Preparation and Characterization of 1,3-Dioplar Cycloaddition of Nitrones to N-Phenyl Maleimide

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Abstract:

It was found that the cycloaddition of α -(4-Methoxy)phenyl-N-Phenyl nitrone (1)to N-Phenyl maleimide gives the syn isoxazolidine(3),whereas α -(2-fluoro)phenyl-N-phenyl nitrone(2)to the same compound gives the antiisoxazolidine(4), which has been identified by the IR spectroscopy, CHN analysis, Mass spectrometry and H-NMR spectra from two isoxazolidines compounds.

Introduction:

Isoxazolidines, readily available via 1,3-dipolar cycloddition of nitrones to olefins, represent an attractive class of compounds which can be utilized in the synthesis of other heterocyclic systems and substituted alkane.¹

A large part of research on stereocontrolled versions of 1,3-dipolar cycloaddition in the last few years was devoted to the influence exerted by a stereocentre located on the two cycloaddition.²

Recently it was reported that the cycloaddition of nitrones to α,β -unsaturated sugar lactones,^r as the bicyclic system is highly functionalized, the adducts offer wide possibilities of formation of selected structures. Scheme (1)



Scheme (1)

Results and Discussion:

The 1,3-dipolar cycloaddition reaction has a nearly singular capability of establishing large number of stereochemical center in one synthetic step.1

In this line an impressive effort has been devoted to the synthetic application of the cycloaddition nitrones to alkenes to give isoxazolidines. خطأ! الإشارة المرجعية, 1 The prepared nitrones was accomplished from the corresponding aldehydes, 1 which were converted to nitrones by treatment with N-phenyl hydroxylamine. Scheme (2)





1,3-dipolar cycloaddition of α -(4-methoxy)phenyl-N-phenyl-nitrone (1) reacts with N-phenyl maleimide in toluene at 110 °C to give the syn isoxazolidine (3) (H-3, H-3a-syn-relationship). In contrast, the α -(2-fluoro) phenyl-N-phenyl nitrone (2)gave the anti-isoxazolidine(4)(H-3,H-3a-anti-relationship). Scheme (3)



(4) anti isoxazolidine

Scheme (3)

The crude residue was chromatographically separated and both cycloaddition assignments of H-3, H-3a and H-6a atoms were made to the condensed isoxazolidines on the basis of spectroscopic data, in particular by using the J3-3a and J3a-6a coupling constant.

Moreover, all up to date known 1,3-dipolar cycloaddition reactions of nitrones to alkenes proceeded with cis-stereo specified.

1H-NMR analysis of isoxazolidines (3) revealed that each a H-3, H-3a syn relationship, Fig (1). In (3) the signal for the H-3a proton appears as a triplet at δ 4.19 with a coupling constant of J3a-6a=9.3 Hz, J3a-3= 7.4 Hz from coupling solely to the H6a, H-3 proton.

While the signal for the H-3 proton appears as a doublet at δ 5.45 with a coupling constant of J3a-3= 7.4 Hz; while proton NMR analysis of anti-isoxazolidine (4) reveals each H-3, H-3a-anti-relationship, Fig (2).

In (4) the signal for the H-3a proton appears as a doublet at δ 5.42 with a coupling solely to J6a-3a the H-6a proton, while H-3 proton appears as a singlet1 at δ 6.05.

As well as, the compounds characterized by the elemental analysis (CHN), IR spectroscopy and Mass spectrometry. As shown in Fig. (3) and (4).

The 1,3-dipolar cycloaddition of nitrones with N-phenyl maleimide gives two diastereoisomeric isoxazolidines on the basis of two possible endo and exo arrangements,⁸ Scheme (4).



Scheme (4)

Stereoselectivity is due to secondary orbital interactions or steric effects. There is clear evidence that nitrones derived from aromatic aldehydes prossess a configuration which the C-aryl and N-phenyl groups are in a trans relationship.⁹

A cycloaddition of Z-nitrone via on exo transition state (exo arrangement between two N-phenyl groups) results in the formation of cis-isoxazolidines. Cycloaddition through the endo transition state (both N-phenyl groups are in the same side) gave the trans isomers.

Experiment:

Melting point was determined on digital Gallenkamp, CHN analysis by CHN-900 in LECO, IR spectra were obtained with SP3-300S in PYE-UNICETHZ and Mass spectra were obtained with an MS USER: SPE DEFAULT.

Preparation of α -aryl-N-phenyl nitrone (1),(2):

The N-phenyl hydroxyl amine was prepared from nitrobenzene according to ref.1 and α -ary-N-phenyl nitrones(1),(2)from the respective substituted benzaldehyde and N-phenyl hydroxyl amine according to ref.¹¹

General for the Preparation of the isoxazolidines (3), (4):

The N-phenyl- α -aryl nitrones(1),(2)(0.005 mole) and (0.005) mole) N-phenyl maleimide in dry toluene(50ml)were heated under reflux for 2-4 h. Column chromatography (chloroform-toluene 6:4 V/V) of each residue on silica gel (mesh 230-400) and crystallization from methanol then gives(3),(4).

The following compound prepared in this manner:

2,5-diphenyl-3-(4-methoxyphenyl)-4,6-di-oxo-2,3,3a,4,6,6a-

hexahydropyrrolo[3,4-d]-isoxazole (3).

Yield: 80%; m.p.=210-212 °C; C24H20N2O4 (400, 43 g/mole) calc: C=71.99%, H=5.03%, N=7.0%, found C= 71.9%, H=5.25%, N= 7.05%; IR: 1700s (C=O), 1600s-1485s (C=C), 1385s, 1245 (C-O), 1180s (N-O); H-NMR: δ 6.95-7.47 (m, 14H, aromatic), 5.45 (d, 1H, H-3, J3-3a= 7.47 Hz), 5.0(d, 1H, H6a, J6a-3a= 9.34 Hz), 4.19 (t, 1H, H-3a), 3.76 (s, 3H, CH3); Ms: m/z= 400.02 (M+).

2,5-diphenyl-3-(2-fluorophenyl)-4,6-di-oxo-2,3,3a,4,6,6a-

hexahydropyrrolo[3,4-d]-isoxazole (4).

Yield: 75%; m.p.=203-205 °C; C23H17N2O3F (388.4 g/mol); calc: C=71.13%, H=4.41%, N=7.21%, found: C=71.13%, H=4.53%, N=7.26%; IR: 1700s (C=O), 1585m, 1480 (C=C), 1390s (C-O), 1205 (N-O); H-NMR: δ 6.62-7.67 (m, 14H, aromatic), 6.055 (s, 1H, H-3), 5.42 (d, 1H, H6a, J3a-6a= 7.31 Hz), 421 (d, 1H, H-3a); Ms: m/z= 388.1 (M+).

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المستخلص: الاضافة الحلقية لمركب الفا-(٤ ميثوكسي)فنيل في فنيل نيترون(١)الى ن فنيل ماليمايد اعطى المركب سن ازوكسازولدين(٣) بينما الاضافة الحلقية له الفا-(٢ فلورو) فنيل-ن فنيل نيترون(٢)الى ن فنيل ماليمايد اعطى المركب انتي ازوكسازولدين(٤)حيث شخص المركبان الناتجان بواسطة طيف الاشعة تحت الحمراء وجهاز تحليل العنصر الدقيق وطيف الكتلة وطيف الرنين النووي المغناطيسي للبروتون

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