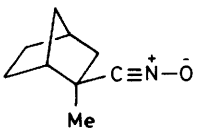
The Nitrile Oxide–Isocyanate Rearrangement

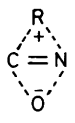
Giles A. Taylor
Department of Chemistry, University of Sheffield, Sheffield S3 7HF

The thermal rearrangement of 2,4,6-trimethylbenzonitrile *N*-oxide to the corresponding isocyanate has been investigated by double isotopic (^2H and ^{18}O) labelling and kinetic experiments. Rearrangement proceeds with exchange of oxygen atoms, and this exchange occurs exclusively between nitrile oxide molecules. Kinetic results suggest that the pathway involves a polymerisation, catalysed either by electrophiles or by nucleophiles, followed by decomposition of the polymer. The rearrangement is catalysed at room temperature by trifluoracetic acid. A synthesis of ^{18}O-labelled hydroxylamine is reported.

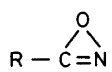
The thermal rearrangement of organic nitrile oxides or their furoxan dimers to isocyanates has been known for over 70 years[1] but the mechanism of the process is still far from clear. The possibility that the reaction involves ionisation to an organic cation and fulminate anion followed by recombination after rearrangement of the anion, was disproved by Grundmann and Kochs[2] who showed that nitrile oxides such as (**1**), in which the alkyl cation, if formed, would be expected to rearrange, undergo thermal rearrangement with preservation of both the constitution and configuration of the alkyl group. The failure to observe a CIDNP effect during the rearrangement of 2,4,6-trimethylbenzonitrile *N*-oxide discounted a radical dissociation–recombination pathway. These authors also showed that when a mixture of ^2H-labelled benzonitrile oxide and ^{13}C-labelled benzonitrile oxide was rearranged, no doubly labelled phenyl isocyanate was formed, and concluded that the reaction was strictly intramolecular. They suggested that the rearrangement might proceed *via* a transition state (**2**) or an oxazirine intermediate (**3**), but it is reported[3] that attempts to detect or trap the oxazirine have been unsuccessful. Theoretical calculations[4] on the thermal conversion of fulminate anion into cyanate ion have suggested that this reaction occurs *via* a three-membered cyclic intermediate (**4**).



(**1**)

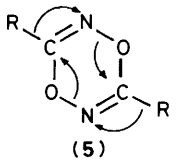


(**2**)



(**3**)

(**4**)



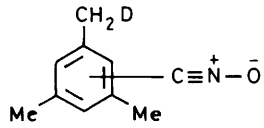
(**5**)

a; R = Ph
b; R = 2,4,6-$Me_3C_6H_2$

It seems improbable that the nitrile oxide–isocyanate rearrangement proceeds *via* either (**2**) or (**3**). Both of these species are very highly strained and additionally (**3**) is expected to be antiaromatic. Also the implied unimolecularity of these reaction mechanisms seems inconsistent with the report[5] that acetonitrile oxide can be formed by flash vacuum pyrolysis at 550 °C of its furoxan dimer. It might have been expected that, under these conditions, a wholly intramolecular rearrangement of the nitrile oxide would have occurred very rapidly. An alternative possibility is a pathway proceeding *via* formation of the dioxadiazine dimers of nitrile oxides (**5**), which are reported to be formed by dimerisation of nitrile oxides in the presence of pyridine[6] or boron trifluoride.[7] The decomposition to isocyanates by the mechanism shown in (**5**) is attractive, but Grundmann has demonstrated[2b] that (**5a**) and (**5b**) are thermally more stable than the parent nitrile oxides and decompose slowly on prolonged heating in xylene to give a complex mixture containing no isocyanate, and from which only the nitrile could be isolated.

It appeared that all wholly intramolecular rearrangement pathways involve intermediates or transition states of very high energy and the possibility of an intermolecular process other than *via* (**5**) was considered. In the light of previous results, any such process would probably involve oxygen atom exchange between rearranging molecules, as in the now discredited mechanism shown in (**5**). This possibility has been tested by a double isotopic labelling experiment similar to that of Grundmann and Kochs, but using ^2H and ^{18}O labels.

