Synthesis of α,β-unsaturated esters from dialkoxyphosphoryl esters and aldehydes in the ionic liquid [bmim][PF_6]

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α,β-Unsaturated esters were synthesised by LiOH·H_2O-promoted reactions of triethyl phosphonoacetate **1** and triethyl 3-methyl-4-phosphono-2-butenoate **2** with aldehydes in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]).

The base-promoted reactions of carbonyl compounds with phosphonic esters containing electron-accepting groups at the α-position (Horner–Emmons reaction) are widely used for the synthesis of di- and tri-substituted alkenes[1] including those with a required configuration of the double bond.[2] This reaction is usually performed in polar organic solvents[1] or in nonpolar solvents under phase-transfer catalysis conditions.[3(a)–(d)]

Recently, a base-promoted synthesis of α-fluoro-α,β-unsaturated esters by the reaction of triethyl 2-fluoro-2-phosphonoacetate with aldehydes in a solution of 8-alkyl-1,8-diazabicyclo[5,4,0]-7-undecenium and 1,3-dialkylimidazolium triflates was reported.[4] These liquid triflates belong to organic ionic liquids, which attract interest as an alternative to common organic solvents.[5] Ionic liquids consisting of an onium organic cation and a poorly coordinating (often fluorine-containing) anion are thermally stable, non-volatile and recyclable.[5(c)]

Here, we report the synthesis of biologically active compounds by the base-promoted Horner–Emmons reaction performed in an ionic liquid. As the starting compounds, we used triethyl phosphonoacetate **1** and triethyl 3-methyl-4-phosphono-2-butenoate **2**, which are known as building blocks for the synthesis of biologically active isoprenoid compounds.[6] 1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), which was applied previously as a reaction medium in C–C coupling reactions,[7(a)–(f)], was chosen as the ionic solvent.

To find optimum reaction conditions, we investigated a reaction between the compound **1** and 3-methylbutanal **3a** in [bmim][PF_6] in the presence of various deprotonating agents. We found that phosphonoester **1** containing less acidic α-hydrogen atoms than the α-hydrogen atom in triethyl 2-fluoro-2-phosphonoacetate does not react with aldehyde **3a** in the ionic solvent in the presence of K_2CO_3 or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (*i.e.*, under conditions described previously[4]). The use of stronger bases, such as NaOH or KOH, led to hydrolysis of the ester group in compound **1**.

We were able to direct the reaction to the formation of alkene **4a** by performing it in the presence of LiOH·H_2O. The reaction of equimolar amounts of compounds **1** and **3a** with an excess of LiOH·H_2O (4–5 equiv.) in [bmim][PF_6] (2–3 equiv.) at 20 °C afforded 5-methyl-2-hexenoic acid ester **4a** in 70% yield (Table 1).† An excess of the base is necessary for the reaction to be completed: the yield of **4a** was reduced to 20% in the presence of 1 equiv. of LiOH·H_2O added to the reaction mixture. The reaction is heterogeneous (LiOH·H_2O is poorly soluble in [bmim][PF_6]); therefore, it is influenced by the particle size of the base. The highest reproducible yields of compound **4a** were obtained when the reaction was carried out in a suspension of LiOH·H_2O in [bmim][PF_6].

The different behaviour of LiOH·H_2O, as compared to other alkali metal hydroxides, in the reaction can probably be explained by the more effective ion–dipole interaction between Li^+ cations and water formed during deprotonation[8] that moves it out of the reaction area and prevents hydrolysis of the ester group.

The found conditions were applied to the synthesis of α,β-unsaturated esters from phosphonoester **1**, **2** and aliphatic, aromatic and heteroaromatic aldehydes. The reactions of compound **1** with benzaldehyde **3b**, cinnamaldehyde **3c**, cyclopropanecarbaldehyde **3d**, picolinaldehyde **3e** and citronellal **3f** in [bmim][PF_6] afforded olefination products **4b–f** in 68–81% yields (Table 1, rows 4–9).† Reactions between triethyl 3-methyl-4-phosphono-2-butenoate **2** and 3-methylbutanal **3a** or 3,7-dimethyloctanal **3g** gave 3,7-dimethyloctadienic ester **5** and hydroprene **6** in 48% and 75% yields, respectively (Table 1, rows 10–11).† To the best of our knowledge, the synthesis of compounds **5** and **6** is the first example of the preparation of biologically active compounds by the Horner–Emmons reaction performed in an ionic liquid. Ester **5** is an effective sterilising agent for spider mite (*Tetranychidae*); hydroprene **6** is an analogue of the insect juvenile hormone.[6]

The reactions were completed within 2–10 h depending on the structure of starting compounds (TLC monitoring). The reactions of phosphonoester **2** with aldehydes take longer times than the corresponding reactions of compound **1**. The reaction time usually increased with the chain length of substituent R in the aldehyde component (Table 1).

