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iso-Propyl phenylacetate: formation of a single enolate with tBuP4 as base

A. Solladié-Cavallo,[a,*] T. Liptaj,[a,b,*] M. Schmitt[a] and A. Solgadi[a]

[a] *Laboratoire de Stéréochimie Organométallique associé au CNRS, ECPM, Unversite Louis Pasteur, 25 rue Becquerel, 67087 Strasbourg, France*

[b] *Central Laboratories, Slovak, Technicals University, Bratislava, Slovakia*

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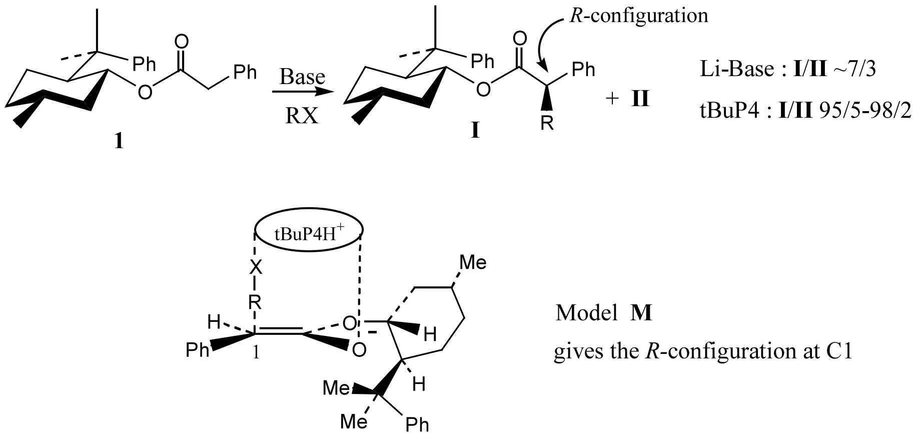
Abstract—Formation of the enolate of *iso*-propyl phenyl acetate using phosphazene bases was studied by ^{1}H, ^{13}C and ^{31}P NMR. It has been shown that: (i) while EtP2 was not strong enough, tBuP4 provided the enolate and (ii) only one isomer of the enolate was formed which was assigned the *Z*-configuration from the stereo-outcome of the reaction. A strong conjugation between the phenyl ring and the enol moiety was observed (with ΔG12 kcal/mol as estimated by NMR) and, in the absence of air/metals, the enol was stable until +40°C. ^{1}H and ^{31}P NMR studies of commercially available phosphazene bases have shown that EtP2 contained less than 5% of an undetermined P2 isomer and that tBuP4 contained up to 12% of another P4 isomer whose structure has been determined. © 2002 Elsevier Science Ltd. All rights reserved.

We have recently shown that the 'naked' enolate of chiral 8-phenylmenthyl phenylacetate **1** generated with tBuP4, a strong phosphazene base,[1] allowed an increase of the diastereoselectivity of *C*-alkylation of up to 95/5–98/2 (as compared to lithium enolate which provided no more than 70/30)[2] (Scheme 1). Moreover, the formation of the *major* diastereomer obtained was rationalized through a model of approach **M** involving a *Z*-enolate and assistance of the base-counter-cation, as suggested by Seebach,[3] to the entrance of the alkylating agent (Scheme 1). The question was then to identify whether the *Z*-enolate was the only one to be formed and to react or if both *Z*- and *E*-enolates were formed but were in rapid equilibrium and that the *Z*-enolate reacted faster than the *E*-enolate.

We present here a ^{1}H NMR (400 MHz) study of enolate formation of *iso*-propyl phenylacetate **2** using EtP2 and/or tBuP4, as well as ^{1}H (400 MHz) and ^{31}P NMR (162 MHz) studies of these two bases.



Scheme 1.

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* Corresponding author.

