, together with a high-melting by-product which is thought to be 6-keto-2,4,7-tris(trichloromethyl)-1,3,5-dioxazaseptane (138).

$$CCl_3CHO + KCN \longrightarrow CHCl_2COOK + CCl_3CHCONHCHCCl_3$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O\,C(CCl_3)\,O$$

These transformations are thought to proceed through the cyanohydrin by a mechanism proposed by Pinner (458) and Kötz (320) and later substantiated by Lapworth (126). In the following generalized expression HA may represent water, alcohols or ammonia, and amines:

$$\diagdown\!\diagup CClCHO + KCN + HA \rightleftharpoons \diagdown\!\diagup CClCH(OH)CN + KA$$

$$\diagdown\!\diagup CClCH(OH)CN \longrightarrow \diagdown\!\diagup C{=}C(OH)CN + HCl$$

$$\diagdown\!\diagup C{=}C(OH)CN \longrightarrow \diagdown\!\diagup CHCOCN$$

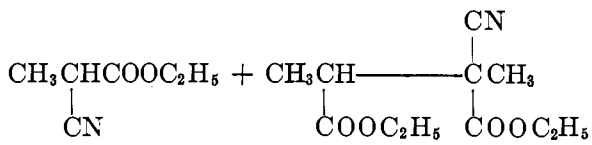
$$\diagdown\!\diagup CHCOCN + 2KA \longrightarrow \diagdown\!\diagup CHCOA + KCN$$

$$HCl + KCN \longrightarrow KCl + HCN$$

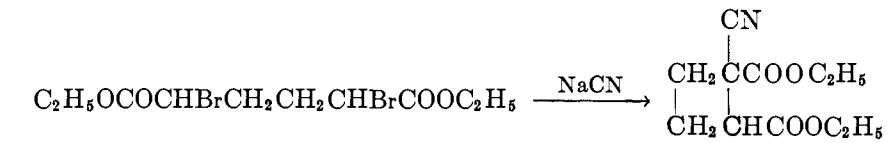
A strong argument for the cyanohydrin intermediate in the Pinner–Kötz mechanism is based on the fact that other materials of similar alkalinity do not effect the transformation. The diethyl acetals of chloral and related compounds are inert in this reaction because of the stability of the acetal linkage to basic media.

Halides containing halogen alpha to a carbonyl group often react with alkali cyanides to give inter- or intra-molecular dehydrohalogenation with the formation of a new carbon–carbon bond. Thus, by-products in the reaction of α-bromopropionic esters are the α,α′-dimethyl-α-cyanosuccinates (619).

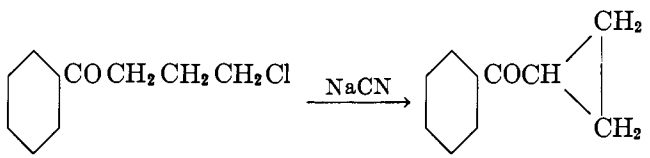
$$CH_3CHBrCOOC_2H_5 + KCN \longrightarrow$$



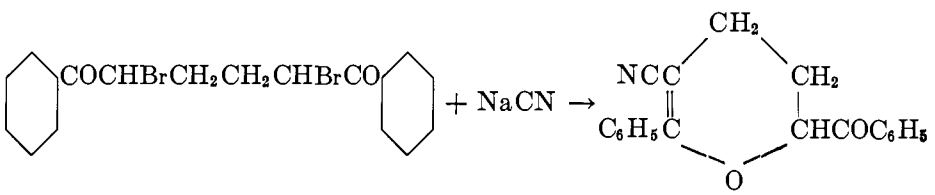
α-Chloroethyl methyl ketone gives a similar by-product (294). α,α′-Dibromoadipates are converted to cyclobutane derivatives (199, 338).

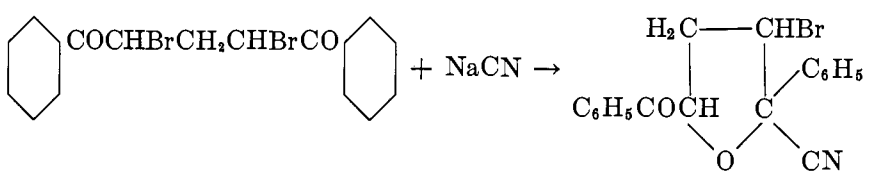


γ-Chlorobutyrophenone is similarly transformed into a cyclopropane derivative (5).



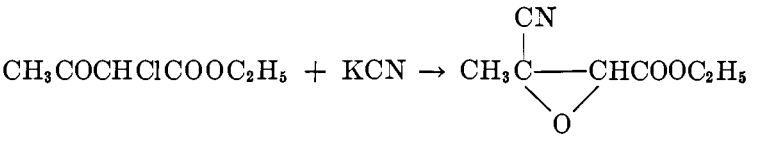
Dehydrohalogenation often occurs with the formation of a new epoxy linkage. This can arise either from the enol form of the ketone or from its cyanohydrin (200, 201).



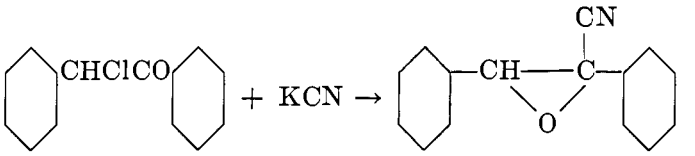


Early investigators assumed that the products resulting from the reaction of α-chloroketones and alkali cyanides were the normal β-ketonitriles. Actually in most cases, especially if the halide has a secondary configuration, the product is a cyanoölefin oxide. Thus, Favrel and Prevost demonstrated in 1931 that

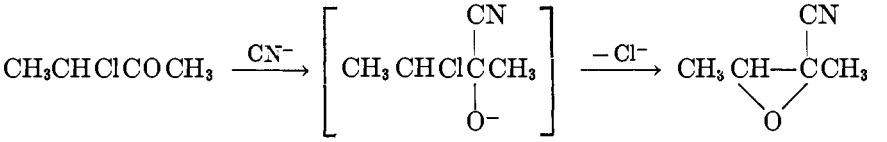
the product from α-chloroacetoacetic ester and potassium cyanide was not the cyanoketo ester, but ethyl α,β-epoxy-β-cyanocrotonate (178).



Desyl chloride reacts similarly (322).

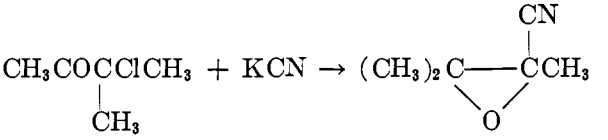


Other chloroketones which have been recently reported to react in this anomalous fashion are α-chlorobenzyl alkyl ketones (468), 2-chloro-3-butanone (215, 300), chloroacetone (300), and γ-chloroacetoacetic ester (318). It is probable that the cyanide ion attacks the carbonyl carbon, followed by elimination of the chloride ion through formation of the epoxide linkage.

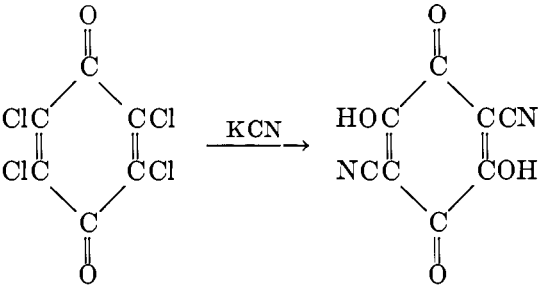


The cyanohydrin of the chloroketone is definitely not the intermediate, since Gerbaux (215) treated this compound (which he isolated by another method) with potassium cyanide and obtained very little of the cyanoepoxide, which was obtained in 70 per cent yield when the chloroketone was used.

Delbaere obtained a cyanoepoxide from 2-chloro-2-methyl-3-butanone. The reaction product in this case was further complicated by the occurrence of a pinacolone-type rearrangement (155).



Olefinic chlorine atoms, if activated by a carbonyl group, will react with potassium cyanide. In the case of chloranil, two of the halogens are replaced and two are hydrolyzed by the basic aqueous solution (487).



2. *Aromatic halides*

In 1877, Merz obtained α-naphthonitrile from α-bromonaphthalene by treatment with potassium ferrocyanide (395). A modified technique involved passing the gaseous aryl halide over the hot ferrocyanide at about 350–400°C. (12). Benzonitrile was also obtained from iodobenzene and silver cyanide (395), but the method has little preparative value.

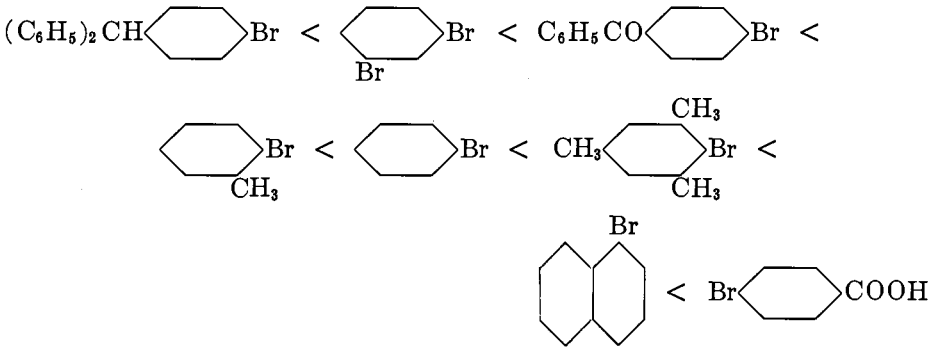
The use of cuprous cyanide dissolved in cyclic aromatic amines was introduced in the German patent literature in 1913 (12, 390). A related reaction was the conversion of bromobenzene to benzonitrile in 23 per cent yield by the action of copper thiocyanate in pyridine solution (493). Considerable diphenyl sulfide was obtained as a by-product.

Later de Diesbach extended the cuprous cyanide reaction and reported yields of 88 per cent for the conversion of a mixture of dibromoxylenes to the dinitriles (162). This technique has proved very popular with later workers. The aryl bromide and a slight excess of dry cuprous cyanide are added to sufficient dry pyridine or quinoline to form a homogeneous complex at reaction temperatures of 150–250°C. Aryl chlorides undergo the reaction satisfactorily if sufficiently activated by appropriate substituents. Thus, Newman converted α-bromonaphthalene with cuprous cyanide in pyridine solution to α-naphthonitrile in 93 per cent yield at 220°C. in 15 hr. α-Chloronaphthalene underwent 92 per cent conversion at 250°C. in 24 hr. (70 per cent in 6 hr.) (431). There appears to be an optimum time and temperature for each type of compound. For example, a substituted chlorobenzene is reported to give an 87 per cent yield at 245°C. in 25 hr., 74 per cent in 35 hr., and 67 per cent in 48 hr. In 60 hr. at 255°C. the yield dropped to 20 per cent (192).

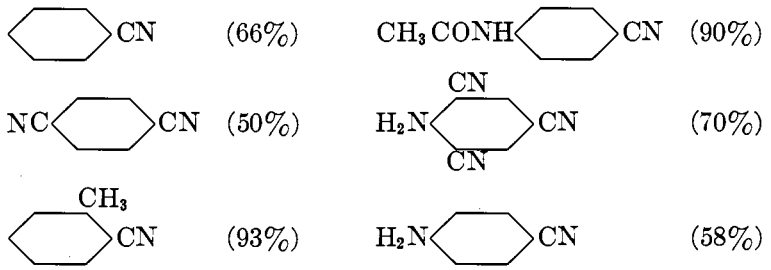
Another technique involves the use of cuprous cyanide in the absence of basic solvents. Thus, Rosenmund observed in 1919 that the addition of cuprous cyanide to aqueous sodium cyanide in the aryl halide reaction exerted a marked catalytic effect and considerably increased the yields of acids formed (494). The nitriles themselves are reported to be obtainable from the mixed sodium cyanide–copper cyanide reagent in the absence of water (217). The efficacy of copper catalysts has been similarly observed in the conversion of chlorobenzene to benzonitrile by zinc cyanide. Similarly, the use of copper, nickel, or cobalt halide catalysts is stated to give high yields at 300°C. in 4 hr., while less than 50 per cent yields are obtained with the zinc cyanide alone (565). von Braun observed that bromo derivatives of high-boiling aromatic hydrocarbons are smoothly converted to the nitriles in very high yield by treatment with a slight excess of cuprous cyanide at 260°C. (76). This method, later called the Rosenmund–von Braun synthesis, has been studied in detail by Koelsch and Whitney (315, 319), who found that the reaction is autocatalytic. Thus, *p*-bromotoluene is only 15 per cent converted at 250°C. in 60 min. but 75 per cent converted in 90 min. Addition of a small amount of a nitrile to the reagents largely eliminates this induction period. Copper sulfate in small amounts also has a marked catalytic effect, while hydroquinone retards the reaction. This observation led to the hypothesis that only the divalent copper ion can react with the aryl halide to form a stable complex. The following mechanism has been proposed (319):

$$ArX + Cu^{++} \rightleftharpoons [ArX \rightarrow Cu]^{++}$$
$$Cu^{+} + [ArX \rightarrow Cu]^{++} \rightarrow Cu^{++} + [ArX \rightarrow Cu]^{+}$$
$$[ArX \rightarrow Cu]^{+} \rightarrow Ar^{+} + CuX$$
$$Ar^{+} + CN^{-} \rightarrow ArCN$$

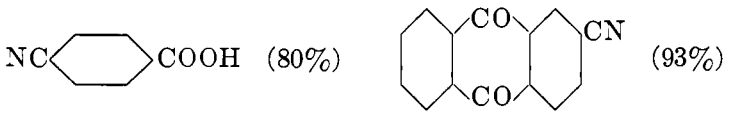
Gradual addition of the halide to the cuprous cyanide and catalysts promotes rapid conversion, since the reacting halide acts as a diluent. A considerable difference in the rate of reaction has been observed with aryl bromides of different structures. The following sequence of increasing reactivity has been established (315):



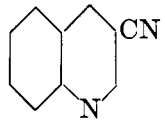
The above two techniques of aryl halide–copper cyanide reactions (with or without a basic solvent) have been discussed by Braun (78). For large-scale runs, as in commercial practice, the use of a solvent or an inert diluent is desirable to assist the dissipation of the heat of reaction. This may be either a solvent for the cuprous cyanide (pyridine, quinoline, or phenylacetonitrile) or a diluent such as nitrobenzene, dichlorobenzene, or naphthalene. In general, the use of a solvent enables the reaction to be effected at lower temperatures. Most bromo compounds will react at 130–180°C., active chlorides at 180–190°C., and inactive chlorides at 190–240°C. The following yields of nitriles are reported to be obtained from the bromides in pyridine solution (78):



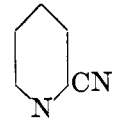
in *o*-dichlorobenzene solution:



and in nitrobenzene solution:



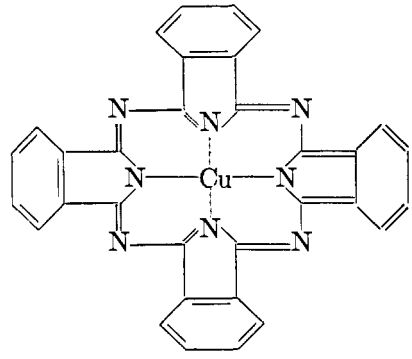
(60%)



(90%)

Active aryl chlorides such as nitrochlorobenzenes, alkoxychlorobenzenes, polyalkylchlorobenzenes, 1-chloronaphthalenes, and 1-chloroanthraquinones are converted smoothly and in high yields under similar conditions (78).

An anomalous reaction was observed by Diesbach (163), who obtained a highly colored insoluble mass when *o*-dibromoxylene was reacted with copper cyanide in pyridine solution. The nature of these materials was elucidated by Linstead and coworkers, who showed them to be phthalocyanines or tetrabenzotetraazaporphins, a class of blue organic pigments which now have acquired considerable commercial importance (506).



Similarly, *o*-bromoacetophenone and other similar ortho derivatives lead to copper complexes of tetrabenzoazaporphins (255).

As would be expected, halogen derivatives of pyridine and quinoline react smoothly without solvents. The 4-, 5-, 6-, and 8-bromoisoquinolines are reported to be converted to the nitriles in 88, 81, 25, and 53 per cent yields, respectively (567).

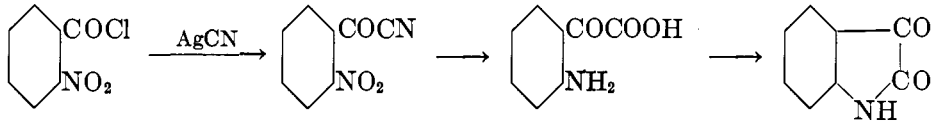
The success of other transformations in the nitrogen heterocyclic series depends on the structures involved. Thus, 2-amino-4-methyl-5-bromopyrimidine was very rapidly converted to the nitrile (465), while 2-methyl-4-hydroxy-5-bromo-6-ethoxymethylpyrimidine was completely inert (372). On the other hand, 1-methyl-4-nitro-5-chloroglyoxaline was so reactive that an 85 per cent yield was obtained by the action of potassium cyanide in absolute alcohol (510).

3. Acid halides

As noted earlier, the first nitrile of recognized constitution to be synthesized was benzoyl cyanide, which Wöhler and Liebig made in 1832 by the distillation of benzoyl chloride over mercuric cyanide (609). The cyanides of mercury, silver (280a, 430), and copper (440, 565a) have continued to be the most useful reagents

for the conversion of aroyl or acyl halides to the corresponding nitriles. When benzoyl chloride and dry cuprous cyanide are heated at 220–230°C. for 1.5 hr., a 60–65 per cent yield of benzoyl cyanide is obtained (440). The *o*-, *m*-, and *p*-phthalyl cyanides have been similarly prepared in 30–50 per cent yields by the action of mercuric chloride (49).

The method is equally applicable to the aliphatic series, but the lower-boiling acyl chlorides must often be treated with metallic cyanides under pressure. The acyl bromides are more reactive than the chlorides. Thus, acetyl bromide and cuprous cyanide are converted in 77 per cent yield to pyruvonitrile after 2 hr. on the steam bath, while acetyl chloride undergoes no reaction in 8 hr. (283). This reaction is applicable to a variety of types of halides, such as pentaacetylgluconyl chloride (13), acetyl mandelyl chloride (380), and disubstituted carbamyl chlorides (618). *o*-Nitrobenzoyl chloride was used in Claisen's classic synthesis of isatin (116):



Another interesting application of the acyl cyanide synthesis is found in Bouveault's preparation of aldehydes from acid chlorides (62):

$$RCOCl \rightarrow RCOCN \rightarrow RCOCOOH \xrightarrow[-CO_2]{C_6H_5NH_2}$$

$$RCH{=}NC_6H_5 \xrightarrow{H_2SO_4} RCHO$$

Anhydrous alkali cyanides do not readily react under the above conditions (283). Most acyl cyanides, while capable of being hydrolyzed by mineral acids to α-ketoamides, are rapidly cleaved by aqueous bases to salts of the acids and hydrocyanic acid.

$$RCOCN + NaOH \rightarrow RCOONa + NaCN$$

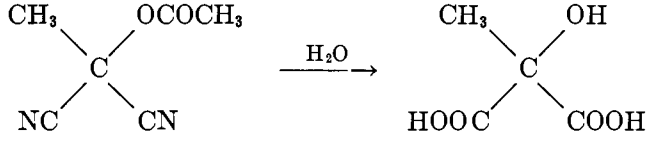
For this reason aqueous or alcoholic solutions of the basic alkali cyanides are rarely used for the conversion of acid halides to α-ketonitriles. However, by working rapidly at temperatures below 0°C. Nef was able to isolate benzoyl cyanide and alkyl cyanoformates (430). The phenylhydrazone of ethyl cyanoglyoxylate also appears to be sufficiently stable to alkaline cleavage to enable its preparation from the corresponding chloro compound and hot alkali cyanide solution (97).

Another popular synthesis of acid cyanides is the method of Claisen (113), who slowly added pyridine to anhydrous ether solutions of acid chlorides and hydrogen cyanide. The reverse order of addition favors the formation of acid cyanide dimers. The precipitation of pyridine hydrochloride from the ether solution aids in effecting high conversions.

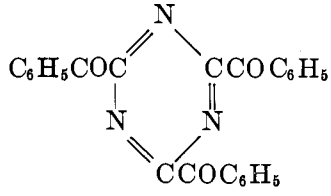
$$RCOCl + HCN + C_5H_5N \rightarrow RCOCN + C_5H_5N{\cdot}HCl$$

The method is of general application, but aroyl cyanides are prepared in much better yields (40–80 per cent) than aliphatic acyl cyanides (161, 185, 291, 386, 554).

As implied above, a complication in the preparation of acyl or aroyl cyanides is the formation of low-molecular-weight polymers. Thus, in the preparation of benzoyl cyanide the monomer, m.p. 32°C., was obtained by the action of mercuric or cuprous cyanide on benzoyl chloride (430, 578); the dimer, m.p. 99–100°C., was obtained by the action of cold sodium cyanide or pyridinium cyanide on benzoyl chloride (161, 430); while the trimer, m.p. 195°C., was obtained from benzoyl bromide and silver cyanide in ether solution (430). The structure of the dimer (which can also be made from the monomer by the action of sodium in absolute ether) is obscure. In this connection, the dimer of pyruvonitrile, obtained from acetic anhydride and potassium cyanide, was shown to have the following structure by virtue of its hydrolysis to isomalic acid (86):



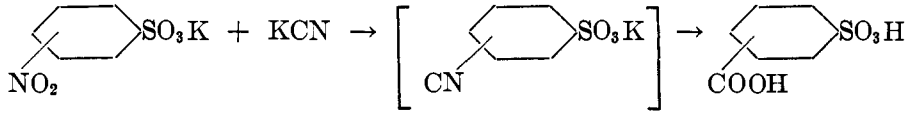
Benzoylcyanide trimer is probably 2,4,6-tribenzoyl-1,3,5-triazine.



A recent patent indicates that acyl cyanides may be prepared in low conversion but good yield by the action of acid anhydrides on hydrogen cyanide at 240–270°C. (221a).

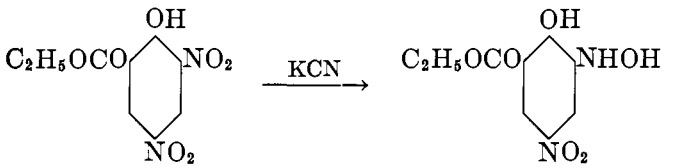
D. NITRO OR AMINO COMPOUNDS AND METAL CYANIDES

The replacement of nitro or amino groups by the action of metallic cyanides is not of general application. It will however be discussed briefly, since it appears to be an excellent preparative method for certain types of compounds. Fittig and Ramsay first observed that potassium nitrobenzenesulfonates were converted by hot aqueous potassium cyanide to a complex mixture of sulfonated carboxylic acids. The reaction must have proceeded through the unisolated nitrile intermediate (188).

