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Synthesis of difluoromethylphosphonamidates by direct addition of amine

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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

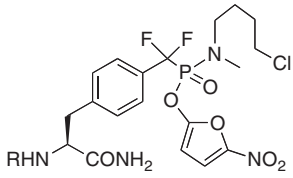
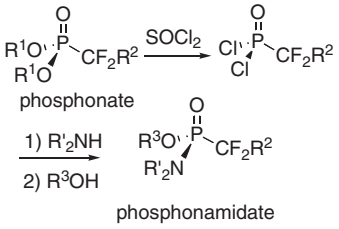


Figure 1. Prodrug of PTP 1B inhibitor.



Scheme 1. Synthesis of phosphonamidates as prodrugs.

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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.

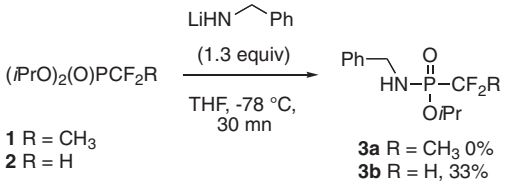
Taking into account that the presence of a difluoromethylene group enhances the electrophilic character of the phosphorus center,[8] the direct transformation of phosphonates into the corresponding phosphonamidates from amines and difluoromethylphosphonate dialkyl esters was explored and our progress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

2. Results and discussion

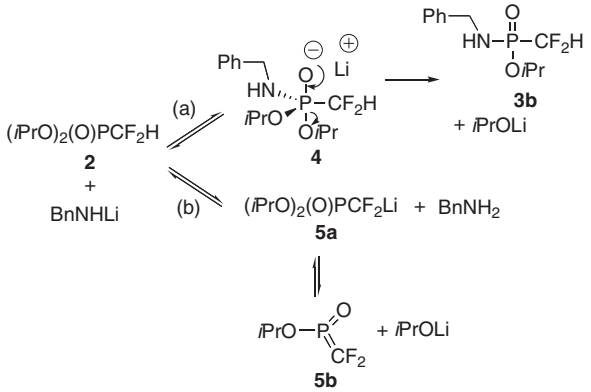
In a first approach the addition of lithium benzylamide onto difluoroethylphosphonate **1** was realized (Scheme 2). However, no addition reaction was observed at −78 °C, and partial decomposition occurred at 20 °C, affording a mixture of unidentified products. A similar reaction was then realized from 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]

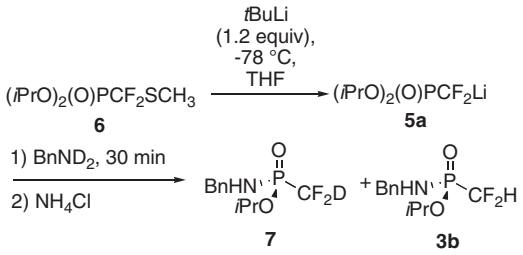
With less hindered lithium amide, the rearrangement of the phosphorane intermediate **4** can occur, placing the isopropyl group in the apical position, favorable for its elimination.[10] Since the reaction eventually ends up with a reasonable global yield, this could be possible if the different species 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.

phosphonamidate **3b**. This protonation of the starting carbanion **5a** prior to the addition reaction was also confirmed when the reaction was performed with deuterated benzylamine (Scheme 4). Carbanion **5a** was treated with $PhCH_2ND_2$ at −78 °C over 30 min. After hydrolysis, the ^{19}F NMR analysis of the crude mixture presented a ABXZ system (−135.4 ppm, ddt, $^2J_{FF}$ = 345.8 Hz, $^2J_{FP}$ = 88.1 Hz, $^2J_{FD}$ = 7.5 Hz), as the major signal corresponding to the CF_2D compound **7**. This compound **7** was obtained in a ratio of 7:3 with the corresponding phosphonamidate **3b**. We assumed that the formation of **3b** was due to the quality of the deuterated amine (deuterated at 80%). As mentioned early, in this case the formation of the isopropylphosphinico difluoromethane **5b** cannot be excluded, although a S_N2 mechanism is more probable.[9a]

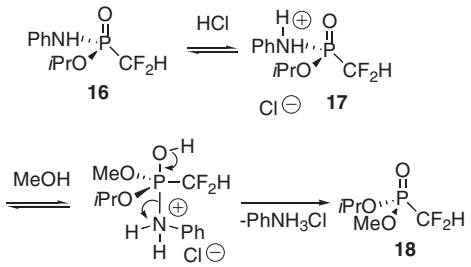
The scope and limitations of the synthesis of phosphonamidates were next explored from primary and secondary amines and sulfide **6**.[12,13] Carbanion **5a** formed in situ was immediately protonated by the amine and reacted with the corresponding lithiated amide during 0.5 h at −78 °C. From primary aliphatic amines, products **8**–**11** were isolated by flash chromatography in 63–66% yield (Table 1). However, the addition reaction was unsuccessful from diethylamine at this temperature.

