In Situ Generation of 1,5-Dipoles by Concerted [1,6] Hydrogen Transfer. Stereoselective Thermal Rearrangement of 1-(1-Pyrrolidinyl)-1,3-butadienes to Pyrrolizines

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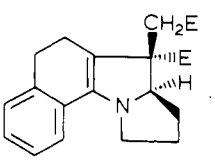
Abstract: 1-(1-Pyrrolidinyl)-1,3-butadienes (**2**, **3**, **5**, and **7**), all having an electron-withdrawing substituent at C-3, undergo a thermal rearrangement to pyrrolizine derivatives (**1**, and **10–14**). The rate of reaction generally increases with increasing polarity of the solvent; in aprotic solvents Lewis acids act as catalysts. The rate of reaction is also dependent on the configuration of the 1-(1-pyrrolidinyl)-1,3-butadiene ($k_{(E)\text{-}5}/k_{(Z)\text{-}5} = 5.2$). These thermal rearrangements take place in two steps. The first step comprises a concerted antarafacial [1,6] hydrogen shift that generates a 1,5-dipolar species, e.g., **15a**, that may undergo stereomutation to **15b**; in the second step a disrotatory electrocyclization takes place to give the corresponding pyrrolizines (**11** and **12**). The stereospecific transformation of (*E*)-**8** to **16a** and **17a** and of (*Z*)-**8** to **16b** and **17b** proves that the cyclization takes place from the helical conformation in which the antarafacial [1,6] hydrogen shift has taken place.

We have recently found that the reactions of 3-(1-pyrrolidinyl)thiophenes[1] and of enamines, e.g., 1-(1-pyrrolidinyl)cycloalkenes,[2,3] with electron-deficient acetylenes such as dimethyl acetylenedicarboxylate (DMAD) give pyrrolizines in *polar* protic solvents. This result contrasts to the well-known reactions of these compounds in *apolar* solvents that give 3-(1-pyrrolidinyl)cyclobutenes by a thermal (2 + 2) cycloaddition. Moreover we have found that the products of the reaction in apolar solvent in some cases rearrange to the corresponding pyrrolizines when they are dissolved in methanol.[4] The formation of pyrrolizines in polar solvents was accounted for by a reaction of a 1,4-dipole via two consecutive hydrogen-transfer reactions to give a 1,5-dipole that then undergoes a concerted 1,5-dipolar cyclization. By specific deuterium labeling of the 2- and 5-positions of the pyrrolidinyl moiety we have proven that one hydrogen transfer occurs intramolecularly and the other proceeds via the solvent.[1]

In this paper we report the elucidation of the mechanism of the pyrrolizine formation, which reveals a novel principle that may be useful more generally for the synthesis of five-membered rings.

Results[5] and Discussion

As reported previously the reaction of 1-(3,4-dihydro-1-naphthalenyl)pyrrolidine and DMAD in methanol at room temperature gave the corresponding pyrrolizine **1**.[3] However, when we monitored the same reaction at −7 °C by ^{1}H NMR spectroscopy we observed two transient absorptions of unequal intensities at δ 6.33 and 5.95, respectively. After prolonged reaction time these signals disappeared, and ultimately we only isolated compound **1**. The two observed signals can be assigned to the *E* and *Z* isomers of the Michael adducts **2** of DMAD and the enamine, because these values agree with those reported for similar compounds.[6] This observation suggested that one or both of the Michael adducts, containing the 1-(1-pyrrolidinyl)-1,3-butadiene moiety, might be intermediates in the formation of the pyrrolizine **1**. Therefore we decided to investigate if the conversion of 1-(1-pyrrolidinyl)-1,3-butadienes into pyrrolizines is a general reaction, because this would enlarge the scope of our pyrrolizine synthesis, since other routes to compounds like **2** are possible.



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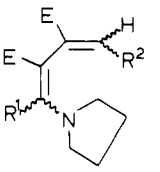
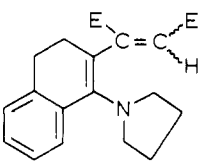


3

a, R^1 = Ph, R^2 = OPh
b, R^1 = Ph, R^2 = Ph
c, R^1 = Ph, R^2 = SPh



2

E = COOMe

Synthesis of 1-(1-Pyrrolidinyl)-1,3-butadienes. The literature[7-11] reports only a few examples of 1-(1-pyrrolidinyl)-1,3-butadienes with the general structure **3**. We had obtained compounds **3a–c** previously as the products of the thermal isomerization of the corresponding 3-(1-pyrrolidinyl)cyclobutene derivatives.[10] For this particular study we have also prepared the 1-(1-pyrrolidinyl)-1,3-butadienes **5–7** in which one of the double bonds constitutes part of a heteroaromatic system. Reaction of 2-(1-pyrrolidinyl)benzo[*b*]thiophene (**4**) with DMAD in methanol at room temperature afforded a 3:1 mixture of the *E* and *Z* isomers of dimethyl [2-(1-pyrrolidinyl)benzo[*b*]thien-3-yl]-2-butenedioate (**5**) in a total yield of 86%. We could separate the two isomers by column chromatography and assign the structures on the basis of ^{1}H NMR spectroscopy. The absorptions of the vinylic hydrogen atom at δ 7.07 and 5.93 respectively are in good agreement with the values reported for dimethyl (*E*)- and (*Z*)-2-(1,3-dimethylindole-2-yl)butenedioate at δ 7.7-7.1 and 6.12, respectively.[12] As will become clear in the second part of this paper it was essential for our work to have 1-(1-pyrrolidinyl)-1,3-butadienes of unambiguous stereochemistry. Methyl propiolate reacted with **4** more

(1) Reinhoudt, D. N.; Geevers, J.; Trompenaars, W. P.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1981**, *46*, 424.
(2) Geevers, J.; Visser, G. W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 251.
(3) Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *Tetrahedron* **1981**, *37*, 3525.
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(5) The results of this investigation have been partly published in a preliminary communication, see: Visser, G. W.; Verboom, W.; Benders, P. H.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1982**, 669.
(6) Noland, W. E.; Lee, C. K. *J. Chem. Eng. Data* **1981**, *26*, 91.
(7) A number of 1-(1-pyrrolidinyl)-1,3-butadienes has been obtained by reaction of enamines with methyl propiolate.[8,9]
(8) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 818.
(9) Tsuge, O.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 641.
(10) Reinhoudt, D. N.; Geevers, J.; Trompenaars, W. P.; *Tetrahedron Lett.* **1978**, 1351.
(11) Huebner, C. F.; Donoghue, E. *J. Org. Chem.* **1963**, *28*, 1732.
(12) Fried, F.; Taylor, J. F.; Westwood, R. *J. Chem. Soc., Chem. Commun.* **1971**, 1226.

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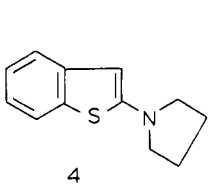
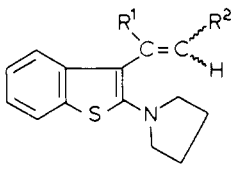
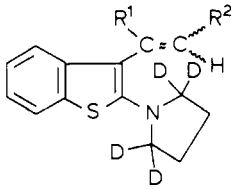


