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HYDROPHILIC IONIC LIQUIDS IN THE SYNTHESIS OF HANTZSCH ESTER

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Hantzsch ester synthesis was investigated using (2-hydroxyethyl)-ammonium carboxylates, polar and hydrophilic ionic liquids possessing low toxicity and high biodegradability. The reaction rates and yields of the products in ionic liquids were greater than those in common organic solvents. The relationship between the structure of the ionic liquid used and the structure of the heterocyclic compound was investigated.

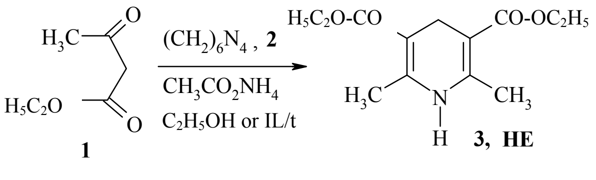
Key words: *ionic liquids, Hantzsch ester, synthesis.*

INTRODUCTION

Ionic liquids (ILs) have replaced successfully common organic solvents in syntheses of different organic compounds. The utilization of ILs provides many advantages in comparison with the use of conventional solvents [1]. The possibility of designing the optimal structures for the chosen application, protection of the environment, higher reaction yields and shorter reaction times are most common advantages of the utilization of ILs.

ILs are also used for formation of various heterocyclic systems. A comprehensive review of the benefits of the application of ILs in these reactions has been published recently [2]. Hantzsch ester (HE) is an important heterocyclic compound [3], particularly it serves as a raw material for the preparation of pyridine derivatives and medicines. Several methods of HE synthesis have been described in the literature; the most convenient one involves utilization of hexamethylenetetramine instead of formaldehyde and ammonia. Ethyl 3-oxobutanoate (**1**, acetoacetic ester), hexamethylenetetramine (**2**) and ammonium acetate transform into the Hantzsch ester (**3**, HE) when stirred at elevated temperature in ethanol or in different ILs [4]. Scheme 1 shows the chemical reaction leading to the production of HE:

Scheme 1



The application of traditional ILs [4] has shown the possibility of producing HE in IL media and some benefits of the method. 1-Alkylpyridinium, 1,3-di-alkylimidazolium and tetraalkylammonium salts were examined as ILs in these experiments. The structures of ILs have demonstrated an essential impact on the yields and rates of this cyclization reaction: the increasing of hydrophobicity of the cation decreases the yield of HE; more nucleophilic anions provide higher yields than other anions; aromatic and aliphatic cations show a similar behaviour, etc. [4]. Although acceptable yields of HE were obtained in ILs [4], the relatively high toxicity and low biodegradability of the used ILs have decreased the significance of these materials for use in the large-scale production of HE. In this paper, the application of novel ILs with better performance for HE syntheses is presented.

EXPERIMENTAL

Materials

Ionic liquids (**6**, **7**, **8**) were prepared by the reaction of a corresponding amine with a carboxylic acid as described elsewhere [5, 6]. Ammonium acetate, ethyl acetoacetate, and hexamethylenetetramine were of analytical grade (*Aldrich*) and were used as received without any purification.

Syntheses

Synthesis of hydrophilic ionic liquid (2-hydroxyethyl)ammonium formate (6a). Formic acid (90%, 4.08 g; 79.9 mmol) was added dropwise to 2-hydroxyethylamine (**4a,** 4.88 g; 79.9 mmol) at ~0 °C while stirring vigorously. The mixture was stirred for an extra 24 h at room temperature and then was dried for approximately 3 h at 50 °C under vacuum (1–2 Torr). The colorless viscous liquid (**6a)** was obtained (8.47 g; 99 %); the content of the basestock was ≥99% (examined by HPLC/MS). ^{1}H NMR spectrum (400 MHz; D_2O; Me_4Si) δ, ppm: 8.4 (1 H, s, $\underline{H}$–CO_2), 6.1 (4 H, m, $N\underline{H_3}$ + $O\underline{H}$), 3.5 (2 H, t, $C\underline{H_2}$–O), 2.8 (2 H, t, $C\underline{H_2}$–N); IR spectrum (Nujol) υ_{max}, cm^{-1}: 3500–3100 (NH + OH); 1750–1600 (C=O + NH). Water (moisture) content was 2.2 % (measured by the Karl Fisher method). Other ILs (**6 - 8**) were prepared and characterized in a similar way.

