Short and Stereoselective Synthesis of δ-Functionalized *E*-α,α-Difluoroallylphosphonates

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New functionalized *E*-α,α-difluoroallylphosphonates including purine derivatives have been prepared from α,β-unsaturated carbonyl compounds and diethylphosphinyldifluoromethyllithium.

There are wide biological and therapeutic applications for potent, readily available and stable phosphate surrogates.[1,2] Among all the strategies studied to date, the replacement of oxygen in phosphate esters by a CF_2 group has been recognized[3] as a method of choice to mimic a phosphate monoester. Physicochemical studies (^{31}P NMR spectroscopy,[4,5] pH measurement[4,5] or X-ray crystallography[6]) have clearly demonstrated the superior structural analogy between difluoromethylene phosphonates and phosphate monoester when compared with methylene phosphonates. Following the pioneering work of Blackburn[4,7] where the β,γ bridging oxygen atoms of nucleoside triphosphates has been replaced by a CF_2 group, this concept has been recently applied to the design of difluoromethylene phosphonate analogues of isoprenoid pyrophosphates,[8] glycolytic phosphates,[9] phosphonoacetyl-L-aspartic acid,[10] carbocyclic nucleotides,[11] AZT-triphosphate (AZT = 3′-azido-3′-deoxythymidine; zidovudine),[12] phosphonacetates[13] and recently, difluoromethylene phosphonate derivatives of guanine have been

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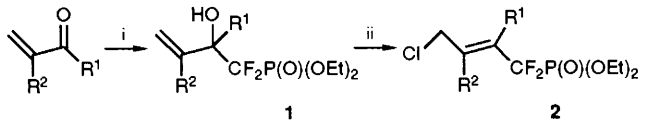


	1	2
a; $R^1 = R^2 = H$	72%	76%
b; $R^1 = Me$, $R^2 = H$	72%	82%
c; $R^1 = H$, $R^2 = Me$	81%	68%

Scheme 1 *Reagents and conditions*: i, $LiCF_2P(O)(OEt)_2$, −78 °C, THF; ii, $SOCl_2$, 20 °C, CH_2Cl_2

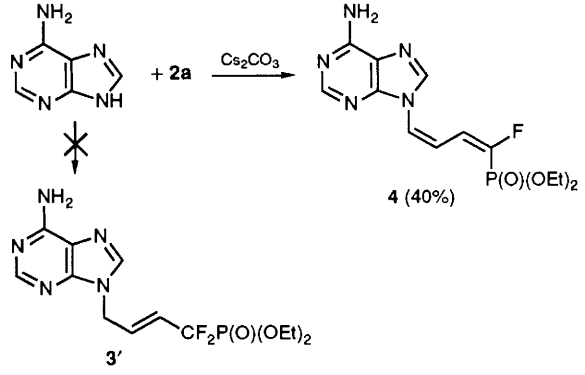
identified as very potent inhibitors of purine nucleoside phosphorylase.[14]

Only a few synthetic methods have been described to prepare difluoromethylene phosphonate derivatives; these include the coupling of electrophiles with difluoromethylene phosphonate anions,[15] the palladium catalysed addition of iododifluoromethyl phosphonates to alkenes[16] or electrophilic fluorinations of methylene phosphonates using *N*-fluorobenzenesulfonamide.[17] However, the synthesis of compounds in which the difluoromethylene phosphonate group is directly attached to an unsaturated carbon atom, *i.e.* α,α-difluoroallylphosphonates, has never been reported. Such compounds could be of great interest as conformationally restricted analogues of phosphate monoesters but also as versatile synthetic intermediates towards new difluoromethylene phosphonates as the double bond can be considered as a latent functionality. In this paper, we report the first examples of a convenient and flexible route to prepare the alkyl chlorides **2a–c** stereoselectively, in addition to their use to prepare the functionalized α,α-difluoroallylphosphonate **3a–c**.

