

1,3-DIALKYLIMIDAZOLIUM DIMETHYL PHOSPHATES – EFFECTIVE SOLVENTS AND CATALYSTS FOR CONDENSATION REACTIONS

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We report the preparation, characterization and exploitation of 1,3-dialkylimidazolium dimethyl phosphates. Condensation reactions of benzaldehyde with ethyl cyanoacetate and with malonic acid were performed in these ionic liquids either in absence or in presence of other catalysts. The effect of ionic liquid structure on the condensation reaction rates and yields was discussed.

Key words: *ionic liquids, dialkyl phosphates, condensation reactions.*

INTRODUCTION

Ionic liquids (ILs) have been used as solvents for organic syntheses for more than twenty years, 1-alkylpyridinium and 1,3-dialkylimidazolium salts being the most frequently used materials of this type [1, 2]. Recently, the family of ILs was enlarged by the introduction of 1,3-dialkylimidazolium dialkyl phosphates [3]. 1,3-Dialkylimidazolium phosphates have not been frequently used as solvents for organic transformations. We disclosed a novel possibility of using 1,3-dialkylimidazolium dialkyl phosphates as solvents for condensation reactions, where the catalytic activity of these materials offers an additional advantage.

EXPERIMENTAL

Materials

1,2-Dimethylimidazole, trimethyl phosphate, and other reagents were analytical grade commercial products (Sigma-Aldrich). 1-Butyl-2-methylimidazole was prepared by alkylation of 2-methylimidazole (purchased from Sigma-Aldrich) with 1-bromobutane (purchased from Alfa Aesar).

Measurements

The ^1H NMR spectra were recorded on a Varian 400 MR spectrometer, using DMSO-d_6 as a solvent and TMS as an internal standard. The water (moisture) content of the ILs was measured by the Karl Fischer method using a Metrohm 836 Titrando Karl Fischer titrator, cylinder volume 20 mL. The reagent Hydranal-Composite 5 and the data-processing program Tiamo (version 1.2.1) were used in these analyses. The Karl Fischer titrator was calibrated with distilled water before each measurement series. The polarity of ILs was evaluated (and E_T^N calculated) according to the described [4] method using

Reichardt's dye and a PerkinElmer Lambda 25 UV/Vis spectrophotometer. Data were processed with the Lambda 25 UV WinLab software. Thermogravimetric analysis was performed on an SII Exstar6000 TG/DTA 6300 instrument at a heating rate of 10 °C/min.

Syntheses of ionic liquids

1,3-Dimethylimidazolium dimethyl phosphate (3a). 1-Methylimidazole (8.2 g, 0.10 mol) and trimethyl phosphate (14 g, 0.10 mol) were mixed at room temperature under argon and with vigorous stirring, then heated to 80 °C and stirred at this temperature for 24 h. The mixture was cooled, then washed with dry diethyl ether, the liquid was separated and dried in vacuum (0.5 Torr) for 4 h at 80 °C. The IL (**3a**, 22 g, 99%) was obtained as a yellow liquid. ¹H NMR spectrum (400 MHz, DMSO-d₆, ppm) δ = 9.32 (1H, s, NCHN); 7.72 (2H, dd, NCH=CHN, *J* = 1.4 Hz, 0.9 Hz); 3.85 (6H, s, CH₃NCHNCH₃); 3.25 (6H, d, P(OCH₃)₂, *J* = 10.3 Hz).

1,2,3-Trimethylimidazolium dimethyl phosphate (3b). 1,2-Dimethylimidazole (9.6 g 0.10 mol) and trimethyl phosphate (14 g, 0.10 mol) were mixed at room temperature under argon and with vigorous stirring, then heated to 80 °C and stirred at this temperature for 1 h. Acetonitrile (20 mL) was added and the mixture was stirred at 80 °C for 23 h. The mixture was left for 16 h, the precipitate was separated and dried in vacuum (0.5 Torr) for 4 h at 80 °C. The IL (**3b**, 22 g, 95%) was obtained as a colorless powder with m.p. 86–88 °C. ¹H NMR spectrum (400 MHz, DMSO-d₆, ppm) δ = 7.62 (2H, s, NCH=CHN); 3.75 (6H, s, CH₃NCH₂NCH₃); 3.23 (6H, d, P(OCH₃)₂, *J* = 10.3 Hz); 2.55 (3H, s, NC(CH₃)N).

