ANNELATION BY INTRAMOLECULAR 1,3-DIPOLAR ADDITION OF NITRONES

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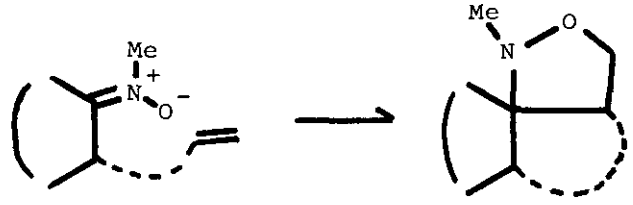
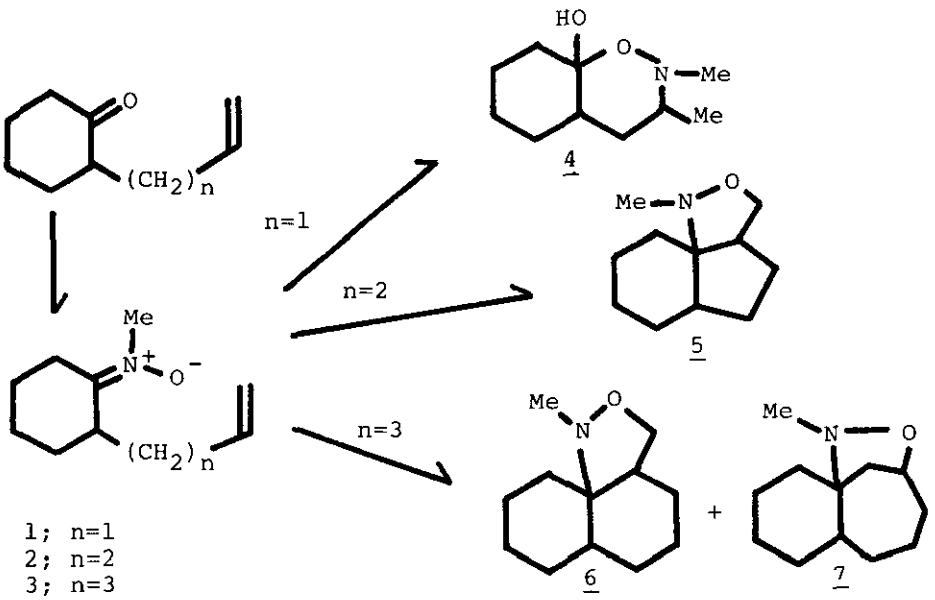
Intramolecular 1,3-dipolar cyclization of the nitrone 2 gave the perhydroindane 5 as a regio and stereoselective product.

Annelation reaction, construction of a new carbon ring, is important especially in the synthesis of natural products. Intramolecular 1,3-dipolar addition[1,2] *of a nitrone group* to an olefinic bond in the following system can build up a new carbon ring together with an isoxazolidine ring. The present paper describes the cyclization of the nitrones 1-3.



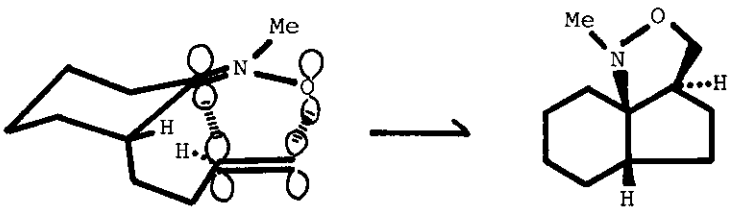
The nitrones were prepared from the corresponding cycloalkanones and N-methylhydroxylamine[3].



On standing at room temperature, the nitrone 1 [$\delta(CDCl_3)$3.73 (3H,s,Me-N(-O)=)] changed into an abnormal cyclization product 4[4] [bp 59°/0.3 mm, $\nu(CHCl_3)$ 3450, 1050 cm^{-1}, $\delta(CDCl_3)$ 4.28 (1H,s,OH) 2.60 (3H,s,N-Me), 2.5 (1H,m,Me-CH-N), 1.05 (3/2H,d,J=6.5 Hz,Me-CH-N), 0.97 (3/2H,d,J=6.5 Hz, isomeric Me-CH-N)]. The normal 1,3-dipolar cyclization product was not obtained even when 1 was heated in refluxing benzene.

On the other hand, the nitrone 2 smoothly gave the expected 1,3-dipolar cyclization product 5 in quantitative yield at room temperature. The nmr spectrum of 5 exhibited a multiplet around 3.8 ppm which was an AB part of an ABX system due to the methylene group of the isoxazolidine ring of 5. This product was found to be a single isomer, showing that the cyclization reaction proceeded regio and stereoselectively.

The stereochemistry of 5 was tentatively described as in 9; thus, the most favorable transition state leading to 5 seemed to be 8, because it permitted the maximum overlapping of the π orbitals of the nitrone and the side chain olefine groups.



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The selective formation of the hydrindane skeleton of 5 is noteworthy, because the operations involved are simple and easy to perform; thus, 1 mole of 2-(3-butenyl)cyclohexanone was treated with N-methylhydroxylamine hydrochloride (1.5 mole) and potassium hydroxide (1.5 mole) in methanol. After the mixture was stirred for 18 hr at room temperature, it was diluted with ether, and the precipitate (KCl) was removed by filtration. The filtrate was concentrated, and the crude nitrone was allowed to stand at room temperature for several days, affording 5 after simple chromatography.

The nitrone 3 somewhat resisted cyclization; however, when it was heated in benzene, the cyclization products 6 and 7 (1:1) were obtained in a good yield. These isomers were separable chromatographycally, and their structures were determined on the basis of their spectral properties; 6 [$\delta(C_6D_6)$ 2.46 (3H,s,N-Me), 3.48 (1H, dd,J=9 and 7 Hz, CH_X-CH_AH_B-O), 3.99 (1H,dd,J=10 and 7Hz,CH_X-CH_AH_B-

O)], 7 [δ(C_6D_6) 1.61 (1H,dd,J=12 and 3 Hz,C-CH_AH_B-CH_X-O), 1.97 (1H,dd,J=12 and 9 Hz,C-H_AH_B-CH_X-O), 2.40 (3H,s,N-Me), 4.45 (1H,m, CH_AH_B-CH_X-O)].

REFERENCES

1 R. Huisgen, Angew. Chem., 75, 604 (1963).

2 For 1,3-dipolar addition of nitrones, see D. S. C. Black, R. F. Crozier and V. C. Davis, Synthesis, 1975, 205. For intramolecular cyclization of nitrones, see W. Oppolzzer, Angew. Chem. Int. Ed. 16, 10 (1977), and references cited therein.

3 Purchased from Aldrich Chemical Company, Inc.

4 This product consisted of two stereoisomers, which were separated by chromatography. ^{13}C-nmr of the one isomer showed the signals at δ($CDCl_3$) 98.21(s), 61.54(d), 43.54(d), 42.88(q), 35.46(t), 35.13(t), 28.80(t), 23.04(t), 19.03(q), 25.79(t).

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