Solvent Effects in Thermal (2 + 2) Cycloaddition Reactions. Intramolecular Capture of 1,4-Dipolar Intermediates vs. (2 + 2) Cycloaddition in Reactions of 3-(1-Pyrrolidinyl)thiophenes with Electron-Deficient Acetylenes

David N. Reinhoudt,* Jan Geevers, and Willem P. Trompenaars

Laboratory of Organic Chemistry, Twente University of Technology, Enschede, The Netherlands

Sybolt Harkema and Gerrit J. van Hummel

Laboratory of Chemical Physics, Twente University of Technology, Enschede, The Netherlands

Received June 4, 1980

3-(1-Pyrrolidinyl)thiophenes (1) react as "pseudo" enamines with electron-deficient acetylenes, such as dimethyl acetylenedicarboxylate (DMAD), dicyanoacetylene, and methyl propiolate. In apolar solvents with DMAD (2 + 2) cycloadducts are formed. These cycloadducts (2) isomerize under the reaction conditions to yield thiepins (3), which are also thermally unstable and eliminate sulfur via the isomeric norcaradienes (4) to give the benzene derivatives (5), the isolated products. In protic polar solvents with DMAD, 6,7,7a,8-tetrahydro-5*H*-thieno[2,3-*b*]pyrrolizines (6) are formed by intramolecular abstraction of hydrogen, or deuterium in specifically labeled **1d**, in the initially formed 1,4-dipolar intermediate. In aprotic polar solvents the two modes of reaction compete and in these solvents and with excess of DMAD present, thiophenol derivatives (12) and a 4*H*-1-benzothiapyran-4-one (13) were also isolated. Compounds **12** and **13** arise from S-alkylation of the thianorcaradienes (4), the valence isomers of the thiepins (3), by DMAD. The structures of the 5*H*-thieno[2,3-*b*]pyrrolizine **6e** and the thiophenol derivative **12d** (*E* isomer) were proven by single-crystal X-ray analyses. A 1,4-dipolar intermediate formed from **1d** and DMAD in acetonitrile has been intercepted by phenyl isocyanate; the 1:1:1 reaction product was obtained in 15% yield. Dicyanoacetylene reacts with **1f** in apolar solvent (CH_2Cl_2) to give a 6,7,7a,8-tetrahydro-5*H*-thieno[2,3-*b*]pyrrolizine (17). Methyl propiolate and **1d** and DMAD and 4-(4-morpholinyl)-2-phenylthiophene afford linear Michael adducts (**19** and **20**, respectively) in methanol.

Thermal (2 + 2) cycloadditions can take place by either the concerted formation of the two σ bonds or by a nonconcerted reaction via a diradical or 1,4-dipolar intermediate. Theoretical predictions about the mechanism are not unequivocal. Woodward and Hoffmann[1] concluded that, on the basis of the concept of conservation of orbital symmetry, (2 + 2) cycloaddition of two 2π systems cannot take place in a concerted suprafacial manner and that the symmetry allowed $[{}_\pi 2_s + {}_\pi 2_a]$ process is unlikely for steric reasons, leaving the two-step process as the only possible low-energy pathway. However Epiotis claims that the concerted suprafacial mode of reaction does not necessarily comprise a high activation energy,[2-4] when the contributions of polar substituents at the two 2π systems are taken into account.

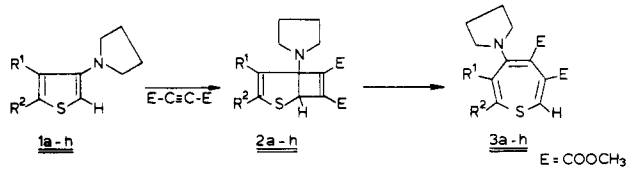
For reactions between two alkenes both the scope of (2 + 2) cycloadditions and their mechanism have been studied in great detail. The formation of cyclobutanes by the reaction of alkenes and 1,3-dienes with fluoroalkenes at high temperature clearly proceeds through a 1,4-diradical intermediate, as shown by the partial loss of configuration of the alkenes.[5-7] Thermal (2 + 2) cycloadditions proceeding via the other two-step process but through 1,4-dipolar intermediates include the reactions of tetracyanoethylene with electron-rich alkenes such as enol ethers,[8] tetraalkoxyethylenes,[9] and thio enol ethers.[10,11] Huisgen et al.[12] demonstrated the existence of 1,4-dipolar intermediates in these reactions by intermolecular trapping reactions with alcohols and 1,4-dipolarophiles such as acetonitrile and acetone. However, Epiotis[4] claims that the observed high degree of stereospecificity in the reactions with alcohols indicates the presence of some 1,4-bonding in the intermediate.

The mechanism of the corresponding (2 + 2) cycloadditions of alkenes with acetylenes is less well studied although a large number of these reactions are known which are of value in organic synthesis. Formation of cyclobutenes,[13] ring enlargement of (hetero)cyclic enamines by two carbon atoms,[14,15] and the synthesis of natural products such as steganacin[16] utilize facile thermal (2 + 2) cycloaddition reactions of enamines with electron-deficient acetylenes. Similarly nitrocyclobutanes[17] and 3-nitrocyclobutenes[18,19] are obtained as the (2 + 2) cycloadducts of nitroalkenes or nitro-substituted heteroaromatics with electron-rich alkenes and acetylenes, respectively. Further, the Lewis acid catalyzed (2 + 2) cycloadditions of alkenes[20-22] and alkylthiophenes[23] with

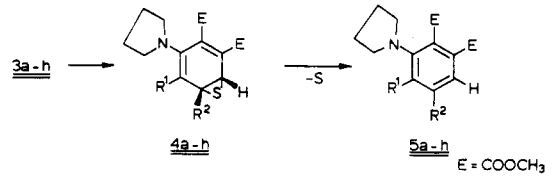
(1) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 8, 781 (1969).
(2) N. D. Epiotis, *Angew. Chem., Int. Ed. Engl.*, **13**, 751 (1974).
(3) N. D. Epiotis, R. L. Yates, D. Carlberg, and F. Bernardi, *J. Am. Chem. Soc.*, **98**, 453 (1976).
(4) N. D. Epiotis and S. Shaik, *J. Am. Chem. Soc.*, **100**, 9 (1978).
(5) P. D. Bartlett, *Q. Rev., Chem. Soc.*, **24**, 473 (1970).
(6) P. D. Bartlett, K. Hummel, S. P. Elliott, and R. A. Minns, *J. Am. Chem. Soc.*, **94**, 2898 (1972).
(7) P. D. Bartlett, G. M. Cohen, S. P. Elliott, K. Hummel, R. A. Minns, C. M. Sharts, and J. Y. Fukunaga, *J. Am. Chem. Soc.*, **94**, 2899 (1972).
(8) R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).
(9) R. W. Hoffmann, U. Bressel, J. Gehlhaus, and H. Häuser, *Chem. Ber.*, **104**, 873 (1971).
(10) H. Graf and R. Huisgen, *J. Org. Chem.*, **44**, 2594 (1979).
(11) R. Huisgen and H. Graf, *J. Org. Chem.*, **44**, 2595 (1979).
(12) R. Huisgen, *Acc. Chem. Res.*, **10**, 199 (1977).
(13) A. G. Cook, Ed., "Enamines: Synthesis, Structure and Reactions", Marcel Dekker, New York, 1969, p 211.
(14) D. N. Reinhoudt, *Adv. Heterocycl. Chem.*, **21**, 253 (1977).
(15) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963).
(16) D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1674 (1977).
(17) Reference 13, p 223.
(18) A. D. de Wit, M. L. M. Pennings, W. P. Trompenaars, D. N. Reinhoudt, S. Harkema, and O. Nevestveit, *J. Chem. Soc., Chem. Commun.*, 993 (1979).
(19) D. N. Reinhoudt and C. G. Kouwenhoven, *Recl. Trav. Chim. Pays-Bas*, **95**, 67 (1976).
(20) J. H. Lukas, F. Baardman, and A. P. Kouwenhoven, *Angew. Chem., Int. Ed. Engl.*, **15**, 369 (1976).
(21) B. B. Snider, D. J. Rodini, R. S. E. Conn, and S. Sealfon, *J. Am. Chem. Soc.*, **101**, 5283 (1979).
(22) H. Fienemann and H. M. R. Hoffmann, *J. Org. Chem.*, **44**, 2802 (1979).

0022-3263/81/1946-0424$01.00/0

Scheme I



Scheme II



electron-deficient acetylenes have been reported recently.

By analogy with polar (2 + 2) cycloadditions of alkenes with alkenes, 1,4-dipolar intermediates have been proposed for the reactions of electron-deficient acetylenes and alkenes.[21,24,25] The only indirect experimental evidence that supports the claim that these reactions proceed via 1,4-dipolar intermediates is limited to the observation that in many of the reactions linear Michael adducts are obtained, presumably by hydrogen transfer in such intermediates.[26,27] The fact that chlorocyanoacetylene reacts with 7-oxa-2,3-benzobicyclo[2.2.1]hepta-2,5-diene to yield, in addition to the (2 + 2) cycloadduct, an isomeric species which can be explained by a Wagner–Meerwein type rearrangement of a 1,4-dipolar intermediate can only be regarded as circumstantial evidence.[25]

In this paper we describe the effect of solvent polarity on reactions of "pseudo" enamines, namely, 3-(1-pyrrolidinyl)thiophenes (1),[28] with electron-deficient acetylenes. Whereas in apolar solvents (2 + 2) cycloaddition takes place, pyrrolizine derivatives (6) are formed by intramolecular capture of a discrete 1,4-dipolar or 1,4-diradical intermediate in polar solvents. To our knowledge, these results provide the first direct experimental evidence for an intermediate in reactions of "alkenes" with acetylenes.

Results[32] and Discussion

Our approach for the synthesis of monocyclic thiepins comprises two steps, namely, (2 + 2) cycloaddition of a thiophene derivative (1) and an acetylene, followed by thermal isomerization of the resulting 2-thiabicyclo-[3.2.0]hepta-3,6-diene (2)[35] (Scheme I).

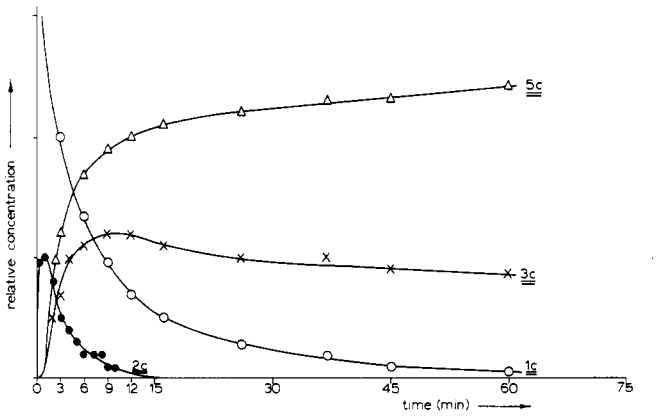


Figure 1. Relative concentrations of **1c**, **2c**, **3c**, and **5c** as a function of time in the reaction of **1c** with an equimolar amount of DMAD in tetrachloromethane at 25 °C.

