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CROWN ETHERS IN ORGANIC SYNTHESIS. II.[1] CATALYTIC DEHYDRATION OF ALDOXIMES

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Phase transfer (crown ether or quaternary ammonium salt) catalyzed reaction of benzaldoxime with potassium salts (cyanide or halide) produces a 3:1 mixture of benzonitrile and benzamide. A base-catalyzed mechanism is proposed. Extension of the procedure to provide a general, one-pot conversion of aldehydes to nitriles is indicated.

In an attempt to extend our recently reported[1] procedure for in situ cyanosilylation of carbonyl compounds to the imine system, we were surprised to observe that benzaldoxime **1** was transformed into a 73:27 mixture of benzonitrile and O - trimethylsilylbenzaldoxime **2**. This extremely mild conversion of oxime to

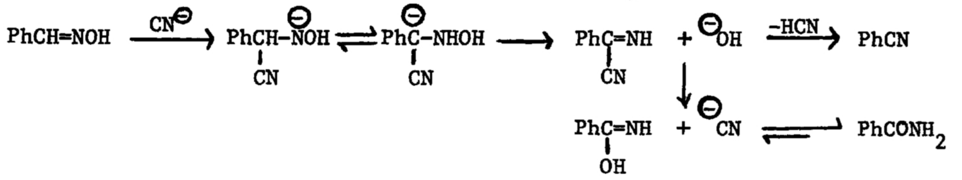
$$\underset{\mathbf{1}}{PhCH{=}NOH} + \underset{(3\ equiv)}{KCN} + \underset{(2.5\ equiv)}{(CH_3)_3SiCl} + \underset{(.05\ equiv)}{\text{18-Crown-6}} \xrightarrow{CH_3CN,\ \text{reflux 4 days}}$$

$$PhCN + \underset{\mathbf{2}}{PhCH{=}NOSi(CH_3)_3}$$

nitrile was intriguing, and led us to investigate the reaction in further detail. We subsequently found that treatment of either **1** or **2** (25 mmol in 5 ml acetonitrile at reflux) with a catalytic amount (0.05 equiv each) of potassium cyanide and 18-crown-6[2] resulted in a 3:1 mixture of benzonitrile and benzamide in almost quantitative yield. In addition, reaction of **2** with 0.2 equiv each of the two catalysts resulted in a four-fold increase in the rate of benzonitrile production, thus establishing a direct dependence upon the amount of cyanide ion in solution.

$$\underset{\mathbf{1}}{PhCH{=}NOH} \text{ or } \underset{\mathbf{2}}{PhCH{=}NOSi(CH_3)_3} \xrightarrow[\substack{\text{18-crown-6}\\ CH_3CN,\ \Delta}]{KCN} PhCN + PhCONH_2$$

It turns out that in 1926 Passerini reported[3] the conversion of benzaldoxime into benzonitrile in "moderate" yield by the action of potassium cyanide in aqueous ethanol. We repeated his work, and were able to obtain 33% yield. Passerini considered the reaction to occur via primary addition of KCN to the oxime double bond followed by loss of water from the labile addition product. Although such a mechanism could account for both of our products[4] (Scheme I), we did not favor hydroxide as a leaving group. We therefore decided to try other potassium salts, hoping to derive pertinent information by comparing the relative reaction rates with the relative basicities or nucleophilicities of the various anions.



$$\mathrm{PhCH{=}NOH} \xrightarrow{\mathrm{CN}^{\ominus}} \underset{\mathrm{CN}}{\mathrm{PhCH{-}\overset{\ominus}{N}OH}} \rightleftarrows \underset{\mathrm{CN}}{\mathrm{Ph\overset{\ominus}{C}{-}NHOH}} \longrightarrow \underset{\mathrm{CN}}{\mathrm{PhC{=}NH}} + {}^{\ominus}\mathrm{OH} \xrightarrow{-\mathrm{HCN}} \mathrm{PhCN}$$

$$\downarrow$$

$$\underset{\mathrm{OH}}{\mathrm{PhC{=}NH}} + {}^{\ominus}\mathrm{CN} \rightleftarrows \mathrm{PhCONH_2}$$

SCHEME I

The results obtained (Table), when taken in conjunction with Liotta's recent work[5] on the relative nucleophilicities of "naked" anions in acetonitrile, rule out a nucleophilic rationale such as Passerini's, at least as the rate determining step. Interestingly, $CN^{\ominus}$, $I^{\ominus}$ and $Br^{\ominus}$ catalyze the reaction at virtually identical rates, $Cl^{\ominus}$ works at a much reduced rate, and $F^{\ominus}$ is slower yet.

TABLE

Reaction[a] of Benzaldoxime with $K^{\oplus}X^{\ominus}$/18-Crown-6

Solvent	$X^{\ominus}$	Product Ratio[b,c]	
		PhCN	$PhCONH_2$
CH_3CN	$CN^{\ominus}$	76	24
PhH	$CN^{\ominus}$	54	46 (@ 80% conversion)
CH_3CN	$I^{\ominus}$	81	19
"	$Br^{\ominus}$	77	23
"	$Cl^{\ominus}$	79	21 (slow)
"	$F^{\ominus}$	Very slow reaction	
"	$OAc^{\ominus}$	No reaction	
"	$OH^{\ominus}$	Slight reaction	

[a] Reaction times, under the conditions listed in text above, ranged from 3 to 10 days.

