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REACTIONS OF THIOPHENES WITH ACETYLENES IN POLAR SOLVENTS; A NOVEL ANNULATION REACTION

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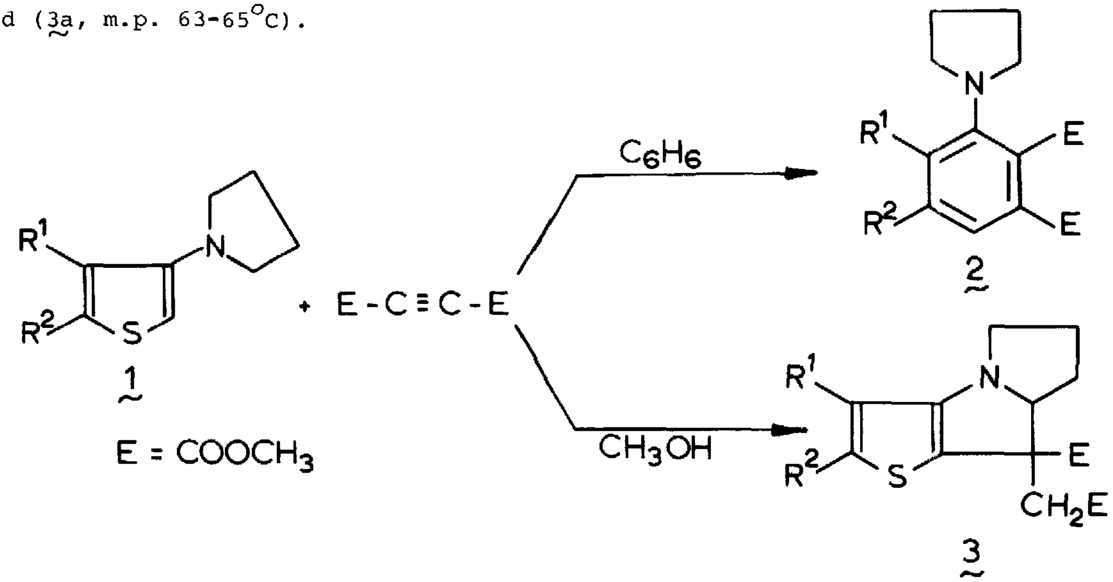
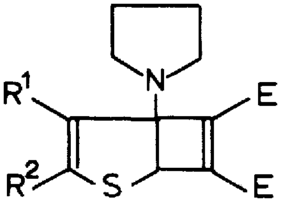
Although for a long time thiophenes have been considered to be inert in cycloaddition reactions, recently some have been reported to react with acetylenes via either a (2+2)- or a (4+2)-cycloaddition reaction[1-4]. Particularly some of the (2+2)-cycloadditions of thiophenes[1,2], and of benzo[*b*]thiophenes[5-7], proved to be versatile reactions in the synthesis of 1-heterocycloheptatrienes. For example, reaction of 3-pyrrolidinothiophenes (**1**) with dimethyl acetylenedicarboxylate in apolar solvents at low temperature yielded the corresponding thiepins (**5**), a class of anti-aromatic compounds that could not be obtained by other routes. We now report that in polar solvents the reactions of **1** with dimethyl acetylenedicarboxylate take an entirely different course.

From the reaction of **1a** (R^1=H and R^2=Me) with dimethyl acetylenedicarboxylate in chloroform (16 hours/25°C) we obtained not only the expected benzene derivative (**2a**) - formed by (2+2)-cycloaddition, isomerization and subsequent desulphurization of the corresponding thiepin - but also a small amount of an unknown compound (**3a**, m.p. 63-65°C).





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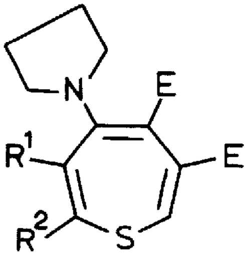

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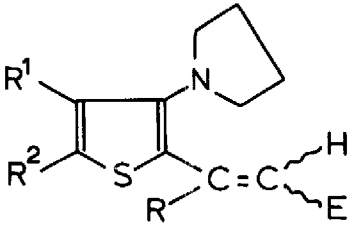


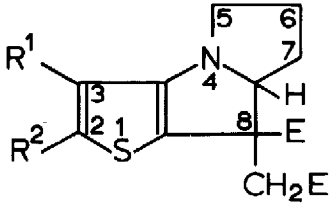
6a, R=E 6b, R=H

In other solvents the two compounds (2a and 3a) were formed in totally different ratios. In benzene the reaction yielded exclusively the benzene derivative (2a), but in methanol the other type of compound (3a) was selectively produced. Several other 3-pyrrolidinothiophenes[8] underwent the same type of reaction with dimethyl acetylenedicarboxylate in methanol (see Table).

The mass spectra and elemental analyses indicated that compounds 3 had been formed from one molecule of 3-pyrrolidinothiophene and one molecule of dimethyl acetylenedicarboxylate. ^{1}H- and ^{13}C-NMR data and the high thermal stability were not consistent with structures of the expected products: (2+2)-cycloadducts (4), thiepins (5) or Michael adducts (6a). Surprisingly they pointed to a tricyclic structure (3), which was subsequently confirmed by an X-ray analysis of 3d (see Figure).

