Ring-enlargement of Isoxazol-5-ones to 1,3-Oxazin-6-ones

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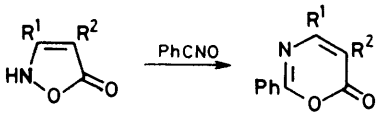
Isoxazol-5-ones undergo ring-enlargement by reaction with nitrile oxides to give 1,3-oxazin-6-ones. The mechanism is discussed. Some chemical transformations of the oxazinone ring are described.

In continuation of our studies [1,2] of the behaviour of nitrile oxides above the limits of their thermal stability, we have investigated the reaction with isoxazol-5-ones (NH form) under these conditions and now report the products isolated and discuss the mechanism of the reaction.



(1) (2)

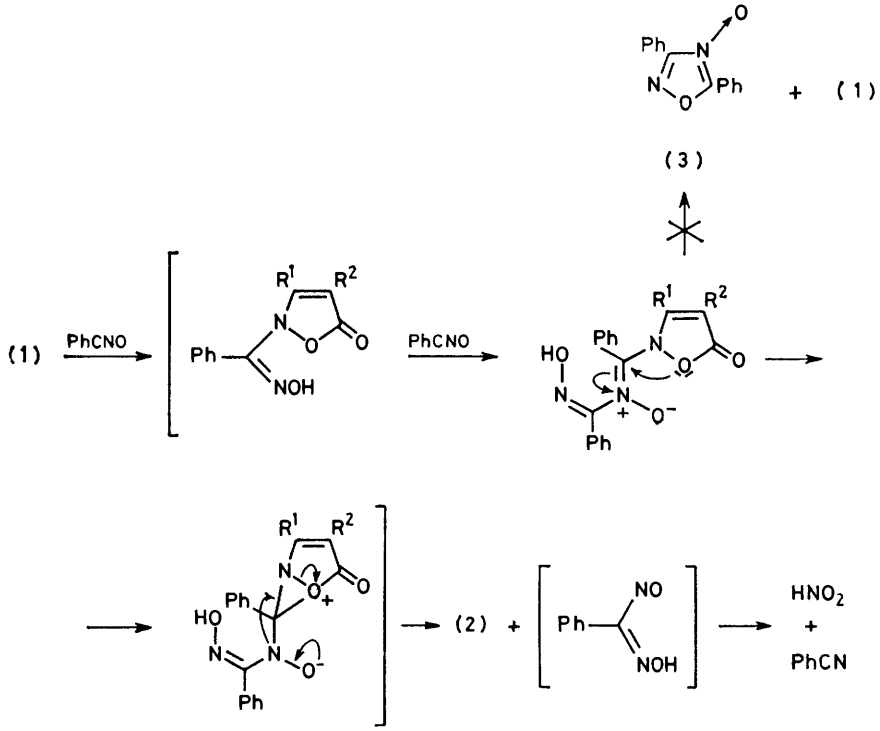
Isoxazol-5-ones (1) reacted with an excess of benzonitrile oxide (BNO) in boiling benzene to give 1,3-oxazin-6-ones (2) with loss of HNO_2 and formation of PhCN; in all cases the reaction competed obviously with the unavoidable dimerisation of the nitrile oxide. The products were isolated by chromatography on silica gel; yields of (2), which were not optimized, were in the range 30—85%.

The formation of compounds (2a—e) involves an initial attack of BNO, most likely as phenylnitrosocarbene,[1,2] on the NH lone pair of the isoxazolonic ring to give open-chain intermediates which then subsequently undergo ring expansion.

We suggest that the reaction proceeds with BNO in two successive steps. The first, similar to that occurring under mild conditions with ammonia and its inorganic or organic derivatives,[3] leads to an oxime intermediate which undergoes further reaction with BNO.[1b] Rearrangement of the second intermediate (see Scheme) gives rise to (2) and the unstable (at reaction temperature) nitrosobenzhydroximic acid which finally decomposes into HNO_2 and PhCN (1 : 1).[4,5,†]

Analogous reaction of *O*-unsubstituted oximes with BNO involves the same open-chain intermediate (it could not be isolated), the evidence for which has been provided by the two paths of the previously described mechanism,[1b] one of which leads to the 3,5-diphenyl-1,2,4-oxadiazole 4-oxide (3).

The latter, a dimer of BNO, was never found in neutral



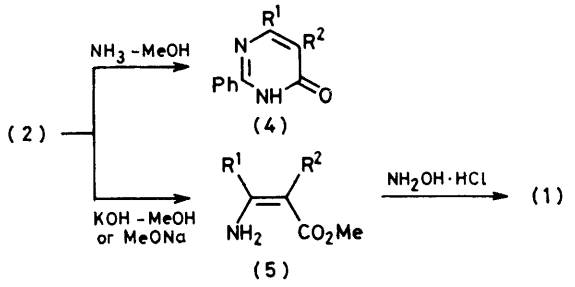
Scheme

† If BNO ethereal solution is added after no more HNO_2 is evolved, PhCN will react also to give 3,5-diphenyl-1,2,4-oxadiazole.