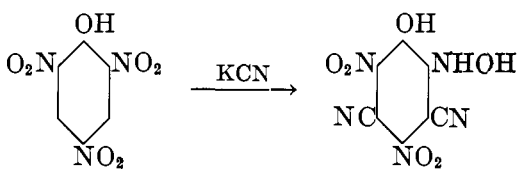


The compounds most amenable to reaction with potassium cyanide are the polynitrobenzenes and the polynitrophenols. The structure of the products of

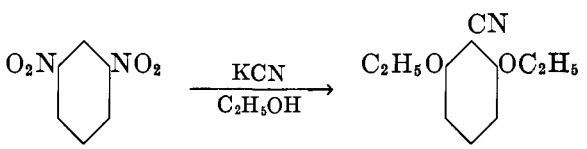
the latter reaction, loosely called "purpuric acids", has been elucidated principally by de Bruyn (93) and Borsche (57, 58). Four distinct types of action take place, often simultaneously: (*a*) reduction of a nitro group to an azo, azoxy, nitroso, or hydroxylamino group, (*b*) replacement of a nitro group by an alkoxy group if the reaction is conducted in alcoholic solution, (*c*) replacement of a hydrogen by the cyano group, and (*d*) replacement of the nitro group by the cyano group. The last type requires very reactive nitro groups. de Bruyn reports an example of an alkoxydinitrobenzonitrile being converted to a phthalonitrile derivative by the action of potassium cyanide (93). Representative examples of the other types of reactions are given below:



(57)

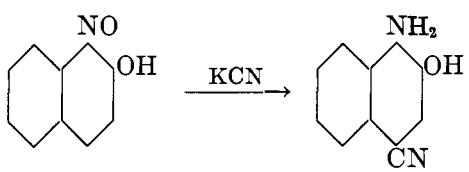


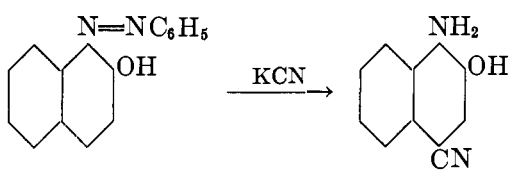
(57)



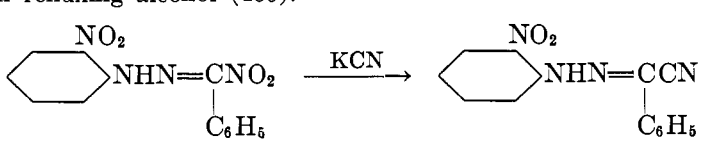
(566)

Nitroso- or azo-naphthols react similarly (65).





Reports of replacement of an aliphatic nitro group by a cyano group are rare. The *o*-nitrophenylhydrazone of phenylnitroformaldehyde reacts with potassium cyanide in refluxing alcohol (460).

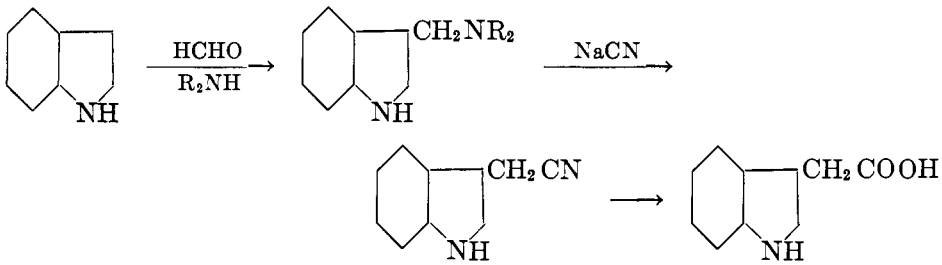


From 1,1,1-trinitroethane is formed the potassium salt of β,β-dinitropropionitrile. The reaction probably involves the formation of *asym*-dinitroethylene, followed by addition of potassium cyanide (389).

$$(NO_2)_3CCH_3 + KCN \rightarrow KNO_2 + HCN +$$

$$[(NO_2)_2C{=}CH_2] \xrightarrow{KCN} NO_2C(NO_2K)CH_2CN$$

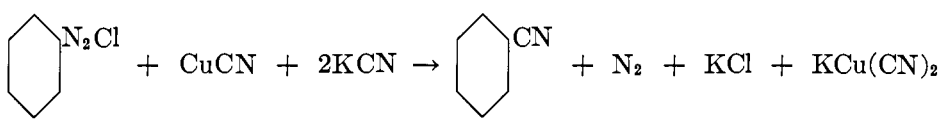
A synthesis of indoleacetic acid has recently been reported in which the key reaction is the conversion of 3-(dialkylaminomethyl)indole to indole-3-acetonitrile in 30 per cent yield by the action of sodium cyanide (505).



If this reaction proves to be typical of Mannich bases, it may be a very useful method for the introduction of a cyanomethyl group.

E. DIAZONIUM HALIDES AND METAL CYANIDES (SANDMEYER SYNTHESIS)

The preparation of aromatic nitriles by the reaction of cold solutions of diazonium salts with a cuprous cyanide–potassium cyanide solution was discovered by Sandmeyer in 1884 (507).



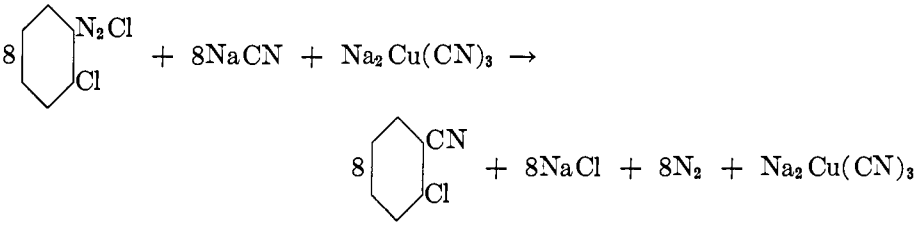
The Gattermann modification involving the use of an alkali cyanide and metallic copper was stated to be feasible (208), but apparently has not been widely adopted as a preparative method. Korczynski found in 1920 that the use of the double salt obtained from potassium cyanide and nickel cyanide gives equivalent or slightly better yields and purer products than the standard Sandmeyer technique (156, 326, 327, 499). This is one of the few instances in which a Sandmeyer reaction succeeds in the absence of cuprous salts. However, the cyanides of cobalt, iron, chromium, zinc, and numerous other metals are not effective.

Clarke and Reade found that the reaction could be effected in neutral or slightly basic solution. By neutralizing the excess acidity of the diazonium solution before addition to the cyanide solution slightly better yields are sometimes obtained and the liberation and loss of hydrogen cyanide by excessive acidity are avoided (118). Diazonium or tetrazonium borofluorides are converted to nitriles by treatment with the cyanide reagent (497).

Subsequent developments have been in the direction of decreasing the ratio of copper cyanide to diazonium compound. By the reaction of the diazonium solution with a sodium cupriammonium cyanide (prepared from copper sulfate, ammonium hydroxide, and sodium cyanide), Hagenest was able to reduce the consumption of both copper and sodium cyanide (234, 285). Yields of 65 per cent of benzonitrile and 83 per cent of *p*-tolunitrile based on the following equation are claimed:

$$3C_6H_5N_2Cl + Na_3Cu(CN)_5NH_3 \rightarrow 3C_6H_5CN + 3NaCl + \tfrac{1}{2}(CN)_2 + CuCN + NH_3$$

Still greater efficiencies are stated to have been accomplished in recent German industrial practice, simply by the use of excess sodium cyanide. The following reaction was conducted at 16°C. at a pH of 7 in 75–80 per cent yields.



Furthermore, acidification of the cyanide solution after removal of the product permitted a 90 per cent recovery of cuprous cyanide (576).

In recent years the mechanism of the Sandmeyer and Gattermann reactions has been the subject of polemic discussions, the principal question being whether the diazonium halide reacts through an aryl free radical or through an entirely ionic mechanism. The non-ionic *syn-* and *anti*-diazocyanides (now thought by Hodgson (269) to have isonitrile and nitrile structures, respectively) are probably not intermediates in the preparation of nitriles, as originally assumed by Hantzsch (507). In studies on the decomposition of the diazocyanides by copper powder in non-polar solvents, Stephenson and Waters found that the reactive *syn*-compound gave only traces of the nitrile and considerable reduction to aryl and diaryl hydrocarbons. In polar solvents, such as alcohol, an equilibrium between the *syn*-diazocyanide and the diazonium salt was thought to exist. Decomposition with copper in this medium gave somewhat larger quantities of the nitrile whose precursor must have been the salt $[ArN_2]^+CN^-$ (540). In a normal diazonium halide–cuprous cyanide reaction the salt is probably in the form of a copper complex, $[ArN_2]^+[Cu(CN)_2]^-$. In the mechanism proposed by Waters, a non-ionic decomposition of the cation proceeds through the aryl free radical in the following manner (586):

$$Cu^+ + [Ar{:}N{:}{:}{:}N{:}]^+ \rightarrow Cu^{++} + Ar\cdot + N_2$$

$$Ar\cdot + CN^- \rightarrow ArCN + e$$

$$e + Cu^{++} \rightarrow Cu^+$$

An alternative mechanism, involving ionic reactions of complex double salts of the type $[(ArN_2)Cu_2]X_3$, has been recently discussed in detail by Hodgson (269a).

Practical laboratory procedures for the synthesis of nitriles by the Sandmeyer method are given by Weygand (591) and Clarke and Reade (119). The principal variations are in the manner of preparing the fresh cuprous cyanide solution. A method of preparing dry cuprous cyanide which can be kept indefinitely and used as needed by dissolving in sodium cyanide solution has been published recently. The method also avoids loss of cyanide through evolution of cyanogen (31).

$$2CuSO_4 + 2NaCN + NaHSO_3 + H_2O \rightarrow 2CuCN + 2NaHSO_4$$

Occasionally, difficultly convertible compounds will react if the diazonium compound is added to a refluxing solution of the cyanide (17).

A few aromatic amino compounds such as *o*-aminobenzaldehyde and its derivatives (106), *o*-aminophenol (499), and 2-methyl-3-aminofuran (541) could not be converted to the nitrile by the Sandmeyer technique. However, literally hundreds of nitriles of widely varying structure have been prepared in this manner. A few selected types are listed in table 2 to illustrate the general non-interference of extraneous substituents even when in the ortho position.

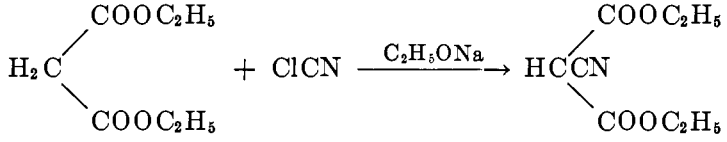
F. ORGANOMETALLIC COMPOUNDS AND CYANOGEN DERIVATIVES (GRIGNARD SYNTHESIS)

The first reaction of organometallic compounds and cyanogen derivatives was reported in 1868 by Gal, who obtained propionitrile by treating diethylzinc with cyanogen chloride (205).

$$(C_2H_5)_2Zn + 2ClCN \rightarrow 2C_2H_5CN + ZnCl_2$$

Frankland and Graham conducted a similar reaction with cyanogen in 1880 (195), and shortly afterwards Calmels extended the reaction to triethylaluminum (102). These syntheses, however, proved to be of theoretical rather than practical interest.

The reaction of cyanogen chloride with the sodium derivative of malonic ester to give ethyl cyanomalonate was reported by Haller in 1879 (236):



The reaction has been extended to the synthesis of cyanoform, $CH(CN)_3$, from malononitrile (241, 516) and of ethyl α-cyano-β-ketobutyrate from acetoacetic ester (238). A more detailed study of the malonic ester reaction indicates that it may be conveniently effected by passing gaseous cyanogen chloride into a re-

fluxing alcoholic solution of the salt. At 12–15°C., the principal products are the ester of ethylmalonic acid and sodium cyanate. The best yields (80–90 per cent) of a purer product are obtained with the dry sodium derivative and cyanogen chloride in anhydrous ether. The use of cyanogen bromide results only in

TABLE 2

Preparation of nitriles from diazonium halides

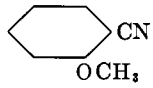
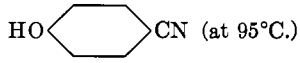
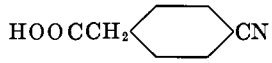
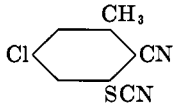
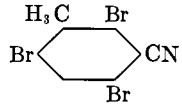
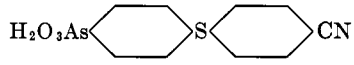
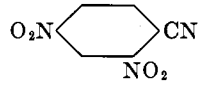
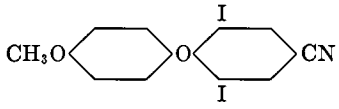
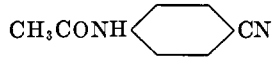
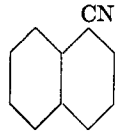
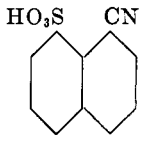
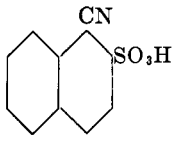
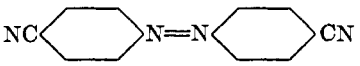
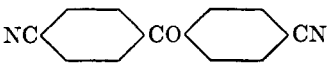
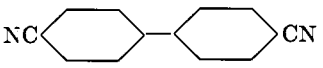
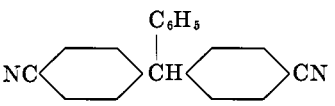
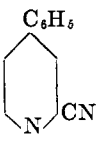
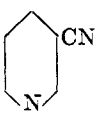
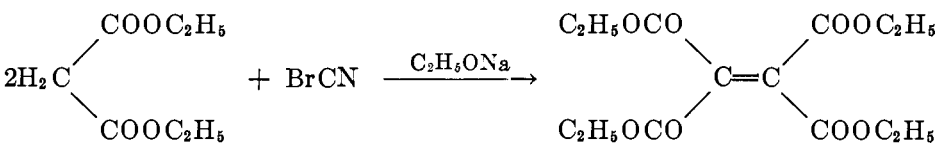
PRODUCT	YIELD	REFERENCE
	per cent	
	80	(326)
	70	(17)
	50	(290)
	"Very good"	(262)
	48	(589)
	32	(165)
	85	(546)
		(244)
	69	(55)
	78	(499)

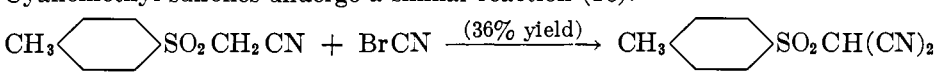
TABLE 2—*Concluded*

PRODUCT	YIELD	REFERENCE
	per cent	
	77	(64)
	92	(64)
	45	(17)
	68	(17)
	66	(156)
	5	(17)
		(100)
	50	(48)

the formation of tetracarbethoxyethylene, while cyanogen iodide gives the saturated analogue (402).



Cyanomethyl sulfones undergo a similar reaction (16).



The silver salt of diethyl cyanomalonate has been converted by cyanogen chloride to the dicyanomalonate (402).

Sodium derivatives of acetylenic compounds undergo an analogous metathetical reaction. Moureu and Delange in 1901 found that sodium phenylacetylide was converted to phenylpropiolonitrile by the action of cyanogen, while cyanogen bromide gave only the bromo derivative (412).

$$C_6H_5C{\equiv}CBr \xleftarrow{BrCN} C_6H_5C{\equiv}CNa \xrightarrow{(CN)_2} C_6H_5C{\equiv}CCN$$

In 1911 Grignard applied the versatile organomagnesium reagent that bears his name to the above reactions (222). Together with his coworkers (223, 225) he found that the reaction with cyanogen halides invariably took two simultaneous courses, resulting in the formation of a halide and a nitrile. In the latter case, the mechanism is assumed to involve the same type of intermediates that have been isolated in the reaction of Grignard reagents with nitriles.

$$RMgX + X'CN \longrightarrow RX' + MgXCN$$

$$RMgX + X'CN \longrightarrow \left[\begin{array}{l} X' \\ | \\ RC{=}N{-}MgX \end{array}\right] \xrightarrow{H_2O} \begin{array}{l} X' \\ | \\ RC{=}NH \end{array} \xrightarrow{-HX'} RCN$$

With primary aliphatic, acetylenic, or aryl Grignard reagents, cyanogen chloride leads primarily to the formation of nitriles, together with minor amounts of the chlorides (226). Secondary, alicyclic, and tertiary aliphatic reagents, on the other hand, lead largely to the formation of chlorides.

$$(CH_3)_2CHMgBr + ClCN \longrightarrow \underset{\text{(67 per cent)}}{(CH_3)_2CHCl} + \underset{\text{(9 per cent)}}{(CH_3)_2CHCN}$$

$$C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HMgBr + ClCN \longrightarrow \underset{\text{(47 per cent)}}{C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCl} + \underset{\text{(10 per cent)}}{C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCN}$$

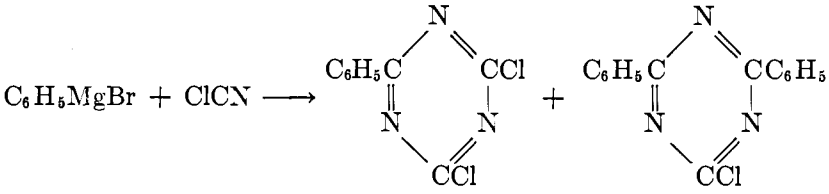
$$+ \underset{\text{(5 per cent)}}{C_6H_5\underset{\displaystyle H_3C}{\underset{|}{C}}H\underset{\displaystyle CH_3}{\underset{|}{C}}HC_6H_5}$$

$$(C_6H_5)_2CHMgBr + ClCN \longrightarrow \underset{\text{(42 per cent)}}{(C_6H_5)_2CHCl} + \underset{\text{(8 per cent)}}{(C_6H_5)_2CHCN}$$

$$+ \underset{\text{(5 per cent)}}{(C_6H_5)_2CHCH(C_6H_5)_2}$$

Cyanogen bromide and cyanogen iodide lead almost entirely to the organic halogen compounds with all types of reagents. This reaction, incidentally, has proven useful for the conversion of unsaturated Grignard reagents to unsaturated halides (chlorine or bromine cannot be used without addition to the olefinic linkage). By dropping the Grignard reagent into a solution of cyanogen chlo-

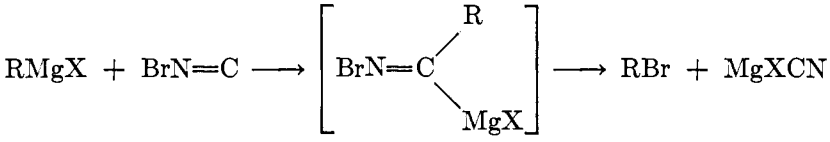
ride, 55–80 per cent yields of benzonitrile, α-naphthonitrile, anisonitrile, phenylpropionitrile, amylpropiolonitrile, and other similar compounds have been obtained (222, 225, 227, 228). In the presence of hydrogen chloride, the reaction leads to phenylchlorotriazines (444).



If the Grignard reagent is present in excess during the reaction, formation of a diketone will result. For example, *o*-ditolylketone was formed in yields of 70 per cent based on cyanogen chloride and over 50 per cent based on the Grignard reagent when the latter was present in excess (224).

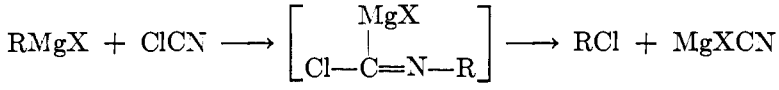
Cyanogen chloride reacts with butylmagnesium bromide to give slightly higher yields of nitrile (47 per cent) than when dibutylmagnesium is used (34 per cent) (130).

Grignard hypothesized that the difference between the behavior of cyanogen chloride and that of cyanogen bromide or iodide was due to the predominant existence of the latter two compounds in the isocyanide form, C=N—X (223).

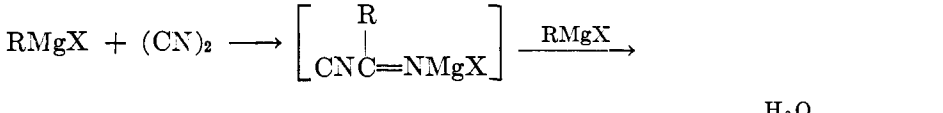


The difference between the action of primary and of tertiary reagents was more vaguely explained on the basis of a preferred "affinity" of a tertiary radical for the halogen.

It is known, however, that certain tertiary alcohols and their derivatives will add to organic nitriles in an abnormal fashion, with the resultant formation of *N*-substituted amides, while primary alcohols lead in the normal fashion to imino ethers and esters. It seems more probable, therefore, that a tertiary Grignard reagent would add in abnormal fashion to cyanogen chloride to produce an intermediate of the following type:



In view of the limitations of the reaction with cyanogen halides, it was natural to turn to the use of cyanogen. Blaise had used these reagents in 1901 but the sole products obtained were ketones (50).



However, by using the above-mentioned technique of keeping the cyanogen in excess, Grignard was able to obtain the nitriles as products (222, 223, 224). The yields were not quite as good as those obtained with cyanogen chloride for primary aliphatic and aromatic Grignard reagents. However, secondary and alicyclic reagents were found to give nitriles in 30–60 per cent yields. This technique is especially valuable, since nitriles of this type are not easily obtained in good yield by other direct syntheses.

Dimethyl cyanamide has been reported to react with benzylmagnesium chloride to give phenylacetonitrile in addition to the normal amidine, but only the latter is obtained from benzylmagnesium bromide (579).

$$C_6H_5CH_2MgCl + (CH_3)_2NCN \longrightarrow (CH_3)_2NC(=NH)CH_2C_6H_5 + C_6H_5CH_2CN + (CH_3)_2NH$$

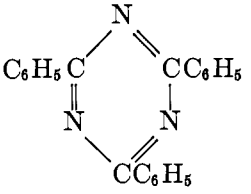
III. Cyanogenation of Aromatic Compounds

A. The Friedel–Crafts–Karrer Synthesis

Friedel and Crafts in 1878 extended their technique of acetylation of aromatic hydrocarbons with anhydrous aluminum chloride catalysts to include cyanogen chloride as a reagent (198).

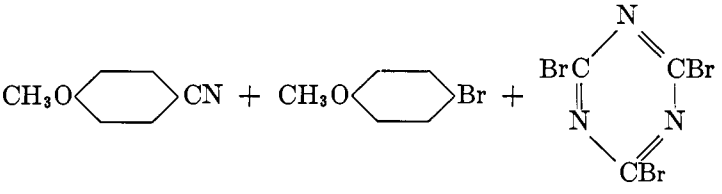
$$C_6H_6 + ClCN \xrightarrow{AlCl_3} C_6H_5CN + HCl$$

In their hands, the yield of benzonitrile was very poor and considerable amounts of high-boiling complex by-products were formed. A little later Scholl and Nörr studied the reaction of cyanogen bromide and benzene in carbon bisulfide solution and found that the principal product was the trimer of benzonitrile, *sym*-triphenyltriazine or cyaphenin (519).



When the reaction was extended to more reactive compounds such as anisole, only 4 per cent of *p*-methoxybenzonitrile was formed together with some trimer, about 30 per cent of *p*-bromoanisole, and some cyanuryl bromide.

$$CH_3OC_6H_5 + BrCN \xrightarrow[CS_2]{AlCl_3}$$



Further investigation revealed that benzonitrile was obtained when benzene was treated with mercuric fulminate and anhydrous aluminum chloride, whereas the use of hydrated aluminum chloride yielded benzaldehyde oxime (518).

Degrez, working in Friedel's laboratory, observed that the use of cyanogen in place of cyanogen chloride gave rise to benzonitrile upon distillation of the reaction complex (152). When the reaction complex was hydrolyzed with dilute acids, however, it was found that benzoyl cyanide was the principal product, some benzil being obtained also (578).

$$C_6H_6 + (CN)_2 \xrightarrow{AlCl_3} \left[C_6H_5C(=NH)CN + C_6H_5C(=NH)C(=NH)C_6H_5 \right] \xrightarrow{heat} C_6H_5CN$$

$$\left[\text{above} \right] \xrightarrow{H_2O} C_6H_5COCN + C_6H_5COCOC_6H_5$$

The value of the Friedel–Crafts synthesis as a preparative method did not become apparent until Karrer examined the reaction in 1919 (303, 304). His technique differed from that of earlier workers only in that finely ground aluminum chloride and freshly prepared cyanogen bromide were employed. These simple precautions led to the preparation of benzonitrile in 69 per cent yield, whereas three-week-old cyanogen bromide led exclusively to the formation of the trimeric form. Phenol ethers gave even better yields. The reaction is also applicable to hydrocarbons such as toluene, acenaphthene, and anthracene. Phenanthrene, however, is unreactive (408). Thiophene is converted to the α-cyano derivative, but if both α-positions are occupied, the β-nitrile is formed (300). Furan does not undergo the reaction in satisfactory yield (312). A certain amount of the aryl bromide is formed as a by-product in all of these reactions (32). Cyanogen chloride may be used with equally satisfactory results, but cyanogen iodide is partially degraded to free iodine.

