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POLAR CYCLOADDITION IN THE PYRAZINE SYSTEM.

PREPARATION OF NEW HETEROPOLYCYCLES

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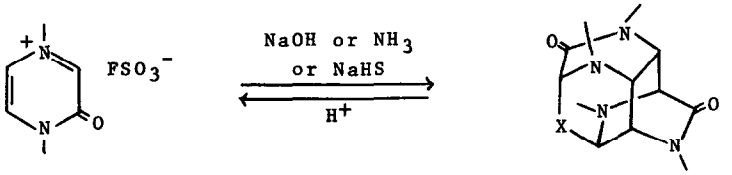
1,2-Dihydro-1,4-dimethyl-2-oxopyrazinium fluorosulfonate reacts in high yields with a variety of nucleophiles (OH^-, NH_3, SH^-) to give interesting new cage systems.

Polar cycloaddition reactions differ from classical 4+2 Diels-Alder reactions in that the diene bears a positive charge and acts as an electrophile. The positive charge influences the formation and geometry of charge transfer complexes and hence the regioselectivity and stereochemistry of the reaction (1).

We have found that 1,2-dihydro-1,4-dimethyl-2-oxopyrazinium fluorosulfonate I (prepared from 1,2-dihydro-1-methylpyrazin-2-one in quantitative yield by reaction with methylfluorosulfonate) reacts instantaneously and exothermically at room temperature and in high yields (70-80% isolated yield) with a variety of nucleophiles (OH^-, NH_3, SH^-) to give interesting new cage systems II which have incorporated 2 equivalents of I with 1 equivalent of the nucleophile (Scheme 1).

Scheme 1



IIa X=O
b X=NH
c X=S

The reaction conditions for the preparation of II(a,b,c) are, respectively, $NaOH/H_2O$, NH_3/CH_3CN, and NaSH (anhydrous)/CH_3CN. In aqueous ammonia a mixture of II(a) and (b) is obtained. Compounds II(a,b,c) are crystalline solids

(m.p. 172-174°, 160-162°, 200-201°, respectively, all with decomposition), stable in organic solvents, water and base. On treatment with aqueous acid they revert completely to I.

All compounds gave correct analyses and consistent mass spectra (2) with molecular ion peaks. The 220 MHz NMR (3) provided unambiguous structure proof. Analysis of tertiary proton resonance of the 220 MHz NMR spectrum of II(a) (for example) gave the results shown in Table I.

Table I

Proton No.	1	2	3	4	5	6
1	3.39δ	3.2 Hz	0	0	<1 Hz	0
2		4.05δ	10.0 Hz	0	0	0
3			3.37δ	3.0 Hz	1.7 Hz	1.4 Hz
4				3.87δ	4.3 Hz	0
5					4.68δ	0
6						4.43δ

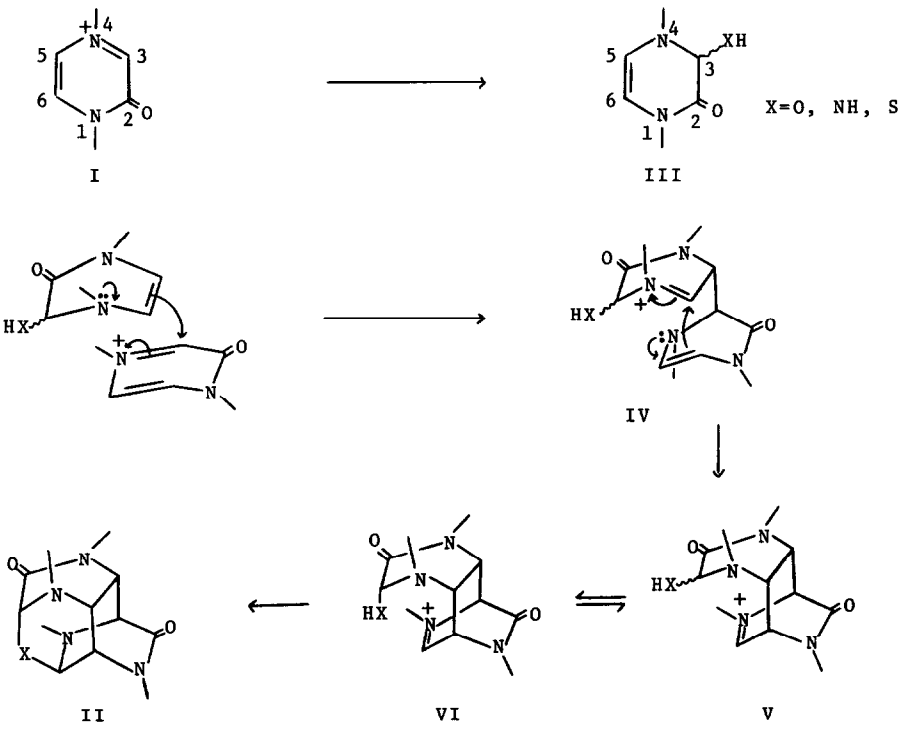
Diagonal elements are chemical shifts, off diagonal are coupling constants.

