

Chiral ionic liquid based on N-(2-hydroxyethyl) pyrrolidine and its use in Diels-Alder reaction

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Introduction

Among many possible applications of ionic liquids, there is one that particularly brings plenty of advantages. Replacing popular solvents in the organic synthesis and catalysis increases the yield, reaction rate, selectivity, as well as allows the recovery and reuse of both the ionic liquid and the catalyst. The asymmetric catalysis is one of the most important fields in organic chemistry. In this regard, chiral ionic liquids are an interesting option over chiral solvents [1]. Not only are they non-volatile and inflammable, but they are also highly ordered, while specific interactions, including hydrogen bonds and the van der Waals interactions with substrates, may greatly affect the transition complex in the reaction. In case of using chiral ionic liquids, it may be expected that the chirality will be transferred to substrates.

The normal electron demand Diels-Alder reaction is a reaction where the solvent significantly affects its outcome. The previous research on this reaction in ionic liquids mainly showed that the interactions of dienophile with an ionic liquid cation [2], and particularly their increase in the proton-donor properties, greatly increases the reaction rate and stereoselectivity of the reaction [3, 4]. Therefore, locating chirality in the cation section, with a simultaneous presence of proton-donor groups in a cation, seems a very promising measure for controlling asymmetry in the Diels-Alder product. However, as the strength of interactions between the cation and dienophile also depends on an ionic liquid anion, thus the combination of such anions that are weak bases is most desirable. An example of such an anion may be bis(trifluoromethylsulfonyl)imide (NTf_2), which at the same time provides the fluidity of the ionic liquid at ambient temperatures, or even lower.

The aim of the study was the incorporation of a chiral substituent to a nitrogen atom in the pyrrolidine ring with a hydroxyethyl substituent that can form a hydrogen bond and also the determination of the effect of such a chiral ionic liquid obtained on the Diels-Alder reaction of selected reagents. In this case, a chiral substituent in the cation was a (1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl group derived from (-)-menthol. So far, such a substituent was introduced to nitrogen in the imidazole ring [5], pyridine [6], as well as in quaternary ammonium salts [7].

Experimental part

Synthesis of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]-pyrrolidinium chloride, [M(2HEt)pyrr][Cl]

120 cm³ of anhydrous diethyl ether was added to a 250 ml round-bottomed flask equipped with a magnetic stirrer, a reflux condenser with a tube containing desiccant at its end. While stirring vigorously, 3.45 g (0.030 mole) of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]-pyrrolidinium was added and 6.3 g (0.031 mole) of chloromethyl (1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohex-1-yl ether obtained according to the [7].

The reaction was conducted for 24 hours at 25°C. The solid product was filtered off using a vacuum funnel and rinsed threefold portionwise with 20 cm³ of diethyl ether. Then the product was crystallised from the mixture diethyl ether/hexane and dried in a vacuum drier at 40°C for 24 hours. The yield of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium chloride was 93%. The product had a melting point of 112°C and its specific rotation $[\alpha]_D^{20}$ was -63.9 ($c=1\%$ (m/v) in MeOH). HRMS (ESI+) spectra and ¹H NMR and ¹³C NMR confirmed the structure of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium chloride.

HRMS (TOF MS ES+): measured value 284.2591 (value calculated for $\text{C}_{17}\text{H}_{34}\text{NO}_2$: 284.2590).

¹H NMR (600 MHz, CDCl_3) δ in ppm: 4.91 (d, $J=7.1$ Hz, 1H), 4.89 (d, $J=7.0$ Hz, 1H); 4.06 (br s, 2H); 3.86 (m, 4H); 3.70 (m, 2H); 3.53 (td, $J=10.59$ Hz, 4.20 Hz, 1H); 2.31 (m, 2H); 2.14 (m, 3H); 2.04 (pent. d, $J=7.0$ Hz, 2.60 Hz, 1H); 1.68 (m, 1H); 1.65 (m, 1H); 1.42 (m, 1H); 1.32 (m, 1H); 0.99 (m, 2H); 0.93 (t, $J=6.6$ Hz, 6H); 0.86 (td, $J=12.4$ Hz, 3.4 Hz, 1H); 0.80 (d, $J=6.9$ Hz, 3H).

¹³C NMR (CDCl_3) δ in ppm: 83.5; 81.0; 61.4; 60.7; 60.5; 56.1; 48.1; 40.4; 33.95; 31.2; 25.8; 22.7; 22.2; 22.1; 22.0; 21.0; 15.85.

