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SHORT COMMUNICATIONS

Silica-Alumina Catalyzed of 2,4-Pentanedione with Formaldehyde and α,ω-Dithiols

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Depending on the character of initial reagents the condensation of 2,4-pentanedione with aldehydes and thiols in water environment leads to the formation in 15–98% yields of β -sulfanyldiketones exhibiting a wide range of pharmacologic characteristics [1, 2].

We presumed that the condensation of 2,4-pentanedione (I) with formaldehyde and α,ω -dithiols would allow the synthesis of cyclic III [3] or linearly bound β,β' -disulfanyldiketones IV (see the scheme). Preliminary experiments showed that the reaction without catalyst of diketone I with formaldehyde and 1,2-ethanedithiol (IIb) (H₂O, 80–100°C, 8 h [1]) afforded 3,10-diacetyl-5,8-dithiadodecane-2,11-dione (IVb) in a yield $\leq 20\%$ (conversion ~30%). Aiming at increasing the yield we carried out the reaction in the presence of heterogeneous catalysts. Poly-(4-vinylpyridine)alumina-silica (PVP/Al₂O₃–SiO₂) at the molar ratio Al₂O₃–SiO₂ 0.31–0.83 catalyzed the Knoevenagel condensation of 1,3-dicarbonyl compounds with aldehydes [4]. In view of these data we applied to the reaction alumina-silica catalysts obtained from ethyl silicate-40 [5] in the presence of surfactant Reapon-4 (see the table, samples nos. 1-4), and samarium silicates (samples nos. 10, 11), and also catalysts obtained by annealing and deposition of elements in the pores of thermohydrated silica gel (samples nos. 5-9, 12). Among the tested alumina-silica catalysts (samples nos. 1-5) the sample Al₂O₃–SiO₂ with the molar ratio 0.0125 : 1 exhib-



II, R = H (a), C₂H₄SH (b), (CH₂)₂O(CH₂)₂O(CH₂)₂SH (c), p-C₆H₄OC₆H₄SH-p (d); **III**, **IV**, **X** = (CH₂)_n, n = 1 (a), 2 (b); (CH₂)₂O(CH₂

Sample no.	Catalyst composition (molar ratio)	Surfactant consumption per weight unit of catalyst, %	Yield, %	
			IVc	IVd
1	Al_2O_3 -SiO ₂ (0.050 : 1)	1.5	36	27
2	Al_2O_3 -SiO ₂ (0.025 : 1)	1.5	21	15
3	Al ₂ O ₃ -SiO ₂ (0.0125 : 1)	1.5	86	91
4	Al ₂ O ₃ -SiO ₂ (0.0125 : 1)	3.0	81	87
5	Al_2O_3 -Si $O_2(0.0429:1)$	_	71	68
6	11.7 wt % $FeCl_3 \cdot 6H_2O/Al_2O_3 - SiO_2(0.0125:1)$	_	63	79
7	8.9 wt % $MnCl_2 \cdot 4H_2O/Al_2O_3$ -SiO ₂ (0.0125 : 1)	_	67	42
8	4.1 wt % MnO ₂ /Al ₂ O ₃ -SiO ₂ (0.0125 : 1)	_	74	39
9	4.1 wt % CoO/Al ₂ O ₃ -SiO ₂ (0.0125 : 1)	_	49	33
10	Sm_2O_3 -SiO ₂ (0.0125 : 1)	1.5	72	65
11	Sm_2O_3 -SiO ₂ (0.0125 : 1)	3.0	78	74
12	Sm_2O_3 -SiO ₂ (0.0429 : 1)	_	63	79

Yield of compounds IVc and IVd depending on the used catalyst

ited the highest activity (sample no. 3). In the presence of this catalyst (5 mol %) the reaction (H₂O, 80–100°C, 8 h) afforded compound **IVb** in 43% yield. When the reaction was carried out in a mixture H₂O–C₂H₅OH–CHCl₃ the yield of compound **IVb** grew to 60%. Under the developed conditions the three-component condensation of diketone **I**, formaldehyde and H₂S in the presence of the catalyst Al₂O₃–SiO₂, 0.0125 : 1, gave thiomethylated diketone **IVa** in 47% yield. No formation of cyclic compounds **IIIa**, **IIIb** was observed in any runs.