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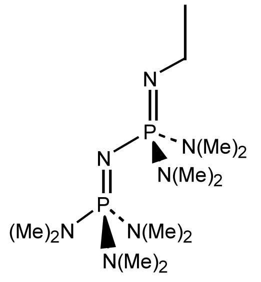
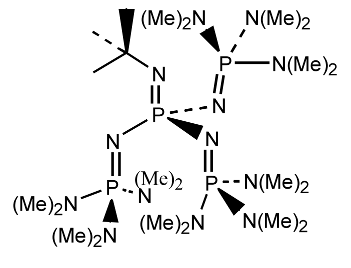
Less expensive isopropyl ester **2** (similar to **1**, as derived also from a secondary alcohol), Scheme 2, has been used together with deuterated THF (solvent used for the alkylation reactions) and commercially available EtP2 (solid) and/or tBuP4 (1 M hexane solution). The enolates have been generated directly in an NMR tube at −78°C from a known THF-d_8 solution of ester **2** and known THF-d_8 solutions of EtP2 and/or tBuP4.

1. The bases

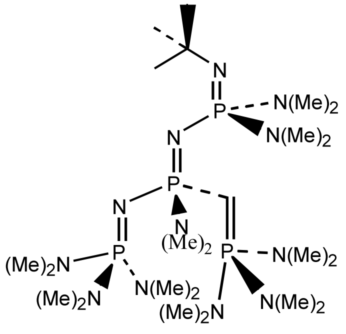
The ^{1}H NMR spectrum (in C_6D_6) of EtP2 exhibited, as expected, four signals: a double quadruplet at 3.50 ppm (2H, $3\times{}^3J_{HH}=7$ Hz, $^3J_{PH}=16$ Hz), a doublet at 2.82 ppm (12H, $^3J_{PH}=10$ Hz), a doublet at 2.41 ppm (18H, $^3J_{PH}=10$ Hz) and a double triplet at 1.59 ppm (3H, $2\times{}^3J_{HH}=7$ Hz, $^4J_{PH}=2$ Hz). An unidentified impurity was, however, detected with a multiplet at about 2.45 ppm. The {^{1}H-decoupled} ^{31}P NMR spectrum (in C_6D_6) exhibited the two expected doublets at 17.59 (1P, $^2J_{PP}=47$ Hz) and 14.95 ppm (1P, $^2J_{PP}=47$ Hz) as well as two other doublets at 23.69 ppm ($^2J_{PP}=44$ Hz)[4] and 13.63 ppm ($^2J_{PP}=44$ Hz)[4] which could correspond to another kind of P2 base (~4%).



EtP2



tBuP4, **I**



tBuP4, **II**

The ^{1}H NMR spectrum (in C_6D_6) of tBuP4 exhibited two signals: a doublet at 2.70 ppm (54H, $^3J_{PH}=10$ Hz) and a singlet at 1.74 ppm (9H) for the expected structure **I** of the base together with the hexane signals at 1.22 ppm (broad) and 0.87 ppm (t) in a 4/3 ratio. However, four other signals: a doublet at 2.93 ppm (12H, $^3J_{PH}=10$ Hz), a doublet at 2.85 ppm (6H, $^3J_{PH}=$ 10 Hz), a doublet at 2.57 ppm (46H, $^3J_{PH}=10$ Hz) and a singlet at 1.57 ppm (9H) which corresponded to structure **II** (12%) were also observed. The {^{1}H-decoupled} ^{31}P NMR spectrum (in C_6D_6) was in accord and exhibited the signals of both structures (**I** and **II**) in the same ratio (88/12); the two expected signals for **I**: a doublet at 8.75 ppm (3P, $^2J_{PP}=29$ Hz) and a quadruplet at −23.45 ppm (1P, $3\times{}^2J_{PP}=29$ Hz) as well as the three expected signals for **II**: a doublet at 13.49 (1P, $^2J_{PP}=32$ Hz), a doublet at 12.61 (2P, $^2J_{PP}=45$ Hz) and a double triplet at −12.67 (1P, $2\times{}^2J_{PP}=45$ Hz, $^2J_{PP}=32$ Hz).

