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Synthesis of Di- and Triphosphate Ester Analogs *via* a Modified Michaelis-Arbuzov Reaction

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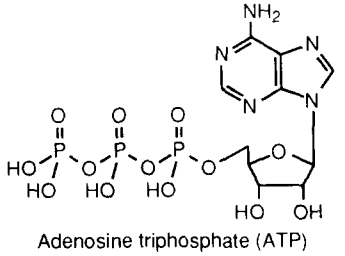
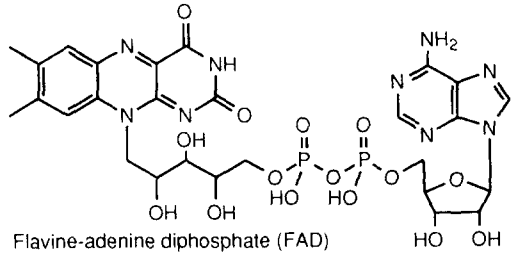
Abstract: For the first time, benzyl phosphites allowed the preparation of a set of polyphosphonates from chloromethyl halides *via* the Michaelis-Arbuzov reaction performed under vacuum. Regioselective mono-deprotection or complete deprotection of these phosphonates provide useful building blocks for the synthesis of biological phosphate analogs.

Many biological compounds (nucleosides, isoprenoids, some vitamins or coenzymes) have to be polyphosphorylated inside the cell to be active or to act in a different manner. By successive action of different cellular kinases, nucleosides are transformed into nucleoside triphosphates that can be incorporated into growing DNA or RNA by polymerases.[1] Similarly, many isoprenoids are phosphorylated into diphosphates that are then involved into post-translational modifications of specific proteins, modifying their regulation, functional activation and intracellular targeting.[2] Dinucleotides and related compounds such as diadenosine triphosphate (AP3A)[3] or flavine-adenine diphosphate (FAD)[4] constitute another class of functionally important polyphosphorylated compounds.

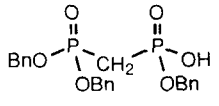


Adenosine triphosphate (ATP)

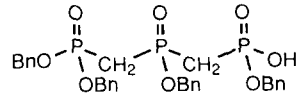


Flavine-adenine diphosphate (FAD)

In order to obtain stable analogs of such structures, especially *versus* enzymatic hydrolysis, we aimed to replace pyrophosphate moieties with methylene bis-phosphonates. We imagined to couple a fully protected phosphorus-containing building block (**1**, **2**) with an aglycon moiety prior to ultimate deprotection of benzyl esters.



1

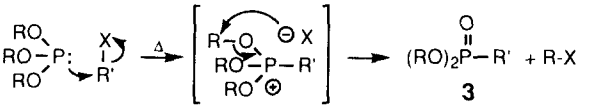


2

The benzyl ester protective group on phosphorus was selected with regard to the mild reaction conditions necessary for its final removal, either by catalytic hydrogenolysis or by action of bromotrimethylsilane.[5] Herein

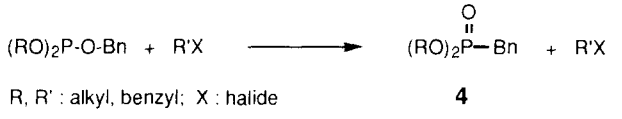
we describe the synthesis of compounds **1** and **2** using a modified procedure of the Michaelis-Arbuzov rearrangement.

The Michaelis-Arbuzov rearrangement, also known as the Arbuzov reaction, is a very versatile way to create a phosphorus-carbon bond from a trialkyl phosphite and an alkyl halide (scheme 1).[6]



Scheme 1

This reaction is one of the most extensively investigated in organophosphorus chemistry and is widely used to prepare phosphonates, phosphinates and phosphine oxides.[7] Basically, the trialkyl phosphites usually used are $(MeO)_3P$, $(EtO)_3P$ or $(i\text{-}PrO)_3P$. The rearrangement involves the formation of the corresponding alkyl halide (MeX, EtX, *i*-PrX) that is volatile in the general experimental conditions of the Arbuzov reaction. To our knowledge, there is no report in the literature on a Michaelis-Arbuzov reaction using benzyl phosphites except for the photo-Arbuzov rearrangement.[8,9] In fact benzyl phosphites are very reactive species and, in the presence of an alkyl halide R'X, there is formation of the highly reactive and non-volatile benzyl halide BnX. This one competes with the less reactive remaining R'X and immediately reacts with benzyl phosphite and generates another benzyl halide molecule. The reaction is then autocatalyzed so the benzyl phosphite is rapidly and totally transformed into the undesirable benzyl phosphonate **4** (scheme 2).

