1,2,3 -TRIAZOLO[5,1-*b*]THIAZOLES. PART 3.[1] THE REACTION BETWEEN A TRIAZOLOTHIAZOLIUM YLIDE AND ACETYLENIC DIPOLAROPHILES

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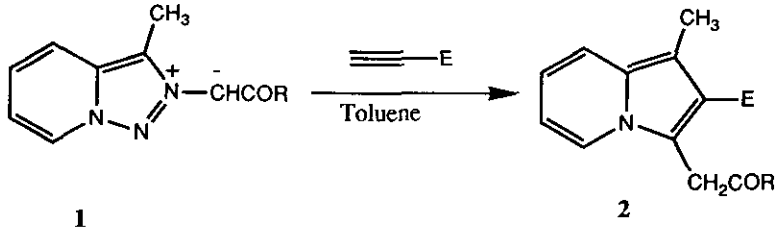
Abstract - The reaction between 2-methoxycarbonylmethyl-3-methyl- 1,2,3-triazolo[5,1-*b*]thiazolium ylide (**5**) and methyl propiolate gives the dienes (**7**) and (**8**). Existence of this type of diene was postulated in previous papers but they were not isolated. However the reaction of **5** with dimethyl acetylendicarboxylate gives a simple pyrrolo[2,1-*b*]thiazole system (**13**).

Recently we reported a novel synthesis of trisubstituted indolizines (**2**) from triazolopyridinium ylides (**1**) and methyl propiolate (Scheme 1) and we have proposed a mechanism which involves a diazene as intermediate for this transformation.[2]



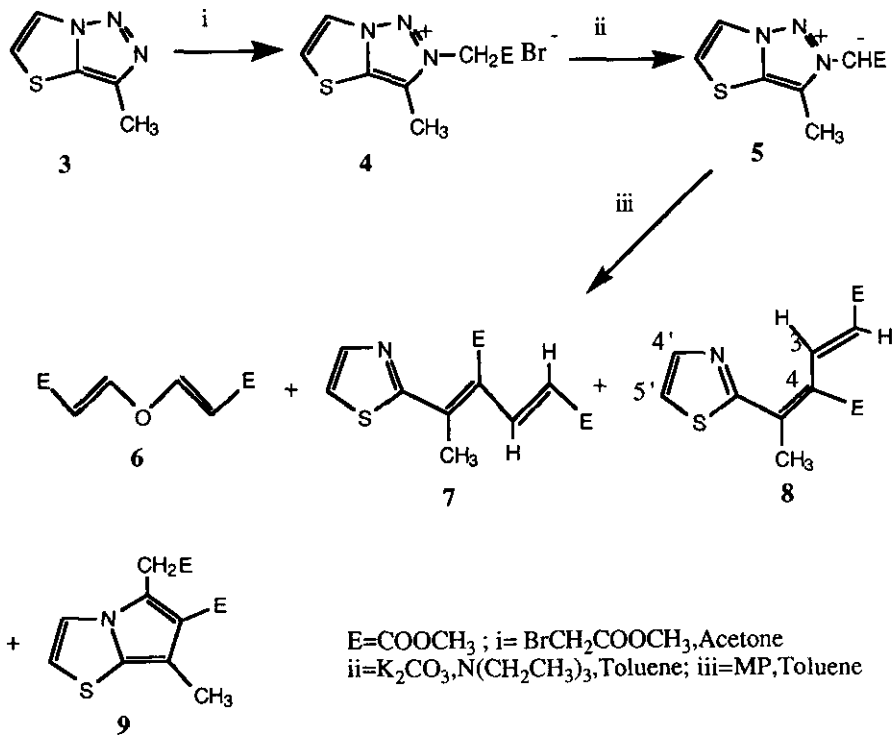
1 **2**

Scheme 1

We report here a new study with the 1,2,3-triazolo[5,1-*b*]thiazole system[1] (**3**). The change of the pyridine ring for a ring such as thiazole offers interesting possibilities to study the scope of the reaction and to explore the mechanism previously proposed.

