An Effective Borate-Mediated Approach to 1-Trifluoromethyl-1-hydroxy-3-ketophosphonates, Phosphinates, and Phosphine Oxides

Dmitrii L. Chizhov,*[a] Vera Vogel,[b] Sergey N. Tverdomed,[b] Valery N. Charushin,[a] Gerd-Volker Röschenthaler[b]

[a] I. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, GSP-147, Russia
Fax +7(343)3693058; E-mail: dlchizhov@ios.uran.ru

[b] School of Engineering and Science, Jacobs University Bremen, P.O. Box 750561, 28725 Bremen, Germany

Received 27 January 2011

Abstract: Ethyl 1-trifluoromethyl-1-hydroxy-3-oxo-phosphonates, the related (methyl)phosphinates and (phenyl)phosphinates, and phosphine oxides were obtained in good yield via direct phosphonylation of acyltrifluoroacetones with diethyl phosphite, ethyl (methyl)phosphonite, ethyl (phenyl)phosphonite, and diphenylphosphine oxide in the presence of triethyl borate. The subsequent dehydration of the selected phosphonates and phosphinates proceeds smoothly affording previously unknown diethyl 1,2-unsaturated 1-trifluoromethyl-3-oxophosphonates, ethyl 1-trifluoromethyl-3-oxo(methyl)-, and ethyl 1-trifluoromethyl-3-oxo(phenyl) phosphinates in good yields.

Key words: acyltrifluoroacetones, phosphonylation, triethyl borate, fluorinated phosphonate, fluorinated phosphinate, fluorinated phosphine oxides

Dialkyl 1-hydroxyphosphonates and related alkyl 1-hydroxyphosphinates are esters of 1-hydroxyphosphonic (phosphinic) acids which constitute a prominent group of organophosphorus compounds that could be found in nature and exhibit attractive biological properties. They are very potent inhibitors of enzymes such as renin,[1] human immunodeficiency virus (HIV) protease, and polymerase.[2] They have also been reported to possess antiviral[3] and antitumor[4] activity. Therefore the design of α-hydroxyphosphonates and their derivatives are of practical importance.

From this point of view, 1-hydroxy-3-ketophosphonates **1** (Figure 1) seem to be precursor for tailor-made compounds due to the presence of the versatile carbonyl group. Moreover, the aldol (1-hydroxy-3-keto) fragment is rather common in the structure of nonaromatic polyketide metabolites.[5]

On the other hand, fluoro-containing phosphonates are important, taking into account the well-known influence of fluorine or fluorinated groups in organic molecules on their physical, chemical, and biological properties.[6] Thus, the development of useful methods for the synthesis of fluorine-containing phosphonates is of interest for the synthesis of potentially bioactive substances.[7]

Methods for nonfluorinated phosphonates with separated 1-hydroxyphosphonate and 3-ketophosphonate units are well developed.[8] Pudovik and phospha-Michael reactions can be correspondingly used. However, reports on the synthesis of 1-hydroxy-3-ketophosphonates and their properties are scarce. Though, an effective approach to these compounds via a novel cross aldol reaction of acylphosphonates (α-ketophosphonates) and ketones has been recently reported.[9]

As far as fluorinated 1-hydroxy-3-ketophosphonates **2** (Figure 1, $R^3 = R^4 = OAlk$) are concerned, it has been shown that these compounds can be the product of phosphonylating fluorinated 1,3-diketones with *O*-trimethylsilyl-substituted phosphites.[10] Nevertheless, the given moisture sensitivity of these phosphorus reagents, the application of dialkyl phosphites in this reaction, seems to be more attractive. However, there is only one report on the reaction of dialkylphosphites with the highly reactive hexafluoroacetylacetone.[11]

In the view of the possible biological activity of fluorine-containing phosphonates and as an extension of our continuing synthetic studies on the reactivity of R^F-containing di- and polycarbonyl compounds, and their derivatives,[10–12] we have focused our attention on 1-R^F-1-hydroxy-3-ketophosphonates **2** ($R^1 \neq R^F$). Despite their potential interest as a promising building block for the construction of more complex fluorine phosphorus containing compounds, they have not received much attention, probably owing to the lack of general methods for the synthesis of these compounds.