2,4,6-Trimethylbenzonitrile *N*-oxide was chosen for the work since it is stable at room temperature. ^2H-Labelling of the methyl groups was chosen since aromatic protons might have exchanged under strongly acidic reaction conditions, and exclusively singly labelled mesitylene could be easily obtained by zinc and acetic acid ($MeCO_2D$) reduction of 3,5-dimethylbenzyl bromide. The [^2H]-mesitylene so obtained was converted into trimethylbenzaldehyde by a Gatterman reaction and then *via* the oxime into the nitrile oxide (**6**) in which there was random labelling of one of the methyl groups.



(**6**)

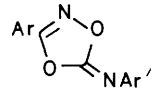
The synthesis of the ^{18}O-labelled nitrile oxide required ^{18}O-labelled hydroxylamine for which no preparation appeared to be on record. The formation of hydroxylamine from nitrite anion seemed to be the only feasible route since hydroxylamine O-sulphonic acid is known to give hydroxylamine by O–S cleavage under acidic conditions[8] and alkaline hydrolysis gives mainly nitrogen and ammonia.[9] However, the use of nitrite anion requires non-aqueous conditions since isotopic exchange of oxygen between nitrite ion and water is expected to be rapid at the pH normally employed for direct reduction.[10] The

method chosen involved conversion of isotopically enriched water into hydroxide ion in dry methanol and use of this to cleave an alkyl nitrite forming ^{18}O-labelled nitrite anion. Nitrosation of ethyl acetoacetate in acetic acid and hydrolysis of the oxime produced gave a moderate overall yield of hydroxylamine hydrochloride, but with substantial loss of the isotopic label. Conversion of hydroxide into nitrite ion dilutes the isotopic label and half of the heavy isotope is inevitably lost in the nitrosation step. However, having started with 20% enriched $H_2^{18}O$, the final 5.5% ^{18}O-labelling in the hydroxylamine, measured *via* fluorenone oxime, means that a significant loss occurred by unidentified causes, possibly due to traces of water in the nitrosation medium. Subsequent conversion of the hydroxylamine into the nitrile oxide gave a product with a 5.5% ^{18}O label.

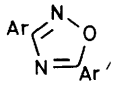
For the rearrangement experiment a mixture of equal weights of the ^2H and ^{18}O labelled nitrile oxides with a little benzene were heated in a sealed tube in a xylene-vapour jacket (*ca.* 140 °C) for 1 h. Simultaneously, an identical sample of unlabelled material was also heated in the same apparatus. Samples of the products were introduced into a mass spectrometer *via* a capillary g.l.c. column and the intensities of the peaks *m/z* 158—164 in the mass spectrum of the trimethylphenyl isocyanate were measured directly as ion currents under standard operating conditions. The mass spectrum observed for the mixed rearrangement product consists of three or four overlapping spectra. If it is assumed that the intensity distribution of the peaks $(M - 3)^+$ to $(M + 3)^+$ for the individual, isotopically substituted compounds is the same as that observed for the spectrum of the unlabelled isocyanate for fixed operating conditions of the spectrometer, then the observed intensities of the peaks *m/z* 161—164 can be interpreted in terms of the proportions of the various isotopically substituted species present in the reaction mixture. To check the stability of the spectrometer performance, the unlabelled material was measured immediately before and after the mixed rearrangement proudct, and an average value of the relative peak intensities was used to analyse the results from the mixed rearrangement.

