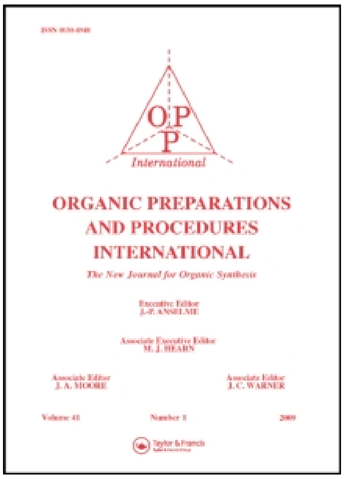

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THE REACTION OF 3,5-DIMETHYLISOXAZOLE WITH NITRITES AND NITROSO COMPOUNDS

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OPPI BRIEFS

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THE REACTION OF 3,5-DIMETHYLISOXAZOLE WITH NITRITES AND NITROSO COMPOUNDS

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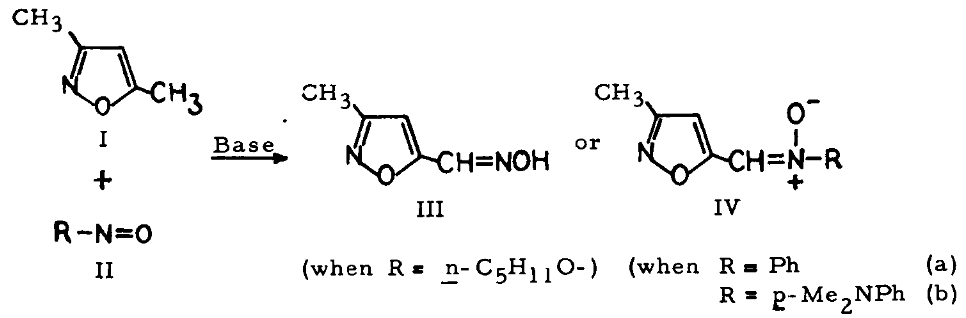
The reaction of 3,5-dimethylisoxazole (I) with n-amyl nitrite and with nitrosoarenes in the presence of strong bases gives 3-methyl-5-isoxazolecarboxaldehyde derivatives in a regiospecific reaction.[1]



In addition to recovered I (40%) and 3-methyl-5-isoxazolecarboxamide (15%), III[2] was obtained in 19% yield from the reaction of n-amyl nitrite with I in the presence of sodium amide. Nitrones IVa (17%) and IVb (2%) were obtained from the reaction of I with nitrosobenzene and p-dimethylaminonitrosobenzene respectively, with either sodium amide or butyllithium as the base; the corresponding azoxy compounds (V) were also characterized as by-products. Compound IVa was converted to III by treatment with hydroxylamine hydrochloride and sodium acetate.[3]

EXPERIMENTAL[4]

The Reaction of 3,5-Dimethylisoxazole with Amyl Nitrite. - To a sodium amide suspension in liquid ammonia, prepared from sodium (0.01 g atom), a solution of I (0.01 mole) in 15 ml of anhydrous ether was added. After stirring for 1-1.5 hr. under nitrogen stream, amyl nitrite (0.01 mole) in 15 ml of anhydrous ether was added and the stirring was continued for another 5 hrs. at -78°. The reaction mixture was neutralized with solid ammonium chloride (6.0 g). Ammonia was removed at room temperature. The residual ethereal solution was extracted with dichloromethane. After the removal of the solvent, the residue was purified by silica gel column chromatography with a benzene-ethyl acetate mixture and recrystallization.

3-Methyl-5-isoxazolecarboxaldoxime (III), mp. 126-128° (recrystallized from chloroform), was obtained in 19% yield. IR (KBr): 3200, 1590, 1010 and 805 cm^{-1}. Nmr ($CDCl_3$): 2.35 (s, 0.84H), 2.38 (s, 2.16H), 6.38 (s, 0.28H), 6.98 (s, 0.72H) and 8.09 ppm (s, 0.28H).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.90; N, 22.22 .