H_5 and H_6 are assigned the lowest field resonances as their carbons bear oxygen. Furthermore, H_6 is expected to be a singlet while H_5 should be a doublet with a 3.4 vicinal gauche coupling to the bridgehead H_4 proton. The simultaneous double irradiation of the resonances at ~3.38 ppm (resonances for H_1 and H_3) resulted in the collapse of the peak at 4.43 to a singlet and that at 4.68 to a doublet (coupling 4.3 Hz). Thus H_5 and H_6 are assigned to the resonances at 4.68δ and 4.43δ, respectively.

The long-range coupling constants enable us to unambiguously assign chemical shifts to each tertiary hydrogen (Table I). II(b) and II(c) have 220 MHz NMR spectra with very similar patterns and coupling constants.

A reasonable mechanism for the formation of II is shown in Scheme 2.

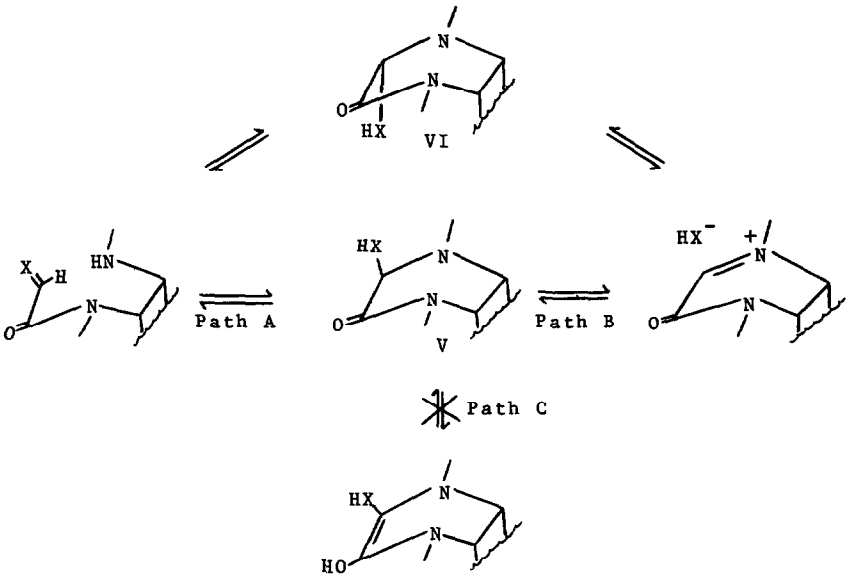
Scheme 2



The orientation in the reaction can possibly be explained by the initial formation of a charge transfer complex due to the interaction of the positive charge in I and the unshared valence electrons of the amide nitrogen (N_1) or the heteroatom (X) in structure III. The alternative orientation is apparently less favoured due to carbonyl-carbonyl interaction as well as lone pair repulsion between N_1 of I and N_4 of III. Epimerization from V to VI could occur either via ring opening (Scheme 3) (path A) or through an iminium ion (path B).

Epimerization via keto-enol tautomerism (path C) does not occur, at least where X=O, since when the reaction was carried out with $NaOD/D_2O$, no deuterium was incorporated in the final product.

Scheme 3



Work is underway to evaluate the scope and synthetic utility of the reaction.

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References

1. C. K. Bradsher, Adv. in Heterocyclic Chem., 1974, 16, 289.

2. Mass spectral analyses have been performed by the Morgan Schaffer Corporation, Montreal.

3. We wish to thank Dr. A. A. Grey of the "Canadian 220 MHz NMR Centre", Ontario Research Foundation, Sheridan Park, Ontario, for the NMR spectra.