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Condensation of Propan-2-one with Formaldehyde and Propane-2-thiol

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Abstract—Three-component condensation of propan-2-one with formaldehyde and propane-2-thiol in the presence of sodium hydroxide afforded 3-{[(propan-2-yl)sulfanyl)]methyl}but-3-en-2-one or 4-[(propan-2-yl)-sulfanyl]-3-{[(propan-2-yl)sulfanyl]methyl}butan-2-one, depending on the amount of the base. The formation of 4-[(propan-2-yl)sulfanyl]-3-{[(propan-2-yl)sulfanyl]methyl}butan-2-one from 4-[(propan-2-yl)sulfanyl]-butan-2-one involved aldol condensation of the latter with formaldehyde and subsequent nucleophilic addition of propane-2-thiol to the C=C double bond of intermediate 3-{[(propan-2-yl)sulfanyl]methyl}but-3-en-2-one in the presence of sodium hydroxide.

Keywords: thiol, formaldehyde, γ-keto sulfide, β-mercaptoketone, three-component condensation, thia-Michael reaction

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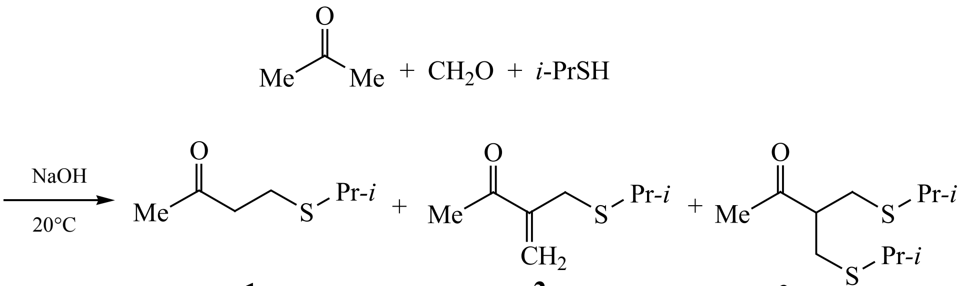
In recent time, multicomponent reactions satisfying the “green chemistry” principles have been widely used in organic synthesis. Such reactions include three-component condensations of ketones and diketones with aldehydes and amines [1–4] or thiols [5–10]. Reactions of ketones with aldehydes and thiols give rise to polyfunctionalized γ-keto sulfides (β-mercaptoketones) which can be used as noble metal extractants [11, 12], flotation agents for gold-containing sulfide ores [13], hydrogen sulfide corrosion inhibitors [14], and intermediate products in medicinal, extraction, agricultural, and heterocyclic chemistry [8, 10, 15–18]. Since the reactions can be performed in the presence of a base, the source of thiols may be alkaline sulfide solutions obtained upon alkaline treatment of gas condensates and petrochemicals to remove sulfur-containing compounds [19].

Ketones with a methylene group at the carbonyl carbon atom (e.g., butan-2-one, 1-phenylpropan-1-one) were reported to react with formaldehyde and thiols to produce alkylsulfanylmethyl ketones [19, 20]. Under the same conditions, reactions of methyl ketones (propan-2-one, 1-phenylethanone) afforded bis(alkylsulfanylmethyl) derivatives. The yields of monosubstituted compounds did not exceed 31%. In order to find out optimal conditions for the formation of various γ-keto sulfides, in this work we studied the condensation of accessible propan-2-one (acetone) with formaldehyde and propane-2-thiol in alkaline medium.

The three-component condensation of propan-2-one with equimolar amounts of formaldehyde and propane-2-thiol in the presence of 0.03–1.25 equiv of sodium hydroxide at 20°C gave a mixture of 4-[(propan-2-yl)sulfanyl]butan-2-one (**1**), previously unknown 3-{[(propan-2-yl)sulfanyl]methyl}but-3-en-2-one (**2**), and 4-[(propan-2-yl)sulfanyl]-3-{[(propan-2-yl)sulfanyl]-methyl}butan-2-one (**3**) (Scheme 1).