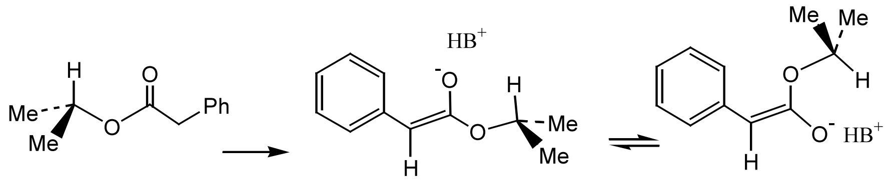
2. The enolate

Ester **2** in the presence of an excess of EtP2 (1.15 equivalent, as seen from the ratio of the methyls signals of the base and of the ester) did not lead to formation of the enolate. The CH_2 singlet shifted but slightly (from 3.5 to 3.6 ppm), retained a 2H-integration but broadened ($\Delta\nu_{1/2}=12$ Hz instead of ~3 Hz), indicating the presence of an exchange of the CH_2-protons between the ester and the base.

However, in the presence of tBuP4, the CH_2 singlet (2H) at 3.50 ppm is replaced by a 1H- singlet at 3.90 ppm. Moreover, one main species **A** together with two minor species **B** (**A**/**B** ~95/5) and **C** (Fig. 1(a)) were observed. The main species **A** exhibits seven signals integrating for one each (the above CH-singlet, a septuplet, three aromatic triplets and two aromatic doublets) and one doublet integrating for six (isopropyl methyls), as expected for an enolate species.

After removing part of the solution with a syringe, it appeared that (probably because of air and metal catalysis) species **B** increased (**A**/**B** ~2/1) (Fig. 1(b)) suggesting a decomposition of **A** into **B**.

Variation of the temperature between −40°C and +40°C showed an exchange process within species **A**, the two



Scheme 2.

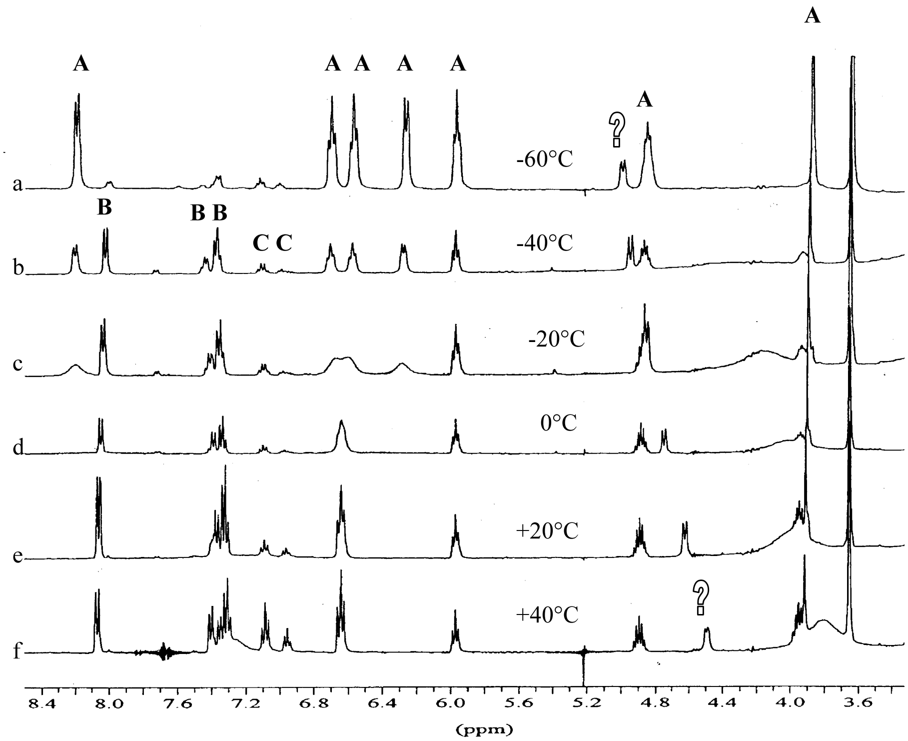


Figure 1.

