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Aryl H-Phosphonates. 7. Studies on the Formation of Phosphorus-Carbon Bond in the Reaction of Trityl and Benzyl Halides with Dialkyl and Diphenyl H-Phosphonates

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Abstract: The reactions of H-phosphonate diesters with trityl and benzyl halides were investigated using ^{31}P NMR spectroscopy. It was found that extensive oxidation, which usually accompanies the formation of trityl- or *p*-nitrobenzylphosphonates from the corresponding alkyl bromides in the Michaelis-Becker reaction, can be considerably suppressed or completely eliminated by reacting *p*-nitrobenzyl or trityl bromides with diphenyl H-phosphonate in acetonitrile in the presence of DBU.

INTRODUCTION

Although phosphorus compounds containing the P–C bond are not particularly abundant in nature, their diverse biological activity[1,2] has for a long time attracted considerable synthetic[3] and pharmacological interest[4].

A primary rationale of using C-phosphonates as analogues of natural phosphates lies in the fact that, due to the presence of the P–C bond, these compounds are usually resistant to enzymatic hydrolysis under conditions used for cleavage of phosphate esters[3]. Despite this favourable property, C-phosphonate derivatives of natural products are less frequently used in biological studies than other phosphate analogues, mainly due to difficulties in their preparation[3].

For the formation of the P–C bond the most common approaches are probably those involving Michaelis-Arbuzov[5,6] and Michaelis-Becker[7] reactions. They make use of nucleophilic properties of tervalent P(III) compounds (*e.g.* trialkyl phosphites or alkali metal salts of dialkyl phosphites), which react with alkyl halides to produce the corresponding alkylphosphonate derivatives. Due to mildness of the reaction conditions, the choice of trialkyl *vs* dialkyl phosphite derivatives, is often resolved in favour of the latter one[8] (*i.e.* a Michaelis-Becker reaction).

Although a Michaelis-Becker reaction is quite a general one, it usually fails with tertiary alkyl halides[9,10] or with substrates having pseudohalide[11] character, *e.g.* with *p*-nitrobenzyl bromide[12,13], triphenylmethyl bromide[14], bromomalonate[15], *etc*[16]. With the latter type of substrates, complicated mixtures of products are often formed with no (or very little) compounds containing P–C bonds. Rachoń *et al.*[12,13,16-18] have delineated the mechanism of these "unusual" Michaelis-Becker reactions and showed, that they usually consist of X-philic substitution on bromine, followed by a single-electron transfer (SET mechanism) from the produced carbanion to the appropriate alkyl bromide. The latter process results in the formation of various products depending on stoichiometry and the chemical nature of the substrates used. Although compounds with P–C bonds can also be formed *via* this pathway, this usually requires a high concentration of a phosphite anion (ca 10 molar excess) to efficiently capture the generated alkyl radicals[13].

Considering the biological and synthetic importance of organophosphorus compounds, we investigated as part of our studies on aryl H-phosphonates as synthetic intermediates[19-21] the possibility to overcome some of the above limitations of the Michaelis-Becker reaction. For this purpose we embarked on exploration of diphenyl H-phosphonate/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) reagent system as a source of a phosphite anion. There were two main rationales behind this. Firstly, higher acidity of the P–H bond in aryl *vs* alkyl H-phosphonates, should make it possible to generate the corresponding diaryl phosphite anions in an appreciable concentration in the presence of DBU and this would alleviate problems connected with the preparation of alkali metal salts of the phosphite diesters[8]. Secondly, due to the presence of two aromatic rings, diaryl phosphite anions should be less susceptible to oxidation (X-philic substitution) and thus S_N2 attack on the sp^3 carbon of alkyl halides to produce C-phosphonates may become the predominant process. We tried to verify the validity of these assumptions by monitoring the formation of the P–C bond under various reaction conditions using ^{31}P NMR spectroscopy. To make a reliable inventory of phosphorus compounds formed in these reactions (C-phosphonate formation *vs* oxidation due to a possible attack on a bromine centre), equimolar amounts of H-phosphonates and alkyl halides were used in all instances.