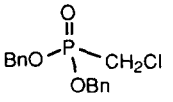
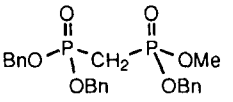
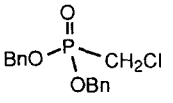
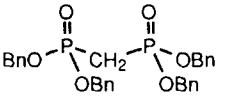
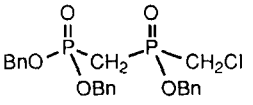
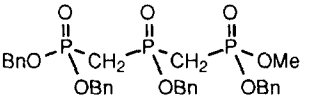
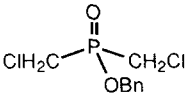
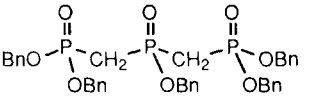
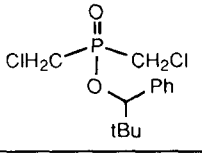
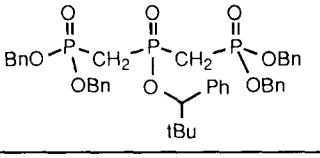


Scheme 2

However, efficient removal of benzyl halide generated *in situ*, performing the reaction at high temperature and reduced pressure, allows the formation of the desired phosphonate **3** with good to excellent yields. Working out the Michaelis-Arbuzov reaction in these conditions using halomethylene phosphonic or bis-halomethylene phosphinic esters,[10] it was possible to prepare differently functionalized diphosphate and triphosphate analogs with benzyl esters as protective groups.

In a typical experiment, the halomethylene derivative (c.a. 5 mmol) was vigorously stirred under vacuum (4-20 mmHg) with benzyl phosphite (10-20 mmol) and heated at 140°C for 2 to 8 hours. The crude residue was chromatographed on silica gel.

Results obtained with different halomethylene derivatives and various benzyl phosphites are summarized in table 1.

RX	Phosphite	Product		Yield* (%)
	$(BnO)_2P$-OMe		**5**	65
	$(BnO)_3P$		**6**	92
	$(BnO)_2P$-OMe		**7**	85
	$(BnO)_3P$		**8**	71
	$(BnO)_3P$		**9**	84

* The yields are based upon pure isolated material.

Table 1

The use of mixed phosphites, like dibenzyl methyl phosphite, allows the preparation of mixed di- and triphosphate analogs (**5** and **7**). Compound **5** (resp. **7**) is then easily and selectively monodeprotected at the methyl ester in 95% yield (resp. 94%) to give **1** (resp. **2**) using a well established procedure.[11,12]

Building blocks such as **1** and **2** allow direct esterification with various alcohols of interest (nucleosides, isoprenoids, vitamins...), using a Mitsunobu coupling reaction for example.[13,14] The selective removal of all benzyl groups can be achieved *via* catalytic hydrogenolysis or using bromotrimethylsilane.[5] This provides a new synthetic pathway to stable analogs of polyphosphorylated biochemicals. On the other hand, compound **6** and **8** can be fully deprotected *via* hydrogenolysis using Pd/C and then specifically esterified following previously reported procedures.[15]

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References and Notes

1. Lehninger, A.L. "Biochemistry" **1975**, 2nd Ed. Worth Publishers, Inc. New York, Chap 12.
2. Schafer, W.R.; Rine, J. *Annu. Rev. Genet.* **1992**, *30*, 209-237.
3. (a) Ralevic, V.; Burnstock, G. *Br. J. Pharmacol.* **1988**, *95*, 637-645. (b) Hoyle, C.H.V. *Gen. Pharmacol.* **1990**, *21*, 827-831.
4. Rivlin, R.S. "Riboflavin" **1975**, Plenum Press, New York.
5. McKenna, C.E.; Higa, M.T.; Cheung, N.H.; McKenna, M.C. *Tetrahedron Lett.* **1977**, 155-158.