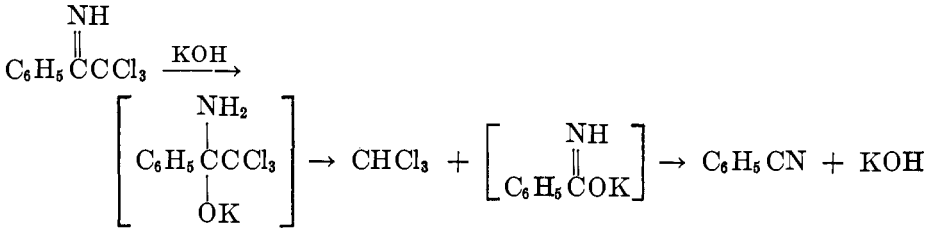
B. THE HOUBEN–FISCHER SYNTHESIS

An extremely facile method for the preparation of aromatic nitriles was introduced by Houben and Fischer in 1929 (277). These authors, while investigating the formation of aryl ketones from nitriles, noted that trichloroacetonitrile led to the expected intermediate, the ketimine hydrochloride. This intermediate was hydrolyzed by dilute acids in the normal fashion to the trichloromethyl aryl ketone, but treatment with potassium hydroxide led to the aromatic nitrile in excellent yield.

$$C_6H_6 + CCl_3CN \rightarrow C_6H_5C(=NH\cdot HCl)CCl_3 \xrightarrow{acids} C_6H_5COCCl_3$$

$$C_6H_5C(=NH\cdot HCl)CCl_3 \xrightarrow{KOH} C_6H_5CN + CHCl_3$$

Houben has stated that the alkali acts catalytically by the following mechanism, which involves the potassium salt of the pseudo amide as an intermediate:



Trichloroacetonitrile appears to be a highly specific reagent, as alkaline hydrolysis of the ketimines from dichloroacetonitrile and chloroacetonitrile leads only to the ketone. The conditions and catalysts needed for formation of the intermediate ketimine depend on the reactivity of the aromatic compound. Phenols and their ethers require only dry hydrogen chloride, while the more inert hydrocarbons require the addition of the chlorides of zinc or aluminum. The intermediate ketimine need not be isolated, and the use of ammonia gas in the degradation step inhibits ketone formation and gives improved yields.

Since the $-CCl_3$ group commonly behaves as a pseudo-halogen, the over-all reaction resembles the Friedel–Crafts synthesis. More widespread adoption of this method as a synthetic technique is probably dependent upon the future availability of trichloroacetonitrile.

The products and yields obtained from some typical aromatic compounds and trichloroacetonitrile are listed in table 3 (277).

IV. Addition of Hydrogen Cyanide

A. Addition of hydrogen cyanide to olefinic and acetylenic compounds

The addition of hydrogen cyanide to simple olefins does not take place satisfactorily, although propionitrile has been isolated by passing ethylene and hydrogen cyanide through an ozonizer or silent electric discharge (104). Recent patents describe the formation in low yields of higher homologues at 250–350°C. and 10–100 atm. pressure in the presence of metal catalysts (557). Trimethylacetonitrile is obtained in 46 per cent yield from isobutylene and hydrogen cyanide at 350–400°C. over alumina gel (244a). The highly reactive diolefin, allene, is reported to add hydrogen cyanide at 425°C. over a zinc oxide catalyst to give 20 per cent conversion and 55 per cent yields of a mixture of nitriles consisting predominantly of methacrylonitrile and lesser amounts of *cis*- and *trans*-crotononitriles (99). The use of aluminum chloride catalyst enabled Wieland and Dorrer to cause 1,1-diphenylethylene to add hydrogen cyanide. Considerable dimerization and reduction of the hydrocarbon occurred concurrently. The chloroaldimine was hypothesized as the intermediate.

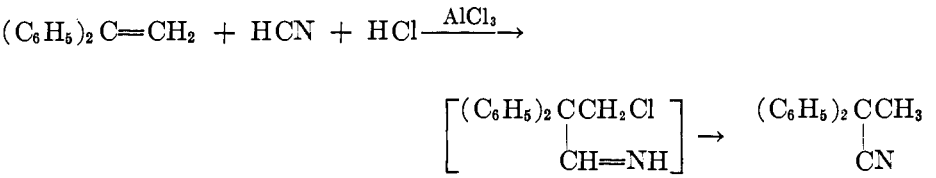
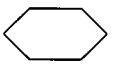
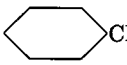
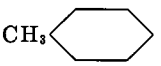
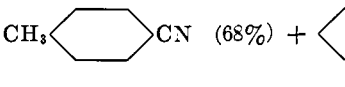
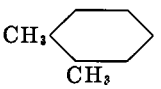
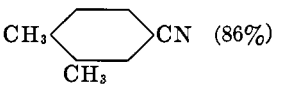
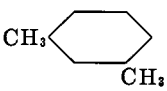
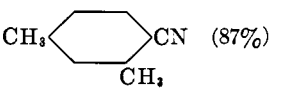
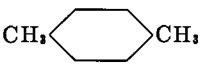
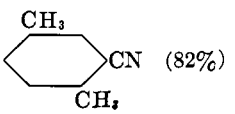
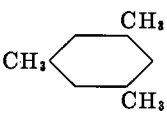
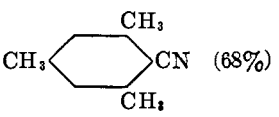
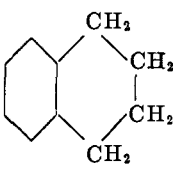
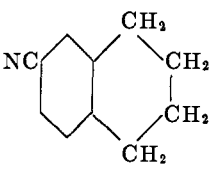
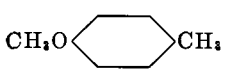
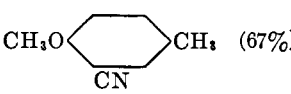
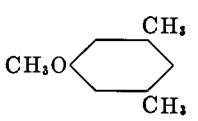
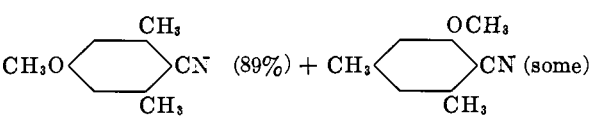
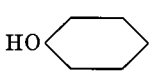
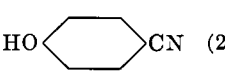
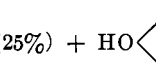
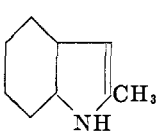
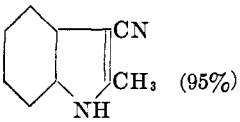
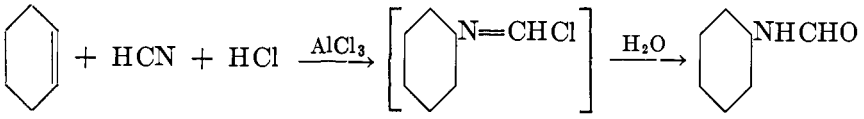


TABLE 3

Nitriles prepared with trichloroacetonitrile

REAGENT	PRODUCTS AND YIELDS
	 (69%)
	 (68%) + (15%)
	 (86%)
	 (87%)
	 (82%)
	 (68%)
	 (65%) and some α-isomer
	 (67%)
	 (89%) + (some)
	 (25%) + 
	 (95%)

Under similar conditions, stilbene gave low yields of an unidentified basic compound, while cyclohexene added hydrogen cyanide in an abnormal fashion to give a 30 per cent yield of *N*-cyclohexylformamide (598).



Butadiene also reacts with hydrogen cyanide under the influence of a strong acidic catalyst such as boron trifluoride, but the structures of the products have not been elucidated (129). A recent patent describes the formation of 3-pentenonitrile in 21 per cent yield from butadiene and hydrogen cyanide at 90–100°C. in an aqueous acidic ammonium chloride–cuprous chloride solution.

$$CH_2{=}CHCH{=}CH_2 + HCN \rightarrow CH_3CH{=}CHCH_2CN$$

Isoprene and cyclopentadiene react similarly (523a).

The addition of hydrogen cyanide to acetylene was observed in 1911 when a 5 per cent yield of succinic acid was formed from a mixture of calcium carbide, potassium cyanide, and dilute sulfuric acid (132). Although a purely thermal vapor-phase reaction of acetylene and hydrogen cyanide leads to a complex mixture of bases including pyrrole, pyridine, aniline, and quinoline (396), succinonitrile and some acrylonitrile are obtained in about 60 per cent yield at 355°C. over cadmium and magnesium oxide catalysts (104).

$$CH{\equiv}CH + HCN \rightarrow CH_2{=}CHCN \xrightarrow{HCN} CNCH_2CH_2CN$$

An early development in the vapor-phase process included the use of alkali or alkaline earth catalysts at 400–500°C., a procedure which enabled the intermediate acrylonitrile to be isolated in about 10 per cent yield (35). It has been demonstrated recently that these conditions actually produce acrylonitrile in much higher yields and that the low recovery of product was caused by secondary reactions promoted by basic by-products. Thus 70 per cent yields are obtained by condensing the product gases in acetic acid or monosodium hydrogen phosphate solution (170). Similar yields of acrylonitrile are stated to be obtained when the oxides of zinc, cadmium, or magnesium are employed as catalysts (535). A novel process involves the simultaneous reaction of ammonia and methane to form acetylene and hydrogen cyanide. The latter two compounds then combine to give acrylonitrile (171).

The most satisfactory reaction conditions involve the use of a Nieuwland-type catalyst,—a concentrated aqueous solution of cuprous chloride and ammonium chloride (346, 503). This process has been operated very successfully in commercial production and about 25,000,000 pounds of acrylonitrile were reported to have been produced in Germany in 1944. Acetylene and hydrogen cyanide in a 10:1 ratio are passed through a rubber-lined catalyst chamber containing a liquid mixture of cuprous chloride (65 parts), ammonium chloride (35 parts), concentrated hydrochloric acid (2 parts) in water (56 parts) held at 70–90°C.

Yields of acrylonitrile of 80–95 per cent based on hydrogen cyanide are obtained. By-products include 4 per cent acetaldehyde, 1 per cent chloroprene, 4 per cent 1-cyanobutadiene, 2 per cent lactonitrile, and traces of acetylene polymers (103, 247).

The addition of hydrogen cyanide to vinylacetylene proceeds by a 1,4-addition mechanism, the intermediate undergoing a prototropic rearrangement to 1-cyanobutadiene. This is in contrast to the 1,4-addition of hydrogen chloride, followed by an anionotropic rearrangement resulting in 2-chlorobutadiene (127).

$$CH{\equiv}CCH{=}CH_2 + HCN \rightarrow [CH_2{=}C{=}CCH_2CN] \rightarrow CH_2{=}CHCH{=}CHCN$$

$$\xrightarrow{HCl} [CH_2{=}C{=}CCH_2Cl] \rightarrow CH_2{=}CClCH{=}CH_2$$

The addition of hydrogen cyanide to ketene was first reported by Deakin and Wilsmore in 1910 (150), although later investigators were unable to duplicate the results (283). Further study of the reaction has indicated that alkaline catalysts and relatively low temperatures are required. A by-product, acetyl cyanide dimer, is also obtained.

$$HCN + CH_2{=}C{=}O \rightarrow [CH_3COCN] \xrightarrow{CH_2=C=O}$$

$$CH_2{=}C(CN)COCOCH_3 \xrightarrow{HCN} CH_3C(CN)COCOCH_3$$

The reaction is best carried out in a solvent at −50°C. to 30°C. in the presence of a tertiary amine or alkali metal acetate. A variation in yields of 8–82 per cent for α-cyanovinyl acetate and 5–72 per cent for acetyl cyanide dimer are obtained, depending on the conditions of the reaction. High yields of the first product are favored by acetic anhydride as a solvent and low reaction temperatures (299, 350, 577). The structure of acetyl cyanide dimer, which had been previously prepared from potassium cyanide and acetic anhydride or from monomeric pyruvonitrile by the catalytic action of sodium, has been established by hydrolysis to isomalic acid (86, 350). The intermediate pyruvonitrile is obtained by reaction in the vapor phase at 200–400°C. (476).

Diphenylketene fails to give an adduct with hydrogen cyanide in ether or in pressure tubes, but the effect of alkaline catalysts apparently has not been investigated (219).

An olefinic double bond is made highly susceptible to hydrogen cyanide addition by an alkoxy or acyloxy substituent. Thus, vinyl ethers of methyl, ethyl, butyl, and octadecyl alcohols are reported to add hydrogen cyanide in good yield in pyridine solution at 100–150°C. (34).

$$CH_2{=}CHOR + HCN \rightarrow CH_3CH(OR)CN$$

The use of stronger bases or primary and secondary amines results in poorer yields.

Vinyl acetate and related compounds react similarly at lower temperatures (25–60°C.) in the presence of tertiary amine or alkali metal cyanide catalysts. The exothermic reaction (25.5 kg.-cal. per mole) is promoted by the presence of acetaldehyde and gives 90–95 per cent yields (174, 239, 344).

$$CH_2{=}CHOCOCH_3 + HCN \rightarrow CH_3CH(CN)OCOCH_3$$

The addition of hydrogen cyanide to the double bond of an α,β-unsaturated acid or its derivatives proceeds very readily. The addition of hydrogen cyanide to crotononitrile was observed by Claus in 1878 (120).

$$CH_3CH{=}CHCN + HCN \rightarrow CH_3CH(CN)CH_2CN$$

In 1903, Lapworth demonstrated that the reaction required basic catalysis; under these conditions he developed a method which has become a very useful synthesis for a large variety of succinic acid derivatives (265, 352, 354).

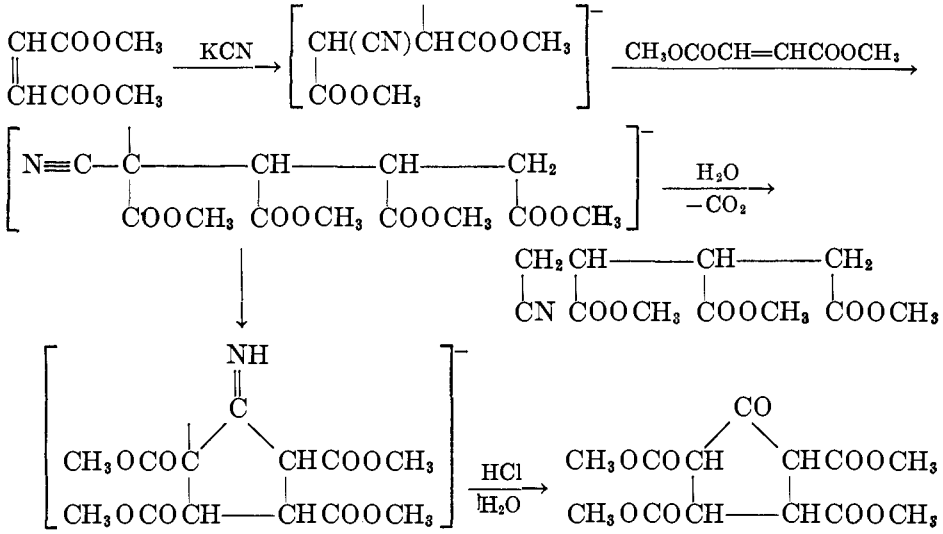
In absolute methanol as solvent Michael and Weiner have isolated the potassium salt of the adduct derived from benzalmalonic ester, although they failed to recognize the ionic nature of the reaction (399).

$$C_6H_5CH{=}C(COOCH_3)_2 + KCN \rightarrow C_6H_5CH(CN)C(COOCH_3){=}C(COCH_3)OK$$

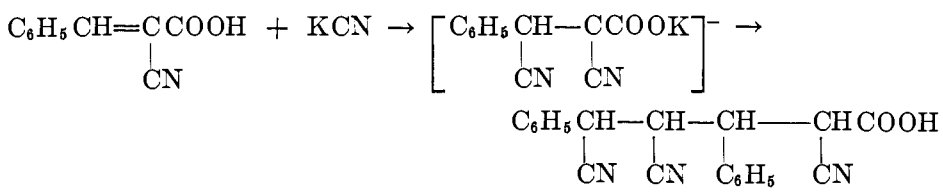
The mechanism has been shown by Ingold and coworkers to be initiated by attack of the cyanide ion at the β-carbon (essentially a 1,4-addition to the conjugated C=C—C=O system). As such it is entirely analogous to the Michael addition of alkali salts of malonic esters. It differs from additions of compounds like hydrogen bromide in that hydrogen cyanide acts as a nucleophilic reagent. The cyanide ion is strongly attracted to the β-carbon atom of the double bond because of the greatly decreased electron density at that location. This situation is due to electron withdrawal and polarization toward the α-carbon under the influence of the carbonyl group (53, 98, 168).

In general, additions proceed with greater ease and in higher yield if the reacting acrylic acid, ester, or nitrile is substituted in the α-position by another negative group (carbalkoxy, cyano, or phenyl), while the accumulation of substituents in the β-position lowers the yield (168, 265, 399). The presence of a negative substituent in the β-position favors the occurrence of side-reactions. Thus, from potassium cyanide and methyl fumarate is obtained an intermediate which undergoes a Michael-type addition to a second molecule of fumaric ester. This product is either partially saponified and decarboxylated if water is present

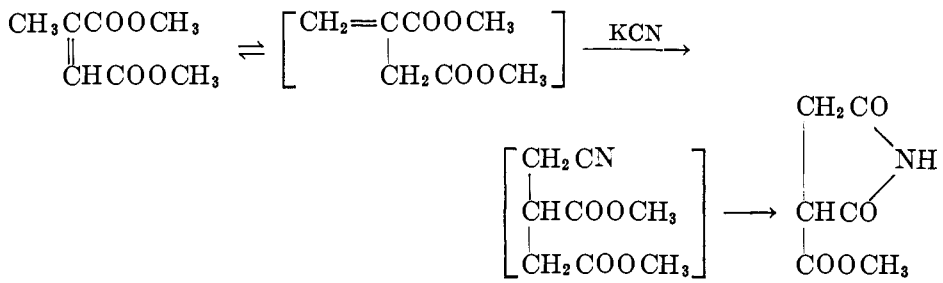
or undergoes a Dieckmann condensation with the formation of a cyclopentanone derivative in absolute methanol (399).



α-Cyanocinnamic acid is converted by a similar mechanism to 3,5-diphenyl-2,4,5-tricyanovaleric acid (560).



Ethyl itaconate quantitatively forms the expected cyanomethylsuccinic ester (275). However, methyl citraconate apparently isomerizes to the itaconic ester before addition. The final product is the methyl ester-imide of tricarballylic acid (399).



The basicity of the reaction is increased by the formation of alkali hydroxides. If carried out in the presence of water this usually results in at least partial

saponification of an ester or nitrile group. Decarboxylation frequently follows, as in the preparation of phenylsuccinonitrile from ethyl α-cyanocinnamate (415).

$$C_6H_5CH{=}\underset{\displaystyle CN}{\overset{|}{C}}COOC_2H_5 + NaCN + H_2O \rightarrow C_6H_5\underset{\displaystyle CN}{\overset{|}{C}}HCH_2CN + NaHCO_3 + C_2H_5OH$$

This hydrolysis and decarboxylation may be diminished by the presence of acetic acid (614).

$$CH_3CH_2CH{=}\overset{\displaystyle COOC_2H_5}{\overset{\diagup}{\underset{\displaystyle COOC_2H_5}{\overset{\diagdown}{C}}}} + KCN \xrightarrow[\text{(62 per cent yield)}]{CH_3COOH} CH_3CH_2\underset{\displaystyle CN}{\overset{|}{C}}H{-}\underset{\displaystyle COOC_2H_5}{\overset{|}{C}}HCOOC_2H_5$$

The alkali may also induce cleavage of a formyl group, as in the quantitative conversion of the half-aldehyde of maleic acid to succinic acid (179).

$$CHOCH{=}CHCOONa \xrightarrow{KCN} HOOCCH_2CH_2COOH + HCOOH$$

2-Cyano-3,4-diphenyl-4-crotonolactone is reported to be inert toward hydrogen cyanide addition (376).

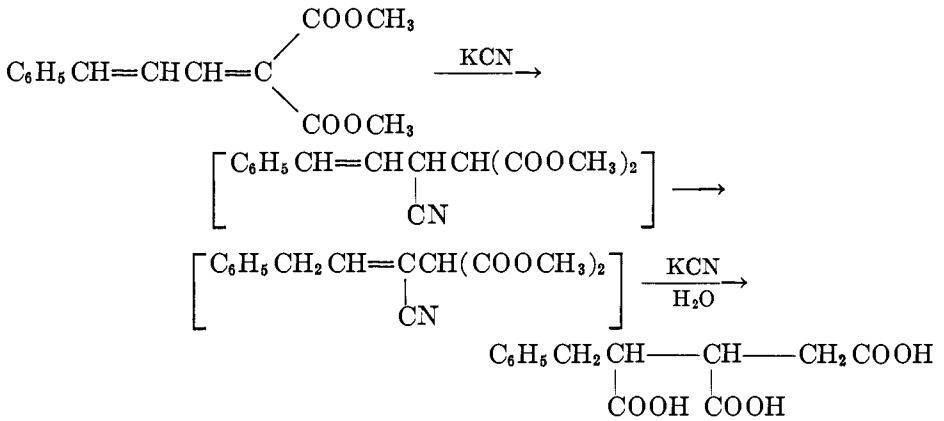
α,β-Triple-bonded compounds such as phenylpropiolic esters add two molecules of hydrogen cyanide with concurrent saponification of the ester group and decarboxylation. The intermediate α-cyanocinnamate was not isolated, but phenyl succinonitrile was obtained in 20 per cent yield (124, 399).

$$C_6H_5C{\equiv}CCOOC_2H_5 \xrightarrow{KCN} \left[\underset{\displaystyle CN}{\overset{|}{C_6H_5CH}}{=}CHCOOC_2H_5\right] \xrightarrow{KCN} \underset{\displaystyle CN}{\overset{|}{C_6H_5CH}}CH_2CN$$

The intermediate mononitrile has been isolated in fair yield from methyl propiolate (343).

$$CH{\equiv}CCOOCH_3 + HCN \rightarrow CNCH{=}CHCOOCH_3$$

Cinnamalmalonic ester reacts with 1 mole of potassium cyanide, with the ultimate formation of styrylsuccinic acid, an α,β-addition (560). The tricarboxylic acid obtained by use of an excess of cyanide was shown to be 4-phenyl-1,2,3-butanetricarboxylic acid, which resulted from two such α,β-additions made possible by an intermediate prototropic shift of the double bond (168).

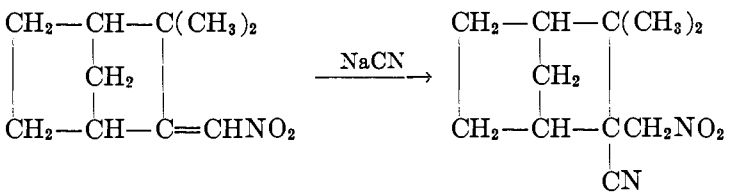


In the absence of water the predominant product is one formed by a Michael addition of the first intermediate to unchanged cinnamylidenemalonic ester (399).

The presence of an acid or ester group is not essential for the success of this addition, since α,β-unsaturated nitriles, sulfones, or nitro compounds react with equal facility. For example, acrylonitrile is converted by the action of sodium cyanide in aqueous solution at 80°C. to succinimide in 70 per cent yield (614), while the use of anhydrous hydrogen cyanide in the presence of 1–3 per cent of sodium cyanide at 30–50°C. leads to succinonitrile in 95 per cent yield (385a, 530a). Alkylidenemalononitriles yield saturated trinitriles in excellent yield (134).

$$RCH{=}C(CN)_2 \xrightarrow{KCN} RCH(CN)CH(CN)_2$$

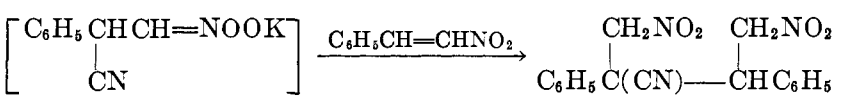
Reactions of this type are reversed at high temperatures (477). Nitrocamphene is converted by alcoholic sodium cyanide to nitroisocamphanyl cyanide (366).



Buckley has shown recently that the lower nitroölefins react similarly in yields ranging from 15 to 90 per cent (96a).

