Synthesis of Allenic (α,α-Difluoromethylene)phosphonates from Propargylic Tosylates and Acetates

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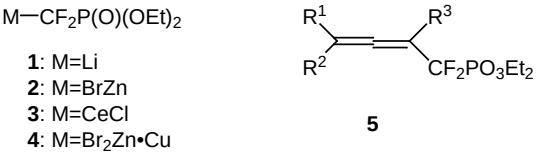
Abstract: Copper (I) bromide−promoted reactions of bromo[(diethoxyphosphoryl)difluoromethyl]zinc reagent **2** with propargylic tosylates and acetates were examined. The reaction proceeded in an S_N2' manner to give allenic (α,α-difluoromethylene)phosphonates in good to excellent yield.

Key words: allenes, addition reaction, organometallic reagents, phosphate mimics, fluorine

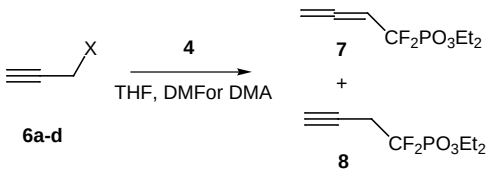


(α,α-Difluoromethylene)phosphonic acids (DFMPA) as hydrolytically stable analogues of naturally occurring phosphate esters have attracted much attention because they mimic parental biophosphates more accurately than analogous non-fluorinated phosphonates in their isosteric and isopolar properties.[1] Therefore, interest is growing in the development of general methods that allow the synthesis of compounds in which the DFMPA is borne within a functionalized array of biological interest.[2]

Numerous literature citations involve the preparation of DFMPA−ester derivatives through carbon−carbon bond formation of metallated diethyl difluoromethylphosphonates **1**-**3**.[3-5] Our group's contribution to this research field resulted in the discovery of the novel reactivity of the zinc reagent **2** in DMF or DMA in the presence of copper (I) bromide.[6] The presumed organocopper species **4**, generated by the transmetalation of **2** with copper (I) bromide in DMF and DMA, readily cross-coupled with a variety of iodoalkenes and iodobenzene derivatives to give (α,α-difluoroallyl)- and (α,α-difluorobenzyl)-phosphonate derivatives in high yield.[6] The methods have been recently applied to synthesize a number of biologically active compounds on the basis of the DFMPA−functional group by ourselves and others.[7,8]

In our continuous efforts to expand the utility of the organocopper species **4** derived from **2**, we have pursued the reaction with propargylic substrates in expectation of the reaction giving allenic (α,α-difluoromethylene)phosphonates **5**.[9] The structural novelty of **5** and the latent reactivity of the allenyl moiety would be potentially useful for developing new DFMPA−derivatives of biological interest. Here, we describe the results of our studies.

Our initial experiments focused on finding suitable leaving groups for the transformation of propargylic substrates to the target allenic (α,α-difluoromethylene)phosphonates **5** and the allene/acetylene product distribution for the reactions was verified (Table 1). The organocopper species **4**, generated from the zinc reagent **2** and stoichiometric amounts of copper (I) bromide in THF, DMF or DMA as usual,[4,6] were treated with the representative propargylic substrates **6a-d** at room temperature for 12 h. In either THF or DMF, propargyl bromide **6a** reacted with **4** to give the allenic (α,α-difluoromethylene)phosphonate **7** in moderate to good yield (entries 1 and 2). The products from the reaction in THF were contaminated by a trace amount of the acetylene derivative **8** (entry 1). The choice of solvent was critical for the selective formation of the allene, when propargyl tosylate **6b** was used as a substrate (entries 3 and 4). Upon treatment of **6b** with **4** in THF, an inseparable mixture of the allene **7** and the acetylene **8** was produced in a ratio of 85:15.[10] The allene/acetylene distribution ratio was significantly improved



a: X=Br; **b**: X=OTs; **c**: X=OCOOMe; **d**: X=OAc

Scheme 1

Table 1 Reaction of **4** with propargylic substrates **6a-c**[a]

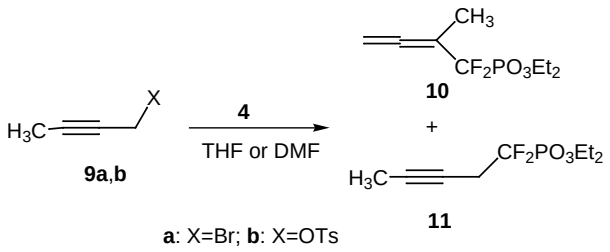
Entry	**6** (X)	Solvent	**7**/**8**[b]	Yield (%)
1	**6 a** (Br)	THF	98/2	53
2	**6 a** (Br)	DMF	>99/1<	89
3	**6 b** (OTs)	THF	85/15	80
4	**6 b** (OTs)	DMF	>99/1<	80
5[c]	**6 c** (OCOOMe)	DMA	>99/1<	26

