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STEREOCHEMICAL FEATURES OF CYCLOADDITION OF HETEROAROMATIC N-YLIDES. SELECTIVE PARTICIPATION OF THE ANTI AND SYN YLIDES

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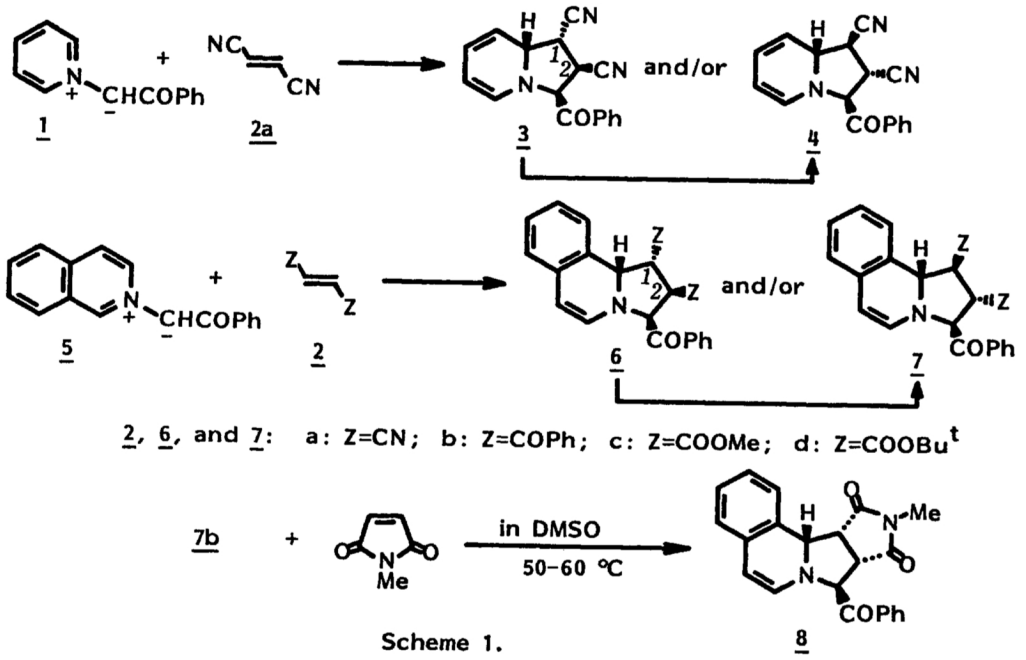
In the cycloaddition of heteroaromatic N-ylides to symmetrically substituted trans olefins, the anti ylide exclusively participates if the ylide is carbonyl-stabilized, while the syn ylide does if it has a substituent of non-carbonyl type. The cycloadducts isomerize into thermodynamically more stable isomers through a retro reaction.

Regardless of great importance of the cycloaddition of heteroaromatic N-ylides as a synthetic method of fused heterocycles, only scattered examples are known for the cycloaddition to olefinic dipolarophiles.[1] This reaction involves some important features of regioselectivity, stereospecificity, and stereoselectivity of olefin- (endo and exo) and ylide-substituents. Only recently it has been gradually revealed that cycloaddition of these ylides to symmetrically substituted cis olefins takes place through the endo approach of anti form of the ylides,[2] however, limited reliable informations are available so far on the cycloaddition to other types of olefinic dipolarophiles.[3]

In the course of our study on the cycloaddition of heteroaromatic N-ylides to a variety of olefinic dipolarophiles, some stereochemical features of this reaction have been figured out. The present communication describes new findings of the endo-exo selectivity and the selectivity of ylide-substituent in the cycloaddition of heteroaromatic N-ylides.

The reaction of pyridinium phenacylide 1 with an equivalent of fumaronitrile 2a in chloroform at 0 °C for 5 min furnished a mixture of two stereoisomeric cycloadducts 3 and 4 (7:3) in a quantitative yield (Scheme 1 and Table 1). Their structures were confirmed as the 1-endo-2-exo for 3 and 1-exo-2-endo cycloadduct for 4 to the anti form of 1 on the basis of spectral data[4] and elementary analyses.[5] On standing in solution at room temperature, 3 gradually changed into 4 and this clean isomerization was completed in 1 h, indicating that 3 and 4 are kinetically and thermodynamically controlled products, respectively.

