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ADDITION OF 1,2- AND 1,3-DITHIOLS TO 2-ALKOXYPROPENALS – A NEW METHOD FOR THE PRODUCTION OF SUBSTITUTED DITHIACYCLOALKANES*

N. A. Keiko, E. A. Funtikova, L. G. Stepanova, Yu. A. Chuvashev, and L. I. Larina

The reaction of 2-alkoxypropenals with ethane-1,2-dithiols and propane-1,3-dithiols under various conditions was studied by ^1H NMR and chromato-mass spectrometry. Under kinetically controlled conditions at 20°C in the absence of catalysts the addition of dithiols takes place according to the Markovnikov rule. The primary adducts are unstable and are quickly converted into the corresponding substituted 1,4-dithiacycloheptane or 1,4-dithiane. The latter in turn can be converted under the reaction conditions or at high temperature into a thiolane derivative. The reaction of 2-ethoxypropenal with a twofold excess of ethane-1,2-dithiol at 60°C in the presence of p-toluenesulfonic acid leads to 2-methyl-2,2'-bi(dithiolane).

Keywords: 2-alkoxypropenals, 1,3- and 1,4-dithiane, 1,3-dithiolane, 1,2- and 1,3-dithiols.

The synthesis of 1,3-dithiacycloalkanes is a promising direction in organic chemistry [1-6]. Interest in the mentioned compounds is due to fact that in these cyclic dithioacetals the carbon atom of the former aldehyde group becomes nucleophilic during metallation ("umpolung" – "inversion of polarization"). As result of this the carbanions generated from 1,3-dithiacycloalkanes are widely used as equivalents of acyl groups at the construction of new C–C bonds [7-9]. In addition, the dithiolane or dithiane protection of the carbonyl group is more stable than acetal protection and makes it possible to use other methods for dithioacetalization [1]. For example, 2-formyl-1,3-dithianes have greater synthetic potentialities on account of the numerous reactions of the aldehyde group. The dithiane protection of the vicinal keto group in the reaction products is easily removed at the end of the multistage synthesis [10].

The aim of the present work was to study the possibilities of the formation of various 2-substituted dithiacycloalkanes from 2-alkoxypropenals.

1,3-Dithiolanes and 1,3-dithianes are generally obtained by the condensation of carbonyl compounds with alkane-1,2-dithiols [1, 11, 12] and alkane-1,3-dithiols [13] respectively. It is the carbonyl group that takes part in the reaction of α,β-unsaturated aldehydes with dithiols [14-16].

The results of our work showed that unlike the reaction with acrolein or crotonaldehyde [14-16] the reaction of α-alkoxyacroleins (**1a**, **b**) with ethane-1,2-dithiol (**2a**) and propane-1,3-dithiol (**2b**) begins with electrophilic addition of one of the sulfhydryl groups to the double bond of the substrate (according to the

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A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, Irkutsk, Russia; e-mail: keiko@irioch.irk.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 455-460, April, 2002. Original article submitted July 11, 2001. Revision submitted September 19, 2001.

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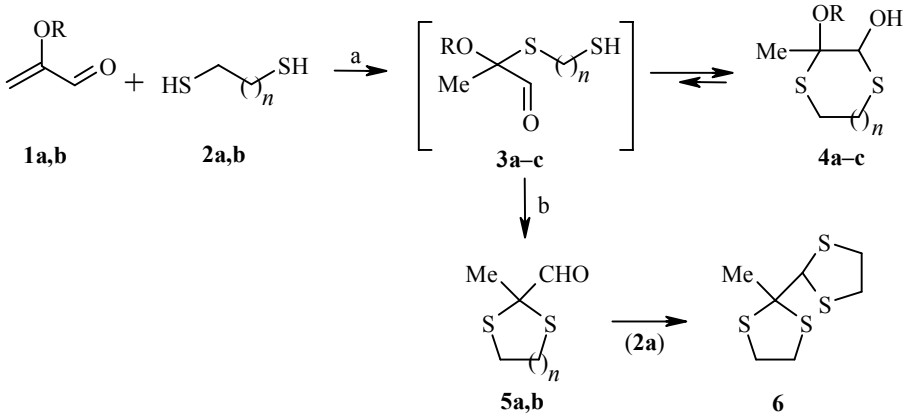
Markovnikov rule). The reaction takes place at room temperature without a catalyst. The formed 2-(2'-mercaptoalkylthio)-2-alkoxypropanals **3** are unstable. They are readily stabilized by intramolecular addition of the remaining sulfhydryl group to the aldehyde group, and are transformed into 2-alkoxy-3-hydroxy-2-methyl-1,4-dithiacycloalkanes **4**. The duration of the reaction to complete conversion of the initial compounds in equimolar ratio amounts to 5-9 days (expts. 1-2). The data of the individual experiments are given in Table 1.



