JOC*Note*

Addition of Trifluoromethyltrimethylsilane to Acyl Phosphonates: Synthesis of TMS-Protected 1-Alkyl-1-trifluoromethyl-1-hydroxyphosphonates and 1-Aryldifluoroethenyl Phosphates

Ayhan S. Demir* and Serkan Eymur

Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

asdemir@metu.edu.tr

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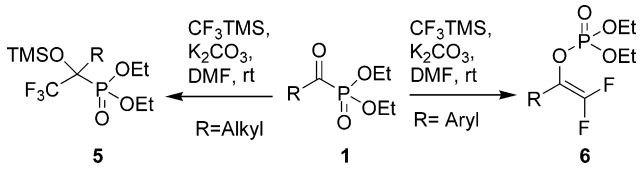

Addition reactions of nucleophilic CF_3TMS to acyl phosphonates were investigated. Various acyl phosphonates reacted readily with CF_3TMS in the presence of K_2CO_3 in DMF at rt to give 1-alkyl-2,2,2-trifluoro-1-trimethylsilyloxyethylphosphonate in 70−90% yields. When benzoyl phosphonates were used as starting material, after addition of CF_3, the formed alcoholate undergoes phosphonate−phosphate rearrangement to form the acyl anion, followed by elimination of F^- to give 1-aryldifluoroethenyl phosphates in 87−97% yields. As a representative example, vinylphosphate **6a** was converted into 2,2-difluoro-1-phenylethanone **7** with 6 N HCl/EtOH/reflux or CAN/NaOH/MeOH/0 °C in 82−90% yields.

Organofluorine compounds exhibit unique properties[1] which are of great interest in a wide range of applications[2] and justify the steadily growing number of new organofluorine products which appear every year.[3] Thus, these molecules are very useful not only in the pharmaceutical[2a,d] and agrochemical[2d,e] fields but also for material design.[2e,f]

Trifluoromethylation using Ruppert−Prakash reagent[4] is one of the most widely used methods to incorporate a trifluoromethyl moiety into organic molecules.[5] Prakash et al.[6] carried out extensive studies to develop varieties of easily accessible nucleophilic catalysts to promote such reactions. TMS-protected trifluoromethylated alcohols were prepared from both aldehydes and ketones in excellent yields using a catalytic amount of amine *N*-oxide. Carbonate and phosphate salts also showed efficient catalytic activity toward this reaction.[4b] This reagent was also used for the effective formation of difluoroenol silyl ethers.[7] These enoxysilanes were also synthesized by Portella et al.[8] starting from trifluoromethyltrimethylsilane and acylsilanes via the Brook rearrangement of the alcohol adduct. Several approaches to difluoroenol silyl ethers have appeared in the literature.[8] Ishihara et al. prepared them by silylation of a zinc difluoroenolate derived from chlorodifluoromethyl ketone.[9] Other approaches, based on intermediate trialkylsilyltrifluoromethyl carbinolate adducts, used silyllithium reagents either to prepare a needed trifluoroacetylsilane[10] or to add to a trifluoromethyl ketone.[11] In situ silylation of a difluoroenolate obtained by electroreduction of a trifluoromethyl ketone has also been reported.[12]

Recently, we and others[13] have shown that acyl phosphonates are potent acyl anion precursors and undergo nucleophile-promoted phosphonate−phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates. Acyl phosphonates **1**, which are easily synthesized from acyl chloride and trialkyl phosphite in high yields, as the acyl anion precursors, and aldehydes as the electrophiles in the presence of a cyanide catalyst provide cross-benzoin products. Aromatic−aromatic cross-benzoin synthesis, benzoyl phosphonates with

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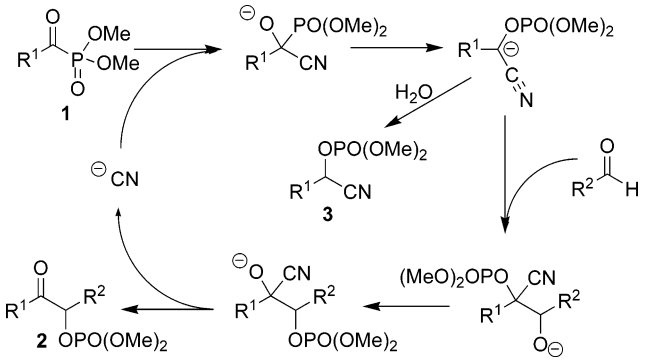
SCHEME 1



