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A New Horner−Wadsworth−Emmons Type Coupling Reaction between Nonstabilized β-Hydroxy Phosphonates and Aldehydes or Ketones

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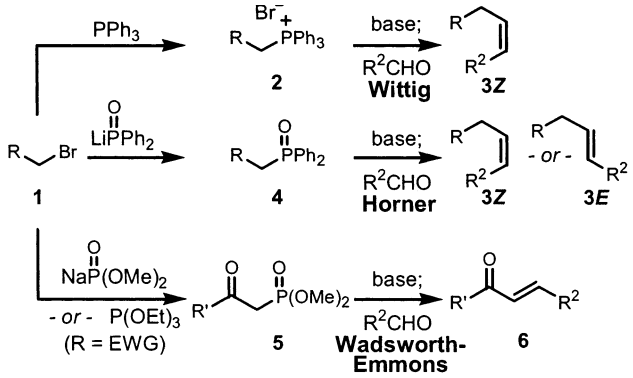
Abstract: Treatment of nonstabilized β-hydroxy phosphonic acid mono methyl esters with diisopropyl carbodiimide at ambient temperature leads to clean stereospecific elimination. The phosphonic acid mono alkyl esters are accessible by the selective partial saponification of dimethyl or diethyl alkyl phosphonates with NaOH or $MgBr_2$. Isolated yields over both hydrolysis and elimination steps average 55−75%.

Introduction

The Wittig,[1,2] Horner,[3,4] and Wadsworth−Emmons[5,6] reactions are classic methods for joining two complex molecular fragments through relatively simple functional groups, and these reliable olefin-forming reactions are well-accepted transformations in both academia and industry (Scheme 1).[7] The synthetic power inherent with these kinds of coupling and homologation reactions has spurred research into optimizing, modifying, or supplanting[8] these methods with others that operate under different reaction conditions,[9] can be prepared from alternative starting materials,[10] or that enhance stereochemical control.[11,12]

The dialkyl phosphonates of the Wadsworth−Emmons reaction can be prepared by Arbuzov, Michaelis−Becker,[13,14] or other methods,[14] and the alkylation of α-lithio phosphonates with aldehydes is well known. However, a carbanion-stabilizing group in the β-position is necessary for elimination and olefin formation, without which addition to aldehydes gives stable β-hydroxyphosphonates.[6,7,15] The elimination of nonstabilized β-hydroxy phosphonates to olefins has long been recognized as a difficult transformation. In pioneering studies on the formation of olefins from nonstabilized β-hydroxy phosphonates derived from benzophenone, Corey and Kwiatkowski reported that the optimal yield of 1,1-diphenylethylene was at best 30%, and benzophenone, unsaturated phosphonate, and acidic materials were also formed.[16] To overcome these difficulties, Corey et al. ingeniously developed phosphonic bisamides[17] and thiophosphonates[16] as alternative coupling reagents.[18] During the intervening decades, a general protocol for the elimination of nonstabilized β-hydroxyphosphonates has not been advanced. In this paper, we describe a novel method for the utilization of nonstabilized β-hydroxyphosphonates in Horner−Wadsworth−

Scheme 1



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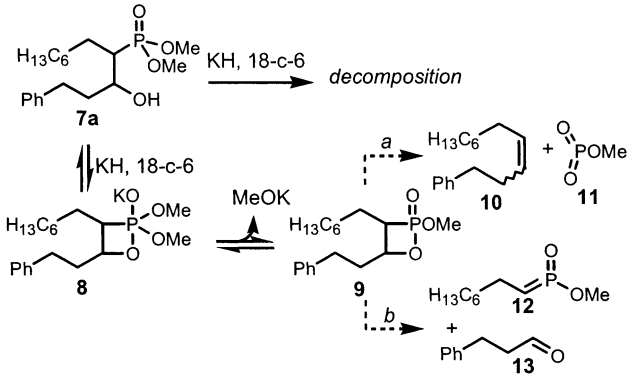
Scheme 2



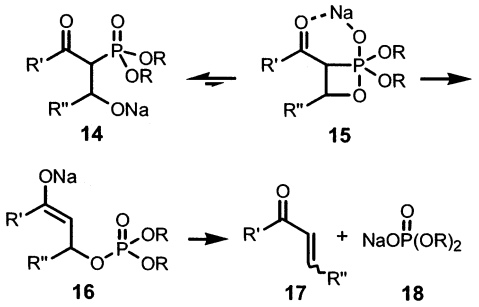
Emmons type reactions under ambient conditions using mild dehydrating reagents.

