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Selective Synthesis of α-Fluoro-β-keto- and α-Fluoro-β-aminophosphonates via Electrophilic Fluorination by Selectfluor

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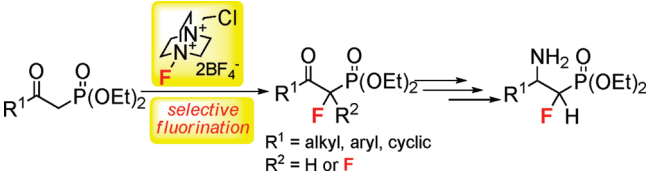
Received November 15, 2010



A series of α-mono- and α,α-difluoro-β-ketophosphonates were synthesized in moderate to good yields with excellent selectivities via electrophilic fluorination by Selectfluor. Subsequently, synthetic potential of the obtained α-monofluoro-β-ketophosphonates was demonstrated by their application in synthesis of α-monofluoro-β-aminophosphonates, useful building blocks in the preparation of phosphapeptides.

As phosphorus analogues of natural aminocarboxylic acids, the α- and β-aminophosphonic acids and their phosphonate esters exhibit a variety of intriguing biological properties, and thus they have found diverse applications in many areas of modern medicine and agriculture.[1] On the other hand, the introduction of the fluorine atom is often adopted as a measure to usher in great changes in the physicochemical and biological properties of the molecules and impact and utilization of fluorine span areas as diverse as pharmaceuticals, agrochemicals, and polymers.[2] In particular, interest in fluorine substitution of organic groups attached to phosphorus stems from the possible effect of such substitution on physical, chemical, and biological properties of the resulting fluorinated phosphonates.[3] Additionally, it is worth noting, that the union of fluorine and phosphorus has natural origin.[4] As a result, it is desirable to devise novel methods to allow easy access to fluoro-containing phosphonates in view of their great utility, and thus, the development of selective procedures producing exclusively mono- or difluorinated products would well serve this purpose.

Fluorination of phosphonates is not a trivial issue and usually requires complex chemistry based on scarce synthetic precursors and demanding reaction conditions.[5] Recently, a number of new fluorinating agents appeared, especially electrophilic agents with an N−F structure, to introduce fluorine atom into organic molecules and especially Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) began to gain popularity as an exceptionally stable, virtually nonhydroscopic crystalline solid and inexpensive electrophilic fluorinating agent.[6] To the best of our knowledge, there are only a few examples in the literature dealing with the application of this reagent for the preparation of fluorinated-β-ketophosphonates. Hamilton et al. and later on Marma et al. have reported the synthesis of various α-fluorinated phosphonoacetate derivatives via electrophilic fluorination by Selectfluor however, with poor yields in range of 17% and 40−50%, respectively.[7] Later on, Selectfluor was used by Landame and co-workers for preparation of functionalized dibenzyl α,α-difloromethylene-β-ketophosphonates (40−60%), although the monofluorinated products were obtained in minor amounts (5−10%).[8] Recently, Cox et al. have used Selectfluor for the preparation of inhibitors of bacterial aspartate semialdehyde dehydrogenase, containing α-fluoro-β-ketophosphonate unit.[9] The

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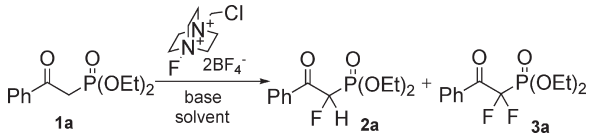
Published on Web 01/18/2011 DOI: 10.1021/jo102276y

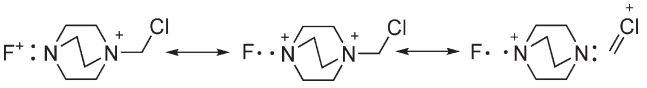
TABLE 1. Effect of Amount of Selectfluor and Additives on the Fluorination of β-Ketophosphonate 1a[a]



entry	base	Selectfluor (equiv)	solvent	**1a**[b] (%)	**2a**[b] (%)	**3a**[b] (%)
1	NaH	1	THF	**1a** (0)[c]	**2a** (31)[c]	**3a** (69)[c]
2	LDA	1	THF	**1a** (100)[c]	**2a** (-)[c]	**3a** (-)[c]
3	none	1	CH_3CN	**1a** (70)	**2a** (30)	**3a** (0)
4	none	2	CH_3CN	**1a** (0)	**2a** (95)	**3a** (< 5)
5	none	2	THF	**1a** (95)	**2a** (< 5)	**3a** (0)
6	none	2	DMF	**1a** (90)	**2a** (10)	**3a** (0)
7	none	4	CH_3CN	**1a** (0)	**2a** (35)	**3a** (65)
8	none	6	CH_3CN	**1a** (0)	**2a** (< 5)	**3a** (95)