Keto sulfides **1** and **3** are products resulting from successive introduction of alkylsulfanylmethyl group into the propan-2-one molecule. Compound **2** is formed via aldol condensation of keto sulfide **1** with formaldehyde. Compounds **1**–**3** were isolated by vacuum distillation (**3**) or column chromatography (**1**, **2**), and their structure was determined on the basis of their elemental analyses and spectral data. The ^{1}H NMR spectrum of **2** contained singlets at δ 5.94 and 6.08 ppm due to nonequivalent olefinic protons, which were not observed in the spectrum of initial keto sulfide **1**, and signals at δ 145.6 (C^3) and 125.9 ppm (C^4) were present in its ^{13}C NMR spectrum. The IR spectrum of **2** showed C=O, C=S, and =C–H stretching bands at 1681, 1626, and 3096 cm^{-1},

Scheme 1.



1 **2** **3**

respectively. The spectral characteristics of **1** and **3** were in a good agreement with those reported in [21, 22].

According to the data of functional group analysis and GLC analysis of the reaction mixtures, the conversion of propane-2-thiol and the product ratio depended on the amount of sodium hydroxide. When the molar ratio acetone : CH$_2$O : *i*-PrSH : NaOH was 1 : 1 : 1 : 0.03, the conversion of propane-2-thiol did not exceed 47% (1 h). After 5 min, the reaction mixture contained mainly keto sulfide **1**, whereas no appreciable amount of **2** or **3** was detected (Fig. 1a). After 10 min, the concentration of **1** decreased due to its transformation into compounds **2** and **3**, and the yields of the latter reached 37 and 5% (calculated on the initial thiol), respectively, after 30 min. The concentrations of **2** and **3** did not change significantly during the subsequent 30 min. Increase of the amount of sodium hydroxide to 0.13 mol led to increase of the conversion of *i*-PrSH to 58% (2 h). The yields of **1**, **2**, and **3** were, respectively, 4, 34, and 18% in 1 h and 5, 30, and 23% in 2 h, and they did not change further to an appreciable extent.

The maximum conversion of *i*-PrSH (99%) was attain in 5 h at a ketone : CH$_2$O : *i*-PrSH : NaOH molar ratio of 1 : 1 : 1 : 0.4; in this case, the major product was bis-sulfide **3** (Fig. 2). In 1 h after the reaction started, the yields of **2** and **3** were 33 and 35%, respectively. As the reaction progressed further, the yield of **2** decreased due to its transformation to **3**. In the presence of an equimolar amount of sodium hydroxide, the conversion of propane-2-thiol was almost complete, and maximum yield of **3** (65%) was attained in 15 min (Table 1, run no. 3).

Our results indicated that propan-2-one reacted with equimolar amounts of formaldehyde and propane-2-thiol in the presence of 0.03 equiv to give in 5 min keto sulfide **1** as the primary product which was then converted almost completely into compound **2** (60 min). The yield of **2** was 40% (calculated on *i*-PrSH) or 81% (with respect to formaldehyde), and the conversion of formaldehyde was

