

ONE-POT SYNTHESIS OF HETEROCAGE COMPOUNDS¹

Akikazu Kakehi* and Suketaka Ito

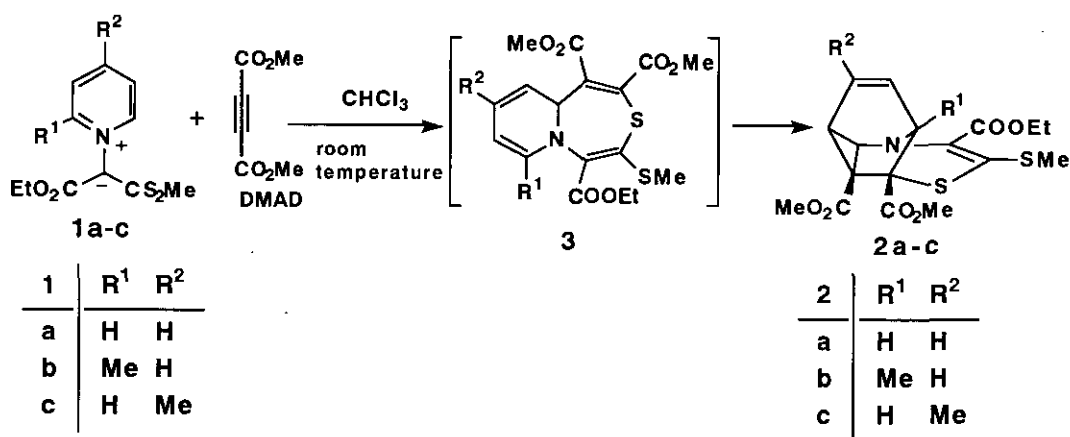
Department of Chemistry and Material Engineering, Faculty of Engineering,
Shinshu University, Wakasato, Nagano 380, Japan

Abstract--- The reaction of some pyridinium 1-(methylthiothiocarbonyl)-methylides bearing an ethoxycarbonyl group at the ylidic carbanion with dimethyl acetylenedicarboxylate in chloroform at room temperature gave smoothly 3-methylthio-4-thia-1-azatetracyclo[5.4.0.0^{5,11}.0^{6,8}]undeca-2,9-diene-2,5,6-tricarboxylic esters in moderate yields.

Recently we have reported the smooth preparation of 10a*H*-pyrido[1,2-*d*]-1,4-thiazepine derivatives from the reaction of pyridinium 1-(methylthiothiocarbonyl)methylides, substituted with a cyano group at the ylidic carbanion, with dimethyl acetylenedicarboxylate (DMAD).² This [5+2] type of reaction between 1,5-dipoles and DMAD as a dipolarophile or electrophile,³ though it is still unclear whether this reaction proceeds *via* concerted 1,5-dipolar cycloaddition⁴ or stepwise addition-cyclization route, is the first case and is of high synthetic and theoretical value, because such 7-membered heterocycles cannot be easily obtained by other methods. In order to obtain further information for this reaction, we attempted next to examine the reactions of other types of pyridinium 1-thiocarbonylmethylides with DMAD, and found a one-pot synthesis of the title compounds. In this paper we wish to report a smooth formation of 4-thia-1-azatetracyclo[5.4.0.0^{5,11}.0^{6,8}]undeca-2,9-diene derivatives from the reaction of pyridinium 1-(1-ethoxycarbonyl-1-methylthiothiocarbonyl)methylides with DMAD.

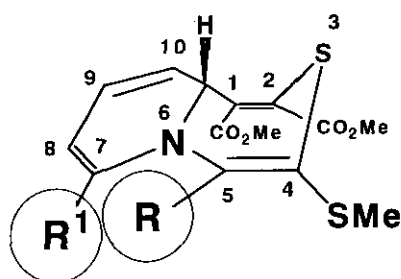
When a solution of pyridinium 1-(1-ethoxycarbonyl-1-methylthiothiocarbonyl)methylide (**1a**)⁵ in chloroform and a small excess of DMAD was allowed to react at room temperature for 12 h and the resulting reaction mixture was separated by column chromatography on alumina using chloroform as an eluent, a colorless crystalline product (**2a**), mp 135-136 °C (from chloroform-ether), ν (KBr) 1674 and 1721 cm⁻¹ (CO), m/z 397 (M⁺), δ (CDCl₃)⁶ 1.29 (3H, t, *J*=7.0 Hz, OCH₂CH₃), 2.43 (3H, s, SMe), 2.66 (1H, m, 8-H), 3.58 (1H, dd, *J*=7.0 and 1.0 Hz, 7-H), 3.66 (6H, s, 2xOMe), 3.88 (1H, br d, *J*=7.0 Hz, 11-H), 3.9-4.4 (2H, m, OCH₂CH₃), 5.96 (1H, br t, *J*=8.5 and 7.0 Hz, 10-H), and 6.20 (1H,

