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First synthesis of diethyl N-acetyl-glycosamine-1-difluoromethylphosphonate from 2-nitroglycals as phosphate analog

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ABSTRACT

Herein, we report the first access to diethyl glycosamine-1-difluoromethylphosphate as phosphate mimic. The diethyl 2-nitro-glycosides-β-1-difluoromethylphosphonate were obtained from a Michael addition of diethyl(difluoro-(trimethylsilyl)methyl)phosphonate on 2-nitroglycals in the presence of a fluoride promoter in good to excellent yields. A subsequent reduction of the nitro group leads to the *N*-acetyl glycosides derivative giving a straightforward access to phosphate analogs.

1. Introduction

Carbohydrates are ubiquitous compounds present in several bioactive compounds [1]. Glycosides and their derivatives are involved in several biological events like cell recognition for instance. As a result, these compounds have been widely explored in the development of new therapeutics like anticancer vaccines for instance [2]. Among these carbohydrate derivatives, glycosamines are an important class of compound among which glycosylaminephosphates constitute an important sub-class. Indeed, glycosaminephosphates are key element of the lipopolysaccharides (e.g. Lipid A and its precursor: Lipid X) [3], which form the outer membrane of the gram-negative bacteria and are responsible for the endotoxic properties of these bacteria. To elucidate the key role of the phosphate residue present on these glycolipids several efforts have been devoted to design isosteric and non-isosteric phosphonate analogs. For instance, Vasella [4], Schmidt [5] and von Itzstein [6] later, depicted the non-isosteric phosphonate analogs where the P-atom is directly bound to the glycoside residue. This strategy is suitable for the study of analogs, since the C–P bound could not be hydrolyzed in vivo by enzymes involved in the phosphate cleavage. As part of our ongoing research program devoted to the synthesis of fluorinated glycomimetics, we were interested in the synthesis of the C-difluorinated-phosphonate as a mimic of the natural phosphate. Indeed, the CF_2 moiety is well recognized as an isoster of the oxygen atom [7] and its replacement by the difluorinated moiety should avoid an in vivo hydrolysis of the glycoside–phosphonate link [8], which is the major drawback for their use as potent biologically active compounds. Recently, we reported the Michael addition of various organolithium species onto 2-nitroglucals, giving selectively the α-additions products. [9] Thus, we were wondering if such strategy could be applied toward the synthesis of 1-difluoromethylated glycosamines by using a fluorinated nucleophile i.e. difluorinated phosphonate. Herein, we reported our efforts toward the synthesis of 1-difluoromethylphosphonateglycosamine through a Michael addition of $TMSCF_2P(O)(OEt)_2$ on 2-nitroglycals (Fig. 1).

2. Results and discussion

At the beginning of the project, we used tri-O-benzyl-2-nitroglucals **1a** as a model substrate. Initial attempts to introduce the $-CF_2P(O)(OEt)_2$ moiety by using the corresponding lithiated species did not afford even a trace of the product **2a**. Indeed, whatever the method of formation (*n*-BuLi, *t*-BuLi...) of the corresponding lithiated difluorinated species, only degradation products were observed (Scheme 1).

In our quest to find a more suitable nucleophile, we thought that the corresponding silylated species i.e. $TMSCF_2P(O)(OEt)_2$ might be a suitable alternative to its lithiated congeners. Indeed,

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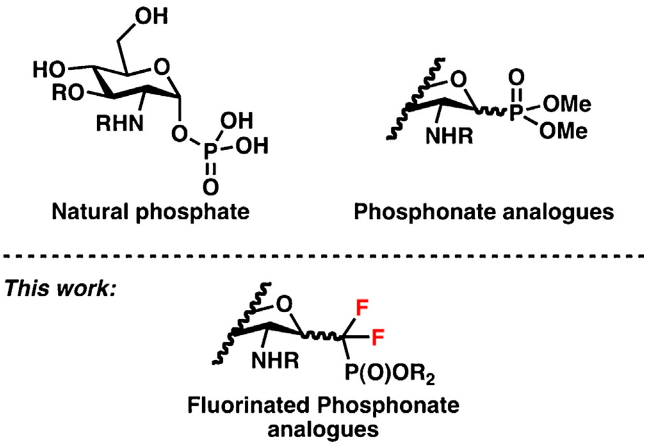
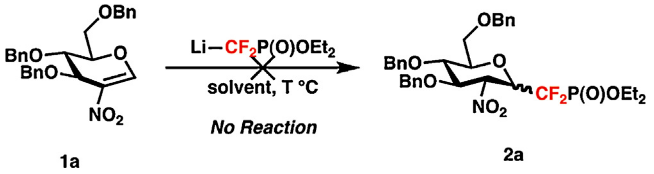


Fig. 1. Difluorophosphonate as a phosphate mimic.



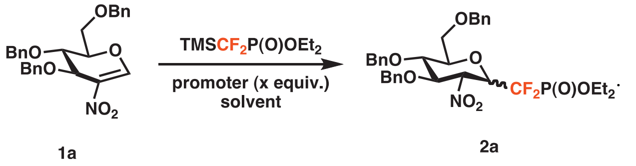
Scheme 1. Initial attempts using lithium fluorinated phosphonate.

