SHORT COMMUNICATION

Ultrasonic and Lewis acid ionic liquid catalytic system for Kabachnik–Fields reaction

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A combination of ultrasonic (US) and $[bmim]AlCl_4$ ionic liquid is used as an alternative to conventional acid catalysts in the Kabachnik–Fields reaction of an amine and aryl aldehyde with phosphite leading to the formation of aminophosphonates. The reaction time was significantly reduced and the reaction progressed very smoothly.

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Intense research has recently focused on the application of ionic liquids as catalysts for a wide variety of organic synthetic processes. Ionic liquids provide vapour-free, thermally stable and "green" auxiliary substances for chemical reactions (Fumino et al., 2011). Active Lewis acid catalysis based on ionic liquids is regarded as important because of the widespread air- and solvent-stable demand for the use of Lewis acid catalysts in synthetic and industrial chemical applications (Dupont et al., 2002). Very recently, Lewis acidic ionic liquids have attracted increased attention as replacements for conventional mineral acid catalysts because of their negligible vapour pressure, outstanding acidity and predetermined solubility for some organic species (Gordon et al., 2001). On the other hand, ultrasound has been shown to have potential applications in organic synthesis, "green" chemistry and industry. Compared with traditional methods, this method is more convenient and more readily controlled (Rostamnia, 2011).

Due to the importance of aminophosphonates, the synthesis of these units is important in their use as inhibitors and a wide range of antibacterial or antifungal applications (Pratt, 1989; Rostamnia & Lamei, 2003). Several methods of synthesising α -aminophosphonate have been reported in the literature (Ranu & Hajra, 2002; Azizi & Saidi, 2003; Ramalingam & Kumar 2008; Niralwad et al., 2010; Ordoñez et al., 2010; Mandhane et al., 2011). However, the use of IL and ultrasound (US) contributes to a clean environment. The current study reports the results of the application of the US/IL catalytic system (Fig. 1) as a rapid catalyst for the three-component condensation of an amine, aldehyde and phosphite with excellent yields of α -aminophosphonates.

The ongoing programme (Rostamnia & Zabardasti, 2003; Rostamnia et al., 2012a, 2012b) focuses on the development of efficient and environmentally friendly methods in synthetic organic chemistry. The aim has been to investigate and design a catalyst and energy resources to achieve the desired chemical transformations with minimal formation of by-products or waste, as well as to decrease reaction time using ultrasound and porous catalysts. Building on earlier success in the "green" application of ultrasound in organic synthesis, we sought to combine achievements in the IL area with ultrasound. The current study presents the results of an extended investigation into the simultaneous use of the $[bmim]AlCl_4$ and ultrasound as a rapid approach to synthesis of the α aminophosphonate III via three-component coupling (Fig. 1).

The reaction of aniline and p-chlorobenzaldehyde with dimethyl phosphite was precisely monitored. The

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Solvent	Temperature/ $^{\circ}C$	Time/min	Yield/%		
			HSS	US	
MeOH	50	10	22	75	
EtOH	50	5	19	87	
EtOH	a.t.	5	14	93	
PhMe	a.t.	10	33	74	
PhMe	60	10	45	93	
CH_3CN	60	10	40	92	

Table 1. Study of optimised conditions for model reaction (high-speed stirrer vs ultrasound) a

a) Reaction scale: aniline (2 mmol), p-chlorobenzaldehyde (2.2 mmol), dimethyl phosphite (2 mmol) and catalyst (10 mol %) in 10 mL of solvent.

Table 2. Clean one-pot synthesis of IIIa-IIIi by US/IL catalytic system^a

Entry	Amine	Ar(R')CHO	Time/min	Product	Isolated yield/ $\%$
1	$PhNH_2$	4-Cl-C ₆ H ₄	5	IIIa	93
2	$PhNH_2$	C_6H_5	5	IIIb	91
3	$PhNH_2$	$3-NO_2-C_6H_4$	6	IIIc	92
4	$4-Me-C_6H_4NH_2$	$2-Cl-C_6H_4$	5	IIId	91
5	$4-Me-C_6H_4NH_2$	$4-NO_2-C_6H_4$	4	IIIe	90
6	$4-Me-C_6H_4NH_2$	2-MeO-C ₆ H ₄	7	IIIf	89
7	Et_2NH	$3-NO_2-C_6H_4$	5	IIIg	92
8	$(CH_2)_4NH$	$2-MeO-C_6H_4$	5	IIIh	87
9	$PhNH_2$	$(CH_2)_5CO$	10	IIIi	88

a) Reaction scale: amine (1 mmol), aldehyde (1 mmol), dimethyl phosphite (1.1 mmol) and catalyst (10 mol %) in 5 mL EtOH.