6. (a) Michaelis, A.; Kachene, R. *Chem. Ber.* **1898**, *31*, 1408. (b) Arbuzov, A.E. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687.
7. (a) Kosolapov, G. "*Organophosphorus Compounds*" **1950**, Wiley, New York, chapter 7. (b) Harvey, R.G.; DeSombre, E.R. "*Topics in Phosphorus Chemistry*" **1964**, vol I, Grayson, M.; Griffith, E.J. Ed., Interscience, New York, p57. (c) Arbuzov, B.A. *Pure Appl. Chem.* **1964**, *9*, 307-335. (d) Henning, H.G.; Hilgetag, G. *Z. Chem.* **1967**, *7*, 169-176. (e) Arbuzov, B.A. *Z. Chem.* **1974**, *14*, 41-49. (f) Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.
8. Omelanzcuk, J.; Sopchik, A.E.; Lee, S.G.; Akutagawa, K.; Cairns, S.M.; Bentrude, W.G. *J. Am. Chem. Soc.* **1988**, *110*, 6908-6909.
9. A non-classical Arbuzov reaction involving tribenzyl phosphite and an activated acetate on a β-lactam has been reported: Campbell, M.M.; Carruthers, N. *J. Chem. Soc. Chem. Commun.* **1980**, 730-731.
10. (a) Bannard, R.A.B.; Gilpin, J.R.; Vavasour, G.R.; McKay, A.F. *Can. J. Chem.* **1953**, *31*, 976-983. (b) Frank, A.W.; Gordon, I. *ibid* **1966**, *44*, 2593-2596. (c) Ivanov, B.E.; Pantaleeva, A.R.; Shagidullin, R.R.; Shermergorn, I.M. *Zh. Obshch. Khim.* **1967**, *37*, 1856-1862 (*CA 68 29797e*). (d) Maier, L. *Helv. Chim. Acta* **1969**, *52*, 827-845. (e) Maier, L. *ibid* **1969**, *52*, 845-857.
11. Savignac, P.; Lavielle, G. *Bull. Soc. Chim. Fr.* **1974**, 1506-1508.
12. Selected analytical data. (**1**): ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.36-7.28 (*m*, 15 H); 5.10 (*d*, *J* = 11.9, 2 H); 5.02 (*d*, *J* = 12.0, 4 H); 2.57 (*t*, *J* = 21.1, 2 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 136.21 (*d*, *J* = 7.0); 135.86 (*d*, *J* = 6.5); 128.36; 128.31; 128.23; 128.02; 127.87; 127.46; 68.11 (*d*, *J* = 6.5); 67.30 (*d*, *J* = 6.0); 26.06 (*t*, *J* = 134.5). ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 22.06 (*d*, *J* = 6.2); 19.79 (*d*, *J* = 6.2). (**2**): (Mixture of diastereomers) ^{1}H-NMR (DMSO d_6, 200 MHz): 7.37-7.31 (*m*, 20 H); 5.07 (*d*, *J* = 7.2, 2 H); 4.97 (*d*, *J* = 7.4, 6 H); 2.77 (*t*, *J* = 20.1, 4 H). ^{13}C-NMR (CD_3OD, 50 MHz): 137.82-137.38 (*m*); 129.60-128.85 (*m*); 69.38 (*d*, *J* = 5.7); 68.63 (*d*, *J* = 5.7); 68.34 (*d*, *J* = 6.3); 29.61 (*dd*, *J* = 87.1, 130.6). ^{31}P-NMR ($CDCl_3$, 81.015 MHz): 41.21 (*t*, *J* = 4.9, 1 P); 18.59 (*d*, *J* = 4.9, 2 P).
13. Saady, M.; Lebeau, L.; Mioskowski, C. "Analogues stables, non-hydrolysables, de diphosphates ou de triphosphates et leurs procédés de fabrication". Fr. Patent n° 94 08091, June 30, 1994.
14. Saady, M.; Lebeau, L.; Mioskowski, C. *Tetrahedron Lett.* **1995**, *36*, 2239-2242.
15. (a) Myers, T.C.; Nakamura, K.; Flesher, J.W. *J. Am. Chem. Soc.* **1963**, *85*, 3292-3295. (b) Myers, T.C.; Nakamura, K.; Danielzadeh, A.B. *J. Org. Chem.* **1965**, *30*, 1517-1520. (c) Stock, J.A. *J. Org. Chem.* **1979**, *44*, 3997-4000. (d) Blackburn, G.M.; Kent, D.E.; Kolkmann, F. *J. Chem. Soc. Chem. Commun.* **1981**, 1188-1190. (e) Dixit, V.M.; Poulter, C.D. *Tetrahedron Lett.* **1984**, *25*, 4055-4058. (f) Blackburn, G.M.; Taylor, G.E.; Thatcher, G.R.J.; Prescott, M.; McLennan, A.G. *Nucleic Acids Res.* **1987**, *15*, 6991-7004. (g) Davisson, V.J.; Davis, D.R.; Dixit, V.M.; Poulter, C.D. *J. Org. Chem.* **1987**, *52*, 1794-1801. (h) Blackburn, G.M.; Guo, M.J.; Langston, S.P.; Taylor, G.E. *Tetrahedron Lett.* **1990**, *31*, 5637-5640. (i) Blackburn, G.M.; Langston, S.P. *Tetrahedron Lett.* **1991**, *32*, 6425-6428. (j) Hebel, D.; Kirk, K.L.; Kinjo, J.; Kovács, T.; Lesiak, K.; Balzarini, J.; De Clercq, E.; Torrence, P.F. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 357-360.

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