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THIEPIN CHEMISTRY. 1:2 REACTION PRODUCTS FROM 3-(1-PYRROLIDINYL)THIOPHENS AND DIMETHYL ACETYLENEDICARBOXYLATE (DMAD)

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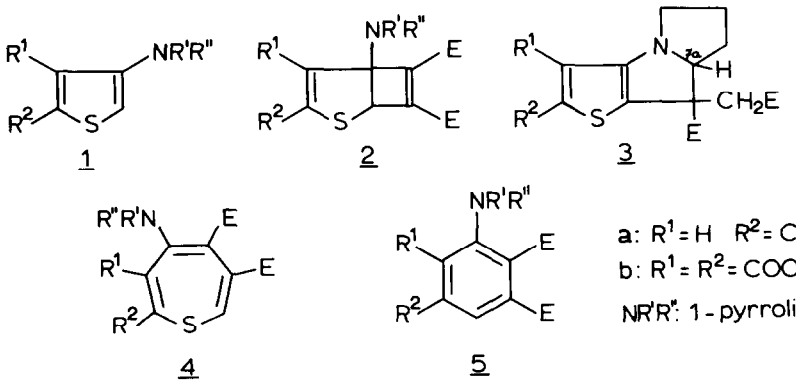
Abstract. Thiepins are intercepted before desulfurization can occur when 3-(1-pyrrolidinyl)thiophens are reacted with excess of DMAD. The structure of one of the reaction products was established by single-crystal X-ray analysis.

Previously[1,2] we have reported that 3-(1-pyrrolidinyl)thiophens (1) react with dimethyl acetylenedicarboxylate (DMAD) to give 1:1 reaction products. The products are 2-thiabicyclo[3,2,0]hepta-3,6-dienes (2) when the reactions are carried out in apolar solvents and 6,7,7a,8-tetrahydro-5*H*-thieno[3,2-*b*]pyrrolizines (3) when the reactions take place in methanol. In both reactions we use the "enamine" type of reactivity of 1. The reactions in apolar solvents are of particular interest to us because 2-thiabycyclo[3,2,0]hepta-3,6-dienes (2) are the bicyclic isomers of thiepins. These 8π-electron heterocycles have hitherto not been isolated although several years ago we have shown that thiepins are formed by valence isomerization of 5-(1-pyrrolidinyl)-2-thiabicyclo[3,2,0]hepta-3,6-dienes at -30°C. However, these thiepins (4) eliminate sulfur under reaction conditions and the corresponding benzene derivatives (5) were obtained.



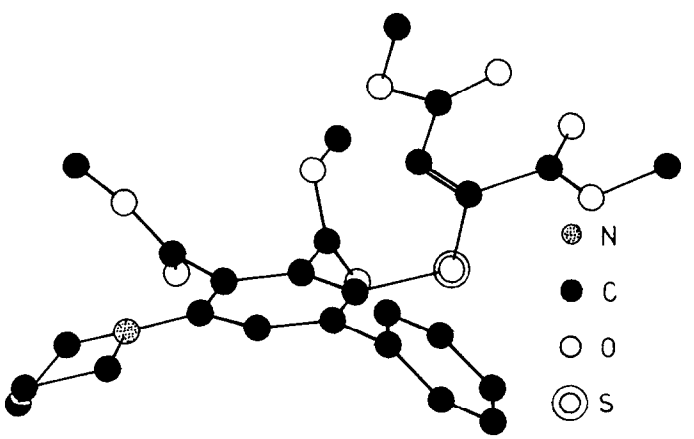
1 2 3

4 5

a: R^1 = H R^2 = C_6H_5
b: R^1 = R^2 = $COOCH_3$(E)
NR'R": 1-pyrrolidinyl

As part of our programme aimed at the synthesis of more stable thiepins we have investigated the possible conversion of 2-phenyl- and 2,3-bis(methoxycarbonyl)-4-(1-pyrrolidinyl)thiophens (1a and 1b) with DMAD into the corresponding thiepins[3]. When 2-phenyl-4-(1-pyrrolidinyl)thiophen (1a) was reacted with DMAD in various solvents we found that a rapid conversion took place even at room temperature.

