Synthesis of β-Hydroxy Esters from Ketene Acetals and Aldehydes or Ketones. An Acidic Alternative for the Reformatsky Reaction and Crossed Aldol Condensation

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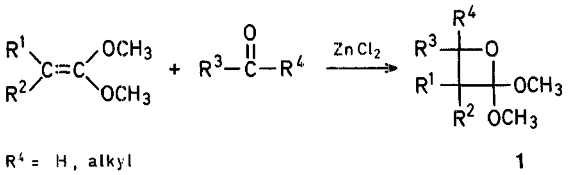
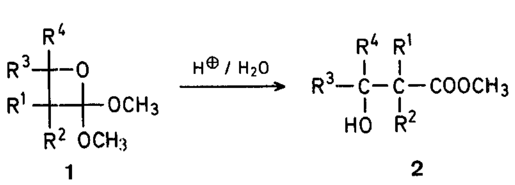
From the various methods available for the preparation of β-hydroxy esters the Reformatsky reaction[1], performed with several variations, can be considered as the most useful procedure. In other methods lithium salts of esters generated in several ways are allowed to react with an aldehyde or ketone[1,2,3]. Recently it was reported that aldehydes and ketones could be converted with vinyloxyboranes or via ketene alkyl trialkylsilyl acetals[3a].

In a recent paper[4] we reported that all types of aldehydes and also ketones can be converted into 2,2-dialkoxyoxetanes **1** by reaction with a ketene acetal in the presence of a Lewis acid, preferably zinc chloride, according to Scheme **A**.



Scheme **A**

It appeared that the oxetanes can easily be hydrolysed to β-hydroxy esters **2** under weakly acidic conditions (Scheme **B**).



Scheme **B**

The mild, acidic conditions make these reactions potentially useful for the preparation of β-hydroxy esters from aldehydes or ketones having base-labile groups.

In this paper we describe the scope of this preparative method, which can be carried out as a "one pot" synthesis. The ketene dimethyl acetals used in this investigation were the compounds having $R^1 = H$, $R^2 = CH_3$; $R^1 = R^2 = CH_3$; or $R^1 = R^2 = OCH_3$. As shown previously ketene acetals with $R^1 = R^2 = H$ fail to give oxetanes.

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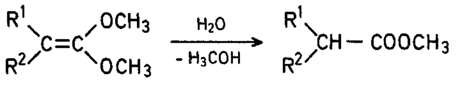
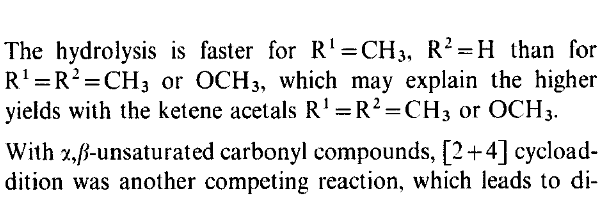
Best results were obtained with simple aldehydes, which often give poorer yields in the Reformatsky reaction[5]. In general, the yield for aldehydes R—CHO varies in the order R = alkyl ≥ aryl > alkenyl. When the reaction was followed with N.M.R. it appeared that the formation of oxetanes (step 1) leads in all cases to more than 95% conversion after a suitable reaction time. Under the polar conditions of the hydrolytic step, however, the cycloaddition is reversed, and this may occur faster as the starting carbonyl compound is more stable. The ketene acetal itself is then removed from the reaction mixture by hydrolysis according to Scheme **C**.



Scheme **C**

The hydrolysis is faster for $R^1 = CH_3$, $R^2 = H$ than for $R^1 = R^2 = CH_3$ or OCH_3, which may explain the higher yields with the ketene acetals $R^1 = R^2 = CH_3$ or OCH_3.

With α,β-unsaturated carbonyl compounds, [2+4] cycloaddition was another competing reaction, which leads to dihydropyrans (Scheme **D**).



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Scheme **D**

When the carbonyl compound contains only substituents in the β-position, the formation of **3** could be suppressed by working at low temperature. With unsaturated aldehydes having α-substituents and with unsaturated ketones, however, a dihydropyran was always obtained as the main product. The factors which influence the ratio between [2+2]- and [2+4]cycloaddition of ketene acetals and α,β-unsaturated carbonyl compounds will be discussed in more detail in a subsequent paper.

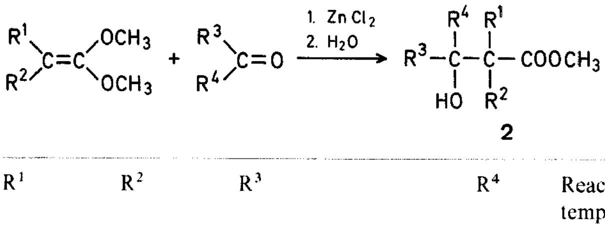
In syntheses with $CH_3CH{=}C(OCH_3)_2$ as the ketene acetal, a mixture of an *erythro* and a *threo* product was always formed. The product ratio could be determined from the N.M.R. spectrum, in which the α-methyl groups of the diastereomeric β-hydroxy esters show different shifts. In this connection it is interesting to note that in the Reformatsky reaction of methyl 2-bromopropanoate and benzaldehyde methyl *erythro*-3-hydroxy-2-methyl-3-phenylpropanoate is the main product[6, 7], whereas the *threo* compound is mainly formed in the synthesis via a more stable oxetane.