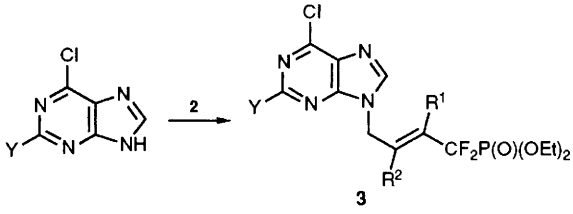
Condensation of diethylphosphinyldifluoromethyllithium[15a] with α,β-unsaturated aldehydes or ketones at −78 °C in tetrahydrofuran (THF) followed by hydrolysis with saturated aqueous ammonium chloride at −45 °C regioselectively produces the 1,2 adducts **1a–c** as no 1-4 adduct could be detected in the crude reaction mixture (Scheme 1). The allyl alcohols **1a–c** proved to be very sensitive to basic conditions at temperatures above 0 °C, giving decomposition products analogous to their known saturated analogues.[15a] Therefore, activation of the alcohols **1** was studied using thionyl chloride without tertiary amine or pyridine,[18] and it was found that these conditions allowed the regio- and stereo-selective formation of the allyl chlorides **2a–c**.‡ No detectable amounts of β-chloro-α,α-difluorohomoallylphosphonates coming from direct S_Ni reaction could be identified in the crude reaction mixtures. The *E* stereochemistry of the rearranged allylic chlorides **2a–c** has been established unequivocally by ^1H NMR spectroscopy including 2D NOESY (nuclear Overhauser effect spectroscopy) experiments. It is noteworthy that the formation of the allyl chlorides **2a–c** by reacting the alcohol **1a–c** with thionyl chloride, is clearly accelerated by the addition of tetrabutylammonium chloride whereas addition of tetrabutylammonium bromide, when reacting **2c** with thionyl chloride, gives a mixture of **2c** and the corresponding allyl bromide. A large excess of tetrabutylammonium salts or higher reaction temperatures must be avoided as these conditions lead to the mono deesterification of the phosphonate diester.

The two-step procedure described in Scheme 1 offers a very short and practical access to electrophilic allylic difluoro-

‡ All new compounds **2**, **3** and **4** have been isolated in a pure analytical form after flash-chromatography purification on silica gel using chloroform and increasing amounts of methanol as eluents. Compound **4** was isolated as a white solid (m.p. 86–88 °C).



Scheme 2



	Y	R^1	R^2	Method	Yield (%)
3a	H	H	H	K_2CO_3	42
3b	NH_2	Me	H	KF	55
3c	NH_2	H	Me	KF	30

Scheme 3

phosphonates. In order to illustrate the synthetic potential of such derivatives, the nucleophilic substitution of the allyl chlorides **2a–c** by purine nucleophiles has been studied since several types of acyclic phosphonate derivatives of purines have been identified as potent enzyme inhibitors[14] or antiviral agents.[19] In a first attempt to prepare compound **3'** by reacting adenine with the intermediate **2a** in the presence of an excess of caesium carbonate, the dienic monofluoro phosphonate derivative **4** (Scheme 2) was isolated in 40% yield together with some N-7 regioisomers. Compound **4** was obtained as a 60 : 22 : 12 : 6 mixture of four stereoisomers and ^1H, ^{19}F NMR analyses have shown that the major isomer was the depicted *Z,Z*-isomer **4**. The formation of **4** is easily explained by a base-catalysed dehydrofluorination of the expected nucleophilic substitution product **3'**.

In order to avoid these problems, the reaction was run using 6-chloropurine as a nucleophile (in order to increase the N-9 regioselectivity) and only 1.1 equiv. of potassium carbonate (Scheme 3). These conditions allowed the preparation of the expected adduct **3a** in 42% yield and only traces of dienic analogues. The use of the neutral fluoride ion catalysed procedure[20] allowed the preparation of the unsaturated difluorophosphonate derivative of guanine **3b** in 55% yield from 2-amino-6-chloropurine and the allyl chloride **2b** (KF, *N,N'*-dimethylformamide, 60 °C, 4 h). The same conditions used to prepare **3c** were found to be less satisfactory as only 30% of product were obtained after flash-chromatography purification on silica gel.

In conclusion, the condensation of difluoromethylene phosphonate anion with α,β unsaturated aldehydes or ketones followed by reaction of the adduct with thionyl chloride offers a short method of access to functionalized *E*-α,α-difluoroallylphosphonates. Work is in progress to determine the scope

and limitations of the nucleophilic displacement of the allyl chlorides of type **2**.

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