1 2

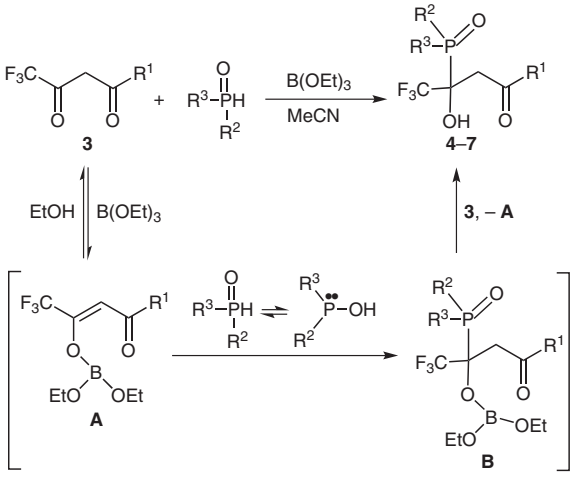
Figure 1 1-Hydroxy-3-ketophosphonates **1** and target 1-R^F-1-hydroxy-3-ketophosphonates **2**

This prompted us to develop a new general and efficient method for the preparation of 1-R^F-1-hydroxy-3-ketophosphonates **2** as useful precursors of a wide variety of tailor-made phosphonates with fluoroalkyl groups. We reasoned that 1,3-diketones bearing both fluorinated and nonfluorinated terminal substituents would directly react with dialkylphosphites and related phosphorus reagents as it has been shown for hexafluoroacetylacetone.[11] However, to the best of our knowledge, no data of such a reaction has been reported.

SYNLETT 2011, No. 12, pp 1735–1739
Advanced online publication: 05.07.2011
DOI: 10.1055/s-0030-1260935; Art ID: B02811ST

In this communication, we wish to report the successful approach to ethyl esters of 1-trifluoromethyl-1-hydroxy-3-oxo-phosphonates **4a–g**, (methyl)phosphinates **5a–c**,**e–g**, (phenyl)phosphinates **6a–c**,**f**,**g**, and tertiary diphenylphosphine oxides 7**a**,**c**,**d**,**g** involving the direct phosphonylation of acyltrifluoroacetones **3** with diethyl phosphite, ethyl (methyl)phosphonite, ethyl (phenyl)phosphonite, and diphenylphosphine oxide, and the subsequent dehydration of the selected phosphonates and phosphinates to the corresponding unsaturated ketophosphonates **8a–c** and phosphinates **9a–c** and **10a–c**.

We have found that phosphonylation of benzoyltrifluoroacetone (**3a**) with diethyl phosphite occurred in acetonitrile solution in the presence of 3–5 mol% of triethyl borate at ambient temperature affording diethyl 1-trifluoromethyl-1-hydroxy-3-oxo-phosphonate (**4a**) as the sole product (Scheme 1, $R^2 = R^3 = OEt$). The conversion of the diketone was ca. 100% (based on the ^{19}F NMR spectrum) in 3 days, when at least a three-fold excess of diethyl phosphite was used (Table 1, entry 1). Increasing the triethyl borate content up to one equivalent accelerated the reaction but had no influence on the essential amount of the phosphorus reagent (Table 1, entry 2). However, when an acetonitrile solution of **3a**, diethyl phosphite, and triethyl borate in the ratio 1:1.1:1.1 was refluxed for 2 days, phosphonate **4a** was obtained in ca. 100% NMR and 78% isolated yield (Table 1, entry 3). It should be noted, that in the absence of borate the phosphonylation did not occur at all.



R^1 = Ph (**a**), 4-$O_2NC_6H_4$ (**b**), 2-thienyl (**c**), 4-$EtOC_6H_4$ (**d**), Me (**e**), Et (**f**), *t*-Bu (**g**)
R^2, R^3 = EtO, EtO (**4**); Me, EtO (**5**); Ph, EtO (**6**); Ph, Ph (**7**)

Scheme 1 Triethyl borate mediated reaction of acyltrifluoroacetones **3** with derivatives of phosphorous, phosphonous, and phosphinous acids

