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Synthesis of new ionic liquids based on (5*Z*,9*Z*)-alkadienoic acids and choline

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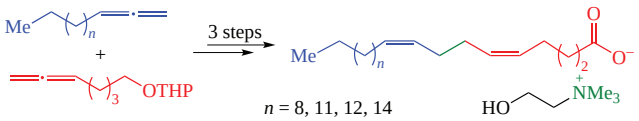
Efficient synthesis of ionic liquids based on stereoisomerically pure natural and synthetic higher (5*Z*,9*Z*)-alkadienoic acids and choline hydroxide was developed. The key unsaturated carboxylic acids were prepared using the stereoselective cross-cyclomagnesiation reaction of aliphatic and oxygen-containing 1,2-dienes with EtMgBr in the presence of Mg metal and Cp_2TiCl_2 catalyst.



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Numerous recent studies have shown that ionic organic compounds have an enormous scope of potential applications, in particular, in medicine and pharmaceutics. Today, the synthesis of ionic liquids (ILs) or ionic derivatives (organic salts) based on known pharmaceutical drugs is considered to be a simple and convenient tool for tuning the physical properties of drugs, including water solubility and bioavailability, and the conversion of a neutral agent to an appropriate ionic species often improves physical, chemical, and biological characteristics of the drug.[1–7] Ionic compounds prepared from active pharmaceutical ingredients (APIs) can serve for both overcoming the drawbacks of known drugs (such as polymorphism, low solubility, poor bioavailability, *etc*.) and developing absolutely new biologically active hybrid compounds (bio-ILs) with specified properties.[8,9] Analysis of recent published data on the synthesis of bio-ILs suggests that the unique possibility of tuning and optimizing ILs for particular tasks at the molecular level, together with their biological activity, would make biomedical application of these ionic derivatives a primary line of research in the next decade.[10]

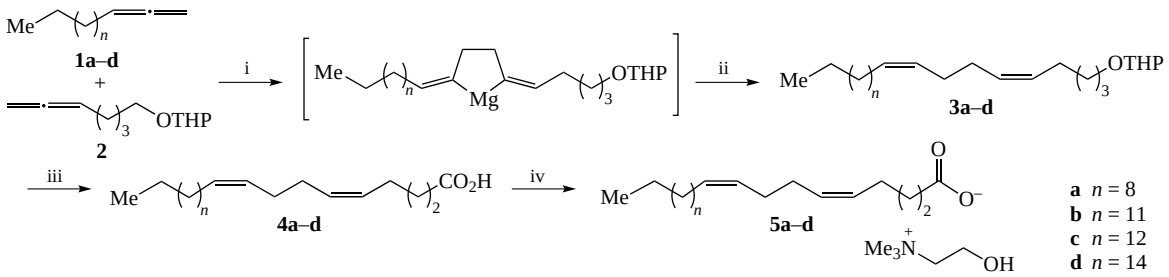
The synthetic strategy towards ionic liquids is similar to that used to prepare common pharmaceutical salts, but combining large organic ions leads to lower melting point, high thermal stability, and low ignitability, thus making this strategy attractive.[11] Over the last 20 years, quite a few scientific publications described the use of the choline cation in combination with API anions (including anions of amino acids and various biologically active carboxylic acids).[12–14] The API-bio-IL systems thus developed are highly soluble in water and in physiological fluids and are able to penetrate cell membranes.

Furthermore, it was shown that choline-based ILs can act as safe compounds, as they are non-toxic and enhance the solubility of APIs, while maintaining their pharmacological activity.[15–18] Choline improves the brain functioning, prevents the development of Alzheimer's disease, serves as a precursor of the neurotransmitter acetylcholine, and also functions as a precursor in trimethylglycine (betaine) and phospholipid biosynthesis in the human body. Choline is widely used as a pharmaceutical excipient since it is considered to be safe. Ionic liquids with choline cations are less toxic and more biodegradable than imidazolium or pyridinium ILs because of the biological origin of choline. Also, choline has a synergistic action enhancing the pharmacological effect of active substances upon topical administration and can be used to boost the solubility for increasing the absorption of insoluble small molecules and as a carrier for targeted drug delivery.[19–24]