Synthesis of the Hantzsch ester (3) in the ionic liquid (2-hydroxyethyl)-ammonium formate (6a). (2-Hydroxyethyl)ammonium formate (**6a**, 0.68 g, 6.3 mmol), ammonium acetate (200 mg, 2.6 mmol) and hexamethylenetetramine (**2**, 80 mg, 0.57 mmol) were stirred at slightly elevated temperature (≤30 °C) until a homogeneous solution was formed. Ethyl acetoacetate (**1**, 0.8 ml, 6.3 mmol) was added and the mixture was stirred at 100 °C for 1 h. After cooling to 80 °C, water (50 ml) was added to the reaction mixture. The mixture was heated to 100 °C under vigorous stirring to dissolve the ionic liquid in water. After cooling to room temperature, the precipitate was separated, washed with water (2×4 ml) on the filter and dried. Pure HE (360 mg, 45 %) was obtained after crystallization from ethanol with m.p. 177–178 °C (m.p. 176–183 °C reported in [7]). ^{1}H NMR spectrum (400 MHz; $CDCl_3$; Me_4Si), δ, ppm: 1.30 (t, 6H, $C\underline{H_3}$–CH_2), 2.22 (s, 6H, =C(NH)–$C\underline{H_3}$), 3.28 (s, 2H, =$C(CO_2C_2H_5)$–$C\underline{H_2}$–$C(CO_2C_2H_5)$=), 4.20 (q, 4H, $C\underline{H_2}$–O); 5.18 (s, 1H, N–$\underline{H}$).

Other syntheses of HE were performed in a similar manner in ILs **6**, **7** and **8**. The results are presented in Figs. 1–4, respectively.

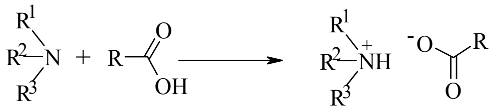
Measurements

^{1}H NMR spectra were examined with a Varian 400 MR spectrometer, using D_2O or $CDCl_3$ as solvents and TMS as an internal standard. FT-IR spectra were examined on an *Avatar 330 FT-IR* Thermo Nicolet spectrometer in Nujol mineral oil. HPLC/MS analyses were performed on chromatograph (*Waters Alliance 2690*). The stationary phase was Atlantis HILIC Silica (2.1×150 mm, particle size of the sorbent 3 μm). The mobile phase was water–methanol (3/7; v/v), with a flow rate of 0.2 ml/min at 30 °C. The detector was the mass spectrometer (*Micromass® Quattro Micro™ API*) with electrospray ionization. Water (moisture) content in the ILs was measured by the Karl Fisher method using the Karl Fischer titrator *836 Titrant Metrohm*. Reagent *Hydranal-Composite 5*, cylinder volume 20 ml and the data processing program *Tiamo* (version 1.2.1.) were used in these analyses. The Karl Fischer titration instrument was calibrated with distilled water before each measurement series. The pH of the ILs in water solution (0.10 mol/l) were measured using pH meter (*Adrona AD1 405*) equipped with a *Hamilton POLYPLASTIC BNC* glass electrode; the accuracy of the instrument was 0.01 pH units. Theoretical pH values were calculated as described in the literature [8]. The polarity of the ILs was evaluated (and E_T^N was calculated) according to the method using Reichardt's dye and a *Perkin Elmer Lambda 25* UV/VIS spectrometer [9]. Data were processed with the program *Lambda 25 UV Win Lab*.

