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One-Pot Three Component Synthesis of α, β-Unsaturated Ketones

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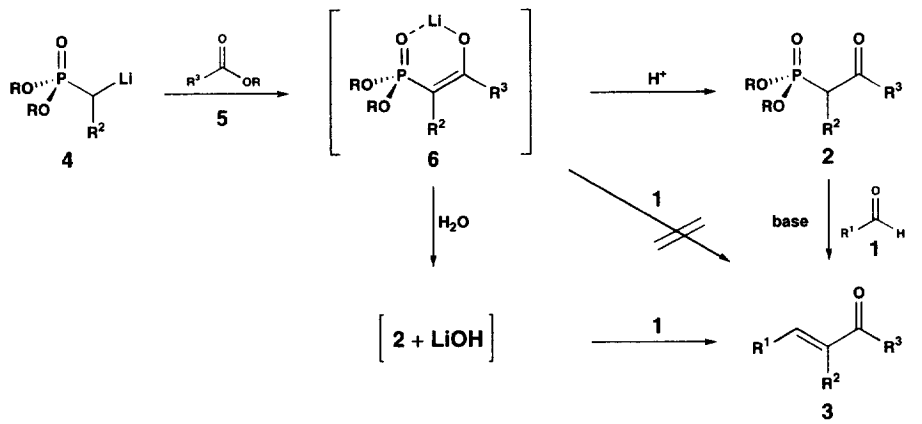
Abstract: A highly stereoselective synthesis of di- and trisubstituted enones via the tandem-sequence Corey-Kwiatkowski and Horner-Wadsworth-Emmons reaction has been developed. Six examples are given.

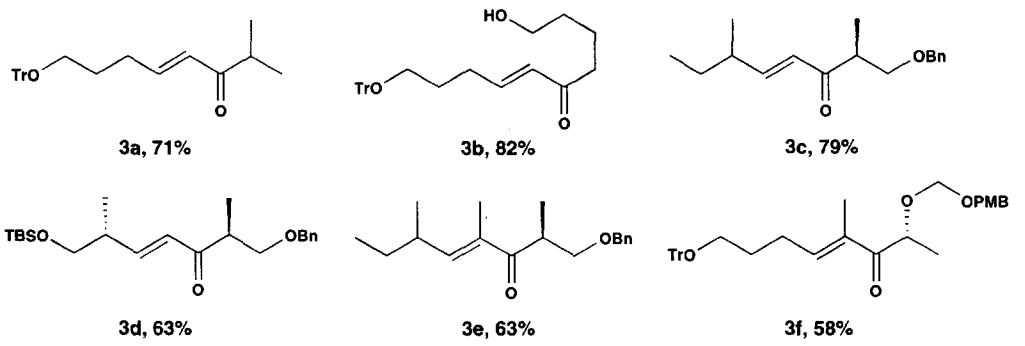
The Horner-Wadsworth-Emmons (HWE) reaction between aldehydes **1** and β-ketophosphonates **2** leading to α,β–unsaturated carbonyl compounds **3** has a prominent place among the C-C-bond forming reactions.[1] This has mainly three reasons. First, α,β–unsaturated carbonyl compounds **3** are of great synthetic value for further manipulations. Second, the reaction is generally highly stereoselective, giving access to both E- and Z-enones.[2] Finally, ketophosphonates **2** are easily prepared via Corey-Kwiatkowski reaction from lithioalkyl-phosphonates **4** (from *n*-butyllithium and alkylphosphonates) and esters **5**.[3]

In the Corey-Kwiatkowski reaction it is likely that the deprotonated species **6** is formed by fragmentation of a tetrahedral intermediate and deprotonation with liberated lithium alkoxide. After acidic work-up ketophosphonates **2** are isolated. At the same time, intermediate **6** has been assumed to be the reactive species in the HWE reaction. Therefore, it should be possible to combine the Corey-Kwiatkowski and the HWE reaction in a one pot procedure by treating intermediate **6** with an aldehyde instead of an acid.[4] However our first experiments in this direction failed.(Scheme 1)



Scheme 1

On the other hand, treatment of **6** with water should result in the formation of LiOH and ketophosphonate **2** (Scheme1), a mixture which has been successfully applied in HWE reactions.[5,6] The solution of the problem was thus surprisingly simple and effective: treatment of the Corey-Kwiatkowski reaction mixture with equimolar amounts of water and subsequently with aldehydes **1** gave enones **3** highly stereoselective (E/Z > 95:5) and in good yields. A general experimental procedure has been developed. Some of the α,β-unsaturated ketones[7,8], prepared via this new tandem sequence are shown in scheme 2.



Scheme 2

General procedure: a solution of alkylphosphonate (18 mmol) in 25 ml dry ether was treated at -78 °C with 11.25 ml (18 mmol) of *n*-butyllithium (1.6 M in hexanes). After 30 min, a solution of ester **5** (10 mmol in 3 ml ether) was added dropwise via syringe. After another 90 min the mixture was warmed to 0 °C and a solution of 0.36 ml water (20 mmol) in 20 ml THF was added under vigorous stirring. The resulting suspension was treated with aldehyde **1** (12-14 mmol) in 5 ml THF and stirred for 2-6 h at room temperature. Usual work-up and purification by silica gel column chromatography afforded pure compounds **3**.

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References and Notes

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3. Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.
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5. a) Lewis, C.N. et al, *J. Org. Chem.* **1992**, *57*, 1935. b) Mulzer, J.; List, B. *Tetrahedron Lett.* **1994**, *48*, 9021.
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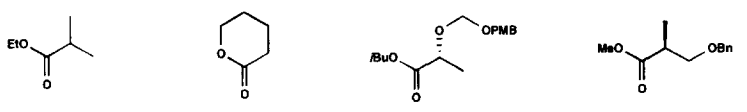
7. All new compounds gave satisfactory analytical data (^{1}H-NMR, ^{13}C-NMR, IR, MS, EA).
   ^{1}H-NMR (270 MHz, $CDCl_3$) of **3f**: δ = 1.22 (d, *J*= 6.8, 3 H), 1.71 (d, *J*= 1.3, 3 H), 1.79 (m, 2 H), 2.38 (m, 2 H), 3.11 (m, 2 H), 3.75 (s, 3 H), 4.44 (d, *J*= 11.4, 1 H), 4.48 (d, *J*= 11.4, 1 H), 4.59 (d, *J*= 7.0, 1 H), 4.67 (d, *J*= 7.0, 1 H), 4.85 (q, *J*= 6.8, 1 H), 6.75 (dt, *J*= 1.3, 7.3, 1 H), 6.87 (m, 2 H), 7.23 (m, 5 H), 7.31 (m, 6 H), 7.44 (m, 6 H).
8. From esters and lactones:



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