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CYCLOADDITION EXTRUSION REACTION OF 2- OR 4-(METHYLTHIO)-THIOCARBONYLIMINO-1,2 OR 1,4-DIHYDROPYRIDINE DERIVATIVES WITH DIMETHYL ACETYLENEDICARBOXYLATE.

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Reaction of (methylthio)thiocarbonylimino derivatives of pyridine(Ia-d, IV) with dimethyl acetylenedicarboxylate(DMAD) afforded 2 or 4-(1,2-dimethoxycarbonyl-2-thioxoethylidene)-1,2 or 1,4-dihydropyridine derivatives(IIa-d, V), accompanied with extrusion of methyl thiocyanate[1] from 1,4-cycloadduct, spiro-1,3-thiazine derivatives.

Further, reaction of IV with DMAD(2 mole) gave cyclobuteno[1,2-b]azocine derivative(VI). Reaction of (methylthio)thiocarbonylimino derivative of benzothiazole(VII) with DMAD afforded 4H-pyrrole-2-spiro-2-(2,3-dihydrobenzothiazole)(VIII), accompanied with desulfrization.

In connection with our studies on reactions of enaminodithiocarboxylate derivatives, we have investigated the cycloaddition reactions of enaminodithiocarboxylate derivatives with dimethyl acetylenedicarboxylate(DMAD)[2-5].

The present investigation is undertaken to compare enaminodithiocarboxylates with iminodithiocarboxylates in the 1,4-cycloaddition reactions with DMAD. The iminodithiocarboxylates have a dihetero diene system, thiocarbonyl group of its dithiocarboxylate and a carbon-nitrogen double bond(schiff base).

A solution of 1-methyl-2-(methylthio)thiocarbonylimino-1,2-dihydropyridine(Ia)(0.43 g) and DMAD(0.3 g) in 50 ml of dioxane was stirred at room temperature. The color of the mixture changed into black from yellow within 5 min. After stirring for 12 hr, the appeared dark-yellow precipitate was collected by filtration and recrystallized from methanol to give yellow needles of mp 217-218°(decomp) in 80% yield. Elemental analysis of this product corresponded to $C_{12}H_{13}O_4NS$=267.23(Calcd.: C, 53.93; H, 4.90; N, 5.24; S, 11.97. Found: C, 53.78; H, 4.77; N, 5.11; S, 11.92.). The molecular weight of this compound was also supported by mass spectrometry(M^+: 267). The nuclear magnetic resonance(NMR) spectrum(in DMSO-d_6) of this compound displayed two singlet peaks of methoxy groups at 3.45 and 3.64 ppm. The infrared(IR) spectrum of this compound showed absorptions due to ester carbonyl groups at 1670 and 1720 cm^{-1}. The ultraviolet(UV) spectrum revealed maxima, nm(logε), at 220(3.82), 264(3.81), and 332(4.26). From these spectral data and elemental analysis, this compound was found to be 1-methyl-2-(1,2-dimethoxycarbonyl-2-thioxoethylidene)-1,2-dihydropyridine(IIa).

In a similar manner, treatment of other methyl iminodithiocarboxylate derivatives(Ib-d, IV) with DMAD, shown in Chart 1 and 2, afforded the corresponding (2-thioxoethylidene)-1,2 or 1,4-dihydropyridine derivatives (IIb-d, V) respectively, accompanied with the elimination of methyl thiocyanate[1)], in fairly good yields. Spectral data of these products are summarized in Table.

