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REGIOCHEMICAL ASPECTS ASSOCIATED WITH THE INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION REACTIONS OF MUNCHNONE DERIVATIVES

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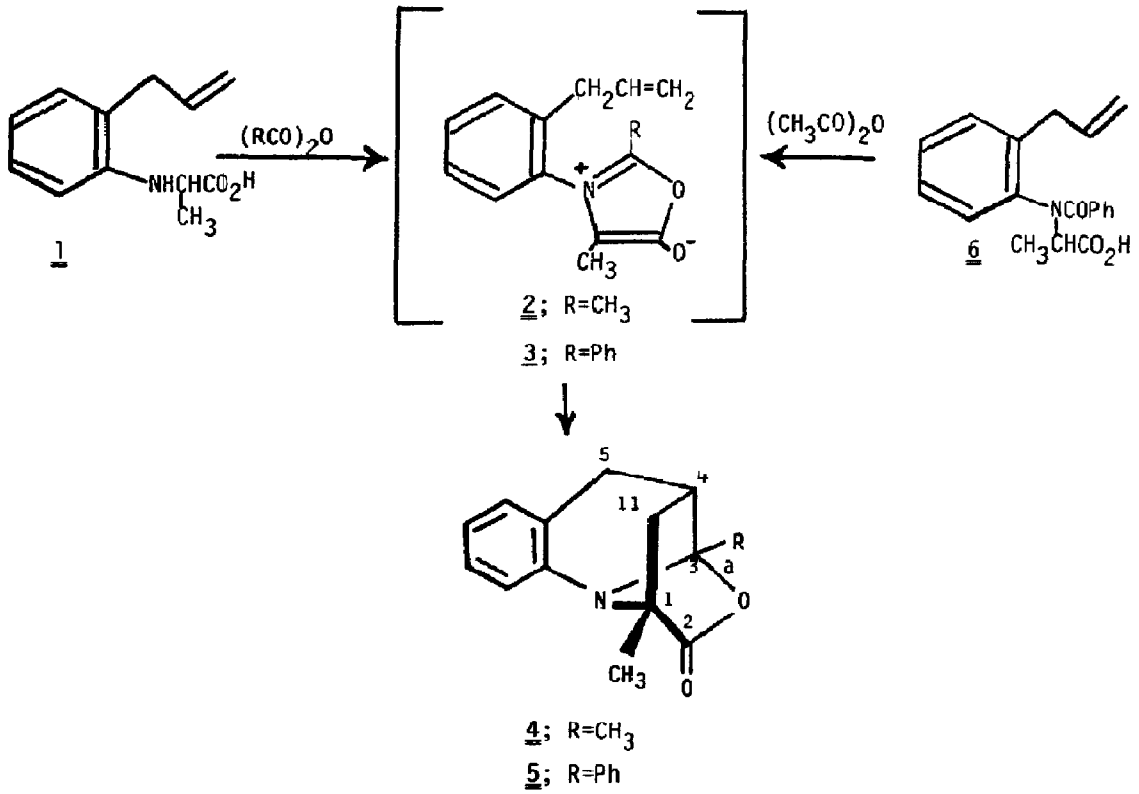
Abstract: The regioselectivity of the internal cycloaddition of a series of N-(o-allylphenyl) substituted munchnones has been found to be markedly dependent on the substituent groups present.

The mesoionic Δ^2-oxazolium-5-oxides, often referred to as "munchnones", are a well characterized mesoionic system.[1] Huisgen and coworkers have studied the cycloaddition reaction of munchnones with various dipolarophiles in detail and have shown that the reaction constitutes a general synthesis of pyrroles[2] and pyrrolines.[3] The reaction involves a 1,3-dipolar cycloaddition of the munchnone, behaving like a cyclic azomethine ylide, to the corresponding acetylenic or olefinic dipolarophile followed by CO_2 evolution and aromatization or tautomerization.[4,5] In this communication we wish to report that munchnones having a dipolarophilic function suitably spaced within the molecule undergo smooth intramolecular 1,3-dipolar cycloaddition to form novel heterocyclic compounds.[6]

Treatment of N-(o-allylphenyl)alanine (1) with acetic anhydride at 55°C for 3 hr afforded a single compound in 54% isolated yield whose structure is assigned as (1R*,3aS*,4R*)-3a,4-dihydro-1,3a-dimethyl-1,4-methano-5H-oxazolo[3,2-a]quinolin-2(1H)-one (4), mp 115-116°C; NMR ($CDCl_3$, 100 MHz) δ 1.25 (dd, 1H, J=13.0 and 2.0 Hz), 1.31 (s, 3H), 1.53 (s, 3H), 1.95 (dd, 1H, J=13.0 and 7.5 Hz), 2.58-2.82 (m, 1H), 2.81 (dd, 1H, J=16.5 and 2.5 Hz), 3.16 (dd, 1H, J=16.5 and 4.0 Hz), 6.96-7.14 (m, 1H), 7.14-7.36 (m, 3H). Similarly, treatment of 1 with two equivalents of benzoic anhydride in refluxing benzene also yielded a single cycloadduct (5) in 84% isolated yield. This same cycloadduct was obtained by treating N-benzoyl-N-(o-allylphenyl)alanine (6) with acetic anhydride at 55°C for several hours. In neither case



