

# Efficient Synthesis of Fluorophosphonylated Alkyles by Ring-Opening Reaction of Cyclic Sulfates

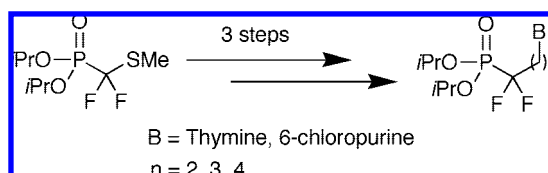
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## ABSTRACT



Ring-opening reactions of functionalized 1,2-cyclic sulfates and oxetanes with the phosphonodifluoromethyl carbanion are reported. This approach allows an easy access to fluorinated  $\beta$ -hydroxyphosphonates that are building blocks in the synthesis of acyclic nucleosides. Synthesis of precursors of nucleoside phosphorylase inhibitors from these alcohols is described.

Due to the importance of the phosphate moiety in the living world, a variety of stable phosphate mimics have been developed and used to either assign its exact role in biological pathways or inhibit enzymes responsible for several diseases.<sup>1</sup> Since the pioneering work of Blackburn<sup>2</sup> and Chambers,<sup>3</sup> difluoromethylphosphonates are known as the best isosteric and isoacidic phosphate analogues. Thus, many derivatives containing a difluoromethylphosphonate function were designed as potential enzyme inhibitors<sup>4</sup> and as useful probes for the elucidation of biochemical processes.<sup>5</sup> Among the different preparation methods of phosphonodifluorom-

ethyl derivatives described in the literature, the carbanionic method starting from the diethyl difluoromethylphosphonate is the most common.<sup>6</sup> However, since Montreal's protocol, this approach is compromised due to the regulation of HCFC and CFC needed to synthesize the starting materials. To overcome this major limitation, we developed an alternative route to form this fluorinated carbanion from the diisopropyl

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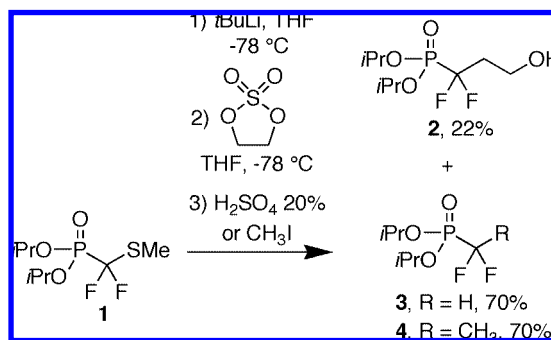
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phosphonodifluoromethyl sulfide **1** prepared by nucleophilic fluorination.<sup>7</sup> In contrast, this new method allowed the use of Lewis acid, and we showed that the anion reacted with a weaker electrophile such as THF, trimethylene oxide, and epoxides to produce hydroxydifluoromethylphosphonates in moderate to good yields.<sup>8</sup>

As resulting alcohols are known to be of great interest for the preparation of highly sophisticated difluoromethylphosphonates by C–C bond formation,<sup>9</sup> other ring-opening reactions of functionalized cyclic sulfates and oxetanes were explored and are reported in this paper. Derivation of the obtained alcohols in acyclic nucleoside precursors is also described.

We previously showed that the phosphonodifluoromethyl anion could react with epoxides in the presence of Lewis acid (BF<sub>3</sub>·Et<sub>2</sub>O) to afford β-hydroxydifluoromethylphosphonates in moderate to good yields.<sup>8</sup> However, this reaction was limited due to a retro-reaction, and an excess of anion or epoxide was needed to obtain the desired products in good yields. To circumvent this limitation, we focused our study on the more reactive 1,2-cyclic sulfates. These synthetic equivalents of epoxides are known to be more electrophilic.<sup>10</sup> Up to date, only three successful examples dealing with the preparation of fluorinated alcohols from 1,2-cyclic sulfates have been reported. These include their ring-opening reactions with fluoride (TBAF),<sup>10a</sup> trifluoromethyl (CF<sub>3</sub>I/TDAE),<sup>11</sup> and sulfonodifluoromethyl (PhSO<sub>2</sub>CF<sub>2</sub><sup>–</sup>) anions.<sup>12</sup> To the best of our knowledge, no attempt using the phosphonodifluoromethyl anion has been described. First, ethane 1,2-cyclic sulfate, easily prepared from ethyleneglycol,<sup>13</sup> was tested. The fluorinated carbanion was reacted at –78 °C with ethane 1,2-cyclic sulfate (1.2 equiv) over 2 h. After acidic treatment with H<sub>2</sub>SO<sub>4</sub>, the corresponding fluorinated β-hydroxyphosphonate **2** was isolated in 22% yield, while about 70% of diisopropyl difluoromethylphosphonate **3** was recovered (Scheme 1). Attempts to optimize the ring-opening reaction by changing the reaction time or the temperature or by adding a Lewis acid<sup>8</sup> or HMPA<sup>12</sup> were unsuccessful. In each case, phosphonate **3** was obtained as the major compound after acidic hydrolysis. On the other hand, workup with methyl iodide instead of H<sub>2</sub>SO<sub>4</sub> resulted in the formation of diisopropyl 1,1-difluoroethylphosphonate **4** as the main product. This result suggested that the formation of the hydrolysis product **3** occurred during the

