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A NEW MICROSCALE METHOD FOR THE CONVERSION OF PHOSPHORUS OXYACIDS TO THEIR FLUORINATED ANALOGUES, USING CYANURIC FLUORIDE IN SOLUTION AND ON SOLID SUPPORT

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Cyanuric fluoride, in solution or loaded onto a Wang resin, is successfully used as a fluorinating agent for phosphorus oxy acids. The reaction is very efficient with high yields and easy workup procedures, thereby in general generating products in quantitative yields. The cyanuric fluoride is proven suitable for micromolar scale synthesis of analytical standards, particularly in its resin-bound form.

Keywords Cyanuric fluoride; micro scale; phosphorus fluoridates; solid phase synthesis

INTRODUCTION

In connection with the work concerning the identification of fluorinated phosphorus compounds related to the Chemical Weapons Convention (CWC),[1] there is an interest in developing new and more effective synthetic methods appropriate for production on a micromolar scale. Such methods would, if reliable, diminish the need for storage of the compounds as analytical references. Instead, the compounds could be synthesized "on demand" in the amounts and concentrations needed for the analytical work.

The most common production methods of phosphorus fluoridates are by halogen exchange of the corresponding chloridate using, for instance, a fluoride ion.[2–4] There are also other methods to produce the fluoro analogues from various starting materials.[5–7] By avoiding the phosphorus chloridates as intermediates and directly synthesizing the phosphorus fluoridate, it is possible to bypass one reaction step and shorten the synthetic route. Furthermore, halogen exchange reactions are equilibria, with which it is difficult to reach completion, and the use of fluoride ions often involves salt slurries that make performance on a small scale problematic. Since the phosphorus chloridates are very reactive, phosphorus anhydrides are often formed in a considerable amount during their production, if synthesized from phosphorus oxy acids. This can also be seen in the fluorination of phosphorus oxyacids if a unit of the starting compound manages to react with a unit of product (Scheme 1).

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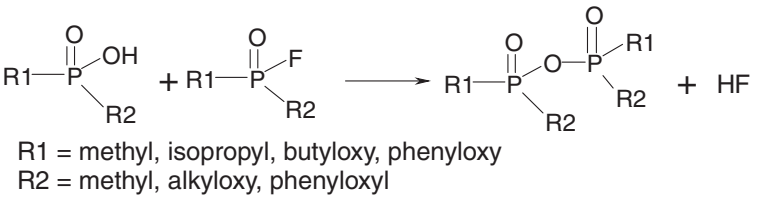
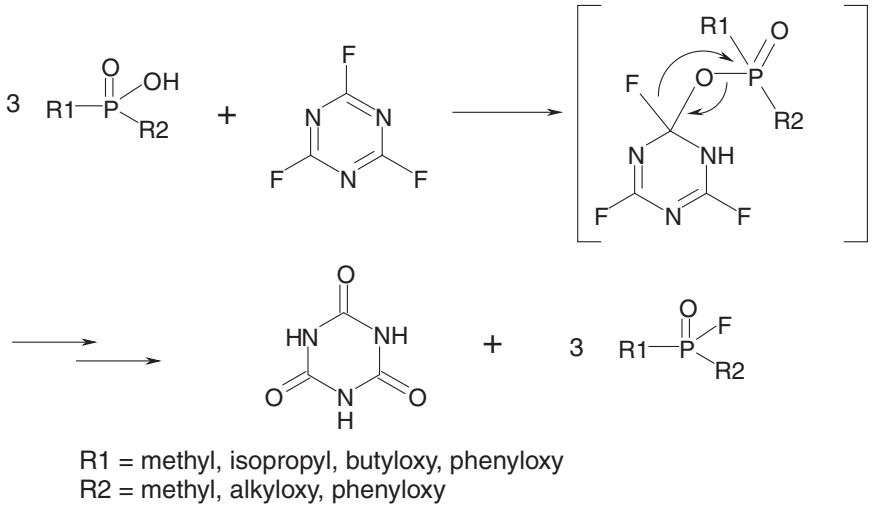


Scheme 1 The formation of pyrophosphonates is sometimes a significant problem, hampering the yields.

