Novel Nitroimidazo[2,1-*b*]oxazole Formation from Reaction of 2,4(5)-Dinitroimidazole with Oxiranes (1)

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Received July 23,1979

A novel reaction for the synthesis of 2,3-dihydroimidazo[2,1-*b*]oxazoles has been described by condensation of 2,4(5)-dinitroimidazole with a series of oxiranes.

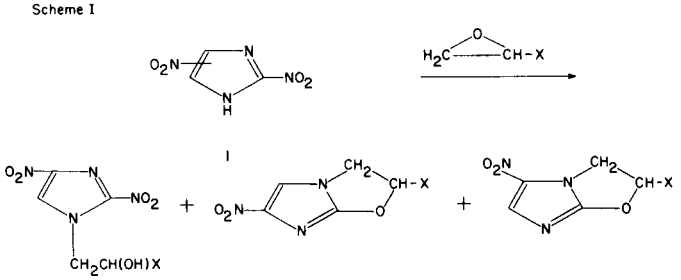
J. Heterocyclic Chem., **16**, 1499 (1979).

Sir:

In our continuing search for effective radiosensitizers of hypoxic tumor cells, we attempted to incorporate an additional nitro function into the 2-nitroimidazole nucleus to increase its electron affinity, and then to alkylate the 2,4(5)-dinitroimidazole (**1**) by reaction with oxiranes. During such attempts we obtained not only 1-(2-hydroxyalkyl)-2,4-dinitroimidazoles but also novel nitroimidazo[2,1-*b*]oxazoles as products by elimination of the 2-nitro group. An intramolecular displacement of the 2-nitro function in 1(α-D-ribofuranosyl)-2-nitroimidazole upon treatment with methanolic sodium methoxide has recently been reported (2). 1-Bromoisoquinolines have also been shown to undergo ethylene oxide mediated isoquinolone conversion presumably *vis* oxazolidine intermediate (3). In the present report we wish to describe the formation of nitroimidazo[2,1-*b*]oxazoles by the reaction of **1** with oxiranes.

The reaction of ethylene oxide with **1** to afford 1-(2-hydroxyethyl)-2,4-dinitroimidazole (**2a**) [Scheme I] was recently reported from our laboratory (4). We were able to isolate a labile compound from this reaction which was found to be 5-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (**4a**). The structure of **4a** was confirmed by X-ray crystallography, ir, nmr and mass spectral analyses. This reaction is now found to be of a general type in that a variety of substituted, stable imidazo[2,1-*b*]oxazoles can be synthesized by reaction of **1** with oxiranes. Accordingly,

Scheme I



2a, X = H
2b, X = CH_3
2c, X = CH_2Cl
2d, X = CH_2OCH_3

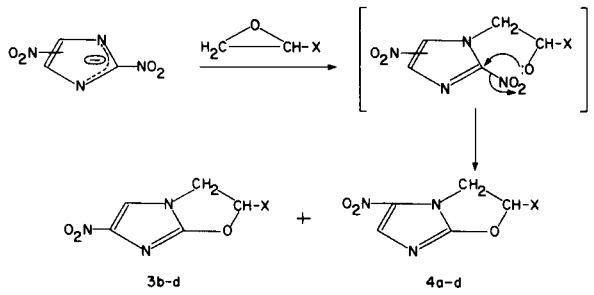
3b, X = CH_3
3c, X = CH_2Cl
3d, X = CH_2OCH_3
3e, X = CH_2OH