4



5, $R^1 = R^2 = E$
6, $R^1 = H; R^2 = E$ (E)
7, $R^1 = R^2 = CN$



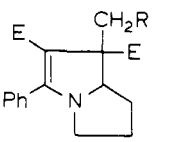
8, $R^1 = R^2 = E$
9, $R^1 = H; R^2 = E$ (E)

slowly at room temperature than DMAD. After 18 h only 40% was converted into a 3:2 mixture of methyl (*E*)-3-[2-(1-pyrrolidinyl)benzo[*b*]thien-3-yl]propenoate (**6**) and methyl (*Z*)-2-methoxypropenoate.[13] However, when the reaction was carried out in 1-butanol at 50 °C we isolated only **6** in a yield of 69%. In the ^{1}H NMR spectrum of **6**, the vinylic hydrogen atoms at δ 8.14 and 6.19 exhibit a coupling constant of 15.9 Hz; therefore we concluded that the stereochemistry of **6** was *E*. Dicyanoacetylene[14] is extremely reactive; within 2 h at −50 °C **4** was converted in dichloromethane as the solvent into a mixture of (*E*)- and (*Z*)-2-[2-(1-pyrrolidinyl)benzo[*b*]thien-3-yl]-2-butenedinitrile (**7**). In this case reaction in alcoholic solvents may give addition of the solvent to dicyanoacetylene.[15] The *E* isomer of **7** [δ 6.05 (s, =CHCN)] could be isolated in a yield of 34%. The yield of the *Z* isomer was only 3% (δ 5.70). The stereochemistry assignment is based on the fact that in the ^{1}H NMR spectra of the addition products of both alcohols and piperidine to dicyanoacetylene, the vinylic protons of the *Z* isomers always absorb at a higher field than those of the *E* isomers.[15]

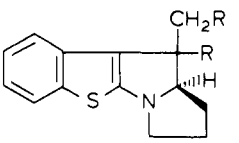
For mechanistic studies of the reactions of 1-(1-pyrrolidinyl)-1,3-butadienes, we prepared compounds (*E*)-**8**, (*Z*)-**8**, and **9** in which the 2- and the 5-positions of the pyrrolidinyl group are substituted with deuterium (vide infra). These compounds were prepared by similar procedures and with comparable yields as found for **5** and **6**.

Thermal Rearrangement of 1-(1-Pyrrolidinyl)-1,3-butadienes. According to our working hypothesis the compounds containing a 1-(1-pyrrolidinyl)-1,3-butadiene moiety should undergo a conversion into the corresponding pyrrolizines, and therefore they were reacted at higher temperatures than those used in their synthesis.

Dimethyl 3-(phenoxymethylene)-2-(phenyl-1-pyrrolidinylmethylene)butanedioate (**3a**, mixture of isomers) was heated in 1-butanol at 118 °C for 20 h. After column chromatography a pure compound was obtained in a yield of 26%. The mass spectrum and elemental analysis showed that this compound had the same molecular composition as **3a**. In the ^{1}H NMR spectrum a characteristic absorption at δ 4.7–4.5 (m) was present, whereas the ^{13}C NMR spectrum showed absorptions at δ 70.6 (d), 59.2 (s), and 67.3 (t, OCH_2). On the basis of these and other spectroscopic data, which all agree with those of pyrrolizines of which the X-ray structures have been determined,[1,3] we concluded that the reaction product was one diastereoisomer of dimethyl 5,6,7,7a-tetrahydro-1-(phenoxymethyl)-3-phenyl-1*H*-pyrrolizine-1,2-dicarboxylate (**10a**). Under the same conditions dimethyl 3-(phenylmethylene)-2-(phenyl-1-pyrrolidinylmethylene)butanedioate (**3b**, mixture of isomers) gave rise only to the formation of other stereoisomers.[16] However, when the



10a, R = OPh
b, R = Ph



11, R = E (α-E)
12, R = E (β-E)
13, R = CN (α-CN)
14, R = CN (β-CN)

reaction was performed in refluxing acetonitrile in the presence of a Lewis acid ($ZnCl_2$) for 16 h, dimethyl 5,6,7,7a-tetrahydro-3-phenyl-1-(phenylmethyl)-1*H*-pyrrolizine-1,2-dicarboxylate (**10b**) was obtained in 66% yield. The structure was proven by comparison of the ^{1}H and ^{13}C NMR spectra with those of **10a** and other pyrrolizine derivatives. The values of δ 4.7–4.4 (m, 1 H, NCH) and 71.4 (d, NCH) and 59.0 [s, *C*(E)CH_2Ph] point to only one diastereoisomer. Reaction of the 1-(1-pyrrolidinyl)-1,3-butadiene **3c** in refluxing 1-butanol or acetonitrile in the presence of zinc chloride only resulted in the formation of other stereoisomers without further reaction to pyrrolizines.

Heating of (*E*)-**5** in 1-butanol at 118 °C for 15 h resulted in a complete conversion into a mixture of two isomers in a ratio of 2:1 with a total yield of 86%. According to ^{1}H and ^{13}C NMR spectroscopy this mixture consisted of the two diastereoisomeric 2,3,10,10a-tetrahydro-10-(methoxycarbonyl)-1*H*-[1]benzothieno[3,2-*b*]pyrrolizine-10-acetates (**11** and **12**). The major diastereoisomer exhibited in the ^{1}H NMR spectrum characteristic signals that are in agreement with those of the pyrrolizines prepared in methanol,[1-4] viz., δ 5.15 (dd, J = 6 and 10 Hz, NCH), 4.02 and 2.77 (AB q, J = 17.8 Hz, CH_2E), and 3.72 and 3.71 (s, OCH_3). The same correlation could be obtained from the ^{13}C NMR spectra with absorptions at δ 78.4 (d, NCH) and 36.6 (t, CH_2E). The minor isomer showed substantially different values for the chemical shifts of these groups: δ 4.4–4.0 (m, NCH), 3.86 and 3.56 (s, OCH_3), 3.19 and 2.94 (AB q, J = 15.5 Hz, CH_2E), 81.2 (d, NCH) and 43.3 (t, CH_2E). The assignment of the stereochemistry can be based on the following considerations: Previously we have elucidated the structure of two pyrrolizines, viz., *cis*-methyl 6,7,7a,8-tetrahydro-8-(methoxycarbonyl)-2-(2-methoxyphenyl)-5*H*-thieno[2,3-*b*]pyrrolizine-8-acetate[1] and dimethyl 1,2,3,5,6,7,7a,8-octahydro-8-(methoxycarbonyl)-8-[(methoxycarbonyl)methyl]cyclopenta[*b*]pyrrolizin-3-ylidenebutanedioate,[3] by single-crystal X-ray analysis. In these compounds both the CH_2E group and the pyrrolidine ring are on the same face of the molecule. In the ^{13}C NMR spectra of these cis diastereoisomers the methylene carbon atom of the CH_2E group absorbs at δ 38.9 and ~36, respectively. In addition it is known that the methyl carbon atoms in *cis*-1,2-dimethylcyclopentane and -cyclohexane in the ^{13}C NMR spectra absorb at higher field than in the corresponding trans isomers ($\Delta\delta$ 3.6[17] and 4.5,[18] respectively). Hence, we can assign to the major isomer in which the CH_2E group absorbs at δ 36.6 structure **11** (cis) and consequently to the minor isomer in which this carbon atom is less shielded (δ 43.3) structure **12** (trans). A second argument can be found in the different absorptions of the NCH hydrogen atoms in the ^{1}H NMR spectrum. In all the *cis*-thienopyrrolizines[1] obtained so far this hydrogen atom exhibits an absorption in the range of δ 4.8 ± 0.1 (dd, J = 6 ± 1 and 10 ± 1 Hz). This relatively low-field value is due to the deshielding by the *cis*-methoxycarbonyl group. Therefore the assignment of the structures **11** and **12** is supported by the respective positions of the NCH absorptions at δ 5.15 and 4.4–4.0.

The other isomer [(*Z*)-**5**] was also reacted in 1-butanol at 118 °C. After 15 h (*Z*)-**5** was only converted 85% but the products **11** and **12** were formed in the same ratio (2:1).

