# The Halogen-Catalyzed Pyridine N-Oxide Oxidation of Isonitriles to Isocyanates

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The reactions of isopropylisonitrile with pyridine N-oxide in the presence of chlorine, bromine, and iodine have been studied. Reaction with iodine yields isopropyl isocyanate; the kinetics of the reaction were found to be over-all third order. Reaction with bromine yields an initial adduct (II) whose structure has been determined. Further reaction of II with isonitrile yielded isopropyl isocyanate. Reaction of chlorine with isopropylisonitrile and pyridine N-oxide gave the isocyanate in a very slow reaction. Phenyl- and *p*-anisylisonitriles also gave isocyanates with pyridine N-oxide and iodine; the kinetics were measured and compared with those of isopropyl isocyanate.

Recently the oxidations of isopropyl- and phenylisonitriles to the corresponding isocyanates with dimethyl sulfoxide in the presence of halogen were reported.[1] Previously the oxidation of isonitriles to isocyanates with mercuric oxide[2] and ozone[3] and the reaction of isonitrile dihalides with water (which yields the amine, presumably *via* the isocyanate)[4] have been reported. In this paper are reported the results of studies on the mechanism of isonitrile oxidation.

Reaction temperatures for the isopropylisonitrile–iodine–dimethyl sulfoxide reaction were undesirably high for kinetic studies. Preliminary studies showed that pyridine N-oxide, iodine, and isopropylisonitrile also yielded isopropyl isocyanate in chloroform. The kinetics of the reaction of isopropyl-, phenyl-, and *p*-anisylisonitriles with pyridine N-oxide and iodine in chloroform solvent were determined using infrared spectroscopy to follow the increase in intensity of the product peak at 2250 cm$^{-1}$. The reactions appeared to be cleanly third order (first order in isonitrile, pyridine N-oxide, and iodine). Iodine was not consumed, and pseudo-second-order kinetics were observed experimentally. The reaction was run in a normal sealed cell using the thermostating of the instrument (32 ± 0.5°) for temperature control. The 10% agreement of the rate constants appeared satisfactory to establish the order of the reaction. Each run was accurately pseudo second order graphically. The nonconsumption of iodine in the reaction was established using visible absorption measurements. At 90% reaction the iodine was still present at 95% of its original concentration. The results are shown in Table I.

The rate constant of reaction of isopropylisonitrile was about 1.8 × $10^1$ l.$^2$/mole$^2$ sec; those for phenyl- and *p*-anisylisonitriles were 3.3 × $10^1$ and 6.9 × $10^1$ l.$^2$/mole$^2$ sec, respectively. Thus the reaction rate increased, but not dramatically, on going to phenyl- and *p*-anisylisonitriles. Attempts were made to measure the rate of reaction of *p*-nitrophenylisonitrile, but the compound was not sufficiently soluble in chloroform to measure.

Iodine did not react with the isonitrile to form a stable isonitrile diiodide detectable by infrared spectroscopy (the dibromide has a C═N stretching absorption comparable in intensity to a normal ketone carbonyl band). Pyridine N-oxide had no effect on the isonitrile in the absence of a halogen, and the infrared spectrum of a mixture of a pyridine N-oxide and isonitrile appeared to be the sum of the spectra of the two species. A mechanism consistent with the observed data is shown in eq 1–3. Bromine and chlorine form stable isonitrile dihalides of the type shown in eq 1. The kinetics demand that all three reactants participate in the transition state (or prior equilibria). Infrared studies show that the isonitrile diiodide, if formed, cannot be present in large concentrations, a result also demanded by observed kinetics; thus step 1 must be fast with a small equilibrium constant. Either the reaction of the diiodide with pyridine N-oxide or the decomposition of some adduct (*e.g.*, I) can be rate determining. If I is formed reversibly, the equilibrium constant in eq 2 must be small, since no C═N frequency is seen in the infrared spectrum of the reaction.

