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An alternative route for the preparation of α,α-difluoropropargylphosphonates

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Abstract

The organometallic reagent, $(EtO)_2P(O)CF_2ZnBr$, reacts with 1-bromoalkynes in the presence of CuBr to give good yields (50–61%) of α,α-difluoropropargylphosphonates. © 2000 Elsevier Science Ltd. All rights reserved.

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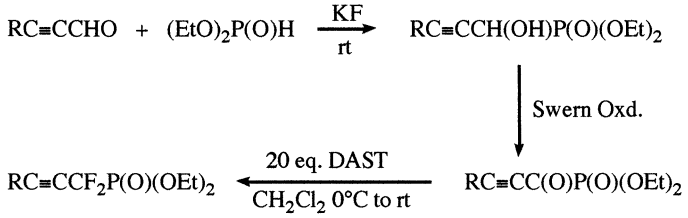
Interest in the preparation and utility of α,α-difluorophosphonates has increased steadily in recent years.[1] Numerous biological and chemical studies have demonstrated that α,α-difluorophosphonates exhibit excellent electronic and structural similarity to phosphate.[2] However, unlike phosphate, the phosphonate linkage is not readily hydrolyzed in a biological environment and this unique property has made α,α-difluorophosphonates attractive for potential utilization in medicinal and pharmaceutical applications. Thus, the development of new methodology for the preparation of functionalized α,α-difluorophosphonate derivatives continues to be an active area of research.

Recently, Hammond reported a successful approach to the preparation of α,α-difluoropropargylphosphonates via fluorination (DAST, Et_2NSF_3) of α-ketophosphonates.[3] Although this approach provides the propargyl phosphonates, it requires a three-step procedure utilizing an α-ketophosphonate of limited stability and a large excess of the fluorinating agent DAST (20 equivalents).



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Since our initial report on the generation of the stable zinc reagent, $(EtO)_2P(O)CF_2ZnBr$, **1**, in 1986, this reagent has been utilized by ourselves and others with various electrophiles, such as allylic halides, vinyl halides, aryl halides and propargyl chloride to provide functionalized α,α-difluorophosphonate derivatives.[4] Herein we report an alternative route for the preparation of α,α-difluoropropargylphosphonates via the CuBr catalyzed reaction of **1** with 1-haloalkynes.[5]

$$(EtO)_2P(O)CF_2Br \xrightarrow[THF,\ rt]{Zn} (EtO)_2P(O)CF_2ZnBr \quad (\mathbf{1})$$

$$\mathbf{1} \xrightarrow[THF]{\text{1) CuBr, -5°C; 2) RC≡CX, -5° to rt, X = I, Br}} RC{\equiv}CCF_2P(O)(OEt)_2$$

Preliminary results indicated that the reaction of **1** in THF with 1-haloalkynes in the presence of CuBr gave two major side reactions; namely, metal exchange and dimerization of the 1-haloalkyne. For example, treatment of a THF solution of **1** with 1-iodophenylacetylene in the presence of CuBr gave not only the propargylphosphonate but also significant amounts of $(EtO)_2P(O)CF_2I$ and $C_6H_5C{\equiv}C{-}C{\equiv}C{-}C_6H_5$ (30%). Although DMF and DMAC $[CH_3C(O)N(CH_3)_2]$ are good solvents for stabilization of the intermediate $(EtO)_2P(O)CF_2Cu$ reagent, **2**, these solvents produced not only the cross-coupled product but also phosphoryl fluoride from the decomposition of **2**. Thus, the best conditions for preparation of the propargylphosphonates were THF solvent at −5°C and the use of 1-bromoalkynes to minimize exchange and dimerization reactions. CuBr catalysis is necessary for useful reaction times, since the reaction of **1** with 1-bromophenylacetylene in the absence of CuBr took 10 days for completion.

Our results are summarized in Table 1.

Table 1
Preparation of α,α-difluoropropargylphosphonates

$$(EtO)_2P(O)CF_2ZnBr \xrightarrow[<5°C,\ THF]{CuBr} \xrightarrow[<5°C\text{ to rt}]{RC{\equiv}CX} RC{\equiv}CCF_2P(O)(OEt)_2$$

Entry	R	X	Reaction time (h)	Isolated yield[a,b] (%)
1	C_4H_9	Br	72	51
2	C_5H_{11}	Br	72	50
3	C_5H_{11}	I	48	30
4	C_6H_{13}	Br	72	51
5	C_6H_{13}	I	48	31
6	C_7H_{15}	Br	72	56
7	C_7H_{15}	I	48	32
8	C_6H_5	Br	36	61
9	C_6H_5	I	24	50

[a] Isolated yield based on alkynyl halide.
[b] All products gave satisfactory ^{19}F, ^{1}H, ^{13}C, ^{31}P NMR and GC-MS data.

In a typical experimental procedure, a 25 mL round bottom flask with a magnetic stir bar, a N_2 tee and ice cooled water bath was charged with 5 mL of pre-generated $(EtO)_2P(O)CF_2ZnBr$ (1.0 M, 5 mmol) in THF.[4a] This solution was cooled at <5°C for about 15 minutes, and the copper(I) bromide (0.64 g, 5 mmol) was added into the reaction mixture all at once. The resulting mixture was stirred at <5°C for an additional 15 minutes, then 0.72 g (4 mmol) of 1-bromophenylacetylene was introduced into the solution, and the reaction mixture was slowly allowed to warm to room temperature with stirring over 36 hours. The mixture was then diluted with 150 mL of ether. The resulting solid was removed by filtration and the solid was washed with 3×25 mL of ether. The combined organic solutions were then mixed with a NaOH (5%) solution (50 mL) and stirred vigorously at room temperature for at least 15 minutes to remove any P–F derivatives. The organic layer was separated and washed with water (3×40 mL), brine solution (40 mL) and dried over anhydrous $MgSO_4$. After removal of ether, the residue was purified further on a silica gel column using a mixture of ethyl acetate and hexanes (1:4) to give 0.70 g (61%) of diethyl 1,1-difluoro-3-phenyl-2-propynephosphonate, GLPC >99%. ^{19}F NMR ($CDCl_3$): −96.8 (d, $J=108$ Hz) ppm. ^1H NMR ($CDCl_3$): 7.24–7.53 (m, 5H), 4.30–4.40 (m, 4H), 1.40 (td, $J=7.1$ Hz, $J=0.7$ Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$): 132.2 (m), 130.4, 128.5, 119.4 (m), 109.44 (td, $J=253.2$ Hz, $J=229.6$ Hz), 91.48 (q, $J=7.3$ Hz), 78.30 (td, $J=33.4$ Hz, $J=17.1$ Hz), 65.38 (d, $J=6.9$ Hz), 16.32 (d, $J=5.4$ Hz) ppm. ^{31}P NMR ($CDCl_3$): 3.89 (t, $J=108$ Hz) ppm. GC-MS: 288 (M+, 3.9), 259 (6.2), 232 (22.5), 216 (4.9), 180 (7.0), 151 (100), 132 (33.8), 1.09 (61.3), 81 (33.1). IR (neat, NaCl plate): 3063 (s), 2986 (w), 2236 (m), 1163 (w), 810 (s). The spectroscopic data is in agreement with the data reported by Hammond.[3] TLC: $R_f=0.30$ (hexanes: ethyl acetate = 1:1).

In conclusion, a short useful preparation of α,α-difluoropropargylphosphonates is easily achieved from readily available reagents via the CuBr catalyzed reaction of $(EtO)_2P(O)CF_2ZnBr$ with 1-haloalkynes.

Acknowledgements

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