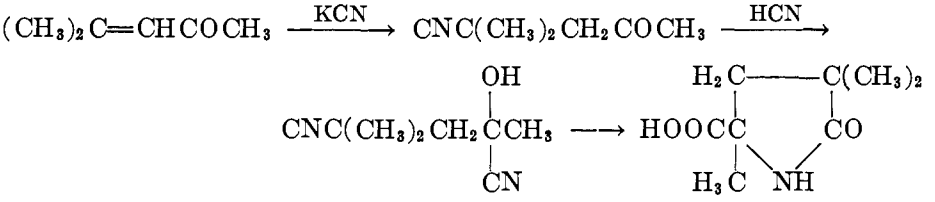
β-Nitrostyrene reacts with potassium cyanide, but the intermediate compound apparently undergoes a condensation of the Michael type with a second molecule of the nitroölefin. The structure of the resultant product, 2,3-diphenyl-2-cyano-1,4-dinitrobutane, was established by degradation to α,β-diphenylsuccinic acid (274).

$C_6H_5CH{=}CHNO_2 + KCN \rightarrow$



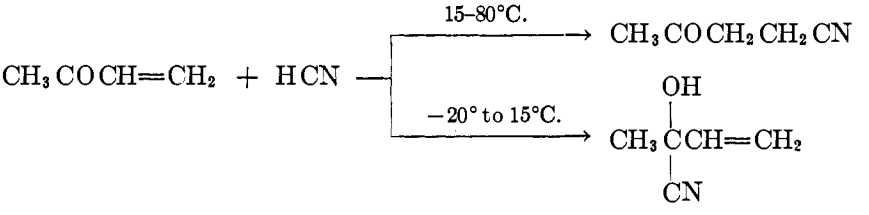
Vinyl sulfones are converted by the same reagent to the β-cyanoethyl sulfones (345).

The reaction of alkali cyanides with a large number of α,β-unsaturated ketones has been investigated. Thus, mesityl oxide and phorone are converted in excellent yield to the ketonitrile and the ketodinitrile, respectively. In the first case, the presence of both potassium cyanide and hydrogen cyanide causes the intermediate ketonitrile to be further converted to its cyanohydrin. This is easily hydrolyzed at higher temperatures to the lactam of mesitylic acid (352).



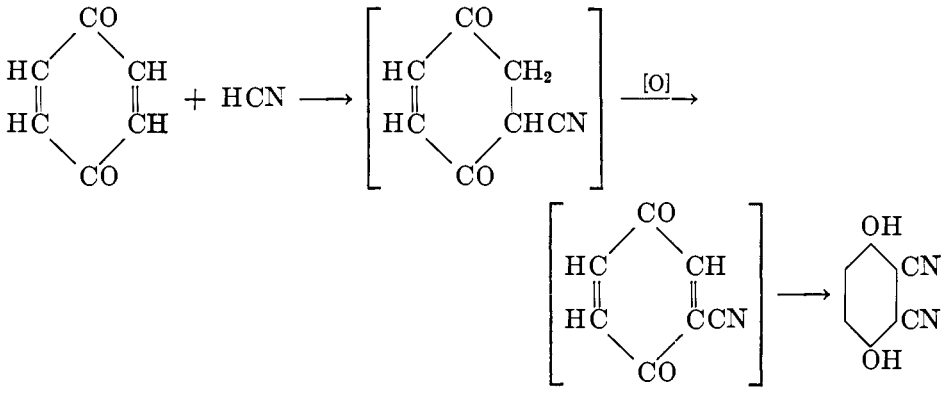
α-Alkylideneacetoacetic esters similarly form monolactones of tricarboxylic acids (280).

In the case of methyl vinyl ketone it is stated that the course of the addition depends largely upon the experimental conditions. At 15–80°C. the predominant reaction product is levulinonitrile, while at −20°C. to 15°C. in the presence of a diluent the cyanohydrin of methyl vinyl ketone is formed (358).



Since aldehydes react more rapidly and completely with hydrogen cyanide than do ketones, cyanohydrin formation is the exclusive reaction with α,β-unsaturated aldehydes (399, 474). Benzalacetophenone is converted in aqueous alcohol to α-cyanobenzylacetophenone in 95 per cent yield (280), but in absolute methanol the chief products are complex cyclic compounds of incompletely elucidated structures which arise through Michael condensations of the intermediate salt and a second mole of unsaturated ketone (399). The p,p'-dimethoxychalcones, however, are reported to be completely unreactive toward potassium cyanide (142).

Two moles of hydrogen cyanide are added to quinone with the formation of 2,3-dicyanohydroquinone. Part of the quinone is simultaneously converted to hydroquinone while oxidizing the first of the unisolated mononitrile intermediates. The absence of 2,5-dicyanohydroquinone in the product is explained by the strong activating influence of the nitrile group in the second intermediate (9).



Although earlier investigators were unable to effect the addition of cyanogen halides to olefins, it has recently been demonstrated that cyanogen chloride will add to acetylene to give β-chloroacrylonitrile in good yields. An acidified aqueous cuprous ammonium chloride solution is used as the catalyst (172a).

$$ClCN + CH{\equiv}CH \rightarrow ClCH{=}CHCN$$

B. ADDITION OF HYDROGEN CYANIDE TO ALDEHYDES AND KETONES

Synthetic mandelonitrile has been known since 1832, when it was prepared from benzaldehyde and hydrogen cyanide by Winkler (602). In 1867 Gautier and Simpson isolated the first aliphatic cyanohydrin, lactonitrile, by allowing acetaldehyde to stand for several days with hydrogen cyanide (211). The method was adapted with erratic results for the preparation of other aldehyde cyanohydrins, but attempted preparations of ketone cyanohydrins were unsuccessful. Urech observed in 1872 that the latter could be formed when equivalent quantities of ketone and alkali cyanide were acidified with acetic or hydrochloric acid (571). Kiliani later noted the catalytic influence of ammonia in preparing carbohydrate cyanohydrins (310). However, it was not until 1903 that Lapworth showed that the rate of reaction was proportional to the concentration of the cyanide ion and that alkali or ammonium cyanides were the active catalysts in the modifications of Urech and Kiliani (352).

Urech's method is still popular because of its simplicity and gives a 77–78 per cent yield in the case of acetone cyanohydrin (136).

Ultee's method involves the addition of anhydrous hydrogen cyanide to the aldehyde or ketone containing a trace of alkali cyanide at about 0°C. Equilibrium is rapidly established under these conditions, and the product is then stabilized by acidification before distillation or recrystallization. Low temperatures favor high conversion (less dissociation of the cyanohydrin). The method is highly successful for most aldehydes and ketones (284, 570), and simplifies the isolation and purification of the cyanohydrin, since water and inorganic salts are present only in trace amounts. In large-scale runs, a little crude product from a previous run is stated to prevent an induction period which may be dangerous because of the highly exothermic nature of the reaction (164).

Another procedure which is a very convenient laboratory method is the sodium bisulfite modification of Pape (450).

$$RCHO + NaHSO_3 \longrightarrow RCHOHSO_3Na \xrightarrow{NaCN} RCHOHCN + Na_2SO_3$$

Several advantages are claimed for this technique. Hydrogen cyanide fumes are largely avoided since the reaction is always basic. Benzoin formation is minimized in the case of aromatic aldehydes, although some *N*-benzylidenemandelamide by-product has been isolated in the preparation of mandelonitrile (521). Very pure cyanohydrins are obtained directly if the crystalline intermediate bisulfite addition compound is washed with alcohol and benzene to remove the carbonyl compound and dried *in vacuo* to remove sulfur dioxide before treatment with a cold saturated solution of alkali cyanide (47). This technique cannot be used for a number of ketones which react with hydrogen cyanide but not with sodium bisulfite. A slight modification of the bisulfite method employs sulfurous acid (4).

The procedure of Albert, in which the aldehyde is dissolved in a water-immiscible solvent and shaken with a mixture of ammonium chloride and an alkali cyanide, is reported to be advantageous for certain aldehydes (4, 111). For example, *o*-nitrobenzaldehyde is converted to the cyanohydrin without the usual formation of tarry by-products. Curiously, the Zelinsky–Stadnikoff formation of aminonitriles does not take place in this two-phase system (see page 237).

An advantageous method for the preparation of lower water-soluble cyanohydrins involves an interchange between a ketone cyanohydrin and an aldehyde. The equilibrium, which is quickly obtained in the presence of a trace of alkali, favors relatively high conversions to the aldehyde cyanohydrin.

$$RCHO + R'_2C\begin{matrix}OH\\ \diagup\\ \diagdown\\ CN\end{matrix} \rightleftharpoons R'_2CO + HCN + RCHO \rightleftharpoons RCHOHCN + R'_2CO$$

This procedure avoids the handling of anhydrous hydrogen cyanide and simplifies the isolation procedure by eliminating aqueous solutions of inorganic salts. The preparation of glycolonitrile, which has a particularly unfavorable distribution coefficient for extraction from aqueous solution by immiscible organic solvents, is obtained from methyl ethyl ketone cyanohydrin and formalin in 70–83 per cent yields (341, 414).

Lapworth's reaction mechanism for cyanohydrin formation (352) involves the attack of the nucleophilic cyanide ion at the point of lowest electron density, which is the carbonyl carbon atom. The intermediate then absorbs a proton from the solution.

$$R_2CO + CN^- \rightleftharpoons R_2C\begin{matrix}O^-\\ \diagup\\ \diagdown\\ CN\end{matrix} \xrightarrow{H^+} R_2C\begin{matrix}OH\\ \diagup\\ \diagdown\\ CN\end{matrix}$$

The first step is bimolecular and the rate-determining reaction, since the over-all reaction velocity is independent of hydrogen-ion concentration (3). Stewart's study of the formation and behavior of cyanohydrins in non-polar solvents has indicated that the reaction can also proceed by a non-ionic mechanism. Under these conditions a cyanohydrin–amine complex is thought to be the active catalyst (361, 542).

TABLE 4

Dissociation constants and thermodynamic stability of cyanohydrins

BENZALDEHYDES RC_6H_4CHO R =	$K \times 10^2$	ΔF
		kg.-cal.
H (99%)	0.47	−3.1
o-Nitro	0.07	−4.2
m-Nitro	0.27	−3.4
p-Nitro	1.81	−2.3
o-Chloro	0.10	−4.0
m-Chloro	0.25	−3.5
p-Chloro	0.49	−3.1
o-Methoxy	0.26	−3.5
m-Methoxy (97%)	0.43	−3.2
p-Methoxy	3.12	−2.0
o-Hydroxy	1.67	−2.4
m-Hydroxy	0.48	−3.1
p-Hydroxy	7.66	−1.5
m-Methyl	0.60	−3.0
p-Methyl	1.03	−2.7
p-Dimethylamino	39.00	−0.5

METHYL KETONES CH_3COR R =	$K \times 10^2$	ΔF
Methyl (97%)	3.05	−2.0
Ethyl	2.65	−2.1
n-Propyl	3.55	−1.9
n-Butyl	3.20	−2.0
Isopropyl	1.55	−2.4
tert-Butyl	3.10	−2.0
Benzyl	2.15	−2.2
β-Phenylethyl	3.50	−2.0
γ-Phenylpropyl	3.60	−1.9

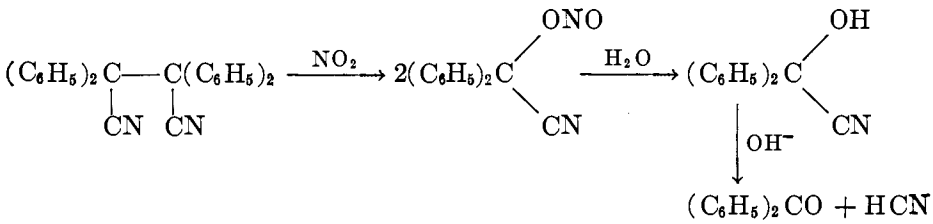
PHENYL KETONES C_6H_5COR R =	$K \times 10^2$	ΔF
		kg.-cal.
Methyl (46%)	130.	+0.2
Ethyl	60	−0.3
n-Propyl (55%)	90	−0.05
n-Butyl	115	+0.1
n-Amyl	130	+0.2
n-Hexyl	145	+0.2
Isopropyl	25	−0.8
Isobutyl	155	+0.3
Isoamyl	155	+0.3
tert-Butyl (91%)	9	−1.4
Cyclohexyl	40	−0.6
Phenyl	No reaction	

CYCLIC KETONES	$K \times 10^2$	ΔF
Cyclopentanone	1.49	−2.4
Cyclohexanone	0.09	−4.1
2-Methylcyclohexanone	0.06	−4.3
3-Methylcyclohexanone	0.30	−3.4
4-Methylcyclohexanone	0.13	−3.9
Cycloheptanone	7.96	−1.5
Menthone	6.54	−1.6
α-Hydrindone	610.0	+1.1
α-Tetralone	806.0	+1.0
Fluorenone	146.	+0.2
Camphor	No appreciable reaction	
Anthrone	No appreciable reaction	
Xanthone	No appreciable reaction	

The conversions obtainable in cyanohydrin formation are largely a function of the structure of the carbonyl compound and are dependent upon the degree of dissociation of the cyanohydrin at equilibrium. The equilibria of a large number of cyanohydrins were first measured by Ultee in the absence of solvents (570) and later with great precision by Lapworth and Manske in 96 per cent ethanol (353). Table 4 presents their data for the dissociation constants (K) and thermo-

dynamic stability of cyanohydrins at 20°C. The per cent of cyanohydrin present at equilibrium is given in parentheses for a few compounds.

In benzaldehyde, *o*-nitro, *o*-chloro, or *o*-methoxy substituents stabilize the cyanohydrin. These substituents have little effect in the meta position but have a marked labilizing influence in the para position. Aliphatic ketone cyanohydrins are more highly dissociated than those derived from aldehydes. Cyclization results in a strong stabilizing influence in the case of alicyclic five- and six-membered rings and a labilizing influence in the case of larger rings. Camphor does not form a cyanohydrin. Aryl alkyl ketones are converted to cyanohydrins in poor yields and diaryl ketones not at all. Benzophenone cyanohydrin, which has been prepared by an indirect synthesis, is instantly and completely decomposed by traces of a basic catalyst (608).



As mentioned earlier, the formation of cyanohydrins from α,β-unsaturated ketones is complicated by the tendency for hydrogen cyanide to add to the olefinic double bond, although no difficulty is encountered with the corresponding aldehydes (399). Cyanohydrin formation of highly enolized ketones such as α-diketones, oxaloacetic esters, and benzoyl acetic esters is usually not successful, although the dicyanohydrin of 1,3-cyclohexanedione is reported (392, 419). While acetoacetic ester readily forms a cyanohydrin, pivaloylacetic ester, $(CH_3)_3COCH_2COOC_2H_5$, does not (582). Similarly, α,α'-dibenzenesulfonylacetone, $C_6H_5SO_2CH_2COCH_2SO_2C_6H_5$, does not add hydrogen cyanide although it gives other ketone reactions (446). α-Dicarbonyl compounds such as camphor quinone and isatin react satisfactorily (80, 256).

In connection with the discussion of methathesis reactions of alkyl halides and alkali cyanides, it was pointed out that many α-haloketones behave anomalously in forming cyanoölefin epoxides rather than β-ketonitriles (see page 205). Formation of the cyanohydrins of ketones of this type is best effected by the use of Ultee's method (anhydrous hydrogen cyanide). This procedure gives excellent yields with chloroacetone and 2-chloro-3-butanone, while the bisulfite modification fails completely (284, 300).

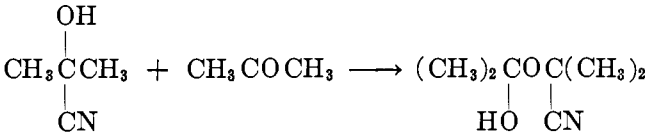
Aromatic aldehydes in the presence of catalytic amounts of potassium cyanide undergo the benzoin condensation.

$$2C_6H_5CHO \xrightarrow{KCN} C_6H_5COCHOHC_6H_5$$

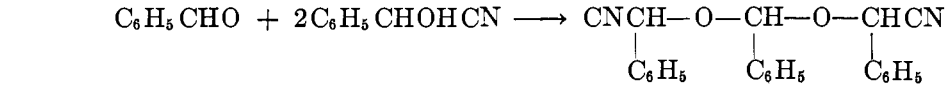
Lapworth (352) and others have felt that this reaction, which cannot be effected by other bases, is closely related to cyanohydrin formation in that the cyanide ion is the active catalyst. This view has been questioned, because the reaction

can be effected in non-ionizing solvents (407). More recent kinetic studies have shown that the reaction in these media proceeds concurrently by two mechanisms, i.e., a fast autocatalytic reaction proportional to the amount of benzoin product present and a slow heterogeneous reaction at the surface of the solid catalyst (426). Since the product benzoin may function as an ionizing solvent, Lapworth's mechanism may be partially correct.

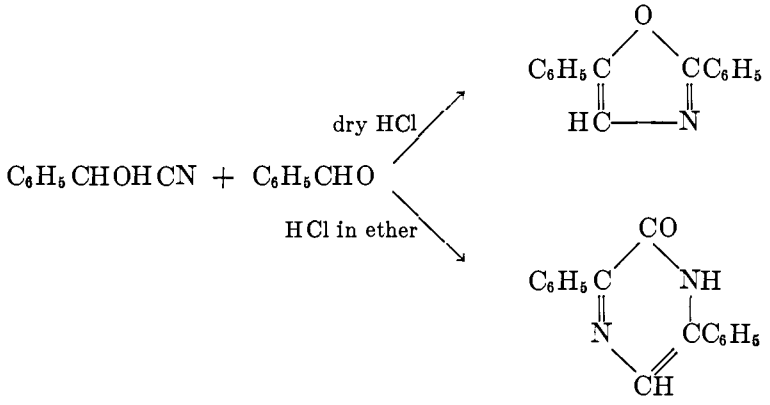
The reaction between carbonyl compounds and cyanides may take other courses which lead to contamination of the product. Under the influence of dilute acids, the cyanohydrin will form fairly stable hemiketals with unreacted ketone (569).



Considerable quantities of this by-product are often formed in the preparation of ketone cyanohydrins having high dissociation constants (419). With aldehydes a similar side reaction leads to acetal formation (545).



The latter compound is also formed through deterioration of mandelonitrile (26). The same reagents with dry hydrogen chloride lead to 2,5-diphenyloxazole (184) or 3-keto-2,5-diphenyl-3,4-dihydro-1,4-diazine (287, 292).



The above products may be formed in minor amounts in Ultee's cyanohydrin preparation when anhydrous conditions are employed. In the bisulfite method for the mandelonitrile preparation, still another by-product, *N*-benzylidenemandelamide, $C_6H_5CH{=}NCOCHOHC_6H_5$, is formed from the same reagents (521).

When the reaction is carried out in aqueous solution a certain amount of hydrolysis may be caused by the basicity of the sodium cyanide. The ammonia liberated by this hydrolysis may react with the cyanohydrin to form a variety

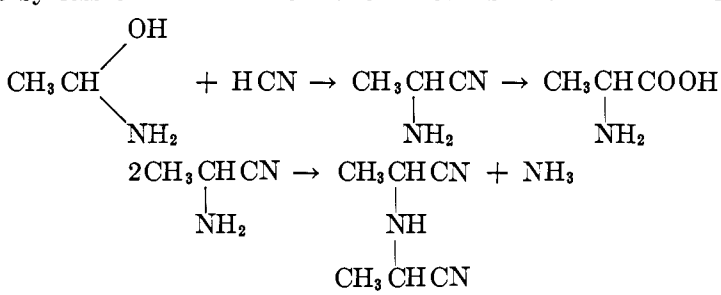
of products. Thus, Franzen allowed 1200 cc. of formalin to stand with 980 g. of potassium cyanide at room temperature and recovered 130 g. of glycolic acid, 21 g. of glycine, 60 g. of iminodiacetic acid, and 145 g. of iminotriacetic acid. The following reactions account for the formation of these materials, which were obtained in a total yield of 34 per cent (196).

$$KCN + CH_2O + H_2O \rightarrow HOCH_2CN + KOH$$
$$HOCH_2CN + KOH + H_2O \rightarrow HOCH_2COOK + NH_3$$
$$HOCH_2CN + NH_3 \rightarrow NH_2CH_2CN + H_2O$$
$$NH_2CH_2CN + KOH + H_2O \rightarrow NH_2CH_2COOK$$
$$NH_2CH_2CN + HOCH_2CN \rightarrow NH(CH_2CN)_2 + H_2O$$
$$NH(CH_2CN)_2 + 2KOH + 2H_2O \rightarrow NH(CH_2COOK)_2$$
$$NH_2CH_2CN + 2HOCH_2CN \rightarrow N(CH_2CN)_3 + 2H_2O$$
$$N(CH_2CN)_3 + 3KOH + 3H_2O \rightarrow N(CH_2COOK)_3 + 3NH_3$$

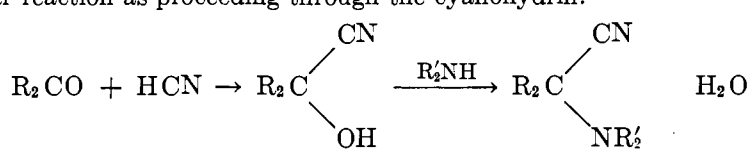
In the presence of equimolar amounts of calcium chloride the same reagents lead rapidly to the formation of hexamethylenetetramine and glycolic acid, which is precipitated as the calcium salt (323).

$$10CH_2O + 4KCN + 2H_2O \xrightarrow{CaCl_2} (CH_2)_6N_4 + 4HOCH_2COOK$$

The above reactions lead logically to a consideration of the Strecker synthesis of amino acids, which has proved to be extremely useful to synthetic organic chemists since its discovery in 1850. Strecker treated acetaldehyde ammonia with hydrogen cyanide and hydrolyzed the product to obtain alanine (549). In 1875 Erlenmeyer showed that the intermediate compound in Strecker's synthesis was the α-aminonitrile and that substantial amounts of the iminodinitrile were also formed (176). He further demonstrated that the iminodinitrile is formed by loss of ammonia from two molecules of the aminonitrile (531).



In 1880 Tiemann reversed Strecker's order of addition of reagents and caused ammonia to react with the cyanohydrin. He also extended the reaction to ketones and primary and secondary amines (562, 563). Since better yields were obtained in this manner, he preferred to regard the mechanism of the generalized Strecker reaction as proceeding through the cyanohydrin.



This difference of opinion initiated a polemic argument that has been taken up by numerous other investigators over a period of sixty years. Zelinsky and Stadnikoff supported Tiemann's mechanism and introduced the use of a mixture of an alkali cyanide and ammonium chloride as reagents for the preparation of α-aminonitriles (620). The isolation of good yields of the cyanohydrin in the non-aqueous layer of a two-phase Zelinsky–Stadnikoff reaction appears to support this view (4, 111). Sannié, in an elaborate kinetic study of the disappearance of ammonia and hydrocyanic acid from a mixture containing acetaldehyde, found that the irregular reaction rates varied between the rates expected for monomolecular and bimolecular reactions (508). He concluded, on the basis of admittedly ambiguous evidence, that the reaction proceeded by the following sequence:

$$CH_3CHO + H_2O \rightarrow CH_3CH(OH)_2$$
$$CH_3CH(OH)_2 + HCN \rightarrow CH_3CHOHCN$$
$$CH_3CHOHCN + NH_3 \rightarrow CH_3CH(NH_2)CN$$

The study of the principal reaction was confused by the regeneration of ammonia through the formation of the iminodinitrile by-product.

Although it has been demonstrated that aldimines and ketimines will add hydrogen cyanide to give α-aminonitriles (245, 404, 563), it seems improbable that this intermediate is formed in an aqueous mixture of the three reagents under mild conditions.

The original views of Erlenmeyer that the aldehyde ammonia is the intermediate has received the support of Lapworth, who notes that a simple cyanohydrin has acidity comparable to the phenols. The carbon–oxygen bond (strengthened by the cyano substituent) could not be broken in a mild metathesis reaction with ammonia or amines. On the other hand, the aldehyde ammonia has a particularly labile hydroxyl group which should be easily replaced by the cyanide ion (126). Furthermore, since camphor does not form a cyanohydrin (353), the quantitative yield of 1-anilino-1-cyanocamphane obtained from a mixture of camphor, aniline, and potassium cyanide in glacial acetic acid must have been formed through this mechanism (157). These views have received additional support in recent years by the observations of Stewart and coworkers, who have made kinetic studies on the behavior of cyanohydrins in anhydrous media. With amines as catalysts, dissociation of the cyanohydrin to the carbonyl compound and hydrogen cyanide is rapid and reversible. In the opinion of these workers the aldehyde ammonia which then forms is converted to the aminonitrile by reaction with either hydrogen cyanide or a molecule of cyanohydrin (3, 543).

