

# 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-organylthiopropenals which spontaneously isomerize to 1-ethoxy-1-organylthiopropenones in storage or in the presence of an acid catalyst.

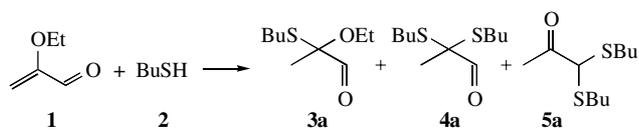
The addition of thiols to acrylic systems, including  $\alpha$ -alkoxy substituted  $\alpha,\beta$ -unsaturated ketones and esters, plays an important role in the anticancer activity of the compounds.<sup>1</sup>

Formally, a combination of structural fragments of acrolein and vinyl ether takes place in the 2-alkoxypropenal molecule. The introduction of an  $\alpha$ -alkoxy group into acrylic systems results in electron density redistribution in the ground state of the molecule. According to the <sup>13</sup>C NMR spectrum, a considerable negative charge is concentrated on the  $\beta$ -carbon atom of  $\alpha$ -ethoxyacrolein **1**.<sup>2</sup> 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<sub>2</sub>O) to the C=C bond to follow the Markovnikov pattern.<sup>3</sup>

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-methylthiopropenal (yield 94%).<sup>4</sup> The butanethiol and thiophenol addition takes place as well.<sup>5,6</sup> 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%.<sup>7</sup>

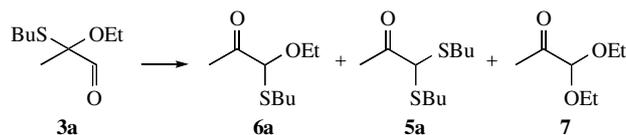
In this work this reaction was monitored by <sup>1</sup>H NMR at 20 °C and by GC–MS. The addition appeared to follow the Markovnikov rule even at this temperature with no catalyst, and 2-butylthio-2-ethoxypropenal makes up 75 mol% of the mixture after the 5-day interaction. The impurities are 2,2-dibutylthiopropenal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



On heating in a solution of CDCl<sub>3</sub> (60 °C, 3 h), monothioacetal **3a** isomerises into thermodynamically more stable 1-butylthio-1-ethoxypropenone **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 monothioacetal **3a** into acetals **5a** and **6a** in the ratio 1:1.

In the presence of *p*-toluenesulfonic acid (*p*-TsOH), the isomerization of monothioacetal **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-diethoxypropenone **7** accomplishes in 24 h. As this takes place, monothioacetal **6a**<sup>‡</sup> is the major reaction product (71 mol%). Compounds **6a**, **5a** and **7**<sup>‡</sup> 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



exothermic. According to <sup>1</sup>H 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%.

<sup>†</sup> The reaction was monitored on a Bruker DPX-400 NMR spectrometer [400 MHz, standard (Me<sub>3</sub>Si)<sub>2</sub>O] 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 <sup>1</sup>H 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<sub>2</sub>CO<sub>3</sub> before distillation. Reactions with *p*-TsOH were carried out in the presence of molecular sieves 4A.

**2-Butylthio-2-ethoxypropenal 3a**: bp 67 °C (1 torr), *n*<sub>D</sub><sup>20</sup> 1.4640. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 0.88 (t, 3H, Me<sub>Bu</sub>, <sup>3</sup>J 7.3 Hz), 1.26 (t, 3H, Me<sub>Et</sub>), 1.35 (m, 2H, CH<sub>2</sub>Me<sub>Bu</sub>), 1.45 (m, 2H, SCH<sub>2</sub>CH<sub>2</sub>), 1.53 [s, 3H, MeC(O)S], 2.35 (t, 2H, SCH<sub>2</sub>, <sup>3</sup>J 7.35 Hz), 3.55 and 3.77 (2dq, 2H, C\*OCH<sub>2</sub>, <sup>2</sup>J 9.09 Hz, <sup>3</sup>J 7.04 Hz), 9.07 (s, 1H, CHO). MS (70 eV), *m/z* (%): 190 ([M]<sup>+</sup>, 1), 161 ([M – CHO]<sup>+</sup>, 100), 133 ([M – Bu]<sup>+</sup>, 45), 101 ([M – SBu]<sup>+</sup>, 14), 73 (46), 59 (24), 43 (78). IR (film,  $\nu$ /cm<sup>-1</sup>): 2955 (s), 2925 (s), 2870, 2820, 1725 (w) (C=O), 1445, 1380, 1200, 1145–1155, 1100, 1070, 1045 (s). Found (%): C, 57.6; H, 9.7; S, 16.48. Calc. for C<sub>9</sub>H<sub>18</sub>O<sub>2</sub>S (%): C, 56.8; H, 9.53; S, 16.85.