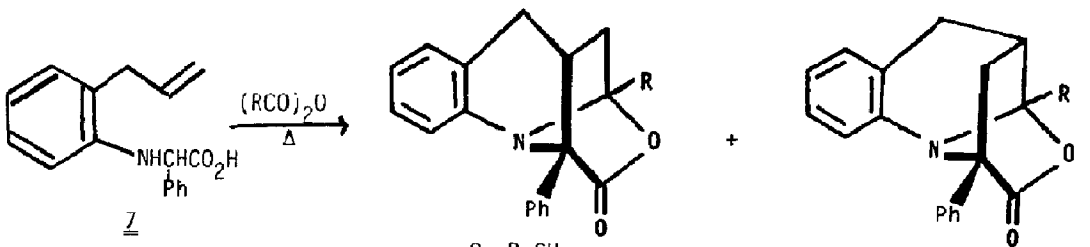
were there any signs of another regioisomer in the crude reaction mixture.

The structure of cycloadduct 5 is assigned as the 1,4-methano-5H-oxazolo[3,2-a]quinolin-2(1H)-one regioisomer, mp 155-156°C, on the basis of its characteristic spectral data. Most noteworthy is the fact that cycloadducts 4 and 5 have virtually identical C^{13} chemical shifts at carbon atoms 1,2,3a,4,5 and 11 (C^{13}NMR, $CDCl_3$) 73 (s), 174 (s), 99 (s), 40 (d), 36 (t) and 35 (t) ppm. The structure of oxazoloquinolinone 5 was unequivocally proved by an X-ray single crystal structure analysis.[7] The crystals of 5 used for X-ray diffraction were monoclinic and belong to space group $p2_1/n$. The unit cell parameters were a=10.522(2) A^0, b=8.858(1) A^0, c=16.5818(2) A^0, β=94.46(1)^0 and the calculated density indicate four molecules per unit cell. The structure was derived from Patterson and Fourier syntheses and refined by least squares to R=0.051 for all the data.

The above cycloaddition reactions proceed via an initial N-acetylation of the amino acid followed by cyclodehydration to give an unstable munchnone intermediate (i.e. 2 or 3). The azomethine ylide functionality of the mesoionic species then participates in an intramolecu-

lar 1,3-dipolar cycloaddition[8] with the unactivated carbon-carbon double bond of the allyl group to give the oxazoloquinolinones 4 and 5.

We have also studied the regiochemical aspects of the cycloaddition of N-(2-allylphenyl)-2-phenylglycine (7) with acetic anhydride. The reaction produced a mixture of two regioisomeric cyloadducts 8 and 9. The isomers were easily separated by fractional crystallization and identification of each regioisomer was made on the basis of their respective proton and C^{13} NMR spectra. Particular attention was given to the chemical shifts of the benzylic and methylenic protons as well as to an appreciably shielded aromatic proton with cycloadduct 9.[9] The major isomer formed (80%) was identified as 1,4-methano-1H-oxazolo[3,4-a]quinolinone 8, mp 165-166°C; NMR ($CDCl_3$, 100 MHz) δ 1.63 (s, 3H), 1.65 (dd, 1H, J=13.0 and 2.0 Hz), 2.34 (dd, 1H, J=13.0 and 7.0 Hz), 2.51 (dd, 1H, J=17.0 and 2.5 Hz), 2.78 (dd, 1H, J=17.0 and 3.0 Hz), 2.80-3.05 (m, 1H), 6.80 (d, 1H, J=7.0 Hz) and 6.89-7.34 (m, 8H). No interconversion of 8 and 9 occurred on heating the isolated regioisomers in boiling toluene for 6 hr, thus indicating the observed regiochemistry to result from kinetic control. The isolation of oxazoloquinolinone 8 as the major cycloadduct stands in marked contrast with the results encountered with the N-(allylphenyl)alanine system (1).



Opposite regioselectivity was encountered in the intramolecular cycloaddition of the munchnone derived from heating 7 with benzoic anhydride in benzene. Under these conditions 7 furnished cycloadducts 10 and 11 in a 1:2 ratio. Regiochemical assignment of the mixture of isomers was easily made by comparison of the proton and C^{13} NMR spectra. The above results clearly indicate that the nature of the substituent groups present on the munchnone ring play an important role in controlling the regioselectivity of cycloaddition. It can be presumed

that both steric and electronic factors are involved.[10] Intramolecular cycloaddition of munchnones thus provide a valuable mechanistic tool for the study of orientational substituent effects.

1,3-Dipolar cycloaddition of mesoionic systems have been suggested to be a LU(1,3-dipole) HO(dipolarophile) controlled process.[11,12] We find it difficult to accommodate our results with a type III process (Sustmann's classification)[13] since this perception cannot easily accommodate the changes in regiochemistry that we observe. Further work is in progress to explore the regiochemistry of munchnone cycloadditions and will be presented at a later date.

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(7) We wish to thank Mr. Jordan Hirshfield of Merck Sharp and Dohme for determination of the X-ray crystal structure of compound 5.

(8) The regioselectivity encountered here is similar to that reported with the related sydnone system, H. Meier, H. Heimgartner, and H. Schmid, Helv. Chim. Acta., 60, 1087 (1977); J. H. Bieri, H. Meier and H. Heimgartner, Helv. Chim. Acta., 61, 1091 (1978).

(9) All compounds gave satisfactory analyses. Complete spectroscopic and degradative detail will be given in our full publication.

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