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Note

# The phosphorofluoroamidite approach to mixed phosphites

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Dedicated to Professor François Mathey on the occasion on his 60th birthday

**Abstract**

A new convenient and general procedure is described for the preparation of mixed phosphites from readily available phosphorofluoroamidites by stepwise replacement of amino and fluoro-groups in the presence of trimethylchlorosilane ($Me_3SiCl$). The reaction mechanism is briefly discussed. © 2002 Elsevier Science B.V. All rights reserved.

*Keywords:* Phosphites; Fluorophosphites; Trimethylchlorosilane; Nucleotides

## 1. Introduction

As a result of recent advances in chemical biology and organometallic chemistry, there is a need to develop efficient methods and strategies for synthesis of esters containing different groups at the tricoordinate phosphorus centre. Recent developments in the chemistry of tricoordinate phosphorus compounds containing a P–F bond show that they are available in a number of structural combinations [1]. We have recently reported a new example of P(III) systems containing amino and fluoro ligands [2]. The pronounced stability of these compounds in comparison with their analogues containing other halogens makes them convenient candidates for the synthesis of other P(III) structures [3].

We now disclose a new synthesis of mixed P(III) esters based on the stepwise exchange of amino and fluoro ligands. Synthesis of simple mixed phosphites is possible in the reaction of corresponding phosphorochloridites with alcohol. However, this method is not useful in the synthesis of nucleosidyl phosphite owing to the limited availability of corresponding nucleosidyl phosphorochloridites.

As reported previously by us, trimethylchlorosilane ($Me_3SiCl$) may act as a highly efficient catalytic activator for the replacement of the amino group by alcohols to form the corresponding ester in almost quantitative yield at room temperature [4]. We have now made the happy discovery that P(III)–F systems can be activated by $Me_3SiCl$. We found that P(III) esters are formed in excellent yield when P(III)–F compounds are allowed to react with an alcohol in the presence of an equivalent amount of $Me_3SiCl$. Two other products formed in this reaction—trimethylfluorosilane ($Me_3SiF$) and hydrogen chloride—are readily separated from the ester formed. In a model study, we observed that simple phosphorofluoridite **1** reacts at room temperature with 2-cyanoethanol and $Me_3SiCl$ to give the ester **2a** in over 90% yield after 12 h (Scheme 1).

We found that this reaction proceeds a similar manner with a number of other alcohols and phosphorofluoridites. This type of reaction is of limited interest in the case of simple phosphorofluoridites. But the situation is very different in the case of P(III) compounds containing amino and fluoro ligands, where $Me_3SiCl$ may act either as activator of the amino group or as a reagent for replacing the fluoro group. The rates of these processes differ greatly. Therefore, replacing of the amino group by an alcohol in the presence of $Me_3SiCl$ proceeds very fast at room temperature, practically without affecting the P(III)–F bond (Scheme 2, reaction a). The reaction of the latter with an alcohol

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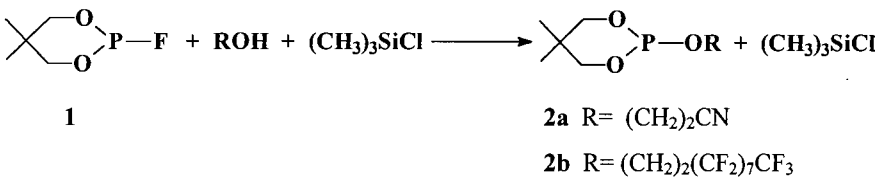
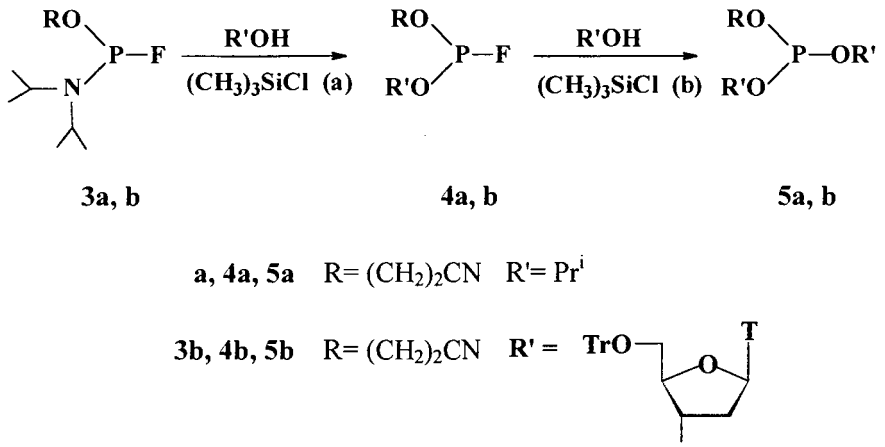
and $Me_3SiCl$ takes several hours at room temperature (reaction b). Therefore, effective stepwise ligand exchange can be achieved in R-P(F)$NR'_2$ systems. This is illustrated by the following examples.

