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REACTION OF (*p*-ALKOXYPHENYL)-ACETOTHIOAMIDES WITH ACETYLENE-DICARBOXYLIC ESTERS*

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The condensation of p-methoxy(ethoxy)phenylacetothioamides with acetylenedicarboxylic esters leads to two condensation products, 2-(alkoxycarbonylmethylene)-4-(4-methoxy(ethoxy)phenyl)-5-morpholino-3H-thiophen-3-ones and 2-(alkoxycarbonylmethylene)-4-(4-methoxy(ethoxy)phenyl)-5-alkoxy-3H-thiophen-3-ones. It was shown that the substitution of the morpholino group is intramolecular.

Keywords: dialkyl acetylenedicarboxylate, thioacetamides, thiophene, condensation.

The reaction of thioureas, thiosemicarbazides, and thioamides with derivatives of acetylenedicarboxylic acid is a convenient method for the synthesis of nitrogen- and sulfur-containing heterocycles [1, 2], such as thiazoles [3-5], thiazines [6, 7], pyrroles [8], and pyrimidines [9, 10]. We showed [11, 12] that N,N-dialkylacetothioamides **1** react with dimethyl acetylenedicarboxylate with the formation of methylidenethiophen-3-ones **2**. In a continuation of our research for compounds **1a**,**b** containing a methoxy or ethoxy group at the *para* position of the aryl substituent, in addition to the thiophenes **2a**,**b** (yields 60-70%) we obtained compounds **3a**,**b** with yields of 4-10% as a minor product of the reaction with acetylenedicarboxylic ester in ethanol.

The ^{1}H and ^{13}C NMR spectra of these compounds did not contain signals for the morpholino group, but there were signals for another methoxy group. On the basis of data from the NMR spectra and also X-ray crystallographic analysis for compound **3b** (Fig. 1) it was concluded that 4-aryl-5-methoxy-2-(methoxycarbonylmethylene)thiophen-3-ones **3a**,**b** are formed as a minor product during the reaction, i.e., substitution of the morpholino group by the methoxy group occurs as a result of the reaction. However, we showed that the fraction of the minor reaction product **3a** does not increase if the acetylenedicarboxylic ester is added to a hot (50-60°C) ethanol solution of the thioamide **1a** and that the ratio of the thiophenes **2** and **3** hardly changes at all if the reaction is carried out with heat.

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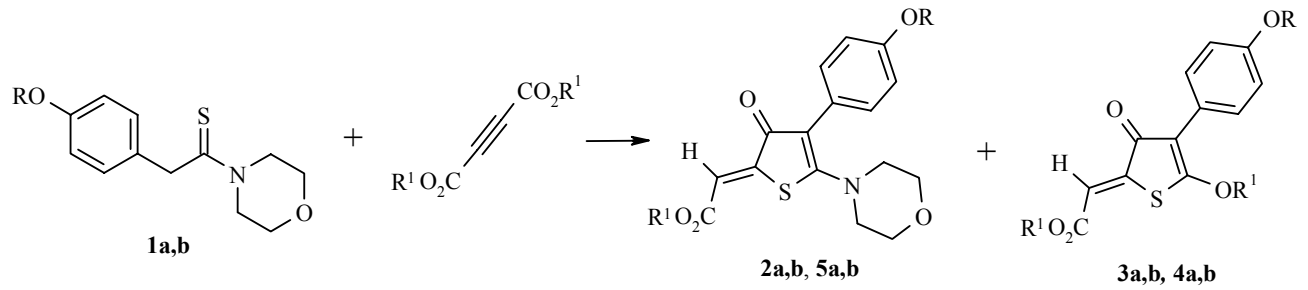

1–5 a R = Me, **b** R = Et; **2**, **3 a**,**b** R^1 = Me; **4**, **5 a**,**b** R^1 = Et

When diethyl acetylenedicarboxylate was used and the reaction was carried out in methanol solution the thiophenes **4a**,**b**, containing an ethoxy group at position 5 of the thiophene ring, were obtained. Thus, we had demonstrated that the substitution of the amino group is intramolecular and involves the alkoxy group of the acetylenedicarboxylic esters. It should be noted that we were unable to detect the formation of compounds **3** and **4** during the reactions of acetylenedicarboxylic acid derivatives with thioamides containing other substituents, such as Cl, Br, Me, and H, in the aromatic ring. The mesomeric effect of the alkoxy group at the *para* position evidently plays a major role.

