The Michael-type addition of organylthiols to 2-alkoxypropenals

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Dedicated to Academician Michael G. Voronkov on the occasion of his 80th birthday
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Abstract
The reaction of 2-alkoxypropenals with organylthiols in the presence of small amounts of a base afforded 3-organylsulfanyl-2-alkoxypropanals. The regiochemistry follows the 1,4-addition pattern and contrasts the orientation of the Markovnikov addition, which takes place in the absence of a base. Microwave irradiation accelerates the 1,4-addition reaction.

Keywords: 2-Alkoxypropenal, 1,4-addition, alkylthiols, arylthiols, base catalysis, microwave irradiation

Introduction

The orientation of the addition of thiols, alcohols, amines, CH-acids to an olefinic double bond activated by geminal substituents of opposite electronic character is a topical problem of the strategy and tactics of organic synthesis.

The 1,4-addition reaction of mercaptans[1] and thiophenol[2] to α,β-unsaturated aldehydes proceeds readily in the absence of a catalyst at room temperature and also in the presence of tertiary amines (triethylamine, piperidine) giving rise to the formation of 1,4-addition products,[2–4] also at elevated temperatures.[5] The addition reaction of alkanethiols to 2-chloro-2-butenal in the presence of potassium carbonate at 80 °C follows the same 1,4-addition pattern.[6]

2-Alkoxypropenals combine structural features of acrolein and vinyl ethers. Depending on reagent and reaction condition, the addition of various reagents to this olefinic system with geminal capto-dative substituents may follow either of three pathways: 4,3-addition according to Markovnikov's rule (H_2O, ROH),[7,8] Michael-type 1,4-addition (CH-acids),[9] and 1.2-addition to the carbonyl group (amines, hydrazines, Grignard reagents, CH-acids).[9–11]

According to ^1H and ^{13}C NMR spectral data, the olefinic bond of 2-alkoxypropenals is

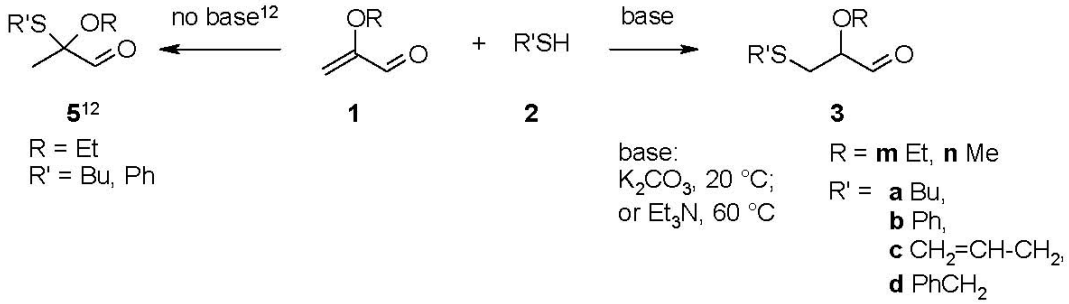
polarized with the β-carbon atom being partially negatively charged.[9] Due to this electron density distribution the reaction of 2-ethoxypropenal (**1m**) with thiols **2a**,**b** at 20 °C yielded 2-organylsulfanyl-substituted 2-ethoxypropanals **5** (Scheme 1) regioselectively following the Markovnikov addition pattern.[12] The initial attack of the thiol group of 2-mercaptoethanol on 2-alkoxypropenals in neutral or acidic media at room temperature also occurs with this orientation.[13]

On the other hand, as we have reported previously[14] the reaction of butane-1-thiol (**2a**) with 2-alkoxypropenals **1** in the presence of bases like BuSNa or NaOH in DMSO (so called "strongly basic" media)[15] or potassium carbonate (5–10 mol%) without solvent afforded 1,4-addition products. The reaction mixture rapidly turned dark (possibly because of polymer formation), and work-up after 1–2 h afforded 3-butylsulfanyl-2-alkoxypropanals **3** in low yields (15–40%).[14]

The goal of the present work was the investigation of the 1,4-addition reaction of alkyl- and arylthiols **2** to 2-alkoxypropenals **1**. This study is of special interest in view of 1,4-addition reaction of thiol groups of key controlling enzymes and some proteins to α,β-unsaturated aldehydes being the basis of the biological effect of the latter,[16–18] in particular, that of antitumor actions.[19–21] The addition of methanethiol[22] and thiophenol[23] to acrolein is the starting reaction in the synthesis of biologically active compounds such as methionine[24] and macrolide antibiotics.[22]

