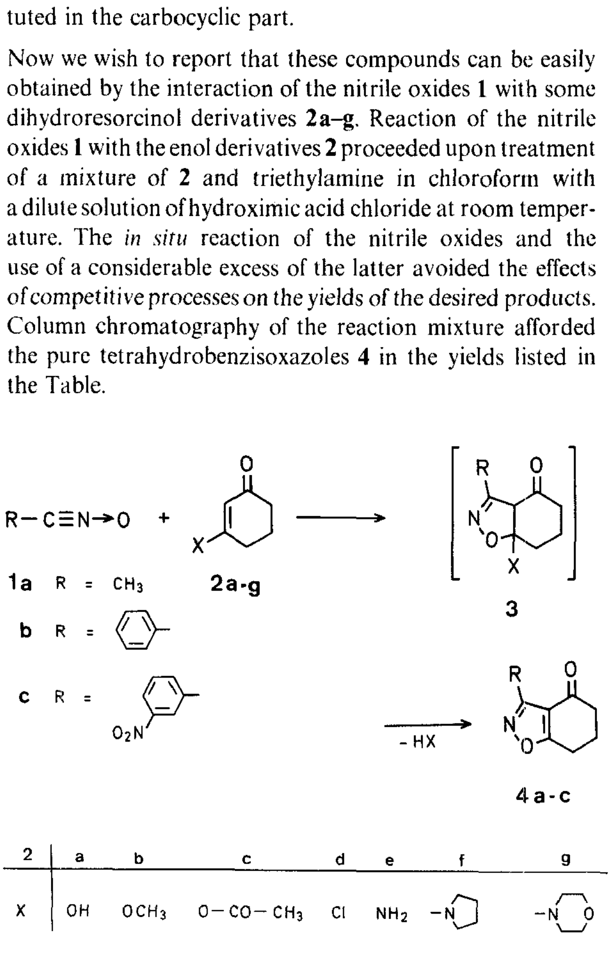
# A Convenient One-Step Synthesis of Tetrahydrobenzisoxazoles via 1,3-Cycloaddition of Nitrile Oxides to Cyclohexane-1,3-dione Derivatives

A. A. Akhrem, F. A. Lakhvich*, V. A. Khripach, A. G. Pozdeyev

Institute of Bioorganic Chemistry, Byelorussian SSR Academy of Sciences, 220600 Minsk, U.S.S.R.

Condensed cyclohexaneisoxazoles such as **4** are of considerable synthetic interest particularly as latent forms of 2-acylcyclohexane-1,3-diones[1,2], whose usefulness in organic synthesis is well documented[3]. The preparation of different 3-substituted 6,6-dimethyltetrahydrobenzisoxazoles via 1,3-cycloaddition of nitrile oxides to 5,5-dimethyl-2-cyclohexen-1-one followed by chloranil dehydration of the corresponding 4-acylisoxazolines was achieved earlier[1]. However, the low regioselectivity of cycloaddition of the nitrile oxides to the cyclohexenone (**2**, X=H)[4] limits the exploitation of this procedure for the preparation of the isoxazoles **4** unsubstituted in the carbocyclic part.

Now we wish to report that these compounds can be easily obtained by the interaction of the nitrile oxides **1** with some dihydroresorcinol derivatives **2a–g**. Reaction of the nitrile oxides **1** with the enol derivatives **2** proceeded upon treatment of a mixture of **2** and triethylamine in chloroform with a dilute solution of hydroximic acid chloride at room temperature. The *in situ* reaction of the nitrile oxides and the use of a considerable excess of the latter avoided the effects of competitive processes on the yields of the desired products. Column chromatography of the reaction mixture afforded the pure tetrahydrobenzisoxazoles **4** in the yields listed in the Table.



Obviously, the formation of the tetrahydrobenzisoxazoles **4** is a result of spontaneous elimination of HX molecule from the $\Delta^2$-isoxazolines **3**, which are the primary products of cycloadditions.

The tetrahydrobenzisoxazole **4a** obtained from the reaction of acetonitrile oxide (**1a**) with **2a–g** was identical in all respects with the authentic sample[5]. The structures of the tetrahydrobenzisoxazoles **4b,c** follow from the analytical and spectral (I.R., $^1$H-N.M.R. and mass spectra) data and chemical behaviour as well as from comparison with the known analogs[1].