The most suitable conditions (Table 1, entry 3) were used to react diketones **3b–g** with diethyl phosphite, and phosphonates **4b–g** were obtained (Table 1, entries 4–9).[13] When ethyl (methyl)phosphonite reacted with diketones **3a–c**,**e–g** under the found conditions (Scheme 1, $R^2 = OEt$, $R^3 = Me$), the expected ethyl 1-trifluoromethyl-1-hydroxy-3-oxo-(methyl)phosphinates **5a–c**,**e–g** were isolated in good yields (Table 1, entries 12–17). Phosphonylation of diketones **3a–c**,**f**,**g** with ethyl (phenyl)phosphonite gave rise to the corresponding ethyl 1-trifluoromethyl-1-hydroxy-3-oxo-(phenyl)phosphinates **6a–c**,**f**,**g** (Table 1, entries 18–22). However, a greater amount of the phosphorus reagent (1.5 equiv) was required for completeness of the reaction that is likely to be due to its reduced nucleophilicity. Thus, reaction of diketones **3a**,**c**,**d**,**g** with less nucleophilic diphenylphosphine oxide was completed in the presence of two equivalents of this reagent to afford the corresponding phosphine oxides **7a**,**c**,**d**,**g** in 60 hours (Table 1, entries 23–26).

In accord to the ^{19}F NMR and ^{31}P NMR spectra of reaction mixtures, compounds **5a–c**,**e–g** and **6a–c**,**f**,**g** were formed as nearly 1:1 mixture of diastereomers due to the presence of carbon and phosphorus stereogenic centers and low diastereoselectivity of the phosphinylation. However, we failed to separate these diastereomeric mixtures by column chromatography in the course of product isolation.

Noticeably, the nature of the terminal substituent R^1 in diketones has no major effect on the reaction outcome. However the replacement of the trifluoromethyl group by difluoromethyl (diketone **3h**) or 1,1,2,2-tetrafluoroethyl (diketone **3i**) substituents changes the reaction course dramatically. In both cases phosphonylation was not complete even with large excess of the phosphorus reagent (10 equiv) or triethyl borate (3 equiv); the NMR yields were less than 30% after 100 hours (Table 1, entries 10–11).

The positive effect of triethyl borate on the course of phosphonylation could be explained by a reversible formation of the more reactive borate derivative **A** followed by a nucleophilic attack of phosphorus under formation of borate **B**, and subsequent regeneration of **A**, as it is outlined in Scheme 1. Surprisingly, there were no reports on reaction of fluorinated diketones with trialkyl borates. Moreover, it had been shown, that diketones bearing an electron-withdrawing ester group did not react with trialkyl borates.[14] Therefore, the ^1H NMR and ^{19}F NMR spectra of mixtures of diketones **3a** and triethyl borate in the ratio 2:1, 1:1, and 1:2 were recorded in CD_3CN solution to confirm the intermediate **A** formation. The yellow color of samples and the appearance of additional low intensity signals in the NMR spectra proved that the reaction had taken place. A singlet at $\delta = 5.45$ ppm and a four-proton quartet at $\delta = 3.53$ ppm in the ^1H NMR spectra were assigned to the olefinic and methylene protons of two ethoxy groups of the enol borate **A**. The upfield shift for olefinic protons of enol ethers of fluorinated 1,3-diketones are well-known.[15]

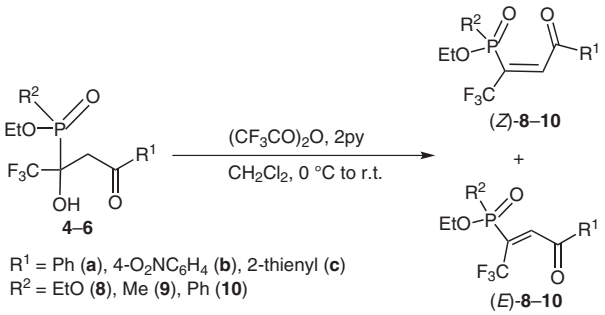
Additionally, it was observed a singlet at $\delta = 7.07$ ppm that was attributed to the olefinic proton signal for the chelate ring of benzoyltrifluoroacetonato boron diethoxide. This signal was deshielded (0.32 ppm) compared to the olefinic proton of the keto-enol tautomer of **3a**, similarly to that of other boron diketonates.[14,16] The trifluoromethyl groups of **A** and the boron chelate were shifted downfield

in comparison to **3a** and appeared as singlets at δ = 87.5 and 87.2 ppm (C_6F_6) in the ^{19}F NMR spectra. The total integration for signals of the enol borate **A** and the boron diketonate increased from ca. 2.5% to 5.0% with increasing of the triethyl borate content.