**2,2-Dibutylthiopropenal 4a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 0.89 (t, 6H, Me), 1.4 (m, 4H, SCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.55 (m, 4H, SCH<sub>2</sub>CH<sub>2</sub>), 1.63 [s, 3H, MeC(S)S], 2.5 (m, 4H, SCH<sub>2</sub>), 9.05 (s, 1H, CHO). MS (70 eV), *m/z* (%): 234 ([M]<sup>+</sup>, 1), 205 ([M – CHO]<sup>+</sup>, 100), 149 (11), 103 (7), 93 (10), 59 (74), 41 (30), 29 ([CHO]<sup>+</sup>, 42).

**1,1-Dibutylthiopropenone 5a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 0.9 (t, 6H, Me), 1.4 (m, 4H, SCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.53 (m, 4H, SCH<sub>2</sub>CH<sub>2</sub>), 2.35 (s, 3H, Me), 2.36 (m, 4H, CH<sub>2</sub>S), 5.28 (s, 1H, SCHS). MS (70 eV), *m/z* (%): 234 ([M]<sup>+</sup>, 1), 205 ([M – CHO]<sup>+</sup>, 2), 191 (100), 135 (27), 89 ([SBu]<sup>+</sup>, 6), 79 (21), 43 (81), 41 (37).

**1-Butylthio-1-ethoxypropenone 6a**: bp 64 °C (3 torr), *n*<sub>D</sub><sup>20</sup> 1.4620. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 0.84 (t, 3H, Me<sub>Bu</sub>, <sup>3</sup>J 7.3 Hz), 1.21 (t, 3H, Me<sub>Et</sub>, <sup>3</sup>J 7.0 Hz), 1.33 (m, 2H, CH<sub>2</sub>Me<sub>Bu</sub>, <sup>3</sup>J 7.5 Hz), 1.48 (m, 2H, SCH<sub>2</sub>CH<sub>2</sub>), 2.21 (s, 3H, MeCO), 2.45 (m, 2H, SCH<sub>2</sub>), 3.45 and 3.84 (2dq, 2H, C\*OCH<sub>2</sub>, <sup>2</sup>J 9.0 Hz, <sup>3</sup>J 7.0 Hz), 4.80 (s, 1H, CH). MS (70 eV), *m/z* (%): 190 ([M]<sup>+</sup>, 1), 147 ([M – MeCO]<sup>+</sup>, 69), 119 ([M – MeCO – C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>, 48), 101 (2), 91 (6), 73 (19), 57 (39), 43 ([MeCO]<sup>+</sup>, 100), 29 ([Et]<sup>+</sup>, 58), 27 (50). Found (%): C, 56.62; H, 9.52; S, 16.11. Calc. for C<sub>9</sub>H<sub>18</sub>O<sub>2</sub>S (%): C, 56.8; H, 9.47; S, 16.85.

**1,1-Diethoxypropenone 7**. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.24 (t, 6H, 2Me <sup>3</sup>J 7.0 Hz), 2.18 (s, 3H, MeCO), 3.69 and 3.56 (AB system, 2dq, 4H, 2OCH<sub>2</sub>, <sup>2</sup>J 9.5 Hz, <sup>3</sup>J 7.0 Hz), 4.52 (s, 1H, CH). MS (70 eV), *m/z* (%): 103 ([M – MeCO]<sup>+</sup>, 24), 75 ([M – MeCO – C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>, 31), 73 (29), 47 (100), 45 (42), 43 (89).

