Kinetic and thermodynamic control in the synthesis of methylglyoxal thioacetals from 2-ethoxypropenal

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Under kinetically controlled conditions, the addition of organylthiols to 2-ethoxypropenal follows the Markovnikov rule to give 2-ethoxy-2-organylthiopropanals which spontaneously isomerize to 1-ethoxy-1-organylthiopropanones in storage or in the presence of an acid catalyst.

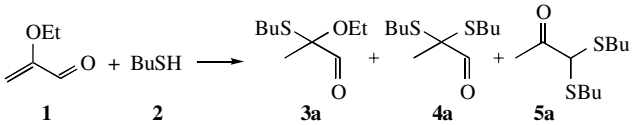
The addition of thiols to acrylic systems, including α-alkoxy substituted α,β-unsaturated ketones and esters, plays an important role in the anticancer activity of the compounds.[1]

Formally, a combination of structural fragments of acrolein and vinyl ether takes place in the 2-alkoxypropenal molecule. The introduction of an α-alkoxy group into acrylic systems results in electron density redistribution in the ground state of the molecule. According to the ^{13}C NMR spectrum, a considerable negative charge is concentrated on the β-carbon atom of α-ethoxyacrolein **1**.[2] The prevailing +M-effect of the alkoxy group in comparison with the –M-effect of the carbonyl group in 2-alkoxypropenals causes the addition of electrophiles (HCl, H_2O) to the C=C bond to follow the Markovnikov pattern.[3]

In order to determine the regioselectivity of 2-ethoxypropenal reactions with thiols, we studied the interactions with butanethiol and thiophenol in neutral and acidic media.

The reaction of acrolein with methanethiol is exothermic even without a catalyst to afford 3-methylthiopropanal (yield 94%).[4] The butanethiol and thiophenol addition takes place as well.[5,6] In contrast, the interaction of 2-ethoxypropenal with butanethiol at 20 °C proceeds with no changes in the first 24 h. Previously, the reaction mixture was heated (90 °C, 11 h) to get 2-butylthio-2-ethoxypropenal **3a** after distillation with a yield of 30%.[7]

In this work this reaction was monitored by ^1H NMR at 20 °C and by GC–MS. The addition appeared to follow the Markovnikov rule even at this temperature with no catalyst, and 2-butylthio-2-ethoxypropanal makes up 75 mol% of the mixture after the 5-day interaction. The impurities are 2,2-dibutylthiopropanal **4a** (10 mol%) and 1,1-dibutylthiopropanone **5a** (5 mol%). The ratio between compounds **3a**, **4a** and **5a**† is 15:2:1. Moreover, about 10% of initial aldehyde **1** remained unreacted (Scheme 1).



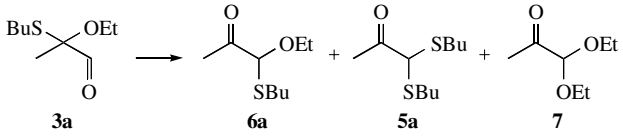
1 **2** **3a** **4a** **5a**

Scheme 1

On heating in a solution of $CDCl_3$ (60 °C, 3 h), monothioketal **3a** isomerises into thermodynamically more stable 1-butylthio-1-ethoxypropanone **6a**. In so doing, the latter partially disproportionates to give symmetrical thioacetal **5a**. The ratio **3a**:**6a**:**5a** is 3:2:1. Additional heating of the obtained reaction mixture (60 °C, 2 h) leads to the complete transformation of monothioketal **3a** into acetals **5a** and **6a** in the ratio 1:1.

In the presence of *p*-toluenesulfonic acid (*p*-TsOH), the isomerization of monothioketal **3a** occurs even more easily. Thus, in the presence of 1 mol% *p*-TsOH at 20 °C the transformation of ketal **3a** to acetals **5a**, **6a** and 1,1-diethoxypropanone **7** accomplishes in 24 h. As this takes place, monothioacetal **6a**‡ is the major reaction product (71 mol%). Compounds **6a**, **5a** and **7**‡ are in the ratio 5:1:1 (Scheme 2).

In order to speed up the butanethiol Markovnikov addition, a catalytic amount of hydrochloric acid (1 mol%) was added to the equimolar mixture of reagents **1** and **2**. The reaction is



3a **6a** **5a** **7**

Scheme 2

exothermic. According to ^1H NMR and GC–MS data, the molar ratio between reaction products **3a**, **6a** and **5a** becomes 1:3:1 in 48 h. This means that the concentration of mixed acetal **6a** in the reaction mixture is 60%.

† The reaction was monitored on a Bruker DPX-400 NMR spectrometer [400 MHz, standard $(Me_3Si)_2O$] and a Hewlett-Packard HP5971A GC–MS instrument.

