Tetrahedron: *Asymmetry* 25 (2014) 1280–1285

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Camphorpyrazolium-based chiral functional ionic liquids

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ARTICLE INFO

*Article history:*
Received 25 June 2014
Accepted 31 July 2014

ABSTRACT

The solvent-less quaternization of *N*-phenyl-camphorpyrazole **4** with $BrC_4H_9$, $IC_2H_4OCH_3$, and $IC_2H_4OC_2H_4OC_4H_9$ afforded the corresponding chiral pyrazolium halides **5a**, **6a**, and **7a** in excellent yields. The anions were modified either by trihalide formation with $Br_2$ and $I_2$, or by salt metathesis with $LiNTf_2$ and $NaCo(CO)_4$. All pyrazolium salts bearing the di-ether side chain **7a–d** were liquids at room temperature, while the X-ray crystal structure of the bis(trifluoromethylsulfonyl)amide salt of the corresponding mono-ether analogue **6c** (mp 97 °C) revealed intermolecular H-bonding interactions. Furthermore, an improved protocol for the well-known but notoriously low-yielding synthesis of (+)-hydroxymethylenecamphor **3** is disclosed.

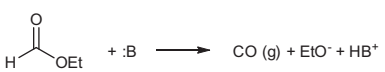


## 1. Introduction

Pyrazolium-based ionic liquids have been receiving relatively little attention compared to their imidazolium-based analogues, in spite of the fact that both cations are structural isomers and have comparable physical properties.[1] Chiral ionic liquids have great potential for a wide range of applications including asymmetric synthesis, enantioselective separation processes, NMR shift reagents, and liquid crystals.[2] Schulz et al. demonstrated an effective transfer of chirality through ion pairing in chiral ionic liquids.[3] For the above reasons, inexpensive camphorpyrazolium-based chiral ionic liquids seemed to be worthwhile synthetic targets. Furthermore, the combination of the role of a chiral ionic liquid with a reactive moiety creates potentially very useful chiral functional ionic liquids. Herein we report on the synthesis of new camphorpyrazolium-based chiral ionic liquids, some of which are accompanied by functional trihalide and cobaltate anions.

## 2. Results and discussion

Camphor is a readily available building block from the 'chiral pool' that can be easily transformed into the corresponding pyrazolium salts. The camphor motif and similar derivatives have previously been used in the anionic part of chiral ionic liquids,[3,4] while herein it is integrated in the cationic part. We first found it necessary to optimize the synthesis of the starting material (+)-hydroxymethylenecamphor **3** (see Scheme 1), a molecule known since the days of Claisen[5] and an important chiral building block. By using standard protocols, compound **3** could be reproducibly obtained in only 20–30% yields from camphor via the in situ formation of the $Na^+$ or $K^+$ enolate of camphor **1**, followed by the addition of formates.[6] Even following an improved protocol that requires excess KH as the endizing base and successive in situ addition of ethyl formate,[7] we were unable to obtain significantly higher yields of **3**. We repeatedly monitored the immediate evolution of a gas when ethyl formate was added to the alkali camphor enolate/KH mixture at room temperature. The formation of CO upon contact of formates and formamides with a base has been described,[8] and in the case of the synthesis of **3** it appears to be a competing side reaction at room temperature (Eq. 1). The low yields obtained by using standard protocols are due to loss of the ethyl formate electrophile in the form of gaseous CO upon reaction with the enolate or excess enolizing base. It should be noted that an excess of KH in the reaction mixture shifts the equilibrium (1) even further by liberating $H_2$.