Beier and co-workers recently reported the Michael addition of this species on several α,β-unsaturated compounds,[10] while the addition of TMSCF$_2$P(O)OEt$_2$ as been explored by Beier and Dilman on aldehydes [11] and imines [12] respectively. Initially we investigated the addition of TMSCF$_2$P(O)OEt$_2$ on glucal **1a** by using CsF as a promoter, unfortunately, no trace of product was observed in THF (Table 1, entry 1). Pleasingly, a survey of promoters revealed that the use of TBAT (tetrabutylammonium triphenyldifluorosilane) gave a decent 40% NMR yield along with a nice 1:12 α:β ratio (Table 1, entry 4), while others inorganic promoters gave no conversion (entries 2 and 3). Noteworthy, the use of DMF, which is well known to have beneficial effect on the conversion with the silylated nucleophile led to a complete degradation of the starting material (Table 1, entry 5). Pleasingly, the replacement of TBAT by TMAF (tetramethylammonium fluoride) provided a significant enhancement of the yield from 40 to 60% with a slight improvement of the α:β ratio from 1:12 to 1:14 (Table 1, entry 6). Then, the stoichiometry of the reaction was investigated. A catalytic amount of activator was found ineffective to promote the reaction (Table 1, entry 7). The use of 3 equiv. of TMAF or TBAT was required to ensure a full conversion, and the desired addition product **2a** was isolated in 48 and 52% yield with a 1:14 and 1:15 α:β ratio respectively (Table 1, entries 8 and 9).

With these optimized conditions in hand, we moved on the extension of the reaction scope on several others glycal derivatives. First, 3,4,6-tri-O-benzyl-2-nitro-galactal **1b** was engaged under our reaction conditions. Surprisingly, the α-talose derivative was obtained as a single isomer 59% yield. Presumably, the addition of the phosphonate derivatives occurred on the α-side of the galactal and the protonation step proceeded on the more hindered face to place the nitro group at the equatorial position. Then the addition of the silylated diethyl difluoromethylphosphonate was performed on the 3,4-di-O-benzyl-2-nitro-rhamnal **1c**. The addition gave a 1:5 mixture of α and β isomers of diethyl 1-difluoromethylphosphonate-2,6-dideoxy-2-nitro-L-glucopyranose **2c**, which was isolated in 33% yield. When reaction was carried out on the 3,4-di-O-benzyl-2-nitro-L-arabinal **1d** the addition products **2d** (diethyl 1-difluoromethylphosphonate-2-deoxy-2-nitro-L-arabinopyranose) were isolated in 51% yield and a decent 1:8 α:β ratio (Scheme 2).

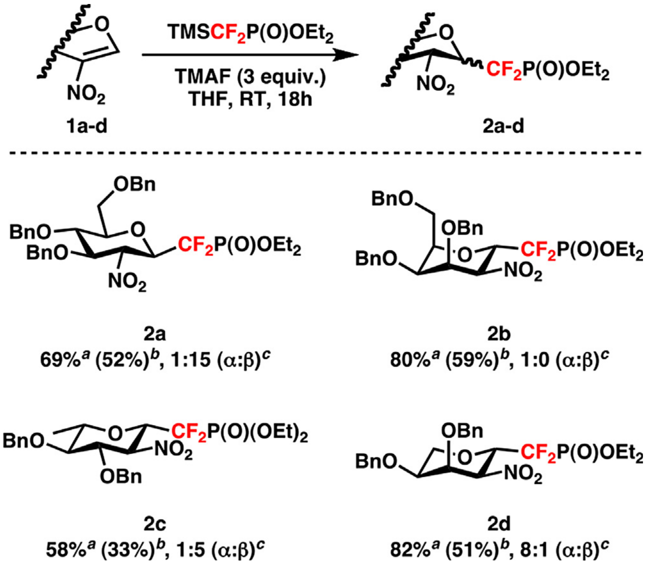
The stereochemistry of Michael adducts **2a-d** were assigned by ^{1}H NMR spectroscopy experiments (Scheme 3). In the case of compound **2a,** the observed value of the J coupling constant between H^1 and H^2 ($J_{1,2}$ = 10.2 Hz) implied a trans relationship resulting from a β-substitution of the glycoside. Then, NOE experiment showed a $^4C_1$ conformation of the difluorinated glycoside since correlations between H^1 and H^5 and between H^2 and H^4 have been observed. A similar set of experiments on addition products **2c** and **2d** unambiguously showed a $^1C_4$ conformation for **2c** and **2d** and confirmed the β-addition as favored reaction pathway in the case of **2c** and an α-addition for **2d** like **2b**. Regarding the conformation of **2b**, the determination of the J coupling constant between H^1 and H^2 ($J_{1,2}$ = 8.5 Hz) points out a trans relationship, while the J coupling constant between H^2 and

Table 1
Optimization of the reaction conditions.



Entry	Promoter	x	Solvent	NMR conversion [%][a]	α:β ratio[b]
1	CsF	1	THF	N. R.	–
2	KF	1	THF	N. R.	–
3	KHF$_2$	1	THF	N. R	–
4	TBAT	1	THF	40	1:12
5	TBAT	1	DMF	Degradation	–
6	TMAF	1	THF	60	1:14
7	TBAT	0.2	THF	Trace	–
8	TBAT	3	THF	100 (48)[c]	1:14
9	TMAF	3	THF	100 (52)[c]	1:15

[a] Conversion was determinate by ^{1}H NMR.
[b] Determined by ^{19}F NMR.
[c] Isolated yield.



Scheme 2. Scope of the reaction. ^{a} Yield determinate by ^{19}F NMR using C_6H_5F as internal standard. ^{b} Isolated Yield. ^{c} ratio was determinate by ^{19}F NMR in crude product.