SYN SELECTIVITY IN THE REACTIONS OF AZOMETHINE IMINES AND AZOMETHINE OXIDES WITH CIS-3,4-DISUBSTITUTED CYCLOBUTENES

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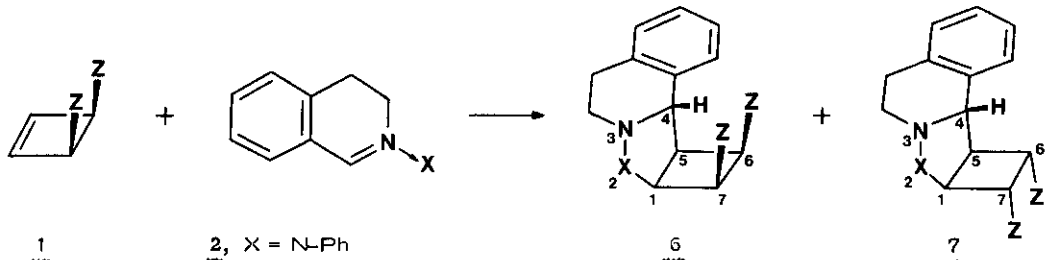
Abstract - 3,4-Dihydroisoquinoline-N-phenylimine reacted with cis-3,4-dichloro, -dihydroxy and -diacetoxycyclobutenes to give the sterically disfavoured syn adducts as dominant products; with carbonyldioxy and dicarbomethoxycyclobutenes repulsive steric interactions led to the prevailence of the anti adducts. An increased syn selectivity was found for the reactions of 3,4-dihydroisoquinoline-N-oxide with diacetoxycyclobutene and of nitro substituted 3,4-dihydroisoquinoline-N-phenylimines with dichlorocyclobutene.

One of the outstanding problems in 1,3-dipolar[1-4] and Diels-Alder[4,5] cycloadditions is the syn-anti isomerism.* In this paper we would like to present the results of the reactions of three azomethine imines (2)-(4) with cis-3,4-disubstituted cyclobutenes (1a)-(1e) and of the azomethine oxide (5) with (1c). The yet unknown cis-3,4-diacetoxycyclobutene (1c) [oil; ν_{max}, 1750 cm^{-1} (OCOMe); δ ($CDCl_3$) 6.43 (m, H-1 and H-2), 5.72 (m, H-3 and H-4), 3.12 (s, Me)] was prepared in quantitative yield by acylation of (1b).[2c]

The pyrazolidines (6)-(11) (Table 1 and Scheme) were obtained by heating the dimers of azomethine imines (2)-(4) and cyclobutenes (1a)-(1e) in boiling benzene. The quantitative composition of the reaction mixtures was obtained by column chromatography separation. The exo,syn-adducts (6), (8) and (10) [with the exception of (6b)] were characterized by a smaller R_F (tlc) than the

* For syn-anti and exo-endo nomenclature see ref. 1, pp. 403-405.



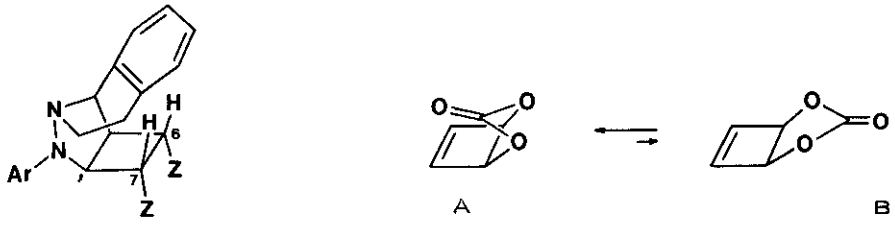
1 | 2, X = N-Ph | 6 | 7

2, X = N-C_6H_4-4-NO_2 | 8 | 9

4, X = N-C_6H_3-2,4-$(NO_2)_2$ | 10 | 11

5, X = O | 12 | 13

a : Z = Cl; b : Z = OH; c : Z = OCOMe; d : Z = -O-C(=O)-O-; e : Z = COOMe



14 | 1d

corresponding exo, anti-adducts (7), (9), (11). This tlc behaviour is in agreement with a predictable larger dipole moment for the syn compounds.[2a] No endo products, e.g. endo, anti adducts (14), were detected in the reaction mixtures showing that the 1,3-dipoles reacted with the cyclobutenes only in the sterically favoured exo disposition.

