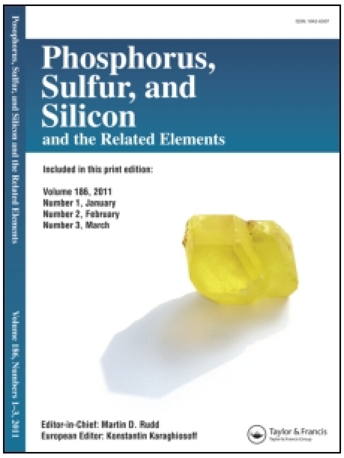

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Advantages of Organophosphorus Synthesis in Ionic Liquids: "Green" Approaches to Useful Phosphorus-Substituted Building Blocks

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Novel examples concerning the application of ionic liquids as a promoting reaction media in organophosphorus chemistry are discussed. Imidazolium ionic liquids were found to accelerate the Michaelis-Arbuzov reaction allowing to perform it under very mild conditions. Both phosphonium and imidazolium ILs give the possibility to perform easily direct amidation of phosphoryl acetic acids by various amines. Nucleophilic displacement reactionin a series of bromoalkylphosphonates was carried out in quantitative yield to afford azidoalkylphosphonates using the [bmim][PF$_6$]/H$_2$O system.

Keywords 1,2,3-triazoles; amidation; azidoalkylphosphonates; carbamoylmethyl phoshine oxides; click chemistry; ionic liquids; nucleophilic displacement reactions; the Michaelis-Arbuzov reaction

INTRODUCTION

Currently, ionic liquids (ILs) due to their potential for recycling, ability to dissolve a variety of organic, inorganic and metal complex materials, to activate different reactions and non-volatile nature, are of interest in the search for "green" alternatives of traditional organic solvents.[1,2] Nevertheless, to the best of our knowledge only a few applications of ionic liquids in organophosphorus chemistry can be found in the literature, namely the Wittig-Horner reaction,[3]

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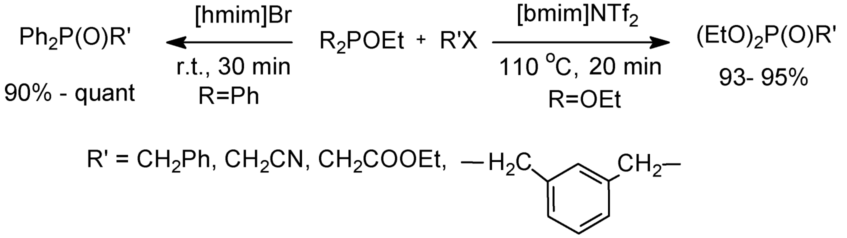
the synthesis of α-aminophosphonates via the Kabachnik-Fields reactions,[4,5] and the esterification of phosphonic(phosphinic) acids by triethyl(methyl) orthoacetate.[6] In this paper, we report on some new examples of ILs' application as activating media for organophosphorus synthesis.

RESULTS AND DISCUSSION

The first reaction under discussion is the Michaelis-Arbuzov rearrangement being a highly important reaction of general value in the conversion of 3-coordinate phosphorus esters to 4-coordinate species. Taking into account that amines are found to be more nucleophilic in ionic liquids than in common organic solvents,[7]we considered that ILs might be used as activating media for this reaction. This is because it involves the attack of a phosphorus lone pair on the electrophilic carbon atom of an alkyl halide at the first stage followed by rapid dealkylation of an intermediate phosphonium salt formed. In fact, the use of room temperature imidazolium ionic liquids [Rmim][X] [X = Br, BF_4, PF_6, NTf_2; Rmim = 1-butyl-3-methylimidazolium (bmim) or 1-hexyl-3-methylimidazolium (hmim)] enhanced significantly the rate of this reaction (Scheme 1). The anion of the ionic liquids affected their catalytic activity considerably, depending on reaction conditions, and the structure of the starting phosphorus ester. Thus, at 110°C (5–30 min) the activity of ILs increased as follows [Equation (1)]:

$$[\text{bmim}][\text{Br}] \leq [\text{bmim}][\text{PF}_6] < [\text{bmim}][\text{BF}_4] < [\text{bmim}][\text{NTf}_2]. \qquad (1)$$

