p-Cyanophenol from p-Nitrobenzaldoxime by an Apparent Dehydration–Displacement, and a Suggested Modification of the Miller–Loudon Conversion of Aldehydes to Nitriles

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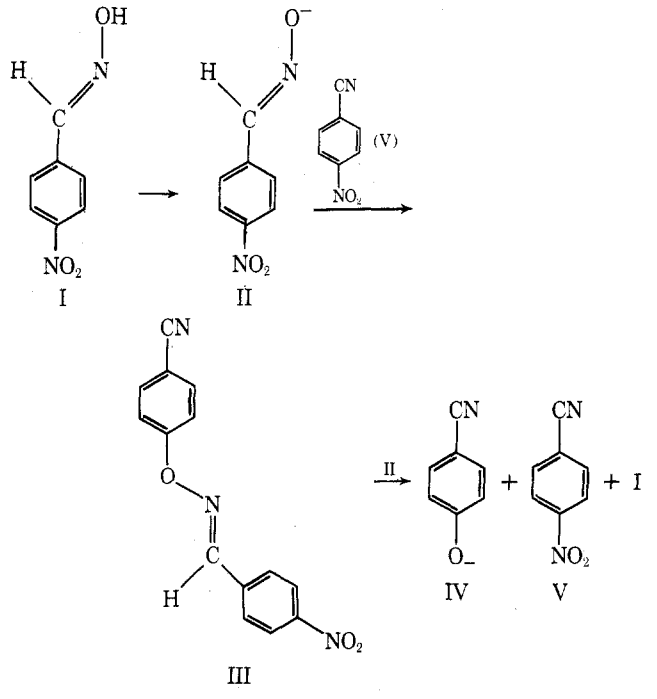
In Me_2SO solution a salt of *syn*-*p*-nitrobenzaldoxime generates the *p*-cyanophenoxide anion via a chain process in which *p*-nitrobenzonitrile, formed in trace amounts from the oximate anion, is attacked by the oximate with displacement of the nitro group to form *O*-(*p*-cyanophenyl)-*p*-nitrobenzaldoxime (III), which undergoes cleavage as a result of attack by a second oximate anion. The cleavage produces the cyanophenoxide anion and *p*-nitrobenzaldoxime and regenerates the *p*-nitrobenzonitrile, which, reentering the cycle, acts as a chain carrier. Addition of a small amount of *p*-nitrobenzonitrile to the mixture permits the reaction to be carried out in a short time, and the further addition of a suitable base, by converting the oxime formed in the cleavage to the reactive oximate ion, permits the high-yield transformation to the cyanophenol. The salt of *syn*-*o*-nitrobenzaldoxime behaves similarly. The cleavage of the *O*-*p*-cyanophenyl ether formed from the anion of an oxime and *p*-nitrobenzonitrile affords a simple means of converting an aldehyde to a nitrile. Thus, in the presence of a suitable base, piperonaldoxime, employed as such or prepared in situ, gives a high yield of piperonylonitrile.

The observation[1] that an oximate anion is sufficiently basic to effect the cleavage of an *O*-arylaldoxime, e.g., III, in aprotic solution, generating a phenoxide anion, e.g., IV, and a nitrile, e.g., V, leads to the prediction that in Me_2SO solution at room temperature the anion (II) of *p*-nitrobenzaldoxime would readily change to the cyanophenoxide anion IV. To initiate the process it would only be necessary for the oximate II to generate a small amount of *p*-nitrobenzonitrile V, which would react with the oximate ion II undergoing displacement of the nitro group and forming the *O*-arylaldoxime[1] III. Cleavage of III by a second oximate anion, II, acting as a base, would produce the cyanophenoxide IV, regenerating the nitronitrile V, which reentering the cycle would become a chain carrier, and also producing the free oxime I. The crucial step, the formation of



the chain-carrying nitronitrile V from the oximate ion II, sufficiently resembles the formation of nitriles from some aldoximes under the influence of aqueous base[2] that it could be expected to occur to the extent necessary to initiate the process. However, if not enough of the nitronitrile V were formed in this way to permit the rapid conversion of II to IV and I, a little of the chain carrier could be added to serve as a "catalyst". Only half of the oximate II used would be converted to the cyanophenoxide IV unless additional base were added to reconvert the free oxime I also formed to the anion II.