**Table.** Tetrahydrobenzisoxazoles **4** from Nitrile Oxides **1** and Dihydroresorcinol Derivatives **2**

| Dipolarophile **2** | Yields of Tetrahydrobenzisoxazoles [%] **4a** | **4b** | **4c** |
|---|---|---|---|
| **a** | 70 | 34 | 56 |
| **b** | 61 | 3 | 22 |
| **c** | 38 | 10 | 30 |
| **d** | 38 | 12 | 36 |
| **e** | 24 | 18 | 40 |
| **f** | 100 | 26 | 52 |
| **g** | 100 | 68 | 93 |

**General Procedure for the Preparation of Tetrahydrobenzisoxazoles 4 from Nitrile Oxides 1 and Cyclohexenones 2:**

To a vigorously stirred solution of **2** in chloroform (30–40 mmol/l) and triethylamine (5-fold excess), a solution of hydroximic acid chloride in chloroform (60–70 mmol/l) is added dropwise at room temperature during 6 h. The reaction mixture is allowed to stand at room temperature for 12 h and then the solvent is removed under reduced pressure. The residue is chromatographed over alumina (by Brockmann, II), using hexane/ether gradient elution. Tetrahydrobenzisoxazoles **4a,b,c** are obtained in yields listed in the Table.

*3-Phenyl-4-oxo-4,5,6,7-tetrahydrobenz[1,2-*d*]isoxazole* (**4b**):
is obtained as described above; m.p. 69–71° (from *n*-hexane).

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{11}NO_2$ | calc. | C 73.24 | H 5.16 | N 6.57 |
| (213.2) | found | 72.99 | 5.19 | 6.44 |

M.S.: *m/e* (relative intensity)=213 (M$^+$, 100%); 185 (16%); 184 (16%); 157 (15%); 156 (12%); 143 (88%).

I.R. (KBr): $\nu_{max}$=1575; 1590; 1690 cm$^{-1}$.

$^1$H-N.M.R. (CDCl$_3$): $\delta$=2.20 (m, 2H); 2.54 (m, 2H); 2.99 (t, 2H, $J$=7 Hz); 7.72 ppm (m, 5H).

*3-(*m*-Nitrophenyl)-4-oxo-4,5,6,7-tetrahydrobenz[1,2-*d*]isoxazole* (**4c**):
is obtained as described above; m.p. 131–134° (from *n*-hexane).

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{10}N_2O_4$ | calc. | C 60.46 | H 3.90 | N 10.85 |
| (258.2) | found | 60.62 | 3.90 | 10.70 |

M.S.: *m/e* (relative intensity)=258 (M$^+$, 93%); 230 (31%); 188 (100%).

I.R. (KBr): $\nu_{max}$=1350; 1530; 1690 cm$^{-1}$.

$^1$H-N.M.R. (CDCl$_3$): $\delta$=2.27 (m, 2H); 2.62 (t, 2H, $J$=6 Hz); 3.10 (t, 2H, $J$=6 Hz); 8.30 ppm (m, 4H).

Received: January 25, 1977
(Revised form: August 22, 1977)

---

[1] A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, I. B. Klebanovich, *Khim. Heterocycl. Soed.* **1975**, 329; *C. A.* **83**, 27669 (1975).

[2] A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, I. B. Klebanovich, *Tetrahedron Lett.* **1976**, 3983.

[3] A. A. Akhrem, A. M. Moiseenkov, F. A. Lakhvich, *Dokl. Akad. Nauk SSSR* **193**, 1053 (1970); C. A. **74**, 23014 (1971).
A. A. Akhrem, A. M. Moiseenkov, V. A. Krivoruchko, F. A. Lakhvich, A. I. Poselenov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, 2078; *C. A.* **78**, 30056 (1973).
A. Martani, A. Flavolini, G. Grandolini, *J. Heterocycl. Chem.* **11**, 453 (1974).
A. A. Akhrem et al., *Dokl. Akad. Nauk SSSR* **226**, 1326 (1976); C. A. **85**, 32487 (1976).
M. Kataoka et al., *Japan Kokai* 7601633 (1976); *C. A.* **84**, 175144 (1976).

[4] G. Bianchi et al., *J. Chem. Soc. Perkin Trans. 1*, **1973**, 1148.

[5] H. Smith, *J. Chem. Soc.* **1953**, 803.

0039-7881/78/0132-0043 $ 03.00