Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 4035

www.rsc.org/obc

COMMUNICATION

A new route to α-alkyl-α-fluoromethylenebisphosphonates†

Petr Beier,*[a] Stanislav Opekar,[a] Mikhail Zibinsky,[b] Inessa Bychinskaya[b] and G. K. Surya Prakash*[b]

Received 18th January 2011, Accepted 10th March 2011
DOI: 10.1039/c1ob05095h

A new route to α-alkyl-α-fluoromethylenebisphosphonates, 2 has been developed starting from commercially available tetraethyl fluoromethylenebisphosphonate (1), and alkyl halides using either caesium carbonate in DMF or sodium dimsyl. De-esterification of 2 provided biologically important α-alkyl-α-fluoromethylenebisphosphonic acid, 3, while alkoxide–induced carbon–phosphorus bond cleavage of 2 gave α-fluorophosphonates, 4, which are useful synthons in organic synthesis.

Phosphonates are important non-hydrolyzable mimics of phosphates and are used in the synthesis of nucleotide analogs as probes for various enzymes,[1,2] in bone cancer treatments as carriers of radioactive ^{153}Sm,[3] in inorganic chemistry as chelating agents, *etc.*[4] They also have found several industrial applications.[5] The replacement of the oxygen bridge of the biological phosphate with the difluoromethylene or monofluoromethylene groups leads to isosteric analogues having acid dissociation constants almost identical with those of the natural phosphate.[6] This concept, introduced by Blackburn and co-workers,[7] led to the synthesis of a variety of biologically active fluorinated phosphonates and their successful deployment in many areas of biological chemistry.[1] Fluorinated phosphonates can be prepared in a number of different ways depending on the nature of organyl moiety. One of the common methods is their synthesis *via* fluorinated phosphonate carbanions. A central issue in nucleophilic displacement chemistry involving α-fluorinated phosphonoalkyl anions is the α-elimination of the phosphite or fluoride to produce carbenoid species leading to decomposition and generally lower yields. In case of difluorophosphonate metal species[8] this problem has been overcome by using either reactive electrophiles such as primary alkyl triflates[9] or by stabilization of the carbanion with cadmium or zinc.[10] The resulting reagents can be directly coupled with reactive alkyl halides or even with aryl halides or alkynyl halides, in the presence of Cu(I). Another way is to introduce a second anion-stabilizing group in addition to the original phosphonate such as trimethylsilyl,[11] arylsulfonyl[12] or a second phosphonate group (*i.e.* using bisphosphonates).[13] These modifications significantly prolong the nucleophile lifetime and prevent α-eliminations.

Bisphosphonates are compounds of interesting biological properties and currently there are a number of approved pharmaceuticals used for the treatment of various bone diseases (Fig. 1). These drugs are non-hydrolysable analogues of the endogenous pyrophosphate in which the oxygen bridge is replaced by a carbon atom bearing two groups. Usually one of these groups is an organic chain that determines the mode of action and the drug's activity. The other group mainly affects pharmacokinetics and it is usually a hydroxyl group.

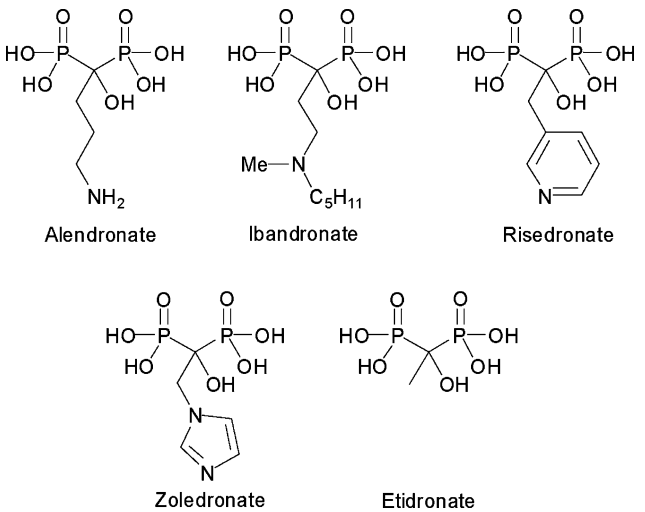


Fig. 1 Structures of bisphosphonate drugs currently used as anti-resorptive agents.