Our work on the reactions of enamines with DMAD had revealed the crucial role of the solvent.[1-4] Therefore we have also

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(15) Winterfeldt, E.; Krohn, W.; Preuss, H. *Chem. Ber.* **1966**, *99*, 2572.
(16) There are four stereoisomers of **3a–c** of which probably only the *E,E* and *E,Z* isomers can cyclize (vide infra).
(17) Christle, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 3463.
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Scheme I

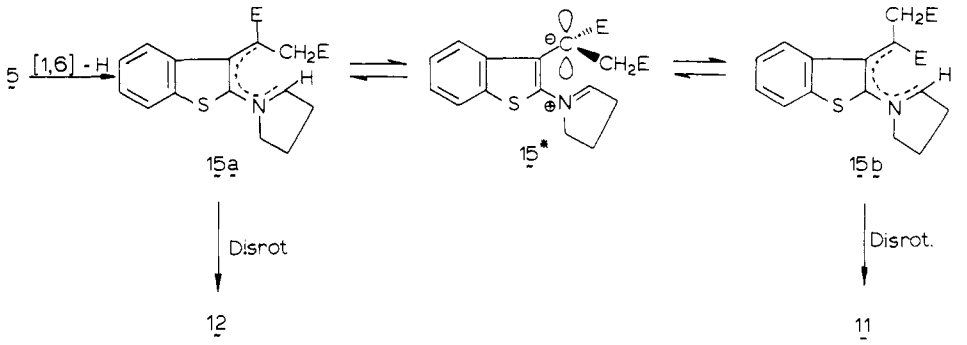

Table I. Reaction of (*E*)-5 in Solvents of Different Polarity[a]

solvent	temp, °C	time, h	ratio of 11:12[b]
toluene	110	15	0:100
toluene/acetic acid[c]	110	15	15:85
acetonitrile	81	48	33:67
acetonitrile ($ZnCl_2$)	81	16	67:33
1-butanol	118	15	67:33
acetic acid	100	15	~94:6

[a] Reactions have been carried out to complete conversion (≥98%). [b] Ratios determined by ^1H NMR spectroscopy and confirmed by isolation (total isolated yield 86% in the case of 1-butanol). [c] Molar ratio (*E*)-5 to acetic acid (5:1).

studied the effect of the solvent on the conversion of (*E*)-**5**. Reaction in toluene at 110 °C resulted in a quantitative conversion of the starting material and the *exclusive formation of the trans diastereoisomer* **12**. The results of a more detailed variation of the solvent on this reaction are summarized in Table I.

Two conclusions can be drawn from the data collected in Table I. Firstly, the ratio **11**:**12** increases with increasing polarity of the solvent, and secondly the rate of the reaction also increases with increasing polarity of the solvent. The latter has been measured for the two extremes of the polarity scale at a constant temperature of 100 °C. Both in toluene and in acetic acid the conversion of (*E*)-**5** and the formation of the pyrrolizines is first order for at least 3 half-lives with reaction rate constants of $(9.7 \pm 0.1) \times 10^{-6}$ s^{-1} (toluene) and $(3.6 \pm 0.1) \times 10^{-4}$ s^{-1} (acetic acid), which means that the rate in acetic acid is 37 times faster.

We have also found a consistent difference in rate of reaction of the *E* and *Z* isomers, with the *E* isomer as the more reactive compound. In polar solvents, e.g., acetic acid, this picture may be obscured by *Z* to *E* isomerization of **5** under reaction conditions, but in toluene we have proven that this is not the case (vide infra). The *E* isomer reacted at 110 °C in toluene with a rate constant of $(2.6 \pm 0.1) \times 10^{-5}$ s^{-1} and the *Z* isomer with a rate constant of $(5.0 \pm 0.1) \times 10^{-6}$ s^{-1}, which means that the *E* isomer reacts about 5 times faster.

Neither bifunctional catalysts[19] such as 1,2,4-triazole, 2-hydroxypyridine, and 8-hydroxyquinoline nor nonnucleophilic bases, e.g., 1,4-diazabicyclo[2.2.2]cyclooctene, affected the rate of reaction nor the product distribution.

Variation of the substituents at the vinyl group revealed that the propenoate **6** did not react at all when heated for 18 h in 1-butanol at 118 °C.

The dinitrile (*E*)-**7** did react in 1-butanol at 118 °C. After 23 h a 1:4 mixture of *cis*- and *trans*-10-cyano-2,3,10,10a-tetrahydro-1*H*-[1]benzothieno[3,2-*b*]pyrrolizine-10-acetonitrile (**13** and **14**, respectively) was obtained. During the cyclization of (*E*)-**7** in toluene at 110 °C, the *Z* isomer could be detected in the ^1H NMR spectrum. However, after 90 h only **14** was isolated. Under the same reaction conditions (*Z*)-**7** also gave **14**. The structures of **13** and **14** were assigned by comparing the ^1H NMR and ^{13}C NMR data with those of **11** and **12**.

We propose that the conversion of 1-(1-pyrrolidinyl)-1,3-butadienes into mixtures of *cis*- and *trans*-pyrrolizines can be explained by two consecutive pericyclic reactions. The first step, a [1,6] hydrogen shift, produces a conjugated 1,5-dipolar species (**15**) that subsequently undergoes a concerted disrotatory electrocyclization of the 6π-electron system and produces the pyrrolizines. The stereochemistry around the carbon–carbon bond that is formed will depend on the structure of the 1,5-dipole as is illustrated for the formation of **11** and **12** from the reaction of **5** (Scheme I). This scheme represents a novel principle for the synthesis of pyrrolizines and would reveal that *1-(1-pyrrolidinyl)-1,3-butadienes are potential 1,5-dipoles*. Moreover this principle seems of a more general applicability. In order to prove that the hydrogen-transfer reaction is indeed an *intra*molecular process we have prepared the two tetradeuterated *E* and *Z* isomers of **8**. Reaction of **8** in 1-butanol at 118 °C gave compounds with the same molecular composition ($C_{18}H_{15}D_4NO_4S$). When **5** was reacted in 1-deuterio-1-butanol no incorporation of deuterium in **11** and **12** was observed. Both experiments prove that during the reaction, even in a protic solvent, the deuterium atom is transferred *intra*molecularly. According to the principle of conservation of orbital symmetry in sigmatropic shifts of hydrogen in triene systems, the allowed low-energy pathway is the antarafacial mode which requires a helical transition state.[20] In all-carbon systems Havinga and co-workers,[21] Schmid and co-workers,[22] and Courtot and Rumin[23] have studied such thermal [1,7] hydrogen migrations and they found that such a reaction requires a cisoid configuration of the triene. The hydrogen shift in **5** and **7** is formally a [1,6] hydrogen shift, but since the lone pair of the nitrogen atom contributes 2π-electrons, the reaction is electronically equivalent with a [1,7] hydrogen shift in the all-carbon system.[24-27]

The observed difference in rate of reaction of the overall reaction between (*E*)-**5** and (*Z*)-**5** ($k_{rel} = 5.2$) is also in agreement with such an antarafacial [1,6] hydrogen shift. This difference is due to the fact that the ester function at C-3 in (*E*)-**5** and the pyrrolidinyl group are in close proximity, thus forcing the 1-(1-pyrrolidinyl)-1,3-butadiene moiety more out of the coplanar conformation as is the case in the *Z* isomer. ^1H NMR spectroscopy of both isomers showed that the signals of the NCH_2 hydrogen atoms of (*E*)-**5** and (*Z*)-**5** differ significantly. The spectrum of (*E*)-**5** shows a broad AA′BB′ signal whereas the *Z*

(19) (a) Beyerman, H. C.; Maassen v.d. Brink, W. *Proc. Chem. Soc.* **1963**, 266. (b) Li, J. P. *Aldrichimica Acta* **1972**, *5*, 5.

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(24) A similar analogy is found in the photochemical [1,16] hydrogen shift in corrins, which is formally also electronically equivalent with a [1,17] sigmatropic reaction.[25]

(25) Yamada, Y.; Miljkovic, D.; Wehrli, P.; Golding, B.; Löliger, P.; Keese, R.; Müller, K.; Eschenmoser, A. *Angew. Chem.* **1969**, *81*, 301.

(26) The [1,4] sigmatropic rearrangement of the *N*-allyl-2-oxyanilinium ylides is another example.[27]

(27) Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 653.

