SYNTHESIS OF PYRROLIZINES BY INTRAMOLECULAR CAPTURE OF 1,4-DIPOLAR INTERMEDIATES IN REACTIONS OF ENAMINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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Abstract—Solvent polarity and reaction temperature strongly influence the reactions of dimethyl acetylenedicarboxylate (DMAD) with 1-pyrrolidinyl enamines of acyclic and cyclic ketones. Whereas DMAD and 1-[1-phenyl-2-(phenylthio)ethenyl]pyrrolidine (3) give only a mixture of the isomeric 1,3-butadienes (5) in apolar solvents, in methanol the main product is the pyrrolizine 7, together with 5. Again in methanol, DMAD reacts at 0–5° with 8, 9 and 10 to give exclusively 1:1 adducts, the pyrrolizines 11, 12 and 13, respectively, whereas at −50° 8 and 9 give 1:2 (enamine:DMAD) adducts, the pyrrolizines 14 and 15, respectively; a single crystal X-ray analysis of 14 gave the structure of the 1:2 adducts. In the same solvent methyl propiolate and 8 give only the linear Michael adduct 17. The enamine-ketone 18 reacts with DMAD in propylene carbonate at 0–5° to give, via (2 + 2)-cycloaddition and ring expansion, 19, and the linear Michael adduct 20. The mechanism of (2 + 2)-cycloaddition and pyrrolizine formation is discussed in terms of a common tied-ion pair intermediate formed in the first, rate-determining step, followed by a second solvent-dependent step.

An obvious and simple synthesis of cyclobutene derivatives comprises the thermal (2 + 2)-cycloaddition reaction of alkenes and acetylenes.[1] In practice it has been found that only reactants in which both 2π-electron systems are strongly polarized and in which the electron densities are opposite undergo this type of cycloaddition under relative mild conditions. Although a few cyclobutenes have been synthesized by reaction of electron-rich acetylenes (ynamines) with electron-deficient olefins such as acrylonitriles[2] and nitro-alkenes,[3] most cyclobutenes have been obtained from electron-deficient acetylenes and electron-rich alkenes either in the presence[4] or in the absence[5,6] of a Lewis acid catalyst. Lewis acid-catalyzed thermal (2 + 2)-cycloaddition of this type can take place with simple unactivated olefins but the non-catalyzed reactions require electron-donating alkoxy or (dialkyl)amino substituents.

The first synthesis of 3-dialkylamino cyclobutenes by the reaction of enamines and acetylenic esters was nearly simultaneously reported by three groups.[7–9] Since the 3-dialkylaminocyclobutenes undergo facile ring opening, the reaction of acetylenic esters with enamines of cyclic ketones has frequently been applied in ring enlargement reactions.[10–14]

An investigation of the effect of solvent polarity on the reaction between 3-(1-pyrrolidinyl)thiophenes (1) and dimethyl acetylenedicarboxylate (DMAD) revealed a remarkable solvent dependency.[15] In apolar solvents such as toluene the expected formation of (2 + 2)-cycloadducts was observed, but in polar protic and aprotic solvents such as methanol and acetonitrile 6,7,7a,8 - tetrahydro - 5H - thieno - [2,3 - b]pyrrolizines (2, E = COOCH₃) were formed. Since we regard 3-(1-pyr-

rolidinyl)thiophenes (1) as heteroaromatics with "enamine" reactivity we have subsequently investigated the influence of solvent polarity on reactions of enamines
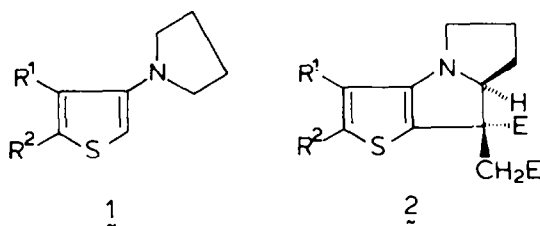
of acyclic and cyclic ketones with acetylenic esters and the results of this work are the subject of this paper.

RESULTS[16]

The C=C double bond of the enamine 1 - [1 - phenyl - 2 - (phenylthio)ethenyl]pyrrolidine (3) is very similar to the reactive C-2–C-3 bond in the 3-(1-pyrrolidinyl)thiophenes (1) that exhibit the spectacular effect of the solvent in reactions with DMAD. This enamine was prepared by acid-catalyzed reaction of 1-phenyl-2-(phenylthio)ethanone[17] with pyrrolidine in a yield of 84%. Subsequent reaction with DMAD in diethyl ether at room temperature gave a mixture of two isomeric 1:1 adducts (73%). ¹H NMR and ¹³C NMR spectroscopic data exclude a cyclobutene structure such as 4 and are in good agreement with two isomeric 1,3-butadiene structures (5, ratio 3:2). Despite careful analysis of the spectra it remains difficult to exclude the alternative 1,3-butadienes 6 that can result from Michael addition of 3 to DMAD. However comparison of our data (Experimental)

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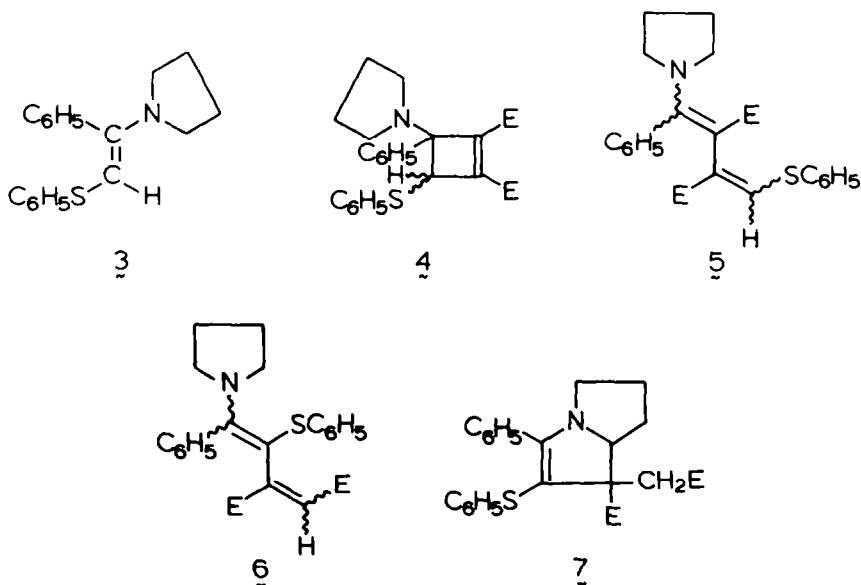
with those reported for the products obtained from a corresponding reaction of 2-dimethylamino-2-methyl-thiostyrene by Karlsson and Sandstroem[18] indicate that the 1,3-butadienes are of type 5.