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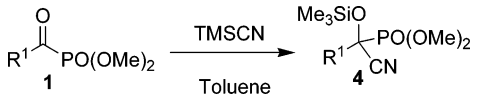
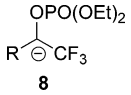


aliphatic aldehydes, aliphatic acyl phosphonates, and aromatic aldehydes furnished the acyloin products **2** in good yields. The protonation of these acyl anion equivalents, generated from acyl phosphonates, furnished cyanohydrin *O*-phosphates **3** in good yields (Scheme 1).[14]

In an additional study, the cyanosilylations of various acyl phosphonates under comparatively mild conditions furnished the trimethylsilyloxycyanophosphonates in high yield. The addition to acyl phosphonate proceeded without the influence of a catalyst (Scheme 2).[15]

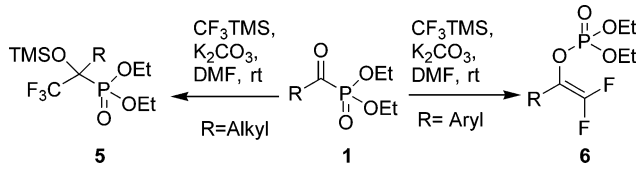
As a general extension of earlier work, we have investigated the reaction of the trifluoromethylation agent CF_3TMS with acyl phosphonates. We planned to gain a direct and uncatalyzed access to α-hydroxytrifluoromethylphosphonates. Moreover, we hoped that the CF_3 group could supply considerable carbanion stabilization to provide **8** that can give a wide range of fluorinated carbinols upon reaction with electrophiles. The addition of TMSCN to acyl phosphonates (Scheme 2) prompted us to apply the same strategy to the addition of CF_3TMS to the acyl phosphonates.



In an initial reaction, acetylphosphonate **1a** was reacted with CF_3SiMe_3 at rt in DMF, but no reaction was observed. Increasing the reaction temperature also failed to give the addition product. Next, nucleophilic trifluoromethylation was used to incorporate a trifluoromethyl moiety into acetylphosphonates.[4b] For generation of nucleophilic CF_3, to the reaction mixture of acetylphosphonate **1a** and CF_3TMS was added a catalytic amount (10%) of K_2CO_3 and the reaction was monitored by TLC (2 h). After workup, the CF_3TMS addition product **5a** was obtained in 82% yield (Scheme 3).

The reaction was repeated by using 15−50% of K_2CO_3, NaOAc, $NaHCO_3$, and Na_2CO_3. While K_2CO_3, NaOAc, and $NaHCO_3$ furnished comparable yields, no reaction was observed by using Na_2CO_3. In all cases DMF, CH_3CN, toluene, and THF

SCHEME 3



were used as solvents at various temperatures, with the best yield being obtained with 1 equiv of phosphonate, 1.5−2 equiv of CF_3TMS, and 20% K_2CO_3 in DMF (100% conversion in 5 min) at rt. With other solvents, the conversion decreased (30−65%, 19−24 h). This reaction was applied to various aliphatic phosphonates, and the 1-alkyl-2,2,2-trifluoro-1-trimethylsilyloxyethylphosphonates **5a**−**d** were obtained in 70−90% yield as summarized in Table 1 (entries 1−4). In all cases, trace amounts of vinyl phosphates **6** were detected by crude NMR.

In the next step, we tried the addition reaction with benzoyl phosphonates. The reaction of benzoyl phosphonate **1e** under the standard procedure described above for aliphatic phosphonates (K_2CO_3 (20%), DMF, CF_3TMS at rt) furnished not the expected addition product **5** but rather 1-phenyl-2,2-difluoroethenyl phosphate (**6a**) in 96% yield (Scheme 3). This reaction was repeated at rt in DMF with various additives. As shown in Table 2, K_2CO_3, NaOAc, and $NaHCO_3$ afforded high conversions compared to tertiary amines (triethylamine and cinchonidinium chloride). As in the previous case, Na_2CO_3 gave no reaction.

When the reaction of benzoyl phosphonate **1e** with CF_3TMS was performed at rt in the presence of K_2CO_3 in various solvents, the best conversion was again obtained with DMF in 15 min. The use of CH_3CN, THF, or toluene decreased the conversion rate, and reaction time was increased (Table 3). By using toluene and THF, the reaction was carried out at −40 and −20 °C and was monitored by TLC; even at −40 °C slow formation of the elimination product was observed. In summary, despite many attempts to obtain the addition product, no successful reaction occurred.

