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A General Method for the Preparation of Benzylic α,α-Difluorophosphonic Acids; Non-Hydrolyzable Mimetics of Phosphotyrosine

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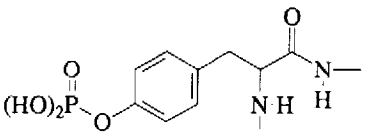
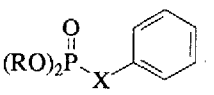
Abstract: Methodology is presented for the preparation of heretofore unreported benzylic α,α-difluorophosphonic acids. Oxidation of benzylic α-hydroxyphosphonates using MnO_2 provided a new route for the synthesis of benzylic α–oxophosphonates, which were then fluorinated using DAST. Hydrolysis of ester protecting groups yielded α,α-difluorophosphonic acids. These represent non-hydrolyzable mimetics of arylphosphates which could be of value in the study of cellular phosphotyrosine-utilizing signal transduction pathways.

The phosphorylation states of strategic tyrosines in a variety of cellular proteins serve as key determinants in the biochemical processes of both normal and pathological physiology. This is particularly true of mitogenic signal transduction where the active, cytoplasmic domains of many growth factor receptors are protein tyrosine kinases[1] (PTKs; enzymes that catalyze the phosphorylation of tyrosine residues within protein substrates). Aberrant expression of PTKs has been associated with a number of tumor viruses and neoplastic disorders,[2] making inhibitors of PTKs potential targets as antiproliferative therapeutics.[3] The actions of PTKs can be modulated by phosphotyrosine phosphatases (PTPs), which catalyze the removal of phosphate from phosphorylated tyrosines.[4] Such modulation can either be positive or negative, endowing inhibitors of PTPs as useful pharmacological tools for studying a range of cellular phenomena.

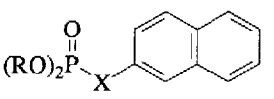
Phosphonic acids have proven to be of general use as non-hydrolyzable phosphate mimetics,[5,6] with **3d** and **2b** being examples which are either PTK[7] or PTP[8] inhibitors. In theory, phosphonic acids act as PTP "dead end substrate" inhibitors by binding within the catalytic site in a manner similar to the parent phosphate. Conceptually, phosphonic acid **3b**, which is a mimetic of the known PTP substrate **3a**,[8] could also serve as a PTP inhibitor in a manner similar to **2b**.[8] However, the ability of isosteric phosphonic acids to serve as biomimetic equivalents of phosphates is limited by the higher pK_a2 values of a phosphonic acid analogue relative to the parent phosphate. Substitution of fluorine atoms at the α-methylene position lowers the phosphonic acid pK_a2 to a value closer to that of the parent phosphate[9] and α, α–difluorophosphonic acids are now commonly used as phosphate biomimetics.[10] While methodology presently exists for the preparation of nonbenzylic α,α-difluorophosphonic acids[11-13] and benzylic α-monofluorophosphonic acids,[9] preparation of the corresponding benzylic α,α-difluorophosphonic acids (which would be direct mimetics of the phenylphosphate moiety of phosphoryltyrosine **1**) is lacking. Herein is reported a general procedure for the synthesis of benzylic α,α-difluorophosphonic acids.



1
Phosphorylated tyrosyl residue



2



3

a R = H; X = O **c** R = *t*-Bu; X = CHOH **e** R = *t*-Bu; X = CO **g** R = H; X = CF_2
b R = H; X = CH_2 **d** R = H; X = CHOH **f** R = *t*-Bu; X = CF_2 **h** R = H; X = CHF