(1)

To avoid these problems, we reacted the isolated and analytically pure potassium enolate **1**[9] (Scheme 1) with ethyl formate at low temperature and on a 50 g scale. This afforded salt **2**, which was isolated and then titrated with HCl in aqueous solution. At equivalence point copious amounts of **3** precipitated, and excellent yields of sublimed, analytically pure material were obtained (ca. 80%, >30 g

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http://dx.doi.org/10.1016/j.tetasy.2014.07.014
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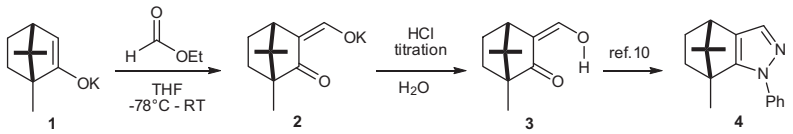



**Scheme 1.**

scale). We are unaware of NMR data for this product, and our material exhibited a characteristic proton resonance of the hydroxymethylene C–H proton at 6.7 ppm in $CDCl_3$ solution (pure *Z* isomer), while in $CD_3OD$ the main resonance was due to the *E*-isomer, which appeared at 7.3 ppm (*E*/*Z* ≈ 88:12). With readily accessible **3** in hand, the multi-gram synthesis of **4** was straightforward, and its X-ray crystal structure (Fig. 1) confirmed the previous structural assignment based on 1D H NMR data.[10] The asymmetric unit of **4** contains two crystallographically independent molecules, each with identical chirality of the stereogenic atoms. Molecular parameters such as torsion angles in each molecule differ significantly [for A: 40.5(3)°; for B: −47.0(3)°].

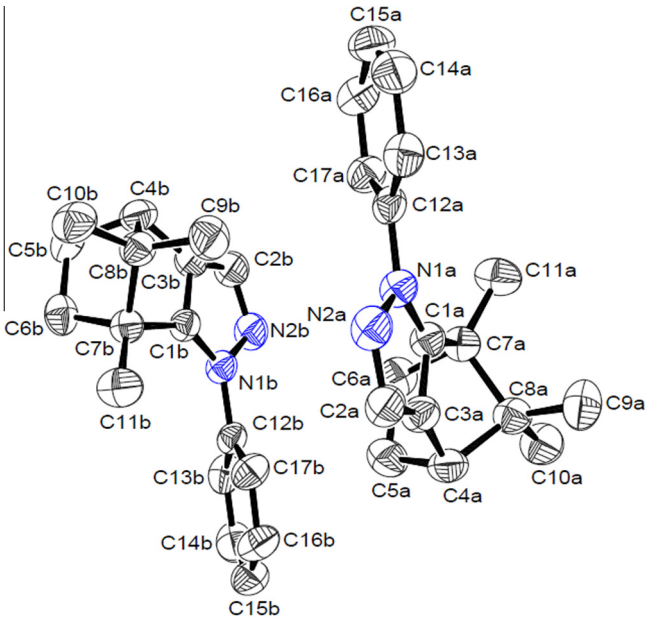
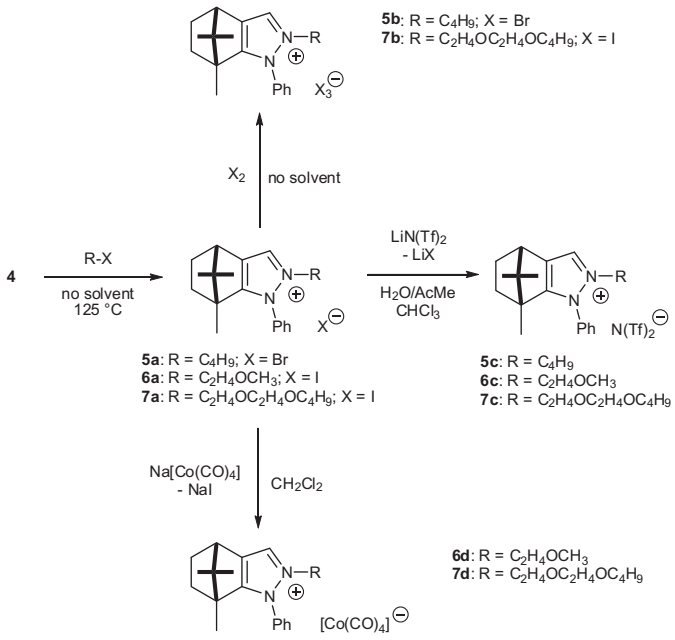