4a, X = H
4b, X = CH_3
4c, X = CH_2Cl
4d, X = CH_2OCH_3

reaction of a solution of 0.5 g. (3.2 mmoles) of **1** in 50 ml. of absolute ethanol with 8 ml. of propylene oxide (stirring at room temperature for 48 hours) produced two fractions separated by preparative tlc (chloroform) and subsequently identified as **2b**, m.p. 72-73° (ethyl ether) [319 mg., 53%] and **4b**, m.p. 68-69° (ethyl ether/hexane) [124 mg., 23%] (5). Attempted reaction of a solution of 0.5 g. of **1** in 50 ml. of absolute ethanol with 5 ml. of epichlorohydrin at room temperature for 48 hours remained incomplete as followed by tlc (chloroform). However, the reaction was completed upon further heating the mixture at 60° for 16 hours; the products were isolated by thin-layer fractionation and/or fractional crystallization and identified by ir, nmr and mass spectrometry as **2c**, m.p. 121-122° (ethyl ether) [116 mg., 15%]; **3c**, m.p. 170-171° (absolute ethanol) [236 mg., 37%] and **4c**, m.p. 98-99° (chloroform/hexane) [158 mg., 25%]. Similarly, reaction of a solution of 0.5 g. of **1** in 50 ml. of absolute ethanol with 5 ml. of 1,2-epoxy-3-methoxypropane at room temperature for 24 hours was negligible. However, on heating this solution at 60° for 16 hours, the reaction was completed; the products were isolated by thin-layer fractionation and/or fractional crystallization, and identified as **2d**, m.p. 68-69° (ethyl ether) [106 mg., 14%], **3d**, m.p. 159-160° (absolute ethanol) [223 mg., 35%], and **4d**, m.p. 71-72° (ethyl ether/hexane) [166 mg., 26%]. Since in these reactions **2c** and **2d** were only minor products, attempts were made to develop conditions for obtaining larger yields of these alcohols for studying biological activity. Indeed, reaction of 0.5 g. of **1** in 10 ml. of epichlorohydrin or 1,2-epoxy-3-methoxypropane (**1** went into solution gradually) without the solvent during 96 and 48 hours at room temperature, respectively, afforded higher yields of **2c** (463 mg., 58%) and **2d** (395 mg., 51%). The products were separated from excess oxiranes by silica gel column chromatography by initial elution of the column with chloroform followed by 1:10 ethyl acetate/chloroform. Reaction of **1** (0.5 g.) with 1,2-epoxy-3-hydroxypropane (5 ml.) was also carried out at room temperature by stirring for 48 hours, since the higher temperatures were

0022-152X/79/071499-02$02.25

Scheme II



found to polymerize the oxirane. This reaction afforded only one isomer, **3e**, m.p. 167-168° dec. (ethyl acetate) [180 mg., 31%]. The product was separated from excess polymerized oxirane on a silica gel column by elution with ethyl acetate.

The generality of the reaction and the unusual nature of these products led us to examine the mechanism by which these products were being formed. It seemed logical that the initial reaction was the formation of the alcohol which could undergo intramolecular cyclization on heating. Indeed, reaction of a solution of 100 mg. of **2b** in 10 ml. of absolute ethanol in the presence of excess propylene oxide (under reflux, 40°) for 48 hours afforded primarily **3b**, m.p. 156-157° (absolute ethanol) [47 mg., 60%]. Similarly, reaction of a solution of 100 mg. of **2c** and **2d** in 10 ml. of absolute ethanol in the presence of 2.5 ml. of epichlorohydrin and 1,2-epoxy-3-methoxypropane, respectively, under reflux at 80°, afforded **3c** (61 mg., 75%) and **3d** (63 mg., 78%), respectively. However, formation of the cyclized products **4b-d** could not be satisfactorily explained by this reaction pathway. To rationalize the formation of **4b-d**, we propose that the alternate pathway might involve initially the abstraction of a proton from **1** to form an anion which is then followed by the direct attack of the oxiranes as depicted in Scheme II.

Thus, the displacement of 2-nitro function from an imidazole ring carrying an activating group such as nitro at 4(5) position, is carried out conveniently by oxiranes and leads to reasonable yields of imidazo[2,1-*b*]oxazoles.

REFERENCES AND NOTES

(1) Presented in part at the 176th National Meeting of the American Chemical Society, Miami, Florida, September, 1978, Abstracts of Papers, MEDI-37; this investigation was supported by grant number CA-21050, awarded by the National Cancer Institute, DHEW.

(2) E. J. Prisbe, J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **43**, 4784 (1978).

(3) C. N. Filler, F. E. Granchelli, A. H. Soloway and J. L. Neumeyer, *ibid.*, **43**, 672 (1978).

(4) K. C. Agrawal, K. B. Bears, R. K. Sehgal, J. N. Brown and P. E. Rist, *J. Med. Chem.*, **22**, 583 (1979).

(5) Satisfactory analytical data (within ± 0.4% of the theoretical values for C, H, and N) were obtained for all new compounds. Their ir, nmr and mass spectra were consistent with the structures shown in Scheme I.