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Synthesis and Face- and Stereo-selective Cycloadditions of α-Alkoxy Cyclic Nitrones

Sk. Asrof Ali*, S. M. Azhar Hashmi and Mohammed I. M. Wazeer

Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

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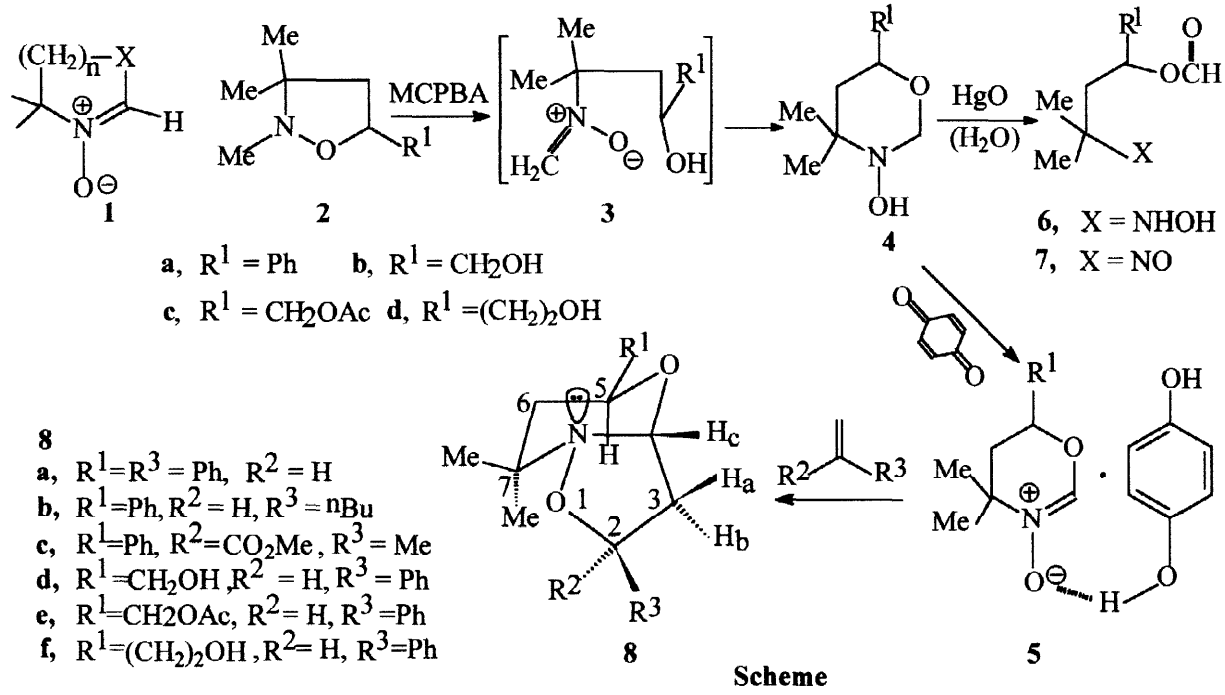
Abstract:: α-Alkoxy cyclic nitrones **(5)**, stabilized by the presence of hydroquinone, underwent face-, regio- and stereo-selective cycloaddition reaction with normal alkenes to afford bicyclic isoxazolidines **(8)** efficiently.

Nitrone's singular capability to incorporate multiple stereocentres in its addition onto dienophile has earned this functionality a place of distinction in organic synthesis.[1] While the cycloaddition reaction of cyclic aldonitrones (**1**, X=CH_2) have been extensively studied,[2] to the best of our knowledge only one report[3] describes the addition reaction of an α- alkoxy cyclic aldonitrone (**1**, n = 1, X= O) with powerful electron



Scheme

deficient alkene maleic anhydride. However its failure to add onto methyl acrylate or phenyl acetylene even at 150 °C led the authors[3] to comment on the limited utility of this synthetically important class of nitrones. Herein we report for the first time the synthesis and addition of nitrones of the type **1** (n=2, X= O) with normal alkenes, let alone the most reactive dienophiles.

The isoxazolidines[4] **2** on peracid induced ring opening (MCPBA, 1 eq, dry CH_2Cl_2, -15 °C) afforded the hydroxylamines **4** *via* intermediate methylenenitrones **3** in 80-90% yields. The oxidation of hydroxylamine **4a**

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with mercury (II) oxide in anhydrous CH_2Cl_2, to our dismay, resulted in the formation of the blue coloured nitroso compound **7a** *via* hydrolysis of the expected nitrone **5a** to hydroxylamine **6a** followed by its oxidation. The oxidation carried out in presence of styrene, linde molecular seives (4 A°) or $MgSO_4$ also led to **7a**. We realized, at this stage, that oxidation should be carried out using oxidant that would not generate water molecules. To our delight, the reaction of the hydroxylamine **4a** (2.0 mmol) in anhydrous benzene (35 cm^3) using p-benzoquinone (2.3 mmol) at 25 °C (15 min) under N_2 gave a blue coloured mixture (presumably a radical-cation-radical-anion pair by SET[5] mechanism) which on heating at 50-60 °C (10 min) resulted in precipitation of a white solid of **5a**-hydroquinone pair. Addition of anhydrous styrene (3 cm^3), 1-hexene (5 cm^3) or methyl methacrylate (3 cm^3) to the reaction mixture and heating at 80 °C for 2 h resulted in the formation of the addition products **8a**, **8b**, and **8c** (and its isomer) in 71, 65 and 90 % yield, respectively, (silica gel chromatography, hexane-ether eluant). Like wise the nitrones **5b, 5c** and **5d** were prepared and reacted with styrene to give the cycloadducts **8d**, **8e** and **8f**, respectively, in 65, 75 and 55 % yields (reaction conditions are not optimized). The addition reactions with styrene and 1-hexene are face-, regio- and stereo-selective, happening at the sterically favoured face of the nitrone *via exo*-mode of approach of the alkenes. The proton H_c in all the isoxazolidines[6] **8** appeared as a doublet ($J_{a,c} \approx 5$ Hz) at around δ 5.1 ppm indicating a dihedral angle of 90° between H_b and H_c. The large coupling constant of 12 Hz reveals the axial nature of the C(5) proton thus forcing the compounds to adopt *cis* geometry around the ring juncture.

While the free nitrone **5a** is expected to be soluble in $CDCl_3$, the pair (mp 151-152°C, closed capillary) remained almost insoluble in $CDCl_3$ but readily dissolves in rigorously dried DMSO-d_6 (δ_H 1.49 (3 H, s), 1.59 (3 H, s), 2.41 (2 H, m), 5.54 (1 H, dd, *J* 5.0, 9.5 Hz), 6.70 (4 H, s, hydroquinone), 7.56 (5 H, m), 8.11 (1 H, s, CH=N), 9.10 (2 H, s, hydroxyls). α Alkoxy-ketonitrones are known[7] to be unstable, but the pair **5a** remained stable and when used after two months it afforded the cycloadducts with the same ease. It is tempting to anticipate that the mere presence of hydroquinone may stabilize various otherwise unstable nitrones. The presence of bridgehead H in **8** is of tremendous importance since it meets the requirement of per acid induced ring opening[8,9] of isoxazolidines to generate new series of nitrones.

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