A novel procedure for microscale synthesis of mono-alkylated phosphonic acids has been developed.[8] The phosphonates produced by this method can be efficiently transformed using the same scale to the corresponding fluorinated analogues, if desired. The latter can be accomplished with, for instance, fluoroenamines as previously shown,[9] or the method that is presented in this paper, cyanuric fluoride (CF).[10] CF (2,4,6-trifluoro-1,3,5-triazine) is a commercially available reagent that has been extensively used in preparation of carboxylic fluorides, as well as for peptide coupling reactions.[11–13] Although being hygroscopic, corrosive, and toxic, the CF is relatively easily handled on micromolar scale, and furthermore, the cyanuric acid (CA) that is formed due to hydrolysis is insoluble and precipitates in the storage bottle, thus keeping the reagent relatively pure over time. High-yielding reactions and convenient workup procedures are always sought by synthesis chemists, and these factors become even more important the smaller the scales of the syntheses are. In this context, the methods developed using CF match the requirements well.

RESULTS AND DISCUSSION

CF reacts with phosphorus oxy acids only to produce phosphorus fluoridates and CA (Scheme 2). CA is a rather stable compound that is almost insoluble in many organic solvents such as chlorinated hydrocarbons, which is taken advantage of in the following method. During the reaction, CA precipitates and can therefore be easily removed by filtration of the solution. All three equivalents of fluorine in the reagent are consumed during the reaction, and our investigations indicate that the reactivity of CF increased after the nucleophilic attack of the first oxy acid. This was supported by spectroscopic ^{19}F NMR data, where it was not possible to detect mono-fluoro analogue of the reagent in the reaction mixture. Furthermore, the reactivity of the resin-bound CF was higher than the unbound CF itself. The CF in solution reacts slowly with the phosphorus oxy acids at room temperature. However, increasing the temperature to the interval 70–100°C, depending on the starting material, was found to accelerate the reaction sufficiently. Chlorinated solvents such as chloroform, 1,2-dichloroethane, tetrachloroetylene, or 1,1,2,2-tetrachlorethane are the most suitable for comparable substitution reactions, according to earlier investigations.[9,14] The final choice of solvent is of course dependent on the starting material and temperature required for the specific reaction. Typically, a reaction time of approximately 20 h will be sufficient to produce approximate yields of more than 95%, with the exception of compounds with severe steric hindrance. For example, isopropylphosphonic acid with a bulky O-alkyl group will need reaction times of at least 48 h to achieve acceptable yields. The dialkyl phosphoric acids (phosphates) are found to be less reactive to CF than the phosphinic or phosphonic acids and require even longer reaction times, if the reaction is feasible at all. For instance, dibutyl phosphorofluoridates were successfully converted after



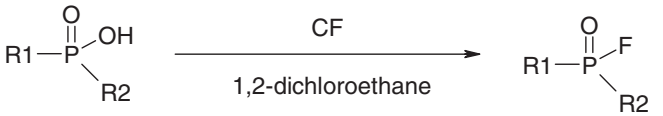
Scheme 2 Schematic representation of the reaction of cyanuric fluoride and phosphorus oxy acid.

72 h of reaction, but we were unable to synthesize diphenyl phosphorofluoridate using this method. It is not possible to synthesize methylphosphonic monofluoride exclusively starting from methylphosphonic acid; the methylphosphonic difluoride is always formed to some extent. An excess of reagent gives methylphosphonic difluoride quantitatively within 72 h. The reagent can be used in large excess without affecting the yields (∼5eq), and if dry conditions are difficult to ensure, the amount of CF can be raised to compensate for loss of reagent.

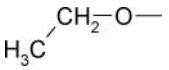
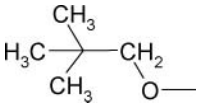
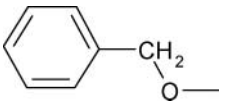
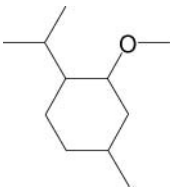
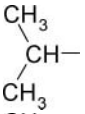
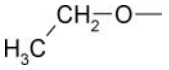
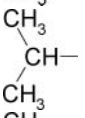
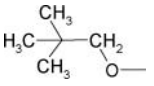
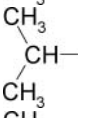
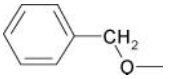
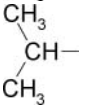
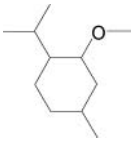
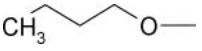
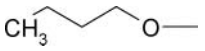
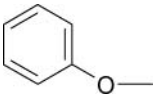
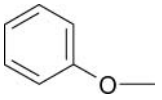
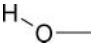
The progress of the reaction can be visually monitored by observing the CA precipitating from the reaction mixture. The various phosphorus oxy acids evaluated as starting materials and the results of the fluorination reactions are presented in Table I. Another important factor contributing to an effective method is the workup procedure, which in this case is both simple and convenient. The workup will be described for three situations: excess of reagent, deficit of reagent, and solid-phase chemistry. If CF is used excessively, superfluous reagent can be removed by filtration through a small amount of citric acid in a short column. The citric acid immediately reacts with the excess of reagent, and the formed CA precipitates within the column. Filtration of the reaction mixture also removes already precipitated CA in the reaction mixture, and the only compound still dissolved in the solvent after the filtration is the product. If the starting material, solvent, or glassware is contaminated with a small amount of water, there will possibly be a deficit of CF due to hydrolysis of the reagent. As a consequence, some phosphorus oxy acid will remain in the reaction mixture. The unreacted acid can be removed by promptly filtering the reaction mixture through a small amount of alumina, although it is necessary to use a proper amount of alumina. Otherwise, some product will be lost.