The reaction of 3 with DMAD in methanol at 35° for 16 hr yielded two fractions. The first was obtained in 60% yield as a yellow crystalline compound that was shown to be 5,6,7,7a - tetrahydro - 1 - (methoxycarbonyl) - 3 - phenyl - 2 - (phenylthio) - 1*H* - pyrrolizine - 1 - acetic acid methyl ester (7). The absorptions in the ^{1}H NMR spectrum at δ 4.72 ppm (dd, $J = 6$ and 10 Hz) and at δ 3.62 and 2.59 ppm (AB-quartet, $J = 17$ Hz) are in excellent agreement with values of the corresponding H-7a and CH$_2$E signals in the ^{1}H NMR spectra of the thieno [2,3-*b*]pyrrolizines (2), the structure of which was unequivocally established by X-ray analysis.[15]

The second fraction (27%) consisted of the two isomeric 1,3-butadiene derivatives (5, ratio 3:2). This result resembles the reactions of 3-(1-pyrrolidinyl)thio-phenes (1) and DMAD in polar aprotic solvents such as nitromethane and acetonitrile in which competitive (2 + 2)-cycloaddition and pyrrolizine formation take place.[19] In these latter reactions a substantial effect of reaction temperature on the ratio of the two products was observed. Consequently, the effect of the reaction temperature on the ratio of 7 to 5 was investigated. Equimolar amounts of 3 and DMAD in methanol were reacted at three different temperatures 0°, 20° and 40° and the ratio of 7 to 5 was determined in the crude reaction mixture by glc. The results given in the table show that the formation of the pyrrolizine 7 is favoured by higher temperatures with the ratio of 7 to 5 increasing from 0.9 at 0° to 1.75 at 40°.

The results of these experiments clearly show that for reactions of enamines and DMAD two different types of reaction are possible and that the relative rates are dependent on the polarity of the solvent and the reaction temperature.[20] The reason why hitherto only one type of reaction *viz* (2 + 2)-cycloaddition had been found is a consequence of the apolar solvents generally employed. Such solvents were used because it was considered that they enhanced (2 + 2)-cycloaddition and suppressed linear addition.[20]

Since the reaction in methanol represents a novel simple synthesis of pyrrolizines and because this

Table 1. Product distribution 7 to 5 in reactions of 3 and DMAD in methanol at different temperatures[a]

Temp.[b] (°C)	Ratio 7/5
0	0.9
20	1.36
40	1.75

[a] Molar ratio 3 to DMAD (1:1); the ratio 7 to 5 was determined by GLC (5% OV-101).

[b] At lower temperatures the reaction of 3 and DMAD becomes to slow.

heterocyclic ring system constitutes a part of many natural products,[24] we have explored the scope of this reaction with particular emphasis on enamines of cyclic ketones. The latter because of our interest in the synthesis of analogues of mitomycin C, a promising anti-cancer agent in which the 1*H*-pyrrolo[1,2-*a*]indole skeleton is present.

Reactions of enamines of cyclic ketones with acetylenic esters in apolar solvents are well documented.[1,5] Huebner *et al.*[9] have reported that 1-(1-pyrrolidinyl)cyclopentene (8) reacts with ethyl propiolate in diethyl ether at 0° to give the corresponding (2 + 2)-cycloadduct and Berchtold and Uhlig[8] and Yoshii and Kimoto[25] have described similar reactions with DMAD and methyl tetrolate in toluene. Reaction of 1-(1-pyrrolidinyl)-cyclohexene (9) with DMAD in diethyl ether at 25–35° gave the corresponding bicyclo[4.2.0]oct - 7 - ene - 7,8 - dicarboxylate in 76% yield, and 1 - (3,4 - dihydro - 1 - naphthyl)pyrrolidine (10) reacted similarly.[16]

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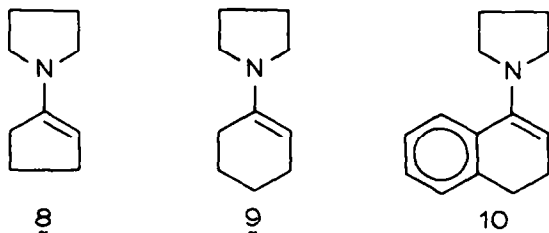
The three enamines (**8**, **9** and **10**) reacted with an equimolar amount of DMAD in methanol at temperatures of 0–5° for 16 hr to give the corresponding cyclopenta[*b*]pyrrolizine (**11**), the 1*H*-pyrrolo[1,2-*a*]indole (**12**) and the 6*H* - benzo[*g*]pyrrolo[1,2 - *a*]indole (**13**) as the only products obtained in yields of 30, 67 and 89%, respectively. The structures were proven by mass spectrometry, ¹H an ¹³C NMR spectroscopy and elemental analysis. The N–CH– and CH₂E signals of **11–13** resonate characteristically at δ 4.55 ± 0.15 ppm (dd, J = 6 and 10 Hz) and at δ 3.35 ± 0.15 ppm and δ 2.55 ± 0.12 ppm (J = 17 Hz), respectively in their ¹H NMR spectra, indicating that in each case only one diastereoisomer has been formed.† These values correspond with those found for thieno[2,3-*b*]pyrrolizines (**2**): δ (H-7a) 4.80 ± 0.10 ppm and δ (CH₂E) 3.30 ± 0.05 ppm and 3.02 ± 0.05 ppm. The large difference (~0.5 ppm) in the chemical shift of one of the CH₂E protons and almost no difference in the chemical shift of the other proton can be attributed to a deshielding effect by the thiophene ring on one of the CH₂E protons of **2**. X-Ray analysis of **2** (R¹ = H and R² = *o*–CH₃OC₆H₄) has shown that the CH₂E group and the pyrrolidine ring are *cis*. Moreover, comparison with the ¹H NMR and ¹³C NMR data of compound **14** (*vide infra*), the stereochemistry of which was assigned by X-ray analysis, point to the same stereochemistry (CH₂E and pyrrolidine ring *cis*).