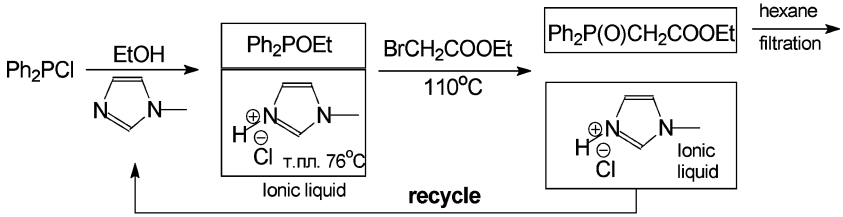


SCHEME 1

For triethyl phosphite, the above reaction temperature was the most suitable and in [bmim][NTf_2] the reaction proceeded in 5 min with dropwise addition of ethyl bromoacetate and was complete in 20 min when using benzyl bromide. In the case of the more nucleophilic ethyl diphenylphosphinite, the reaction was found to proceed easily even under ambient conditions in nearly the same period giving the products in high yields. The most suitable ionic liquid in this case was [hmim]Br, which we used instead of [bmim]Br, which is a solid at room temperature

Phosphorus esters may be reacted with alkyl halides using either the ionic liquid alone as the reaction media followed by ether extraction or the aqueous work-up procedure or in a biphasic system where diethyl ether plays the role of the second immiscible phase. The latter variant seems more advantageous because the amount of ionic liquid may be decreased to 1 mol equivalent and the target products are easily separated along with the ether layer. The recovered ionic liquid may be recycled at least 5 times without any decrease in activity.

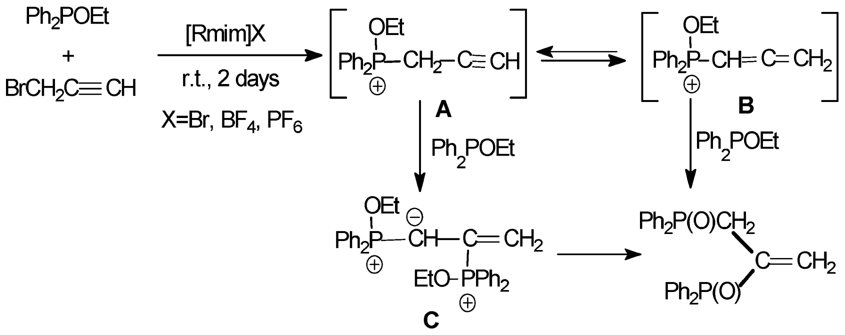
The method described can be successfully combined in a one-pot synthesis with the BASIL^{TM} procedure[9] used for the synthesis of trivalent phosphorus acid esters. In the BASIL^{TM} process, 1-methylimidazole is used as an acid scavenger giving 1-methylimidazolium chloride. This ionic liquid can also serve as an effective media for the Arbuzov reaction similar to the other ILs mentioned above. Thus, the crude reaction mixture of phosphorus(III) ester and 1-methylimidazolium chloride obtained during the first step can be heated above the melting point of the latter (~100°C) followed by the reaction with ethyl bromoacetate (Scheme 2). Starting from chlorodiphenylphosphine, $Ph_2P(O)CH_2COOEt$ was obtained in ca. 93% yield (based on Ph_2PCl) with a purity above 85% after aqueous work-up (not optimized).



SCHEME 2

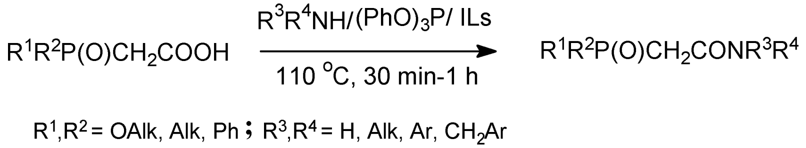
In some cases, the presence of ionic liquid may change the reaction course. Thus, the interaction of diphenylethylphosphynite with propargyl bromide in [hmim]Br surprisingly resulted in 2,3-bis(diphenylphosphoryl)-1-propene independently on the reactant ratio rather than in normal Arbuzov product. Investigation of the reaction in detail allowed us to suggest its mechanism (Scheme 3).

