Tetrahedron Letters,Vol.28,No.10,pp 1059-1062,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

INTRAMOLECULAR OXIDATIVE-CYCLOADDITION OF DIHYDROPYRAZOLONES

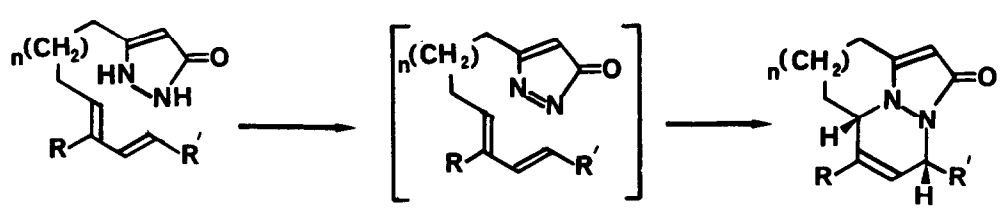
Julio C. Medina, Rodolfo Cadilla and Keith S. Kyler*
Department of Chemistry, University of Miami,
Coral Gables, Florida 33124, U.S.A.

Summary. The hitherto unknown intramolecular cycloaddition reaction of azo dienophiles, as outlined in Scheme I below, is described.

The $4_\pi + 2_\pi$ cycloaddition reaction of azo dienophiles is well established.[1] Dominating these processes are the azodicarbonyl dienophiles of which dialkyl azodicarboxylates[2] or 4-substituted-1,2,4,-triazoline-3,5-diones[3] are exemplary. The intermolecular reactions of these compounds have been of tremendous importance for the preparation of azoalkanes via the oxidative hydrolysis of the Diels-Alder adducts, and considerable effort has focused on developing new azo dienophiles such as 1,3,4-thiadiazole-2,5-dione[4] which can facilitate this transformation.

In contrast to the intermolecular reactions with 1,3-dienes, an intramolecular process is not known for azo dienophiles despite the extensive application of this concept to the Diels-Alder reaction. The demonstrated efficiency of the cycloaddition of azo dienophiles with 1,3-dienes for constructing carbon-nitrogen bonds suggested this situation was likely to change. We now wish to report the *intramolecular* oxidative-cycloaddition reaction of dihydropyrazolones according to Scheme I.

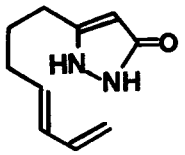
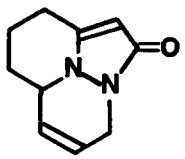
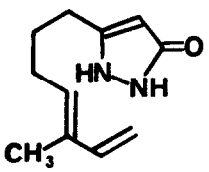
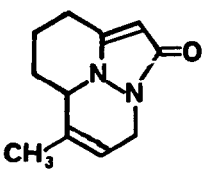
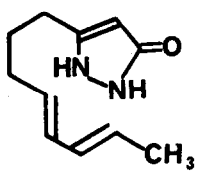
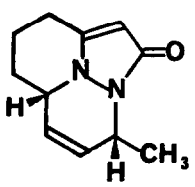
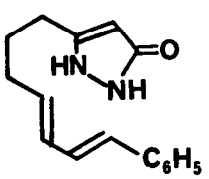
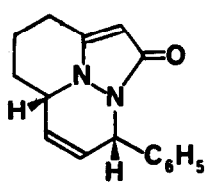
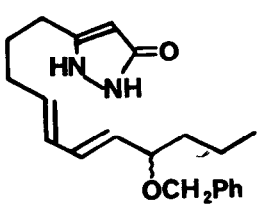
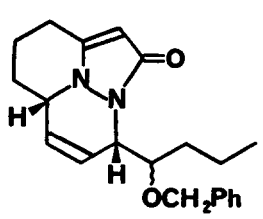
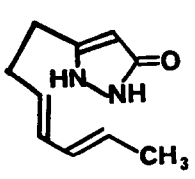
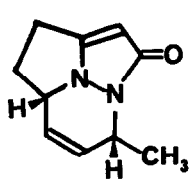
Scheme I