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†The ¹³C NMR spectrum of **12** shows two sets of absorptions; a fact we cannot account for.

The formation of **13** was shown to be largely temperature independent but at − 10° the reaction becomes slow. The same was observed in reaction of **3** with DMAD (Table). However in the case of **8** and **9**, the reaction at − 50° in methanol also produced 2:1 adducts (DMAD: enamine). With two equivalents of DMAD these compounds become the major isolated products in 50% (**14**) and 46% (**15**) yield respectively together with 9% of **11** and 33% of **12**, respectively. The ¹H NMR spectroscopic data of **14** and **15** resemble those of the corresponding pyrrolizines **11** and **12** with absorptions at δ 4.87 ppm (dd, J = 6 and 9 Hz) in **14** and δ 4.51 ppm (dd, J = 6 and 9 Hz) in **15**. The CH₂E groups resonate at δ 3.19 and 2.71 ppm (J = 17 Hz) in **14** and δ 3.30 and 2.51 ppm (J = 17 Hz) in **15** and their ¹³C NMR spectra also indicate the presence of a pyrrolizine ring. An additional AB-quartet was evident in their ¹H NMR spectra as were two additional sp²-hybridized carbon atoms in their ¹³C NMR spectra. However, further structural assignments for the compounds could not be made with the spectral data on hand. X-Ray diffraction showed that the compound obtained from **8** was **14** (see Fig. 1) and it follows that the compound obtained from **9** was **15**. The crystal structure of **14** was solved by direct methods[26] (Experimental).

A perspective view of the molecule is given in Fig. 1 made by ORTEP.[27] The non-equivalence of the protons of the =C–CH₂E group at C-3 in **14** and **15** is due to steric hindrance by the NCH₂ group of the pyrrolizine ring (see **16**). It is interesting to note that also in this pyrrolizine the CH₂E and the pyrrolizine ring are *cis*.[15] The effect of
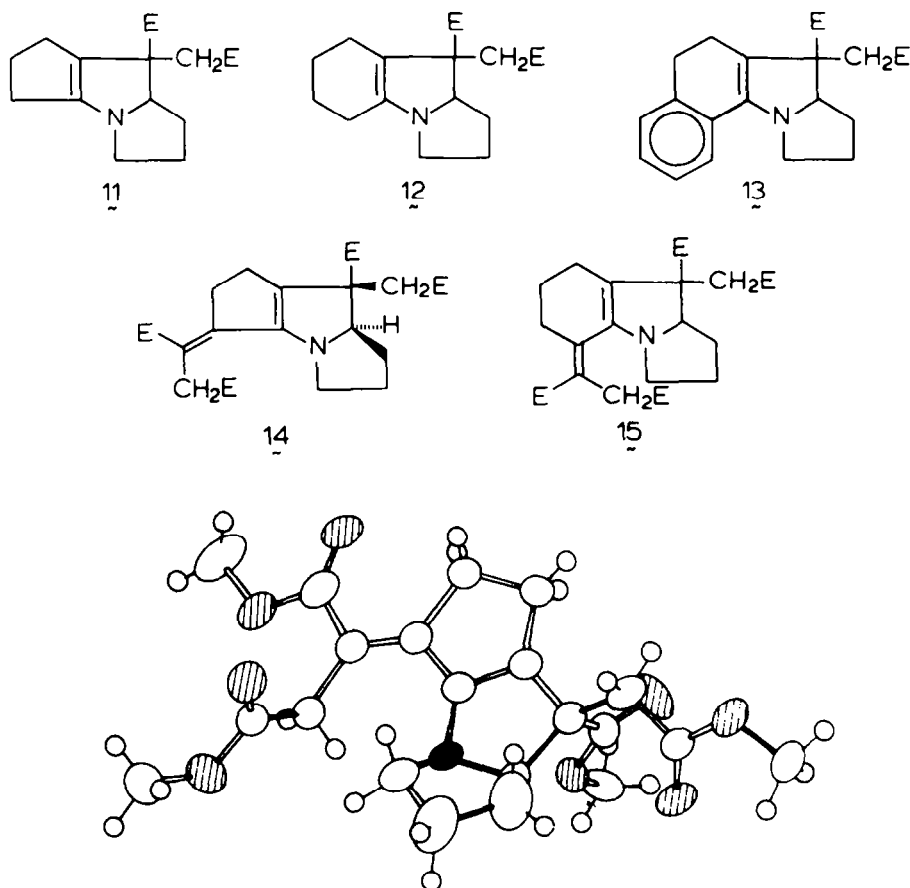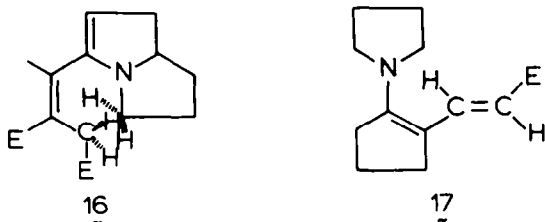

Fig. 1. Computer drawing of compound **14**.

Scheme 1. Frontier molecular orbitals of substituted alkenes and substituted acetylenes.

native orientation would not benefit from the large orbital coefficients in the "perpendicular" overlap.

If we analyze the results we have obtained and when the known reactions of DMAD and enamines are also taken into account we can distinguish three different reaction products: (2 + 2)-cycloadducts, Michael adducts and pyrrolizines. Of the latter two types can be formed, either of a 1:1 or a 1:2 molecular composition. The formation of both the Michael adducts and the pyrrolizines can be rationalized by assuming the intermediacy of a common 1,4-dipolar charge-separated species **21** which results from nucleophilic addition of the electron-rich enamine to the electron-deficient C≡C triple bond of the acetylene. Intermolecular proton transfer, most probably via the solvent, gives the Michael adduct (e.g. **17**) and, where the steric situation is favourable, intramolecular proton abstraction gives an allyl azomethinylid (**22**, for a detailed discussion see Ref. 15).