RESULTS AND DISCUSSION

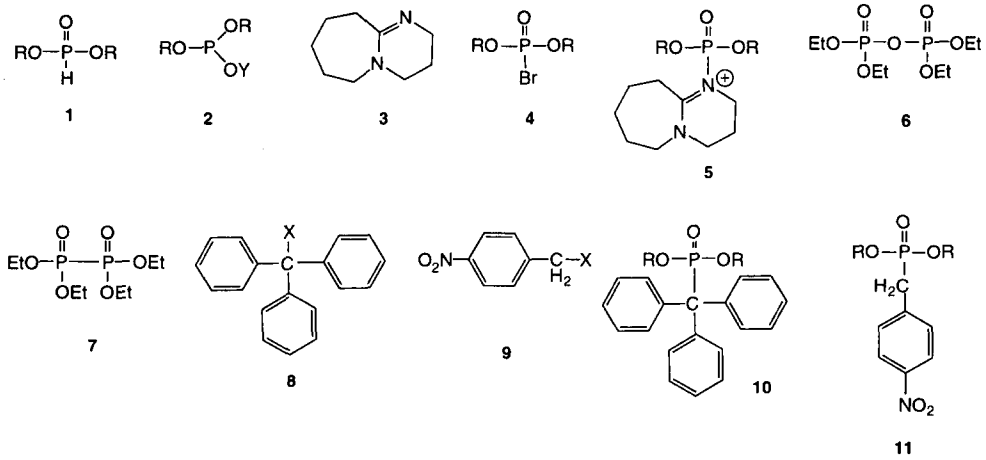
For these studies we chose two alkyl halides, for which the unusual course of a Michaelis-Becker reaction is best documented, namely, triphenylmethyl bromide[14] (trityl bromide, **8b**) and *p*-nitrobenzyl bromide (**9b**)[12,13]. In reactions of these substrates with equimolar amounts of sodium dialkyl phosphites in THF exclusive nucleophilic attack on bromine (X-philic substitution) with no detectable formation of the P–C bond was observed. As reference compounds we used the corresponding chlorides **8a** and **9a**, which are known to react with dialkyl phosphite anions in the expected way, albeit yields of the produced C-phosphonates[14,17], particularly those for the benzyl derivatives, are usually modest (~20%)[17].

Reaction of diethyl H-phosphonate 1a with alkyl halides in the presence of DBU.

To compare the H-phosphonate diester/DBU + alkyl halide reagent system to that of the standard Michaelis-Becker reaction (alkali metal salt of a phosphite diester + alkyl halide), we checked the reactivity of diethyl H-phosphonate towards trityl halides under various experimental conditions. When equimolar

amounts of diethyl H-phosphonate **1a** and trityl chloride **8a** were allowed to react overnight in THF in the presence of 2 equiv. of DBU (**3**), ^{31}P NMR spectroscopy revealed only the presence of the unchanged substrate **1a**. In a similar experiment of sodium salt **2a** with **8a** in THF, formation of the following major species could be detected (^{31}P NMR) in the reaction mixture: unreacted **1a** (~26%), diethyl tritylphosphonate **10a** (~19%), ethyl phosphate (~30%), diethyl phosphate (~10%), tetraethyl hypophosphate 7[22] (~10%).

Scheme 1



1a, 4a, 5a, 10a, 11a, R = Et
1b, 4b, 5b, 10b, 11b, R = Ph

2a R = Et; Y=Na$^+$
2b R = Ph; Y=DBUH$^+$

2c R = Ph; Y=Na$^+$
8a, 9a, X = Cl

8b, 9b, X = Br

In contradistinction to this, trityl bromide **8b** in the reaction of **1a**/ 2 equiv. DBU or with **2a** in THF afforded predominately (>95%) products originated from oxidation of the phosphorus reagent. Rachoń *et al.*[12,13,16-18] postulated, that the initial process in this type of reactions involves X-philic substitution on bromine to produce the corresponding bromophosphate **4**, but no direct evidence for the intermediacy of the latter was provided[23]. We tried to address this issue by reacting **1a** with **8b** in the presence of variable amounts of DBU and monitoring progress of the reaction by ^{31}P NMR spectroscopy. The addition of 0.5 equiv. of DBU to the equimolar amounts of **1a** and **8b** in THF triggered the clean appearance of a singlet at -8.6 ppm (~12%), which on the basis of its chemical shift, the splitting pattern in the P–H coupled spectrum, and by spiking the mixture with an authentic sample of **4a**, was assigned to the expected diethyl bromophosphate. Incremental addition of more DBU (2 equiv.) caused the replacement of the resonance at -8.6 ppm by a singlet at 4.9 ppm, which intensity was gradually increased with time. Since a singlet at 4.9 ppm was formed as an exclusive resonance in the reaction of bromophosphate **4a** or diethyl chlorophosphate in THF with 1-2 equiv. of DBU, we assigned it to the complex **5**. Although DBU has usually been considered as a non-nucleophilic strong base[24], these results and some recent literature reports[25,26] make such an assumption no longer tenable.

