Pergamon

Tetrahedron Letters 40 (1999) 1869–1872

TETRAHEDRON LETTERS

Facile Installation of the Phosphonate and (α,α-Difluoromethyl)phosphonate Functionalities Equipped with Benzyl Protection

David B. Berkowitz*, Debnath Bhuniya and Gorka Peris

Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588-0304

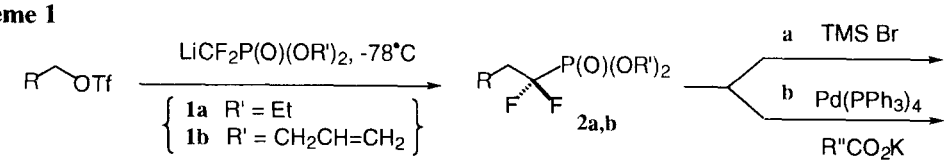
Received 17 December 1998; revised 5 January 1999; accepted 6 January 1999

Abstract: Under appropriate conditions, dibenzyl (lithiomethyl)phosphonate and dibenzyl (lithiodifluoromethyl)phosphonate displace primary triflates to provide convenient access to the corresponding phosphonates, carrying benzyl ester protecting groups. This approach is of particular advantage for phosphonate ester deprotection, which may be achieved by simple hydrogenolysis.

There has been a long-standing interest in the synthesis of phosphonates as hydrolytically stable mimics of biological phosphates.[1] More recently, α-halogenated phosphonates have received considerable attention, particularly those in which the bridging oxygen atom is replaced by a CF_2 unit.[2] Blackburn has predicted that these might be "isosteric and isopolar" analogs of the corresponding phosphonates.[3] The data now unambiguously show that introduction of α-difluorination leads to a reduced second pK_a, resulting in "isoionic" phosphate mimics (at least where the dianion is the relevant species). Indeed, in a recent study, the superiority of α,α-difluorinated (bis)phosphonates as inhibitors of 3-phosphoglycerate kinase has been attributed to this pK_a-lowering effect.[4]

However, from the enzyme kinetic data currently available, it is difficult to predict which phosphate binding sites are best targeted with α,α-difluorinated phosphonates,[5] and which with their non-fluorinated congeners.[6] A rate-limiting step in obtaining such comparative data has been the phosphonate deprotection/purification operation. This Letter provides a simple, yet heretofore unavailable, solution to that problem.

Scheme 1



The most convergent synthetic approaches to (α,α-difluoroalkyl)phosphonates include: (i) PCF_2-C bond construction from $(RO)_2P(O)CF_2M$ reagents via triflate displacement (Scheme 1),[7] carbonyl addition,[8] conjugate addition,[9] or transition metal-mediated cross-coupling reactions[10] and (ii) $(RO)_2P(O)CF_2$-radical-mediated couplings with alkenes,[11a] alkynes[11b] and pyrophosphites (PCF_2-P bond).[11c] Alternatively, Piettre has recently described an elegant radical-mediated approach to P-CF_2C bond formation.[12]

In nearly all of these approaches, the fluorinated phosphonate functionality enters with diethyl ester protection. Such diethyl phosphonates can be deprotected using the Rabinowitz/Jung/McKenna protocol {TMSX} in many cases.[13] However, problems have been encountered with TMSBr(I) when attempting to deblock (diethyl)phosphonato groups appended to certain lactone (dimethyl and dibutyl esters were used here),[14a] pyranose,[14b] or amino acid[14c] frameworks. Piettre has reported major problems with the deprotection of diethyl

* email: dbb@unlinfo.unl.edu; fax: (402) 472-9402.