1-Butyl-3-methylimidazolium dimethyl phosphate (3c). This IL (**3c**) was prepared in a similar way than a previous example of IL (**3a**). The product (**3c**, 26 g, 98%) was obtained from 1-butylimidazole (12 g, 0.10 mol) and trimethyl phosphate (14 g, 0.10 mol). ¹H NMR spectrum (400 MHz, DMSO-d₆, ppm) δ = 9.44 (1H, s, NCHN); 7.82 (1H, s, NCH=CHN); 7.75 (1H, s, NCH=CHN); 4.17 (2H, t, CH₃CH₂CH₂CH₂N, *J* = 7.2 Hz); 3.86 (3H, s, CH₃N); 3.25 (6H, d, P(OCH₃)₂, *J* = 10.3 Hz); 1.76 (2H, quintet, CH₃CH₂CH₂CH₂N, *J* = 7.4 Hz); 1.25 (2H, sextet, CH₃CH₂CH₂CH₂N, *J* = 7.5 Hz); 0.89 (3H, t, CH₃CH₂CH₂CH₂N, *J* = 7.4 Hz).

1-Butyl-2,3-dimethylimidazolium dimethyl phosphate (3d). This IL (**3d**) was prepared in a similar way as (**3b**). The product (**3d**, 9.2 g, 82 %) with m.p. 89–91 °C was obtained from 1-butyl-3-methylimidazole (5.6 g, 0.040 mol) and trimethyl phosphate (5.6 g, 0.040 mol). ¹H NMR spectrum (400 MHz, DMSO-d₆, ppm) δ = 9.44 (1H, s, NCHN); 7.68 (2H, dd, NCH=CHN, *J* = 8.0 Hz, 1.9 Hz); 4.11 (2H, t, CH₃CH₂CH₂CH₂N, *J* = 7.3 Hz); 3.76 (3H, s, CH₃N); 3.24 (6H, d, P(OCH₃)₂, *J* = 10.43 Hz); 2.58 (3H, s, NC(CH₃)N); 1.68 (2H, quintet, CH₃CH₂CH₂CH₂N, *J* = 7.5 Hz); 1.28 (2H, sextet, CH₃CH₂CH₂CH₂N, *J* = 7.5 Hz); 0.90 (3H, t, CH₃CH₂CH₂CH₂N, *J* = 7.4 Hz).

Condensation Reactions in Ionic Liquid Media

Ethyl 2-cyano-3-phenylpropenoate (7). Benzaldehyde (0.53 g, 5.0 mmol), ethyl cyanoacetate (0.57 g, 5.0 mmol), and 1,3-dimethylimidazolium dimethyl-phosphate (**3a**, 1.11 g, 5.0 mmol) were stirred at 90 °C for 1 h. The reaction mixture was cooled to room temperature and extracted with diethyl ether (5×2 mL). The combined ether solution was washed with water (2×2 mL), dried

with sodium sulphate for 16 h and evaporated. The residue was crystallized from ethanol. The colorless product **7** (0.70 g, 69%) was obtained with m.p. 50–51 °C (lit. [5] m.p. 51–53 °C). ¹H NMR spectrum (400 MHz, DMSO-d₆, ppm) δ = 8.13 (s, 1H, HC=); 7.79–7.33 (m, 5H, HC_{Ar}); 4.23 (q, 2H, -CH₂O, *J* = 7.1 Hz); 1.42 (t, 3H, CH₂CH₃, *J* = 7.1 Hz).

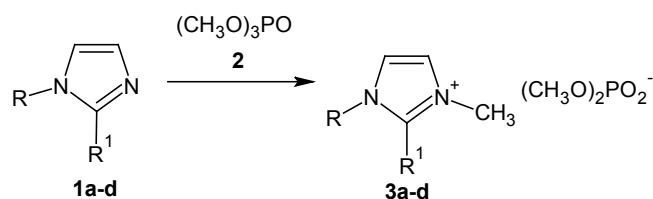
Syntheses in other ILs (**3b–d**, 5 mmol of reagents in every experiment) were performed in a similar way; 0.5 mmol (10 mol %) of catalyst were added in those reactions where extra catalysts were used – ammonium acetate (0.04 g), or sodium acetate (0.04 g), or glycine (0.04 g), or *L*-proline (0.06 g). Results of all experiments are presented on Fig. 1–4.