Results and Discussion

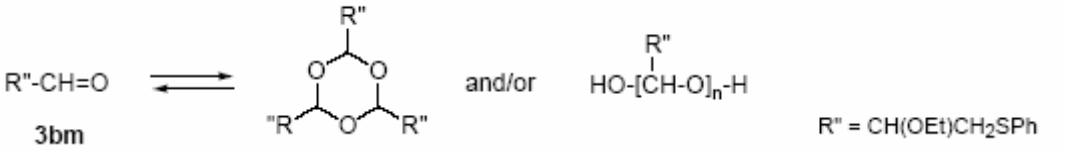
When the reaction of butane-1-thiol (**2a**) with 2-ethoxypropenal (**1m**) in the presence of small amounts of potassium carbonate (5–10 mol%) without solvent was carried out at a prolonged reaction period (20 °C, 24 h) the yield of the 1,4-adduct **3am** increased (70%) (Scheme 1). Using small amounts of triethylamine (60 °C, 3 h) instead of potassium carbonate also induced selectively the 1,4-addition of thiols **2** to 2-alkoxypropenals **1** and furnished adducts **3** in up to 82% yield (Scheme 1).



Scheme 1

The reaction of 2-ethoxypropenal (**1m**) with thiophenol (**2b**) in the presence of small amounts of potassium carbonate (5 mol%) at 20 °C for 24 h furnished exclusively 2-ethoxy-3-

phenylsulfanylpropanal (**3bm**) (Scheme 1). The ^{1}H NMR spectrum of the reaction mixture revealed the coexistence of monomer (**3bm**) and polymer forms (ratio 1:1; Scheme 2): The integration of the aldehyde methine proton signal (R"–CH=O), δ 9.59 (d, J = 1.8 Hz) was about 50% with respect to the integration of the R" signals; an additional signal at δ 3.68 (d, J = 8 Hz) integrating about 50% of the respective R" signals can be attributed to the acetal group [O–CH(R")–O] of the aldehyde polymer (trimer[7, 25] or linear polymer) (Scheme 2).



Scheme 2

In these reactions, triethylamine (0.6–10 mol%) can replace potash as base. When the reaction was carried out in the presence of catalytic amounts of triethylamine without a solvent in a commercial microwave oven the reaction time was reduced to several minutes affording **3** in higher yields (up to 70%).

These experiments suggest that in the presence of a base that renders the thiol reactant **2** more nucleophilic the reaction with 2-alkoxypropenals **1** afforded 1,4-adducts **3** in good yields following the typical orientation of 1,4-addition reactions of nucleophilic reactants with enone systems.

In summary, the reaction of thiols **2** with 2-alkoxypropenals **1** shows the ambident nature of the latter;[12,13] the presence of a base gave rise to the regioselective formation of 1,4-adducts **3**, variation of reaction conditions (solvent, reaction temperature, reaction time) affected the reaction rate and the yield of these products.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer at 25 °C; the signals are referenced to $CHCl_3$ (δH 7.25) in the solvent $CDCl_3$. Mass spectra (EI, 70 eV) were recorded on a chromato-mass spectrometer Hewlett-Packard HP5971A chromatograph HP-5890 (column Ultra-1, 25 m, with SE-30 phase, evaporator temperature 250 °C, temperature gradient 20 °C min^{-1} in the range of 70 to 250 °C). A microwave oven LG Electronics Inc MS-1904H (560 W) was used.

3-Butylsulfanyl-2-ethoxypropanal (3am). Typical procedure. A solution of K_2CO_3 (35 mg, 0.25 mmol) in **2a** (0.52 mL, 438 mg, 4.85 mmol) was combined with **1m** (485 mg, 4.85 mmol). The reaction mixture was allowed to stand at 20 °C for 24 h. Vacuum distillation gave a colourless oil **3am** (645 mg, 70%), bp 93 °C (3 mm Hg); n 1.4625. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (1H, d, J = 2 Hz, 1-HC=O), 3.8 (1H, m, 2-HCO), 3.65 (2H, m, CH_2O), 2.82 (1H, dd, J =

13.82, 5.38 Hz, 3-CH_AS), 2.77 (1H, dd, *J* = 13.82, 6.73 Hz, 3-CH_BS), 2.56 (2H, t, SCH_2[Bu]), 1.57 (2H, m, CH_2[Bu]), 1.39 (2H, m, CH_2[Bu]), 1.19 (3H, t, *J* = 7 Hz, CH_3), 0.90 (3H, t, *J* = 7 Hz, CH_3[Bu]); MS: *m/z* (%) 190 [M+•],(1), 161 $[M-CHO]^+$ (7), 145 $[M-OEt]^+$ (1), 133 $[M-Bu]^+$ (3), 105 (6), 61 (39), 29 (100). Anal. Calcd. for $C_9H_{18}O_2S$ (190.15): C, 56.80; H, 9.53; S, 16.85. Found: C, 56.88; H, 9.40; S, 16.68.

