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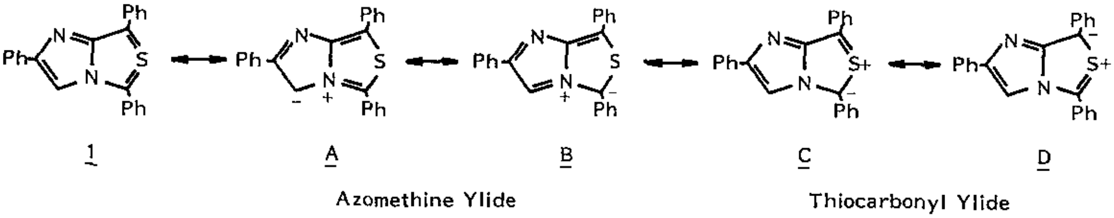
REGIO- AND PERISELECTIVE CYCLOADDITION REACTIONS OF A BIPERIFUNCTIONAL COMPOUND, 1,3,6-TRIPHENYLIMIDAZO[1,2-c]THIA^{IV}ZOLE

Otohiko Tsuge*, Shuji Kanemasa, and Takayoshi Hamamoto
Research Institute of Industrial Science, and Department of Molecular Science
and Technology, Interdesciplinary Graduate School of Engineering Sciences,
Kyushu University, Kasuga, Kasuga-shi, Fukuoka 816, Japan

Abstract ——— In the cycloaddition reactions of a biperifunctional compound, 1,3,6-triphenylimidazo[1,2-c]thia^{IV}zole, to a variety of unsymmetrically substituted olefinic dipolarophiles, one of the two peripheral thiocarbonyl ylides has exclusively contributed affording good yields of the regioselective [3 + 2] cycloadducts.

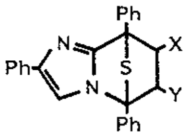
An attractive biperifunctional compound, 1,3,6-*triphenylimidazo*[1,2-c]*thia*^{IV}zole 1, *has been* recently synthesized[1]. This nitrogen-bridged tetravalent sulfur compound reacts with N-(p-tolyl)-maleimide not only as an azomethine ylide but also as a thiocarbonyl ylide 1,3-dipole to give the four isomeric [3 + 2] cycloadducts which undergo retro 1,3-dipolar cycloaddition reactions. It has been also suggested that all of the 1,3-dipolar cycloadditions and the retro reactions proceed in concerted manners, on the basis of the stereochemical investigations using acyclic olefinic dipolarophiles[2].

Each two dipolar forms with opposite directions of dipole are possible for the azomethine ylide (A and B) and the thiocarbonyl ylide 1,3-dipole (C and D) of the imidazothiazole 1. The ylide character of the rare compound 1 may be well understood by seeing which forms of the above two

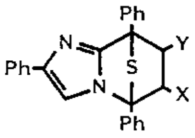


ylides will contribute to the orientation of [3 + 2] cycloadducts obtainable from the reactions with unsymmetrically substituted dipolarophiles.

In the cycloaddition reactions of 1 to unsymmetrically substituted olefinic dipolarophiles (XCH=CHY), it is expected to form the thermodynamically more stable cycloadducts E and/or F to the thiocarbonyl ylide 1,3-dipole[3]. Regardless of the formation of thermodynamically controlled products in this case, the regiochemistry of cycloadducts must result from the contribution of the more predominant dipolar form C or D since little difference of the steric hindrance may be present between the two regioisomeric cycloadducts E and F[4].



E

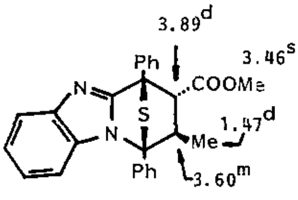


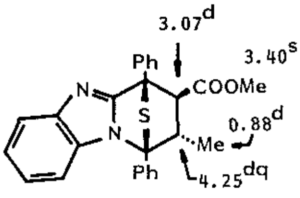
F

This communication describes the highly regioselective and also periselective [3 + 2] cycloaddition reactions of 1,3,6-triphenylimidazo[1,2-c]thia^{IV}zole 1 to a variety of unsymmetrically substituted electron-deficient olefins.

The reaction of 1 with citraconic anhydride 2 in benzene under reflux gave the single 1:1 adduct 3 in 73 % yield. The ^{1}H-NMR spectrum of 3 shows an olefin singlet at 6.85 ppm and a methine singlet at 3.82 ppm which is characteristic to the methine hydrogen at the 8a-endo position in the similar cycloadduct to maleic anhydride[5], indicating that 3 is assignable to be the exo [3 + 2] cycloadduct to the thiocarbonyl ylide of 1 with the methyl group at the 5a-endo position. The molecular model of 3 shows that the rotation of phenyl substituent at the 5-position is hindered by the adjacent carbonyl group so that the methyl group at the 5a-endo position can be deshielded (1.36 ppm). The extremely high regioselectivity of the above reaction is noteworthy since steric stability may be comparable between the two possible regioisomers as mentioned above. The weak polarization of double bond of 2 induced by the methyl substituent may have exclusively selected the only one regiochemical course leading to 3[6].