In addition, we demonstrated that direct amidation of phosphoryl acetic acids by various amines can be easily performed in the presence of triphenylphosphite using both phosphonium and imidazolium ILs. This reaction opens the simple route to carbamoylmethyl phosphine



SCHEME 3

oxides (CMPO) being neutral organophosphorus ligands widely used for processing of liquid radioactive wastes (Scheme 4).



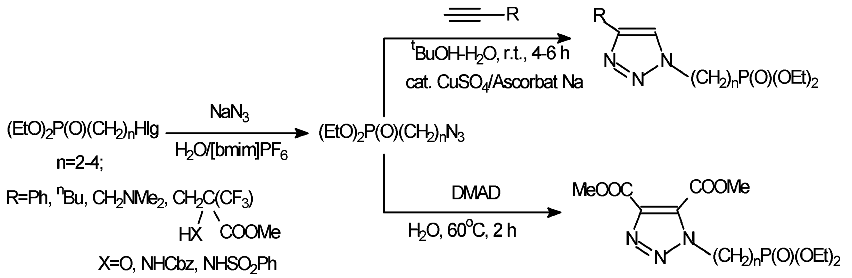
SCHEME 4

We found amidation to proceed via the formation of the intermediate phosphoryl acetic acid phenyl ester followed by transformation of the leaving phenoxy group into the amide function under the action of N-nucleophile. Moreover, as all phosphite groups are reactive under these conditions $(PhO)_3P$ was used in 0.35 molar equivalents.

Under other similar conditions, the rate of the reaction decreases in passing from primary alkylamines to secondary ones and further to aromatic and alkylaromatic amines. Investigation of the ionic liquids tested on the reaction rate demonstrated that for alkylamines it decreases as follows: $[bmim]Br \approx [P(C_6H_{13})_3(C_{14}H_{29})]Cl > [bmim]BF_4 > [bmim]PF_6 > [bmmim]Br > [P(C_6H_{13})_3(C_{14}H_{29})]Br$. For less nucleophilic benzylamine reactivity rate changes for $[bmim]Br \approx [bmim]PF_6 \approx [P(C_6H_{13})_3(C_{14}H_{29})]Cl > [P(C_6H_{13})_3(C_{14}H_{29})]Br > [P(C_6H_{13})_3(C_{14}H_{29})]BF_4$. In all cases the best results in terms of reaction rate were obtained either in [bmim]Br or in phosphonium chloride where it takes ca. 40 min and 100–110°C to obtain the desired products in quantitative yields.

The similar approach was succesfully used to obtain chemically stable membranes bearing CMPO-moieties for water cleaning starting from commercially available polymeric materials modified by amino functions.

Finally, since ILs were found to be efficient promoting media for nucleophilic displacement reactions,[1,2] we elaborate a facile route to azidoalkylphosphonates starting from the corresponding bromides using [bmim][PF_6]/H_2O system (Scheme 5). The reaction proceeds smoothly at room temperature to give the desired compounds in 95–98% yield. The time required for the complete azide formation strongly depends on the alkylene chain length in the starting substrate. For the less reactive 2-bromoethylphosphonate it was *ca.* 5 days (120 h), decreased to 48 h for propyl derivative and to 40 h for n = 4. The increase of the temperature up to 80°C resulted in shortening of the reaction time up to 2 h for n = 2 and to ~30 min for more reactive compounds with n = 3, 4. No side products were observed in these reactions but diethyl(bromomethyl)phosphonate did not undergo azide/halide exchange even under prolonged reaction time.



SCHEME 5

ω-Azidoalkylphosphonates were used as intermediates for Huisgen 1,3-dipolar cycloaddition to alkynes to give triazoles as potential drug-candidates. In the case of terminal alkynes usage of copper(I) catalyst (which can be generated in situ by reduction of Cu(II) salts) allows high rate and complete control of regioselectivity and reactions were performed in organo-aqueous systems while the reaction with DMAD proceeded in H_2O. It should be noted that to impart phosphorylated triazoles better lipophilic and biodegradable properties advantageous in medicinal chemistry we used in the above cycloaddition propargyl substituted CF_3-containing alcohol and protected amino acids (Scheme 5).

It should be noted that in all the above reactions the recovered ionic liquid may be recycled at least 5 times without any decrease in activity.

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