**Scheme 1.** Ring-Opening Reaction of Ethane 1,2-Cyclic Sulfate



hydrolysis step and did not result from a proton transfer via a cyclic sulfate rearrangement.

This preliminary result contrasts with Hu's data concerning the ring-opening reaction of cyclic sulfates with PhSO<sub>2</sub>CF<sub>2</sub><sup>–</sup>.<sup>12</sup> Such a difference of reactivity between both phosphonyl and sulfonyl fluorinated carbanions was unexpected and difficult to rationalize since completely opposite reactivity profiles have been reported in ring-opening reaction of epoxides.<sup>8,14</sup> To explore the scope and limitation of the phosphonodifluoromethyl anion reactivity toward cyclic sulfates, our study was extended to constrained substituted 1,2-cyclic sulfates. Ring-opening reactions were realized following this scheme. The carbanion formed by addition of **1** to a solution of *tert*-butyllithium in THF at –78 °C was trapped by addition of neat 1,2-cyclic sulfate (1.3 equiv). After 15 min of stirring and acidic workup, β-hydroxydifluoromethylphosphonates **5–10** were isolated after flash chromatography in moderate to good yields (Table 1). Ring-opening reactions of functionalized 1,2-cyclic sulfates are relatively fast and do not require any Lewis acid. Unlike epoxides, a low amount of hydrolysis product **3** was observed even by using 1.3 equiv of cyclic sulfate. This reaction was regioselective and occurred on the less substituted carbon atom.<sup>15</sup> From the halogenated cyclic sulfate, no substitution reaction of the chlorine atom was observed. However, in this case, about 25% of product **3** was detected in the crude mixture. The β-hydroxydifluoromethylphosphonate **6** was isolated in 53% yield (Table 1). HMPA addition did not improve the rate and the yield of the reaction. As mentioned by Hu,<sup>12</sup> we also found the reaction supported other functional groups (OBn, OAr) and was efficient with alkyl- or aryl-substituted cyclic sulfates (Table 1, compounds **7–10**). Contrary to epoxides, the absence of Lewis acid allowed the anion formed by LDA deprotonation of HCF<sub>2</sub>P(O)(OEt)<sub>2</sub> to react in a similar manner with cyclic sulfates (Table 1, note a).

The ring-opening reaction was attempted with the 1,2-cyclic sulfamidate derived from benzyl phenylalaninol. After

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(15) Structures of the obtained regioisomers have been easily assigned by <sup>19</sup>F NMR analysis. In these spectra, each fluorine atom exhibits a multiplet (dddd) indicating the presence of a methylene group adjacent to the difluoromethylphosphonate function and an asymmetric carbon.

