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New Synthesis of 2-Acetonyl-4-alkoxymethylbutanolides*

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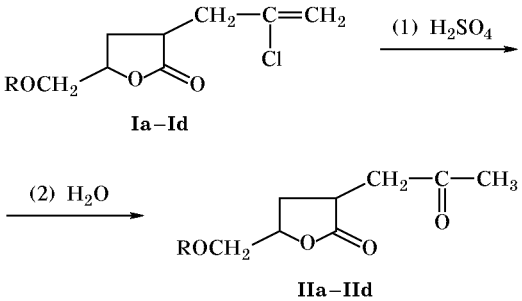
Abstract—A new method was developed for synthesis of 2-acetonyl-4-alkoxymethylbutanolides by treatment of 4-alkoxymethyl-2-(β-chloroallyl)butanolides with concentrated sulfuric acid and subsequent hydrolysis. 4-alkoxymethyl-2-(β-chloroallyl)butanolides are readily obtained by alkylation of accessible 4-alkoxymethyl-2-ethoxycarbonylbutanolides with 2,3-dichloropropene, followed by hydrolysis and decarboxylation of the resulting 4-alkoxymethyl-2-(β-chloroallyl)-2-ethoxycarbonylbutanolides.

Keto lactones, specifically acetonyl lactones, are reactive compounds which can be used for preparation of heterocyclic compounds containing a lactone moiety; the latter are promising from the viewpoint of biological activity [1–3]. We previously proposed [4] a procedure for synthesis of 2-acetonyl-4-alkoxymethylbutanolides by the Kucherov hydration of 4-alkoxymethyl-2-(2-propynyl)butanolides which are obtained from the corresponding acetyl lactones. However, this procedure requires thoroughly dehydrated solvents, otherwise initial acetyl lactones can undergo ring opening with subsequent decarboxylation, and the yield of 2-propynyl lactones sharply decreases. In addition, the required 2-propynyl halides and 2-propynyl alcohol are not readily accessible compounds, and there is the problem of utilization of waste mercury sulfate used as hydration catalyst. These factors reduce the value of the developed procedure.

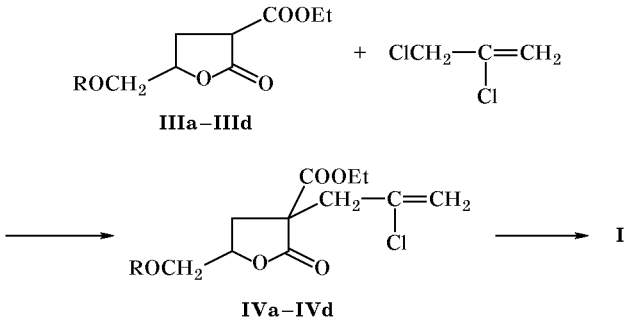
Scheme 1.



R = C_4H_9 (**a**), *iso*-C_4H_9 (**b**), C_5H_{11} (**c**), *iso*-C_5H_{11} (**d**).

We now report on a new method for preparation of 2-acetonyl-4-alkoxymethylbutanolides **II** by hydrolysis of 4-alkoxymethyl-2-(β-chloroallyl)butanolides **I** in sulfuric acid (Scheme 1). Initial β-chloroallyl lactones **I** are readily prepared by alkylation of accessible 4-alkoxymethyl-2-ethoxycarbonylbutanolides **III** with 2,3-dichloropropene, followed by hydrolysis and decarboxylation of 4-alkoxymethyl-2-(β-chlorallyl)-2-ethoxycarbonylbutanolides **IV** thus obtained (Scheme 2).

Scheme 2.



