

ON THE MECHANISM OF THE REACTION OF ENAMINES AND DIMETHYL ACETYLENEDICARBOXYLATE  
(DMAD) IN POLAR AND APOLAR SOLVENTS

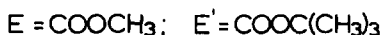
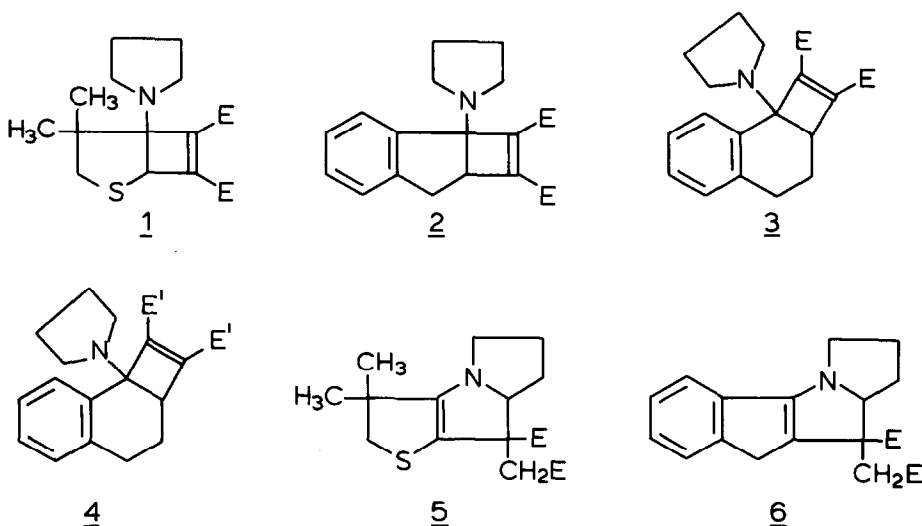
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**Abstract.** [2+2]-Cycloadducts of enamines and DMAD, formed in apolar solvents, isomerize to pyrrolizine derivatives, under mild conditions in protic polar solvents like methanol and 1-butanol.

Recent studies in our laboratories have revealed that the well known reaction of pyrrolidine enamines with electron-deficient acetylenes like dimethyl acetylenedicarboxylate (DMAD) only give cyclobutenes in solvents of low polarity. In polar solvents such as acetonitrile, nitromethane and particularly methanol we found that the same reactants give pyrrolizine derivatives<sup>1</sup>. The same difference was observed in reactions of 3-(1-pyrrolidinyl)thiophene derivatives with DMAD<sup>2</sup>. A qualitative comparison of the rates of these reactions in polar and apolar solvents learned that the rate varies with the electron density of the enamine double bond, but hardly with the polarity of the solvent in which the reaction is carried out<sup>3</sup>. This is strikingly different from the results obtained by Huisgen *et al.*<sup>5</sup> for the reaction of an electron-deficient olefin (tetracyanoethylene) with electron-rich olefins (enol ethers). They found that the rate of the [2+2]-cycloaddition reactions is strongly dependent on the polarity of the solvent ( $k_{\text{(acetonitrile)}}/k_{\text{(cyclohexane)}} 1-6 \times 10^4$ ) and they have attributed this to the stabilization of the transition state of the rate-determining step, which involves the formation of a 1,4-dipolar intermediate. Since the reaction of pyrrolidine enamines and DMAD in polar solvents to give pyrrolizines proceeds most likely *via* a 1,4-dipole, the absence of a substantial solvent effect on the rate let us to suggest that the rate-determining step in the reactions of pyrrolidine enamines and DMAD might be the formation of a tied-ion pair. That different products are obtained in polar and apolar solvents can be rationalized assuming that in polar solvents the tied-ion pair is rapidly converted into a pyrrolizine, *via* a 1,4-dipolar intermediate which is stabilized by solvation in polar solvents<sup>1</sup>. In this communication we describe the conversion of 3-(1-pyrrolidinyl)cyclobutene derivatives into pyrrolizines in polar solvents.