In contrast, the addition of secondary cyclic amines afforded the expected phosphonamidates **12**–**14** in 55–70% yield. From less nucleophilic or secondary linear amines, such as aniline or diethylamine, the reaction reached completion only when the reaction mixture was warmed-up from −78 °C to 20 °C over 1 h. In these cases, the corresponding phosphonamidates **15** and **16** were obtained in 63% and 74% yields, respectively (entries 9 and 10).

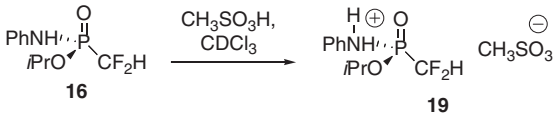
This reaction is highly sensitive to the steric demand of the amine or the phosphorus center, reflecting the ease of the phosphorane rearrangement. Indeed, as expected, the experiment realized with diisopropylamine afforded exclusively phosphonate **2**. In this case, the pentacoordinated intermediate related to **4** was not formed, due to the high steric demand of the amino group. This limitation was also observed from hindered phosphonate. No reaction occurred when the direct addition of lithium benzylamide onto sulfide **6** was realized at −78 °C. We assumed that the steric hindrance due to the presence of the methylsulfanyl group prevented the formation or the rearrangement of the pentacoordinated intermediate.[14]

The stability of compound **16** was evaluated in acidic medium by NMR analysis. A solution of **16** in MeOH was gradually acidified by addition of diluted methanolic HCl solution (0.01 M), and ^{31}P NMR analysis was performed every 1 h or day (Fig. 2). At pH 3.4, the acidity of the medium induced a slight shift of the signal of **16**. As shown in Figure 2, this phosphonamidate **16** was slowly protonated between pH 8 and pH 3 and the intermediate cation **17** was gradually formed (Scheme 5).

This intermediate was exclusive at pH 0.3. The reaction was reversible since **16** was recovered when aqueous NaOH was added to the solution of **17** (see Supplementary data). The most surprising is the remarkable stability of intermediate **17** since no decomposi-



Scheme 5. Stability of **16** in acidic medium.



Scheme 6. Protonation of phosphonamidate **16**.

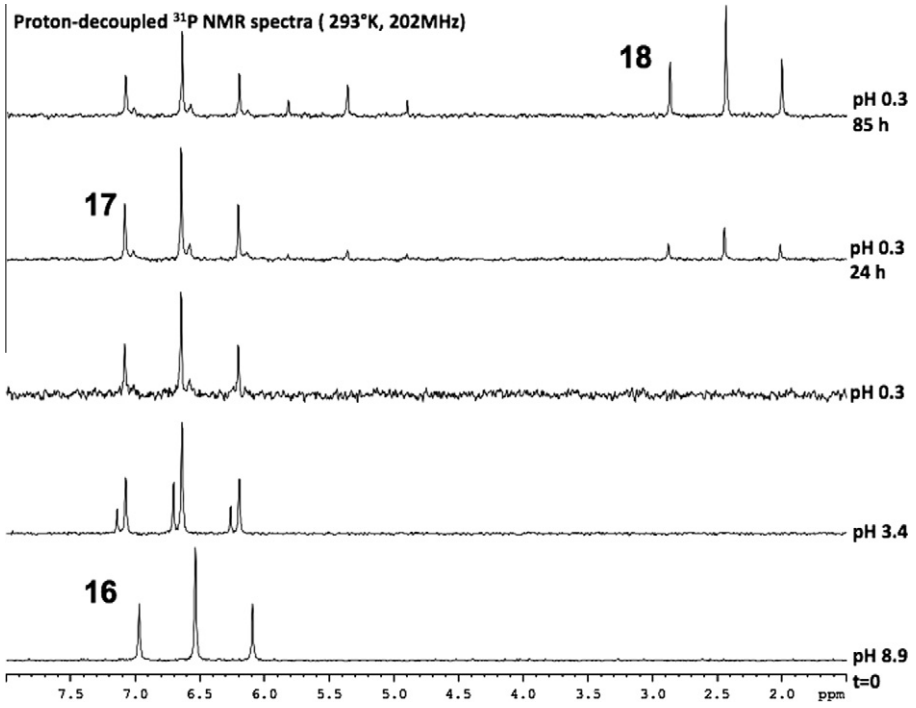


Figure 2. Evolution of **16** in acidic methanolic medium by ^{31}P NMR.