Synthesis of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-menthoxyethyl]-pyrrolidinium bis(trifluoromethylsulfonyl)imide, [M(2HEt)pyrr][NTf₂]

9.6g (0.03 mole) of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium and 40 cm³ of water were placed in a 100 cm³ round-bottomed flask equipped with a magnetic stirrer. While stirring vigorously, 8.61g (0.030 mole) of lithium bis(trifluoromethylsulfonyl)imide dissolved in 4 cm³ of distilled water was added. The flask was stoppered and the reaction was conducted for 15 hours at 35°C, while mixing vigorously with the magnetic stirrer. Then the solution was left until the phase separation and the aqueous layer was removed with a pipette. 20 cm³ of deionized water was added to the ionic liquid layer left in the flask and stirred vigorously for 1 hour, after which the aqueous layer was removed again with the pipette. The operations of washing the organic layer and the separation of the aqueous layer were repeated several times until no presence of chloride ions was found in the aqueous solution from washing (a test with AgNO_3). The product obtained, in a liquid form, was dried at 60°C for 48 hours *in vacuo*. N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium bis(trifluoromethylsulfonyl)imide was obtained at 90% yield. Its density was 1.3156 g/cm³ (at 23°C), the refractive index $n_D=1.4503$, specific rotation $[\alpha]_D^{20}=-56.9$ ($c=1\%$ (m/v) in MeOH) and glass transition temperature $T_g=-50.2^\circ\text{C}$. Onset decomposition temperature: 177°C.

HRMS (ESI+) spectra and ¹H NMR and ¹³C NMR confirmed the structure of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-menthoxyethyl]pyrrolidinium bis(trifluoromethylsulfonyl)imide.

HRMS (TOF MS ES+): measured value 284.2592 (value calculated for $\text{C}_{17}\text{H}_{34}\text{NO}_2$: 284.2590).

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¹H NMR (600 MHz, CDCl₃) δ in ppm: 4.69 (d, *J*=7.12 Hz, 1H); 4.59 (d, *J*=7.12 Hz, 1H); 4.01 (br s, 2H); 3.62 (m, 4H); 3.50 (m, 3H); 2.24 (m, 2H); 2.15 (m, 2H); 2.05 (m, 2H); 1.67 (m, 2H), 1.40 (m, 1H); 1.32 (m, 1H); 0.99 (m, 2H); 0.93 (dd, *J*=6.8 Hz, 6H); 0.87 (m, 1H); 0.79 (d, *J*=6.96 Hz, 3H);

¹³C NMR (CDCl₃) δ in ppm: 122.9; 120.8; 118.7; 116.5; 84.2; 81.2; 60.8; 60.6; 60.5; 56.6; 48.0; 40.1; 33.9; 31.1; 25.8; 22.6; 22.2; 22.0; 21.8; 20.9; 15.5.

Diels-Alder reaction

In a 5 cm³ flask equipped with a magnetic stir bar, the catalyst (if it was applied) and the ionic liquid [M(2HEt)pyrr][NTf₂] were placed. The content was flushed with argon, the flask was sealed with a silicone stopper and placed on the magnetic stirrer. Subsequently, after the catalyst was dissolved, dienophile and cyclopentadiene were added through a needle and stirred at 20°C.

The reaction was conducted at an equimolar quantity of dienophile and ionic liquid, whereas the cyclopentadiene:dienophile ratio was 2:1. Samples of the reaction mixture were collected at specific intervals, extracted with hexane and the hexane extracts were analysed using gas chromatography. The following chromatographic columns were used: Rxi-17, CHIRALDEX G-TA and β-Dex. An example chromatogram showing separation of cycloaddition product stereoisomers into enantiomers is presented in Figure 1. The chromatographic analysis was used to determine the dienophile conversion, endo:exo ratio, and also enantiomer ratio for selected reagents.

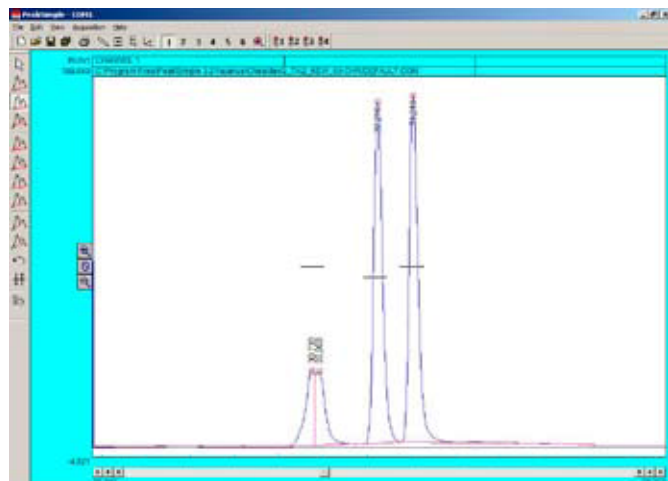


Fig. 1. Sample chromatogram (fragment) showing the separation of products of the reaction between cyclopentadiene with pent-1-en-3-on into stereoisomers and enantiomers

Results and discussion

The chiral ionic liquid N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyl-1-oxymethyl]pyrrolidinium bis(trifluoromethylsulfonyl)imide, [M(2HEt)pyrr][NTf₂], was synthesised starting from (-)-menthol as a substrate according to the presented methods. The subsequent reactions are presented in Figure 2.

