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O-Methyl-bis-*O*-(4-nitrophenyl)phosphite: a novel chemoselective *O*-phosphitylating reagent

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ABSTRACT

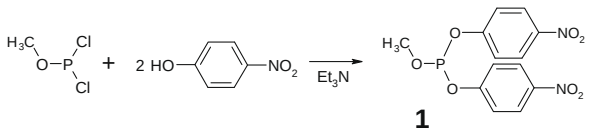
A novel chemoselective *O*-phosphitylating reagent containing two aryloxy leaving groups at a P(III) center is developed for selective formation of P(III) esters from amino alcohols without the need to protect the amino group. The reagent proved to be highly convenient for the synthesis of dinucleotides, P(III)–F structures, and cyclic P(III) nucleotides.

Synthetically available analogues of biological phosphates are of importance for molecular biology, enzymology, and medicine.[1] In contrast to pentavalent phosphorus compounds which are involved in mechanisms of life, trivalent phosphorus compounds have not been found in Nature. However, the introduction of P(III)–X (X = leaving group) type compounds as phosphitylating reagents was a central point in the synthetic chemistry of biophosphates. In comparison to P(O)–X compounds, they are considerably more reactive in nucleophilic displacements at the phosphorus center.[2] The early preference for P(V) reagents was based on their relative stability. Phosphoramidites >P–N< are the most frequently used reagents in the synthesis of various biomolecules.[3] The phosphoroamidite strategy is an extension of the Letsinger[4a] phosphate method and was introduced in nucleotide chemistry by Caruthers,[4b] and later improved by Köster.[4c] This class of compounds react poorly with alcohols unless specifically activated: tetrazole is by far the most commonly used activator in coupling reactions of phosphoroamidite with alcohols and other nucleophiles.[4b,5] This activator suffers from several drawbacks. Tetrazole is expensive, explosive, hygroscopic, and sparingly soluble in acetonitrile, the solvent most often used in coupling reactions.[6] It may also induce transesterification of trialkylphosphites.[7] Tetrazole is ineffective or must be used in large excess when strongly electronegative ligands are attached to the P(III) center.[8] To render the phosphoroamidite approach even more useful, several other activators have been investigated. Examples include substituted 1*H*-azoles such as 5-(4-nitrophenyl)-1*H*-tetrazole,[9a,b,e,g] 5-ethylthio-1*H*-tetrazole,[9c,d,f] 4,5-dicyanoimidazole,[9f,j] trimethylchlorosilane,[9e] and 2,4-dinitrophenol.[9i] Several acid salts have been proposed to replace tetrazole as the activator for phosphoroamidite coupling with alcohols.[10] Our recent efforts were directed toward replacement of phosphoroamidites with suitable phosphitylating reagents which do not require activation by tetrazole or other similar acidic activators.[11] Therefore P(III) compounds containing one or two 4-nitrophenoxy leaving groups attracted our attention.[12]

Aryloxy groups attached to the P(III) center have been employed as leaving groups in phosphitylation processes. Reagents containing the >POAr moiety are relatively stable, and easy to manipulate. They are activated by strong bases such as DBU and NaH and react rapidly with alcohols in very high yield at ambient temperature. Formation of an ArO^- anion, if necessary, may potentially serve to indicate reaction progress.

In this Letter, we describe a new phosphitylating reagent: *O*-methyl-bis-(*O*-4-nitrophenyl)phosphite **1**, which can readily be prepared in excellent yield from commercially available methoxydichlorophosphine using a standard procedure (Scheme 1).[13]

Phosphite **1** is a crystalline, stable compound which can be used and stored without any special precautions. Each of its two aryloxy groups can be replaced by alcohols in a stepwise manner with excellent chemoselectivity. The most important chemical property of phosphite **1** is its O-chemoselectivity. Therefore, as shown in this study, **1** is the phosphitylating reagent of choice for O-phosphitylation of amino alcohols, without the necessity of protecting the amino group. Another advantage of **1** is that the rate of exchange of the second aryloxy group is slow enough for efficient preparation of P(III) esters containing one aryloxy group. This type of compound can be used for further exchange thus allowing syntheses of (di)nucleotide systems containing a >P–F moiety.[8b,14]



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Scheme 1.

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E-mail address: wdabkow@bilbo.cbmm.lodz.pl (W. Dabkowski).

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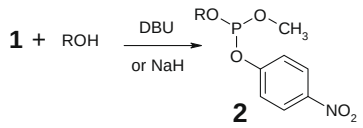


Scheme 2.

Exchange of the first aryloxy group of **1** by an alcohol proceeds smoothly in the presence of DBU or NaH in excellent yield within 10 min (Scheme 2).[15] Examples of products obtained according to Scheme 2 are given in Table 1.