[a] All reactions were carried out at room temperature for 12 h in the presence of 2.0 equiv of **4**. [b] The ratio was determined by ^{1}H NMR (300 MHz) analysis. [c] The reaction was carried out under ultrasound-irradiation.

when the reaction was carried out in DMF in place of THF under similar conditions (entry 4). The reaction is completely regioselective, giving the allene as the sole product in high yield. Propargyl carbonate **6c** showed modest reactivity toward **4**; the allene was formed in low yield through the ultrasound−assisted reaction in DMA (entry 5).[6b] Propargyl acetate **6d** was a poor substrate for this transformation; only a traceable amount of **7** was confirmed by ^{1}H NMR.[11]

The structure of **7** was confirmed by means of ^{1}H NMR and IR spectroscopy.[12] In the ^{1}H NMR spectrum (400 MHz, $CDCl_3$), diagnostic allene−protons were observed at δ 5.56-5.42 (1H, m) and δ 5.20 (2H, dddd, J_{HH} = 5.3 Hz, J_{HP} = 6.7 Hz, J_{FH} = 6.8, 6.8 Hz), respectively, with the characteristic H−H, H−P, and H−F couplings. The antisymmetrical stretch band for the allene was observed at 1981 cm^{-1}.

Terminal substituents on the acetylene are known to affect greatly the regiochemical outcome of the addition of an organocopper species to propargylic substrates.[13,14] Then, we next examined the steric effects of the terminal substituents on the allene/acetylene distribution for these reactions (Table 2). When the 1-bromo-2-butyne **9a** was treated with **4** in DMF; the reaction gave an inseparable mixture of the allene **10** and the acetylene **11** in a ratio of 23:77 in 71% yield (entry 1).[15] Under the same conditions, the propargylic tosylate **9b** gave an almost 1:1 mixture of **10** and **11** (entry 2). 1-Bromo-2-butyne **9a** and the tosylate **9b** showed different reactivity toward **4** in THF (entries 3 and 4). 1-Bromo-2-butyne **9a** reacted with **4** in favor of formation of the allene, whereas the tosylate **9b** gave the acetylene **11** in modest selectivity.



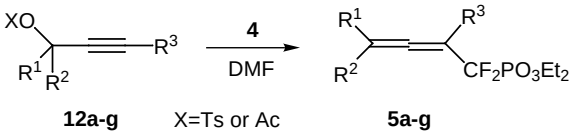
Scheme 2

Table 2 Reaction of **4** with propargylic substrates **9a,b**[a]

Entry	**9** (X)	Solvent	**10**/**11**[b]	Yield(%)
1	**9a** (X=Br)	DMF	23/77	71
2	**9b** (X=OTs)	DMF	48/52	95
3	**9a** (X=Br)	THF	60/40	60
4	**9b** (X=OTs)	THF	15/85	67

[a] All reactions were carried out at room temperature for 12 h in the presence of 2.0 equiv of **4**. [b] The ratio was determined by ^{1}H NMR (300 MHz) analysis.

With these results in hand, we focused on the reaction with propargylic substrates **12a-g**, derived from known propargylic alcohols through the standard tosylation or acetylation,[13,14] to examine the generality and scope of these reactions.[16] As shown in Table 3, propargylic tosylates **12a-c** reacted with **4** in DMF to give di-substituted allenes **5a-c** in good to excellent yield (entries 1−3). Propargylic acetates **12d-f**, in which the acetoxy group is positioned at either the quaternary or benzylic carbon, were good substrates for this transformation (entries 4-6). From these reactions, tri-substituted allenes **5d,e** and the allene **5f** conjugated to phenyl were isolated in good to excellent yield. *Endo*-terminal propargylic acetate **12g** did not react with **4** under the conditions and was recovered (entry 7).



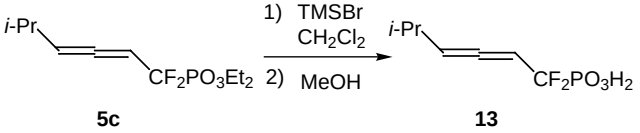
Scheme 3

Table 3 Synthesis of allenic (α,α-difluoromethylene)phosphonates **5**[a]

Entry	Substrate					Product	
	12	R'	R^2	R^3	X	**5**	Yield(%)
1	**12a**	Me	H	H	Ts	**5a**	83
2	**12b**	*n*-Pr	H	H	Ts	**5b**	72
3	**12c**	*i*-Pr	H	H	Ts	**5c**	98
4	**12d**	Me	Me	H	Ac	**5d**	93
5	**12e**	−(CH$_2$)$_5$−		H	Ac	**5e**	73
6	**12f**	Ph	H	H	Ac	**5f**	74
7	**12g**	Ph	H	Ph	Ac	**5g**	0

[a] All reactions were carried out in DMF at room temperature for 12 h.

