LETTER

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Highly selective *O*-phosphitylation of amino alcohols using P^{III}reagents containing 4-nitro and 2,4-dinitro aryloxy leaving groups†

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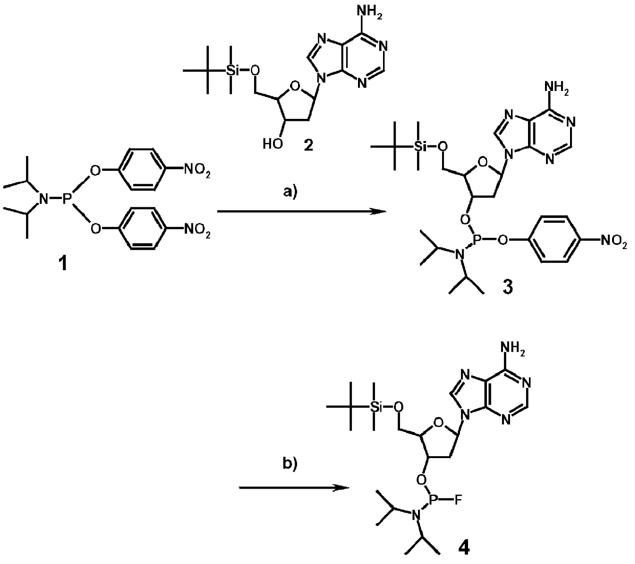
A method for direct highly *O*-selective phosphitylation of amino alcohols by reagents containing a 4-nitrophenoxy or 2,4 dinitrophenoxy leaving group has been developed. This method provides mild reaction conditions to access *O*-phosphitylated amino alcohols. The flexibility of the synthesis is exemplified by the models of simple amino alcohols and of nucleosides containing unprotected NH_2 groups.

Trivalent phosphorus compounds P^{III} are not found in nature. However they play a dominant role in the synthesis of other classes of phosphorus compounds due to their high reactivity.[1] Phosphoramidites are at present the most popular phosphitylating reagents. They are easily handled because of their relative stability and, once suitably activated, the amino group attached to the phosphorus center becomes a good leaving group. Over the past years we have employed P^{III}–OAryl compounds as a novel class of phosphitylating reagents in the synthesis of biophosphates and their analogues.[2] The P^{III}–OAr compounds are stable, and often crystalline phosphitylating reagents. P(III) compounds containing 2,4-dinitrophenoxy living groups react with alcohols without additional activation. In contrast, coupling of phosphite esters containing 4-nitrophenoxy living groups with alcohols requires intervention of strong bases such as DBU or sodium hydride.

In this paper we report that both types of reagents are *O*-selective toward systems containing free HO and NH_2 groups. Significant pieces of information about selective *O*-phosphitylation and *O*-phosphorylation are included in several excellent papers. Most of them deal with tetracoordinate phosphorus compounds and nucleotide chemistry.[3] The bis (*O*-4-nitrophenyl)-*N*,*N*-diisopropylphosphoramidite **1** is a typical reagent of this class in which the 4-nitrophenoxy group can be replaced by *O*-nucleophiles without affecting the amido function. The base of choice, to ensure its *O*-selectivity, is 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In the presence of other bases like sodium hydride a considerable proportion of *N*-phosphitylation products was observed.

The following scheme illustrates *O*-selective phosphitylation procedures of *O*-(5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosine by the bis (*O*-4-nitrophenyl)-*N*,*N*-diisopropylphosphoramidite **1**. In this way *O*-(4-nitrophenyl)-*N*,*N*-diisopropylphosphoramidite **3** was prepared in over 95% yield by the phosphitylation of the 5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosine **2** using reagent **1** in the presence of equimolar amount of DBU (Scheme 1, reaction a).

