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Difluoromethylenediphosphonate: A Convenient, Scalable, and High-Yielding Synthesis

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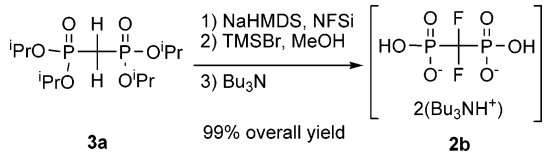
ABSTRACT

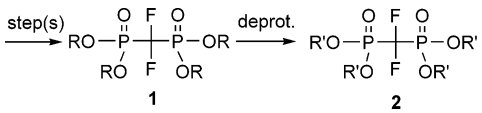


3a **2b**

Since the first disclosure of difluoromethylenediphosphonate, 2, almost 40 years ago, interest in this compound has flourished in several research areas. In this paper, we present a convenient, high-yielding (99% overall) method for the preparation of milligram to multigram quantities of 2 (as the bis(tributylammonium salt, 2b) in a solid form that is easy to handle.

Recently, we began a broad research program which required the synthesis and screening of a diverse collection of nucleoside mono-, di-, and triphosphate mimics for activity against nucleotide-binding protein targets of diseases such as cancer, HIV, and HCV.[1] The mimics comprised nucleoside phosphates, in which one or more bridging or nonbridging oxygen atoms bonded to phosphorus were replaced with moieties such as borano, fluoro, alkyl, aryl, seleno, amino, azido, and thio. In this paper, we focus on the synthesis of a particularly effective diphosphate mimic, namely difluoromethylenediphosphonate, **2** (Scheme 1). For simplicity,

Scheme 1



1 R = alkyl **2** R' = H or neg. charge

structure **2** represents the free acid, salt, or partial salt forms.

Diphosphonate, **2**, was first claimed as the trisodium salt in a Proctor and Gamble patent in 1966.[2] Study of this compound intensified after Blackburn reported that it is an isopolar and isosteric analogue of pyrophosphate.[3] Consequently, the CF_2 group was found to be an effective and non-hydrolyzable replacement for oxygen in phosphate analogues of important biomolecules, such as nucleoside triphosphates,[4] isoprenoid pyrophosphates,[5] and nucleoside diphosphates.[6] Compound **2** has also attracted attention in the study of bone resorption[7] and fuel cell electrolytes.[8]

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(1) (a) Boyle, N. A.; Fagan, P.; Brooks, J. L.; Prhavc, M.; Lambert, J.; Cook, P. D. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, in press. (b) Rajwanshi, V. K,; Prhavc, M.; Fagan, P.; Brooks, J. L.; Hurd, T, Cook, P. D.; Wang, G. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24* (3), 179−189. (c) Boyle, N. A.; Rajwanshi, V.; Prhavc, M.; Wang, G.; Fagan, P.; Chen, F.; Ewing, G.; Brooks, J. L.; Hurd, T.; Bruice, T. W.; Cook, P. D. Synthesis of Dideoxynucleoside. *J. Med. Chem.* **2005**, *48* (7), 2695−2700. (d) Wang, G.; Boyle, N. A.; Chen, F.; Rajappan, V.; Fagan, P.; Brooks, J. L.; Hurd, T.; Leeds, J. M.; Bruice, T. W.; Rajwanshi, V.; Jin, Y.; Prhavc, M.; Cook, P. D. *J. Med. Chem.* **2004**, *47* (27), 6902−6913. (e) Wang, G.; Sakhivel, K.; Rajappan, V.; Bruice, T. W.; Tucker, K.; Fagan, P.; Brooks, J. L.; Hurd, T.; Leeds, J. M.; Cook, R. D. *Nucleosides Nucleotides Nucleic Acids* **2004**, *23* (1−2), 317−337. (f) Cook, P. D.; Ewing, G.; Jin, Y.; Lambert, J.; Prhavc, M.; Rajappan, V.; Rajwanshi, V. K.; Sakthivel, K. PCT Int. Appl. WO2005021568, 2005.

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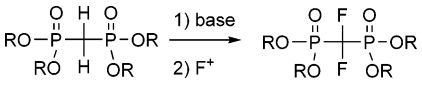
Given the continued and recent interest in this pyrophosphate mimic,[9] we wish to provide an improved and robust method for its preparation.

Generally, the synthesis of **2** requires construction of tetraalkyl difluoromethylenediphosphonate, **1**, followed by deprotection of the phosphate ester groups (Scheme 1).

A standard method for the preparation of **1** is not apparent in the literature, but it has been accomplished using a variety of innovative chemistries over the last 25 years.[10] We set out to improve the synthesis of **1** in order to provide a scalable, robust, high-yielding route to compound **2** using readily available chemicals and minimal synthetic steps.

A general route for the construction of **1** is the reaction between phosphonate carbanions (derived from methylene diphosphonate, **3**, and a strong base) and electrophilic fluorinating reagents which provide a source of electrophilic fluoride (F^+) (Scheme 2).

