Tetrahedron Letters,Vol.23,No.21,pp 2167-2170,1982 0040-4039/82/212167-04$03.00/0
Printed in Great Britain

REGIOCHEMICAL ASPECTS ASSOCIATED WITH THE CYCLOADDITION OF DIAZOPYRAZOLINONES TO ELECTRON DEFICIENT ACETYLENES

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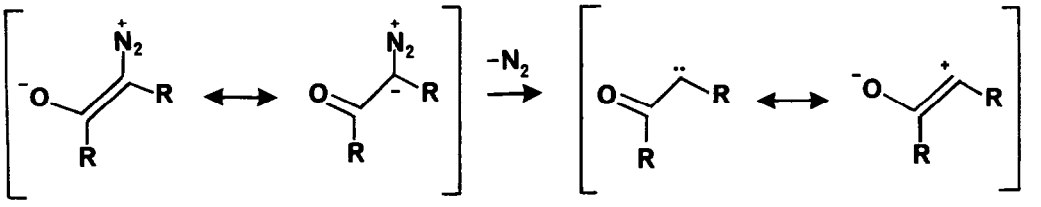
Abstract The regiospecificity with which members of the 4-diazopyrazolin-5-one system undergo intermolecular cycloaddition to propiolate ester has been found to be markedly dependent upon the substituent groups present.

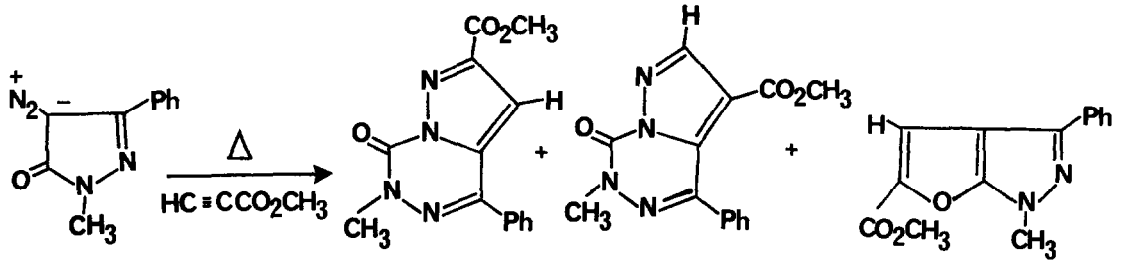
α-Diazoketones represent an interesting class of compounds since several discrete modes of intermolecular cycloaddition are possible.[1] Amongst these are those involving reaction as a 1,3-dipole, either through the diazoalkane moiety or through a reactive intermediate possessing the stoichiometry of a ketocarbene species derived from an initial loss of nitrogen. Much less common modes of addition involving the extended



6π-electron 1,5-dipolar system are also observed with certain quinonoid α-diazoketones.[2] The use of extended diazoalkanes with six or more electrons has received only a minimum amount of attention despite the obvious synthetic and theoretical interest in such processes [3] When the diazoalkane moiety forms part of a heterocyclic system, dipolar cycloadditions can, in principle, provide ready access to more elaborate molecules. This phenomenon has indeed been realized in our recent work[4] and herein we wish to describe an aspect of the interesting profile of reactivity of these heterocyclic α-diazoketones towards an unsymmetrical electron-deficient acetylenic ester.

Cycloaddition reactions were carried out by heating toluene solutions containing the diazopyrazolinone and the acetylenic ester. From the reaction of 4-diazo-1-methyl-3-phenylpyrazolin-5-one (1) with methyl propiolate, three crystalline products were

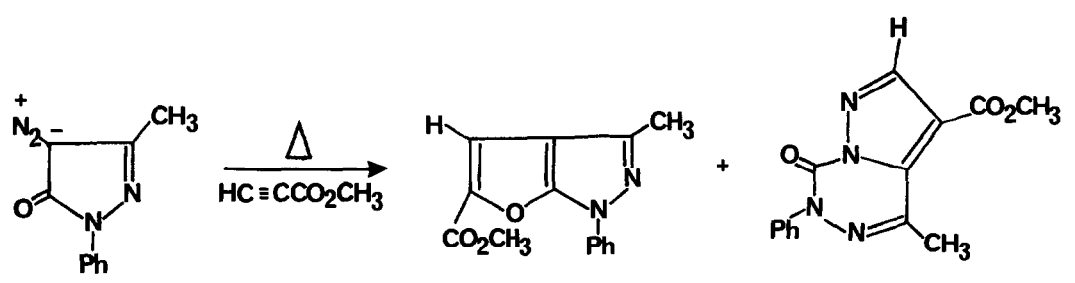
isolated. From a single crystal X-ray structure determination[5] the major (40%) adduct was shown to be pyrazolotriazinone 2, mp 180-181°C, NMR ($CDCl_3$,90 MHz) δ 3.93 (s, 3H), 3.97 (s, 3H), 7.32 (s, 1H). The regioisomeric pyrazolotriazinone 3-carboxylate 3, mp 137-138°C (NMR ($CDCl_3$,90 MHz) δ 3.39 (s, 3H), 3.97 (s, 3H), 8.47 (s, 1H)) was isolated as the next most prevalent product (34%) and was assigned on the basis of both ^1H and



1 2 3 4

^{13}C-NMR data recorded for the methine hydrogen and carbon atoms.[6] The minor (28%) adduct was assigned[7] as methyl 1-methyl-3-phenyl-1H-furo[2,3-c]pyrazole 5-carboxylate (4), mp 137-138°C, NMR ($CDCl_3$,90 MHz) δ 3.93 (s, 3H), 3.96 (s, 3H) and 7.51 (s, 1H).

