

SYNTHESIS OF β -NITROSTYRENE IN HIGHLY HYDROPHILIC IONIC LIQUID MEDIA

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The condensation reaction of benzaldehyde with nitromethane that resulted in the formation of β -nitrostyrene was studied in ionic liquid media - (2-hydroxyethyl)ammonium carboxylates (formates, lactates, acetates) without application of any other catalyst. The dependence of product yield on the ionic liquid cation and anion structure, the polarity of the ionic liquid and the pseudo-pH value of the reaction medium was investigated. The highest yield of the condensation reaction product - β -nitrostyrene was achieved in (2-hydroxyethyl) ammonium formate medium.

Key words: ionic liquids, condensation reaction, β -nitrostyrene.

INTRODUCTION

β -Nitrostyrenes are convenient starting materials for constructing medicinal substances, heterocyclic compounds, etc. [1–3]. Usually these nitroalkenes are obtained by aromatic aldehyde condensation with the corresponding nitroalkanes [4]. The reaction is catalysed by acids or bases, and the best yields have been obtained by using primary or secondary amine catalysts in acetic acid medium. The β -nitrostyrenes usually have been isolated in moderate to good yields. The most significant side reactions were trimerisation of β -nitrostyrenes into 1,3,5 -trisubstituted arenes [5] or polymerisation giving intractable structures [4]. These observations suggest a need for improved methods of β -nitrostyrene synthesis on a preparative scale.

EXPERIMENTAL

Materials

Benzaldehyde and nitromethane (Sigma-Aldrich) were distilled at reduced pressure before use. Ionic liquids were prepared by the reaction of (2-hydroxyethyl) amines with the corresponding carboxylic acids as described earlier [6, 7].

Measurements

The ^1H NMR spectra were recorded on a Varian 400-MR magnetic resonance spectrometer, using DMSO-d_6 as a solvent and TMS as an internal standard. The polarity of ILs was evaluated (and E_T^N calculated) according to a described [8] method using Reichardt's dye and a PerkinElmer Lambda

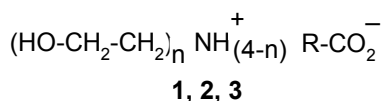
25 UV/VIS spectrophotometer. Data were processed with the Lambda 25 UV WinLab software. The pH of water solutions (1.0 mol/L) of ILs was measured with an Adrona AD1 405 pH meter.

Synthesis in ionic liquid media

***β*-Nitrostyrene.** Benzaldehyde (0.52 g, 5.0 mmol), nitromethane (0.31 g, 5.0 mmol), and (2-hydroxyethyl)ammonium formate (1.51 g, 10.0 mmol) were stirred at room temperature for 24 h. The reaction mixture was transformed into viscous oil. Water (10 mL) was added to the mixture and stirring was continued until the oil transformed into a yellow solid. The latter was separated by filtration, washed with water, dried in air, and crystallized from ethanol. Crystalline ***β*-nitrostyrene** (0.67 g, 90 %) was obtained with m.p. 57.5–58.5 °C (m.p. 58–59 °C in [4]). ¹H NMR spectrum (δ, ppm): 8.23 (1H, d, *J* = 14 Hz); 8.13 (1H, d, *J* = 14 Hz); 7.87 (2H, d, *J* = 5 Hz); 7.55 – 7.45 (3H, m).

RESULTS AND DISCUSSION

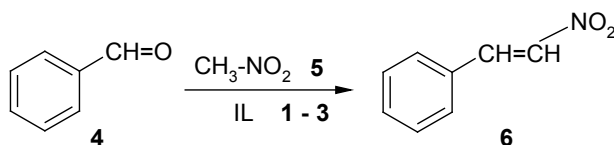
A systematic investigation of highly biodegradable low-toxicity ionic liquids (ILs) – (2-hydroxyethyl)ammonium carboxylates – has demonstrated the usefulness of these materials for condensation reactions. The ILs **1–3** can be easily prepared in high yields by a simple reaction of carboxylic acids with the corresponding (2-hydroxyethyl) amines [6, 7].



where: **1**) *n* = 1; **2**) *n* = 2; **3**) *n* = 3;
a) R = H; **b**) R = CH₃CH(OH); **c**) R = CH₃

The mentioned ILs have been recognized as non-hazardous solvents for organic syntheses that have successfully served both as reaction media and as catalysts for aromatic aldehyde condensation with activated methylene compounds. Therefore we explored the applicability of these ILs for the synthesis of ***β*-nitrostyrene**.