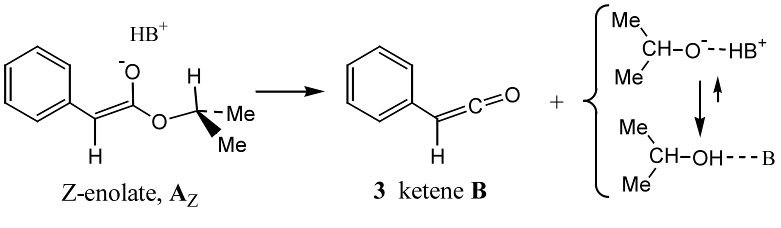
ortho-doublets and the two *meta*-triplets coalesced, while the ratio **A**/**B** did not change much (from ~66/34 at –40°C to ~60/40 at +40°C). At +40°C (Fig. 1(f)) the signal of the *ortho* protons is still a broad singlet which is easily located at about 7.25 ppm overlaping with the *meta* and *para* **B** signals.

Most importantly, no mutual exchange among the three observed species (**A**, **B** and **C**) was observed during the temperature variation, suggesting that neither **B** nor **C** were in dynamic equilibrium with **A**.

Species **A** having all the expected signals was assigned as an enolate species and, from the stereochemical outcome of the reaction, has been assigned the *Z*-configuration ($\mathbf{A}_Z$) (Scheme 2). The barrier to rotation of the phenyl ring found in enolate $\mathbf{A}_Z$ is consistent with an expected strong conjugation. The $\Delta G^\ddagger$ values have been estimated using the approximate formula at coalescence temperature: $\Delta G^\ddagger$ (0°C) = 11.9 kcal/mol (coalescence of *ortho*-protons) and $\Delta G^\ddagger$ (–20°C) = 12.6 kcal/mol (coalescence of the *meta*-protons).

As it is known that ester enolates decompose into ketenes,[5] **B** (which did not exchange with **A** upon heating) was assigned the ketene structure **3** (Scheme 3). The corresponding CH-singlet, expected around 2.1±0.7 ppm for ketene **B**,[6] could not be localized because of solvent and base signals in this domaine, but the ^{13}C NMR spectrum exhibited the two expected singlets at 31 (=CH=) and 201 (C=O) ppm (literature: 30.4 and 201.3 ppm).[6] Moreover, a new signal, which, at higher temperature, appeared as a septuplet (CH-*i*Propyl) was observed at ~4.0 ppm (Fig. 1(e)) and was assigned to the CH of isopropanol linked to tBuP4, which is expected to be formed simultaneously to ketene (Scheme 3).

Species **C** has been assigned to the tBuP4 salt of the corresponding acid (Ph-CH_2-CO_2H) formed from **B** by traces of humidity. Upon addition of traces of water



Scheme 3.

the corresponding aromatic signals increased and a CH_2-singlet appeared at 3.21 ppm.

However, one signal, a doublet, which shifted from 4.95 (at −40°C) to 4.50 ppm (at +40°C) has not been assigned. Using a 2D *J*-resolved experiment it has been shown that this proton was coupled to a phosphorus atom and should therefore belong to a BH^+ species although its surface integration does not correspond to any of the anionic species present (**A**, **B** or **C**).

3. Conclusion

It thus appeared that EtP2 is not strong enough to generate the enolate from ester **2** but that only one enolate, $\mathbf{A}_z$, is formed from ester **2** and the strong tBuP4 base. It is worth noting that this enolate (stable until +40°C in the absence of air and/or metal) is the thermodynamic enolate in THF. The problem of the structure of BH^+ species remains, and this is under study.

Acknowledgements

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