**Table 1** Monitoring of the reactions of 2-ethoxypropenal with thiols by <sup>1</sup>H NMR spectroscopy.

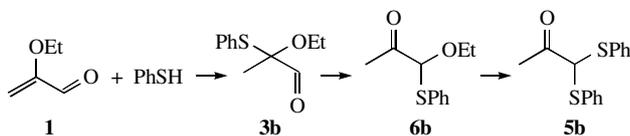
| Compound      | Solvent           | Catalyst       | T/°C | Time    | Product distribution (%) |    |    |    |    |
|---------------|-------------------|----------------|------|---------|--------------------------|----|----|----|----|
|               |                   |                |      |         | 3                        | 4  | 5  | 6  | 7  |
| <b>1 + 2a</b> |                   |                | 20   | 5 days  | 75                       | 10 | 5  |    |    |
| <b>3a</b>     | CDCl <sub>3</sub> |                | 60   | 3 h     | 54                       |    | 16 | 30 |    |
| <b>3a</b>     | CDCl <sub>3</sub> |                | 60   | 5 h     |                          |    | 40 | 40 |    |
| <b>3a</b>     |                   | <i>p</i> -TsOH | 20   | 24 h    |                          |    | 14 | 71 | 14 |
| <b>1 + 2a</b> |                   | HCl            | 20   | 48 h    | 18                       |    | 20 | 57 |    |
| <b>1 + 2a</b> |                   | <i>p</i> -TsOH | 20   | 6 days  | 14                       | 42 |    | 42 |    |
| <b>1 + 2b</b> |                   |                | 20   | 7 days  | 100                      |    |    |    |    |
| <b>3b</b>     |                   |                | 20   | 55 days | 78                       |    | 11 | 11 |    |
| <b>3b</b>     | CDCl <sub>3</sub> |                | 60   | 3 h     |                          |    | 25 | 50 |    |
| <b>3b</b>     | CDCl <sub>3</sub> |                | 60   | 5 h     |                          |    | 20 | 51 |    |
| <b>3b</b>     |                   | <i>p</i> -TsOH | 20   | 24 h    |                          |    | 6  | 70 | 4  |
| <b>1 + 2b</b> |                   | <i>p</i> -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-ethoxypropenal **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-dibutylthio-1-ethoxypropanone **4a**. The ratio of acetals **3a**, **4a** and **6a** is approximately 1:3:3 (Scheme 3).

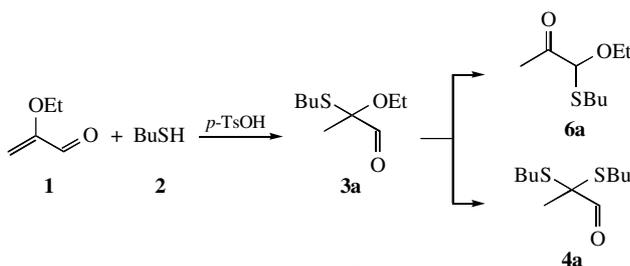
All reactions with *p*-TsOH were carried out in the presence of molecular sieves 4A to avoid the hydrolytic effect of water. Water could form if the aldehyde group of the initial 2-ethoxypropenal **1** took part in the acetal formation, which is characteristic of acrolein.<sup>8</sup>

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-phenylthio-1-ethoxypropanone **3b** and initial substrate **1** is 2:1. In seven days, the conversion of 2-ethoxypropenal into monothioacetal **3b** comprises 100% (Scheme 4).

**Scheme 4**

Like monothioacetal **3a**, monothioacetal **3b** gradually isomerises on keeping at 20 °C to give 1-ethoxy-1-phenylthio-1-ethoxypropanone **6b**. The latter partly undergoes disproportionation into 1,1-diphenylthio-1-ethoxypropanone **5b** and 1,1-diethoxy-1-ethoxypropanone **7**. After storage for two months, the concentration ratio between compounds **3b**, **5b** and **6b**<sup>8</sup> becomes 7:1:1. Acetal **7** cannot be identified in the reaction mixture by NMR; it was detected only by the GC-MS.