The reaction presented in (Scheme 3) demonstrates formation of a complex nucleotide system containing a chiral phosphorus centre. Similar transformation can be performed in a variety of chiral alcohols and phosphorofluoroamidites.

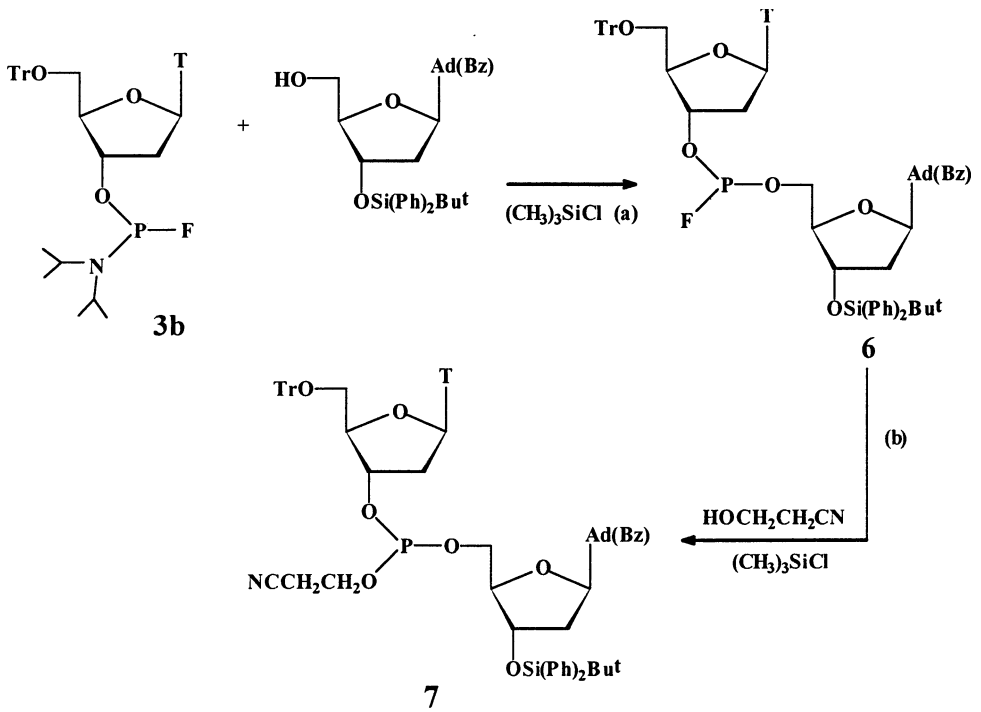
When acid sensitive protective groups are present it is best to neutralise hydrogen chloride with molecular sieves 4 Å.




Scheme 1.




Scheme 2.



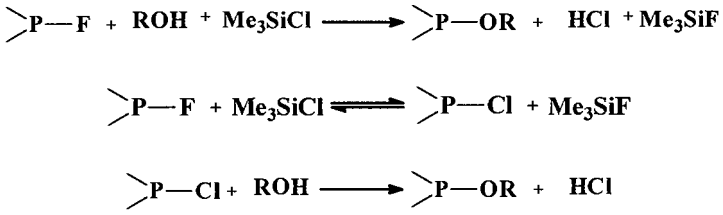

Scheme 3.

Spectroscopic data concerning the compounds **1**–**7** described are given in Table 1.

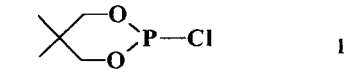
From a mechanistic point of view, the reaction of P(III)F compounds with alcohols and $Me_3SiCl$ leading to P(III)OR esters is most likely to involve intermediate formation of P(III)Cl compounds. The latter react with alcohols to give the desired ester and hydrogen chloride.

In conclusion, we have developed the efficient reaction of phosphorofluoridites with alcohols and $Me_3SiCl$ leading to the corresponding phosphites. This reaction allows stepwise conversion of phosphorofluoroamidites into the corresponding mixed phosphites.

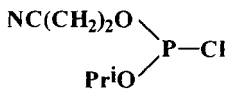
Further studies on the formation of mixed phosphites indicated in this communication are in progress.



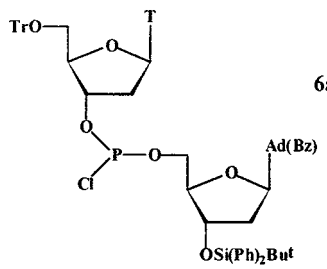

Formation of P(III)–Cl is reversible and the driving force of this reaction is the high energy of the Si–F bond and was observed by $^{31}$P-NMR spectroscopy.