In an earlier paper[30] we described reactions of a number of 3-(1-pyrrolidinyl)thiophenes (1, R^1 = H, CH_3; R^2 = H) with dimethyl acetylenedicarboxylate in chloroform at temperatures of −30 and +25 °C. At 25 °C benzene derivatives were obtained and at −30 °C we could observe by low-temperature ^{1}H NMR both the (2 + 2) cycloadducts (2) and the thiepins (3). The latter eliminate sulfur slowly at −30 °C and rapidly when we tried to isolate the thiepins at 25 °C. This elimination presumably proceeds via the not-observed thianorcaradiene (4) (Scheme II).[36]

Hoffman and Schlessinger[38] have reported that bulky substituents at both the 2 and 7 positions stabilize the thiepin moiety in annulated thiepins by lowering the rate of the symmetry-allowed disrotatory electrocyclization of 3 to 4. Therefore we decided to investigate the effect of C-7 substituents of increasing size on the stability of the thiepins (3). The necessary 5-substituted 3-(1-pyrrolidinyl)thiophenes were prepared via the tetrahydrothiophen-3-ones by methods described previously.[39] The reactivity of **1a–d** with dimethyl acetylenedicarboxylate (DMAD) at room temperature in apolar solvents such as diethyl ether and tetrachloromethane was shown to be similar to that of the parent 3-(1-pyrrolidinyl)thiophene.[30] Complete conversion at 25 °C of starting materials (**1a–d**) took less than 1 h and the corresponding benzene derivatives (**5a–d**) were isolated in yields of 35–77%. However, the reaction of **1c** with DMAD in tetrachloromethane at room temperature was sufficiently retarded to allow permanent monitoring of the characteristic singlet absorptions of **1c** (δ_{H-2} 5.51), **2c** (δ_{H-1} 4.28), **3c** (δ_{H-2} 6.34), and **5c** (δ_{H-arom} 6.86 and 7.12) in the ^{1}H NMR spectrum of the reaction mixture (Figure 1). The appearance and disappearance of these signals showed that the bimolecular (2 + 2) cycloaddition reaction is fast ($c_0 \simeq 0.1$ M), that the isomerization, being a monomolecular process, becomes faster after 2 min, that the rates of isomerization and desulfurization are of the same order

(23) D. N. Reinhoudt, H. C. Volger, C. G. Kouwenhoven, H. Wynberg, and R. Helder, *Tetrahedron Lett.*, 5269 (1972).
(24) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *J. Org. Chem.*, **28**, 3134 (1963).
(25) T. Sasaki, K. Kanematsu, and M. Uchide, *Tetrahedron Lett.*, 4855 (1971).
(26) H. Plieninger and D. Wild, *Chem. Ber.*, **99**, 3070 (1966).
(27) R. M. Acheson, J. N. Brisdon, and T. S. Cameron, *J. Chem. Soc., Perkin Trans. 1*, 968 (1972).
(28) The formal C-2, C-3 double bond in 3-(1-pyrrolidinyl)thiophenes exhibits the reactivity of enamines of cyclic ketones; see ref 29–31.
(29) D. N. Reinhoudt and C. G. Kouwenhoven, *Recl. Trav. Chim. Pays-Bas*, **93**, 321 (1974).
(30) D. N. Reinhoudt and C. G. Kouwenhoven, *Tetrahedron*, **30**, 2093 (1974).
(31) H. C. Mutreja and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas*, in press.
(32) Some of these results have been described in two preliminary communications; see ref 33 and 34.
(33) D. N. Reinhoudt, W. P. Trompenaars, and J. Geevers, *Tetrahedron Lett.*, 4777 (1976).
(34) D. N. Reinhoudt, G. Okay, W. P. Trompenaars, S. Harkema, D. M. W. van den Ham, and G. J. van Hummel, *Tetrahedron Lett.*, 1529 (1979).
(35) For a fast isomerization of **2**, a cis-fused cyclobutene, the presence of an electron-donating substituent, e.g., a 1-pyrrolidinyl group, at the bridgehead carbon atom is essential; cf. ref 23 and 30.
(36) Vogel et al.[37] have captured a thianorcaradiene derivative by a Diels–Alder reaction with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione during the thermal decomposition of *syn*-benzene bisepisulfide.
(37) E. Vogel, E. Schmidbauer, and H.-J. Altenbach, *Angew. Chem., Int. Ed. Engl.*, **13**, 736 (1974).
(38) J. M. Hoffman and R. H. Schlessinger, *J. Am. Chem. Soc.*, **92**, 5263 (1970).
(39) D. N. Reinhoudt, W. P. Trompenaars, and J. Geevers, *Synthesis*, 368 (1978).

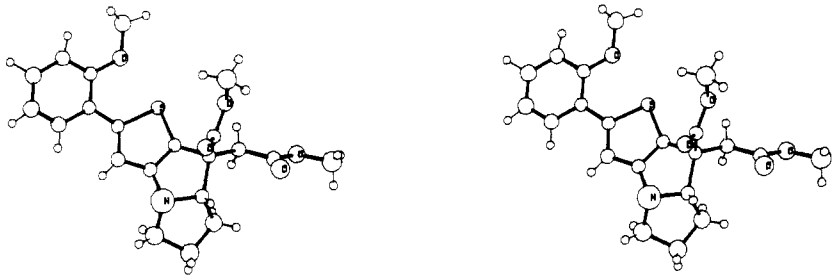
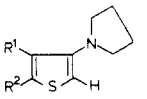


Figure 2. Stereoscopic view of the molecule **6e**.

of magnitude, and that the maximum concentration of thiepin (**3c**) in the reaction mixture is reached after 10 min of reaction time. The reactions of the other thiophenes (**1a,b,d**) with DMAD could only be monitored incompletely at lower temperatures. These experiments indicate that the presence of a bulky *tert*-butyl group at C-7 in nonannulated thiepins enhances their thermal stability by retarding the rate of isomerization to the thianorcaradiene. A thiepin that has *tert*-butyl substituents at both the 2 and 7 positions is likely to be even more stable. However, no attempt was made to prepare such a compound by ring enlargement of 2,5-di-*tert*-butyl-3-(1-pyrrolidinyl)-thiophene because it has been shown that the activation energy of the (2 + 2) cycloaddition strongly increases even when a small methyl group is present at C-2 in the 3-(1-pyrrolidinyl)thiophenes (cf. ref 30).[40] Consequently preparation of the desired thiepin with a bulky *tert*-butyl group at C-2 would require higher temperatures and this will favor elimination of sulfur.

Not only steric factors can influence the stability of thiepins;[43-46] thiepins can be stabilized electronically by substitution and Hückel calculations on substituted thiepins have shown that carboxyl groups substantially decrease the negative value of the resonance energy.[47,48] We therefore attempted to prepare a thiepin with four ester groups (**3f**, $R^1 = R^2 = COOCH_3$) by reacting dimethyl 4-(1-pyrrolidinyl)-2,3-thiophenedicarboxylate (**1f**) with DMAD in nonpolar solvents. However, the reaction only proceeded at 100 °C in toluene and under these conditions only tetramethyl 3-(1-pyrrolidinyl)-1,2,4,5-benzenetetracarboxylate (**5f**) was isolated in 35% yield. Obviously the two ester groups lower the "enamine" type of reactivity of **1f** in the (2 + 2) cycloaddition with DMAD by diminishing the π-electron density of the thiophene nucleus. It is interesting to note the relationship between the electron density at the 2 position, as reflected in the chemical shift of H-2, and the substituents attached to the thiophene ring (Table I).

Table I. ^1H NMR ($CDCl_3$, δ) Chemical Shifts of H-2 in 3-(1-Pyrrolidinyl)thiophenes 1a-h



1

compd	R^1	R^2	δ (H-2)
1a	H	CH_3	5.51
1b	H	i-C_3H_7	5.56
1c	H	t-C_4H_9	5.51
1d	H	C_6H_5	5.74
1e	H	o-CH_3O-C_6H_4	5.84
1f	$COOCH_3$	$COOCH_3$	6.38
1g	C_6H_5	C_6H_5	6.21
1h	CH_3	H	6.15

In order to enhance the rate of the (2 + 2) cycloaddition of **1f** and DMAD we decided to investigate the effect of two other parameters, namely, the polarity of the solvent and the type of acetylene. Huisgen et al.[8,12] have reported that solvent polarity has a very marked effect on the rate of the (2 + 2) cycloaddition of tetracyanoethylene and enol ethers; the rate of formation of the cyclobutanes is approximately 10^4 times faster in acetonitrile than in tetrachloromethane. This is attributed to stabilization of the 1,4-dipolar intermediates. However, when dimethyl 4-(1-pyrrolidinyl)-2,3-thiophenedicarboxylate (**1f**) was reacted with 1 equiv of DMAD in 1-butanol, in place of toluene, no rate enhancement was observed, and again a reaction temperature of 100 °C was required to effect reaction (quantitative conversion of **1f** took 16 h). In addition to the expected benzene derivative (**5f**, 20%), another crystalline compound, mp 96.5–98 °C, was obtained in 45% yield. Mass spectroscopy (M^+, 411.10, $C_{18}H_{21}NO_8S$) and elemental analysis showed that it was a 1:1 reaction product of **1f** and DMAD, and ^1H and ^{13}C NMR spectroscopy clearly showed that it was not a thiepin or a Michael adduct. A series of 3-(1-pyrrolidinyl)thiophenes (**1a–h**) was similarly reacted with DMAD in protic polar solvents and compounds **1a–e** reacted at 25 °C (and some even at −20 °C) in methanol to give the same type of 1:1 reaction product exclusively.

Single-crystal X-ray analysis of the 1:1 adduct obtained from **1e** and DMAD in methanol showed that it was the methyl 5*H*-thieno[2,3-*b*]pyrrolizin-8-acetate **6e** (Figure 2).

On the basis of this X-ray structure determination the other methyl 5*H*-thieno[2,3-*b*]pyrrolizin-8-acetates **6a–h** were readily identified by characteristic absorptions at δ 4.7–4.9 (dd, $J_1 = 10 \pm 1$ Hz and $J_2 = 6 \pm 1$ Hz) and 3.2–3.4 and 2.9–3.1 (AB system, $J_{AB} = 17 \pm 1$ Hz) in their ^1H NMR

(40) After completion of this part of our work Murata et al.[41,42] have synthesized via a different route 2,7-diisopropyl- and 2,7-di-*tert*-butylthiepin derivatives. Whereas the diisopropylthiepin surprisingly desulfurizes at −50 °C, the di-*tert*-butylthiepin is thermally stable (half-life in toluene-d_8 7.1 h at 131 °C). The very remarkable difference in thermal stability might be obscured by the role of palladium present in the synthesis.

(41) S. Yano, K. Nishino, K. Nakasuji, and I. Murata, *Chem. Lett.*, 723 (1978).

(42) K. Nishino, S. Yano, Y. Kohashi, K. Yamamoto, and I. Murata, *J. Am. Chem. Soc.*, **101**, 5059 (1979).

(43) K. Nishino, K. Nakasuji, and I. Murata, *Tetrahedron Lett.*, 3567 (1978).

(44) I. Murata and T. Tatsuoka, *Tetrahedron Lett.*, 2697 (1975).

(45) V. J. Traynelis, J. A. Schield, W. A. Lindley, and D. W. H. MacDowell, *J. Org. Chem.*, **43**, 3379 (1978).

(46) D. N. Reinhoudt and C. G. Kouwenhoven, *Tetrahedron*, **30**, 2431 (1974).

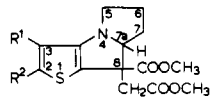
(47) B. A. Hess, L. J. Schaad, and D. N. Reinhoudt, *Tetrahedron*, **33**, 2683 (1977).

(48) The instability of thiepins has been discussed in relation with the potential antiaromaticity of the conjugated, if flat, 8π-electron system. We feel that a more relevant parameter is the rate of electrocyclization of the 6π system.[49,50]

(49) M. J. S. Dewar and N. Trinajstič, *J. Am. Chem. Soc.*, **92**, 1453 (1970).

