Reactions of malonodithioamides with acetylenedicarboxylic esters*

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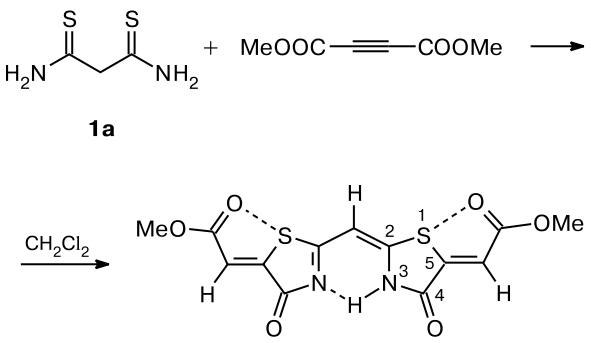
Reactions of malonothioamides with acetylenedicarboxylates proceed as an addition of the sulfur atom at the triple bond with subsequent intramolecular reaction between the ester group and the nitrogen atom, that leads to substituted thiazolidines. Unsubstituted malonodithioamide and *N*-cyclohexylmalonodithioamide give adducts involving both thioamide fragments, whereas *N*,*N*´-bis(4-methoxyphenyl)malonodithioamide forms the 1 : 1 adducts.

Key words: thiazolidinones, malonodithioamides, acetylenedicarboxylates, heterocyclization.

Chemistry of nitrogen- and sulfur-containing heterocycles for the last several decades remains one of the efficiently developing fields of organic synthesis. Oxothiazolidines containing exocyclic C=C double bonds are of special interest among the heterocycles mentioned. Earlier, we have shown that thioacetamides in the reaction with acetylenedicarboxylic esters form 2,5-bis(alkoxycarbonylmethylidene)thiazolidin-4-ones,[1,2] whereas *N*,*N*-disubstituted thioacetamides form 2-(alkoxycarbonylmethylidene)-4-aryl-5-dialkylamino-3*H*-thiophen-3-ones[3]. Unlike malonic monothioamides, malonodithioanilide[4—6] reacts with methyl propiolate and phenyl ethynyl ketones to afford dithiines[7] similarly to the reaction with 1,5-diphenyldithiobiuret,[8] whereas in the presence of triethylamine they give bis(2-benzoylvinyl) disulfide.[9] The present work is devoted to the continuation of the studies on the reactions of malonodithioamides with dialkyl acetylenedicarboxylates.

Unsubstituted malonodithioamide **1a** reacts with dimethyl acetylenedicarboxylate (DMAD) under mild conditions in dichloromethane or ethanol with the formation of the bis-adduct at both carbothioamide groups (Scheme 1). Earlier, we have shown[1—3] that the double bond at position 5 of the thiazole ring has the *Z*-configuration, which is stabilized due to the interaction of the carboxy oxygen atom with the sulfur atom of the ring. Unlike 2,5-dimethylidenethiazolidin-4-ones obtained from thioacetamides,[5] in the case of compound **2**, no isomerization with respect to the exocyclic double bond at position 2 of the thiazole ring is observed. Apparently, this is due to the stabilization through the hydrogen bond formed between the NH proton of the heterocycle and the nitrogen atom of the second ring.

Scheme 1



Introduction of the cyclohexyl group has no effect on the direction of the reaction (Scheme 2). Thus, the reaction of diethyl acetylenedicarboxylate with *N*-cyclohexylmalonodithioamide **1b** leads to the formation of compound **3**. The ^{1}H NMR spectrum of compound **3**, in addition to the signals for the cyclohexyl group, exhibits signals for three protons of the CH groups as singlets at 6.78, 6.85, and 7.15. The reaction initially proceeds at the unsubstituted group, while the intermediate *Z*,*E*-dimethylidenethiazolidinone can easily isomerize to more stable *Z*,*Z*-isomer through the enamine-imine tautomerization.[1]