To test these predictions, the sodium salt of *syn*-*p*-nitrobenzaldoxime[3] (II) was stirred in Me_2SO for 1.25 hr at room temperature. From this solution a small amount (7.5%) of *p*-cyanophenol was isolated and 73% of the *p*-nitrobenzaldoxime was recovered. The mass spectrum of early fractions from the chromatography of the alkali-insoluble residue indicated the presence of traces of the nitronitrile V. When the reaction was repeated with a little (2 mol %, based on the oximate used) added nitronitrile V, the conversion to the cyanophenol was 40% and 44% of the oxime was recovered. Thus, there seems little doubt but that the reactions proceed as indicated.

It should be possible to increase the conversion of the oxime to the cyanophenol by introducing additional base into the solution to reconvert the oxime formed in the last step to the salt I. When an additional equivalent of a base, finely ground potassium hydroxide, was added to a mixture of the sodium salt of *p*-nitrobenzaldoxime (II) and a trace of the nitronitrile V, and the mixture was stirred for 5 hr at room temperature (potassium hydroxide has a limited solubility in Me_2SO and dissolves slowly at room temperature), the yield of the cyanophenol was 79%. With the free oxime and a somewhat weaker base (sodium carbonate, 2 equiv) at a higher temperature (114°) the reaction was essentially complete in 10 hr and the yield of *p*-cyanophenol was 83%. A similar reaction without added *p*-nitrobenzonitrile proceeded more slowly, but gave a good yield (80%) after 18.5 hr. With the very strong base (sodium methylsulfinylmethide, 2 equiv) none of the cyanophenol could be detected.

Similar results were obtained with the salt of *syn*-*o*-nitrobenzaldoxime,[3] although a longer reaction time was required and the yield of product, *o*-cyanophenol, was lower. Thus, when a mixture of *syn*-*o*-nitrobenzaldoxime sodium salt, a small amount of *o*-nitrobenzonitrile, and 1 equiv of finely ground potassium hydroxide was stirred at room temperature for 8 hr, the yield of *o*-cyanophenol was 66% (allowing for conversion of the nitronitrile added). In similar tests with the free oxime and 2 equiv of potassium hydroxide at room temperature and with the sodium salt alone at 100°, but in neither case with the addition of the

nitronitrile, there was very little indication (TLC) of formation of product after long periods (greater than 24 hr). Thus, the o-cyanophenol obtained in the first experiment did not arise by isomerization of the aldoximate ion to the anti form and internal displacement of the nitro group.

In the process under study, an aldoxime is in effect dehydrated to the corresponding nitrile through the cleavage of an O-aryl oxime ether (III) formed by displacement of an activated nitro group. The displacement and cleavage form an attractive[1] means of converting certain nitro compounds to phenols. The cleavage of an oxime ether similar to III is the step which permits the conversion of an aldehyde to a nitrile by the Miller–Loudon[4] process, in which the ether is formed from the aldehyde by reaction with O-2,4-dinitrophenylhydroxylamine. It would seem possible to simplify the latter process by utilizing in situ the ether formed from a salt of the oxime, perhaps also formed in situ, in the displacement reaction with a suitable nitro compound, e.g., V, thus avoiding the need for the use of the dinitrophenylhydroxylamine. The modified process might then be as convenient as the Vonwinkel–Bartel[5] method of converting aldehydes to nitriles by dehydration of the oximes, which need not be isolated, with dicyclohexylcarbodiimide in the presence of a copper catalyst. To test the modified process, piperonaldoxime was stirred in Me_2SO with a slight excess of p-nitrobenzonitrile and 2 equiv of potassium hydroxide at room temperature for 3–4 hr. The expected nitrile was obtained in 92% yield (73% after recrystallization to analytical purity). Furthermore, it is not necessary to isolate the oxime; a similar reaction in which the oxime was prepared in situ also gave a good yield of the nitrile.

Although the modified process has been tested on only one of the aldehydes used by Miller and Loudon,[4] the success with both aromatic and aliphatic oximes in the application[1] of the same reactions for the preparation of phenols and the generality of the Miller–Loudon process suggest a rather broad applicability. An obvious exception is a nitroaromatic aldehyde whose oxime (e.g., I) can participate in the reactions discussed above, leading indirectly to the replacement of the nitro group by hydroxyl as well as to the nitrile formation.