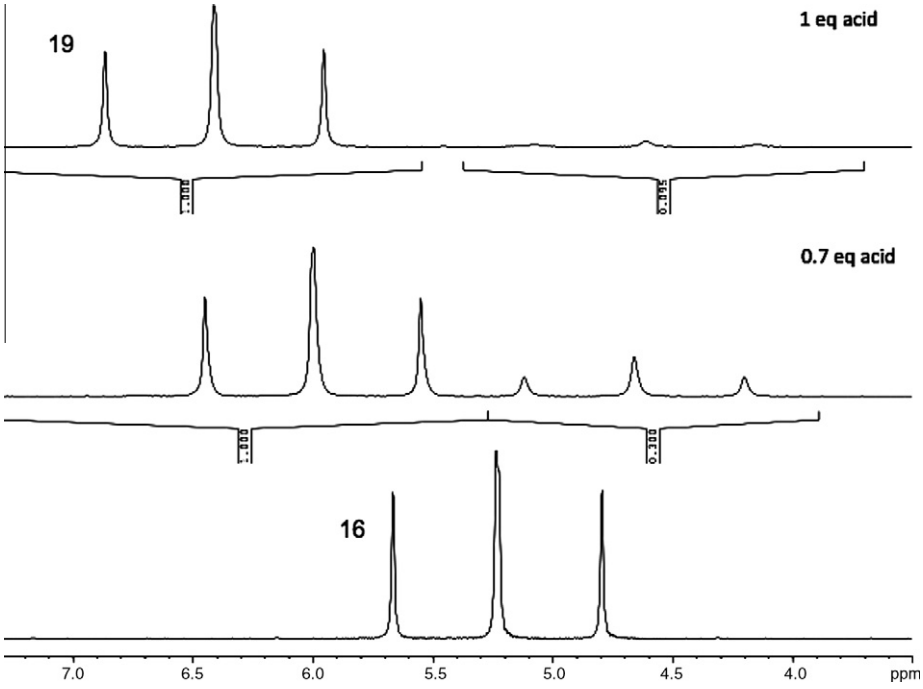
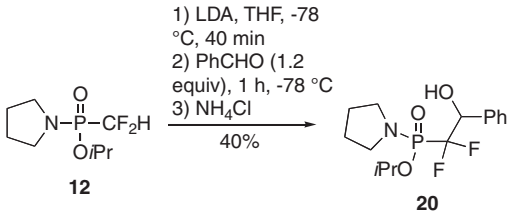


Figure 3. Formation of **19** from **16** and CH_3SO_3H.



Scheme 7. Functionalisation of phosphonamidate **12**.

tion was observed after 5 h at this pH. It is only after several hours in solution at 20 °C that **17** evolved slowly in the medium to form after 85 h the expected dialkoxyphosphonate **18**, illustrating once again the poor ability of the amine to be placed in the apical position of the phosphorane. The trans-esterification reaction of **16** with the solvent was also observed (triplet at 5.5 ppm). This unusual protonated form of phosphonamidate **16** has been confirmed after reaction with sulfonic acid in aprotic solvent. A $CDCl_3$ solution of **16** was treated by a gradual addition of methanesulfonic acid at 20 °C (Scheme 6, Fig. 3). In the presence of 1 equiv of methanesulfonic acid, a new signal appeared at 6.4 ppm (^{31}P NMR), corresponding to the salt **19**.

Finally, a preliminary study of the further functionalization of phosphonamidate **12** was explored by trapping the corresponding carbanion with benzaldehyde at −78 °C. However, in this case the carbanion appeared to be less reactive than anion **5a** and product **20** was isolated in a modest yield (Scheme 7). Further works are underway to further explore the functionalization of these difluorophosphonamidates in order to introduce this function onto a large variety of electrophiles.

3. Conclusion

The particular high electrophilic character of the phosphorus center next to a difluoromethylene group allowed the addition of metalated amides to form in one step a variety of phosphonamidates. It appeared that the steric demand of the amino group is important to perform this reaction, and the steric hindrance around the phosphorus center seems to be crucial, reflecting the apicophilicity of the different groups present on the phosphorus center. High stability of phosphonamidate **16** was observed in methanolic acidic medium, and at pH 0.3, its slow solvolysis occurred at 20 °C. The functionalization of these phosphonamidates and the study of the mechanism involved in their synthesis are underway to explore the synthetic potential of these species, and the exact nature of the intermediates formed during this transformation.

Acknowledgments

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Supplementary data

Supplementary data (experimental section and copies of ^{1}H, ^{13}C NMR spectra of compounds **3b**, **8**–**16**, **19** and NMR experiments with deuterated amine and NaOHaq) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.034.