Although no reaction occurred under reflux in benzene, methyl crotonate 4, an unsymmetrical trans olefin, also yielded the [3 + 2] cycloadduct 5 to the thiocarbonyl ylide of 1 as the sole product when refluxed in toluene. The exo[7] and trans structure of 5 is easily assigned on the basis of the ^{1}H-NMR spectrum which exhibits a small coupling constant between the two methine hydrogens (





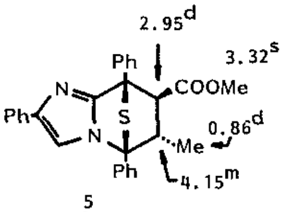


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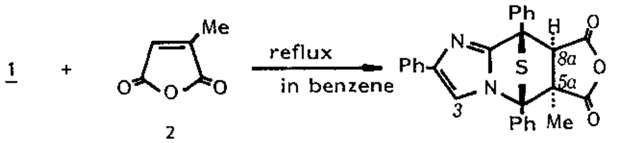
Table 1). The regiochemistry as well as stereochemistry is determined by the close resemblance of its ^{1}H-NMR spectrum to that of a similar cycloadduct of 4 to 1,3-diphenylthia^{IV}zolo[3,4-a]benzimidazole[8] as shown above. Thus, 5 is the exo [3 + 2] cycloadduct to the thiocarbonyl ylide of 1 with the methyl and ester groups at the 6-endo and 7-exo position, respectively.
The highly regiospecific, also periselective and stereospecific in this case, formation of cycloadduct of 1 to 4 means that the the thiocarbonyl ylide 1,3-dipole C has exclusively participated in the cycloaddition reaction.



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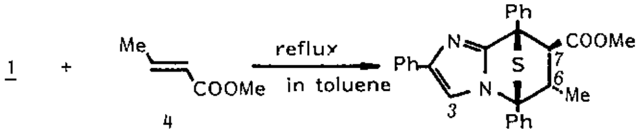
3 (73 %)



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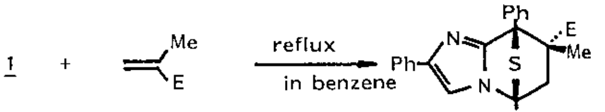
5 (61 %)

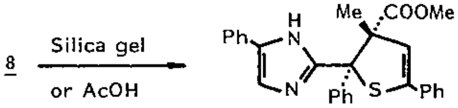


6: E=COOMe

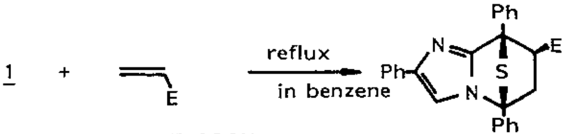
7: E=CN

8: E=COOMe (81 %)

9: E=CN (85 %)



10 (100%)



11: E=COOMe

12: E=CN

13: E=COOMe (89 %)

14: E=CN (80 %)

The reaction of 1 with methyl methacrylate 6 in benzene under reflux gave the thiocarbonyl ylide cycloadduct 8 in a good yield. The structure of 8 is easily confirmed to be the endo [3 + 2] cycloadduct with the two substituents at the 7-position on the basis of the ^{1}H-NMR spectrum and its chemical conversion. Of the two diastereotopic methylene hydrogens observed as each doublet at 2.21 and 4.14 ppm, the exo hydrogen at 4.14 ppm exhibits a remarkable nuclear Overhauser effect on irradiation at the adjacent methyl singlet indicating that the methyl substituent is located exo[9]. When chromatographed over silica gel or treated with acetic acid, 8 was quantitatively converted into its isomer 10, mp 184.5-187 °C, which was determined as a 2-(4-phenyl-2-imidazolyl)-2,3-dihydrothiophene derivative on the ground of the spectral data[10]. The isomer 10 can be derived by a bond cleavage between the 4- and 5-positions of 8 followed by a hydrogen migration.

Similarly methacrylonitrile 7 yielded the regiospecific endo [3 + 2] cycloadduct 9 as a single product under the same conditions. The formation of the endo [3 + 2] cycloadducts 8 and 9 is the only exception in the series of reactions of 1 with unsymmetrically substituted olefins.

Table 1. The Melting Points and Spectral Data of the [3 + 2] Cycloadducts between the Unsymmetrically Substituted Olefinic Dipolarophiles and the Thiocarbonyl Ylide of 1.