[a]Reactions were carried out using 1 mmol of **1a** in 20 mL of solvent at reflux for 24 h. No reaction was observed at room temperature. [b]Selectivity of the fluorination was established on the basis of the integration of signals in the ^{31}P NMR spectra of crude reaction mixture. [c]Deprotonation of **1a** with base was done at 0 °C followed by addition of Selectfluor; next the reaction was stirred at room temperature for 12 h.

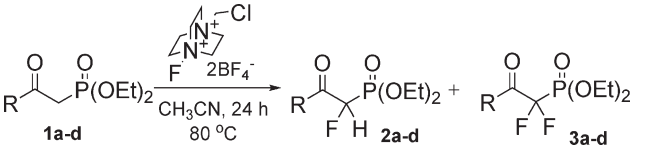
SCHEME 1. Postulated Resonance Structure of Selectfluor



desired α- monofluoro- and α,α-difluorophosphonate derivatives were obtained, after chromatographic separation, with 50% and 16% yield, respectively, along with unreacted starting material (20%). On the basis of these studies and as a part of our continued interest in the synthesis of biologically active phosphonates, we reasoned that fluorinated β-ketophosphonates may be accessible in selective fashion through electrophilic fluorination by Selectfluor. Herein, we report our results with this strategy.

Initially, the electrophilic fluorination by Selectfluor of β-ketophosphonate **1a**, as model substrate, was investigated. The screening of the quantity of the fluorinating agent revealed a pronounced effect on the selectivity of the reaction. To our satisfaction, it was found that the use of a 2-fold excess of Selectfluor leads selectively to monofluorinated product (Table 1, entry 4), whereas the application of 6-fold excess leads exclusively to difluorinated compound (Table 1, entry 8). Knowing that the reactivity of the Selectfluor can be strongly modulated by all the reaction parameters, especially solvent system and the temperature, we carried out an extensive screening of the reaction conditions. Screening of several solvents revealed that CH_3CN was the solvent of choice (Table 1, entries 4−6). Reaction with 1 equiv of fluorinating agent resulted in formation of monofluorinated product, albeit accompanied by large amount of starting material **1a** (Table 1, entry 3). The use of 4 equiv of Selectfluor led to formation of a mixture of mono- and difluorinated products (Table 1, entry 7). Also, experiments of fluorination by Selectfluor in the presence of a base were performed (Table 1, entries 1 and 2), which is the usual protocol described in the literature.[8,9] In the case were LDA was used (Table 1, entry 2), fluorination did not take place and starting material was recovered. The use of NaH (Table 1, entry 1) gave a mixture of mono- and difluorinated products.

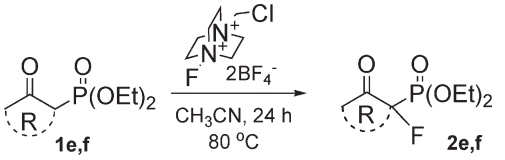
TABLE 2. Scope of the Electrophilic Fluorination of β-Ketophosphonates 1a−d by Selectfluor[a]

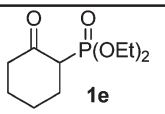
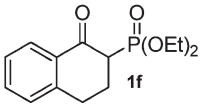


entry	substrate	Selectfluor (equiv)	**2**[b] (%)	**3**[b] (%)
1	**1a**, R = Ph	2	**2a** (65)[b]	**3a** (−)
2	**1b**, R = CH_3	2	**2b** (62)[b]	**3b** (−)
3	**1c**, R = EtO_2C	2	**2c** (40)[b]	**3c** (−)
4	**1d**, R = CF_3	2	**2d** (50)[b]	**3d** (−)
5	**1a**, R = Ph	6	**2a** (−)	**3a** (45)[b]
6	**1b**, R = CH_3	6	**2b** (−)	**3b** (43)[b]
7	**1c**, R = EtO_2C	6	**2c** (−-)	**3c** (40)[b]
8	**1d**, R = CF_3	6	**2d** (−-)	**3d** (42)[b]

[a]Reactions were carried out using 1 mmol of **1** in 20 mL of CH_3CN at 80 °C for 24 h. [b]Isolated yield of purified product after chromatography. Values are an average of three experiments.

