ONE-POT SYNTHESIS OF HETEROCAGE COMPOUNDS[1]

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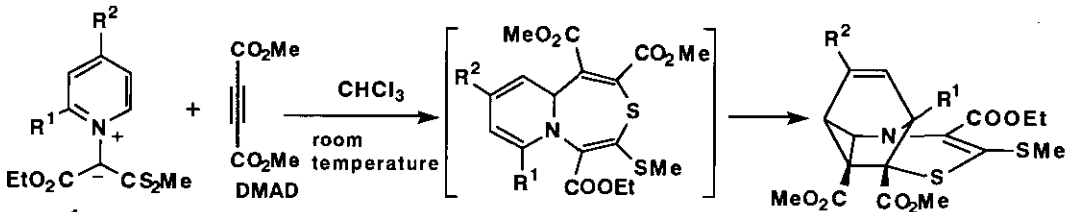
Abstract--- The reaction of some pyridinium 1-(methylthiothiocarbonyl)-methylides bearing an ethoxycarbonyl group at the ylidic carbanion with dimethyl acetylenedicarboxylate in chloroform at room temperature gave smoothly 3-methylthio-4-thia-1-azatetracyclo[5.4.0.0^{5,11}.0^{6,8}]undeca-2,9-diene-2,5,6-tricarboxylic 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 cycloaddition[4] 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-ethoxy-carbonyl-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(CDCl$_3$)[6] 1.29 (3H, t, J=7.0 Hz, OCH$_2$*CH$_3$*), 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, O*CH$_2$*CH$_3$), 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.

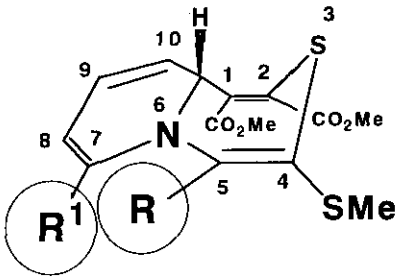


1	R^1	R^2
a	H	H
b	Me	H
c	H	Me

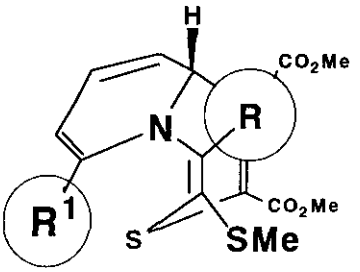
2	R^1	R^2
a	H	H
b	Me	H
c	H	Me

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 the10a*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 pyridothiazepine 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-(methylthio-*thiocarbonyl)methylides* employed here and earlier[2] 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.

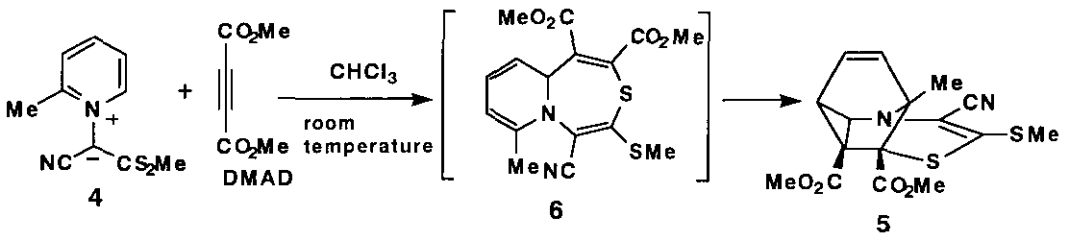


Form **A**



Form **B**

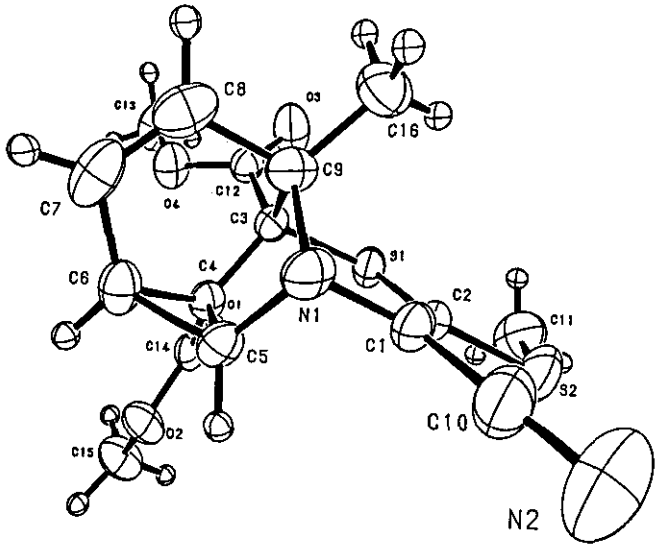
In order to confirm this assumption we attempted the reaction of 2-methylpyridinium 1-(1-cyano-1-methylthiothiocarbonyl)methylide (**4**)[5] with DMAD. As might be expected, this reaction proceeded smoothly at room temperature to give the corresponding product (**5**), 28%, mp 128-130 °C (from ethanol), 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 ^{1}H 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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