The reaction of benzaldehyde (**4**) with nitromethane (**5**) was performed in the highly hydrophilic (2-hydroxyethyl)ammonium carboxylate media at room temperature, and the resulting ***β*-nitrostyrene** (**6**) was separated from the reaction mixture by dissolving the ionic liquid in water. Yields of the isolated and crystallized product (**6**) reached 90 % under optimal conditions.



We tested nine previously described [6, 7] highly hydrophilic ionic liquids (**1a**, **1b**, **1c**, **2a**, **2b**, **2c**, **3a**, **3b**, **3c**) as media for this reaction. The ionic liquids

were characterized by various numbers of hydroxyl groups (1 to 3) and different anions (formate, lactate, acetate). Anions were selected on purpose to increase basicity starting from the less basic formate anion and going to the more basic acetate anion.

The yields of β -nitrostyrene (**6**) in the investigated condensation reaction turned out to be highly dependent on the structure of ILs used (**1a–3c**) (Fig. 1). The experimental comparison of ILs demonstrated a significant advantage of the ILs that were based on 2-aminoethanol (**1**), relative to the more substituted (2-hydroxyethyl)ammonium carboxylates (**2**, **3**). High-melting solids mainly formed when the condensation reaction was performed in media of *bis*- or *tris*-(2-hydroxyethyl)ammonium carboxylates (**2**, **3**). It means that ILs with branched ammonium cations were not favourable for obtaining pure condensation products. A small fraction of the benzaldehyde starting material remained unchanged in these experiments, and a significant amount of high-melting solid could be isolated from the reaction mixture. Most likely, these ILs promoted further transformation of the β -nitrostyrene into its trimers or polymers, as mentioned in literature [4, 5].

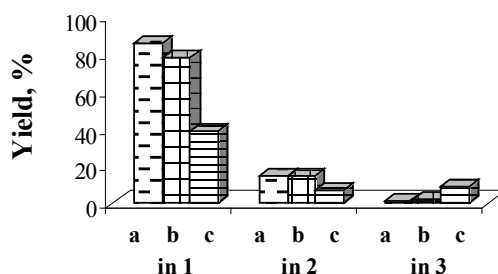


Fig. 1. The impact of the IL action and anion structure on the yield of β -nitrostyrene (**6**) (after 24 h at 25 °C temperature and benzaldehyde: nitromethane: ionic liquid molar ratio of 1:1:2).

In order to explain results, the total polarity of ionic liquids (expressed by the Reichardt's constant, E_T^N) and the obtained yields of β -nitrostyrene (**6**) were compared (Fig. 2). A rather narrow window of the total polarity turns out to be beneficial for the synthesis of the expected product. It corresponds approximately to the polarity of 0.89–0.94 on the Reichardt's scale and is more polar than the polarity of ethanol (0.65) and methanol (0.76) – the commonly used solvents for these reactions.

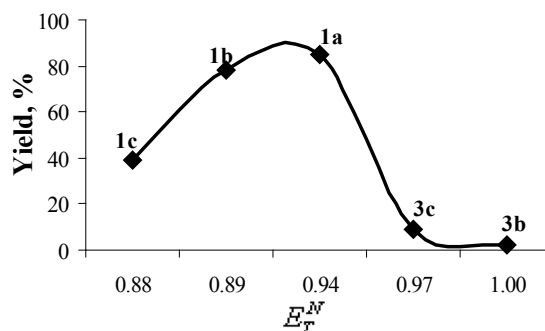


Fig. 2. The impact of the total polarity (E_T^N) of ILs on the yield of β -nitrostyrene (**6**) (after 24 h at 25 °C temperature and benzaldehyde: nitromethane: ionic liquid molar ratio of 1:1:2).

The investigated reaction traditionally has been catalyzed by a base or an acid. At present, no method is available for determination of the true acidity/basicity of ILs. The nearest approximation might be the acidity of the water solutions of investigated ionic liquids – their pseudo-pH values. Such an assumption seems to be valid because the total polarity of used ILs was quite close to that of water. Comparison of β -nitrostyrene (**6**) yields and the measured pseudo-pH of ILs again indicated only a narrow pseudo-pH value region (6.5–6.8) as advantageous for the formation of β -nitrostyrene with acceptable yields in this condensation reaction. The reaction in 1-methylimidazolium acetate (**7**) medium that had pH 6.0 in aqueous solution gave practically zero yield of the condensation product, and served as a comparison to condensation in other ILs.