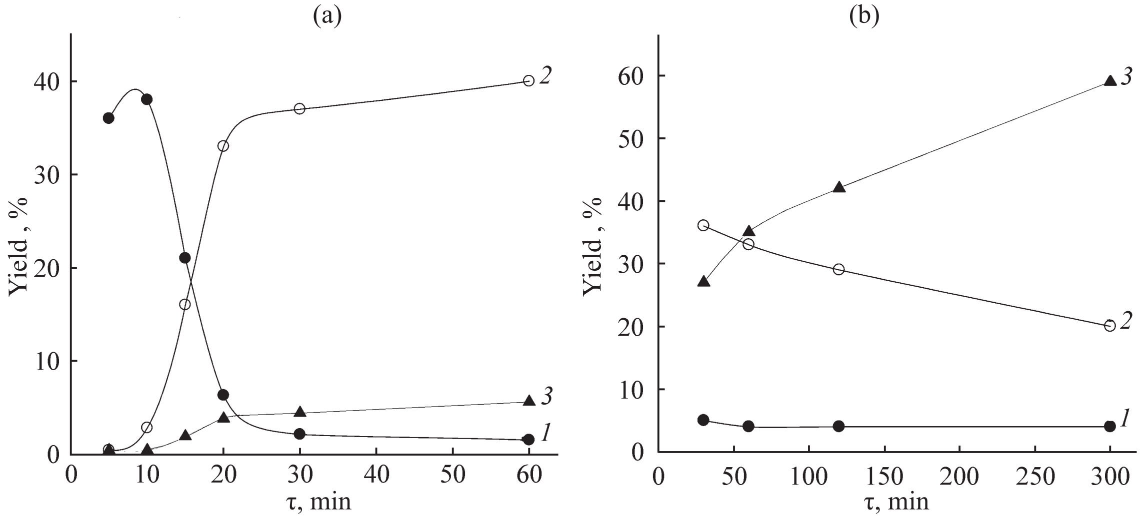


Fig. 1. Yields of compounds (*1*) **1**, (*2*) **2**, and (*3*) **3** in the condensation of propane-2-thiol with formaldehyde and propan-2-one at ketone : CH$_2$O : thiol : NaOH molar ratios of (a) 1 : 1 : 1 : 0.03 and (b) 1 : 1 : 1 : 0.4; temperature 20°C.

Table 1. Condensation of propan-2-one with formaldehyde and propane-2-thiol in the presence of sodium hydroxide at 20°C[a]

Run no.	Molar ratio $Me_2CO : CH_2O :$ *i*-PrSH : NaOH	Conversion of *i*-PrSH, %	Reaction time, min	Yield,[b] %		
				1	**2**	**3**
1	1 : 1 : 1 : 0.13	56	60	4	34	18
2	1 : 2 : 1 : 0.13	73	60	–	67	5
3	1 : 1 : 1 : 1	99	15	8	12	65
5	1 : 1 : 1 : 1.25	99	15	6	11	67
6[c]	1 : 1.25 : 1 : 1	95	30	–	3	86
7[d]	1 : 2 : 1 : 1	99	15	2	40	49
8	1 : 2 : 2 : 2	99	15	2	17	60
9	5 : 1 : 1 : 0.75	97	15	34	2	57
10	10 : 1 : 1 : 0.75	97	15	72	1	6

[a] Diisopropyl disulfide was also detected in 2–4 (run nos. 3–7, 9) and 12% yield (run nos. 8, 10).

[b] Calculated on the initial propane-2-thiol.

[c] The reaction was carried out in ethanol.

[d] The reaction was accompanied by formation of a polymeric product.

87% by that time. In order to improve the selectivity for bis-sulfide **3**, an additional amount of sodium hydroxide (0.4 equiv) should be added, and the reaction time should be prolonged to 5 h. The yield of **3** and the rate of its formation increased in parallel with the amount of alkali (Fig. 1b) and decreased when excess formaldehyde was used (Table 1; run nos. 2, 7).

These findings can be rationalized assuming formation of **3** from **1** according to Scheme 2. Initially, the condensation of propan-2-one with formaldehyde and propane-2-thiol gives keto sulfide **1** which reacts with formaldehyde to produce 3-{[(propan-2-yl)sulfanyl]methyl}but-3-en-2-one (**2**). The final stage is base-catalyzed thia-Michael addition of propane-2-thiol to the C=C double bond of α,β-unsaturated carbonyl compound **2**.

Thus, the optimal conditions for the synthesis of compounds **1**–**3** are as follows. Sulfide **2** is formed as the major product in the presence of 2 equiv of formaldehyde and 0.13 equiv of sodium hydroxyde, whereas 10 equiv of acetone and 0.75 equiv of alkali should be used to obtain preferentially keto sulfide **1** (Table 1, run nos. 2 and 10, respectively). The reaction in ethanol at a ketone : CH_2O : *i*-PrSH : NaOH ratio of 1 : 1.25 : 1 : 1 gives mainly compound **3** in 86% yield (run no. 6).

