Pergamon

Tetrahedron Letters, Vol. 36, No. 16, pp. 2839-2840, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00359-2

An Easy Approach to Butenolides by Horner-Wadsworth-Emmons Olefination of α-Hydroxy Ketones

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Abstract: By treatment with stabilized lithium phosphonates in the presence of activated 4Å molecular sieves, unprotected α-hydroxy ketones **1** undergo a convenient Horner-Wadsworth-Emmons olefination to give directly butenolides **3** as exclusive or predominant products.

Horner-Wadsworth-Emmons (HWE) procedure has been widely employed in organic synthesis for the preparation of α,β-unsaturated esters[1]. As regards α-hydroxy carbonyl compounds, while the reaction of stabilized ylides with unprotected aldehydes is well-known[2-4], rather poor data are available for α-hydroxy ketones[5]. In particular they point out that HWE olefination with stabilized phosphonium ylides proceeds in moderate to good chemical yields with E-stereoselectivity, while very disappointing results have been obtained through the employment of stabilized phosphonates.

We now report that, in the presence of activated[6] 4Å molecular sieves, both linear and cyclic α-hydroxy ketones **1** undergo HWE reaction with stabilized lithium phosphonates **2** to give butenolides **3**, usually as main or exclusive products.The results reported in table can be reasonably explained on the ground of the stereoselective formation of γ-hydroxy-Z-α,β-unsaturated esters (with the exception of entry g where the reverse stereoselectivity has been observed) and their following conversion into **3** in the course of the reaction or work-up procedure.

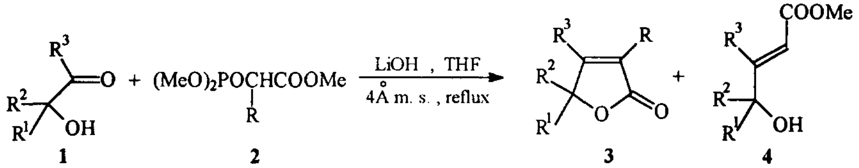

Table - HWE Olefination of Unprotected α-Hydroxy Ketones 1

Entry	R	R1	R2	R3	Reaction Time (h)	3 (%)[a]	4 (%)[a]
a	H	H	$(CH_2)_4$		2	68	17
b	Me	H	$(CH_2)_4$		24	70	-
c	H	H	i-Pr	i-Pr	4	61	-
d	Me	H	i-Pr	i-Pr	24	69	-
e	H	H	H	Et	2	56	-
f	H	H	H	Me	24[b]	30	15
g	H	Me	Me	Me	24[b]	25	50

[a] All the yields refer to isolated, chromatographically pure compounds, whose structures have been confirmed by IR, ^{1}H-NMR, MS data New compounds have given satisfactory elemental analysis. [b] In these cases the reaction has been performed at room temperature.

Furthermore, it has to be noted that, in spite of the rather mild condition involved (no evidence of base catalyzed tautomerization of starting material **1** has been detected in entries e and f), satisfactory results have been obtained both with hindered α-hydroxy ketones and phosphonate (entries b, c and d). Although the mechanistic aspects have not yet been investigated, molecular sieves prove to exert a decisive influence both on efficiency and stereoselectivity of the olefination. In fact, when experiment of entry g is repeated in absence of molecular sieves, the products **3** and **4** are respectively obtained in 10% and 7% yield.

In a typical experimental procedure, solid LiOH $\cdot$ H_2O (2.4 mmol) is slowly added (1 h) to a mixture of **1** (2 mmol), **2** (2.4 mmol), 4Å molecular sieves (3 g) and anhydrous THF (25 ml) under the conditions given in Table. Then, after the usual work-up, pure **3** and **4** are obtained by silica gel column chromatography by elution with n- pentane/diethyl ether mixtures.

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(*Received in UK* 29 *November* 1994; *revised* 17 *February* 1995; *accepted* 24 *February* 1995)