3-Phenylsulfanyl-2-ethoxypropanal (3bm). Typical procedure. A solution of Et_3N (24 mg, 0.27 mmol) in **2b** (0.52 mL, 533 mg, 4.85 mmol) was combined with **1m** (485 mg, 4.85 mmol). The reaction mixture was heated at 60 °C for 3 h. Thereafter, the liquid was distilled to give a colourless oil **3bm** (437 mg, 82%), bp 106 °C (3 mm Hg); *n* 1.5535. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (1 H, d, *J* = 1.8 Hz, 1-HC=O), 7.29 (5H, m, Ph), 3.78 (1H, ddd, *J* = 1.8, 5.3, 7.1 Hz, 2-HCO), 3.61 (1H, dq, *J* = 9.3 Hz, *J* = 6.9 Hz, OCH_B), 3.56 (1H, dq, *J* = 9.3 Hz, *J* = 6.9 Hz, OCH_A), 3.24 (1H, dd, *J* = 13.9, 5.1 Hz, 3-CH_AS), 3.12 (1H, dd, *J* = 13.9, 7.2 Hz, 3-CH_BS), 1.26 (3H, t, *J* = 6.9 Hz, CH_3); MS: m/z (%): 210 [M]+ (11), 181 $[M-CHO]^+$ (11), 152 (4), 135 $[M-OEt]^+$ (100), 123 $[PhSCH_2]^+$ (35), 109 $[PhS]^+$ (34), 65 (21); 45 $[EtO]^+$ (28), 29 (100). Anal. Calcd. for $C_{11}H_{14}O_2S$ (210.17): C, 62.83; H, 6.71; S, 15.25. Found: C, 63.02; H, 6.08; S, 15.25.

3-Phenylsulfanyl-2-ethoxypropanal (3bm). Prepared as described for **3am**. A solution of K_2CO_3 (35 mg, 0.25 mmol) in **2b** (0.5 mL, 534 mg, 4.85 mmol) was combined with **1m** (485 mg, 4.85 mmol) and $Cu(OAc)_2$ (15 mg, 0.25 mmol). After 2 d, the 1H NMR spectrum of the reaction mixture revealed **3bm** as the sole product formed but with an admixture (ratio 1:1) of a polymer form (trimer or linear polymer). ^{1}H NMR: δ 9.59 (1H, d, *J* = 1.8 Hz, 1-HC=O **3bm**), 3.68 (1H, d *J* = 8 Hz, 1-OCHO of trimer or polymer); ratio 1:1 of both signals, each integrating approximately 50% of the respective signals of the remaining groups.

3-Phenylsulfanyl-2-methoxypropanal (3bn). Prepared as described for **3bm**, Et_3N (0.033 mL), **2b** (656 mg, 5.96 mmol) and **1n** (543 mg, 6.31 mmol) gave colourless liquid **3bn** (759 mg, 65%), bp 92 °C (7 mm Hg); *n* 1.5750. ^{1}H NMR (400 MHz, $CDCl_3$): 9.67 (1 H, d, *J* = 1.7 Hz, 1-HC=O), 3.70 (1H, m, 2-HCO), 3.45 (3H, s, OCH_3), 3.24 (1H, dd, *J* = 13.8, 5.3 Hz, 3-CH_AS), 3.13 (1H, dd, *J* = 13.8, 6.9 Hz, 3-CH_BS). MS: *m/z* (%) 167 $[M-CHO]^+$ (15), 135 (100), 123 (81), 110 $[PhSH]^+$ (87), 109 $[PhS]^+$ (67); 77 $[Ph]^+$ (19), 65 (30), 45 (50). Anal. Calcd. for $C_{10}H_{12}O_2S$ (196,16): C, 61.22; H, 6.12; S, 16.32. . Found: C, 61.25; H, 6.12; S, 16.05.

