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Convenient procedure of Horner–Wadsworth–Emmons olefination for the synthesis of simple and functionalized α,β-unsaturated nitriles

Alessandra Lattanzi,[a] Liliana R. Orelli,[b] Patrizia Barone,[a] Antonio Massa,[a] Patrizia Iannece[a] and Arrigo Scettri[a,*]

[a]*Dipartimento di Chimica, Università di Salerno, Via S. Allende 84081 I Baronissi, Salerno, Italy*
[b]*Departamento de Quimica Organica, Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Junin 956 Buenos Aires, 1113 Argentina*

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Abstract—A mild and practical procedure of Horner–Wadsworth–Emmons olefination promoted by lithium hydroxide and α-cyano phosphonates has been set up for the synthesis of α,β-unsaturated nitriles. The reaction conditions are tolerated by functionalized ketones and the exclusive formation of *E*-γ-hydroxy α,β-unsaturated nitriles has been observed.

α,β-Unsaturated nitriles have proved to be versatile intermediates in organic synthesis; in fact they can be converted into carbocycles[1] and heterocycles,[2] and furthermore they constitute the starting compounds for conjugate additions leading to functionalized nitriles.[3] One of the straightforward routes to α,β-unsaturated nitriles is the Horner–Wadsworth–Emmons olefination of carbonyl compounds with α-cyano phosphonates.[4] Several studies have pointed out that from the stereochemical point of view α-cyano phosphonates are less selective compared to carbalkoxy reagents since they furnish mixtures of *Z*/*E* isomers in the range of 1/4 to 2/1.[5] In the case of bis(2,2,2-trifluoroethyl) α-cyano phosphonate the prevalent formation of the *Z* (in some cases exclusive) olefin is generally observed.[6] When a bulky isopropyl group is placed on the α-carbon of α-cyano phosphonate, the *Z*-selectivity is comparable to that obtained using the bis(2,2,2-trifluoroethyl) α-cyano phosphonate.[7]

We reported a useful and simple procedure for the preparation of α,β-unsaturated esters (*E*-isomer highly prevalent), using lithium hydroxide and 4 Å MS to promote the olefination of aldehydes and ketones.[8] The mild reaction conditions allowed the employment of the same system for the HWE olefination of α-hydroxy ketones to butenolides,[9] and of 1,2-diketones to 4-hydroxy-cyclopent-2-en-1-ones.[10] Finally, more recently, Takacs and co-workers11 reported the use of lithium hydroxide/4 Å MS to promote the dienylation of aldehydes and ketones using 4-phosphonocrotonate. LiOH showed to be superior to the classical bases such as LDA, LiHMDS and NaH, commonly used for this type of reaction, furnishing high yields as well as good *E*-stereoselectivity for the dienoates. In all the olefination procedures described, one of the most important features is that even in excess of LiOH no competing ester hydrolysis or keto–enol tautomerization processes have been observed, rendering the methodology simpler and more selective than the one implying the use of strong bases.

These results prompted us to further explore the HWE olefination of carbonyl compounds promoted by LiOH with commercial α-cyano phosphonates **2** (Table 1) for the synthesis of α,β-unsaturated nitriles.

At first, we investigated the reactivity with aldehydes. Aromatic, aliphatic and unsaturated aldehydes were reacted in THF at room temperature with phosphonates **2** (Table 1). Unsaturated nitriles were isolated in quite good yields with satisfactory *E*/*Z* selectivity. At 70°C, reaction times can be further reduced, increasing the yield of the olefin and marginally affecting the *E*/*Z* ratio (compare entries 3 and 4).

Keywords: Horner–Wadsworth–Emmons olefination; α,β-unsaturated nitriles; lithium hydroxide.

* Corresponding author. Tel.: +39-089-965374; fax: +39-089-965296; e-mail: scettri@unisa.it

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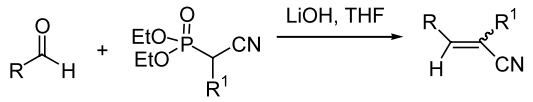
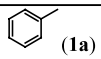
Table 1. LiOH-promoted HWE olefination of aldehydes with α-cyano phosphonates **2**



1 **2** **3**

R^1=H (**2a**), Me (**2b**)

Entry	R	**2**	t (h)	T(°C)	Yield **3**(%)[b]	*E*/*Z* **3**(%)[c]
1	 (**1a**)	**2a**	2	rt	70	90/10
2	"	**2b**	5	rt	85	77/23
3	 (**1b**)	"	2.5	0	78	69/31
4	"	"	0.5	70	85	65/35
5	*n*-C_7H_{15} (**1c**)	**2b**	7	0	72	58/42
6	"	**2a**	4	rt	74	68/32
7	 (**1d**)	**2a**	3	"	72	75/25
8	"	**2b**	6	0	77	63/37

[a]*Typical experimental procedure*: in a screwcap vessel are added under Ar: dry THF (10 mL), **2** (1.1 mmol) LiOH (1.2 mmol). The mixture is stirred at 70°C for 30 minutes. After the reaction mixture is allowed to reach room temperature **1** (1.0 mmol) is added. After completion of the reaction (monitored by TLC) the organic phase is diluted with Et_2O (20 mL) and is washed with HCl solution (1N, 5 mL) and then with saturated brine (2x30 mL). The organic phase is then dried over Na_2SO_4 and the solvent removed by evaporation under vacuum. The crude product is purified by flash chromatography (mixtures of petroleum ether/ Et_2O) to afford **3**. [b]Isolated yield; the structures have been confirmed by ^{1}H- and ^{13}C NMR spectroscopies and by comparison with literature data. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture.