3-Methyl-1,2,3-triazolo[5,1-*b*]thiazole (**3**) is readily available from the oxidation with nickel peroxide of the isomeric hydrazones (*syn* and *anti*) of 2-acetylthiazole.[1a] The reaction of compound (**3**) with methyl bromoacetate in boiling acetone gave, in high yield, the bromide (**4**). The ^{1}H nmr spectrum of the salt (**4**) showed two proton signals in the aromatic region (at δ 9.06 and δ 8.51, J=4 Hz), the methylene signal at δ 6.00, the methoxy signal at δ 3.80 and the methyl signal at δ 2.79. A DIFNOE experiment showed that irradiation at δ 2.79 produced enhancement only of the methylene signal at 6.00 ppm. This result established the position of alkylation as N2.

The yellow ylide (**5**) was formed in toluene solution containing potassium carbonate and triethylamine.[2] The reaction of the ylide (**5**) with methyl propiolate at room temperature gave a dark crude mixture. The toluene soluble products were separated by Chromatotron. The first product eluted was identified as the ether (**6**) (5%) probably formed by reaction of water and methyl propiolate.[3]



3 **4** **5** **6** **7** **8** **9**

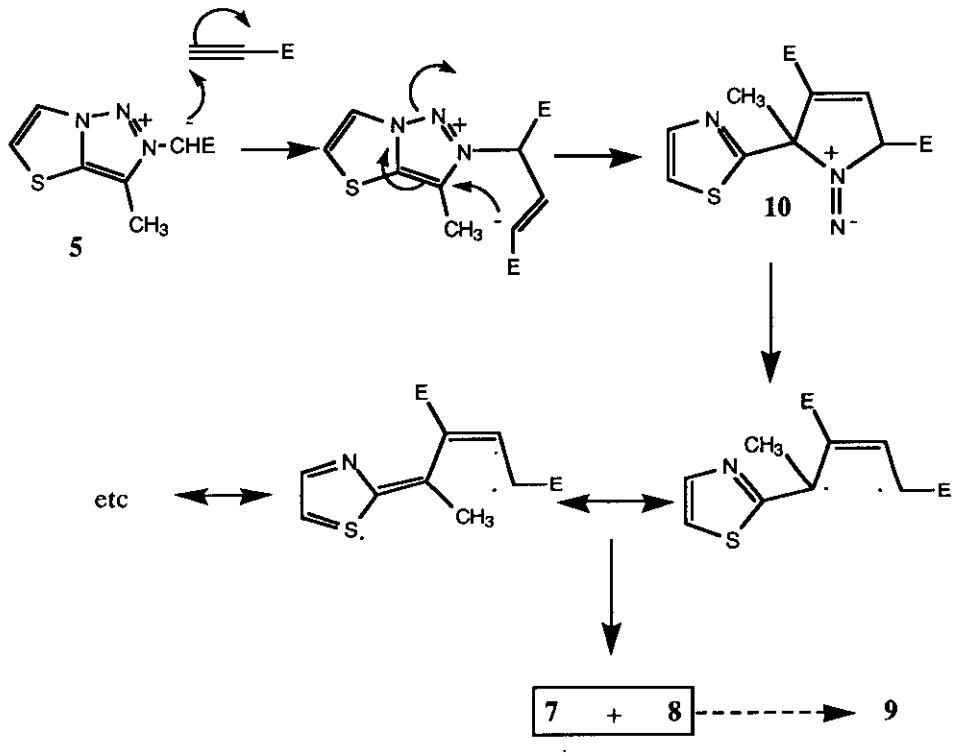
The second fraction was a mixture of the EZ (**7**) and EE (**8**) dienes, and was separated by hplc. The more interesting feature in ^{1}H nmr spectral data (see Table 1) is the deshielding of H3 in the EE isomer.

In the ^{1}H nmr spectrum of the crude reaction mixture , the presence of traces of pyrrolothiazole (**9**) was detected, but not isolated.

Table 1. ^{1}H Nmr(200 MHz) δ $CDCl_3$ (J, Hz)

Compound	H4'	H5'	H2	H3	Me	COOMe
7 (ZE)	7.80(3)	7.75(3)	6.05(16)	7.45(16)	2.50	3.87 3.80
8 (EE)	8.00(3)	7.52(3)	6.00(16)	8.35(16)	2.40	3.90 3.75

The formation of a similar diene was postulated as an intermediate in the indolizine formation from triazolopyridine.[2] The proposed pathway is shown in Scheme 2. The ylide initially reacts with methyl propiolate in a Michael addition, followed by attack on the C3 carbon giving the diazene (**10**). This intermediate (**10**) could fragment to a 1,4-diradical,[4,5] which gives the isomeric dienes (**7**,**8**). The trans configuration of the first double bond is the result of a thermodynamic control.