With the advent of convenient olefin hydrophosphorylation reactions,[19,20] we decided to reinvestigate the conversion of β-hydroxy phosphonates to olefins despite the discouraging heritage for their elimination. Initially we speculated that the use of crown ethers, which were not commercially available three decades ago, would result in a more nucleophilic alkoxide for generating the oxaphosphetane **9**, which could then convert to the desired olefin by a retro [2 + 2] fragmentation pathway (Scheme 2). The more exothermic *pathway a* leads to the desired olefin and meta phosphate **11**,[21] whereas *pathway b* leads to release of aldehyde **13** and the reactive intermediate **12**. However, the alkali salts (NaH, *n*-BuLi, *t*-BuOK) of β-hydroxy phosphonates **7** in the presence of crown ethers[22] showed no reaction at low temperatures, and the substrates underwent decomposition to various dehydrated vinylic and β,γ-unsaturated phosphonates as the reactions warmed to room temperature.[23] Weaker bases (PhONa, wet K_2CO_3) have been reported to result in olefin formation with tertiary β-hydroxy phosphonates,[24] but these methods were ineffective here, even at elevated temperatures (100 °C in DMF).[25] Partial ester hydrolysis occurred in the presence of Lewis acids, and only CsF in hot DMF provided some olefin **10** (8% after 16 h).[26]

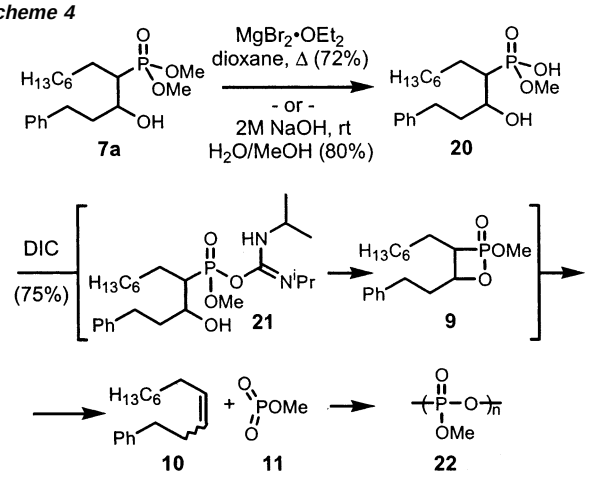
In the Wadsworth−Emmons reaction,[6] the reversible formation of the pentavalent phosphorus species **15** is thought to precede collapse to the stabilized anion **16**, and E1cb elimination leads to release of phosphate and the coupled enone product **17** (Scheme 3). The β-hydroxy phosphonates investigated in this paper also likely form equilibrating pentavalent phosphorus intermediates, but because they lack the β-electron-withdrawing or -stabilizing group, there is no low energy pathway for collapse leading to olefin formation.

It was clear from NMR data that no discernible amounts of the oxephosphetane **9** were formed by treatment of **7a** with alkali

Scheme 3



Scheme 4



metals.[27−29] We postulated that a leaving group superior to methoxide (or methanol) was required for oxephosphetane formation. Dehydration of the free phosphonic acid appeared to be an attractive strategy, and the ideal dehydrating reagent for this task proved to be the peptide coupling reagent diisopropylcarbodiimide (DIC). In this regard, the addition of DIC to a $CHCl_3$[30] solution of the free phosphonic acid **20** resulted in clean formation of olefin **10**.[31] Subsequent NMR investigations revealed that the formation of oxaphosphetane **9** was nearly instantaneous after the addition of DIC to a solution of **20**, whereas the intermediate urea phosphonate **21** could not be detected.[32] The oxaphosphetane **9** slowly converted over 24 h to olefin **10** in 75% yield. The partial saponification of dimethylphosphonate **7a** to **20** was achieved with $MgBr_2$•OEt_2 at 100 °C in dioxane or, more conveniently, by saponification with NaOH in H_2O/MeOH at room temperature (Scheme 4).