br t, $J=8.5$ and 6.5 Hz, 9-H), was obtained in 51% yield. Similar treatment of 2-methyl (**1b**)⁵ and 4-methylpyridinium 1-(1-ethoxycarbonyl-1-methylthiothiocarbonyl)methylides (**1c**)⁵ with DMAD gave the corresponding products (**2b**), 46%, mp 125-126 °C, ν (KBr) 1674 and 1725 cm^{-1} (CO), m/z 411 (M^+), δ (CDCl_3), *inter alia*, 1.52 (3H, s, 11-Me), 2.53 (1H, br t, $J=7.0$ and 6.5 Hz, 8-H), 3.57 (1H, d, $J=7.0$ Hz, 7-H), 5.63 (1H, dd, $J=8.5$ and 7.0 Hz, 10-H), and 6.28 (1H, q, $J=8.5$ and 6.5 Hz, 9-H), and (**2c**), 38%, mp 136-137 °C, ν (KBr) 1680, 1723, and 1748 cm^{-1} (CO), m/z 411 (M^+), δ (CDCl_3), *inter alia*, 1.85 (3H, d, $J=1.5$ Hz, 9-Me), 2.42 (1H, dd, $J=7.0$ and 2.0 Hz, 8-H), 3.51 (1H, dd, $J=7.0$ and 1.0 Hz, 7-H), 3.76 (1H, dd, $J=7.0$ and 1.0 Hz, 11-H), and 5.69 (1H, br d, $J=7.0$ Hz, 10-H), as colorless prisms, respectively. In the above reactions no colored compound such as 10a*H*-pyrido[1,2-*d*][1,4]thiazepine derivatives (**3**) could be detected.

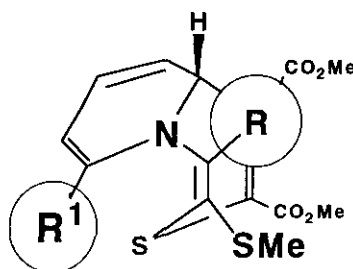


The elemental analyses and mass spectra of products (**2a-c**) showed distinctly that they are 1:1 adducts of pyridinium 1-methylides (**1a-c**) and DMAD, and their ^1H nmr spectra exhibited also the number of proton signals which can be anticipated for the corresponding 1:1 adducts. However, the chemical shifts and signal patterns in ^1H nmr spectra were quite different from those of the 10a*H*-pyrido[1,2-*d*][1,4]thiazepine derivatives prepared by us earlier.² A detailed spectral inspection disclosed the presence of a 1,2,5,6-tetrahydropyridine moiety and a methyl vinyl sulfide structure in these molecules. From this structural information and our previous findings,² in which the reaction of pyridinium 1-(1-cyano-1-methylthiothiocarbonyl)methylides with DMAD afforded the corresponding 10a*H*-pyrido[1,2-*d*][1,4]thiazepine derivatives, we assumed the products (**2a-c**) to be intramolecular Diels-Alder adducts of the initially formed pyrido-thiazepine derivatives such as **3**. The conformational analysis for the 10a*H*-pyrido[1,2-*d*][1,4]thiazepines using Dreiding models suggested the presence of two main conformers, a planar form **A** and an angular form **B** as

shown below. The latter form **B**, which is more suitable for an intramolecular Diels-Alder reaction, can be considered to be enhanced by the peri-interactions between the 1- and 10-positions or the 5- and 7-positions in this molecule. Since the difference between pyridinium 1-(methylthiothiocarbonyl)methylides employed here and earlier² is only the substituent (*R*) on the ylidic carbanion, the peri-interaction between the 5- and 7-position must have contributed largely to this reaction.

