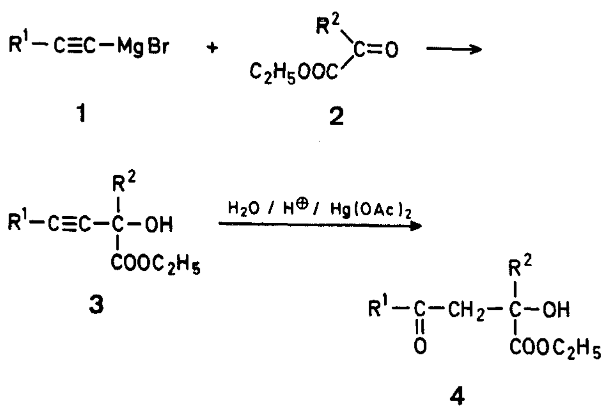
Synthesis of 3-Unsubstituted 2-Hydroxy-4-oxoalkanoates

Antoine MEYER, Michel FLAMMANG, Camille-Georges WERMUTH

Laboratoire de Chimie Organique (ERA 393 du CNRS), U.E.R. des Sciences Pharmaceutiques de l'Université Louis Pasteur, 3, Rue de l'Argonne, F-67083 Strasbourg Cedex, France

Hitherto the synthesis of 2-hydroxy-4-oxoalkanoic acids or esters was generally achieved by an aldolisation reaction between carbonyl derivatives and 2-oxoalkanoic acids or esters. These condensations were realised in presence of potassium hydroxide[1-5], diethylamine[6], or under thermic conditions[7,8]. However, with the exception of the reactions where methyl ketones are used as starting material, the terminal oxoalkanoates were always substituted in the 3-position and, furthermore, the condensations fail with phenylglyoxylic and trimethylpyruvic acids or esters.

In the present communication we wish to report a two-step synthesis of 3-unsubstituted 2-hydroxy-4-oxoalkanoates **4** using addition of the acetylenic Grignard reagent **1** to a 2-oxoalkanoate **2**, followed by hydratation of the resulting acetylenic ester **3**.



The condensation of the substituted alkynyl magnesium bromide **1** with the 2-oxoalkanoates **2** leads to a unique addition to the oxocarbonyl which is consistent with the literature results[9,10]. Mercury(II) acetate promoted hydration of the ester **3** occurs in a specific manner which is in agreement with Stork's and Borch's observations[11] and leads to the expected 2-hydroxy-4-oxoalkanoate **4**. All the compounds **4** (Table) are obtained in medium yields (35–55%), which are dependent on the nature of the R^1 and R^2 substituents.

Table. Preparation of 3-Unsubstituted Ethyl 2-Hydroxy-4-oxoalkanoates **4**

Product	R^1	R^2	b.p./torr or m.p. (from)	Yield [%] 1→4	Molecular formula[a]
4a	C_6H_5	CH_3	130–132°/0.5	55	$C_{13}H_{16}O_4$ (236.3)
4b	C_6H_5	C_2H_5	219°/760	45	$C_{14}H_{18}O_4$ (250.3)
4c	C_6H_5	t-C_4H_9	216°/760	35	$C_{16}H_{22}O_4$ (278.3)
4d	C_6H_5	n-C_5H_{11}	196°/760	40	$C_{17}H_{24}O_4$ (292.4)
4e	C_6H_5	C_6H_5	70° (hexane)	45	$C_{18}H_{18}O_4$ (298.3)
4f	n-C_5H_{11}	CH_3	200°/760	37	$C_{12}H_{22}O_4$ (230.3)
4g	n-C_5H_{11}	C_6H_5	52° (petroleum ether)	38	$C_{16}H_{22}O_4$ (278.3)

[a] All products gave satisfactory microanalyses (C ±0.25%, H ±0.32%).

Preparation of Alkynylmagnesium Bromide 1; General Procedure: Ethylmagnesium bromide [prepared from magnesium (1.2 g) and ethyl bromide (5.50 g)] anhydrous ether (50 ml) is refluxed for 2 h and then added tropwise under stirring to heptyne or phenylacetylene (50 mmol). The resultant solution is refluxed for 2 h. Yield of exchange: 77–80% (Zerewetinoff determination).

Preparation of Ethyl 2-Alkynyl-2-hydroxyalkanoate 3; General Procedure:

The above solution is added dropwise under stirring to ethyl 2-oxoalkanoate (**2**; 100 mmol). The mixture is refluxed for 3 h and, after cooling, hydrolysed with a saturated aqueous solution of ammonium chloride. The organic layer is separated, washed with water, and dried over magnesium sulfate. Solvent, excess of acetylenic compound and the 2-oxoalkanoate **2** are removed by distillation. Purification of the residue is achieved by recrystallisation or by distillation.

Ethyl 2,4-diphenyl-2-hydroxybutynoate (**3e**); yield: 53%; m.p. = 81° (hexane).

I.R. ($CHCl_3$) $\nu = 3500$ (OH), 1735 (C=O ester), 2240 cm^{-1} (C≡C).

^{1}H-N.M.R. ($CDCl_3$) $\delta = 7.75$ and 7.4 (m, $10H_{arom}$): 4.4 (s, 1H, OH), 4.25 (q, 2H, —O—CH_2—), 1.25 ppm (t, 3H, —CH_2—CH_3).

Preparation of Ethyl 2-Hydroxy-4-oxoalkanoates 4; General Procedure:

The ester **3** (50 mmol) is dissolved in acetic acid (10 ml) and the solution poured in to formic acid (10 ml) containing 10% of water. An aqueous mercury(II) acetate solution (5%) is added dropwise, under stirring, till the temperature rises by 6–8°. The mixture is stirred for 2 h, hydrolysed with water, and extracted with ether. The organic layer is washed with water and dried over magnesium sulfate. The solvent is removed in vacuo and the resudue is purified by recrystallisation or by distillation.

Ethyl 2,4-diphenyl-2-hydroxy-4-oxobutanoate (**4e**); yield: 1.23 g (85%); white crystals; m.p. 70°.

I.R. ($CHCl_3$) $\nu = 3500$ (OH), 1735 (C=O ester), 1680 cm^{-1} (C=O ketone).

^{1}H-N.M.R. ($CDCl_3$) $\delta = 7.8$ and 7.5 (m, $10H_{arom}$), 4.5 (s, 1H, OH), 4.25 (q, 2H, —O—CH_2—), 1.25 ppm (t, 3H, —CH_2—CH_3).

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