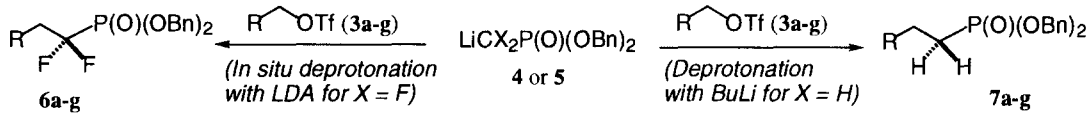
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00077-5

phosphonothioates under these conditions.[14d] Very recently, we and Badet have independently encountered similar difficulties with TMSBr-mediated diethyl phosphonate deprotection in certain furanose systems.[14e]

To expand the repertoire of available deprotection conditions, we introduced **1b** as a new reagent for triflate displacement reactions.[15] Deprotection of allyl esters was done under mild conditions using potassium 2-methyl-hexanoate in the presence of $Pd(PPh_3)_4$, leading to the dipotassium salts of the target phosphonates. For many of our applications in the carbohydrate area, however, multiple protection of sugar hydroxyls is necessary. We have found it especially convenient to use benzyl ether protection there. So, ideally if one could also introduce the phosphonate functionality with benzyl protection, one might be able to unveil the fully deprotected sugar phosphonate in one step, and as the free acid.

In fact, $LiCH_2P(O)(OBn)_2$ (**5**) is known, and has been used to prepare dibenzyl phosphonates via, (a) epoxide ring-opening,[16c,e] (b) acyl substitution reactions at carbonyl centers,[16a,b] and (c) condensations with phosphoryl chlorides.[16d] On the other hand, previous attempts to form $LiCF_2P(O)(OBn)_2$ (**4**) and carry out alkylation reactions with the reagent have apparently been unsuccessful.[14d]

Scheme 2



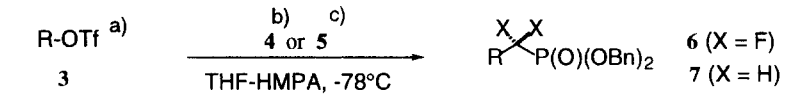
We are pleased to describe here conditions under which both $LiCF_2P(O)(OBn)_2$ (**4**) and $LiCH_2P(O)(OBn)_2$ (**5**) may be deployed in triflate displacement reactions, providing a very direct route for the installation of dibenzylphosphonato and dibenzyl(α,α-difluoro)phosphonato groups (Scheme 2). The phosphonates themselves, $HCF_2P(O)(OBn)_2$ and $CH_3P(O)(OBn)_2$, are easily prepared in 70-80% yield by reaction of HCF_2Cl or CH_3I with $NaP(O)(OBn)_2$ [from NaHMDS and $HP(O)(OBn)_2$] in THF at rt.

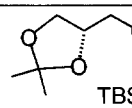
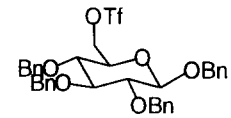
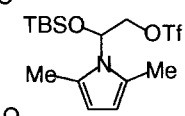
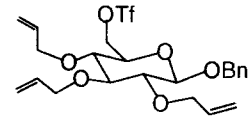
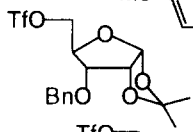
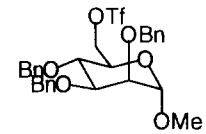
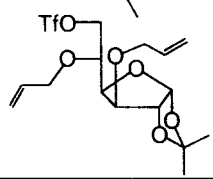
The non-fluorinated anion, $LiCH_2P(O)(OBn)_2$ (**5**) is well-behaved. It may be generated by deprotonation with *n*-BuLi, followed by alkylation with a primary triflate of choice. Yields are generally very good and derivatives of glycerol, serine, glucopyranose, glucofuranose and mannose have been obtained. On the other hand, consistent with Piettre's observations,[14d] the corresponding fluorinated phosphonate anion (**4**) is much more difficult to handle. *However, successful alkylations of this reagent can be achieved by adding a solution of LDA in to a mixture of $HCF_2P(O)(OBn)_2$ and triflate at low T.* Under these conditions, yields are typically in the 50% range, with about 10-15% unreacted triflate remaining, in most cases. For both reagents, we typically employ two equivalents of phosphonate anion, relative to triflate. Yields remain essentially unchanged with greater excesses of phosphonate anion or with longer reaction times.