1a R = Et; **b** R = Me; **2**, **5 a** *n* = 1; **b** *n* = 2; **3**, **4 a** R = Et, *n* = 1; **b** R = Me, *n* = 1; **c** R = Me, *n* = 2

In the reaction of 2-ethoxypropenal **1a** with ethane-1,2-dithiol **2a** without a solvent (expt. 1) 2-ethoxy-3-hydroxy-2-methyl-1,4-dithiane (**4a**) that forms crystallizes on storage. The high yield (90%) and the crystalline form, which makes it easy to isolate the product, demonstrate the high stability of this kinetically controlled cyclic semithioacetal. Its composition and structure are supported by the data from elemental analysis, the ^{1}H and ^{13}C NMR spectra, and the IR spectrum. However, being a semithioacetal, compound **4a** partly decomposes in the evaporator of the chromato-mass spectrometer (200°C) or during distillation, being converted into 2-formyl-2-methyl-1,3-dithiolane (**5a**) and into monothioketal (**3a**), as follows from the results of chromato-mass spectrometry (CMS) of the reaction mixture.

In order to obtain evidence for such isomerization the pure semithioacetal **4a** was kept in solution in DMSO-d_6 in the presence of *p*-toluenesulfonic acid (10 mol %) in the sample tube of the NMR spectrometer at 70, 100, and 150°C. The sample was kept at each temperature for 5 min. In the ^{1}H NMR spectra of the reaction mixture recorded at the indicated time intervals there was a gradual increase in the integral intensity of the signals from dithiolane **5a** and decrease in the intensity of the signals of initial dithiane **4a** up to its complete conversion after 15 min. It is possible that the reaction mechanism includes opening of the dithiane ring of compound **4a** at the semithioacetal center with the formation of the intermediate **3a** and subsequent intramolecular nucleophilic substitution of the EtO group by the RS group.

The reaction of 2-methoxypropenal **1b** with ethane-1,2-dithiol **2a** at 20°C (expt. 2) leads to the formation of the adduct **4b** with a yield of 70% after five days with complete utilization of the reagents. During distillation of the reaction mixture a fraction containing the adducts **4b** and **5a** in a ratio of 5:2 was obtained.

In reaction with 2-ethoxypropenal **1a** without a solvent or catalyst (expt. 3) propane-1,3-dithiol **2b** does not form a kinetically controlled semithioacetal **4b**. After 24 h 2-formyl-2-methyl-1,3-dithiane (**5b**) is formed in a quantitative yield (^{1}H NMR).

Unlike 2-ethoxypropenal **1a**, without a solvent and catalyst 2-methoxypropenal **1b** reacts with propane-1,3-dithiol **2b** (expt. 4) appreciably more slowly, and after a week the reaction mixture contains up to 50% of the initial compounds. Among the reaction products, apart from the dithiane **5b** (25 mol %) 1,4-dithiacycloheptane **4c** is observed (25 mol %). The reaction goes even more slowly in benzene (expt. 5). In this case it was possible by ^{1}H NMR to detect the formation of the intermediate **4c** with a yield of 50 mol %.

According to chromato-mass spectrometry, in the spectrum of the reaction mixture there are two closely located peaks (retention times 10.98 and 11.33 min) for the compounds in a ratio of 3:1. Their total mass in the mixture after 20 days amounted to ~60% (CMS). According to the chromato-mass spectrum, the minor product with a molecular mass of 194 was identical with the cyclic semiacetal **4c**. To judge from the ease of fragmentation with the elimination of the CHO group the major product is probably the unstable isomer **3c** (there is no M^+ 194 in the chromato-mass spectra, but there is a peak at 165 $[M\text{-}CHO]^+$). In addition, the chromato-mass spectrum shows the appearance of dithiane **5b**, the content of which amounts to 5%.