Taking into account that alkylation of lactones **III** proceeds almost quantitatively, final products **I** can be obtained by one-pot synthesis, without isolation of intermediate esters **IV**. The proposed procedure also allows us to obtain 2-acetonyl lactones **V** containing an ester moiety in position *2* (Scheme 3), which extends its synthetic potential. For all reactions we have found optimal conditions, ensuring high yields

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Table 1. Yields, constants, and elemental analyses of 4-alkoxymethyl-2-(β-chloroallyl)butanolides **Ia**–**Id** and 4-alkoxymethyl-2-(β-chloroallyl)-2-ethoxycarbonylbutanolides **IVa**–**IVd**

Comp. no.	Yield, %	bp, °C (*p*, mm)	n_D^{20}	d_4^{20}	R_f (A)	Found, %			Formula	Calculated, %		
						C	H	Cl		C	H	Cl
Ia	90	118 (0.5)	1.4720	1.0892	0.50	58.25	7.75	14.45	$C_{12}H_{19}ClO_3$	58.42	7.71	14.40
Ib	86	114–115 (1)	1.4672	1.0842	0.45	58.60	7.85	14.25	$C_{12}H_{19}ClO_3$	58.42	7.71	14.40
Ic	84	129 (1)	1.4700	1.0729	0.49	60.05	8.12	13.55	$C_{13}H_{21}ClO_3$	59.88	8.06	13.63
Id	85	125 (1)	1.4715	1.0725	0.54	60.00	8.10	13.52	$C_{13}H_{21}ClO_3$	59.88	8.06	13.63
IVa	80	133–134 (1)	1.4700	1.1220	0.40	56.66	7.15	11.00	$C_{15}H_{23}ClO_5$	56.52	7.15	11.15
IVb	80	132 (1)	1.4678	1.1250	0.47	56.65	7.40	11.30	$C_{15}H_{23}ClO_5$	56.52	7.22	11.15
IVc	82	148 (2)	1.4670	1.1099	0.50	57.42	7.45	10.85	$C_{16}H_{25}ClO_5$	57.74	7.52	10.68
IVd	80	134–136 (1)	1.4668	1.1025	0.44	57.66	7.52	10.55	$C_{16}H_{25}ClO_5$	57.74	7.52	10.68

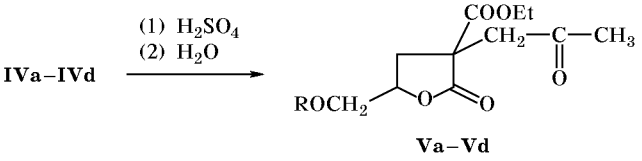
Table 2. Yields, constants, and elemental analyses of 2-acetonyl-4-alkoxymethylbutanolides **IIa**–**IId** and 2-acetonyl-4-alkoxymethyl-2-etoxycarbonylbutanolides **Va**–**Vd**

Comp. no.	Yield, %	bp, °C	n_D^{20}	d_4^{20}	R_f	Found, %		Formula	Calculated, %	
						C	H		C	H
IIa[a]	70	122 (0.5)	1.4592	1.0594	0.47 (A)	63.30	8.85	$C_{12}H_{20}O_4$	63.15	8.77
IIb[a]	80	121 (1)	1.4580	1.0502	0.50 (B)	63.00	8.70	$C_{12}H_{20}O_4$	63.15	8.77
IIc[a]	82	129–130 (1)	1.4570	1.0502	0.53 (B)	64.25	9.00	$C_{13}H_{22}O_4$	64.46	9.09
IId[a]	72	131 (1)	1.4575	1.0385	0.52 (B)	64.35	9.15	$C_{13}H_{22}O_4$	64.46	9.09
Va[b]	64	156–157 (2)	1.4580	1.1072	0.44 (B)	60.15	8.15	$C_{15}H_{24}O_6$	60.00	8.00
Vb	60	145–146 (1)	1.4585	1.1065	0.40 (C)	60.20	8.00	$C_{15}H_{24}O_6$	60.00	8.00
Vc	62	152–153 (1)	1.4590	1.0915	0.45 (C)	61.26	8.21	$C_{16}H_{26}O_6$	61.15	8.28
Vd	60	162–164 (2)	1.4580	1.0823	0.46 (A)	61.28	8.15	$C_{16}H_{26}O_6$	61.15	8.28

[a] For published data, see [4].
[b] For published data, see [5].

of the products. Initial 4-alkoxymethyl-2-ethoxycarbonylbutanolides **IIIa**–**IIId** were synthesized by condensation of alkyl 2,3-epoxypropyl ethers with diethyl malonate according to [5].