From a practical point of view the Zelinsky–Stadnikoff reagent—ammonium chloride and an alkali cyanide—is popular in modern laboratory practice because of its simplicity. Yields commonly range from 30 to 50 per cent (538). The Tiemann technique of using the cyanohydrin gives very good yields when the formation of iminodinitrile is suppressed by the use of a large excess of anhydrous liquid ammonia (96, 391). With acetone cyanohydrin, yields of aminonitriles vary with the structure of the reacting amine: ammonia (80 per cent), dimethyl-

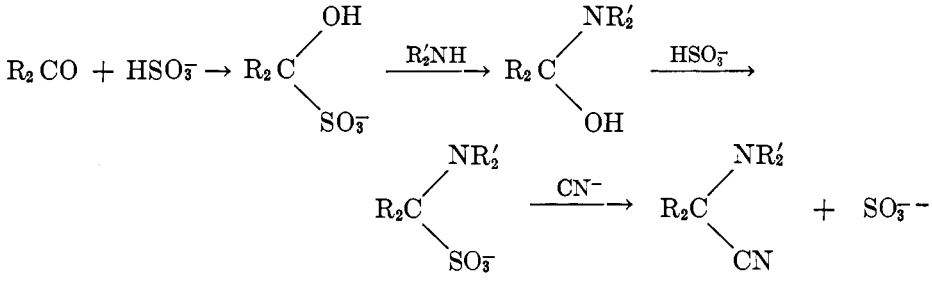
amine (87 per cent), diethylamine (58 per cent), ethylenediamine (40 per cent), cyclohexylamine (70 per cent), and aniline (92 per cent) (289). Methylaniline, however, is reported to be unreactive (420).

The use of ammonium cyanide (232, 526) or of a mixture of hydrogen cyanide and amines (125, 218) is stated to give improved yields. However, α-diketones do not give α-aminonitriles with ammonium cyanide. Benzil is quantitatively cleaved to benzamide and mandelonitrile,

$$C_6H_5COCOC_6H_5 + NH_4CN \rightarrow C_6H_5CONH_2 + C_6H_5CHOHCN$$

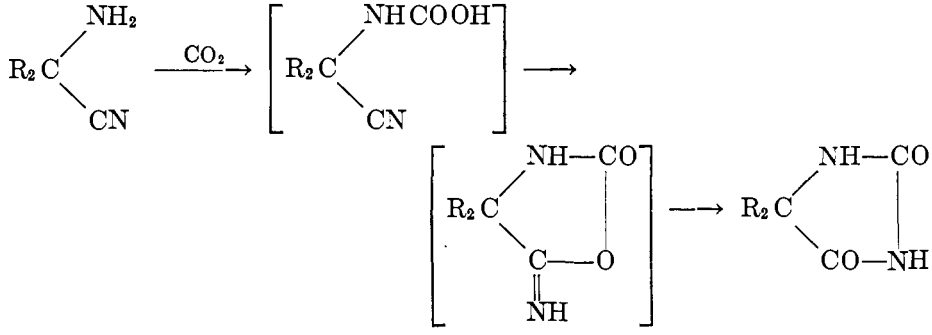
while diacetyl and phenylglyoxal form glyoxaline derivatives (141). The use of glacial acetic acid as a solvent for the reaction of potassium cyanide with the carbonyl compound and the amine gives excellent results (157, 585).

Another modification, which involves the action of an amine and potassium cyanide on the bisulfite addition compound of the aldehyde or ketone, was introduced almost simultaneously by Knoevenagel (313) and Bucherer (94). The method has been used with varying results by a number of investigators (23, 73, 420, 520). In the opinion of Stewart and Li, the mechanism is as follows (543):



Luten has found that the method is best suited to reactions of formaldehyde and lower amines, as indicated in table 5. The yields in parentheses were obtained by the hydrogen cyanide–amine technique (369).

A closely related reaction is the Bucherer synthesis of hydantoins by the interaction of a ketone, hydrogen cyanide, and ammonium carbonate. Since the product is also obtained from the cyanohydrin and ammonium carbonate or from the α-aminonitrile and carbon dioxide, the following mechanism is offered (95):



Ketone cyanohydrins give excellent yields, but aryl and alkyl aldehyde cyanohydrins do not.

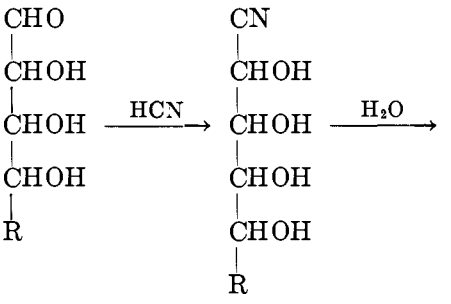
The addition of hydrogen cyanide to the carbonyl group has proved to be a very useful tool in investigations in the field of carbohydrate chemistry. The

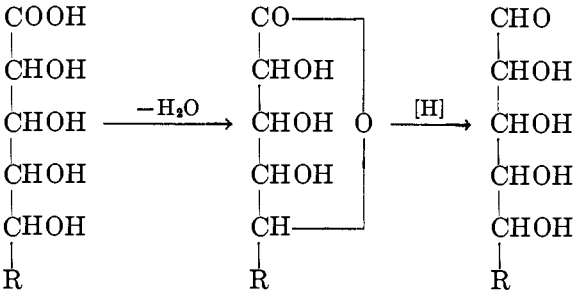
TABLE 5

α-Aminonitriles prepared from bisulfite addition compounds

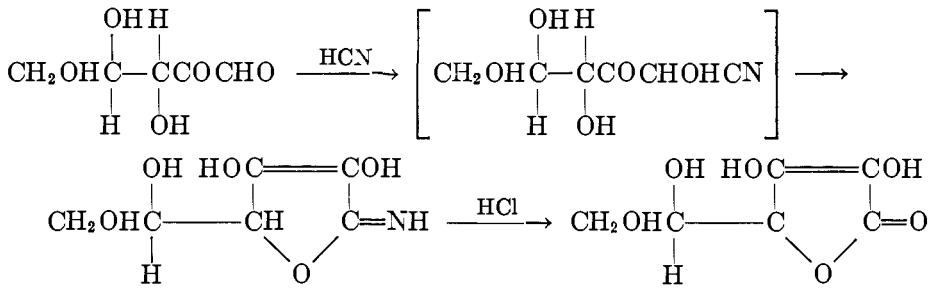
CARBONYL COMPOUND	AMINE	YIELD
		per cent
Formaldehyde	Dimethyl	45–79
Formaldehyde	Diethyl	70–75
Formaldehyde	Di-*n*-propyl	72
Formaldehyde	Diisopropyl	0 (52–65)
Formaldehyde	*n*-Butyl	75
Formaldehyde	Isobutyl	75 (45)
Formaldehyde	*n*-Amyl	84
Formaldehyde	Isoamyl	79
Formaldehyde	*n*-Octyl	0 (31)
Formaldehyde	Methyl phenyl	70–76
Acetaldehyde	Diethyl	25
Acetone	Diethyl	0 (30–39)
Benzaldehyde	Diethyl	56

well-known Kiliani–Fischer cyanohydrin synthesis (183, 310) of higher carbon sugars has been recently reviewed by Hudson (281).

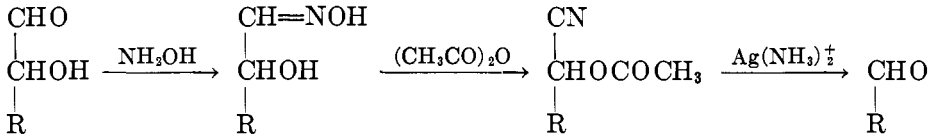




The Kiliani reaction has been applied by Haworth (253) and Reichstein (479) to the synthesis of *l*-ascorbic acid (vitamin C) from *l*-xylosone. The isolated intermediate in this case is thought to have a cyclic imino structure.



The Wohl degradation of sugars is essentially a reversal of the cyanohydrin synthesis (610).



When an aqueous solution of an aldehyde or ketone and an alkali cyanide reacts at low temperatures with benzoyl chloride, the cyanomethyl ester is obtained directly (10, 193).

$$CH_2O + NaCN \rightarrow [CNCH_2ONa] \xrightarrow{C_6H_5COCl} C_6H_5COOCH_2CN$$

This reaction, which is reminiscent of the Schotten–Baumann esterification technique, gives good yields with α,β-unsaturated aliphatic acid chlorides but not with their saturated analogues (414).

The cyanohydrin synthesis has been used as a convenient route for the conversion of aromatic aldehydes to aryl acetonitriles in good over-all yield (266).

$$C_6H_5CHO \xrightarrow{HCN} C_6H_5CHOHCN \xrightarrow{SOCl_2} C_6H_5CHClCN \xrightarrow[CH_3COOH]{Zn} C_6H_5CH_2CN$$

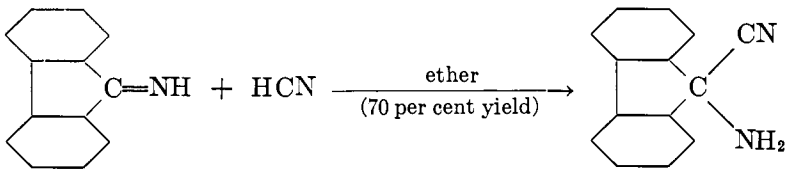
An interesting nitrile synthesis involves the action of hydrogen cyanide and lead tetraacetate upon α-keto acids. The unisolated cyanohydrin is thought to be the intermediate (23a).

$$RCOCOOH + HCN + Pb(OCOCH_3)_4 \rightarrow \left[\begin{array}{c} RCCOOH \\ \diagup\ \diagdown \\ CN \quad OH \end{array}\right] \rightarrow RCOCN + CO_2$$

The cyanohydrin reaction has also been used as an analytical tool for the estimation of formaldehyde and of carbonyl groups in sugars (367, 403).

C. ADDITION OF HYDROGEN CYANIDE TO CARBON–NITROGEN DOUBLE BONDS

As indicated in the discussion of the Strecker synthesis, hydrogen cyanide will add to the carbon–nitrogen bond of aldimines. This was first demonstrated by Tiemann, although under his aqueous alcoholic conditions it is questionable whether the aldimine or the aldehyde ammonia was the actual reagent (563). Subsequently the reaction was carried out under anhydrous conditions which precluded intermediates of the latter type (245).



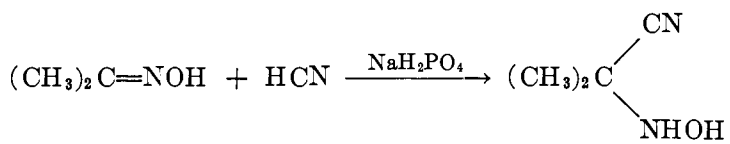
A number of other ketimines behave similarly (404, 530).

Similar additions have been effected with other derivatives of aldehydes and ketones, such as hydrazones (424), semicarbazones, and Schiff bases (221, 404, 492). Methyleneaminoacetonitrile is quantitatively converted to iminodiacetonitrile if catalytic amounts of hydrogen chloride are present (24).

$$(CH_2{=}NCH_2CN)_x + HCN \xrightarrow{(HCl)} NH(CH_2CN)_2$$

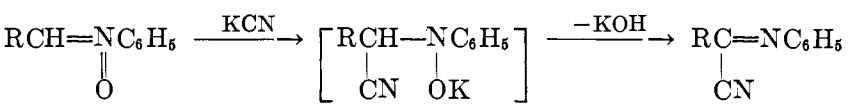
The cyanide group is always directed to the carbon atom of a carbon–nitrogen double bond because of the strongly nucleophilic character of the nitrogen atom.

The addition of hydrogen cyanide to aldoximes and ketoximes was effected by Münch in 1896 (424). His yields have been greatly improved by the use of sodium cyanide in an alkali dihydrogen phosphate buffer solution (362, 461).

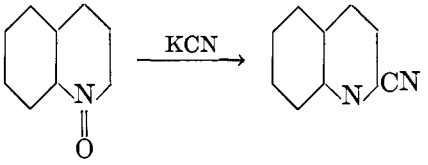


Slightly better results have been obtained by the use of aqueous hydrocyanic acid and a trace of pyridine (2). The use of strongly alkaline potassium cyanide directly usually causes dehydration of the aldoxime to the corresponding nitrile (452).

Bellavita has shown that aldonitrones, the *N*-phenyl ethers of aldoximes, add hydrogen cyanide with the loss of water to form anils of aroyl cyanides. These may be converted by alcoholysis to the anil ester or by hydrolysis to the acyl cyanide (44).



A similar reaction takes place smoothly with pernitroso derivatives of ketones (452) and with quinoline-*N*-oxide (131, 261).



Phenyl isocyanate adds hydrogen cyanide reversibly in non-aqueous solvents in the presence of alkaline catalysts to form the carbamyl cyanide. The action of aqueous potassium cyanide, however, leads to diphenylparabamide (160).

$$C_6H_5NCO + HCN \rightleftharpoons C_6H_5NHCOCN$$

$$2C_6H_5NCO + HCN(aq) \rightarrow C_6H_5N(CO{-}C{=}NH)NC_6H_5CO$$

Aryl isothiocyanates give almost quantitative yields of the thiocarbamyl cyanide even with aqueous potassium cyanide (484).

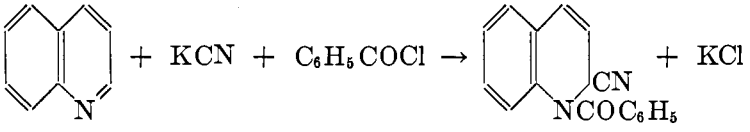
$$C_6H_5NCS + HCN \rightarrow C_6H_5NHCSCN$$

Hydrogen cyanide addition to methyl isothiocyanate must be effected in ether solution with triethylphosphine as a catalyst. Several other basic catalysts are not effective (527).

Diazomethane reacts with hydrogen cyanide to give methyl isocyanide as well as acetonitrile, which was first thought to be the sole product (27, 456).

$$CH_2N_2 + HCN \xrightarrow{-N_2} CH_3CN\ (+CH_3NC)$$

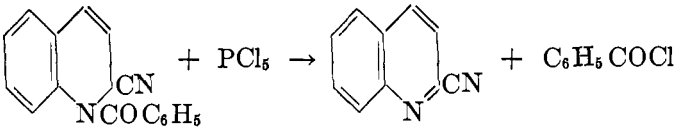
Although it is noted earlier that the reaction of benzoyl chloride, hydrogen cyanide, and pyridine constitutes a convenient synthesis of benzoyl cyanide (see page 210), Reissert discovered that quinoline, benzoyl chloride, and aqueous potassium cyanide led to the formation of 1-benzoyl-2-cyanodihydroquinoline (483).



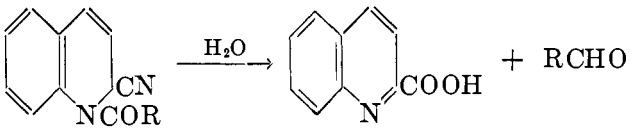
Other cyclic bases such as pyridine, benzothiazole, and acridine did not give satisfactory results, but isoquinoline forms 1-cyano-2-benzoyldihydroisoquinoline. Reissert's reaction has been variously represented as proceeding through such improbable intermediates as 1-benzoyl-2-chlorodihydroquinoline or benzoyl cyanide. Recent studies in non-aqueous solvents, however, indicate that the mechanism probably involves the addition of hydrogen cyanide to the

carbon–nitrogen double bond, followed by acylation of the resultant secondary amine.

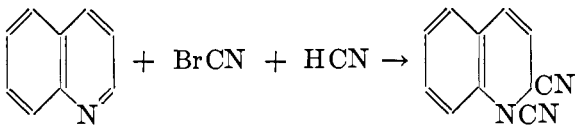
It has been observed that the reaction with potassium cyanide proceeded satisfactorily for aroyl or cinnamoyl chloride in liquid sulfur dioxide solution, but not in benzonitrile, ether, dioxane, acetone, or chloroform (616). Grosheinz and Fischer have extended the reaction to include aliphatic acid chlorides by the use of hydrogen cyanide and 2 moles of quinoline in absolute benzene solution. Yields range from 10 to 74 per cent for these compounds and from 80 to 96 per cent for aroyl chlorides (230). Treatment of Reissert's compound with phosphorus pentachloride in a diluent such as chloroform regenerates the benzoyl chloride with the formation of 2-cyanoquinoline in 55–70 per cent yields (306).



The compound may be hydrolyzed by sulfuric or hydrochloric acid to the aldehyde and quinaldic acid. This convenient aldehyde synthesis has been applied to a large number of acid chlorides in high over-all yield (230, 306, 552).

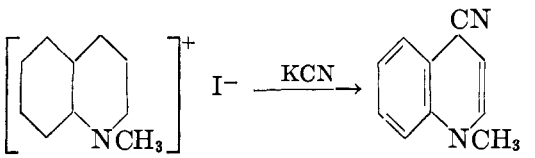


A closely related reaction is that of Mumm and coworkers, who obtained a mixture of *cis*- and *trans*-1,2-dicyanodihydroquinolines from hydrogen cyanide, cyanogen bromide, and excess quinoline in benzene solution.

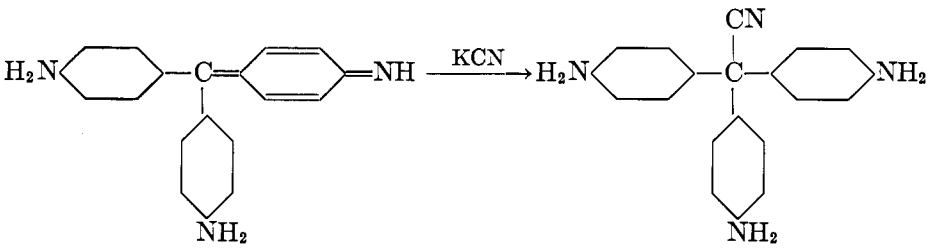


Isoquinoline gives a dicyanide, while 2-substituted quinolines react at higher temperatures to give 4-cyanoquinoline derivatives (422, 423). There are indications that a 1,4-addition of hydrogen cyanide to pyridine takes place, since traces of 4-cyanopyridine have been detected in reactions of organic halides with cuprous cyanide in pyridine solution (419).

Hydrogen cyanide has been reported to add in a 1,4 manner to quinoline methiodide (307).



Pararosaniline and hydrogen cyanide lead to the formation of the highly dissociated tris(*p*-aminophenyl)acetonitrile (360).

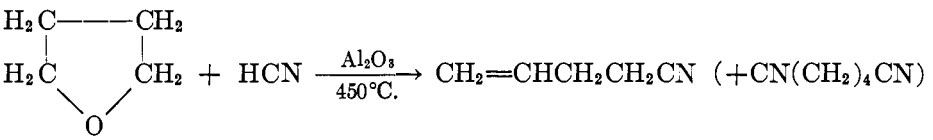


D. HYDROCYANOLYSIS OF CARBON–OXYGEN BONDS

The hydrocyanolysis of simple *aliphatic ethers* apparently occurs only in the vapor phase at elevated temperatures.

$$C_2H_5OC_2H_5 + 2HCN \rightarrow 2C_2H_5CN + H_2O$$

The preferred conditions are temperatures of 300–500°C. and dehydration catalysts such as alumina, silica, thoria, or the phosphate and borate salts of numerous metals (11, 286, 433). Tetrahydrofuran undergoes a similar reaction, forming allylacetonitrile (30 per cent), adiponitrile (8 per cent), pyridine (10 per cent), and α-aminopyridine (2 per cent)(561).



Ethylene oxide is reported to react under similar conditions to give succinonitrile (613).

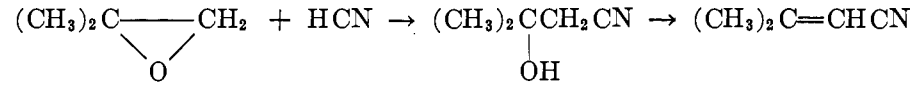
Olefin oxides of the latter type, however, react rapidly and exothermally (40–50 kg.-cal. per mole) with hydrogen cyanide at low temperature to give the corresponding cyanohydrins in nearly quantitative yield.

This reaction was first observed in 1878 by Erlenmeyer, who allowed the reagents to stand for several weeks at room temperature (175). The catalytic effect of bases was not observed until much later (181, 475). In the absence of alkaline catalysts a vigorous reaction is not initiated below about 150°C. (149).

Methods of generating hydrogen cyanide in an aqueous alkali cyanide reaction mixture involve the use of carbon dioxide gas (84) or a saturated solution of magnesium sulfate (556). Modern industrial practice, however, favors the use of anhydrous reagents in the presence of a trace of basic catalysts such as sodium cyanide. This technique was employed for the production of ethylene cyanohydrin in nearly quantitative yield on a very large commercial scale before the

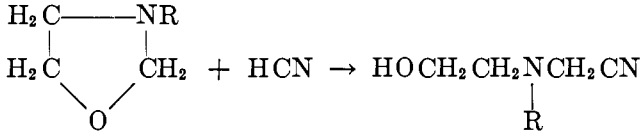
recent adoption of the direct synthesis of acrylonitrile from acetylene and hydrogen cyanide (see page 224).

With substituted olefin oxides, the direction of addition favors the production of secondary or tertiary cyanoalcohols (84, 475). This is demonstrated by the fact that 2-methylpropene epoxide gives a hydroxynitrile which is easily dehydrated on distillation to the unsaturated nitrile (84). The alternate addition product would have been a stable cyanohydrin.



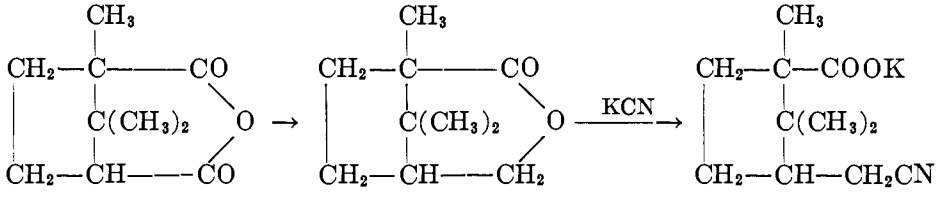
The reaction of 2-chloro-1-propanol with potassium cyanide was thought to proceed through propylene oxide as an intermediate, since β-hydroxy-*n*-butyronitrile was the product (158). Attempts to reverse the direction of addition by the use of acidic catalysts (as has been done in the addition of alcohols to olefin oxides) have not been successful (419). 2-Methyl-2,3-epoxybutyronitrile is stated to be inert toward hydrogen cyanide (215).

Certain heterocyclic compounds, such as oxazolidines, add hydrogen cyanide very easily at low temperatures (568).



The reaction of *lactones* with alkali cyanides was observed in 1886 by Wislicenus, who obtained 90–95 per cent yields of the mononitrile of homophthalic acid from the reaction of phthalide and potassium cyanide at 180–190°C. (466, 603).

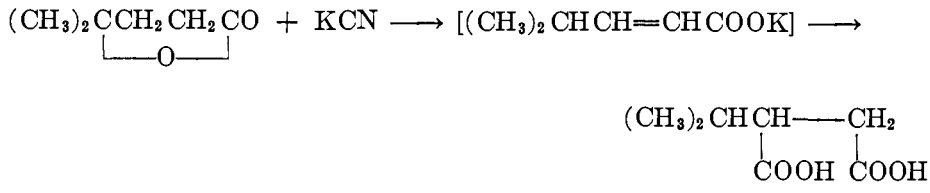
Camphoric anhydride has similarly been converted to campholide and homocamphoric mononitrile, a series of reactions which played a part in the final proof of Brett's structure for camphor (237, 500).



