CHEMISTRY LETTERS, pp. 1533-1536, 1982.

## PERISELECTIVE CYCLOADDITION REACTION OF 3-PHENYLTHIA<sup>IV</sup> ZOLO[4,3-a]ISOINDOLE TO ELECTRON-DEFICIENT OLEFIN

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3-PhenyIthia<sup>IV</sup>zolo[4,3-a]isoindole, generated in situ from 3-phenyI-5H-thiazolo-[4,3-a]isoindolium bromide and triethylamine, reacted with a variety of electrondeficient olefins yielding the regio- and stereoselective 1:1 adducts between the azomethine ylide 1,3-dipole of the isoindole and the olefins.

It has been recently reported that the peripheral cycloaddition reaction of azomethine ylide containing a bridgehead nitrogen atom as a central atom of the 1,3-dipole offers a convenient method for the preparation of cyclazine derivatives.<sup>2</sup> Some mesoionic azapentalenes,<sup>3</sup> indolizines,<sup>4</sup> and their analogs<sup>5</sup> exhibit similar reactions with electron-deficient acetylenes and olefins to give a variety of cyclazine derivatives, while the reaction mechanisms have not been clearly established.<sup>6</sup> On the other hand, a certain nitrogen-bridged tetravalent sulfur compounds such as a thia<sup>IV</sup>zolo[3,4-b]indazole<sup>7</sup> and a pyrrolo[1,2-c]thia<sup>IV</sup>zole<sup>8</sup> have demonstrated the bi-perifunctional properties reacting with dimethyl acetylenedicarboxylate as azomethine ylides and with N-phenylmaleimide as thiocarbonyl ylides.<sup>9</sup> However, the periselective cycloaddition reaction to the azomethine ylide 1,3-dipole of nitrogen-bridged tetravalent sulfur compound is unknown so far.

We have already reported the synthesis of 3-phenyl-5H-thiazolo[4,3-a]isoindolium bromide that might be a precursor of 3-phenylthia<sup>IV</sup>zolo[4,3-a]isoindole <u>1</u> by deprotonation.<sup>10</sup> The present communication describes the cycloaddition reactions of <u>1</u> with a variety of electron-deficient olefins, in which the azomethine ylide 1,3-dipole of <u>1</u> was periselectively engaged to yield the regio- and stereo-selective cycloadducts

An equivalent suspension of 3-phenyl-5H-thiazolo[4,3-a]isoindolium bromide and dimethyl maleate in dry chloroform was warmed at 40 °C and a slight excess of triethylamine in chloroform was slowly added with stirring under nitrogen. Stirring was continued until all the insoluble materials dissolved into a homogeneous solution. The chloroform was evaporated at room temperature and the residue was



washed with ice-water to remove triethylammonium bromide, and then extracted with benzene. Evaporation of the benzene under vacuum afforded a colorless product  $2^{11}$  as a sole product in an excellent yield (Table 1).

The similar reaction with dimethyl fumarate yielded  $\underline{3}$ , an isomer of  $\underline{2}$ , also as a sole product. Both of the products  $\underline{2}$  and  $\underline{3}$  are found to be the 1:1 cycloadducts to an azomethine ylide  $\underline{B}^{12}$  of 3-phenylthia<sup>IV</sup>zolo[4,3-a]isoindole  $\underline{1}$ , that was generated from the bromide by deprotonation, on the basis of the <sup>1</sup>H-NMR spectral data shown in Table 2. The configurations of olefins used should be retained in the structures of cycloadducts,  $\underline{2}$  and  $\underline{3}$ , formed stereoselectively. The stereochemistry of  $\underline{2}$  and  $\underline{3}$  was mainly based on the chemical shifts of ester methyls: the ester methyl ( $\delta$  3.28 ppm) at the 4 position of  $\underline{2}$  appears in a considerably high field due to the shielding effect of the fused benzene ring. <sup>13</sup>

**Dimethyl Maleate** 

Dimethyl Fumarate

N-(p-Tolyl)maleimide



N-(p-Tolyl)maleimide is the only exception among the olefins employed in the cycloaddition reactions, which afforded a mixture of two isomeric 1:1 adducts 4a and 4b in the ratio of 6 to 4. Although it was very difficult to separate either of the adducts in a pure form through a column chromatography, their structures were determined by reading the <sup>1</sup>H-NMR spectrum of the mixture. Thus the product with a rather small coupling constant between 4-H and 4a-H is an endo [3 + 2] cycloadduct 4a and the one with a larger coupling constant is an exo cycloadduct 4b (Table 2).