The products formed (see table) varied with the solvent polarity. In benzene 3,4-bis(methoxycarbonyl)-5-(1-pyrrolidinyl)biphenyl (5a) was formed in 40% yield, m.p. 117-118°, ^{1}H NMR δ($CHCl_3$): 7.10 (s, H_6), 7.3-7.7 (m, 6H, $H_{arom.}$). This reaction does not differ from those of other 3-(1-pyrrolidinyl)thiophens[1] and it indicates that in apolar solvents 5,6-bis(methoxycarbonyl)-2-phenyl-4-(1-pyrrolidinyl)thiepin (4a) has a similar stability to that of the other thiepins obtained previously[1]. With nitromethane as solvent the thieno[3,2-*b*]pyrrolizine (3a)[2] was obtained in 76% yield, but a reaction in acetonitrile yielded a mixture of 3a and two other products in a ratio strongly dependant upon reaction temperature and the ratio of 1a and DMAD. Mass spectrometry showed that these compounds were isomeric 1:2 reaction products; M^+ 513.148 ($C_{26}H_{27}NO_8S$). The compounds were partially separated by column chromatography and TLC resp. (SiO_2, $CHCl_3$). The first was a pure crystalline compound, m.p. 184 -185°. IR(KBr): 1710 cm^{-1} and 1580 cm^{-1} (C=O). ^{1}H NMR δ($CDCl_3$): 5.30 (s, 1H, C=C-H), 6.78 (s, 1H, H_6). ^{13}C NMR δ($CDCl_3$): 106.3 (s) and 114.2 (d) (C=C), 163.9 (s), 165.1 (s), 167.3 (s) and 167.6 (s) (C=O) The other isomer was obtained as an oil. ^{1}H NMR δ($CDCl_3$): 6.16 (s, 1H, C=C-H), 6.74 (s, 1H, H_6). ^{13}C NMR δ($CDCl_3$): 112.3 (s) and 119.8 (d) (C=C), 164.0 (s), 164.7 (s), 167.7 (s) and 167.9 (s) (C=O). Single-crystal X-ray analysis showed that the crystalline compound was the E-isomer of the biphenyl derivative 6.



The crystal structure determination was based on 2497 reflections with a net intensity greater than the standard deviation from counting statistics. These reflections have been measured on an automatic single crystal diffractometer (Philips PW1100, CuK_α radiation, graphite monochromator, $\omega/2\theta$ scan mode, $2.5<\omega<60°$). The space group was $P2_1/n$. The cell constants are : a=11.585 (1), b=28.555 (2), c=8.183 (1) Å; β=108.41 (1)°; Z=4. The structure was solved by direct methods and refined in the usual way[7]. The final R factor after refinement including the non-hydrogen atoms with anisotropic temperature factors was 8.5%[8]. The molecular structure is visualized in the accompanying figure.

Similar types of 1:2 reaction products were formed when 2,3-bis(methoxycarbonyl)-4-(1-pyrrolidinyl)thiophen (1b) was reacted with DMAD in nitromethane at 100°C. From the reaction product we isolated a mixture of E+Z isomers 6b in a yield of 10% m.p. 158-164°. MS: M^+ 553.124 ($C_{24}H_{27}NO_{12}S$). ^{1}H NMR δ($CDCl_3$): 5.40 (s, 1H, C=C-H, E-isomer), 6.50 (s, 1H, C=C-H, Z-isomer). The major product obtained from this reaction however was 2,3,5,7,8-pentakis(methoxycarbonyl)-6-(1-pyrrolidinyl)

-*4H*-1-benzothiopyran-4-on (7) in 40% yield. The orange-red crystals, m.p. 205-206.5°, had a molecular composition of $C_{23}H_{23}NO_{11}S$ (M^+ 521.101). UV[9]: λ_{max}^{EtOH} 230 (log ε=4.33), 265(log ε=4.21) and 361(log ε = 3.89). IR(KBr): 1740 cm^{-1} and 1630 cm^{-1} (C=O). ^1H NMR δ($CDCl_3$): 3.91, 3.95, 3.99 (OCH_3). ^{13}C NMR δ($CDCl_3$): 129.4, 130.0, 132.3, 133.6, 139.1, 139.9, 140.2, 145.1 (s, $C_{arom.}$), 161.5, 164.4, 164.6, 166.3, 167.5, 176.4 (C=O).

