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CYCLOADDITION REACTIONS OF XANTHINIUM N(7)-YLIDES WITH TRANS OLEFINIC DIPOLAROPHILES

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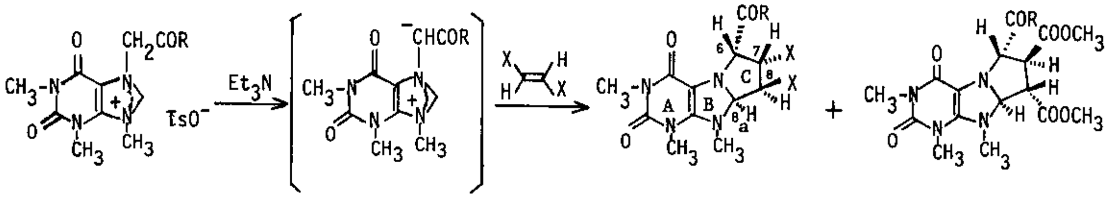
Abstract— The xanthinium N(7)-ylides reacted with olefinic dipolarophiles to give tetrahydropyrrolo[1,2-f]xanthine derivatives. Reaction with dimethyl fumarate gave the mixture of endo and exo adducts. The stereochemistry of these products was elucidated by ^{1}H-NMR and X-ray analysis.
Reaction with other trans olefins afforded solely endo-syn type addition products in excellent yields.

Cycloaddition reactions of azomethine ylides with dipolarophiles have been widely investigated as efficient methods to construct heterocyclic molecules.[1,2] We previously reported that novel xanthinium N-ylides 4 showed high reactivity with the activated acetylenic compounds such as dimethyl acetylenedicarboxylate and methyl propiolate to give 5-pyrrolouracils and pyrrolo[1,2-f]-pteridines through 1,3-dipolar cycloaddition followed by the ring transformation of the adducts.[3] Since the reactions of cyclic azomethine ylides with olefins produce three or four asymmetric carbons in the newly constructed rings at a time, it is very interesting to study these reactions. Stereochemistry of newly constructed rings has been determined mainly based on ^{1}H-NMR coupling constants.[4,5] Determination of stereochemistry is important in the discussion of stereoselectivity of the cycloaddition reaction.

In this paper, we wish to report the cycloaddition reactions of novel xanthinium N(7)-ylides with olefinic dipolarophiles and the stereochemical elucidation of the adducts, whose structure was highly functionalized, by ^{1}H-NMR and X-ray crystallography.

The xanthinium N-ylides 4 were generated from 7-substituted 1,3,9-trimethylxanthinium p-toluenesulfonates (1-3) by the deprotonation with triethylamine[6] in dry acetonitrile at room temperature under a nitrogen atmosphere and allowed to react with dipolarophiles without isolation of ylides 4.



<u>1</u> R = C_6H_5

<u>2</u> R = 4-BrC_6H_4

<u>3</u> R = duryl

<u>4</u>

8-endo adducts <u>5a</u>, <u>6a</u>, <u>8a</u>, <u>9a</u>

8-exo adducts <u>5b</u>, <u>6b</u>, <u>7b</u>

Scheme 1.

Table. Tetrahydropyrrolo[1,2-f]xanthines.

					^{1}H-NMR ppm (Hz)						
Comp.	R	X	yield(%)	mp (°C)	H-6	(J-6,7)	H-7	(J-7,8)	H-8	(J-8,8a)	H-8a
<u>5a</u>	C_6H_5	$COOCH_3$	54.0	136-138	6.13	(7.0)	3.74	(10.8)	4.18	(8.6)	5.13
<u>5b</u>	C_6H_5	$COOCH_3$	36.7	191-193*	6.16	(2.4)	3.79	(4.6)	3.87	(4.6)	5.20
<u>6a</u>	4-BrC_6H_4	$COOCH_3$	62	190-192.5*	6.06	(6.6)	**	(10.5)	4.20	(8.4)	5.12
<u>6b</u>	4-BrC_6H_4	$COOCH_3$	23	174.5-176*	6.09	(2.4)	3.79	(4.6)	3.85	(4.6)	5.18
<u>7b</u>	duryl	$COOCH_3$	62.4	194.5-197*	5.62	(3.0)	3.71	(6.1)	3.77	(5.2)	5.22
<u>8a</u>	C_6H_5	CN	quant.	163-166.5*	6.26	(6.1)	3.34	(10.8)	4.31	(7.3)	5.17
<u>9a</u>	C_6H_5	COC_6H_5	79.4	168-170	6.45	(7.3)	4.90	(10.0)	5.32	(8.6)	5.54

* dec. ** This peak could not be assigned with 60 M-Hz ^{1}H-NMR.