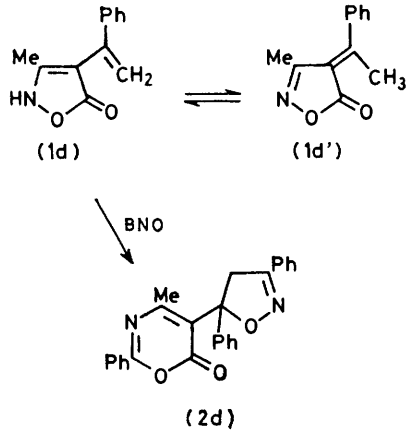
media,[6] although its formation under the catalytic influence of aprotic or protic acids like boron trifluoride–diethyl ether [7] or dry hydrogen chloride,[8] is well established.

Since this dimer was not found in the present work only one path need be taken into account.

Chemical evidence in support of structure (2) includes the following reactions: heating with methanolic ammonia converted (2a, b, d, e) into the corresponding pyrimidones (4);[9,*] treatment of (2a, d, e) with methanolic potassium hydroxide [10] or sodium methoxide led to ring opening to give the enamines (5); and, finally, (5a, e) were reconverted very easily with hydroxylamine hydrochloride into the starting isoxazolones (1).[10]



Our experience with the reactions of 4-arylidene-isoxazol-5-ones with BNO, led us to believe that compound (1d) could react with the tautomeric structure (1d') to give either isoxazolone–isoxazoline [11] or isoxazolone–cyclopropane [10] spiro-compounds by 1,3- or 1,1-cycloaddition, respectively. Instead we obtained as the sole product the 1,3-oxazine-6-one (2d), the result of enlargement of the isoxazolone ring and of 1,3-dipolar cycloaddition to the vinyl double bond of (1d).



EXPERIMENTAL

I.r. spectra were determined for Nujol mulls with a Pye–Unicam SP 1000 and n.m.r. spectra with a Hitachi–Perkin-Elmer R 24 (60 MHz) in the solvent indicated; chemical shifts are relative to $SiMe_4$. BNO was prepared according to the literature:[12] a cold 14% solution of NaOH (75 ml) was slowly added to benzhydroximic acid chloride (0.12 mol) suspended in cold water (150 ml); BNO was extracted with ether (150 ml), dried ($CaCl_2$), and used immediately. Reaction of this ethereal solution (containing *ca.* 0.09 mol of BNO), with the isoxazol-5-ones (1a—e) (0.03 mol) was allowed to go to completion.

The general procedure used for the synthesis of the 1,3-oxazin-6-ones (2) involved further dropwise addition of ethereal BNO to a well-stirred solution, or suspension (1c), of the isoxazolone in boiling benzene (100 ml) under reflux. The reaction mixture was flushed with a stream of nitrogen after each addition of BNO, in order to remove the ether and raise the temperature to 81 °C.[13] Heating was maintained for several hours during which time the colourless solution slowly turned yellow, orange, red-violet, and finally brown, while evolution of N_2O_3 (from HNO_2) was detected at the top of the condenser.† Heating was suspended when no more N_2O_3 was evolved. The solvent was distilled off and the residual oil chromatographed on silica gel (70—230 mesh). Elution with chloroform gave benzonitrile, 3,4-diphenylfuroxan, traces of 3,5-diphenyl-1,2,4-oxadiazole,[5] 1,3-oxazin-6-one (as colourless needles), and starting isoxazolone; coloured resinous by-products remained on the column.

2,4-*Diphenyl*-1,3-*oxazin*-6-*one* (2a), m.p. 137—138 °C (from methanol) (Found: C, 77.2; H, 4.5; N, 5.55. $C_{16}H_{11}NO_2$ requires C, 77.09; H, 4.45; N, 5.62%); $\nu_{C=O}$ 1 764 cm^{-1}; δ($CDCl_3$) 8.3—7.2 (m, 10 H, aromatic) and 6.48 (s, 1 H, =CH).

5-*Benzoyl*-2,4-*diphenyl*-1,3-*oxazin*-6-*one* (2b), m.p. 192—193 °C (from methanol) (Found: C, 78.2; H, 4.1; N, 3.85. $C_{23}H_{15}NO_3$ requires C, 78.17; H, 4.28; N, 3.96%); $\nu_{C=O}$ 1 735 and 1 670 cm^{-1}; δ[$(CD_3)_2CO$] 8.4—7.1 (m, aromatic).

4-*Methyl*-5-(3-*methylisoxazol*-5-*yl*)-2-*phenyl*-1,3-*oxazin*-6-*one* (2c), m.p. 174—175 °C (from benzene–ethanol) (Found: C, 67.4; H, 4.7; N, 10.9. $C_{15}H_{12}N_2O_3$ requires C, 67.15; H, 4.51; N, 10.44%); $\nu_{C=O}$ 1 749 cm^{-1}; δ($CDCl_3$) 8.3—7.3 (m, 5 H, aromatic), 6.84 (s, 1 H, =CH), 2.7 (s, 3 H, Me), and 2.35 (s, 3 H, Me).