The phosphoramidite **3** was obtained as a 1 : 1 mixture of diastereoisomers as estimated from ^{31}P NMR spectroscopy (δ_P: 147.6 ppm, 146.9 ppm) but no signals due to *N*-phosphitylated products (δ_P: 123–127 ppm)[4] were detected. Additionally the structure of **3** was confirmed by its transformation into fluorophosphoramidite **4** [δ_P: 156.0 ppm (d, J_{PF} 1114.9 Hz) and 155.8 ppm (d, J_{PF} 1114.5 Hz), (1 : 1); δ_F: −76.4 ppm (d, J_{PF}: 1116.9 Hz) and −77.0 ppm (d, J_{PF} 1115.6 Hz.)] by tetra-*n*-butyl ammonium fluoride (TBAF) in almost quantitative yield (Scheme 1, reaction b). The replacement of the 4-nitrophenoxy group by fluorine, as demonstrated in our previous studies, proceeds very efficiently giving a convenient access to P^{III}–F systems.[2d] The lack of affinity of the reagent **1** for the amino group of the fully *O*-protected nucleoside 3′,5′-*O*,*O*-di(*tert*-butyldimethylsilyl)-2′-deoxyadenosine **5** was demonstrated in the blank experiment. Compounds **1** and **5** were allowed to interact for 16 h in acetonitrile solution at ambient temperature and no sign of *N*-phosphitylation pathway leading to the compound **6** was observed (Scheme 2).



Scheme 1 Synthesis of *O*-[5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosidin-3′-yl] *N*,*N*-diisopropylfluorophosphoramidite.[4] *Reagents and conditions*: (a) 1 eq DBU CH_3CN, 16 h; (b) 1 eq TBAF, THF, 10 min, rt.

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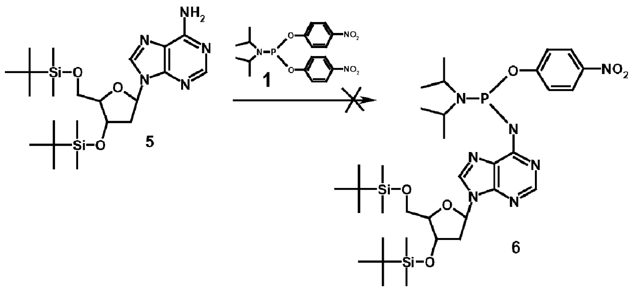
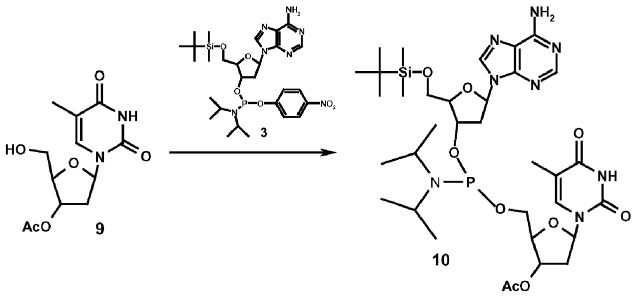


Scheme 2 *Reagents and conditions*: 1 eq DBU, CH_3CN, 16 h, rt.



Scheme 4 Synthesis of *O*-(5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosidin-3′-yl) *O*-(3′-*O*-acetylthymidin-5′-yl)-*N,N*-diisopropylphosphoramidite. *Reagents and conditions*: 1 eq DBU, CH_3CN, 10 h, rt.

The phosphitylating reagent **1** allowed selective *O*-phosphitylation of 9-(2-hydroxyethoxymethyl)guanine (acyclovir, Zovirax ®) **7** in excellent yield without any formation of *N*- or *O*-phosphitylated product on the guanine moiety (Scheme 3).

The ^{31}P NMR spectra data for *O*-(9-[(2-hydroxyethyloxy)-methyl]guanin-4′-yl) *O*-(4-nitrophenyl) *N,N*-diisopropylphosphoramidite **8** [δ_P: 145.0 ppm] are consistent with those observed by us for the *O*-{N^2-(4-methoxytrityl-9-[(2-hydroxyethoxy)methyl]guanin-4′-yl}*O*-(4-nitrophenyl) *N,N*-diisopropylphosphoramidite[5] and the nucleotide analogues containing the protected NH_2 group.

