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# PERISELECTIVE CYCLOADDITION REACTION OF 3-PHENYLTHIA$^{\mathrm{IV}}$ZOLO[4,3-a]ISOINDOLE TO ELECTRON-DEFICIENT OLEFIN

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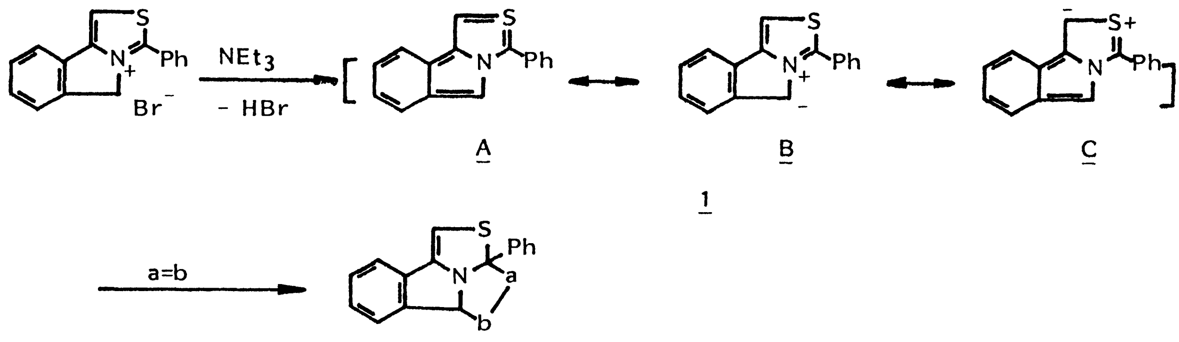
3-Phenylthia$^{\mathrm{IV}}$zolo[4,3-a]isoindole, generated in situ from 3-phenyl-5H-thiazolo-[4,3-a]isoindolium bromide and triethylamine, reacted with a variety of electron-deficient olefins yielding the regio- and stereoselective 1:1 adducts between the azomethine ylide 1,3-dipole of the isoindole 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.[2] Some mesoionic azapentalenes,[3] indolizines,[4] and their analogs[5] 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.[6] On the other hand, a certain nitrogen-bridged tetravalent sulfur compounds such as a thia$^{\mathrm{IV}}$zolo[3,4-b]indazole[7] and a pyrrolo[1,2-c]thia$^{\mathrm{IV}}$zole[8] have demonstrated the bi-perifunctional properties reacting with dimethyl acetylenedicarboxylate as azomethine ylides and with N-phenylmaleimide as thiocarbonyl ylides.[9] 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$^{\mathrm{IV}}$zolo[4,3-a]isoindole 1 by deprotonation.[10] The present communication describes the cycloaddition reactions of 1 with a variety of electron-deficient olefins, in which the azomethine ylide 1,3-dipole of 1 was periselectively engaged to yield the regio- and stereoselective 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



A B C

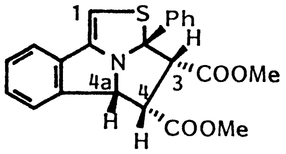
1

2-14

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).

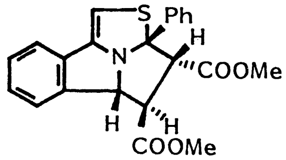
The similar reaction with dimethyl fumarate yielded 3, an isomer of 2, also as a sole product. Both of the products 2 and 3 are found to be the 1:1 cycloadducts to an azomethine ylide B[12] of 3-phenylthia$^{IV}$zolo[4,3-a]isoindole 1, that was generated from the bromide by deprotonation, on the basis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