In all cases, the elimination product was isolated together with trace amounts of **5**. To determine whether the formation of the elimination product takes place during the reaction, at the workup step, or during the purification step, we carried out several control experiments and found that the elimination reaction occurs during the reaction (the reaction was monitored by TLC and ^1H NMR).

Benzoyl phosphonates with both electron-withdrawing and electron-donating groups attached to the phenyl ring affected the yield slightly as shown in Table 1. Under the standard procedures, by using furoyl phosphonate, both products were obtained in almost equivalent amounts with 100% conversion. Careful repetition of this reaction under various conditions (variation of temperature, amount of additives and solvents) resulted in no remarkable change on the product ratio (Scheme 4).

The present approach provides us a straightforward access to these important difluorinated compounds. The synthesis of these types of difluorovinylphosphates has been described only by Ishihara.[9] He reported the preparation of 1-substituted 2,2-difluoroethyl phosphates or 1-hydroxyalkanephosphonates through the reaction of chlorodifluoromethyl ketones with dialkyl or diaryl phosphites. 1-Hydroxyalkanephosphonates are converted to enolphosphates by the treatment with triethylamine or sodium

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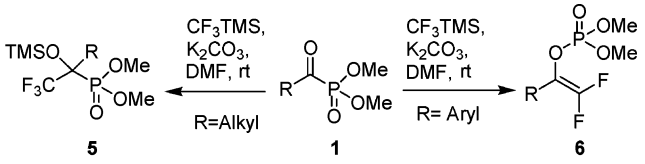
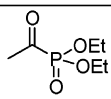
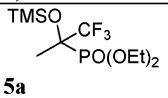
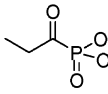
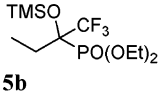
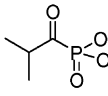
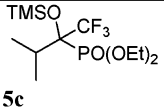
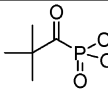
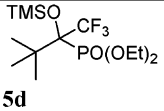
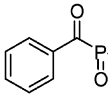
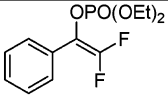
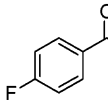
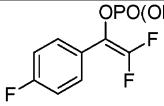
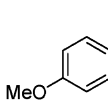
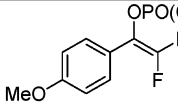
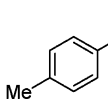
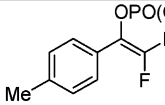
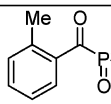
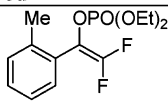
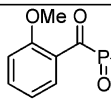
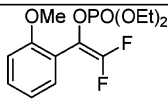
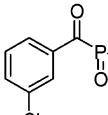
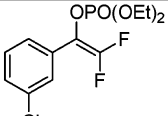
TABLE 1. Addition of CF_3TMS to Acyl Phosphonates



5 **1** **6**

entry	acyl phosphonates **1**	products **5**, **6**	yield (%)
1	 **a**	 **5a**	90[16]
2	 **b**	 **5b**	88[17]
3	 **c**	 **5c**	70
4	 **d**	 **5d**	89
5	 **e**	 **6a**	96[9]
6	 **f**	 **6b**	92
7	 **g**	 **6c**	95
8	 **h**	 **6d**	92
9	 **i**	 **6e**	97
10	 **j**	 **6f**	87
11	 **k**	 **6g**	91

methoxide in refluxing tetrahydrofuran. The applicability of these procedures is limited because of the complexity and difficult availability of the reagents.

The vinylphosphates **6** can be used as electrophilic or nucleophilic reagents depending on the reaction conditions.[7] They are also precursors of difluoroketones. As shown in a representative example (Scheme 5), we found that the vinylphosphate **6a** can be converted to the corresponding 2,2-difluoro-1-phenylethanone **7** by using either 6 N HCl/EtOH/reflux or via cerium ammonium nitrate mediated oxidative cleavage (CAN/NaOH/MeOH/0 °C) in 82−90% yield, respectively.