The presence of the α-OH in bisphosphonates is believed to enhance bone mineral binding compared to their hydrogen derivatives.[14] The bisphosphonate drugs work by inhibiting farnesyl pyrophosphate synthetase (FPPS), one of the key enzymes in the mevalonate pathway. From the crystal structure of the risedronate–FPPS complex it was found that the α-OH group does not chelate magnesium ions in the enzyme active site and contributes indirectly to the phosphonate anion interaction with Mg^{2+} by the electron-withdrawing effect of oxygen.[15] In principle, this effect should be exerted by other electron-withdrawing groups such as fluorine. This substitution might lead to a new class of anti-resorptive agents with better properties. Risedronate analogues shown in Fig. 2 were reported to retain biological activity but

[a]*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10, Prague 6, Czech Republic. E-mail: beier@uochb.cas.cz; Fax: +420 233 331 733; Tel: +420 220 183 409*
[b]*Loker Hydrocarbon Research Institute, Department of Chemistry, University of Southern California, Los Angeles, CA, 90089-1661, USA. E-mail: gprakash@usc.edu; Fax: +1 213 740 6270; Tel: +1 213 740 5984*

† Electronic supplementary information (ESI) available: Experimental procedures and full spectroscopic data for all new compounds. See DOI: 10.1039/c1ob05095h

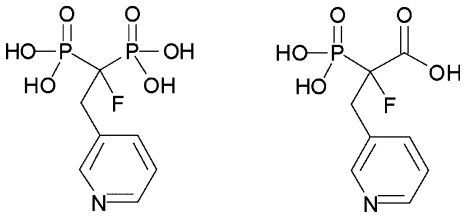


Fig. 2 Biologically active Risedronate analogues.

possess reduced bone affinity, which may be useful therapeutically in certain situations.[16]

Direct installation of an alkyl, aryl or heteroaryl group on CH–acidic bisphosphonate is problematic due to their rather low acidity, significant steric hindrance resulting in lowered nucleophilicity, and their tendency to undergo transesterification.[16,17] Furthermore, as already mentioned, some of CH–acidic compounds bearing fluorine atom undergo loss of fluoride ion upon deprotonation.[18] Due to these reasons, fluorobisphosphonate is considered to be a challenging synthon for undergoing simple alkylation protocols.[1]

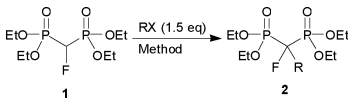
Previously, α-alkyl-α-fluoromethylenebisphosphonates **2** have been prepared by an electrophilic fluorination of α-alkylmethylenebisphosphonates accessible by either alkylation of methylenebisphosphonate[16a] or reaction of bis(diethylphosphono)ethylene with nucleophiles such as potassium imidazolide or aryllithium reagents.[19] The second route makes use of lithium salt of tetraethyl fluoromethylenebisphosphonate (**1**) in reactions with methylating reagents such as iodomethane or dimethylsulfate.[13] The above mentioned methods suffer either from unavailability of starting compounds, low yields or long reaction sequences. Furthermore, the lithium salt of **1** was reported to be unreactive towards other alkylating reagents such as iodoethane.[13a]

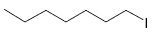
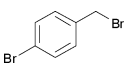
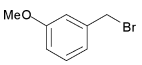
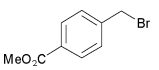
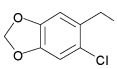
We decided to develop a general methodology towards α-alkyl-α-fluoromethylenebisphosphonates **2**, which would start from tetraethyl fluoromethylenebis-phosphonate (**1**) – a compound commercially available or easily prepared by electrophilic fluorination of tetraethyl methylenebisphosphonate with Selectfluor® in ca 50% yield.[20] Taking into account principal possibility of fluoride elimination and formation of carbene species screening of various bases was performed in the reaction of **1** with two model alkylating reagents: 1-iodoheptane and benzyl bromide. While the use of DBU, *i*-PrNEt$_2$, *t*-BuOK, NaHMDS, CsF or K_2CO_3 in THF or DMF solvents was not met with success, excess of caesium carbonate in DMF or sodium hydride in DMSO were identified as optimal conditions.

Various alkyl halides were used to determine the scope and limitation of the reaction (Table 1). With excess of caesium carbonate in DMF (Method A) primary alkyl iodides reacted well, except for $PhCH_2CH_2I$ which gave styrene by β-elimination as the main product under the reaction conditions. Primary alkyl bromides were also reactive, however, in some cases rather long reaction times were needed to achieve good results. The reactivity of primary alkyl chlorides was significantly reduced compared to iodides and bromides. Finally, 2-iodopropane as an example of a secondary alkyl iodide reacted reasonably well and provided the product **2d** in good yield (Table 1, entry 7). Reaction times could not be shortened by increasing temperature presumably due to limited stability of the caesium salt of **1** under elevated temperatures. For example, in the reaction with allyl bromide at 50 °C the yield of **2c** was only 14% after 18 h and it did not increase further under prolonged reaction times.