**Table 1.** Ring-Opening Reactions of Functionalized 1,2-Cyclic Sulfates and Sulfamidate

heterocycles	products	compounds, yields
	 ( <i>i</i> PrO) <sub>2</sub> (O)PCF <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<b>5</b> , 69% <sup>a</sup>
	 ( <i>i</i> PrO) <sub>2</sub> (O)PCF <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<b>6</b> , 53%
	 ( <i>i</i> PrO) <sub>2</sub> (O)PCF <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<b>7</b> , 79%
	 ( <i>i</i> PrO) <sub>2</sub> (O)PCF <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<b>8</b> , <i>n</i> = 1, 83% <b>9</b> , <i>n</i> = 2, 71%
	 ( <i>i</i> PrO) <sub>2</sub> (O)PCF <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<b>10</b> , 76%
	 ( <i>i</i> PrO) <sub>2</sub> (O)PCF <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	<b>11</b> , 69%

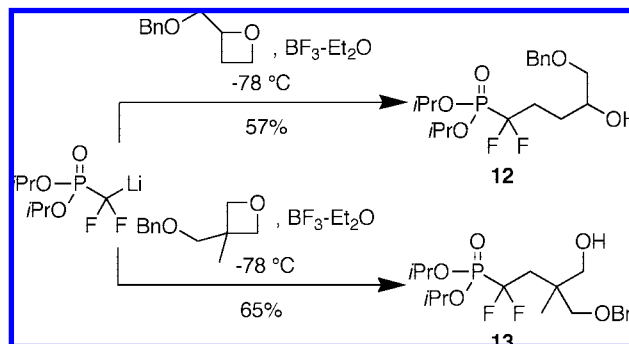
<sup>a</sup> From HCF<sub>2</sub>P(O)(OEt)<sub>2</sub> and LDA, the desired product was isolated in 48% yield under the same experimental conditions.

workup and flash chromatography, the corresponding protected  $\beta$ -amino-difluoromethylphosphonate **11** was isolated in 69% yield.

To cover the scope of the synthesis of functionalized alcohols, we focused our study on the ring-opening reaction of oxetane derivatives. As mentioned, these reactions were realized in the presence of BF<sub>3</sub>·Et<sub>2</sub>O, and diethyl ether was used as solvent. Reactions reached completion after 5 min under stirring at −78 °C. From 2- and 3,3-substituted oxetanes, corresponding fluorinated hydroxyphosphonates **12** and **13** were obtained in 57% and 65% yields, respectively, with traces of **3** (Scheme 2).<sup>16</sup> Due to a lack of general methods for the preparation of functionalized oxetanes, the ring-opening reaction of 1,3-cyclic sulfates was attempted. Unfortunately, only traces (<10%) of  $\gamma$ -hydroxydifluorophosphonates were detected from 1,3-dimethyl 1,3-cyclic sulfate, even in the presence of Lewis acid or HMPA.

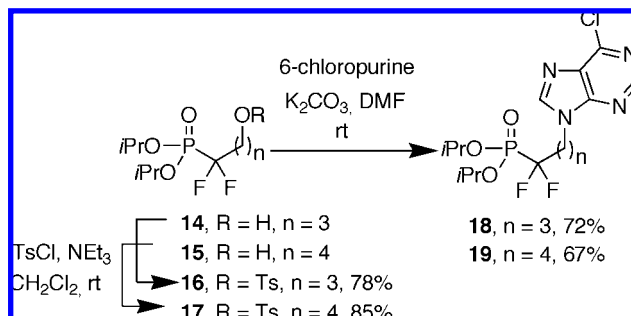
As previously mentioned, the use of  $\beta$ -hydroxydifluorophosphonates was illustrated by the synthesis of acyclic

**Scheme 2.** Ring-Opening Reaction with Substituted Oxetanes



nucleoside analogues. Derivation of alcohols **14** and **15**<sup>8</sup> was realized by introduction of nucleic bases. Alkylation of 6-chloropurine was conducted from their corresponding tosylates **16** and **17** in the presence of K<sub>2</sub>CO<sub>3</sub> in DMF.<sup>4a</sup> Nucleoside precursors **18** and **19** were isolated in good yields (Scheme 3).

**Scheme 3.** 6-Chloropurine Introduction onto Fluorinated Hydroxyphosphonates



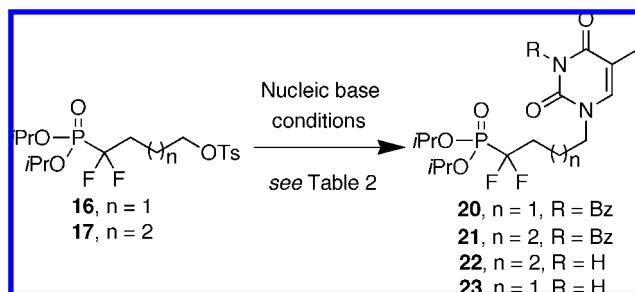
Alkylation of the *N*<sup>3</sup>-benzoylthymine,<sup>17</sup> under these conditions, was not successful due to a weaker nucleophilicity of pyrimidine rings. In the presence of PPh<sub>3</sub> and DEAD, fluorinated alcohols **14** and **15** were converted to their corresponding thymine derivatives **20** and **21** in moderate yields. However, partial deprotection of the thymine occurred, and the residual triphenylphosphine oxide was difficult to remove. Other experimental conditions were explored to optimize the thymine base coupling reaction (Scheme 4 and Table 2).

