

Ionic-liquid-promoted Michaelis–Arbuzov rearrangement

E. V. Matveeva, I. L. Odinets,* V. A. Kozlov, A. S. Shaplov and T. A. Mastryukova

A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova Street, 28, 119991 Moscow GSP-1, Russian Federation

Received 24 May 2006; revised 8 August 2006; accepted 16 August 2006

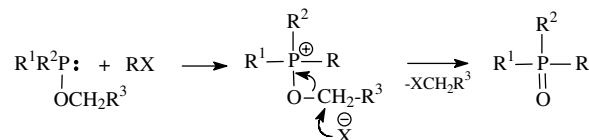
Available online 7 September 2006

Abstract—Room-temperature imidazolium ionic liquids, [Rmim][X], proved to be environmentally benign recyclable solvents promoting the Michaelis–Arbuzov rearrangement, which can be performed even at room temperature in a short period of time. The best ionic liquid of choice depended on the starting phosphorus(III) ester, namely, for triethyl phosphite [bmim][NTf₂] demonstrated better results while for ethyl diphenylphosphinite it was [hmim][Br].

© 2006 Elsevier Ltd. All rights reserved.

Currently, ionic liquids due to their potential for recyclability, ability to dissolve a variety of organic, inorganic and metal complex materials and non-volatile nature, are of interest in chemistry in the search for green alternatives of traditional organic solvents.¹ Despite wide synthetic potential, only a few applications of ionic liquids in organophosphorus chemistry can be found in the literature. The Wittig–Horner reaction of ethyl diethylphosphonoacetate and aldehydes affording β -substituted acrylic esters was carried out in such media in the presence of lithium hydroxide.² α -Aminophosphonates were synthesized via Kabachnik–Fields reactions in ionic liquids by the one-pot, three-component lanthanide triflates-catalyzed reaction of an aromatic aldehyde, aniline and diethyl phosphite.³ Among the catalysts, Sm(OTf)₃ was superior and the reactions in [bmim][PF₆] were the most effective (20 °C, 1 mol % of the catalyst, 27 h, >99% yield). The same reaction can be performed avoiding the use of heavy-metal Lewis acids and in this version [bmim][BF₄] showed better results in terms of reaction rate and yields in comparison to the hydrophobic [bmim][PF₆].⁴ Also, it was reported that the esterification of phosphonic and phosphinic acids occurred with triethyl(methyl) orthoacetate in [bmim][PF₆] in high yields under neutral conditions.⁵

The Michaelis–Arbuzov rearrangement is a highly important reaction of general value in the conversion of 3-coordinate phosphorus esters to 4-coordinate species. In its most common form, the procedure often requires prolonged heating at moderately high temperatures. A variety of simple and complex alkyl groups including functionalized examples have been substituted on the phosphorus using this route.⁶



The mechanism of the Michaelis–Arbuzov rearrangement has been studied widely⁷ and involves the attack of a phosphorus lone pair on the electrophilic carbon atom of an alkyl halide to form an intermediate phosphonium salt followed by its rapid dealkylation via the action of a halide anion. Phosphonium intermediates were observed in the reaction of diethyl phosphinite with an alkyl halide at low temperatures where the two alkyl groups on the phosphorus atom decreased its reactivity⁸ and also in the case of sterically hindered phosphonites.⁹

Weak electrophiles such as vinyl and aryl halides were introduced under the catalysis of various metals and metal halides; nickel(II) halides (5–10 mol %, temperature around 150 °C) appeared to be the most useful.¹⁰

Keywords: Ionic liquids; Michaelis–Arbuzov rearrangement; P–C bond formation.

* Corresponding author. Tel.: +7 495 135 9356; fax: +7 495 135 5085; e-mail: odinets@ineos.ac.ru

The Michaelis–Arbuzov reaction is reported to be effected under microwave irradiation where simple alkyl halides reacted with trialkyl phosphites without solvent in only 5 min.¹¹ This method is suitable for the scale up to 0.2 mol of the halide substrate.