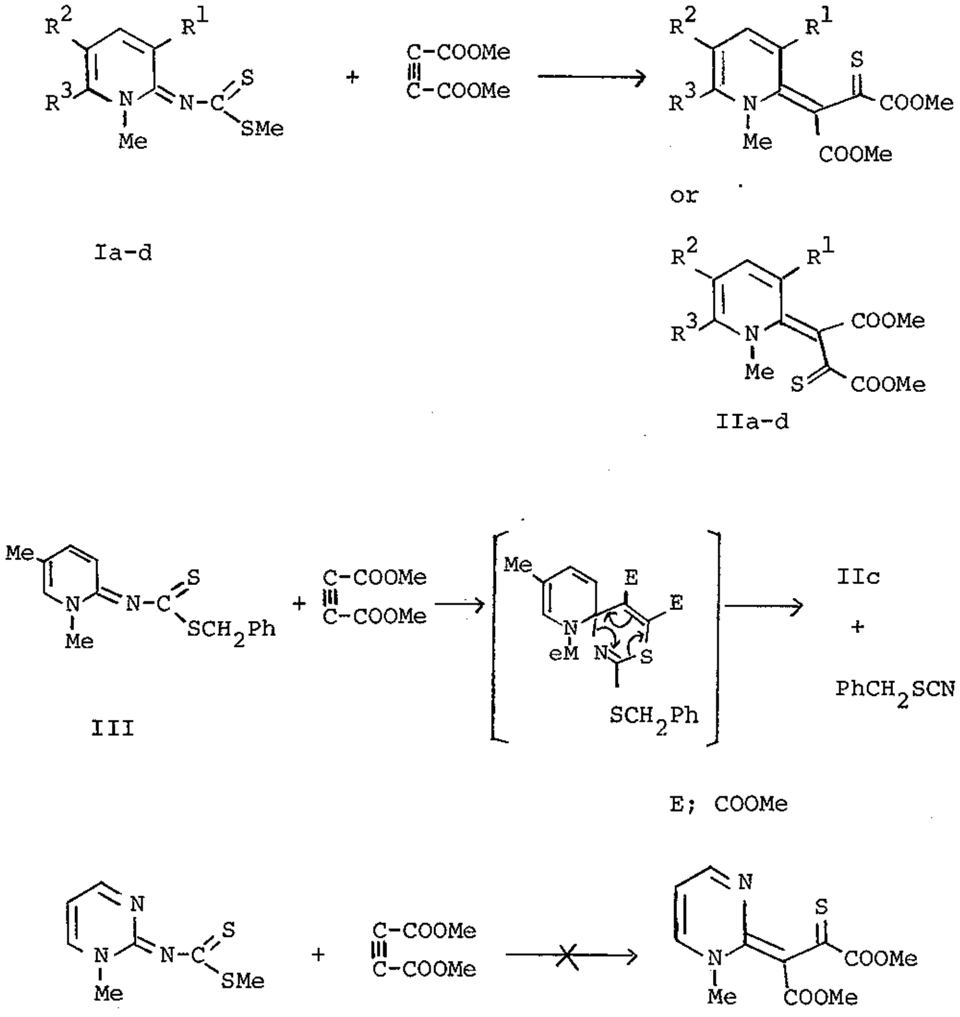


Chart 1

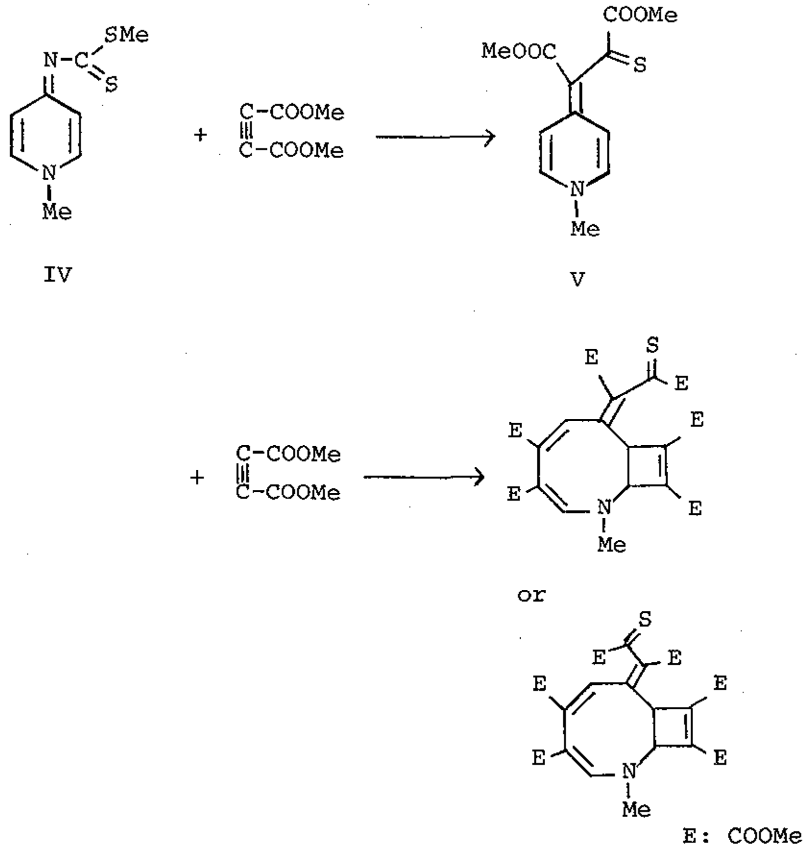
Reaction of 1-methyl-2-(methylthio)thiocarbonylimino-1,2-dihydropyrimidine with DMAD did not occurred under a similar condition.

To presume this reaction's mechanism, the reaction of 1,5-dimethyl-2-(benzylthio)thiocarbonylimino-1,2-dihydropyridine (III) with DMAD was examined in a similar conditions, and two products, IIc and benzyl thiocyanate were obtained. This benzyl thiocyanate was separated by column-chromatography over aluminum-oxide with benzene, of mp 43° as colorless needles and its spectral data were identified with original sample. This preparation of benzyl thiocyanate supported that 1,4-cycloaddition reaction was carried out intermediately.

On the other hand, when this reaction was examined on boiling water-bath, the yields of 2-(2-thioxoethylidene)-1,2-dihydropyridine derivatives decreased and the recovery of starting material increased. From these results, it is thought that the reaction temperature is an important condition in these reactions.

