

THE REACTION OF ENAMINES WITH DIMETHYL ACETYLENEDICARBOXYLATE IN POLAR SOLVENTS

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Reactions of enamines with electron-deficient acetylenes described hitherto proceed almost exclusively via (2+2)-cycloaddition followed by isomerization of the resulting cyclobutene to a 1,3-dienamine¹. This (2+2)-cycloaddition reaction has been employed frequently in organic synthesis as it provides a method of ring enlargement of cyclic ketones by two carbon atoms^{1,2}. It is the key-step in the synthesis of several natural products such as steganacin³ and macrocyclic musks⁴. It should be emphasized that such reactions are usually performed in apolar non-protic solvents.

We have recently reported that the reaction between 3-(1-pyrrolidinyl)thiophenes and the strongly electron-deficient dimethyl acetylenedicarboxylate (DMAD) also proceeds via (2+2)-cycloaddition in apolar solvents⁵. However, when the reaction is carried out in polar solvents such as methanol and acetonitrile the compounds react via a completely different pathway to yield 6,7,7a,8-tetrahydro-5H-thieno [3,2-b]pyrrolizines⁶.

In this communication we report the first results of an investigation of the influence of the solvent on the reaction of enamines of cyclic and acyclic ketones with DMAD. We have found that the enamines (1) reacted with DMAD in apolar solvents such as toluene or diethyl ether at ambient temperature to give a 1,3-dienamine (2) formed by (2+2)-cycloaddition and subsequent isomerization.

In methanol equimolar amounts of 1 and DMAD reacted at temperature of 0-5°C in two different ways to yield mixtures of the 1,3-dienamines (2) and the pyrrolizines 3. The results are given in the table 1.

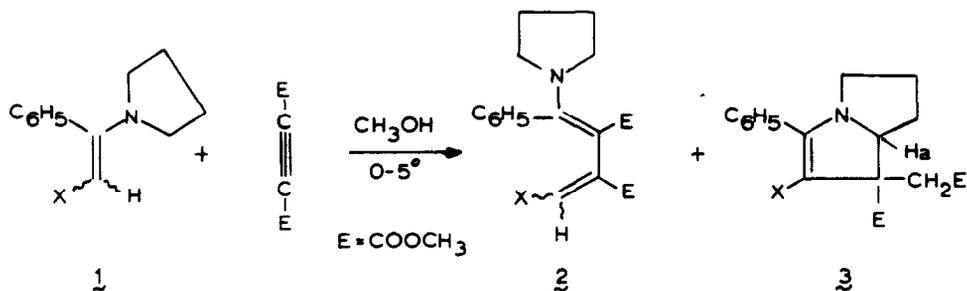
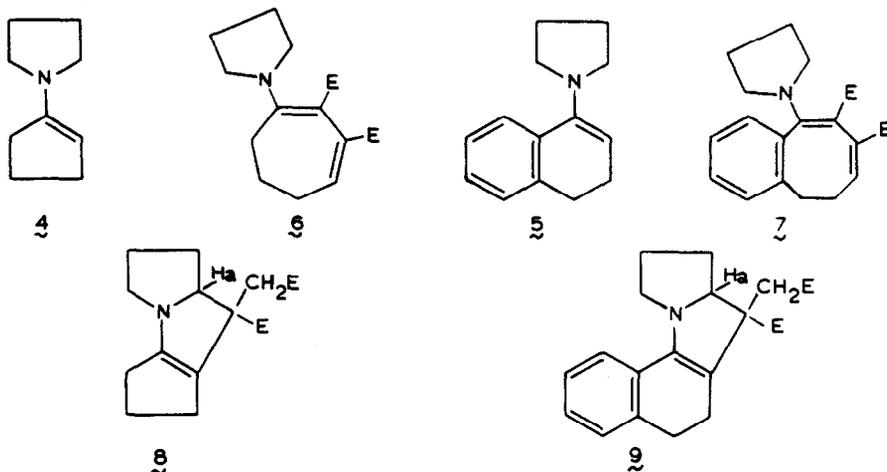


Table 1

Reaction products from enamines <u>1a-c</u> and DMAD in methanol						
	X	m.p. (°C)	yield (%)		m.p. (°C)	yield (%)
<u>2a</u>	SC ₆ H ₅	130 - 132	30	<u>3a</u>	132.5-134	52
<u>2b</u>	OC ₆ H ₅	115 - 116	20	<u>3b</u>	106 - 108	45
<u>2c</u>	C ₆ H ₅	127 - 128	35	<u>3c</u>	94 - 95	23

The pyrrolidino enamines 4 and 5 of cyclopentanone and α -tetralone also exhibited these two different modes of reaction. In toluene or diethyl ether they reacted with DMAD to give 6⁷ and 7 (m.p. 112.5-114.5°C) respectively. The same reagents in methanol afforded the corresponding pyrrolizines 8 and 9 in yields of 30 and 70% respectively.