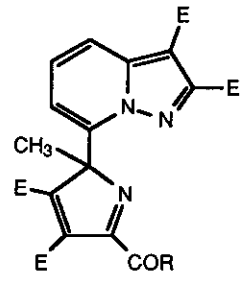


Scheme 2

As reported above we found indication of the formation of pyrrolothiazole (**9**) possibly *via* dienes (**7**) and (**8**) by a cyclization reaction.

To study the cyclization reaction we heated a solution of each of the dienes in DMSO-d_6 and monitored the reaction by ^{1}H nmr. The ZE diene (**7**) gave at 100°C a mixture of ZE (**7**) (70%) and EE (**8**) (30%) in 48 h. The

EE diene (**8**) gave at the same conditions a 50% mixture of EE and ZE isomers. However in no case did we obtain the pyrrolothiazole (**9**). The formation of the product (**9**) (in traces) must be due to another route.
In the reaction of triazolopyridinium ylides with acetylenic esters we have also reported[6] that a change from methyl propiolate to dimethyl acetylenedicarboxylate alters the course of the reaction, producing pyrroleninylpyrazolo[5,1-*a*]pyridines (**11**) in excellent yields.



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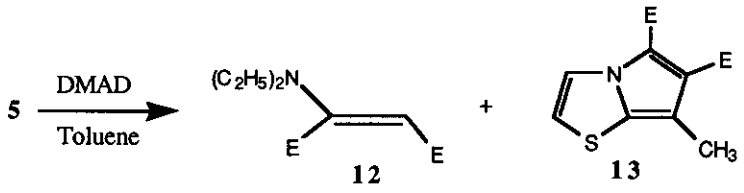

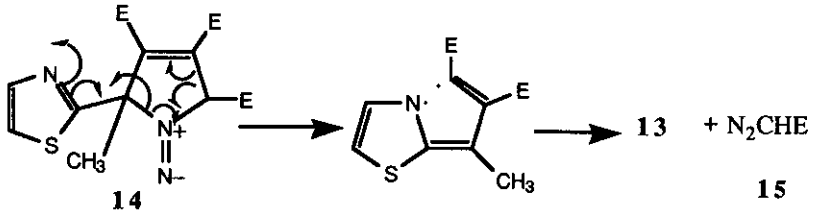

E=$COOCH_3$

We have now studied the reaction of the triazolothiazolium ylide (**5**) with DMAD, and again found unexpected results. Two products were isolated, the aminomaleate (**12**) resulting from the reaction of triethylamine with DMAD,[7] and an oil . The ^1H nmr data of the oil showed an AB system at δ 7.76 and δ 7.39 with a small coupling constant (3 Hz) , two methoxy signals (δ 4.01 and δ 3.90) and a methyl signal at δ 2.11 . The ^{13}C nmr data showed two (CH) signals in the aromatic region , three methyl signals, and five quaternary carbon signals including two carbonyl groups. The ms spectrum has the molecular ion at 253 m/z , and the most important fragmentation is the lost of two ester groups giving a fragment at m/z 135. These data are consistent with 7-methyl-5,6-dimethoxycarbonylpyrrolo[2,1-*b*]thiazole (**13**).

The formation of this adduct could be explained by a mechanism that involves the formation of a similar diazene (**14**) to that described above. In this case the fragmentation of the diazene involves the loss of the diazoacetate (**15**) followed by cyclisation of the diradical so formed, giving the pyrrolo[2,1-*b*]thiazole (**13**).

EXPERIMENTAL

Mp were determined on a Kofler heated stage and are uncorrected. Chromatography on the Chromatotron used 0.2 mm silica (Merck PF_{254})with hexane/ ethyl acetate as eluent. Nmr spectra were determined in $CDCl_3$ solutions, unless otherwise stated, on a Varian Gemini, 200 MHz. Hplc was performed on a Waters instrument, using a semipreparative silica m-porasil P/N 84175,T 50531520 column, eluting with a mixture of ethyl acetate and hexane. Gcms determinations were made using a VG Autospec Fisons.

