Titanium-Mediated Stereoselective Knoevenagel Condensation of Ethyl (Diethoxyphosphoryl)acetate with Aldehydes

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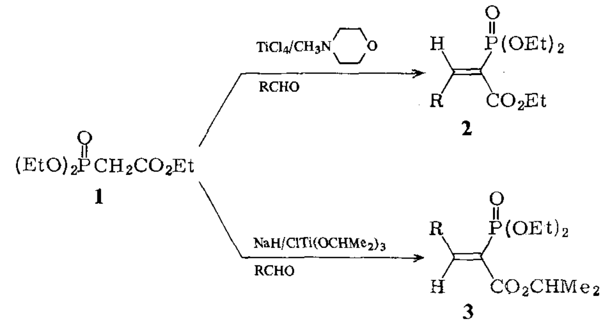
Received August 19, 1986

The titanation of the sodium salt of ethyl (diethoxyphosphoryl)acetate (1) results in a reagent which undergoes a stereoselctive Knoevenagel condensation with aldehydes to form the corresponding trisubstituted olefins 3 having the Z-configuration.

Although the anions of phosphorylacetates such as **1** are generally used for Horner-Wittig olefinations[1], condensation with aldehydes in the presence of *N*-methylmorpholine/$TiCl_4$ is known to yield Knoevenagel products **2** having the thermodynamically more stable *E*-configuration[2].

In this Note we describe a kinetically controlled titanium-mediated Knoevenagel condensation which leads to the opposite stereoselectivity.



a: R = C_6H_5 (57%)
b: R = p-$CH_3OC_6H_4$ (74%)
c: R = p-$NO_2C_6H_4$ (62%)
d: R = $(CH_3)_2CH$ (62%)

Deprotonation of **1** using a suspension of NaH in THF generates the sodium salt of **1**[1], which is titanated[3] with $ClTi(OCMe_2)_3$[4].

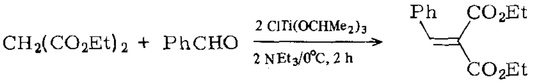
The addition of an aldehyde results in Knoevenagel condensation with preferential formation of the thermodynamically less stable *Z*-isomer **3**. The *E*-isomer is formed to <5% if at all. It is important that the NaH is freshly washed with THF and does not contain NaOH or Na_2O. Small amounts of such bases cause partial isomerization of **3** to the more stable *E*-isomer (20–50%). Also, under the reaction conditions chemoselective transesterification at the carbonyl function sets in[5]. The crude reaction mixture contains <10% of non-transesterified products which are removed during distillation. The ethoxy groups of the phosphonic ester are not exchanged. The *Z*-configuration was assigned on the basis of the large phosphorus/vinyl hydrogen NMR coupling constant of $J_{P\text{-}H} \approx 44$ Hz[6], as opposed to that of ≈23 Hz in case of **2**[2].

Interestingly, upon treating the sodium salt of **1** with $Ti(OCHMe_2)_4$ and adding benzaldehyde, the Horner-Wittig reaction occurs to form the *E*-configurated cinnamic ester (81%)[7]. However, a variation of the above Knoevenagel reaction is possible by using triethylamine in place of NaH as the base. Thus, treating the aldehydes RCHO (R = C_6H_5, p-$CH_3OC_6H_4$, and Me_2CH) with **1** in the presence of two equivalents of $ClTi(OCHMe_2)_3/NEt_3$ at 0°C results in good yields of **3a** (78%), **3b** (89%), and **3d** (72%), respectively. However, in the case of the aromatic aldehydes the NMR spectra show the presence of small amounts of the *E*-isomers (5–10%). If only one equivalent of Et_3N is used at room temperature, the *E*-isomers predominate ($E{:}Z \approx 90{:}10$). Thus, in order to obtain **3** preferentially, kinetic conditions must be used.

$$\mathbf{1} + \mathrm{RCHO} \xrightarrow[2\ NEt_3/2\text{-}3\ h/0°C]{2\ ClTi(OCHMe_2)_3} \mathbf{3}$$

Vinyl-type phosphonates have been utilized in a variety of ways, e.g., Diels-Alder reactions[8], Michael additions[6,9], hydroboration/oxidation[10], reduction[2,11] and ene reactions[12]. Protonation results in the replacement of the phosphonate group by hydrogen[11,13]. In addition to these reports, alternative syntheses have been published[14].