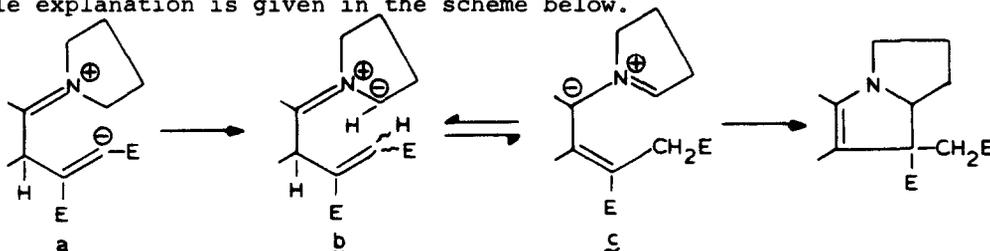
The structures of the new pyrrolizines were confirmed by elemental analysis and mass spectrometry, both revealing that 1:1 adducts had been formed. The relevant data of the ¹H-NMR and ¹³C-NMR spectra of 3, 8 and 9 were compared with those of the 5H-thieno[3,2-*b*]pyrrolizines whose structure had unequivocally been established by an X-ray structure determination⁶. Particularly the absorption of the tertiary protons Ha at 4.6-4.8 ppm (dd, *J*=6_±1 and 10_±1Hz) and of the methoxycarbonylmethyl group (AB-system, *J*=17_±1Hz) are very characteristic. The ¹³C-NMR spectra revealed the presence of two sp³-hybridized carbon atoms corresponding to the original acetylene moiety (see Table 2).

Table 2

Characteristic ¹ H- and ¹³ C-NMR absorptions of compounds <u>3</u> , <u>8</u> and <u>9</u> in CDCl ₃ .						
	δ H a	δ H(CH ₂ E)	δ C(C-Ha)	δ C(C-E)	δ C(CH ₂ E)	
<u>3a</u>	4.72	3.62 2.59	69.95	57.48	37.88	
<u>3b</u>	4.68	3.50 2.77	67.86	55.51	36.63	
<u>3c</u>	4.64	3.35 2.76	69.67	59.43	38.31	
<u>8</u>	4.65	3.21 2.53	{ 70.92 58.17	{ 53.93 49.74	{ 36.56 34.77	
<u>9</u>	4.72	3.49 2.66	70.54	65.71	37.56	

Pyrrolizine rings are present in various alkaloids and in mitomycins, which are potent anti-tumor and anti-bacterial agents⁸. Although several syntheses of pyrrolizines exist⁹ our method represents a very simple and direct route to these heterocycles.

So far, we have not cleared the mechanism of the pyrrolizine formation but a possible explanation is given in the scheme below.



We assume that initially a nucleophilic addition of the enamine to the acetylene triple bond takes place to give a dipolar intermediate (**a**). The second step comprises the intramolecular abstraction of one of the α -methylene protons of the pyrrolidinium group by the carbanionic centre, resulting in the formation of a 1,3-dipole, an azomethine ylid (**b**). By a second proton transfer **b** is converted into its tautomeric form **c** in which the 1,3-dipole is extended to a 1,5-dipole. In this intermediate a symmetry-allowed disrotatory 1,5-dipolar cyclization may occur to give the pyrrolizine. Analogies of all three proposed steps can be found in the literature. Dipolar intermediates of type **a** have been postulated before in (2+2)-cycloaddition reactions of enamines with electron-deficient acetylenes or olefins, because a concerted (2+2)-cycloaddition would violate the Woodward-Hoffmann rules¹⁰. Furthermore, various groups have proposed that benzthiazoles react with DMAD in anhydrous methanol via a 1,4-dipolar addition of a similar intermediate¹¹. The feasibility of intramolecular proton transfer in such 1,4-dipolar species has been shown in reactions of 3-carboxy-1,4-dihydropyridine and DMAD¹². Finally a number of 1,5-dipolar cyclizations to yield 5-membered heterocycles have been reported after this reaction type had been identified as such by Reimlinger¹³.

This mechanism would also account for the observed difference of reaction pathways in polar and apolar solvents. Polar solvents will favour the generation of charge-separated intermediates like **a** in which there is sufficient mobility to allow a conformation in which the hydrogen abstraction can occur. In apolar solvents the development of such dipolar species will be disfavoured and the formation of two carbon-carbon bonds may proceed in a "concerted" mode via a highly polarized transition state. This would be in conflict with the prediction by Woodward and Hoffmann that concerted $[\pi 2_s + \pi 2_s]$ cycloadditions are thermally forbidden and are consequently high-energy processes¹⁰. However recently Epiotis et al. have stated that (2+2)-cycloadditions of electron-rich and electron-deficient π -systems may well proceed in a concerted $[\pi 2_s + \pi 2_s]$ mode¹⁴.

Our results are different from those obtained with electron-deficient olefins (tetracyanoethylene) and electron-rich olefins (vinyl ethers) by Huisgen et al.¹⁵

The formation of the cyclobutane in these reactions is fast and virtually quantitative. Huisgen et al. have postulated a 1,4-dipolar intermediate for this (2+2)-cycloaddition and they have presented evidence that in methanol this intermediate is intercepted by reaction with the solvent.

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