CLEAVAGE OF ISOXAZOLINES BY DIMSYLSODIUM

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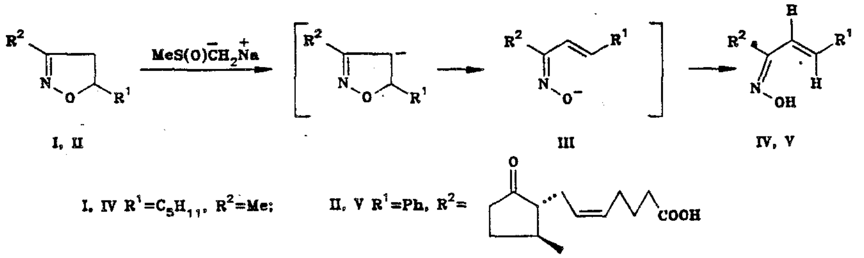
The conversion of 2-isoxazolines to noncyclic, bifunctional derivatives is a widely used strategy in organic synthesis [1-3]. Among the many methods used to exploit the latest functionality of isoxazoline rings, the most advantageous are variations of the reductive cleavage of the N-O bond. The feasibility of syntheses of functionalized compounds involving cleavage of the isoxazoline ring by bases has been limited due to the nonselectivity of this reaction in cases where several potential reactive sites are present. Thus, the cleavage of this heterocycle using diisopropylamide has been described only for 2-isoxazoline derivatives which do not contain active allylic hydrogen atoms within the ring substituents [4, 5].

During the course of our investigations into the use of the isoxazoline approach for the synthesis of prostanoids we discovered that 3,5-disubstituted 2-isoxazolines I and II are readily cleaved by treatment with dimsylsodium to give the α,β-unsaturated oximes IV and V in preparative yields. These reactions apparently occur via intermediate deprotonation of the C(4) atom in the heterocyclic ring, followed by cleavage of the C-O bond and the formation of an enoximate anion III. In contrast to the known examples of base-induced cleavage of 2-isoxazolines [1, 4], ring cleavage by dimsylsodium takes place with a single regiochemical result, regardless of the structure of the starting isoxazoline; the α,β-unsaturated oxime which is formed is the one which retains the configuration of the starting isoxazoline:



To a freshly prepared solution of dimsylsodium (from 10 ml DMSO and 12 mmole sodium hydride, which was heated at 70°C in an argon stream for 45 min, until no more hydrogen gas was evolved) was added a solution of 2 mmole isoxazoline I or II in 2 ml DMSO, and the resulting mixture was stirred at room temperature for 3-4 h; the reaction mixture was then worked up with water and extracted with a 2:1 mixture of benzene—ether. The aqueous portion was acidified with 20% aqueous NaH_2PO_4 to pH 5.5 and extracted with ether; the extract was then dried over Na_2SO_4 and evaporated. The oxime of non-3-en-2-one (IV) was isolated in 92% yield from isoxazoline I. IR spectrum (film): 3270, 1615, 1600 cm^{-1}. PMR spectrum ($CDCl_3$): 0.89 (3H, t, Me), 1.3 (4H, m, 2CH$_2$), 1.42 (2H, m, CH$_2$), 1.97 (3H, s, Me—C=N), 2.18 (2H, q, J = 7.2; 14.6 Hz, —CH$_2$—C=C), 6.13 (1H, dt, J = 7.2; 15.6 Hz, 4-H), 6.83 (1H, d, J = 15.6 Hz, 3-H), 9.9 ppm (1H, br.s, N—OH).

7-[2β-(1-Oximino-3-phenyl-2-propenyl)-5-oxo-1α-cyclopentenyl]-5Z-hexenoic acid (V) was obtained in 80% yield from isoxazoline II. IR spectrum (film): 3470, 3280-2700, 1738, 1710, 1620, 1600 cm^{-1}. PMR spectrum ($CDCl_3$): 1.63-2.5 (12H, m, chain and ring CH$_2$), 2.7 (1H, quint, 1-H ring), 3.2 (1H, m, 2-H ring), 5.41 (2H, m, 5- and 6-H), 7.05 (1H, d, J = 16.5 Hz, =CH—Ph), 7.3-7.6 (6H, m, Ph, N=C—HC=), 8.3 ppm (2H, br.s, COOH, OH).

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UNUSUAL EXAMPLE OF THE FORMATION OF A 1-AZA-3,6-DIOXABICYCLO[3.2.1]OCTANE DERIVATIVE

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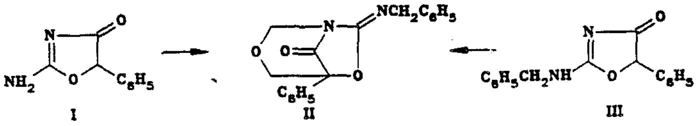
We have found that 2-amino-5-phenyl-4-oxazolinone (I) upon treatment with benzylamine and paraform does not undergo the expected aminomethylation reaction, but rather undergoes successive transamination [1], bishydroxymethylation, and dehydration reactions, to give 7-benzylimino-8-oxo-5-phenyl-1-aza-3,6-dioxabicyclo[3.2.1]octane (II). Compound II was also obtained by an independent synthesis from 2-benzylamino-5-phenyl-4-oxazolinone (III) and formalin



Compound II. A. A mixture of 10.6 g (0.06 mole) compound I, 9.6 g (0.09 mole) benzylamine, 7.7 g (0.25 mole) paraform, and 34.3 ml (0.60 mole) acetic acid in 180 ml methanol was refluxed for 2 h; the reaction mixture was then cooled to 20°C and neutralized with 20% aqueous potassium hydroxide. The resulting precipitate was crystallized from ethanol. Yield 2.0 g (11%), mp 190°C. IR spectrum (in KBr): 1825 (C=O), 1740 cm^{-1} (C=N). PMR spectrum (CCl_4): 7.00-7.42 (10H, m, C_6H_5), 4.03-4.70 (2H, m, 2-CH_2), 2.90-4.03 ppm (4H, m, 4-CH_2, CH_2Ph).

B. A mixture of 0.85 g (0.03 mole) compound III, 0.95 ml (0.013 mole) formalin, and 1.5 ml (0.027 mole) acetic acid in 4.5 ml methanol was refluxed for 0.5 h and worked up to give compound II, as described above. Yield 0.05 g (5%), mp 188°C. The results of elemental analysis were consistent with the calculated values.

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