RESULTS AND DISCUSSION

We have recently shown that significantly hydrophilic and highly polar (2-hydroxyethyl)ammonium carboxylates can perform well as reaction media and catalysts in condensation reactions [5, 6]. Their use in HE production was expected to have similar good results. The (2-hydroxyethyl)ammonium carboxylates are not only the cheapest ILs available, but also have high biodegradability (60–95% during 5 days) and low toxicity (LC_{50} ~ 5–9 g/l) [5, 6] when determined according to the standard methods [10, 11]. These properties may be explained by the close similarity of the ILs with choline, a water-soluble natural product. The ILs used in this work were prepared with high yields (≥97 %) by a simple reaction between the corresponding amine and a carboxylic acid (Scheme 2).

Scheme 2



4 **5** **6, 7, 8**

6a) $R^1 = CH_2CH_2OH$; $R^2 = R^3 = H$; $R = H$
6b) $R^1 = R^2 = CH_2CH_2OH$; $R^3 = H$; $R = H$
6c) $R^1 = R^2 = R^3 = CH_2CH_2OH$; $R = H$
7a) $R^1 = CH_2CH_2OH$; $R^2 = R^3 = H$; $R = CH_3$
7b) $R^1 = R^2 = CH_2CH_2OH$; $R^3 = H$; $R = CH_3$
7c) $R^1 = R^2 = R^3 = CH_2CH_2OH$; $R = CH_3$
8a) $R^1 = CH_2CH_2OH$; $R^2 = R^3 = H$; $R = CH_3CH(OH)$
8b) $R^1 = R^2 = CH_2CH_2OH$; $R^3 = H$; $R = CH_3CH(OH)$
8c) $R^1 = R^2 = R^3 = CH_2CH_2OH$; $R = CH_3CH(OH)$

The ILs were characterized by ^1H NMR and IR, and HPLC/MS analytical methods.

Hydrophilic and polar ILs (**6**, **7**, **8**) perform well as tunable reaction media in the reactions investigated. HE forms in high yields and rapidly in the ionic liquid media (Fig. 1). Acceptable yields of the isolated and crystallized product (75–80%) in ILs can be reached in 30 min, and the product does not contain the corresponding pyridine derivative – the oxidized form of HE.

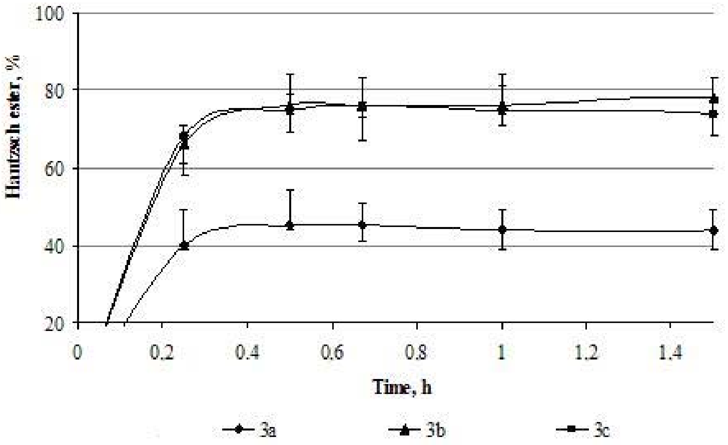


Fig. 1. HE (**3**) formation rates in three (2-hydroxyethyl)ammonium formates (**6a-c**) (molar ratio acetoacetic ester : hexamethylenetetramine : ammonium acetate : IL = 6.3 : 0.57 : 2.6 : 6.3; 100 °C, yields of the isolated product).

Extra catalysts (sodium hydrogen phosphate, glycine, etc.), which used to be beneficial in the Hantzsch synthesis even in common ILs [4], had no effect on these hydrophilic ILs (**6**, **7**, **8**). It is not unexpected, as these ILs are ammonium salts capable of forming a buffer system. Calculated (according to [8]) and measured pH values of ILs (**6**, **7**, **8**) in water solutions differ only slightly and cover with a pH range of 5.8–7.2. Obviously, pH values are valid only for water solutions, and ILs form a completely different environment around dissolved

Table 1. **pH values of water solutions of ionic liquids (6, 7, 8)**[a].

