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Structural study of titanated phosphonoacetates: reagents for stereoconvergent Knoevenagel condensations

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Abstract

The titanation of the sodium salt of phosphonoacetates occurs at the oxygen of the ester function to produce equal amounts of chelated and non-chelated titanium enolates (*Z* and *E*, respectively), as shown by detailed ^{13}C and ^{31}P NMR studies. No sign of the C-titanated species was detected. This means that the previously described Knoevenagel condensation of the intermediate titanium reagents with aldehydes to form *Z*-configurated vinylphosphonates is a fully stereoconvergent process.

Introduction

Whereas the anions of phosphonoacetates (**1**) are generally used for Horner–Wittig olefinations [1], condensation with aldehydes in the presence of $TiCl_4$/*N*-methylmorpholine gives the Knoevenagel products **2** having the thermodynamically more stable *E*-configuration [2].

We have recently described a kinetically controlled titanium-based Knoevenagel condensation which leads to the opposite stereoselectivity [3]. Accordingly, the sodium salt of **1** is titanated with $ClTi(OCHMe_2)_3$ and the resulting reagent of unknown structure allowed to react with aldehydes to produce good yields of **3** with > 95% stereoselectivity. The overall process is accompanied by chemoselective transesterification at the carbonyl function [4 **].

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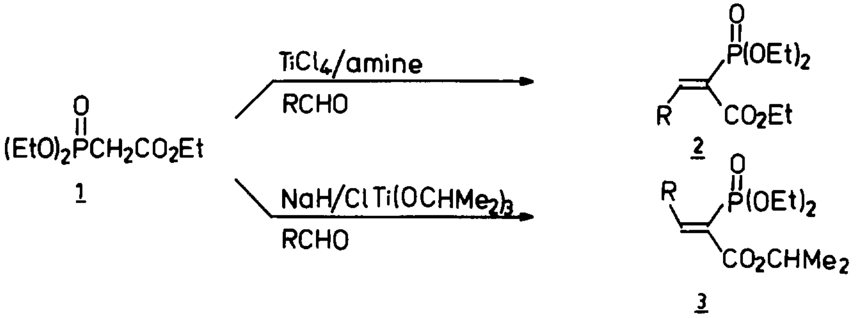
** Reference number with asterisk indicates a note in the list of references.

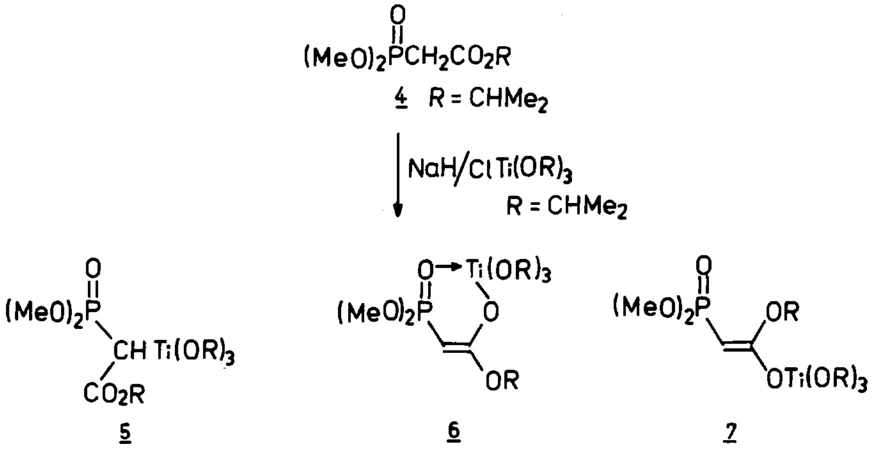


Although the titanation of classical "carbanions" has been shown to increase chemo- and stereo-selectivity in reactions with carbonyl compounds and alkyl halides, few structural data of the intermediate organotitanium reagents are known [5]. Here we present a ^{13}C and ^{31}P NMR study of the intermediate titanium reagents of the above *Z*-selective Knoevenagel condensation. Ambient temperatures and THF as the solvent were chosen because these correspond to the conditions of the previously reported Knoevenagel condensation [3].

Results

In order to circumvent the added feature of transesterification and to simplify the NMR spectra, we first studied the titanation of the isopropyl ester (**4**). In principle this can lead either to *C*-titanation (cf. **5**) and/or *O*-titanation (cf. **6**/**7**).