Extensive oxidation of phosphorus reagents during the course of a Michaelis-Becker reaction involving trityl or *p*-nitrobenzyl bromides in THF is most likely due to the presence of a partial positive charge on the

bromine. This, and the possibility of forming a resonance-stabilized trityl or *p*-nitrobenzyl anion, facilitates nucleophilic attack on bromine. One can argue, that in polar aprotic solvents a polarization of the carbon-bromine bond should generate a partial negative charge on the halide, and thus retards oxidation. Indeed, in the reaction of sodium salt **2a** with trityl bromide **8b** in acetonitrile, a significant suppression of the oxidation of **2a** and a considerable increase in the P–C bond formation (**10a**, ~40%) was observed. In this solvent, also diethyl H-phosphonate **1a** in the presence of 5 equiv. DBU was found to be completely resistant to oxidation by **8b** (48 h, ^{31}P NMR spectroscopy), in contradistinction to the analogous reaction in THF (*vide supra*).

Stability of diphenyl H-phosphonate 1b in acetonitrile in the presence of DBU.

Recently, we have reported that diphenyl H-phosphonate under anhydrous reaction conditions undergoes a base-promoted disproportionation[20] to triphenyl phosphite and phenyl H-phosphonate. Since this reaction is fast[20,27] and may impose some limitations on possible applications of diphenyl H-phosphonate as a substrate in Michaelis-Becker reactions, it was essential to evaluate stability of **1b** in acetonitrile and THF in the presence of DBU.

When 1 equiv. of DBU was added to **1b** in acetonitrile a broad singlet, assigned to diphenyl phosphite anion[28], appeared at ~139 ppm (40%) (first spectrum, ca 5 min). This signal sharpened and became the major one (ca 75%) when 5 equiv. of DBU was used for the reaction. Its intensity gradually decreased (after 1.5 h 20% still present), while those from the disproportionation products[20] (singlets at 129.7 and -1.1 ppm) increased. The latter process seemed to be somewhat slower than that when 0.25-0.5 equiv. of DBU was used. In THF the disproportionation of **1b** was found to be faster (~90% completion after 10 min in the presence of 5 equiv. of DBU) than in acetonitrile.

The above results can be rationalized as follows. In acetonitrile there is a slow equilibrium between **1b** and its $DBUH^+$ salt **2b**. It is shifted to the right with the increasing concentration of DBU (~0.1 - 0.75 M) and this, apparently, also increases the rate of exchangeof the protonated amine moiety in **2b** (sharpening of the resonance at ~139 ppm). Since disproportionation of **1b** , according to the previously proposed mechanism[20], occurs *via* an attact of the corresponding phosphite anion on the phosphonate centre in **1b**, its rate should be at maximum with equal concentration of both species. Formation of considerable amounts of the salt **2b** depletes concentration of the phosphonate **1b**, and thus, the disproportionation reaction may proceed slower. This interpretation was supported by experiments involving sodium salt **2c**, generated from diphenyl H-phosphonate and sodium hydride. The salt **2c** was stable both in acetonitrile and in THF (~25% disproportionation after overnight), however, the addition of equimolar amounts of **1b** to the reaction mixtures containing salt **2c** resulted in fast disproportionation (completion within ca 50 min in THF).

Reaction of diphenyl H-phosphonate 1b with alkyl halides in the presence of DBU.

To assess the synthetic utility of diphenyl H-phosphonate **1b** for the purpose of the P–C bond formation, we investigated the efficiency of trityl- and *p*-nitrobenzylphosphonates formation (**10b** and **11b**, respectively) under various reaction conditions. First, equimolar amounts of trityl halides **8a** or **8b** and diphenyl H-phosphonate **1b** were reacted separately in THF and in acetonitrile, in the presence of DBU (2

equiv.). In THF, trityl chloride **8a** did not afford any detectable amounts of the C-phosphonate **11b** (overnight reaction, see Table 1). The formation of only triphenyl phosphite and phenyl H-phosphonate (^{31}P NMR) indicated, that apparently under the reaction conditions the disproportionation of **1b** was significantly faster than the reaction of the phosphite anion **2b** with halide **8a** to produce the P–C bond. In contradistinction to this, the reaction in acetonitrile furnished rapid and clean formation of trityl phosphonate **10b** (> 90%, 5 min). Other products detected in the reaction mixture (^{31}P NMR) were only those due to disproportionation of **1b**.