In order to study the regioselectivity of the reaction under thermodynamically controlled conditions the reaction of 2-ethoxypropenal **1a** with ethane-1,2-dithiol **2a** was studied at 60°C (expt. 6) and also in the presence of acids (expts. 7-10). At 60°C (3 h, in benzene) rapid and complete conversion of the initial propenal **1a** and dithiol **2a** is observed, but here addition takes place nonselectively, and compounds with larger molecular masses are also formed (CMS). Under the same conditions in the presence of catalytic amounts of trifluoroacetic acid (1 mol %) (expt. 7) semithioacetal **4a** is formed with a yield of 96% (^{1}H NMR). According to the chromato-mass spectrum, the reaction product consists of two isomers with molecular mass of 194 in a ratio of 5:1. It is possible that these are compounds **3a** and **4a**, since it is possible to imagine that the ring in semithioacetal **4a** is opened during passage through the evaporator.

In the presence of *p*-toluenesulfonic acid (5 mol %) from equimolar amounts of the reagents **1a** and **2a** even at 20°C after 2 days (expt. 8) a mixture of compound **5a** and 2-methyl-2,2'-bi(1,3-dithiolane) (**6**), not containing the initial compounds, is formed in a ratio of 5:3 (^{1}H NMR). The result is confirmed by the CMS data.

The formation of bi(dithiolane) **6** with a yield of 35%, even with a significant stoichiometric deficiency of ethane-1,2-dithiol for its formation indicates that in the presence of a catalyst the rate of condensation at the carbonyl group becomes commensurable with the rate of addition of the sulfhydryl group at the C=C bond followed by substitution (stages a and b).

TABLE 1. The Conditions and the Results of the Reaction of 2-Alkoxypropenals **1a**,**b** with Dithiols **2a**,**b**

Experiment	Initial compounds	Solvent	Catalyst	T, °C	Duration	Reaction products and their content in the reaction mixture (mol %) according to ^{1}H NMR		
						4	**5**	**6**
1	**1a** + **2a**	—	—	20	9 days	**4a**, 90		
2	**1b** + **2a**	—	—	20	5 days	**4b**, 69		
3	**1a** + **2b**	—	—	20	24 h		**5b**, ~100	
4*	**1b** + **2b**	—	—	20	7 days	**4c**, 25	**5b**, 25	
5	**1b** + **2b**	C_6H_6	—	20	20 days	**4c**, 50*[2]		
6	**1a** + **2a**	C_6H_6	—	60	3 h	**4a**, 56	**5a**, 5	
7	**1a** + **2a**	C_6H_6	CF_3COOH (1 mol %)	60	3 h	**4a**, 96		
8	**1a** + **2a**	Et_2O	*p*-TsOH (5 mol %)	20	2 days		**5a**, 60	**6**, 35
9	**1a** + **2a**	C_6H_6	CF_3COOH (5 mol %)	20	5 days	**4a**, 50	**5a**, 25	**6**, 25
10*[3]	**1a** + **2a**	C_6H_6	*p*-TsOH (5 mol %)	60	2 h			**6**, 80

* The reaction mixture contains 50% of the initial compound **2b**.

*[2] According to CMS, apart from compound **4c**, dithiane **5b** (mass fraction 5%) is also observed.

*[3] (**1a**)–(**2a**) ratio 1:2.

Trifluoroacetic acid (5 mol %) accelerates this reaction somewhat more mildly with the formation of a large amount of adducts from monoaddition. Here after five days (expt. 9) compounds **4a**, **5a**, **6** are formed in a ratio of 2:1:1 with complete conversion of the reagents.

The action of twofold excess of ethane-1,2-dithiol **2a** on 2-ethoxypropenal **1a** at 60°C (2 h) in the presence of *p*-toluenesulfonic acid (5 mol %) (expt. 10) leads to bi(dithiolane) **6** with a yield of 80% (^{1}H NMR). The high yields of the new dithiacycloalkanes **4-6** (Table 1) makes it possible to use the proposed methods for their preparation.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 and 100.61 MHz in DMSO-d_6 and deuterochloroform with HMDS as internal standard. The signals of CH_3, CH_2 and CH, and Cquat in the ^{13}C NMR spectra were assigned using the standard Jmod software. The IR spectra were obtained on a Specord IR-75 spectrometer. The chromato-mass spectrometric analysis was conducted on a Hewlett-Packard HP 5971A chromato-mass spectrometer (EI 70 eV, mass-selective detector), HP-5890 chromatograph, Ultra-2 column (5% of phenylmethylsilicone), evaporator temperature 250°C, column thermostat temperature 70-280°C (20 deg/min).