IL	pH	
	found	calculated[b]
6a	6.3 ± 0.5	6.65
6b	6.5 ± 0.2	6.34
6c	5.7 ± 0.6	5.78
7a	6.9 ± 0.3	7.15
7b	7.1 ± 0.5	6.84
7c	6.4 ± 0.1	6.28
8a	6.7 ± 0.5	6.68
8b	7.1 ± 0.4	6.38
8c	6.1 ± 0.5	5.83

Notes: [a] concentrations of ILs in water 0.10 mol/l;
[b] calculated according to [8].

substances. Meanwhile, the ILs investigated (**6**, **7**, **8**) were highly polar substances – their Reichardt's polarity indices E_T^N were in the range of 0.89–1.00 [5, 6]. These values are close to that of water (E_T^N = 1.00). Therefore it is reasonable to assume that acid–base properties of ILs might form a dependence similar to that measured in water solutions (Table 1) and form their own pseudo-pH range.

Small differences in pH values of ILs cause substantial differences in the yields of HE prepared in various ILs (Fig. 2). The formation of the heterocycle HE goes through various single steps, all being pH dependent. Therefore, the observed relationship between the yield of HE and the mentioned pseudo-pH level in the ILs used shows that an acidic medium is more favorable for the HE synthesis. The optimal pseudo-pH value is a bit more lower (acidic) than the pH value in molecular liquids, in which the acetic acid is the first.

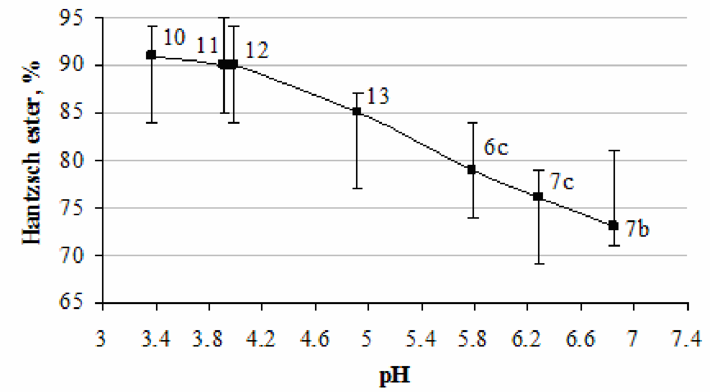


Fig. 2. The impact of the pH of ILs (measured in water) on yields of the isolated HE synthesized in IL media (after 1 h at 100 °C; molar ratio ethyl acetoacetate : hexamethylenetetramine : ammonium acetate : IL = 6.3 : 0.57 : 2.6 : 6.3): **6c** – tris(2-hydroxyethyl)ammonium formate; **7b** – bis(2-hydroxyethyl)ammonium acetate; **7c** – tris(2-hydroxyethyl)ammonium acetate; **10** – butylmethylimidazolium tetrafluoroborate; **11** – butylmethylimidazolium bromide; **12** – butyldimethylimidazolium bromide; **13** – dodecylmethylimidazolium bromide.

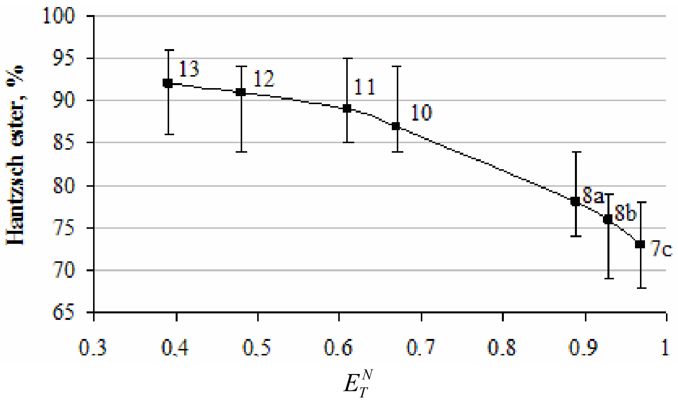


Fig. 3. The impact of the polarity of ILs on the yields of the isolated HE (after 1 h at 100 °C; molar ratio ethyl acetoacetate : hexamethylenetetramine : ammonium acetate : IL = 6.3 : 0.57 : 2.6 : 6.3): **7c** – tris(2-hydroxyethyl)ammonium acetate; **8a** – (2-hydroxyethyl)ammonium lactate; **8b** – bis(2-hydroxyethyl)-ammonium lactate**;** **10** – butylmethylimidazolium tetrafluoroborate; **11** – butylmethylimidazolium bromide; **12** – butyldimethylimidazolium bromide; **13** – tetrabutylammonium bromide.