The reaction of trityl bromide **8b** with **1b**/DBU reagent system in THF was rapid, but afforded predominately the oxidation products of **1b** (~80%) together with triphenyl phosphite (<10%), and small amounts of tritylphosphonate **10b** (<10%). Similarly to the reaction of **1a**/DBU with **8a** in THF (*vide supra*), also in this instance the initial step involved, most likely, X-philic attack on the bromine centre, as it was apparent from the presence in the ^{31}P NMR spectrum a predominant signal at ~-4.8 ppm, assigned to the adduct **5b**[29]. Under analogous reaction conditions in acetonitrile, however, very clean and fast formation of the tritylphosphonate **10b** was observed (> 98%). No traces of the oxidation or disproportionation products of **1b** could be detected (^{31}P NMR) in the reaction mixture.

As to a possible role of DBU in the suppression of oxidation of **1b** during the formation of tritylphosphonate **10b** from bromide **8b**, some further observations are pertinent. Trityl bromide **8b** is poorly soluble in acetonitrile, however, its solubility markedly increased when 1 mole equiv. of DBU was added. This may indicate the formation of a complex or an onium salt of **8b** and DBU, in which the base is neutralized. In agreement with this, upon addition of diphenyl H-phosphonate **1b** (1 equiv.) to such a mixture, neither disproportionation nor tritylphosphonate **10b** formation was observed (^{31}P NMR, 24 h). As expected, however, another equivalent of DBU triggered fast and clean formation of the C-phosphonate **10b**. Since in an onium salt of **8b** and DBU, bromine plays a role of a counter anion, it is not any more susceptible to X-philic substitution. Thus, the observed differences in the course of the reaction of **1b**/DBU and **8b** in THF *vs* acetonitrile can be explained (at least partly) by different degree of complexation occurring in these solvents. Most likely, the equilibrium onium salt ⁻ DBU + **8b**, is to the right in THF while in acetonitrile, it is significantly shifted to the left. Formation of considerably stronger complexes of DBU in acetonitrile, compared to those in THF, was recently reported for some tervalent P(III) compounds[25].

Somewhat surprisingly, the reaction of *p*-nitrobenzyl bromide **9b** with **1b**/ 2 equiv. DBU reagent system, was found to be rather insensitive to the nature of the solvent used. It proceeded smoothly in acetonitrile or in THF to the benzylphosphonate **11b** as the major product (5 min, ~90%). In both instances, the oxidation and disproportionation of **1b** did not exceed 10% (^{31}P NMR). The reaction of *p*-nitrobenzyl chloride **9a** with **1b**/ 2 equiv. DBU in acetonitrile was slower than that of the bromide **9b**, and consequently, together with the desired C-phosphonate **11b** (~70%, 10 min), significant amounts of the disproportionation products (~30%) were also formed. Similar results were obtained in THF as a solvent (see, Table 1).

Although **9a** and **9b** in the reaction with **1b**/ 2 equiv. DBU reagent system produced **11b** as the sole P–C containing product (the ^{31}P NMR spectra acquired after 5-10 min), we noticed that the latter was partially unstable in acetonitrile, as inferred from gradual changes occurring in the reaction mixtures (^{31}P NMR).

However, when the amount of DBU used for the reaction was reduced to 1-1.2 equiv., the produced *p*-nitrobenzylphosphonate **11b** was completely stable and did not undergo any subsequent transformations (24 h, ^{31}P NMR)[30]. It is worth noting that the analogous reactions in THF with limited amounts of DBU were significantly less efficient and produced only 5-10% of the desired C-phosphonate **11b**.

