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A STUDY OF THE 5-EXO METHYLENE-ISOXAZOLIDINE TO 3-PYRROLIDINONE REARRANGEMENT

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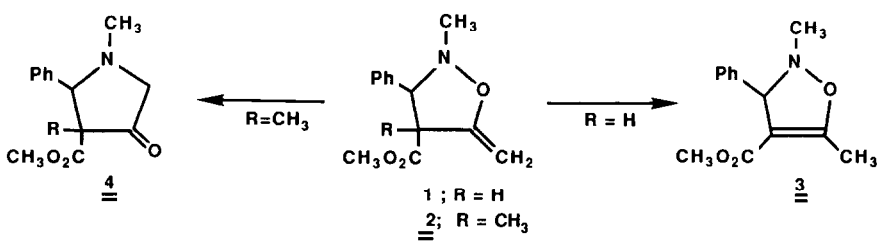
Abstract: Dipolar cycloaddition of nitrones with carbomethoxy substituted allenes gives 5-exo methylene substituted isoxazolidines which rearrange upon thermolysis to 3-pyrrolidinones.

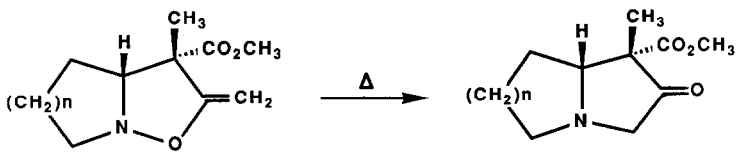
The preparation of five-membered nitrogen heterocycles has received considerable attention from synthetic chemists in recent years,[1-8] in part due to the interesting biological activities exhibited by several polysubstituted pyrrolidines.[9] The 1,3-sigmatropic rearrangement of 5-methylene isoxazolidines attracted our attention as a particularly appealing vehicle for developing a new pyrrolidine synthesis. The reaction of nitrones with simple allenes was previously reported to provide 3-pyrrolidinones.[10-12] The formation of the pyrrolidinone ring was attributed to an initial 1,3-dipolar cycloaddition reaction followed by a spontaneous rearrangement of a transient isoxazolidine intermediate. In this communication, we report the first study dealing with the actual isolation and thermal reorganization of several 5-methylene substituted isoxazolidines.

1-Carbomethoxyallene reacted smoothly with C-phenyl-N-methylnitrone in benzene at 40°C to produce isoxazolidine 1 in 80% yield.[13] The isolation of cycloadduct 1 is of considerable interest since related 5-exo methylene substituted isoxazolidines have only been reported as transient species. Based on FMO theory, allenes possessing electron withdrawing substituents are expected to undergo dipolar cycloaddition across the activated π-bond. MNDO calculations indicated that the introduction of a carbomethoxy group causes a significant lowering of the MO energy level compared with allene and the largest LUMO coefficient resides on the central carbon and the next on the position bearing the carbomethoxy group. We have studied the thermolysis of 1 at 90°C and find that it reacts via a 1,3-hydrogen shift to give 3 rather than by N-O bond scission.



Reaction of 1-methyl-1-carbomethoxyallene with C-phenyl-N-methylnitrone gave rise to cycloadduct 2 in 96% yield.[14] This material can not rearrange via a 1,3-hydrogen shift. Instead, at 90°C, in either benzene, DMF or cyclohexane, 2 undergoes quantitative reorganization to give pyrrolidinone 4. The progress of the reaction can be conveniently monitored by ^{1}H NMR spectroscopy. The rate of rearrangement was found to be 8.75 X 10^{-6} sec^{-1} at 80°C. The reaction was determined to have an activation energy of 30.2 kcal/mole. The small response of the rate (i.e. less than five-fold) to a variation of the solvent polarity rules out a dipolar intermediate and is more consistent with either a concerted reaction or homolytic cleavage of the N-O bond.[15]

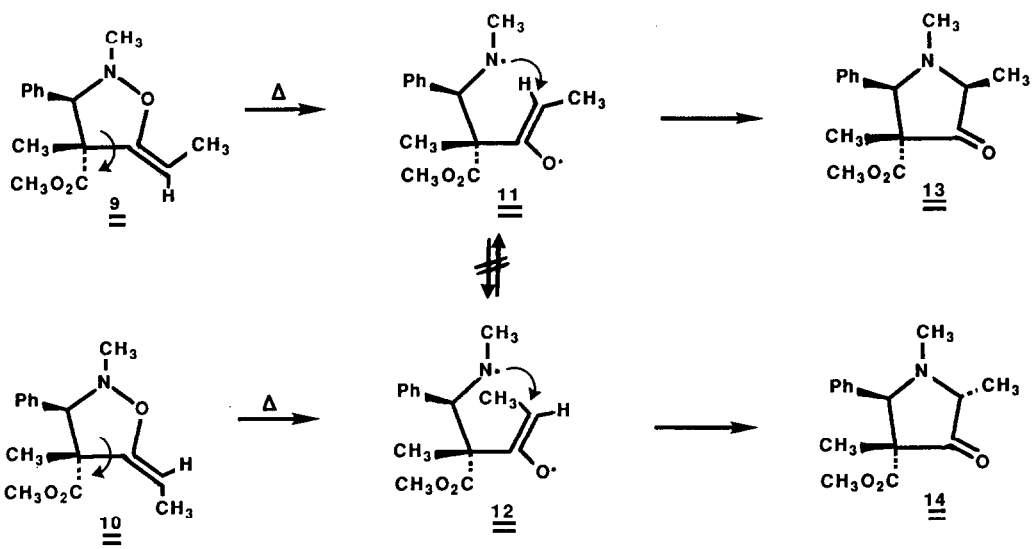
The 5-methylene isoxazolidine-pyrrolidinone rearrangement was also observed to occur with cycloadducts 5 and 6. These compounds were quantitatively converted to pyrrolidinones 7 and 8 upon heating in DMF at 80°C for 8-10 hr.