A further complication arose from the use of a capillary g.l.c. column to ensure that the recorded mass spectrum was due only to the aryl isocyanate. For each sample injected, several mass spectra were recorded as the isocyanate peak emerged from the column, and it was clear that significant isotopic fractionation was occurring in the capillary column, with ^2H labelled material being concentrated at the leading edge of the emerging sample. In the absence of accurate knowledge of the pattern of elution of material from the column and the timing of the recorded mass spectra in relation to the emergence of the peak, it was impossible to calculate an average value for the proportion of the various labelled components. All that could be done was to calculate the percentage molecular contribution of each species for each recorded spectrum. These figures for the doubly labelled (^2H and ^{18}O) isocyanate ($M^+ = 164$) started at 1.8% molecular proportion and declined over nine spectra to 0.2%. The high initial figure is consistent with ^2H-labelling; the corresponding figures for the singly ^2H-labelled isocyanate started at 77% and fell to 14%. Since the interpretation of results depends critically upon the relative peak intensities measured in the spectrum of the unlabelled material, the results were recalculated using selected least-favourable figures from this source rather than average ones. The corresponding molecular proportions of doubly labelled isocyanate started at 1.5% and fell to 0.2%. If random exchange of oxygen atoms occurs during the rearrangement from nitrile oxide to isocyanate, then with 85.7% ^2H label in one component and 5.5% ^{18}O label in the other, a 1.2% proportion of doubly labelled isocyanate is expected to be formed. The experimental results seem to establish unequivocally that oxygen atom exchange occurs during the rearrangement.

Prior to the measurement of the mass spectra, rearrangement of unlabelled material under identical conditions had been performed and the formation of the aryl isocyanate was proved by conversion into the diaryl urea by reaction with aniline.[11] G.l.c. analysis of the crude mixture showed the presence of a small quantity of another compound, which was shown by mass spectrometry and g.l.c. peak enhancement to be 2,4,6-trimethylbenzonitrile. Three different types of process might, therefore, participate in the rearrangement, with the nitrile oxide exchanging its oxygen atom with either another nitrile oxide molecule or with a molecule of phenyl isocyanate *via* the formation and fragmentation of an intermediate such as (**7**), or with a catalytic amount of nitrile *via* (**8**). Neither of the last two alternatives seemed very probable as trimethylbenzonitrile *N*-oxide is reported to add to phenyl isocyanate to give (**9**) not (**7**),[12] and though nitrile oxides add to nitriles to give adducts like (**8**)[12] these are not reported to decompose readily to isocyanates, although prolonged heating of 3,5-diphenyl-1,2,4-oxadiazole is reported to cause decomposition to benzonitrile and phenyl isocyanate.[13] To eliminate the latter possibilities

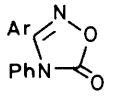


(**7**)



(**8**)

a; Ar = 2,4,6-$Me_3C_6H_2$
Ar′ = Ph



(**9**)

Ar = 2,4,6-$Me_3C_6H_2$

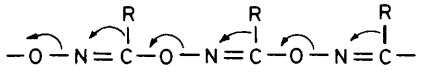
^{18}O-labelled trimethylbenzonitrile oxide was heated with phenyl isocyanate under conditions identical with those used previously. The mass spectrum of the phenyl isocyanate isolated after this experiment showed no significant change in the intensity ratio of peaks *m/z* 119 and 121. Oxygen exchange between nitrile oxides and isocyanates can therefore be discounted. Likewise, the nitrile oxide when heated with benzonitrile at 140 °C gave an adduct (**8a**) which was stable at that temperature. No trace of phenyl isocyanate and very little trimethylphenyl isocyanate could be detected in the reaction mixture by g.l.c. Oxygen exchange between nitrile oxide molecules appears to be the only remaining process which can account for the observations.

In the hope of discovering something further about the rearrangement pathway the decomposition of trimethylbenzonitrile oxide was studied kinetically. The ^1H n.m.r. spectrum of this compound has two signals at δ 2.4 and 2.3 due to methyl groups, the two methyl groups *ortho* to the nitrile oxide group resonating at lower field presumably due to the magnetic anisotropy of the adjacent triple bond.[14] The methyl signals in the n.m.r. spectrum of the isocyanate are at δ 2.3 and 2.25 and clear of the low-field signal in the nitrile oxide spectrum. Disappearance of the nitrile oxide can therefore be followed by the decrease in the integrated signal at δ 2.4. This method was not sufficiently accurate to give high quality data but was, nevertheless, very revealing. The decomposition was studied in a mixture of 1,2,4-trichlorobenzene and [$^2H_5$]-nitrobenzene at 110 °C. 2-Methoxynaphthalene was added and the methoxy signal was used as a standard for the integration.