Thymine alkylation via its sodium salts was limited, and from tosylate **17** derivative **21** was isolated in 35% yield (Table 2, entry 1). The use of a nonmetallic base such as 1,1,3,3-tetramethylguanidine (TMG), known to enhance the yield of nucleophilic substitution reactions,<sup>18</sup> was then tested.

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**Scheme 4.** Thymine Alkylation with Fluorophosphonylated Tosylates



A mixture of tosylate **17** and thymine was treated with TMG in DMSO or acetonitrile at room temperature (Table 2, entry 2). After 15 h of stirring, the corresponding fluorophosphonylated thymine **22** was isolated in 86% yield as a mixture of two regioisomers (77/23) in favor of the *N*<sup>1</sup>-isomer.

**Table 2.** Different Conditions for Thymine Alkylation

entries	condition	product (yield) <i>N</i> <sup>1</sup> / <i>N</i> <sup>3</sup> isomers
1	<i>N</i> <sup>3</sup> -benzoylthymine, NaH, DMF, 80 °C, 4 h	<b>21</b> (35%), nd
2	thymine, TMG, DMSO, rt, 15 h	<b>22</b> (86%), 77/23
3	bis(trimethylsilyl)thymine, TBAF, THF, rt, 22 h	<b>22</b> (71%), 68/32
4	bis(trimethylsilyl)thymine, TMG, DMSO, rt, 15 h	<b>22</b> (69%), 60/40
5	<i>N</i> <sup>3</sup> -benzoylthymine, TMG, DMSO, rt, 15 h	<b>20</b> (75%), <b>21</b> (81%), 100/0

From the bis(trimethylsilyl)thymine and tosylate **17** in the presence of tetrabutylammonium fluoride (TBAF),<sup>19</sup> derivative **22** was obtained in 71% yield, also as a mixture of regioisomers (Table 2, entry 3).

On the basis of few reports describing the nucleophilic properties of TMG toward strong electrophiles,<sup>20</sup> tosylate **17** was treated by the silylated thymine in the presence of TMG (1.5 equiv). As for TBAF, TMG reacted on the silicon center, and after 15 h of stirring at room temperature, the

desired compound **22** was isolated in 69% yield (Table 2, entry 4). Although this is the first reported example of nucleic base introduction using the nucleophilic property of TMG, this reaction occurred without increased regioselectivity. Finally, these new coupling conditions have also been applied to the *N*<sup>3</sup>-benzoylthymine (Table 2, entry 5). In this case, tosylates **16** and **17** were converted into their corresponding thymine derivatives **20** and **21** in good yields with excellent regioselectivities when treated in the presence of TMG. Finally, thymine derivatives **22** and **23** were obtained in 67 and 71% yield, respectively, after treatment of **20** and **21** with methylamine in ethanol. This first room-temperature alkylation of protected thymine with primary alkylsulfonate is highly competitive with previous known methods.

In summary, we reported the synthesis of functionalized hydroxyphosphonates by new ring-opening reactions of 1,2-cyclic sulfates and oxetanes. From monosubstituted cyclic sulfates, the products were obtained in high yields, while from ethane 1,2-cyclic sulfate low yield was observed. The decreasing torsional strain ingoing to the transition state could be attributed to this high difference of reactivity. Oxetanes reacted as well as 1,2-cyclic sulfates to produce the expected alcohols in good yields. The synthetic interest of hydroxydifluorophosphonates was illustrated by their derivation into precursors of acyclonucleotides by using mild nucleic base coupling reactions. The biological evaluation of the fully deprotected acyclic nucleoside is under investigation and will be reported in due course.

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**Supporting Information Available:** Experimental procedures for the preparation of **2** and **5–23** and NMR spectra for compounds **5–9**, **11–13**, and **23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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