The ideal base for use in the present processes would be one strong enough to permit the desired reactions but not capable itself of displacing the nitro group from the nitronitrile V. The success with potassium hydroxide may result from its low solubility and low rate of solution in Me_2SO, with the result that as it enters the solution it is largely neutralized by the free oxime present or produced and hence does not attack the nitronitrile to a damaging extent. The use of strenuous conditions may promote the displacement of the nitro group by other anions; in the reaction employing sodium carbonate at 114° a trace of p,p′-dicyanodiphenyl ether,[6] presumably formed from the nitronitrile V and the cyanophenoxide ion IV, was isolated. Miller and Loudon[4] found ethanolic triethylamine to be a sufficiently strong base to cleave the isolated O-aryloxime, corresponding to III, in their conversion of aldoxime ethers to nitriles. This observation suggests the possibility of using triethylamine as the only base in the reaction of piperonaldoxime with p-nitrobenzonitrile. However, a trial gave none of the nitrile, and the mixture did not develop the transient deep red color characteristic of the successful runs with potassium hydroxide. The similar color in the cyanide ion reactions[1] has been attributed to the presence of Jackson–Meisenheimer complexes,[7] which, although formed reversibly and not necessarily leading to the observed products, give indication through the color formation that the anion is sufficiently basic to give an addition product with the aromatic nitro compound. In Me_2SO triethylamine evidently is not sufficiently basic to develop the necessary concentration of the oximate anion.

Experimental Section

Either a Perkin-Elmer 521 or a Beckman IR-12 spectrophotometer was used for ir spectra, which were run as KBr disks. NMR spectra were recorded on a Varian A-60A or A-56/60 spectrometer. Mass spectra were recorded by Mr. J. Wrona and associates on an Atlas CH5 spectrometer at 70 eV. Microanalyses were performed by Mr. J. Nemeth and associates. Products were identified by comparison of ir and NMR spectra unless otherwise noted. All starting materials were either commercially available reagent grade and were used as received or were prepared in the laboratory by well-known synthetic routes. Me_2SO was stored over Linde Type 4A molecular sieves for 2 weeks before use.

1. p-Cyanophenol from the Sodium Salt of *syn*-p-Nitrobenzaldoxime. A. With No Added Reagents. The sodium salt was prepared by adding *syn*-p-nitrobenzaldoxime[8] to 1 equiv of sodium ethoxide in absolute ethanol. After dilution with absolute ether the precipitated salt was collected and dried. A solution of 1.88 g (10 mmol) of the salt in 35 ml of Me_2SO was stirred at room temperature for 1.25 hr and then poured into 150 ml of ice–water containing 2 ml of concentrated hydrochloric acid. The solution was extracted with ether and the ether extract was washed with water, dried ($MgSO_4$), and evaporated. The light yellow residue was chromatographed on silica gel. Elution with hexane–benzene (1:1) produced 1.21 g (73% recovery) of p-nitrobenzaldoxime (NMR spectrum identical with that of an authentic sample). Elution with benzene produced 0.09 g (7.5% conversion) of p-cyanophenol (NMR spectrum identical with that of an authentic sample).

B. With Added p-Nitrobenzonitrile. A mixture of the sodium salt (1.88 g, 10 mmol), p-nitrobenzonitrile (0.09 g, 0.06 mmol), and 35 ml of Me_2SO was stirred at room temperature for 1.25 hr and treated as described above. From the chromatography 0.74 g (44% recovery) of the p-nitrobenzaldoxime and 0.48 g (40% conversion) of p-cyanophenol, both identified by NMR spectra identical with those of authentic samples, were obtained.

C. With Added p-Nitrobenzonitrile and Potassium Hydroxide. A mixture of the sodium salt (1.13 g, 6 mmol), p-nitrobenzonitrile (20 mg, 0.14 mmol), freshly ground potassium hydroxide (338 mg, 6 mmol), and Me_2SO (20 ml) was stirred at room temperature for 5 hr. The mixture was poured into 120 ml of ice–water and the acidified solution was extracted with ether. The ether solution was extracted with 5% aqueous sodium hydroxide and the alkaline solutions were acidified and reextracted with ether. Evaporation of the dried ($MgSO_4$) ether solution gave 566 mg (79%) of slightly impure p-cyanophenol, mp 97–102° (lit.[9] mp 112°).