**Figure 1.** View of the two independent molecules of **4** in the unit cell. H atoms are omitted. Selected bond lengths (Å) and angles (°) are: N1a–C12a 1.422(2), N1a–N2a 1.382(3), N2a–C2a 1.333(3), N1b–C12b 1.426(2), N1b–C1b 1.378(3), N2b–C2b 1.332(3), C12a–N1a–N2a 118.7(2), C1a–N1a–C12a 130.9(2), N2a–N1a–C1a 110.3(2), C12b–N1b–N2b 119.0(2), C12b–N1b–C1b 130.0(2), N2b–N1b–C1b 110.9(2).

Alkylation of **4** with a slight excess of butylbromide, methoxyethyliodide, and 1-butoxy-2-diethyl-ether-iodide afforded the camphorpyrazolium salts **5a**, **6a**, and **7a** in fair to good yields (36–77%, see Scheme 2). These salts were then used as starting materials for anion exchange reactions as outlined in Scheme 2. The X-ray crystal structure of **6a** along with a selection of structural parameters is presented in Figure 2. The torsion angle between the phenyl ring and the pyrazole ring is 74.2° (measured along N2–N1–C12–C13), and the structure shows disordered methoxy-ethyl side chains. No H-bridging interactions with the ether function or the anion are present.

In an attempt to lower the melting points and viscosities of **5a**, **6a**, and **7a**, we decided to introduce the bis(trifluoromethylsulfonyl)amide ($NTf_2$) anion by metathetical exchange with $LiN(Tf)_2$ in a water–acetone–$CHCl_3$ mixture. Chiral ionic liquids **5c**, **6c**, and




**Scheme 2.**

**7c** were thus obtained in good to excellent yields (67–92%). Single crystals of **6c** were grown by slow evaporation of an ethanol solution. A partial view of the crystal structure is depicted in Figure 3. The bis(trifluoromethanesulfonyl)amide anion was found to be disordered over two sets of positions. Self-assembly between the cations and anions is obtained from multiple supramolecular interactions, which showed five types of interactions. First, the hydrogen atoms of the phenyl ring of the chiral cation bridge the fluorine atoms of the anion. The $CF_3$ groups also show F···H contacts with the bridge-head methyl groups of the camphor units. Thirdly, we observed O···H bridging between the sulfonyl group of the anion and the H-atom of the pyrazolium ring. Fourthly, the H-atom of one of the non-bridgehead methyl groups of the camphor unit bridges the O-atom of the ether side chain of a neighboring cation. Finally, the $CF_3$ groups also show F···F interactions that are known to play a vital role in directing molecular assemblies.[11] The cooperative effect of all of these H-bonding and F···F interactions may explain why, in this case, the $NTf_2$ anion does not cause **6c** to become a room temperature ionic liquid. It should be noted that the torsion angle between the phenyl and pyrazole rings in **6c** is smaller than in **6a** (66.9° vs 74.2°).

Our interest in functional ionic liquids prompted us to synthesize the corresponding trihalide chiral ionic liquids **5b** and **7b**[12] by reacting the bromide and iodide **5a** and **7a** with $Br_2$ or $I_2$, respectively. These reactions were high-yielding (91–93%) and tri-iodide **7b** turned out to be a liquid at RT. The Co-containing chiral ionic liquids **6d** and **7d** were prepared by salt metathesis with $Na[Co(CO)_4]$ in $CH_2Cl_2$ in good isolated yields (87–88%) (Scheme 2).[13] To the best of our knowledge, these are the first examples of transition metal based chiral ionic liquids. The results in Table 1 show that with the exception of **6a**, all of the compounds may be classified as ionic liquids, even though only derivatives **7**