In contrast with the maleimide, an another cyclic dipolarophile, citraconic anhydride, gave the only isomeric cycloadduct 5 in the reaction with 1. The product 5 was assigned to be an endo cyclo-adduct with a 4-exo-methyl group on the basis of the splitting pattern of methine hydrogens (Table 2).

The formation of 5 as a sole product might be explained from a viewpoint of steric hindrance: the approach between 1 and the anhydride leading to 5 seems to be sterically least hindered among the all possible approaches.

With an unsymmetrical dipolarophile with one electron-withdrawing substituent, the question of regioselectivity in the cycloaddition reaction arises. Such electron-deficient olefins as acrylonitrile, methy and ethyl acrylates, methacrylonitrile, methyl methacrylate, crotononitrile, methyl crotonate, methyl cinnamate, and trans-p-methoxy- $\beta$ -nitrostyrene were found to cycloadd to <u>1</u> in a highly peri-,

Products	Yields (१)	mp (℃)	IR (cm <sup>-1</sup> )	MS (m/e) <sup>a)</sup>
2	84	122-124	1730 (CO)	393*, 249
<u>3</u>	67	160-161(d)	1725 (CO)	393*, 249
<u>4</u>	87 ( <u>4a:4b</u> =	6:4)	1775, 1710 (CO)	
5	87	133.5-135(d)	1830, 1775 (CO)	361*, 288, 249
<u>6</u>	59	71-73	2230 (CN)	302*, 249
<u>7</u>	60	140-142	1740 (CO)	335*, 249
<u>8</u>	59	133-135	1730 (CO)	349*, 249
9	73	161-164	2215 (CN)	316*, 249
<u>10</u>	47	129-132	1727 (CO)	349*, 249
<u>11</u>	50	101-103	2230 (CN)	316*, 249
<u>12</u>	43	143-146	1730 (CO)	349*, 249
13	46	142.5-144.5	1740 (CO)	411*, 249
<u>14</u>	60	144.5-147	155, 1350 (NO <sub>2</sub> )	382 (M <sup>+</sup> -NO <sub>2</sub> ), 263, 249

Table 1. The [3 + 2] Cycloadducts of 1 to Electron-deficient Olefins.

a)	The ion	peaks	with	asterisk	are	parent	peaks	and	the	fragment	ion	at	249 is	assigned	to	1.