This azomethinylid undergoes tautomerization and the tautomeric 1,5-dipolar intermediate **23** then cyclizes via a symmetry-allowed disrotatory electrocyclization.[37] The spectroscopic data of **2** and **14** show that only one isomer is formed, and this means that the stereochemistry in the 1,5-dipolar intermediate **23** must be as depicted in Scheme 2.

In addition to these two proton abstraction processes by the carbanion in **21** a third possibility exists if the enamine has a proton (or two) at the β'-position. This is the case in enamines **8** and **9** but not in **1**, **3** or **10**. For reasons discussed below, at lower temperatures in the intermediates formed by the addition of **8** or **9** to DMAD a third type of prototropic shift (Scheme 3) which converts the dipolar intermediate into **24**, is a faster reaction than the formation of **22**. The dienamine **24** finally reacts via route b (Scheme 2) with a second molecule of DMAD to give the pyrrolizines **14** and **15**.
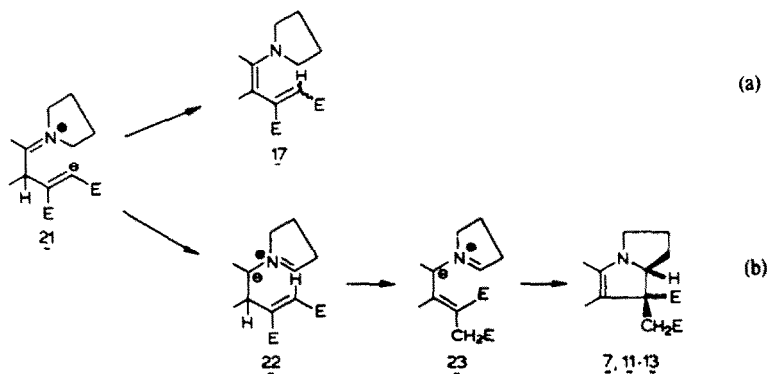
Scheme 2.
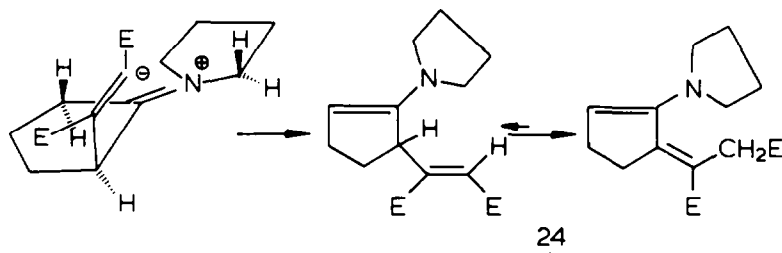
Scheme 3.

As mentioned before, 1,4-dipolar intermediates like **21** have been proposed by Huebner et al.,[9] Hafner et al.,[30] Anghelide et al.,[39] Fleury et al.[22] and others as the intermediates in the formation of the (2 + 2)-cycloadducts. However, convincing evidence for this type of mechanism has not been provided. Eberbach and Carré[23] found that the *ratio* in which the Michael adduct and the (2 + 2)-cycloadduct are formed depends on the polarity of the solvent but that the *rate* of conversion of DMAD and the enamine was almost independent of the solvent polarity. This led them to conclude that a common 1,4-dipolar intermediate is formed in the rate determining step, followed by a second step in which the products are formed which is solvent dependent. Although we did not measure the rates of the reactions of enamines and DMAD it was evident that the rate of conversion hardly differs in a strongly polar solvent like methanol and in solvents such as toluene or benzene.[15] Based on this observation and the fact that Huisgen found enormous rate differences for the reaction of tetracyanoethylene (TCNE) with enol ethers in polar and apolar solvents $(k_{(acetonitrile)}/k_{(cyclohexane)}\ 1 - 6 \times 10^4)^{33}$ it can be concluded that the formation of a charge-separated 1,4-dipolar intermediate is not the rate determining step in our case. Further, Huisgen showed that the 1,4-dipolar intermediates formed in the reaction of enol ethers and TCNE, under conditions of kinetic control, in apolar solvents could be trapped by an *inter*molecular reaction with 1,4-dipolarophiles.[33] In our reactions, if such 1,4-dipolar intermediates were involved, interception by an *intra*molecular proton abstraction process in apolar solvents should be evident in cases where this is the prefered process in polar solvents. Since we have shown[15] that the proton abstraction is an *intra*molecular process it will be virtually independent of the polarity of the solvent. Therefore we conclude that in apolar solvents the reaction of enamines and DMAD does not proceed via a charge-separated 1,4-dipolar intermediate as has always been hi '...to proposed in the literature. If the reaction is a two-step process there must be, to some degree, restricted rotation of the two poles of the 1,4-dipole, probably caused by electrostatic interaction (e.g. in a tied-ion pair as depicted in Scheme 3). Alternatively, the reaction in apolar solvents might be a near-concerted process which means that there is some degree of bonding in both σ-bonds in a highly polarized transition state. We regard the difference between both possible pathways as being philosophical because it concerns the definition of bonding.

In polar solvents the conversion of an initially formed tied-ion pair type of 1,4-dipolar intermediate into a charge-separated type will be assisted by solvation by solvent molecules. This process can become the favoured pathway over (2 + 2)-cycloaddition and this would explain how the different products are formed.