In extension of the synthesis to compounds where the 2,4-dioxopentane-3-yl fragments are bound with chains containing oxygen and sulfur atoms we studied the reaction of diketone **I** with formaldehyde and heterochain α,ω -dithiols. In reactions of acetylacetone with formaldehyde, 3,6-dioxaoctane-1,8-dithiol (**IIc**) or 4-(4-sulfanylphenoxy) thiophenol (**IId**) a high catalytic activity was exhibited by alumina-silica Al₂O₃–SiO₂, 0.0125 : 1 (sample no. *3*) and 0.0429 : 1 (sample no. *4*), and also catalysts based on deposited on alumina-silica FeCl₃ (sample no. *6*) and Sm₂O₃ (samples nos. *10–12*). With these catalysts the yields of 3,16-diacetyl-8,11-dioxa-5,14-dithiaoctadecane-2,17-dione (**IVc**) and 3-{4-[4-(2-acetyl-3-oxobutylsulfanyl)-phenoxy]phenylsulfanylmethyl} pentane-2,4-dione (**IVd**) reached 63–90%.

Obviously the reactivity of the heterochain α,ω -dithiols in the alumina-silica catalyzed reaction of acetylacetone with formaldehyde is higher than the reactivity of aliphatic dithiols.

3,9-Diacetyl-5,7-dithiaundecene-2,10-dione (IVa). 2.21 mL (30 mmol) of 37% water solution of formaldehyde was at room temperature (~20°C) saturated with hydrogen sulfide (obtained from the calculated amount of Na₂S and HCl) in the course of 30 min. Then to the reaction mixture 2.5 mL of CHCl₃ and 2.5 mL of C₂H₅OH, 1.95 mL (20 mmol) of acetylacetone, and 0.11 g (1.63 mmol) of Al₂O₃-SiO₂ was added. The mixture was stirred at ~20°C for 6 h. The reaction mixture was filtered through a silica gel bed, the reaction products were extracted with ethyl acetate $(3 \times 15 \text{ mL})$, the extract was dried with Na₂SO₄, evaporated on a rotary evaporator, and the reaction products were separated by column chromatography on silica gel (eluent hexane-chloroform-ethyl acetate, 1:1:4). Yield 47%, oily substance, n_D^{20} 1.5124. IR spectrum, cm⁻¹: 1726 (C=O), 1420 (CH₂), 1074 (C–O), 720 (C–S). ¹H NMR spectrum, δ, ppm: 2.12 s (12H, H₃C^{14,17,18,19}), 2.82 m (4H, H₂C^{4,8}), 3.65 t (2H, HC^{5,9}, J 7.1 Hz), 4.32 br.s (2H, H₂C²). ¹³C NMR spectrum, δ, ppm: 24.31 (C^{14,17,18,19}), 29.61 (C^{4,8}), 33.27 (C²), 69.15 (C^{5,9}), 192.73 (C^{6,10,12,15}). Mass spectrum: m/z327.241 [*M*+Na]⁺. Found, %: C 50.82; H 6.44; S 20.91.

C₁₃H₂₀O₄S₂. Calculated, %: C 51.29; H 6.62; S 21.07. *M* 304.427.

Catalytic thiomethylation of acetylacetone with formaldehyde and α,ω -dithiols. Into a Schlenk vessel under argon atmosphere at room temperature (~20°C) was charged 1.47 mL (20 mmol) of 37% water solution of formaldehyde, 10 mmol of an appropriate α,ω dithiol, and the mixture was stirred for 30 min. Then to the mixture was added 2.5 mL of CHCl₃ and 2.5 mL of C₂H₅OH, 1.95 mL (20 mmol) of acetylacetone, and 1 mmol of alumina-silica catalyst, the reaction mixture was stirred at ~20°C for 6 h. The reaction mixture was filtered through a bed of silica gel, the filtrate was dried with Na₂SO₄. The reaction products were separated by column chromatography on silica gel (eluent hexane– chloroform–ethyl acetate, 1 : 1 : 4).