Scheme 3.



Va–Vd

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in mineral oil. Thin-layer chromatography was performed on Silufol UV-254 plates using the following solvent systems: ethanol–benzene–hexane, 3:3:10 (A), 1:1:1 (B), and 3:3:5 (C); the spots were developed with iodine vapor.

4-Alkoxymethyl-2-(β-chloroallyl)butanolides Ia–Id. *a*. A 20% solution of 10 g (0.25 mol) of sodium hydroxide was mixed with 10 ml of a 50% solution of Katamin AB [dimethylbenzylamine–(C_{10}–C_{18})–ammonium chloride], 0.1 mol of appropriate 4-alkoxymethyl-2-(β-chloroallyl)-2-ethoxycarbonylbutanolide was added, and the mixture was stirred for 2 h at 55–60°C (water bath). The resulting transparent solution was cooled, acdidifed with hydrochloric acid to pH 1–2, and extracted with ether. The extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was subjected to decarboxylation by heating under reduced pressure (15–20 mm, water-jet pump). The products was distilled twice in vacuo (Table 1). IR spectrum,

ν, cm^{-1}: 3050 (=C−H); 1770 (C=O, lactone); 1640 (C=C); 1240, 1190 (C−O−C), 700 (C−Cl).

b. The procedure was analogous to that given below for the synthesis of 4-alkoxymethyl-2-(β-chloroallyl)-2-ethoxycarbonylbutanolides **IVa**–**IVd** with the difference that the residue, obtained by removal of alcohol, was cooled, a 20% solution of 10 g (0.25 mol) of sodium hydroxide and 10 ml of a 50% solution of Katamin AB were added, and the process was continued as described above in *a*. Yield 85–90% (Table 1). The IR spectra of the products obtained as described in *a* and *b* were identical.

4-Alkoxymethyl-2-(β-chloroallyl)-2-ethoxycarbonylbutanolides IVa–IVd. 4-Alkoxymethyl-2-ethoxycarbonylbutanolide **IIIa**–**IIId**, 0.1 mol, was added dropwise under stirring and cooling with water to a solution of sodium ethoxide, prepared from 2.3 g (0.1 mol) of metallic sodium and 90 ml of anhydrous ethanol. The mixture was stirred for about 1 h, and 11.1 g (0.1 mol) of 2,3-dichloropropene was added dropwise. After 15–20 min, the mixture was heated on a water bath until it became neutral (pH paper), and the solvent was distilled off. The residue was cooled, acdi water (pH 3–4) was added, and the mixture was extracted with ether. The extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was twice distilled in vacuo (Table 1). IR spectrum, ν, cm^{-1}: 3050 (=CH); 1770 (C=O, lactone); 1640 (C=C); 1230, 1190 (C−O−C); 700 (C−Cl).

2-Acetonyl-4-alkoxymethylbutanolides IIa–IId and 2-acetonyl-4-alkoxymethyl-2-ethoxycarbonylbutanolides Va–Vd. Concentrated sulfuric acid, 24 ml, was slowly added to 0.1 mol of appropriate β-chloroallyl butanolide **Ia**–**Id** or **IVa**–**IVd** under stirring and cooling with water. Vigorous evolution of hydrogen chloride was observed. The mixture was stirred at room temperature until hydrogen chloride no longer evolved (10–12 h), carefully poured into ice water, partially neutralized with potassium carbonate, and extracted with ether. The ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was twice distilled in vacuo (Table 2). IR spectrum, ν, cm^{-1}: 1770 (C=O, lactone); 1720, 1710 (C=O, ketone); 1240, 1185 (C−O−C); the IR spectrum of **V** also contained ester carbonyl band at 1730 cm^{-1}.

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