Products	1-H <sup>s</sup>	3-exo	3-endo	4-exo	4-endo	4a-H	J <sub>3-4</sub>	J 4-4a	Jgem
2	5.60	H 4.39 <sup>d</sup>	OMe 3.61 <sup>S</sup>	H 3.15 <sup>dd</sup>	OMe 3.28 <sup>s</sup>	5.29 <sup>d</sup>	10.0	8.1	
<u>3</u>	5.33	H 4.12 <sup>d</sup>	OMe 3.59 <sup>S</sup>	OMe 3.81 <sup>s</sup>	H 3.39 <sup>dd</sup>	4.66 <sup>d</sup>	8.8	8.4	
<u>4a</u>	5.46	H 3.84 <sup>d</sup>		H 3.28 <sup>dd</sup>		5.06 <sup>d</sup>	8.2	9.3	
<u>4b</u>	5.62		H 4.22 <sup>d</sup>		H 3.08 <sup>dd</sup>	5.38 <sup>d</sup>	9.9	3.2	
<u>5</u>	5.56	H 3.67 <sup>S</sup>		Me 1.35 <sup>S</sup>		4.68 <sup>5</sup>			
<u>6</u>	5.59	H 3.66 <sup>dd</sup>		H 2.26 <sup>dt</sup>	H 1.94 <sup>dt</sup>	4.77 <sup>dd</sup>	9.4 5.2	8.8	11.9
<u>7</u>	5.42	H 3.80 <sup>t</sup>	OMe 3.84 <sup>S</sup>	Н 2.16 <sup>dd</sup>	H 2.16 <sup>dd</sup>	4.72 <sup>t</sup>	7.8	7.3	
<u>8</u>	5.43	н 3.75 <sup>t</sup>	$OEt \frac{1.32^{t}}{4.30^{q}}$	H 2.17 <sup>t</sup>	H 2.17 <sup>t</sup>	4.73 <sup>t</sup>	8.1	8.0	
<u>9</u>	5.72	Me 1.23 <sup>S</sup>		H 2.05 <sup>dd</sup>	H 2.42 <sup>dd</sup>	5.21 <sup>dd</sup>		8.6 4.0	14.6
<u>10</u>	5.39	Me 0.99 <sup>s</sup>	OMe 3.78 <sup>s</sup>	H 2.61 <sup>dd</sup>	H 1.93 <sup>dd</sup>	4.76 <sup>dd</sup>		9.8 5.8	12.6
<u>11</u>	5.40	H 3.31 <sup>d</sup>		Me 1.07 <sup>d</sup>	H 2.18 <sup>m</sup>	4.01 <sup>d</sup>	9.2	8.2	
<u>12</u>	5.51	H 3.59 <sup>d</sup>	OMe 3.99 <sup>S</sup>	Me 1.12 <sup>d</sup>	H 2.58 <sup>m</sup>	4.20 <sup>d</sup>	10.0	9.2	
<u>13</u>	5.41	H 3.97 <sup>d</sup>	OMe 3.78 <sup>s</sup>		H 3.58 <sup>dd</sup>	4.56 <sup>d</sup>	9.2	8.8	
<u>14</u>	5.56	H 5.80 <sup>d</sup>			H 3.88 <sup>t</sup>	4.72 <sup>d</sup>	8.5	8.5	

Table 2. The <sup>1</sup>H-NMR spectra of  $2-\underline{14}$ ,<sup>a)</sup>

a) All the spectra were taken in CDCl  $_{3}$  (5 ppm) and the coupling constants are expressed in Hz.

regio- and yet stereoselective manner to give the corresponding cycloadducts <u>6-14</u>. Regardless of the structures of olefins, all the products are endo [3 + 2] cycloadducts to an azomethine ylide <u>B</u> with electron-withdrawing substituents at their 3-endo positions. The structural elucidation of them were accomplished on the basis of the spectral data shown in Table 1 and 2, especially of the <sup>1</sup>H-NMR spectra.

Regio- and stereochemistry of the cycloadducts  $\underline{6-14}$  coincides with the orientations derived from the combination of polarized structures of olefins with <u>B</u>, and also from an attractive interaction between the electron-withdrawing groups and the thiazole ring of <u>1</u> as has been demonstrated in the reaction with dimethyl fumarate. These aproaches leading to the regioselective endo cycloadducts are not sterically hindered either.

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- 11. This experiment offers the typical procedure for the reactions of 1 with electron-deficient olefins.
- 12. According to the inspection using a Dreiding model, in the [3 + 2] cycloadduct to a thiocarbonyl ylide C of 1, if an endo or an exo isomer, the bridgehead hydrogen should have exhibited a very small vicinal coupling.
- 13. The inspection of a Dreiding model shows that it seems rather difficult to estimate the dihedral angles, hence vicinal coupling constants, between the 3-H and 4-H and between the 4-H and 4a-H since the skeleton of the cycloadduct is not tightly fixed. The structures of 2 and 3 are also supported by the consideration of reaction modes in which the other olefins except for the maleimide were participated.

(Received August 4, 1982)