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Synthesis of Benzylic Mono(α,α-Difluoromethylphosphonates) and Benzylic Bis(α,α-Difluoromethylphosphonates) via Electrophilic Fluorination

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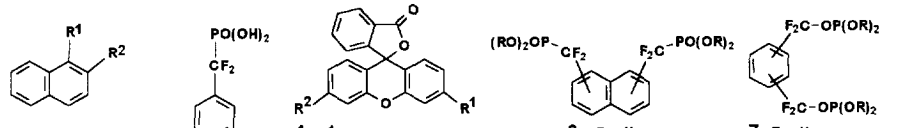
Abstract: A series of benzylic mono(α,α-difluoromethylphosphonates) and benzylic bis(α,α-difluoromethylphosphonates) have been prepared via electrophilic fluorination of the corresponding benzylic phosphonates.

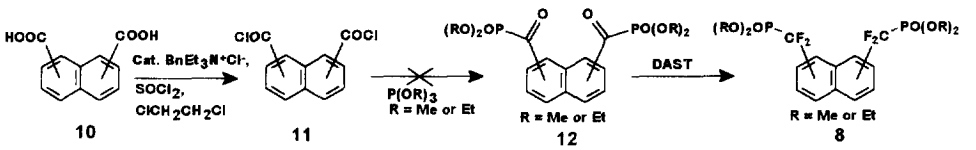
Protein tyrosine phosphatases (PTPases) are enzymes that catalyze the removal of phosphate groups from phosphotyrosine residues in proteins. These enzymes are crucial for the regulation of a wide variety of biochemical processes such as intracellular signaling, cell growth and differentiation to name but a few. In addition, recent studies have suggested that overexpression of certain PTPases results in a number of disease states such as diabetes[1a] and ovarian cancer.[1b] Consequently, there has been much interest in the development of PTPase-specific inhibitors.[2a,b] The most common approach towards the rational development of PTP-specific inhibitors has been to incorporate non-hydrolyzable phosphotyrosine mimetics into synthetic PTPase peptide substrates.[3a,3b] Although peptide-based inhibitors are useful in determining important properties for substrate-



1, $R^1 = CF_2PO(OH)_2$, $R_2 = H$
2, $R^1 = H$, $R^2 = CF_2PO(OH)_2$
3
4, $R^1 = OPO(OH)_2$, $R_2 = H$
5, $R^1 = R^2 = OPO(OH)_2$
6, R = H
8, R = Me or Et
7, R = H
9, R = Me or Et

PTPase interactions, their use as probes for cellular studies and as therapeutics is limited due to their susceptibility to proteolytic degradation. However, very little has been reported on the development of reversible, organic, non-peptidyl inhibitors of PTPases. Recently, Burke and coworkers reported that naphthyl derivatives having the difluoromethylphosphonyl (DFMP) group, **1** and **2**, were relatively good but non-specific competitive inhibitors of the PTPase, PTP1B,[2b] while the phenyl derivative, **3**, was a very poor inhibitor of PTP1B.[2b] Recent studies with non-peptidyl PTPase substrates, such as **4** and **5**, have demonstrated that the presence of two phosphate groups significantly enhances substrate binding and specificity[4a,b] (with PTP1B, K_m for **4** > 200 uM, K_m for **5** = 10 uM[4b]). Consequently, we reasoned that incorporation of two DFMP moieties into a naphthyl or phenyl ring (**6** and **7**) may increase the selectivity and potency of the naphthyl- and phenyl-based inhibitors towards PTPases. Thus, we have undertaken the syntheses of a series of benzylic bis(α,α-difluoromethylphosphonates), **8** and **9**. Herein we report that these species, as well as a variety of benzylic mono(α,α-difluoromethylphosphonates), can be readily obtained via electrophilic fluorination of the corresponding benzylic phosphonates.