2-Methoxycarbonylmethyl-3-methyl-1,2,3-triazolo[5,1-*b*]thiazolium Bromide (**4**). A solution of 3-methyl-1,2,3-triazolo[1,5-*b*]thiazole[1a] (2.59 g 12 mmol) and methyl bromoacetate (2.85 g,19 mmol) in dried acetone (20 ml) was boiled under reflux (3 days). The precipitated salt was filtered, washed with chloroform and recrystallized from ethanol (2.8 g, 50%). mp 167-170 °C. Anal.Calcd for $C_8H_{10}N_3O_2BrS$: C,32.89; H,3.42; N,14.18. Found: C,32.69; H,3.53; N,14.18. ^{1}H Nmr (DMSO-d_6) δ 2.79(s, 3H), 3.80(s, 3H), 6.00(s, 2H), 8.51(d, J=4 Hz, 1H), 9.06 (d, J=4 Hz, 1H). ^{13}C Nmr δ 9.33(q), 52.25(t), 53.46(q), 120.90(d), 131.25(d), 138.75(s), 166.74(s).

Reaction between the ylide (**5**) and MP. A suspension of the salt (**4**) (0.8 g , 2.7 mmol) in anhydrous toluene (24 ml) with triethylamine (0.38 ml,2.7 mmol) and potasium carbonate (0.50 g,3.5 mmol) was strirred vigorously at room temperature (4 h) during which a yellow paste formed. Methyl propiolate (MP) (0.26 g, 3 mmol) was added , and stirring continued overnight (12 h). The mixture was filtered, the filtrate was evaporated under reduced pressure and the residue was separated by Chromatotron. The first fraction was dimethyl E,E-oxydipropenoate (**6**)[3] (25 mg, 9%). The second fraction eluted was a equimolecular mixture (0.21 g, 28%) of methyl 2E,4Z-4-methoxycarbonyl-5-(2-thiazolyl)-2,4-hexadienoate (**7**) and the 2E,4E isomer (**8**). Anal.Calcd for $C_{12}H_{13}NO_4S$: C,53.93; H,4.90; N,5.24; S,11.98. Found: C,53.87; H,5.07; N,5.32; S,12.06; Ms(%) 267(0.5) 208(100). This mixture of isomers (**7**) and (**8**) was separated by hplc. The first fraction eluted was the 2E,4E isomer (**8**) (4 ml/min retention time 7.95 min)(65 mg, 9%). ^{1}H Nmr (see Table 1). ^{13}C Nmr δ 21.90 (q), 51.70(q), 52.30(q), 121.14(d), 122.35(d), 132.26(s), 135.85(s), 138.80(d), 144.24(d), 166.60(s) 166.90(s), 170.20(s). The second isomer eluted was the 2E,4Z compound (**7**) (retention time 8.51 min) (108 mg, 15%). ^{1}H Nmr (see Table 1) .^{13}C Nmr δ 18.10(q), 51.85(q), 52.50(q), 120.80(d), 122.75(d), 130.70(s), 133.70(s), 137.10(d), 144.36(d), 166.60(s), 166.90(s), 168.90(s). Traces of the pyrrolothiazole (**9**) were observed only in the ^{1}H nmr of crude reaction mixture. ^{1}H Nmr δ 2.70(s, 3H), 3.62(s, 3H), 3.37(s, 3H), 4.20(s, 2H), 7.20(d, J=3 Hz, 1H), 7.90(d, J=3 Hz, 1H).

Rection between the ylide (**5**) and DMAD. The ylide (**5**) generated from the salt (**4**) (1 g, 3,4 mmol), in identical conditions that those described for the preceding reaction, was reacted with DMAD (0.49 g 3.5 mmol) at room

temperature during 12 h. The mixture was filtered , the filtrate evaporated under reduced pressure and the residue was separated by Chromatotron .The first fraction eluted was identified as the dimethyl 2- diethylaminomaleate (**12**)[7] (0.2 g , 31%) . The second fraction eluted was the 7-methyl-5,6-dimethoxycarbonylpyrrolo[2,1-*b*]thiazole (0.13 g,16%) (**13**) . Ms: 253 (32), 238(13), 222(18), 221(33), 206(24), 194(56), 178(25), 164(29), 163(70), 162(80), 136(36), 135(100), 134(33), 59(57), 58(62). ^{1}H Nmr δ 2.11(s, 3H), 3.90(s, 3H), 4.01(s, 3H), 7.39(d, J=3 Hz, 1H), 7.76(d, J=3 Hz, 1H). ^{13}C Nmr , δ 22.04(q), 53.20(q), 53.25(q), 120.72(d), 143.14(d), 145.82(s), 150.99(s), 159.42(s), 160.19(s), 161.94(s).

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