Since nonbenzylic α-fluorophosphonates have been converted to α,α-difluorophosphonates using electrophilic fluorinating reagents,[12] and benzylic α-fluorophosphonates have been prepared from α-hydroxyphosphonates using (diethylamino)sulfur trifluoride (DAST),[9] we sought to prepare benzylic α,α-difluorophosphonates from the corresponding benzylic α-hydroxyphosphonates through the intermediacy of the α-fluorophosphonates. This appeared particularly appealing because benzylic α-hydroxyphosphonates are easily obtained by reaction of arylaldehydes with dialkyl phosphites under alkaline conditions.[14] However, we were unable to convert the benzylic monofluoro to the difluorophosphonates by this approach. Alternatively, conversion of α-oxoarylacetates to α,α-difluoroarylacetates using DAST[15] provided precedence for the transformation of benzylic α-oxophosphonates to the corresponding benzylic α,α-difluorophosphonates. While α-oxophosphonates are normally prepared by the Michaelis-Arbuzov reaction of acyl chlorides with trialkyl phosphites,[16,17] an approach utilizing benzylic α-hydroxyphosphonates was examined. It was determined that oxidation of the α-hydroxyphosphonates **2c** and **3c** to α-oxophosphonates **2e** and **3e** could be cleanly achieved in high yields employing MnO_2, thereby establishing a new method for the synthesis of α-oxophosphonates. A variety of other oxidizing agents, including pyridinium chlorochromate, dichloro-dicyanobenzoquinone (DDQ) and the Swern oxidation were also found to yield the α-oxophosphonates. It should be noted that use of phosphite esters other than *tert*-butyl (ie., methyl or benzyl) was incompatible with this transformation, as reversion of the hydroxyphosphonate to the aldehyde resulted. Conversion of the resulting α-oxophosphonates to the benzylic α,α-difluorophosphonates **2f** and **3f** with DAST was explored using a variety of solvents and temperatures. As with the preparation of α,α-difluoroarylacetates from α-oxoarylacetates,[15] the most satisfactory results were obtained by running the reactions neat (15 equivalents DAST) at room temperature. Labile *tert*-butyl groups (which were utilized in order to allow facile deprotection of the phosphonate under exposure to mild acid) were stable to the fluorination reaction, but required the maintenance of an alkaline pH during quenching and work up. Treatment of the resulting *tert*-butyl esters **2f** and **3f** with trifluoroacetic acid (TFA) cleanly yielded the free benzylic α,α-difluorophosphonic acids **2g** and **3g**.

Since benzylic α,α-difluorophosphonic acids would be of particular importance pharmacologically due to their ability to mimic the phenylphosphate moiety of phosphorylated tyrosine **1**, pK_a2 value for α,α-difluorophosphonic acid **2g** was compared to phenylphosphate **2a** and phosphonic acids **2b** and **2h** (Table 1). It is important to note that monofluorophosphonic acids such as **2h** possess a center of asymmetry at the α-fluoromethylene which has the potential of introducing diastereomeric interactions with enzymatic systems. The lack of asymmetry in α,α-difluorophosphonic acids such as **2g** could be an additional advantage of the difluoro analogue.

In conclusion, this paper reports the first methodology for the preparation of benzylic α,α-difluorophosphonic acids. In so doing it establishes a new route for the synthesis of α-oxophosphonates which proceeds under neutral or alkaline conditions. This may afford versatility over previously reported methods which used acid chlorides,

and which may have been incompatible with acid-sensitive functionality in other parts of the molecule. This work also reports the first direct conversion of an α-ketophosphonate to a difluorophosphonate. The use of *tert*-butyl esters allows deprotection to the free phosphonic acid under mild, non-nucleophilic conditions.

Table 1. Comparison of pK_a2 values for phenylphosphate **2a** and related phosphonic acids.

Compound	X	pK_a2[a]	Lit.[b]
2a	O	6.22	6.20
2b[c]	CH_2	7.72	7.60
2h[d]	CHF	6.60	6.50
2g	CF_2	5.71	-

a) Values were by potentiometric titration.[18] Variation from the average was <0.09.
b) Values were reported[9] as ±0.2 units.
c) Prepared starting from benzyl bromide using di-*tert*-butyl phosphite; mp 163-166°C (Lit.[19] mp 167-169°C).
d) Prepared starting from **2c** using DAST; mp 113-115°C (previously reported[9] as the biscyclohexylammonium salt; mp 196-198°C.)