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12. *Typical procedure*: *Isopropyl N-benzyl difluoromethylphosphonamidate* **3b**. To a cold solution of *t*-butyllithium (1.3 M in THF, 0.76 mL, 0.99 mmol, 1.3 equiv), in dried THF (5 mL) at −78 °C was added dropwise diisopropyl methylsulfanyl difluoromethylphosphonate **6** (200 mg, 0.76 mmol, 1.0 equiv) and the solution was stirred over 15 min. To this anion, benzylamine (0.108 mL, 0.99 mmol, 1.3 equiv) was slowly added, and after 30 min at −78 °C, the reaction mixture was quenched by addition of aqueous solution of NH_4Cl and then slowly warmed to room temperature. The aqueous layer was extracted with diethyl ether and combined organic layers were washed with aqueous solution of $NaHCO_3$ and dried over $MgSO_4$. Solvents were evaporated under reduced pressure and crude product was purified by flash column chromatography to afford compound **3b** as a yellow oil (155 mg, 0.59 mL, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, $^3J_{HH}$ = 6.4 Hz, CH_3, 3H), 1.29 (d, $^3J_{HH}$ = 6.2 Hz, CH_3, 3H), 3.56 (s, NH, 1H), 4.13 (m, 2H), 4.75 (m, 1H), 5.76 (ddd, $^2J_{HP}$ = 25.6 Hz, $^2J_{HF}$ = $^2J_{HF}$ = 49.4 Hz, CF_2H, 1H), 7.17–7.27 (m, Ar, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0 (d, $^3J_{CP}$ = 3.8 Hz), 23.1 (d, $^3J_{CP}$ = 4.2 Hz), 43.9, 71.8 (d, $^2J_{CP}$ = 6.7 Hz), 112.0 (ddd, $^1J_{CF}$ = 254.7 Hz, $^1J_{CF}$ = 259.8 Hz, $^1J_{CP}$ = 198.7 Hz, CF_2), 126.2, 126.5, 127.6, 138.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −135.6 (ddd, $^2J_{FH}$ = 49.4 Hz, $^2J_{FP}$ = 86.2 Hz, $^2J_{FF}$ = 347.2 Hz, 1F), −133.8 (ddd, $^2J_{FH}$ = 49.4 Hz, $^2J_{FP}$ = 86.3 Hz, $^2J_{FF}$ = 347.2 Hz, 1F); ^{31}P NMR (162 MHz, $CDCl_3$) δ 9.73 (dd, $^2J_{PF}$ = 86.2 Hz, $^2J_{PF}$ = 86.3 Hz, 1P); HRMS (ESI) *m*/*z* [M+H]$^+$ calcd for $C_{11}H_{17}F_2NO_2P$ 264.0965, found 264.0973.
13. *Isopropyl N-phenyl difluoromethylphosphonamidate* **16**. Following the typical procedure from phosphonate **6** (200 mg, 0.76 mmol), and aniline (0.09 mL, 0.99 mmol), the reaction mixture was stirred from −78 °C to 20 °C over 1 h, and phosphonamidate **16** was obtained as a yellow oil (141 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, $^3J_{HH}$ = 6.2 Hz, CH_3, 3H), 1.37 (d, $^3J_{HH}$ = 6.2 Hz, CH_3, 3H), 4.87 (m, 1H), 5.93 (ddd, $^2J_{HP}$ = 27.3 Hz, $^2J_{HF}$ = $^2J_{HF}$ = 48.7 Hz, CF_2H, 1H), 6.91–7.28 (m, Ar, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (d, $^3J_{CP}$ = 4.4 Hz), 24.1 (d, $^3J_{CP}$ = 4.3 Hz), 73.4 (d, $^2J_{CP}$ = 7.1 Hz), 112.2 (ddd, $^1J_{CF}$ = 259.7 Hz, $^1J_{CF}$ = 259.7 Hz, $^1J_{CP}$ = 195.7 Hz, CF_2), 118.9 (d, $^3J_{CP}$ = 5.9 Hz), 122.8, 129.3, 138.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −133.9 (ddd, $^2J_{FH}$ = 48.7 Hz, $^2J_{FP}$ = 87.7 Hz, $^2J_{FF}$ = 345.1 Hz, 1F), −135.5 (ddd, $^2J_{FH}$ = 48.7 Hz, $^2J_{FP}$ = 88.9 Hz, $^2J_{FF}$ = 345.1 Hz, 1F); ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.51 (dd, $^2J_{PF}$ = 87.7 Hz, $^2J_{PF}$ = 88.9 Hz, 1P); HRMS (ESI) *m*/*z* [M+H]$^+$ calcd for $C_{10}H_{15}F_2NO_2P$ 250.0808, found 250.0820.
14. The experiment realized with **6** and BnNHLi at 20 °C over 2 h afforded the expected corresponding phosphonamidate, but this latter was accompanied with other unidentified products.