The reactions of <u>4</u> with dimethyl fumarate afforded two isomers of 1:1 adducts (<u>5a</u>, <u>5b</u>) in the ratio of 6:4. These isomers were separated by column chromatography on silica gel. The assignments of NMR spectra were made on the basis of the chemical shifts, coupling constants and spin-spin decoupling (Table).

In the adduct (<u>5a</u> or <u>5b</u>) a doublet at about δ 6.1 ppm was assigned to be 6-H by the spin-decoupling technique (400 MHz); the 6-H was coupled to the adjacent 7-H (J=7.0 and 2.4 Hz) and the coupling constants between the 7-H and 8-H were 10.8 and 4.6 Hz, respectively. Likewise another doublets at about δ 5.1 ppm assigned to be 8a-H and the coupling constants between 8a-H and 8-H were 8.6 and 4.6 Hz for <u>5a</u> and <u>5b</u>, respectively. Considering the reported coupling constants of stereoisomers of pyrrolidine derivatives,[7] the structure of major isomer (<u>5a</u>) is tentatively assigned to be the H6, H7-cis-H7,H8-trans-H8,H8a-cis configuration (8-endo adduct) and minor isomer (<u>5b</u>) was assigned to the all trans stereochemistry (8-exo adduct). But in the case of J-7,8 of <u>5a</u>, unreliable assignment was made because the value (J= 10.8 Hz) is on the border of cis or trans coupling constants.

In order to elucidate the stereochemistry and conformations of pyrrolidine moiety (ring C), X-ray

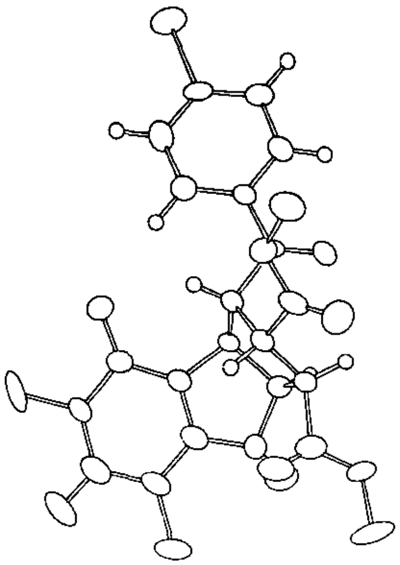


Figure ORTEP Drawing of 6a

4A 4B

Scheme 2.

analysis of bromo derivative (6a) which corresponds to the major isomer (5a) was made. As shown in the ORTEP drawing (Figure) of 6a, the stereochemistry of ring C was cis-trans-cis (8-endo adduct) and well accorded with that speculated from the ^{1}H-NMR data.

These stereochemistry of 5a and 5b revealed that dipolarophiles reacted only with the conformer 4B of the ylide (as shown in Scheme 2) to give endo and exo addition products. The less hindered conformer 4B might predominantly exist in the transition states because of steric and electrostatic repulsion between uracil moiety and benzoyl groups (R). Since the isomerization between 5a and 5b was not observed under the reaction conditions,[10] the minor product (5b) was obviously derived through less hindered exo approach to the ylide conformer 4B.

Interestingly other trans olefins (trans 1,2-dibenzoylethylene and fumaronitrile) afforded solely cis-trans-cis isomers (8-endo adducts 8a and 9a) in excellent yields as shown in the Table.

Very recently Tsuge et al. reported that 3+2 cycloaddition reactions in pyridinium and thiazolinium systems proceeded only in stereoselective-endo type addition process.[11] They emphasized that secondary orbital interaction favored the endo addition and steric repulsion in the transition state might control the ylide conformation.

On the other hand, Toth et al. reported an interesting result similar to ours that 2,3-dihydroisoquinolinium methylide reacted with dimethyl fumarate in the presence of pyridine to afford endo and exo isomers.[8] *From these results the reactions with dimethyl fumarate was practically un-*

affected by the secondary orbital interaction and dimethyl fumarate might be a susceptive dipolarophile to the steric hindrance.

In order to clarify the efficiency of secondary orbital interaction and steric effect in the xanthinium N(7)-ylide system (4), highly sterically-hindered ylide (4 R= duryl) generated from N-7 duroylmethylxanthine (3) was allowed to react with dimethyl fumarate under the same conditions. The only one product (7b) was obtained in 62,4 % yield and the stereostructure of ring C was assigned to be trans-trans-trans (8-exo adduct).

Our results clearly show that not only the secondary orbital interaction but also steric hindrance controls the reaction modes of cyclic azomethine ylides with olefins.

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