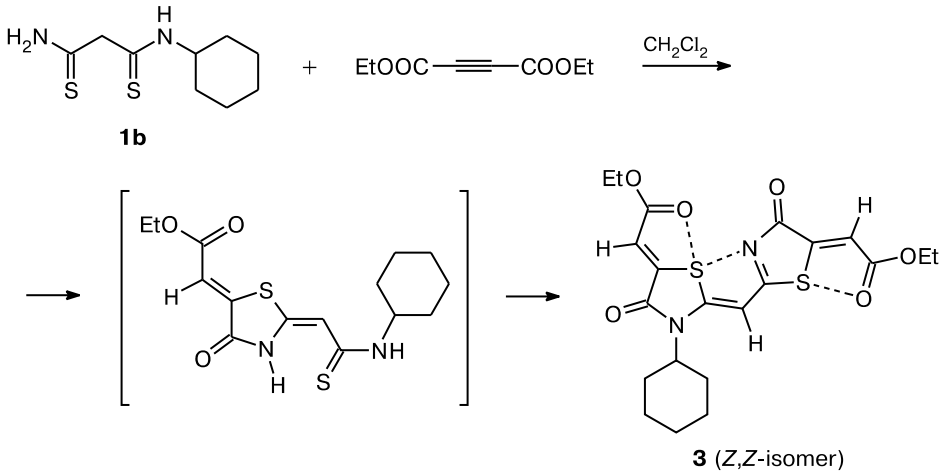
Unlike compounds **1a,b**, *N*,*N*´-bis(4-methoxyphenyl)-malonodithioamide **1c** reacts with DMAD at only one thioamide group to form thiazolidinone **4** (Scheme 3). The reaction proceeds at 0 °C, while elevated temperatures lead to resinification of the reaction mixture.

We suggest that initially only one thioamide group is involved into the reaction to yield *Z*,*Z*-isomer **4**. Its reaction with DMAD at the remained thioamide group with the formation of the second thiazole ring is hindered because of low reactivity and steric effect of the neighboring groups.

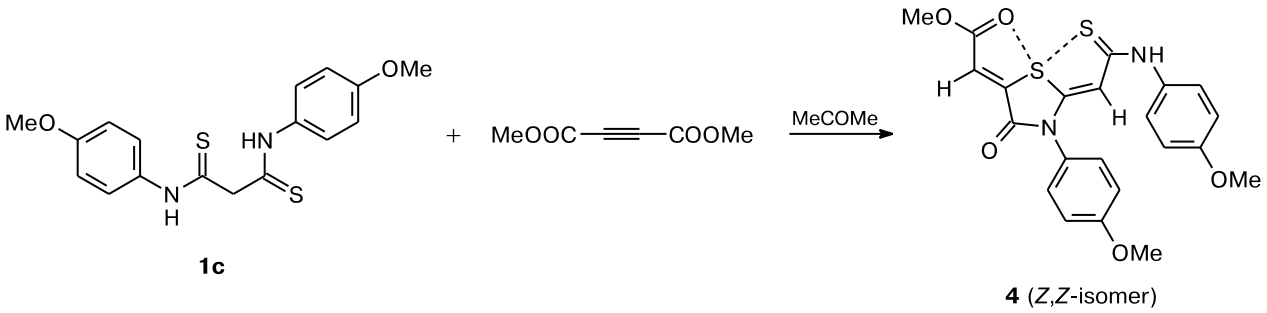
* Dedicated to Academician V. N. Charushin in honor of his 60th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 991—993, May, 2011.

Scheme 2



Scheme 3



In conclusion, we showed that unsubstituted malonodithioamide **1a** and *N*-substituted malonodithioamide **1b** react with acetylenedicarboxylates to form a system of two conjugated thiazolidine heterocycles containing exocyclic double bonds, whereas *N*,*N*´-disubstituted malonodithioamide **1c** forms only one thiazole ring.

Experimental

Reaction progress and individuality of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the ethyl acetate—hexane (1 : 10 and 1 : 5) solvent systems. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 and 100 MHz, respectively) relatively to Me_4Si as an internal standard. Mass spectra were recorded on a Varian MAT 311A instrument (70 eV) with the direct injection of a sample into the source of ions.

Malonodithioamide (1a) was synthesized according to the reported procedure,[10] the yield was 69%, m.p. 207 °C (*cf.* Ref. 10: 207 °C).

Dithioamides 1b,c (general procedure). Finely powdered P_2S_5 (2.0 g, 9.0 mmol) was added to a suspension of the corresponding malonodiamide[11,12] (2.0 g) in anhydrous dioxane[13] (100 mL) with stirring. The reaction mixture was heated for 2 h at 50 °C, cooled, and concentrated at reduced pressure. The residue was diluted with water (100 mL), and the mixture was stirred for 20 min at 60 °C, followed by addition of activated charcoal (1—2 g) and maintaining for 10 min. After filtering, the filtrate was cooled to room temperature and left at –20 °C until it was completely frozen. While melting, a precipitate was filtered off and recrystallized from EtOH. The obtained malonodithioamide was dried over P_2O_5.

***N*-Cyclohexylmalonodithioamide (1b).** The yield was 0.85 g (33%), m.p. 80 °C. MS, m/z (I_{rel} (%)): 216 $[M]^+$ (100). Found (%): C, 50.1; H, 7.5; N, 13.2; S, 29.9. $C_9H_{16}N_2S_2$. Calculated (%): C, 49.96; H, 7.45; N, 12.95; S, 29.64.