For construction of the bis-substituted naphthyl compounds, **8**, we wished to use a methodology that would allow us to start with readily available, isomerically pure, naphthyl starting materials. Consequently, we first attempted to synthesize these species via DAST fluorination of the bis(α-ketophosphonates), **12**, since this procedure has been used extensively in the synthesis DFMP-containing inhibitors[5] and the diacid precursors, **10**, could be prepared in high yields via oxidation[6] of commercially available, isomerically pure dimethylnaphthalenes (Scheme 1). We first attempted the synthesis of the 2,6-naphthyl derivative using this



Scheme 1

procedure. However, numerous attempts to synthesize the bis(α-ketophosphonate) precursor by reacting the bis(acid chloride)[7], **11**, with trimethyl or triethyl phosphite were unsuccessful.[8] Similar attempts to form the para-bis(α-ketophosphonate) phenyl derivative by reacting triethyl phosphite with terephthaloyl chloride were also unsuccessful. Therefore, we turned to other methods, most notably the fluorination of phosphonate carbanions with the electrophilic fluorinating agent, N-fluorobenzenesulfonimide (NFBS), a reagent that had been previously used by Differding and coworkers for the synthesis of non-benzylic α,α-difluorophosphonates.[9] We first attempted this procedure on benzylic monophosphonates. Although it had been previously reported[5] that similar benzylic α,α-difluoromethylphosphonates could not be obtained by electrophilic fluorination, we found that we could readily obtain a variety benzylic α,α-difluoromethylphosphonates in good to excellent yields by reacting benzylic phosphonates[10] with 2.2 equivalents of NaHMDS[11] at -78°C in THF followed by the addition of 2.5 equivalents of NFBS (Table 1). A number of functional groups (halo, nitro, ether) could be tolerated

Table 1. Preparation of Benzylic mono(α,α-Difluorophosphonates).[a]

entry	substrate	product[b]	yield
1	$PhCH_2PO(OEt)_2$	$PhCF_2PO(OEt)_2$	79
2	$PhCH_2PO(OEt)_2$	$PhCFHPO(OEt)_2$	69
3	*p*-$BrPhCH_2PO(OMe)_2$	*p*-$BrPhCF_2PO(OMe)_2$	79
4	*p*-$NO_2PhCH_2PO(OMe)_2$	*p*-$NO_2PhCF_2PO(OMe)_2$	74
5	*p*-$MeOPhCH_2PO(OMe)_2$	*p*-$MeOPhCF_2PO(OMe)_2$	80
6	β-naphthyl-$CH_2PO(OMe)_2$	β-naphthyl$CF_2PO(OMe)_2$	90
7	α-naphthyl-$CH_2PO(OMe)_2$	α-naphthyl$CF_2PO(OMe)_2$	85

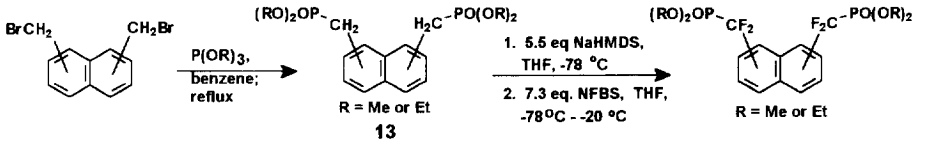
(a) Characterized by MS and ^1H-, ^{31}P- ^{19}F- and ^{13}C-NMR

(b) All products were obtained using 2.2 equivalents of NaHMDS and 2.5 equivalents of NFBS with the exception of entry 2 in which 1.1 eq. of NaHMDS and NFBS were used.

and both methyl and ethyl phosphonate esters could be employed. We have also found that this method is superior to the DAST procedure[5] for synthesizing these mono substituted derivatives[12] and yields are comparable with CuCl-promoted coupling of (diethylphosphonyl)difluoromethylcadmium reagent with aryl iodides.[13] Although the monofluoro derivatives could be readily obtained in reasonable yields (for example see

entry 2, Table 1) by reducing the number of equivalents of base and NFBS (1.1 eq) we found that isolation of the monofluoro derivatives, followed by another fluorination reaction at -85 °C did not improve yields. This is in contrast to Differding's original report[9] on the fluorination of non-benzylic phosphonates in which the best yields of α,α-difluorophosphonates were obtained by a two step procedure involving formation and isolation of the monofluoro species followed by another fluorination reaction at -85 °C.