The aryloxyphosphoramidite **8** obtained in excellent yield is an example of a useful ambident phosphitylating reagent which can react with a variety of nucleophiles in a chemoselective manner by the replacement of either the 4-nitrophenoxy group or the diisopropylamino group to give compounds of potential interest as antivirus agents.[6]

Another example of *O*-phosphitylation not interfering with the NH_2 group attached to the adenine ring is the highly efficient synthesis of *O*-(5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosidin-3′-yl) *O*-(3′-*O*-acetylthymidin-5′-yl)-*N,N*-diisopropylphosphoramidite **10** (Scheme 4). The latter dinucleotide **10** was prepared in 98% yield by coupling of compound **3** with 3′-*O*-acetylthymidine **9** in acetonitrile solution in the presence of an equimolar amount of DBU (Scheme 4). The structure of **10** and the purity of the crude material were confirmed by the ^{31}P NMR spectrum, which shows two prominent signals at 149.2 ppm and 148.8 ppm supporting the presence of the diastereomeric phosphotriester functions, but no detectable signals due to *N*-phosphitylated products (δ_P: 123–127 ppm)[3f].

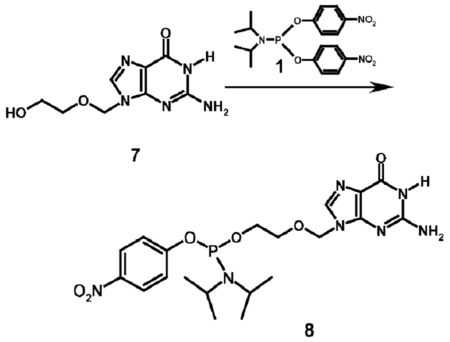
The question is: what is the origin of the observed *O*-selective phosphitylation in the presence of DBU? The same reaction carried out in the presence of sodium hydride or triethylamine led to a mixture of *O*- and *N*-phosphitylated products. This could indicate that DBU acts in this case not only as base but also as nucleophilic activator by formation of the intermediate species **11**. The reaction of compound **3** with an equimolar amount of DBU was monitored at room temperature by ^{31}P NMR spectroscopy. Generation of the cationic P(III) species **11** is observed in the region expected for the tricoordinate phosphorus compounds values: δ: 127.39 ppm 128.11 ppm (Scheme 5).

Involvement of DBU in the phosphitylation procedure is supported by the fact that when 3′-*O*-acetylthymidine **9** is added the complex **11** disappears forming the corresponding dinucleotide **10**. The ability of the tricoordinate phosphorus species to form complexes with DBU has recently been described by Bertrand *et al.*[7] and also recently observed by us in the case of tricoordinate systems containing an aryl ligand.[8]

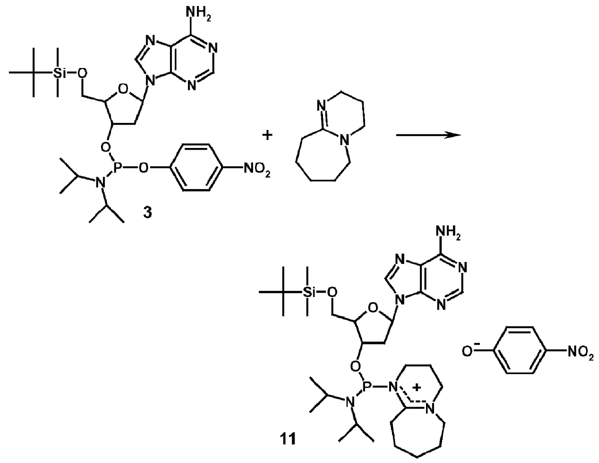
Having defined the methodology of *O*-phosphitylation *via* reagents containing the 4-nitrophenoxy group we turned our attention to their analogues bearing the 2,4-dinitrophenoxy group. Recently it was demonstrated in this laboratory that the latter class of compounds phosphitylates alcohols without any need for activation.[9] This approach has been successfully applied to the preparation of cyclic phosphate triesters.[10] The phosphite **12** is readily formed in almost quantitative yield from the phosphoramidite **3** by the reaction with one equivalent of 2,4-dinitrophenol.[11] Because of its low stability the phosphite **12** was used *in situ* to phosphitylate the nucleoside **9** to give the final phosphate **13** in over 95% yield without attacking the NH_2 group attached to the adenine ring (Scheme 6).