Finally, the $ClTi(OCHMe_2)_3$-based Knoevenagel condensation can also be applied in case of other CH-acidic compounds such as malonic ester **4**. In this case, the conditions used do *not* lead to transesterification. The reaction is faster and milder than the $TiCl_4$-mediated process which requires 16 hours[15].



4 **5** (84%)

We thank the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* for support of this work.

Experimental

All reactions were carried out under an atmosphere of nitrogen using dry THF. Sodium hydride in oil was washed twice with THF. NaH in bottles which have been opened several times and which thus contain $NaOH/Na_2O$ should not be used. – NMR: Varian XL-100; $DCCl_3$/TMS internal. – Combustion analyses: Analytisches Labor/Fachbereich Chemie, Marburg.

Knoevenagel Condensation. Procedure A: The suspension of 0.25 g (10.5 mmol) of NaH in 30 ml of THF is treated with 2.24 g (10.0 mmol) of ethyl (diethoxyphosphoryl)acetate (**1**) at room temperature and the mixture stirred until an almost clear solution forms. It is refluxed for 1 h, cooled to −78°C and treated with 2.73 g (10.5 mmol) of chlorotriisopropoxytitanium[4]. The cooling bath is removed and the mixture stirred for 1.5 h at room temper-

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Chem. Ber. **120**, 121–122 (1987) © VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1987 0009–2940/87/0101–0121 $ 02.50/0

ature. After the addition of an aldehyde (9.5 mmol), the mixture is stirred at room temperature for 4 h (in case of 4-methoxybenzaldehyde: overnight) and poured on dilute hydrochloric acid. The aqueous phase is extracted twice with ether and the combined organic phase washed with water and dried over $MgSO_4$. After stripping off the solvent, the crude product is distilled using a Kugelrohr (**3a**: 200°C/0.05 Torr; **3b**: 200°C/0.05 Torr; **3c**: 230°C/0.05 Torr; **3d**: 140°C/0.05 Torr). Other data see Table 1.

Table 1. Data of compounds **3**

Compound	Molecular formula	Analysis Calcd.	Analysis Found	^{1}H NMR[a] δ [ppm] CH=C
3a	$C_{16}H_{23}O_5P$ (326.3)	C 58.89 H 7.10	C 58.69 H 7.00	8.14 ($J_{P\text{-}H}$ = 43 Hz)
3b	$C_{17}H_{25}O_6P$ (356.4)	C 57.30 H 7.07	C 57.18 H 6.93	8.08 ($J_{P\text{-}H}$ = 44 Hz)
3c	$C_{16}H_{22}NO_7P$ (371.3)	C 51.75 H 5.97 N 3.77	C 51.50 H 5.97 N 3.80	8.13 ($J_{P\text{-}H}$ = 43 Hz)
3d[b]	$C_{13}H_{25}O_5P$ (292.3)	C 53.42 H 8.62	C 53.15 H 8.52	7.19 ($J_{P\text{-}H}$ = 46 Hz)

[a] ^{1}H and ^{13}C NMR as well as mass spectra are in accord with the proposed structures[7]. — [b] Compound solidifies (m.p. 66–69°C).

Procedure B: The mixture of 5.2 g (20 mmol) of chlorotriisopropoxytitanium[4], 2.24 g (10.0 mmol) of ethyl (diethoxyphosphoryl)acetate (**1**) and 10.0 mmol of an aldehyde in 30–40 ml of THF is treated with 2.02 g (20 mmol) of triethylamine at 0°C. The amine hydrochloride precipitates and the mixture is stirred at 0°C for 2–3 h; workup according to Procedure A.

Procedure B can be applied to the synthesis of **5** (84%; isolated by Kugelrohr distillation at 200°C/0.1 Torr).

CAS Registry Numbers

1: 867-13-0 / **3a**: 104779-88-6 / **3b**: 104779-89-7 / **3c**: 104779-90-0 / **3d**: 104779-91-1 / **4**: 105-53-3 / **5**: 5292-53-5 / C_6H_5CHO: 100-52-7 / p-$CH_3OC_6H_4CHO$: 123-11-5 / p-$NO_2C_6H_4CHO$: 555-16-8 / $(CH_3)_2CHCHO$: 78-84-2 / $(EtO)_2P(O)CHCO_2Et \cdot Na$: 22822-85-1

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