Distinguishing between the *C*- and *O*-titanated forms should be possible on the basis of the magnitude of the ^{13}C–H (methine) coupling constant. It is well known that $^{1}J(^{13}\text{C–H})$ depends upon the hybridization of the C-atom, i.e., it increases with increasing *s*-character [6]. In **5**, the methine carbon atom is approximately sp^3-hybridized, whereas in **6** and **7** sp^2 hybridization pertains. Thus, in going from **4** to **5**, little change in $^{1}J(^{13}\text{C–H})$ is expected, in contrast to the situation encountered in **4** → **6**/**7**. Experimentally, the ^{13}C NMR spectrum (THF, room temperature) shows two clean sets of signals for two different species in a ratio of about 1/1. The



signals of the methine carbon atoms occur at 40.9 and 45.1 ppm, and the coupling constants ${}^1J({}^{13}C\text{–}H)$ are 159.9 and 159.5 Hz, respectively. Comparing these values with those of the neutral precursor **4** (δ 33.1 ppm and ${}^1J({}^{13}P\text{–}C)$ 137.4 Hz), leads to the conclusion that only *O*-titanation has occurred.

The assignment regarding **6** vs. **7** is more difficult. The species having the absorption of the methine carbon atom at 40.9 ppm may tentatively be assigned to the chelated structure **6**. It is reasonable to expect that upon coordination of the phosphoryl oxygen to titanium, electron density at the metal should increase. Consequently, the donor effect of the enolate oxygen onto the metal should correspondingly be lowered, resulting in a slight upfield shift of the ${}^{13}C$ resonance of C(1) relative to that of the non-chelated species **7**. NOE studies were not successful. Finally, the spectra at lower temperatures begin to become extremely complex, indicative of aggregation.

The conclusion of *O*-titanation vs. *C*-titanation was substantiated by a ${}^{31}P$ NMR study. In going from phosphonium salts to ylides, the coupling constant ${}^1J({}^{31}P\text{–}C)$ is known to increase owing to an increase in percent *s*-character [7]. In the present case, the ${}^{31}P$ NMR spectrum shows the existence of two titanated species in a ratio of about 1/1, as expected. The chemical shifts are 39.1 and 43.0 ppm downfield from 85% H_3PO_4 (external). The ${}^1J(P\text{–}C)$ values are 219.3 and 222.0 Hz, respectively. These data can be compared to the values of the precursor **4**: δ 21.9 ppm, ${}^1J(P\text{–}C)$ 137.4 Hz. These results are in complete agreement with *O*-titanation. Taken together, both NMR studies constitute unambiguous proof that the two species have the structure **6**/**7**. The distinction between **6** and **7** on the basis of the ${}^{31}P$ NMR data is tentative: however, it is logical to assume that the species with δ at lower field (43.0 ppm) is **6**, because chelation is expected to remove electron density away from phosphorus.

It is interesting to compare our results with those of Seyden-Penne, who studied the lithiated form of diethyl[(carbomethoxy)methyl]phosphonate [8]. Using n-butyllithium as the base, a single (chelated) species analogous to **6** was obtained. Similar trends in ${}^{13}C$ and ${}^{31}P$ NMR spectra were observed, and the same criteria regarding coupling constants as a means to distinguish between *C*- and *O*-metallation were used. The non-chelated form analogous to **7** was not observed. However, in the case of the potassium salt of the related diphenylphosphine oxide, two species were detected corresponding to the *Z*- and *E*-forms; the lithiated compound turned out to be chelated (*Z*) [9].

In further ${}^{13}C$ and ${}^{31}P$ NMR experiments we subjected compound **8** to titanation. In this case transesterification at the carbonyl function is an additional process which complicates the interpretation. Indeed, the ${}^{13}C$ and ${}^{31}P$ NMR spectra are complex and point to the existence of four species in an almost statistical ratio of 1/1/1/1. The data (Table 1) in conjunction with the previous results and assignments are in accord with species **9**, **10**, **11** and **12**. At ambient temperature the ligands at titanium may well scramble, but alkoxy exchange at the vinyl position does not occur, at least not on the NMR timescale.