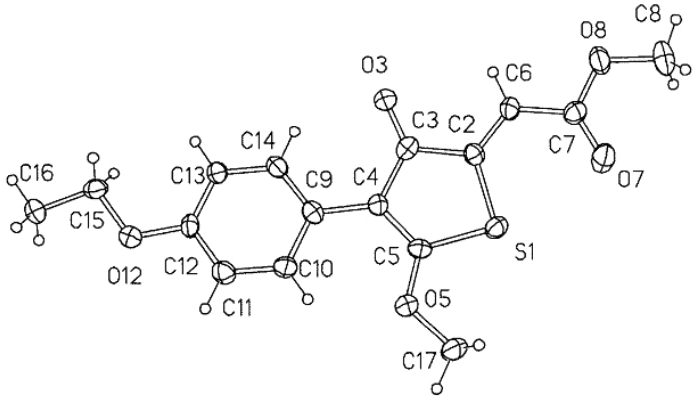

Fig. 1. The structure of compound **3b** according to data from X-ray crystallographic analysis.

EXPERIMENTAL

The reactions and the individuality of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the 1:10 and 1:5 ethyl acetate–hexane systems. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 spectrometer (400 and 100 MHz respectively) in DMSO-d_6 (compounds **2b**, **3a**, **4a**,**b**, and **5a**) and $CDCl_3$ (compound **3b**) with TMS as internal standard. The mass spectra were obtained on a Varian MAT 311A spectrometer at 70 eV with direct injection into the source. The UV spectra were obtained on a Perkin–Elmer Lambda 45 UV-vis spectrometer in ethanol at sample concentrations of ~$5\cdot10^{-5}$ M.

The thioamides **1a**,**b** and thiophenes **2a** and **5b** were obtained by the method in [11].

Methyl [5-Methoxy-4-(4-methoxyphenyl)-3-oxo-3H-thiophen-2-ylidene]acetate (3a). To a warm solution of the thioamide **1a** (0.251 g, 1.0 mmol) in 96% ethanol (10 ml) at 55°C with vigorous stirring we added dimethyl acetylenedicarboxylate (0.42 ml, 142 mg, 1.0 mmol). The mixture was stirred at 45-65°C for

4 h. After cooling to room temperature for 20 min compound **3a** was precipitated (dark-red crystals). The precipitate was filtered off and washed with alcohol. After 1 h at room temperature compound **2a** was precipitated (bright-orange crystals). The yield of compound **3a** was 10 mg (4%); mp 132-133°C. UV spectrum, λ_{max}, nm (log ε): 277 (4.40), 448 (3.14). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.15 (2H, d, *J* = 6.0, ArH); 6.98 (2H, d, *J* = 6.0, ArH); 6.36 (H, s, CH=); 4.08 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 3.73 (3H, s, OCH_3). Mass spectrum, *m/z (I,* %): 306 (100). Found, %: C 59.06; H 4.81; S 10.55. $C_{15}H_{14}O_5S$. Calculated, %: C 58.81; H 4.61; S 10.47.

Methyl [4-(4-Ethoxyphenyl)-5-methoxy-3-oxo-3H-thiophen-2-ylidene]acetate (3b) and Methyl [4-4-(Ethoxyphenyl)-5-morpholino-3-oxo-3H-thiophen-2-ylidene]acetate (2b) were obtained similarly from the thioamide **1b**.

Compound 3b. The yield was 25 mg (8%); mp 150°C. UV spectrum, λ_{max}, nm (log ε): 277 (4.44), 448.6 (3.14). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.55 (2H, d, *J* = 8.8, ArH); 7.06 (H, s, CH=); 6.89 (2H, d, *J* = 8.8, ArH); 4.21 (3H, s, OCH_3); 4.05 (2H, q, *J* = 7.1, OCH_2); 3.87 (3H, s, OCH_3); 1.40 (3H, t, *J* = 7.1, CH_3). ^{13}C NMR spectrum, δ, ppm: 184.30 (d, *J* = 4.8, C(3)=O); 184.15 (q, *J* = 5.1, C-5); 165.75 (qd, *J* = 4.0, *J* = 1.5, $COOCH_3$); 157.33 (m, Ar_p); 143.91 (d, *J* = 1.8, C-2); 129.20 (dd, *J* = 160.6, *J* = 7.5, Ar_mH); 122.24 (t, *J* = 7.8, C-4); 117.54 (d, *J* = 171.3, CH=); 113.86 (dd, *J* = 159.7, *J* = 4.9, Ar_oH); 109.98 (t, *J* = 3.5, Ar_iH); 62.92 (td, *J* = 144.3, *J* = 4.5, OCH_2); 60.97 (q, *J* = 149.3, OCH_3); 52.66 (q, *J* = 148.3, OCH_3); 14.59 (qt, *J* = 126.7, *J* = 2.8, CH_3). Mass spectrum, *m/z (I,* %): 320 (100). Found, %: C 60.09; H 5.18; S 10.22. $C_{16}H_{16}O_5S$. Calculated, %: C 59.99; H 5.03; S 10.01.

