STEREOSELECTIVE [3 + 2] CYCLOADDITION REACTION OF PYRIDINIUM AND THIAZOLIUM METHYLIDES TO ELECTRON-DEFICIENT OLEFINIC DIPOLAROPHILES

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Abstract —— The cycloaddition reaction of pyridinium and thiazolium methylides to electron-deficient olefinic dipolarophiles has been found to take place through an endo approach of the anti-ylides to the dipolarophiles affording the stereoselective [3 + 2] cycloadducts in quantitative yields.

It has been recently reported that methylenecyclopropenes bearing unsaturated substituents at the 4-position react with a variety of ylides of nitrogen heterocycles such as thiazolium[1,2], pyridinium[3], and imidazolium methylides[4] giving pentacyclic cage compounds. An intermolecular 1,3-dipolar cycloaddition and an intramolecular Diels-Alder reaction are comprised in this double cycloaddition reaction; a diene moiety for the latter reaction originates from the dipolarophile (the methylenecyclopropenes).

Another type of double cycloaddition reaction could be realized by the reaction of heterocyclic N-ylides in which the ylide carbon carries a diene moiety. Pyridinium and thiazolium (2-furoyl)methylides are the ylides of our choice. According to the molecular model inspection, only the cis [3 + 2] cycloadduct that is available in the reaction of a syn form of the ylide with dipolarophiles is favored for the second intramolecular Diels-Alder reaction[5].

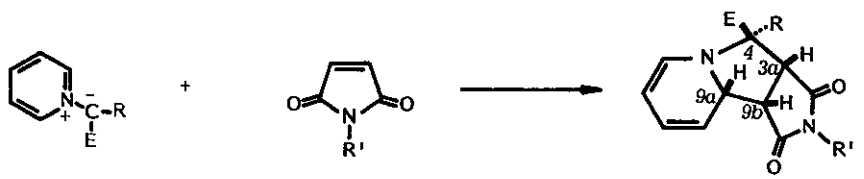
However, few studies on the stereochemical course of 1,3-dipolar cycloaddition reaction of pyridinium and thiazolium methylides to olefinic dipolarophiles have been reported so far[6]. The stereostructure of the only isolated [3 + 2] cyclo-

adduct of pyridinium phenacylide to acrylonitrile was not determined[7]. We have recently reported the formation of endo [3 + 2] cycloadduct between the anti form of thiazolium phenacylide and a methylenecyclopropene[2].

In the present communication, we would like to describe the 1,3-dipolar cycloaddition reaction of pyridinium and thiazolium methylides to several olefinic dipolarophiles leading to the quantitative formation of endo [3 + 2] cycloadducts between the corresponding anti-ylides and dipolarophiles.

The reaction of pyridinium (2-furoyl)methylide 1a, which was generated in situ from N-(2-furoylmethyl)pyridinium bromide[8] and triethylamine, with N-methylmaleimide 2a in chloroform at room temperature for 10 min gave the 1:1 adduct 3a in a quantitative yield. The structure of 3a was determined as an endo adduct between the anti form of 1a and 2a on the basis of the spectral data[9]. The coupling constants of J_{4-3a} (0 Hz), J_{3a-9b} (7.9 Hz), and J_{9b-9a} (7.9 Hz) rule out the other stereoisomers.

Similarly the endo [3 + 2] cycloadducts 3b-3j of anti forms of the various pyridinium methylides 1a-1f were obtained also in almost quantitative yields in the reaction with N-substituted maleimides 2a-2d under the reaction conditions shown in Table 1 (Scheme 1).



1 2 3

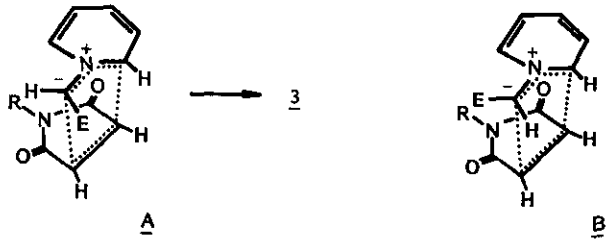
1a: E=2-furoyl, R=H
1b: E=PhCO, R=H
1c: E=COOMe, R=H
1d: E=COOEt, R=H
1e: E=p-$NO_2C_6H_4$, R=H
1f: E=R=COOEt

2a: R'=Me
2b: R'=p-MeC_6H_4
2c: R'=Ph
2d: R'=CH_2=$CHCH_2$

3a: E=2-furoyl, R=H, R'=Me
3b: E=2-furoyl, R=H, R'=p-MeC_6H_4
3c: E=PhCO, R=H, R'=Me
3d: E=PhCO, R=H, R'=Ph
3e: E=PhCO, R=H, R'=CH_2CH=CH_2
3f: E=COOMe, R=H, R'=p-MeC_6H_4
3g: E=COOEt, R=H, R'=p-MeC_6H_4
3h: E=p-$NO_2C_6H_4$, R=H, R'=p-MeC_6H_4
3i: E=R=COOEt, R'=Me
3j: E=R=COOEt, R'=p-MeC_6H_4

