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Synthesis of difluoromethylphosphonamidates by direct addition of amine

Lucie Aliouane [a], Baptiste Rigaud [a], Emmanuel Pfund [a], Ludovic Jean [b], Pierre-Yves Renard [b], Thierry Lequeux [a,*]

[a] Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507 & FR3038, ENSICAEN, Université de Caen Basse-Normandie, 6 Bd du Maréchal Juin, Caen 14050, France
[b] Chimie Organique Bioorganique Réactivité et Analyses, UMR CNRS 6014 & FR3038, Université de Rouen, rue Tesnière Mont St., Aignan 76000, France

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ABSTRACT

The one step synthesis of difluoromethylphosphonamidates from dialkylphosphonates is reported. The addition of lithiated amides onto dialkyl difluoromethylphosphonates afforded the corresponding phosphonamidates, as potential prodrug precursors. The remarkable high stability of these phosphonamidates in acidic medium was studied by ^{31}P NMR.

1. Introduction

Phosphoramidates are important in medicinal chemistry and have been developed to prepare prodrugs containing mainly nucleoside derivatives, or to design new transition state analogues as enzyme inhibitors.[1] However, in order to prevent the rapid cleavage of the carbon–oxygen bond of a monophosphate function by phosphatases, the replacement of the bridging oxygen atom by a difluoromethylene group has been intensively studied.[2] In addition, the replacement of a hydroxyl group of a phosphate by a difluoromethylene group stabilizes the phosphate bond, as exemplified by the synthesis of modified inositol or nonionic dinucleotide derivatives.[3] It is well established that the difluoromethylphosphonate function (DFMP) can be introduced as a stable phosphate mimic, but its derivation into the corresponding phosphonamidate as a prodrug has been scarcely studied. Phosphonamidates have been used as potential transition-state analogues of peptidases,[4] and difluorophosphonamidates were designed as new prodrugs to facilitate the transportation of PTB 1B inhibitors (Fig. 1).[5]

The importance of the difluoromethylene group has been demonstrated, and the presence of such electron attracting group attached onto the phosphorus center enhanced the stability of the P–N bond by two units of pH: difluorophosphonamidates are stable above pH 5, and slowly decompose at pH 2.[6,7] Yet, the main limitation for further use of those phosphonamidate derivatives lies in the fact that their synthesis requires the tricky activation of the phosphorus center. In most cases, it is realized by formation of intermediate phosphonyl dichloride derivatives produced upon treatment of the corresponding dialkyl phosphonic ester with oxalyl chloride or thionyl chloride (Scheme 1). These phosphonyl dichlorides were directly converted by addition of primary or secondary amines, or transformed in their activated species by addition of aromatic or tertiary amines.[5,7] This approach is of great

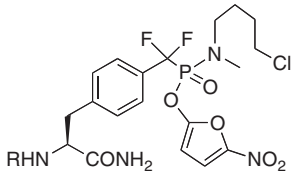
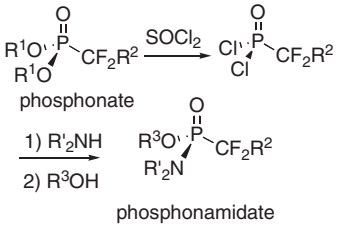


Figure 1. Prodrug of PTP 1B inhibitor.



Scheme 1. Synthesis of phosphonamidates as prodrugs.

* Corresponding author. Tel.: +33 231452854; fax: +33 231452865.
E-mail address: Thierry.Lequeux@ensicaen.fr (T. Lequeux).

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interest but limited to structures containing chemical functions stable toward these strong electrophilic reagents ($SOCl_2$, $(ClCO)_2O$), and often gives moderate yields.

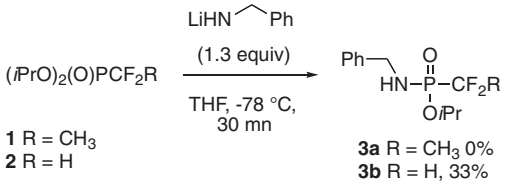
Taking into account that the presence of a difluoromethylene group enhances the electrophilic character of the phosphorus center,[8] the direct transformation of phosphonates into the corresponding phosphonamidates from amines and difluoromethylphosphonate dialkyl esters was explored and our progress in this field is reported.