		^{1}H-NMR in $CDCl_3$ (δ ppm, Hz)[b)]						IR	M^{+}
Compds.	Mp(°C)[a)]	3-H	6-exo	6-endo	7-exo	7-endo	J(A-B)	(cm^{-1})	(m/e)
3	194-196	6.85^{s}		1.36^{s} (5a-Me)		3.82^{s} (8a-H)		1845 1780	464
5	104.5-105	-[c)]	4.15^{m}	0.86^{d} (Me)	3.27^{s} (COOMe)	2.95^{d}	4.5(6ex-7en) 7.0(6ex-Me)	1730	452
8	187-191	6.85^{s}	4.14^{d}	2.21^{d}	1.05^{s} (Me)	3.32^{s} (COOMe)	12.0(gem)	1730	452
9	202.5-206	6.82^{s}	3.82^{d}	2.40^{d}	1.21^{s} (Me)	- (CN)	12.0(gem)	2220	419
13	136-139	6.84^{s}	3.54^{dd}	2.70^{dd}	3.28^{s} (COOMe)	3.40^{dd}	5.0(6ex-7en) 8.0(6en-7en) 12.0(gem)	1740	438
14	185-186	6.76^{s}	3.44^{dd}	2.76^{dd}	- (CN)	3.35^{dd}	4.5(6ex-7en) 9.0(6en-7en) 13.0(gem)	2220	405

a) All the compounds melt with decomposition.

b) The chemical shifts are given for hydrogens otherwise shown in parentheses.

c) The signal is overlapping with the aromatic signals.

Methyl acrylate 11 readily reacted with 1 under reflux in benzene to give the single 1:1 adduct 13 in an excellent yield. The upfield (endo) and downfield methylene hydrogens (exo) couple with the adjacent methine hydrogen with the coupling constants of 8.0 and 5.0 Hz, respectively, showing that

13 is the exo [3 + 2] cycloadduct to the thiocarbonyl ylide of 1 (Table 1). The regiochemical assignment of 13 is based on the comparison of the ^{1}H-NMR spectrum with that of the confirmed cycloadduct of 11 to 1,3-diphenylthia^{IV}zolo[3,4-a]benzimidazole[8].

The similar cycloadduct 14 was obtained in a good yield in the reaction of 1 with acrylonitrile 12. As shown above, the cycloaddition reactions of 1,3,6-triphenylimidazo[1,2-c]thia^{IV}zole 1 to a variety of unsymmetrically substituted olefinic dipolarophiles form the highly regioselective [3 + 2] cycloadducts to the thiocarbonyl ylide of 1 in spite of the comparable stability between the two possible regioisomers. It would be concluded that this extremely high regioselectivity results from the selective contribution of the dipole C.

REFERENCES AND NOTES

1. O. Tsuge, S. Kanemasa, and T. Hamamoto, Chem. Lett., 1982, 1491.
2. O. Tsuge, S. Kanemasa, and T. Hamamoto, ibid., in press.
3. Only the thiocarbonyl ylide cycloadducts have been obtained in the reactions of 1 with symmetrically substituted olefins under reflux in benzene (see ref. 2).
4. Structural inspection of the Dreiding model indicates that the steric environment around the 6-position is almost the same to that around the 7-position.
5. The exo [3 + 2] cycloadduct of maleic anhydride to the thiocarbonyl ylide of 1 shows the methine hydrogen at the 5a-endo position (4.12 ppm) downfield of the one at the 8a-endo position (3.89 ppm) owing to the deshielding effect from the bridgehead nitrogen. The similar deshielding has been observed in the corresponding cycloadducts to N-(p-tolyl)maleimide and dimethyl maleate (see ref. 1 and 2).
6. Similar high regioselectivity of 2 in a cycloaddition reaction has been recently reported: S. Kanemasa, S. Ikeda, H. Shimoharada, and S. Kajigaeshi, Chem. Lett., 1982, 1533.
7. The term, an exo cycloadduct, is used for the cycloadduct with an electron withdrawing substituent at the endo position.
8. O. Tsuge, H. Shiraishi, and T. Takata, Chem. Lett., 1980, 1369.
9. The signal intensity for the doublet at 4.14 ppm was enhanced by 12 % on the irradiation at the methyl singlet at 1.05 ppm, while a few percent of the enhancement was observed for the doublet at 2.21 ppm.
10. The compound 10: IR (KBr) 3350 (NH) and 1710 cm^{-1} (CO); ^{1}H-NMR (CDCl$_3$) δ1.50 (3H, s, Me), 3.71 (3H, s, COOMe), 6.45 (1H, s, 4-H), and 7.00-8.00 ppm (17H, m, aromatic and NH); ^{13}C-NMR (CDCl$_3$) δ22.35 (q, Me), 53.06 (q, COOMe), 64.39 (s, 3-C), 68.95 (s, 2-C), 112.47 (d, 4-H), 120.79 (d, HN-C=N), and 177.19 ppm (s, COOMe); MS (m/e) 452 (M$^+$).

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