It was found that the cycloadducts of 1 to some other trans olefins were so labile as to suffer from a ready elimination of pyridine,[6] while stable cycloadducts were found to form from isoquinolinium phenacylide 5. A similar reaction of 5 with 2a in dimethyl sulfoxide precipitated out the 1-endo-2-exo cycloadduct 6a as a major product, and in chloroform the thermodynamically controlled 1-exo-2-endo



Scheme 1.

isomer 7a was predominant in an equilibrium with 6a.[7] With trans-dibenzoylethene 2b bearing two bulky substituents, 7b was the only product. Exclusive formation of 7b would be because the kinetic path to its isomer 6b has been sterically closed and/or through a rapid isomerization of 6b. Heating 7b with N-methylmaleimide at 50-60 °C led to an excellent yield of the cycloadduct 8 to the maleimide,[8] indicating that the isomerization of the 1-endo-2-exo cycloadducts into the 1-exo-2-endo isomers occurs through a retro cycloaddition.[9]

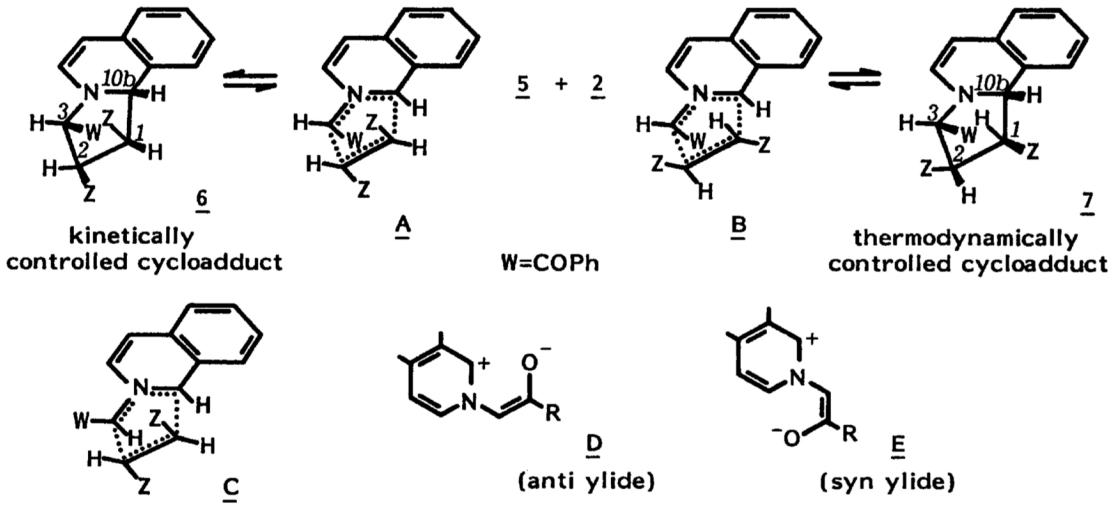
It was found that this retro reaction was suppressed when the dipolarophile-activating substituents are esteric.[10] Accordingly, the formation of comparable

Table 1. Cycloadditions of Heteroaromatic N-Ylides to trans Olefins

Ylides	Olefins	Reaction conditions			Products (isolated yield/%)		
		Temperature	Solvent[a]	Time			
1	2a	0 °C	C	5 min	3 (70)	4 (30)	
		0 °C	C	1 h		4 (100)	
5	2a	rt	D	5 min	6a (67)	7a (33)	
		rt	C	5 min	6a (14)	7a (86)	
		rt	C	18 h	6a (14)	7a (86)	
5	2b	rt	C or A	10 min		7b (100)	
5	2c	rt	C or A	10 min	6c (50)	7c (50)	
5	2d	rt	C	2 h		7d (100)	
9	2b	rt	A	12 h			10b (100)
9	2c	reflux	A	3 min			10c (71)[b]
9	2d	rt	A	17 h			10d (97)