(50) R. H. Schlessinger, *Aromat., Pseudo-Aromat., Anti-Aromat., Proc. Int. Symp.* 158 (1970).

Table II. Physical and Spectral Properties of 6,7,7a,8-Tetrahydro-5*H*-thieno[2,3-*b*]pyrrolizines (6)



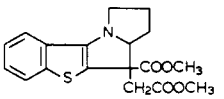
6

compd	R^1	R^2	% yield	mp, °C (solvent)	mass spectrum, M^+ found, formula (M^+ calcd)	^{1}H NMR ($CDCl_3$), δ H-7a (dd)[a]	CH_2	AB q[b]	^{13}C NMR ($CDCl_3$), δ C-7a (d)	CH_2 (t)
6a	H	CH_3	52	63-65 (pentane)	309.104, $C_{15}H_{19}NO_4S$ (309.104)[c]	4.72	3.25	2.97	77.5	39.0
6b	H	*i*-C_3H_7	61	86-88 (ether/pentane 1:1)	337.136, $C_{17}H_{23}NO_4S$ (337.135)[d]	4.73	3.25	2.95	77.5	39.1
6c	H	*t*-C_4H_9	69	92-93 (ether/pentane 1:1)	351.150, $C_{18}H_{25}NO_4S$ (351.150)[e]	4.77	3.29	2.97	77.3	38.9
6d	H	C_6H_5	63	130-131.5 (methanol)	371.131, $C_{20}H_{21}NO_4S$ (371.119)[f]	4.74	3.27	3.03	77.6	38.8
6e	H	*o*-$CH_3OC_6H_4$	64	181-183 (methanol)	401.131, $C_{21}H_{23}NO_5S$ (401.130)[g]	4.84	3.36	3.00	77.6	38.9
6f	$COOCH_3$	$COOCH_3$	46	96.5-98 (methanol)	411.100, $C_{18}H_{21}NO_8S$ (411.099)[h]	4.70	3.08[i]		78.4	39.0
6g	C_6H_5	C_6H_5	31	160-162 (ethanol)	447.149, $C_{26}H_{25}NO_4S$ (447.150)[j]	4.90	3.30	3.06	77.4	39.4
6h	CH_3	H	50	77-79 (diisopropyl ether)	309.104, $C_{15}H_{19}NO_4S$ (309.104)[k]	4.91	3.25	2.97	78.4	39.3

[a] Doublet of doublets J(7-7a) = 6 ± 1 and 10 ± 1 Hz. [b] AB system, J = 17 ± 1 Hz. [c] Anal. Calcd: C, 58.23; H, 6.19; N, 4.53; S, 10.36. Found: C, 58.41; H, 6.23; N, 4.51; S, 10.27. [d] Anal. Calcd: C, 60.51; H, 6.87; N, 4.15; S, 9.50. Found: C, 60.37; H, 6.73; N, 4.16; S, 9.42. [e] Anal. Calcd: C, 61.51; H, 7.17; N, 3.99; S, 9.12. Found: C, 61.26; H, 7.17; N, 3.91; S, 9.04. [f] Anal. Calcd: C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.37; H, 5.64; N, 3.75; S, 8.67. [g] Anal. Calcd: C, 62.82; H, 5.77; N, 3.49; S, 7.98. Found: C, 62.78; H, 5.86; N, 3.44; S, 8.04. [h] Anal. Calcd: C, 52.55; H, 5.14; N, 3.40; S, 7.79. Found: C, 52.14; H, 5.15; N, 3.26; S, 7.47. [i] In this particular case no AB quartet was found, only a broad singlet. [j] Anal. Calcd: C, 69.78; H, 5.63; N, 3.13; S, 7.16. Found: C, 69.63, H, 5.69; N, 3.23; S, 7.13. [k] Anal. Calcd: C, 58.23; H, 6.19; N, 4.53; S, 10.36. Found: C, 58.29; H, 6.23; N, 4.49; S, 10.33.

spectra. In their ^{13}C NMR spectra absorptions at δ 78 (d) and 39 (t) were present in every case (Table II).

3-(1-Pyrrolidinyl)benzo[*b*]thiophene, which reacts with DMAD to give the (2 + 2) cycloadduct at −30 °C or the corresponding 1-benzothiepin at +25 °C in diethyl ether, reacted with DMAD in methanol selectively to give methyl 2,3,3a,4-tetrahydro-4-(methoxycarbonyl)-1*H*-[1]benzothieno[2,3-*b*]pyrrolizin-4-acetate (**7**). To our knowledge these reactions represent the first synthesis of the heterocyclic systems **6** and **7**.

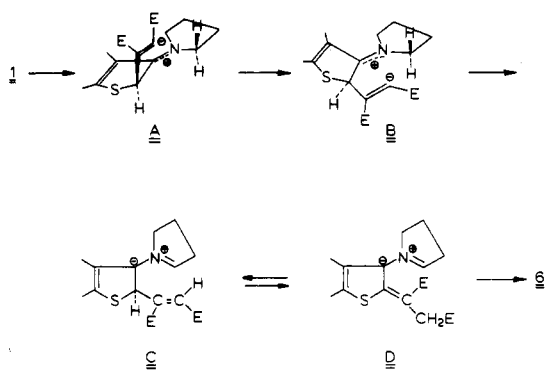


7

The effect of the polarity of the solvent on these reactions differs from that observed in the corresponding "polar" (2 + 2) cycloadditions of electron-deficient alkenes with electron-rich alkenes.[8,12] In those cases the rate increases with the solvent polarity but the product, a cyclobutane, remains the same. We find that whereas the rates of reaction of the acetylenes and the thiophenes (reacting as electron-rich alkenes) are hardly affected by the polarity of the solvent, different products are formed. A possible mechanism for the formation of the 5*H*-thieno[2,3-*b*]pyrrolizine is depicted in Scheme III.

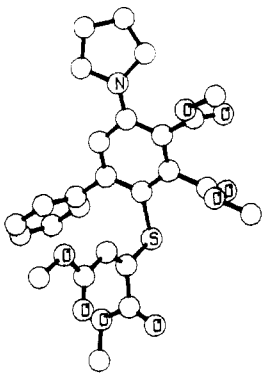
The initial step is the nucleophilic addition of **1** to the electron-deficient triple bond of the acetylene to give an intermediate A that is the tied ion pair form of a 1,4-dipolar intermediate. This step will be rate determining since it involves the loss of the thiophene aromaticity. Differentiation in the reaction pathway occurs in the

Scheme III



second step and it is this step that is solvent dependent. In apolar solvents a second σ bond is formed and in polar solvents rotation around the newly formed σ bond takes place to give the solvent-stabilized charge-separated ion pair B. In apolar solvents such a separation of (partial) charges will be unfavorable. Molecular models show that in B the developing carbanion is ideally situated from a steric point of view for abstraction of one of the α-aminomethylene hydrogen atoms. Further, a developing positive charge at nitrogen will facilitate hydrogen abstraction via an acid–base reaction. Huisgen et al.[51] have shown that azomethine ylides are generated by the action of triethylamine on *N*-(4-nitrobenzyl)-3,4-dihydroisoquinolinium bromide; i.e., the aminomethylene protons in

(51) R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).



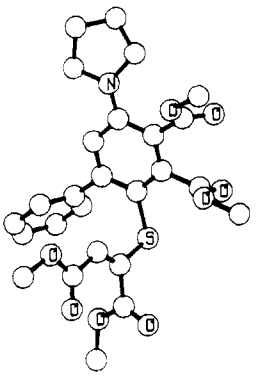


Figure 3. Stereoscopic view of the molecule **12d**.

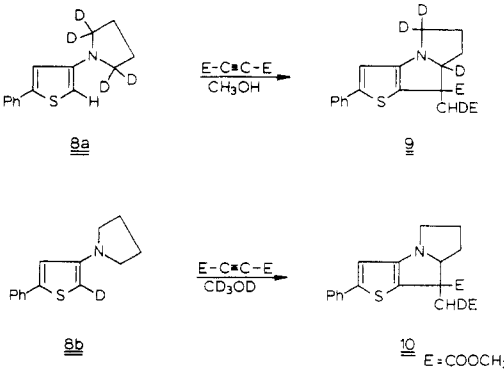
B are more acidic than the hydroxyl protons of methanol. The azomethine ylide D then undergoes a hydrogen shift, probably via the solvent, to give the conjugated 1,5-dipolar tautomer D, which finally undergoes a symmetry-allowed disrotatory electrocyclization to give **6**. Similar 1,5-dipolar cyclizations have been reported by Reimlinger[52] and Sasaki et al.[53] The formation of **6** always occurs stereospecifically since we have never observed two diastereoisomers in their ^{1}H NMR spectra. The X-ray structure of **6e** shows that the CH_2E group and the pyrrolidinyl group have the cis configuration, which one would expect from a symmetry-allowed disrotatory electrocyclization of D. The corresponding *Z* isomer of D would give rise to the other diastereoisomer.

We have proven that the proton abstraction from the aminomethylene group by the developing carbanionic center does not occur via the solvent but intramolecularly by reacting the specifically tetradeuterated 2-phenyl-4-(1-pyrrolidinyl-2,2,5,5-d_4)thiophene (**8a**) with DMAD in methanol. ^{1}H NMR spectroscopy clearly showed that the resulting tetradeuterated pyrrolizine **9** contained a CHDE-group. In the reverse experiment **8b** was reacted with DMAD in deuteriomethanol and the resulting pyrrolizine **10** also contains a CHDE-group (Scheme IV). Since we have proven by independent experiments that under similar reaction conditions compound **6d** does not react with the solvent, this means that one hydrogen transfer occurs intramolecularly. Attempts to prove how the other hydrogen is transferred from C-2 to the acetylene carbon atom were unsuccessful because the rate of hydrogen exchange of H-2 in **1d** is fast compared with the rate of reaction with DMAD.

This difference in reaction when the "pseudo" enamines **1** are reacted with DMAD in apolar or protic polar solvents had not been reported for simple enamines.[54]

Our results, in particular the insensitivity of the *rate* of the reaction to solvent polarity, might also point to a 1,4-diradical intermediate instead of a 1,4-dipolar intermediate A (Scheme III). However, if such were the case, it would be difficult to understand how further reaction of a 1,4-diradical would lead to the two different type of products, depending on the polarity of the solvent. Consequently we prefer a mechanism, as depicted in Scheme III, with the formation of a tied ion pair type of intermediate in the rate-determining step with formation of different products in the subsequent, non-rate-determining, solvent-dependent step (B in polar solvents and a (2 + 2) cycloadduct in apolar solvents).

Scheme IV



8a 9 8b 10

The reaction of **1d** and **1f** was also investigated in aprotic polar solvents such as acetonitrile and nitromethane which are also capable of stabilizing dipolar intermediates. 2-Phenyl-4-(1-pyrrolidinyl)thiophene (**1d**) reacted with DMAD in nitromethane at room temperature to give the corresponding 5*H*-thieno[2,3-*b*]pyrrolizine (**6d**), which was also obtained in methanol, in 76% yield. The same reaction in acetonitrile afforded a mixture of products: **6d** in a yield of 34% and in addition two isomeric 1:2 reaction products in 26% yield; M^+, 513.148 ($C_{26}H_{27}NO_8S$). Column chromatography and preparative TLC gave the pure isomers as crystals, mp 184–185 °C, and as an oil, with vinylic protons (s) at 5.30 and 6.16 ppm, respectively, in their ^{1}H NMR spectra. Single-crystal X-ray analysis showed that the crystalline 1:2 reaction product was the *E* isomer of the biphenyl **12d** (Figure 3).