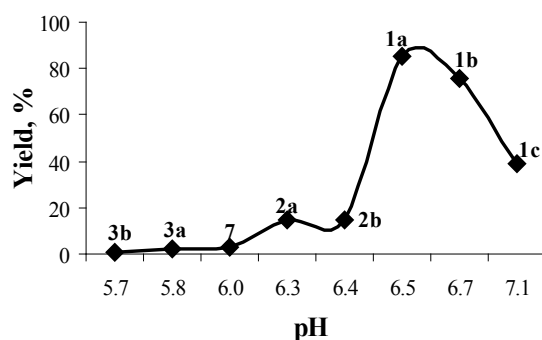


Fig.3. The impact of the IL pseudo-pH value on the yield of β -nitrostyrene (**6**) after 24 h at 25 °C temperature and benzaldehyde:nitromethane:ionic liquid molar ratio of 1:1:2; IL (**7**) – 1-methylimidazolium acetate).

At the end of synthesis in *bis*- and *tris*-(2-hydroxyethyl) ammonium carboxylates (**2**, **3**), the benzaldehyde - starting material could be detected in the reaction mixtures by HPLC only in negligible amounts. The main product of these reactions was a high-melting substance; most likely, it was the type of polymer mentioned in literature [4, 5] for similar condensation reactions. Apparently the formation of β -nitrostyrene occurred in these media, but the conditions were beneficial for its further transformations. Structural characterization of these polymeric side products was not attempted.

Hence, it can be asserted that (2-hydroxyethyl)ammonium formate is by far the best medium for β -nitrostyrene synthesis from benzaldehyde and nitromethane at room temperature and in the absence of any catalyst.

CONCLUSIONS

The condensation reaction of benzaldehyde with nitromethane proceeded in mild conditions – at room temperature and without any catalyst in media of highly polar ionic liquids – (2-hydroxyethyl)ammonium carboxylates. The β -nitrostyrene yield completely depended on the structure of used ionic liquid, its total polarity and the pseudo-pH value. The best yield of β -nitrostyrene could be obtained in the medium of (2-hydroxyethyl)ammonium formate.

REFERENCES

1. Milhazes, N., Calheiros, R., Marques, M.P., Garrido, J., Cordeiro, M.N.D.S, Rodrigues, C., Quinteira, S., Novais, C., Peixe, L., Borges, F. (2006). β -Nitrostyrene derivatives as potential antibacterial agents: A structure-property-activity relationship study. *Bioorg. Med. Chem.*, 14, 4078–4088.
2. Wang, W.Y., Hsieh, P.W., Wu, Y.C., Wu C.C. (2007). Synthesis and pharmacological evaluation of novel β -nitrostyrene derivatives as tyrosine kinase inhibitors with potent antiplatelet activity. *Biochem. Pharmacol.*, 74, 601–611.
3. Kotrusz, P., Toma, S., Schmalz, H.G., Adler, A. (2004). Michael additions of aldehydes and ketones to β -nitrostyrenes in an ionic liquid. *Eur. J. Org. Chem.*, 1577–1583.
4. Gairaud, C.B., Lappin, G.R. (1953). The synthesis of ω - nitrostyrenes. *J. Org. Chem.*, 18, 1–3.
5. Kim, T.Y., Kim, H.S., Lee, K.Y., Kim, J.N. (2000). Improved synthesis of 1,3,5-triarylbenzenes from α,β -unsaturated nitro compounds. *Bull. Korean Chem. Soc.*, 21, 521–522.
6. Zicmanis, A., Pavlovica, S., Gzibovska, E., Mekss, P., Klavins, M. (2010). 2-Hydroxyethylammonium carboxylates – highly biodegradable and slightly toxic ionic liquids. *Latv. J. Chem.*, 269–276.
7. Pavlovica, S., Zicmanis, A., Gzibovska, E., Klavins, M., Mekss, P. (2011). (2-Hydroxyethyl)-ammonium lactates – highly biodegradable and essentially non-toxic ionic liquids. *Green and Sustainable Chem.*, 1, 103–110.
8. Reichardt, C. (2005). Polarity of ionic liquids determined empirically by means of solvatochromic pyridinium *N*-phenolate betaine dyes. *Green Chem.* 7, 339–351.

β -NITROSTIROLA SINTĒZE STIPRI HIDROFĪLU JONU ŠĶIDRUMU VIDĒS

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

Pētīta β -nitrostirola sintēze benzaldehīda kondensācijas reakcijā ar nitrometānu jonu šķīdumu (2-hidroksietil)amonija karboksilātu (formiātu, laktātu, acetātu) vidēs bez citu katalizatoru lietošanas. Pētīta reakcijas produkta iznākuma atkarība no jonu šķīdumu katjona un anjona uzbūves, jonu šķīdumu kopējās polaritātes un reakcijas vides pseido-pH vērtības. Visaugstāko β -nitrostirola iznākumu nodrošināja (2-hidroksietil)amonija formiāta lietošana par reakcijas vidi.

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