For further reaction of a charge-separated ion pair type of intermediate **21** there are various possibilities: intermolecular prototropic processes will produce Michael adducts and intramolecular proton abstraction gives either the alkylated enamine **24** or the allyl azomethinylid **22** which subsequently leads to the pyrrolizines. According to our results the mode of intramolecular proton abstraction depends on the temperature and alkylation takes place only at low temperature. This can be explained if we compare the acidity of the two methylene groups that donate the protons. In the 1,4-dipolar species we assume that most of the positive charge is located on the nitrogen atom and consequently the $-\overset{\oplus}{\underset{|}{C}}=\overset{}{\underset{|}{N}}-CH_2-$ protons will be more acidic than the protons of the $CH_2-\overset{}{\underset{|}{C}}=\overset{\oplus}{N}\diagdown$ group. On the other hand proton abstraction of the latter protons requires less rotation of the intermediate (Fig. 2). Therefore at low temperature
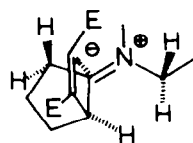
Fig. 2.

the proton abstraction takes place under kinetic control and at high temperature under conditions of thermodynamic control. When the steric situation for *intra*molecular proton abstraction is not favourable, intermolecular protontransfer will be the preferred pathway. This would explain why only pyrrolidine enamines are capable of undergoing intramolecular proton abstraction in contrast with enamines of 6-membered amines.[15]

The reaction of **18** and DMAD both in methanol and propylene carbonate illustrates a further possibility. As shown in Fig. 3 in this case an alternative proton donor, *viz* the enol group, is available and in this situation the formation of a Michael adduct is more favourable than pyrrolizine formation.
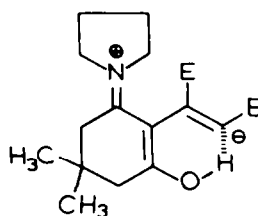
Fig. 3.

The effect of the temperature on the ratio of (2 + 2)-cycloadduct **5** and pyrrolizine **7** (Table) reflects the differences, at various temperatures, in energy barriers that separate the tied-ion pair 1,4-dipolar intermediate and the charge-separated 1,4-dipole and (2 + 2)-cycloadduct, respectively. It can be expected that the activation entropy for the (2 + 2)-cycloaddition has a larger negative value than for the formation of a "linear" 1,4-dipole in protic polar solvents[40] and this agrees with the observed increase of pyrrolizine formation with increasing reaction temperature.

EXPERIMENTAL

M.ps were determined with a Mettler FP1 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker WP80-FT and a Varian XL-100 spectrometer, respectively, in CDCl$_3$ with TMS as internal standard. Mass spectra were obtained with a Varian Mat 311A spectrometer and IR spectra with a Perkin Elmer 257 spectrophotometer. Elemental analyses were carried out by the Element Analytical section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of W. J. Buis.

Dimethyl acetylenedicarboxylate (DMAD) refers to Aldrich reagent and was distilled before use. Methyl propiolate (Fluka) was used without further purification. Compounds **8**,[42] **9**,[42] **16**[43] and **18**[44] were prepared according to known methods.

Preparation of 1 - [1 - phenyl - 2(phenylthio)ethenyl]pyrrolidine (3)
A soln of 1 - phenyl - 2 - (phenylthio)ethanone[17] (4.56 g, 0.20 mol), pyrrolidine (21.3 g, 0.30 mol) and p-toluenesulfonic acid (1 g) in 125 ml benzene was refluxed for 5 hr; 4.2 ml water was separated in a Dean-Stark trap. After evaporation of the solvent and most of the excess of pyrrolidine under reduced pressure, the light brown enamine **3** was purified by elution with MeOH. Recrystallization from petroleum-ether (60/80) afforded white crystals.
Yield 84%; m.p. 88.6–89.8°; ^{1}H NMR: δ 7.4–7.0 (m, 10 H, Ar), δ 4.79 (s, =CH), δ 3.25–3.05 (m, 4 H, N–CH$_2$) and δ 2.0–1.8 (m, 4 H, –CH$_2$–). ^{13}C NMR: δ 157.0 (s, N–C=), δ 142.4 and 137.1 (s, Ar), δ 128.3, 128.1, 127.7, 124.8 and 123.6 (d, Ar), δ 80.5 (d, N–C=C–), δ 48.9 (t, N–CH$_2$) and δ 25.1 (t, –CH$_2$–). MS: M$^+$ 281.124, calc. 281.124. (Found: C, 76.77; H, 6.81; N, 4.90 and S, 11.40. Calc. for C$_{18}$H$_{19}$NS (281.42): C, 76.82; H, 6.81; N, 4.98 and S, 11.39%).

Reactions of 1 - [1 - phenyl - 2 - (phenylthio)ethenyl]pyrrolidine (3) with DMAD in diethyl ether and methanol. Formation of 1 - phenyl - 4 - (phenylthio) - 1 - (1 - pyrrolidinyl) - 1,3 - butadiene - 2,3 - dicarboxylic acid dimethyl ester (5) and 5,6,7,7a - tetrahydro - 1 - (methoxycarbonyl) - 3 - phenyl - 2 - (phenylthio) - 1H - pyrrolizine - 1 - acetic acid methyl ester (7)
Diethyl ether as a solvent. A soln of DMAD (4.69 g, 33 mmol) in 30 ml dry diethyl ether was added to a suspension of **3** (8.43 g, 30 mmol) in 70 ml dry diethyl ether under N$_2$ at room temp. The orange-red soln was stirred overnight at room temp and the resulting ppt was collected by filtration. Purification by elution with MeOH afforded the pure **5** as a mixture of isomers (2:3) in 73% yield.
Methanol as a solvent.[45] A soln of DMAD (8.5 g, 60 mmol) in 50 ml MeOH was added to a suspension of **3** (8.43 g, 30 mmol) in 100 ml MeOH under N$_2$ at 35°. After stirring overnight of the orange-red soln at 35°, the resulting ppt was collected by filtration. Purification by elution with MeOH yielded the light yellow **7** (yield 60%). On standing overnight at – 20° a yellow solid crystallized from the filtrate. Elution with MeOH and then recrystallization from MeOH gave the yellow **5** (yield 27%) as a mixture of isomers (2:3).
Compound **5**; m.p. 127–128°; ^{1}H NMR: δ 7.5–6.9 (m, 10 H, Ar), δ 6.98 and 6.40 (s, =CH), δ 3.79, 3.65 and 3.79, 3.32 (s, OCH$_3$), δ 3.3–3.1 (m, 4 H, N–CH$_2$) and 2.0–1.7 (m, 4 H, –CH$_2$–). ^{13}C NMR: δ 169.1, 167.9, 167.7 and 166.5 (s, C=O), δ 159.6 and 157.8 (s, N–C=), δ 147.7 and 146.0 (d, =CH–), δ 125.8 and 124.4 [s,