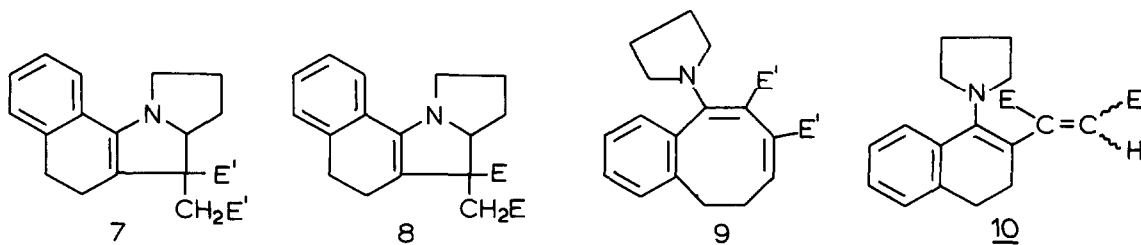
3-(1-Pyrrolidinyl)cyclobutenes generally are reactive compounds, since they

easily undergo ring opening often at temperatures below 20<sup>o</sup>. However, compounds 1-3 have been prepared by reaction of the corresponding enamines with DMAD in



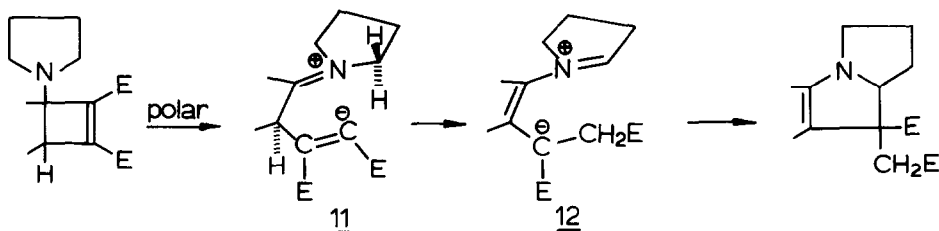
apolar solvents such as diethyl ether or benzene<sup>7-9</sup>. Under similar conditions the reaction of the pyrrolidine enamine of  $\alpha$ -tetralone and di-*tert*-butyl acetylenedicarboxylate in acetonitrile gave 4<sup>10</sup> in a yield of 83% [mp 104-105<sup>o</sup>;  $m/e$  425.257 ( $M^+$ );  $^1\text{H NMR } \delta(\text{CDCl}_3)$  3.40-3.60 (m, 1H,  $-\overset{\cdot}{\text{C}}\text{H}-$ ), 1.51 and 1.38 (s, 9H,  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C NMR } \delta(\text{CDCl}_3)$  65.5 (s,  $\text{N}-\overset{\cdot}{\text{C}}$ ), 40.8 (d,  $-\overset{\cdot}{\text{C}}\text{H}-$ )].

When the [2+2]-adduct 1<sup>7</sup> was dissolved in methanol at 20<sup>o</sup> we observed a quantitative conversion ( $\geq 95\%$ ) into the corresponding pyrrolizine 5 within two hours [oil;  $m/e$  325.132 ( $M^+$ );  $^1\text{H NMR } \delta(\text{CDCl}_3)$  4.85 (dd,  $J=6$  and 10Hz, 1H,  $\text{N}-\overset{\cdot}{\text{C}}\text{H}-$ ), 3.23 and 2.67 (AB-q,  $J=17\text{Hz}$ , 2H,  $\text{CH}_2\text{E}$ );  $^{13}\text{C NMR } \delta(\text{CDCl}_3)$  155.2 (s,  $\text{N}-\overset{\cdot}{\text{C}}=\text{C}$ ), 76.8 (d,  $\text{N}-\overset{\cdot}{\text{C}}\text{H}-$ ), 54.4 (s,  $-\overset{\cdot}{\text{C}}(\text{E})\text{CH}_2\text{E}$ )]. The same pyrrolizine was obtained by reaction of 2,3-dihydro-3,3-dimethyl-4-(1-pyrrolidinyl)thiophene and DMAD in methanol at 0<sup>o</sup> in a yield of 37%. In a similar way compound 6 was formed within two hours when 2 was dissolved in methanol, in a yield of 78% [mp 114-115<sup>o</sup>;  $m/e$  327.147 ( $M^+$ );  $^1\text{H NMR } \delta(\text{CDCl}_3)$  4.91 (dd,  $J=6$  and 9Hz, 1H,  $\text{N}-\overset{\cdot}{\text{C}}\text{H}-$ ), 3.24 and 2.78 (AB-q,  $J=17\text{Hz}$ , 2H,  $\text{CH}_2\text{E}$ );  $^{13}\text{C NMR } \delta(\text{CDCl}_3)$  157.5 (s,  $\text{N}-\overset{\cdot}{\text{C}}=\text{C}$ ), 77.9 (d,  $\text{N}-\overset{\cdot}{\text{C}}\text{H}-$ ), 54.8 (s,  $-\overset{\cdot}{\text{C}}(\text{E})\text{CH}_2\text{E}$ )]<sup>11</sup>. Isomerization of compound