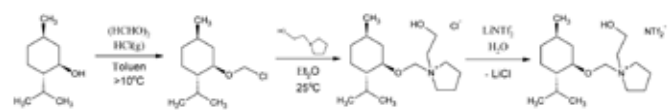


Fig. 2. Synthesis scheme of N-(2-hydroxyethyl)-N-[(1R,2S,5R)-(-)-2-isopropyl-5-methylcyclohexyloxymethyl]pyrrolidinium bis(trifluoromethylsulfonyl)imide

[M(2HEt)pyrr][NTf₂] is in a liquid state at ambient temperature and undergoes the glass phase transition at -50.2°C. It shows high thermal stability – extrapolated onset decomposition temperature is 201.9°C. The liquid undergoes the thermal decomposition in two steps, where the first weight loss corresponds to the elimination of a 2-isopropyl-5-methylcyclohexyl-1-oxymethyl group. The results of the thermogravimetric analysis are presented in Figure 3.

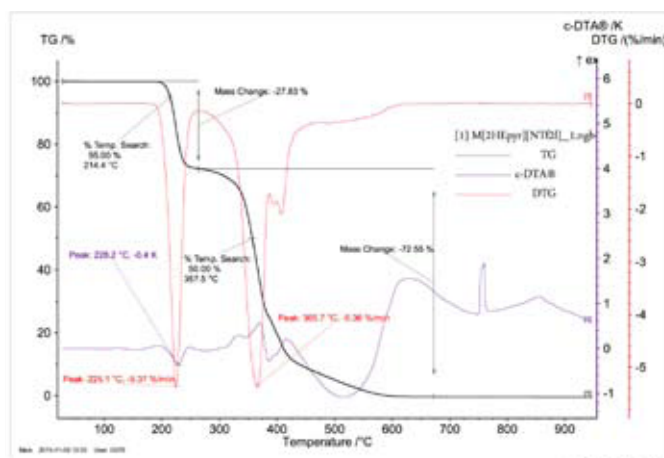


Fig. 3. TG, DTG and c-DTA curves recorded for the chiral ionic liquid [M(2HEt)pyrr][NTf₂] (analysis conditions: Al₂O₃ crucible, sample weight 5 mg, temperature range: 25°C ÷ 1000°C; 5°/min; N₂: 10 ml/min, air: 25 ml/min)

The chiral ionic liquid [M(2HEt)pyrr][NTf₂] was used in the Diels-Alder reaction as a solvent. The reaction of cyclopentadiene with such dienophiles as prop-2-enal (**1a**), (*E*)-but-2-enal (**1b**), (*E*)-pent-2-enal (**1c**), (*E*)-hex-2-enal (**1d**), 2-methylpent-2-enal (**1e**), pent-1-en-3-on (**1f**), 5-methylhex-3-en-2-on (**1g**) was conducted (Fig. 4). The ionic liquid was used in an equimolar quantity to dienophile. The reactions were performed with or without Lewis acids – Zn(OTf)₂ and Cu(OTf)₂, which were used at a concentration of 1% and 0.1%-mole of dienophile respectively.



Fig. 4. Diels-Alder reaction between cyclopentadiene and various dienophiles

Table I
Dienophile conversion and the endo/exo diastereomer ratio for the Diels-Alder reaction between cyclopentadiene and various dienophiles

Dienophile	Reaction time	α, %	endo/exo
1a	60 min	97	4.1
1b	24 h	32	3.4
1c	24 h	9	2.1
1d	24 h	8	2.1
1e	24 h	0	-
1f	30 min	95	5.0
1g	24 h	5	-

For the ionic liquid environment without Lewis acid (Tab. 1), high conversions exceeding 90% were obtained for prop-2-enal (**1a**) and pent-1-en-3-on (**1f**), as dienophiles, whereas a moderate conversion was observed for **1b**. Other dienophiles showed low reactivity in the reaction with cyclopentadiene with conversions below 10%. The endo/exo stereoisomer ratio depended on the type of dienophile. The highest stereoselectivity was obtained for the reaction of cyclopentadiene with pent-1-en-3-on (**1f**). Small differences in areas of peaks corresponding to enantiomeric products for dienophiles **1f** and **1b** indicated that the ionic liquid used did not induce chirality in the reaction product. The reaction of cyclopentadiene with pent-1-en-3-on (**1f**) was conducted using the ionic liquid in twice or threefold higher amount than the amount of dienophile; however, no enantiomeric excess was observed here as well.