Typical displacement procedure with **4**: To a solution of **3g** (352 mg, 0.59 mmol) and $HCF_2P(O)POBn)_2$ (369 mg, 1.2 mmol) in THF (6 mL) at –78°C is added, dropwise and via cannula, a (–78°C) solution of LDA (1.18 mmol) and HMPA (0.21 mL, 1.2 mmol) in THF (6 mL). After stirring for 15 min at –78°C, the reaction is quenched with NH_4Cl (aq) and diluted with Et_2O (20 mL). The organic layer is washed again with NH_4Cl (aq), followed by water and brine. After drying (Na_2SO_4), filtration and evaporation, flash chromatography (ethyl acetate/hexanes) affords **6g** (210 mg, 47%).

Typical displacement procedure with **5**: To a solution of *n*-BuLi (0.62 mL of a titrated 2.4 M solution in hexanes, 1.5 mmol) in THF (5 mL) at –78°C, is slowly added, via cannula, a solution of $CH_3P(O)(OBn)_2$ (416 mg, 1.5 mmol) and HMPA (0.26 mL, 1.5 mmol) in THF (5 mL) at –78°C. After 5 min, a solution of **3g** (449 mg, 0.75 mmol) in THF (5 mL) at –78°C is added dropwise, via cannula. After 20 min, the reaction is quenched with NH_4Cl (aq) and worked up as described for **6g**. Following SiO_2 chromatography, one obtains **7g** (380 mg, 70%).

Table

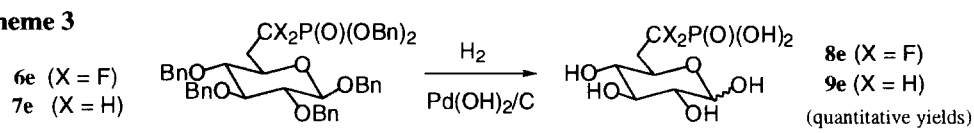


3		6 [d]	7 [d]	3		6 [d]	7 [d]
a		56	76	e		52	72
b		55	78	f		50	72
c		50	75	g		47 [f]	70 [g]
d		52	74				