We then turned our attention to the formation of the bis-substituted derivatives **8** and **9**. The phosphonate precursors were readily obtained in excellent yields by reacting trimethyl- or triethyl phosphite with



Scheme 2

bis(bromomethyl)naphthalenes[14] or α,α'-dibromoxylenes. We found that a variety of benzylic bis(α,α-difluoromethylphosphonates) could be obtained in a single fluorination reaction by reacting bis-phosphonates, such as **13**, with 5.5 eq of NaHMDS at -78 °C followed by addition of 7.3 eq. of NFBS in THF (Scheme 2).[15] The results are summarized in Table 2. With the exception of the 2,6 naphthyl isomer (23 %, entries 3 and 4, Table 2), the yields were in the range of 46-74 %.[16] The yields were not improved by stepwise fluorination and both methyl and ethyl phosphonates gave similar yields (entries 1-6, Table 2). By reducing the number of equivalents of NaHMDS (2.5 eq) and NFBS (3.0 eq), benzylic bis(α-monofluorophosphonates) could be

Table 2. Preparation of Benzylic Bis(α,α-Difluorophosphonates).[a]

entry	naphthyl	R[b]	Yield (%)
1	2,7	Me	57
2	"	Et	49
3	2,6	Me	23
4	"	Et	23
5	1,5	Me	46
6	"	Et	48
7	1,3	Me	55
8	1,6	Me	51
9	1,7	Et	46
	phenyl		
10	meta	Me	46
11	"	Et	74

(a) Characterized by MS and ^{1}H-, ^{31}P- , ^{19}F- and ^{13}C-NMR spectra.
(b) R refers to the ethyl or methyl ester in Scheme 2.

isolated as the major product from a mixture of mono- and bis-substituted products. Under no circumstances were we able to detect any benzylic mono(α,α-difluoromethylphosphonate) product, suggesting that the reaction, in the presence of 5.5 eq of NaHMDS and 7.3 eq. of NFBS, proceeds exclusively via initial formation of the dianion and the benzylic bis(α-monofluoromethylphosphonate).

To summarize, we have demonstrated that a variety of benzylic mono- and bis(α,α-difluoromethylphos-

phonates) can be readily prepared via electrophilic fluorination of the corresponding benzyl phosphonate derivatives. Conversion of these esters into the corresponding acids and their evaluation as inhibitors of PTPases is in progress.