Next, we turned out our attention to the olefination of ketones, which are known to be considerably less reactive than aldehydes. On the basis of our previous work[8] for the synthesis of α,β-unsaturated esters we carried out the reactions in the presence of activated 4 Å MS. Unfunctionalized ketones were converted in high yields (entries 1–2) into the corresponding olefins with moderate to good *E*/*Z* stereoselectivities.

Treatment of cyclohexanone with phosphonate **2b** (1.1 mmol) in the presence of LiOH (2.4 mmol)/4 Å MS at 70°C for 21 h furnished the corresponding nitrile in 80% yield.

Interestingly, in absence of molecular sieves (entry 3) at room temperature, acetophenone was converted into **5b** in good yield and with the same *E*/*Z* ratio. Surprisingly, the presence of molecular sieves was not strictly necessary in order to obtain satisfactory yields of alkenes as we indeed found in the case of the olefination[8] of ketones with triethyl phosphonoacetate.

In fact, this was further confirmed comparing experiments in entries 4–6, where the functionalized ketones (with the acetal moiety in α and β position) were transformed in short reaction times to **3** in high yields and satisfactory stereoselectivities at 70°C in absence of 4 Å MS. The *E*-stereoselective monolefination of 2,3-butandione was accomplished when using 1 equiv. of **2a**.

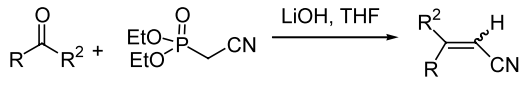
More interestingly, the mono-olefination (entry 7) or diolefination of 1,2-dicarbonyl compounds could be achieved by a suitable choice of the stoichiometric ratios, allowing an easy and convenient approach to muconontriles[15] (entries 8–9).

Remarkable results, from the synthetic point of view, were observed in the olefination of α-hydroxy ketones (entries 10–13): γ-hydroxy unsaturated nitriles were obtained with complete *E*-stereoselectivity. A previous report[16] on the Wittig olefination of α-hydroxyketones with stabilized phosphonium ylides (Ph_3PCHCO_2Me) and HWE reaction envisaged the hydroxyl-directed[17] effect to account for the formation of *E*-trisubstituted olefins. Two plausible transition states which may justify the stereochemical results in Table 2 (entries 10–13) are depicted in Scheme 1.

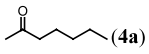
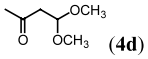
The possible interaction of the OH group of the ketone with the phosphonate oxygen in **I** gives rise to a stabilized transition state, which after *syn* elimination of phosphate group would furnish the *E* olefin. An alternative possibility is that the hydrogen-bond between the OH group and the carbonyl function could activate it toward the ylide attack, affording the less sterically encumbered transition state **II**. This provides, after elimination, the *E* olefin.

Some experiments were performed on α-hydroxycyclohexanone **4j** to ascertain the involvement of the OH directing effect (Table 3).

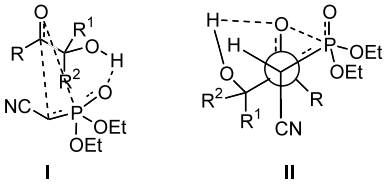
Table 2. LiOH-promoted HWE olefination of ketones with α-cyano phosphonate **2a**[a]



4 **2a** **5**

Entry	**4**	Additives	t (h)	T(°C)	Yield **5**(%)[b]	*E*/*Z* **5**(%)[c]
1	 (**4a**)	4Å MS	4	rt	90	67/33
2	 (**4b**)	"	24	0	85	90/10
3	"	-	28	rt	70	90/10
4	 (**4c**)	4Å MS	5	rt	70[12]	80/20
5	"	-	2.5	70	77	80/20
6	 (**4d**)	-	3	"	88[13]	75/25
7	 (**4e**)	4Å MS	0.5	70	57	*E*
8[d]	"	"	2	"	90	*EE*/*EZ* 50/50
9[d]	 (**4f**)	"	21	"	61	*EE*/*EZ* 40/60
10	 (**4g**)	-	1	"	86	*E*
11	 (**4h**)	-	"	"	58	"
12	 (**4i**)	-	"	"	71[14]	"
13	 (**4j**)	-	3	"	67	"

[a]The experimental procedure is the same as reported for the aldehydes with the exception that activated 4 Å MS (0.5 g /mmol of **4**) were added before **2a**. The work up procedure requires the filtration of molecular sieves before the aqueous extraction. [b]Isolated yield; the structures have been confirmed by ^{1}H- and ^{13}C NMR spectroscopies and by comparison with literature data. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]2.2 equiv of **2a** were employed in order to obtain the corresponding diolefination products (muconontriles).