Satisfactory results have also been obtained using sodium hydride in DMSO (Method B). Reactions proceeded faster under these conditions, however they gave lower yields in some cases. In case of using chloromethylthiirane as the alkylating reagent (Table 1, entry 12), the formation of thietane substituted fluorobisphosphonate was not observed, which points to substitution process close to S_N2. It was thus shown that the caesium or sodium salt of **1** could be formed using a suitable base, the salts do not expel fluoride and are stable at ambient temperature in DMSO or

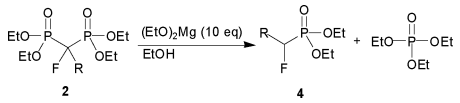
Table 1 Synthesis of **2** from **1** by alkylation



Entry	RX	Method[a]	Time (h)	**2**, Yield (%)[b]
1	MeI	A	22	**2a**, 85
2	MeI	B	1	**2a**, 62
3		A	144	**2b**, 57
4		A	72	**2c**, 50
5		A	160	**2c**, 78
6		B	1	**2c**, 59
7		A	96	**2d**, 57
8		A	85	**2e**, 22
9		A	19	**2e**, 74
10		A	120	**2f**, 82
11		A	20	**2g**, 0[c]
12		B	12	**2h**, 59
13		A	20	**2i**, 74
14		B	1	**2i**, 83
15		B	2	**2j**, 43
16		B	2	**2k**, 45
17		B	1	**2l**, 50
18		B	3	**2m**, 46
19		B	12	**2n**, 43

[a] Method A: Cs_2CO_3 (2 eq), DMF, rt; Method B: NaH (1.1 eq), DMSO, 0 °C to rt. [b] Isolated yield. [c] Styrene formed instead of **2g**.

Table 2 Synthesis of **4** from **2** by the action of magnesium ethoxide



Entry	**2**, R	Temp. (°C)	Time (h)	**4**, Yield (%)[a]
1	**2a**, Me	145	22	**4a**, 26[b]
2	**2c**, $CH_2{=}CHCH_2$	90	18	**4c**, 5[c]
3	**2e**, *n*-Bu	150	20	**4e**, 61
4	**2f**, *n*-C_7H_{15}	155	44	**4f**, 62
5	**2i**, Bn	100	20	**4i**, 50

[a] Isolated yield. [b] **4a** was obtained as inseparable mixture with triethylphosphate. [c] Number of side products were formed.

DMF and nucleophilic enough to undergo the desired alkylation reactions unlike the lithium salt of **1**.

De-esterification of selected phosphonates **2** using literature conditions[21] gave α-alkyl-α-fluoromethylenebisphosphonic acids, **3** in excellent yields (**3a**, R = Me, 97%; **3i**, R = Bn, 92%). This two step protocol starting from **1** represents the method of choice for the synthesis of phosphonic acids **3**.

A possibility of cleavage of one of the phosphoryl groups of bisphosphonates **2** to α-fluorophosphonates **4** was also investigated. This transformation would be analogous to the reductive cleavage of the sulfonyl group in fluorinated sulfones by sodium amalgam or magnesium metal in the presence of protic solvent.[12,22] Alkoxide induced P–CF_3 bond cleavage has been reported in the nucleophilic trifluoromethylations using diethyl trifluoromethylphosphonate.[23] It was expected that a nucleophile such as alkoxide anion would attack one phosphorus atom of **2**, followed by the cleavage of carbon–phosphorus bond to give α-fluorophosphonates **4**. Reaction of **2e** with EtONa (20 eq) in EtOH at ambient temperature gave only traces of expected diethyl (1-fluoropentyl)phosphonate (**4e**) after 17 h. At 50 °C under otherwise identical conditions the product conversions were 55% after 5 h and 30% after 17 h with the formation of many side products. Reaction of **2e** with Mg (10 eq) in MeOH at ambient temperature provided a mixture of methyl and ethyl bisphosphonates after 1.5 h and a mixture of methyl and ethyl (1-fluoropentyl)phosphonate after 17 h. Finally, it was decided to use magnesium ethoxide in ethanol[24] to avoid the formation of mixture of products by transesterification and the results are summarized in Table 2. It was found that excess (10 eq) of magnesium ethoxide and elevated temperature are needed to achieve moderate to good yields of fluorophosphonates **4**. Careful temperature control plays a crucial role. For example, with the benzyl derivative **2i**, the optimal temperature was found to be 100 °C. Below 90 °C the reaction was very sluggish, while above 120 °C there was a number of side-products formed. For alkyl derivatives **2a**, **2e**, **2f** the optimal temperature was 145–155 °C. This process represents novel and interesting C–P bond cleavage of fluorinated bisphosphonates to give fluorophosphonates **4**, however, it is not as efficient as some other literature methods.[11,12,25]