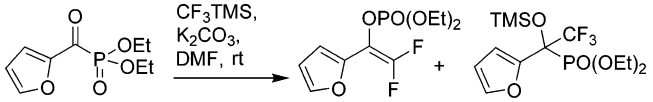
TABLE 2. Addition of CF_3TMS to 1e

catalyst (20%)	time	conversion (%)
K_2CO_3	15 min	100
CH_3COONa	30 min	100
$NaHCO_3$	24 h	90
cinchonidinium chloride	24 h	35
Et_3N	24 h	25
Na_2CO_3	24 h	0

TABLE 3. CF_3TMS Addition to 1f in Different Solvents

solvent	time (h)	*T* (°C)	conversion (%)
DMF	15 min	rt	100
CH_3CN	16	rt	70
THF	24	rt	65
THF	24	−20	10
THF	24	−40	10
toluene	24	rt	40
toluene	24	−20	15

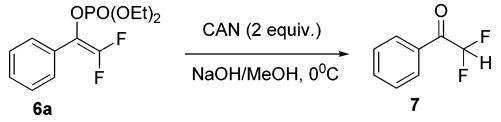
SCHEME 4



1l **6h** **6i**

1:1

SCHEME 5



6a **7**

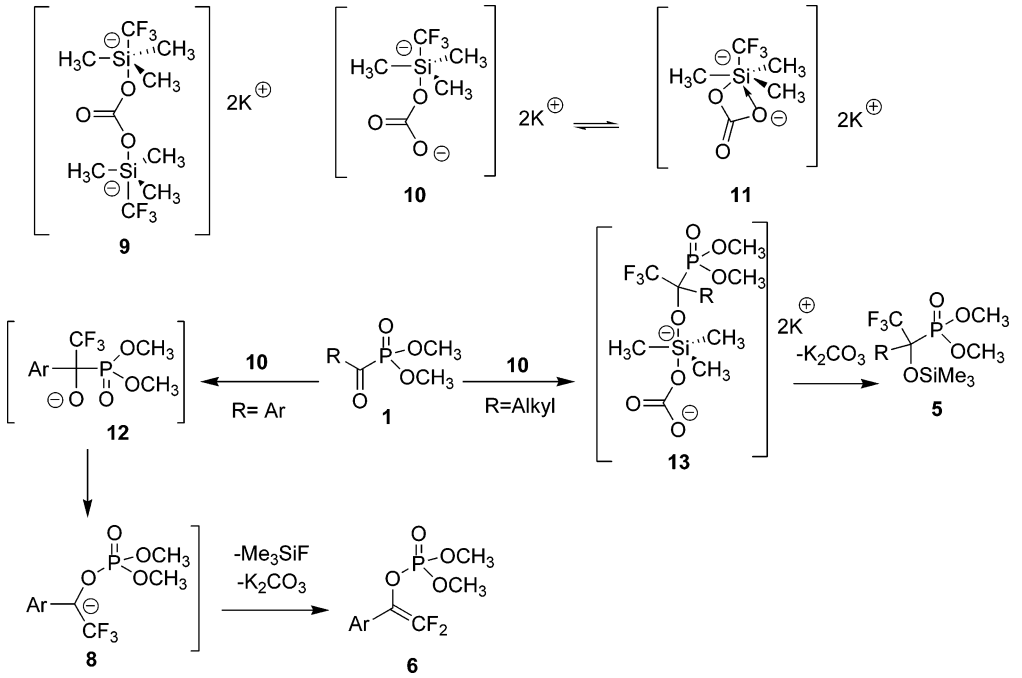
A possible mechanism for the bidentate, potassium carbonate catalyzed reaction is shown in Scheme 6. Prakash et al.[4b] described the formation of intermediates **9**−**11** from $TMSCF_3$ and potassium carbonate. Subsequently, either intermediate **9**, **10**, or **11** can undergo an attack by the acyl phosphonate to form the corresponding intermediate **13** (in Scheme 6, **10** is taken as an example), which can then decompose to give the product **5** and regenerate the catalyst. In the case of benzoyl phosphonate, after the addition of CF_3, a phosphonate−phosphate rearrangement occurs to generate 1-phosphonoxy-2,2,2-trifluoroethyl carbanion **8**, which was stabilized by the aryl ring. Then, the elimination of F^- is preferred to form the stable conjugate product **6** as described. By the computational studies on enantioselective thiazolium-catalyzed benzoin reaction, Goldfuss et al.[18] reported that alkyl substitution disfavors but π-conjugation favors formation of the carbanionic d^1-intermediate. The mixed product formation with furoyl phosphonate, which destabilized the carbanion, supported this suggestion. More detailed work for the mechanism of the elimination step is currently in progress.