Examples of the *O*-phosphitylating ability of simple P^{III}-compound **14** containing a 2,4-dinitrophenoxy leaving group is given in Scheme 7.

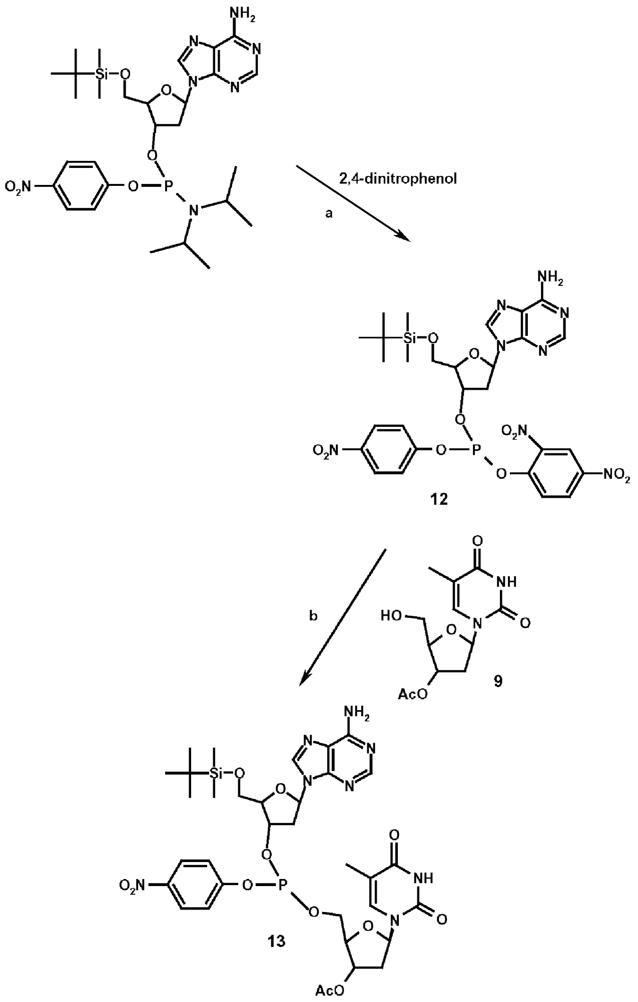
Both reactions b and c (Scheme 7) proceeded very fast at room temperature in THF or acetonitrile solution yielding the *O*-phosphitylated product: 3-[(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)oxy]-propylamine **15** (δ_P: 122.0 ppm) or



Scheme 3 Preparation of *O*-{9-[(2-hydroxyethyloxy)methyl]guanin-4′-yl} *O*-(4-nitrophenyl) *N,N*-diisopropylphosphoramidite. *Reagents and conditions*: 1 eq. DBU, CH_3CN, 2 h, rt.

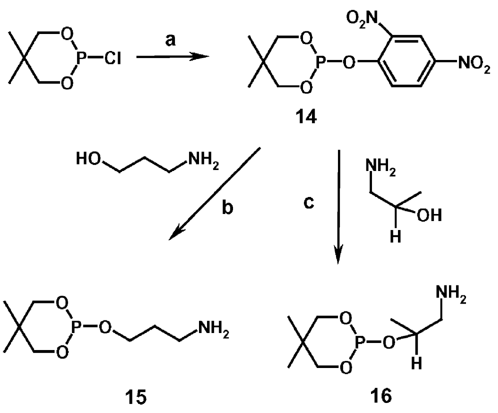


Scheme 5 Formation of the intermediate species **11** between *O*-[5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosidin-3′-yl] *O*-(4-nitrophenyl)-*N,N*-diisopropylphosphoramidite **3** and DBU.