5-(3,5-*Diphenyl*-2-*isoxazolin*-5-*yl*)-4-*methyl*-2-*phenyl*-1,3-*oxazin*-6-one (2d), m.p. 215 °C (from benzene–ethanol) (Found: C, 76.4; H, 4.95; N, 6.85. $C_{26}H_{20}N_2O_3$ requires C, 76.45; H, 4.94; N, 6.86%); $\nu_{C=O}$ 1 735 cm^{-1}; δ($CDCl_3$) 8.3—7.2 (m, 15 H, aromatic), 4.37 and 4.02 (ABq, 2 H, *J* 18 Hz, CH_2 isoxazoline ring), and 2.54 (s, 3 H, Me).

The method used for the conversion of 1,3-oxazin-6-ones into *pyrimidin*-4-*ones* consisted of dissolving a sample of the oxazinone in methanol with an excess of ammonia. The reaction mixture, stirred for 2 h at room temperature and concentrated, gave the product in quantitative yield.

2,6-*Diphenylpyrimidin*-4-*one* (4a), m.p. 293—294 °C (from methanol) (lit.,[9,14] m.p. 291 °C) (Found: C, 77.3; H,

* The products obtained from the reaction mentioned are now explained by the mechanism here proposed, that appears to be more consistent.

† Without nitrogen the gaseous product underwent aerial oxidation and N_2O_4 was well observed in the reflux condenser. While production of coloured by-products occurred in this reaction with isoxazol-5-ones, we observed that, only in this light, the analogous reaction with oximes (*i.e.*, acetone oxime, acetophenone oxime, *etc.*) proceeded very cleanly: red-violet solution colour turned, by heating, to colourless in the precise moment when N_2O_3 was cast off; further addition of BNO to the colourless solution changed it again to red-violet, and then to colourless under other N_2O_3 evolution. This should be explained with a coloured transient oxime salt of the unstable nitrosobenzhydroximic acid that splits by heating into HNO_2, PhCN, and the starting oxime; the latter reacts again. Unpublished results from this laboratory.

4.8; N, 11.3. Calc. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28%); $\nu_{C=O}$ 1 663 cm^{-1}.

5-Benzoyl-2,6-diphenylpyrimidin-4-one (4b), m.p. 230—232 °C (from methanol) (Found: C, 78.1; H, 4.7; N, 7.75. $C_{23}H_{16}N_2O_2$ requires C, 78.39; H, 4.58; N, 7.95%; $\nu_{C=O}$ 1 694 cm^{-1}; δ[$(CD_3)_2CO$] 8.7—7.4 (m, aromatic).

5-(3,5-Diphenyl-2-isoxazolin-5-yl)-6-methyl-2-phenylpyrimidin-4-one (4d), m.p. 283 °C (from methanol) (Found: C, 76.4; H, 5.4; N, 10.5. $C_{26}H_{21}N_3O_2$ requires C, 76.64; H, 5.20; N, 10.31%); $\nu_{C=O}$ 1 623 cm^{-1}; δ($CDCl_3$) 8.4—7.2 (m, 15 H, aromatic), 4.46 and 3.99 (ABq, 2 H, *J* 18 Hz, CH_2 isoxazoline ring), and 2.63 (s, 3 H, Me).

Methyl 3-Aminocinnamate (5a).—A sample of (2a) dissolved in a solution of 2% potassium hydroxide in dry methanol and kept at room temperature for 24 h yielded the product in good amount (70%), m.p. 58 °C (from methanol) (Found: C, 67.7; H, 6.35; N, 8.0. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.91%); $\nu_{max.}$ 1 654 (C=O), 1 620 (C=C), and 3 318 and 3 410 (NH_2) cm^{-1}; δ($CDCl_3$) 7.34 (s, 5 H, aromatic), 6.5br (NH_2) (disappears with D_2O), 4.96 (m, 1 H, =CH), and 3.65 (s, 3 H, Me).

Methyl 3-Amino-2-(3,5-diphenyl-2-isoxazolin-5-yl)-crotonate (5d), m.p. 167 °C (from methanol). This compound was prepared from (2d) as described in the preceding experiment in excellent yield (81%) (Found: C, 71.35; H, 5.95; N, 8.4. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%); $\nu_{max.}$ 1 660 (C=O), 1 610 (C=C), and 3 290 and 3 420 cm^{-1} (NH_2); δ($CDCl_3$) 7.8—7.1 (m, 10 H, aromatic), 6.66br (NH_2) (disappears with D_2O), 3.94 and 3.6 (ABq, 2 H, *J* 17 Hz, CH_2 isoxazoline ring), 3.74 (s, 3 H, Me), and 1.98 (s, 3 H, Me).

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