Variations of this mechanism not precluded by the observed third-order kinetics are possible. One varia-

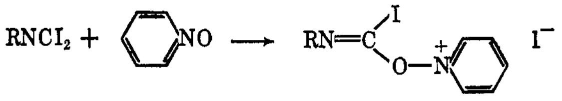
Table I

Rates of Reaction of Isonitriles with Iodine and Pyridine N-Oxide (PNO)

| R | [RNC] × $10^3$ *M* | [PNO] × $10^3$ *M* | [$I_2$] × $10^3$ *M* | $k_3$ × $10^{-1}$, l.$^2$/mole$^2$ sec |
|---|---|---|---|---|
| $C_6H_5$ | 4.97 | 5.31 | 2.65 | 3.30 |
| | 4.73 | 10.1 | 2.53 | 2.73 |
| | 9.47 | 5.06 | 2.53 | 3.22 |
| | 5.37 | 5.07 | 5.16 | 2.87 |
| | | | Av | 3.0 ± 0.3 |
| *p*-OMe$C_6H_4$ | 3.74 | 2.74 | 10.1 | 6.38 |
| | 3.85 | 5.64 | 5.20 | 6.11 |
| | 7.48 | 2.74 | 5.07 | 6.96 |
| | 3.56 | 2.62 | 4.82 | 7.61 |
| | 7.48 | 2.74 | 5.07 | 7.30 |
| | | | Av | 6.9 ± 0.7 |
| $(CH_3)_2CH$ | 1.01 | 1.24 | 1.02[a] | 1.84 |
| | 0.96 | 1.19 | 4.86 | 1.50 |
| | 0.817 | 1.03 | 4.87 | 2.05 |
| | 1.63 | 1.03 | 4.87 | 1.77 |
| | 0.817 | 2.05 | 4.87 | 2.05 |
| | | | Av | 1.84 ± 0.2 |

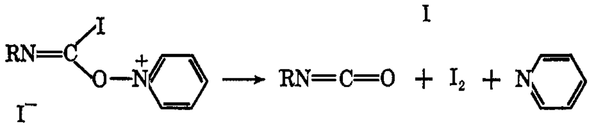
[a] × $10^2$ *M*.

$$RNC + I_2 \rightleftharpoons RN{=}CI_2 \qquad (1)$$



(2)

I



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[1] H. W. Johnson, Jr., and P. H. Daughhetee, Jr., *J. Org. Chem.*, **29**, 264 (1964).

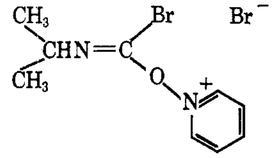
[2] A. Gautier, *Ann. Chim.* (Paris), [4] **17**, 229 (1869).

[3] H. Feuer, H. Rubinstein, and A. T. Nielsen, *J. Org. Chem.*, **23**, 1107 (1958).

[4] H. Guillemard, *Ann. Chim.* (Paris), [8] **14**, 311 (1908); *Bull. Soc. Chim. France*, **31**, 605 (1904); J. U. Nef, *Ann.*, **270**, 257 (1892).

tion is the attack of an $I^+$ donor ($I_2$ presumably) on the isonitrile to yield an iodocarbonium ion, which in turn reacts with pyridine N-oxide to yield intermediate I. In a second variation the iodocarbonium could react with pyridine N-oxide to yield the product directly. In this work it has not been thought necessary to distinguish these possibilities, since they are essentially variations of the scheme shown. Mechanisms utilizing attack by pyridine N-oxide as an initial step have been excluded, since no detectable interaction of the isonitrile with pyridine N-oxide occurs, and since it is known that isonitriles are much more susceptible to electrophilic than to nucleophilic attack.

Reaction of pyridine N-oxide with isopropylisonitrile and bromine in chloroform gave an immediate yellow precipitate (II), mp 95–96°. This precipitate showed a correct analysis for a 1:1:1 adduct of isonitrile, pyridine N-oxide, and bromine. The infrared spectrum showed a bond at 5.86 $\mu$ (Nujol mull); the C=N frequency in isonitrile halides occurs in this region. Pyridine ring vibrations at 6.25 and 6.78 $\mu$ were also present. Reaction of II with potassium hydroxide gave *sym*-diisopropylurea; reaction with *sec*-butylamine in methanol gave N-isopropyl-N′-*sec*-butylurea. Upon heating *in vacuo*, a complex mixture of products including pyridine, isopropyl isocyanate, isopropylisonitrile, isopropylisonitrile dibromide, and much higher boiling material was formed. Upon treatment of the compound with lithium aluminum hydride, there were formed pyridine and methylisopropylamine. No alkylated pyridines were detected by vapor phase chromatography. The unknown gave an immediate precipitate with silver nitrate. It thus appears that no new C–C or C–N bond was established between the isonitrile and pyridine residues in the formation of the unknown, and it is formulated as shown below.