In summary, a new route to α-alkyl-α-fluoromethylenebisphosphonates **2** starting from commercial tetraethyl fluoromethylenebisphosphonate (**1**) and alkyl halides has been developed. This protocol is operationally very simple one-step reaction, which takes place at ambient temperature and under mild reaction conditions. Straightforward de-esterification of **2** provides important biologically active α-alkyl-α-fluoromethylenebisphosphonic acids **3**. Alkoxide–induced carbon–phosphorus bond cleavage of **2** provides a new way to α-fluorophosphonates **4**.

Support of this work at the Institute of Organic Chemistry by the Grant Agency of the Czech Republic (203/08/P310) and the Academy of Sciences of the Czech Republic (Research Plan AVZ40550506) is gratefully acknowledged. Work at the University of Southern California (USA) was supported by the NIH grant, 5-U19-CA105010 and the Loker Hydrocarbon Research Institute.

Notes and references

1 V. D. Romanenko and V. P. Kukhar, *Chem. Rev.*, 2006, **106**, 3868.
2 (*a*) G. K. S. Prakash, M. Z. Zibinsky, T. G. Upton, B. A. Kashemirov, C. E. McKenna, K. Oertell, M. F. Goodman, V. K. Batra, L. C. Pederson, W. A. Beard, D. D. Shock, S. H. Wilson and G. A. Olah, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 15693; (*b*) A. C. Sucato, T. G. Upton, B. A. Kashemirov, J. Osuna, K. Oertell, W. A. Beard, S. H. Wilson, J. Florian, A. Warshel, C. E. McKenna and M. F. Goodman, *Biochemistry*, 2008, **47**, 870; (*c*) C. A. Sucato, T. G. Upton, B. A. Kashemirov, V. K. Batra, V. Martinek, Y. Xiang, W. A. Beard, L. C. Pedersen, S. H. Wilson, C. E. McKenna, J. Florian, A. Warshel and M. F. Goodman, *Biochemistry*, 2007, **46**, 461; (*d*) C. E. McKenna, B. A. Kashemirov, T. G. Upton, V. K. Batra, M. F. Goodman, L. C. Pedersen, W. A. Beard and S. H. Wilson, *J. Am. Chem. Soc.*, 2007, **129**, 15412; (*e*) S. D. Taylor, F. Mirzaei and S. L. Bearne, *J. Org. Chem.*, 2008, **73**, 1403; (*f*) T. R. Burke, M. S. Smyth, M. Nomizu, A. Otaka and P. P. Roller, *J. Org. Chem.*, 1993, **58**, 1336; (*g*) A. V. Shipitsin, L. S. Victorova, E. A. Shirokova, N. B. Dyatkina, L. E. Goryunova, R. S. Beabealashvilli, C. J. Hamilton, S. M. Roberts and A. Krayevsky, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1039.
3 A. Singh, R. A. Holmes, M. Farhangi, W. A. Volkert, A. Williams, L. M. Stringham and A. R. Ketring, *J. Nucl. Med.*, 1989, **30**, 1814.
4 (*a*) V. Chandrasekhar, T. Senapati, E. C. Sanudo and R. Clerac, *Inorg. Chem.*, 2009, **48**, 6198; (*b*) D. Ostovic, C. Stelmach and B. Hulshizer, *Pharm. Res.*, 1993, **10**, 470; (*c*) E. Gumienna-Kontecka, R. Silvagni, R. Lipinski, M. Lecouvey, F. C. Marincola, G. Crisponi, V. M. Nurchi, Y. Leroux and H. Kozlowski, *Inorg. Chim. Acta*, 2002, **339**, 111.
5 B. Nowack, *Water Res.*, 2003, **37**, 2533.
6 D. B. Berkowitz and M. Bose, *J. Fluorine Chem.*, 2001, **112**, 13.
7 (*a*) G. M. Blackburn, *Chem,. Ind. (London)*, 1981, 134; (*b*) G. M. Blackburn, D. A. England and F. Kolkmann, *J. Chem. Soc., Chem. Commun.*, 1981, 930; (*c*) G. M. Blackburn, D. E. Kent and F. Kolkmann, *J. Chem. Soc., Chem. Commun.*, 1981, 1188.
8 K. S. Chunikhin, A. A. Kadyrov, P. V. Pasternak and N. D. Chkanikov, *Russ. Chem. Rev.*, 2010, **79**, 371.
9 D. B. Berkowitz, D. Bhuniya and G. Peris, *Tetrahedron Lett.*, 1999, **40**, 1869.
10 (*a*) D. J. Burton, R. Takei and S. Shin-Ya, *J. Fluorine Chem.*, 1981, **18**, 197; (*b*) W. Qiu and D. J. Burton, *Tetrahedron Lett.*, 1996, **37**, 2745; (*c*) T. Yokomatsu, K. Suemune, T. Murano and S. Shibuya, *J. Org. Chem.*, 1996, **61**, 7207; (*d*) X. Zhang and D. J. Burton, *Tetrahedron Lett.*, 2000, **41**, 7791.
11 R. Waschbüsch, J. Carran and P. Savignac, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1135.
12 D. B. Berkowitz, M. Bose and N. G. Asher, *Org. Lett.*, 2001, **3**, 2009.
13 (*a*) B. Iorga, F. Eymery and P. Savignac, *Tetrahedron Lett.*, 1998, **39**, 4477; (*b*) B. I. Martynov, V. B. Sokolov, A. Yu,. Aksinenko, T. V. Goreva, T. A. Epishina and A. N. Pushin, *Russ. Chem. Bull.*, 1998, **47**, 1983.
14 (*a*) A. Jung, S. Bisaz, P. Bartholdi and H. Fleisch, *Calcif. Tissue Res.*, 1973, **13**, 27; (*b*) E. Van Beek, C. Lowik, I. Que and S. Papapoulos, *J. Bone Miner. Res.*, 1996, **11**, 1492; (*c*) F. H. Ebetino, M. D. Francis, M. J. Rogers and R. G. G. Russell, *Rev. Contemp. Pharmacother.*, 1998, **9**, 233; (*d*) A. Jung, S. Bisaz and H. Fleisch, *Calcif. Tissue Res.*, 1973, **11**, 269.
15 K. L. Kavanagh, K. Guo, J. E. Dunford, X. Wu, S. Knapp, F. H. Ebetino, M. J. Rogers, R. G. G. Russell and U. Oppermann, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 7829.