[a] Prepared according to ref. 7a. [b] For $HCF_2P(O)(OBn)_2$: purified by SiO_2 chromatography (5→15% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) 5.15 (d, *J*=8 Hz, 4H), 5.82 (dt, *J*=28, 48 Hz, 1H), 7.35 (10H); ^{13}C NMR ($CDCl_3$, 125 MHz) 70.16 (d, *J*=6 Hz), 112.0 (dt, *J*=212, 257 Hz), 128.8, 129.3, 129.5, 135.6 (d, *J*=5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz) 5.4 (t, *J*=93 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) -135.3 (dd, *J*=48, 93 Hz). [c] For $H_3CP(O)(OBn)_2$: bp 160°C (0.01 torr); ^1H NMR ($CDCl_3$, 300 MHz) 1.43 (d, *J*=18 Hz, 3H), 4.96 (dd, *J*=6, 12 Hz, 2H), 5.06 (dd, *J*=6, 13 Hz, 2H), 7.38 (10H); ^{13}C NMR ($CDCl_3$, 75 MHz) 12.13 (d, *J*=144 Hz), 67.6 (d, *J*=6 Hz), 128.4, 128.9, 129.1, 136.8 (d, *J*=7 Hz); ^{31}P NMR ($CDCl_3$, 122 MHz) 31.5. [d] Isolated yields (%) of pure products with satisfactory ^1H, ^{13}C, and ^{31}P NMR spectra. [e] From racemic serine. See ref. 7c for details. [f] For **6g**: ^1H NMR ($CDCl_3$, 500 MHz) 2.22-2.40 (m, 1H), 2.44-2.71(m, 1H), 3.31(s, 3H), 3.64 (t, *J*=9 Hz, 1H), 3.78 (br, 1H), 3.87 (dd, *J*=3, 9 Hz, 1H), 4.07 (t, *J*=9 Hz, 1H), 4.54-4.76 (m, 6H), 4.96 (d, *J*=11 Hz, 1H), 5.01-5.19 (m, 4H), 7.2-7.4 (25H); ^{13}C NMR ($CDCl_3$, 75 MHz) 35.9-36 (m), 55.5, 66.2, 70.1 (d, *J*=7 Hz, 2C), 72.7, 73.4, 75.1, 75.7, 77.8, 80.9, 99.5, 128.3-129.1 (aromatics, 25C), 135.9 (d, *J*=6 Hz, 2C), 138.7, 138.8, 139.0; ^{31}P NMR ($CDCl_3$, 122 MHz) 7.65 (t, *J*=109 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) -112.8 (dddd, *J*=13, 20, 109, 302 Hz), -110.2 (dddd, *J*=13, 33, 109, 302 Hz). [g] For **7g**: ^1H NMR ($CDCl_3$, 500 MHz). 1.75-1.90 (m, 2H), 2.1-2.3 (m, 1H), 3.25 (s, 3H), 3.52 (dt, *J*=9, 2 Hz, 1H), 3.68 (t, *J*=9 Hz, 1H), 3.81 (br s, 1H), 3.86 (dd, *J*=9, 2 Hz, 1H), 4.62 (d, *J*=12 Hz, 1H), 4.63 (br s, 2H), 4.68 (br s, 1H), 4.73 (d, *J*=12 Hz, 1H), 4.78 (d, *J*=12, 1H), 4.94 (d, *J*=11 Hz, 1H), 4.98-5.10 (m, 4H), 7.2-7.4 (25H); ^{13}C NMR ($CDCl_3$, 125 MHz) 22.7 (d, *J*=143 Hz), 25.3 (d, *J*=4 Hz), 55.2, 67.6 (d, *J*=4 Hz), 67.7, 71.7, 71.8, 72.7, 73.4, 75.7, 78.8, 80.8, 99.6, 128.1-129.2 (aromatics, 25C), 137.1 (d, *J*=5 Hz, 2C), 138.9, 139.0, 139.1; ^{31}P NMR ($CDCl_3$, 202 MHz) 32.98.

To illustrate the advantage of this new approach in accessing free sugar phosphonates, all ether and phosphate ester protecting groups in both **6e** and **7e** were cleaved under standard hydrogenolytic conditions (Scheme 3). The free glucose-6-phosphate analogs, **8e** and **9e**, respectively, were obtained as the expected α/β anomeric pairs, without need for further purification. The application of this approach to the synthesis of other (fluorinated) sugar phosphonates, as well as their biochemical evaluation, is under investigation and will be reported in due course.

Scheme 3



Acknowledgements. The authors are grateful to the American Heart Association for financial support. D.B.B. is an Alfred P. Sloan Fellow. G.P. thanks the Howard Hughes Medical Institute for a summer undergraduate research fellowship (UNL SURE program). Thanks are due to R.K. Shoemaker (UNL) for assistance, and to the NIH (SIG 1-S10-RR06301) & NSF (CHE-93000831) for NMR and GC/MS instrumentation, respectively.