Scheme 1

The exclusive formation of stereoselective [3 + 2] cycloadducts in the above reaction is of great surprise. The pyrrolidine ring formed in the cycloaddition reaction of azomethine ylide 1,3-dipoles to olefinic dipolarophiles is known to suffer an epimerization by heating or on the treatment with base[10, 11]. However, neither an epimerization nor a deuterium exchange reaction occurred[12] by heating the cycloadduct 3a in benzene in the presence or absence of triethylamine, or when 3a was treated with triethylamine-D_2O in deuteriochloroform. The spectroscopic follow (^{1}H-NMR) of the reaction of 1b with 2a and that of N-phenacylpyridinium bromide with 2a in the presence of triethylamine in deuteriochloroform showed that these reactions were completed within a few minutes even at 0 °C forming the cycloadduct 3c both in quantitative yields, indicating that all the isolated [3 + 2] cycloadducts 3 are kinetically controlled.

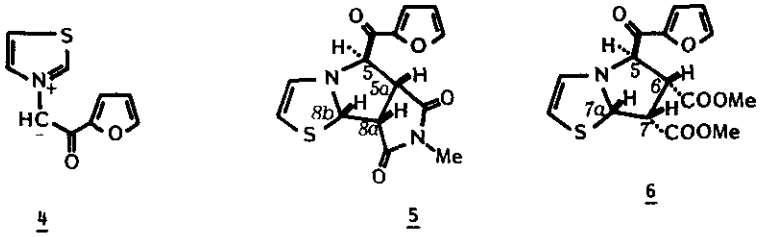


A B

Scheme 2

The highly selective participation of the anti form of pyridinium ylides 1 in the 1,3-dipolar cycloaddition reaction can be explained by the relative stability between the transition state A from an endo approach of the anti-ylide and the one B from the syn ylide. The former A leading to the observed products 3 may be less crowded and thus more stable than the latter B as shown in Scheme 2.

The reaction of thiazolium (2-furoyl)methylide 4, which was generated in situ from N-(2-furoylmethyl)thiazolium bromide[13] and triethylamine, with 2a in chloroform at



4 5 6

Scheme 3

room temperature for 10 min gave the 1:1 adduct 5 as the single product in a quantitative yield (Scheme 3). The structure of 5 was again easily assigned as the endo [3 + 2] cycloadduct between the anti form of 4 and 2a on the basis of the coupling constants among the hydrogens on the newly formed pyrrolidine ring (Table 1). The similar endo [3 + 2] cycloadduct 6 was obtained in the reaction of 4 with dimethyl maleate under similar reaction conditions.

Table 1. endo [3 + 2] Cycloadducts 3, 5, and 6.

	Reaction Conditions[a]	Yield [%]	Mp [°C]	$\nu_{C=O}$ [cm^{-1}]	Coupling Constants			M^+ [m/e]
					J_{4-3a}	J_{3a-9b}	J_{9b-9a}	
3a	r.t. 10 min	quant.	127-130[b]	1760, 1690, 1660	0 Hz	7.9 Hz	7.9 Hz	298
3b	r.t. 10 min	quant.	145-153	1770, 1705, 1670	0.5	7.9	7.9	374
3c	r.t. 10 min	quant.	150-153[b]	1780, 1695, 1678	0.6	7.7	7.7	308
3d	r.t. 10 min	quant.	72-73	1776, 1720, 1705	0.8	8.0	8.0	370
3e	r.t. 10 min	quant.	oil	1775, 1710, 1690	0.7	7.8	7.8	334
3f	r.t. 10 min	quant.	133-136	1780, 1740, 1710	0	8.0	8.0	338
3g	r.t. 10 min	quant.	94-97	1775, 1730, 1705	0	8.0	8.0	352
3h	r.t. 24 h	59[c]	146-149	1770, 1720, 1705	0.8	8.0	8.0	401
3i	reflux 4 h	quant.	oil	1770, 1730, 1710	-	8.1	8.1	348
3j	reflux 4 h	quant.	65-67	1760, 1730, 1710	-	7.8	7.8	424
5	r.t. 10 min	quant.	178-179	1770, 1705, 1680	0 (J_{5-5a}	8.0 J_{5a-8a}	8.0 J_{8a-8b})	304
6	r.t. 10 min	92	oil	1740, 1720, 1670	0 (J_{5-6}	7.0 J_{6-7}	7.0 J_{7-7a})	337

a) All the reactions were carried out in chloroform.

b) Melted with decomposition.

c) The unreacted pyridinium salt was recovered in 40 % yield.

