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THE 1,3-MIGRATION OF PHOSPHORUS FROM OXYGEN TO CARBON: A NEW SYNTHESIS OF β-KETOPHOSPHONATES FROM ENOL PHOSPHATES

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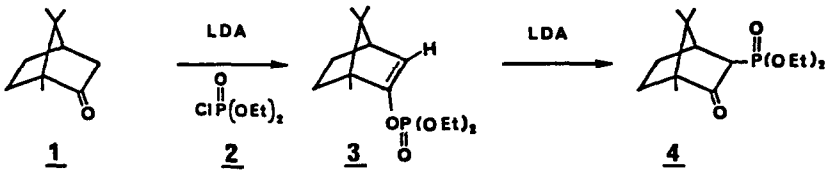
Abstract: Enol phosphates, readily prepared from ketone enolates and dialkyl phosphorochloridate, can be converted to the analogous β-ketophosphonates by treatment with strong base.

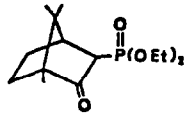
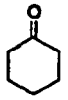
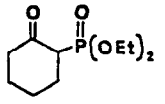
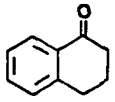
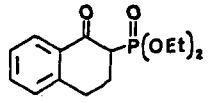
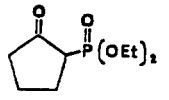
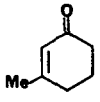
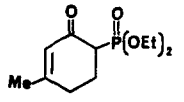
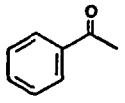
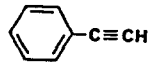
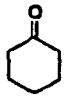
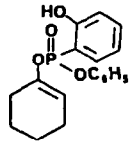
In the 25 years since its discovery,[2,3] the Wadsworth-Horner-Emmons condensation has become an important method for the synthesis of conjugated olefins from carbonyl compounds and β-ketophosphonates. This reaction gives primarily the thermodynamically favored olefin isomer,[4] but recent modifications have extended its range to allow stereoselective synthesis of both Z- and E-trisubstituted olefins in at least some cases.[5,6] Unfortunately, methodology for the synthesis of β-ketophosphonates has not advanced to the same degree. The most common approach, the classical Arbuzov synthesis,[7] involves reaction of a trialkylphosphite with an α-haloketone. This reaction works best with nucleophilic phosphites[8] and α-iodoketones which readily undergo substitution reactions. When the Arbuzov and other standard approaches[9] could not meet our needs,[10] we sought new, general routes to β-ketophosphonates based on electrophilic rather than nucleophilic phosphorus reagents. Here we report a procedure which affords β-ketophosphonates from ketones via simple, readily available enol phosphates.[11]

The reaction of dialkyl phosphorochloridates with enolates is well known, and results in clean formation of the enol phosphate rather than the ketophosphonate.[12] For example, sequential treatment of camphor (1) with LDA and diethyl phosphorochloridate (2) at -78° in THF, results in near quantitative formation of the enol phosphate (3), which, if desired, can be isolated and characterized. However, if it were converted to its own anion, rearrangement to the desired phosphonate appeared reasonable,[13] since this would afford the highly stabilized



1 2 3 4

Table: Synthesis of β-Ketophosphonates.

	KETONE	PRODUCT	YIELD[a]
1			71
2			72
3			88
4			55
5			75
6			75[b]
7			90

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a) Isolated yields for the conversion of ketone to phosphonate. Satisfactory ^{1}H and ^{31}P NMR spectra, and mass spectra were obtained for all compounds. Satisfactory combustion analyses were obtained for all new phosphonates. b) GC yield.

ketophosphonate anion from a much less stable species. In fact, treatment of the enol phosphate 3 with LDA (-78° to RT), results in smooth rearrangement to the desired β-ketophosphonate 4, as evidenced by a dramatic change in the ^{31}P NMR spectrum (from -4.24 ppm to +23.07 ppm). The overall isolated yield for the two step sequence from camphor to the ketophosphonate is quite reasonable (62%). Furthermore, it is not essential to isolate the intermediate enol phosphate: the phosphonate can be obtained by sequential treatment of camphor with LDA, the phosphorochloridate, and LDA in a single reaction vessel. By this latter approach, compound 4 was obtained in 71% isolated yield, after the addition of acetic acid in ether to quench the reaction and purification by filtration through a Florisil pad.

This methodology works best with cyclic ketones (see Table), yielding precisely those β-ketophosphonates which are least accessible via other methods. In fact, even the α,β-unsaturated ketone 3-methyl-2-cyclohexenone is readily converted to its α′-phosphonate analogue by this procedure. When enolates derived from acyclic ketones are treated under the same experimental conditions, the results are more complex. With methyl ketones, such as acetophenone, a known phosphate elimination resulting in alkyne formation[14] predominates. With more substituted, acyclic ketones, such as 3-pentanone or propiophenone, complicated product mixtures are obtained, although ^{31}P NMR analysis of the reaction mixtures indicates the formation of some phosphonate products. It is possible that formation of the desired ketophosphonate is a function of enolate stereochemistry,[15,16] but this remains to be established. Finally, when the diphenyl enol phosphate of cyclohexanone was treated with LDA under the standard conditions (entry 7), phosphorus migration was observed to the ortho position of an aromatic ring[13] instead of to the vinylic position.

This new route to β-ketophosphonates is short, high yielding, and offers ready access to structural variety not previously available in these compounds. As a consequence, this procedure should find wide use, and allow for creative new applications of β-ketophosphonates.

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