Noteworthy that, in addition to the doublet signals of products at δ = 86–88 (J_{FP} = ca. 3–4 Hz) in the ^{19}F NMR spectra of reaction mixtures (Table 1, entries 2–5), additional low intensive doublets (J_{FP} = ca. 3–5 Hz) with similar shifts were observed. Their disappearance after hydrolysis could stand for the presence of borates **B** in the reaction mixtures.

This approach is the first example of successful syntheses of diethyl 1-trifluoromethyl-1-hydroxy-3-oxo-phosphonates **4**, related phosphinates **5**, **6**, and tertiary phosphinoxides **7** and has advantages with regard to the ease of operation and the ready availability of starting materials. In addition, compounds **4**–**7** could be considered as analogues of β-trifluoromethyl-β-hydroxy ketones, which proved to be useful building blocks.[17]

Thus, dehydration of selected compounds **4**–**6**(**a**–**c**) by means of $(CF_3CO)_2O$ in the presence of pyridine at 0 °C affords the respective trifluoromethyl-containing unsaturated 3-oxo-phosphonates **8a**–**c**, (methyl)phosphinates **9a**–**c**, and (phenyl)phosphinates **10a**–**c** (Scheme 2, Table 2).



Scheme 2 Dehydration of 1-trifluoromethyl-1-hydroxy-3-oxo-phosphonates **4a**–**c**, (methyl)phosphinates **5a**–**c**, and (phenyl)phosphinates **6a**–**c**

Compounds **8**–**10** were isolated in 63–88% yields as a mixture of *E*- and *Z*-isomers with a predominant amount of *Z*-isomer (≥90%).[18] Noteworthy, when the dehydration occurred at room temperature, the content of the *E*-isomer increased up to ca. 20%.

Since phosphonates **8** and phosphinates **9**, **10** could be regarded as α,β-unsaturated trifluoromethylketones[19] and vinylphosphonates,[8b,c,20] this experimentally simple method may be of great value in R^F-phosphorus-containing building-block chemistry.

The structures of compounds **4**–**10** were confirmed by elemental analysis, ^1H NMR, ^{19}F NMR, ^{31}P NMR, and ^{13}C NMR spectroscopy.[13,18] A characteristic feature of the ^1H NMR spectra for phosphonates **4** and tertiary phosphine oxides **7** in $CDCl_3$ is the presence of an AB system of doublets at δ = 2.7–3.6 ppm ($^2J_{Ha–Hb}$ = 15–19 Hz, $^3J_{Ha–P}$ = 11–

Table 1 Triethyl Borate Mediated Reaction of Diketones **3a**–**i** with Diethyl Phosphite, Ethyl (Methyl)phosphonite, Ethyl (Phenyl)phosphonite, and Diphenylphosphine Oxide

Entry	Diketone	R^1	R^2, R^3	Catalyst amount[a–c]	Time (h)[d]	Yield (%)[e]
1	**3a**	Ph	OEt, OEt	5 mol%, r.t.[f]	72	100[g]
2	**3a**	Ph	OEt, OEt	3 equiv, r.t.[f]	48	100[g]
3	**3a**	Ph	OEt, OEt	1.1 equiv	48	78
4	**3b**	4-$O_2NC_6H_4$	OEt, OEt	1.1 equiv	48	83
5	**3c**	2-thienyl	OEt, OEt	1.1 equiv	48	90
6	**3d**	4-$EtOC_6H_4$	OEt, OEt	1.1 equiv	48	86
7	**3e**	Me	OEt, OEt	1.1 equiv	48	56
8	**3f**	Et	OEt, OEt	1.1 equiv	48	75
9	**3g**	*t*-Bu	OEt, OEt	1.1 equiv	48	91
10	**3h**[h]	Ph	OEt, OEt	3.0 equiv[j]	100	29[g]
11	**3i**[i]	Ph	OEt, OEt	3.0 equiv[j]	100	17[g]
12	**3a**	Ph	Me, OEt	1.1 equiv	24	68
13	**3b**	4-$O_2NC_6H_4$	Me, OEt	1.1 equiv	24	87
14	**3c**	2-thienyl	Me, OEt	1.1 equiv	24	85
15	**3e**	Me	Me, OEt	1.1 equiv	24	59
16	**3f**	Et	Me, OEt	1.1 equiv	24	70
17	**3g**	*t*-Bu	Me, OEt	1.1 equiv	24	62
18	**3a**	Ph	Ph, OEt	1.1 equiv[k]	48	61
19	**3b**	4-$O_2NC_6H_4$	Ph, OEt	1.1 equiv[k]	48	78
20	**3c**	2-thienyl	Ph, OEt	1.1 equiv[k]	48	70
21	**3f**	Et	Ph, OEt	1.1 equiv[k]	48	49
22	**3g**	*t*-Bu	Ph, OEt	1.1 equiv[k]	48	70
23	**3a**	Ph	Ph, Ph	1.5 equiv[l]	60	53
24	**3c**	2-thienyl	Ph, Ph	1.5 equiv[l]	60	47
25	**3d**	4-$EtOC_6H_4$	Ph, Ph	1.5 equiv[l]	60	52
26	**3g**	*t*-Bu	Ph, Ph	1.5 equiv[l]	60	63