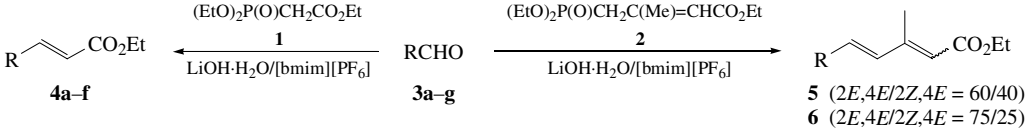
The reactions are stereoselective. According to ^{1}H NMR spectra, the newly formed double bond in compounds **4a–f**, **5** and **6** has the *E*-configuration ($^3J_{H–C=C–H}$ ~ 16 Hz, which is typical of *E*-olefins[1(c),9]). Isomerization takes place in compounds **5** and **6** regarding to the C^2=C^3 (Δ^2) double bond previously existing in starting phosphonoester **2**. The 2*E*,4*E*/2*Z*,4*E* isomer ratio determined by the ratio of Me protons at C^3 and olefinic protons at C^2 in the ^{1}H NMR spectra of the compounds **5** and **6**, as well as by GLC, is 60/40 or 75/25, respectively. It is comparable with the isomer distribution in compounds **5** and **6** obtained under phase-transfer catalysis conditions.[2,6]

The stereoselectivity of C=C bond formation distinguishes the studied reaction from the appropriate reactions between aldehydes and α-fluorophosphonoesters[4] or α-substituted phosphoranes[10] in the ionic liquids that afforded the mixtures of *E*- and *Z*-isomers in various proportions. A synthetic advantage of the method compared to the Wittig olefination reaction[10] is that there is no need to separate the reaction products from Ph_3PO.

As a whole, the reaction of phosphonoesters **1**, **2** with aldehydes and LiOH·H_2O in [bmim][PF_6] resembles those per-

† *General procedure.* The ionic solvent was synthesised according to the reported method.[7(b)] The ^{1}H, ^{31}P and ^{19}F NMR spectra of the melt recorded in [$^2H_6$]acetone contained only signals of the ionic liquid. ^{1}H NMR, δ: 0.93 (t, 3H, *J* 7.2 Hz), 1.36 (sep, 2H, *J* 7.5 Hz), 1.89 (pent, 2H, *J* 7.6 Hz), 4.0 (s, 3H), 4.3 (t, 2H, *J* 4.0 Hz), 7.62 (t, 1H, *J* 1.8 Hz), 7.68 (t, 1H, *J* 1.8 Hz), 8.82 (s, 1H). ^{31}P NMR, δ: –142.4 relative to H_3PO_4 (heptet, $^1J_{P–F}$ 708 Hz). ^{19}F NMR, δ: –71.0 relative to $CFCl_3$ (d, $^1J_{P–F}$ 708 Hz). To [bmim][PF_6] (11–15 mmol) was added LiOH·H_2O (22–25 mmol) and the mixture was vigorously stirred at 20 °C for 0.5–1.0 h. To the resulting suspension were added successively **1** or **2** (5 mmol) and **3a–g** (5 mmol). The reaction mixture was stirred at 20 °C for 2–10 h (TLC monitoring) and extracted with Et_2O (4×10 ml). The combined ether extracts were dried with anhydrous $MgSO_4$. The solvent was evaporated, and remaining products **4a–f**, **5** and **6** were distilled *in vacuo*. Compound **4d** was also isolated by direct distillation from the reaction mixture. The boiling points, n_D^{20} and ^{1}H NMR spectra of the compounds **4a–f**, **5** and **6** were in accordance with reported data. The remaining ionic liquid was filtered from inorganic salts, washed with water (3×10 ml) and kept at 40–60 °C (2 Torr) for 2 h to afford 89–94% of [bmim][PF_6]. The ^{1}H, ^{31}P and ^{19}F NMR spectra of thus recovered melt were identical to the spectra of freshly prepared [bmim][PF_6].