Table 1. *Summary of the reactions of H-phosphonates* **1** *with alkyl halides under various experimental conditions.*

Reagent system	Trityl chloride **8a**		Trityl bromide **8b**		*p*-Nitrobenzyl chloride **9a**		*p*-Nitrobenzyl bromide **9b**	
	THF	CH_3CN	THF	CH_3CN	THF	CH_3CN	THF	CH_3CN
1a/DBU	(a)	(a)	(c)	(a)	(d)	(d)	(d)	(d)
1b/DBU	(b)	**10b** (>90%)	(c)	**10b** (>98%)	**11b** (~60%)[e]	**11b** (~70%)[e]	**11b** (>90%)	**11b** (>90%)

In all instances, equimolar amounts of phosphorus reagents (**1**) and alkyl halides (**8**, **9**) in the presence of 2 equiv. of DBU were used. Compositions of the reaction mixtures were evaluated using ^{31}P NMR (see also the Experimental Part). [a] No oxidation of **1a** nor the P–C bond formation (24h). [b] Disproportionation of **1b**, only (10 min). [c] Exclusively oxidation of the phosphorus reagent occurred (24h). [d] Only oxidation of the phosphorus reagent (10-30%, 24h). [e] The rest constituted products of the disproportionation and hydrolysis of **1b** by spurious water (10 min).

In conclusion, these studies indicate that the scope of the Michaelis-Becker reaction can be broadened to encompass pseudohalide substrates, by using aryl H-phosphonates/DBU system as a source of phosphite anions. Solvent often exerts considerable influence on the course of a Michaelis-Becker reaction, irrespective of the reagent system used. Tetrahydrofuran, a common solvent for this reaction, usually promotes oxidation of a phosphite anion *via* X-philic substitution on a partially positive halides (pseudohalide substrates), while acetonitrile tends to favour the nucleophilic attact on a carbon centre of alkyl halides to produce the desired C-phosphonate derivatives. DBU was found to be an indispensable component of the reagent system. It, apparently, plays a dual role in the Michaelis-Becker reaction, acting both (i) as a base to generate the appropriate phosphite anion from the phosphorus reagent and (ii) as a nucleophile, that modulate properties and reactivity of the alkyl halides used.

EXPERIMENTAL PART

Reactions were carried out in 10-mm NMR tubes and spectra were recorded on a Jeol GSX-270 FT spectrometer. For ^{31}P NMR experiments 2% H_3PO_4 in D_2O was used as external standard (coaxial inner tube). The values of the chemical shifts for the intermediates produced *in situ*, in some experiments varied (±1 ppm) depending on the reaction conditions. A systematic trend of shifting ^{31}P NMR resonances to the lower field (~1.5-2 ppm) was observed upon changing the solvent from THF to acetonitrile.

Acetonitrile (Merck) was made anhydrous by storing over molecular sieves (4Å). Tetrahydrofuran (Merck) was refluxed over $LiAlH_4$ and freshly distilled before use. Diethyl H-phosphonate, diphenyl H-phosphonate, trityl chloride, trityl bromide (all from Aldrich), *p*-nitrobenzyl chloride (BDH), and *p*-nitrobenzyl bromide (Lancaster) were commercial grade. DBU (Aldrich) was distilled before use.

The reference compounds **4**, **5**, **7**, **10b**, and **11b**, which have been used for the identification of some of the reaction products, were produced as follows. Diethyl bromophosphate **4a** was produced from equimolar amounts of triethyl phosphite and bromine in THF[31]; diphenyl bromophosphate **4b**, analogously, from equimolar amounts of diphenyl H-phosphonate **1b** and bromine in THF, in the presence of triethylamine (1.2 equiv.). The DBU adducts **5a** and **5b**, were formed *in situ* by the addition of equimolar amounts of the base to

the corresponding bromophosphates (**4a** and **4b**) or similarly from diethyl and diphenyl chlorophosphates, respectively. Diethyl hypophosphate **7** was produced as described by Stec *et al.*[32] from **2a** (2 equiv) and

Table 2. *^{31}P NMR data of some H-phosphonates, phosphites, C-phosphonates*[a]

Cmpd	δ (ppm)	$^1J_{PH}$ (Hz)	$^3J_{PH}$ (Hz)	Cmpd	δ (ppm)	$^1J_{PH}$ (Hz)	$^3J_{PH}$ (Hz)
1a	8.37	692.2	8.3 (q)	**5a**	4.91	-	(m)
1b	2.10	741.0	-	**5b**	-4.82[b]	-	10.2 (t)
2a	150.8[b]	-	(m)	**6**	-12.51[a]		8.13[c]
2b	139.00	-	(m)	**7**	7.29[b]	-	(m)
2c	148.90	-	-	**10a**	25.97[b]	-	7.3 (q)
4a	-8.65	-	10.2 (q)	**10b**	19.47	-	-
4b	-16.42	-	-	**11b**	19.51	-	22.0 (t)