[a] Refluxing, if not indicated otherwise.
[b] MeCN as solvent.
[c] 1.1 Equiv of phosphorus reagent, if not indicated otherwise.
[d] Monitoring by ^{19}F NMR.
[e] Isolated yield.
[f] 3 Equiv of diethyl phosphite.
[g] NMR yield.
[h] $R^F = HCF_2$.
[i] $R^F = HCF_2CF_2$.
[j] 10 Equiv of diethyl phosphite.
[k] 1.5 Equiv of ethyl (phenyl)phosphonite.
[l] 2.0 Equiv of diphenylphosphine oxide.

Table 2 Dehydration of Compounds **4a–c**, **5a–c**, and **6a–c**

Entry	Compd	R^1	R^2	Yield (%)
1	**8a**	Ph	OEt	69
2	**8b**	4-$O_2NC_6H_4$	OEt	70
3	**8c**	2-thienyl	OEt	74
4	**9a**	Ph	Me	77
5	**9b**	4-$O_2NC_6H_4$	Me	63
6	**9c**	2-thienyl	Me	81
4	**10a**	Ph	Ph	88
5	**10b**	4-$O_2NC_6H_4$	Ph	72
6	**10c**	2-thienyl	Ph	65

17 Hz, $^3J_{Hb–P}$ = 2–9 Hz) for the methylene protons and doublet at δ = 6.5–6.8 ppm ($^3J_{H–P}$ = 8–15 Hz) for the OH group, which disappeared in the presence of CD_3CO_2D. In the ^{19}F NMR spectra of **4** and **7** the trifluoromethyl group appeared as a doublet with J_{FP} = ca. 2–5 Hz at δ = 86–90 ppm (C_6F_6). In the case of phosphinates **5** and **6**, two sets of characteristic signals were observed. Noteworthy that, in contrast to phosphonate **4**, the CF_3 and the phosphinate groups of **5** and **6** manifest themselves as broadened singlets at δ = 86–87 ppm (C_6F_6) and at δ = 48–50 ppm (for compounds **5**) and 34–42 ppm (for compounds **6**, 85% H_3PO_4) in the ^{19}F NMR and $^{31}P–^1H$ decoupled spectra, correspondingly.

The presence of a double bond in compounds **8–10** was confirmed by the appearance of a doublet of quartets at δ = 7.5–7.7 ppm ($J_{H–P}$ = 31–39 Hz, $J_{H–F}$ = 1–2 Hz) and a doublet at δ = 7.8–7.9 ($J_{H–P}$ = 19–24 Hz) for olefinic protons of the major and the minor isomer in their ^1H NMR spectra, respectively. The *Z* configuration of the double bond in the predominant isomer was established uniquely since the range of the $J_{H–P}$ values is characteristic for *trans* position of hydrogen and phosphorus around a double bond.[21] In the ^{19}F NMR spectra the trifluoromethyl group of the *Z*-configured compounds **8–10** appeared as a singlet at δ = 99–101 ppm (C_6F_6), whereas the signal of *E*-isomers is shifted downfield (Δ = ca. 5 ppm), due to the deshielding effect of the aroyl group.