4 required heating for 24 hours in methanol at reflux temperature. We obtained a 3:5 mixture of the pyrrolizine 7 [mp 117.5-118.5°;  $m/e$  425.255 ( $M^+$ );  $^1H$  NMR  $\delta$  ( $CDCl_3$ ) 4.75 (dd,  $J=6$  and 9 Hz, 1H,  $N-CH-$ ), 3.35 and 2.51 (AB-q,  $J=17.5$  Hz, 2H,  $CH_2E^A$ );  $^{13}C$  NMR  $\delta$  ( $CDCl_3$ ) 146.9 (s,  $N-C=$ ), 70.5 (d,  $N-CH-$ ), 57.0 (s,  $-C(E^A)CH_2E^B$ )]<sup>12</sup> and the benzocyclooctene 9 [mp 131.5-133.5°;  $m/e$  425.253 ( $M^+$ );  $^1H$  NMR  $\delta$  ( $CDCl_3$ ) 6.28 (m, 1H,  $=CH-$ );  $^{13}C$  NMR  $\delta$  ( $CDCl_3$ ) 157.2 (s,  $N-C=$ ), 136.8 (d,  $-CH=$ )]. Pyrrolizine 7 could also be prepared by reaction of the enamine and the acetylene in methanol at 65° for 16 hours in a yield of 41% and 9 was obtained almost quantitatively by heating 4 in toluene for 2.5 hours at 110°.

We can explain these isomerization reactions of the cyclobutene derivatives to pyrrolizine derivatives in polar solvents in terms of a conversion of the cyclobutene in a strongly solvated 1,4-dipolar intermediate 11 (Scheme)<sup>13</sup>. Subsequent transfer of two hydrogen atoms gives the 1,5-dipole 12 which cyclizes to give a pyrrolizine<sup>1</sup>.



In the literature<sup>8,9,15</sup> isomerization reactions of [2+2]-cycloadducts of enamines and acetylenic esters to the corresponding Michael adducts (structures of type 10) have been reported. Brannock *et al.*<sup>9</sup> have explained this reaction by a [2+2]-cycloreversion followed by a slow, irreversible formation of the Michael adduct. We have repeated such a reaction *viz.* the isomerization of methyl 1-(1-pyrrolidiny1)bicyclo[3.2.0]hept-6-ene-7-carboxylate in methanol and observed after 45 hours at 20° a 1:5 mixture of the starting material and the Michael adducts ( $E:Z=2:1$ ). In view of these results, the Michael adduct obtained in methanol by Eberbach and Carré<sup>4</sup> might well have been formed *via* the [2+2]-cycloadduct, since the rates of formation are the same.

During the isomerization of 3 to 8 the  $^1H$  NMR spectrum showed a transient singlet absorption at  $\delta$  5.95. When the reaction of the pyrrolidine enamine of  $\alpha$ -tetralone and DMAD in methanol at 0° was stopped after 15 minutes the  $^1H$  NMR spectrum of the reaction mixture exhibited two signals at  $\delta$  6.33 and  $\delta$  5.95 respectively but after a prolonged reaction time these signals disappeared and we only isolated the known pyrrolizine 8<sup>1</sup>. We assign the signals at  $\delta$  6.33 and  $\delta$  5.95 to the *E*- and *Z*-isomers of the Michael adducts 10 respectively, because these values are in agreement with values reported for such compounds<sup>16</sup>. Therefore it seems that in the isomerization of 3 to 8 the Michael adduct is an intermediate.

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## References and notes

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3. We have measured the rates of the reaction of dimethyl 4-(1-pyrrolidiny1)-2,3-thiophenedicarboxylate with DMAD at 100° both in 1-butanol and in toluene and we found that the reaction in the polar solvent is only about twenty times faster than that in the apolar solvent. Eberbach and Carré<sup>4</sup> also reported no difference in the rate of reaction of a dihydroazepine with DMAD in solvents of different polarity although in acetonitrile the rearranged [2+2]-cycloadduct is formed exclusively, whereas in methanol only the Michael adduct was obtained.
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10. Satisfactory elemental analyses were obtained for all new compounds (C,H,N ± 0.3%).
11. Compound 6 was formed independently in the reaction of the pyrrolidine enamine of  $\alpha$ -indanone and DMAD in methanol at 0-5°.
12. The NMR spectra of the pyrrolizines 7 and 8<sup>1</sup> are similar.
13. Huisgen *et al.*<sup>14</sup> have intercepted a 1,4-dipole when the acetone solution of the cyclobutane, derived from ethyl vinyl ether and tetracyanoethylene was kept for one week at room temperature.
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