Synthesis of chiral bicyclo[3.3.1]nonane derivative
as ionic liquid and using it for asymmetric Michael’s
addition reaction

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In this study a chiral bicyclo[3.3.1]nonane derivative as an ionic liquid was synthesized starting from (+)-(1S,5S)-bicyclo[3.3.1]nonane-2,6-dione (1a). Resulting compound (+)-(1S,2R,5S,6R)-2,6-di[(N-methylimidazol-3-ium-3-yl)acetyl]oxybicyclo[3.3.1]nonane di(tetrafluoroborate) (4) was used as a chiral catalyst for the asymmetric Michael’s addition reaction of 1,3-diphenyl-2-propan-1-one (chalcone 5) with diethyl malonate.

In that case (+)-(S)-diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (7) was obtained. Optical purity of purposive compound 7 was 57%, the enantiomeric excess calculated according to spectral data (1H NMR) ee = 35%. This difference can be explained by the Horeau effect.

Key words: bicyclo[3.3.1]nonane, chiral ionic liquid, imidazolium cation, asymmetric Michael’s addition reaction

Abbreviations: CIL – chiral ionic liquids, DCC – dicyclohexylcarbodiimide, DMAP – N,N-dimethylaminopyridine, Eu(TFC)₃ – Europium (III) tris[3-(trifluoromethylhydroxymethyl)camphorate]
In this way we have obtained (+)-(1S,5S)-bicyclo[3.3.1]nonane-2,6-dione (1a) with a specific light polarization rotation angle $[\alpha]_{D}^{25} = +171\degree$ (c 1.5, EtOH), (lit. data +176°).

The compound 1a was used in other chiral ionic liquid synthesis stages [9] (Fig. 2).

We synthesized compound 3 according to the chosen CIL synthesis scheme. Firstly, we got diol 2 (determined $[\alpha]_{D}^{25} = +49\degree$ (c 1.9, EtOH; lit. data +55°). The product was reacted with monobromoacetic acid (DCC/DMAP in dichloromethane). We got compound 3 ($[\alpha]_{D}^{25} = +19.6\degree$) which was reacted with N-methylimidazole. After the ion exchange reaction we obtained (+)-(1S,2R,5S,6R)-2,6-di[[(N-methylimidazol-3-ium-3-yl)acetyl]oxy]bicyclo[3.3.1]nonane di(tetrafluoroborate) (4) ($[\alpha]_{D}^{25} = +9.0\degree$; c 2.0, in EtOH) (Fig. 3).

The ionic liquid 4 was used in further asymmetric synthesis.

There is an interesting case of the catalysis when asymmetric synthesis is being induced by simple chiral ionic liquids having two imidazolium cations. In literature this case is shown in the asymmetric Michael’s addition reaction [10]. According to the literature sources, we have chosen the reaction which was being made with the use of the chiral catalyst of the similar structure and we got satisfactory exposures and enantiomeric excess (Fig. 4).

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The reaction was made by stirring at room temperature a mixture of chalcone (1,3-diphenyl-2-propen-1-one) 5 with diethyl malonate and adding K₂CO₃. After 12 hours we got product 6. During this reaction a synthesized chiral catalyst 4 (amount – 15%) was being added. The thin-layer chromatography indicated the completed reaction and the resulting optical active diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (6) was separated successfully from the catalyst using the flash chromatography with ethyl acetate. The structure was proved by the analysis of ¹H-NMR, ¹³C-NMR and IR spectrums [11]. Rotation angle measurements were done. CHCl₃ was chosen as a solvent (in order to compare with the data indicated in the references [12]). The indicated rotation angle showed the following results: [α]D²⁵ = +13° (lit. data +23°) and optical purity was about 57% according to the calculations by the rotation angle:

\[
\text{Optical purity} = \left( \frac{\alpha_{\text{observed}}}{\alpha_{\text{pure enantiomer}}} \right) \times 100% = \left( \frac{13}{23} \right) \times 100% = 57%.
\]

After analysing the results and comparing them to those indicated in the references [12], we found out that S-configuration enantiomer 7 was in excess unambiguous (Fig. 5).

The ideal equivalence between the optical purity and enantiomeric excess (ee) does not always hold. It is known as the Horeau effect [13], i.e. the relationship between the mole based ee and the optical rotation based ee (optical purity) can be non-linear. It depends on different effects, for example, dimerization of chiral compounds, virtue of the forming meso diastereomer, which allows for removal of racemic material, etc.

In that case we also calculated the enantiomeric excess according to ¹H-NMR spectral analysis. Firstly, the spectrum of optical active compound 6 was written, then a small amount (about 15% mol) of chiral shift reagent Eu(TFC)₃ was added.