In conclusion, we have shown that the reaction of acyltrifluoroacetones **3** with several derivatives of phosphorous, phosphonous, and phosphinous acids such as diethyl phosphite, ethyl (methyl)phosphonite, ethyl (phenyl)phosphonite, and diphenilphosphine oxide in the presence of triethyl borate provides a simple and convenient approach from readily available starting material to 1-trifluoromethyl-1-hydroxy-3-oxo-phosphonates, 1,2-unsaturated 1-trfluoromethyl-3-ketophosphonates and their (methyl)phosphinate and (phenyl)phosphinate analogues, and 3-(diphenylphosphoryl)-3-trifluoromethyl-3-hydroxyketones, which may be considered as a CF_3-containing substrate for the synthesis of a wide variety of phosphonates, phosphinates, and phosphine oxides with potential biological activity. Further studies on the scope of this approach and synthetic application of the obtained compounds are now in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

D.L.C. is grateful to the Deutsche Forschungsgemeinschaft for generous financial support (Grant DFG 436 RUS 113/911/0-1).

References and Notes

(1) (a) Dellaria, J. F. Jr.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 534. (b) Tao, M.; Bihovsky, R.; Wells, G. J.; Mallamo, J. P. *J. Med. Chem.* **1998**, *41*, 3912.
(2) Stowasser, B.; Budt, K.-H.; Li, J.-Q.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625.
(3) Snoeck, R.; Holy, A.; Dewolf-Peeters, C.; Van Den Oord, J.; De Clercq, E.; Andrei, G. *Antimicrob. Agents Chemother.* **2002**, *46*, 3356.
(4) (a) Peters, M. L.; Leonard, M.; Licata, A. A. *Cleve Clin. J. Med.* **2001**, *68*, 945. (b) Leder, B. Z.; Kronenberg, H. M. *Gastroenterology* **2000**, *119*, 866.
(5) (a) Rawlings, J. B. *Nat. Prod. Rep.* **1999**, *16*, 425. (b) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380. (c) Paterson, I.; Scott, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1003. (d) Keck, D.; Bräse, S. *Org. Biomol. Chem.* **2006**, *4*, 3574.
(6) (a) Kirsch, P. *Modern Organofluorine Chemistry*; Wiley-VCH: Weinheim, **2004**. (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons: Hoboken / NJ, **2008**. (c) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, **2009**.
(7) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868.
(8) (a) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, **2000**. (b) Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*; CRC Press: Boca Raton / FL, **2003**. (c) Atmani, A.; Memmou, F.; Bouillon, J.-Ph. *C. R. Chim.* **2009**, *12*, 963. (d) Albrecht, Ł.; Albrecht, A.; Krawczyk, H.; Jørgensen, K. A. *Chem. Eur. J.* **2010**, *16*, 28. (e) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29.
(9) (a) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442. (b) Samanta, S.; Perera, S.; Zhao, C.-G. *J. Org. Chem.* **2010**, *75*, 1101. (c) Dodda, R.; Zhao, C.-G. *Org. Lett.* **2006**, *8*, 4911.
(10) (a) Schoth, R.-M.; Sevenard, D.; Pashkevich, K.; Röschenthaler, G.-V. *Coord. Chem. Rev.* **2000**, *210*, 101. (b) Sevenard, D. V.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. *Heteroat. Chem.* **2002**, *13*, 97. (c) Chizhov, D. L.; Slepukhin, P. A.; Charushin, V. N.; Röschenthaler G.-V. *J. Fluorine Chem.*, submitted.
(11) Francke, R.; Röschenthaler, G.-V. *Chemiker-Ztg.* **1989**, *113*, 115.

(12) (a) Chizhov, D. L.; Ratner, V. G.; Pashkevich, K. I. *Russ. Chem. Bull.* **1999**, *48*, 758. (b) Yachevskii, D. S.; Chizhov, D. L.; Ratner, V. G.; Pashkevich, K. I. *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 1233. (c) Chizhov, D. L.; Pashkevich, K. I.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2003**, *123*, 267. (d) Chizhov, D. L.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2006**, *127*, 235. (e) Sevenard, D. V.; Kazakova, O.; Schoth, R.-M.; Lork, E.; Chizhov, D. L.; Poveleit, J.; Röschenthaler, G.-V. *Synthesis* **2008**, 1867.