Reduction of (6d) and (7d) with $LiAlH_4$ afforded (6b) and (7b), respectively.

The structures were assigned on the basis of ^{1}Hnmr spectra whose characteristic patterns are illustrated by the data of three pairs of adducts reported in Table 2. In the anti adducts H-7 resonated at higher field values than H-6 while in the syn isomers H-7 appeared at similar or lower field values than H-6. This finding is consistent with the exo, anti structures (7), (9) and (11) where H-7 is shielded by the N-Ar group. The alternative endo, anti structure (14) should be excluded because for that structure H-6 would have appeared at higher field values than H-7 as a result of the strong shielding by the phenyl moiety of the tetrahydroisoquinoline system. Moreover H-4 resonated at lower field values in the syn series than in the anti one and in the former resul-

Table 1

Comp.	Mp (°C)	Syn / Anti ratio[a]	Comp.	Mp (°C)	Syn / Anti ratio[a]
(6a)	170 - 172	1.35	(6b)	185 - 187	≥ 16
(7a)	120 - 122		(7b)[b]	158 - 160	
(8a)[c]	256 - 257	3.0	(6c)	192 - 196	1.5
(9a)[c]	209 - 211		(7c)	149 - 150	
(10a)[c]	238 - 239	2.1	(6d)	223 - 225	0.15
(11a)[c]	236 - 237		(7d)	215 - 217	
(12c)	162 - 163	4.6	(6e)	d	< 0.05
(13c)	106 - 107		(7e)	146 - 149	

[a]The values represent the mean of two indipendent runs. Overall yields were ≥ 80%. Lower yields have been found for the reaction of (4) with (1a) (25%) owing to competitive isomerization of (4) to a benzotriazole-1-oxide derivative[9] and for reaction of (2) with (1e) (40%) owing to isomerization of (1e) to 1,4-dicarbomethoxybutadiene.

[b]Detected (trace amounts) by tlc analysis of the crude reaction mixture

[c]Yellow [d]Not detected

ted practically unaffected changing $CDCl_3$ with C_6D_6. This result was expected for a proton which is deshielded and whose solvation is hindered by the neighbouring groups at positions 6 and 7. Exo, syn structures (6), (8) and (10) are consequently assured.

The $J_{4,5}$ found for the pyrazolidines (6)-(11) was ≥ 6.8 Hz a value unexpectedly quite different from those found for the corresponding isoxazolidines [adducts of (5) to cyclobutenes; cf. $J_{4,5}$ = 6.0 for (13c) and < 3.0 Hz for (12a)-(12e) and (13a), (13b), (13d), (13e)].[2b, 2c] Therefore $J_{4,5}$ should be used with caution when choosing between cis, trans structures for compounds of this type.

X-ray analysis of (6a), (6d) and (10a) confirmed our structural assignement.[6]

Nitrone (5) has been reacted at room temperature with (1c) to give a mixture of the adducts (12c)

Table 2

^{1}Hnmr [δ ($CDCl_3$)] data and (in parentheses) $\Delta\delta = \delta(CDCl_3) - \delta(C_6D_6)$. [a,b]

Comp.	H-1	H-4	H-5	H-6	H-7	$J_{4,5}$
(6c)	4.48	5.13	3.58	5.43	5.86	8.5
	(0.63)	(-0.07)	(>0.48)	(0.28)	(0.08)	
(7c)	4.67	4.53	3.30	5.44	5.10	8.0
	(0.17)	(0.33)	(0.31)	(0.22)	(0.12)	
(6d)	4.59	5.23	3.77	5.49		6.8
	(0.79)	(-0.10)	(>0.50)	(1.05)		
(7d)	4.47	4.41	3.52	5.13	4.84	7.4
	(0.65)	(0.66)	(0.75)	(1.05)	(0.76)	
(8a)	4.97	5.40	3.97	5.33		8.0
	(1.33)	(0.01)	(>0.77)	(0.97)		
(9a)	4.70	4.48	3.58	4.70	4.52	8.5
	(0.32)	(0.35)	(0.26)	(0.42)	(0.50)	