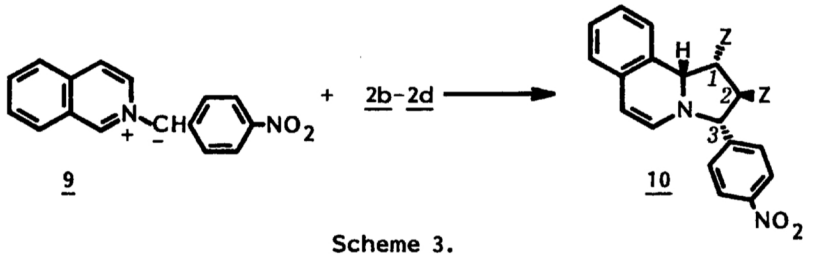
a) C: chloroform; D: dimethyl sulfoxide; A: acetonitrile. b) Containing 17% of the 1,10b-dehydrogenated derivative of 10c.

amounts of 6c and 7c in the reaction with dimethyl fumarate 2c indicates that both the 1-endo-2-exo and 1-exo-2-endo approaches have competed. It is understandable that di(tert-butyl) fumarate 2d as a bulky dipolarophile produced the sterically more favored isomer 7d through a kinetical path.



Scheme 2.

As shown in Scheme 2, the reaction of 5 with 2 has proceeded through either or both of the two approaches, the 1-endo-2-exo A and 1-exo-2-endo approach B to the anti form of 5, depending upon the nature of substituents Z and W. The approach A leading to 6 is favored if an attractive interaction between Z and the heteroaromatic plane overwhelms steric repulsions of all sorts. But the approach B leading to 7 predominates over the other when steric repulsions between Z and the plane and between Z and W suppress the endo interaction.[11] As the 1-endo-2-exo cycloadduct 6 is rather crowded around the 2- and 3-positions, it undergoes the retro reaction back to 5 and 2 which then recombine in the other fashion leading to the thermodynamically more favored 1-exo-2-endo cycloadduct 7.



Scheme 3.

It is noteworthy that only the anti form has participated in the cycloaddition of such carbonyl-stabilized ylides as 1 and 5.[12] To our surprise, however, the selective participation of syn ylide was observed in the reaction of isoquinolinium p-nitrobenzylide 9 as a ylide stabilized by a non-carbonyl substituent. Thus, the reaction of 9 with 2b to 2d provided the single stereoisomers of cycloadducts 10 (10b: Z=COPh; 10c: Z=COOMe; 10d: Z=COOBu^t) which were assigned as the 1-endo-2-exo cycloadducts to the syn form of 9 on the basis of spectral data and elementary analyses (Scheme 3 and Table 1).[13]

On the 1-endo-2-exo approach of trans olefins, the ylide-stabilizing substituent is arranged syn so as to go through a sterically less hindered transition state (C in Scheme 2). On the other hand, when the ylide is carbonyl-stabilized type, the anti form is more highly stabilized than the syn form getting a chance of participating exclusively to the cycloaddition. This stabilization may be caused by a proximate interaction of the both poles of 1,5-dipole which arises from an extended conjugation of 1,3-dipole with the carbonyl (D and E in Scheme 2).