A variety of β-hydroxy phosphonates prepared from aldehydes and ketones were made for exploring the generality of the elimination protocol (Table 1). An important consideration when evaluating the alkylation yields in Table 1 is that the ratio of phosphonate anion to carbonyl electrophile was maintained at 1:1, and the reaction stoichiometry was not adjusted to increase efficiency. The alkylation of octyl dimethyl phosphonate **19a** with aliphatic or aromatic aldehydes provided the β-hydroxy phosphonates **7a**,**b** in 81 and 84% isolated yields,

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(23) Based on ^{1}H and ^{31}P NMR.
(24) Dimethyl 2-hydroxy-2,2-dibenzylethylphosphonate, K_2CO_3 (8 equiv) and H_2O (8 equiv) in DMF at 95 °C for 48 h gave 80% olefin: Kawashima, T.; Ichii, T.; Inamoto, N. *Chem. Lett.* **1984**, 1097−1100; ref 35.
(25) Abbreviations used: BHT = 2,6-di-*tert*-butyl-1-hydroxy toluene, DMF = *N*,*N*-dimethylformamide, DIC = 1,3-diisopropylcarbodiimide.
(26) Dimethyl 2-hydroxy-2,2-diphenylethylphosphonate, CsF (3.5 equiv) and H_2O (3.5 equiv) in DMF at 55 °C for 16 h gave 83% olefin: Kawashima, T.; Ichii, T.; Inamoto, N. *Chem. Lett.* **1983**, 1375−1378; ref 35.
(27) Oxaphosphetane structures analogous to **9** have been isolated, some even by distillation. See refs 28 and 29.
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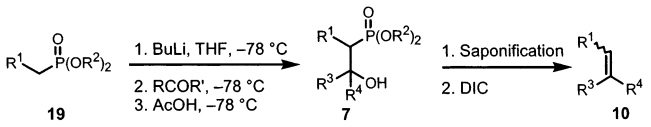
(30) Chloroform was found to be the ideal solvent, see Supporting Information.
(31) A similar observation was reported for DCC: Kawashima, T.; Nakamura, M.; Nakajo, A.; Inamoto, N. *Chem. Lett.* **1994**, 1843−1486.
(32) Mitsunobu conditions were equally effective, whereas other dehydration reagents were not: P_2O_5, PPh_3BrBr, and 2-chloro-*N*-methylpyridine iodide in the presence of Et_3N or 2,6-di-*tert*-butyl-4-methyl-pyridine.

Table 1. Phosphonate Alkylation, Saponification, and Elimination



entry	19	R^1	R^2	R^3COR^4	yield 7[a]	7	saponification[b]	yield 10[c]	10
1	**19a**	C_7H_{15}	Me	$PhCH_2CH_2CHO$	81%[b]	**7a**	A	55%	**10a**
2	**19a**	C_7H_{15}	Me	PhCHO	84%[b]	**7b**	A	59%	**10b**
3	**19a**	C_7H_{15}	Me	*c*HexCHO	42%	**7c**	B	54%	**10c**
4	**19a**	C_7H_{15}	Me	Et_2CO	60%	**7d**	A or B		**10d**
5	**19b**	H	Me	$PhCH_2CH_2CHO$	79%	**7e**	B	55%	**10e**
6	**19c**	H	Et	PhCHO	83%[b]	**7f**	B		**10f**
7	**19c**	H	Et	$PhCH_2CH_2CHO$	86%[b]	**7g**	B	75%	**10e**

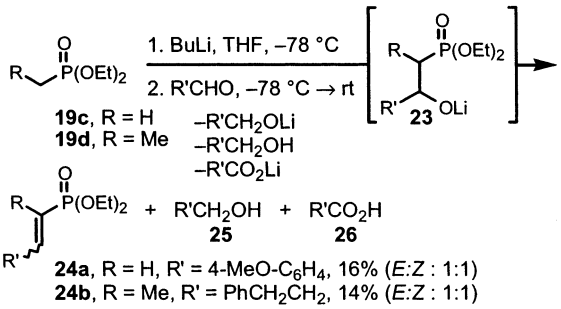
[a] Isolated yields. [b] Saponification methods: A, $MgBr_2$; B, NaOH. [c] Isolated yields for two steps.

but the alkylation was less efficient when β-branching was present (entry 3). Both the aromatic and the aliphatic β-hydroxy phosphonates underwent saponification and elimination equally well (entries 1−3). In contrast, ketone alkylation tended to be less efficient, and the reaction with 3-pentanone afforded the β-hydroxy phosphonate **7d** in 42% yield (entry 4). Moreover, the saponification of **7d** caused disconcerting substrate decomposition.[33] The alkylation of commercially available methyl dimethyl phosphonate **19b** or ethyl diethyl phosphonate **19c** with aliphatic or aromatic aldehydes gave >79% yield in each case (entries 5−7), but the user must be cautioned that the use of low molecular weight phosphonates can be complicated by poor solubility of the anion at low temperature. The reaction of ethyl diethylphosphonate **19c** (entries 6 and 7) illustrates that phosphonates easily accessible by Arbuzov[13] reaction can also be saponified for use in the coupling reaction. While alkylation of the lower molecular weight phosphonates proceeded without incident, the subsequent saponification proved problematic with benzylic β-hydroxy phosphonates (entry 6). From the table, it appears that in the absence of steric bulk or enolizable ketones, high reaction efficiency is observed in the alkylation step. However, these test substrates revealed that to avoid substrate decomposition with certain benzylic β-hydroxy phosphonates, milder saponification methods are required.[33]

