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A novel facile synthesis of carbamoylmethylphosphine oxides in ionic liquids

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Abstract

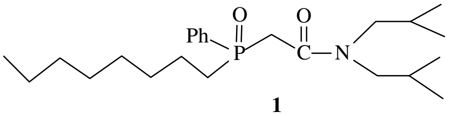
A convenient access to carbamoylmethylphosphine oxides (CMPO) in up to 96% isolated yield is developed via direct amidation of diphenylphosphoryl acetic acid in an ionic liquid as a recyclable reaction medium in the presence of triphenyl phosphite. The influence of the nature of the amine and anion and cation structure in the ionic liquid on the reaction rate and yields of the products are also investigated. 1-Butyl-3-methylimidazolium bromide [bmim]Br and trihexyltetradecylphosphonium chloride $[P(C_6H_{13})_3(C_{14}H_{29})]Cl$ proved to be the best media for carrying out this reaction.

Keywords: Carbamoylmethylphosphine oxides; Phosphorylacetic acid; Amidation; Ionic liquids; Triphenyl phosphite

The development of the nuclear industry and processing of accumulated liquid acidic radioactive wastes necessitates selective extraction of long-lived isotopes (primarily actinides). For this purpose, liquid–liquid extraction procedures using neutral organophosphorus compounds, such as carbamoylmethylphosphine oxides (CMPO), for example, (*N*,*N*-diisobutylcarbamoylmethyl)octylphenylphosphine oxide **1**[1] or *N*,*N*-dibutylcarbamoylmethyl-diphenylphosphine oxide **2**,[2] are used in current practice in the so-called TRUEX process.

Typical synthetic approaches to such compounds are based on the Arbuzov[2a,3] or Michaelis–Bekker[4] reactions starting from three valent phosphorus species. Other CMPO syntheses comprise the amidation of either ethyl diphenylphosphorylacetate[5] or *p*-nitrophenyl diphenylphosphorylacetate[6] by primary alkylamines including those based on calix[*n*]arene or resorcinarene platforms, or transformation of diphenylphosphorylacetic acid to the corresponding amides under the action of triamidophosphites[7] or via the corresponding acid chloride.[8]

Ionic liquids (ILs) are of interest in synthetic organic chemistry due to their non-volatile nature, potential for recycling, ability to dissolve a variety of organic, inorganic, and metal complex materials, and especially due to their ability to activate various reactions.[9] Nevertheless, and to the best of our knowledge, ILs have been used for 'green'



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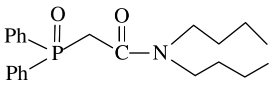

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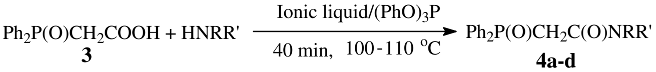


$$\underset{\mathbf{3}}{Ph_2P(O)CH_2COOH} + HNRR' \xrightarrow[\text{40 min, 100-110 °C}]{\text{Ionic liquid/(PhO)}_3\text{P}} \underset{\mathbf{4a\text{-}d}}{Ph_2P(O)CH_2C(O)NRR'}$$

R=H, R'=Ph (**4a**), CH_2Ph (**4b**), Bu (**4c**); R=R'=Bu (**4d**)

Scheme 1.

organophosphorus synthesis rather restrictedly.[10,11] In this Letter, we report the application of ionic liquids as an activation medium for the synthesis of carbamoylmethylphosphine oxides. This method represents an effective approach to a variety of CMPOs starting from a single phosphorus substrate and a wide range of amines.

Diphenylphosphorylacetic acid **3** was shown to react easily with aromatic and aliphatic amines in the presence of triphenyl phosphite both in imidazolium and in phosphonium ionic liquids to yield the corresponding amides (CMPO) in high yields and purity (Scheme 1).[12]

Thus, in 1-butyl-3-methylimidazolium bromide ([bmim]Br) the reaction of **3** with the amines investigated was complete after 40 min at 100–110 °C. The nature of the counterion of the ionic liquids affected the reactivity. Use of [bmim]BF_4 led to a decrease in the yield of the corresponding product, while in [bmim]PF_6 the reaction proceeded quantitatively over 40 min only with benzylamine. In the reaction with dibutylamine yielding (*N*,*N*-dibutylcarbamoylmethyl)diphenylphosphine oxide **4d**, it was demonstrated that introduction of an additional methyl group into the imidazolium cation ([bmmim]BF_4) resulted in a decrease of the product yield to 81% under the same conditions.