Previously, it was shown that (5*Z*,9*Z*)-alkadienoic acids belonging to the chemotype of non-methylene-interrupted fatty acids exhibit antimalarial, antimicrobial, antibacterial, and antitumor activities[25–29] and inhibit cell cycle enzymes, topoisomerases, which regulate vital processes in cells.[30–32] These acids are present in sea sponges and gymnosperm fruits in only trace amounts.[33–35] Together with the complexity of isolation of individual (5*Z*,9*Z*)-alkadienoic acids and the absence of efficient methods for their synthesis, this considerably hampered studies of their structure–biological activity relationships. A stereoselective method comprising a small number of steps has been recently developed for the preparation of natural and synthetic (5*Z*,9*Z*)-alkadienoic acids, with the key step being the catalytic cross-cyclomagnesiation of aliphatic and oxygen-containing 1,2-dienes.[36] This approach made it possible to synthesize a range of dienoic acids with different hydrocarbon chain lengths containing a (1*Z*,5*Z*)-diene moiety in a specified position relative to the carboxyl group. It was shown that the synthesized unsaturated acids and new derivatives based on them exhibit a high inhibitory activity against topoisomerases and an antitumor activity *in vitro* against a number of cancer cell lines.[37–41]

Herein, we performed the first synthesis of new ionic liquids comprising anions of 5*Z*,9*Z*-alkadienoic acids and choline cation. To implement this plan, we synthesized the key (5*Z*,9*Z*)-alka-5,9-dienoic acids from allenes **1a**–**d** and **2** by the sequence of reactions developed previously (Scheme 1).[36]

The target ILs were synthesized *via* a two-step metathesis reaction, with slight modification of the previously published



Scheme 1 *Reagents and conditions*: i, EtMgBr, Mg, Cp_2TiCl_2 (10 mol%); ii, NH_4Cl, H_2O; iii, Jones reagent; iv, $[HO(CH_2)_2NMe_3]^+OH^-$, acetone or methanol, H_2O, 45 °C, 24 h.

procedure.[42] Initially, choline chloride $[HO(CH_2)_2NMe_3]^+Cl^-$ was treated with silver oxide Ag_2O in water and stirred for 2 h to generate choline hydroxide. After removal of the AgCl and Ag_2O precipitation, the most of water was evaporated to leave a concentrated solution containing choline hydroxide (over 90% yield). In the second step, ILs were obtained by neutralization of the equimolar amounts of carboxylic acids **4a**–**d** with choline hydroxide in acetone or methanol (see Scheme 1). During the reaction, the colour of the reaction mixture changed from brown to light yellow. Evaporation of the solvent and removal of water gave organic salts **5a**–**d** as highly viscous liquids in quantitative yields.

The purity and the structure of the resulting organic salts were confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and high-resolution mass spectrometry. In the ^1H and ^{13}C NMR spectra of compound **5a**, the proton and carbon signals of the methylene group in the α-position to the carboxylate anion (CH_2–COO^-) are located at 2.08–2.14 and 38.4 ppm, respectively, whereas the analogous atoms in the free acid (CH_2–COOH) resonate at 2.35–2.40 and 33.5 ppm, respectively. As the distance between an atom and the carboxylate anion increases, the deshielding effect gradually decreases: the proton signals for the β-methylene group are observed at 1.52–1.62 ppm *versus* 1.69–1.76 ppm for the free acid. There are also slight changes in the proton (5.30–5.41 ppm) and carbon (129.1–130.3 ppm) chemical shifts for the unsaturated part of IL, which is attributable to free movement of π-electrons.[43] In the IR spectra, the C–O stretching modes of the carboxyl group of acid **4a**, which are manifested at 1739 cm^{-1}, shift to 1566 cm^{-1} upon the formation of compound **5a**. For the IL **5a**, a new weak peak was observed at 1649 cm^{-1}, the characteristic peak of the quaternary ammonium group spectrum indicating a strong interaction between the carboxylic proton of the fatty acid and the amine group of the choline. Similar changes in the NMR and IR spectra were found for all ionic compounds prepared from acids **4b**–**d** and choline.

In conclusion, we accomplished the synthesis of novel ionic liquids based on isomerically pure biologically active (5*Z*,9*Z*)-alkadienoic acids and choline. We believe that the developed synthetic route possesses considerable potential for the preparation of polyfunctional ILs by varying the structures of the initial acids and the counterions, which have a potential pharmacological activity. Active studies along this line are in progress and, in the near future, we intend to considerably expand the range of prepared ILs, produce necessary amounts of compounds, and assess their antitumor and antibacterial activities using advanced cell technologies and flow cytometry.

Synthesis of (5*Z*,9*Z*)-alka-5,9-dienoic acids was supported by the budget of the UFRSC RAS State Targets (FMRS-2022-0075). The structural studies of the synthesized compounds were performed with the use of Collective Usage Centre ‘Agidel’ at the Institute of Petrochemistry and Catalysis of RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.015.

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