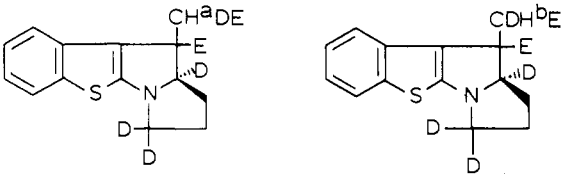
isomer exhibits a much sharper one. This is in agreement with a larger steric interaction between the ester and the pyrrolidinyl group in (*E*)-**5**. As a result of this prefixed helix type of conformation in the *E* isomer, the [1,6] hydrogen shift will be faster than in the *Z* isomer. Our results are in agreement with the different rates of [1,7] hydrogen transfer in 1,3,5-undecatrienes. Ohloff and co-workers[28] reported a faster reaction when all double bonds have the *Z* configuration.

We could show that the [1,6] hydrogen shift is the rate-determining step in the overall reaction. Firstly, we have measured a noticeable primary kinetic isotope effect for the conversion of (*E*)-**5** in toluene at 110 °C (k_H/k_D = 1.44).[29] Secondly, when **9** was heated in 1-butanol we found no reaction but also no incorporation of hydrogen in the pyrrolidinyl group of **9**. Finally, the effect of the solvent on the rate of the reaction, increasing in more polar solvents, also agrees with the formation of a 1,5-dipole being the rate-determining step. The mechanism also explains why an electron-withdrawing group at the "negative" end of the 1,5-dipole is required for this reaction (compare **5** and **6**). A simple FMO treatment of the [1,7] hydrogen shift[31] shows that such an electron-withdrawing group gives rise to a large orbital coefficient at the terminal carbon atom of the 1,5-dipole to which the hydrogen atom is transferred. For the same reason zinc chloride will enhance the rate of the reaction because coordination of a Lewis acid to an ester group is known to enhance concerted electrocyclic reactions.[32,33]

The second step in the conversion of 1-(1-pyrrolidinyl)-1,3-butadienes into pyrrolizines is the formation of a carbon–carbon bond with the introduction of two chiral centers. There are two ways to interprete this reaction. The first one is the addition of a carbanion to an iminium salt; the second involves a concerted disrotatory electrocyclization of the 6π-electron 1,5-dipole **15**. The latter type of reaction is now well documented[34,35] and should be stereoselective. Previously we have shown that reactions of enamines and DMAD in methanol[1-4] are indeed stereoselective; only the cis diastereoisomer with H and E on the same face is formed. The present results of the reaction of **5** in a range of solvents allow us to discuss the stereochemistry of the formation of **11** and **12** in more detail. According to ^{1}H NMR spectroscopy in the apolar solvent toluene, both (*E*)- and (*Z*)-**5** exclusively give **12**. This product is expected when the 1,5-dipole **15a** cyclizes in a disrotatory fashion (Scheme I). As shown in Scheme I the concerted [1,6] hydrogen shift will give **15a** with CH_2E in the endo position. With increasing polarity of the solvent the stereospecificity of the reaction is lost and mixtures of **11** and **12** are obtained (Table I). This seems to exclude that the conversion of the 1,5-dipole **15** into **11** and **12** is a concerted reaction. However, this is not the case because stereomutation of **15a** to **15b** cannot be a priori excluded.[34] Since the process must proceed via a nonconjugated dipolar species **15***, the rate of stereomutation should increase with increasing polarity of the solvent. Molecular models show that the planar ester group will preferentially occupy the endo position like in **15b**, because the CH_2E group will interfere more with the pyrrolidinium group. In the analogous 1,5-dipolar cyclization of heteropentadienyl anions, cyclization under conditions of both thermodynamic and kinetic control have been reported to give products with different stereochemistry.[36] Therefore the ratio of the products formed (**11**:**12**) will depend on the relative rates of stereomutation and on the relative rates of electrocyclization of **15a** and **15b**.

At this point we should refer to the striking analogy of these reactions of 1-(1-pyrrolidinyl)-1,3-butadienes and the 1,3-dipolar reactivity of imines of α-amino acid esters,[37] arylhydrazones,[38] and oxazolinones.[39] These compounds can undergo a prototropic shift and react as 1,3-dipoles with alkenes. These reactions are always stereospecific with respect to the alkenes, but with decreasing dipolarophilic reactivity or increasing polarity of the solvent, the stereospecificity with respect to the imine is lost. Grigg and Kemp[40] explained this in terms of *stereomutation of the in situ generated 1,3-dipole*. The two-step sequence of concerted reactions of 1-(1-pyrrolidinyl)-1,3-butadienes may be regarded as the *intra*molecular equivalent of the above reaction.

Definite proof that the pyrrolizines are indeed formed directly from a *helical conformation* by disrotatory 1,5-cyclization was obtained from experiments with tetradeuterio (*E*)- and (*Z*)-**8** in 1-butanol. When the individual isomers were converted into a mixture of corresponding pyrrolizines (**16** and **17**) the analysis of the ^{1}H NMR spectra surprizingly revealed that the CHDE group of each isomer only gave *one broad singlet*. Moreover, the *E* and *Z* isomer gave products with different complementary absorptions, *each corresponding to one part of the AB quartet* of the nondeuterated compounds **11** and **12**. The *E* isomer gave the two products **16a** and **17a** in a ratio of 7:3 with absorptions



16a (α-E) 16b (α-E)
17a (β-E) 17b (β-E)

of the CHDE groups at δ 2.77 and 3.12, respectively. The *Z* isomer also gave a mixture of two products in a ratio of 7:3. These two pyrrolizines, **16b** and **17b**, exhibited broad singlets corresponding to the CHDE group at δ 3.99 and 2.97, respectively. This means that the (*E*)- and (*Z*)-**8** isomers have reacted in a stereospecific fashion with respect to the third chiral center, the CHDE group, that is now introduced in the tetradeuterated pyrrolizines. In all four compounds *one hydrogen* atom is stereospecifically replaced by deuterium because otherwise in **16** and **17** the CHDE group would have given *two* broad singlets corresponding to the A and B part of the CH_2E group in **11** and **12**. Moreover, the (*E*)- and (*Z*)-**8** isomers would have given identical products, viz., a mixture of **16a**, **16b**, **17a**, and **17b**.

Only a mechanism in which cyclization takes place from the unique helix in which the hydrogen (or deuterium) is transferred, *without the equilibration of clockwise and anticlockwise helixes of the 1,5-dipole prior to cyclization*, can possibly explain these results (Scheme II).[41] We will illustrate this starting from the (*E*)-**8** isomer. The [1,6] hydrogen shift can take place in a clockwise helix to give a (*R*)-CHDE group or in an anticlockwise helix to give a (*S*)-CHDE group. If we assume that the 1,5-electrocyclization from a helix conformation takes place in only one of the two disrotatory modes, viz., in such a way that the endo CHDE group rotates outward, we obtain the (*RRR*)-**17a**[46] and the (*SSS*)-**17a** stereoisomers from the clockwise and the anti-