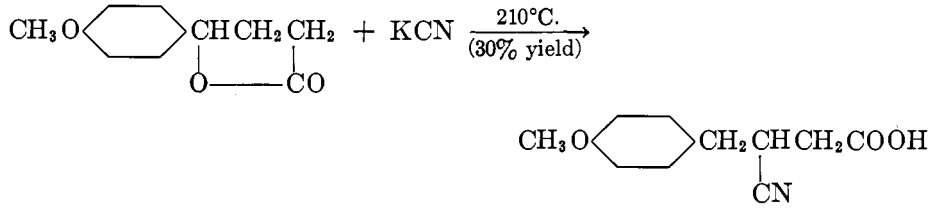
A number of other phthalide derivatives and aliphatic lactones react similarly (1, 51, 52, 328, 332).

Blaise observed that isocapro-γ-lactone gave rise to isopropylsuccinic acid instead of the expected α,α-dimethylglutaric acid (51). This material undoubtedly

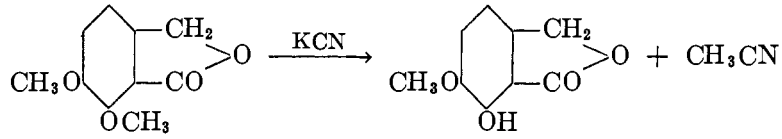
arose through formation of the α,β-unsaturated acid (by dehydration and isomerization), which added hydrogen cyanide in the normal α,β fashion.



γ-*p*-Anisyl-γ-butyrolactone undergoes a similar rearrangement before addition (464).



The rather drastic alkaline conditions of this reaction sometimes cause other side-reactions. Meconin does not react at the lactone group but does lose one of its methoxy groups (490).



(47 per cent yield)

Aliphatic esters do not appear to have been investigated. In this connection, propionitrile has been isolated in a study of the action of potassium cyanide on isobutyraldehyde in alcohol solution. Presumably it was formed by the action of potassium cyanide on ethyl isobutyrate, which arose through disproportionation and esterification of the aldehyde (555).

V. Isocyanide Isomerization and Related Syntheses

The isomerization of isocyanides to nitriles by the action of heat was first observed by Gautier in 1867 (210) in connection with his studies on the reaction of alkyl halides with metal cyanides (see page 195). Further studies by Nef indicated that ethyl isocyanide is completely converted to propionitrile in 3 hr. at 230–255°C., while phenyl isocyanide forms benzonitrile in 2 hr. at 200–220°C. (429). In 1907 Guillemard investigated the molecular weights and products of the reaction at various temperatures and found that isomerization and reversible polymerization of isocyanides proceed simultaneously. With ethyl isocyanide the polymerization reaction begins at 120°C., reaches a maximum at 160°C., and is reversed at 220°C. Isomerization to nitriles begins at 140°C. and is complete

at 240°C. These findings led to the hypothesis that the isomerization reaction proceeds through the trimer (231).

$$RNC \rightarrow (RNC)_3 \rightarrow RCN$$

The heats of combustion of isocyanides range from 15 to 20 cal. per mole higher than for the corresponding nitriles (356). The thermodynamic aspects of the structures of these two classes of compounds have been discussed by Pauling and Hendricks (454).

A number of syntheses of nitriles have been effected which utilize amines and their derivatives. Some of these reactions involve a carbon–nitrogen rearrangement of the type discussed above. Moderate yields of aromatic nitriles are obtained, but the methods are of very little value in the aliphatic series.

Pyrolysis of *N*-ethylaniline at 560°C. results in the production of a 35 per cent yield of benzonitrile, together with hydrogen and unsaturated hydrocarbons. This derivative is a more satisfactory reagent than the *N*-methyl- (8 per cent yield of benzonitrile), *N*-propyl- (24 per cent yield), *N*-butyl- (4 per cent yield), or *N*,*N*-dimethyl-anilines (4 per cent yield)(595).

$$C_6H_5NHC_2H_5 \rightarrow C_6H_5CN + H_2 + CH_4$$

Hofmann noted in 1867 that formanilide when heated with zinc dust gave rise to benzonitrile (270). This method has attracted the interest of subsequent workers, and it is stated in the patent literature that aniline is transformed by formic acid over activated carbon or silica gel at 450°C. to benzonitrile in conversions of 25 per cent. By similar techniques phenylacetonitrile is obtained from benzylamine (42 per cent conversion), *m*-tolunitrile from *m*-toluidine (40 per cent conversion and 88 per cent yield), and *o*-tolunitrile from *o*-toluidine (55 per cent conversion and 82 per cent yield)(434).

$$C_6H_5NH_2 + HCOOH \xrightarrow{-H_2O} C_6H_5NHCHO \xrightarrow{-H_2O} C_6H_5CN$$

Distillation of aniline oxalate also gives low yields of benzonitrile (271, 564).

The distillation of aryl isothiocyanates or diarylthioureas over metals such as copper, zinc, or iron produces aryl cyanides, with the simultaneous formation of metallic sulfides (432, 522, 590).

$$C_6H_5SCN + Cu \rightarrow C_6H_5CN + CuS$$

A similar result is obtained by heating bromobenzene with copper thiocyanate at 180°C. for 8–9 hr. in pyridine solution. Benzonitrile is obtained in 23 per cent yield in the presence of pyridine, together with 39 per cent of a mixture of diphenyl sulfide and diphenyl disulfide (493).

VI. Amine Dehydrogenation

Interest in the dehydrogenation of amines as a method of preparing nitriles was initiated in 1884 when Hofmann published the results of his studies of the action of bromine and aqueous alkali on the amides of carboxylic acids. With aliphatic amides of five carbon atoms or less, the principal product of the reaction is the

amine of one less carbon atom. With amides of more than five carbon atoms the resultant amine is further attacked by the reagent and, by a bromination–dehydrobromination mechanism, is converted to the nitrile.

The reaction has limitations as a preparative method because the yields are not high, reaching a maximum of 25–30 per cent with the amides of pelargonic and capric acids. Substituted ureas are by-products in the Hofmann degradation (273).

$$RCH_2CONH_2 + Br_2 + KOH \rightarrow RCH_2CONHBr + KBr + H_2O$$

$$RCH_2CONHBr + KOH \rightarrow [RCH_2CON] + KBr + H_2O$$

$$[RCH_2CON] \rightarrow RCH_2NCO$$

$$RCH_2NCO + 2KOH \rightarrow RCH_2NH_2 + K_2CO_3$$

$$RCH_2NH_2 + 2Br_2 + 2KOH \rightarrow RCH_2NBr_2 + 2KBr + 2H_2O$$

$$RCH_2NBr_2 + 2KOH \rightarrow RCN + 2KBr + 2H_2O$$

Phenylpropiolamide is a special case in which good yields of phenylacetonitrile are obtained.

$$C_6H_5C{\equiv}CCONH_2 \xrightarrow{NaOBr} [C_6H_5C{\equiv}CNH_2] \longrightarrow C_6H_5CH_2CN$$

The dehydrochlorination of alkyldichloroamines, which parallels the last phase of the Hofmann degradation, has been effected by alkalies (29, 39) and by magnesium (101).

Closely related to the above is Dakin's reaction of chloramine T (sodio-*p*-toluenesulfochloroamide) with α-amino acids. In weakly alkaline solution at 20°C. the degradation leads to the aldehyde, but in slightly stronger alkali (0.2 *N*) at 35°C. the nitrile is the principal product. Histidine, glycine, alanine, and α-aminophenylacetic acid are all converted to the nitriles in varying yields by this reaction, which is illustrated below for glutamic acid (83, 139, 140).

$$H_2NCOCH_2CHCOOH \xrightarrow[0.1\ N\ NaOH]{\text{chloramine T}} NH_2COCH_2CHO$$

$$\begin{array}{l} \quad | \\ NH_2 \end{array}$$

$$\xrightarrow[0.2\ N\ NaOH]{\text{chloramine T}} HOOCCH_2CH_2CN$$

Bamberger has observed that monopersulfuric acid oxidizes aliphatic amines to nitriles in rather low yields. Oximino acids and nitro compounds are by-products and the latter are formed exclusively in the aromatic series (28).

$$CH_3CH_2NH_2 \xrightarrow{[O]} CH_3CH_2NHOH \longrightarrow CH_3CH{=}NOH \longrightarrow CH_3CN$$

$$\begin{array}{l} \quad | \\ \quad\quad NOH \\ \quad\quad \| \\ \rightarrow CH_3COH \end{array} + CH_3CH_2NO_2$$

The vapor-phase dehydrogenation of amines was studied first by Sabatier (502) and Maihle (379) in 1917. The amine is passed over hydrogenation catalysts

such as finely divided nickel at 300–350°C. or copper at 450°C. Benzylamine forms about 30 per cent benzonitrile, together with by-product toluene which arises through hydrogenolysis of the amine.

$$C_6H_5CH_2NH_2 \begin{cases} \xrightarrow{-2H_2} C_6H_5CN \\ \xrightarrow{+H_2} C_6H_5CH_3 + NH_3 \end{cases}$$

Except for the lowest members of the series, the aliphatic amines give much better yields of nitriles, a nearly quantitative yield being obtained from isoamylamine. In general, copper was found to be a less satisfactory catalyst than nickel. Secondary and tertiary amines are pyrolyzed to olefins and nitriles.

$$((CH_3)_2CHCH_2CH_2)_2NH \rightarrow (CH_3)_2CHCH_2CN + (CH_3)_2CHCH{=}CH_2 + H_2$$

Schiff bases behave similarly, a mixture of toluene, ethylene, benzonitrile, and acetonitrile being obtained from *N*-ethylbenzaldimine.

By passing the amine and ammonia simultaneously over the catalyst, the nitrile–hydrocarbon ratio in the product is increased (36). Other catalysts for this reaction are the sulfides or arsenides of zinc and cadmium, which are effective at 500°C. (370). Although the intermediate aldimine has never been isolated, its presence was detected when the reaction vapors were diluted with steam, which caused hydrolysis to the aldehyde (401).

The formation of by-product hydrocarbons through hydrogenolysis of the amine has also been effectively reduced by simultaneously introducing a controlled amount of oxygen or air into the system. By this oxidation technique, methallylamine has been converted to methacrylonitrile in 72–76 per cent conversions and 85–88 per cent yields at 500–575°C. over a silver catalyst. Acrylonitrile is similarly obtained from allylamine (385). Nicotine is oxidized over vanadium pentoxide to nicotinonitrile in 52 per cent yield (615).

Another technique for removing the by-product hydrogen is by the use of an acceptor such as an easily hydrogenated olefin. From butylamine, ammonia, and 2-pentene at 180–200°C. in an autoclave in the presence of a cobalt catalyst is obtained a 70 per cent yield of butyronitrile (442).

Several similar high-temperature dehydrogenation techniques are reported in which the amine or aldimine is undoubtedly formed but not isolated. Thus, amides when passed over nickel catalysts at high temperatures are degraded to the amines through loss of carbon monoxide. If the amine formed is primary and aliphatic, it is simultaneously dehydrogenated to the nitrile. The reaction is essentially a vapor-phase catalytic degradation of the Hofmann type (377).

$$RCH_2CONH_2 \xrightarrow{Ni} CO + [RCH_2NH_2] \longrightarrow RCN + H_2$$

Isobutyraldehyde, isovaleraldehyde, propionaldehyde, benzaldehyde, and anisaldehyde have been converted in 30–40 per cent yields by ammonia over thoria at 220–240°C. to the nitriles through the aldimine intermediates (379).

$$RCHO + NH_3 \xrightarrow{-H_2O} [RCH{=}NH] \xrightarrow{-H_2} RCN$$

Similarly, alcohols and ammonia are converted to nitriles by the method of Hara and Komatsu over finely divided copper or silver catalysts at 300–400°C. Amines and aldimines are assumed to be intermediates in this synthesis, which gives 55–90 per cent yields (243, 536).

$$RCH_2OH + NH_3 \xrightarrow[300\text{–}400°C.]{Cu} [RCH_2NH_2] \longrightarrow$$
$$[RCH{=}NH] \longrightarrow RCN + H_2O + 2H_2$$

Maihle has found that alkyl nitrites and nitroalkanes may be converted by hydrogen at 300°C. over nickel catalysts to the corresponding nitriles by an ingenious hydrogenation–dehydrogenation technique (379).

$$RCH_2NO_2 \xrightarrow{3H_2} [RCH_2NH_2] \xrightarrow{-2H_2} RCN$$

The preparation of acetonitrile from acetylene and ammonia was studied by Chichibabin (110) and has been voluminously discussed in the patent literature (435, 513, 550, 551).

$$CH{\equiv}CH + NH_3 \rightarrow [CH_2{=}CHNH_2] \rightarrow [CH_3CH{=}NH] \rightarrow CH_3CN$$

Considerable amounts of pyridine, picolines, pyrrole, and related compounds are also formed. A recent publication indicates that a 66 per cent yield of acetonitrile is obtained over a zirconium oxide catalyst at 400–500°C. A trace of water vapor is essential for high yields (10a). A special case is found in the action of ammonia on an ether solution of dichloroacetylene. Chloroacetonitrile results by dehydrohalogenation of the unisolated intermediate iminochloride (445).

$$ClC{\equiv}CCl + NH_3 \longrightarrow \left[CHCl{=}C\begin{matrix} NH_2 \\ \diagup \\ \diagdown \\ Cl \end{matrix} \right] \longrightarrow$$
$$\left[CH_2ClC{=}NH \atop \quad | \atop \quad Cl \right] \longrightarrow ClCH_2CN$$

A recent development involves the amination of olefins with the simultaneous formation of amines and the nitriles resulting from their dehydrogenation. Temperatures of 200–350°C., pressures up to 500 p.s.i., and a supported cobalt catalyst promoted by manganese dioxide are stated to give the best results (558).

The commercial production of benzonitrile from toluene and ammonia by a high-temperature catalytic vapor-phase process has recently been announced (12b). Undoubtedly benzylamine and benzaldimine are intermediates.

$$C_6H_5CH_3 + NH_3 \rightarrow [C_6H_5CH_2NH_2] \rightarrow [C_6H_5CH{=}NH] \rightarrow C_6H_5CN + 3H_2$$

VII. Dehydration of Oximes

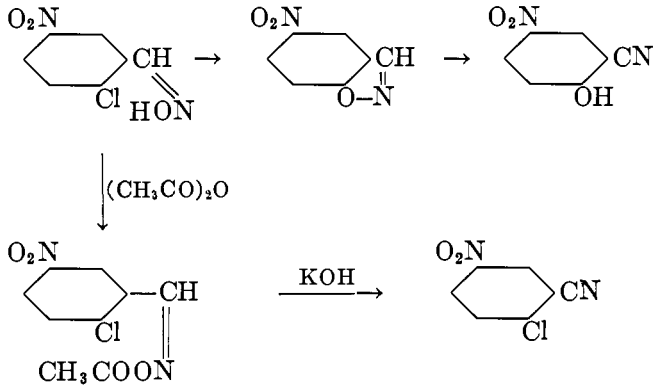
The dehydration of aldoximes is a facile method of synthesis which permits the transformation of an aldehyde to the corresponding nitrile under mild reaction conditions in high over-all yield. The reaction was first observed by Gabriel and Meyer in 1881, who used refluxing acetic anhydride (203). This is still the most popular reagent for effecting the dehydration, but thionyl chloride (409), ethyl

chloroformate (67), lead oxide (56), phosphorus pentoxide (517), benzenesulfonyl chloride (192), alkalies (115), and heat alone (115, 379) are representative of the many types of reagents that have been used.

In 1891 Hantzsch studied the two isomeric forms of aldoximes and noted that the acetyl derivative of one form (α) regenerated the aldehyde on treatment with alkali, whereas the other form (β) was converted to the nitrile. On the assumption that nitrile formation was the result of a "*cis*" elimination of acetic acid, he arbitrarily assigned the *syn*-structure to the β-oxime.

$$\begin{matrix} \mathrm{ArCH} \\ \| \\ \mathrm{NOCOCH_3} \end{matrix} + \mathrm{KOH} \rightarrow \mathrm{ArCN} + \mathrm{H_2O} + \mathrm{CH_3COOK}$$

Subsequently, evidence of various types has been accumulated to show that the structures of Hantzsch were erroneous. For example, Brady and Bishop showed that the isomer of 2-chloro-5-nitrobenzaldoxime, whose acetate lost acetic acid readily, also was the one which underwent ring closure to form the isoxazole and ultimately the hydroxynitrile (66). Since neighboring groups undoubtedly react most readily in ring closures, the acetic acid elimination must proceed by a "*trans*" elimination mechanism.

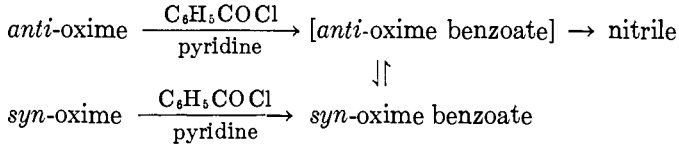


Acetic anhydride does not cause inversion during acetate formation (67). This structural problem has attracted the attention of numerous investigators, most of whom now appear to be in agreement that the α-oxime has the *syn*-configuration (250).

Hauser and coworkers have studied in considerable detail the effect of alkaline agents on *syn*- and *anti*-oximes and their derivatives. The products obtained from each isomer depend largely upon the conditions employed. Thus *anti*-benzaldoxime acetate forms the nitrile predominantly at 30°C., but at 0°C. principally regenerates the oxime.

Furthermore, even the *syn*-compounds will react at 100°C. to give nitriles (250). In general, the oxime carbonates give higher yields of nitriles than the acetates (251). Studies of the action of benzoyl chloride on *syn*- and *anti*-oximes have led to the conclusion that an equilibrium exists under basic conditions between the *syn*- and *anti*-benzoates. The *anti*-benzoate is thought to be the immediate

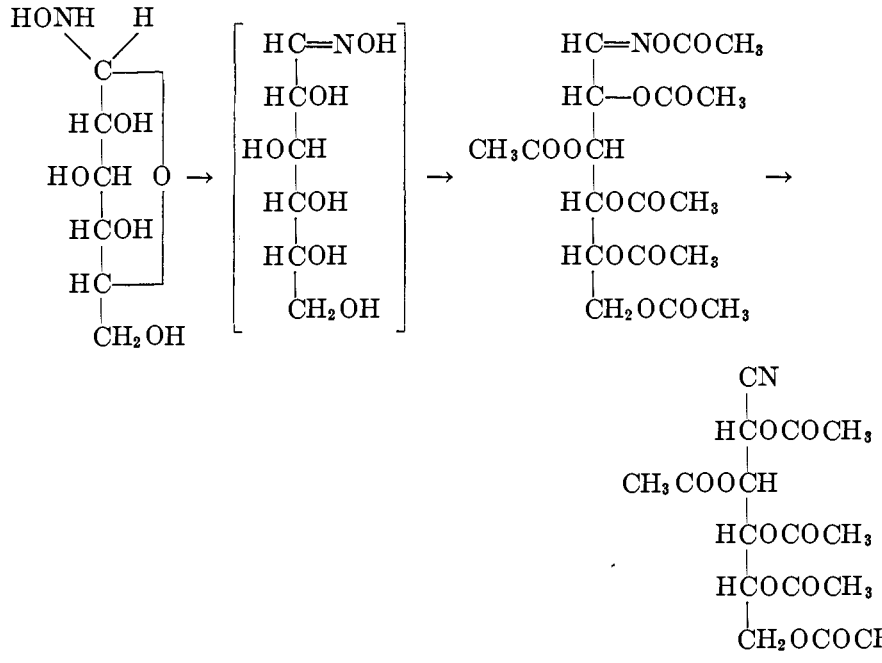
precursor of the nitrile, although it could not be isolated under the reaction conditions employed (252).



Hauser has also studied chloramine as a reagent for converting aromatic aldehydes to nitriles. The intermediate aldchlorimine is converted almost instantaneously at 0°C. by bases to the nitrile in high yield (249).

$$ArCHO + NH_2Cl \rightarrow ArCH{=}NCl \xrightarrow{base} ArCN$$

The oxime dehydration method is particularly useful for nitrile synthesis in cases where the molecule contains sensitive groups that would be attacked under more drastic reaction conditions. In many cases it is the only method of preparation available. The reaction is the first step in the Wohl degradation of sugars, and glucose may be converted in 50–55 per cent over-all yield to pentaacetyl-*d*-gluconononitrile (117, 610). By suitable modifications gluconononitrile itself may be obtained in similar yield (611, 621). Wolfrom has shown that glucose oxime, which normally exists in a ring-type structure, is cleaved to form the open-chain hexaacetate before the nitrile is formed by loss of acetic acid (612a).



Nitroacetonitrile had been the structure erroneously proposed by Kekulé for fulminic acid, and its independent synthesis was attempted unsuccessfully by a large number of investigators. This was ultimately accomplished by the thionyl

chloride dehydration of nitroacetaldehyde oxime and was shown to be an unstable oil which had no relation to fulminic acid (539).

$$NO_2CH_2CH{=}NOH \xrightarrow{SOCl_2} NO_2CH_2CN$$

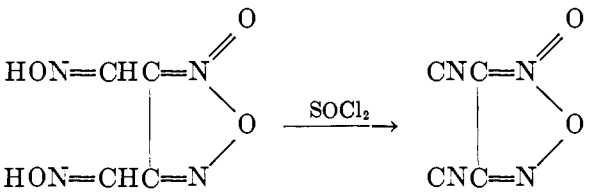
The oxime dehydration method is advantageous for the preparation of acyl cyanides. This is especially true for aroyl cyanides, since the requisite intermediates for these preparations are easily obtained from aryl methyl ketones (60, 63, 115, 517).

$$ArCOCH_3 \xrightarrow{C_5H_{11}ONO} ArCOCH{=}NOH \rightarrow ArCOCN$$

Carbonyl cyanide is obtained from dioximinoacetone (381).

$$HON{=}CHCOCH{=}NOH \xrightarrow{(CH_3CO)_2O} CH_3COON{=}CHCOOCH{=}NOCOCH_3 \rightarrow CNCOCN$$

Cyano derivatives of various heterocyclic compounds such as pyrroles (186), quinolines (59), furans (599), and thiophenes (166) are prepared by this method. Dicyanofuroxan is obtained from the appropriate dioxime in 30–40 per cent yields (504).

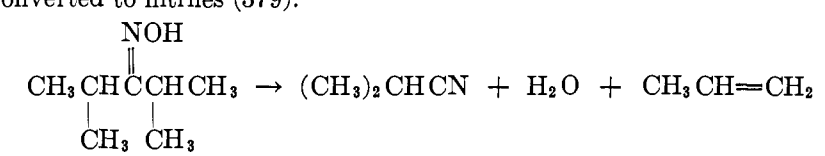


Oximes of unsaturated aldehydes are dehydrated without causing polymerization or isomerization in the configuration or position of the double bond (417, 624). Propionaldoxime undergoes simultaneous catalytic dehydration and dehydrogenation to acrylonitrile (172).

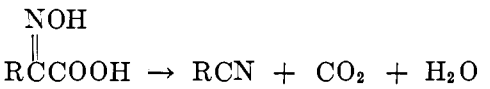
$$CH_3CH_2CH{=}NOH \xrightarrow[400°C.]{Cr_2O_3} CH_2{=}CHCN + H_2O + H_2$$

It is possible to distinguish between aldehydes and ketones and separate them on the basis of the stability of their oximes. This procedure has proved to be useful in structural studies of certain natural products (337).

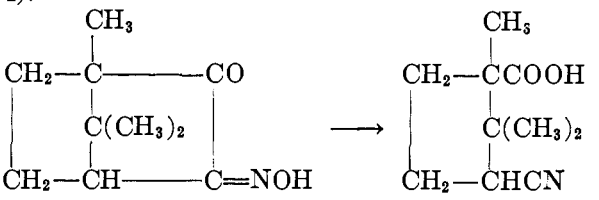
When subjected to drastic pyrolytic conditions, however, even ketoximes can be converted to nitriles (379).