–C(E)=], δ 99.1 and 99.0 (s, N–C=C) and δ 51.6, 51.5, 50.9 and 50.6 (OCH$_3$ and N–CH$_2$–). IR (KBr): 1688 cm^{-1} (C=O). MS: M$^+$ 423.152, Calc. 423.150. (Found: C, 67.99; H, 5.93; N, 3.28. Calc. for C$_{24}$H$_{25}$NO$_4$S (423.54): C, 68.06; H, 5.95; N, 3.31%).
Compound **7**; m.p. 134.5–135.5°; ^{1}H NMR: δ 7.7–7.55 (m, 2 H, Ar), δ 7.45–7.25 (m, 3 H, Ar), δ 7.25–7.0 (m, 5 H, Ar), δ 4.72 (dd, $J = 6 \pm 1$ and 10 ± 1 Hz, N–CH–), δ 3.65 and 3.23 (s, OCH$_3$), δ 3.62 and 2.59 (AB-q, $J = 17$ Hz, CH$_2$E). ^{13}C NMR: δ 173.6 and 172.3 (s, C=O), δ 164.6 (s, N–C=), δ 138.9 and 131.9 (s, Ar), δ 129.1, 128.4, 127.8, 125.6 and 124.7 (d, Ar), δ 96.1 (s, N–C=C), δ 70.0 (d, N–CH–), δ 57.5 [s, C(E)CH$_2$E], δ 51.7 and 51.6 (q, OCH$_3$), δ 50.2 (t, N–CH$_2$), δ 37.9 (t, CH$_2$E) and δ 27.1 and 24.6 (t, –CH$_2$–). IR (KBr): 1736 cm^{-1} (C=O). MS: M$^+$ 423.147, Calc. 423.150. (Found: C, 67.99; H, 6.02; N, 3.31; O, 15.37; S, 7.59. Calc. for C$_{24}$H$_{25}$NO$_4$S (423.54): C, 68.06; H, 5.95; N, 3.31; O, 15.11; S, 7.57%).

Reaction of 1 - (1 - pyrrolidinyl)cyclopentene (8), - cyclohexene (9) and 1 - (3,4 - dihydro - 1 - naphthyl) - pyrrolidine (10) with one equivalent of DMAD
Formation of the pyrrolizines 11–13. A soln of DMAD (7.38 g, 52 mmol) in 25 ml MeOH was added dropwise to a soln of **8–10** (50 mmol) in 75 ml MeOH under N$_2$ at 0–5°. The red-colored soln was stirred overnight at room temp. For each enamine **8–10** a different workup-procedure was necessary. Compounds **11–13** were recrystallized from MeOH.
1,2,3,5,6,7,7a,8 - Octahydro - 8 - (methoxycarbonyl) - cyclopenta[b]pyrrolizine - 8 - acetic acid methyl ester (11). After removing the MeOH under reduced pressure, repeated crystallization from MeOH at – 20° gave a solid which on washing (3 × 10 ml MeOH, 1 × 10 ml hexane) afforded **11**. Yield 30%; m.p. 134–135°; ^{1}H NMR: δ 4.65 (dd, $J = 6 \pm 1$ and 10 ± 1 Hz, N–CH–), δ 3.68 and 3.66 (s, OCH$_3$), δ 3.21 and 2.53 (AB-q, $J = 17$ Hz, CH$_2$E). ^{13}C NMR: δ 176.4, 174.1, 172.5 and 172.1 (s, C=O), δ 159.1 (s, N–C=), δ 119.1 (s, N–C=C–), δ 70.9 and 58.2 (d, N–CH–), δ 53.9 and 49.7 [s, –C(E)CH$_2$E], δ 51.8 and 51.6 (q, OCH$_3$) and δ 36.6 and 34.8 (t, CH$_2$E). IR(KBr): 1740 and 1720 cm^{-1} (C=O) and 1660 cm^{-1} (–C=C–). MS: M$^+$ 279.151, Calc. 279.147. (Found: C, 63.60; H, 7.57; N, 4.81. Calc. for C$_{15}$H$_{21}$NO$_4$ (279.34): C, 64.50; H, 7.58; N, 5.01%).
2,3,5,6,7,8,9,9a - Octahydro - 9 - (methoxycarbonyl) - 1H - pyrrolo[1,2 - a]indole - 9 - acetic acid methyl ester (12). After evaporation of the solvent under reduced pressure, distillation of the crude mixture yielded **12** (b.p. 160–165°/0.7 mm Hg) as an oil which was crystallized from hexane as white crystals. Yield 67%; m.p. 62–65°; ^{1}H NMR: δ 4.45 (dd, $J = 6 \pm 1$ and 10 ± 1 Hz, N–CH–), δ 3.74 and 3.68 (s, OCH$_3$), δ 3.32 and 2.43 (AB-q, $J = 17$ Hz, CH$_2$E). ^{13}C NMR: δ 174.2 and 172.2 (s, C=O), δ 146.9 (s, N–C=), δ 107.9 (s, N–C=C–), δ 69.6 (d, N–CH–), δ 57.4 [s, –C(E)CH$_2$E], δ 51.9 and 51.5 (q, OCH$_3$), δ 48.5 (t, N–CH$_2$–) and δ 36.9 (t, CH$_2$E). IR (KBr): 1741 and 1718 cm^{-1} (C=O) and 1670 cm^{-1} (–C=C–). MS: M$^+$ 293.162, Calc. 293.163. (Found: C, 65.41; H, 7.82; N, 4.78; O, 22.02. Calc. for C$_{16}$H$_{23}$NO$_4$ (293.37): C, 65.51; H, 7.90; N, 4.77; O, 21.82%).
5,7,7a,8,9,10 - Hexahydro - 7 - methoxycarbonyl - 6H - benzo[g]pyrrolo[1,2-a]indole - 7 - acetic acid methyl ester (13). In this case **13** crystallized spontaneously from the crude mixture. Filtration and washing (3 × 10 ml MeOH) afforded **13** as white crystals. Concentration of the filtrate afforded another crop of **13**. Yield 89%; m.p. 133–134°; ^{1}H NMR: δ 7.45–7.1 (m, 4 H, Ar), δ 4.72 (dd, $J = 6 \pm 1$ and 10 ± 1 Hz, N–CH–), δ 3.70 and 3.68 (s, OCH$_3$), δ 3.50 and 2.66 (AB-q, $J = 17$ Hz, CH$_2$E). ^{13}C NMR: δ 173.5 and 172.1 (s, C=O), δ 147.6 (s, N–C=), δ 137.1 (s), 129.4 (s), 127.4 (d), 127.1 (d) and 123.2 (d) (Ar), δ 112.9 (s, N–C=C–), δ 70.5 (d, N–CH–), δ 56.7 [s, –C(E)CH$_2$E], δ 52.3 and 51.8 (q, OCH$_3$), δ 51.8 (t, N–CH$_2$–) and δ 37.5 (t, CH$_2$E). IR (KBr): 1748 and 1720 cm^{-1} (C=O) and 1643 cm^{-1} (–C=C–). MS: M$^+$ 341.164, Calc. 341.163. (Found: C, 70.23; H, 6.86; N, 4.03. Calc. for C$_{20}$H$_{23}$NO$_4$ (341.41): C, 70.36; H, 6.79; N, 4.10%).