REFERENCES

1. Reviews: (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349-367; (b) Wiemer, D.F. *Tetrahedron* **1997**, *53*, 16609-16644.
2. For overviews of recent work in the area, see: (a) Tozer, M.J.; Herpin, T.F. *Tetrahedron* **1996**, *52*, 8619-8683; (b) Burton, D.J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641-1715.
3. (a) Blackburn, G.M. *Chem. Ind. (London)* **1981**, 134-138; (b) Blackburn, G.M.; Kent, D.E.; Kolkmann, F. *J. Chem. Soc. Perkin Trans. I* **1984**, 1119-1125; (c) Blackburn, G.M.; Perrée, T. D.; Rashid, A. *Chem. Scripta* **1986**, *26*, 21-24.
4. Caplan, N.A.; Pogson, C.I.; Hayes, D.J.; Blackburn, G.M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 515-520.
5. For cases in which α,α-difluorination enhances enzyme-binding, see: (a) Stremler, K.E.; Poulter, C.D. *J. Am. Chem. Soc.* **1987**, *109*, 5542-5544 (geranyl diphosphate analogs as FDP synthase pseudo-substrates); (b) Arabshahi, L.; Khan, N.N.; Butler, M.; Noonan, T.; Brown, N.C.; Wright, G.E. *Biochemistry* **1990**, *29*, 8620-8626 [β,γ-CF_2-dGTP as a substrate for *B. subtilis* DNA pol III; $K_m < K_m$(dGTP)]; (c) Hebel, D.; Kirk, K.L.; Kinjo, J.; Kovacs, T.; Lesiak, K.; Balzarini, J.; De Clercq, E.; Torrence, P.F. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 357-360 (RT inhibitors); (d) Phillion, D.P.; Cleary, D.G. *J. Org. Chem.* **1992**, *57*, 2763-2764 (EPSP synthase inactivator); (e) Burke, T.R., Jr.; Kole, H.K.; Roller, P.P. *Biochem. Biophys. Res. Commun.* **1994**, *204*, 129-134 and (f) Kole, H.K.; Smyth, M.S.; Russ, P.L.; Burke, T.R., Jr. *Biochem. J.* **1995**, *311*, 1025-1031 (PTP inhibitors); (g) Halazy, S.; Ehrhard, A.; Eggenspiller, A.; Berges-Gross, V.; Danzin, C. *Tetrahedron* **1996**, *51*, 177-184 (PNP inhibitors).
6. For instances in which simple phosphonates perform better than their difluorinated analogs, see: (a) Martin, S.F.; Wong, Y.-L.; Wagman, A.S. *J. Org. Chem.* **1994**, *59*, 4821-4831 (PC-PLC inhibitors); (b) Gzik, L.; Langston, S.P.; Brown, P.; Blackburn, G.M. *Nucleosides & Nucleotides* **1995**, *14*, 731-734 (Ap_4A-hydrolase substrates); (c) Nieschalk, J.; Batsanov, A.S.; O'Hagan, D.; Howard, J.A.K. *Tetrahedron* **1996**, *51*, 165-176 (G3PDH substrates).
7. For examples of the triflate displacement approach to PCF_2-C bond formation, see: (a) Berkowitz, D.B.; Eggen, M.; Shen, Q.; Sloss, D.G. *J. Org. Chem.* **1993**, *58*, 6174-6176; (b) Vinod, T.K.; Griffith, O.H.; Keana, J.F.W. *Tetrahedron Lett.* **1994**, *35*, 7193-7196; (c) Berkowitz, D.B.; Shen, Q.; Maeng, J.-H. *Tetrahedron Lett.* **1994**, *35*, 6445-6448. (d) Matulic-Adamic, J.; Haeberli, P.; Usman, N. *J. Org. Chem.* **1995**, *60*, 2563-2569.
