A DAST-free route to aryl(difluoromethyl)phosphonic esters

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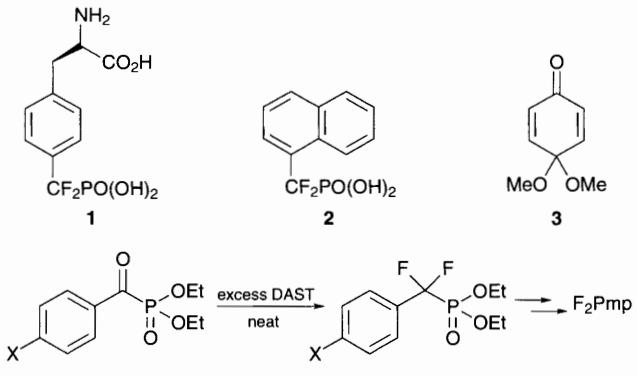
The cerium(III)-mediated addition of diethyl (lithiodifluoromethyl)phosphonate to a benzoquinone monoketal allows the synthesis of phenol bearing the (diethoxyphosphonyl)difluoromethyl group *via* short, scaleable reaction sequences which avoid the use of the DAST reagent.

The chemical mimicry of reactive phosphate esters by stable phosphonic acid derivatives[1] is proving to be an interesting tactic for the medicinal chemist, because the phosphonate mimics, or isosteres, can act as ligands or inhibitors for some of the key enzymes involved in cell signalling. The most significant and pioneering developments have been reported by the Burke group, who have described the synthesis[2] of phosphotyrosine analogue F_2Pmp **1** and its incorporation within hexapeptide ligands for protein tyrosine kinase SH-2 domains.[3] Small molecule protein tyrosine phosphatase inhibitors such as **2** have also been developed by the same group.[4] The current synthetic routes[5] to these interesting compounds rely on the transformation of an aryl α-ketophosphonate to the corresponding difluoromethylenephosphonate using a large excess of the DAST reagent (Scheme 1).[6] Though there are many reports of syntheses of difluoromethylenephosphonates, none of the published methods had been applied to targets of this type. We anticipated that F_2Pmp (and potentially, a much wider range of targets) could be prepared from phenol **8** *via* conversion to the triflate and palladium-catalysed coupling with a serine-derived iodozinc reagent.[7] We have therefore prepared phenol **8** and its triflate ester **9** from commercial[8] benzoquinone monoketal **3** and diethyl difluoromethanephosphonate (Scheme 2).



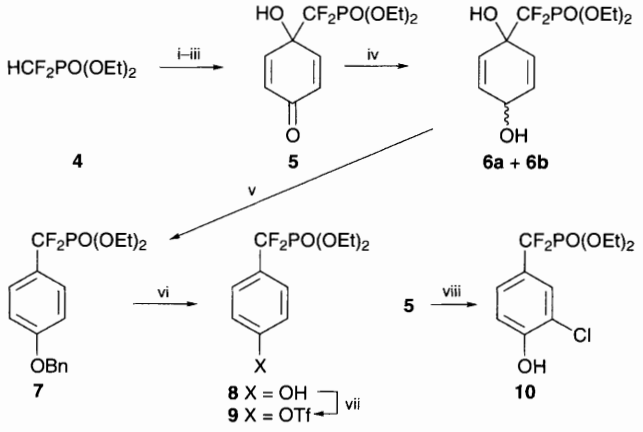
Scheme 1

Initially, the addition of the lithiophosphonate to **3** proceeded in moderate yield; however, when difluoromethanephosphonate was added slowly to lithium diisopropylamide which contained cerium(III) chloride,[9] an efficient addition occurred to afford **5** in excellent (92%) yield, after quantitative hydrolysis of the ketal (HCl, acetone, water). Luche reduction[10] afforded a 1 : 1 mixture of *cis*- and *trans*-diols **6a** and **b** in good (87%) yield. Exposure of the mixture to freshly-prepared[11] benzyl trichloroacetimidate (3 equiv.), resulted in selective benzylation of the secondary hydroxy group, and aromatisation *via* dehydration† to afford aryl benzyl ether **7** (62%). Deprotection occurred smoothly under a balloon of hydrogen at room temperature (10% palladium-on-carbon catalyst, 18 h, 92%) to afford phenol‡ **8** and triflate **9** was prepared using a standard procedure (Tf_2O, pyridine, CH_2Cl_2, 82%).[12]

If an allylic transposition[13] is performed before reduction of the dienone carbonyl group, chlorophenol **10** is obtained. To date, we have failed to perform transpositive bromination[14] or iodination,[15] which would lead to products capable of undergoing two different coupling reactions adding to the structural diversity of compounds available *via* this route.

Experiments to determine the reactivity of **9** in palladium catalysed coupling reactions are underway in our laboratory.

The authors wish to thank the European Community (HCM Network on Synthesis and Molecular Recognition of Selectively Fluorinated Bioactive Molecules, ERBCHRXCT930279, Fellowship to T. P. L.), the EPSRC (Quota Studentship to K. B., CASE Studentship to H. J. E.) and GlaxoWellcome (CASE support to H. J. E.) for financial support.



Scheme 2. *Reagents and conditions*: i, LDA (1 equiv.), $CeCl_3$ (1 equiv.), THF, −78 °C; ii, **3**; iii, HCl, acetone, H_2O; iv, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, v, $PhCH_2OC(=NH)CCl_3$ (3 equiv.), TfOH (cat.), C_6H_{12}, CH_2Cl_2, 40 °C, 18 h; vi, H_2, 10%Pd–C, EtOH, room temp., 18 h; vii, Tf_2O, C_5H_5N, CH_2Cl_2, 0 °C to room temp., 18 h; viii, $SOCl_2$, CH_2Cl_2, room temp., 72 h.

Footnotes

† We assume that benzylation precedes protonation on the tertiary hydroxy group and formation of a dienyl cation from which proton loss occurs regenerating the triflic acid catalyst.

‡ *Spectroscopic data* for phenol: δ_H (300 MHz; $CDCl_3$) 8.47 (1 H, s, OH), 7.35 (2 H, d, $^3J_{H-H}$ 9.0 Hz, H^a), 6.78 (2 H, d, $^3J_{H-H}$ 9.0 Hz, Hb), 4.31–4.06 (4 H, m, OCH_2CH_3) and 1.30 (6 H, t, $^3J_{HN}$ 7.3 H_3 OCH_2CH_3) δ_C (75 MHz; $CDCl_3$) 159.0, 127.6, 123.1, 117.5 (dt, $^2J_{C-F}$ 275 Hz, $^2J_{C-P}$ 205 Hz), 115.7, 65.1, 16.3; δ_F (90 MHz, $CDCl_3$) −107.11 (d, $^2J_{F-P}$ 122 Hz); *m/z* (CI, NH_3) 298 (100%, $[M + NH_4]^+$) 281 (55, $[M + H]^+$) (HRMS: calc. for $C_{11}H_{16}F_2PO_4$ ($[M + H]^+$) 281.075836. Found, 281.075429).

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Received, 29th April 1996; Com. 6/03005J