(13) **Typical Procedure for the Preparation of Compounds 4–7**

A mixture of diketone **3** (10.0 mmol), phosphorus reagent [11.0 mmol in the case of diethyl phosphite or ethyl(methyl)phosphonite, 15 mmol in the case of ethyl(phenyl)phosphonite, or 20 mmol in the case of diphenylphosphine oxide], and triethylborate (1.60 g, 11.0 mmol in the case of phosphite and phosphonites or 2.92 g, 20.0 mmol in the case of diphenylphosphine oxide) was refluxed in MeCN (20 mL) for the respective time (Table 1). All volatile materials were removed in vacuo, and the residue was dissolved in Et_2O (30 mL). The ether solution was washed with H_2O (10 mL) and 10% solution of Na_2CO_3 (3 × 10 mL). For compounds **6** and **7** a sat. solution of $NaHCO_3$ was used. Et_2O was removed, the crude product was dissolved in $CHCl_3$ (10 mL) and filtered through a layer of silica (3 sm). The solvent was evaporated, and the residue was dried in vacuo for 12 h. For compounds **6** and **7**, the products were purified by column chromatography (EtOAc–hexane = 1:2).

Data for Diethyl 1-Hydroxy-3-(4-nitrophenyl)-3-oxo-1-(trifluoromethyl)propylphosphonate (4b)

Yellowish viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, 3 H, Me, *J* = 7.1 Hz), 1.27 (t, 3 H, Me, *J* = 7.1 Hz), 3.21 (dd, 1 H, $J_{Ha–Hb}$ = 16.1 Hz, $J_{Ha–P}$ = 18.6 Hz, C*H*H), 3.82 (dd, 1 H, $J_{Ha–Hb}$ = 16.1 Hz, $J_{Hb–P}$ = 7.3 Hz, CH*H*), 4.10–4.36 (m, 4 H, 2 OCH_2), 6.74 (d, 1 H, $J_{H–P}$ = 8.3 Hz, OH) 7.61–7.66 (m, 2 H, Ar), 7.88–7.93 (m, 2 H, Ar). ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ = 88.96 (d, $J_{F–P}$ = 5.2 Hz, CF_3). ^{31}P–^{1}H decoupled (81 MHz, $CDCl_3$, 85% H_3PO_4): δ = 16.68 (q, $J_{P–F}$ = 5.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 16.13 (d, $^3J_{C–P}$ = 5.2 Hz, Me), 38.64 (s, CH_2), 63.58 (d, $^2J_{C–P}$ = 7.4 Hz, OCH_2), 63.63 (d, $^2J_{C–P}$ = 7.4 Hz, OCH_2), 75.58 (dq, $^1J_{C–P}$ = 164.6 Hz, $^2J_{C–F}$ = 29.0 Hz), 124.41 (qd, CF_3, $^1J_{C–F}$ = 285.4 Hz, $^2J_{C–P}$ = 12.6 Hz), 124.42, (CH, Ar), 130.87 (CH, Ar), 143.03 (Ar), 150.70 (Ar), 195.94 (d, $^3J_{C–P}$ = 8.5 Hz, C=O). Anal. Calcd for $C_{14}H_{17}NPF_3O_7$: C, 42.12; H, 4.29; F, 14.28. Found: C, 42.31; H, 4.17; F, 14.42.

(14) Singh, Y. P.; Saxena, S.; Rai, A. K. *Synth. React. Inorg. Met.-Org. Chem.* **1982**, *12*, 867.

(15) (a) Jullien, J.; Pechine, J. M.; Perez, F.; Piade, J. J. *Tetrahedron* **1982**, *38*, 1413. (b) Pavlov, A. M.; Chizhov, D. L.; Charushin, V. N. *Russ. J. Org. Chem.* **2005**, *41*, 1449. (c) Bonacorso, H. G.; Martins, M. A. P.; Bittencourt, S. R. T.; Lourega, R. V.; Zanatta, N.; Flores, A. F. C. *J. Fluorine Chem.* **1999**, *99*, 177. (d) Mkrtchyan, E. G.; Yachevskii, D. S.; Chizhov, D. L.; Charushin, V. N. *Russ. Chem. Bull.* **2005**, *54*, 2150.

(16) (a) Mikhailov, B. M. *Pure Appl. Chem.* **1977**, *49*, 749. (b) Kunstle, G.; Siegel, H. DE 2402426, **1975**; *Chem. Abstr.* **1975**, *83*, 193406. (c) Balaban, A. T.; Rentea, C. N.; Mocanu, M. *Tetrahedron Lett.* **1964**, *5*, 2049. (d) Chaturvedi, A.; Nagar, P. N.; Srivastava, G. *Synth. React. Inorg. Met.-Org. Chem.* **1993**, *23*, 1599.

