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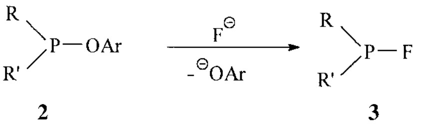
Synthesis of Tri- and Tetracoordinate Phosphorus Compounds Containing a PCF_3 Group by Nucleophilic Trifluoromethylation of the Corresponding PF Compounds

Izabela Tworowska, Wojciech Dąbkowski, and Jan Michalski*

Dedicated to Professor Marianne Baudler on the occasion of her 80th birthday

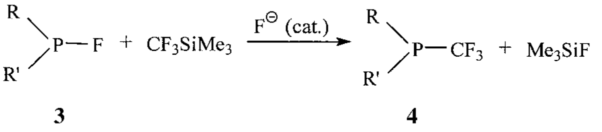
The introduction of a trifluoromethyl group into an organic compound can bring about remarkable changes in physical, chemical, and biological properties.[1] Therefore, the importance of fluorinated compounds in life sciences is rapidly increasing. Modification of the backbone of biophosphates by replacement of the anionic phosphodiester group with the neutral trifluoromethylphosphonato group should have steric, polar, and electronic effects similar to those of a hydroxyl group. Additionally, the lipophilicity should be enhanced.[2] Tricoordinate $P^{III}-CF_3$ compounds may act as useful ligands in organometallic chemistry.[3] Among the variety of methods for introducing a CF_3 group into organic compounds, the application of (trifluoromethyl)trimethylsilane CF_3SiMe_3 (**1**) as nucleophilic trifluoromethylating reagent is rapidly becoming the method of choice. CF_3SiMe_3 was first synthesized by Ruppert et al. in 1984[4] and is commercially available. In contrast to organic compounds containing a CF_3 group, little is known about $P^{III}-CF_3$ compounds. $P^{V}-F$ compounds, which are apparent candidates for nucleophilic trifluoromethylation by **1**, have been used for this purpose in only two cases.[5] So far no reaction of this kind has been described for $P^{III}-F$ compounds.

Our interest in $P-CF_3$ compounds is related to our recent studies on phosphorus–fluorine compounds derived from alcohols of biological interest. The method of choice for preparing $P^{III}-F$ groups is based on nucleophilic displacement of OAr^- from a $P^{III}-OAr$ group by a fluoride ion [Eq. (1)].[6] Both types of P^{III} compounds, **2** and **3**, are available in excellent yield and exhibit a high degree of chemical and stereochemical stability.[7]



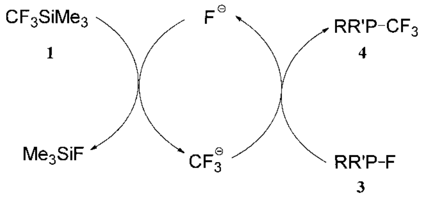
(1)

We found that $P^{III}-F$ compounds react with the Ruppert reagent **1** at 20 °C in THF or acetonitrile in almost quantitative yield [Eq. (2)].[8] The reaction is catalyzed by fluoride ions.



(2)

Cesium fluoride is a convenient fluoride donor, but other donors such as tetrabutylammonium fluoride (TBAF) can also be used. As the fluoride ion is used in catalytic amounts, the catalytic cycle shown in Scheme 1 is proposed.



Scheme 1. Proposed cycle for the nucleophilic trifluoromethylation of $P^{III}-F$ compounds by **1**.

The strength of the P–F bond is compensated by the high affinity of fluorine for the silicon center. An analogous mechanism should operate in the case of tetracoordinate phosphorus–fluorine compounds RR′P(X)F (X = O, S). The optimized protocol for this reaction was applied to a variety of

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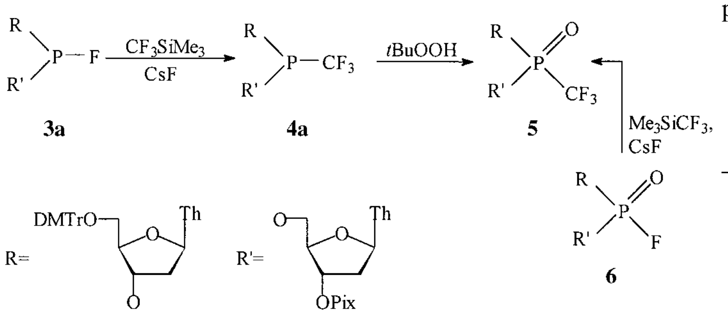
P^{III}–F structures **3** containing alkoxy, alkylsulfanyl, amino, and aryl ligands and led to the corresponding P^{III}–CF_3 compounds **4** in good yield (Table 1). Compounds **4** derived from nucleosides can also be prepared efficiently by this method. Note that the high toxicity of some P^{III}–F and P^{III}–CF_3 compounds calls for special precautions.

Table 1. ^{31}P NMR and FAB-MS data of selected compounds.