As amines are found to be more nucleophilic in ionic liquids than in common organic solvents¹² we considered that ILs might be used as activating media for the above reaction. In fact, the use of room-temperature imidazolium ionic liquids [Rmim][X] [X = Br, BF₄, PF₆, NTf₂; Rmim = 1-butyl-3-methylimidazolium (bmim) or 1-hexyl-3-methylimidazolium (hmim)] significantly enhanced the rate of the Michaelis–Arbuzov rearrangement. However, the counteranion of the ionic liquids affected their catalytic activity considerably depending on the structure of the starting phosphorus ester and reaction conditions. The results are summarized in Tables 1 and 2.¹³

Thus, [bmim][NTf₂] appeared to be the most suitable ionic liquid to perform the rearrangement of triethyl phosphite where the reaction proceeded in 5 min with dropwise addition of ethyl bromoacetate and was completed in 20 min when using benzyl bromide (Table 1). Good results were achieved using [bmim][BF₄]. [Bmim][Br] accelerated the side dealkylation process resulting in hydrophosphoryl compounds rather than the Arbuzov rearrangement giving diethylphosphonoacetate in 25% yield only (Table 1, run 3). It should be noted that triethyl phosphite rapidly underwent dealkylation in [bmim][Br] in the absence of alkyl halide giving ca. 60% (EtO)₂P(O)H and ca. 40% (EtO)(HO)P(O)H in 1 h at 110 °C while in [bmim][NTf₂] under identical conditions, only traces of dealkylated products were registered by ³¹P NMR. [Bmim][PF₆] accelerated not only the Arbuzov rearrangement but also further dealkylation of the final product resulting mostly in C₆H₅CH₂P(O)(OH)(OEt) (65% vs 25% of C₆H₅CH₂P(O)(OEt)₂) (Table 1, run 4). Phosphonium ionic liquids gave undesired results in this reaction. Thus, when using [(C₁₄H₂₉)(C₆H₁₃)₃P]Cl for the reaction of (EtO)₃P with benzyl bromide, only

dealkylated products were observed in the reaction mixture [(EtO)₂P(O)H and (EtO)(HO)P(O)H in a 1:1 ratio]. The same reaction in [(C₁₄H₂₉)(C₆H₁₃)₃P]BF₄ gave the desired product in 50% yield after heating for 1 h while the second product was (EtO)₂P(O)H (yield 48%).

If ethyl diphenylphosphinite was used instead of the less reactive triethyl phosphite in the reaction with ethyl bromoacetate under similar conditions (110 °C), the effect of ionic liquids on the reaction rate did not change in the above series, that is, [bmim]Br ≤ [bmim]PF₆ < [bmim]BF₄ < [bmim]NTf₂ (Table 2, runs 1–4). However, this reaction was found to proceed easily under ambient conditions in nearly the same period of time giving the product in higher yields. The most suitable ionic liquid in this case was [hmim]Br which we had used instead of [bmim]Br, a solid at room temperature. For ethyl diphenylphosphorylacetate formation, all the ionic liquids were comparable in terms of the final yields. In [bmim]Br and [bmim]NTf₂, about 10% of the starting ester did not react over 20 min, but the reaction was completed within half an hour (Table 2, runs 5 and 8). In [bmim]BF₄, following the reaction course by ³¹P NMR, we did not observe the signals of the starting substrate after 20 min but a signal at δ_P 65.3 ppm was assigned to the corresponding intermediate phosphonium salt stabilized by the non-nucleophilic tetrafluoroborate anion. Over time, the phosphonium salt was transformed into the final product (Table 2, run 7). The application of [bmim]PF₆ as the reaction media resulted in the formation of Ph₂P(O)H as a side product in 10% yield (δ_P 20.2 ppm, ¹J_{PH} 483 Hz).

Extension of these reaction conditions to the other types of haloalkanes led to a decrease in the reaction rate to some extent in the case of benzyl halides and a drastic decline in product yields in the case of the weaker electrophiles such as chloroacetonitrile or ethyl chloroacetate. For the latter, it was necessary to perform the reaction at an elevated temperature.