[a] Spectra in acetonitrile. 2% H_3PO4 in D_2O as an external reference; [b] Spectra in THF; [c] Calculated for the spin system AA'X4X'4, $^2J_{PP}$ = 15.03 and $^5J_{HP}$ = 0.44 Hz; t = triplet; q = quintet; (m) broad, not fully resolved multiplet.

diethyl chlorophosphate in THF. The reaction mixture contained **7**, along with roughly equivalent amounts of tetraethyl pyrophosphite, monoethyl and diethyl H-phosphonate and unreacted **2a** (^{31}P NMR). Diphenyl tritylphosphonate **10b** was obtained in the reaction of equimolar amounts the sodium salt **2c** and trityl chloride **8a**, followed by silica gel chromatography. Diphenyl *p*-nitrobenzylphosphonate **11b**, was obtained analogously to the phosphonate **10b** using *p*-nitrobenzyl chloride **9a** and **2c**.

Stability of diphenyl H-phosphonate **1b** in acetonitrile in the presence of DBU.

1b (0.25 mmol) was dissolved in acetonitrile (1.8 mL) and DBU (0.25 - 5 equiv.) was added. Progress of the reaction was followed by ^{31}P NMR spectroscopy (for the results, see in the text).

Reactions of diphenyl H-phosphonate **1b** with alkyl halides **8** or **9**.

1b (0.25 mmol) and the alkyl halides **8a**, **8b**, **9a** or **9b** were dissolved in the appropriate solvent (1.8 mL, acetonitrile or THF) and DBU (1-2 equiv., or as stated in the text) was added. Progress of the reaction was followed by ^{31}P NMR spectroscopy. In all reactions involving *p*-nitrobenzyl halides coloration of the reaction mixtures (pink red in acetonitrile and yellow in THF) was observed. The colors developed immediately upon the addition of DBU, and underwent gradual changes to become light brown after ca 1 h.

The produced diphenyl tritylphosphonate **10b** and diphenyl *p*-nitrobenzylphosphonate **11b** from selected experiments were isolated and found to be identical (^1H, ^{13}C and ^{31}P NMR) with the corresponding authentic samples obtained on another routes (*vide supra*).

Diphenyl tritylphosphonate **10b**, ^1H NMR ($CDCl_3$, δ in ppm): 6.6 - 7.5 (m, aromatic protons); ^{13}C NMR, ($CDCl_3$, δ in ppm): 63.8 (d, 135.6 Hz), 120.8 (d, 3.6 Hz), 125.1, 127.5, 128.2, 129.4, 130.9 (d, 7.4 Hz), 140.8 (d, 5.5 Hz), 150.7 (d, 11.0 Hz); ^{31}P NMR data (see Table 2).

Diphenyl *p*-nitrobenzylphosphonate **11b**, ^1H NMR ($CDCl_3$, δ in ppm): 8.19 (d, ^3J = 8.1 Hz, 2H), 7.56 (dd, ^3J = 8.1 Hz, $^4J_{PH}$ = 2.5 Hz, 2H), 7.04 - 7.32 (m, 10H), 3.60 (d, $^2J_{PH}$ = 22.4 Hz, 2H); ^{13}C NMR, ($CDCl_3$, δ in ppm): 33.8 (d, 149.3 Hz), 120.2 (d, 3.7 Hz), 123.9, 125.5 129.9, 130.9 (d, 7.4 Hz), 138.3 (d, 9.1 Hz), 147.4 (d, 3.7 Hz), 150.0 (d, 9.1 Hz); ^{31}P NMR data (see Table 2).

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27. In acetonitrile in the presence of TEA (15 equiv.) the disproportionation of **1b** goes to completion within few minutes.
28. To the present time, only formation of alkali metal salts of H-phosphonate diesters have been reported. The absence of detectable P–H couplings prevents more detail NMR analysis of the signal at ~139 ppm. However, the value of its chemical shift and the observed reactivity of a species that gave rise to it, are in agreement with the postulated structure **2b**.
29. The bromophosphate **4b** is not stable under the reaction conditions and undergoes some further transformations. However, the pattern of resonances in the reaction mixture paralleled those produced upon treatment of an authentic sample of **4b** with DBU. In the initial stages of the latter reaction, the formation of a singlet at ~-4.8 ppm, assigned to **5b**, was observed. As expected, an analogous signal was also detected upon treatment of diphenyl phosphorochloridate with DBU in THF.
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