On the basis of ^{1}H and ^{13}C NMR spectroscopic data the other isomer was assigned the *Z* configuration. We found that the reaction temperature had a marked effect on the ratio in which **6d** and **12d** were formed in acetonitrile. At low temperature **6d** was the predominant reaction product (see Table III).

Dimethyl 4-(1-pyrrolidinyl)-2,3-thiophenedicarboxylate (**1f**) did not react with DMAD at 25 °C in either acetonitrile or nitromethane, but in nitromethane it was consumed at reflux temperature within 2 h. The expected 5*H*-thieno[2,3-*b*]pyrrolizine (**6f**) could be detected in the crude reaction mixture and only 10% **12f** (*E* + *Z*), mp 158–164 °C, was isolated. The two isomers were not further separated but identified on the basis of their ^{1}H NMR spectroscopic data (absorptions of the vinylic protons in **12f**: δ 5.40 (s) for the *E* isomer and δ 6.50 (s) for the *Z* isomer) and by mass spectrometry; M^+, 553.124 ($C_{24}H_{27}NO_{12}S$). The major reaction product was 2,3,5,7,8-pentakis(methoxycarbonyl)-6-(1-pyrrolidinyl)-4*H*-1-benzothiopyran-4-one (**13**). The orange-red crystalline compound,

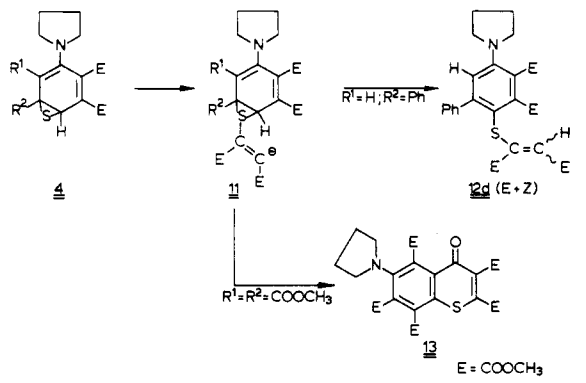
(52) H. Reimlinger, *Chem. Ber.*, **103**, 1900 (1970).
(53) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **37**, 3106 (1972).
(54) More recently we have shown that pyrrolidine enamines of cyclic and acyclic ketones also show these deviating reaction pathways in polar and apolar solvents.[55]
(55) D. N. Reinhoudt, J. Geevers, and W. P. Trompenaars, *Tetrahedron Lett.*, 1351 (1978).

Table III. Reactions of (1-Pyrrolidinyl)thiophenes 1d and 1f with DMAD in Various Solvents

reactant	solvent	mol ratio, DMAD/1	temp, °C	isolated % yield of product 5	6	12	13
1d	C_6H_6	1.1	20[a]	40	-	-	
1d	CH_3CN	2.0	20[a]	-	34	26[c]	
1d	CH_3CN	5.0	20[a]	-	20	47[c]	
1d	CH_3CN	5.0	-30[a]	-	46	14[c]	
1d	CH_3NO_2	1.1	20[a]	-	76	-	
1d	CH_3OH	1.1	20[a]	-	63	-	
1f	$C_6H_5CH_3$	1.1	100[b]	35	-	-	-
1f	CH_3NO_2	4.0	100[b]	-	-	10[c]	40
1f	C_4H_9OH	1.1	100[b]	20	60	-	-

[a] Reaction time 16 h. [b] Reaction time 2 h. [c] Mixture of two isomers.

Scheme V



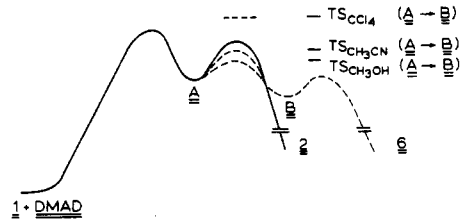


Figure 4. Possible energy profiles for reactions of 1 and DMAD in solvents of different polarity.

mp 205–206.5 °C, shows a characteristic absorption in the UV spectrum. λ_{max} 230 (log ϵ 4.33), 265 (4.21), 361 nm (3.89), which agrees well with the spectroscopic data reported by Schmutz et al.[56] for a number of substituted 4*H*-1-benzothiopyran-4-ones. Further, the absorption at 1740 cm^{-1} in the IR spectrum of **13** and a low-field absorption in the ^{13}C NMR spectrum at 176.4 ppm reveal the presence of a carbonyl group. Finally a parent peak, M^+, 521.101, which corresponds to a molecular composition of $C_{23}H_{23}NO_{11}S$ in in full agreement with the proposed structure.

How do we account for the results of the reactions in these aprotic polar solvents that differ both from those obtained in apolar and polar protic solvents? Obviously, in these solvents with polarities or better acceptor numbers[57] in between those of methanol (AN 41.3) and tetrachloromethane (AN 8.6), the activation energy of the two competing pathways, (2 + 2) cycloaddition to yield 2-thiabicyclo[3.2.0]hepta-3,6-dienes (**2**) and intramolecular capture of a 1,4-dipolar intermediate, is almost the same. For the more reactive **1d** we were able to study the reaction over a wider range of temperatures than with the less reactive **1f** and, again, the reaction temperature was shown to affect the product ratio (**6d**:**12d**). A rationalization for the formation of **12d** is given in Scheme V. We assume that the initially formed thiepin undergoes S-alkylation by DMAD in these solvents to yield **11**. Hydrogen transfer and formation of the benzene ring then give **12**. Although we cannot explain why the rate of alkylation in acetonitrile is faster than the elimination of sulfur it is known that with benzo[*b*]thiepins S-alkylation, acylation, or protonation competes in many cases with the elimination of sulfur.[46,58]

Further, Hofmann and Molnar[59] have reported that *S*-methyl-1-benzothiepinium salts rearrange to the corresponding methylthionaphthalenes via the *S*-methylthianorcaradienes, and Kobayashi and Mutai[60] have described the S-alkylation of 2,5-diphenyl-1,4-dithiin 1,1-dioxide with DMAD. In the S-alkylated thianorcaradiene **11f** ($R^1 = R^2 = COOCH_3$) an alternative pathway for the hydrogen-transfer step is possible, namely, the nucleophilic attack of the carbanionic center at the adjacent ester group. This is only possibly in **11f** because it requires a five-membered transition state that is not accessible in other intermediates of this type, e.g., **11d**. The methoxy group of the ester function acts as the leaving group and will subsequently abstract a proton to give methanol.

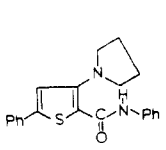
These experiments provide additional evidence that thiepins are formed by reaction of 3-(1-pyrrolidinyl)-thiophenes and DMAD and they are the first examples where the thiepins can be captured as their valence isomers, thianorcaradienes, before they undergo desulfurization. In this reaction the most likely role of the polar solvent is to stabilize the dipolar intermediates of type **11**. These results also complete the picture of the intermediates depicted in Scheme III. The conclusions at this stage are the following. (i) The rate-determining step, formation of a tied (1,4-dipolar) ion pair like A (Scheme III) is virtually independent of the solvent polarity.[61] (ii) Solvent-stabilized conversion of the tied (1,4-dipolar) ion pair in a charge-separated ion pair B (Scheme III) occurs only in solvents with a high acceptor number, otherwise the (2 + 2) cycloaddition is the preferred pathway with alcohols as one extreme and tetrachloromethane as the other; acetonitrile represents a solvent with an intermediate acceptor number. (iii) Higher temperatures favor (2 + 2) cycloaddition, probably because the activation entropy of (2 + 2) cycloaddition has a smaller negative value than that of the formation of a charge-separated

(56) J. Schmutz, H. Lauener, R. Hirt, and M. Sanz, *Helv. Chim. Acta*, **34**, 767 (1951).
(57) V. Gutmann, "The Donor-Acceptor Approach to Molecular Interactions", Plenum Press, New York, 1978, Chapter 2.
(58) H. Hofmann, H. Westernacher, and H.-J. Haberstroh, *Chem. Ber.*, **102**, 2595 (1969).
(59) H. Hofmann and A. Molnar, *Tetrahedron Lett.*, 1985 (1977).
(60) K. Kobayashi and K. Mutai, *Tetrahedron Lett.*, 905 (1978).
(61) It is not unlikely that 1 forms first a CT complex with DMAD since upon mixing of the reagents a deep red color appears. After completion of the reaction the mixture has, depending on the substrate and solvent, often an orange to yellow color (see ref 62).
(62) R. Huisgen and G. Steiner, *Tetrahedron Lett.*, 3763 (1973).

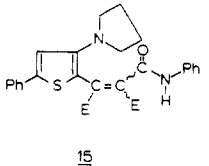
intermediate (B)[63] (Scheme III).

The question remains as to whether the intermediates A and B are real 1,4-dipoles or whether some degree of 1,4-bonding already exists in A. This question is related to the more fundamental question of how concerted are (2 + 2) cycloaddition reactions (cf. ref 12, p 206). To help answer this question we attempted to capture the proposed 1,4-dipolar intermediates (A or B, see Scheme III) by an intermolecular reaction with a 1,4-dipolarophile.[64] Assuming that the energy profiles for reaction of **1** with DMAD are as shown in Figure 4, the best chance to achieve this is in a solvent like acetonitrile because there the rate of conversion of A to B will be slower than in methanol, and in such solvents intermolecular 1,4-dipolar addition will have the best chance to compete with the intramolecular abstraction of hydrogen.

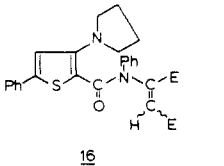
The reaction of **1d** with DMAD in the presence of 4 equiv of phenyl isocyanate at room temperature gave three products. The major product was the 5*H*-thieno[2,3-*b*]-pyrrolizine **6d** and only small amounts of 5-phenyl-2-(phenylcarbamoyl)-3-(1-pyrrolidinyl)thiophene (**14**) were obtained. (Compound **14** was prepared independently by reaction of **1d** with phenyl isocyanate.[65]) In addition to these 1:1 addition products a crystalline 1:1:1 reaction product was isolated in 15% yield. The structure of this 1:1:1 reaction product was shown by ^1H and ^{13}C NMR spectroscopy, elemental analysis, and mass spectrometry to be compound **15**. The $M^+ - C_6H_5NCO$ peak in the mass spectrum proves that the compound was **15** and excludes the alternative structure **16**. The fact that **14** is formed



14



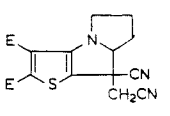
15



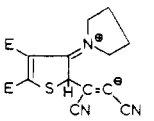
16 E = $COOCH_3$

in low yield despite the presence of a fourfold excess of phenyl isocyanate compared with 1 equiv of DMAD proves that DMAD reacts with **1d** much faster than does phenyl isocyanate. Similarly, the formation of **6d** as the major product demonstrates the fast rate of the intramolecular hydrogen-transfer step compared with the intermolecular 1,4-dipolar addition. Whether **15** is formed by addition of the carbanionic center of intermediate B (Scheme III) to the O=C=N bond of phenyl isocyanate or by 1,4-dipolar addition followed by cleavage of the N—C bond in the 1,4-dipolar adduct[29] remains unanswered. However, this trapping experiment proves that in acetonitrile the 1,4-dipolar species, formed by reaction of **1d** with DMAD, can be intercepted before it undergoes an intramolecular hydrogen transfer.