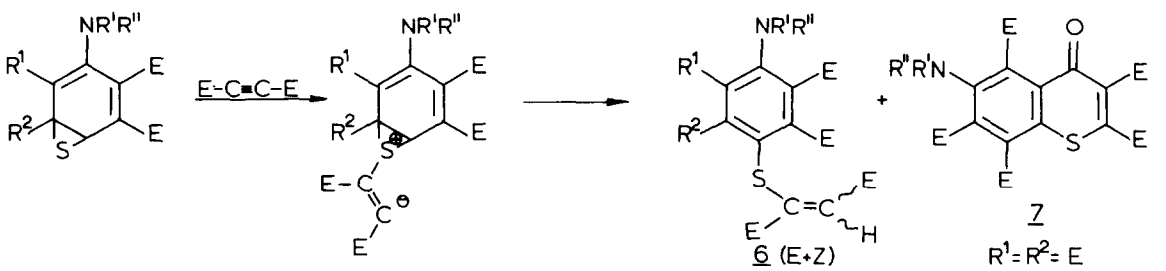
The reaction of 1b with DMAD in toluene at 100° gave 1,2,4,5-tetrakis(methoxycarbonyl)-3-(1-pyrrolidinyl)benzene 5b as main product in 35% yield, m.p. 168.5-170.5°. MS: M^+ 379.125. ($C_{18}H_{21}NO_8$). IR(KBr): 1735 cm^{-1} (C=O). ^1H NMR δ($CDCl_3$): 3.94 (s, OCH_3), 8.46 (s, 1H, $H_{arom.}$). ^{13}C NMR δ($CDCl_3$): 128.3 (d), 129.3 (s), 141.4 (s), 145.4 (s) ($C_{arom.}$), 164.3 and 167.5 (C=O). Reaction of 1b in *n*-butanol gave a mixture of 5b (20%) together with *5H*-thieno[3,2-*b*]pyrrolizine 3b which was isolated in a yield of 60%, m.p. 96.5-98°. M^+ 411.100 ($C_{18}H_{21}NO_8S$). ^1H NMR δ($CDCl_3$): 3.75, 3.85 and 3.93 (OCH_3), 4.70 (dd, 1H, H_{7a}, J(7-7a)=6±1 and 10±1H_z).

Table. Reactions of (1-pyrrolidinyl)thiophens with DMAD

Reactant	Solvent	Mol.Ratio DMAD/1	Temp °C	Product isolated (%) 5	3	6	7
1a	C_6H_6	1.1	20[a]	40	-	-	
1a	CH_3CN	2.0	20[a]	-	34	26[c]	
1a	CH_3CN	5.0	20[a]	-	20	47[c]	
1a	CH_3CN	5.0	-30[a]	-	46	14[c]	
1a	CH_3NO_2	1.1	20[a]	-	76	-	
1a	CH_3OH	1.1	20[a]	-	63	-	
1b	$C_6H_5CH_3$	1.1	100[b]	35	-	-	-
1b	CH_3NO_2	4.0	100[b]	-	-	10[c]	40
1b	n-C_4H_9OH	1.1	100[b]	20	60	-	-

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

From this result we conclude that the ester groups in thiepin 4b provide insufficient stability to prevent desulphurization at 100° in toluene or n-butanol.



The thiepin 4b cannot be synthesized by this method at lower temperature because the ester groups in 1b lower the "enamine" reactivity[11]. Obviously in our approach the desired effect of the ester groups in the thiepin conflicts with the necessary reactivity of the thiophen in the (2+2)-cycloaddition with DMAD in apolar solvents Formation of 6 and 7 in polar aprotic solvents can be rationalized as the initial interception of the thiepin (4a or 4b) before elimination of sulphur can occur. The S-alkylation of 4 by a second molecule of DMAD or alternatively S-alkylation of the corresponding thianorcaradiene followed by proton transfer and aromatization gives 6 (E+Z). In the reaction of 1b (R^1=R^2=$COOCH_3$) there are two competing pathways in operation, one to give 6b (E+Z) and a second which proceeds via a nucleophilic attack at the ester group (R^2) adjacent to sulphur. Elimination of methanol yields the 1-benzothiopyran-4-on (7).

S-alkylation by DMAD has been reported recently by Kobayashi and Mutai[12] for 2,5-diphenyl-1,4-dithiin-1,1-dioxide. In addition Hofmann and Molnar[13] have reported that S-methyl-1-benzothiepinium salts rearrange to the corresponding methylthionaphthalenes at higher temperatures through intermediacy of the S-methylthianorcaradienes.

The formation of 6 and 7 are the first examples of reactions in which thiepin intermediates are captured before desulphurization[14]. This behaviour of thiepins is completely analogous to that of 1-benzothiepins for which both desulphurization and rearrangement without the loss of sulfur has been reported[16,17].

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