II

Treatment of II with isopropylisonitrile gave isopropyl isocyanate and isopropylisonitrile dibromide. On standing at room temperature, II decomposed to bromine and polymer. Structure II is somewhat analogous to intermediates postulated in the reaction of pyridine N-oxide with acetic anhydride.[5] A transient precipitate was observed upon mixing phenylisonitrile with bromine and pyridine N-oxide in chloroform. The precipitate was not sufficiently stable to permit structure determination thus far.

The reaction of isopropylisonitrile with chlorine and pyridine N-oxide in chloroform was conducted initially by bubbling chlorine through a solution of the other reactants at room temperature. Under these conditions a precipitate of pyridine N-oxide hydrochloride formed after 5 min. The structure was determined by comparison of melting points, infrared spectra, and nmr spectra with those of an authentic sample. Vapor phase chromatography and infrared spectroscopy demonstrated that carbon tetrachloride was formed as the other product. In subsequent experiments isopropylisonitrile dichloride was prepared by reaction of chlorine with the isonitrile. Excess chlorine was removed by evaporation of the solvent and pumping the residue. Reaction of the dichloride with pyridine N-oxide in chloroform gave isopropyl isocyanate in a very slow reaction.

Pyridine N-oxide had no effect on the rate of the chloroform chlorine reaction as judged by the half-life of loss of chlorine in parallel reactions with and without the N-oxide.

The necessity for the halogen in the pyridine N-oxide and dimethyl sulfoxide reactions made it of interest to determine its necessity in previously reported reactions of isonitriles with mercuric oxide.[2] Oxidation of isopropylisonitrile with mercuric oxide occurred simply by refluxing the mixture in chloroform; thus, elemental halogen is not required for the oxidation with mercuric oxide. No reaction occurred with pyridine N-oxide in the absence of halogen with another sample of the same preparation of the isonitrile.

Benzoyl peroxide, dimethyl sulfone, and triphenylphosphine oxide also react with isopropylisonitrile in chloroform in the presence of iodine or bromine to form isopropyl isocyanate.

## Experimental Section

**Isopropylisonitrile** was prepared in the same manner described in the previous report.[1,6]

**Phenylisonitrile** was prepared by the reaction of aniline (0.1 mole) with bromoform (0.105 mole) and sodium hydride (0.33 mole as a dispersion in mineral oil) in tetrahydrofuran (THF). The mixture of aniline and bromoform was added to a suspension of sodium hydride in THF. After the reaction was complete, water was added dropwise to destroy any excess sodium hydride. Ether was added, and the ether solution was washed with four 50-ml portions of water, three 20-ml portions of dilute hydrochloric acid, and water. After drying over sodium sulfate, the ether was evaporated and the residue distilled to yield 4.65 g (45%) of phenylisonitrile, bp 50–55° (13 mm). Redistillation gave 3.5 g, bp 52–53° (13 mm). The material was light green, but became colorless upon bulb-to-bulb distillation at $10^{-5}$ mm.

**Kinetic Determinations.**—The chloroform was purified by washing with sulfuric acid, water, dilute sodium hydroxide, and water. It was dried over calcium hydride, and distilled just prior to use. Pyridine N-oxide was obtained from a commercial source and distilled under reduced pressure. It was kept in a dessicator over phosphorus pentoxide until used. Iodine was a freshly sublimed sample of analytical reagent grade material. The isonitriles were purified by bulb-to-bulb distillation at $10^{-5}$ mm just prior to use.

