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A New Procedure for Horner-Wadsworth-Emmons Olefination of Carbonyl Compounds

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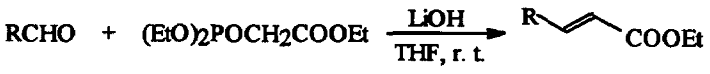
Abstract: aldehydes undergo an efficient E-stereoselective Horner-Wadsworth-Emmons olefination by generation of phosphonate carbanion with lithium hydroxide. The reaction proceeds satisfactorily with linear, cyclic, polifunctional ketones in the presence of activated zeolites and and by the slow addition of the base.

Horner-Wadsworth-Emmons reaction is widely employed in organic synthesis for the preparation of acrylic esters. However, most of the available methodologies proceeds with high efficiency and stereoselectivity only with aldehydes, while they often prove to be unsatisfactory in the case of ketones, which usually require more vigorous conditions.[1]

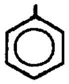
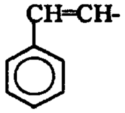
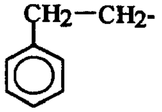
An interesting methodology, based on the generation of phosphonate carbanion with tertiary amine, R_3N, in the presence of lithium halides, LiX, proved to be applicable to ketones only by the employment of more reactive bis(trifluoroethyl)phosphonates.[2,3]

We have found that the above procedure can be conveniently modified through the substitution of R_3N/LiX system by lithium hydroxide, a reagent which includes both the required basic properties and the presence of the lithium cation. In fact, aldehydes **1**, submitted to the treatment with a slight excess of phosphonate carbanion (1,1 eq), generated by reaction of **2** (1,1 eq) with $LiOH{\cdot}H_2O$ (1,1 eq) in THF solution, at room temperature, are converted into α,β-unsaturated esters **3** with high yields and E-stereoselectivity (Table 1).



1 **2** **3**

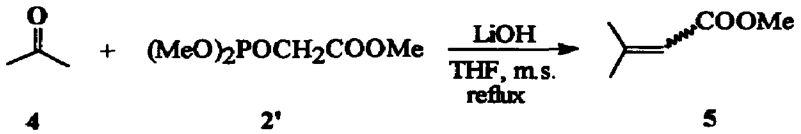
Table 1- HWE Olefination of Aldehydes

Entry	R	Reaction time (h)	Yield (%)[a]	E (%)	Z (%)
1		6	91	100	-
2		24	63	96	4
3		6	73	95	5
4		3.5	86	100	-
5		6	91	99	1
6	n-C_5H_{11}-	6	69	98	2

[a] All the yields refer to isolated chromatografically pure compounds. The composition of the diastereoisomeric mixtures has been determined on the ground of isolated pure E and Z isomers. All the structures have been confirmed by IR and ^{1}H-NMR spectroscopy.

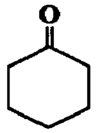
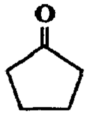
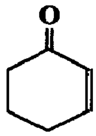
Unfortunately, the same methodology has afforded poor results when ketones have been used as starting materials; for example, under the usual conditions, heptan-2-one has been converted into the expected α,β-unsaturated ester only in 10% yield, as 3/1 E/Z mixture.

A significant improvement has been obtained through a modification involving the combined employment of pre-activated 4Å molecular sieves and lithium hydroxide and the slow addition of the base to the reaction mixture. In fact, under the conditions reported in Table 2, the formation of products **5** took place in satisfactory way with the usual predominance of E isomers.



4 2' 5

Table 2- HWE Olefination of Ketones

Entry	Ketone	Reaction time (h)	Yield(%)[a,b]
1		4	85
2	$CH_3CO(CH_2)_4CH_3$	24	65 (3/1)[d]
3	$CH_3(CH_2)_2CO(CH_2)_2CH_3$	24	42
4		24	48
5		24	29 (2/1)[d]
6	$CH_3COCOOC_2H_5$	4	67 (1/6)[d]
7	$CH_3COCH_2CH(OCH_3)_2$	24	44 (2/1)[d]
8	$CH_3COCH(OCH_3)_2$	4	80 (1.6/1)[d]
9	$CH_3COCHBrCH_3$	4	77[c] (3/1)[d]

[a] The yields refer to isolated chromatographically pure compounds. All the structures have been confirmed by IR, ^{1}H-NMR and MS data. All new compounds have given satisfactory elemental analysis. [b] Values in parentheses refer to E/Z ratios. [c] In this case the reaction has been performed at room temperature. [d] E/Z ratios have been determined by ^{1}H-NMR analysis.

Furthermore, it has to be noted that this methodology proves to be compatible with the presence of additional functional groups in the carbonyl compounds such as acetals (entries 7, 8), esters (entry 6) and halogens (entry 9).

Further investigations, devoted to broaden the field of applicability, are in progress.

Experimental:

General procedure for compounds of type 3: a suspension of **1** (2 mmol), phosphonoacetate **2** (2,2 mmol) and lithium hydroxide monohydrate (2.2 mmol) in distilled THF (2 ml) was stirred at room temperature under argon atmosphere until disappearance of starting material. After the usual work-up, purification by silica gel column chromatography affords pure products **3** by elution with n-hexane/diethyl ether mixtures.

General procedure for compounds of type 5: to a suspension of **4** (2mmol), phosphonoacetate **2'** (2.2 mmol) and activated 4 Å molecular sieves (3 g) in anhydrous THF (20 ml) was added, under stirring at reflux temperature (room temperature for entry 9, Table 2), lithium hydroxide monohydrate (2,2 mmol)previously submitted to heating at 120 °C for 2 hours, in three portions, during the reaction course. After the usual work-up, purification by silica gel column chromatography affords pure compounds **5** by elution with n-hexane/diethyl ether mixtures.

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