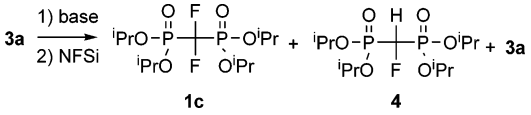
Scheme 2



The synthesis of **1** using NFSi was first reported by Gosselin (>34% yield).[11] Blackburn (50% yield)[12] and Lebeau (68−78% yield)[8c] have also reported this method. Tetraalkyl methylenediphosphonates and other reagents used in this route are readily available commercially and are relatively inexpensive. With the added convenience of a single step, we decided to choose this method for improvement.

In our initial study, tetraisopropyl methylenediphosphonate, **3a**, was treated with 2.0−3.3 equiv of base (e.g., KHMDS, NaHMDS, LiHMDS, NaH, KH) followed by 2.0−3.6 equiv of NFSi (Scheme 3). Crude reaction mixtures

Scheme 3



were analyzed by ^{31}P NMR for the presence of product **1c**, starting[10] material **3a**, partial product fluoromethylenediphosphonate, **4**, and unidentified impurities. In all cases, varied, but persistent, amounts of unreacted **3a** and **4** were observed in the reaction mixtures. Furthermore, compound **4** has an R_f similar to that of the desired product, and as a result, efficient removal of this impurity by flash chromatography, particularly on a multigram scale, was not trivial.

With similar results from different bases, it was apparent that the choice of base was not a critical factor for minimizing undesired **3a** or **4**; therefore, we chose to continue our study with the convenient NaHMDS solution.

Because NaHMDS is a strong base, reactions using this reagent are typically performed at −78 °C to allow more control of the reaction and to minimize the formation of side products. However, since diphosphonate **3a** is relatively stable, we decided to explore higher reaction temperatures, while maintaining the equivalents of NaHMDS and NFSi at 3 and 3.3, respectively. Encouragingly, the ratio of **1c** to **3a** and **4** improved with increased temperature (−20 °C, 0 °C, 25 °C, and reflux), but compounds **3a** and **4** still remained. Significantly, no additional impurities were observed by ^{31}P NMR under these conditions, therefore it was evident that cooling the reaction mixture was not necessary.

We then experimented with incremental, alternate additions of NaHMDS and NFSi without cooling the reaction mixture. Thus, **3a** was treated with 3.3 equiv of NaHMDS

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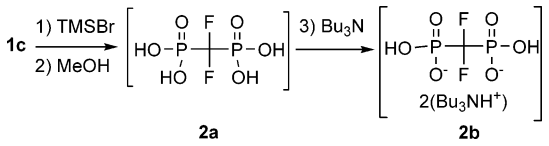
(12) Blackburn, G. M.; Thompson, M. Personal communication.

and 3.6 equiv of NFSi, which were added, alternately, in 2, 4, and 10 portions. For example, for 10 incremental additions, **3a** was treated 10 times with alternate additions of 0.33 equiv of NaHMDS followed by 0.36 equiv of NFSi. The ratio of **1c** to **3a** and **4** increased with 2 and 4 incremental additions, but with 10 incremental additions, negligible amounts of compounds **3a** or **4** were observed by ^{31}P NMR. The reaction was repeated several times with similar results and compound **1c** was isolated in yields ranging from 81 to 92% on a 0.5−27 g scale.[1d] After further method development (see the experimental details), a quantitative yield of **1c** was achieved on a 192 g scale.

Deprotection of 1. Bromotrimethylsilane (TMSBr) is the standard reagent for the deprotection of alkyl phosphate esters.[10a] This reaction is quite robust, and yields are typically very high. Treatment of **1c** with TMSBr, followed by quenching the resulting TMS esters with water or methanol, gives intermediate **2a** (Scheme 4). Desired salts, such as

Scheme 4



metal or quaternary ammonium, are readily prepared using equivalents of metal hydroxides or tertiary amines, respectively. The number of equivalents and the choice of counterion(s) influence the physical form and extent of hydration of **2**. In this paper we describe the preparation of **2** as the bis(tributylammonium) salt, **2b** (Scheme 4) in a solid form which is not highly hygroscopic and can be weighed accurately. This is particularly convenient where **2** is required for anhydrous reactions.

Difluoromethylenebis(phosphonic dichloride), **5**,[13] can be prepared from phosphonic acid **2a** via oxalyl chloride and catalytic DMF (Scheme 5). After purification by distillation, oil **5** was used immediately or stored in the freezer.

Scheme 5 [a]

[a] **5** was collected at 65 °C at 0.5 mmHg.

In summary, we investigated a number of different chemistries during our research on fluorinated phosphinates, phosphonates, and diphosphonates, and in one example, described in this manuscript, we developed a high-yielding route to compounds **1c** and **2b**. We believe that the methods described herein present the most convenient and efficient reported route and allow ready access to milligram to multigram quantities of such compounds. Furthermore, the chemistry described for the preparation of **1c** may also be useful in the synthesis of other fluorinated compounds, such as difluoromethanedisulfonate derivatives,[14] difluoro(phosphono)acetic acid derivatives,[15] or difluoromethanesulfonamide derivatives.[16]

Supporting Information Available: Experimental procedures and spectroscopic data for **1c** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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