(16) (a) Francke, R.; Roeschenthaler, G-V. *Chem.-Ztg.* **1987**, *111*, 307. (b) Kibardin, A.; M.; Gazizov, T. K.; Pudovik, A. N. *Zh. Obshch. Khim.* **1975**, *45*, 1982.

(17) Dieckbreder, U.; Roschenthaler, G. V. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *116*, 101.

(18) Goldfuss, B.; Schumacher, M. *J. Mol. Model.* **2006**, *12*, 591.

SCHEME 6



In conclusion, we have developed a convenient, one-pot procedure for preparing various 1-alkyl-2,2,2-trifluoro-1-trimethylsilyloxyethylphosphonate and 1-aryldifluoroethenyl phosphate compounds starting from readily available acyl phosphonates and trifluoromethyltrimethylsilane under very mild conditions. K_2CO_3 has been used successfully as an effective catalyst in the nucleophilic trifluoromethylation reactions, and its catalytic property has been improved further by using DMF as a solvent. Addition of the nucleophilic CF_3 to acyl phosphonate furnished **5** in 70−90% yields. By using benzoyl phosphonates for the addition, phosphonate−phosphate rearrangement followed by fluorine elimination afforded **6** in 87−97% yields. As a representative example, the vinylphosphate **6a** was converted to difluoroketone **7** by using either 6 N HCl/MeOH or CAN/NaOH/MeOH in 82−90% yields.

Experimental Section

General Procedure for the Addition of $TMSCF_3$ to Acyl Phosphonates. Acyl phosphonate (1 mmol) and $TMSCF_3$ (1.5 mmol) in dry DMF (5 mL) were placed in a 10 mL Schlenk flask. To this solution was added dry K_2CO_3 (20%), and the mixture was stirred vigorously at room temperature. Completion of the reaction was monitored by TLC. The reaction mixture was then poured into brine solution (15 mL) and extracted with diethyl ether (2 × 25 mL). The combined organic layers were finally washed with brine solution and dried over anhydrous Na_2SO_4, and then solvent was removed under reduced pressure. The crude product was further purified by column chromatography (silica eluted with 4:1 hexane/ethyl acetate) to afford pure TMS-protected 1-alkyl-1-trifluoromethyl-1-hydroxyphosphonate and 1-aryl-difluoroethenyl phosphate.

Diethyl 1,1,1-trifluoro-2-trimethylsilyloxy-3,3-dimethylbutan-2-ylphosphonate (5d): yield 323 mg (89%); colorless liquid; IR (neat) ν = 2992, 1445, 1388, 1254, 1171, 1061, 1039, 991, 853, 755, 581, 497 s cm-1.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (9H, s), 1.11 (9H, s), 1.28 (6H, q, J = 14.6, 7.3 Hz), 4.00−4.21 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0, 14.6 (m), 25.2, 37.5 (d, J = 4.4 Hz), 60.6 (d, J = 7.7 Hz), 61.1 (d, J = 7.6 Hz), 82.5 (dq, J = 160, J = 26.2 Hz), 123.6 (dq, J = 292, J = 10.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 17.0. Anal. Calcd for $C_{13}H_{28}F_3O_4PSi$: C, 42.85; H, 7.74. Found: C, 42.88; H, 7.78.

Diethyl 2,2-difluoro-1-(2-methylphenyl)ethenyl phosphate (6e): yield 296 mg (97%); colorless liquid; IR (KBr) ν = 2986, 2933, 1766, 1575, 1445, 1394, 1267, 1143, 1029, 983, 886 s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (6H, t, J = 7.0 Hz), 2.32 (3H, s), 3.78−4.00 (4H, m), 7.11−7.36 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (d, J = 6.8 Hz), 19.4, 64.2 (d, J = 5.8 Hz), 111.8 (ddd, J = 48.6, J = 17.7, J = 8.3 Hz), 125.6, 129.9, 130.3, 130.4, 137.2, 138.1, 154.2 (ddd, J = 291, J = 277, J = 9.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −4.5. Anal. Calcd for $C_{13}H_{17}F_2O_4P$: C, 50.99; H, 5.60. Found: C, 50.96; H, 5.62.

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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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