General Procedure for Expts. 1-10. Equimolar mixture of compounds **1** and **2** was kept at the temperature (see Table 1) for the specified time (see Table 1). In the experiments with a solvent the mixture was dissolved in the solvent (2-3 ml to 4.85 mmol of **1**), which was evaporated at the end of the experiment. In the experiments with a catalyst the reaction mixture was filtered through a layer of potassium carbonate for purification from the catalyst. After the experiment the reaction mixture was analyzed by ^{1}H NMR and CMS.

The details of the isolation of the products in some experiments and their characteristics are given below.

Expt. 1. We obtained 0.37 g of the reaction mass, which gradually crystallized, and 0.34 g of compound **4a** was filtered off; mp 74°C. IR spectrum (potassium bromide), ν, cm^{-1}: 860 (C–S–C), 1100 (C–O–C), 3420 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.15 (3H, t, CH_2CH_3); 1.32 (3H, s, CH_3); 2.90 (2H, ddd, $J_{a\text{-}a}$ = 13.6, $J_{a\text{-}e}$ = 12.1, $J_{e\text{-}e}$ = 2.0, SCH_2); 3.06 (2H, ddd, $J_{a\text{-}a}$ = 13.6, $J_{a\text{-}e}$ = 12.1, $J_{e\text{-}e}$ = 2.0, SCH_2); 3.45 (1H, dq, ^3J = 7.0, ^2J = 9.2, OCH_2); 3.75 (1H, dq, ^3J = 7.0, ^2J = 9.2, OCH_2); 4.31 (1H, d, *J* = 6.0, C<u>H</u>OH); 6.10 (1H, d, *J* = 6.0, CHO<u>H</u>). ^{13}C NMR spectrum (deuterochloroform), δ, ppm: 15.47 (CH_3 in Et); 22.46 and 26.70 (SCH_2); 23.81 (CH_3); 57.95 (OCH_2); 75.48 (SCHO); 84.21 (SCO). Mass spectrum, *m/z* (I_{rel}, %): 177 $[M - OH]^+$ (11), 149 $[M - OEt]^+$ (9), 132 $[M - OH - OEt]^+$ (2), 119 (39), 103 (100), 75 (71), 59 (51), 47 (92). Found, %: C 43.45; H 6.67; S 33.09. $C_7H_{14}O_2S_2$. Calculated, %: C 43.27; H 7.26; S 33.00.

Expt. 2. We obtained 0.8 g of reaction mixture, vacuum distillation of which gave 0.3 g of a fraction boiling at 109°C (3 mm Hg), n_D^{20} 1.5582, and containing (^{1}H NMR) semithioacetal **4b** (55 mol %) and dithiolane **5a** (22 mol %). ^{1}H NMR spectrum of compound **4b**, (DMSO-d_6), δ, ppm: 1.45 (3H, s, CH_3); 2.46 (2H, m, SCH_2); 3.47 (3H, m, OCH_3); 4.45 (1H, d, C<u>H</u>OH); 5.02 (1H, d, CHO<u>H</u>). Mass spectrum, *m/z* (I_{rel}, %): 163 $[M - OH]^+$ (9), 119 (27), 105 (9), 75 (100), 59 (41), 31 $[OCH_3]^+$ (8). ^{1}H NMR spectrum of compound **5a**, (DMSO-d_6), δ, ppm: 1.76 (3H, s, CH_3); 3.39 (4H, m, CH_2S); 9.10 (1H, s, CHO). Mass spectrum, *m/z* (I_{rel}): 148 $[M]^+$ (1), 119 (100), 59 (72).

Expt. 3. By distilling 1.0 g of the reaction mixture we isolated 0.69 g (69%) of compound **5b**; bp 112-113°C (4 mm Hg), n_D^{20} 1.5432. ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 1.48 (3H, s, CH_3); 1.77 (1H, m, CH_2); 2.1 (1H, m, CH_2); 2.6 (2H, dt, ^2J = 14, ^3J = 4, SCH_2); 3.05 (2H, m, SCH_2); 9.04 (1H, s, CHO). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.60 (CH_3); 23.23 (CH_2); 26.12 (SCH_2); 72.00 (C); 189.91 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 162 $[M]^+$ (4), 133 $[M - CHO]^+$ (100), 105 (2), 59 (63). Found, %: C 44.48; H 6.40; S 39.70. $C_6H_{10}OS_2$. Calculated, %: C 44.43; H 6.16; S 39.53.

