Tetrahedron Letters 54 (2013) 817-820

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet



The phosphorus-Claisen condensation

Laurent Gavara, Fabien Gelat, Jean-Luc Montchamp*

Department of Chemistry, Box 298860, Texas Christian University, Fort Worth, TX 76129, United States

ARTICLE INFO

Article history: Received 14 November 2012 Accepted 16 November 2012 Available online 2 December 2012

Keywords: 1,1-Bisphosphorus compound Phosphonate Phosphinate Claisen condensation

ABSTRACT

1,1-Bisphosphorus compounds are easily synthesized through the phosphorus-Claisen (phospha-Claisen) condensation between a phosphorus-stabilized anion and a phosphorus electrophile. The preliminary scope of this reaction is investigated in terms of employable phosphorus reagents. Valuable intermediates are conveniently prepared in a single step. Overall, the method is competitive with multistep procedures which require the preparation of PCI intermediates derived from the P(OR) reagents we instead employ directly, and it delivers complex organophosphorus compounds in moderate to good isolated yields. An example of the intramolecular version of the reaction, the phospha-Dieckmann condensation, is also reported.

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Because of our laboratory's continued efforts in the preparation of 1,1-bisphosphorus compounds,¹ we became interested in investigating the condensation between a phosphonate-stabilized anion and a phosphonate electrophile, a process analogous to the Claisen ester condensation. Because phosphorus compounds provide much more structural variety than their carboxylic ester counterparts, we decided to explore this reaction, and its generalized version: the phosphorus-Claisen condensation (heretofore referred to as 'phospha-Claisen').

Examination of the literature revealed surprisingly few examples of this reaction, always limited to the self-condensation of a phosphonate diester anion. In pioneering research nearly thirty years ago, Savignac and co-workers studied the thermal stability of various phosphonate diester α -anions (RO)₂P(O)CHLiR¹ and reported on their generally undesirable self-condensation (Eq. 1).² As in the classic Claisen condensation, the driving force is the formation of a stabilized anion with lower basicity. Further, realizing the potential of this type of intermediate, Savignac and co-workers also described some synthetic application through the Wadsworth–Horner–Emmons (WHE) olefination.²

$$2 \xrightarrow{\text{RO}, P}_{\text{RO}, P-\text{CHLi}}^{\text{O}} \xrightarrow{\Delta}_{\text{RO}, P}^{\text{O}, Q} \xrightarrow{Q}_{\text{RO}, P}^{\text{O}, Q} \xrightarrow{P}_{\text{CH}_2\text{RI}}^{\text{P}, \text{OR}} + \text{ROLi}$$
(1)

However, very little work has appeared concerning the use of the autocondensation products, except in the simplest case $(RO)_2P(O)CH_2P(O)(OR)CH_3$. For example, McClard³ reported the alkylation of $(RO)_2P(O)CHMP(O)(OR)CH_3$, and the corresponding

dianion $(RO)_2P(O)CHMP(O)(OR)CH_2M$.⁴ On the other hand, the condensation between a phosphonate anion and a P–Cl electrophile has been used more commonly to prepare various 1,1-bisphosphorus compounds.^{1b–d,5} Of course, this approach necessitates a reactive electrophile, which is either commercially/readily available R₂P(Y)Cl (Y = lone pair, O, BH₃, etc.), or requires prior synthesis of a chlorophosphonate R¹P(O)(OR)Cl from the corresponding phosphonate diester. Alternatively, another approach has been the Arbuzov or Michaelis–Becker reactions between P(O)CH₂X and P(OR)₃, or MOP(O)(OR)₂, respectively.^{1a,6}

Thus, it occurred to us that the general phospha-Claisen condensation between a nucleophile **1** and an electrophile **2** would be a convenient and powerful tool for the synthesis of methylene-1,1-bisphosphorus compounds **3** (Eq. 2), with enormous versatility in terms of substitution pattern and functional groups. Preliminary studies of the feasibility of the reaction are presented below.

$$\begin{array}{c} R^{4} \stackrel{\gamma}{I} \\ R^{2} \stackrel{P}{\xrightarrow{}} CH_{2}M \end{array} \xrightarrow[R^{4} \stackrel{\pi^{3}}{\xrightarrow{}} P^{-}OR \stackrel{2}{\xrightarrow{}} R^{1} \stackrel{\gamma}{\xrightarrow{}} \stackrel{Z}{\underset{R^{2}}{\xrightarrow{}} P^{-}R^{3}} \\ \begin{array}{c} 1 \\ then H_{3}O^{+} \end{array} \xrightarrow[R^{2} \stackrel{P}{\xrightarrow{}} R^{2} \stackrel{P}{\xrightarrow{}} R^{3} \\ \end{array}$$
(2)

Because the condensation product is a stabilized anion and alcohol, nucleophile **1** either needs to be used in excess, or the base to generate it must be present in at least two molar equivalents (Eq. 1). Based on this requirement and on Savignac's autocondensation studies, the first nucleophile we selected was $(i-\text{PrO})_2\text{P}(\text{O})$ -CH₂Li **1a**. This compound is generated easily from the deprotonation of the corresponding phosphonate with *n*-BuLi at low temperature.