Scheme 6 Synthesis of *O*-(5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosidin-3′-yl) *O*-(3′-*O*-acetylthymidin-5′-yl) *O*-(4-nitrophenyl)phosphite **13** using 2,4-dinitrophenyl as the activator. *Reagents and conditions*: (a) 2,4-dinitrophenol, CH_3CN, (b) CH_3CN, 1 h, rt.

2-[(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)oxy]propylamine **16** (δ_P: 122.6 ppm) in very good yield. A similar chemical shift was observed for *O*-phosphitylated derivatives of 5,5-dimethyl-1,3,2-dioxaphosphorinane.[12] The reactions b and c (Scheme 7) were monitored by ^{31}P NMR. In the case of the reaction b, the spectrum showed a signal at 122.0 ppm supporting the presence of the *O*-phosphitylated product, but no detectable signal around δ_P: 140 ppm, which could be assigned to an *N*-phosphitylated derivative. Some *N*-phosphitylated product (δ_P: 137.5 ppm, 1% yield as determined by ^{31}P NMR) was observed in the synthesis of **16**.[13]



Scheme 7 Synthesis of 3-[(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)oxy]-propylamine **15** and 2-[(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)oxy]-propylamine **16**. *Reagents and conditions*: (a) 2,4-dinitrophenol, NEt_3, THF, 1 h; (b) CH_3CN, 2 h; (c) CH_3CN, 2 h, rt.

Smooth formation of P^{III}-*O*-2,4-dinitrophenoxy structures from the corresponding phosphoramidites is a principal element of the catalytic action of 2,4-dinitrophenol described by us in earlier study.[9] Most recently this catalyst was used in the *O*-selective phosphitylations leading to oligonucleotides.[14]

In summary we have uncovered a mild and efficient method for selective *O*-phosphitylation of amino alcohols. This method is applicable for a wide range of amino alcohols. The full scope and reaction mechanism will be reported in due course.

Experimental

General

The solvents were reagent grade and were distilled and dried by conventional methods before use. The products were purified by flash chromatography on silica gel 60 (Merck 0.063 mm, 230–400 mesh ASTM). NMR spectra were obtained on a Bruker AC 200 and MSL 300 MHz spectrometers. δ-Values are reported in ppm relative to Me_4Si as standard for ^{1}H NMR (200.13 and 300.13 MHz), relative to H_3PO_4 as external standard for ^{31}P NMR (80.96 and 121.49 MHz), and relative to $CFCl_3$ as external standard for ^{19}F NMR (188.15 MHz). The signals are expressed as s (singlet), d (doublet), t (triplet) or m (multiplet). Coupling constants (*J*) are in Hz.

General syntheses

A solution of the appropriate amino alcohol (10 mmol) and DBU (10 mmol) in dry CH_3CN was added at room temperature under N_2 atmosphere to a solution of corresponding *O*-arylphosphite (10 mmol) in dry CH_3CN. The progress of the reaction was monitored by ^{31}P NMR and TLC. When the reaction was complete the reaction mixture was evaporated *in vacuo*. The residue was purified by flash chromatography or distillation.

Acknowledgements

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5 Compound *O*-{N^2-(4-methoxytrityl)-9-[(2-hydroxyethoxy)-methyl]-guanin-4′-yl} *O*-(4-nitrophenyl) *N,N*-diisopropylphosphoramidite was prepared in an analogous way as described for compound **8**. ^{31}P-NMR ($CDCl_3$) 145.9, 146.0.

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