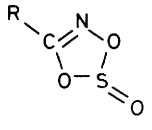
Plotting the integrated intensity of the signal at δ 2.4 against time showed that after an initial induction period the graph was virtually linear until the reaction was more than 80% complete. A five-fold decrease in the concentration of the nitrile oxide produced only a 30% decrease in the gradient of the linear section of the graph with a rather longer initial induction period. It is clear that the rate law is neither first nor second order in nitrile oxide and the linearity suggests a zero order process such as a polymerisation initiated by some adventitious means. Addition of 2,5-di-t-butylhydroquinone had no significant effect on the rate of reaction, so it is clearly not a radical process. Addition of a catalytic amount of 4-dimethylaminopyridine produced a significant acceleration, but addition of catalytic quantities of either trifluoroacetic acid or boron tribromide caused virtually instantaneous disappearance of the nitrile oxide at 110 °C. Trifluoroacetic acid also catalysed the disappearance of the nitrile oxide at room temperature, but boron tribromide was much less effective. That this acid-catalysed process at room temperature led to formation of the isocyanate was proved by conversion of the product into the diaryl urea by reaction with aniline.

The conclusion reached from the isotopic labelling and kinetic studies is that the thermal rearrangement of nitrile oxides to isocyanates occurs via an initial polymerisation to a linear, or possibly cyclic polymer of structure (**10**) which breaks down by N–O fission and migration of the R group from C to N. This polymeric structure is identical with that now accepted for Wieland's 'trifulmin' and its derivatives[15] which are known to decompose thermally to isocyanates. Macrocyclic polymers of acetonitrile oxide of this constititution are also known.[16] Initiation of polymerisation might arise either by nucleophilic attack on the carbon atom of the CNO group or electrophilic attack on oxygen. The lower efficiency of nucleophilic catalysis in the case studied may be due to steric hindrance by the *ortho* methyl groups. The decomposition process shown in (**10**) leaves uncertain the fate of the terminal groups, but it is conceivable that the traces of nitrile detected in the product of thermolysis of trimethylbenzonitrile oxide may arise from some end-group process.

In the light of these results, and notwithstanding the theoretical calculations,[4] it seems possible that the rearrangement of fulminate anion to cyanate anion might also occur *via* an intermediate like (**10**). Despite the relatively low energy of (**4**) with respect to fulminate anion, the calculated activation energies for the steps fulminate anion→(**4**) and (**4**)→cyanate anion are 341 and 370 kJ mol^{-1} respectively with an overall decrease in energy of 77 kJ mol^{-1}. These do not seem to be the components of a potentially explosive process.



(10)



(11)

The isomerisation of nitrile oxides to isocyanates can also be achieved *via* addition of sulphur dioxide to form the heterocyclic adduct (**11**) which decomposes to sulphur dioxide and an isocyanate on heating.[5,17] Oxygen exchange between the nitrile oxide and sulphur dioxide is expected to occur in this process, and an attempt was made to check this by a sulphur dioxide-catalysed rearrangement of ^{18}O-labelled nitrile oxide. However in this case the abundance of $^{32}S^{18}O^{16}O$ has to be measured in the presence of naturally occurring $^{34}S^{16}O_2$. The relative intensities of the peaks 66^+ and 64^+ were measured for commercial sulphur dioxide and sulphur dioxide isolated (by g.l.c.) after the isomerisation. The results were 5.1:100 and 5.9:100 respectively. Although this is a rather smaller difference than was hoped for, it supports the proposed mechanism.[17a]

Experimental

Mass spectra were measured with a Kratos MS25 spectrometer using a DS55 data system. Kinetic n.m.r. experiments were performed with a Bruker AM250 spectrometer.