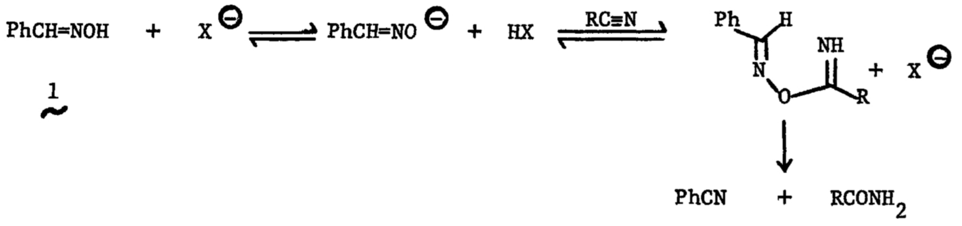
[b] Analyzed by glpc, 10% UCW 98 on Chromosorb W-AW-DMCS.

[c] Isolated yield (silica gel chromatography with ether, followed by 10% MeOH/ether) and product ratio were shown to be nearly identical.

The real clue to the reaction mechanism came when we were able to identify acetamide as a by-product. This allowed us to propose the mechanism outlined in Scheme II. A completely analogous sequence explains the conversion of the silylated oxime into benzonitrile and benzamide, the only difference being an initial nucleophilic displacement at silicon.

Ample precedent for a scheme of this type is to be found in the work of Ho on the dehydration of aldoximes using nitrilium salts[6a] and the reaction of aryl aldoximes with trichloroacetonitrile at reflux.[6b] Additional support for the mechanism proposed in Scheme II was provided by our observation that the methyl ether of benzaldoxime, $PhCH=NOCH_3$, is stable to our reaction conditions, with less than 5% conversion to benzonitrile after 6 days reaction time. This result is inconsistent with the Passerini mechanism, which would predict little difference between elimination of water vs elimination of methanol. The possibility that the reaction proceeds via acid catalyzed O-acylation by acetonitrile (or HCN) appears to be contradicted by a number of observations, including the fact that addition of acid retards the reaction rate dramatically.

SCHEME II



Having satisfied ourselves with a reasonable mechanistic explanation, we turned our attention to the generality of the reaction and to the development of a more synthetically useful procedure.

Quaternary ammonium and phosphonium salt phase-transfer catalysts exhibit known similarities to crown ethers in promoting two-phase reactions.[7] We therefore treated benzaldoxime (0.1 mol) in benzene (1 ml) with saturated aqueous sodium cyanide (12 ml) in the presence of Aliquat 336 (methyltricaprylylammonium chloride from General Mills, 0.02 equiv). Heating at 80°C for 10 hours with rapid stirring produced benzonitrile and benzamide in 66.1% and 22.2% isolated yields respectively. Hoping to obviate the use of cyanide, we then studied the catalytic effect of other anions. For this study, benzaldoxime (50mmol) in refluxing acetonitrile (5 ml) was treated, in the presence of Aliquat 336 (0.04 equiv), with a sufficient amount of saturated salt solution to provide a 2-fold excess of the anion. The following order of reaction rates was found:

$$NaCN >> KI \approx NaSCN >> NaBr >>> NaCl$$

Unfortunately, the cyanide-catalyzed reaction was the only one which appeared to proceed at a preparatively useful rate under these conditions (30 hours to completion), and produced an 85:15 mixture of benzonitrile/benzamide. Reasonable reaction times (24 hours) could be obtained with the KBr/18-crown-6 system also, provided that the amount of solvent was reduced from 5 ml to 1 ml per 25 mmol benzaldoxime. Understandably, this also affected the product ratio, giving 64:36 benzonitrile/benzamide. These results indicate the versatility which can be obtained by proper adjustment of the reaction variables.

Glass and Hoy have recently communicated[8] a mild procedure for the conversion of aromatic aldehydes into aromatic nitriles by treatment of the corresponding N-tosylimines with sodium cyanide in hexamethylphosphoric triamide. Whereas the Glass-Hoy method appeared at this point to be superior to our procedure, it had an inherent disadvantage in that it could not be applied to aliphatic aldehydes. This was found to be not the case with our system. For example, treatment of n-butyraldoxime with KBr/18-crown-6 under identical conditions to those indicated in Table I for 14 days resulted in an extremely clean conversion to butyronitrile (> 90% yield). No butyramide was observable in the reaction mixture. The conversion of aldehyde to nitrile can also be accomplished without isolation of the aldoxime. The following procedure is representative:

> p-Tolualdehyde (0.1 mol), hydroxylamine hydrochloride (0.11 mol) and sodium hydroxide (0.11 mol) in water (15 ml) were stirred for 30 minutes. Acetonitrile (10 ml), NaCN (0.2 mol) and Aliquat 336 (0.08 equiv) were added, and rapidly stirred mixture was refluxed for 27 hours. Extraction with ether, followed by distillation provided p-tolunitrile in 94.2% overall yield (88% was obtained by Glass and Hoy[8]). Glpc of the crude reaction mixture also indicated the presence of 4-5% p-toluamide.

A similar procedure allowed clean conversion of n-valeraldehyde to valeronitrile.

Our continuing studies into the generality and synthetic potential of these procedures will be reported in due course.

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