In summary, we have found that the product ratio in the three-component condensation of propan-2-one with formaldehyde and propane-2-thiol depends on the amount of sodium hydroxide. 3-{[(Propan-2-yl)sulfanyl]methyl}but-3-en-2-one is formed as a result of aldol condensation of 4-[(propan-2-yl)sulfanyl]butan-2-one with formaldehyde, and 4-[(propan-2-yl)sulfanyl]-3-{[(propan-2-yl)sulfanyl]methyl}butan-2-one is the product of addition of propane-2-thiol to 3-{[(propan-2-yl)sulfanyl]methyl}but-3-en-2-one.

EXPERIMENTAL

Freshly distilled propane-2-thiol (reagent-grade), 32% aqueous formaldehyde (GOST 1625-2016), and analytical-grade propan-2-one, sodium hydroxide, and chloroform were used.

The IR spectra were recorded from films on a Shimadzu IR Prestige-21 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer at 500.13 and 125.76 MHz, respectively, using $CDCl_3$ as

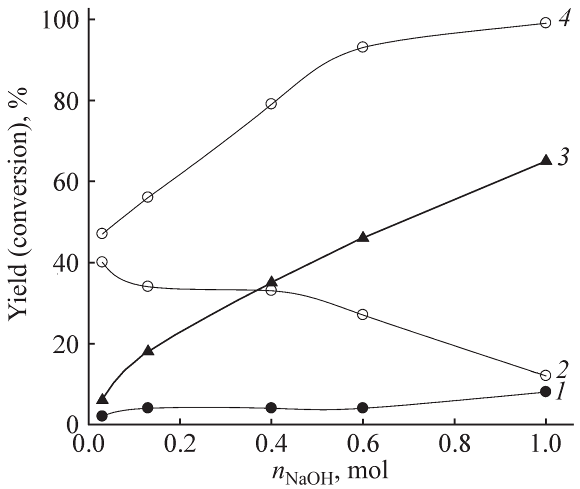
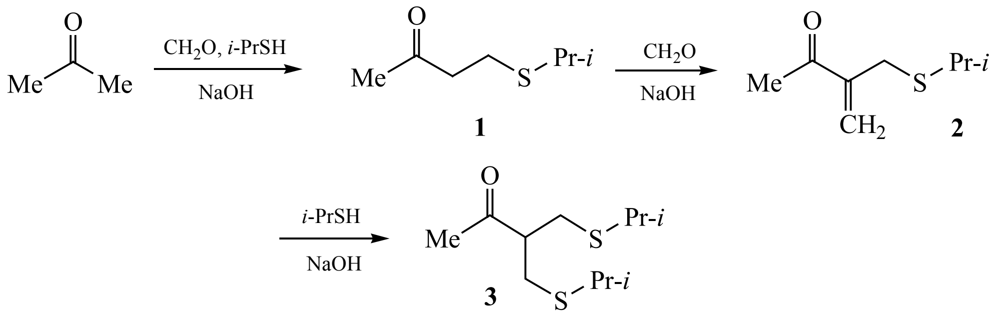


Fig. 2. Yields of compounds (*1*) **1**, (*2*) **2**, and (*3*) **3** and (*4*) conversion of propane-2-thiol in the condensation of propane-2-thiol with formaldehyde and propan-2-one at a molar ratio of 1 : 1 : 1 versus amount of sodium hydroxide; temperature 20°C.

Scheme 2.



solvent and reference. GLC analyses were performed on a Chrom 5 chromatograph equipped with a flame ionization detector and a 2.4-m × 3-mm column packed with 5% SE-30 on Chromaton N-AW-DMCS (0.16–0.20 mm), oven temperature 50–300°C, carrier gas helium; compounds **1**–**3** were quantitated by the internal standard method using hexadecane as internal standard. The calibrating factors were determined using artificial mixtures of **1**–**3** and internal standard. The mass spectra (electron impact, 70 eV) were obtained on a Thermo Finnigan MAT 95 XP instrument with direct sample admission into the ion source. Column chromatography was performed on MN Kieselgel 60 silica gel (0.063–0.2 μm). The progress of reactions was monitored by potentiometric titration with ammoniacal silver nitrate to determine thiol sulfur [23]. The spectral and analytical data were obtained at the Chemistry joint center, Ufa Institute of Chemistry, Russian Academy of Sciences.