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(29) We are aware of the fact that a single-temperature kinetic isotope effect holds no significance for the geometry of the transition state, but we can conclude that hydrogen transfer is involved in the rate-determining step.[30]
(30) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401.
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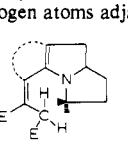
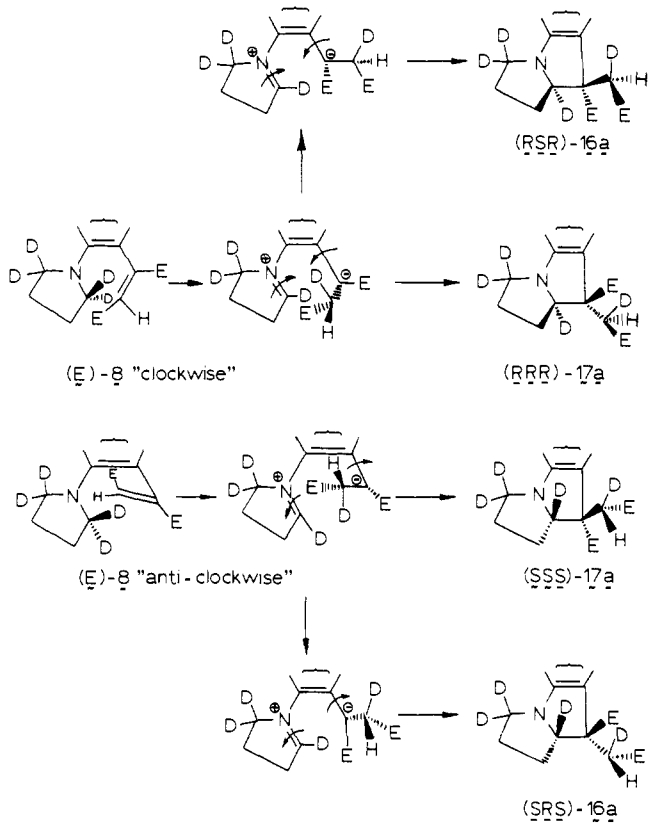
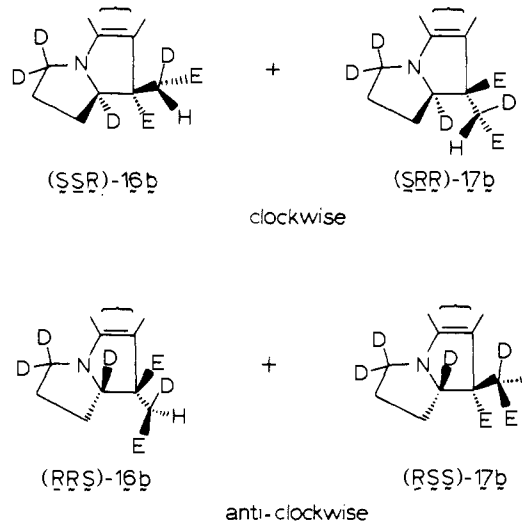
(40) Grigg, R.; Kemp, J. *Tetrahedron Lett.* **1980**, *21*, 2461.
(41) It is not likely that equilibration between the two helixes is possible in a fairly crowded 1,5-dipole. In a system with a closely related geometry we have observed hindered rotation, due to the severe interactions of the CH_2E group with the methylene hydrogen atoms adjacent to nitrogen.[3]



Scheme II



clockwise helixes, respectively. *These are enantiomers and give rise to identical spectra.* If stereomutation occurs before cyclization, again without interconversion of the clockwise and the anticlockwise helixes, we obtain (*RSR*)-**16a** and (*SRS*)-**16a**, respectively. *Again these are enantiomers.* Following the same reasoning, (*Z*)-**8** gives two pairs of enantiomers, (*SSR*)- and (*RRS*)-**16b** and (*SRR*)- and (*RSS*)-**17b**.[42]



A final conclusion of our present results must be that the mechanism proposed previously for the formation of pyrrolizines from enamines and DMAD in methanol[1-4] has to be revised with respect to the order of the two hydrogen-transfer reactions. Most likely Michael adducts are also formed in those reactions, but the subsequent [1,6] hydrogen shift followed by cyclization is obviously much faster in those compounds than is the case in **5**.

Several reactions that have recently been published may be interpreted in terms of consecutive [1,6] hydrogen transfer and 1,5-dipolar cyclization.[43-45] Therefore we feel that this principle has a much wider scope than the chemistry reported in this paper.

Experimental Section

Melting points were determined with a Leitz Wetzlar 1121 or a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with a Bruker WP-80 spectrometer, and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 spectrometer (Me_4Si as an internal standard). Mass spectra were obtained with a Varian Matt 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 supervision of W. J. Buis and G. J. Rotscheid.

Dimethyl acetylenedicarboxylate (DMAD) refers to Aldrich reagent and was distilled before use. Methyl propiolate (Fluka) was used without further purification. Medium-pressure chromatography was performed with a Lobar silica gel column obtained from Merck. All reactions were carried out under a nitrogen atmosphere.

Reaction of 1-(3,4-Dihydro-1-naphthalenyl)pyrrolidine with DMAD. This reaction was carried out following the procedure described previously[3] at a temperature of −7 °C. After 30 min and 1 h an aliquot was taken from which the methanol and DMAD were removed at reduced pressure at 0 °C. ^{1}H NMR spectroscopy revealed, beside absorptions of pyrrolizine **1**, the presence of signals at δ 6.33 (s) and 5.95 (s). After 3 h the temperature of the reaction mixture was raised to 25 °C and stirred for an additional 15 h. After removal of the solvent the ^{1}H NMR spectrum showed only the absorptions of **1**.

Dimethyl (*E*)- and (*Z*)-[2-(1-Pyrrolidinyl)benzo[*b*]thien-3-yl]-2-butenedioate (5). A solution of DMAD (0.71 g, 5 mmol) in 5 mL of methanol was added dropwise to a suspension of **4**[47] (1.02 g, 5 mmol) in 20 mL of methanol at 20 °C. The mixture was stirred for 6 h, and subsequently the solvent was removed under reduced pressure. The residue, dissolved in dichloromethane, was passed through a short column of silica gel. After removal of the solvent, medium-pressure chromatography of the residue (silica gel, dichloromethane/tetrachloromethane 4:1) afforded the pure (*E*)-**5** and (*Z*)-**5**.

(*E*)-**5**: yield 64%; mp 96.5–98.5 °C (ethanol; red); ^{1}H NMR δ 7.65–7.45 (m, 1 H, Ar H), 7.35–6.9 (m, 3 H, Ar H), 7.07 (s, 1 H, =CHE), 3.77 and 3.56 (s, 3 H, OCH_3), 3.5–3.1 (m, 4 H, NCH_2), 2.1–1.75 (m, 4 H, NCH_2CH_2); ^{13}C NMR δ 167.6 and 164.9 (s, C=O), 153.2 (s, NC=), 140.3 (s, EC=), 139.5 and 130.2 (s, Ar C), 127.7 (d, =CHE), 124.3, 121.1, 120.3 and 118.5 (d, Ar C), 101.6 (s, NC=*C*), 52.8 and 51.6 (q, OCH_3), 52.2 (t, NCH_2), 25.9 (t, NCH_2CH_2); IR (KBr) 1715 (C=O) cm^{-1}; mass spectrum, *m/e* 345.104 (M^+; calcd 345.104).

Anal. Calcd for $C_{18}H_{19}NO_4S$ (M_r 345.421): C, 62.59; H, 5.54; N, 4.06. Found: C, 62.57; H, 5.61; N, 4.09.

(*Z*)-**5**: yield 22%; mp 114–116 °C (ethanol; yellow); ^{1}H NMR δ 7.65–6.9 (m, 4 H, Ar H), 5.93 (s, 1 H, =CHE), 3.84 and 3.80 (s, 3 H, OCH_3), 3.55–3.2 (m, 4 H, NCH_2), 2.15–1.8 (m, 4 H, NCH_2CH_2); ^{13}C NMR δ 167.9 and 165.8 (s, C=O), 154.6 (s, NC=), 142.8 (s, EC=), 139.6 (s), 130.4 (s), 124.7 (d), 121.1 (d), 119.4 (d) (Ar C), 122.6 (d, =CHE), 103.4 (s, NC=*C*), 53.2 (t, NCH_2), 52.5 and 51.8 (q, OCH_3), 25.9 (t, NCH_2CH_2); IR (KBr) 1740 and 1710 (C=O), 1615 (C=C) cm^{-1}; mass spectrum, *m/e* 345.103 (M^+; calcd 345.104).

Anal. Calcd for $C_{18}H_{19}NO_4S$ (M_r 345.421): C, 62.59; H, 5.54; N, 4.06. Found: C, 62.75; H, 5.50; N, 4.02.