Next, a solution of 1-methyl-4-(methylthio)thiocarbonylimino-1,4-dihydropyridine(IV), 2 equivalent mole of DMAD, and 30 ml of dimethylformamide(DMF) was stirred for 72 hr at room temperature. After the evaporation of reaction solvent, white needles of mp 183-184° were separated from the residue by column-chromatography over aluminum-oxide with chloroform in 40% yield. Elemental analysis of this product corresponded to $C_{24}H_{25}O_{12}NS$ =551.45(Calcd.: C, 52.27; H, 4.57; N, 2.54; S, 5.80. Found: C, 52.14; H, 4.56; N, 2.31; S, 5.58). The molecular weight of this product was also supported by mass spectrometry(M^+: 551).

The NMR spectrum(in $CDCl_3$) of this product displayed two doublet signals due to methine protons at $C_{1a,\ 3a}$-position of azocine ring at 3.36(1H, doublet, J=6Hz) and 4.04 ppm(1H,doublet, J=6Hz) and four sharp singlets due to methyl protons at 2.54(3H, singlet, NCH_3), 3.76(6H, singlet, OCH_3), 3.84(6H, singlet, OCH_3), and 3.88 ppm(6H, singlet, OCH_3). IR(in KBr): 1702 and 1728-1742 cm^{-1}(ester carbonyl). UV λ_{max}^{EtOH} nm(logε): 220(4.54) and 298(3.80). From these spectral data and elemental analysis, this compound was assigned to be 1,1a,3a,4-tetrahydro-1′,2′,2,3,6,7-hexamethoxycarbonyl-1-methyl-4-(2′-thioxoethylidene)-cyclobuteno[1,2-b]azocine(VI).



IV

V

VI

Chart 2

	R^1	R^2	R^3	Reaction1) time(hr)	Yield (%)	dp (°C)	Crystal2) form
IIa	H	H	H	12	80	217-218	pale yellow needles
IIb	Me	H	H	48	40	214-215	yellow needles
IIc	H	Me	H	2	98	230-232	yellow crystals
IId	H	H	Me	12	70	239-240	pale yellow needles
V				12	30	202 (mp)	orange leaflets

1) All these reactions were carried out at room temperature.

2) All crystalline compounds were recrystallized from MeOH.

	N M R3) (OCH_3) ppm	I R(in KBr) (C=O) cm^{-1}	UV λ_{max}^{EtOH} nm(logε)
IIa	3.45 3.64	1720 1670	220(3.82), 264(3.81), 332(4.26)
IIb	3.42 3.62	1725 1660	220(3.94), 272(3.89), 334(4.33)
IIc	3.44 3.64	1710 1660	220(4.03), 272(3.87), 332(4.28)
IId	3.48 3.67	1730 1660	220(3.80), 272(3.92), 330(4.28)
V	3.52 3.56	1705 1660	260(3.99), 320(4.11), 445(4.04)

3) Measured in deutero-dimethyl sulfoxide using tetramethylsilane as internal standard.

Table

Reaction of VII with DMAD under heating at 150° for 5hr afforded yellow needles of mp 245°, in 30% yield, which had an empirical formula $C_{16}H_{16}O_4N_2S_2$=364.30 in agreement with the desulfurization product[3,5] from 1,4-cycloaddition reaction product and its mass spectrometry showed a molecular ion peak at 364(M^+). NMR spectrum(in pyridine) ppm: 2.60(3H, singlet, SCH_3), 3.32(3H, singlet, OCH_3), 3.62(3H, singlet, OCH_3). IR(in KBr): 1670, 1705 cm^{-1}(ester carbonyl). UV λ_{max}^{EtOH} nm(logε): 220(4.23), 254(4.23), 286(4.42), 300(4.29), 405(3.78). From these spectral data and elemental analysis, this compound was found to be 3,4-dimethoxycarbonyl-5-methylthio-4H-pyrrole-2-spiro-2-(3-methyl-2,3-dihydrobenzothiazole)(VIII)

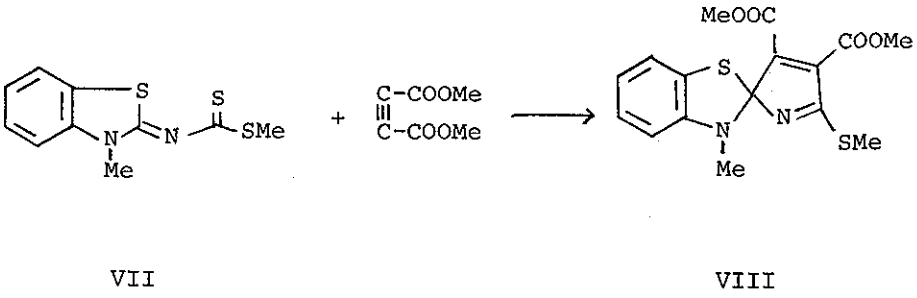


Chart 3

There have been many reports of Diels-Alder reactions containing carbon-nitrogen double bond as diene but there are very few reports about the cycloaddition reaction of a dihetero diene containing a thioketone and a carbon-nitrogen double bond(schiff base) with dipolarophiles.

REFERENCES

1) *Methyl thiocyanate(bp 130.5°/756mmHg) was not isolated* from the residue.

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7) All new compounds reported herein afforded satisfactory elemental analysis and spectral data. And the synthetic methods of these compounds will be reported in our future paper, in detail.

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