Table 1 $LiOH·H_2O$-Promoted reaction of phosphonoesters **1**, **2** with aldehydes **3a–g** in [bmim][PF_6].



	Compound	R	*t*/h	Yield of **4a–f**, **5**, **6** (%)[a]	Cycle no.	Recovered [bmim][PF_6] (%)	Ratio **1**:**3**:[bmim][PF_6]:$LiOH·H_2O$	Reported yield **4a–f**, **5**, **6** (%)	
								NaH/ glyme	PTC conditions
1	**4a**	Me_2CHCH_2	2	70	1	89	1:1:3:5		
2	**4a**	Me_2CHCH_2	2	68	2	94	1:1:2.6:4.4		
3	**4a**	Me_2CHCH_2	2	72	3	94	1:1:2.5:4.2		
4	**4b**	Ph	4	78	4	92	1:1:2.3:3.8	84[1(b)]	56[b]
5	**4b**	Ph	4	81	1	91	1:1:3:5		
6	**4c**	(*E*) PhCH=CH	6	71	2	93	1:1:2.7:4.5	72[1(b)]	
7	**4d**	cyclopropyl	2	68 (65[c])	3	94	1:1:2.5:4.2	73[1(b)]	
8	**4e**	2-pyridyl	3	74	4	93	1:1:2.4:3.9		
9	**4f**	$Me_2C=CHCH_2CH_2CH(Me)CH_2$	7	63	5	92	1:1:2.2:3.6	75[1(b)]	
10	**5**	Me_2CHCH_2	6	48	1	91	1:1:3:5		67[d]
11	**6**	$Me_2CH(CH_2)_3CH(Me)CH_2$	10	75	2	93	1:1:2.7:4.5		74[d]

[a]Yields of compounds **4–6** isolated by extraction from the reaction mixture with Et_2O followed by distillation. [b]Ratio **1**:**3**:$NaOH_{aq}$:TBAI = 1:1:10:0.1, CH_2Cl_2, 20 °C, 15 min.[11] [c]Yield of compound **4d** obtained by direct distillation from the reaction mixture. [d]Ratio **2**:**3**:KOH:TBAB = 1:1:2:0.1, PhH, 20 °C, 2–3 h.[6,9]

formed in common organic solvents regarding the yields of products and *E*-stereoselectivity (Table 1). The reaction in an ionic liquid is preferable because of the simplicity of product isolation and solvent regeneration. Olefins **4–6** can be isolated by direct evaporation under reduced pressure (2 Torr) from their solutions in the non-volatile ionic liquid or (more conveniently in laboratory conditions) by extraction with diethyl ether (which is immiscible with [bmim][PF_6]) followed by distillation. The ionic liquid was recovered by filtration from inorganic salts followed by washing with water (which is also practically immiscible with [bmim][PF_6]), and by the removal of volatile impurities under reduced pressure.

Thus, recovered [bmim][PF_6] was identical, according to ^{1}H, ^{31}P and ^{19}F NMR spectra, to the sample prepared by the reported method.[7(b)] The recovery of the ionic liquid was 89–94% (Table 1). The limited loss (6–11%) of the solvent is probably due to a slow ion exchange between [bmim][PF_6] and LiOH, which leads to the formation of [bmim][OH].

The use of the recovered [bmim][PF_6] in several consecutive cycles of the reaction between **1** and **3a** does not lead to a reduction in the yields of compound **4a** (Table 1, rows 1–3). Moreover, the regenerated solvent, which does not contain, according to ^{1}H and ^{31}P NMR spectra, even traces of compounds dissolved in previous experiment, can be reused in new reactions involving other aldehydes (Table 1, rows 4–9) and phosphoesters (Table 1, rows 10–11). After several regeneration cycles, the ionic solvent was pure enough to be reused for synthesis of olefins **4c–f**, **5**, **6** with characteristics identical to the published data. The reduction of [bmim][PF_6] in the course of regeneration (from 3.0 to 2.2 equiv.) does not reduce the yields of products.

In summary, we developed a simple and efficient synthesis of α,β-unsaturated esters (including biologically active compounds) based on the $LiOH·H_2O$-promoted reactions of triethylphosphonoacetate **1** and triethyl 3-methyl-4-phosphono-2-butenoate **2** with aldehydes in [bmim][PF_6]; the ionic solvent can be recycled.

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