In order to improve the reagent and synthetic procedures even further, the potential of CF as a polymer-supported reagent was investigated. To the best of our knowledge, this is the first report demonstrating the use of solid-phase–supported CF in organic synthesis. A Wang resin was used in accordance with the findings of Luo et al.,[15] who used polymer-supported cyanuric chloride in the synthesis of acyl chlorides. Contrary to these findings, which indicated that a linker was needed in order to achieve acceptable yields, the reagent

Table I Synthesis of fluorinated analogues of phosphorus oxy acids



R1 = methyl, isopropyl, butyloxy, phenyloxy
R2 = alkyloxy, phenyloxy, methyl, hydroxy

R1	R2	% Conversion	Yield (NMR)	^{31}P shift ($CDCl_3$)	J_{P-F}
CH_3-		100	Quant	29.8	1048 Hz
CH_3-		92	Quant	29.6	1047 Hz
CH_3-		100	Quant	30.3	1054 Hz
CH_3-		100	Quant	29.1 28.4	1049 Hz 1047 Hz
		59	89%[a]	34.9	1088 Hz
		100	77%[a]	34.4	1086 Hz
		51	85%[b]	35.4	1094 Hz
		83	30%[b]	34.1 33.5	1087 Hz 1091 Hz
CH_3-	CH_3-	100	Quant	64.9	990 Hz
			94%[c]	–8.7	978 Hz
		0	0%		
CH_3-		100	Quant[c]	24.1	1109 Hz

Reaction with CF (0.37 eq.) in dichloroethane at 100°C during 23 h.

[a]One additional unknown product containing phosphorus.

[b]Isopropylphosphonic mono- and difluoride were formed indicating cleavage of the alkyloxy group.

[c]For difluoride, the reaction time must be at least 72 h.

can in this case be directly connected to the resin in a one-pot synthesis. There is no need to use linkers in order to distance the reagent from the polymer to achieve good results. The resin was characterized by IR spectroscopy, and by weighing the dried polymer, a yield of 82% was determined. By using one of CF's reactive sites to attach the reagent to the polymer, two free sites are left to be consumed in the fluorination reactions. One of the advantages is that the reactivity of this polymer-bound reagent is higher than that of the free CF, resulting in the possibility of lowering the temperature. The enhanced reactivity makes it possible to change the reaction medium to the more volatile chloroform, which is easier to evaporate than 1,2-dichloroethane, after completion of the reaction. The phosphono fluoridates (entry 1–8, Table I) were all afforded in quantitative yields. The most significant byproduct in the reactions is phosphorus difluoride, which originates from contamination of alkylphosphonic acid within the starting material. Hence, by starting with highly purified phosphorus oxyacids, it is possible to synthesize small amounts of phosphonic fluoridates of high quality by an immediate filtration of the reaction mixture followed by an evaporation of the solvent.

EXPERIMENTAL

All phosphorus fluoridates were analyzed and characterized by NMR on a Bruker Avance 500 spectrometer. The spectral data recorded were compared with previously published data, including the following nuclei: ^{1}H, ^{31}P and ^{19}F.[3] The IR spectra of the resin were recorded on a Thermo Nicolet Avatar 370. All equipment and solvents were dried before use. The phosphonic acids, except for ethyl methylphosphonic acid, which was obtained from Aldrich, were synthesized by the method of Petrov et al.[16] The phosphinic as well as the phosphoric acids were purchased from Aldrich and were used without further purification. The purity of the phosphinic-, phosphonic-, and phosphoric acids was at least 95% regardless of their origin. Chloroform was obtained from Fluka, and 1,2-dichloroethane was obtained from BDH. All solvents were of p.a. quality and were dried before use. DIPEA was purchased from Fluka and was freshly distilled before use. The Wang resin was obtained from Fluka with a loading of 1 mmol/g, and the particle size was 200–400 mesh.