Compound	$\delta(^{31}P)$[a]	J_{PCF} [Hz]	FAB-MS [M+H]	Yield [%][b]
4 (R, R′: $-SCH_2CH_2S-$)	40.82 (q)	63.515	193.2	65
4a[c]	111.91 (q)	76.987	1143.1	82
	112.02 (q)	77.012		
5[c]	−2.42 (q)	129.431	1159.1	90
	−2.50 (q)	127.963		
8	31.41 (sept)	87.901	270.2	75

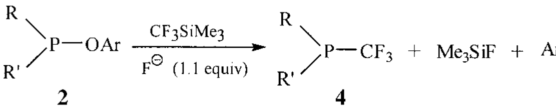
[a] 81.014 MHz, $CDCl_3$, H_3PO_4 external standard. [b] Yields of isolated product after purification. [c] Mixture of two diastereoisomers (1:1).

The trifluoromethylphosphonate analogues of nucleotides were prepared from CF_3PBr_2 and nucleosides.[9] Dinucleoside trimethylsilylphosphonates were prepared by Ugi et al. from $CF_3P(NEt_2)_2$ in a multistep synthesis with low yield.[2] Our synthesis of dinucleoside trifluoromethylphosphonate **4a** derived from thymidine starts either from the dinucleotide phosphorofluoridite **3a** or from the corresponding phosphorofluoridate **6** (Scheme 2). Compounds **4a** and **5** were clearly revealed by ^{31}P NMR spectroscopy to be 1:1 mixtures of diastereoisomers (Table 1). The spectroscopic properties of the CF_3 phosphonate **5** are identical with those described by Ugi et al. The intermediate phosphonite **4a** undergoes slow ligand exchange in solution. Therefore its oxidation to the CF_3 phosphonate **5** should be performed without delay. Oxidation of **3a** to **6** and of **4a** to **5** was performed with *tert*-butyl hydroperoxide. The reactions shown in Scheme 2 proceed in high yield.

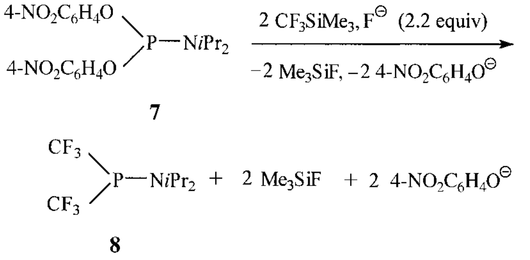


Scheme 2. Synthesis of **4a** and **5**. DMTr = 4,4′-dimethoxytrityl, Pix = 9-(9-phenyl)xanthenyl, Th = thymine residue.

An important part of these studies was to develop a sequential procedure that combines formation of RR′P–F (**3**) with their transformation into the corresponding $RR'PCF_3$ [**4**; Eq. (3)]. We assume that in this case the intermediate **3** is formed and reacts at once with **1** to give **4**. The combined procedure takes place at 20 °C in high yield. An illustrative example of the sequential procedure is the synthesis of (diisopropylamino)bis(trifluoromethyl)phosphine **8** [Eq. (4), Table 1].[10]



(3)



(4)

In conclusion, we have developed a general and highly efficient procedure for the conversion of P^{III}–F compounds into the corresponding P^{III}–CF_3 compounds by reaction with CF_3SiMe_3. The tricoordinate compounds are readily oxidized by *tert*-butylhydroperoxide to $P(O)CF_3$ compounds. The method is particularly useful as it is compatible with a sequential procedure combining formation of phosphorus–fluorine compounds from P^{III}-aryloxy precursors with the reaction leading to P^{III}–CF_3 groups. Both reactions require the presence of fluoride ions as substrate or catalyst. Our procedure is superior to those described previously.[2, 9]

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[8] Typical procedure for **4**: A solution of CF_3SiMe_3 (10 mmol) in dry THF (20 mL) was added dropwise at room temperature under nitrogen to a stirred mixture of **3** (10 mmol) and CsF (0.1 mmol) in dry THF (20 mL). After 4 h the solvent was evaporated in vacuo. The residue was purified by column chromatography (250–400 mesh silica gel, Merck 9385) or distilled under reduced pressure.

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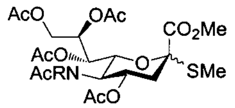
[10] Typical procedure for **8**. A solution of CF_3SiMe_3 (10 mmol) in dry THF (20 mL) was added dropwise at room temperature under nitrogen to a stirred mixture of bis(4-nitrophenyl) *N*,*N*-diisopropylphosphoramidite **7** (5 mmol) and cesium fluoride (11 mmol) in dry THF (20 mL). After 4 h the cesium 4-nitrophenoxide salt was removed by filtration. The filtrate was concentrated in vacuo, and the residue was purified by distillation under reduced pressure.