I II

Scheme 1.

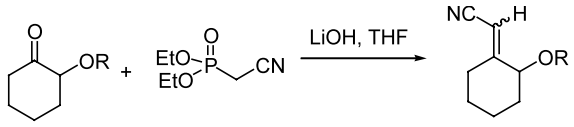
No solvent dependence of the stereoselectivity was observed when using acetonitrile and methanol (entries 2–3) which furnished the *E*-isomer. These results appear to be consistent with a directed reaction.[18]

Other experimental support for the above hypothesis was obtained in entries 4 and 5 on the OH-protected acetate and silylated derivatives. The rate of reaction (compare with entry 1) decreased and more importantly a substantial erosion of *E*-stereoselectivity was observed. Next, we performed two reactions in the presence of lithium chelating agents (entries 6–7), in order to verify whether the stereoselectivity would be affected by the lithium cation coordinating effect. In both cases, the *E*-unsaturated nitrile was isolated in very good yield, confirming the hypothesis of the unique OH group directing-effect.

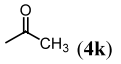
In conclusion, a practical procedure of HWE olefination of aldehydes and ketones for the synthesis of α,β-unsaturated nitriles has been developed using LiOH as a mild base. The *E*-stereoselectivity is predominant and the olefins are obtained in good to high yields.

Activated 4 Å MS have been shown to shorten reaction times with ketones, but they are not necessary to secure

Table 3. LiOH-promoted HWE olefination of **4** with **2a**[a]



4 **2a** **5**

Entry	R	Solvent	Additives	t (h)	T(°C)	Yield **5**(%)[b]	*E*/*Z* **5**(%)[c]
1	H (**4j**)	THF	-	3	70	70	*E*
2	"	CH_3CN	-	"	"	78	"
3	"	CH_3OH	-	"	"	47	"
4	 (**4k**)	THF	-	8	"	59	64/36
5	-Si(CH_3)$_2$*t*-Bu (**4l**)	"	-	6.5	"	51	76/24
6[d]	H (**4j**)	"	HMPA	24	rt	77	*E*
7[e]	H (**4j**)	"	12-crown-4	24	"	80	*E*

[a]See the experimental procedure in Table 1 note a. [b]Isolated yields; the structures have been confirmed by ^{1}H- and ^{13}C NMR spectroscopies and by comparison with literature data. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]2.5 equiv of HMPA were added with respect to LiOH. [e]5.5 equiv of crown ether were added with respect to LiOH.

good yields of the final products, rendering the methodology even simpler. Finally, a complete control of the stereoselectivity has been achieved in the case of α-hydroxy ketones, where the directing effect of the hydroxyl group is reasonably considered to be responsible of the observed exclusive formation of the *E*-isomer.

Acknowledgements

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12. **5c**: unseparable mixture of *E*/*Z* isomers. IR (KBr) 2937, 2835, 2222, 1444, 1156, 969 cm^{-1}; *E distinct signals*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (q, 1H, J=1.3 Hz), 4.70 (s, 1H), 3.27 (s, 6H), 2.00 (d, 3H, J=1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 116.3, 102.0, 98.6, 52.9, 16.9. *Z distinct signals*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (q, 1H, J=1.4 Hz), 5.03 (s, 1H), 3.41 (s, 6H), 1.88 (d, 3H, J=1.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 103.4, 97.8, 55.2. Anal. calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N 9.92. Found: C, 59.70; H, 7.71; N 9.80. In general the vinylic proton of the *Z*-isomer exhibits signal that is upfield compared to the *E*-isomer. See: Ando, K. *J. Org. Chem*. **1998**, *63*, 8411.
13. **5d**: unseparable mixture of *E*/*Z* isomers. IR (KBr) 2938, 2834, 2218, 1443, 1082, 965 cm^{-1}; *E distinct signals*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22–5.20 (m, 1H,), 4.49 (t, 1H, J=5.7 Hz), 3.32 (s, 6H), 2.46 (dd, 2H, J=5.7, 0.8 Hz), 2.08 (d, 3H, J=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 116.3, 101.7, 97.0, 52.6, 40.9, 21.0. *Z distinct signals*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (t, 1H, J=5.6 Hz), 3.36 (s, 6H), 2.70 (dd, 2H, J=5.6, 0.8 Hz), 1.96 (d, 3H, J=1.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 116.2, 102.0, 97.2, 52.8, 38.9, 23.4. Anal. calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N 9.03. Found: C, 61.74; H, 8.35; N, 9.15.
14. **(*E*)-5i**: IR (KBr) 3445, 2981, 2935, 2220, 1626, 1440, 1185, 966 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (q, 1H, J=1.1 Hz), 2.08 (d, 3H, J=1.1 Hz), 1.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 117.5, 93.6, 73.3, 28.1, 17.6. Anal. calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N 11.19. Found: C, 67.00; H, 8.95; N 11.30. Olefin stereochemical assignment was determined by NOE measurement.

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