TABLE 3. Electrophilic Fluorination of Cyclic β-Ketophosphonates by Selectfluor[a]



entry	substrate	Selectfluor	**2** (%)[b]
1	 **1e**	2 equiv.	**2e** (60)[b]
2	 **1f**	2 equiv.	**2f** (56)[b]

[a]Reactions were carried out using 1 mmol of **1e**,**f** in 20 mL of CH_3CN at 80 °C for 24 h. [b]Isolated yield of purified product after chromatography. Values are an average of three experiments.

The mechanism of electrophilic fluorination of β-ketophosphonates is believed to involve an enolate intermediate resulting from deprotonation of β-ketophosphonate moiety by a base.[8,9] The fluorination method we report here however, does not require the presence of additional base and this fact caused us to postulate that the Selectfluor itself play a role of a base as a result of its original structure that involves 1,4-diazabicyclo[2.2.2]octane (DABCO), known to be a strong base (Scheme 1).[6b,10] That is why the presence of 1 equiv of Selectfluor is not enough to force the fluorination reaction to proceed to completion and a lot of starting material remains unreacted (Table 1, entry 3). In turn, with 2 equiv, total conversion of starting material into the selectively

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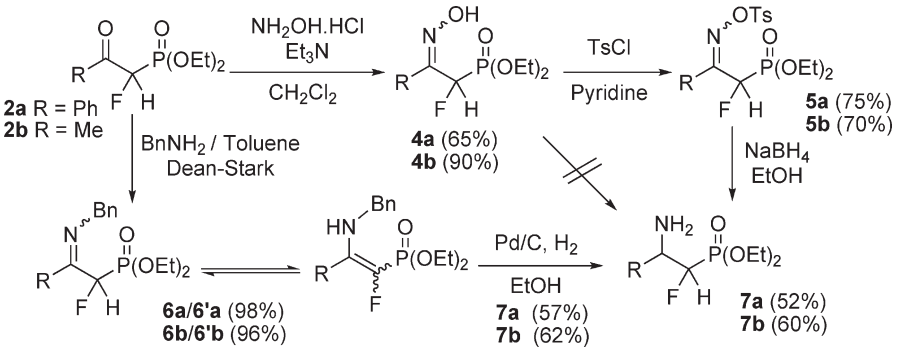
SCHEME 2. Preparation of α-Monofluorinated β-Ketophosphonates 7



monofluorinated product is obtained (Table 1, entry 4). When 4 equiv of fluorinating agent (Table 1, entry 7) is used, the difluorinated product appears, this is presumably because the monofluorinated product is more acidic than the starting material and deprotonates and fluorinates a second time to finally yield selectively difluorinated β-ketophosphonate when 6 equiv. of Selectfluor is added (Table 1, entry 8).

Subsequently, a selected spectrum of β-ketophosphonates was examined to test the scope of the presented protocol (Table 2). Different aromatic-, aliphatic-, ester-, and trifluoromethyl-substituted β-ketophosphonates were tolerated under the presented, optimized reaction conditions. Pure mono- and difluorinated β-ketophosphonates **2a**−**d** (Table 2, entries 1−4) and **3a**−**d** (Table 2, entries 5−8) were selectively obtained in moderate to good yields.

Notably, cyclic β-ketophosphonates **1e**,**f** also proved to be suitable substrates for the electrophilic fluorination by Selectfluor (Table 3, entries 1 and 2), giving the corresponding fluorinated products **2e** and **2f** in 60% and 56% yield, respectively.

In continuation, we examined the synthetic utility of the obtained fluorinated-β-ketophosphonates as starting materials in the preparation α-fluoro-β-aminophosphonates. Although it is well-known that monofluorinated aminophosphonates are better mimics of natural phosphonates with matched pK_a values,[3] their synthesis is scarcely described in the literature.[11]