Ketones delivered β-hydroxy esters in lower yields than aldehydes due to the easy reversal of the reaction shown in Scheme **A**. For this reason and because of their lower reaction rate it was possible to transform selectively the aldehyde group of the δ-keto aldehyde, 3-(2-oxocyclohexyl)-propanal.

General Procedure for the Preparation of β-Hydroxy Esters:

A 50% solution of an aldehyde or ketone in acetonitrile is mixed with a ketene acetal (1.2 equiv). Addition of ~1 mol-% of zinc chloride causes evolution of heat, and in reactions with simple aldehydes the mixture has to be cooled to keep the temperature below 40°. After standing for the time and at the temperature given in the Table, water (3 equiv) and a trace of *p*-toluenesulphonic acid are added. The mixture is kept at room temperature for 0.5 h (2 h at −10° for the conversion of α,β-unsaturated aldehydes with 1,1-dimethoxy-1-propene), and then concentrated at a pressure of 20 torr. Pentane is added, the pentane layer is separated, filtered, and dried. Evaporation of the solvent and distillation of the residue through a Vigreux column (25 × 1.2 cm) yields the β-hydroxy ester.

Table. Preparation of β-Hydroxy Esters **2** from Aldehydes or Ketones and Ketene Dimethyl Acetals



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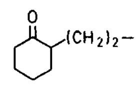
R^1	R^2	R^3	R^4	Reaction conditions temperature/time	Yield [%]	b.p./torr	Molecular formula[a]
CH_3	H	C_2H_5	H	25°/1 h	75	82°/15	$C_7H_{14}O_3$ (146.2)
CH_3	H	$i\text{-}C_3H_7$	H	25°/1 h	65	86°/15	$C_8H_{16}O_3$ (160.2)
CH_3	CH_3	$i\text{-}C_3H_7$	H	25°/1 h	50	91°/15	$C_9H_{18}O_3$ (174.2)
CH_3O	CH_3O	$i\text{-}C_3H_7$	H	25°/1 h	70	74°/0.4	$C_9H_{18}O_5$ (206.2)
CH_3	H	$H_3C{-}CH{=}CH$	H	10°/2 h	40	98°/15	$C_8H_{14}O_3$ (158.2)
CH_3	CH_3	$H_3C{-}CH{=}CH$	H	25°/36 h	45	104°/15	$C_9H_{16}O_3$ (172.2)
CH_3O	CH_3O	$H_3C{-}CH{=}CH$	H	25°/1 h	70	76°/0.1	$C_9H_{16}O_5$ (204.2)
CH_3	H	$C_6H_5{-}CH{=}CH$	H	−15°/48 h	40	138°/0.5	$C_{13}H_{16}O_3$ (220.3)
CH_3	CH_3	$C_6H_5{-}CH{=}CH$	H	25°/48 h	55	128°/0.3	$C_{14}H_{18}O_3$ (234.3)
CH_3O	CH_3O	$C_6H_5{-}CH{=}CH$	H	25°/24 h	55	144°/0.4	$C_{14}H_{18}O_5$ (266.3)
CH_3	H	C_6H_5	H	25°/1 h	55	94–98°/0.5	$C_{11}H_{14}O_3$ (194.2)
CH_3	CH_3	C_6H_5	H	25°/1 h	80	96°/0.3	$C_{12}H_{16}O_3$ (208.3)
CH_3O	CH_3O	C_6H_5	H	25°/1 h	80	128°/0.8[b]	$C_{12}H_{16}O_5$ (240.3)
CH_3	H	$-(CH_2)_5-$		25°/3 h	55	80°/0.8	$C_{10}H_{18}O_3$ (186.2)
CH_3	H		H	25°/1 h	45	130°/0.5	$C_{12}H_{22}O_4$ (230.3)

[a] All compounds gave satisfactory microanalyses (C ±0.5%, H ±0.2%).
[b] Lit.[8] b.p. 120–121°/10 torr.

The compounds were identified by M.S., I.R. ($\nu_{C=O}$ between 1715 and 1730 cm^{-1}) and N.M.R. The N.M.R. spectrum was also used for determination of the ratio of diastereoisomers if present. Microanalysis (C,H) of all compounds were in accordance with calculated values. Yields and boiling points are given in the Table.

In one case (C_6H_5—CHOH—CH(CH_3)—$COOCH_3$) the *threo*-product, accounting for 80 % of the product mixture, was isolated. It crystallized from petroleum ether (40/60°); m.p. 52° (Lit.[6] 50.5–51.5°).

In the preparation of methyl 2-methyl-3-hydroxy-5-(2-oxocyclohexyl)pentanoate the product after distillation was purified by preparative chromatography (Jobin Yvon Chromatospac prep. 100) over silica gel H (type 60) and elution with chloroform/toluene (3:1).

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