Fig. 1. US/[bmim]AlCl₄ system in Kabachnik–Fields reaction.



Fig. 2. Catalyst amounts of IL in synthesis of IIIa.

model reaction (60 °C) was carried out using different amounts of IL as the catalyst and irradiation with ultrasound. A high yield of α -aminophosphonate *IIIa* (93 %) was obtained with 10 mol % of the catalyst over 15 min in toluene. A further increase in the amount of catalyst (from 6 mol % to 20 mol %) had no significant effect on the product yield or reaction time (Fig. 2).

The model reaction in the presence of 10 mol % of [bmim]AlCl₄ was examined in different media (Table 1). Remarkably, in the comparative study of a one-pot, three-component synthesis of *IIIa*, the ultrasonically-mediated (US) procedure was completed in 5 minutes and the reaction time using the high-speed stirrer (HSS) method was 3 hours. Sonication in the model reaction led to reduced time and higher yield.

To demonstrate the diversity of this combined ultrasonic and IL catalytic system and to expand the scope of the process, the optimised conditions (EtOH, a.t. and US irradiation with 10 mol % of IL) were applied to a series of *III* via a three-component condensation. The results are summarised in Table 2.

The synthesis of IIIa with high level (5 mmol) of reactant was carried out in 25 mL EtOH. When the *p*-chlorobenzaldehyde and aniline were coupled with dimethylphosphite under optimal conditions, a yield of 89 % was obtained, demonstrating the efficiency of this method in large amount of substrates.

For a chemoselectivity investigation, the reactivity of dimethyl phosphite in the presence of the mixture of aldehydes, ketones and aniline may demonstrate the chemoselectivity in the present method. To demonstrate the chemoselectivity, dimethyl phosphite was treated with the mixture of aniline, benzaldehyde and

 Table 3. Spectral data of Kabachnik–Fields products

Compound	Spectral data
IIIa	¹ H NMR (CDCl ₃), δ : 3.55 (d, ³ $J_{\rm HP}$ = 10.8 Hz, 3 H), 3.77 (d, ³ $J_{\rm HP}$ = 10.8 Hz, 3 H), 4.52 (br, 1 NH), 4.79 (d, ² $J_{\rm HP}$ = 24.3 Hz, 1 H), 6.59–7.44 (m, 9 H)
IIIb	¹ H NMR (CDCl ₃), δ : 3.47 (d, ³ $J_{\rm HP}$ = 10.5 Hz, 3 H), 3.78 (d, ³ $J_{\rm HP}$ = 10.5 Hz, 3 H), 4.84 (d, ² $J_{\rm HP}$ = 24.3 Hz, 1 H), 5.02 (br, 1 NH), 6.51–7.51 (m, 10 H)
IIIc	$^{1}\mathrm{H}$ NMR (CDCl_3), $\delta:$ 3.64 (d, $^{3}J_{\mathrm{HP}}$ = 10.8 Hz, 3 H), 3.83 (d, $^{3}J_{\mathrm{HP}}$ = 10.4 Hz, 3H), 5.00 (d, $^{2}J_{\mathrm{HP}}$ = 25.1 Hz, 1 H), 5.25 (br, 1 NH), 6.62–8.41 (m, 9 H)
IIId	$^{1}\mathrm{H}$ NMR (CDCl ₃), $\delta:$ 2.16 (m, 3 H), 3.43 (d, $^{3}J_{\mathrm{HP}}$ = 9.9 Hz, 3 H), 3.83 (d, $^{3}J_{\mathrm{HP}}$ = 9.9 Hz, 3 H), 4.85 (br, 1 NH), 5.39 (d, $^{2}J_{\mathrm{HP}}$ = 24.9 Hz, 1 H), 6.49–7.56 (m, 8 H) $^{13}\mathrm{C}$ NMR (CDCl ₃), $\delta:$ 20.34, 50.39 (d, $^{3}J_{\mathrm{CP}}$ = 6.6 Hz), 53.03 (d, $^{1}J_{\mathrm{CP}}$ = 152.1 Hz), 113.67, 127.42, 127.46, 127.97, 129.78, 133.83, 137.78, 146.00
IIIe	$^{1}\mathrm{H}$ NMR (CDCl ₃), $\delta:$ 2.24 (m, 3 H), 3.50 (d, $^{3}J_{\mathrm{HP}}$ = 10.5 Hz, 3 H), 3.78 (d, $^{3}J_{\mathrm{HP}}$ = 10.5 Hz, 3 H), 4.80 (d, $^{2}J_{\mathrm{HP}}$ = 24.3 Hz, 1 H), 6.02 (br, 1 NH), 6.54–7.38 (m, 8 H) $^{13}\mathrm{C}$ NMR (CDCl ₃), $\delta:$ 21.15, 53.84 (d, $^{3}J_{\mathrm{CP}}$ = 6.9 Hz), 55.43 (d, $^{1}J_{\mathrm{CP}}$ = 152.1 Hz), 113.92, 118.49, 127.66, 127.74, 129.49, 132.43, 137.78, 149.26
IIIf	$^{1}\mathrm{H}$ NMR (CDCl ₃), δ : 2.18 (m, 3 H), 3.45 (d, $^{3}J_{\mathrm{HP}}$ = 10.5 Hz, 3 H), 3.82 (d, $^{3}J_{\mathrm{HP}}$ = 10.5 Hz, 3 H), 3.93 (s, 3 H), 4.06 (br, 1 NH), 5.43 (d, $^{2}J_{\mathrm{HP}}$ = 24.0 Hz, 1 H), 6.54–7.49 (m, 8 H)
IIIg	$^1{\rm H}$ NMR (CDCl ₃), δ : 0.95 (t, J = 7.2 Hz, 6 H), 2.21 (m, 2 H), 2.88 (m, 2 H), 3.37 (d, $^3J_{\rm HP}$ = 9.3 Hz, 3 H), 3.77 (d, $^3J_{\rm HP}$ = 9.3 Hz, 3 H), 4.12 (d, $^2J_{\rm HP}$ = 24.9 Hz, 1 H), 7.17–7.38 (m, 5 H)
IIIh	¹ H NMR (CDCl ₃), δ : 31.69 (m, 4 H), 2.16 (m, 2 H), 2.64 (m, 2 H), 3.46 (d, ³ J _{HP} = 6.3 Hz, 3 H), 3.77 (d, ³ J _{HP} = 6.3 Hz, 3 H), 3.85 (s, 3 H), 4.66 (d, ² J _{HP} = 18.0 Hz, 1 H), 6.89–7.75 (m, 4 H)
IIIi	¹ H NMR (CDCl ₃), δ : 1.13–2.13 (m, 10 H), 3.45 (br, 1 NH), 3.55 (d, ³ J _{HP} = 10.5 Hz, 6 H), 6.66–7.06 (m, 5 H)