Condensation of propan-2-one with formaldehyde and propane-2-thiol. The reactions were carried out in a glass reactor equipped with a magnetic stirrer, maintaining the temperature at 20°C. The reactor was charged with 1.23 mL (13 mmol) of propane-2-thiol, and 0.30 mL (0.39 mmol) of 5% aqueous sodium hydroxide was added with stirring. The mixture was stirred for 15 min, 0.97 mL (13 mmol) of propan-2-one and 1.13 mL (13 mmol) of 32% aqueous formaldehyde were added in succession, and the mixture was stirred for a required time (5 min to 5 h). The mixture was then treated with brine (1 : 1), the organic layer was separated, washed with water (2 mL), dried over $MgSO_4$, and analyzed by GLC, and the products were isolated by silica gel column chromatography (EtOAc–hexane, 1 : 15) or vacuum distillation.

If an equimolar or larger amount of sodium hydroxide was used, the mixture was treated in a different way. After completion of the reaction, the organic layer was separated, and the alkaline aqueous layer was diluted with water (1 : 1) and extracted with chloroform (2×5 mL). The extracts were combined with the organic layer, washed with 10% aqueous HCl (4 mL) and water (2×4 mL), and dried over $MgSO_4$, the solvent was distilled off, and the residue was analyzed as described above.

The molar ratio ketone–formaldehyde–propane-2-thiol–sodium hydroxide was varied in the ranges (0.5–10) : (1–2) : (1–2) : (0.03–2).

4-[(Propan-2-yl)sulfanyl]butan-2-one (1). Mass spectrum, *m*/*z* (I_{rel}, %): 146 (62) $[M]^{+\cdot}$, 131 (2) $[M - CH_3]^+$, 113 (2) $[M - SH]^+$, 103 (12) $[M - C_3H_7]^+$, 89 (8), 75 (40) $[SC_3H_7]^+$, 71 (46) $[C_4H_7O]^+$, 61 (32), 43 (100) $[C_2H_3O]^+$, $[C_3H_7]^+$. The IR and ^{1}H and ^{13}C NMR spectra were identical to those reported in [21].

3-{[(Propan-2-yl)sulfanyl]methyl}but-3-en-2-one (2). IR spectrum, ν, cm^{-1}: 3096 w (=CH), 1681 s (C=O), 1626 w (C=C), 883 w (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 1.25 d [6H, $SCH(CH_3)_2$, $^3J = 6.7$ Hz], 2.36 s (3H, C^1H_3), 2.84 sept (1H, SCH, $^3J = 6.7$ Hz), 3.39 s (2H, CH_2S), 5.94 s and 6.08 s (1H each, $=CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 23.1 [$CH(\mathbf{C}H_3)_2$], 26.0 (C^1H_3), 29.9 (CH_2S), 34.9 (SCH), 125.9 (C^4), 145.6 (C^3), 198.5 (C^2). Found, %: C 60.78; H 8.97; S 20.31. $C_8H_{14}OS$. Calculated, %: C 60.71; H 8.92; S 20.26. The mass spectrum of **2** was similar to that reported in [24].

4-[(Propan-2-yl)sulfanyl]-3-{[(propan-2-yl)-sulfanyl]methyl}butan-2-one (3). $n_D^{20} = 1.4956$, $d_4^{20} = 0.994$. The IR and ^{1}H and ^{13}C NMR spectra were identical to those reported in [22].

2,2′-(Disulfanediyl)dipropane (diisopropyl disulfide) was identified by comparing with an authentic sample.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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