CAUTION: Phosphorus fluoridates are highly toxic, and the reaction must take place in an effectively vented hood using the appropriate protecting equipment.

Synthesis of Resin-Bound Cyanuric Fluoride

Wang resin (250 mg, 0.25 mmol) was mixed with dry $CHCl_3$ (6 mL). The reaction flask was flushed with argon and sealed with a rubber septum. CF (250 μL, $\sim$7 eq) and N-diisopropyl-ethylamine (DIPEA) (50 μL, $\sim$1 eq) were injected through a syringe. After a reaction time of 24 h at room temperature, the resin was filtered and washed 3–4 times with dried $CHCl_3$ (3 mL). The resin was then dried thoroughly under reduced pressure and characterized by IR. The yield of the reaction was 274 mg, 82%.

Synthesis of Phosphonofluoridates Using Cyanuric Fluoride in Solution—General Procedure

Phosphorus oxyacid (50 μmol) was dissolved in of 1,2-dichloroethane (1 mL) in a 4 mL vial equipped with a magnetic stirring bar under argon atmosphere. CF (19 μmol,

active fluorine 1.14 eq) was added from a stock solution (CF 20% in $CHCl_3$). The vial was carefully sealed, and the solution was stirred in an oil bath at 100°C for approximately 20 h. After cooling to room temperature, the reaction mixture was filtered through a small column, size 5 mm in diameter, of citric acid (less than 0.25 g). The solvent was evaporated under reduced pressure, and the product was isolated. For individual yields, see Table I.

Alternatively, if the reagent, due to improperly dried starting material, equipment, or solvent, was consumed by hydrolysis, and the subsequent deficit of CF left some oxyacid unreacted, this was removed by filtration of the reaction mixture through a 5 mm wide column of alumina (typically 0.25 g). The solvent was evaporated, and the product isolated.

Synthesis of Phosphonofluoridates Using Polymer Supported Reagent, General Procedure

To a solution of phosphonic acid (50 μmol) in $CHCl_3$ (2.0 mL) in a 4 mL vial, CF-resin (corresponding to CF 100–150 μmol, 2–3 eq.) was added, and the vial was sealed and placed in an oil bath at 70°C under slow stirring for 20 h. If the stirring was too vigorous, the stirring bar might grind the polystyrene beads, which might lower the yield and obstruct the workup procedure. When cooled to room temperature, the resin was removed by filtration, and the filtrate was evaporated to give the product in quantitative yield.

Synthesis of Dimethylphosphinofluoridate

To a solution of dimethylphosphinic acid (10 mg, 0.11 mmol) in dry $CHCl_3$ (1 mL), CF (40 μmol) was added in one portion from a prepared stock solution (CF 20% in $CHCl_3$). After sealing the vial, the solution was stirred at 100°C for 8 h. The workup was identical to the one described above in the general procedure of the phosphonates. Dimethyl phosphinofluoridate was afforded in quantitative yield.

Synthesis of Dibutyl Phosphorofluoridate

CF (19 μmol, 1.14 eq.) was added to a solution of dibutyl phosphoric acid (10 mg, 50 μmol) in dry $CHCl_3$ (1 mL). The CF was added from a stock solution (CF 20% in $CHCl_3$) in order to facilitate the exact amount to be transferred. The reaction vessel was sealed, and the temperature was set to 100°C, whereupon the reaction was stirred for 72 h. The workup was identical to the one described above in the general procedure of the phosphonates. The yield of dibutyl phosphorofluoridate achived was at this time 94%

Synthesis of Diphenyl Phosphorofluoridate

Even after a week at 100°C in $CHCl_3$, no fluorination was observed.

Synthesis of Methylphosphonic Difluoride

To a solution of methylphosphonic acid (10 mg, 0.1 mmol) in dry $CHCl_3$ (1 mL), CF (6.2 μL, active fluorine $\sim$2.2 eq.) was added in one portion. After sealing the vial, the solution was stirred at 100°C for 72 h. The workup was identical to the one described above in the general procedure of the phosphonates. Methylphosphonic difluoride was afforded in quantitative yield.

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