Reaction of 1 - (1 - pyrrolidinyl)cyclopentene (8) with two equivalents of DMAD

Formation of [1,2,3,5,6,7,7a,8 - octahydro - 8 - (methoxycarbonyl) - 8 - (methoxycarbonylmethyl) - cyclopenta[b]pyrrolizin - 3 - ylidene] - butanedioic acid dimethyl ester (14). A soln of **8** (1.37 g, 10 mmol) in 20 ml MeOH was added dropwise to a soln of DMAD (2.84 g, 20 mmol) in 30 ml MeOH under N_2 at $-50°$. The red-colored soln was stirred overnight at room temp. The MeOH was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, $CHCl_3$: EtOAc = 25:7) yielding **14** as an oil which was crystallized from diethyl ether. GC-analysis (10% SE-30) of the crude mixture showed in addition to **14** the presence of 8–10% of **11**, which could not be isolated by chromatography because of decomposition on silica. Yield 50%; m.p. 144–145°; ^1H NMR: δ 4.87 (dd, $J = 6 \pm 1$ and 9 ± 1 Hz, N–CH–), δ 3.75 and 3.72 (s, 3 H, OCH_3), δ 3.69 (s, 6 H, OCH_3), δ 4.05[46] (AB-q, $J = 17$ Hz, =C–CH_2E), δ 3.19 and 2.71 (AB-q, $J = 17$ Hz, –CH_2E). ^{13}C NMR: δ 173.1, 172.2, 171.4 and 167.9 (s, C=O), δ 157.0, 151.3 and 140.6 (s, C=C), δ 113.9 (s, N–C=C–), δ 77.2 (d, N–CH–), δ = 54.9 [s, –C(E)CH_2E], δ 52.6, 52.4, 51.7 and 51.3 (q, OCH_3), δ 51.9 (t, N–CH_2–), δ 36.9, 36.6 and 35.0 (t, 2x CH_2E and =C–C–), δ 26.1, 25.7 and 24.1 (t, other –CH_2–). IR (KBr): 1710, 1732 and 1742 (sh) cm^{-1} (C=O), 1612 cm^{-1} (–C=C–). MS: M$^+$ 421.174, Calc. 421.174. (Found: C, 60.17; H, 6.55; N, 3.26. Calc. for $C_{21}H_{27}NO_8$ (421.45): C, 59.85; H, 6.46; N, 3.32%).

Reaction of 1 - (1 - pyrrolidinyl)cyclohexene (9) with two equivalents of DMAD

Formation of [2,3,5,6,7,8,9,9a - octahydro - 9 - (methoxycarbonyl) - 9 - (methoxycarbonylmethyl) - 1 H - pyrrolo[1,2-a]indol - 5 - ylidene] - butanedioic acid dimethyl ester (15). Compound **15** was prepared as described for **14**. GC-analysis (10% SE-30) of the crude mixture showed, in addition to **15**, the presence of 33% of **12**, which could not be isolated by chromatography because of decomposition on silica. Yield 46%; m.p. 133.5–134°; ^1H NMR: δ 4.51 (dd, $J = 6 \pm 1$ and 9 ± 1 Hz, N–CH–), δ 4.48 and 3.73 (AB-q, $J = 17$ Hz, =C–CH_2E), δ 3.73 and 3.68 (s, 12 H, OCH_3), δ 3.30 and 2.51 (AB-q, $J = 17$ Hz, –CH_2E). ^{13}C NMR: δ 173.5, 172.2, 171.8 and 168.7 (s, C=O), δ 146.7 and 141.9 (s, N–C= and C=C), δ 121.6 and 119.1 (s, N–C=C and C=C), δ 69.1 (d, N–CH–), δ 57.7 [s, –C(E)CH_2E], δ 52.4, 52.2, 51.8 and 51.3 (q, OCH_3), δ 51.6 (t, N–CH_2), δ 36.4 and 36.1 (t, CH_2E), δ 30.0, 27.3, 24.9, 24.3 and 21.6 (t, other –CH_2–). IR (KBr): 1740 and 1748 (sh) cm^{-1} (C=C), 1608 and 1631 cm^{-1} (–C=C–). MS: M$^+$ 435.191, Calc. 435.189. (Found: C, 60.70; H, 6.81; N, 3.17. Calc. for $C_{22}H_{29}NO_8$ (435.48): C, 60.68; H, 6.71; N, 3.22%).

