

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}, pyridinium³, and imidazolium methylides⁴ 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 reaction⁵.

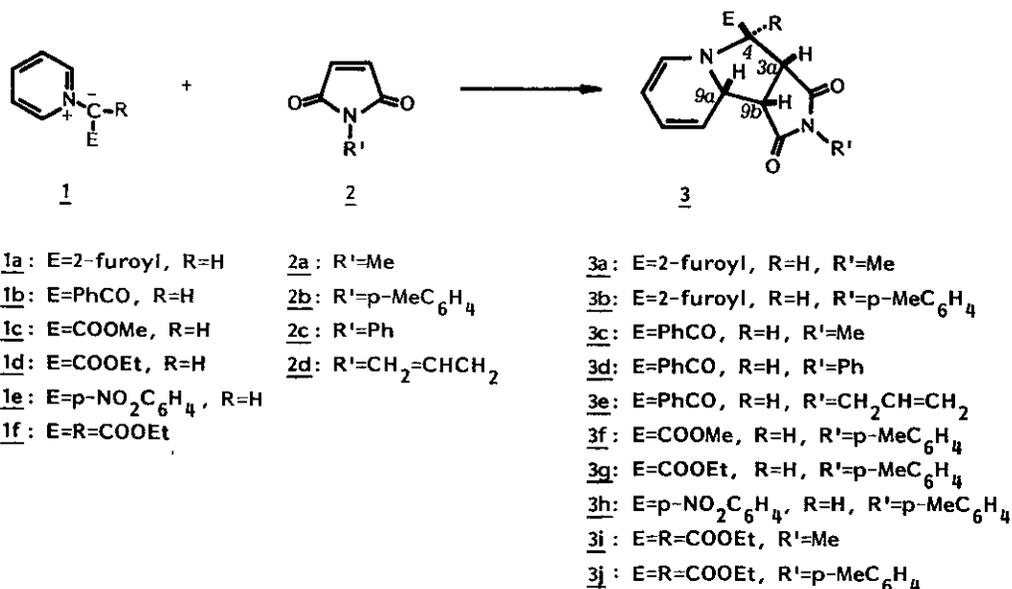
However, few studies on the stereochemical course of 1,3-dipolar cycloaddition reaction of pyridinium and thiazolium methylides to olefinic dipolarophiles have been reported so far⁶. The stereostructure of the only isolated [3 + 2] cyclo-

adduct of pyridinium phenacylide to acrylonitrile was not determined⁷. We have recently reported the formation of endo [3 + 2] cycloadduct between the anti form of thiazolium phenacylide and a methylenecyclopropene².

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.

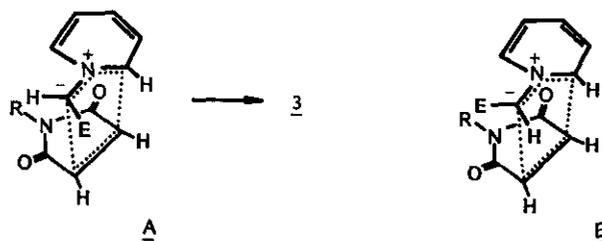
The reaction of pyridinium (2-furoyl)methylide 1a, which was generated in situ from N-(2-furoylmethyl)pyridinium bromide⁸ and triethylamine, with N-methylmaleimide 2a in chloroform at room temperature for 10 min gave the 1:1 adduct 3a in a quantitative yield. The structure of 3a was determined as an endo adduct between the anti form of 1a and 2a on the basis of the spectral data⁹. 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).



Scheme 1

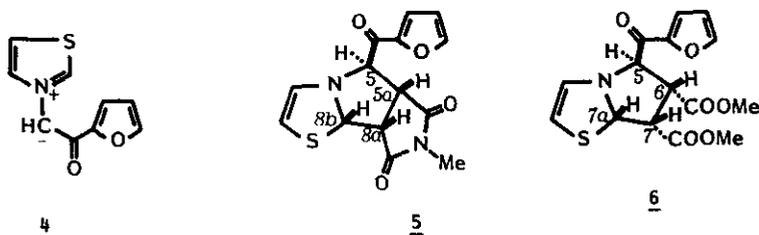
The exclusive formation of stereoselective [3 + 2] cycloadducts in the above reaction is of great surprise. The pyrrolidine ring formed in the cycloaddition reaction of azomethine ylide 1,3-dipoles to olefinic dipolarophiles is known to suffer an epimerization by heating or on the treatment with base^{10, 11}. However, neither an epimerization nor a deuterium exchange reaction occurred¹² by heating the cycloadduct 3a in benzene in the presence or absence of triethylamine, or when 3a was treated with triethylamine-D₂O in deuteriochloroform. The spectroscopic follow (¹H-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.



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 bromide¹³ and triethylamine, with 2a in chloroform at



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}	
<u>3a</u>	r. t.	10 min	quant.	127-130 ^{b)}	1760, 1690, 1660	0 Hz	7.9 Hz	7.9 Hz	298
<u>3b</u>	r. t.	10 min	quant.	145-153	1770, 1705, 1670	0.5	7.9	7.9	374
<u>3c</u>	r. t.	10 min	quant.	150-153 ^{b)}	1780, 1695, 1678	0.6	7.7	7.7	308
<u>3d</u>	r. t.	10 min	quant.	72-73	1776, 1720, 1705	0.8	8.0	8.0	370
<u>3e</u>	r. t.	10 min	quant.	oil	1775, 1710, 1690	0.7	7.8	7.8	334
<u>3f</u>	r. t.	10 min	quant.	133-136	1780, 1740, 1710	0	8.0	8.0	338
<u>3g</u>	r. t.	10 min	quant.	94-97	1775, 1730, 1705	0	8.0	8.0	352
<u>3h</u>	r. t.	24 h	59 ^{c)}	146-149	1770, 1720, 1705	0.8	8.0	8.0	401
<u>3i</u>	reflux	4 h	quant.	oil	1770, 1730, 1710	-	8.1	8.1	348
<u>3j</u>	reflux	4 h	quant.	65-67	1760, 1730, 1710	-	7.8	7.8	424
<u>5</u>	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
<u>6</u>	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.

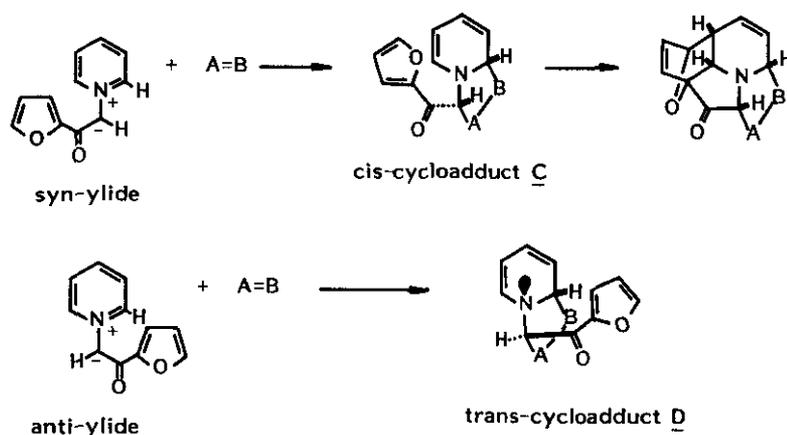
b) Melted with decomposition.

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

Thus, it has been found that the anti form of pyridinium and thiazolium methyldes 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.

REFERENCES

- 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. ¹H-NMR (CDCl₃) 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.

Received, 6th June, 1983