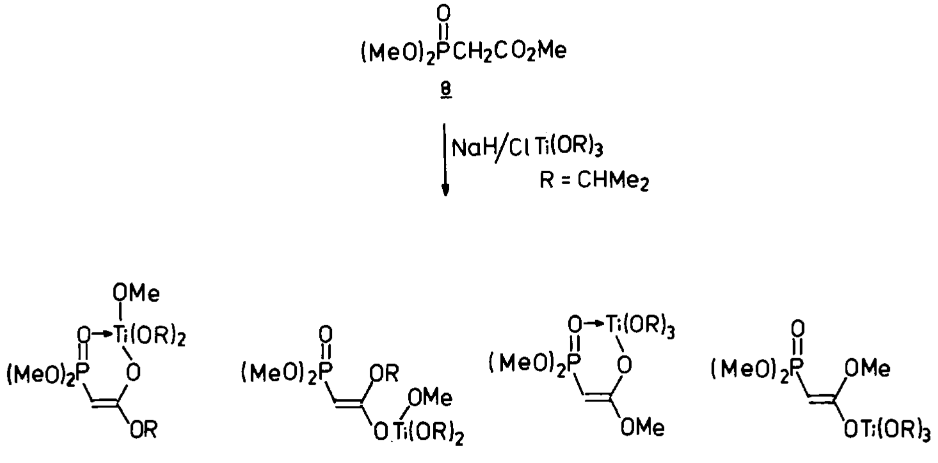
The basic conclusion of this work is that titanation of phosphonoacetates leads to equal amounts of chelated and non-chelated titanium enolates having the *Z*- and *E*-configuration, respectively. The Knoevenagel condensation with various aliphatic and aromatic aldehydes then produces the vinylphosphonates (**3**) with > 95% stereoselectivity. The reaction is thus completely stereoconvergent. How can this be

Table 1

^{13}C and ^{31}P NMR Data [a]

Compound	δ(C(1))	δ(C(2))	δ(P)	$^{1}J(^{13}C{-}H)$	^{1}J(P–C)
8	32.6	166.2	22.1	– [b]	133.2
9	40.9	174.2	43.1	159.9	221.9
10	45.2	174.6	39.2	159.5	219.3
11	40.5	175.0 [c]	42.9	– [d]	222.3
12	44.5	175 [c]	39.5	– [d]	219.4

[a] Numbering system $(EtO)_2P(O)\overset{1}{C}H_2\overset{2}{C}O_2Me$. [b] $^{1}J(^{13}C{-}H)$ for the methylene carbon atom in $(EtO)_2P(O)CH_2CO_2Me$: 130.0 Hz (Lit. [9]). [c] Estimation due to the complexity of the spectrum. [d] Not measured.



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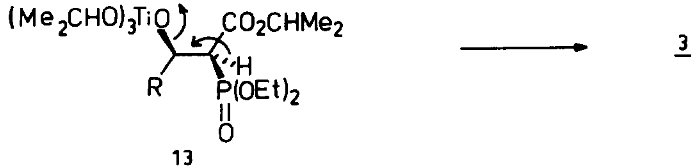
9 10 11 12

explained? *Z*- and *E*-titanium enolates derived from ketones are known to add to aldehydes with preferential formation of the *syn*-configurated aldol adducts, although the degree of stereoselectivity is not uniformly high [10]. The fact that the same aldol adduct is formed preferentially irrespective of the geometry of the ketone enolate, is unusual and may be indicative of either an acyclic transition state [10,11] or a switch from chair to boat cyclic transition states [12,13]. In the present case, a similar *syn*-selective aldol addition of the titanated phosphonoacetates as the initial step of the Knoevenagel condensation seems reasonable. Base induced *trans*-elimination **13** → **3** would then lead to the observed product.



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Experimental

Instruments

^{13}C NMR spectra were recorded on a Bruker WH 400 spectrometer (100 MHz) using THF as the solvent and internal reference. ^{31}P NMR spectra were recorded on a Varian XL-100 spectrometer (40.5 MHz) using THF as the solvent and 85% H_3PO_4 as an external reference.

Preparation of titanated phosphonoacetates

Sodium hydride (91.1 mg, 3.8 mmol) was washed with dry pentane, then with dry THF under an atmosphere of nitrogen, and then stirred in about 7 ml of THF in a flask equipped with a serum cap and nitrogen inlet. At room temperature, the equivalent amount of the phosphonoacetate was added dropwise via a syringe. After 10 min, the flask was fitted with a reflux condenser and the mixture refluxed for 1 h. It was then cooled to −78 °C and chlorotriisopropoxytitanium (99.0 mg, 3.8 mmol) was slowly added. The mixture was warmed to room temperature and stirred for an additional 2 h. A 1 ml aliquot of the pale yellow solution was introduced under a nitrogen atmosphere into an NMR tube.

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