A general experimental procedure for the reaction of 2-ethoxypropenal with thiols. An equimolar mixture (4.85–27.5 mmol) of an organylthiol and 2-ethoxypropenal stabilised by hydroquinone (0.001 g) was allowed to stand at ambient temperature for 5–7 days to the disappearance of the substrate. The reaction was monitored by ^1H NMR. To isolate pure adducts, the reaction mixture was distilled *in vacuo* (1–3 torr).

To accelerate the interaction, acid catalysts were used and after completion of reaction they were neutralised by K_2CO_3 before distillation. Reactions with *p*-TsOH were carried out in the presence of molecular sieves 4A.

2-Butylthio-2-ethoxypropanal **3a**: bp 67 °C (1 torr), n_D^{20} 1.4640. ^1H NMR ($CDCl_3$) δ: 0.88 (t, 3H, Me_{Bu}, ^3J 7.3 Hz), 1.26 (t, 3H, Me_{Et}), 1.35 (m, 2H, CH_2Me_{Bu}), 1.45 (m, 2H, SCH_2CH_2), 1.53 [s, 3H, MeC(O)S], 2.35 (t, 2H, SCH_2, ^3J 7.35 Hz), 3.55 and 3.77 (2dq, 2H, C*OCH_2, ^2J 9.09 Hz, ^3J 7.04 Hz), 9.07 (s, 1H, CHO). MS (70 eV), *m/z* (%): 190 ([M]$^+$, 1), 161 ([M – CHO]$^+$, 100), 133 ([M – Bu]$^+$, 45), 101 ([M – SBu]$^+$, 14), 73 (46), 59 (24), 43 (78). IR (film, ν/cm^{-1}): 2955 (s), 2925 (s), 2870, 2820, 1725 (ws) (C=O), 1445, 1380, 1200, 1145–1155, 1100, 1070, 1045 (s). Found (%): C, 57.6; H, 9.7; S, 16.48. Calc. for $C_9H_{18}O_2S$ (%): C, 56.8; H, 9.53; S, 16.85.

2,2-Dibutylthiopropanal **4a**: ^1H NMR ($CDCl_3$) δ: 0.89 (t, 6H, Me), 1.4 (m, 4H, $SCH_2CH_2CH_2$), 1.55 (m, 4H, SCH_2CH_2), 1.63 [s, 3H, Me–C(S)S], 2.5 (m, 4H, SCH_2), 9.05 (s, 1H, CHO). MS (70 eV), *m/z* (%): 234 ([M]$^+$, 1), 205 ([M – CHO]$^+$, 100), 149 (11), 103 (7), 93 (10), 59 (74), 41 (30), 29 ([CHO]$^+$, 42).

1,1-Dibutylthiopropanone **5a**: ^1H NMR ($CDCl_3$) δ: 0.9 (t, 6H, Me), 1.4 (m, 4H, $SCH_2CH_2CH_2$), 1.53 (m, 4H, SCH_2CH_2), 2.35 (s, 3H, Me), 2.36 (m, 4H, CH_2S), 5.28 (s, 1H, SCHS). MS (70 eV), *m/z* (%): 234 ([M]$^+$, 1), 205 ([M – CHO]$^+$, 2), 191 (100), 135 (27), 89 ([SBu]$^+$, 6), 79 (21), 43 (81), 41 (37).

‡ *1-Butylthio-1-ethoxypropanone* **6a**: bp 64 °C (3 torr), n_D^{20} 1.4620. ^1H NMR ($CDCl_3$) δ: 0.84 (t, 3H, Me_{Bu}, *J* 7.3 Hz), 1.21 (t, 3H, Me_{Et}, *J* 7.0 Hz), 1.33 (m, 2H, CH_2Me_{Bu}, ^3J 7.5 Hz), 1.48 (m, 2H, SCH_2CH_2), 2.21 (s, 3H, MeCO), 2.45 (m, 2H, SCH_2), 3.45 and 3.84 (2dq, 2H, C*OCH_2, ^2J 9.0 Hz, ^3J 7.0 Hz), 4.80 (s, 1H, CH). MS (70 eV), *m/z* (%): 190 ([M]$^+$, 1), 147 ([M – MeCO]$^+$, 69), 119 ([M – MeCO – C_2H_4]$^+$, 48), 101 (2), 91 (6), 73 (19), 57 (39), 43 ([MeCO]$^+$, 100), 29 ([Et]$^+$, 58), 27 (50). Found (%): C, 56.62; H, 9.52; S, 16.11. Calc. for $C_9H_{18}O_2S$ (%): C, 56.8; H, 9.47; S, 16.85.