5; n =1
6; n = 2

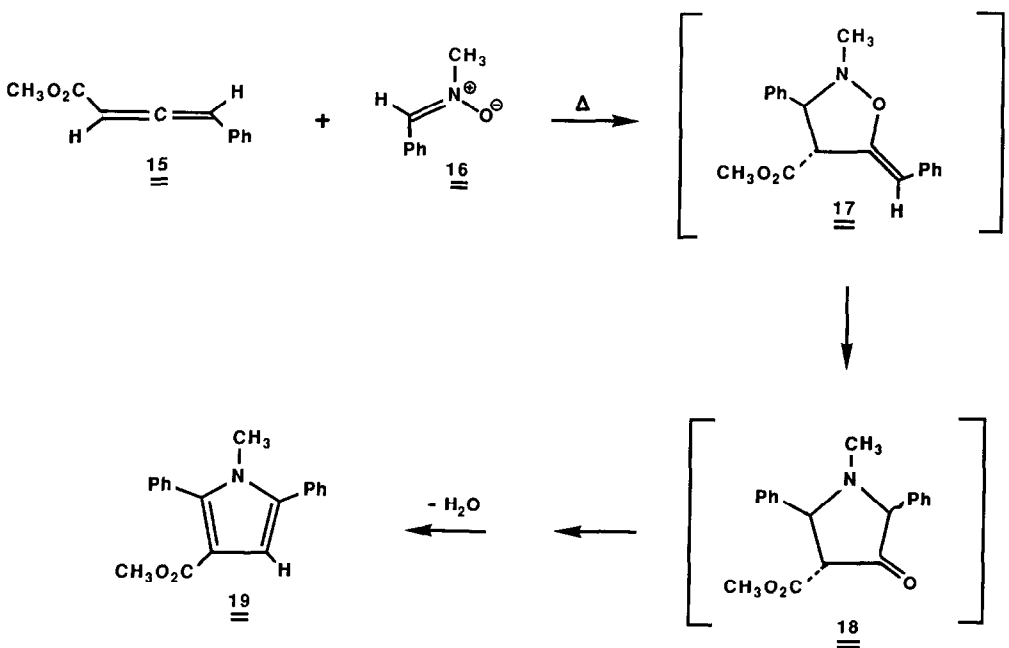
7; n = 1
8; n = 2

In order to probe the stereochemical aspects of the reaction, we have studied the thermal behavior of isoxazolidines 9 and 10. These compounds were prepared by treating C-phenyl-N-methylnitrone with 1-carbomethoxy-2,3-propadiene at 50°C for 12 hr. The two isomeric cycloadducts were separated by silica gel chromatography. Thermolysis of 9 gave rise to a single pyrrolidinone



(i.e. 13). Heating a sample of 10 produced the isomeric structure 14 as the exclusive product in quantitative yield. These results clearly establish that the thermal rearrangement of the 5-exo methylene isoxazolidine system is totally stereospecific. The stereochemical results obtained may be most simply interpreted on the basis of a concerted 1,3-sigmatropic rearrangement.[16] The results can also be rationalized on the basis of a rapid readdition of the nitrogen radical derived from N-O bond scission onto the enol radical pi system. The latter possibility would require that rotation about the 4,5 bond occur exclusively in a clockwise direction. The preferred direction of rotation is probably due to a minimization of nonbonded interactions with the methyl group on the 4-position of the ring. MNDO calculations indicate a 54 kcal/mol difference in the heat of formation of the parent 5-exo methylene isoxazolidine with the 3-pyrrolidinone ring thereby providing the thermodynamic driving force for the reaction.

We also examined the reaction of 1-carbomethoxy-3-phenylpropadiene with C-phenyl-N-methylnitrone. Stirring a mixture of these two compounds in benzene at 50°C for 6 hr gave N-methyl-1,5-diphenyl-3-carbomethoxypyrrole (19)[17] in 67% yield. In this case, the initially formed cycloadduct (17) rapidly rearranges since the reaction is facilitated by the conjugative stabilization of the oxygen radical by the phenyl group. The subsequent conversion of the pyrrolidinone to the pyrrole nucleus probably proceeds via a series of proton shifts followed by loss of water.



Studies of the rearrangement reaction with other systems and its application toward the synthesis of alkaloids are in progress and will be reported on at a later date.

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(13) To our knowledge, the spectroscopic and chemical data associated with 1 and 2 represent the first direct characterization of a 5-exo methylene isoxazolidine obtained from cycloaddition of a nitrone with an allene; NMR 1 (90 MHz,$CDCl_3$) δ 2.68 (s, 3H), 3.72 (s, 3H), 3.9-4.2 (m, 3H), 4.25 (t, 1H, J=2.5 Hz) and 7.30 (m, 5H).

(14) Cycloadduct 2 corresponded to the major diastereomer isolated in 75% yield; NMR (90 MHz,$CDCl_3$) δ 1.20 (s, 3H), 2.70 (s, 3H), 3.75 (s, 3H), 3.95 (d, 1H, J=2.5 Hz), 4.23 (d, 1H, J=2.5 Hz), 4.50 (s, 1H) and 7.2 (s, 5H); NMR 4 (90 MHz,$CDCl_3$) δ 1.0 (s, 3H), 2.25 (s, 3H), 3.03 (d, 1H, J=17.0 Hz), 3.68 (d, 1H, J=17.0 Hz), 3.72 (s, 3H), 4.25 (s, 1H) and 7.3 (m, 5H).

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