16 (*a*) M. S. Marma, Z. Xia, C. Stewart, F. Coxon, J. E. Dunford, R. Baron, B. A. Kashemirov, F. H. Ebetino, J. T. Triffitt, R. G. G. Russell and C. E. McKenna, *J. Med. Chem.*, 2007, **50**, 5967; (*b*) C. E. McKenna *US*, *Patent* 4,478,763, 1984.
17 (*a*) I. Greiner, A. Grün, K. Ludányi and G. Keglevich, *Heteroatom Chemistry*, 2011, **22**, 11; (*b*) G. M. Kosolapoff, *J. Am. Chem. Soc.*, 1953, **75**, 1500.
18 (*a*) J. Hein van Steenis and A. van der Gen, *Eur. J. Org. Chem.*, 2001, 897; (*b*) N. Ishikawa, A. Takaoka and K. Ibrahim, *J. Fluorine Chem.*, 1984, **25**, 203; (*c*) M. Obayashi, E. Ito, K. Matsui and K. Kondo, *Tetrahedron Lett.*, 1982, **23**, 2323.
19 S. Inoue, T. Okauchi and T. Minami, *Synthesis*, 2003, 1791.
20 Y. Xu, L. Qian and G. D. Prestwich, *Org. Lett.*, 2003, **5**, 2267.
21 (*a*) V. M. D'yakov, M. G. Voronkov and N. F. Orlov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 1972, **21**, 2417; (*b*) C. E. McKenna and P. Shen, *J. Org. Chem.*, 1981, **46**, 4573.
22 J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465.
23 P. Cherkupally and P. Beier, *Tetrahedron Lett.*, 2010, **51**, 252.
24 Magnesium ethoxide in ethanol was applied since the reaction of magnesium metal requires the use of rigorously anhydrous ethanol and special magnesium activation. (*a*) A. Lenz, O. Bleh, E. Termin DE, 1806549, 1970; (*b*) E. Nakamoto, T. Kuniyuki JP, 61260086, 1986.
25 (*a*) G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1982, 1270; (*b*) G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1417; (*c*) G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1425; (*d*) C. Patois and P. Savignac, *J. Chem. Soc., Chem. Commun.*, 1993, 1711; (*e*) E. Differding, R. O. Duthaler, A. Krieger, G. M. Rüegg and C. Schmit, *Synlett*, 1991, 395; (*f*) G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Chem. Commun.*, 1981, 511; (*g*) X. Zhang, W. Qiu and D. J. Burton, *Tetrahedron Lett.*, 1999, **40**, 2681.