Cinnamic acid (9). Benzaldehyde (0.53 g, 5.0 mmol), malonic acid (0.78 g, 7.5 mmol, added in several small portions to the reaction mixture), and 1,3-dimethylimidazolium dimethylphosphate (**3a**, 1.11 g, 5.0 mmol) were stirred at 140 °C for 1 h, then the mixture was cooled to 90 °C. Water (5 mL) was added to the stirred mixture, then the solution was allowed to cool down at 4 °C. The precipitate was separated and dried in air for 24 h. The product (**9**, 0.36 g, 48%) was obtained with m.p. 134–135 °C (reported m.p. 133 °C [6]). ¹H NMR spectrum (400 MHz, DMSO-d₆, ppm) δ = 7.96 (1H, d, C_{Ar}-CH=, *J* = 16.0 Hz); 7.73–7.44 (5H, m, HC_{Ar}); 6.75 (1H, d, =CH-COOH, *J* = 16.0 Hz).

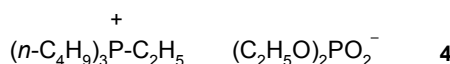
Syntheses of cinnamic acid in other ILs (**3b–d**, 5 mmol in every experiment) as well as in a commercially available phosphonium ionic liquid CYPHOS IL 169 (**4**) were performed in a similar way, with the results presented in Figure 5.

RESULTS AND DISCUSSION

Imidazolium dialkyl phosphates with different length of alkyl group at N(1) atom (Me or Bu) and different substituents at C(2) atom (H or Me) (**3a–d**) were investigated in order to assess the utility of these ILs in organic synthesis, especially the impact of their hydrophobicity and possible hydrogen bonding on the yields of investigated reactions. Alkylation of substituted imidazoles (**1**) with trimethyl phosphate (**2**) were used for the syntheses of ILs (**3**) according to a method slightly modified from that previously published [3], the yields of ILs (**3**) reaching 96–99%. The syntheses were performed without any solvent, and the products (**3**) were purified by washing with diethyl ether or by crystallisation from acetonitrile.



- a) R = CH₃; R¹ = H; b) R = CH₃; R¹ = CH₃;
c) R = *n*-C₄H₉; R¹ = H; d) R = *n*-C₄H₉; R¹ = CH₃



ILs (**3**) are viscous liquids if the substituent at the C(2) atom is hydrogen and solids if it is a methyl group. All ILs (**3**) are highly hygroscopic compounds, and were dried *in vacuo* at 80 °C for 4 hours. Imidazolium dialkylphosphates (**3**) were characterized by ¹H NMR spectra, Karl Fischer titration, thermogravimetry and polarity measurements according to Reichardt's method [4] (Table 1). ¹H NMR spectra of two described ILs (**3a,c**) fully corresponded to the published data [3]. Spectra of two other ILs (**3b,d**) were different from the spectra of **3a,c** – the C(2)–H proton signals were absent and new signals of C(2)–CH₃ protons appeared.

Table 1. Characteristics of the used imidazolium dialkyl phosphates

IL	Yield, %	m.p., °C	pH	Water, %	Decomposition temperature, °C	E_T^N
3a	99	liquid	2.3	0.54	302	0.576
3b	95	86–88	2.8	0.43	290	n/a**
3c	98	liquid	2.5	1.23	315	0.601
3d	96	89–91	3.1	0.85	297	n/a**
4	*	liquid	1.9	0.42	n/a**	n/a**

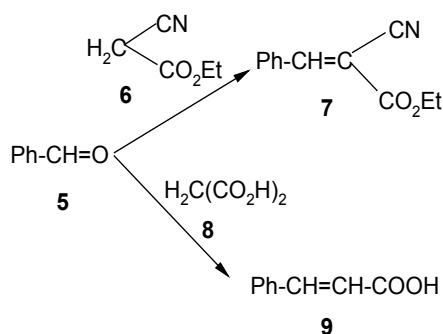
* Commercially purchased ionic liquid CYPHOS® IL 169, produced by Cytec Industries, Inc.