Experimental

Preparation of benzylic α-hydroxyphosphonates (2c and 3c)

To an ice-cold stirred suspension of NaH (1.2 equiv.; 0.3 M in THF) is added a solution of di-*tert*-butyl phosphite (1.2 equiv.; 0.3 M in THF) over 5 minutes and the mixture stirred under argon at 0° C (0.5 hr).[20] A solution of aldehyde (1 equiv.; 1 M in THF) is rapidly added and the reaction is then stirred at rt (1.5 hr). The reaction is quenched (H_2O), subjected to an extractive work up (brine/$CHCl_3$) and purified by silica gel chromatography, yielding pure benzylic α–hydroxyphosphonates: **2c** (86% from benzaldehyde), mp 110-113° C (gas); **3c** (75% from 2-naphthaldehyde), mp 123.5-124.5° C (lit.[14] 124-127°C).

Preparation of benzylic α–ketophosphonates (2e and 3e)

A solution of benzylic α–hydroxyphosphonate (15 mM in toluene) is stirred at reflux with activated MnO_2 (10 equiv.; 1.5 hr). The reaction mixture is cooled (0° C), filtered through celite, taken to dryness and purified by silica gel chromatography to yield pure benzylic α–ketophosphonates: **2e** (87% from **2c**), oil; **3e** (74% from **3c**), mp 74-76° C (62° soften).

Conversion of benzylic α–ketophosphonates to benzylic α,α– difluorophosphonates (2f and3f)

A solution of benzylic α–ketophosphonate (0.5 M in DAST) is stirred at rt overnight. It is then cooled (0° C), diluted with $CHCl_3$, added dropwise to cold (0°C) concentrated KOH, then subjected to an extractive work up and purified by silica gel chromatography to yield pure benzylic difluorophosphonates: **2f** (79% from **2e**), oil; **3f** (43% from **3e**), mp 73-76° C.

Ester hydrolysis [conversion to free benzylic α,α–difluorophosphonic acids (2g and 3g)]

A solution of di-*tert*-butyl difluorophosphonate (100 mM in TFA) is stirred at rt (1.5 hr) with anisole (5 equiv.). Excess TFA is blown off under argon (gentle warming), with residual traces of TFA being removed under high vacuum. The resulting crude difluorophosphonic acid is crystallized from $CHCl_3$: pet. ether to yield benzylic α,α–difluorophosphonic acids: **2g**[21] (61% from **2f**), mp 109-111°C (gas; soften 106°C); **3g**[22] (51% from **3f**), mp 111-112° C (gas; soften 79°C).

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20. Note:The use of NaH is superior to that which we previously reported using basic alumina (see ref. 14). The phosphite should be added to a suspension of NaH. Reverse addition of NaH to phosphite gives much poorer results. Additionally, generation of the di-*tert*-butyl phosphite anion above 0°C affords little or no desired product.
21. Analysis calcd. for $C_7H_7F_2O_3P$•1/4 H_2O: C, 39.55; H, 3.56. Found: C, 39.52; H, 3.83. FABMS m/z: 415 (M_2-H); 299 (M-H + glycerol); 207 (M-H). ^{19}F NMR (vs. $CFCl_3$ in DMSO-d_6) δ: -107.6 (d, J = 106.7 Hz).
22. Analysis calcd. for $C_{11}H_9F_2O_3P$•H_2O: C, 47.84; H, 4.01. Found: C, 47.77; H, 4.00. FABMS m/z: 349 (M-H + glycerol); 257 (M-H). ^{19}F NMR (vs. $CFCl_3$ in DMSO-d_6) δ: -107.2 (d, J = 105.8 Hz).

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