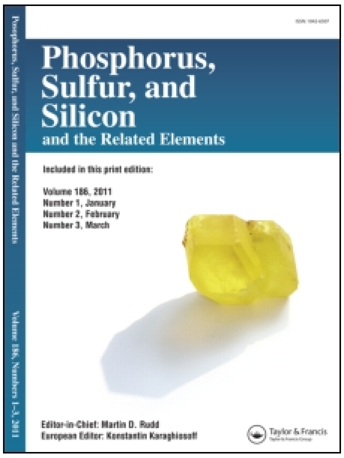

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New Reagents for Halogenation of Phosphorus

Rikard Wärme[a]; Lars Juhlin[a]; Lars Trogen[a]
[a] Swedish Defence Research Agency CBRN Defence and Security, UMEÅ, Sweden

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New Reagents for Halogenation of Phosphorus

Rikard Wärme, Lars Juhlin, and Lars Trogen
Swedish Defence Research Agency CBRN Defence and Security,
UMEÅ, Sweden

Syntheses of phosphorus halides are of interest in many genres of organic chemistry,[1–4] *but the development of new methods and reagents for their synthesis is presently scarcely explored. Working in small scale put extra demands on reactions as well as purification procedures to ensure that losses can be kept at a minimum. New reagents for these reactions with properties compatible with micro scale synthesis will be presented.*

The versatility of the reagents is further explored by the synthesis and use of solid supported reagents. The reagents are mild, compatible with many functional groups, and selective towards phosphorus oxy acids, which enable the reactions to be used in a variety of applications. Clean reactions and easy work-up procedures ensures excellent yields, which, only with a few exceptions, are quantitative. These reagents have proven suitable for micro scale synthesis especially in the solid phase application.

Keywords Chlorine; cyanuric fluoride; fluorine; fluorination; haloenamines; phosphorus; phosphonofluoridate

INTRODUCTION

The methods used for synthesis of phosphorus fluorides are often industrial methods which are not suited for small scale laboratory synthesis. Since the products are highly toxic the reactions are often done on micro scale. This calls for development of new methods of synthesis and purification procedures. Our objective is to develop new reagents for these reactions which have better properties on micro scale. Two types of reagents have been developed, haloenamines (i.e. N-(1-chloro-2-methylprop-1-enyl)-N,N-diisopropylamine) and cyanuric fluoride (2,4,6,trifluoro[1,3,5]triazine). These reagents have been used successfully in coupling reactions in peptide chemistry but never in phosphorus chemistry.

Address correspondence to Rikard Wärme, Swedish Defence Research Agency CBRN Defence and Security, Cementvägen 20, 901 82 UMEÅ, Sweden. E-mail: rikard.warme@foi.se

α- Haloenamines and cyanuric fluoride are hygroscopic hydrolysis sensitive liquids in room temperature. They are toxic and corrosive but compared to other fluorinating reagents relatively easily handled.

Phosphorus oxy acids were converted to their halogenated counterparts in this study. This is a new approach to the synthesis of the halides of mono alkylated phosphonic acids which are usually synthesised from the di-halides. The fluoro analogues may, with these reagents, be synthesized without using the chloro compounds as intermediates which is the case in most methods for their preparation. Care must be taken handling these compounds, especially the phosphono fluoridates. They are highly toxic and will damage the nervous system if exposed to the substances.

RESULTS AND DISCUSSION

In this article, we have investigated the potential of α-haloenamines as reagents for the transfer of halogen[5] (Cl and F) and cyanuric fluoride for the transfer of fluoride[6] to phosphorus.

The α-haloenamines do not give rise to HCl gas or water during the reaction but simply revert to the stable amide from which they are prepared.

Cyanuric fluoride reacts with the phosphorus oxy acids only to produce phosphorus fluoride and cyanuric acid. Cyanuric acid is a stable compound that precipitates from the solution, which is of great advantage in purification.

Enamines

Our investigations prove the α-haloenamines to be very efficient reagents, which react fast at mild conditions to produce the desired products. Yields are usually high and few impurities are formed. The method is applicable to all types of phosphorus oxy acids, i.e., phosphinic, phosphonic, and phosphoric acids. Furthermore, it is compatible with a variety of functional groups.