Table 1. The Michaelis–Arbuzov rearrangement of triethyl phosphite in ionic liquids

$$(\text{EtO})_3\text{P} + \text{RX} \longrightarrow (\text{EtO})_2\text{P}(\text{O})\text{R}$$

Run	RX	Temp (°C)	Solvent or ionic liquid	Time	Yield (%) ^a
1 ^b	BrCH ₂ Ph	120–150	Xylene ^{14a}	3 h	92
2 ^b	BrCH ₂ Ph	150	(EtO) ₃ P ^{14b}	4 h	87
3	BrCH ₂ Ph	110	[bmim]Br	20 min	25 ^c
4	BrCH ₂ Ph	110	[bmim]PF ₆	20 min	25 ^d
5	BrCH ₂ Ph	110	[bmim]BF ₄	20 min	78
6	BrCH ₂ Ph	110	[bmim]NTf ₂	5 min	80
				20 min	94
7 ^b	BrCH ₂ COOEt	110	Toluene ^{14c}	6 h	87
8 ^b	BrCH ₂ COOEt	130–140	Xylene ^{14d}	3 h	93
9 ^b	BrCH ₂ COOEt	60–80	(EtO) ₃ P ^{14c}	30 min	Quant
10	BrCH ₂ COOEt	110	[bmim]NTf ₂	5 min	94

^a Isolated yield.

^b Literature data provided for comparison.

^c 40% (EtO)₂P(O)H, 25% (EtO)(HO)P(O)H, and 10% (EtO)₃P were obtained.

^d 10% (EtO)₂P(O)H and 65% C₆H₅CH₂P(O)(OH)(OEt) were obtained.

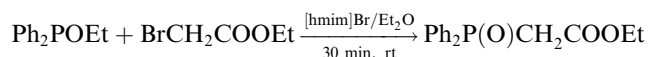
Table 2. The Michaelis–Arbuzov rearrangement of diphenylethylphosphinite in ionic liquids

$\text{Ph}_2\text{POEt} + \text{RX} \longrightarrow \text{Ph}_2\text{P}(\text{O})\text{R}$					
Run	RX	Temp (°C)	Ionic liquid	Time	Yield (%) ^a
1	BrCH ₂ COOEt	110	[bmim]Br	5 min	53
				20 min	77
2	BrCH ₂ COOEt	110	[bmim]PF ₆	5 min	27
				20 min	61
3	BrCH ₂ COOEt	110	[bmim]BF ₄	5 min	63
				20 min	78
4	BrCH ₂ COOEt	110	[bmim]NTf ₂	5 min	69
				20 min	83
5	BrCH ₂ COOEt	20	[hmim]Br	20 min	91
				30 min	Quant (70)
6	BrCH ₂ COOEt	20	[hmim]Br/Et ₂ O	30 min	98 (76)
7	BrCH ₂ COOEt	20	[bmim]BF ₄	20 min	85
				24 h	Quant
8	BrCH ₂ COOEt	20	[bmim]PF ₆	20 min	90 ^b
9	BrCH ₂ COOEt	20	[bmim]NTf ₂	20 min	90
				40 min	Quant
10	BrCH ₂ Ph	20	[hmim]Br	20 min	77 (70) ^b
11	BrCH ₂ Ph	20	[hmim]Br/Et ₂ O	30 min	Quant (98)
				20 min	54
12	BrCH ₂ Ph	20	[bmim]BF ₄	20 min	54
				40 min	70
				24 h	Quant (95)
13	1,3-(BrCH ₂) ₂ C ₆ H ₄	140	Xylene ¹⁵	3 h	58
14	1,3-(BrCH ₂) ₂ C ₆ H ₄	20	[hmim]Br	20 min	25
				24 h	81 (76) ^b
15	ClCH ₂ COOEt	20	[hmim]Br	20 min	27
16	ClCH ₂ CN	20	[hmim]Br	20 min	2.5
				24 h	11
17	ClCH ₂ CN	110	[hmim]Br	20 min	70 (64)

^a Yield according to ³¹P NMR data, isolated yield are shown in brackets.

^b Formation of Ph₂P(O)H in 10%, 23% and 19% yields for runs 8, 10 and 14 was observed.

Ph₂POEt can 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 can be decreased to 1 mol equiv and the target products are easily separated along with the ether layer (Table 2, runs 6 and 11). The recovered ionic liquid may be recycled at least 5 times without any decrease in activity as shown using the reaction with ethyl bromoacetate as an example (Table 3).