3-Butylsulfanyl-2-methoxypropanal (3an). Prepared as described for **3bm**, Et_3N (0.033 mL), **2a** (0.54 mL, 454 mg, 5.03mmol) and **1n** (0.4 mL, 434 mg, 4.81 mmol) afforded **3an** as a colourless liquid (339 mg, 40%), bp 60 °C (3 mm Hg); *n* 1.4675. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (1H, d, *J* = 1.8 Hz, 1-HC=O), 3.74 (1H, m, 2-HCO), 3.50 (3H, s, OCH_3), 2.83 (1H, dd, *J* = 13.9, 5.3 Hz 3-CH_AS), 2.77 (1H, dd, *J* = 13.9, 6.6 Hz 3-CH_BS), 2.57 (2H, t, *J* = 7.4 Hz, CH_2S[Bu]), 1.40 (2H, m, CH_2[Bu]), 1.55 (2H, m, CH_2[Bu]), 0.91 (3H, t, *J* = 7.3 Hz, CH_3). Anal. Calcd. for $C_8H_{16}O_2S$ (176,14): C, 54.51; H, 9.15; S, 18.15. Found: C, 56.47; H, 9.63 S, 19.55.

3-Allylsulfanyl-2-ethoxypropanal (3cm). Prepared as described for **3bm**, Et_3N (0.033 mL), **2c** (358 mg, 4.85 mmol) and **1m** (485 mg, 4.85 mmol) yielded a colourless liquid **3cm** (310 mg,

36%), bp 82 °C (3 mm Hg); *n* 1.4900. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (1 H, d, *J* = 2.0 Hz, 1-HC=O), 5.75 (1H, m, =CH), 5.12 (1H, m, $=CH_2$),5.10 (1H, m, $=CH_2$)3.75 (1H, m, 2-HCO), 3.64 (2H, m, OCH_2), 3.18 (2H, d, *J* = 7.22 Hz, SCH_2), 2.75 (1H, dd, *J* = 13.9, 5.2 Hz, 3-CH_AS), 2.69 (1H, dd, *J* = 13.9, 6.7 Hz, 3-CH_BS), 1.27 (3H, t, *J* = 6.99 Hz, CH_3). MS: *m/z* (%) 145 [M –CHO]$^+$ (25), 113 (32), 103 (42), 87 [M –EtOCHCHO]$^+$ (35), 73 [M –CH_2=$CHCH_2S$]$^+$ (41), 72 (63), 41 (100). Anal. Calcd. for $C_8H_{14}O_2S$ (174,14): C, 55.14; H, 8.85; S, 18.40. Found: C, 53.14; H, 8.10; S, 18.27.

3-Benzylsulfanyl-2-ethoxypropanal (3dm). Prepared as described for **3bm**, Et_3N (0.033 mL), **2d** (601 mg, 4.85 mmol) and **1m** (485 mg, 4.85 mmol) gave a colourless liquid **3dm** (550 mg, 51%), bp 146 °C (3 mm Hg); *n* 1.546. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (1 H, d, *J* = 1.92 Hz, 1-HC=O), 7.29 (5H, m, Ph), 3.76 (2H, s, Ph-CH_2S), 3.69 (1H, m, 2-HCO), 3.58 (2H, m, OCH_2), 2.67 (1H, dd, *J* = 13.9, 5.1 Hz, 3-CH_AS), 2.62 (1H, dd, *J* = 13.9, 6.8 Hz, 3-CH_BS), 1.26 (3 H, t, *J* = 6.95 Hz, CH_3). MS: *m/z* (%) 224 [M]$^+$ (1), 195 [M –CHO]$^+$ (9), 150 [M –CHO –OEt]$^+$ (9), 137 [M –EtOCHCHO]$^+$ (11), 123 [M –$PhCH_2S$]+ (9), 91 (100). Anal. Calcd. for $C_{12}H_{16}O_2S$ (224,18): C, 64.25; H, 7.19; S, 14.29. Found: C, 64.15;H, 7.10; S 14.05.

Reaction of 2-ethoxypropenal (1m) with thiols 2c,**d under microwave irradiation.** To a solution of Et_3N (4.9 mg, 0.05 mmol) in **1m** (0.1 ml, 97mg, 0.97 mmol) was added thiol **2c** (71.8 mg, 0.97mmol) or **2d** (120 mg. 0.97 mmol). The reaction mixture was exposed to microwave irradiation for 2 min. ^{1}H NMR evaluation of the reaction mixture indicated the formation of the main products **3cm** (45%) and **3dm** (70%), respectively.

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