** Data not available.

The obtained ILs (**3**) contained a small amount of water ($\leq 1.5\%$), most likely due to the high hygroscopicity of these compounds. Thermal decomposition thresholds for the investigated ILs were determined by thermogravimetric analysis (TGA). All ILs (**3**) were thermally stable up to 290 °C, the decomposition temperature rising with the increasing length of alkyl chains in the cations ((**3c,d**) versus (**3a,b**)). The total polarity of ILs (**3**) was measured according to the published method [4] for liquid ILs (**3a,c**) and their Reichardt's constant values (E_T^N) were found to be 0.6, making these materials of similar polarity to lower alcohols. Ethanol has been the most frequently used molecular liquid (organic solvent) for the condensation reactions that we planned to perform in ILs (**3**), so the observed similarity seemed to us quite beneficial. Condensation reactions usually demand the presence of a basic or acidic catalyst. It is difficult to characterize the true acid-base properties of neat ILs. Therefore the acidity was determined for 0.1 M aqueous solutions. We found that these solutions were acidic (pH 2.3–3.1), a similar phosphonium dialkyl phosphate (**4**) demonstrating even higher acidity. It remains to assume that hydrolysis of dialkylphosphate anion took place in water solutions, resulting in increased acidity. Water is also expected to be present during the use of ILs in condensation reactions and therefore catalytic amounts of acids should always be present in these reactions.

ILs are quite frequently used as reaction media (solvents) or as catalysts in organic syntheses. Both of these functions have rarely been performed by one type of IL. Such reactions are discussed in the present investigation, where the

ILs (**3**) served both as solvents and as catalysts. Reactions of benzaldehyde with ethyl cyanoacetate (**6**) and with malonic acid (**8**) were tested and the yields of isolated products (**7** and **9**) were measured in order to appreciate the impact of IL (**3**) structure on the reaction progress.



Condensation reactions of benzaldehyde with ethyl cyanoacetate (**6**) were performed at the same temperature (90 °C) in the media of all ILs (**3**) and some organic solvents – 1-butanol and pyridine, either in absence or in the presence of other catalysts which have been traditionally used in these reactions. A reaction was also performed in the medium of a phosphonium IL – tributylethylphosphonium diethyl phosphate (**4**), in order to have some insight about the role of the cation. Yields of isolated product (**7**) from these experiments are presented in the Fig. 1.

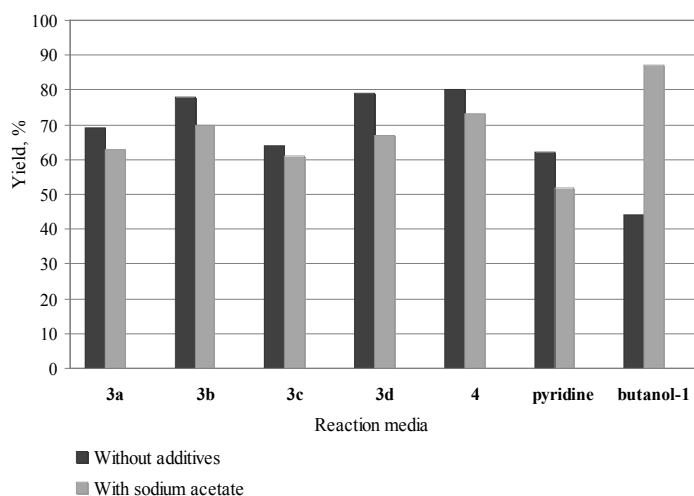


Fig. 1. Yields of isolated ethyl 2-cyano-3-phenylpropenoate (**7**) in various media (in the absence or presence of sodium acetate catalyst (10 mol %)).