Thus, it has been found that the anti form of pyridinium and thiazolium methylides with an electron-withdrawing substituent at the ylide carbon exclusively contributes to the cycloaddition reaction with olefinic dipolarophiles forming the stereoselective endo [3 + 2] cycloadducts. These cycloadducts have an unfavored configuration for the intramolecular Diels-Alder reaction (the cycloadducts 3a, 3b, 5, and 6 are the case). We are now studying the formation of syn-ylide cycloadducts.

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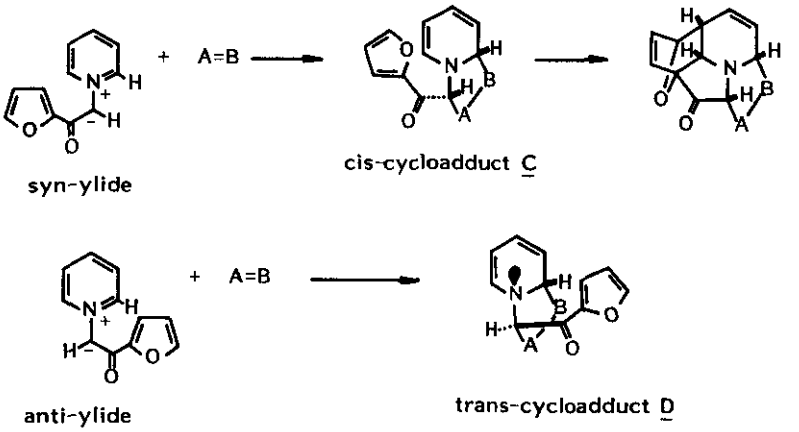
1) O. Tsuge and H. Shimoharada, Chem. Pharm. Bull., 1982, 30, 1903.

2) O. Tsuge, H. Shimoharada, M. Noguchi, and S. Kanemasa, Chem. Lett., 1982, 711.

3) O. Tsuge, S. Kanemasa, and S. Takenaka, Chem. Lett., 1983, 519.

4) O. Tsuge, S. Kanemasa, and S. Takenaka, Bull. Chem. Soc. Jpn., in press.

5) The diene and dienophile in the cis-cycloadduct C which is obtainable from the syn-ylide are located close enough to interact each other. However, the similar interaction is not expected in the trans-cycloadduct D that corresponds to the one between the anti-ylide and the dipolarophile (A=B).



6) The cycloaddition reaction of isoquinolinium (p-chlorophenyl)methylide to electron-deficient olefins has been reported: B. E. Landberg and J. W. Lown, J. Chem. Soc., Perkin I, 1975, 1326.

7) J. Fröhnlich and F. Kröhnke, Chem. Ber., 1971, 104, 1621.

8) The bromide was obtained in the reaction of pyridine with 2-(bromoacetyl)furan in acetone at 0 °C in 68 % yield. mp 208-209 °C.

9) The IR and mass spectra of 3a are given in Table 1. ^{1}H-NMR ($CDCl_3$) δ 2.90 (3H, s, Me), 3.40 (1H, t, J = 7.9 Hz, 9b-H), 3.64 (1H, d, J = 7.9, 3a-H), 4.54 (1H, ddd, J = 7.8, 3.9, and 1.4 Hz, 7-H), 4.70 (1H, ddd, J = 7.9, 5.8, and 1.4 Hz, 9a-H), 5.15 (1H, s, 2-H), 5.44 (1H, ddt, J = 10.0, 3.9, and 1.4 Hz, 8-H), 5.91 (1H, ddt, J = 10.0, 5.8, and 1.4 Hz, 9-H), 6.09 (1H, dt, J = 7.8 and 1.4 Hz, 6-H), 6.58, 7.38, and 7.64 ppm (each 1H, dd, furyl). The other cycloadducts 3b-3j, 5, and 6 gave the satisfactory spectral data.

10) P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, 1969, 35, 888. See also the literature in ref. 6.

11) O. Tsuge, H. Shimoharada, and M. Noguchi, *Heterocycles*, 1981, 15, 807.

12) Heating 3a in benzene under reflux for 4 h gave a complex mixture of products from which no epimerized isomers were detected. The treatment of 3a as well as the other cycloadducts 3 with silica gel or acetic acid gave the pyridine-eliminated products in good yields. This result will be published soon.

13) N-(2-Furoylmethyl)thiazolium bromide was obtained in the reaction of thiazole with 2-(bromoacetyl)furan in acetone at 0 °C in 49 % yield. mp 204-205 °C.

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