[a] Signal multiplicity: doublets for H-4 and multiplets for other protons

[b] J in Hz

and (13c) (Table 1), which have also been obtained on acetylation with acetylchloride of the previously described (12b) and (13b).[2c] The following syn/anti ratios were obtained[2b, 2c] in the reactions of (5) with cyclobutenes: 2.7 for (1a), ≥16 for (1b), 0.05 for (1d) and 0.14 for (1e). The syn/anti ratios found in the reactions of (2) and (5) with cyclobutenes (1) are, in our opinion, determined by positive electronic interactions which lead to syn approach whereas steric repulsion between 1,3-dipoles and the cyclobutene substituents (steric size: COOMe > Cl > OCOMe > OH) favours the anti approach. The results suggest a loose correlation between the former effect and substituent electronegativity (electronegativity OCOMe > OH > Cl > COOMe).[7] In addition, the high syn selectivity observed for (1b) may be due also to hydrogen bond in the transition state between OH and N-Ph group of the 1,3-dipole.[2c] Moreover the prevailence of anti attack for (1d) [in which the electronegativity of the substituent group is similar to that of (1c)] can be rationa-

lized by a preferential attainement of conformation of type A over that of type B (Scheme). Conformation A is possibly stabilized by a through space interaction between π^*_{CO} and π_{CC} orbitals. The present work has also evidenced that the introduction of an electron withdrawing substituent in the 1,3-dipole, on going from (2) to (3) and (4), resulted in an enhanced syn selectivity in the cycloaddition with (1a). A similar effect was previously observed in the reaction of nitrile oxides with (1a).[2a] In the case of (4), however, electronic effect is to some extent neutralized by steric hindrance brought in by o-NO_2 group.

Our conclusion is that 1,3-dipolar cycloaddition on 3,4-disubstituted cyclobutenes is rather sensitive to both two previously proposed electronic effect: (i) the intramolecular perturbation between σ^* and π orbitals of dipolarophile;[3] (ii) the intermolecular interaction between $LUMO_{1,3\text{-dipole}}$ and lone pairs of Z substituents.[2a] Qualitatively, the higher the electronegativity of Z the stronger is the (i) effect which allows a better dispersion of the partial negative charge, arising on the dipolarophile in the oriented complexes as a consequence of the dominant $HOMO_{1,3\text{-dipole}} - LUMO_{cyclobutene}$ interaction, when 1,3-dipole attacks on the syn face than when the attack is on the anti face.[3] As regards (ii) effect electronwithdrawing substituents on the 1,3-dipole will lower its LUMO and consequently syn attack results accelerated.[2a]

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REFERENCES

1 G. Bianchi, C. De Micheli and R. Gandolfi, ' 1,3-Dipolar Cycloadditions involving X-Y Groups', in 'The Chemistry of Functional Groups, Supplement A', eds. by S. Patai, John Wiley and Sons, inc., New York, 1977, pp. 369-532.

2 a) G. Bianchi, C. De Micheli, A. Gamba and R. Gandolfi, J.C.S.Perkin I, 1974, 137; b) C. De Micheli, A. Gamba and R. Gandolfi, Tetrahedron Letters, 1975, 2493; c) C. De Micheli, A. Gamba, R. Gandolfi and L. Scevola, J.C.S.Chem.Comm., 246, 1976.

3 M. Franck-Neumann and M. Sedrati, Angew.Chem.Int.Ed.Engl., 1974, 13, 606.

4 P.V. Alston and R.M. Ottenbrite, J.Heterocyclic Chem., 1977, 14, 1443.

5 Nguyen Trong Anh, Tetrahedron, 1973, 29, 3227 and references cited therein.

6 R. Oberti and R. Gandolfi, Cryst.Struct.Comm., 1978, 7, 15 and 21; A. Coda and R. Oberti, private communication.

7 R.W. Taft, 'Separation of Polar, Steric and Resonance Effects in Reactivity', in 'Steric Effects in Organic Chemistry' eds. by M.S. Newmann, John Wiley and Sons, New York, 1956, pp. 613-618. The difference between electronegativity and electronwithdrawing power $\left[\text{electronwithdrawing power, Cl} > \text{OCOMe} > \text{COOMe} > \text{OH}\right]^{\delta}$ is therein discussed.

8 P.R. Wells, 'Linear Free Energy Relationship', Academic Press, London - New York, 1968, p. 38.

9 R. Grashey, Angew.Chem.Int.Ed.Engl., 1962, 1, 158.

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