1 2 3

n = 0, 1

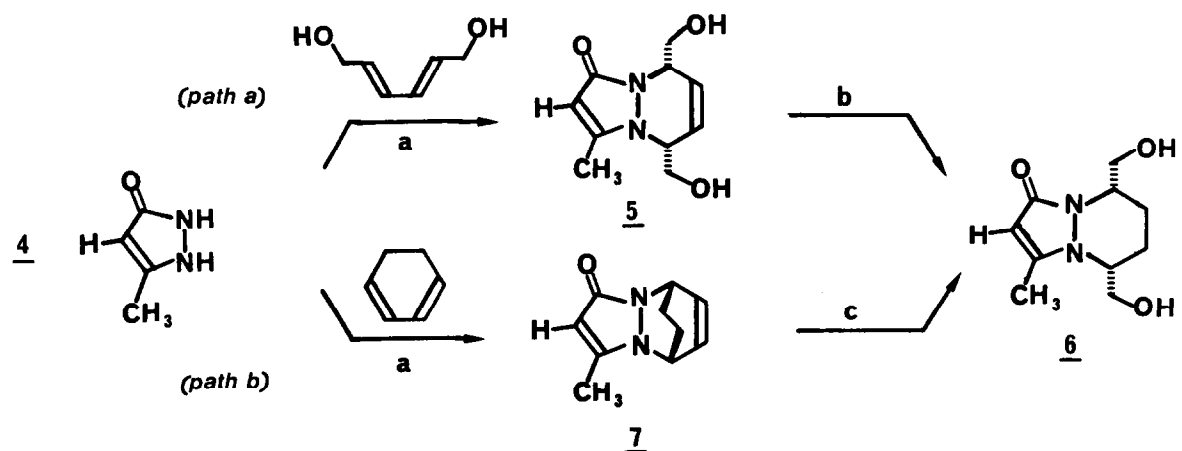
Table I. Intramolecular Oxidative-Cycloaddition of 1,2-Dihydro-3H-pyrazol-3-ones 1.

n	entry	substrate 1	adduct 3	reaction time(min)	isolated yield,%
1	a			5	77
1	b			5	57
1	c			15	61
1	d			3	74
1	e			10	60
0	f			5	25

The addition of 1.2 equivalents of $Pb(OAc)_4$[5] to a suspension of the 1,2-dihydro-3H-pyrazol-3-one[6] 1a (2 mmol) in 10 mL of dichloromethane at 23° led to immediate consumption of 1a and afforded the intramolecular adduct 3a[7] in 72% yield after silica gel chromatography (1:4 methanol-ethyl acetate). In addition to the intramolecular adduct, we also isolated a small amount (17%) of 1,3-decadien-9-yne which presumably arises from fragmentation of the intermediate azo dienophile (2a) with loss of dinitrogen and carbon monoxide.[8] We briefly examined a number of other oxidants[9] (mercuric oxide and manganese dioxide) and solvents (acetonitrile, THF, ether, benzene), but all were less satisfactory than $Pb(OAc)_4$ in dichloromethane.

Extension of the intramolecular oxidative-cycloaddition using $Pb(OAc)_4$ to the dihydropyrazolones listed in Table I afforded moderate yields of adducts 3b-3f[7]. Both chromatographic and spectral data (^1H-and ^{13}C-NMR) showed that a single stereoisomer was produced for adducts 3c, 3d and 3f, whereas an approximately 1:1 mixture of diastereomers was obtained for 3e due to the asymmetric center in the diene side-chain of 1e. An unequivocal assignment of the *cis*-stereochemistry as shown for these adducts could not be made directly from either the ^1H- or ^{13}C-NMR spectra. Consequently, these assignments were established from the series of transformations shown in Scheme II.

Scheme II



(a) $Pb(OAc)_4$, CH_2Cl_2 ; **(b)** H_2, Pd/C, $MeOH$; **(c)** *1.* O_3, -78^o, CH_2Cl_2 ; *2.* $NaBH_4$, $MeOH$.

The oxidative-cycloaddition of dihydropyrazolone 4[10] (5 mmol) to the labile 2,4-hexadien-1,6-diol[11] (1.3 eq.) using $Pb(OAc)_4$ (1.2 eq) in 20 mL of dichloromethane at 23° afforded the adduct 5 in 66% isolated yield, and to the exclusion of any diastereomeric adduct as determined by analytical thin-layer chromatography and ^1H- and ^{13}C-NMR spectra. Hydrogenation (1 atm) of diol 5

over 10% Pd on carbon in methanol gave a new diol 6 (path a) in essentially quantitative yield. We anticipated that diol 6 could also be obtained from an alternate route, (path b), via the oxidative cleavage and subsequent reduction of the previously known adduct 7[10]. Thus, ozonolysis of adduct 7 (5 mmol) in 50 mL of dichloromethane at -78°, followed by the addition of methanol (10 mL), and direct reduction of the crude mixture with $NaBH_4$ (5 mmol) afforded diol 6 which was identical in all respects to the diol obtained from path a.

These results suggest that the oxidative-cycloaddition reaction proceeds with exclusive *syn*-addition, and most likely *endo*-attack, of the transient azo dienophile to 1,3-dienes. Hence, we assigned the *cis*-stereochemistry to the adducts 3c-3f.

The *intramolecular* oxidative-cycloaddition of 1,2-dihydro-3H-pyrazol-3-ones described herein conceptionally offers a novel route for the preparation of 2,6-disubstituted-N-acylaminopiperidines (3a-3e,) or the analogously substituted pyrrolidines (3f). Additionally, the overall bis(amination) of the diene termini proceeds with exclusive *syn*-addition and offers a stereocontrolled route to these heterocyclic compounds. These facts coupled with the simplicity of the method should contribute to further development and future applications of intramolecular azo cycloaddition reactions to the synthesis of nitrogen heterocycles.[12]

References and Notes

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12. We gratefully acknowledge support of this work by the American Cancer Society.

(Received in USA 26 December 1986)