8. For carbonyl condensation routes, see: (a) Obayashi, M.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2327-8; (b) Martin, S.F.; Dean, D.W.; Wagman, A.S. *Ibid.* **1992**, *33*, 1839-1842. (c) Lequeux, T.P.; Percy, J.M. *J.C.S. Chem. Commun.* **1995**, 2111-2112; (d) Berkowitz, D.B.; Eggen, M.; Shen, Q.; Shoemaker, R.K. *J. Org. Chem.* **1996**, *61*, 4666-4675; (e) Piettre, S.R.; Girol, C.; Schelcher, C.G. *Tetrahedron Lett.* **1996**, *37*, 4711-4712.
9. For conjugate addition approaches, see: (a) Lequeux, T.P.; Percy, J.M. *Synlett* **1995**, 361-362; (b) Campbell, M.M.; Kawamoto, A.M. *J. Fluorine Chem.* **1997**, *81*, 181-186; (c) Blades, K.; Lapôtre, D.; Percy, J.M. *Tetrahedron Lett.* **1997**, *38*, 5895-5898; (d) Blades, K.; Percy, J. M. *Tetrahedron Lett.* **1998**, *39*, 9085-9088.
10. For transition metal-mediated PCF_2-C(sp^2) bond formation, see: (a) Burton, D.J.; Sprague, L.G. *J. Org. Chem.* **1988**, *53*, 1523-1527; (b) Qiu, W.; Burton, D. J. *Tetrahedron Lett.* **1996**, *37*, 2745-2748; (c) Yokomatsu, T.; Suemune, K.; Murano, T.; Shibuya, S. *J. Org. Chem.* **1996**, *61*, 7207-7211; (d) Yokomatsu, T.; Murano, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1997**, *53*, 815-822.
11. For radical-mediated approaches to PCF_2-C or PCF_2-P bond formation, see: (a) Yang, Z.-Y.; Burton, D.J. *J. Org. Chem.* **1992**, *57*, 4676-4683; (b) Li, A.-R.; Chen, Q.Y. *Synthesis*, **1996**, 606-608; (c) Nair, H.K.; Burton, D.J. *J. Am. Chem. Soc.* **1997**, *119*, 9137-9143.
12. For P-CF_2C bond formation, see: (a) Piettre, S.R. *Tetrahedron Lett.* **1996**, *37*, 2233-2236; (b) Herpin, T.F.; Motherwell, W.B.; Roberts, B.P.; Ronald, S.; Weibel, J.-M. *Tetrahedron* **1997**, *53*, 15085-15100.
13. (a) Rabinowitz, R. *J. Org. Chem.* **1963**, *28*, 2975-2978; (b) Jung, M.E.; Lyster, M.A. *J. Am. Chem. Soc.* **1977**, *99*, 968-9; (c) McKenna, C.E.; Higa, M.T.; Cheung, N.H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, *18*, 155-8.
14. (a) Kamber, M.; Just, G. *Can. J. Chem.* **1985**, *63*, 823-827; (b) Wang, M. F.; Crilley, M.M.L.; Golding, B.T.; McInally, T.; Robinson, D.H.; Tinker, A. *J.C.S. Chem. Commun.* **1991**, 667-66; (c) Gordeev, M.F.; Patel, D.V.; Barker, P. L.; Gordon, E.M. *Tetrahedron Lett.* **1994**, *35*, 7585-7588; (d) Piettre, S.R.; Raboisson, P. *Ibid.* **1996**, *37*, 2229-2232; (e) Le Camus, C. Doctoral Thesis, Univ. Rene Descartes, **1998** (B. Badet, Advisor).
15. Berkowitz, D.B.; Sloss, D.G. *J. Org. Chem.* **1995**, *60*, 7047-7050.
16. (a) Andrus, A.; Christensen, B.G.; Heck, J.V. *Tetrahedron Lett.* **1984**, *25*, 595-598; (b) Chakravarty, P.K.; Comb, P.; Roth, A.; Greenlee, W.J. *Ibid.* **1987**, *28*, 611-612; (c) Li, Z.; Racha, S.; Dan, L.; El-Subbagh, H.; Abushanab, E. *J. Org. Chem.* **1993**, *58*, 5779-5783; (d) Grison, C.; Charbonnier, F.; Coutrot, Ph. *Tetrahedron Lett.* **1994**, *35*, 5425-5428; (e) Migand, M.E.; Frost, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 495-501.