α-Deuterio-1,3,5-trimethylbenzene.—A mixture of deuterium oxide (99.8% D_2O; 18 ml) and acetic anhydride (85 ml) was heated on a steam bath, under reflux for several hours. After cooling, the product was added to dry ether (1 l) and zinc dust (140 g), and 3,5-dimethylbenzyl bromide (93 g) in dry ether (300 ml) was added dropwise with vigorous stirring. After the addition was complete the mixture was stirred and boiled under reflux for 0.5 h. Filtration and standard work-up of the ethereal solution, followed by fractional distillation gave ^{2}H labelled mesitylene b.p. 160—170 °C (78%, 20% utilisation of ^{2}H; 44 g).

α-Deuterio-2,4,6-trimethylbenzonitrile N-*Oxide* (**6**).—α-^{2}H-Labelled mesitylene was converted into 2,4,6-trimethylbenzaldehyde[18] and thence, *via* the oxime, to the nitrile oxide[11] by standard procedures. Mass spectrometry showed the product to be 85.7% [^{2}H]-labelled.

^{18}O-*Labelled Hydroxylamine Hydrochloride.*—Dry methanol (25 ml) was added slowly to sodium hydride powder (2 g) in a bomb tube cooled in ice. When the evolution of hydrogen had ceased, water (20%^{18}O; 1 g) and isopropyl nitrite (10 ml, 8.6 g) were added and the bomb tube was sealed. After being heated at 55 °C for 4.5 days the bomb tube was cooled and opened and the contents evaporated to dryness under reduced pressure to leave a slightly sticky brown solid. This crude sodium nitrite was added in small portions with stirring to an ice-cooled mixture of glacial acetic acid (45 ml) and ethyl acetoacetate (15 ml), the temperature being maintained below 5 °C. The mixture was stirred at 5 °C for 0.5 h after which the cooling bath was removed and stirring continued for 2.5 h. By this time all the suspended solid had dissolved and the temperature had risen to 23—25 °C. This solution was added to hydrochloric acid (5M; 50 ml) and boiled for 17 h. The mixture was then steam-distilled until about 1 l. of distillate had been collected after which the residual dark solution was boiled with active charcoal, filtered, and evaporated to dryness under reduced pressure. Extraction of the residue with boiling ethanol and evaporation of the extract gave crude hydroxylamine hydrochloride (3.8 g, theory 3.9 g) which was not further purified. The purity, estimated volumetrically by potassium bromate oxidation,[19] was 55%. A small sample was converted into fluorenone oxime by heating with fluorenone and an acetate buffer in aqueous methanol. The mass spectrum of the product compared with that of a normal sample showed a peak at 197^+ whose intensity relative to the 195^+ peak corresponded to 5.5% ^{18}O-isotopic labelling. The hydroxylamine was not purified, but used in this crude form for the subsequent preparation.

^{18}O-*Labelled* 2,4,6-*Trimethylbenzonitrile* N-*Oxide.*—The labelled hydroxylamine hydrochloride was converted into trimethylbenzaldoxime and thence into the nitrile oxide by standard procedures.[11]

Reaction of 2,3,6-*Trimethylbenzonitrile* N-*Oxide with Benzonitrile*.—A mixture of trimethylbenzonitrile *N*-oxide (0.3 g) and benzonitrile (0.4 ml) was heated in a sealed tube at 140 °C in xylene vapour for 1 h. On cooling, the mixture solidified giving 5-phenyl-3-(2,4,6-trimethylphenyl)-1,2,4-oxadiazole (**8a**), m.p. 86—87 °C (from methanol) (Found: C, 77.0; H, 6.2; N, 10.6. Calc. for $C_{17}H_{16}N_2O$: C, 77.3; H, 6.1; N, 10.6%); $\delta_H(CDCl_3)$ 2.24 (6 H, s), 2.33 (3 H, s), 6.97 (2 H, s), 7.5—7.7 (3 H, m), and 8.1—8.3 (2 H, m); $\delta_C(CDCl_3)$ 19.3 (CH_3), 20.4 (CH_3), 123.0 (C), 123.5 (C), 127.3 (CH), 127.7 (CH), 128.2 (CH), 131.8 (CH), 136.9 (C), 138.9 (C), 168.0 (C), and 174.5 (C).