Methyl (*E*)-3-[2-(1-Pyrrolidinyl)benzo[*b*]thien-3-yl]propenoate (6). A mixture of methyl propiolate (0.25 g, 3 mmol) and **4** (0.51 g, 2.5 mmol) dissolved in 12.5 mL of 1-butanol was heated at 50 °C for 20 h. Removal of the solvent followed by medium-pressure chromatography of the residue (silica gel, dichloromethane) gave pure **6** as yellow crystals: yield 69%; mp 100–102 °C (ethanol); ^{1}H NMR δ 8.14 (d, J = 15.9 Hz, 1 H, =CCH=), 7.9–7.0 (m, 4 H, Ar H), 6.19 (d, J = 15.9 Hz, 1 H, =CHE),

(42) In a previous paper[1] we have described the reaction of 2-phenyl-4-(1-pyrrolidinyl-2,2,5,5-d_4) thiophene with DMAD in methanol. The ^{1}H NMR spectrum of the resulting pyrrolizine derivative showed two broad singlets. Careful inspection of the spectra showed that the intensities of the two peaks are not exactly the same: δ 3.25 (relative intensity 43%) and δ 3.00 (relative intensity 57%). This means that reaction must have taken place from both the *E* and *Z* isomer of the corresponding Michael adducts with complete stereomutation.

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(46) The configuration assignments refer to CHDE, C-10, and C-10a, respectively.

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3.80 (s, 3 H, OCH_3), 3.8–3.4 (m, 4 H, NCH_2), 2.2–1.8 (m, 4 H, NCH_2CH_2); ^{13}C NMR δ 168.9 (s, C=O), 159.1 (s, NC=), 138.7 and 131.0 (s, Ar C), 138.1 (d, CH=), 125.0, 121.6, 121.3 and 120.3 (d, Ar C), 111.3 (d, =CHE), 106.6 (s, NC=*C*), 54.1 (t, NCH_2), 51.2 (q, OCH_3), 26.0 (t, NCH_2CH_2); IR (KBr) 1692 (C=O), 1600 (C=C) cm^{-1}; mass spectrum, *m/e* 287.096 (M^+; calcd 287.098).

Anal. Calcd for $C_{16}H_{17}NO_2S$ (M_r 287.383): C, 66.87; H, 5.96; N, 4.87. Found: C, 66.76; H, 6.07; N, 4.84.

(*E*)- and (*Z*)-2-[2-(1-Pyrrolidinyl)benzo[*b*]thien-3-yl]-2-butenedinitrile (7). A solution of freshly prepared dicyanoacetylene[14] (2-butyndinitrile, 1.10 g, 14 mmol) in 10 mL of dichloromethane was added in 10 min to a solution of **4** (2.94 g, 14 mmol) in 40 mL of dichloromethane at about −55 °C. After 3 h, the mixture was allowed to reach room temperature and subsequently stirred overnight. After removal of the solvent under reduced pressure, the residue, dissolved in chloroform, was passed through a silica gel (40 g) column. The solvent was evaporated and the residue of the red fraction was treated with a small amount of diethyl ether to give a solid from which the red (*E*)-**7** was isolated by trituration with diethyl ether: yield 34%; mp 125–127 °C (methanol); ^1H NMR δ 7.7–7.0 (m, 4 H, Ar H), 6.05 (s, 1 H, =CHCN), 3.5–3.15 (m, 4 H, NCH_2), 2.3–1.9 (m, 4 H, NCH_2CH_2); ^{13}C NMR δ 157.6 (s, NC=), 137.2 and 129.9 (s, Ar C), 125.7 (s, NC=*C*), 125.6, 122.2, 121.5 and 119.0 (d, Ar C), 116.2 and 114.2 (s, C≡N), 105.6 (d, =*C*HCN), 53.2 (t, NCH_2), 26.1 (t, NCH_2CH_2); IR (KBr) 2210 (C≡N) cm^{-1}; mass spectrum, *m/e* 279.082 (M^+; calcd 279.083).

Anal. Calcd for $C_{16}H_{13}N_3S$ (M_r 279.365): C, 68.79; H, 4.69; N, 15.04. Found: C, 68.80; H, 4.74; N, 14.92.

From the mother liquors another fraction was isolated by medium-pressure chromatography (silica gel, dichloromethane) to yield the yellow (*Z*)-**7**: yield 3%; mp 135–136 °C (methanol); ^1H NMR δ 7.9–7.05 (m, 4 H, Ar H), 5.70 (s, 1 H, =CHCN), 3.6–3.2 (m, 4 H, NCH_2), 2.2–1.8 (m, 4 H, NCH_2CH_2); ^{13}C NMR δ 158.7 (s, NC=), 137.3 and 130.1 (s, Ar C), 126.1 (s, NC=*C*), 125.6, 122.6, 121.7 and 118.6 (d, Ar C), 115.5 and 115.0 (s, C≡N), 107.0 (d, =*C*HCN), 54.3 (t, NCH_2), 26.1 (t, NCH_2CH_2); IR (KBr) 2210 (C≡N) cm^{-1}; mass spectrum, *m/e* 279.082 (M^+; calcd 279.083).

Anal. Calcd for $C_{16}H_{13}N_3S$ (M_r 279.365): C, 68.79; H, 4.69; N, 15.04. Found: C, 68.73; H, 4.78; N, 14.92.

Dimethyl (*E*)- and (*Z*)-[2-(1-Pyrrolidinyl-*2,2,5,5-d*$_4$)benzo[*b*]thien-3-yl]-2-butenedioate (8). Using 2-(1-pyrrolidinyl-*2,2,5,5-d*$_4$)benzo[*b*]-thiophene (see below), the reaction with DMAD was carried out as described for **5**.

(*E*)-**8**: yield 65%; mp 71–73 °C (ethanol; red); ^1H NMR δ 7.65–7.45 (m, 1 H, Ar H), 7.3–6.9 (m, 3 H, Ar H), 7.07 (s, 1 H, =CHE), 3.77 and 3.56 (s, 3 H, OCH_3), 1.94 (s, 4 H, NCD_2CH_2).

Anal. Calcd for $C_{18}H_{15}D_4NO_4S$ (M_r 349.453): C, 61.87; H + D, 6.63; N, 4.01. Found: C, 62.06; H + D, 6.49; N, 3.93.

(*Z*)-**8**: yield 19%; mp 115–116 °C (ethanol; yellow); ^1H NMR δ 7.65–6.95 (m, 4 H, Ar H), 5.94 (s, 1 H, =CHE), 3.84 and 3.80 (s, 3 H, OCH_3), 1.98 (s, 4 H, NCD_2CH_2).

Anal. Calcd for $C_{18}H_{15}D_4NO_4S$ (M_r 349.453): C, 61.87; H + D, 6.63; N, 4.01. Found: C, 61.93; H + D, 6.56; N, 3.92.

Methyl (*E*)-3-[2-(1-Pyrrolidinyl-*2,2,5,5-d*$_4$)benzo[*b*]thien-3-yl]-propenoate (9). 2-(1-Pyrrolidinyl-*2,2,5,5-d*$_4$)benzo[*b*]thiophene was reacted with methyl propiolate, using the procedure described for the preparation of **6**, to give **9** as yellow crystals: yield 71%; mp 103–104 °C (ethanol); ^1H NMR δ 8.14 (d, *J* = 15.9 Hz, 1 H, =CCH=), 7.9–7.0 (m, 4 H, Ar H), 6.19 (d, *J* = 15.9 Hz, 1 H, =CHE), 3.80 (s, 3 H, OCH_3), 2.02 (s, 4 H, NCD_2CH_2).

Anal. Calcd for $C_{16}H_{13}D_4NO_2S$ (M_r 291.415): C, 65.95; H + D, 7.26; N, 4.81. Found: C, 66.05; H + D, 7.19; N, 4.74.

2-(1-Pyrrolidinyl-*2,2,5,5-d*$_4$)benzo[*b*]thiophene. 2-Mercaptobenzo-[*b*]thiophene[49] was reacted with pyrrolidine-*2,2,5,5-d*$_4$,[48] using the procedure reported for the preparation of **4**, to afford 2-(1-pyrrolidinyl-*2,2,5,5-d*$_4$)benzo[*b*]thiophene as a yellow solid that was only triturated with methanol and used without further purification: yield 77%; mp 87–92 °C; ^1H NMR δ 7.7–6.8 (m, 4 H, Ar H), 5.82 (s, 1 H, NC=CH), 2.00 (br s, 4 H, NCD_2CH_2); mass spectrum, *m/e* 207.102 (M^+; Calcd for $C_{12}H_9D_4NS$ 207.102).