Nucleoside 3′-phosphites **2a**,[12a] **2b**, **2c**, and **2d** were obtained as 1:1 mixtures of diastereoisomers as determined from ^{31}P NMR spectroscopy. No signals were found in the region 145–150 ppm, which could have indicated the formation of N-phosphitylated products.[16]

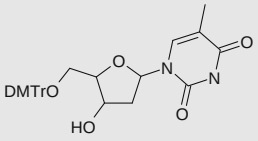
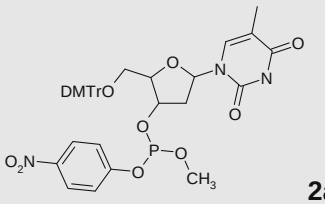
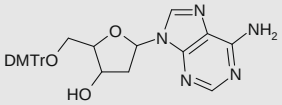
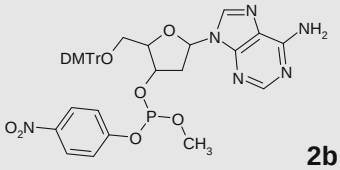
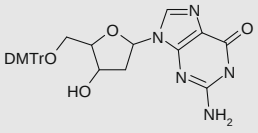
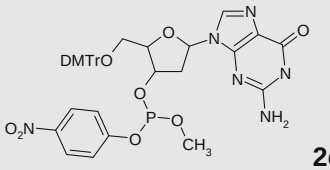
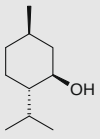
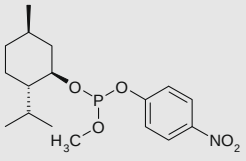
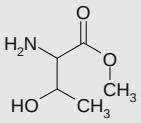
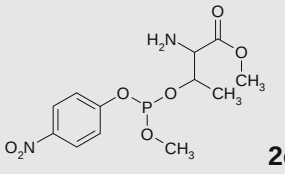
Compounds **2a**, **2b**, and **2c** were allowed to react with another nucleoside in the presence of DBU or NaH to give dinucleosidyl phosphites **3** (Scheme 3).[17]

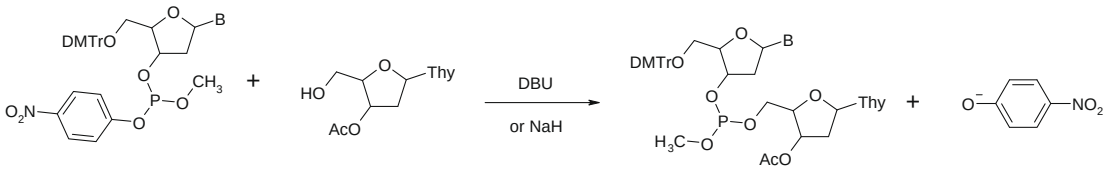
The condensations leading to the dinucleotides **3a–c** (Scheme 3) proceeded in excellent yield in the presence of DBU at 20 °C. The reaction rates were distinctly lower than the exchange reactions presented in Scheme 2. The minimum time necessary to complete the above coupling was ca. 4 h, the reaction being monitored by ^{31}P NMR.

Phosphites **3** were readily oxidized by adding elemental sulfur or selenium to give the corresponding thio **4**[18] or seleno **5**[19] dinucleotides (Scheme 4).

Interestingly, compound **1** can be readily transformed, via three steps (Scheme 5), into the corresponding salts **6** after removal of the methyl group. In this way we were able to confirm our earlier discovery that such demethylation occurs via the action of 4-nitrophenolate under mild conditions.[12a]

Table 1
Synthesis of phosphites **2a–e**

Entry	ROH	Product	^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm)	Yield (%)
1		 **2a**	134.9, 133.8 (1:1)	98
2		 **2b**	138.9, 138.0 (1:1)	95
3		 **2c**	141.0, 139.2 (1:1)	95
4		 **2d**	136.1, 135.6 (1:1)	98
5		 **2e**	135.4	90



2a, B = Thy
2b, B = Ad
2c, B = Gu

3a, B = Thy
3b, B = Ad
3c, B = Gu

Entry	Product	^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm)	Yield (%)
1	**3a**	141.5, 140.5	95
2	**3b**	140.4, 144.0	90
3	**3c**	141.9, 140.1	90

Scheme 3.