3,10-Diacetyl-5,8-dithiadodecane-2,11-dione (IVb). Yield 59%, white crystals, mp 138–140°C. IR spectrum v, cm⁻¹: 3434 (O–H), 1691 (C=O), 1418 (CH₂), 1020 (C–O), 724 (C–S). ¹H NMR spectrum, δ , ppm: 2.27 s (12H, H₃C^{15,18,19,20}), 2.80 s (4H, H₂C^{6,7}), 3.51 br.s (4H, H₂C^{2,9}), 16.74 s (2H, OH). ¹³C NMR spectrum, δ , ppm: 22.68 (C^{15,18,19,20}), 30.35 (C^{9,5}), 32.33 (C^{2,3}), 106.21 (C^{6,10}), 191.82 (C^{7,11,13,16}). Mass spectrum: *m*/*z* 341.255 [*M* + Na]⁺. Found, %: C 51.86; H 6.80; S 20.60. C₁₄H₂₂O₄S₂. Calculated, %: C 52.80; H 6.96; S 20.14. *M* 318.454.

3,16-Diacetyl-8,11-dioxa-5,14-dithiaoctadecane-2,17-dione (IVc). Yield 86%, oily substance, n_D^{20} 1.5348. IR spectrum v, cm⁻¹: 1699 (C=O), 1599, 1418 (CH₂), 1110 (C–O–C), 1022 (C–O), 716 (C–S). ¹H NMR spectrum, δ , ppm: 2.24 s (12H, H₃C^{21,24,25,26}), 2.70 t (4H, H₂C^{2,9}, *J* 6.4 Hz), 3.52 d (4H, H₂C^{11,15}, *J* 5.6 Hz), 3.64 d (4H, H₂C^{5,6}, *J* 3.2 Hz), 3.67 t (4H, H₂C^{3,8}, *J* 6.6 Hz). ¹³C NMR spectrum, δ , ppm: 22.87 (C^{21,24,25,26}), 29.46 (C^{11,15}), 30.89 (C^{2,9}), 70.32 (C^{3,8}), 71.01 and 106.6 (C^{12,16}), 71.60 (C^{5,6}), 192.13 (C^{13,17,19,22}). Mass spectrum: *m/z* 429.134 [*M* + Na]⁺. Found, %: C 52.71; H 8.13; S 15.59. C₁₈H₃₀O₆S₂. Calculated, %: C 53.18; H 7.44; S 15.77. *M* 406.559.

3-{4-[4-(2-Acetyl-3-oxobutylsulfanyl)phenoxy]phenylsulfanylmethyl}pentane-2,4-dione (IVd). Yield 91%, oily substance, n_D^{20} 1.6092. IR spectrum v, cm⁻¹: 1697 and 1581 (C=O), 1485 μ 1555 (Ar), 1416 (CH₂), 1238 (Ar–O–Ar), 1012 (C–O), 714 (C–S). ¹H NMR spectrum, δ, ppm: 2.16 s (12H, H₃C^{21,27,30,31}), 3.76 s (4H, H₂C^{8,23}), 3.85 t (2H, HC^{9,24}, *J* 6.8 Hz), 6.92–7.50 m (8H, HC^{4r}). ¹³C NMR spectrum, δ, ppm: 22.67 (C^{21,27,30,31}), 34.58 (C^{8,23}), 69.15 (C^{9,24}), 119.58–156.64 (C^{4r}), 192.44 (C^{10,19,25,28}). Mass spectrum: *m*/*z* 481.196 [*M* + Na]⁺. Found, %: C 61.60; H 5.56; S 14.24. C₂₄H₂₆O₅S₂. Calculated, %: C 62.86; H 5.71; S 13.98. *M* 458.592.

NMR spectra were registered on a spectrometer Bruker Avance-400 in CDCl₃, operating frequencies 400.13 (¹H) and 100.62 (¹³C) MHz. Mass spectra were obtained on an instrument MALDI-TOF Autoflex III, matrices α -cyano-4-hydroxycinnamic and 2,5-dihydrobenzoic acids. IR spectra were recorded on a spectrophotometer Bruker Vertex 70V from mulls in mineral oil. Elemental analysis was performed on an analyzer Carlo Erba 1106. Column chromatography was carried out on silica gel (50–160 µm), TLC analysis was done with the use of Silufol UV-254 plates, development in iodine vapor.

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