Development of new protocols leading to those derivatives is therefore, especially desirable. Here we present two alternative synthetic pathways leading to α-fluoro-β-aminophosphonates **7** using α-fluoro-β-ketophosphonates **2** as substrates (Scheme 2). In the first approach, the synthesis of α-fluoro-β-aminophosphonates **7** was accomplished by a simple three-step protocol involving in the first step condensation of hydroxylamine hydrochloride with appropriate α-fluoro-β-ketophosphonate **2** in the presence of Et_3N to obtain the α-fluorinated-β-oximes **4**. All attempts to directly reduce oximes **4** to amines **7** using known literature procedures failed in our case.[12] Oximes **4** were, therefore, transformed into the corresponding *p*-toluenesulfonyloximes **5** by reaction with *p*-toluenesulfonyl chloride in pyridine and, subsequently, reduction by means of $NaBH_4$ to afford the desired α-fluoro-β-aminophosphonates **7** with acceptable yields (Scheme 2). It is noteworthy that oximes **4** and *p*-toluenesulfonyloxime **5** were obtained as a mixture of *E* and *Z* stereoisomers. By analogy with our previous works, both stereoisomers could be easily distinguished using ^{31}P NMR spectroscopy where the *E* stereoisomer presented an upfield and Z stereoisomer a downfield signals respectively.[13] In the second, successful strategy, the desired α-fluorinated β-aminophosphonates **7** were obtained with good yields by catalytic hydrogenation of a crude mixture composed of α-fluoro-β-iminophosphonate **6** and α-fluoro-β-enaminophosphonate **6′** due to existence of such a tautomeric equilibrium.[14] The presence of both tautomeric forms was confirmed by NMR analysis and by comparison of the obtained data in the literature values.[15] The **6**/**6′** mixture was produced, in almost quantitative yield, by simple condensation of corresponding α-fluoro-β-ketophosphonates **2** with benzylamine in refluxing toluene using a Dean−Stark apparatus.

In conclusion, we have developed an efficient and selective protocol for the synthesis of a palette of α-monofluoro- and α,α-difluoro-β-ketophosphonates via electrophilic fluorination by Selectfluor. This method is featured with relatively mild reaction conditions, simple operation, good substrate scope, and excellent selectivity. The synthetic utility of the obtained α-monofluoro-β-ketophosphonates was demonstrated by efficient preparation of α-monofluoro-β-aminophosphonates, compounds otherwise difficult to obtain, and useful building blocks in the synthesis of phosphapeptides.

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(14) (a) Palacios, F.; Aparicio, D.; de los Santos, J. M.; Rodriguez, E. *Tetrahedron* **1998**, *54*, 599–614. (b) Palacios, F.; Aparicio, D.; Garcia, J. *Tetrahedron* **1996**, *52*, 9609–9628.

(15) Zapata, A. J.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227–234.

Experimental Section

General Procedure for Selective Fluorination of β-Ketophosphonates by Selectfluor. To a stirred solution of appropriate β-ketophosphonate **1** (1.0 mmol) in dry acetonitrile (20 mL) at room temperature was added Selectfluor (2.0 mmol, 0.71 g for monofluorination or 6.0 mmol, 2.1 g to obtain difluorinated product), and stirring was continued for 10 min. After that reaction time, the vessel was heated to reflux, and the heating was continued for 24 h. Next, the reaction mixture was cooled to room temperature, and Et_2O (30 mL) was added followed by addition of saturated aqueous NH_4Cl (20 mL). The layers were separated, and the organic layer was washed with brine (2×15 mL) and H_2O (1×15 mL), dried over anhyd $MgSO_4$, and concentrated under reduced pressure affording the crude product that was further purified by column chromatography (SiO_2, EOAc/hexane).

Diethyl 1-fluoro-2-oxopropylphosphonate (2b): colorless oil (131 mg, 62%); R_f = 0.40 (EtOAc/pentane 2:1); ^{1}H NMR ($CDCl_3$) δ_H 1.31−1.39 (m, 6H), 2.36 (s, 3H), 4.19−4.25(m, 4H), 5.13 (dd, 1H, $^2J_{HF}$ = 47.30 Hz, $^2J_{HP}$ = 14.32 Hz); ^{13}C NMR ($CDCl_3$) δ_C 16.3, 26.7, 64.1, 91.6 (dd, J_{CP} = 152.61 Hz, J_{CF} = 197.54 Hz), 200.7 (d, J_{CF} = 20.37 Hz); ^{31}P NMR ($CDCl_3$) δ_P 10.1 (d, $^2J_{PF}$ = 71.47 Hz); FTIR (neat) ν_{max} (cm^{-1}) 1734 (C=O), 1258 (P=O); CIMS *m*/*z* 212 ([M^+], 25); HRMS calcd for $C_7H_{15}FO_4P$ $(M + H)^+$ 213.0614, found 213.0615.

Acknowledgment. Polish State Committee for Scientific Research (K.B.N.) is acknowledged for financial support (Grant No. 1297/T09/2005/29). K.R.-O. is grateful to Wroclaw University of Technology and University of the Basque Country for predoctoral scholarship.

Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **2**−**5** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org