Compound 2b. The yield was 0.15 g (40%); mp 155°C. UV spectrum, λ_{max}, nm (log ε): 322 (4.34), 440 (3.57). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.12 (2H, d, *J* = 9.1, ArH); 6.88 (2H, d, *J* = 9.1, ArH); 6.63 (1H, s, CH=); 4.02 (2H, q, *J* = 6.5, OCH_2); 3.77 (3H, s, OCH_3); 3.60-3.63 (4H, m, $2OCH_2$); 3.40-3.46 (4H, m, $2NCH_2$); 1.33 (3H, t, *J* = 6.5, CH_3). Mass spectrum, *m/z (I,* %): 375 (100). Found, %: C 60.88; H 5.82; N 3.88; S 8.62. $C_{19}H_{21}NO_5S$. Calculated, %: C 60.78; H 5.64; N 3.73; S 8.54.

Ethyl [5-Ethoxy-4-(4-methoxyphenyl)-3-oxo-3H-thiophen-2-ylidene]acetate (4a) was obtained similarly from the thioamide **1a** and diethyl acetylenedicarboxylate. The reaction products were separated by column chromatography with chloroform as eluent. The yield was 20 mg (6%); mp 135-138°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56 (2H, d, *J* = 8.0, ArH); 6.86 (H, s, CH=); 6.82 (2H, d, *J* = 8.0, ArH); 4.08 (2H, q, *J* = 7.0, OCH_2); 4.01 (2H, q, *J* = 7.1, OCH_2); 3.87 (3H, s, OCH_3); 1.38 (3H, t, *J* = 7.1, CH_3); 1.33 (3H, t, *J* = 7.0, CH_3). Mass spectrum, *m/z (I,* %): 334 (100). Found, %: C 60.99; H 5.55; S 9.60. $C_{17}H_{18}O_5S$. Calculated, %: C 61.06; H 5.43; S 9.59.

Ethyl [5-Ethoxy-4-(4-ethoxyphenyl)-3-oxo-3H-thiophen-2-ylidene]acetate (4b) was obtained similarly to the previous compound from the thioamide **1b**. The reaction products were separated by column chromatography with chloroform as eluent. The yield was 35 mg (10%); mp 125°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.24 (2H, d, *J* = 8.0, ArH); 7.02 (2H, d, *J* = 8.0, ArH); 6.86 (H, s, CH=); 4.00-4.20 (6H, m, $3OCH_2$); 1.38 (3H, t, *J* = 7.1, CH_3); 1.35 (3H, t, *J* = 7.0, CH_3); 1.31 (3H, t, *J* = 7.0, CH_3). Mass spectrum, *m/z (I,* %): 348 (100). Found, %: C 62.12; H 5.88; S 9.26. $C_{18}H_{20}O_5S$. Calculated, %: C 62.05; H 5.79; S 9.20.

Ethyl [4-(4-Methoxyphenyl)-5-morpholino-3-oxo-3H-thiophen-2-ylidene]acetate (5a). The yield was 0.22 g (58%); mp 175°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.15 (2H, d, *J* = 8.0, ArH); 6.88 (2H, d, *J* = 8.0, ArH); 6.66 (H, s, CH=); 4.08 (2H, q, *J* = 6.5, OCH_2); 3.86 (3H, s, OCH_3); 3.60-3.63 (4H, m, $2OCH_2$); 3.40-3.46 (4H, m, $2NCH_2$); 1.31 (3H, t, *J* = 6.5, CH_3). Mass spectrum, *m/z* (*I*, %): 375 (100). Found, %: C 60.92; H 5.65; N 3.78; S 8.56. $C_{19}H_{21}N0_5S$. Calculated, %: C 60.78; H 5.64; N 3.73; S 8.54.

The X-ray crystallographic analysis of compound 3b was conducted on a Bruker P4 diffractometer (MoK_α radiation, λ = 0.71073 Å, graphite monochromator, θ/2θ scan, 2θ < 50°). The structure was interpreted by the direct method using SHELXL-97 software and refined by least-squares treatment in anisotropic-isotropic approximation using SHELXS-97 software. Absorption was not included. Crystallographic data: $C_{16}H_{16}O_5S$, M = 320.35, crystal dimensions 0.1×0.16×0.55 mm, triclinic, grown from a mixture of methanol and hexane,

space group $P\bar{1}$, a = 7.674(3), b = 11.023(4), c = 18.135(4) Å, α = 95.98(2), β = 90.85(2), γ = 99.44(3)°, V = 1504.2 (8) Å^3, Z = 4, d_{calc} = 1.415 g/cm^3, μ = 0.236 mm^{-1}, F(000) = 672. The intensities of 4230 reflections were measured, of which 2227 were observed intensities ($I > 2\sigma$), S = 1.080, wR_2 = 0.2063, R_1 = 0.1433 for all reflections; wR_2 = 0.1769, R = 0.0729 (for 2227 reflections with $I > 2\sigma$). The positions of the hydrogen atoms were assigned by geometry and were refined isotropically consistent with the positions of the carbons to which they are attached. The molecular structure of compound **3b** is shown in Fig. 1. The atomic coordinates, bond lengths, and angles have been deposited at the Cambridge Crystallographic Data Centre CCDC 683181.

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