The Thioglycoside and Glycosyl Phosphite of 5-Azido Sialic Acid: Excellent Donors for the *α*-Glycosylation of Primary Hydroxy Groups[**]

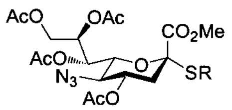
Chung-Shan Yu, Kenichi Niikura, Chun-Cheng Lin,[*] and Chi-Huey Wong[*]

N-Acetylneuraminic acid (sialic acid, NeuAc) is often found at the nonreducing end of glycoconjugates associated with important biological recognition events.[1] Although many glycosylation reagents are available for the synthesis of sialosides, addition of sialic acid with absolute *α*-glycosidic linkage remains a significant challenge.[2] Because of the sterically hindered tertiary anomeric center, the presence of an electron-withdrawing carboxyl group, and the lack of a participating auxiliary substituent adjacent to the anomeric center, most of the existing sialyl donors often have relatively low anomeric reactivities, and the sialylation reaction often proceeds with low yield, low *α*-stereoselectivity and significant undesirable elimination.

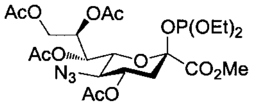
In order to tackle these problems, various new sialyl donors, including sialyl phosphites,[3] thioglycosides,[4] and xanthates,[5] have been developed. These donors give high *α*-selectivity in reactions with secondary hydroxyl groups, but they exhibit low *α*-selectivity, when primary hydroxyl groups are used as acceptors.[2a] In most cases, the content of undesirable *β* isomer ranged from 10 to 50% when secondary hydroxyl groups were used as acceptors and was more than 50% with primary hydroxy groups like the 9-OH group of sialic acid as acceptors. Anchimeric assistance by an auxiliary group at C-3[2d, 6] has been demonstrated to improve *α*-selectivity. Recently, the di-*N*-acetyl sialyl donor **1** has been shown to exhibit increased reactivity and yield in reaction with the 9- or 8-OH group of an appropriate acceptor,[7] and in certain cases with higher *α*-selectivity.[8] The sialic acid 8-OH group was thought to engage in an intramolecular hydrogen bonding interaction with the O atom of the C-1 carbonyl or the 2-OR group, or to interact with the 5-NHAc group of **2**, thus weakening the nucleophilic activity.[7]



1α, β R = Ac
2α, β R = H



3 R = *p*-methylphenyl (Tol)
4α R = Me



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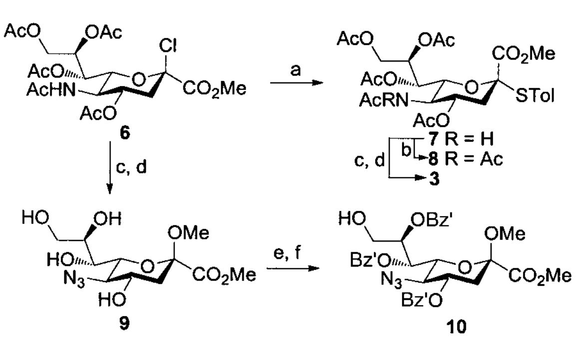
This undesirable interaction was circumvented by further acetylation of the NHAc group, and the NAc_2 derivative **1** gave an increased glycosylation yield;[7a] however, the *α*-selectivity was not improved, and a significant amount of *β* isomer was present in the product (ca. 30%). We report here the use of the thiosialosides **3** and **4** and the corresponding phosphite **5**, in which the 5-NHAc of **2** is replaced with the azido group, as *α*-selective glycosylation reagents for primary and secondary hydroxyl groups as acceptors. Sialylation reagents with a 5-azido group have been described in the literature,[9] but their effect on reactivity or stereoselectivity has not been studied, except that a low-yield (ca. 26%) sialylation was reported.[9b]

To prepare the glycosyl donors, the sialyl chloride **6**[10a] was treated with *p*-thiocresol in the presence of Hünig's base to give the *α*-thioglycoside **7**[10b] in crystalline form (Scheme 1). Subsequent N acetylation of **7** to give **8** could be easily achieved in high yield by treatment with isopropenyl acetate and a catalytic amount of TsOH.[7a] Complete deacetylation[11] of **7** followed by a catalytic diazo transfer[12] and acetylation of the hydroxyl groups gave **3**. The methylsulfanyl-substituted



Scheme 1. a) Thiocresol, $NEt\textit{i}Pr_2$, CH_2Cl_2, RT, 18 h, 85%. b) Isopropenyl acetate, cat. TsOH, 60°C, 15 h, 95%. c) MsOH, MeOH, 60°C, 24 h, 55%. d) 1) TfN_3, $CuSO_4 \cdot 5H_2O$, MeOH, RT, 18 h; 2) Ac_2O, py, RT, 4 h (66% for two steps). e) $\textit{t}BuMe_2SiCl$, py, DMAP, CH_2Cl_2, RT, 24 h, then *p*-ClC_6H_4COCl (Bz'Cl), RT, 18 h, 86%. f) HF/py, AcOH, THF, RT, 1 h, 94%.

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