Dimethyl Maleate



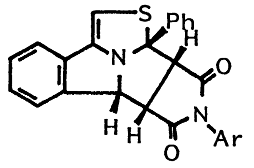
2

Dimethyl Fumarate

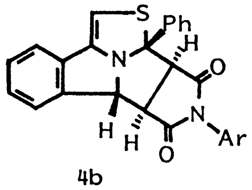


3

N-(p-Tolyl)maleimide



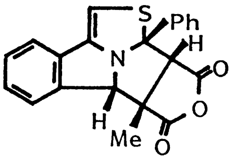
4a



4b

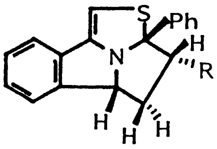
Ar: p-Tolyl

Citraconic Anhydride

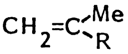


5

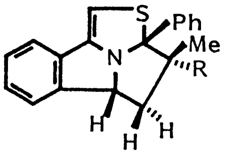
$CH_2=CH-R$



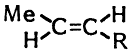
6: R=CN
7: R=COOMe
8: R=COOEt



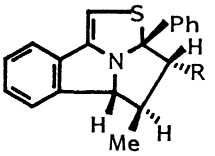
$CH_2=C\begin{smallmatrix}Me\\R\end{smallmatrix}$



9: R=CN
10: R=COOMe

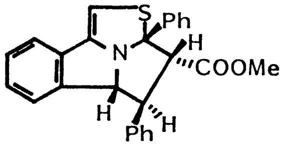


$\begin{smallmatrix}Me\\H\end{smallmatrix}C=C\begin{smallmatrix}H\\R\end{smallmatrix}$



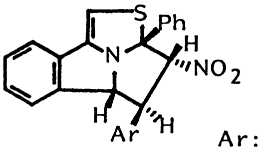
11: R=CN
12: R=COOMe

Methyl Cinnamate



13

trans-p-Methoxy-
β-nitrostyrene



14

Ar: p-Methoxyphenyl

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 $^1$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 cycloadduct 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-β-nitrostyrene were found to cycloadd to 1 in a highly peri-,

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

| Products | Yields (%) | mp (℃) | IR ($cm^{-1}$) | MS (m/e)[a] |
|---|---|---|---|---|
| 2 | 84 | 122-124 | 1730 (CO) | 393*, 249 |
| 3 | 67 | 160-161(d) | 1725 (CO) | 393*, 249 |
| 4 | 87 (4a:4b=6:4) | | 1775, 1710 (CO) | |
| 5 | 87 | 133.5-135(d) | 1830, 1775 (CO) | 361*, 288, 249 |
| 6 | 59 | 71-73 | 2230 (CN) | 302*, 249 |
| 7 | 60 | 140-142 | 1740 (CO) | 335*, 249 |
| 8 | 59 | 133-135 | 1730 (CO) | 349*, 249 |
| 9 | 73 | 161-164 | 2215 (CN) | 316*, 249 |
| 10 | 47 | 129-132 | 1727 (CO) | 349*, 249 |
| 11 | 50 | 101-103 | 2230 (CN) | 316*, 249 |
| 12 | 43 | 143-146 | 1730 (CO) | 349*, 249 |
| 13 | 46 | 142.5-144.5 | 1740 (CO) | 411*, 249 |
| 14 | 60 | 144.5-147 | 155, 1350 ($NO_2$) | 382 ($M^+-NO_2$), 263, 249 |

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

Table 2. The $^1$H-NMR spectra of 2-14.[a]

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

a) All the spectra were taken in $CDCl_3$ (δ ppm) and the coupling constants are expressed in Hz.

regio- and yet stereoselective manner to give the corresponding cycloadducts 6-14. Regardless of the structures of olefins, all the products are endo [ 3 + 2] cycloadducts to an azomethine ylide B 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 $^{1}$H-NMR spectra.

Regio- and stereochemistry of the cycloadducts 6-14 coincides with the orientations derived from the combination of polarized structures of olefins with B, and also from an attractive interaction between the electron-withdrawing groups and the thiazole ring of 1 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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9. Bi-perifunctional property of imidazo[ 1,2-c]thia$^{IV}$zole derivative in the reaction with N-(p-tolyl)-maleimide will be reported: O. Tsuge, S. Kanemasa, and T. Hamamoto, Chem. Lett.,(1982) submitted.
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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.

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