Table

6,7,7a,8-Tetrahydro-5*H*-thieno[3,2-*b*]pyrrolizines (3)



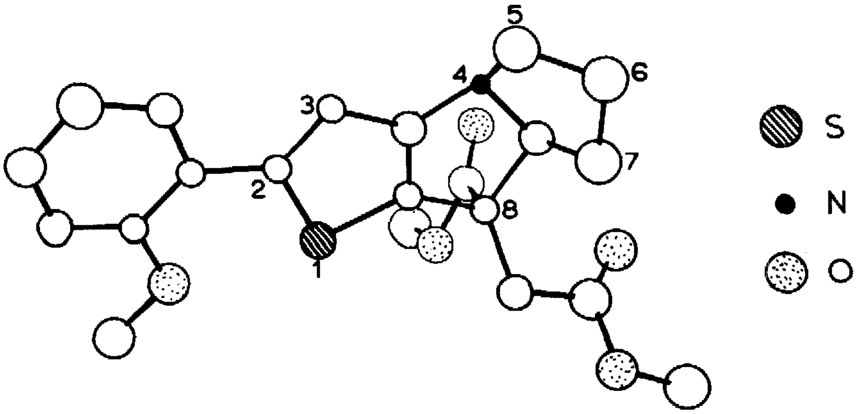
	R^1,	R^2	m.p. (^{o}C)	yield (%)	δH(2)/H(3)[a]	δH(7a)[b]	δ(CH_2E)[c]
3a	H ,	Me	63-65	52	6.25(s)	4.72	3.25;2.97
3b	Me,	H	oil	50	6.53(s)	4.69	3.01;2.82
3c	H ,	Ph	130-131.5	45	6.76(s)	4.74	3.27;3.03
3d	H ,	o-(MeO)Ph	181-183	64	6.96(s)	4.84	3.36;3.00
3e	Ph,	Ph	180(dec)	50	--	4.90	3.30;3.06

a In deuteriochloroform with TMS as the internal reference compound

b Doublet of doublet, *J*(7-7a) = 6 ± 1 and 10 ± 1 Hz

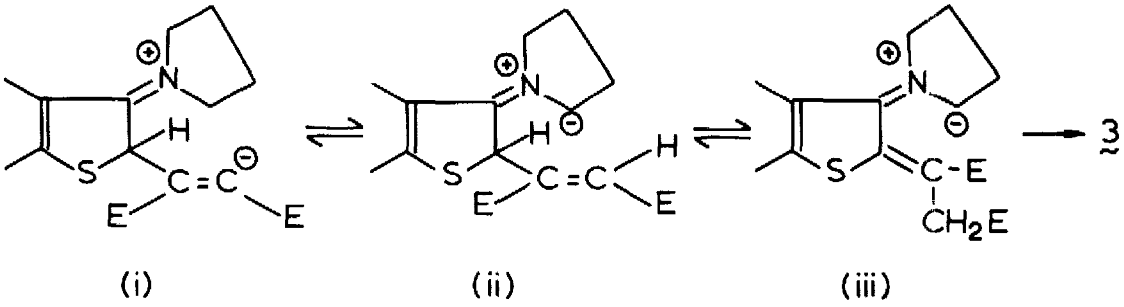
c AB-system, *J* = 17 ± 1 Hz

Figure



Structure of 3d

The formation of **3** can be rationalized by assuming initial attack at C(2) by dimethyl acetylenedicarboxylate to give a dipolar intermediate (*i*). Subsequent proton transfer to the strongly basic centre yields an azomethinylid which can be present in two tautomeric forms (*ii* and *iii*). In one of these (*iii*) a rapid intramolecular 1,3-dipolar addition with the electron-deficient double bond might occur to give **3**:



Arguments supporting this mechanism are the known reactions of azomethinylids (*e.g.* generated from 2-(4-nitrobenzyl)-3,4-dihydroisoquinolinium bromide by reaction with triethylamine) with electron-poor dipolarophiles (*e.g.* dimethyl fumarate)[9]. Further experimental evidence was provided by the results of the reaction of **1c** with methyl propiolate, which gave a mixture of Michael adducts (**6b**) rather than a tricyclic compound. The crucial intermediate in this reaction (compare with *iii*) does not have an electron-deficient carbon-carbon double bond required for a fast 1,3-dipolar addition[10].

The striking difference in the course of the reaction of 3-pyrrolidinothiophenes with electron-deficient acetylenes in polar and in apolar solvents might be attributed to the fact that in polar solvents one σ-bond is initially formed to give a dipolar intermediate (*i*) that is stabilized by solvation, whereas in apolar solvents two σ-bonds are formed in a nearly concerted fashion, to yield a (2+2)-cycloadduct (4). Although such a concerted thermal $[{}_{\pi}2_s + {}_{\pi}2_s]$-cycloaddition is expected to be a non-allowed high-energy process[11], the recent work of Epiotis[12] on the theory of (2+2)-cycloaddition predicts that when the reacting double bonds are substituted with strongly electron-donating or electron-withdrawing groups the activation energy of such a "forbidden" reaction will be lowered.

A similar reasoning can be used to explain the results of some other reactions of electron-rich heterocycles with electron-deficient acetylenes[13,14]. These also yielded mixtures of (2+2)-cycloadducts and products that are most likely derived from dipolar intermediates.

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