The yields are poor unless the oximino group is adjacent to another carbonyl, carboxyl, or carbinol group. In these cases cleavage of the carbon–carbon bond proceeds at lower temperatures and in much better yield. Thus, α-oximino acids are readily degraded by dilute acids to a nitrile having one less carbon atom (586a):



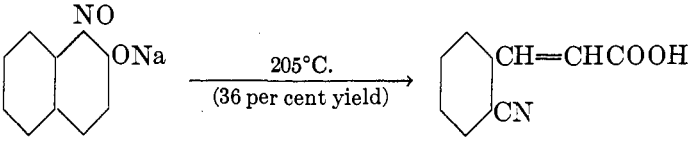
Isonitrosocamphor is converted in 85 per cent yield to camphoric acid mononitrile (324, 504).



The following sequence of reactions has been used for the synthesis of aliphatic nitriles of more than five carbon atoms (145):

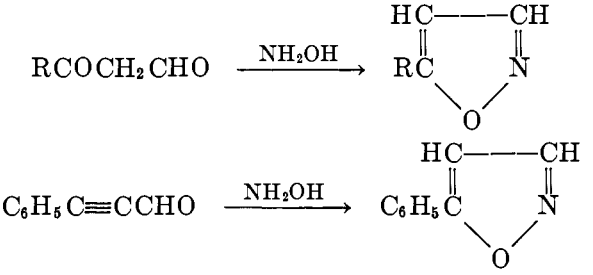
$$RCH_2COOH \xrightarrow{SOCl_2} RCH_2COCl \xrightarrow{C_6H_6} RCH_2COC_6H_5 \xrightarrow{NH_4ONO} RC(=NOH)COC_6H_5 \xrightarrow{210°C.} RCN + C_6H_5COOH$$

The preparation of *o*-cyanocinnamic acid by heating the sodium salt of α-nitroso-β-naphthol is a related reaction (148).

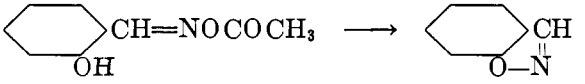


The older literature on the pyrolysis of ketoximes has been discussed at length by Hurd (282).

β-Ketoaldehydes and derivatives of propiolaldehyde form isoxazoles when treated with hydroxylamine (22, 114).



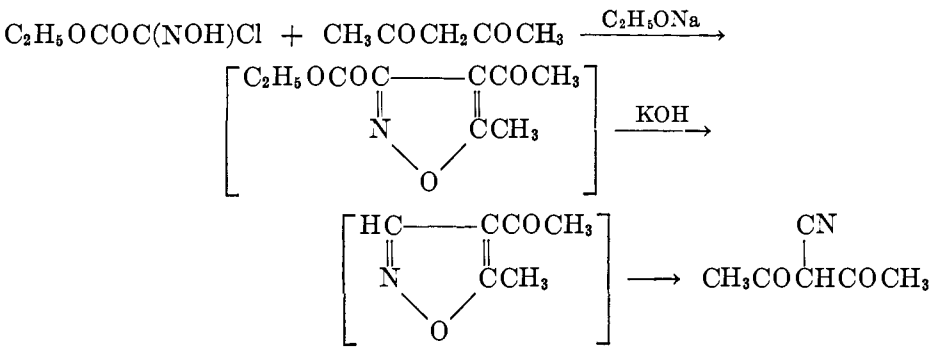
A similar reaction takes place with *o*-hydroxybenzaldoxime derivatives (363).



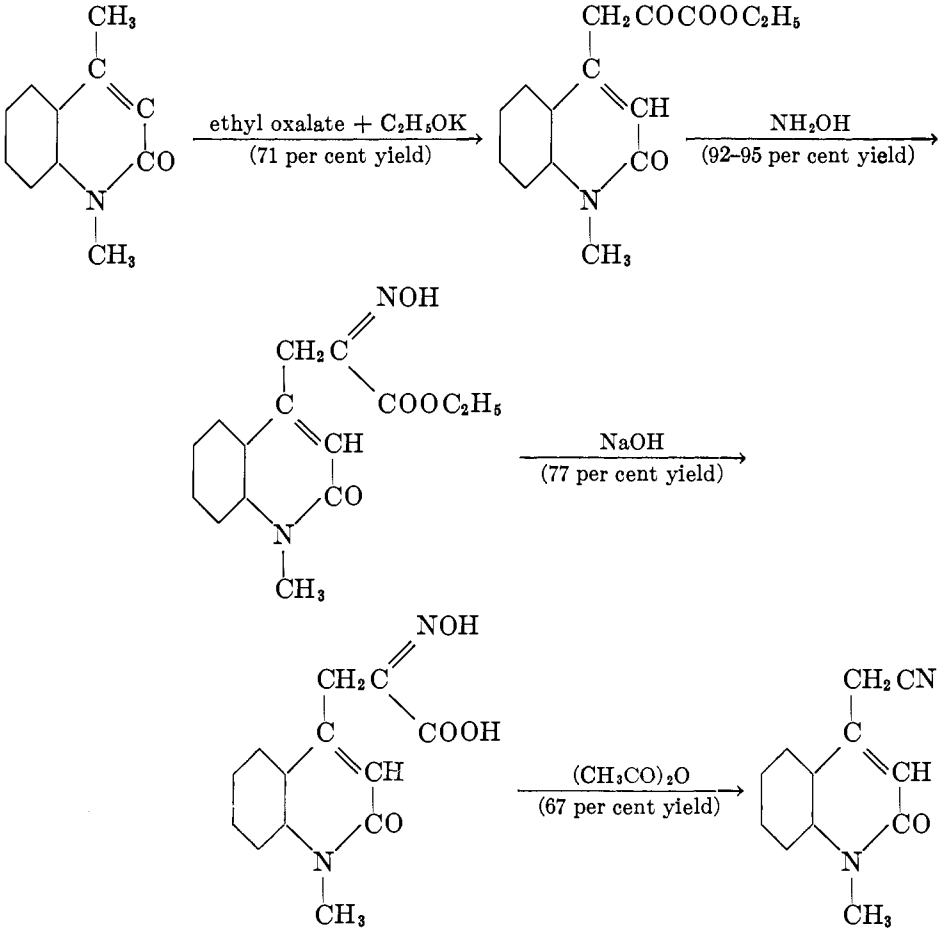
Products of this type when heated or when treated with alkali form the corresponding nitriles in good yield unless the isoxazole ring is stabilized by a substituent in the 3-position.

Since the reaction of alkali cyanides and many α-haloketones leads to cyano derivatives of ethylene oxide (see page 205), the methods involving oxime dehydration have been used to prepare previously unavailable β-ketonitriles. By treating the oximinochloride of monoethyl oxalate with sodium salts of active

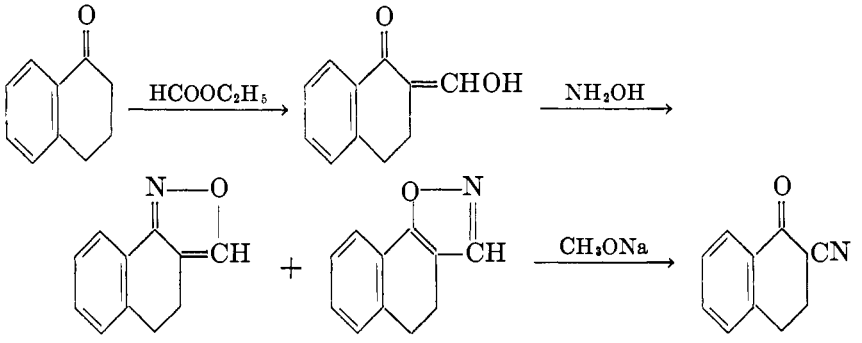
hydrogen compounds, Musante was able to prepare the corresponding isoxazoles. These intermediates, usually not isolated, were converted by hot alcoholic alkali to the nitriles. The reaction is applicable to β-keto esters, cyanoacetic esters, and β-diketones (425).



A similar technique is illustrated for 1,4-dimethylcarbostyryl (305).



A related synthesis involving the formylation of ketones with alkoxides and ethyl formate has been studied by Johnson and Shelberg. Treatment of the β-ketoaldehyde with hydroxylamine gives two isoxazoles. The neutral isomer is inert to the action of sodium methoxide and is easily separated from the ketonitrile which is formed from the reactive isomer. α-Tetralone is converted in 79 per cent over-all yield to its β-cyano derivative, with the concurrent formation of 9 per cent of the neutral isoxazole.



l-Menthone gives 57 per cent ketonitrile and 21 per cent stable isoxazole isomer, while only the nitrile is obtained from camphor. Since the reaction fails completely with cyclopentanone rings, Johnson and Shelberg have suggested that it be used as a basis for proof of structure in sterol chemistry. Even sterically hindered open-chain ketones, such as acetomesitylene, are converted in very high yields to the ketonitriles (298).

The principal side-reaction in the dehydration of oximes is a thermal rearrangement of the Beckmann type which leads to amides and acids. Thus, certain monoöximes of arylglyoxals are converted to acids and hydrogen cyanide (61).

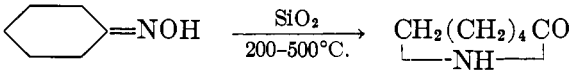
$$ArCOCH{=}NOH \rightarrow ArCOOH + HCN$$

The formation of amides by rearrangement of oximes is catalyzed by Raney nickel at 80–150°C. (453).

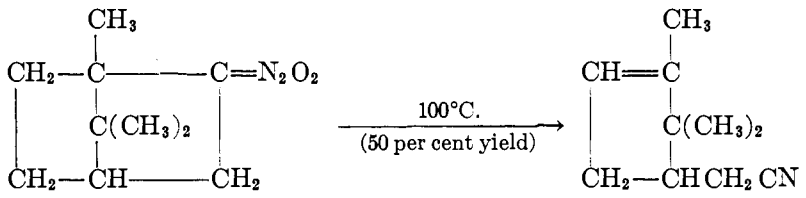
$$RCH{=}NOH \rightarrow RCONH_2$$

In this manner the appropriate aldoximes are converted to acetamide (86 per cent yield), benzamide (75 per cent yield), furoamide (88 per cent yield), caprylamide (90 per cent yield), and β-phenylpropionamide (30 per cent yield).

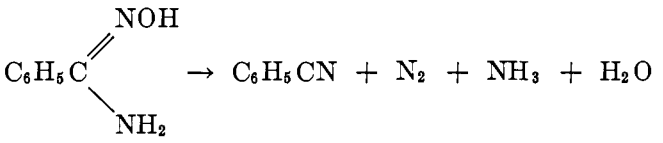
Monoöximes of diketones such as acenaphthenequinone give the cyano acid or the related imide, depending on the reaction conditions (37). Ketoxime pyrolysis may lead to mixtures of various products (282, 321). Under controlled conditions the vapor-phase pyrolysis of cyclohexanone oxime in industrial practice gives high yields of ε-aminocaprolactam, an intermediate for the preparation of polyamide plastics and fibers (355).



A reaction closely related to ketoxime pyrolysis is the transformation of pernitrosocamphor to campholenonitrile (207).



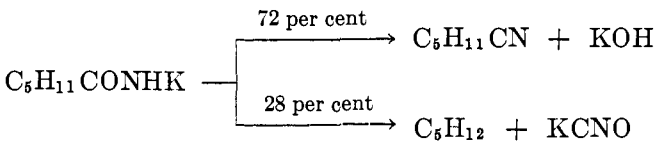
Benzamidoxime is similarly pyrolyzed to benzonitrile (333).



VIII. Dehydration of Amides

A. Dehydration of Amides by Chemical Reagents

In 1832 Wöhler and Liebig distilled benzamide over barium oxide and obtained an oil which was subsequently recognized as benzonitrile, the first nitrile to be synthesized. The use of basic reagents for effecting amide dehydrations has not proved desirable, although pyrolysis of the sodium derivative of benzamide has been reported to give 85 per cent yields of benzonitrile (324). It has also been observed that the potassium derivatives of amides of two to six carbon atoms are converted by heat to the nitriles. Appreciable amounts of by-product hydrocarbon are also formed (40).



The most useful chemical reagents for effecting the dehydration of amides are without exception the halides or anhydrides of organic or inorganic acids. The use of *phosphorus pentoxide* to dehydrate ammonium salts or amides in both the aliphatic and the aromatic series was introduced by Dumas in 1847 (169).

$$RCONH_2 + P_2O_5 \rightarrow RCN + 2HPO_3$$

Customarily the reaction is carried out by dry distillation of an intimate mixture of the solid amide and finely divided phosphorus pentoxide. Yields are improved if the temperature (usually 100–200°C.) and pressure are adjusted so that the product is distilled from the metaphosphoric acid as rapidly as formed. Stirring of the reaction is often complicated by frothing and by the pasty, semisolid consistency of the mixture. An inert diluent such as sand or mineral oil is often employed to facilitate heat transfer.

In spite of the seemingly drastic conditions and intractable nature of the reaction mixture, the method is exceptionally versatile and provides excellent yields of a large variety of nitriles. Aliphatic monoamides are dehydrated in nearly

quantitative yields (309, 329). Substituents such as halo, cyano, nitro, alkoxy, and carbalkoxy groups are not affected, but free hydroxyl or primary or secondary amino groups lead to side-reactions. Aliphatic diamides and polyamides have been successfully converted as, for example, in the classic proof of structure of cyanogen by the dehydration of oxamide (42):

$$NH_2COCONH_2 \xrightarrow{P_2O_5} (CN)_2$$

N,*N*-Dipropyloxamide, however, is converted to the corresponding cyanoformamide in 65 per cent yield (18).

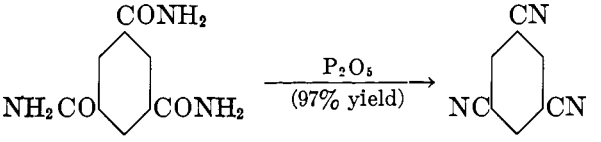
$$(n\text{-}C_3H_7)_2NCOCONH_2 \xrightarrow{P_2O_5} (n\text{-}C_3H_7)_2NCOCN$$

Optically active α-haloamides are not racemized or inverted by this reagent during their conversion to nitriles (41, 529). Olefinic and acetylenic amides are converted smoothly to the corresponding nitriles, some of which are not obtainable by other syntheses. For example, Moureu has obtained the unstable, highly reactive mono- and di-cyanoacetylenes in this manner (411).

$$NH_2COC{\equiv}CCONH_2 \xrightarrow{P_2O_5} CNC{\equiv}CCN$$

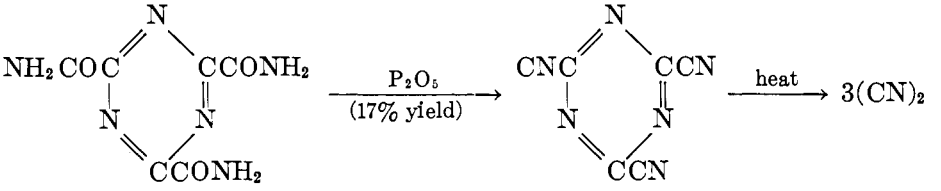
Succinic or maleic amides and their derivatives, however, are converted predominantly to the cyclic imides by loss of ammonia rather than to the dinitrile by dehydration (419, 612). Amides containing acid-sensitive acetal groups are smoothly converted in 75–80 per cent yield to the corresponding nitriles by phosphorus pentoxide in triethylamine solution. Quinoline, *N*-hexylpiperidine, and *N*-ethylmorpholine were less satisfactory solvents (373a).

As would be expected, the reactions of aromatic amides and phosphorus pentoxide give high yields of nitriles. *o*-Diamides have a tendency to form cyclic imides but no difficulty is encountered with polyamides of other configurations such as trimesic amide (38).



Salicylamide, however, forms disalicylamide by intermolecular loss of ammonia when treated with phosphorus pentoxide (135).

Pyridine-monocarboxamides and -dicarboxamides are smoothly converted to the nitriles by the action of phosphorus pentoxide (339, 347). 1,3,5-Tricyanotriazine, which can be pyrolyzed to cyanogen, is similarly obtained from the triamide (216).



Phosphorus pentasulfide and benzamide are stated to give 40–50 per cent yields of benzonitrile according to the following equation (257):

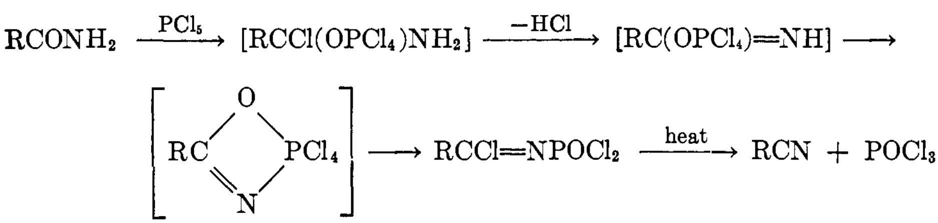
$$5C_6H_5CONH_2 + P_2S_5 \rightarrow 5C_6H_5CN + 5H_2S + P_2O_5$$

The use of *phosphorus pentachloride* as a reagent for the dehydration of amides was introduced by Gebhart in 1858 (216). Carboxamides were originally thought to be dehydrated through the following mechanism (585):

$$RCONH_2 \xrightarrow{PCl_5} RCCl_2NH_2 \xrightarrow{-HCl} \underset{\displaystyle Cl}{\underset{|}{RC}}{=}NH \xrightarrow{-HCl} RCN$$

Since carboxamides are thought to exist partially in the imino acid form (21), the unstable amide dichloride is not necessarily an intermediate. Hantzsch prefers to regard the amide dichloride and iminochloride (which may be obtained by the addition of hydrogen chloride to the nitrile) as nitrilium salts, $[RC{\equiv}NH]^+Cl \cdot HCl$ and $[RC{\equiv}NH]^+Cl^-$ (240).

The actual precursor of the nitrile is probably a phosphochloride derivative of the iminochloride. This intermediate has been isolated in excellent yield in the trichloroacetamide–phosphorus pentachloride reaction, but it has only a transitory existence in the case of amides of less negatively substituted aliphatic acids. According to von Braun and Rudolph the intermediate is formed by the following mechanism:



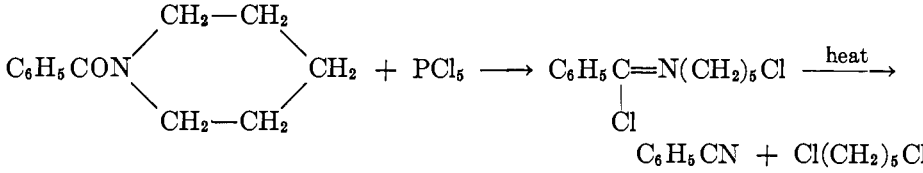
Since this intermediate could not be isolated in the dehydration of the amide by phosphorus oxychloride, it is felt that the previously proposed mechanism involving dehydrochlorination of the iminochloride is erroneous (77).

von Braun has studied the action of phosphorus pentachloride on the amides derived from primary and secondary amines (70, 75). The following transformations have been established for various benzamide derivatives:

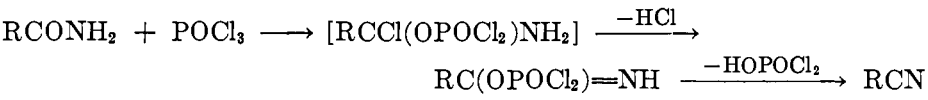
$$C_6H_5CONR_2 \xrightarrow{PCl_5} C_6H_5CCl_2NR_2 \xrightarrow[-RCl]{heat} \overset{\displaystyle Cl}{\overset{|}{C_6H_5C}}{=}NR \xleftarrow{PCl_5} C_6H_5CONHR$$

$$C_6H_5C(Cl){=}NR \xrightarrow{heat} C_6H_5CN + RCl$$

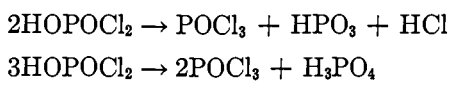
If *N*-benzoylpiperidine is used, the reaction provides a convenient synthesis of 1,5-dihalides.



A solution of phosphorus pentachloride in *phosphorus oxychloride* has been advocated as a convenient reagent for nitrile dehydration (301, 410). Phosphorus oxychloride alone, however, is especially advantageous for amides containing the hydroxyl and keto groups, since these are not affected by the reagent. Only 30 to 50 mole per cent of the oxychloride is needed for complete conversion to the nitrile. The reaction is thought to proceed by the following mechanism (68, 77):

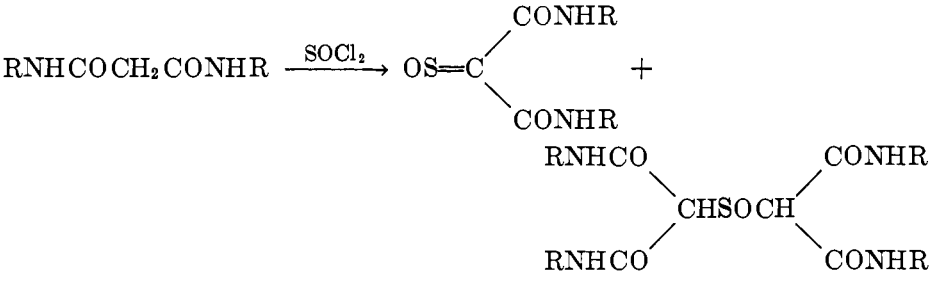


Phosphorus oxychloride is regenerated by one of the following routes:



Benzonitrile and *o*-nitrobenzonitrile are obtained in 95 per cent yield with 25 mole per cent of the oxychloride, but higher ratios are required for equivalent yields of aliphatic nitriles such as lauronitrile or adiponitrile (68). Acetylated amides in the carbohydrate series are converted in 90–95 per cent yields to the corresponding nitriles (348). The addition of sodium chloride to the reaction mixture increases the yield (302, 553). The use of strongly nucleophilic solvents as hydrogen chloride acceptors has proved to be particularly advantageous. Pyridine, dimethylaniline, or other tertiary amines have been recommended (187). Equally good results are claimed for less basic solvents, such as *N*-alkylformanilides (544). These solvents permit the conversion of phthalamide to phthalonitrile, instead of phthalimide which is often formed by acidic dehydrating agents (147, 544).

Thionyl chloride is a popular reagent for the dehydration of amides, since the by-product hydrogen chloride and sulfur dioxide are gaseous and an excess of the volatile reagent is easily removed (400). The reagent fails to dehydrate malonamide, while *N*-substituted malonamides are converted to sulfoxides (428).



Compounds such as α,α-ditosylacetamide (15) and 3-carbamidophthalide (573) are reported to be resistant to dehydration by thionyl chloride, and the reagent causes partial demethylation of mandelamide methyl ether (528). Aromatic sulfonic acids (447) and sulfonyl chlorides (233) are also reported to effect the dehydration of amides in high yields.

$$C_6H_5CONH_2 \xrightarrow{ArSO_3H} C_6H_5CN + H_2O$$

$$C_6H_5CONH_2 \xrightarrow{ArSO_2Cl} C_6H_5CN + ArSO_3H + HCl$$

Anhydrous *aluminum chloride* has been studied as a reagent for amide dehydration. The double salt obtained from equimolar amounts of aluminum chloride and sodium chloride gives better results. The following yields are obtained, using a 10 to 50 per cent molar excess of the double salt: acetonitrile (91 per cent), diphenylacetonitrile (52 per cent), *n*-valeronitrile (63 per cent), benzonitrile (97 per cent), *o*-chlorobenzonitrile (93 per cent), *p*-chlorobenzonitrile (89 per cent), 2,6-dichlorobenzonitrile (67 per cent), *p*-nitrobenzonitrile (20 per cent), α-naphthonitrile (79 per cent), and β-naphthonitrile (80 per cent). Dibasic amides and ammonium salts gave less satisfactory results (437).

Molecular complexes of *boron trifluoride* are effective reagents for amide dehydration (534).

Among the organic acid chlorides, *phosgene* has received considerable attention, probably because of its low cost and availability. Pyridine or other tertiary amines (147, 173) or *N*-alkylformanilides (147) are advantageous nucleophilic solvents for this reaction. The acyl isocyanate has been proposed as an intermediate, since the reaction of benzoyl chloride and potassium isocyanate also gives benzonitrile (405). This has not been confirmed by other evidence.

$$\begin{matrix} C_6H_5CONH_2 + COCl_2 \\ \qquad\qquad\qquad\quad \searrow \\ \qquad\qquad\qquad\qquad [C_6H_5CONCO] \xrightarrow{-CO_2} C_6H_5CN \\ \qquad\qquad\qquad\quad \nearrow \\ C_6H_5COCl + KNCO \end{matrix}$$

Trichloromethyl chloroformate, obtainable by the photochemical chlorination of methyl formate, is a satisfactory dehydrating reagent (259).