Since our original objective, the synthesis of a stable thiepin by reaction of **1f** with DMAD, could not be achieved by reaction in protic polar solvents and the reaction in nitromethane leads only to products **12f** and **13** derived from the desired thiepin, the effect of two other parameters was investigated. Firstly, we studied reactions of other acetylenes, namely, dicyanoacetylene and methyl propiolate, with **1f**. Reaction of equimolar amounts of **1f** and dicyanoacetylene in dichloromethane takes place at −60 °C and is complete in 2 h. The 1:1 reaction product that was isolated still contained sulfur but it was not the desired thiepin **3f**. ^1H and ^{13}C NMR spectroscopy identified this product unambigously as the 5*H*-thieno[2,3-*b*]pyrrolizine **17** ($\delta_{H\text{-}7a}$ 4.84 (dd) and δ_{CH_2CN} 3.02 (s); $\delta_{C\text{-}7a}$ 79.8 (d) and δ_{CH_2CN} 25.0 (t)). This demonstrates not only that dicyanoacetylene is a more reactive acetylene than DMAD but also that even in such an apolar solvent as dichloromethane the 1,4-dipolar pathway is preferred to the (2 + 2) cycloaddition. We attribute this difference with DMAD to a better intramolecular stabilization of the carbanionic center of the 1,4-dipole **18** by two cyano groups. External stabilization of the intermediate **18** by solvent molecules is no longer required to make the 1,4-dipolar reaction path the most favorable.

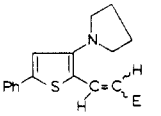


17

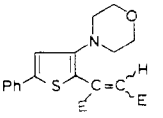


18 E = $COOCH_3$

Reaction of **1f** with methyl propiolate at room temperature does not take place. Even the more reactive 3-(1-pyrrolidinyl)thiophenes (e.g., **1d**) reacted slowly with methyl propiolate. Both in the absence of solvent and with methanol as solvent the same 1:1 reaction product was obtained. ^1H and ^{13}C NMR spectroscopy revealed that it was the Michael adduct **19** (*E* + *Z*); one of the isomers disappeared on chromatography or recrystallization. This represents an example where the intermediate (B, Scheme III) abstracts a proton from the solvent faster than from the methylenamino group. Because there is only one electron-withdrawing group present in this intermediate, it will definitely be less stable compared with A, B, or **18** and therefore more reactive toward the solvent.



19 (E + Z)



20 (E + Z)

A similar mixture of *E* and *Z* isomers of Michael adducts was also obtained when 4-(4-morpholinyl)-2-phenylthiophene was reacted with DMAD in methanol. Again on purification one of the isomers was converted into the other isomer, mp 144–146 °C ($\delta_{H\text{-}vinyl}$ 6.38 (s)). It would appear that the formation of products (e.g., **6**) by hydrogen abstraction of aminomethylene protons seems to be restricted to 3-(1-pyrrolidinyl)thiophenes.[55,66]

Conclusion

Most cycloadditions are discussed in terms of concerted or stepwise formation of the two new σ bonds and, when a stepwise mechanism is proposed, the capture of the intermediate is then the subject of further studies. The main conclusion from our work is that another factor has to be taken in account in these discussions, namely, the role of the solvent, because this can completely alter the reaction pathway. Our observations neither confirm nor disprove Epiotis' prediction[4] that thermal $[{}_\pi 2_s + {}_\pi 2_s]$ cycloadditions of highly polarized π systems are concerted processes with relative low activation energies, and a concerted pathway in apolar solvents has not been disproved. It is possible

(63) G. Steiner and R. Huisgen, *Tetrahedron Lett.*, 3769 (1973).

(64) For a leading reference on 1,4-dipolar additions, see R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkenes", S. Patai, Ed., Interscience, London, p 739.

(65) Similar reactions of 3-(1-pyrrolidinyl)benzo[*b*]thiophene with phenyl isocyanate and isothiocyanate gave the same type of 2-substituted benzo[*b*]thiophene.[29]

(66) Similar reactions of enamines of cyclic and acyclic ketones with DMAD in methanol show the same limitation (to be published).

that acetylenes are, like ketenes, a special case of 2π systems in thermal (2 + 2) cycloadditions because acetylenes have two perpendicular π systems, and it should be mentioned that tetracyanoethylene does not react with 3-(1-pyrrolidinyl)thiophenes under the same mild conditions. Further the question as to whether the intermediate A that is formed in the (2 + 2) cycloaddition pathway is a true intermediate or a more highly polarized transition state of a concerted process must also be left open. However, since the alternative hydrogen abstraction is an intramolecular process it would offer, also in apolar solvents, the best system to capture a possible 1,4-dipolar intermediate if these (2 + 2) cycloadditions would follow a two-step pathway. It will be difficult to design a more sensitive experiment that could distinguish between a concerted and a two-step reaction. In polar solvents, particularly alcohols, the 1,4-dipolar intermediate fully develops and these reactions have opened an attractive route for the synthesis of pyrrolizine systems. Application of this reaction for the synthesis of analogues of the antitumor antibiotic mitomycin is under investigation.[67] As far as the primary objective of the reactions between 3-(1-pyrrolidinyl)-thiophenes and electron-deficient acetylenes is concerned, i.e., the synthesis of "stable" thiepins, the reaction in apolar solvents is shown to have its limitations. Substitution by one bulky *tert*-butyl group at C-2 leads to a substantial enhancement of the thermal stability of thiepins and we can observe such thiepins at 25 °C by ^{1}H NMR spectroscopy. However, the steric constraints of the facile (2 + 2) cycloaddition will not allow the synthesis of thiepins with two bulky groups, both at C-2 and C-7, by this method. The amount of stabilization of thiepins by four electron-withdrawing ester groups could not be investigated because the two ester groups in the thiophene reduce the "pseudo" enamine type of reactivity of 3-(1-pyrrolidinyl)thiophenes drastically.

Experimental Section

Melting points were determined with a Mettler FP1 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 spectrometer (Me_4Si as internal standard). Mass spectra were obtained with a Varian Mat 311A spectrometer. 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.

Dimethyl acetylenedicarboxylate (DMAD) refers to Merck reagent and was distilled immediately before use.

Preparation of 3-(1-Pyrrolidinyl)thiophenes 1. Compounds **1a**, **1d**, and **1f–h** were prepared as described previously.[39]

2-(1-Methylethyl)-4-(1-pyrrolidinyl)thiophene (1b) (1-[5-(1-methylethyl)-3-thienyl]pyrrolidine) was prepared in a multistep synthesis starting from 4-methyl-2-pentenoic acid.[68,69] Addition of mercaptoacetic acid to 4-methyl-2-pentenoic acid in a manner as described before[39] afforded 3-[(carboxymethyl)-thio]-4-methylpentanoic acid (65%) as a yellow oil, bp 190–195 °C (0.4 torr), and ring closure yielded 4,5-dihydro-5-(1-methylethyl)-3(2*H*)-thiophenone (70%), bp 94–98 °C (15 torr). The corresponding oxime was prepared by refluxing the ketone with an excess of hydroxylamine hydrochloride and barium carbonate in methanol during 4 h (95%), mp 30–35 °C. Semmler–Wolff aromatization, according to the procedure reported by Binder and Stanetty,[70] yielded 3-amino-5-(1-methylethyl)thiophene hydrochloride (65%), mp 134–136 °C dec, which was reacted with 1,4-dibromobutane and diisopropylethylamine (Hünig base[71]), in a manner as described before,[39] to give **1b** (46%): bp 80–84 °C (0.01 torr); ^{1}H NMR δ 6.46 (br s, 1 H, H-3), 5.56 (br s, 1 H, H-5), 3.35–2.95 (m, 5 H, $C(CH_3)_2$-H and Pyrr H(α)), 2.10–1.80 (m, 4 H, Pyrr H(β)), 1.30 (d, 6 H, CH_3).

Anal. Calcd for $C_{11}H_{17}NS$ (mol wt 195.11): C, 67.64; H, 8.77. Found: C, 67.54; H, 8.81.

2-(1,1-Dimethylethyl)-4-(1-pyrrolidinyl)thiophene (1c) (1-[5-(1,1-Dimethylethyl)-3-thienyl]pyrrolidine). By the procedure described for the preparation of **1b**, 4,4-dimethyl-2-pentenoic acid[68,69] yielded, respectively, 3-[(carboxymethyl)-thio]-4,4-dimethylpentanoic acid (80%; mp 103–105 °C), 4,5-dihydro-5-(1,1-dimethylethyl)-3(2*H*)-thiophenone [50%; bp 106–110 °C (18 torr)], the corresponding oxime (85%; mp 109–111 °C), 3-amino-5-(1,1-dimethylethyl)thiophene hydrochloride (80%; mp 156–158 °C), and finally **1c** (68%): bp 98–102 °C (0.1 torr); ^{1}H NMR δ 6.37 (d, J = 2 Hz, 1 H, H-3), 5.51 (d, J = 2 Hz, 1 H, H-5), 3.35–3.0 (m, 4 H, Pyrr H(α)), 2.05–1.70 (m, 4 H, Pyrr H(β)), 1.34 (s, 6 H, CH_3).

Anal. Calcd for $C_{12}H_{19}NS$ (mol wt 209.35): C, 68.85; H, 9.15; N, 6.69. Found: C, 68.57; H, 9.31; N, 6.80.

2-(2-Methoxyphenyl)-4-(1-pyrrolidinyl)thiophene (1e) (1-[5-(2-Methoxyphenyl)-3-thienyl]pyrrolidine). By the procedure described for the preparation od **1d**, 3-(2-methoxyphenyl)propenoic acid[72] yielded, respectively, 3-[(carboxymethyl)thio]-3-(2-methoxyphenyl)propanoic acid (65%; mp 119.5–121.5 °C), 4,5-dihydro-5-(2-methoxyphenyl)-3(2*H*)-thiophenone [70%; bp 131–134 °C (0.01 torr)], 2,3-dihydro-2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)thiophene (65%; mp 85–87 °C), and finally **1e** (40%): mp 74–75 °C; ^{1}H NMR δ 7.75–7.55 (m, 1 H, Ar H), 7.25–6.75 (m, 4 H, Ar H), 5.84 (br s, 1 H, H-5), 3.88 (s, 3 H, OCH_3), 3.40–3.15 (m, 4 H, Pyrr H(α)), 2.10–1.85 (m, 4 H, Pyrr H(β)).

Anal. Calcd for $C_{15}H_{17}NOS$ (mol wt 243.37): C, 69.46; H, 6.61; N, 5.40. Found: C, 69.51; H, 6.48; N, 5.36.

Reaction of (1-Pyrrolidinyl)thiophenes (1) with Dimethyl Acetylenedicarboxylate (DMAD) in Apolar Solvents. Preparation of 5c, 5d, and 5f. Compounds **5c** and **5d** were prepared by reacting the corresponding 3-(1-pyrrolidinyl)-thiophenes (1, 5 mmol) with DMAD (5.5 mmol) in 15 mL of dry benzene or ether at room temperature under a nitrogen atmosphere for 20 h. After removal of solvent under reduced pressure, chromatography of the residue (silica gel, chloroform) afforded the pure products. Compound **5f** was prepared by stirring **1f** (5 mmol) and DMAD (5.5 mmol) in 15 mL of dry refluxing toluene during 20 h. After removal of solvent under reduced pressure, trituration of the residue with a few milliliters of methanol afforded **5f**.

Dimethyl 5-(1,1-dimethylethyl)-3-(1-pyrrolidinyl)-1,2-benzenedicarboxylate (5c): yield 77%; mp 67–68 °C; ^{1}H NMR δ 7.25 and 6.92 (1 H, d, J = 3 Hz, Ar H-6 and Ar H-4), 3.86 (s, 6 H, OCH_3), 3.40–3.20 (m, 4 H, Pyrr H(α)), 2.00–1.80 (m, 4 H, Pyrr H(β)), 1.31 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 170.4 and 167.7 (s, C=O), 152.5 (s, Ar C-3), 145.9 (s, Ar C-1), 130.3 (s, Ar C-2), 116.7 (s, Ar C-5), 115.1 (d, Ar C-4 and C-6), 52.3 and 52.2 (q, OCH_3), 49.7 (t, Pyrr C(α)), 34.9 (s, $C(CH_3)_3$), 31.1 (q, CH_3), 25.7 (t, Pyrr C(β)); mass spectrum, m/e 319.178 (M^+; calcd 319.78).