1a $^{31}$P NMR ($CDCl_3$): 147.1 ppm




4c $^{31}$P NMR($CDCl_3$): 165.4 ppm




6a $^{31}$P NMR($CDCl_3$): 166.0, 165.7 ppm

This reaction proceeds either via intermediate phosphonium salt **8** or the four centre transition state **9**.

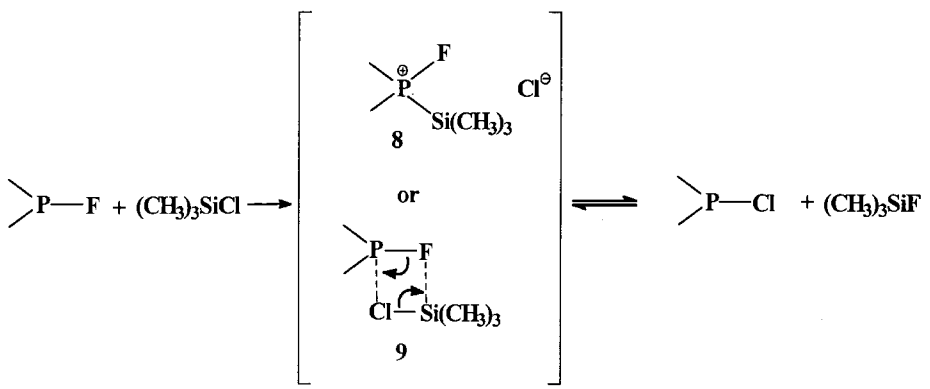


Table 1
$^{31}$P-NMR of compounds **1**–**7**

| Compound | $^{31}$P-NMR ($\delta$ ppm) [a] | ($J_{P-F}$ Hz) |
|---|---|---|
| **1** | 121.7, 105.6 | 1305, 1 |
| **2a** | 121.6 | – |
| **2b** | 122.5 | – |
| **3a** | 161.5, 147.8 | 1104, 2 |
| **3b** | 162.9, 149.1 162.7, 148.9 | 1117.5, 1115.4 |
| **4a** | 138.9, 122.9 | 1297,8 |
| **4b** | 139.8, 124.8, 139.6, 124.6 | 1215.2, 1216.8 |
| **5a** | 140.4 | – |
| **5b** | 140.1 | – |
| **6** | 139.9, 124.9, 138.1, 123.1 | 1220.8, 1220.0 |
| **7** | 140.1, 139.3 | – |

[a] Eighty five percent $H_3PO_4$ external references at 121 49 MHz in $CDCl_3$.

## 2. Experimental

### 2.1. Typical synthetic procedures

#### 2.1.1. 1-(2-Cyanoethoxy)-4,4-dimethyl-1-phospha-2,6-dioxacyclohexane (**2a**)

$Me_3SiCl$ (10 mmol) in THF (10 ml) was added to a solution of 1-fluoro-4,4-dimethyl-1-phospha-2,6-dioxacyclohexane (10 mmol) and 2-cyanoethanol (10 mmol) in THF (20 ml). The reaction was run at 20 °C for 12 h. After evaporation of THF in vacuo the crude **2a** was purified by distillation (b.p. 89/16 mmHg). Yield 90%. $^1$H-NMR (Bruker AC 200.13 MHz) 0.19 (s, 3H), 0.97 (s, 3H), 2.40–2.65 (m, 2H), 3.04 (t, 2H), 3.79–3.84 (m, 2H), 4.25–4.50 (m, 2H); Anal. Calc. for $C_8H_{14}O_3NP$: C, 47.29; H, 6.95; N, 6.89%. Found: C, 47.35; H, 7.00; N, 7.00%.

#### 2.1.2. O-[5′-O-tritylthymidin-3′-yl] O-[$N^6$-benzoyl-3′-O-(tert-butyldiphenylsilyl) 2′-deoxy-adenosin-5′-yl] o-(2-cyanoethyl)phosphite (**7**)

The fluorophosphoramidite **3b** (10 mmol) was allowed to react with $N^6$-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl)-2′-dexyadenosine (11 mmol) in the presence of $Me_3SiCl$ (0.3 mmol) in THF solution (20 ml) to give after 5 min at 20 °C the fluorophosphite **6**.

Consequently 2-cyanoethanol (10 mmol) and $Me_3SiCl$ (10 mmol) were added. The reaction was run at 20 °C for 20 h. The nucleotide **7** formed was purified by silica gel column chromatography ($CH_2Cl_2$: $CH_3C(O)CH_3$ 10:1 v/v). Yield 95%. $^1$H-NMR (Bruker AC 200.13 MHz) 1.00 (s, 9H *t*-butyl), 1.59 (d, 3H, thymine), 2.50–2.70 (m, 2H, P–$OCH_2$), 4.10–4.30 (m, 2H, $CH_2CN$), 8.57, (1H, br. s, NH). MS (FAB$^-$) Calc. 1178.5 [M]. Found: 1177.1 [M − 1].

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