3,5-Dinitrobenzoyl chloride in pyridine solution has been proposed as a reagent for the quantitative determination of amides. The hydrogen chloride liberated is titrated to determine the amount of nitrile formed (405).

Benzotrichloride has been used as a reagent for the dehydration of aromatic and aliphatic amides. The reaction temperature may be lowered from 200° to 100°C. by the use of traces of the chlorides of zinc, aluminum, or iron (276).

Acetic anhydride is the most popular of the organic anhydrides for amide dehydration (68). The reaction is reversible. At equilibrium acetamide is 83 per cent converted to the nitrile at 98°C. (87 per cent at 78°C.) by an equimolar quantity of acetic anhydride.

$$CH_3CONH_2 + (CH_3CO)_2O \rightleftharpoons CH_3CN + 2CH_3COOH$$

The distribution of products from 1 mole of benzamide and 1 mole of acetic anhydride was observed to be as follows at equilibrium (330):

$$\underset{(0.48\ \text{mole})}{C_6H_5CONH_2} + \underset{(0.48\ \text{mole})}{(CH_3CO)_2O} \rightleftharpoons \underset{(0.38\ \text{mole})}{C_6H_5CONHCOCH_3} + \underset{(0.66\ \text{mole})}{CH_3COOH} + \underset{(0.14\ \text{mole})}{C_6H_5CN}$$

Traces of cobalt, copper, nickel, molybdenum, and zinc salts are effective catalysts in promoting this reaction, and high conversions may be attained by distilling the acetic acid from the reaction mixture as formed (325, 419, 532).

Trisubstituted acetamides react with aliphatic *Grignard reagents* to give mixtures of ketones and nitriles. The latter predominate if the reagent is an arylacetamide. The following mechanism has been proposed (473):

$$ArCR_2CONH_2 \rightleftharpoons ArCR_2C(OH)(=NH) \xrightarrow{R'MgX} ArCR_2C(OMgX)(=NMgX) \rightarrow ArCR_2CN + MgO + MgX_2$$

Aryl Grignard reagents give relatively larger amounts of the ketone, but the *tert*-butyl Grignard reagent leads to a 73 per cent yield of pivalonitrile from the corresponding amide (594).

B. DEHYDRATION OF AMIDES BY CATALYTIC METHODS

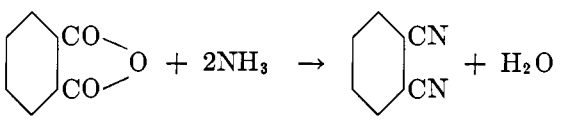
It has long been known that compounds such as ammonium acetate or acetamide will be dehydrated if heated strongly. However, in the absence of catalysts the conversion is low and considerable quantities of the acid and ammonia are regenerated through hydrolysis of the amide by the water liberated in the principal reaction. For example, distillation of stearamide at atmospheric pressure gives 33 per cent stearic acid, 30 per cent stearonitrile, and 5 per cent unchanged stearamide (471). Similarly, distillation of sebacic diamide gives predominantly 9-cyanononoic acid (45). It was observed by Boehner in 1916 that if acetamide were refluxed at 250–260°C. over alumina, lamp black, pumice, or silica improved yields (65–68 per cent) of acetonitrile were obtained. Still better results were obtained if the reaction was carried out in the vapor phase at 420°C. Under these conditions a pumice catalyst gave a 91 per cent yield (54).

Conditions similar to the above are now used for the large-scale commercial production of hydrogen cyanide (and sodium cyanide) from formamide. The amide vapors are passed over catalysts such as aluminum phosphate at 350–370°C. and absorbed in aqueous alkali (371). Acrylamide and methacrylamide are dehydrated in 67–75 per cent yields to the corresponding nitriles at 490°C.

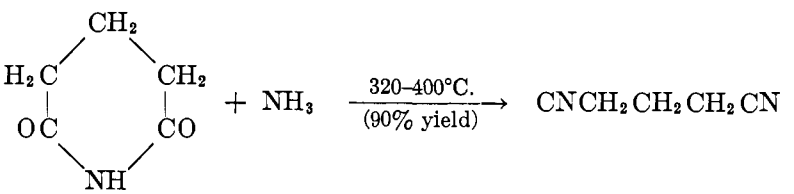
over fused manganese dioxide. Reduced pressures contribute toward the attainment of high yields (342).

At the same time that Boehner was investigating the catalytic dehydration of amides, Reid announced a similar synthesis in which the acid and ammonia are passed in the vapor phase over dehydration catalysts to give the nitrile directly without isolation of the intermediate ammonium salt or amide (572). When acetic acid and an excess of ammonia are passed at 500°C. over a catalyst of thoria or alumina supported on pumice, an 85 per cent yield of acetonitrile is obtained. Silica gel as a catalyst at 500–525°C. gives 95 per cent yields (406). The following nitriles were similarly obtained in the yields indicated: propionitrile (85 per cent), *n*-butyronitrile (90 per cent), *n*-valeronitrile (80 per cent), isovaleronitrile (94 per cent), capronitrile (90 per cent), heptonitrile (93 per cent), lauronitrile (55 per cent), phenylacetonitrile (87 per cent), and β-phenylpropionitrile (81 per cent).

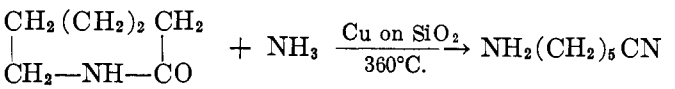
A liquid-phase technique for aliphatic monobasic or dibasic acids involves blowing ammonia into the molten acid at elevated temperatures. Amide formation occurs above 100°C. and nitrile formation occurs in the 200–350°C. range. Of numerous catalysts mentioned for the latter step about 2–5 per cent of phosphoric acid appears to be the most popular. This technique has been employed for the production on a commercial scale of long-chain fatty acid nitriles (472) and adiponitrile (189). With phthalic acid the liquid-phase technique, however, leads to the production of phthalimide rather than phthalonitrile. The latter is obtained at higher temperatures (350–500°C.) in the vapor phase over various dehydration catalysts (365).



A relatively short contact time (2–5 sec.) and an eight- to ten-fold excess of ammonia enable yields of 80–90 per cent to be obtained. Lower temperatures favor higher amounts of phthalimide formation, while higher temperatures lead to increasing amounts of benzonitrile, which arises through decarboxylation (365, 419). Phthalimide undergoes the reaction as readily as phthalic anhydride, and glutarimide is similarly converted to glutaronitrile (382).



ε-Aminocaprolactam is similarly converted to ε-aminocapronitrile (355).



Other catalysts that have been recommended for vapor-phase dehydration of amides are Japanese acid clay (314), sulfates, phosphates, borates, and molybdates of aluminum, boron, vanadium, beryllium, and zirconium (16a, 279).

Another variation involving the simultaneous preparation and dehydration of amides was introduced by Maihle, who passed ammonia and carboxylic esters over dehydration catalysts at elevated temperatures.

$$RCOOR' + NH_3 \xrightarrow[500°C.]{Al_2O_3} RCN + R'OH + H_2O$$

The by-product alcohol is often converted to the corresponding ether or olefin. The reaction has been applied to both the aliphatic and the aromatic series, the yields being somewhat better in the latter case.

Unsaturated nitriles such as crotononitrile, oleonitrile, and cinnamonitrile have also been prepared in this manner. A nearly quantitative yield of hydrogen cyanide is reported to be obtained from the reaction of carbon monoxide and ammonia at 400°C. Alumina and thoria are the preferred catalysts. Primary aliphatic amines may be substituted for ammonia as a nitrogen source.

$$RCOOR' + R''CH_2CH_2NH_2 \xrightarrow{-R'OH} [RCONHCH_2CH_2R''] \rightarrow RCN + R''CH{=}CH_2 + H_2O$$

Acid chlorides may be substituted for esters in this method of nitrile synthesis (378).

The use of nickel catalysts causes a side-reaction reminiscent of the Hofmann degradation. Aromatic esters are degraded to the aromatic amines, but the corresponding aliphatic amines usually undergo dehydrogenation to the lower nitriles (377).

$$ArCOOR + NH_3 \xrightarrow{Ni} ArNH_2 + CO + ROH$$

$$RCH_2COOR' + NH_3 \xrightarrow{Ni} [RCH_2NH_2] \rightarrow RCN + H_2$$

Methyl iminobenzoate is converted to benzonitrile by heating at 250–280°C. for 26 hr. The trimer of benzonitrile, cyaphenine, may be the intermediate in this reaction (296, 604).

IX. Miscellaneous Syntheses

A large number of nitrile syntheses have been proposed which involve heating an acid or one of its derivatives with some nitrogen-containing compound. Only those methods will be mentioned in this section which have preparative value or are of theoretical interest.

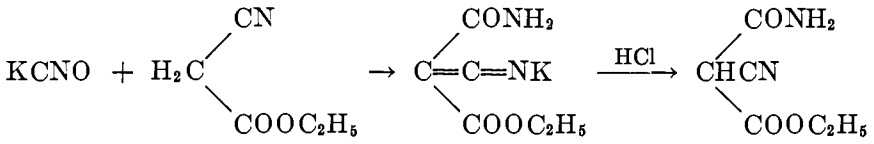
Schiff observed in 1857 that the reaction of benzoyl chloride with potassium cyanide gave some benzonitrile (512). The fusion of an aromatic acid with potassium thiocyanate was introduced by Letts in 1872 as a preparative method (357). It was subsequently observed that Letts's method gave better yields if lead thiocyanate was employed (334). A systematic study of the reaction by

Reid has shown that dry distillation of the zinc salt of the acid with a 20 per cent excess of lead thiocyanate gives the best yield of benzonitrile (86 per cent conversion and 91 per cent yield), although lead, barium, or potassium ferrocyanide, lead cyanate, and silver cyanide all give yields in excess of 50 per cent. The reaction fails with amino-, nitro-, or hydroxy-benzoic acids.

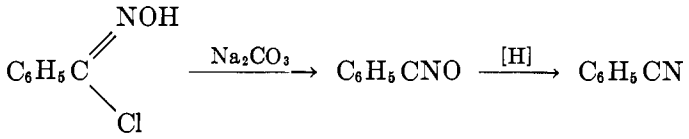
$$(C_6H_5COO)_2Zn + Pb(CNS)_2 \rightarrow 2C_6H_5CN + PbS + ZnS + 2CO_2$$

In the aliphatic series the yields are poorer. Several metallic salts of acetic acid were investigated. Manganese and zinc acetates are converted by lead thiocyanate to acetonitrile in 70 per cent and 46–57 per cent yields, respectively. Yields of 16 to 29 per cent are obtained from the acetates of cobalt, strontium, barium, copper, and lead, while the use of magnesium, nickel, tin, and iron salts gives definitely inferior results (572).

Potassium cyanate reacts with the reactive methylene group of cyanoacetic ester in a different fashion, but this type of synthesis does not appear to have been investigated further (197).



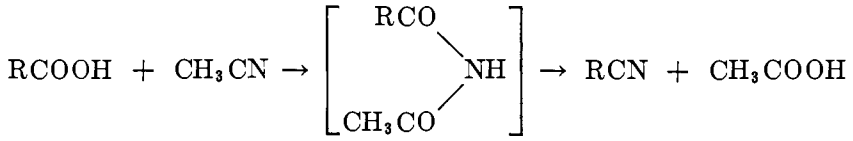
Nitrile oxides which are obtained by dehydrochlorination of hydroxamic chlorides can be reduced with zinc and acetic acid to the nitriles (597).



In a somewhat related reaction dithio acids and hydroxylamine hydrochloride in pyridine solution give rise to aliphatic nitriles directly. In the aromatic series aldoximes are formed (617).

$$RCSSH + NH_2OH \rightarrow RCN + H_2S + H_2O + S$$

A nitrile interchange reaction between excess acetonitrile and a higher acid takes place at 250–300°C. under pressure. Acidic substances act as catalysts and the mechanism undoubtedly involves the mixed imide as an intermediate (368).



Aliphatic acid chlorides are converted by acetonitrile in the presence of aluminum chloride to the corresponding nitrile (431a).

A synthesis of considerable utility which involves the fusion of an acid with benzenesulfonamide was introduced by Remsen in 1896 (485, 496). This reac-

tion has been studied in considerable detail recently by Oxley and coworkers, who have shown that the mechanism involves the following sequence of reactions. Under slightly modified conditions the amidines may be obtained as the principal reaction products.

$$RCOOH + R'SO_2NH_2 \rightleftharpoons RCONH_2 + R'SO_2OH$$

$$RCONH_2 + R'SO_2NH_2 + R'SO_2OH \rightarrow R\overset{\overset{NH}{\|}}{C}OSO_2R' + R'SO_2ONH_4$$

$$R\overset{\overset{NH}{\|}}{C}\diagdown_{OSO_2R} \rightarrow RCN + R'SO_2OH$$

$$RCN + R'SO_2ONH_4 \rightleftharpoons R\overset{\overset{NH}{\|}}{C}\diagdown_{NH_2}\cdot RSO_3H$$

With 2 moles of benzenesulfonamide at 220°C. ± 10° in 1 or 2 hr. the following conversions of acids to nitriles are obtained: benzonitrile (90 per cent), *o*-nitrobenzonitrile (11 per cent), *p*-nitrobenzonitrile (81 per cent), 2,4-dinitrobenzonitrile (79 per cent), *p*-chlorobenzonitrile (66 per cent), 2,4-dichlorobenzonitrile (80 per cent), *o*-cyanophenyl methyl sulfone (83 per cent), *m*-cyanophenyl methyl sulfone (61 per cent), *p*-cyanophenyl methyl sulfone (75 per cent), *p*-cyanophenyl phenyl sulfone (74 per cent), *p*-anisonitrile (10 per cent), di-*p*-cyanophenyl ether (45 per cent), phenylacetonitrile (22 per cent). The reaction fails with chloroacetic, oxalic, malonic, tartaric, salicylic, *o*-anisic, *p*-hydroxybenzoic, anthranilic, and *p*-aminobenzoic acids (447).

Fusion of phospham with aliphatic acids is stated to give the nitriles (574).

$$2RCOOH + PN_2H \xrightarrow{150\text{–}200°C.} 2RCN + H_3PO_4$$

Dicyandiamide (143) and urea (46) have been proposed as convenient nitrogen sources for the conversion of acids to their nitriles.

Phenylhydrazones of aldehydes are converted to nitriles by pyrolysis at 180–200°C. in the presence of catalytic amounts of the chlorides of copper, lead, or zinc.

$$RCH{=}NNHC_6H_5 \rightarrow RCN + C_6H_5NH_2$$

The lower aliphatic aldehydes lead principally to derivatives of indole, but yields of nitriles increase with higher molecular weight. Isobutyronitrile and isoheptanonitrile are obtained in 37 per cent and 60 per cent yields from their respective aldehyde phenylhydrazones (14).

The pyrolysis of Schiff bases also leads to nitriles. The reaction is conducted in the vapor phase at 420°C. over finely divided nickel. From *N*-ethylbenzaldimine are obtained principally benzonitrile and ethane, although appreciable quantities of toluene and acetonitrile are also obtained (379).

$$C_6H_5CH{=}NC_2H_5 \rightarrow C_6H_5CN + C_2H_6 \ (+ \ C_6H_5CH_3 + CH_3CN)$$

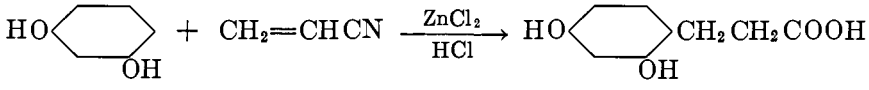
Benzaldehyde may also be converted to benzonitrile through the action of a benzene solution of hydrazoic acid in the presence of dry hydrogen chloride (514).

$$C_6H_5CHO + HN_3 \xrightarrow{HCl} C_6H_5CN + H_2O + N_2$$

The scope of this review has been limited to those reactions in which the cyano group is formed or introduced into an existing organic nucleus. However, brief mention should be made of recently developed techniques for the introduction of the cyanoethyl group according to the general reaction:

$$RH + CH_2{=}CHCN \rightarrow RCH_2CH_2CN$$

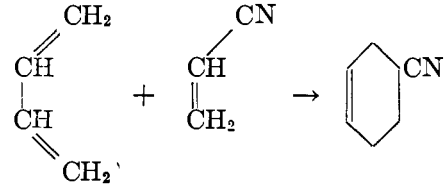
The reaction is effected by traces of alkaline catalysts under mild conditions. Alcohols, amines, mercaptans, and related compounds lead to the corresponding β-substituted propionitriles. Bruson has found that in the case of compounds containing reactive carbon–hydrogen bonds a true carbon synthesis of the Michael type is effected. Thus, hydrocarbons such as fluorene, cyclopentadiene, and indene (87), chlorinated hydrocarbons such as chloroform (90), and nitro compounds such as nitromethane (91) are cyanoethylated in good yield. Other compounds having reactive hydrogens in the α-position, such as esters (88, 317), nitriles (91), ketones (91), aldehydes (92) and sulfones (92), easily add one or more molecules of acrylonitrile. Reactive aromatic hydrocarbons such as resorcinol react similarly in the presence of acidic catalysts (351).



Acrylonitrile and its derivatives are conveniently attached to aromatic groups by reaction with diazonium halides (316, 388, 421).

$$ArN_2Cl + CH_2{=}CHCN \xrightarrow{-N_2} ArCH_2CHClCN \xrightarrow{-HCl} ArCH{=}CHCN$$

Another technique for the introduction of cyanoethyl or dicyanoethyl groups into a molecule involves the Diels–Alder condensation of 1,3-dienoic compounds with acrylonitrile, fumaronitrile, and their derivatives (416, 438).



X. Toxicity of Hydrogen Cyanide and Nitriles

Insofar as hydrogen cyanide and its derivatives are commonly employed in the synthesis of nitriles, a few observations on the toxicity and physiological action of these compounds should be of interest.

A single dose of 50 mg. of hydrogen cyanide may be fatal to a human being, although a great difference in individual susceptibility exists. For example, it has been reported that an attempt to poison Rasputin in 1916 by placing a large overdose of potassium cyanide in his wine failed because he had an alkaline stomach condition caused by acute alcoholic gastritis. Since rats, fed nine times the lethal dose of sodium cyanide, will recover if glucose and colloidal sulfur are injected intravenously, it would be reasonable to assume that diabetics would also be less susceptible to cyanide poisoning.

The average chemist, however, must rely on careful manipulative technique and adequate ventilation. Hydrogen cyanide has a distinctive odor. It is more easily detected while smoking, because of the disagreeable acrid taste it leaves in the mouth. The warning afforded by the sense of smell is not durable, however, since the olfactory nerves are rapidly paralyzed. Death by asphyxiation often occurs in a relatively short time. This is caused by paralysis of the central nervous system through inhibition of a single enzyme, cytochrome oxidase (40a) rather than by the accumulation of cyanohemoglobin in the blood stream, as has been commonly supposed.

The following lethal concentrations of hydrogen cyanide in air for human beings are cited by Fabre (176a):

Instantly fatal	0.3 mg. per liter
Fatal in 30 to 60 min	0.12–0.15 mg. per liter
Fatal after several hours	0.02–0.04 mg. per liter
Tolerable for 6 hr	0.01 mg. per liter

Supposedly, hydrogen cyanide poisoning is not cumulative and the spell passes quickly in fresh air. Actually, repeated sublethal exposures leave lesions of the central nervous system leading to difficulty of speech, paralysis, anemia, vertigo, heart trouble, and larynx trouble.

Recommendations for the treatment of cyanide poisoning have been made by Chen, Rose, and Clowes (109). These include inhalation of amyl nitrite as a preliminary adjuvant, alternate intravenous injection of solutions of sodium nitrite and sodium thiosulfate, and artificial respiration if necessary to restore breathing. The use of *p*-aminopropiophenone and sodium thiosulfate is equally effective. It is recommended that pearls of amyl nitrite be kept in the laboratory and that a kit containing ampoules of sterile solutions of sodium nitrite and sodium thiosulfate and syringes be kept at a nearby first aid station.

Cyanogen, cyanogen halides, and certain nitriles are almost as toxic as hydrogen cyanide. In general, the saturated aliphatic and aromatic nitriles are no more toxic than many chemicals commonly regarded as relatively harmless. Unsaturated nitriles, cyanohydrins, and α-aminonitriles, however, approach hydrogen cyanide in toxicity. Halogenated nitriles are also quite toxic and some are extremely lachrymatory. Unsaturated nitriles, such as acrylonitrile and fumaro-

nitrile, cause extensive and painful dermatitis when the liquid, dust, or vapors are brought in contact with the skin. In general, the mechanism and symptoms of poisoning by nitriles are similar to those caused by hydrogen cyanide. Table 6 indicates the relative toxicity of some of these materials.

A concentration of 20 p.p.m. of acrylonitrile in the atmosphere of industrial plants has been recommended as a maximum (167).

XI. Conclusion

In the preceding review an attempt has been made to describe the principal techniques which are available for the synthesis of nitriles. Specific procedural details have been omitted, since these may easily be obtained from original sources. However, the scope, limitations, and postulated reaction mechanisms

TABLE 6

Toxicity of nitriles

COMPOUND	MEDIAN LETHAL DOSE	DOSAGE METHOD	TEST ANIMAL	REFERENCE
	grams/kilogram			
HCN	0.006	Oral	Mouse	(214)
$CNCOOCH_3$	*ca.* 0.01	Inhalation	Mouse	(190)
CH_3CN	2.65	Intravenous	Rabbit	(153)
CH_3CH_2CN	1.08	Intravenous	Rabbit	(153)
$CH_2{=}CHCN$	0.085	Intravenous	Rabbit	(153)
$CH{\equiv}CHCN$	0.0147	Intravenous	Rabbit	(153)
$CH_3CH_2CH_2CN$	0.98	Intravenous	Rabbit	(153)
$CH_2{=}CHCH_2CN$	0.06	Intravenous	Rabbit	(153)
$C_6H_5CH_2CH_2CN$	0.039	Intravenous	Rabbit	(153)
$C_6H_5CH{=}CHCN$	0.034	Intravenous	Rabbit	(153)
$C_6H_5C{\equiv}CCN$	0.01	Intravenous	Rabbit	(153)
$C_5H_{11}C{\equiv}CCN$	0.19	Intravenous	Rabbit	(153)
$CNC{\equiv}CCN$	0.195	Intravenous	Rabbit	(153)
$RCH(NH_2)CN$	0.02–0.16		Rabbit	(509)
$C_5H_{11}CN$	0.31	Subcutaneous	Guinea pig	(153)

of each reaction have been presented as a guide to chemists who are confronted with the choice of a method for specific synthetic problems.

In general, the aliphatic nitriles are most conveniently prepared from alkyl halides or sulfates by metathesis reactions with alkali cyanides. With alicyclic, secondary, and tertiary halides, it may be preferable to employ the Grignard reagent and cyanogen or cyanogen chloride. If the requisite aldehyde or acid is available, the procedures involving oxime and amide dehydration are to be recommended.

A comparison of various laboratory techniques for the preparation of aromatic nitriles was made by Tingle in 1906 (564). In the preparation of benzonitrile the following yields were recorded: Sandmeyer reaction from aniline (64 per cent), phosphorus pentoxide dehydration of benzamide (95 per cent), modified Letts reaction of benzoic acid and lead thiocyanate (71 per cent), fusion of sodium

benzenesulfonate and potassium cyanide (26 per cent). Subsequent developments have improved some of the above yields and provided other methods that are to be recommended. These include the Rosenmund–von Braun reaction of halides and copper cyanide, the Friedel–Crafts–Karrer cyanogenation of hydrocarbons with cyanogen chloride and aluminum chloride, and the fusion of acids with benzenesulfonamide.

Acyl or aroyl cyanides are best obtained by metathesis reactions of the acid halides with copper or pyridinium cyanide or from methyl ketones through dehydration of the oximino derivative with acetic anhydride.

XII. References

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