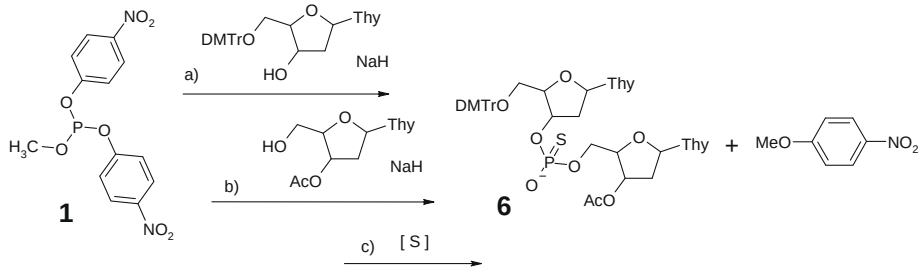
3

4a X = S, B = Thy
4b X = S, B = Ad
4c X = S, B = Gu

5a X = Se, B = Thy
5b X = Se, B = Ad
5c X = Se, B = Gu

Entry	Product	^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm)	Yield (%)	Entry	Product	^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm)	Yield (%)
1	**4a**	69.5, 69.8	90	4	**5a**	74.6; $J_{P\text{-}Se}$ = 976.3 Hz 74.3; $J_{P\text{-}Se}$ = 980.0 Hz	95
2	**4b**	69.9, 68.0	90	5	**5b**	74.3; $J_{P\text{-}Se}$= 976.3 Hz 74.0; $J_{P\text{-}Se}$= 976.3 Hz	85
3	**4c**	69.8, 68.9	95	6	**5c**	74.3; $J_{P\text{-}Se}$= 977.3 Hz 73.9; $J_{P\text{-}Se}$= 975.3 Hz	90

Scheme 4.



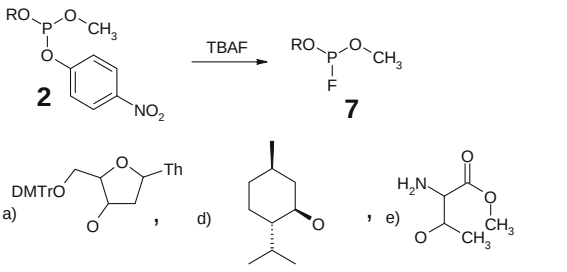
1 **6**

Scheme 5.

The coupling described in Scheme 3 involves the formation of 4-nitrophenolate. Therefore, the addition of sulfur (selenium) (Scheme 4) and demethylation (Scheme 5) can be performed together efficiently (Scheme 5).[20]

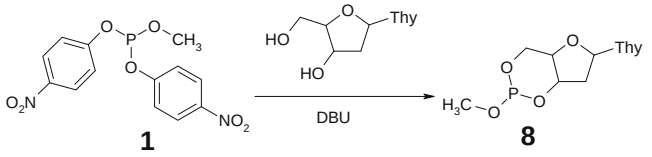
Compounds **2a**,**e**, as well as that derived from L-(−)-menthol **2d** are excellent substrates for the synthesis of fluorophosphites **7**. Exchange of an aryloxy group attached to the P(III) center by a fluorine ligand has been demonstrated previously in this laboratory.[8b,14] This method was successfully applied in the present study as shown in Scheme 6.

Exchange of an aryloxy group for the fluorine using TBAF proceeds at room temperature in THF solution in over 90% yield.[21]



Entry	Product	^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm)	Yield (%)
1	**7a**	131.7; $J_{P\text{-}F}$ = 1212.2 Hz 131.3; $J_{P\text{-}F}$ = 1208.6 Hz	95
2	**7d**	132.4; $J_{P\text{-}F}$ = 1207.3 Hz 132.3; $J_{P\text{-}F}$ = 1199.2 Hz	95
3	**7e**	136.2; $J_{P\text{-}F}$ = 1200.2 Hz	90

Scheme 6.



Scheme 7.

Products **7a–c**, after flash silica gel chromatography, can be used for further transformations such as selective exchange of the fluorine group with organometallic reagents to give P(III)–R structures.[22]

An additional example of the utility of phosphitylating reagent **1** is its application in the synthesis of cyclic phosphate triesters,[23,24] for example, thymidine nucleoside 3′,5′-cyclic methyl phosphite **8**[25,26] (Scheme 7).

In summary, we have developed *O*-methyl-bis-*O*-(4-nitrophenyl)phosphate as an efficient reagent for the preparation of P(III) esters of amino alcohols without the necessity of protecting the amino group, and for the preparation of P(III)–F systems.