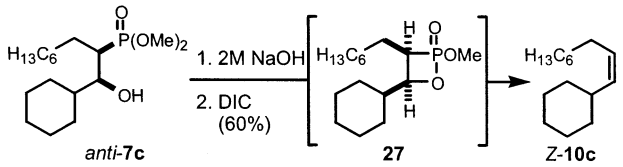
For efficient yields in the aldehyde or ketone alkylation reactions, it was necessary to perform the entire sequence at −78 °C, including the final addition of a proton source to neutralize the lithium alkoxide. At higher temperatures, Tischenko type products[34] were formed, along with vinylic phosphonates **24**,[16,35] especially with electron-rich aldehydes (Scheme 5). For example, with anisaldehyde, the redox products *p*-$MeOC_6H_4CH_2OH$ (**25**) and *p*-MeO $C_6H_4CO_2H$ (**26**) were isolated from reaction mixtures that were allowed to warm to room temperature prior to a protic workup.

In most instances, the β-hydroxy phosphonates were obtained as nearly 1:1 mixtures of syn and anti diastereomers. However, when the stereochemically pure anti diastereomer of **7c** was saponified and eliminated under the standard reaction conditions, the *Z* stereoisomer **10c** was formed exclusively (Scheme 6). This observation is consistent with formation of the oxaphosphetane

Scheme 5



Scheme 6



intermediated **27** followed by a stereospecific collapse to the olefin. Moreover, this method resembles the powerful Horner reaction in that the stereochemical purity of the olefin directly correlates with that of the intermediate β-hydroxy phosphonate that precedes the elimination. No detectable racemization occurred during the saponification, and the more easily handled diesters **7** can be separated instead of the highly hydrophilic phosphonic acids.

In summary, the first general method for the stereospecific dehydrative elimination of secondary, tertiary, and benzylic β-hydroxy phosphonates has been developed. The intermediate β-hydroxy phosphonates are fairly robust under neutral reaction conditions, which may allow them to be carried intact through a synthetic sequence before revealing the olefin. Alkyl dimethyl or diethyl phosphonates, accessible from Arbuzov or Michaelis−Becker reactions, can participate in the coupling reaction, and no special functionality on the β-hydroxy phosphonate is required for olefin formation.

Experimental Section[36]

Compound **19c** was obtained from commercial sources and distilled prior to use. Compounds **19a**,[37] **19b**,[37] and **19d**[37] were prepared according to literature procedures. Compounds **7** and **10** were prepared by one of the following general methods.

***β*-Hydroxy-phosphonic Acid Dialkyl Esters 7 from 19.** To a cooled (−78 °C) solution of **19** (0.80 mmol) in THF (2.5 mL) was added *n*-BuLi in hexanes (0.80 mmol). After being stirred at −78 °C for 15 min, the aldehyde (0.80 mmol) in THF (1 mL) was added. After 60 min at −78 °C, aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Purification by flash chromatography afforded **7** as a colorless oil.

Olefins 10 from 7. To a solution of **7** (1.1 mmol) in MeOH (5 mL) was added 4 M NaOH (5 mL). After being stirred at room temperature for 16 h, the reaction mixture was acidified to pH < 2 with 1 M HCl, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo. The reaction residue containing crude **20** was dissolved in $CHCl_3$ (5 mL) and treated with DIC (2.2 mmol), and after being stirred at room temperature for 4 h, the reaction mixture was concentrated in vacuo.

(33) The mild saponification of orthogonal protective groups will be reported elsewhere. See: Reichwein, J. F.; Pagenkopf, B. L. *J. Org. Chem.* **2003**, *68*, in press.
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(37) Prepared via Arbuzov reaction analogously to: Ford-Moore, A. H.; Perry, B. J. *Org. Synth. Coll. Vol. 4* **1963**, 325−327.

Purification of the residue by flash chromatography afforded **10** as a colorless oil.

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Supporting Information Available: Table of solvents tested for the elimination. Preparation and characterization data for **7**, **10**, and **19** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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