2. Results and discussion

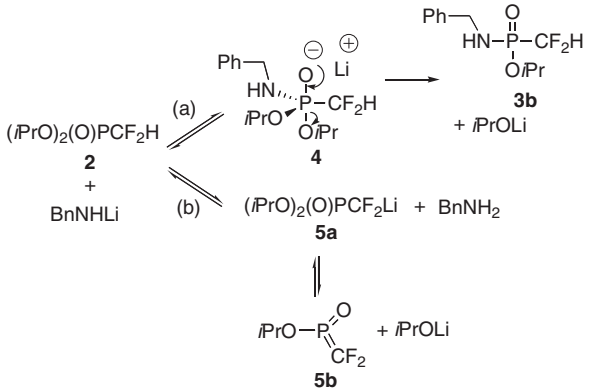
In a first approach the addition of lithium benzylamide onto difluoroethylphosphonate **1** was realized (Scheme 2). However, no addition reaction was observed at −78 °C, and partial decomposition occurred at 20 °C, affording a mixture of unidentified products. A similar reaction was then realized from the difluoromethylphosphonate **2**. In contrast with the first assay, we were pleased to observe that the corresponding phosphonamidate **3b** was formed after 30 min under stirring at −78 °C (yield 33%). When the reaction mixture was allowed to warm up from −78 °C to room temperature, the isolated yield was increased up to 49%. Similar results were obtained from diisopropyl and diethyl phosphonate esters, and use of an excess of lithiated amide (2.5 equiv) induced a partial decomposition of the reagents.

As LDA is the usual base used to deprotonate **2**,[2] it is assumed that in the present case a competitive addition reaction (path a) to a deprotonation reaction (path b) appeared (Scheme 3). Another mechanism involving the formation of the intermediate isopropylphosphinico difluoromethane **5b** from anion **5a** after ejection of one isopropyl group is not excluded.[9]

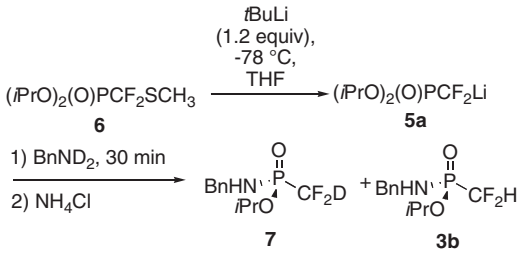
With less hindered lithium amide, the rearrangement of the phosphorane intermediate **4** can occur, placing the isopropyl group in the apical position, favorable for its elimination.[10] Since the reaction eventually ends up with a reasonable global yield, this could be possible if the different species are in equilibrium as depicted in Scheme 3. To confirm this hypothesis the lithiated anion **5a** was formed from sulfide **6** (Scheme 4),[11] and directly treated



Scheme 2. Addition of lithium amide onto difluorophosphonates.



Scheme 3. Suggested mechanism.



Scheme 4. Reaction with deuterated amine.

with benzylamine (1.3 equiv) over 30 min at −78 °C. Under these conditions, the addition reaction reached completion after 30 min at −78 °C, and phosphonamidate **3b** was isolated in 77% yield. In this mechanism, the protonation of carbanion **5a** by the amine must be achieved prior to the addition reaction. Indeed, addition of MeI to the crude mixture before hydrolysis afforded exclusively

Table 1
Formation of difluoromethylphosphonamidates[12,13]

Entry	Amine	Product	Yields (%)
1	Benzylamine	Ph–HN–P(O)(OiPr)–CF2H **3b**	77
2	Ethylamine	HN–P(O)(OiPr)–CF2H **8**	63
3	Phenylethylamine	Ph–HN–P(O)(OiPr)–CF2H **9**	68
4	Allylamine	HN–P(O)(OiPr)–CF2H **10**	63
5	Cyclohexylamine	HN–P(O)(OiPr)–CF2H **11**	66
6	Pyrrolidine	N–P(O)(OiPr)–CF2H **12**	55
7	Piperidine	N–P(O)(OiPr)–CF2H **13**	60
8	Morpholine	O, N–P(O)(OiPr)–CF2H **14**	70
9	Diethylamine	N–P(O)(OiPr)–CF2H **15**	63[a]
10	Aniline	HN–P(O)(OiPr)–CF2H **16**	74[a]

[a] Reaction performed from −78 °C to 20 °C over 1 h.