Anal. Calcd for $C_{18}H_{25}NO_4$ (mol wt 319.41): C, 67.69; H, 7.89; N, 4.39. Found: C, 67.61; H, 7.81; N, 4.31.

Dimethyl 5-(1-pyrrolidinyl)-[1,1′-biphenyl]-3,4-dicarboxylate (5d): yield 42%; mp 116.5–117.5 °C; ^{1}H NMR δ 7.75–7.35 (m, 6 H, Ar), 7.10 (s, 1 H, Ar H-2), 3.90 and 3.86 (s, 6 H, OCH_3), 3.50–3.25 (m, 4 H, Pyrr H(α)), 2.15–1.85 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 170.3 and 167.3 (s, C=O), 146.3 (s, Ar C-5), 142.6 (s, Ar C-3), 140.2 (s, Ar C-1′), 131.0 (s, Ar C-4), 128.6, 127.7, and 127.0 (d, Ar C-2′, -3′, and -4′), 118.0 (s, Ar C-1), 116.6 (d, Ar C-2 and -6), 52.5 and 52.3 (q, OCH_3), 49.8 (t, Pyrr C(α)), 25.8 (t, Pyrr C(β)); mass spectrum, m/e 339.150 (M^+; calcd for 339.147).

Anal. Calcd for $C_{20}H_{21}NO_4$ (mol wt 339.40): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.92; H, 6.03; N, 3.82.

Tetramethyl 3-(1-pyrrolidinyl)-1,2,4,5-benzenetetracarboxylate (5f): yield 35%; mp 169–170.5 °C; ^{1}H NMR δ 8.46 (s, 1 H, Ar H-6), 3.94 (br s, 12 H, OCH_3), 3.30–3.10 (m, 4 H, Pyrr H(α)), 2.00–1.75 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 167.5 and 164.3

(67) J. Geevers, G. W. Visser, and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas*, **98**, 251 (1979).
(68) C. Rappe, *Org. Synth.*, **53**, 123 (1973).
(69) C. Rappe and R. Adestrôm, *Acta Chem. Scand.*, **19**, 383 (1965).
(70) D. Binder and P. Stanetty, *Synthesis*, 200 (1977).
(71) S. Hünig and M. Kiessel, *Chem. Ber.*, **91**, 380 (1958).
(72) A. I. Vogel, "A Text-book of Practical Organic Chemistry", Longmans, New York, 1964, p 719.

(s, C=O), 145.4 (s, Ar C-3), 141.4 (s, Ar C-1 and -5), 129.3 (s, Ar C-2 and -4), 128.3 (d, Ar C-6), 52.7 and 52.6 (q, OCH_3), 52.3 (t, Pyrr C(α)), 26.3 (t, Pyrr C(β)); mass spectrum, m/e 379.127 (M^+; calcd 379.127).

Anal. Calcd for $C_{18}H_{21}NO_8$ (mol wt 379.37): C, 56.99; H, 5.58; N, 3.69. Found: C, 57.15; H, 5.67; N, 3.59.

Reaction of (1-Pyrrolidinyl)thiophenes (1a–h) with Dimethyl Acetylenedicarboxylate (DMAD) in Polar Solvents. Preparation of 6,7,7a,8-Tetrahydro-5*H*-thieno[2,3-*b*]pyrrolizines (6a–h). A solution of DMAD (11 mmol) in 10 mL of methanol was added dropwise to a solution of 1 (10 mmol) in 10 mL of methanol under a nitrogen atmosphere at 0 °C. The red-colored solution was stirred overnight at room temperature (**6a–e**) or at reflux temperature (**6f–h**). (Compound **6f** was prepared in 1-butanol.) The solvent was removed under reduced pressure and the product, dissolved in chloroform, was purified by passing it through a short column of silica gel (**6a–c,g,h**). The chloroform was removed and the product crystallized (see Table II). Compounds **6d** and **6e** crystallized during the reaction, while the crude reaction mixture of **6f** was purified by column chromatography (silica gel, chloroform) yielding, successively, **5f** (20%) and **6f** (see Table II).

Methyl 2,3,3a,4-Tetrahydro-4-(methoxycarbonyl)-1*H*-[1]benzothieno[2,3-*b*]pyrrolizine-4-acetate (7). A solution of DMAD (1.56 g, 11 mmol) in 10 mL of methanol was added dropwise to a solution of 3-(1-pyrrolidinyl)benzo[*b*]thiophene[39,46] (2.03 g, 10 mmol) in 10 mL of methanol at 0 °C under a nitrogen atmosphere and the red-colored solution was stirred overnight at room temperature. The methanol was removed under reduced pressure and the residue was purified by column chromatography (silica gel, chloroform), yielding pure **7** (1.55 g, 40%): mp 118.5–120.5 °C (methanol); ^{1}H NMR δ 7.90–7.70 (m, 2 H, Ar H), 7.45–7.25 (m, 2 H, Ar H), 4.96 (dd, J(3-3a) = 6 ± 1 and 10 ± 1 Hz, 1 H, H-3a), 3.74 (s, 6 H, OCH_3), 3.36 and 3.08 (AB q, J = 17 Hz, 2 H, CH_2(E)) in broad multiplet 3.60–3.00 (2 H, H-1), 2.2–1.6 (m, 4 H, H-2 and H-3); ^{13}C NMR δ 173.8 and 171.4 (s, C=O), 150.7 (s), 144.4 (s), 128.4 (s), 124.2 (d), 123.9 (d), 123.8 (d), 120.9 (d) and 118.7 (s) (Ar C), 77.9 (d, C-3a), 55.1 (s, C-4), 52.9 and 52.0 (q, OCH_3), 51.4 (t, C-1), 38.9 (t, CH_2E), 27.1 and 26.5 (t, C-2 and C-3); mass spectrum, m/e 345.100 (M^+; calcd 345.103).

Anal. Calcd for $C_{18}H_{19}NO_4S$ (mol wt 345.42): C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.53; H, 5.59; N, 3.88; S, 9.18.

2-Phenyl-4-(1-pyrrolidinyl-*2,2,5,5-d*$_4$)thiophene (8a). 4,5-Dihydro-5-phenyl-3(2*H*)-thiophenone[39] was reacted with hydroxylamine hydrochloride, by the procedure described for the preparation of **1b**, to give the oxime (90%), mp 104–105 °C. Semmler–Wolff aromatization of this oxime, according to the procedure described for the preparation of **1b**, yielded 3-amino-5-phenylthiophene hydrochloride (80%), mp 168–170 °C dec. Reaction with 1,4-dibromobutane-*1,1,4,4-d*$_4$ and diisopropylethylamine, in a manner as described before,[39] afforded **8a** (50%): ^{1}H NMR δ 7.75–7.20 (m, 5 H, Ar H), 6.92 (br s, 1 H, H-3), 5.75 (br s, 1 H, H-5), 1.94 (br s, 4 H, Pyrr (H(β)); mass spectrum, m/e 233.119 (M^+; calcd for $C_{14}H_{11}D_4NS$ 233.118).

1,4-Dibromobutane-*1,1,4,4-d*$_4$. Reduction of diethyl butanedioate with $LiAlD_4$ according to the procedure reported by Woller and Garbisch[73] afforded 1,4-butane-*1,1,4,4-d*$_4$-diol, which was treated with hydrobromic acid[74] to yield 1,4-dibromobutane-*1,1,4,4-d*$_4$.

2-Phenyl-4-(1-pyrrolidinyl)thiophene-*5-d* (8b). 2-Phenyl-4-(1-pyrrolidinyl)thiophene (**1d**, 0.5 g) was dissolved in 5 mL of dry tetrachloromethane and stirred vigorously with 2 mL of D_2O for 30 min. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield **8b**. It was demonstrated by ^{1}H NMR that **8b** was at least 90% pure: ^{1}H NMR δ 7.65–7.10 (m, 5 H, Ar H), 6.92 (s, 1 H, H-3), 3.40–3.00 (m, 4 H, Pyrr H(α)), 2.15–1.80 (m, 4 H, Pyrr H(β)).

Methyl 6,7,7a,8-Tetrahydro-8-(methoxycarbonyl)-2-phenyl-5*H*-thieno[2,3-*b*]pyrrolizine-*5,5,7a-d*$_3$-8-acetate-*d* (9). Reaction of **8a** with DMAD in methanol, according to the procedure described for **6d**, yielded **9** (50%): mp 128–130 °C; ^{1}H NMR δ 7.70–7.20 (m, 5 H, Ar H), 6.76 (s, 1 H, H-3), 3.75 (br s, 6 H, OCH_3), 3.25, 3.00 (2 br s, 1 H, CHDCOOCH$_3$), 2.10–1.50 (m, 4 H, H-6 and H-7); mass spectrum, m/e 375.144 (M^+; calcd for $C_{20}H_{17}D_4NO_4S$ 375.144).

Methyl 6,7,7a,8-Tetrahydro-8-(methoxycarbonyl)-2-phenyl-5*H*-thieno[2,3-*b*]pyrrolizine-8-acetate-*d* (10). Reaction of **8b** with DMAD in methanol-d_4, according to the procedure described for **6d**, yielded **10** (63%): mp 129.5–131 °C; ^{1}H NMR δ 7.65–7.20 (m, 5 H, Ar H), 6.76 (s, 1 H, H-3), 4.73 (dd, J(7-7a) = 6 ± 1 and 10 ± 1 Hz, 1 H, H-7a), 3.73 (br s, OCH_3), 3.25, 3.01 (2 br s, 1 H, CHDCOOCH$_3$) in broad multiplet 3.65–2.95 (2 H, H-5), 2.15–1.50 (m, 4 H, H-6 and H-7). It is seen both from the ^{1}H NMR and the mass spectrum that a part of compound **10** is transesterified by CD_3OD.

Reaction of 1d with Excess DMAD in Acetonitrile. Dimethyl (*E*)- and (*Z*)-2-[[3,4-Bis(methoxycarbonyl)-5-(1-pyrrolidinyl)-[1,1′-biphenyl]-2-yl]thio]-2-butenedioate (12d). In a typical experiment (see Table III) a solution of **1d** (5 mmol) in 10 mL of acetonitrile was added slowly to a solution of DMAD (11 mmol) in 10 mL of acetonitrile under a nitrogen atmosphere at 20 °C and the solution was stirred overnight at room temperature. The acetonitrile was removed under reduced pressure and the residue was purified by column chromatography (silica gel, chloroform), yielding **6d** (34%) and a mixture of the *E* and *Z* isomers of **12d** (26%). The isomers were separated by preparative TLC (silica gel, chloroform). (*E*)-**12d**: mp 184–185 °C; ^{1}H NMR δ 7.55–7.30 (m, 5 H, Ar′ H), 6.78 (s, 1 H, H-6), 5.30 (s, 1 H, C=CH), 3.88, 3.85, 3.72, and 3.64 (s, 3 H, OCH_3), 3.40–3.15 (m, 4 H, Pyrr H(α)), 2.10–1.85 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 167.6, 167.3, 165.1, and 163.9 (s, C=O), 151.3 (s), 150.7 (s), 147.8 (s), 143.0 (s), 139.5 (s), 128.6 (d), 127.9 (d), 127.7 (d), 117.1 (d), 115.4 (s), 114.2 (d), and 106.3 (s) (Ar C and C=CH), 52.8, 52.6, 52.5, and 51.6 (q, OCH_3), 50.4 (t, Pyrr C(α)), 25.8 (t, Pyrr C(β)); mass spectrum, m/e 513.149 (M^+; calcd for $C_{26}H_{27}NO_8S$ 513.146).