Table 3. Recyclability of [hmim]Br ionic liquid

Run	Yield (%) ^a	Purity (%) ^b
1	98	93
2	99	97
3	93	98
4	94	89
5	99	87

^a Isolated yield.

^b Estimated from ³¹P and ¹H NMR spectra.

In principle, when using a biphasic system, a catalytic amount of [hmim]Br ionic liquid (5–10 mol %) can be used to obtain ethyl diphenylphosphorylacetate. The use of 5 mol % of ionic liquid resulted in 85% of the product in 20 min but its purity was only 77% according to the ³¹P NMR data (11% of Ph₂POEt, 8% of Ph₂P(O)Et and 4% Ph₂P(O)H). If the amount of [hmim]Br was increased up to 10 mol %, the yield of the desired product in the 1st run was 96% (98% purity) but in the second run the yield decreased to 78% (95% purity). It is interesting to note that the biphasic [hmim]Br/Et₂O system did not work for the reaction of bromoacetate with the less nucleophilic triethyl phosphite, which remained unreacted in the ether layer for at least 3 days followed by a slow dealkylation after a prolonged period of time.

Furthermore, for the synthesis of phosphoryl acetic acid esters the method described can be successfully achieved in a one-step procedure employing the BASIL™ method¹⁶ used for the synthesis of trivalent phosphorus acid esters. In the BASIL™ 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 step of Arbuzov rearrangement similar to the other above mentioned ILs. 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. Starting from chlorodiphenylphosphine, $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{-COOEt}$ was obtained in ca. 93% yield (based on $\text{Ph}_2\text{P}(\text{O})\text{Cl}$) with a purity above 85% after aqueous work-up (unoptimized). It should be noted that our attempt to carry out the reaction with $\text{BrCH}_2\text{COOEt}$ at room temperature in a biphasic system with diethyl ether failed. Under such conditions, the ionic liquid-promoted oxidation of the phosphinite to the corresponding phosphinate, $\text{Ph}_2\text{P}(\text{O})\text{OEt}$, which was isolated in ca. 75% yield.

The general influence of ionic liquids on the rate of the Michaelis–Arbuzov rearrangement may be connected either with the polarity of these solvents which is similar for most RTILs¹⁷ or with solvent–solute interactions increasing the nucleophilicity of the phosphorus lone pair. The difference in the reactivity between triethyl phosphite and the more nucleophilic diphenylethyl phosphinite is still well pronounced in the ionic liquids being similar to common organic solvents. Therefore, it can be suggested that ILs accelerate the second reaction step (formal nucleophilic substitution process),¹⁸ to a greater extent than the first nucleophilic attack of phosphite (phosphinite). In $[\text{bmim}]\text{Br}$ the anion of the ionic liquid may assist the dealkylation due to the increase in its concentration. However, the same factor assists the side dealkylation reaction of the less reactive starting phosphorus substrate $(\text{EtO})_3\text{P}$. In ionic liquids such as $[\text{bmim}]\text{BF}_4$, $[\text{bmim}]\text{PF}_6$ and $[\text{bmim}]\text{NTf}_2$, dealkylation should proceed with the halide anion and reactions in these media proceed slowly and even allow the possibility to observe the unstable phosphonium species stabilized by non-nucleophilic anions.

In conclusion, we have found that 1-methyl-3-alkylimidazolium ionic liquids promote the Michaelis–Arbuzov rearrangement in high yields under mild conditions. $[\text{Bmim}]\text{NTf}_2$ is the ionic liquid of choice for triethyl phosphite reactions while $[\text{hmim}]\text{Br}$ is the best for the rearrangement of diphenylethylphosphinite. Finally, all these reactions were performed without any protective atmosphere of an inert gas.

Acknowledgements

This work was supported by the Russian Basic Research Foundation (Grant No. 05-03-32692) and the German Science Foundation (436 RUS 113/766/1-1). A.S.S. thanks the Fund for Russian Science Assistance for the financial support.

References and notes

1. *Ionic Liquids as Green Solvents: Progress and Prospects*; Rogers, R. D., Seddon K. R., Eds.; ASC Symposium Series; American Chemical Society: Washington, DC, 2003.
2. Kryshchal, G. V.; Zhdankina, G. M.; Zlotin, S. G. *Mendeleev Commun.* **2002**, 176.