Found: C, 47.97; H, 4.90; N, 22.32 .

The yield of III was 15% with n-butyllithium in dry THF (reaction time 5 hrs.).

The Reaction of I with Nitrosoarenes. - To a solution of I (0.01 mole) in dry THF (70 ml), n-butyllithium (0.01 mole, 15% in n-hexane) was added at -78° . The mixture was stirred for 1-1.5 hr. under nitrogen stream. After the addition of the nitrosoarene (0.01 mole), the stirring was continued for another 1-2 hrs. at -78°. The solution was then warmed to room temperature and water was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography with a benzene-ethyl mixture and/or recrystallization.

N-(3-Methyl-5-isoxazolymethylidene)anilile N-Oxide (IVa) was obtained in 17% yield, mp. 146-7° from carbon tetrachloride by using sodium amide in liquid ammonia. IR (KBr): 3430, 3210, 3130, 1585, 1545, 1250, 890 and 830 cm^{-1}; nmr ($CDCl_3$): 2.41 (s, 3H), 7.4-7.9 (m, 6H) and 8.27 ppm (s, 1H).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86 .
Found: C, 65.20; H, 4.93; N, 13.44 .

Azoxybenzene (V): Yield 26%, mp. 35.5-36°.

N-(3-Methyl-5-isoxazolymethylidene)-p-dimethylaminoaniline N-Oxide (IVb) was obtained in 2% yield, mp. 167-169° from carbon tetrachloride. IR (KBr): 3300, 1605, 1580, 1230, 875 and 815 cm^{-1}; nmr ($CDCl_3$): 2.40 (s, 3H), 3.04 (s, 6H), 7.45 (s, 1H), 6.68 (d, 2H, J=9.2 Hz), 7.70 (d, 2H, J=9.2 Hz) and

8.19 ppm (s, 1H).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13 .
Found: C, 63.59; H, 6.04; N, 16.74 .

p,p'-Bis-dimethylaminoazoxybenzene (Vb): Yield 7%, mp. 236-8°.

The Transformation of IVa to III. - Hydroxylamine (38 mg) and an aqueous solution (0.25 ml) of sodium acetate (75 mg) was added to an acetic acid solution (25 ml) of IVa (100 mg). After the mixture was stirred for 1 hr. at room temperature, water was added. The precipitate was filtered and recrystallized from an n-hexane-benzene mixture. The product (21%) was identical to an authentic sample of III.

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1. C. Kashima, S. Tobe, N. Sugiyama and M. Yamamoto, Bull. Chem. Soc. Japan, 46, 310 (1973); C. Kashima, N. Mukai and Y. Tsuda, Chem. Letters, 1973, 539.

2. The structure of the oxime was confirmed by comparison with the nmr spectrum of 2-furancarboxaldoxime [R. Wasylishen and T. Schaefer, Can. J. Chem., 50, 274 (1972)]. It was found that the oximes were mixtures of syn- and anti-isomers by comparing the chemical shifts of the methine protons of C-4 and hydroxyimino group. The methine protons of II at δ 8.09 and 7.64 ppm were assigned to those of syn- and anti- isomers, respectively. The ratio of syn- and anti- isomers varied appreciably depending on the solvents: DMSO: 8.3; EtOH: 5.1; CH_2Cl_2: 2.6; $CHCl_3$: 0.8.

3. The structure of the amide was deduced from the spectral data and was confirmed by a mixture melting point with an authentic sample, from ethyl acetopyruvate and hydroxylamine in 18% yield. [S. Sumimoto, Kogyo Kaguku Zasshi, 66, 1831 (1963); Chem. Abst., 60, 14489e (1964)].

4. Melting points are uncorrected and yields are given after the purification. The ir and nmr spectra were measured by Hitachi ESP-S2 type infrared absorption spectrometer and a Hitachi H-60 type or a JEOL H-100 type nmr spectrometer, respectively. Chemical shifts are in ppm (δ) from TMS as an internal standard.