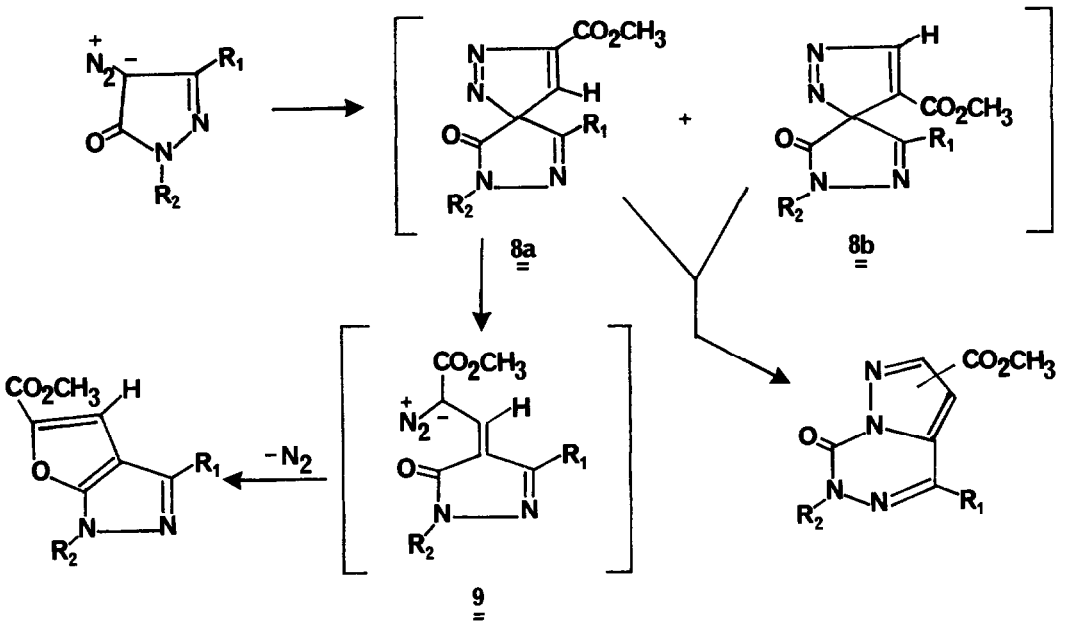
Addition of propiolate ester to 4-diazo-3-methyl-1-phenylpyrazolin-5-one (5) furnished two products resulting from cycloaddition. The structure of the major (44%) adduct was again determined by a single crystal X-ray structure analysis[5] and shown to be the 1H-furo-[2,3-c]pyrazole 6, mp 119-120°C, NMR ($CDCl_3$,90 MHz) δ 2.69 (s, 3H), 3.90 (s, 3H) and 7.22 (s, 1H). Together with derivative 4, these compounds are the first reported representatives of the heteroaromatic 1H-furo[2,3-c]pyrazole ring system. The minor (31%) adduct 7, mp 142-143°C, (NMR ($CDCl_3$,90 MHz) δ 2.84 (s, 3H), 3.94 (s, 3H) and 8.48 (s, 1H)), has



5 6 7

been determined principally from a comparison of ^{1}H and ^{13}C-NMR data with those recorded for isomers 2 and 3.

The mechanism by which these reactions proceed is worthy of comment in view of the subtle variations in product distribution. That only a marginal regiochemical preference is demonstrated is in accord with expectation from a consideration of simple frontier MO theory. The diazopyrazolinone ring, being flanked by two electron-withdrawing residues, would be expected[8] to exhibit type III (Sustmann's classification)[9] behavior in which the dominant interaction is dictated by the LUMO (dipole), which is known[10] to have almost equal terminal orbital coefficients Thus, cycloaddition to the propiolate ester will give adducts resulting from both spiro 3H-pyrazolo-3,4-pyrazolinones (8) The fate of such species is markedly dependent upon the overall pattern of substitution in 8 and



involves either aromatization (van Alphen-Huttel rearrangement)[11] via a single 1,5-acyl migration to give the pyrazolotriazinones or ring opening to an acyclic diazoalkane 9[12] which then rapidly loses nitrogen under these conditions to give the furopyrazoles.

Diazoalkane formation is favored from 8a because of resonance stabilization of the anionic portion of the diazoalkane (e.g. 9). When such resonance is inhibited by steric factors, such as that which would be incurred between substituents at C_3' and C_4 in 8b, the van Alphen-Huttel route predominates.

Studies to probe additional mechanistic details of these reactions are continuing.

Acknowledgement, We wish to thank the National Cancer Institute, DHEW for generous support of this work.

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*John Simon Guggenheim Memorial Fellow, 1981-1982.

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(5) We wish to thank Dr. J. F. Blount of Hoffmann-LaRoche for the single crystal X-ray structure determinations of cycloadducts 2 and 6. Crystals of 2 were monoclinic, space group $P2_1$ with unit cell parameters a=7.215 (4), b=12.217 (5), c=15.074 (7) A^o, B=94.36 (4^o) and d_{calcd} =1.425 gcm^{-3} for Z=4 Similarly, crystals of 6 were monoclinic, $P2_{1/c}$ with a=7.393 (3), b=10.618 (3), c=16.065 (5) A^o, B=99.52 $(3)^o$ and d_{calcd}=1.368 gcm^{-3} for Z=4.

(6) All compounds gave satisfactory analyses. Complete spectroscopic details will be given in our full publication.

(7) Structure 4 has been assigned by analogy to that of 6 for which an X-ray structure determination was performed.

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(Received in USA 5 March 1982)