An Efficient and Stereoselective Wittig–Horner Synthesis of Acyclic α-Enones with Barium Hydroxide as Solid Catalyst

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Wittig–Horner reactions under interfacial solid–liquid conditions using activated barium hydroxide catalyst C-200 produce acyclic α-enones with high yields and selectivities.

The Wittig–Horner reaction is a versatile method for preparation of unsaturated compounds and its synthetic aspects have been widely studied[1]. Recently, the process has been carried out using two-phase liquid–liquid[2] or solid–liquid conditions[3—8] and better yields were obtained than those achieved under classical conditions. Nevertheless, undesired side reactions of starting materials (crotonization, Cannizzaro reaction, *etc.*) and products (*e.g.* double bond shifts) have often been observed.[2,4—7]

We recently described a new microcrystalline solid basic catalyst, C-200 [$Ba(OH)_2{\cdot}0.8H_2O$][9] and its catalytic activity in several organic reactions in solid–liquid media, *e.g.* aldol

Table 1. Wittig–Horner reactions of 2-oxoalkanephosphonates with barium hydroxide C-200 and sodium hydride.

Run	$PhCHR^1CH{=}O$ R^1	$(EtO)_2POCH_2COR^2$ (**3**) R^2	Method[a]	Reaction time	Product α-Enone	Yield(%)[b]
1	Me	Me	A	10 min	(**4a**)	96
2	Me	Me	B	3 h	(**4a**)	90
3	Me	Bu^t	A	10 min	(**4b**)	98[c]
4	Me	Bu^t	B	3 h	(**4b**)	91[c]
5	Me	Ph	A	10 min	(**4c**)	84
6	Me	Ph	B	3 h	(**4c**)	75
7	Bu^t	Me	A	15 min	(**5a**)	96
8	Bu^t	Me	B	3 h	(**5a**)	94
9	Bu^t	Bu^t	A	15 min	(**5b**)	96
10	Bu^t	Bu^t	B	3 h	(**5b**)	94
11	Bu^t	Ph	A	15 min	(**5c**)	96
12	Bu^t	Ph	B	4 h	(**5c**)	95

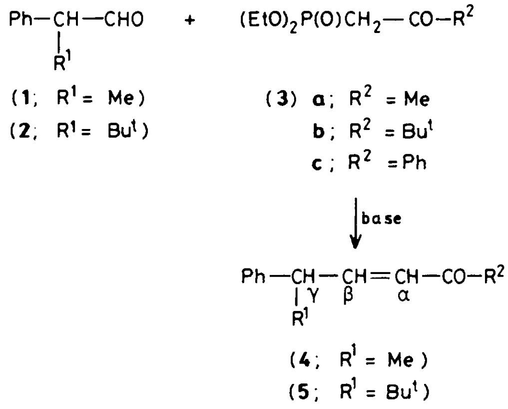
[a] *Reaction conditions*: Method A: C-200 in 1,4-dioxane, molar ratio catalyst : aldehyde 0.52, 70 °C; Method B: sodium hydride in 1,2-dimethoxyethane, molar ratio base : aldehyde 1, 25 °C for (**4**) and 40 °C for (**5**) [at 25 °C the yield of (**5b**) was only 67%]. [b] Determined by gas chromatography (± 2%) (except runs 3 and 4). [c] Deduced by ^1H n.m.r.

condensation,[10] Michael addition,[11] Claisen–Schmidt condensation,[12] and Wittig–Horner reaction with triethyl phosphonoacetate and diethyl cyanomethanephosphonate.[8] In order to get a general view of the catalytic activity of barium hydroxide C-200 in the heterogeneous Wittig–Horner reaction, we have now carried out the process using 2-oxoalkanephosphonates and aliphatic aldehydes with different degrees of steric hindrance (Scheme 1).