Dimethyl 5,6,7,7a-Tetrahydro-1-(phenoxymethyl)-3-phenyl-1*H*-pyrrolizine-1,2-dicarboxylate (10a). A solution of **3a**[10] (a mixture of isomers, 1.00 g, 2.5 mmol) in 15 mL of 1-butanol was heated at 118 °C for 20 h. The solvent was removed under reduced pressure and the residue was separated by column chromatography (silica gel, chloroform/ethylacetate 95:5), yielding a solid from which pure **10a** was isolated as a white solid by trituration with diisopropyl ether: yield 26%; mp 143–144.5 °C (diisopropyl ether); ^1H NMR δ 7.4 (s, 5 H, Ar H), 7.4–7.2 (m, 2 H, Ar H), 7.1–6.8 (m, 3 H, Ar H), 4.7–4.5 (m, 1 H, NCH), 4.68 and 4.42 (AB q, *J* = 10 Hz, 2 H, CH_2OPh), 3.76 and 3.43 (s, 3 H, OCH_3), 3.2–2.7 (m, 2 H, NCH_2), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 174.8, 165.5, 164.6 and 158.4 (s, CC=O, =CC=O, NC=, and OPh C-1), 129.5, 129.2, 127.6, 120.6 and 114.4 (d, Ar C), 100.8 (s, NC=*C*), 70.6 (d, NCH), 67.3 (t, OCH_2), 59.2 [s, *C*(E)CH_2OPh], 52.3 and 50.1 (q, OCH_3), 47.7 (t, NCH_2), 26.5 and 25.3 (t, CH_2); IR (KBr) 1741 (C=O), 1657 (C=C) cm^{-1}; mass spectrum, *m/e* 407.172 (M^+; calcd 407.173).

Anal. Calcd for $C_{24}H_{25}NO_5$ (M_r 407.471): C, 70.74; H, 6.18; N, 3.44. Found: C, 70.83; H, 6.22; N, 3.42.

Dimethyl 5,6,7,7a-Tetrahydro-3-phenyl-1-(phenylmethyl)-1*H*-pyrrolizine-1,2-dicarboxylate (10b). A suspension of **3b**[10] (a mixture of isomers, 0.51 g, 1.3 mmol) and $ZnCl_2$ (0.53 g, 3.9 mmol) in 15 mL of acetonitrile was heated at 81 °C for 16 h. After removal of the acetonitrile under reduced pressure, 25 mL of water was added to the residue. The product was isolated by extraction with chloroform (3 × 25 mL). The combined extracts were washed twice with water and dried with $MgSO_4$, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, chloroform/ethylacetate 95:5) to give **10b** as an oil: yield 66%; ^1H NMR δ 7.35 (s, 5 H, Ar H), 7.4–7.1 (m, 5 H, Ar H), 4.7–4.4 (m, 1 H, NCH), 3.81 and 3.25 (AB q, *J* = 15 Hz, 2 H, CH_2Ph), 3.71 and 3.34 (s, 3 H, OCH_3), 2.0–1.6 (m, 4 H, CH_2); ^{13}C NMR δ 175.7, 165.9 and 163.2 (s, C*C*=O, =C*C*=O, and NC=), 138.6 and 132.3 (s, Ar C), 129.8, 129.2, 129.1, 127.7, 127.6 and 125.8 (d, Ar C), 103.3 (s, NC=*C*), 71.4 (d, NCH), 59.0 [s, *C*(E)CH_2Ph], 52.2 and 49.9 (q, OCH_3), 47.4 (t, NCH_2), 38.6 (t, CH_2Ph), 25.8 and 25.7 (t, CH_2); IR (KBr) 1725 (C=O) cm^{-1}; mass spectrum, *m/e* 391.175 (M^+; calcd for $C_{24}H_{25}NO_4$ 391.178).

Methyl *cis*-2,3,10,10a-Tetrahydro-10-(methoxycarbonyl)-1*H*-[1]-benzothieno[3,2-*b*]pyrrolizine-10-acetate (11). A solution of (*E*)-**5** (1.75 g, 5 mmol) in 50 mL of 1-butanol was heated at 118 °C for 15 h. After removal of the solvent under reduced pressure, the remaining solid was triturated with methanol to give a 2:1 mixture of **11** and **12**, respectively, in a total yield of 86%. Recrystallization of the mixture from methanol afforded pure **11** as white crystals (for the preparation of pure **12** see below): mp 137–138 °C; ^1H NMR δ 7.7–6.9 (m, 4 H, Ar H), 5.15 (dd, *J* = 6 and 10 Hz, 1 H, NCH), 4.02 and 2.77 (AB q, *J* = 17.8 Hz, 2 H, CH_2E), 3.72 and 3.71 (s, 3 H, OCH_3); ^{13}C NMR δ 172.9 and 171.8 (s, C=O), 159.8 (s, NC=), 138.2 and 133.6 (s, Ar C), 124.8, 123.3, 120.7 and 118.4 (d, Ar C), 114.1 (s, NC=*C*), 78.4 (d, NCH), 53.9 [s, *C*(E)-CH_2E], 52.7 and 52.0 (q, OCH_3), 52.7 (t, NCH_2), 36.6 (t, CH_2E), 27.0 and 26.1 (t, CH_2); IR (KBr) 1720 (C=O) cm^{-1}; mass spectrum, *m/e* 345.101 (M^+; calcd 345.104).

Anal. Calcd for $C_{18}H_{19}NO_4S$ (M_r 345.421): C, 62.59; H, 5.54; N, 4.06. Found: C, 62.38; H, 5.63; N, 3.99.

Methyl *trans*-2,3,10,10a-Tetrahydro-10-(methoxycarbonyl)-1*H*-[1]-benzothieno[3,2-*b*]pyrrolizine-10-acetate (12). A solution of (*E*)-**5** (0.50 g, 1.4 mmol) in 10 mL of toluene was heated at 110 °C for 15 h. The solvent was removed under reduced pressure to give an oil that solidified upon the addition of a few drops of ethanol. Purification by trituration with ethanol gave pure **12** as a white solid: yield 73%; mp 94–96 °C (ethanol); ^1H NMR δ 7.7–6.9 (m, 4 H, Ar H), 4.4–4.0 (m, 1 H, NCH), 3.80 and 3.56 (s, 3 H, OCH_3), 3.19 and 2.94 (AB q, *J* = 15.5 Hz, 2 H, CH_2E); ^{13}C NMR δ 171.9 and 171.2 (s, C=O), 159.5 (s, NC=), 138.2 and 134.3 (s, Ar C), 124.5, 122.9 and 120.9 (d, Ar C), 117.2 (s, NC=*C*), 81.2 (d, NCH), 55.5 [s, *C*(E)CH_2E], 53.1 (t, NCH_2), 52.0 and 51.7 (q, OCH_3), 43.3 (t, CH_2E), 26.9 and 25.6 (t, CH_2); IR (KBr) 1730 (C=O) cm^{-1}; mass spectrum, *m/e* 345.101 (M^+; calcd 345.104).

Anal. Calcd for $C_{18}H_{19}NO_4S$ (M_r 345.421): C, 62.59; H, 5.54; N, 4.06. Found: C, 62.57; H, 5.63; N, 3.94.

***cis*- and *trans*-10-Cyano-2,3,10,10a-tetrahydro-1*H*-[1]benzothieno-[3,2-*b*]pyrrolizine-10-acetonitrile (13 and 14). Reaction of (*E*)-7 in 1-Butanol.** A solution of (*E*)-**7** (0.50 g, 1.8 mmol) in 10 mL of 1-butanol was heated at 118 °C for 23 h. After removal of the solvent under reduced pressure a 1:4 mixture of **13** and **14**, respectively, was obtained, which could not be separated by column chromatography. Recrystallization of the mixture from ethanol or methanol afforded pure **14**. The resulting mother liquor consisted of a 1:1 mixture of **13** and **14**, respectively.