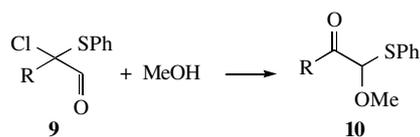
On heating to 60 °C, monothioacetal **3b** (pure or in a CDCl<sub>3</sub> solution) totally disappears in 3 h. This resulted partly from the rearrangement to acetal **6b** and then to thioacetal **5b** and partly from the thermal decomposition of PhS-containing acetals to form diphenyl disulfide (25–30%).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

**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-diphenylthio-1-ethoxypropanone **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 monothioacetals 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-phenylthioalkanal **9** with methanol to give 1-methoxy-1-phenylthioalkanal-2-ones **10** rather than the expected ketals<sup>9</sup> (Scheme 5).

**Scheme 5**

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<sup>2</sup>-Ethoxy-2-phenylthio-1-ethoxypropanone **3b**: bp 120–124 °C (3 torr), *n*<sub>D</sub><sup>20</sup> 1.5560. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.28 (t, 3H, OCH<sub>2</sub>Me, <sup>3</sup>J 7.0 Hz), 1.55 [s, 3H, MeC(O)S], 3.7 (dq, 1H, OCH<sub>2</sub>, <sup>2</sup>J 7.3 Hz, <sup>3</sup>J 7.0 Hz), 4.05 (dq, 1H, OCH<sub>2</sub>, <sup>2</sup>J 7.3 Hz, <sup>3</sup>J 7.0 Hz), 7.29 (m, 3H, *p*-, *m*-Ph), 7.43 (d, 2H, *o*-Ph, <sup>3</sup>J 8.0 Hz), 9.17 (s, 1H, CHO). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 15.06 (Me), 19.44 (Me), 58.81 (CH<sub>2</sub>), 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]<sup>+</sup>, 1), 181 ([M - CHO]<sup>+</sup>, 100), 165 ([M - OEt]<sup>+</sup>, 2), 153 (8), 137 (3), 123 (6), 110 ([HSPh]<sup>+</sup>, 50), 109 ([SPh]<sup>+</sup>, 66), 101 ([M - SPh]<sup>+</sup>, 34), 73 (100), 65 (43), 45 ([OEt]<sup>+</sup>, 67), 43 (70). Found (%): C, 62.64; H, 6.3; S, 15.66. Calc. for C<sub>11</sub>H<sub>14</sub>O<sub>2</sub>S (%): C, 62.83; H, 6.71; S, 15.25.

1-Ethoxy-1-phenylthio-1-ethoxypropanone **6b**: bp 120 °C (2 torr), *n*<sub>D</sub><sup>20</sup> 1.5515. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.29 (t, 3H, OCH<sub>2</sub>Me, <sup>3</sup>J 7.0 Hz), 2.07 (s, 3H, MeCO), 3.54 (dq, 1H, OCH<sub>2</sub>, <sup>2</sup>J 7.3 Hz, <sup>3</sup>J 7.0 Hz), 4.05 (dq, 1H, OCH<sub>2</sub>, <sup>2</sup>J 7.3 Hz, <sup>3</sup>J 7.0 Hz), 5.03 (s, 1H, OCHS), 7.29 and 7.44 (2m, 5H, Ph). MS (70 eV), *m/z* (%): 210 ([M]<sup>+</sup>, 4), 167 ([M - MeCO]<sup>+</sup>, 100), 139 ([M - MeCO - C<sub>2</sub>H<sub>4</sub>]<sup>+</sup>, 84), 111 (65), 109 ([SPh]<sup>+</sup>, 40), 77 ([Ph]<sup>+</sup>, 41), 73 (26), 45 ([OEt]<sup>+</sup>, 69), 43 (85). Found (%): C, 62.45; H, 7.18; S, 15.68. Calc. for C<sub>11</sub>H<sub>14</sub>O<sub>2</sub>S (%): C, 62.83; H, 6.71; S, 15.25.

1,1-Diphenylthio-1-ethoxypropanone **5b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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]<sup>+</sup>, 41), 165 ([M - SPh]<sup>+</sup>, 28), 121 (46), 109 ([SPh]<sup>+</sup>, 41), 77 ([Ph]<sup>+</sup>, 31), 43 ([MeCO]<sup>+</sup>, 100), 28 ([CO]<sup>+</sup>, 87).