Stock solutions of iodine and pyridine N-oxide of approximately 0.01 $M$ were prepared by direct weighing. A solution of the isonitrile was also prepared by direct weighing. These solutions were equilibrated in a constant-temperature bath to the temperature of the Perkin-Elmer 421 spectrophotometer cell compartment (32°). The sealed liquid cells (0.5- and 1.0-mm path length) were allowed to equilibrate in the instrument for at least 1 hr prior to the kinetic run. The iodine and pyridine N-oxide solutions were mixed in appropriate ratios; to begin the run, a solution of isonitrile was added and mixed, and the three-component solution was transferred rapidly to the infrared cell using an all-glass syringe preequilibrated to 32°. The infrared spectrophotometer was fixed on the isocyanate frequency, and the absorbance was measured as a function of time. The final absorbance was compared with the concentration determined by direct weighing; agreement was usually within 2%. Concentration–absorbance plots of the isocyanates were prepared and used

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(5) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953); I. J. Pachter, *J. Am. Chem. Soc.*, **75**, 3026 (1953); V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1286 (1954); O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954); J. A. Berson and T. Cohen, *ibid.*, **77**, 1281 (1955).

(6) J. Casanova, Jr., R. O. Schuster, and N. D. Verner, *J. Chem. Soc.*, 4280 (1963).

to estimate the concentration of isocyanate in the reaction system. Iodine was not consumed in the reaction (visible absorption band was of constant intensity when checked on a Cary Model 14.) Thus the data were treated in a conventional manner using a pseudo-second-order treatment.

Each run was accurately pseudo second order. A typical run was complete in approximately 10 min. Trinitrobenzene had no effect on the reaction, nor did small amounts of AIBN.

**Reaction of Isopropylisonitrile with Bromine and Pyridine N-Oxide.**—A solution of isopropylisonitrile (0.69 g, 0.01 mole) and pyridine N-oxide (0.95 g, 0.01 mole) in 100 ml of chloroform was treated with an equmolar amount of bromine in chloroform. A colorless precipitate appeared, 2.40 g (75%), mp 95–96° dec; the material darkened rapidly at room temperature, but appeared to be stable at 0°. The precipitate II was soluble in water and methanol, slightly soluble in acetonitrile, and insoluble in ether, tetrahydrofuran, carbon disulfide, chloroform, and petroleum ether (bp 30–60°). II gave an immediate precipitate with silver nitrate solution.

*Anal.* Calcd for $C_9H_{12}Br_2N_2O$: C, 33.36; H, 3.73; N, 8.65; Br, 49.32. Found: C, 33.30; H, 3.76; N, 8.58; Br, 48.16 (after 24 hr of standing at room temperature: Br, 46.19).

Infrared maxima were 3.30 (m), 3.42 (m), 3.51 (m), 5.88 (s), 6.25 (m), 6.79 (s), 6.86 (s), 7.28 (w), 7.35 (w), 7.46 (w), 7.81 (w), 8.15 (w), 8.40 (w), 8.51 (w), 8.80 (w), 8.88 (w), 9.12 (w), 9.75 (w), 10.04 (m), 10.25 (vs), 11.42 (w), 12.0 (w), 12.78 (s), 14.00 (w) (in KBr Pellet). In Nujol some prominent peaks were 5.85 (s), 6.25 (m), 10.25 (vs); no peaks were in the 4.0–5.7-μ region.

Treatment of II with water gave a precipitate of *sym*-diisopropylurea, mp 193–194° after sublimation.[7] Its infrared spectrum was identical with that of an authentic sample, and the melting point was not depressed on admixture. Reaction with *sec*-butylamine in methanol gave 1-isopropyl-3-*sec*-butylurea, mp and mmp 135–136°.[8] Infrared spectra of material from an unknown and an authentic sample were superimposable. Heating the unknown under high vacuum gave a complex mixture; volatiles had pyridine (vpc and infrared spectrum), isopropylisonitrile (vpc and mass spectrum), and isopropyl isocyanate (vpc mass spectrum, and infrared spectrum) present. Some pyridine N-oxide was also formed and indications of isopropylisonitrile dibromide (infrared spectrum) were also found. Treatment of the unknown with isopropylisonitrile gave isopropyl isocyanate and isopropylisonitrile dibromide (infrared spectrum). Reduction of 0.25 g of unknown with 3 g of lithium aluminum hydride in ether gave a mixture of pyridine and methylisopropylamine (vpc and infrared spectra).