In the case of phosphonium ionic liquids, amidation proceeded quantitatively in 40 min only with $PhCH_2NH_2$ and Bu_2NH in the ionic liquid containing chloride as the anion, while the application of ILs bearing other counteranions resulted in longer reaction times (1.5–2.5 h).

Therefore, in the case of dibutylamine and benzylamine the effect of the nature of the IL on the amidation reaction rate is as follows:

For Bu_2NH: [bmim]Br ≈ $[P(C_6H_{13})_3(C_{14}H_{29})]Cl$ > [bmim]BF_4 > [bmim]PF_6 > [bmmim]BF_4 > $[P(C_8H_{17})_4]Br$.

For $PhCH_2NH_2$: [bmim]Br ≈ [bmim]PF_6 ≈ $[P(C_6H_{13})_3(C_{14}H_{29})]Cl$ > $[P(C_8H_{17})_4]Br$ > $[P(C_6H_{13})_3(C_{14}H_{29})]BF_4$.

The results are summarized in Table 1.

Table 1
Reaction of **3** with various amines

IL/amine	CMPO yield (%)			
	$PhNH_2$	$PhCH_2NH_2$	$BuNH_2$	Bu_2NH
[bmim]Br	100	100	100	99
[bmim]PF_6	83	100	88	88
[bmim]BF_4[a]	67	91	87	96
[bmmim]BF_4[a]	—	—	—	81
$[P(C_6H_{13})_3(C_{14}H_{29})]Cl$	90[b]	100	95[c]	100
$[P(C_8H_{17})_4]Br$	93%[d]	75[c]	—	68
$[P(C_6H_{13})_3(C_{14}H_{29})]BF_4$[a]	—	72[c]	—	—

[a] Co-solvent CH_3CN.
[b] The reaction proceeds quantitatively over 1.5 h.
[c] The reaction proceeds quantitatively over 2.5 h.
[d] The reaction proceeds quantitatively over 2 h.

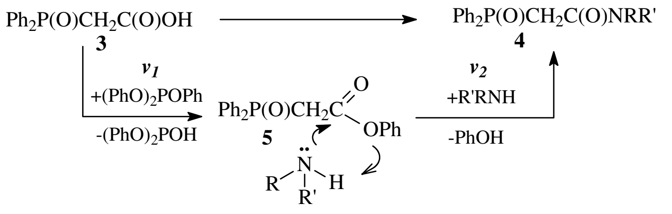
For comparison, in the absence of an ionic liquid the reaction of acid **3** with dibutylamine in the presence of triphenyl phosphite (toluene, 110 °C) resulted in amide **4d** in 15% yield over 1.5 h and the yield was increased only to ca. 40% over 3 h.

Upon completion of the reaction, the products were isolated either through precipitation from the reaction mixtures using diethyl ether/methanol = 95:5 (**4a** from $[P(C_8H_{17})_4)]Br$, **4b** from $[P(C_6H_{13})_3(C_{14}H_{29})]BF_4$ or water (**4a**,**c** from [bmim]Br, **4b** from [bmim]Br, [bmim]PF_6), or through extraction with diethyl ether (**4d** from [bmim]Br, [bmim]PF_6, [bmim]BF_4, [bmmim]BF_4) with yields in the range of 93–96% and high purity (>95%) according to ^{31}P and ^{1}H NMR spectroscopy. It should be noted that we failed to isolate compounds **4a** and **4c** from $[P(C_6H_{13})_3(C_{14}H_{29})]Cl$ and **4d** from $[P(C_8H_{17})_4]Br$ medium in pure state by standard isolation procedures as in this case stable solvate complexes of the CMPO and the corresponding IL were formed.