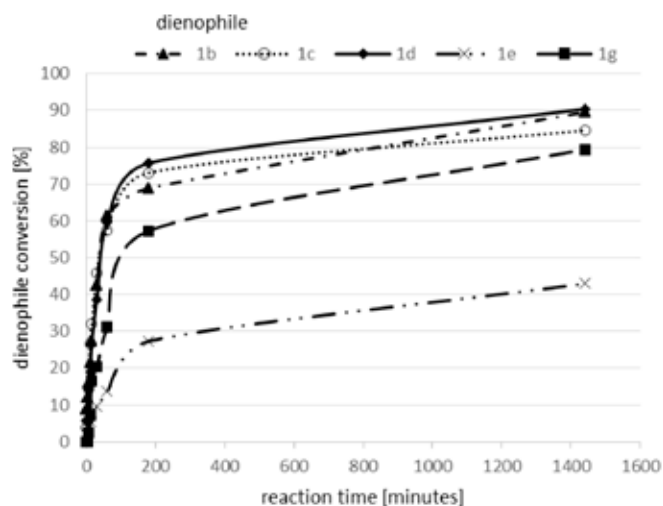


Fig. 5. Dienophile conversion in the Diels-Alder reaction with cyclopentadiene in the ionic liquid [M(2HEt)pyrr][NTf₂] with Cu(OTf)₂ (0.1% mole/dienophile)

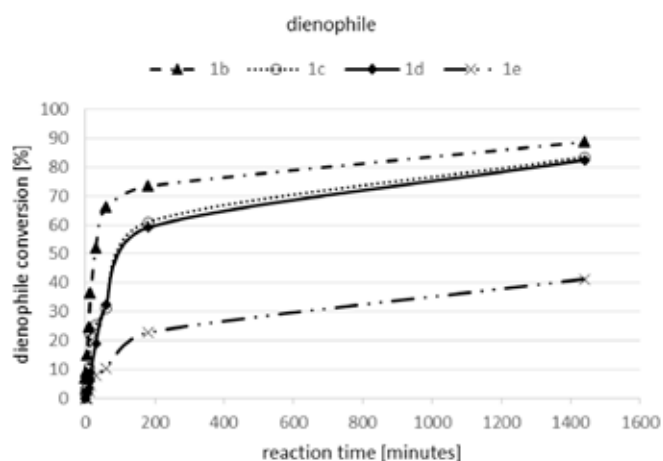


Fig. 6. Dienophile conversion in the Diels-Alder reaction with cyclopentadiene in the ionic liquid [M(2HEt)pyrr][NTf₂] with Zn(OTf)₂ (1% mole/dienophile)

In the next step, a reaction with catalytic systems was conducted for less reactive dienophiles. The systems were prepared by dissolving selected Lewis acids in the chiral ionic liquid. In the early tests, both Cu(OTf)₂ and Zn(OTf)₂ were used in quantity of 1% mole of dienophile. However, for the copper catalyst the reaction was very violent, thus it was decided to reduce its concentration 10-fold. The use of Lewis acids has greatly increased the reaction rate, which indicates the catalytic activity of the metal salts selected in the ionic liquid used (Figs. 5 and 6). The conversions of dienophiles **1b**, **1c** and **1d** were

over 80% for the copper and zinc catalysts. The endo/exo ratio did not change significantly in comparison to the reaction conducted only in the ionic liquid: 2.6 for reaction of cyclopentadiene with **1b**, 2.5 for **1c**, and 2.6 for **1d**. For the dienophile **1g**, the conversion of 79% and 43% was achieved after 24 hours in the presence of Cu(OTf)₂ and Zn(OTf)₂, respectively, with the endo/exo ratio of 5.7 and 3.4. In the reaction of **1e** with cyclopentadiene, the conversion of approx. 40% was obtained for both Lewis acids with a distinct excess of the exo stereoisomer – the exo/endo ratio was 11.5 for the copper catalyst and 9.5 for the zinc one. However, the chromatographic analysis with the chiral column showed no distinct enantiomeric excess.

Conclusions

The chiral ionic liquid was synthesised at high yield containing a bistriflimide anion and pyrrolidinium cation with a hydroxyethyl group and a chiral substituent derived from natural (-)-menthol at the nitrogen atom. Although the use of this liquid in the Diels-Alder reaction failed to give an enantiomeric excess, which indicates that the ionic liquid used introduces too low asymmetry, it is a very good solvent for both Lewis acids and substrates of the Diels-Alder reaction. For reactions of lower ketones and aldehydes with cyclopentadiene, high conversions were achieved without the addition of a catalyst. In case of higher α,β -unsaturated aldehydes and ketones, high conversions were ensured by the application of the catalytic system composed of a chiral ionic liquid and Cu(OTf)₂ or Zn(OTf)₂. The further studies shall focus on creating the complexes of Lewis acids with chiral ligands in a chiral ionic liquid and the application of such systems in the Diels-Alder reaction.

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