Deprotection of diethyl ester **5c** under the conventional conditions (i TMSBr, CH_2Cl_2; ii MeOH) gave the free acid **13** in virtually quantitative yield without affecting the allenic moiety. In the ^{1}H NMR spectrum (300 MHz, MeOH-d_4), diagnostic allene−protons were obserbed at δ 5.71-5.60 (1H, m) and δ 5.57-5.43 (1H, m) with the characteristic H−H, H−P, and H−F couplings. The structure of **13** was also confirmed by FABMS analysis (m/z 213 (MH^+)).



Scheme 4

In summary, a facile preparation of novel allenic (α,α-difluoromethylene)phosphonates is achieved by CuBr-promoted reaction of $BrZnCF_2PO_3Et_2$ with readily available propargylic substrates.

Acknowledgement

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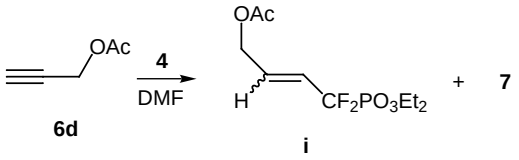
(9) Burton briefly described a reaction of propargyl chloride with **2** in THF in the presence of copper (I) bromide to give an allene.[4a] However, the details of the reaction were not disclosed.
(10) The propargylic methylene and terminal acetylenic protons of **8** were observed at δ 3.02 (tdd, J = 17.5, 5.8, 2.7 Hz) and 2.16 (t, J = 2.8 Hz), respectively, in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$).
(11) The reaction between **4** and the aceteate **6d** in DMF gave an *E*/*Z* mixture (1:1) of (α,α-difluoroallyl)phosphonates **i** as major products:[6a]



Scheme 5

(12) All new compounds gave satisfactory spectroscopic (^{1}H-, ^{19}F-, ^{31}P-, ^{13}C NMR, MS and IR) and analytical data.
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(15) The allenyl and methyl protons of **10** were observed at δ 5.10-5.01 (m) and 1.87 (t with multiple small splits, J = 4.4 Hz); the propargylic methylene and terminal methyl protons of **11** were observed at δ 2.96 (tdd, J = 17.7, 6.0, 2.6 Hz) and 1.81 (t, J = 2.6 Hz), respectively, in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of a mixture of **10** and **11**.
(16) Typical experimental procedure for the synthesis of **5c**: Copper species **4** was generated in DMF (10 mL) from zinc dust (650 mg, 10 mmol), diethyl bromodifluoromethylphosphonate (2.67 g, 10 mmol), and copper (I) bromide (1.43 g, 10 mmol) as described previously.[6] To the solution of **4** thus generated in DMF was added a solution of **12c** (1.0 g, 5 mmol) in DMF (10 mL) at room temperature. After being stirred at room temperature for 12 h, water was added to quench the reaction. The biphasic mixture was passed through Celite, and extracted with Et_2O. The extracts were washed with brine, dried over $MgSO_4$ and evaporated. The volatile components of the residue were removed in vacuo (0.05 mmHg, 80 °C) to leave **5c** (1.31 g, 98%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66-5.59 (1H, m), 5.51-5.43 (1H, m), 4.40-4.19 (4H, m), 2.51-2.35 (1H, m), 1.38 (6H, t, J = 7.0 Hz), 1.07 (6H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.28 (m), 115.88 (td, J_{CP} = 221.5 Hz, J_{CF} = 258.6 Hz), 104.51, 88.45 (dt, J_{CP} = 15.8 Hz, J_{CF} = 26.1 Hz), 64.55 (d, J_{CP} = 8.9 Hz), 64.47 (d, J_{CP} = 8.9 Hz), 27.63, 22.00, 21.94, 16.33 (d, J_{CP} = 5.27 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.89 (t, J_{PF} = 115.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, relative to BTF) δ −42.52 (2F, dddd, J_{PF} = 115.1 Hz, J_{HF} = 11.7, 5.6, 5.6 Hz), IR (film) 1971, 1273 cm^{-1}. MS (EI) m/z 269 (M^++1), 268 (M^+). HRMS (EI) calcd for $C_{11}H_{19}F_2O_3P$ (M^+): 268.1040. Observed: 268.1041.

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