1,1-Diethoxypropanone **7**. ^1H NMR ($CDCl_3$) δ: 1.24 (t, 6H, 2Me ^3J 7.0 Hz), 2.18 (s, 3H, MeCO), 3.69 and 3.56 (AB system, 2dq, 4H, $2OCH_2$, ^2J 9.5 Hz, ^3J 7.0 Hz), 4.52 (s, 1H, CH). MS (70 eV), *m/z* (%): 103 ([M – MeCO]$^+$, 24), 75 ([M – MeCO – C_2H_4]$^+$, 31), 73 (29), 47 (100), 45 (42), 43 (89).

Table 1 Monitoring of the reactions of 2-ethoxypropenal with thiols by ^{1}H NMR spectroscopy.

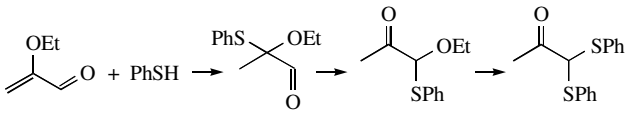
Compound	Solvent	Catalyst	*T*/°C	Time	Product distribution (%)				
					3	**4**	**5**	**6**	**7**
1 + **2a**			20	5 days	75	10	5		
3a	$CDCl_3$		60	3 h	54		16	30	
3a	$CDCl_3$		60	5 h			40	40	
3a		*p*-TsOH	20	24 h			14	71	14
1 + **2a**		HCl	20	48 h	18		20	57	
1 + **2a**		*p*-TsOH	20	6 days	14	42		42	
1 + **2b**			20	7 days	100				
3b			20	55 days	78		11	11	
3b	$CDCl_3$		60	3 h			25	50	
3b	$CDCl_3$		60	5 h			20	51	
3b		*p*-TsOH	20	24 h			6	70	4
1 + **2b**		*p*-TsOH	20	5 days	20		20	60	

Hence, hydrochloric acid not only promotes the initial addition to the C=C bond, but also facilitates the isomerization of 2-butylthio-2-ethoxypropanal **3a** into 1-butylthio-1-ethoxypropanone **6a**, which transforms then into symmetrical thioacetal **5a** as a result of disproportionation.

p-Toluenesulfonic acid accelerates this reaction in a different way. The addition of 1 mol% of the acid to an equimolar mixture of reagents **1** and **2** leads to the formation of O,S-ketal **3a** (20 °C, 6 days). The latter undergoes isomerization into O,S-acetal **6a** along with disproportionation to give 2,2-dibutylthiopropanal **4a**. The ratio of acetals **3a**, **4a** and **6a** is approximately 1:3:3 (Scheme 3).

All reactions with *p*-TsOH were carried out in the presence of molecular sieves 4A to avoid the hydrolytic effect of water. Water could form if the aldehyde group of the initial 2-ethoxypropenal **1** took part in the acetal formation, which is characteristic of acrolein.[8]

The uncatalysed reaction of thiophenol with 2-ethoxypropenal at room temperature also follows the Markovnikov rule, but it is more selective and faster. Thus, in one day, the ratio between 2-ethoxy-2-phenylthiopropanal **3b** and initial substrate **1** is 2:1. In seven days, the conversion of 2-ethoxypropenal into monothioacetal **3b** comprises 100% (Scheme 4).

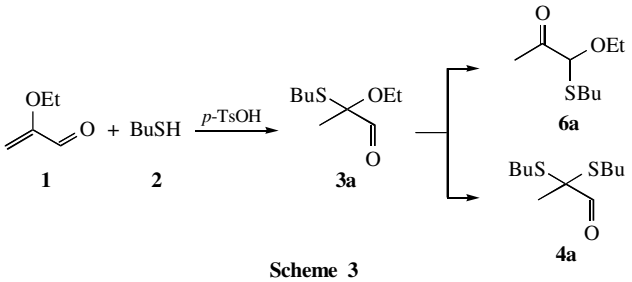


1 **3b** **6b** **5b**

Scheme 4

Like monothioketal **3a**, monothioketal **3b** gradually isomerises on keeping at 20 °C to give 1-ethoxy-1-phenylthiopropanone **6b**. The latter partly undergoes disproportionation into 1,1-diphenylthiopropanone **5b** and 1,1-diethoxypropanone **7**. After storage for two months, the concentration ratio between compounds **3b**, **5b** and **6b**§ becomes 7:1:1. Acetal **7** cannot be identified in the reaction mixture by NMR; it was detected only by the GC–MS.