13: ^1H NMR δ 7.8–7.0 (m, 4 H, Ar H), 5.05–4.75 (m, 1 H, NCH), 3.31 and 2.98 (AB q, *J* = 17.1 Hz, 2 H, CH_2CN).

14: mp 120–122 °C (methanol); ^1H NMR δ 7.8–7.0 (m, 4 H, Ar H), 4.5–4.2 (m, 1 H, NCH), 3.28 and 2.87 (AB q, *J* = 16.8 Hz, 2 H, CH_2CN); ^{13}C NMR δ 161.0 (s, NC=), 138.4 and 131.8 (s, Ar C), 125.6, 123.6, 122.3 and 118.4 (d, Ar C), 116.2 and 112.7 (s, C≡N), 115.0 (s, NC=*C*), 80.2 (d, NCH), 44.4 [s, *C*(CN)CH_2CN], 29.5, 28.4 and 25.7

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(t, CH_2); IR (KBr) 2225 and 2220 (C≡N) cm^{-1}; mass spectrum, *m/e* 279.082 (M^+; calcd 279.083).

Anal. Calcd for $C_{16}H_{13}N_3S$ (M_r 279.365): C, 68.79; H, 4.69; N, 15.04. Found: C, 68.65; H, 4.88; N, 14.86.

Reaction of (*E*)-7 in Toluene. A solution of (*E*)-**7** (0.35 g, 1.3 mmol) in 10 mL of toluene was heated at 110 °C for 90 h. After removal of the solvent under reduced pressure, the remaining solid was triturated with methanol to yield pure **14** in a yield of 90%.

Methyl *cis*-2,3,10,10a-Tetrahydro-10-(methoxycarbonyl)-1*H*-[1]-benzothieno[3,2-*b*]pyrrolizine-*3,3,10a*-d_3-10-acetate-*d* (16a). A solution of (*E*)-**8** (0.35 g, 1 mmol) in 10 mL of 1-butanol was heated at 118 °C for 15 h. After removal of the solvent under reduced pressure a 7:3 mixture of **16a** and **17a**, respectively, was obtained from which **16a** was isolated as a white solid by trituration with methanol: yield 48%; mp 137–139 °C (methanol); ^1H NMR δ 7.7–6.9 (m, 4 H, Ar H), 3.73 and 3.72 (s, 3 H, OCH_3), 2.77 (br s, 1 H, CHDE), 2.2–1.4 (m, 4 H, CH_2); mass spectrum, *m/e* 349.129 (M^+; calcd 349.129).

Anal. Calcd for $C_{18}H_{15}D_4NO_4S$ (M_r 349.453): C, 61.87; H + D, 6.63; N, 4.01. Found: C, 61.95; H + D, 6.53; N, 3.94.

Methyl *trans*-2,3,10,10a-Tetrahydro-10-(methoxycarbonyl)-1*H*-[1]-benzothieno[3,2-*b*]pyrrolizine-*3,3,10a*-d_3-10-acetate-*d* (17a). A solution of (*E*)-**8** (0.35 g, 1 mmol) in 10 mL of toluene was heated at 110 °C for 78 h. After removal of the solvent under reduced pressure, the remaining solid was triturated with ethanol to give **17a** as a white crystalline compound: yield 72%; mp 95–97 °C (ethanol); ^1H NMR δ 7.7–6.9 (m, 4 H, Ar H), 3.80 and 3.56 (s, 3 H, OCH_3), 3.12 (br s, 1 H, CHDE), 2.1–1.5 (m, 4 H, CH_2); mass spectrum, *m/e* 349.126 (M^+; calcd 349.129).

Anal. Calcd for $C_{18}H_{15}D_4NO_4S$ (M_r 349.453): C, 61.87; H + D, 6.63; N, 4.01. Found: C, 61.88; H + D, 6.55; N, 3.94.

Thermal Rearrangement of (*Z*)-8 in 1-Butanol. A solution of (*Z*)-**8** (35 mg, 0.1 mmol) in 3 mL of 1-butanol was heated at 118 °C for 16 h. After removal of the solvent, the ^1H NMR spectrum of the crude reaction mixture revealed the presence of (*Z*)-**8**, **16b**, and **17b** in a ratio of 4:7:3, respectively.

16b: ^1H NMR δ 3.99 (br s, 1 H, CHDE).

17b: ^1H NMR δ 2.97 (br s, 1 H, CHDE).

Kinetic Studies of the Thermal Rearrangement of (*E*)-5, (*Z*)-5, and (*E*)-8. A sealed ^1H NMR tube containing a solution of (*E*)-**5**, (*Z*)-**5**, or (*E*)-**8** (30 mg) in 0.4 mL of toluene-d_8 was heated in an oil bath at 110 °C and withdrawn at regular intervals for ^1H NMR analysis. The rate of conversion was monitored by measuring the ratio of the intensity of the low-field methoxy signals of the starting material and of the corresponding benzothieno[3,2-*b*]pyrrolizine. All the reactions fitted first-order kinetics and for the rate constants *k* of the rearrangements of (*E*)-**5**, (*Z*)-**5**, and (*E*)-**8**, values of $(2.6 \pm 0.1) \times 10^{-5}$, $(5.0 \pm 0.1) \times 10^{-6}$, and $(1.8 \pm 0.1) \times 10^{-5}$ s^{-1}, respectively, were calculated. The same procedure was followed using a solution of (*E*)-**5** (30 mg) in 0.4 mL of toluene-d_8 and acetic acid-d_4, respectively, but these reactions were performed at 100 °C. For the rate constants of the rearrangement of (*E*)-**5** in toluene-d_8 and acetic acid-d_4 values of $(9.7 \pm 0.1) \times 10^{-6}$ and $(3.6 \pm 0.1) \times 10^{-4}$ s^{-1}, respectively, were calculated.

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Transition-State Geometries and Stereoselectivity of Alkylidenecarbene Addition to Olefins. An Experimental and Theoretical Investigation

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Abstract: A careful investigation of the addition of unsymmetrical alkylidenecarbenes $R(CH_3)C{=}C{:}$, where R = Et, *i*-Pr, and *t*-Bu, to two unsymmetrical olefins, isobutylene and *tert*-butylethylene, was carried out. In all cases, the *E* adduct predominated over the *Z* adduct, with increasing stereoselectivity being observed upon going from R = Et to R = *t*-Bu in the carbene. Greater stereoselectivity was also observed with *tert*-butylethylene as substrate compared with isobutylene. Detailed theoretical calculations were carried out on the reaction pathways and transition-state geometries of unsaturated carbene–olefin interactions. Model studies on the $H_2C{=}C{:} + H_2C{=}CH_2$ system were done both by MNDO and by standard ab initio methods at the STO-3G level, whereas the more substituted systems were evaluated by the MNDO method. These calculations indicate that attack of $R(CH_3)C{=}C{:}$ on $(CH_3)_2C{=}CH_2$ leads to favored "C_2-inward" transition states, which yield the observed *E* adducts. For *t*-$BuCH{=}CH_2$, the preferred pathway is through anti "C_2-semiperpendicular" transition states that collapse to "C_2-inward" conformations and then to the *E* products. This pathway also nicely explains the observed relative reactivities of alkylidenecarbenes.

Carbenes are mechanistically interesting as well as synthetically useful reactive intermediates.[1] Recently unsaturated carbenes have been extensively investigated.[2] Two of the major unanswered questions in unsaturated carbene chemistry are the exact mode of approach of the carbene toward the π-system of olefins and the precise nature of the transition state in carbene–alkene addition reactions. Whereas the potential surfaces of methylene and related carbene additions to olefins have been investigated theoretically,[3,4]

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