The very first test showed noticeable changes. The momentum can be seen which showed us interfering hydrogen atoms and helped to calculate the enantiomeric excess. Below there are the parts of spectrums where the received spectral data can be compared. Fig. 6 shows the protons spectrum of compound 6 and Fig. 7 shows it after adding 15% mol of Eu(TFC)₃.

In Fig. 6 we see the signals of protons at the chiral centre together (3.65–3.75 ppm, multiplet). After addition of Eu(TFC)₃, those signals of R and S enantiomers are separated, i.e. the signal of S enantiomers’ proton is at 3.98 ppm (quartet, \(J = 7\) Hz), the signal of R enantiomers’ proton is at 3.87 ppm (doublet, \(J = 7\) Hz). Integrals of the signals give quantities of R and S enantiomers, i.e. the mole ratio is 1.31/0.63 (Fig. 7).
Calculation of the enantiomeric excess was made according to the formula:

\[
ee = \left( \frac{R-S}{R+S} \right) \times 100\% = \\
= \left( \frac{1.31-0.63}{1.31 + 0.65} \right) \times 100\% = 35\%.
\]

It was proved that our catalyst 4 induced the given reaction, but ee was only 35%, so the Horeau effect has the evidence.

**EXPERIMENTAL**

Spectra \(^1\)H and \(^1^3\)C NMR were written with a Varian Unity Inova 300 MHz spectrometer by using residual solvent (CDCl3) signals. Chemical shifts are given in the scale m. d. In descriptions of the spectra \(^1\)H NMR the following abbreviations are used: s – singlet, d – doublet, dd – doublet duplicate, t – triplet and m – multiplet.

IR spectra were registered with a Perkin-Elmer Spectrum BX II spectrometer (nujol or KBr pellets). Melting points were determined with a Gallenkamp melting apparatus in capillary tubes and are not corrected. Optical rotations were measured in a 10 cm cell on a polarimeter Polamat-A (Carl Zeiss) at 546 nm.

\(^1\)H NMR (CDCl3) ppm: 7.48 (s, 2H), 7.01 (s, 2H), 3.97 (m, 4H), 2.86 (m, 2H), 1.91 (m, 4H), 1.31 (m, 2H), 1.7 (m, 2H).

\(^1^3\)C NMR (CDCl3) ppm: 160.8, 137.9, 129.1, 120.5, 47.2, 34.1, 33.6, 33.1, 25.6, 25.1, 24.9.


\[\text{ee} \times \left( \frac{1.31-0.63}{1.31 + 0.65} \right) \times 100\% = \left( \frac{1.31-0.63}{1.31 + 0.65} \right) \times 100\% = 35\%.
\]

(+)-(1S,2S,5S,6R)-2,6-di{(bromoacetyl)oxy}bicyclo[3.3.1]nonane di(tetrafluoroborate) (4)

100 mg (0.5 mmol) of compound 3 and 168 mg (1 mmol) of N-methylimidazole were melted in a round-bottomed flask. The mixture was heated and stirred overnight at the constant temperature of 150 °C. Then 50 mg of water were poured into the mixture, 50 mg of KBF 4 were added and everything was continued to stir for an hour. After the reaction, the water was reduced and a few ml of dichloromethane were poured into the mixture. After the residue melted, the product was filtered through the Celite filter and the filtrate was dried over the anhydrous Na2SO4. The rest part was crystallized from ethanol. The amount of the given product was 0.6 g (yield – 72%).

**Calculations**

\[\text{ee} = \left( \frac{R-S}{R+S} \right) \times 100\% = \\
= \left( \frac{1.31-0.63}{1.31 + 0.65} \right) \times 100\% = 35\%.
\]

\[\text{Melting point} 25–26 \degree C.
\]

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\[\text{Melting point} 25–26 \degree C.
\]

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the product was purified by the flash chromatography (silica gel, EtOAc). Yield – 81%.

\[ \alpha_{D}^{25} = +13^\circ \text{ (c 2.1, EtOH), (lit. data } +23^\circ) \]; calc. optical purity 57%; calc. ee 35%.

CONCLUSIONS

1. A new chiral ionic liquid with two imidazolium cations – (+)-\((1S,2R,5S,6R\)-2,6-di\{[(N-methylimidazol-3-ium-3-yl)acetyl]oxy\}bicyclo[3.3.1]nonane di(tetrafluoroborate) was synthesized starting from (+)-\((1S,5S\)-bicyclo[3.3.1]nonane-2,6-dione.

2. A small amount (15% mol) of the chiral ionic liquid induced the asymmetric Michael’s addition reaction of 1,3-diphenyl-2-propen-1-one with diethyl malonate.

3. The resulting adduct – diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate showed a satisfactory optical activity. The optical purity of the (+)-(S)-enantiomer was 57% according to the calculations by the rotation angle and the enantiomeric excess calculated based on the 1H-NMR spectral analysis was 35%. This inadequacy depends, doubtless, on the so-called Horeau effect.

References