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5. Smyth, M. S.; Ford, H. Jr.; Burke, T.R. Jr. *Tetrahedron. Lett* **1992**, *33*, 4137. These workers also attempted to synthesize similar benzylic α,α-difluoromethylphosphonates (entries 1 and 6 in Table 1 protected with t-butyl groups) by converting the α-monofluorophosphonates, obtained by DAST fluorination of the α-hydroxy phosphonates, to the difluorophosphonates using NFBS but were unsuccessful.
6. Friedman, L.; Fishel, D. L; Shechter, D. *J. Org. Chem.* **1965**, *30*, 1453.
7. Burdett, K. A. *Synthesis* **1991**, 441.
8. ^{31}P NMR analysis of the crude reaction mixtures showed a multitude of peaks. We also considered synthesizing the bis(α-ketophosphonates) by converting naphthalenedicarboxaldehydes into bis(α-hydroxyphosphonates) followed by oxidation to the desired ketones (see ref. 5). However, this approach was not taken due to the potential difficulties in obtaining all of the various isomers of naphthalenedicarboxaldehyde.
9. Differding, E.; Duthaler, R. O.; Kreiger, A.; Ruegg, G. M.; Schmit, C. *Synlett* **1991**, 395.
10. The benzylic phosphonates were either purchased or could be readily prepared in high yields by reacting trimethyl phosphite with benzylic halides (Arbuzov reaction).
11. Successful fluorinations were also performed using KDA and KHMDS, however, NaHMDS consistently gave the highest yields. LDA also worked but much more poorly than the other bases.
12. We also synthesized entries 1, 6 and 7 in Table 1 using the DAST procedure (reference 5) from the corresponding α-ketophosphonates. However, in our hands, yields ranged from 32-50 % and purification required several columns.
13. While this work was in progress Burton and Qui reported the synthesis of a series of benzylic α,α-difluoromethylphosphonates via CuCl-promoted coupling of (diethylphosphonyl)difluoromethylcadmium reagent with aryl iodides. See Qui, W.; Burton, D.J. *Tetrahedron Lett.* **1996**, *37*, 2745.
14. The bis(bromomethyl)naphthalenes were prepared by photochemical bromination of isomers of dimethylnaphthalene. See Futamara, S.; Zong, Z-M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 345.
15. A typical procedure is as follows: To a solution of NaHMDS (Aldrich, 4.4 mL of a 1.0 M in THF, 4.4 mmol, 5.5 eq.) in dry THF (10 mL, total volume 14.4 mL) at -78 °C was added a solution of 2,7-bis(dimethyl methylphosphonyl)naphthalene (300 mg, 0.806 mmol) in dry THF (15 mL) over a period of 2 min. The resulting suspension was stirred for 1 h at -78 °C and then a solution of NFBS (Aldrich, 1.85 g, 5.88 mmol, 7.3 eq) in dry THF (5 mL) was added over a period of two min, during which time the suspension became a clear solution and turned from dark red to yellow-brown. After addition the solution was stirred for 2h and allowed to warm to -20 °C during which time a precipitate formed. The reaction was quenched with 0.01 N HCl (20 mL) and the resulting solution extracted with EtOAc (3 x 50 mL). The organics were combined and washed with 5 % $NaHCO_3$ (1 x 30 mL), brine (1 x 50 mL), dried ($MgSO_4$) and concentrated by rotary evaporation to give a yellow oil. Pure 2,7-bis(dimethyl α,α-difluoromethylphosphonyl)naphthalene was obtained using silica gel chromatography (EtOAc/hexane 80/20, R_f = 0.45). Yield = 202 mg, 57 %, pale yellow solid. ^{1}H NMR ($CDCl_3$,): δ 8.19 (s, 2H, aromatic), 7.8 (d, J = 8.7 Hz, 2 H, aromatic), 7.7 (d, J = 8.8 Hz, 2H, aromatic), 3.8 (d, J = 10.7 Hz, 12H, $POCH_3$); ^{31}P NMR ($CDCl_3$, 85 % H_3PO_4 ext. standard): δ 6.23 (t, J = 115.9 Hz); ^{19}F NMR ($CDCl_3$, fluorobenzene ext. std.): δ 5.6 (d, J = 115.2 Hz); ^{13}C NMR ($CDCl_3$): δ 55.0 (d, J = 6.6 Hz), 118 (dt, J = 219 Hz), 124.4 (t, J = 5.5 Hz), 127.2 (dt, J = 3.6 Hz), 128.4 (s), 130.7 (dt, J = 13.1 Hz), 131.4 (s), 134.9 (s); MS (m/e, rel. int.): 444 (M^+, 22); 335 (M^+ - $PO(OMe)_2$, 100); 226 (M^+ - 2[$PO(OMe)_2$], 32). HRMS calcd for $C_{16}H_{18}F_4O_6P_2$ [M^+] 444.051. found 444.051.
16. We were unable to obtain the para-phenyl derivative or the 1,4-naphthyl derivative using this procedure. Only unidentified polymeric products were obtained. While this work was in progress, Burton and Qui reported the synthesis of the paraphenyl derivative in 75 % yield by CuCl promoted coupling of para-diiodobenzene with (diethylphosphonyl)difluoromethylcadmium reagent. See reference 13.

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