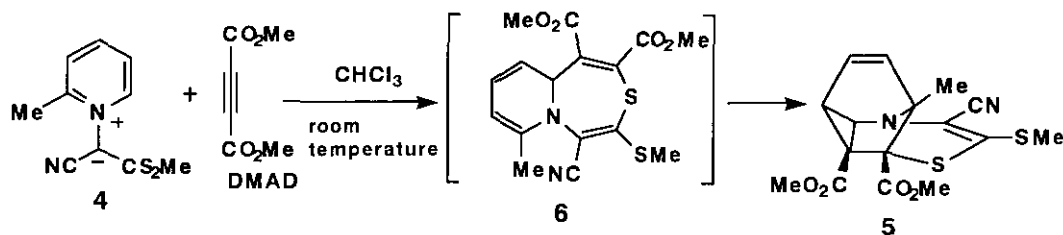


Form A



Form B

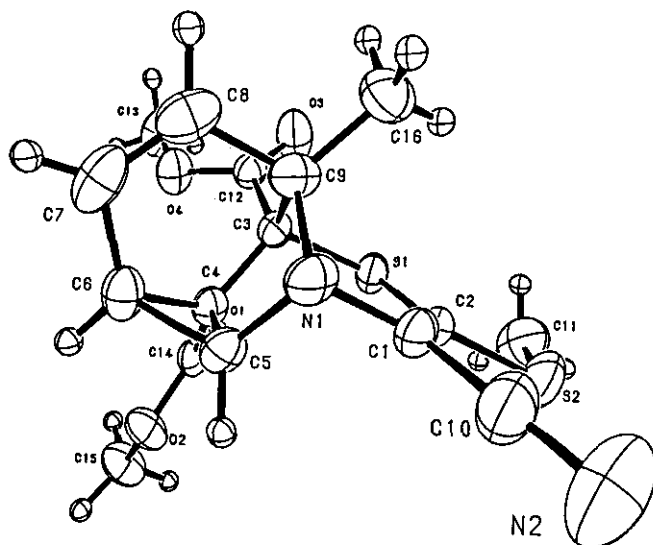
In order to confirm this assumption we attempted the reaction of 2-methylpyridinium 1-(1-cyano-1-methylthiothiocarbonyl)methylide (**4**)⁵ with DMAD. As might be expected, this reaction proceeded smoothly at room temperature to give the corresponding product (**5**), 28%, mp 128-130 °C (from ethanol), ν (KBr) 1721 (CO) and 2191 cm^{-1} (CN), δ (CDCl_3) 1.59 (3H, s, 11-Me), 2.48 (3H, s, SMe), 2.56 (1H, br t, $J=7.0$ and 6.5 Hz, 8-H), 3.66 and 3.70 (each 3H, s, OMe),⁶ 5.61 (1H, dd, $J=8.5$ and 2.0 Hz, 10-H), and 6.26 (1H, q, $J=8.5$ and 6.5 Hz, 9-H), as colorless prisms. Again, in this reaction dimethyl 5-cyano-8-methyl-5-methylthio-10a*H*-pyrido[1,2-*d*][1,4]thiazepine-2,3-dicarboxylate (**6**) could not be obtained.



Fortunately, single crystals of this product (**5**) were grown from the ethanolic solution and its X-ray analysis could be performed. The structural data of compound (**5**) indeed shows it to be the proposed structure that products (**2a-c**) and (**5**) are intramolecular Diels-Alder adducts between the

1,2-dihydropyridine moiety and the electron deficient 1,2-double bond in 10a*H*-pyrido[1,2-*d*][1,4]-thiazepine molecule, as shown in its ORTEP drawing.

The scope and limitation of this reaction will be reported in the near future.



REFERENCES AND NOTES

- 1) Preparation of New Nitrogen-bridged Heterocycles, part 32. For part 31 of this series, see A. Kakehi, S. Ito, T. Fujii, T. Ueda, and T. Hirata, *Chem. Pharm. Bull.*, 1992, **40**, 2313.
- 2) A. Kakehi, S. Ito, and J. Hakui, *Chem. Lett.*, 1992, 777.
- 3) For the reactivity of DMAD, see the following reviews; R. M. Acheson, *Adv. Heterocycl. Chem.*, 1963, **1**, p.125; M. V. George, S. K. Khetan, and R. K. Gupta, *ibid.*, 1976, **19**, p.279; R. M. Acheson and N. F. Elmore, *ibid.*, 1978, **23**, p.263; T. Uchida and K. Matsumoto, *Synthesis*, 1976, 209.
- 4) If this reaction proceeds *via* concerted process, its reaction mode should be $\pi 6a + \pi 2s$. The fact that the approach in an antarafacial fashion is, in general, difficult, except in cases with special steric requirement is well known; See R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Academic Press Inc., 1970, p.66.
- 5) Y. Tominaga, Y. Miyake, H. Hujito, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1977, **97**, 927.
- 6) These ^1H nmr spectra were measured with a Varian EM360 spectrometer (60 MHz).
- 7) The signal of the 7-H was overlapped by the signals of the two methoxy groups appearing at δ 3.66 and 3.70.

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