The Acid-Catalysed Rearrangement of 2,4,6-*Trimethylbenzonitrile* N-*Oxide*.—The nitrile oxide (0.5 g, 3.1 mmol) was dissolved in dry benzene (3 ml), trifluoroacetic acid (0.05 ml, 0.65 mmol) was added, and the mixture left at room temperature for 3 h. A solution of aniline (2 ml) in dry diethyl ether (5 ml) was then added and the mixture left at room temperature overnight. The solvent was evaporated and the residue washed with dilute hydrochloric acid to leave crude *N*-(2,4,6-trimethylphenyl)-*N'*-phenylurea (0.6 g, 76%) identified by i.r. comparison with an authentic sample.

Acknowledgements

I thank Dr. B. F. Taylor for help with the kinetic n.m.r. experiments, Mr. P. R. Ashton and Mr. I. R. Johnstone for the mass spectrometry, Mr. M. Grayson for help with the calculations, and Dr. J. Crosby of ICI for discussion.

References

1 C. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer-Verlag, New York, 1971, ch. IV.
2 (*a*) C. Grundmann and P. Kochs, *Angew. Chem.*, 1970, **82**, 637; *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 635. (*b*) C. Grundmann, P. Kochs, and J. R. Boal, *Justus Liebigs Ann. Chem.*, 1972, **761**, 162.
3 Ref. 1, p. 65.
4 F. J. Holsboer and W. Beck, *J. Chem. Soc., Chem. Commun.*, 1970, 262.
5 W. R. Mitchell and R. M. Paton, *Chem. Ind. (London)*, 1980, 665.
6 F. De Sarlo, *J. Chem. Soc., Perkin Trans 1*, 1974, 1951; W. J. Middleton, *J. Org. Chem.*, 1984, **49**, 919.
7 S. Morrochi, A. Ricca, A. Selva, and A. Zanarotti, *Gazz. Chim. Ital.*, 1969, **99**, 165 (*Chem. Abstr.*, 1969, **70**, 115072n).
8 J. P. Candlin and R. G. Wilkins, *J. Am. Chem. Soc.*, 1965, **87**, 1490.
9 H. J. Matsuguma and L. F. Audrieth, *J. Inorg. Nucl. Chem.*, 1959, **12**, 186.
10 G. K. Rollefson and C. F. Oldershaw, *J. Am. Chem. Soc.*, 1932, **54**, 977.
11 C. Grundmann and J. M. Dean, *J. Org. Chem.*, 1965, **30**, 2809.
12 K. Bast, M. Christl, R. Huisgen, and W. Mack, *Chem. Ber.*, 1972, **105**, 2825.
13 F. D. Dodge, *Justus Liebigs Ann. Chem.*, 1891, **264**, 178.
14 F. B. Mallory and M. B. Baker, *J. Org. Chem.*, 1984, **49**, 1323.
15 Ref. 1, p. 83; H. Wieland, *Chem. Ber.*, 1909, **42**, 803, 816; C. Grundmann and H. D. Frommeld, *J. Org. Chem.*, 1961, **31**, 4235.
16 A. Brandi, F. De Sarlo, and A. Guarna, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1827.
17 (*a*) E. H. Burk and D. D. Carlos, *J. Heterocycl. Chem.*, 1970, **7**, 177; (*b*) G. Trickes and H. Meier, *Angew. Chem.*, 1977, **89**, 562; *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 555; (*c*) J. F. Barnes, R. M. Paton, P. L. Ashcroft, R. Bradbury, J. Crosby, C. J. Joyce, D. R. Holmes, and J. A. Milner, *J. Chem. Soc., Chem. Commun.*, 1978, 113.
18 R. C. Fuson, E. C. Horning, S. P. Rowland, and M. L. Ward, *Org. Synth.*, 1955, Coll. vol. III, p. 549.
19 A. I. Vogel, 'Quantitative Inorganic Analysis,' Longman, Green and Co., London, 2nd edn., 1951, p. 375.

Received 12*th October* 1984; *Paper* 4/1748