The total polarity of the reaction medium is another important factor that affects the reaction results in ILs. Our previous experiments [4] have confirmed that higher HE yields provide more hydrophilic ILs. Unfortunately, the hydrophilicity comprises only part of the total polarity of every solvent. Experiments in investigated ILs (**6**, **7**, **8**) indicated the fact that ILs possessing mild polarity are more suitable for reaching high yields of HE than high polarity ILs, the increased total polarity decreasing the product yields by 10–15% (Fig. 3).

Both the cation and the anion of an IL affect reacting substances (including the transition state), but each in a different way. A comparison of investigated ILs discloses two tendencies: monosubstituted (2-hydroxyethyl)ammonium salts as well as all ammonium salts containing the formate anion are less applicable media for the Hantzsch ester synthesis (Fig. 4).

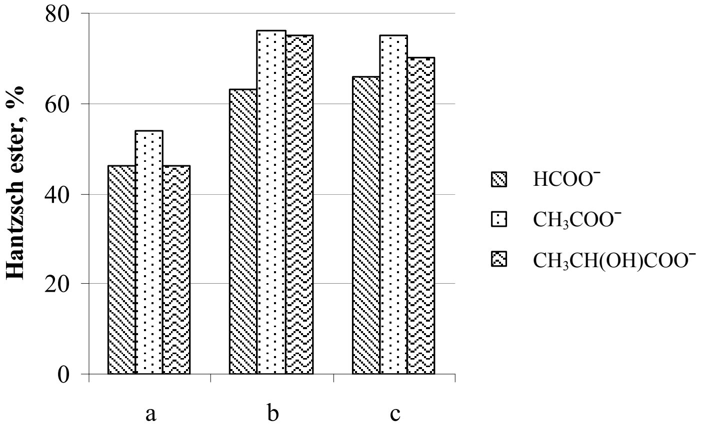


Fig. 4. Comparison of the HE (**3**) yields in investigated ILs – formates (**6 a**–**c**), acetates (**7 a**–**c**) and lactates (**8 a**–**c**) (yields of isolated and crystallized product after 15 min at 100 °C).

The different basicity of carboxylate anions and acidity of substituted ammonium cations as well as steric hindrances in di- and trisubstituted ammonium cations that form close ion pairs with their anions are likely to be responsible for the observed phenomenon. Accordingly, the application of cheap, nontoxic and highly biodegradable ILs in the preparation of 1,4-dihydropyridines allows the use of harmful and dangerous organic solvents to be avoided.

CONCLUSIONS

Yields of the Hantzsch ester syntheses in hydrophilic, polar, practically nontoxic and highly biodegradable ionic liquids – (2-hydroxy-ethyl)ammonium carboxylates – proceed more rapidly than in ethanol solution; the yields of isolated pure product reach 70–80 % in 15–30 min. The highest yields are provided by more acidic and less polar ionic liquids. Acetate and lactate anions as well as bis- and tris-(2-hydroxyethyl)ammonium cations are appropriate structures of ionic liquids for the synthesis of 1,4-dihydropyridine derivatives.

Acknowledgements

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HIDROFILIE JONU ŠĶIDRUMI HANČA ESTERA SINTĒZĒ

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KOPSAVILKUMS

Pētīta Hanča estera sintēze (2-hidroksietil)amonija karboksilātu (jonu šķidrumi ar zemu toksiskumu un augstu biodegradācijas līmeni) vidēs. Reakciju ātrumi un iznākumi jonu šķidrumos ir augstāki nekā parastajos organiskajos šķīdinātājos. Demonstrēta iespēja vislabākā veidā pielāgot jonu šķidrumu struktūru šī nozīmīgā heterocikliskā savienojuma sintēzei.

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