***N*,*N*´-Bis(4-methoxyphenyl)malonodithioamide (1c).** The yield was 0.77 g (35%), m.p. 142—143 °C (*cf.* Ref. 14: 142 °C). MS, m/z (I_{rel} (%)): 346 $[M]^+$ (100).

5-Methoxycarbonylmethylidene-2-[(5-methoxycarbonylmethylidene-4-oxo-4,5-dihydrothiazol-2-yl)methylidene]thiazolidin-4-one (2). Dimethyl acetylenedicarboxylate (0.728 mL, 6.0 mmol) was added to a solution of malonodithioamide **1a** (0.40 g, 3.0 mmol) in dichloromethane (50 mL) at 0 °C with stirring. The reaction mixture was kept at this temperature for 3 h, the product was filtered off and recrystallized from EtOH. The yield was 0.85 g (80%), m.p. 201 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ: 3.79 (s, 6 H, 2 MeO); 6.44 (s, 1 H, CH=); 6.82 (s, 2 H, 2 CH=); 9.0—9.2 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 53.19 (CH_3);

97.51 (CH=); 100.01 (CH=); 142.22 (C(5)); 160.00 (C(2)); 165.74 (CO); 166.24 (CO). MS, m/z (I_{rel} (%)): 354 $[M]^+$ (100). Found (%): C, 44.1; H, 2.9; N, 7.9; S, 18.0. $C_{13}H_{10}N_2O_6S_2$. Calculated (%): C, 44.06; H, 2.84; N, 7.91; S, 18.10.

3-Cyclohexyl-5-ethoxycarbonylmethylidene-2-[(5-ethoxycarbonylmethylidene-4-oxo-4,5-dihydrothiazol-2-yl)methylidene]thiazolidin-4-one (3) was obtained similarly from thioamide **1b** (0.61 g, 3 mmol) and diethyl acetylenedicarboxylate. The yield was 0.89 g (68%), m.p. 165 °C. ^{1}H NMR (DMSO-d_6), δ: 1.28 (m, 7 H, 2 CH_3, H_{cy}); 1.46—1.40 (m, 2 H, H_{cy}); 1.84—1.63 (m, 5 H, H_{cy}); 2.32—2.21 (m, 2 H, H_{cy}); 4.28 (q, 4 H, 2 OCH_2, J = 7.1 Hz); 4.40—4.29 (m, 1 H, H_{cy}); 6.78 (s, 1 H, CH); 6.85 (s, 1 H, CH); 7.15 (s, 1 H, CH). MS, m/z (I_{rel} (%)): 464 $[M]^+$ (25.58). Found (%): C, 54.3; H, 5.2; N, 5.9; S, 13.6. $C_{21}H_{24}N_2O_6S_2$. Calculated (%): C, 54.29; H, 5.21; N, 6.03; S, 13.80.

5-Methoxycarbonylmethylidene-3-(4-methoxyphenyl)-2-{[*N*-(4-methoxyphenyl)thiocarbamoyl]methylidene}thiazolidin-4-one (4). Dimethyl acetylenedicarboxylate (0.364 mL, 3.0 mmol) was added to a solution of malonodithioamide **1c** (1.04 g, 3.0 mmol) in acetone (50 mL) at 0 °C with stirring. The reaction mixture was stirred at this temperature for 3 h, then kept for 48 h at −20 °C. A precipitate was filtered off and recrystallized from EtOH. The yield was 0.62 g (45%), m.p. 130 °C. ^{1}H NMR (DMSO-d_6), δ: 3.76 (s, 3 H, CH_3O); 3.83 (s, 3 H, CH_3O); 3.87 (s, 3 H, CH_3O); 6.18 (s, 1 H, CH); 6.66 (s, 1 H, CH); 6.85 (d, 2 H, Ar, J = 9.0 Hz); 7.15 (d, 2 H, Ar, J = 9.0 Hz); 7.31 (d, 2 H, Ar, J = 9.0 Hz); 7.58 (d, 2 H, Ar, J = 9.0 Hz); 11.15 (s, 1 H, NH). MS, m/z (I_{rel} (%)): 456 $[M]^+$ (33). Found (%): C, 57.88; H, 4.42; N, 6.14; S, 14.05. $C_{22}H_{20}N_2O_5S_2$. Calculated (%): C, 57.88; H, 4.22; N, 6.14; S, 14.05.

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Received February 11, 2011;
in revised form April 13, 2011