Table 1 shows the results obtained for the condensation between **1a** and a range of phosphorus electrophiles **2**. Various



^{*} Corresponding author. Tel.: +1 817 257 6201; fax: +1 817 257 5851. *E-mail address:* j.montchamp@tcu.edu (J.-L. Montchamp).

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Table 1

Phospha-Claisen condensation between $(i-PrO)_2 P(O)CH_2 Li$ and some phosphorus electrophiles 2^a

	i-PrO∑B i-PrO∑P−CH₂L i-PrO 1a	$i \xrightarrow{R^{0} P - OR 2}{R^{2} P - OR 2} \xrightarrow{i PrO H R^{2}} P = OR 2$ - 78 °C to rt $i PrO H R^{2}$ then H ₃ O ⁺ 3	
Entry	Electrophile 2	Product 3	Isolated (³¹ P NMR) yield %
1	EtO = D = D = D = D $EtO = 2a$	OOU (i-PrO) ₂ P-Ph OEt 3a	71 (89)
2	$EtO = C_{14}H_{29}$ $EtO = C_{14}H_{29}$ $2b$	3a $O O O O O O O O O O O O O O O O O O O$	56 (75)
3	$EtO \stackrel{O}{\stackrel{H}{\rightarrow}} CF_2H$ $EtO \stackrel{O}{2c}$	$ \begin{array}{c} \mathbf{3b} \\ O \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \mathbf{c} \\ c$	80 (99) ^b
4	EtO EtO 2d	$(i+10)_2 i \bigvee 1_1 G i_2 i i_2$ OEt 3c $(i-PrO)_2 P \bigvee P - CH_2 OH$ OEt 3d O G G G G G G G G G G	76 (85) ^{b,c}
5	MeO ^O MeO ^P -CH ₂ OH MeO ² e	(<i>i</i> -PrO) ₂ P P-CH ₂ OAc	39 (56) ^d
6	$EtO = CH_2CH(OEt)_2$ $EtO = CH_2CH(OEt)_2$ $2f$	$3e$ $(i \cdot PrO)_2 P$ V $O = P$ $O = P$ $O = O$ $O = O$ $O = O$ $O = O$	52 (64)
7	BuO、Ü Ph [∕] P−CH₂OH 2g	(∔PrO)₂P̈́, P̈́−CH₂OH Ph	70 (82) ^e
8	Ph、P-OEt Ph ² 2h	3g O O (<i>i</i> -PrO)₂P P-Ph Ph 3h	66 (89)
9	MeO, P MeO 2i	$(i-PrO)_2 P \xrightarrow{P}_{i} P \xrightarrow{P}_{i} P(Oi-Pr)_2$ H 3i	10 (64)

^a General conditions: (*i*-PrO)₂P(O)CH₃ (2 equiv), *nBuLi* (2.2 equiv), THF, -78 °C, 1 h, then electrophile **2**, 1 h at -78 °C, then 2 h at rt. See Supplementary data for details. Product purity varies between 92% and 98+%.

^b Isolated without any chromatography.

^c (*i*-PrO)₂P(O)CH₃ (1 equiv), LDA (3.2 equiv), THF, -78 °C, 30 min, then electrophile **2d** (1.2 equiv), 30 min at -78 °C, then 4 h at rt. The isolated yield was adjusted to take into account the presence of a small amount of starting materials.

^d The crude mixture was quenched with AcOH and treated with TsCl (2 equiv), *i*-Pr₂NEt (3 equiv), CH₂Cl₂, rt 16 h.

^e *n*BuLi (3.3 equiv).

phosphonate diesters **2** reacted in good to high yields (entries 1–3), and as expected the more activated electrophiles (electronwithdrawing group on the phosphorus atom in **2**) gave higher yields (entries 1 and 3, vs entry 2). Compound **3c** was isolated in good purity without the need for chromatographic purification.

Diethyl (hydroxymethyl)phosphonate also reacted successfully, provided an additional equivalent of base is employed in order to deprotonate the alcohol functionality in **2d** (entry 4). Although **3d** is contaminated with a small amount of reagents, it was obtained without chromatography. Compounds related to **3d** have been prepared before but through lengthy and cumbersome synthetic sequences via chlorophosphonate BnOCH₂P(O)(OEt)Cl, or phosphonite (RO)₂P(Y)CH₂P(OR)₂ (Y = lone pair, O).⁷ Various compounds with the general structure (RO)₂P(O)CH₂P(O)(OR)CH₂OR¹ have been used in the synthesis of biologically active compounds.

Our method circumvents the need for protection of the alcohol and for the preparation of chlorophosphonate (or a structurally complex phosphonite) and should be useful for a variety of applications using **3d**.

A similar reaction with acetic acid as the quenching reagent and in the presence of tosyl chloride gave acetate **3e** directly, albeit in moderate yield (entry 5). Interestingly, diethyl (2,2-diethoxy)ethylphosphonate **2f** underwent condensation with concomitant elimination of ethoxide producing 2-ethoxyvinyl phosphinate **3f** (entry 6). This type of functionality is known to be versatile toward nucleophilic addition and other functionalization.⁸

Other phosphorus electrophiles can also be employed: (hydroxymethyl)phosphinate **2g** gave the corresponding product **3g** in good yield (entry 7), whereas phosphinate **2h** gave phosphine oxide **3h** (entry 8). Reaction with dimethyl H-phosphonate Download English Version:

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