Acknowledgments

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12. (a) Helinski, J.; Dabkowski, W.; Michalski, J. *Nucleosides Nucleotides* **1993**, *12*, 596; (b) Helinski, J.; Dabkowski, W.; Michalski, J. *Tetrahedron Lett.* **1993**, *34*, 6451; (c) Dabkowski, W.; Tworowska, I.; Michalski, J. *New J. Chem.* **2005**, *29*, 1396.
13. *O-Methyl-bis-O-(4-nitrophenyl)phosphate*: A solution of 4-nitrophenol (20 mmol) and triethylamine (20 mmol) in dry THF (10 ml) was added dropwise at rt under a nitrogen atmosphere to a solution of methoxydichlorophosphine (10 mmol) in dry THF (20 ml). After 2 h, triethylamine hydrochloride was removed by filtration. The filtrate was evaporated to dryness to give *O*-methyl-bis-(*O*-4-nitrophenyl)phosphite. [^{31}P NMR (121.49 MHz, $CDCl_3$) δ: 150.19 ppm; yield 95%].
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15. *General procedure for the preparation of RO-P(OMe)(OC$_6$H$_4$-m-NO$_2$)* **2**: A solution of the appropriate alcohol (10 mmol) and DBU (10 mmol) in dry CH_3CN was added at rt under an N_2 atmosphere to a solution of *O*-methyl-bis-(*O*-4-nitrophenyl)phosphite (10 mmol) in dry CH_3CN. The progress of the reaction was monitored by ^{31}P NMR and TLC. On completion, the reaction mixture was evaporated in vacuo. The residue was purified by flash column chromatography.
16. W. Dabkowski, unpublished results.
17. *General procedure for the preparation of RO-P(OMe)(OR′′)* **3**: To a solution of RO-P-(OMe)(OAr) (10 mmol) and DBU (10 mmol) in dry CH_3CN (20 mL) was added a solution of 3′′-*O*-acetylthymidine (10 mmol) in CH_3CN (10 mL). The progress of the reaction was monitored by ^{31}P NMR and TLC. On completion, the reaction mixture was evaporated in vacuo. The residue was purified by flash column chromatography to give **3**.
18. *General procedure for the preparation of RO-P(S)(OMe)(OR′′)* **4**: To a solution of ROP(OMe)(OR′′) (10 mmol) in dry THF (15 ml) was added a saturated solution of sulfur in *N*,*N*-diisopropylamine (5 ml) and the reaction was stirred for 2 h at rt. The crude product **4** was chromatographed on silica gel, using a gradient of 0–10% $CH_3C(O)CH_3$ in CH_2Cl_2 as eluent.
19. *General procedure for the preparation of RO-P(Se)(OMe)(OR′′)* **5**: To a solution of ROP(OMe)(OR′) (10 mmol) in dry THF (15 ml) was added a saturated solution of selenium in *N*,*N*-diisopropylamine (5 ml). The mixture was stirred for 2 h at rt, and then concentrated in vacuo. Purification by column chromatography, using a gradient of 0–10% $CH_3C(O)CH_3$ in CH_2Cl_2 as eluent gave **5**.

20. *5′′-O-Dimethoxytritylthymidine-3′′-O-(5′′-O-thymidyl-3′′-O-acetyl)phosphorothioate* **6**: A solution of 5′-*O*-dimethixytritylthymidine (10 mmol) and NaH (10 mmol) in dry THF was added, at rt under an N_2 atmosphere, to a solution of *O*-methyl bis(*O*-4-nitrophenyl)phosphite (10 mmol) in dry THF. The reaction was complete within 0.5 h to yield **2b** in 95% yield (^{31}P NMR). This reaction mixture was allowed to react with 3′′-*O*-acetylthymidine (1.1 mmol) and NaH (2.2 mmol dissolved in dry THF (10 mL). After 10 min, the phosphite **3a** had formed in 90% yield (^{31}P NMR). The reaction mixture was treated with a saturated solution of sulfur in *N*,*N*-diisopropylamine (5 ml). After 2 h, the crude solution of **6** was purified by silica gel column chromatography [^{31}P NMR (81 MHz, C_5D_5N) δ: 55.7, 55.0 ppm (1:1); yield 85%].
21. *General procedure for the preparation of RO-P(OMe)F* **7**: To a solution of aryl phosphite **2** (10 mmol) in dry THF (10 mL) was added TBAF (12 mmol) at rt. After 10 min, tetrabutylammonium 4-nitrophenolate was removed by filtration. The filtrate was concentrated in vacuo and the residue was purified by column chromatography using a gradient of 0–15% $CH_3C(O)CH_3$ in CH_2Cl_2 as eluent to give pure fluoridate **7**.
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25. *Thymidine 3′′,5′′-cyclic methyl phosphite* **8**. A solution of thymidine (10 mmol) and DBU (11 mmol) in dry acetonitrile (10 mL) was added dropwise at rt under a nitrogen atmosphere to a solution of *O*-methyl-bis-(*O*-4-nitrophenyl) phosphate **1** (5 mmol) in dry acetonitrile (10 mL) with stirring for 10 h. The mixture was evaporated to dryness and the resulting residue was purified by column chromatography using CH_2Cl_2–$CH_3C(O)CH_3$ (10:3 v/v) as eluent to give pure thymidine nucleoside 3′,5′-cyclic methyl phosphite **8**. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 120.2, 128.0 ppm. Yield 84%.
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