2. p-Cyanophenol from *syn*-p-Nitrobenzaldoxime via Salt Formation in Situ. A. Use of Sodium Carbonate with Added p-Nitrobenzonitrile. Anhydrous powdered sodium carbonate (4.24 g, 40 mmol) was added to Me_2SO (25 ml) and the mixture was heated to 70°. A solution of *syn*-p-nitrobenzaldoxime (3.32 g, 20 mmol) and p-nitrobenzonitrile (0.15 g, 1 mmol) in Me_2SO (35 ml) was added and the resulting bright orange mixture was heated at 114° for 10.5 hr. The cooled mixture was poured into 150 ml of ice–water containing 5 ml of concentrated hydrochloric acid. Ether extraction followed by reextraction into aqueous 5% sodium hydroxide and acidification gave an oil which soon crystallized to give 1.97 g (83%) of p-cyanophenol, mp 103–107°. Recrystallization from benzene raised the melting point to 111–112° (lit.[9] mp 112°). The spectra (ir and NMR) were identical with those of an authentic sample, and the molecular weight as determined by mass spectrometry was 119 (calcd 119).

The ether solution above which had been extracted with alkali was washed with water, dried, and evaporated and the residue was chromatographed on silica gel. Benzene elution gave 0.07 g (3%) of p,p′-dicyanodiphenyl ether: mp 178–180° (lit.[6] mp 180°); ir (KBr) 2230, 1595, 1495, 1253, 1160, 1175, 880, 845 cm^{-1}; NMR ($CDCl_3$) δ 7.66 (d, 2 H), 7.08 (d, 2 H); mass spectrum *m/e* (rel intensity) (I) 51 (11), 75 (17), 76 (10), 102 (41), 192 (24), 220 (100).

B. Use of Sodium Carbonate without Added p-Nitrobenzonitrile. A similar reaction with no added p-nitrobenzonitrile proceeded more slowly at the same temperature as judged by the color change and the composition as followed by TLC. After a few hours a spot with retention time identical with that of p-nitrobenzonitrile was observed in the TLC. After 18.5 hr at 114° the reaction appeared complete (TLC) and the mixture was worked up as described above, giving 1.90 g (80%) of p-cyanophenol.

3. o-Cyanophenol from the Sodium Salt of *syn*-o-Nitrobenzaldoxime. A reaction mixture similar to 1c employing the sodium salt of *syn*-o-nitrobenzaldoxime[8] (1.13 g, 6 mmol), o-nitrobenzonitrile (20 mg, 0.14 mmol), freshly ground potassium hydroxide (338 mg, 6 mmol), and Me_2SO (20 ml) stirred at room temperature for 8 hr and worked up as in 1c gave 500 mg (66%) of o-cyanophenol, mp 94–95° (lit.[10] mp 98°).

4. Piperonylonitrile. A. From Isolated Piperonaldoxime. The oxime employed, prepared quantitatively in aqueous ethanol, melted at 107–110° (lit.[11] syn isomer 112°, anti isomer 146°); NMR [$(CD_3)_2SO$] δ 8.07 (s, 1, HC=N), 11.01 (s, 1, NOH). A mixture of the oxime (1 g, 6 mmol), p-nitrobenzonitrile (900 mg, 6.1 mmol), freshly ground potassium hydroxide (676 mg, 12 mmol), and 20 ml of Me_2SO was stirred at room temperature for 3–4 hr. The mixture was poured into ice water (150 ml) and the solution was acidified and extracted with ether. The ethereal extract was successively washed with cold 5% aqueous sodium hydroxide and water. After drying ($MgSO_4$) and removal of the solvent in vacuo, 807 mg (92%) of the nitrile was obtained. Recrystallization from ethanol–water gave analytically pure material (645 mg, 73%), mp 87–89° (lit.[4] mp 91–93°).

Anal. Calcd for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.16; H, 3.46; N, 9.66.