(*Z*)-**12d**: oil; ^{1}H NMR δ 7.50–7.25 (m, 5 H, Ar′ H), 6.74 (s, 1 H, H-6), 6.16 (s, 1 H, C=CH), 3.86, 3.84, 3.66, and 3.52 (s, 3 H, OCH_3), 3.40–3.15 (m, 4 H, Pyrr H(α)), 2.10–1.85 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 167.9, 167.7, 164.7, and 164.0 (s, C=O), 149.3 (s), 148.8 (s), 146.6 (s), 141.0 (s), 140.0 (s), 129.5 (d), 127.5 (d), 127.3 (d), 119.8 (d), 117.0 (d), 115.6 (s), 112.3 (s) (Ar C and C=CH), 52.6, 52.5, 52.3, and 51.5 (q, OCH_3), 50.2 (t, Pyrr C(α)), 25.8 (t, Pyrr C(β)); mass spectrum, m/e 513.148 (M^+; calcd for $C_{26}H_{27}NO_8S$ 513.146).

Reaction of 1f with Excess DMAD in Nitromethane. Dimethyl 2-[[4-(1-Pyrrolidinyl)-2,3,5,6-tetrakis(methoxycarbonyl)phenyl]thio]-2-butenedioate (12f) and 2,3,5,7,8-Pentakis(methoxycarbonyl)-6-(1-pyrrolidinyl)-4*H*-1-benzothiopyran-4-one (13). A solution of **1f** (1.35 g, 5 mmol) and DMAD (2.82 g, 20 mmol) was stirred in 10 mL of refluxing nitromethane for 2 h under a nitrogen atmosphere. The solvent and excess DMAD were removed under reduced pressure (0.1 torr) and 2 mL of methanol was added to the resulting residue, yielding **13** (0.85 g, 33%, mp 200–202.5 °C). Column chromatography (silica gel, chloroform) of the mother liquor afforded **13** (0.20 g, 8%, mp 200.5–202 °C) and **12f** (0.30 g, 11%, mp 158–164 °C), respectively. (*E*)- and (*Z*)-**12f**: ^{1}H NMR 6.50 (s, C=CH, *Z* isomer), 5.40 (s, C=CH, *E* isomer); mass spectrum, m/e 553.124 (M^+; calcd for $C_{24}H_{27}NO_{12}S$ 553.128).

13: mp 205–206 °C (2-butanone); ^{1}H NMR δ 3.99, 3.95, and 3.91 (br s, 15 H, OCH_3), 3.35–3.15 (m, 4 H, Pyrr H(α)), 2.00–1.70 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 176.4 (s, C=O), 167.5, 166.3, 164.6, 164.4, 161.5 (s, C=O(OCH_3)), 145.1, 140.2, 139.9, 139.1, 133.6, 132.3, 130.0, 129.4 (s, Ar C), 54.1, 53.4, 53.1, 52.9, 52.7 (q, OCH_3), 52.4 (t, Pyrr C(α)), 26.4 (t, Pyrr C(β)); mass spectrum, m/e 521.101 (M^+; calcd 521.099).

Anal. Calcd for $C_{23}H_{23}NO_{11}S$ (mol wt 521.50): C, 52.97; H, 4.45; N, 2.69; S, 6.15. Found: C, 53.06; H, 4.45; N, 2.60; S, 5.97.

5-Phenyl-2-(phenylcarbamoyl)-3-(1-pyrrolidinyl)-thiophene (14). A solution of phenyl isocyanate (0.65 g, 5.5 mmol) in 5 mL of acetonitrile was added dropwise to a solution of **1d** (1.15 g, 5 mmol) in 15 mL of acetonitrile at 0 °C and the mixture was stirred overnight at room temperature. After cooling, the mixture was filtered to yield 1.5 g of **14** (86%): mp 155–156 °C (ethyl acetate); ^{1}H NMR δ 10.82 (br s, 1 H, N-H), 7.80–7.00 (m, 11 H, Ar H), 3.40–3.10 (m, 4 H, Pyrr H(α)), 2.25–1.95 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 160.0 (s, C=O), 150.3 (s), 146.8 (s), 138.6 (s), 133.6 (s), 129.0 (d), 128.5 (d), 125.6 (d), 123.5 (d), 119.3 (d),

(73) P. B. Woller and E. W. Garbisch, *J. Am. Chem. Soc.*, **94**, 5310 (1972).
(74) Reference 72, p 280.

Table IV. Crystallographic Data of 6e and 12d

compound	6e	12d
formula	$C_{21}H_{23}NO_5S$	$C_{26}H_{27}NO_8S$
radiation used	Mo Kα (0.7107 Å)	Cu Kα (1.5418 Å)
maximum θ, deg	30	60
space group	$P2_1/c$	$P2_1/n$
a, Å	10.835 (3)	11.584 (1)
b, Å	11.803 (3)	28.555 (2)
c, Å	15.950 (4)	8.183 (1)
β, deg	105.61 (3)	108.41 (1)
d_x, g cm^{-3}	1.36	1.33
Z	4	4
no. of refl. measured	3587	4114
observed refl. ($I > \sigma(I)$)	3022	2497
R, %	7.7	8.3

and 117.6 (d) (Ar C and H-4), 54.1 (t, Pyrr C(α)), 24.8 (t, Pyrr C(β)); mass spectrum, m/e 348.128 (M$^+$; calcd 348.130).

Anal. Calcd for $C_{21}H_{20}N_2OS$ (mol wt 348.46): C, 72.38; H, 5.79; N, 8.04; S, 9.20. Found: C, 72.40; H, 5.79; N, 7.97; S, 9.02.

Reaction of 1d with DMAD and Phenyl Isocyanate. Synthesis of 1:1:1 Addition Product 15. A solution of phenyl isocyanate (2.38 g, 20 mmol) in 10 mL of acetonitrile and a solution of DMAD (0.71 g, 5 mmol) in 10 mL of acetonitrile were added dropwise and simultaneously to a solution of **1d** (1.15 g, 5 mmol) in 10 mL of acetonitrile at 10 °C and the mixture was stirred overnight at room temperature. The acetonitrile and excess phenyl isocyanate were removed under reduced pressure (0.1 torr) and the residue was separated by column chromatography (silica gel, chloroform) to give successively **14** (0.2 g, 11%), **15** (0.65 g, 15%), and **6d** (1.10 g, 30%). **15**: mp 180–185 °C dec; ^{1}H NMR δ 7.55–7.00 (m, 11 H, Ar H and NH), 6.80 (s, 1 H, thiophene H), 3.88 (s, 6 H, OCH_3), 3.45–3.15 (m, 4 H, Pyrr H(α)), 2.10–1.80 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 168.2, 167.5, and 164.4 (s, C=O), 150.9 (s), 147.7 (s), 142.8 (s), 140.3 (s), 137.5 (s), 128.8 (d), 127.7 (d), 124.2 (d), 119.6 (d), 116.9 (d), 115.0 (s), and 108.4 (s) (Ar C and thiophene C), 52.6 (q, OCH_3), 50.5 (t, Pyrr C(α)), 25.8 (t, Pyrr C(β)); mass spectrum, m/e 371.120 (M$^+$ - C_6H_5NCO; calcd 371.119), 119.037 (calcd for C_6H_5NCO 119.037).

Anal. Calcd for $C_{27}H_{26}N_2O_5S$ (mol wt 490.58): C, 66.10; H, 5.34; N, 5.71; S, 6.54. Found: C, 65.71; H, 5.36; N, 5.70; S, 6.38.

Reaction of 1f with Dicyanoacetylene in Dichloromethane. 6,7,7a,8-Tetrahydro-2,3-bis(methoxycarbonyl)-8-cyano-5*H*-thieno[2,3-*b*]pyrrolizine-8-acetonitrile (17). A solution of dicyanoacetylene[75] (7 mmol) in 10 mL of dichloromethane was added dropwise to a solution of **1f** (6 mmol) in 15 mL of dichloromethane at −60 °C. After 2 h, the mixture was allowed to warm to room temperature. After removal of the solvent, the residue was purified by column chromatography (silica gel, toluene–ethyl acetate, 3:1) to yield **17** (15%): mp 136.5–137.5 °C; ^{1}H NMR δ 4.84 (dd, J(7-7a) = 6 ± 1 and 10 ± 1 Hz, 1 H, H-7a), 3.94 and 3.88 (s, 6 H, OCH_3), 3.02 (s, 2 H, CH_2CN) in broad multiplet 3.80–2.80 (2 H, H-5), 2.25–1.80 (m, 4 H, H-6 and H-7); ^{13}C NMR δ 163.3 and 160.4 (s, C=O), 156.0, 138.3, 124.6, and 121.1 (s, thiophene C), 119.1 and 114.7 (s, CN), 79.8 (d, C-7a), 52.9 and 52.8 (q, OCH_3), 51.5 (t, C-5), 43.8 (s, C-8), 26.8 and 26.1 (t, C-6 and C-7), 25.0 (t, $CH_2(CN)$); mass spectrum, m/e 345.079 (M$^+$; calcd 345.078).

Anal. Calcd for $C_{16}H_{15}N_3O_4S$ (mol wt 345.33): C, 55.64; H, 4.38; N, 12.17. Found: C, 55.10; H, 4.43; N, 11.80.

Reaction of 1d with Methyl Propiolate. Methyl (*E*)- and (*Z*)-3-[5-Phenyl-3-(1-pyrrolidinyl)-2-thienyl]-2-propenoate (19). A solution of methyl propiolate (12 mmol) in 10 mL of methanol was added to a solution of **1d** (10 mmol) in 15 mL of methanol under a nitrogen atmosphere at 0 °C. The mixture was stirred overnight at room temperature and the solvent was then removed under reduced pressure. The ^{1}H NMR spectrum of the crude product showed two doublets at δ 5.70 and 5.10, indicating the formation of a mixture of the *E* and *Z* isomers. Preparative TLC (silica gel, dichloromethane) afforded one of the isomers as an orange-colored crystalline product (60%): mp 120–122 °C dec; ^{1}H NMR δ 7.90 and 5.72 (d, J = 14 Hz, 2 H, HC=CH), 7.60–7.10 (m, 5 H, Ar H), 6.72 (s, 1 H, thiophene H-4), 3.82 (s, 3 H, OCH_3), 3.80–3.30 (m, 4 H, Pyrr H(α)), 2.20–1.80 (m, 4 H, Pyrr H(β)); ^{13}C NMR δ 168.4 (s, C=O), 150.4 (s), 145.0 (s), 138.2 (d), 133.4 (s), 128.7 (d), 128.4 (d), 125.6 (d), 115.4 (d), 109.7 (s), and 107.4 (d) (Ar C, thiophene C, and C=C), 51.7 (t, Pyrr C(α)), 51.1 (q, OCH_3), 25.7 (t, Pyrr C(β)).