**Reaction of Isopropylisonitrile with Chlorine and Pyridine N-Oxide.**—Chlorine gas was bubbled into a solution of pyridine N-oxide and isopropylisonitrile (0.01 *M* in each) in chloroform. After about 5 min, a colorless precipitate formed which was removed by filtration. The material was crystallized from ethanol to yield pyridine N-oxide hydrochloride, mp 179–180, whose infrared and nmr spectra were identical with those of an authentic sample prepared by bubbling anhydrous hydrogen chloride through a chloroform solution of pyridine N-oxide. It was possible to recover 85% of the pyridine N-oxide as solid hydrochloride by allowing the solution to stand for about 1 hr at room temperature.

In a separate experiment chlorine was bubbled through a solution of isopropylisonitrile (0.50 g) in chloroform (25 ml) for 3–5 min. The solvent was removed using a vacuum pump, and the residue was pumped until no more material seemed to be removed. The residue was dissolved in chloroform and an equimolar amount of pyridine N-oxide was added. No reaction occurred immediately; after standing for about 24 hr approximately 25% of the isonitrile dichloride had been converted to the isocyanate as shown by infrared spectra.

In a third experiment a solution of chlorine in chloroform was prepared which gave an optical density of 1.0 in a 1-cm cell at the visible maximum. This solution was divided into two parts; one part was diluted with an equal volume of chloroform; the other was diluted with 0.1 *M* pyridine N-oxide in chloroform. The time for the reduction in optical density by 0.2 and 0.4 unit was identical for the two solutions.

**Reaction of Isopropylisonitrile with Miscellaneous Materials.**—A solution of isopropylisonitrile (10%) in chloroform was allowed to react with mercuric oxide at reflux for 1 hr; infrared spectra showed that complete conversion to the isocyanate occurred during this time. A second portion of the isonitrile was allowed to react with pyridine N-oxide in chloroform in the absence of added halogen. No reaction had occurred after 3 hr.

Solutions of the isonitrile in chloroform (10%) were allowed to react with dimethyl sulfone, benzoyl peroxide, and triphenylphosphine oxide (approximately equimolar proportions) in the presence of small amounts of bromine. Infrared spectra were recorded after a 1-hr reaction. In all instances the isocyanate had formed. In the absence of bromine, no isocyanate formed, except in the case of benzoyl peroxide. With benzoyl peroxide a small amount of isocyanate formed after several days of refluxing.

**Registry No.**—II, 10349-37-8; pyridine N-oxide, 694-59-7; phenylisonitrile, 931-54-4; *p*-anisylisonitrile, 10349-38-9; isopropylisonitrile, 598-45-8.

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(7) A. W. Hofmann [*Ber.*, **15**, 756 (1882)] reports mp 192°.

(8) Urban, *Arch. Pharm.*, **242**, 70 (1892).

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# Trifluoromethylmalononitrile. The Reaction of 1,1-Dichloro-2,2-dicyanoethylene with Argentous Fluoride[1]

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Reaction of 1,1-dichloro-2,2-dicyanoethylene with 4 equiv of argentous fluoride provides the silver salt of trifluoromethylmalononitrile, which can be converted to trifluoromethylmalononitrile by treatment with hydrogen chloride. Under the same conditions, reaction of the chloro cyano olefin with 2 equiv of argentous fluoride provides solutions from which the yellow dye 1-fluoro-1-(4-dimethylaminophenyl)-2,2-dicyanoethylene can be isolated by treatment with N,N-dimethylaniline.

Monoperfluoroalkyl derivatives of malononitrile have not previously been reported.[2] We discovered the parent member of the series, trifluoromethylmalononitrile (IV), during an attempt to convert 1,1-dichloro-2,2-dicyanoethylene (I) to 1,1-difluoro-2,2-dicyanoethylene (II) by treatment with an excess (4 molar equiv) of argentous fluoride. None of the difluoro compound was obtained. Instead, we isolated the silver salt of trifluoromethylmalononitrile (III), which was readily converted to trifluoromethylmalononitrile (IV) by reaction with hydrogen chloride.

As the equations of Scheme I indicate, we believe that 1,1-difluoro-2,2-dicyanoethylene (II) is an intermediate in the reaction. This remarkable addition of

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(1) Presented at the First Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1966.

(2) S. Proskow (U. S. Patent 3,170,949) describes bis(trifluoromethyl)-malononitrile.