Expt. 4. In the reaction mixture we identified compound **5b**, identical with the sample obtained in expt. 3 (^{1}H NMR spectrum and mass spectrum) and also compound **4c**. ^{1}H NMR spectrum (deuterochloroform), δ, ppm: 1.46 (3H, s, CH_3); 1.77 (2H, m, CH_2); 2.50 (4H, m, SCH_2); 3.50 (3H, m, OCH_3); 4.62 (1H, s, CHOH). Mass spectrum of product **4c**, *m/z* (I_{rel}, %): 194 $[M]^+$ (5), 165 (20), 133 (17), 108 (100), 88 $[M - SCH_2CH_2CH_2S]^+$ (42), 73 (72), 57 (79).

Expt. 5. According to ^{1}H NMR data, 50% of the reaction mixture consisted of the product **4c**, identical with the product from expt. 4 (^{1}H NMR and mass spectrum). According to CMS, 60% of the mixture consisted (presumably) of the isomeric products **3c** and **4c** (**3c**:**4c** 3:1), retention time 10.98 and 11.33 min respectively. Mass spectrum of compound **3c**, *m/z* (I_{rel}, %): 165 $[M - CHO]^+$ (62), 151 $[M - CH_3CO]^+$ (1), 133 $[M - HSCH_2CH_2]^+$ (8), 106 $[SCH_2CH_2CH_2S]^+$ (32), 88 $[M - SCH_2CH_2CH_2S]^+$ (100), 75 $[HSCH_2CH_2CH_2]^+$ (41), 64 (84). The mass spectrum of compound **4c** was described above.

Expt. 6. The ^{1}H NMR spectrum of the reaction mixture contained signals of the product **4a** (see expt. 1) and compound **5a** (see expt. 2).

Expt. 7. After evaporating the reaction mixture under vacuum we obtained 0.9 g of the needle crystals of compound **4a**, identical with the sample obtained in expt. 1 (mp, ^{1}H NMR). According to CMS, the reaction product consisted of two isomers **3a** and **4a** with M^+ 194 (retention time 10.46 and 10.61 min). Mass spectrum of supposed compound **3a**, *m/z* (I_{rel}, %): 194 $[M]^+$ (3), 165 $[M - CHO]^+$ (2), 119 $[CH_3CSCH_2CH_2S]^+$ (72), 91 (15), 72 $[M - SCH_2CH_2S - CHO]^+$ (54), 61 (100), 45 $[CH_3CH_2O]^+$ (33).

When compound **4a** was kept in solution of DMSO-d_6 in the NMR sample tube in the presence of *p*-toluenesulfonic acid (10 mol %) at 70, 100, and 150°C (5 min at each) it was converted by 98% into compound **5a**, the ^{1}H NMR spectrum of which was identical with the spectrum of the compound obtained in expt. 6.

Expt. 9. From 0.94 g of the reaction mixture we isolated 0.2 g of the product **5a**; bp 105°C (3 mm Hg), n_D^{20} 1.5540. The compound **5a** was identical with the sample obtained in expt. 2 (^{1}H NMR spectrum and mass spectrum). Found, %: C 40.90; H 5.55; S 42.96. $C_5H_8OS_2$. Calculated, %: C 40.51; H 5.44; S 43.26.

Expt 10. During vacuum distillation of 1.39 g of the reaction mixture we isolated 0.43 g of 1,3-dithiolane **6**; bp 160°C (3 mm Hg), n_D^{20} 1.6425. ^{1}H NMR spectrum (deuterochloroform), δ, ppm: 1.94 (3H, s, CH_3); 3.20-3.56 (8H, m, SCH_2); 5.17 (1H, s, CH). ^{13}C NMR spectrum (deuterochloroform), δ, ppm: 28.7 (CH_3); 40.06, and 40.75 (SCH_2); 68.0 (CH); 96.12 (C). Mass spectrum, *m/z* (I_{rel}, %): 224 $[M]^+$ (21), 119 $[M - CH(SCH_2)_2]^+$ (100), 105 $[M - CH_3C(SCH_2)_2]^+$ (29), 59 (81). Found, %: C 38.64; H 5.45; S 55.59. $C_7H_{12}S_4$. Calculated, %: C 37.46; H 5.39; S 57.15.

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