Fig. 3. Chemoselective addition of phosphite to different carbonyl compounds.

cyclohexanone. Analysis of the mixture after 10 min showed that only benzaldehyde reacted with aniline to form IIIb (Fig. 3).

Many of the synthetic protocols reported for the synthesis of aminophosphonates suffer from one or more disadvantages such as harsh reaction conditions, lengthy reaction time and use of hazardous heavy metal catalysts (Beers et al., 1996; Danila et al., 2008; Cativiela et al., 2009; Gallardo-Macias & Nakayama., 2010; Ohara et al., 2011; Orsini et al., 2010; Tibhe et al., 2012; Disale et al., 2012; Ordóñez et al., 2012). These results clearly indicate the efficiency of the proposed methodology in both the activity and efficiency of the US/IL's catalytic system as compared with literature reports involving several homogeneous and heterogeneous systems under various conditions.

In conclusion, the results reported here concern the simultaneous application of ultrasound and an ionic liquid as a combined catalytic system in the preparation of some biologically interesting organic molecules of aminophosphonates via the threecomponent Kabachnik–Fields reaction. Undoubtedly, as part of the continuing investigation of ultrasonic/IL system for organic synthesis, these reaction methods represent potential applications in organic syntheses, pharmacy and industrial processes, hence this report opens an important field for use of the Lewis acidmediated strategy in the organic process.

All reagents were obtained from Merck (Germany) and Fluka (Switzerland) and used without further purification. [Bmim][AlCl₄] > 95 mass % was obtained from Sigma–Aldrich (China). Melting points were measured on an Electrothermal 9100 apparatus. ¹H NMR spectra were recorded on a Bruker AV-300 instrument (300 MHz) with CDCl₃ as solvent. A multi-wave ultrasonic generator (Sonicator_3000; Misonix, Farmingdale, NY, USA), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, generating continuous irradiation with a maximum power output of 600 W, was used for the ultrasonic irradiation.

General procedure for preparation of compound *III*: A mixture of *p*-chlorobenzaldehyde (140 mg, 1 mmol), aniline (93 mg, 1 mmol), dimethyl phosphite (121 mg, 1.1 mmol) and [Bmim][AlCl₄] (31 mg, 10 mol %) in EtOH (5 mL in a small-diameter beaker) was irradiated with ultrasound at ambient temperature (initial temperature value) for the required reaction time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). Evaporation of the solvent followed by purification on silica gel (EtOH : hexane, 1 : 5

vol.) afforded pure α -aminophosphonate IIIa (303 mg gum, 93 %). All products listed in Table 3 were known and characterised by comparison of their physical and spectral data with those already reported.

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