3. Lee, S.-gi.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commun.* **2001**, 1698.
4. Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P. *Green Chem.* **2002**, *4*, 436.
5. Yoshino, T.; Imori, S.; Togo, H. *Tetrahedron Lett.* **2006**, *62*, 1309.
6. Quin, L. D. A. *Guide to Organophosphorus Chemistry*; John Wiley & Sons, 2000.
7. Hudson, H. R. *Top. Phosphorus Chem.* **1983**, *11*, 339.
8. Razumov, A. I.; Bankovskaya, N. N. *Zh. Obshch. Khim.* **1964**, *34*, 1859.
9. (a) Razumov, A. I.; Bankovskaya, N. N. *Dokl. Akad. Nauk USSR* **1957**, *116*, 241; (b) Hudson, H. R.; Rees, R. G.; Weekes, J. E. *J. Chem. Soc., Perkin Trans. 1* **1974**, 982.
10. Tavs, P. *Chem. Ber.* **1970**, *103*, 2428.
11. (a) Villemin, D.; Simeon, F.; Decreus, H.; Jaffres, P.-A. *Phosphorus Sulfur Silicon* **1998**, *133*, 209; (b) Kiddle, J. J. *Synth. Commun.* **2001**, *31*, 3377.
12. Crowhurst, L.; Lancaster, N. L.; Pérez Arlandis, J. M.; Welton, T. *J. Am. Chem. Soc.* **2004**, *126*, 11549.
13. General procedure: The corresponding phosphorus(III) ester (1 mmol) was added to a solution of alkyl halide (1 mmol) in an ionic liquid (0.5 g) either at 110 °C or at room temperature as indicated. The mixture was stirred at the same temperature over the time mentioned in Tables 1 or 2, respectively. If the reaction was performed at an elevated temperature, the reaction mixture was cooled to ambient conditions before the work-up procedure. The products, excluding 1,3-bis(diphenylphosphorylmethyl)benzene, were extracted with diethyl ether (3 × 10 ml) followed by solvent evaporation. 1,3-Bis(diphenylphosphorylmethyl)benzene, which is not soluble in ether, was precipitated by the addition of water (5 ml) then collected by filtration and dried under vacuum. 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(III) substrate indicating the possibility of further scaling up if necessary. All the compounds obtained are known and after isolation, their physicochemical constants and spectral data compared well with the literature data. The conversion was determined by the integration of signals in the ³¹P NMR spectra [85% H_3PO_4 (³¹P) as an external standard].
14. (a) Gronowitz, S.; Stenhammar, K.; Svensson, L. *Heterocycles* **1981**, *15*, 947; (b) Egbe, D. A. M.; Cornelia, B.; Nowożyński, J.; Klemm, E. *Macromolecules* **2003**, *36*, 5459; (c) Rodrigues, J. M.; DaCosta, J. B. N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 137; (d) Shrestha-Dawadi, P. B.; Lugtenburg, J. *Eur. J. Org. Chem.* **2003**, *23*, 4654; (e) van der Klei, A.; deJong, R. L. P.; Lugtenburg, J.; Aloysius, A. G. M. *Eur. J. Org. Chem.* **2002**, *17*, 3015.
15. Bodrin, G. V.; Kabachnik, M. I.; Kochetkova, N. E.; Medved', T. Ya.; Myasoedov, B. F.; Polikarpov, Yu. M.; Chmutova, M. K. *Izv. Akad. Nauk SSSR, Ser. Khim (Russ.)* **1984**, 1841, [*Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)*, **1984**, *33*, 1682].
16. Volland, M.; Seitz, V.; Maase, M.; Flores, M.; Papp, R.; Massonne, K.; Stegmann, V.; Halbritter, K.; Noe, R.; Bartsch, M.; Siegel, W.; Becker, M.; Huttenloch, O. PCT Int. Appl. 2003, WO 2003062251; *Chem. Abstr.* **2003**, *139*, 149757.
17. Anderson, J. L.; Ding, J.; Welton, T.; Armstrong, D. W. *J. Am. Chem. Soc.* **2002**, *124*, 14247.
18. Regularities of nucleophilic substitution reactions in ionic liquids were recently published: Jorapur, Y. R.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 345.