The obtained results indicated that higher yields of the product (**7**) were achieved in ILs with a methyl group at the C₂ atom of the cation (**3b** and **3d**), compared to those with a C(2)–H bond (**3a**, **3c**). The IL (**3**) media offered higher yields of the product (**7**) without using other catalysts than the reactions in organic solvents, especially in 1-butanol where these yields were lower by almost two times. The yields after addition of sodium acetate as an extra

catalyst to IL media did not improve, but rather slightly decreased, while the same catalyst nearly doubled the yield in BuOH medium. This observation confirmed the hypothesis that ILs (**3**) serve both as reaction media and as catalysts in the investigated Knoevenagel reactions, with the highest yields reached in the ILs **3d** and **4**. The latter observation directed our attention towards considering the impact of IL cation structures on these reactions. It is worth mentioning that the addition of sodium acetate catalyst to the reaction mixture in pyridine also resulted in a lower yield of the product (**7**), similar to what was observed in ILs.

Four traditional condensation reaction catalysts have been tested in IL media (Fig. 2). Apart from L-proline, these extra catalysts slightly lowered yields of the product.

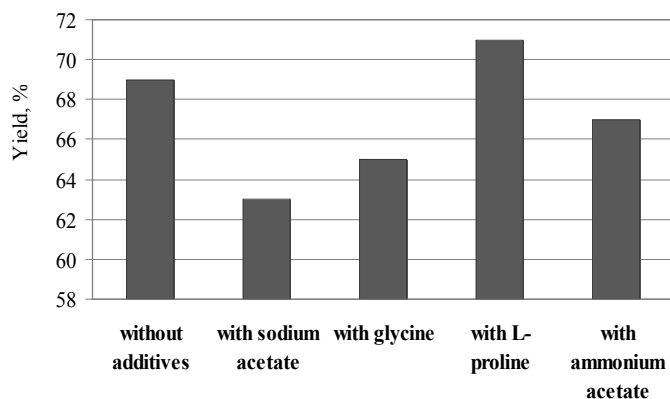


Fig. 2. Yields of isolated ethyl 2-cyano-3-phenylpropenoate in the medium of 1,3-dimethylimidazolium dimethyl phosphate (**3a**) in the absence or presence of various extra catalysts (10 mol %).

Concentrations of reagents in IL media were significantly higher than in traditional solvents, and a decrease of reaction time was therefore expected. Experiments in IL (**3b**) confirmed this hypothesis – the reaction was accomplished in 15–20 min (Fig. 3), and high yields of the product were isolated (75–78%). Longer heating of the reaction mixture even caused a slight decrease of the yield, most likely from degradation of the IL and, consequently, the more difficult purification of the product.

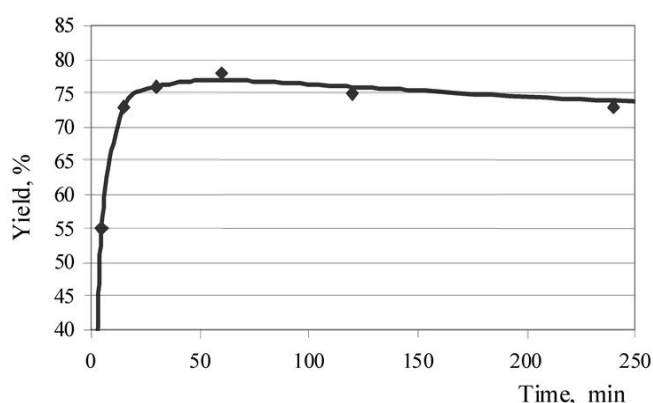


Fig. 3. Yields of isolated ethyl 2-cyano-3-phenylpropenoate (**7**) as a function of time in 1,2,3-trimethylimidazolium dimethyl phosphate (**3b**) medium without any extra catalyst.

A reported [1, 2] advantage of ILs over traditional low-molecular solvents is the possibility to use ILs several times without any purification, which was checked also in this investigation. The yield of the isolated product (**7**) remained unchanged over five uses of the the same IL portion (**3b**) (Fig. 4). The product was isolated from reaction mixture by extraction with diethyl ether, followed by an evaporation of extracts. The IL (**3b**) remained pure enough for further use after each experiment. Hence, the option of reusing ILs (**3**) in condensation reactions is a real advantage for practical application of such reactions.