References

1) The cycloaddition of heteroaromatic N-ylide: a) O. Tsuge, S. Kanemasa, and S. Takenaka, Heterocycles, 20, 1907 (1983); b) G. A. Craus and J. O. Nagy, Tetrahedron Lett., 24, 3427 (1983); c) O. Tsuge, Y. Shimizu, H. Shimoharada, and S. Kanemasa, Heterocycles, 19, 2259 (1982); d) O. Tsuge, H. Shimoharada, and M. Noguchi, ibid., 15, 807 (1981); e) M. Petrovanu, C. Luchian, G. Suprăteanu, and V. Bărboiu, Rev. Roum. Chim., 24, 733 and 1053 (1979); f) M. Petrovanu, I. Drută, and M. V. Tri, ibid., 23, 781 (1978); g) K. T. Potts, D. R. Choudhury, and T. R. Westby, J. Org. Chem., 41, 187 (1976); h) B. E. Landberg and J. W. Lown, J. Chem. Soc., Perkin Trans. 1, 1975, 1326. The cycloaddition of non-aromatic heterocyclic N-ylide: i) Z. Bende, L. Töke, L. Weber, G. Tóth, F. Janke, and G. Csonka, Tetrahedron, 40, 369 (1984); j) G. Tóth, J. Frank, Z. Bende, L. Weber, and K. Simon, J. Chem. Soc., Perkin Trans. 1, 1983, 1961.

2) In the present communication, the word "anti ylide" or "anti form of ylide" is used for a localized 1,3-dipolar structure in which a ylide-stabilizing group occupies the inner position.

3) As the endo cycloaddition to cis olefins: Refs. 1a, 1d, 1e, 1f, and 1j. As the cycloaddition to trans olefins: Refs. 1b, 1d, 1e, 1f, 1h, 1i, and 1j. Most of the latters involve more or less uncorrectly assigned structures of cycloadducts (Refs. 1b and 1i are exceptions).

4) ^{1}H-NMR data of 3: 3.16 (2-H), 3.82 (1-H), 5.41 (3-H), and 5.02 ppm (8a-H) with J_{1-2}=7.8, J_{2-3}=6.4, J_{1-8a}=6.8 Hz. 4: 3.31 (1-H), 3.98 (2-H), 5.37 (3-H), and 5.08 ppm (8a-H) with J_{1-2}=7.3, J_{2-3}=2.8, J_{1-8a}=9.0 Hz. These spectra were analyzed by the comparison with the spectrum for the endo cycloadduct of maleonitrile to the anti form of 1.

5) All new compounds reported herein gave satisfactory elemental analyses.

6) O. Tsuge, S. Kanemasa, S. Kuraoka, and S. Takenaka, Chem. Lett., 1984, 281; O. Tsuge, S. Kanemasa, S. Takenaka, and S. Kuraoka, ibid., 1984, 465.

7) In dimethyl sulfoxide the isomerization of 6a was suppressed because of its precipitation out of the solution. ^{1}H-NMR data of 6a: 4.43 (1-H), 4.25 (2-H), 6.00 (3-H), and 5.06 ppm (10b-H) with J_{1-2}=4.8, J_{2-3}=7.5, J_{1-10b}=6.4 Hz. 7a: 3.38 (1-H), 4.26 (2-H), 5.42 (3-H), and 4.33 ppm (10b-H) with J_{1-2}=8.0, J_{2-3}=2.8, J_{1-10b}=9.5 Hz.

8) N-Methylmaleimide reacts with 5 to give a quantitative yield of 8. A similar retro cycloaddition has been reported previously (See Ref. 1h).

9) It is not always the case that the 1-endo-2-exo cycloadducts undergo a clean isomerization into the thermodynamically more stable isomers. Dehydrogenation and elimination of the heterocycles are the major side reactions.

10) In this case also, the retro reaction occurs in the presence of palladium on chacoal. Thus, 6c isomerized into 7c in this way.

11) In the approach A, an attractive interaction would be possible between Z and W, however, it does not seem prominent enough to overcome the steric repulsion.

12) Other carbonyl-stabilized isoquinolinium ylides carrying an acetyl or methoxycarbonyl substituent show the same tendency.

13) ^{1}H-NMR spectrum of 10b is given as an example: 4.61 (1-H), 4.80 (2-H), 5.10 (3-H), and 5.37 ppm (10b-H) with J_{1-2}=8.0, J_{2-3}=8.0, J_{1-10b}=5.0 Hz. Other spectral data were all satisfied for the assigned structure.

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