An improved synthesis of α,β-unsaturated ketones by the Wittig–Horner reaction under interfacial solid–liquid conditions using barium hydroxide C-200 as catalyst in 1,4-dioxane is reported† (Method A, Table 1). Although the selected α-enones can undergo isomerization easily,[6] this undesirable side reaction is completely avoided under these conditions.

The synthetic method has been used to prepare the β-monosubstituted acyclic α-enones (**4**) and (**5**) with an asymmetric carbon at γ-position, useful model compounds for the study of diastereofacial selectivity in nucleophilic addition reactions.[13,14] This is the first time α-enones (**5**) have been obtained and (**4b**) and (**4c**) have only been reported in connection with stereoselection studies.[14]

In Table 1 the results are compared with those obtained with the sodium hydride–1,2-dimethoxyethane system[15] in homogeneous media (Method B). Under heterogeneous solid–liquid conditions with activated barium hydroxide C-200 (Method A) the process is an interfacial solid–liquid reaction controlled by the solid structure and small amounts of water must be added in order to increase the reaction rate as in the acrylate synthesis.[8] Using Method A lower molar ratios of catalyst : aldehyde and shorter reaction times are necessary to obtain similar yields,[3—7] and isolation of the products and experimental procedure are easier (anhydrous medium and inert atmosphere are avoided). The steric hindrance of the groups R^1 and R^2 does not affect the catalyst's effectiveness and no side reactions were observed.



Scheme 1

However, a higher reaction temperature was needed for (±)-3,3-dimethyl-2-phenylbutanal (**2**) than for (±)-2-phenylpropanal (**1**) with the sodium hydride–1,2-dimethoxyethene system (Method B). Its lower reactivity can be explained by the greater steric hindrance of the Bu^t group in the α-position to the –CHO (Bu^t *cf.* Me). On the other hand, isomerization[4,6] of the α-enones (**4**) was observed at reaction temperatures higher than 25 °C. This side reaction was not observed for (**5**) because of the presence of the bulkier Bu^t substituent at the γ-position which diminishes the stabilization of the β,γ-unsaturated system by steric inhibition of conjugation between the $C_β$–$C_γ$ double bond and the γ-Ph group.

The stereoselectivity of the reaction is the same in all cases. Only the (*E,RS*) isomer was obtained (vicinal coupling constant for olefinic protons $^3J_{αβ}$ 15.4 Hz). Hence our method is efficient, highly stereoselective, and remarkably free of competing side reactions. The novel α-enones (**5**) are proposed as better model compounds for stereoselection studies

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† The following procedure was typical. Barium hydroxide C-200 (activated at 140 °C for 1 h) [0.250 g, 1.30 mmol <>1.5 × 10^{-6} equiv. of strong basic sides, $pK_a > 11.7$], diethyl 2-oxoalkanephosphonate (**3**) (2.5 mmol) and 1,4-dioxane (6 ml) were mixed and stirred at 70 °C for 10 min. A mixture of aldehyde (**1**) or (**2**) (2.5 mmol) in 1,4-dioxane (2 ml) with water (0.05 ml) was added and the reaction mixture stirred at 70 °C (times given in Table 1). Aqueous HCl (10%) was then added to give acidic pH and the mixture was filtered. The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 30 ml). The combined organic layers were washed with water and saturated $NaHCO_3$, and dried ($MgSO_4$). The solvent was removed and the residue analysed by gas chromatography (BDS 10% on Chromosorb W-AW-DMCS) and ^1H n.m.r. spectroscopy. The product was purified by silica gel chromatography (light petroleum–diethyl ether, 97:3 v/v, as eluent) and characterized by i.r. and ^1H and ^{13}C n.m.r. spectroscopy.

than (**4**), given their higher stability towards isomerization and their monoconformational character with respect to rotation around the C_β–C_γ bond.‡

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‡ This character was deduced from analysis of ^{1}H and ^{13}C n.m.r. spectra, in particular coupling constants $^{3}J_{\beta\alpha}$ and $^{4}J_{\alpha\gamma}$ in the ^{1}H n.m.r. spectra. (Unpublished results.)