Dimethyl (*E*)- and (*Z*)-2-[3-(4-Morpholinyl)-5-phenyl-2-thienyl]-2-butenedioate (20). A solution of DMAD (5.5 mmol) in 10 mL of methanol was added to a solution of 4-(4-morpholinyl)-2-phenylthiophene (**21**, 5 mmol) in 10 mL of methanol under a nitrogen atmosphere at 0 °C. The mixture was stirred overnight at room temperature and the solvent was then removed under reduced pressure. The ^{1}H NMR spectrum of the crude product showed two vinylic protons at δ 6.40 and 6.18, indicating the formation of a mixture of the *E* and *Z* isomers. Preparative TLC (silica gel, chloroform) yielded one of the isomers as a pure product: mp 144–146 °C; ^{1}H NMR δ 7.70–7.30 (m, 5 H, Ar H), 7.24 (s, 1 H, thiophene H), 6.38 (s, 1 H, C=CH), 3.97 and 3.76 (s, 6 H, OCH_3), 3.90–3.70 (m, 4 H, morph H(β)), 3.10–2.90 (m, 4 H, morph H(α)); mass spectrum, 387.112 (M$^+$; calcd 387.114).

Anal. Calcd for $C_{20}H_{21}NO_5S$ (mol wt 387.46): C, 62.00; H, 5.46; N, 3.61; S, 8.28. Found: C, 62.11; H, 5.44; N, 3.71; S, 8.40.

4-(4-Morpholinyl)-2-phenylthiophene (21). Reaction of morpholine with 4,5-dihydro-5-phenyl-3(2*H*)-thiophenone and aromatization of the product formed, by the procedure described for **1d**, gave compound **21**: bp 165–175 °C (0.2 torr); mp 87–88 °C (ethanol) (lit.[76] mp 87 °C); ^{1}H NMR δ 7.65–7.10 (m, 5 H, Ar H), 6.96 (d, J = 2 Hz, 1 H, H-3), 6.00 (d, J = 2 Hz, 1 H, H-5), 3.90–3.60 (m, 4 H, morph H(β)), 3.20–2.80 (m, 4 H, morph H(α)).

Crystallographic Data and X-ray Structure Analysis of 6e and 12d. X-ray intensities of suitable crystals of **6e** and **12d** were measured with a Philips PW 1100 diffractometer (graphite monochromated radiation). General information on the data collection and the unit cells is given in Table IV. No absorption corrections have been applied to the measured intensities. The structures were solved by direct methods[77] (MULTAN 78) and refined by the full-matrix least-squares method (ORFLS).[78] Parameters refined in the last cycles for **6e** were positional and isotropic thermal parameters of all atoms (including hydrogen). The sulfur atom was refined with anisotropic thermal parameters. In the case of **12d** the parameters refined were positional and anisotropic thermal parameters of all non-hydrogen atoms. A difference Fourier synthesis made at this stage (R = 8.3%) clearly revealed the hydrogen atoms except some of them belonging to methyl groups.

Acknowledgment. We express our gratitude to Mr. B. Kaptein, Dr. A. C. Marcelis, Dr. H. C. Mutreja, and Dr. G. Okay for their contributions to parts of the experimental work. We also acknowledge Mr. T. W. Stevens for recording the mass spectra and Mrs. J. L. M. Klop-Vrielink and Miss J. M. Visser for recording the NMR spectra. We are indebted to Dr. R. Visser for discussion of the spectroscopic properties of the new compounds.

Registry No. **1a**, 62785-93-7; **1b**, 75782-51-3; **1c**, 75782-52-4; **1d**, 62785-94-8; **1e**, 62785-95-9; **1f**, 67242-97-1; **1g**, 62785-96-0; **1h**, 39713-58-1; **2c**, 75782-53-5; **3c**, 75782-54-6; **5c**, 75782-55-7; **5d**, 72238-47-2; **5f**, 72238-52-9; **6a**, 62785-97-1; **6b**, 75782-56-8; **6c**, 75782-57-9; **6d**, 62785-99-3; **6e**, 62828-21-1; **6f**, 72238-53-0; **6g**, 62786-00-9; **6h**, 62785-98-2; **7**, 75782-58-0; **8a**, 75782-59-1; **8b**, 75782-60-4; **9**, 75782-61-5; **10**, 75782-62-6; (*E*)-**12d**, 72238-34-7; (*Z*)-**12d**, 72238-51-8; (*E*)-**12f**, 72238-49-4; (*Z*)-**12f**, 72238-48-3; **13**, 72238-50-7; **14**, 75782-63-7; **15**, 75782-64-8; **17**, 75782-65-9; (*E*)-**19**, 75782-66-0; (*Z*)-**19**, 75782-67-1; (*E*)-**20**, 75782-68-2; (*Z*)-**20**, 75782-69-3; **21**, 2832-97-5; mercaptoacetic acid, 68-11-1; 4-methyl-2-pentenoic acid,

(75) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

(76) T. Bacchetti, A. Alemagna, and B. Danieli, *Tetrahedron Lett.*, 2001 (1965).

(77) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970); P. Main, "Recent Developments in MULTAN, Computing in Crystallography", H. Schenk, Ed., Delft University Press, The Netherlands, 1978.

(78) W. R. Busing, K. O. Martin, and H. A. Levy, ORFLS, Oak Ridge National Laboratory, Report ORNL-TM-305 (1962).

10321-71-8; 3-[(carboxymethyl)thio]-4-methylpentanoic acid, 75782-70-6; 4,5-dihydro-5-(1-methylethyl)-3(2*H*)-thiophenone, 75782-71-7; 4,5-dihydro-5-(1-methylethyl)-3(2*H*)-thiophenone oxime, 75782-72-8; 3-amino-5-(1-methylethyl)thiophene HCl, 75782-73-9; 1,4-dibromobutane, 110-52-1; 4,4-dimethyl-2-pentenoic acid, 6945-35-3; 3-[(carboxymethyl)thio]-4,4-dimethylpentanoic acid, 75782-74-0; 4,5-dihydro-5-(1,1-dimethylethyl)-3(2*H*)-thiophenone, 75782-75-1; 4,5-dihydro-5-(1,1-dimethylethyl)-3(2*H*)-thiophenone oxime, 75782-76-2; 3-amino-5-(1,1-dimethylethyl)thiophene HCl, 75782-77-3; 3-(2-methoxyphenyl)propenoic acid, 6099-03-2; 3-[(carboxymethyl)-thio]-3-(2-methoxyphenyl)propanoic acid, 75782-78-4; 4,5-dihydro-5-(2-methoxyphenyl)-3(2*H*)-thiophenone, 75782-79-5; 2,3-dihydro-2-(2-methoxyphenyl)-4-(1-pyrrolidinyl)thiophene, 75790-45-3; 3-(1-pyrrolidinyl)benzo[*b*]thiophene, 40311-37-3; 4,5-dihydro-5-phenyl-3-(2*H*)-thiophenone, 36748-19-3; 4,5-dihydro-5-phenyl-3(2*H*)-thiophenone oxime, 75782-80-8; 3-amino-5-phenylthiophene, 75782-81-9; 1,4-dibromobutane-*1,1,4,4-d*$_4$, 36684-45-4; phenyl isocyanate, 103-71-9; dicyanoacetylene, 1071-98-3; methyl propiolate, 922-67-8; morpholine, 110-91-8; DMAD, 762-42-5.

Supplementary Material Available: X-ray structure, fractional atomic coordinates, mean square amplitudes of thermal vibration, bond distances, and bond angles of **6e** (6 pages). Ordering information is given on any current masthead page.

Effect of an Alkynyl Group on the Regio- and Stereochemistry of the Ring Opening of 1,2-Epoxides. Ring-Opening Reactions of 1-Ethynyl-1,2-epoxycyclohexane

Carlo Battistini, Paolo Crotti, and Franco Macchia*

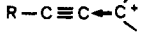
Istituto di Chimica Organica della Facoltà di Farmacia, 56100 Pisa, Italy

Received May 16, 1980

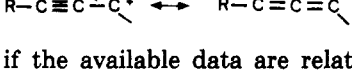
The regio- and stereochemistry of the ring-opening reactions of 1-ethynyl-1,2-epoxycyclohexane (**1**) under acidic conditions have been examined. The reactions were almost completely regiospecific, giving mainly products arising from attack by the nucleophile on the tertiary carbon. The stereoselectivity was not completely anti, affording mixtures of syn and anti addition products, which vary markedly with the reaction conditions (a maximum of 65% syn addition was observed in the reaction of **1** with CCl_3COOH in CH_2Cl_2). The results were rationalized through a mechanism analogous to that previously admitted for aryloxiranes, which implies intermediate structures with a discrete carbocationic character and shows that the ethynyl group has a discrete capability of stabilizing an adjacent carbenium ion. Comparison of the relative percentages of syn opening observed in the reactions of **1** with the corresponding ones obtained in the reactions of the analogous phenyl-substituted (**9**) and methyl-substituted (**10**) epoxides seems to indicate that the stabilizing effect of an ethynyl group is lower than that of a phenyl but, contrary to expectations, higher than that of a methyl.

It is well-known that the ring opening of aliphatic and cycloaliphatic oxiranes under acidic conditions occurs with almost complete inversion of configuration.[1,2] However, when substituents as double bonds or aromatic systems are directly linked to the epoxide ring, the steric course of the ring-opening reactions is not entirely anti.[1,3] The stereoselectivity of these reactions is highly variable, depending to a large extent on the structure of the epoxide and on the reaction conditions in general. It can range from an excess of anti ring opening to complete syn stereoselectivity. As with the reactions of 1-aryl-substituted 1,2-epoxides, it has been found that there is strict relationship between the capability of the aromatic system to stabilize the carbocationic center at the time of the breaking of the benzylic C–O bond of the protonated oxirane and the percentage of syn opening.[1b,c]

The effect of an alkynyl group in stabilizing an adjacent carbenium ion should result from the sum of two conflicting effects: its electron withdrawing effect (expression 1) and its mesomeric electron releasing effect (expression 2).[4]



(1)



(2)

Even if the available data are relatively scarce, the solvolysis rates for tertiary halides (2-substituted 2-propyl halides)[4] reflect the capability of an ethynyl group to stabilize an adjacent carbocation is much lower not only than that of an ethenyl or phenyl group but also than that of an alkyl group.[4] The same order could be also derived from the σ_p^+ values of the same groups[5,6] (see Table I). The σ_m substituent constant for the ethynyl group,[5] 0.205,

Table I. Selected Substituent Constants

substituent	σ_p^+	σ_m^+	σ_m
C_2H_5	−0.265[a]	−0.064[a]	−0.07[c]
C_6H_5	−0.179[a]	0.109[a]	0.06[c]
HC≡C	0.179[b]	0.330[b]	0.205[b]

[a] Reference 6. [b] Reference 5. [c] Reference 7.

(1) Buchanan, J. G.; Sable, H. Z. in "Selective Organic Transformations"; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 1, p 1.
(2) Barili, P. L.; Bellucci, G.; Macchia, B.; Macchia, F.; Parmigiani, G. *Gazz. Chim. Ital.* **1971**, *101*, 300.
(3) (a) Battistini, C.; Crotti, P.; Ferretti, M.; Macchia F. *J. Org. Chem.* **1977**, *42*, 4067. (b) Battistini, C.; Balsamo, A.; Berti, G.; Crotti, P.; Macchia, B.; Macchia, F. *J. Chem. Soc., Chem. Commun.* **1974**, 712. (c) Balsamo, A., Crotti, P.; Macchia, B.; Macchia, F. *Tetrahedron* **1973**, *29*, 199 and references therein cited.
(4) Richey, H. G., Jr.; Richey, J. M. In "Carbenium Ions"; Olah, G. A., Schleyer, P. R., Eds.; Wiley-Interscience: New York, 1970; Vol. 2, p 931.
(5) Landgrebe, J. A.; Rynbrandt, R. H. *J. Org. Chem.* **1966**, *31*, 2585.
(6) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
(7) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420.

0022-3263/81/1946-0434$01.00/0