Therefore, in terms of reaction rate along with the cost of ionic liquid, [bmim]Br and $[P(C_6H_{13})_3(C_{14}H_{29})]Cl$ are the best ionic liquids for these reactions.

Taking into account that sorption methods of isolation and concentration of radioactive elements have attracted significant attention due to their simplicity and technological effectiveness, we attached the CMPO moiety to a polystyrene matrix modified by aminomethyl groups (loading 1.2–1.5 mmol/g, reaction time 1.5 h, 100–110 °C). Without optimization of this analogous polymer transformation, the phosphorylation percent was ca. 25% for [bmim]Br, 35% for $[P(C_6H_{13})_3(C_{14}H_{29})]Cl$, and 45% for [bmim]$NTf_2$ and [bmim]BF_4. Despite phosphorylation not being quantitative, modification of amines of high molecular weight by complexing CMPO moieties can be performed using the described procedure. The rather low yields in this particular case might be connected with steric hindrance to reagent approach due to the presence of a methylene unit between the nitrogen atom and the polymer matrix.

In the absence of triphenyl phosphite, amidation did not take place. Thus, we suggest that the reaction proceeds via the formation of the intermediate phenyl ester **5** of diphenylphosphoryl acetic acid comprising a phenoxy moiety as a good leaving group. The latter is transformed easily to an amide functionality upon reaction with an N-nucleophile



Scheme 2.

(Scheme 2); amines are found to be more nucleophilic in ionic liquids than in common organic solvents.[13] Triphenyl phosphite is converted into diphenylphosphite as confirmed by a signal ($\delta_P \sim 2$ ppm, $^1J_{PH} = 580$ Hz; the location of the signal is slightly shifted depending on the type of ionic liquid and the nature of its anion) in the ^{31}P NMR spectra of the reaction mixtures along with the signals of the CMPO product.

Acid **3** reacts with triphenyl phosphite (model reaction in [bmim]Br) to furnish phenyl ester **5** in about 4 h. This fact as well as the absence of the ester signal in the ^{31}P NMR spectra of the reaction mixture in the presence of the amine suggests the higher rate, v_2, of the second step of the process.

Monitoring the reaction course by ^{31}P NMR spectroscopy showed that when using triphenyl phosphite in an equimolar amount, not all of it was consumed in the reaction (a signal at 127 ppm was always observed corresponding to $(PhO)_3P$). With the proviso that the reaction proceeds according to the mechanism proposed, it may be that all the ester groups of the phosphite are reactive. In fact, the amount of triphenyl phosphite may be reduced to 0.35 M equiv without any negative effect on the reaction rate and the product yield.

Since in most cases extraction of the product with an organic solvent is a convenient isolation procedures, we considered the possibility of performing the CMPO synthesis in a two-phase system where an organic solvent plays the role of the second immiscible phase. Under such conditions, the product was isolated with the organic solvent after separation of the layers and simple evaporation of the solvent gave the desired CMPO. Despite the use of the [bmim]Br/toluene system resulted in practically the same reaction rate (e.g., the reaction of **3** with Bu_2NH in [bmim]Br was completed over 40 min) and the drawback of such a system was connected with the partial solubility of the ionic liquid in toluene. Therefore, a portion of the ionic liquid was lost, which might be the reason for the decreased yield of the product (~70%) at the third recycle. Better results were obtained using the [bmim]Br/dibutyl ether two-phase system. In addition to the isolation of more pure CMPO (>98%) with the ether layer, this two-phase system retained its activity over at least five repeat cycles (Table 2). It should be mentioned that on applying a two-phase system, the amount of the ionic liquid may be reduced up to 1 M equiv with no effect on the product yield and the reaction rate.

Table 2
Recyclability of [bmim]Br in a two-phase system

$$\underset{\textbf{3}}{Ph_2P(O)CH_2COOH + Bu_2NH} \xrightarrow[110\text{-}120\ ^{\circ}C,\ 2\ h]{[bmim]Br/BuOBu,\ 0.35\ equiv\ (PhO)_3P} \underset{\textbf{4d}}{Ph_2P(O)CH_2C(O)NBu_2}$$

Cycle no.	Time	Yield[a] (%)
1	40 min	92
	1 h	95
	2 h	99 (94)
2	2 h	99 (93)
3	2 h	99 (95)
4	2 h	99 (95)
5	2 h	99 (95)

[a] According to ^{31}P NMR spectroscopy; isolated yield shown in brackets.