Reaction of 1 - (1 - pyrrolidinyl)cyclopentene (8) with methyl propiolate

Formation of 2 - (1 - pyrrolidinyl) - 1 - cyclopentene - 1 - propenoic acid methyl ester (17). A soln of methyl propiolate (0.67 g, 8 mmol) in 10 ml MeOH was added to a soln of **8** (0.69 g, 5 mmol) in 15 ml MeOH under N_2 at $-20°$. (The resulting solid dissolved at about 0°.) After stirring for 2 hr at room temp, the MeOH was removed under reduced pressure. The red oil was crystallized from diethyl ether at $-20°$ yielding the pure **17** as orange needles. Yield 73%; m.p. 77–77.5°; ^1H NMR: δ 7.99 (d, $J = 14$ Hz, =C–HC=), δ 5.16 (d, $J = 14$ Hz, =CHE), δ 3.70 (s, OCH_3), δ 3.7–3.5 (m, 4 H, N–CH_2–), δ 2.8–2.45 (m, 4 H, =C–CH_2) and δ 2.1–1.75 (m, 6 H, –CH_2–). ^{13}C NMR: δ 169.5 (s, C=O), δ 154.6 (s, N–C=), δ 141.5 (d, =C–HC=), δ 104.2 (s, N–C=C), δ 103.9 (d, =CHE), δ 5.11 (t, N–CH_2–), δ 50.6 (q, OCH_3), δ 36.6 and 32.3 (t, =C–CH_2) and δ 25.4 and 20.7 (t, –CH_2–). IR (KBr): 1695 cm^{-1} (C=O). MS: M$^+$ 221.141, Calc. 221.142. (Found: C, 70.46; H, 8.60; N, 6.22. Calc. for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33%).

Reaction of 5,5 - dimethyl - 3 - (1 - pyrrolidinyl) - 2 - cyclohexen - 1 - one (18) with DMAD in propylene carbonate

Formation of 5,5 - dimethyl - 7 - oxo - 3 - (1 - pyrrolidinyl) - 2,8 - cyclooctadiene - 1,2 - dicarboxylic acid dimethyl ester (19) and 4,4 - dimethyl - 6 - oxo - 2 - (1 - pyrrolidinyl) - 1 - cyclohexene - 1 - butenedioic acid dimethyl ester (20). DMAD (2.84 g, 20 mmol) was added dropwise to a soln of **18** (3.86 g, 20 mmol) in 25 ml propylene carbonate under N_2 at 0–5°. After 1 hr at 0°, the soln was stirred overnight at room temp. The solvent was removed under reduced pressure (0.01 mm Hg) and the residue was separated by column chromatography (silica gel, EtOAc) yielding **19** (10%) and **20** (37%). Compound **19** was purified by recrystallization from hexane and **20** by elution with EtOAc.

Compound **19**;[30] Yield 10%; m.p. 120.5–122.5°. ^1H NMR (Py-d_5): δ 6.87 (s, =CH), δ 3.81 and 3.73 (s, OCH_3), δ 3.6 – 3.3 (m, N–CH_2–), δ 3.14 and 2.08 (AB-q, $J = 11$ Hz, CH_2–C=), δ 2.61 and 2.34 (AB-q, $J = 14$ Hz, CH_2–C=O), δ 1.8 – 1.5 (m, 4 H, N–CH_2–CH_2), δ 1.00 (s, 6 H, CH_3). ^{13}C NMR: δ 170.4 and 164.6 (s, C=O), δ 161.3 (s, N–C=), δ 144.2 (s, N–C=C–C=), δ 130.1 (d, =CH), δ 96.0 (s, N–C=C), δ 52.6 and 50.9 (q, OCH_3), δ 52.0 (t, N–CH_2–), δ 39.0 [s, $C(CH_3)_2$], δ 29.4 and 28.5 (q, CH_3), δ 25.2 (t, N–CH_2–CH_2). IR (KBr): 1723 and 1708 cm^{-1} (C=O, ester), 1640 cm^{-1} (C=O, ketone). MS: M$^+$ 335.173, Calc. 335.173.

Compound **20**; Yield 37%; m.p. 132–134°. ^1H NMR: δ 5.35 (s, =CH), δ 3.80 and 3.73 (s, OCH_3), δ 3.36 (s, br, 4 H, N–CH_2–), δ 2.54 (s, CH_2–C=), δ 2.20 (s, CH_2–C=O), δ 1.95 (s, br, 4 H, N–CH_2–CH_2), δ 1.08 (s, 6 H, CH_3). ^{13}C NMR: δ 193.9 (s, C=O, ketone), δ 168.5 and 166.1 (s, C=O, esters), δ 161.9 (s, N–C=), δ 144.0 (s, –EC=), δ 120.0 (d, =CH), δ 106.7 (s, N–C=C), δ 51.9 and 51.5 (q, OCH_3), δ 49.8 (t, N–CH_2–), δ 30.6 [s, –C(CH_3)$_2$], δ 28.3 and 28.2 (q, CH_3). IR (KBr): 1745 and 1715 cm^{-1} (C=O, ester) and 1620 cm^{-1} (C=O, ketone). MS: M$^+$ 335.173, Calc. 335.173. (Found: C, 64.66; H, 7.57; N, 4.05. Calc. for $C_{18}H_{25}NO_5$ (335.41): C, 64.46; H, 7.51; N, 4.18%).

X-Ray structure determination of **14**. The structure of **14** was determined from 2882 significant intensities $(I > \sigma(I))$ measured on a Philips PW 1100 diffractometer, using graphite-monochromated MoKα radiation. The $\theta/2\theta$ scan mode was used in the range $3 < \theta < 25°$. The total number of independent reflections measured was 3139. The unit cell parameters found were: a = 13.269 (4), b = 22.413 (4), c = 7.293 (2) Å, β = 102.90 (3)°, Z = 4, d_c = 1.33 g cm^{-3}. The space group is P2$_1$/c. The structure was solved by direct methods[26] and refined with anisotropic temp factors for the non-H atoms. A difference Fourier Synthesis made at this stage revealed maxima at the positions of all possible H positions. In the next cycles of refinement all H atoms were included. During these refinements two H atoms got very high temp factors and shifted to physically unacceptable positions. For this reason the temp factors of these atoms were kept constant and only their position parameters were refined.† The resulting R-factor was 5.4%.

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