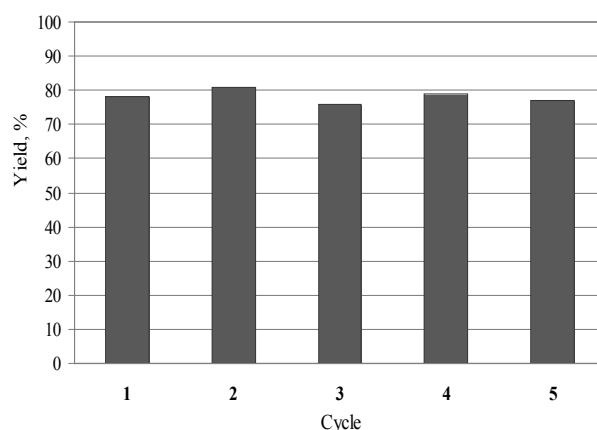


Fig. 4. Yields of isolated ethyl 2-cyano-3-phenylpropenoate (**7**) in experiments where 1,2,3-trimethylimidazolium dimethyl phosphate (**3b**) was reused several times as the reaction medium.

Cinnamic acid (**9**) also was prepared by condensation of benzaldehyde with malonic acid in the investigated IL media, albeit in modest yields (Fig. 5). Higher temperature (140 °C) was used in this reaction than in the reaction with ethyl cyanoacetate to provide full decarboxylation of the intermediate dicarboxylic acid. The product (**9**) was isolated by treating the reaction mixture with boiling water, followed by cooling the mixture to room temperature and separating the precipitate.

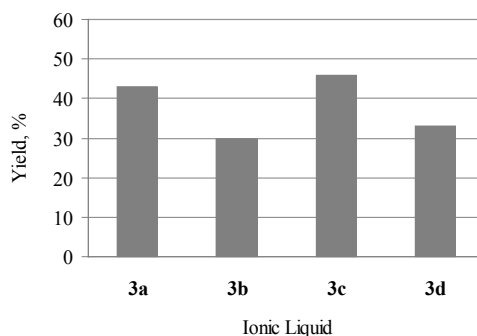


Fig. 5. Yields of isolated cinnamic acid (**9**) in the investigated ionic liquid media.

The moderate yields in ILs (only 30–48%) were clearly lower than the yields obtained in common organic solvents. The higher yields among ILs were observed in those cases when the imidazolium cation was not substituted at C(2) (**3a,c**). The modest yields of the product might be partly explained by the faster decarboxylation of malonic acid, compared to its condensation with benzaldehyde. The overall yield could not be increased above 30–48% with

longer reaction time (up to two hours), stepwise addition of malonic acid to the reaction mixture in small portions, heating the reaction mixture for one hour at 90 °C before raising the temperature to 140 °C and further heating for another hour, as well as the addition of extra catalysts (glycine or sodium acetate).

Hence, we have presented a proof that the structure of ILs is the most important factor that determines condensation reaction outcome, and ILs must therefore be optimally selected for every particular case.

CONCLUSIONS

1,3-Dialkylimidazolium dimethyl phosphates are stable ionic liquids at temperatures ≤ 290 °C, their polarity being comparable with that of ethanol. Benzaldehyde condensation with ethyl cyanoacetate provided 75-80% yields in the mentioned media and the reaction was complete in 15–20 minutes at 90 °C. Higher yields were achieved in less polar ionic liquids. The similar reaction with malonic acid was less effective, the yields of cinnamic acid reaching only 30–48% at 140 °C.

Acknowledgement

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1,3-DIALKILIMIDAZOLIJA DIMETILFOSFĀTI – EFEKTĪVI KONDENSĀCIJAS REAKCIJU ŠĶĪDINĀTĀJI UN KATALIZATORI

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K O P S A V I L K U M S

Aprakstīta 1,3-dialkilimidazolijs dimetilfosfātu sintēze un noteikti to raksturlielumi – mitrums, sadalīšanās temperatūra, ūdens šķīduma pH vērtības un polaritātes novērtējums pēc Reiharta skalas. Benzaldehīda kondensācijas reakcijas ar etilciānacetātu un ar malonskābi pētītajos jonu šķīdumos parādīja, ka jonu šķīdumi izmantojami vienlaikus par kondensācijas reakciju vidi un to katalizatoriem. Citu šīm reakcijām raksturīgo katalizatoru (glicīna, L-prolīna, amonija acetāta vai nātrija acetāta) pievienošana neveicināja reakcijas produktu iznākumu palielināšanos, bet pat izsauca nelielu to samazināšanos.

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