Table 3
Influence of the amine nature on the rate of amidation in the 0.35 equiv $[(PhO)_3P]$/1 equiv [bmim]Br/toluene system

Time	Amine/yield[a] (%)				
	$BuNH_2$	n-$C_9H_{19}NH_2$	Bu_2NH	$PhNH_2$	$PhCH_2NH_2$
40 min	100	100	75	38	20
1.5 h	—	—	100	60	55
3 h	—	—	—	80	100

[a] According to ^{31}P NMR spectroscopy of the reaction mixtures.

It is interesting to note that using 0.35 M equiv of $(PhO)_3P$ in the two-phase system with toluene, the difference in the reactivity of amines was clearly evident: primary aliphatic amines reacted faster than dialkylamines while benzylamine and aniline were significantly less active (Table 3). Thus the reactivity of the amines decreased in the following order: $AlkNH_2 > Alk_2NH > PhCH_2NH_2 > PhNH_2$.

In summary, the method reported for the direct amidation of phosphoryl acetic acids in ionic liquids may be applied effectively for the synthesis of CMPOs. Finally, it should be mentioned that ionic liquids with the addition of CMPO extractant (organic solvent) are promising for use in liquid/liquid separation processes for actinides.[14] Therefore, we suggest that crude reaction mixtures obtained in the course of CMPO synthesis in ILs may be successfully applied for such purpose.

Acknowledgements

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12. *General procedure*: (a) A mixture of an ionic liquid (3 g), 1.2 mmol of the corresponding amine and 0.3 g (1.15 mmol) of diphenylphosphorylacetic acid **3** was heated to ~100 °C under stirring. After dissolution of the starting substrates (ca. 5 min), the mixture was cooled to 50 °C and 358 mg (1.15 mmol) of triphenyl phosphite was added. It should be noted that the starting diphenylphosphoryl acetic acid **3** is insoluble in phosphonium and imidazolium tetrafluoroborate ionic liquids even at 100 °C. In these cases, acetonitrile was used as a co-solvent (100 vol %). Addition of this co-solvent had no detrimental effect on the yield and reaction rate in the case of other ionic liquids. The mixture was heated at 100–110 °C and then allowed to cool to room temperature. Compound **4a** obtained from $[P(C_8H_{17})_4]Br$ and compound **4b** obtained from $[P(C_6H_{13})_3(C_{14}H_{29})]BF_4$ were precipitated by the addition of 20 ml of $Et_2O/MeOH$ (95:5) followed by filtration and drying in vacuo. Compound **4a** obtained from [bmim]Br, and compound **4b** obtained from [bmim]Br and $[bmim]PF_6$ were precipitated by the addition of water (10 ml). Dibutylamide **4d** was isolated by extraction with diethyl ether (3 × 10 ml) followed by solvent evaporation.
    (b) To a mixture of 253 mg (1.15 mmol) of [bmim]Br, 0.3 g (1.15 mmol) of **3**, 1.2 mmol of the corresponding amine and 15 ml of toluene or dibutyl ether as a second-phase after dilution of the phosphorus substrate as described above, 109 mg (0.35 mmol) of triphenyl phosphite was added at ~50 °C. The mixture was heated for 40 min–2.5 h as appropriate, cooled to room temperature and the layers were separated. The solvent layer was evaporated to dryness to afford the final product having purity >95% according to NMR data. In the recycling experiments, reactants were added to the ionic liquid solution remaining in the reaction vessel to start the next run. Similar results were obtained using 0.1 mol of phosphorus substrate, indicating the possibility of further scaling up if necessary. Compounds **4a**,**b**,[8] **4c**[5] and **4d**[2a] are known and after isolation, their physicochemical constants and spectral data compared well with the literature data. Conversion was determined by integration of the signals in the ^{31}P NMR spectra [85% H_3PO_4 (^{31}P) as an external standard].
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