(17) Pashkevich, K. I.; Filyakova, V. I.; Ratner, V. G.; Khomutov, O. G. *Russ. Chem. Bull.* **1998**, *47*, 1239; and references cited therein.

(18) **General Procedure for the Preparation of Compounds 8–10**

To a vigorously stirred solution of phosphonate **4** or phosphinate **5** or **6** (5.0 mmol) and dry pyridine (0.79 g, 10 mmol) in dry CH_2Cl_2 (20 mL) a solution of TFAA (2.10 g, 10 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 4 h at the same temperature, warmed to r.t., washed with cold H_2O (ca. 5 °C, 3 × 10 mL), and filtered through layer of silica (4 sm). The solvent was evaporated and residue was dried in vacuo for 12 h.

Data for Diethyl 3-(4-Nitrophenyl)-3-oxo-1-(trifluoromethyl)prop-1-enylphosphonate (8b)

Yellow viscous oil; *E*/*Z* = 10:1.

Compound (***Z***)**-8b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, 6 H, 2 Me, *J* = 7.1 Hz), 4.01–4.17 (m, 4 H, 2 OCH_2), 7.57 (dq, 1 H, $J_{H–P}$ = 39.0 Hz, $J_{H–F}$ = 1.5 Hz, =CH), 8.02–8.06 (m, 2 H, Ar), 8.31–8.36 (m, 2 H, Ar). ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ = 99.27 (s). ^{31}P–^{1}H coupled (81 MHz, $CDCl_3$, 85% H_3PO_4): δ = 6.67 (dm, $J_{P–H}$ = 39.0 Hz). ^{31}P–^{1}H decoupled (81 MHz, $CDCl_3$, 85% H_3PO_4): δ = 6.67 (q, $J_{P–F}$ = 2.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.00 (d, $^3J_{C–P}$ = 7.1 Hz, Me), 63.80 (d, $^2J_{C–P}$ = 5.7 Hz, OCH_2), 121.65 (qd, CF_3, $^1J_{C–F}$ = 275.5 Hz, $^2J_{C–P}$ = 15.5 Hz), 124.06 (CH, Ar), 129.00 (dq, $^1J_{C–P}$ = 182.3 Hz, $^2J_{C–F}$ = 32.5 Hz), 129.82, (CH, Ar), 139.48 (Ar), 147.39 (m, =CH), 150.82 (Ar), 190.20 (d, $^3J_{C–P}$ = 7.1 Hz, C=O).

Compound (***E***)**-8b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 (t, 6 H, 2 Me, *J* = 7.1 Hz), 4.19–4.35 (m, 4 H, 2 OCH_2), 7.77 (d, 1 H, $J_{H–P}$ = 24.0 Hz, =CH), 8.02–8.06 (m, 2 H, Ar), 8.31–8.36 (m, 2 H, Ar). ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ = 104.36 (d, $J_{F–P}$ = 5.5 Hz). ^{31}P–^{1}H decoupled (81 MHz, $CDCl_3$, 85% H_3PO_4): δ = 9.06 (q, $J_{P–F}$ = 5.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.20 (d, $^3J_{C–P}$ = 7.0 Hz, Me), 64.09 (d, $^2J_{C–P}$ = 5.7 Hz, OCH_2), 124.26 (CH, Ar), 130.04, (CH, Ar), 148.66 (m, =CH). Signals of carbon without hydrogen were not found. Anal. Calcd for $C_{14}H_{15}NPF_3O_6$: C, 44.11; H, 3.97; F, 14.95. Found: C, 44.03; H, 3.75; F, 15.10.

(19) Nenajdenko, V. G.; Druzhinin, S. V.; Balenkova, E. S. *Chemistry of α,β-Unsaturated Trifluoromethyl Ketones*; Nova Sci. Publ.: New York, **2007**.

(20) Dembitsky, V. M.; Al Quntar, A. A. A.; Haj-Yehiaa, A.; Srebnik, M. *Mini-Rev. Org. Chem.* **2005**, *2*, 91.

(21) (a) Kenyon, G. L.; Westheimer, F. N. *J. Am. Chem. Soc.* **1966**, *88*, 3557. (b) Costisella, B.; Keitel, I.; Gross, H. *Tetrahedron* **1981**, *37*, 1227.