During chlorination the phosphonic acids, unlike carboxylic acids, readily form pyro phosphonates. Every molecule of pyrophosphate formed in this way will reduce the highest possible yield of the desired product with two units. The phosphonic acids were added to the halo enamine in chloroform at 50°C. Higher temperatures did not improve the outcome of the reaction and addition of the phosphonic acid at a lower temperature was inferior concerning the yield of desired product. If, for instance, the reaction mixture was cooled to 0°C before addition of the reactant, as suggested by others,[7] a quantitative yield of the corresponding pyro phosphonate was obtained. As predicted the phosphoric acids were less reactive and consequently produced lower yields at longer reaction times. To overcome this problem the temperature had to be raised significantly which excluded chloroform as solvent. Among the investigated solvents were chlorobenzene, tetrachloroethylene, dichloroethane, dioxane, toluene, and benzene. This investigation clearly indicated the chlorinated solvents to be the better ones, which Ernst et al.[8] found in their studies also. Tetrachloroethane finally proved to be the best alternative giving yields as high as 95%, due to the possibility to apply a higher reaction temperature. For diphenylphosphoric acid we were unable to find reaction conditions producing satisfactory yields. Only 57% product was obtained at 120°C in tetrachloroethane. Higher temperatures were not applicable since the boiling point of the enamine, 130°C, constitutes a practical limit unless pressurized equipment is considered, which was not done due to the toxicity of the compounds studied. N-(1-chloro-2-methylprop-1-enyl)-N,N-diisopropylamine[9] was evaluated as an alternative α-haloenamine due to the higher boiling point but proved less effective.

Cyanuric Fluoride

There are three equivalents of fluorine in each molecule of cyanuric fluoride which all react when used in solution. Our investigations indicate that when the first fluorine reacts the others are activated. This is supported by the fact that no products with one or two fluorine's are found in the reaction mixture, there is only cyanuric fluoride and cyanuric acid. Compared to the enamines the cyanuric fluoride reacts slowly with phosphorus oxy acids but since the reaction proceeds smoothly this is not a great problem. Enamines and other reagents produce pyro phosphonates if the reaction doesn't proceed quickly but this is not the case with cyanuric fluoride. If the reaction temperature is raised to 80 degrees Celsius the reaction is finished within 12 h and proceeds with close to quantitative yields. The phosphinic acid is much more reactive towards cyanuric fluoride and reacts within minutes and the phosphoric acids have slightly longer reaction times. One exception is diphenylphosphoric acid which does not react at all with cyanuric fluoride. The reaction can be visually followed by observing the cyanuric acid precipitating. The workup procedure can be done in two ways depending on how the reaction has been carried out. The first method is used when cyanuric fluoride is added in slight excess and hence there is unreacted reagent left after the reaction is complete. The reaction mixture is filtrated threw a small amount of citric acid which react with the cyanuric fluoride which then becomes insoluble and precipitates in the filter. The solvent is removed and the product is isolated. The other method is using a slight deficit of reagent which leaves some phosphonic acid in the reaction mixture. This can easily be removed by filtration through a short alumina column, but it is important to have the right amount of alumina otherwise product will be lost.

Polymer Supported Reagents

Since polymer-supported chemistry is a fast developing chemistry with increasing applications, we investigated the potential of the reagents as a polymer supported reagents. Unfortunately, the enamines proved to be unstable, and it did not perform well on solid support, so we discarded them as reagents. Cyanuric fluoride on the other hand proved to be both excellent as reagent as well as easily connected to the resin. In solid phase chemistry, cyanuric fluoride can be attached directly to the resin using one of the fluorine's as leaving group,[10] which leaves two more to be used in the further synthesis. We used Wang resin because the reagent could be directly connected to the resin in a one-pot synthesis. The reaction temperature, relative to the reaction in solution, was lowered due to the activation of the cyanuric fluoride when one of the fluorine's is reacted in the connecting step. This made a change of solvent to chloroform possible which is more easily handled during workup and evaporation.

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