B. From Piperonaldoxime Prepared in Situ. A mixture of hydroxylamine hydrochloride (462 mg, 6.5 mmol), sodium methoxide (350 mg, 6.5 mmol), and 20 ml of Me_2SO was stirred at room temperature for 15 min. Piperonal (1 g, 6.5 mmol) was added and the mixture was heated at 70° for 2 hr. Heating was then discontinued, p-nitrobenzonitrile (980 mg, 6.5 mmol) and freshly ground potassium hydroxide (758 mg, 13 mmol) were added, and the mixture was stirred at room temperature for 3–4 hr. Work-up as in part A and recrystallization from ethanol–water afforded 742 mg (78%) of piperonylonitrile, mp 87–89[10] (lit.[4] mp 92–93°).

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Registry No.—I sodium salt, 56086-86-3; V, 619-72-7; p-cyanophenol, 767-00-0; potassium hydroxide, 1310-58-3; sodium carbonate, 497-19-8; p,p'-dicyanodiphenyl ether, 6508-04-9; o-cyanophenol, 611-20-1; *syn*-o-nitrobenzaldoxime sodium salt, 56086-87-4; o-nitrobenzonitrile, 612-24-8; piperonylonitrile, 4421-09-4; *syn*-piperonaldoxime, 20747-41-5; *anti*-piperonaldoxime, 20747-42-6.

References and Notes

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Photoreaction of Benzofurazan and Dimethyl Acetylenedicarboxylate. Synthesis of Isomeric Isoxazoles. Carbon-13 Nuclear Magnetic Resonance Spectra of Isoxazoles and Oxazoles[1]

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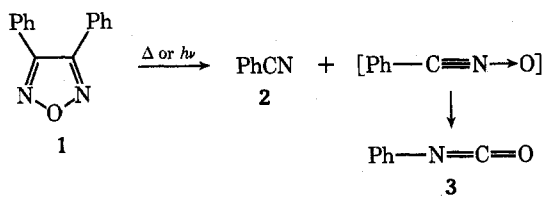
When benzofurazan is irradiated by ultraviolet light (3000 Å), a reactive nitrile oxide intermediate is produced. In order to trap this intermediate, benzofurazan has been irradiated in dimethyl acetylenedicarboxylate (DAD). The nitrile oxide reacts with DAD to produce various geometrical isomers of dimethyl 3-(4-cyanobuta-1,3-dienyl)isoxazole-4,5-dicarboxylate (8). The isoxazoles have been characterized by their ^{13}C NMR spectra. All the isomers have been degraded to the same dimethyl 3-carboxaldehydeisoxazole-4,5-dicarboxylate (9) by ozonolysis. Cis,cis, trans,cis, and trans,trans isomers of 8 have been identified.

The thermal splitting of diphenylfurazan (1) to give benzonitrile (2) and phenyl isocyanate (3) has been known since 1888.[3,4] Ultraviolet irradiation of a 5% ethereal solution of 1 produces the same two compounds.[5]



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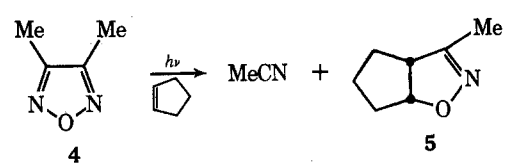
In order to prove the presence of the highly reactive nitrile oxide intermediate, dimethylfurazan (4) was irradiated in the presence of excess cyclopentene to yield 3-methyl-4,5-trimethylene-2-isoxazoline (5).[5] Irradiation of 1 in cyclopentene produced only 2 and 3 in yields similar to those obtained in the absence of cyclopentene. It has been suggested that this failure to trap the benzonitrile oxide by 1,3-dipolar addition is due to a rearrangement of the intermediate to the isocyanate which is faster than the ground-state 1,3-dipolar addition to cyclopentene.[5] Photolysis of 1 in benzene has yielded diphenylfuroxan, 3,5-diphenyl-1,2,4-oxadiazole, and 3.[6]



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It has been shown recently that the irradiation of benzo-, naphthalo-, and phenanthrofurazan derivatives in the presence of triethyl phosphite affords 1,4-dinitrile derivatives in high yields.[7] An azepide 7 has been isolated from the reaction mixture after irradiation of benzofurazan in ben-