On heating to 60 °C, monothioketal **3b** (pure or in a $CDCl_3$ solution) totally disappears in 3 h. This resulted partly from the rearrangement to acetal **6b** and then to thioacetal **5b** and partly from the thermal decomposition of PhS-containing acetals to form diphenyl disulfide (25–30%). The ratio between compounds **6b** and **5b** in a $CDCl_3$ solution is 2.5:1 after heating for 5 h.



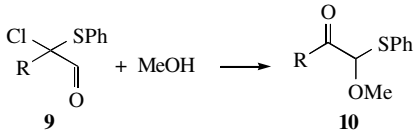
1 **2** **3a** **6a** **4a**

Scheme 3

In the presence of 1 mol% *p*-TsOH, isomerization of ketals **3b** at 20 °C completes in 24 h. The product of symmetrization of acetal **6b**, 1,1-diphenylthiopropanone **5b**, was detected. The ratio between compounds **6b** and **5b** was 12:1. The concentration of diphenyl disulfide was about 10%.

To promote the addition of thiophenol to 2-ethoxypropenal, 5 mol% *p*-TsOH was added to an equimolar mixture of the reactants. In five days, a mixture of acetals in the ratio **3b**:**6b**:**5b** equal to 1:3:1 was obtained after the complete conversion of the initial propenal.

The rearrangement of monothioketals of methylglyoxal **3a**, **3b** to monothioacetals **6a**, **6b** was not yet observed. However, a similar isomerization was reported in the interaction of 2-chloro-2-phenylthioalkanals **9** with methanol to give 1-methoxy-1-phenylthioalkan-2-ones **10** rather than the expected ketals[9] (Scheme 5).



9 **10**

Scheme 5

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§ *2-Ethoxy-2-phenylthiopropanal* **3b**: bp 120–124 °C (3 torr), n_D^{20} 1.5560. ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3H, OCH_2Me, ^3J 7.0 Hz), 1.55 [s, 3H, MeC(O)S], 3.7 (dq, 1H, OCH_2, ^2J 7.3 Hz, ^3J 7.0 Hz), 4.05 (dq, 1H, OCH_2, ^2J 7.3 Hz, ^3J 7.0 Hz), 7.29 (m, 3H, *p*-, *m*-Ph), 7.43 (d, 2H, *o*-Ph, ^3J 8.0 Hz), 9.17 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ: 15.06 (Me), 19.44 (Me), 58.81 (CH_2), 128.87 (*m*-C, Ph), 128.92 (*p*-C, Ph), 135.42 (*o*-C, Ph), 193.47 (CHO). MS (70 eV), *m*/*z* (%): 210 ([M]$^+$, 1), 181 ([M – CHO]$^+$, 100), 165 ([M – OEt]$^+$, 2), 153 (8), 137 (3), 123 (6), 110 ([HSPh]$^+$, 50), 109 ([SPh]$^+$, 66), 101 ([M – SPh]$^+$, 34), 73 (100), 65 (43), 45 ([OEt]$^+$, 67), 43 (70). Found (%): C, 62.64; H, 6.3; S, 15.66. Calc. for $C_{11}H_{14}O_2S$ (%): C, 62.83; H, 6.71; S, 15.25.

1-Ethoxy-1-phenylthiopropanone **6b**: bp 120 °C (2 torr), n_D^{20} 1.5515. ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, OCH_2Me, ^3J 7.0 Hz), 2.07 (s, 3H, MeCO), 3.54 (dq, 1H, OCH_2, ^2J 7.3 Hz, ^3J 7.0 Hz), 4.05 (dq, 1H, OCH_2, ^2J 7.3 Hz, ^3J 7.0 Hz), 5.03 (s, 1H, OCHS), 7.29 and 7.44 (2m, 5H, Ph). MS (70 eV), *m*/*z* (%): 210 ([M]$^+$, 4), 167 ([M – MeCO]$^+$, 100), 139 ([M – MeCO – C_2H_4]$^+$, 84), 111 (65), 109 ([SPh]$^+$, 40), 77 ([Ph]$^+$, 41), 73 (26), 45 ([OEt]$^+$, 69), 43 (85). Found (%): C, 62.45; H, 7.18; S, 15.68. Calc. for $C_{11}H_{14}O_2S$ (%): C, 62.83; H, 6.71; S, 15.25.

1,1-Diphenylthiopropanone **5b**: ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, Me), 5.45 (s, 1H, SCHS), 7.29 and 7.44 (2m, 10H, Ph). MS (70 eV), *m*/*z* (%): 231 ([M – MeCO]$^+$, 41), 165 ([M – SPh]$^+$, 28), 121 (46), 109 ([SPh]$^+$, 41), 77 ([Ph]$^+$, 31), 43 ([MeCO]$^+$, 100), 28 ([CO]$^+$, 87).