

Sugar-Derived Ionic Liquids

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Abstract: Ionic liquids (ILs) are special molten salts with melting points below 100 °C that are typically constituted of organic cations (imidazolium, pyridinium, sulfonium, phosphonium, etc.) and inorganic anions. Due to their ionic nature, they are endowed with high chemical and thermal stability, good solvent properties, and non-measurable vapor pressure. Although the recycling of ILs partly compensates their rather high cost, it is important to develop new synthetic approaches to less expensive and environmentally sustainable ILs based on renewable raw materials. In fact, most of these alternative solvents are still prepared starting from fossil feedstocks. Until now, only a limited number of ionic liquids have been prepared from renewable sources (e.g. hydroxy acids, amino acids, terpenes), and even less from naturally occurring carbohydrates. This short review describes the synthesis and applications of chiral and achiral ILs obtained from inexpensive sugars.

Keywords: Arabinose · Diels-Alder cycloaddition · Fructose · Glycosylation · Supported synthesis

Introduction

The design of environmentally benign solvents and solventless systems is one of the most active areas of green chemistry. Ionic liquids (ILs) are, together with water and supercritical fluids, one of the few alternative media for environmentally friendly processes.^[1] The range of demonstrated or proposed applications of ILs is extremely large, going from their use as non-volatile, non-flammable solvents in organic synthesis to catalysts, materials for aiding separations and gas capture, advanced heat transfer fluids, lubricants, anti-statics and so on. The term 'ionic liquids' includes all compounds composed exclusively by ions that are liquid at a temperature below 100 °C. The ionic nature induces in these compounds unique physico-chemical properties that make them suitable materials for industrially

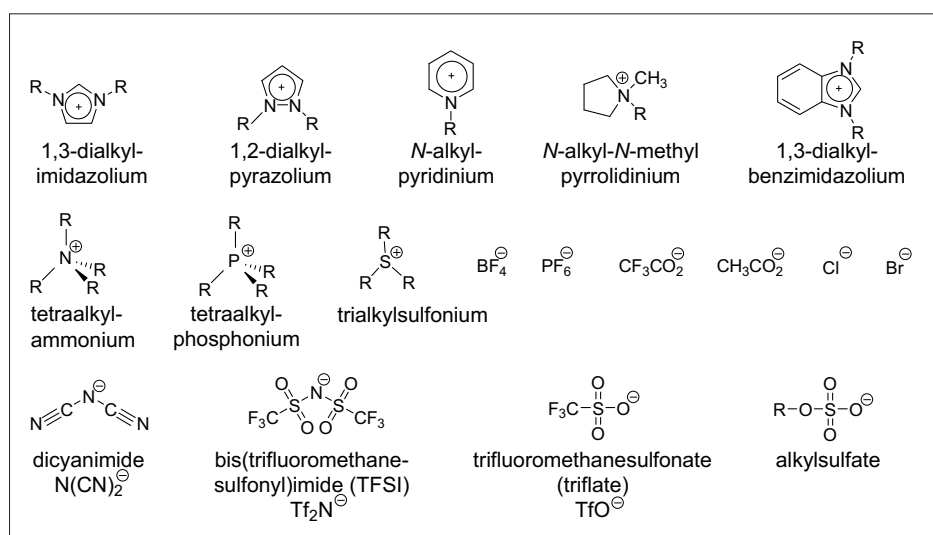


Fig. 1.

relevant processes.^[2] Moreover, their physical and chemical properties can be modified and finely modulated by structural modifications on anion and cation. ILs are generally characterized by the following properties: no effective vapor pressure; high thermal stability; wide liquid range; very good solvent properties for a wide range of inorganic, organic and polymeric materials; easy recycling; hydrophobic or hydrophilic behaviors. Moreover, they may show Brønsted, Lewis, and Franklin acidity, as well as Brønsted and Lewis basicity. However, some features of ILs require improvement. In particular, ionic liquids are as yet relatively expensive.

The ILs are generally based on ammonium, sulfonium, phosphonium, imidazolium, pyridinium, picolinium and pyrrolidinium cations, with the *N,N*-dialkylimidazolium salts representing the most studied and applied class of ionic

compounds (Fig. 1). Inorganic and organic anions have been used to obtain low melting salts and historically ILs are classified into four groups based on anion nature: a) systems based on AlCl_3 and organic salts, like 1-butyl-3-methylimidazolium chloride, $[\text{bmim}][\text{Cl}]$; b) systems based on anions like PF_6^- , BF_4^- ; c) systems based on anions like CF_3SO_3^- , $(\text{CF}_3\text{SO}_2)_2\text{N}^-$ $[\text{NTf}_2]^-$; d) systems based on anions like alkylsulfates and alkylsulfonates (Fig. 1). However, other anions have been used more recently to obtain ILs (dicyanamide, lactate, saccharinates, boronates, etc.).^[3] In addition, also ILs bearing functional groups on the cation or anion able to impart specific properties, defined task-specific ionic liquids (TS-ILs), have been synthesized and applied as designer media in catalysis and material sciences.^[4]

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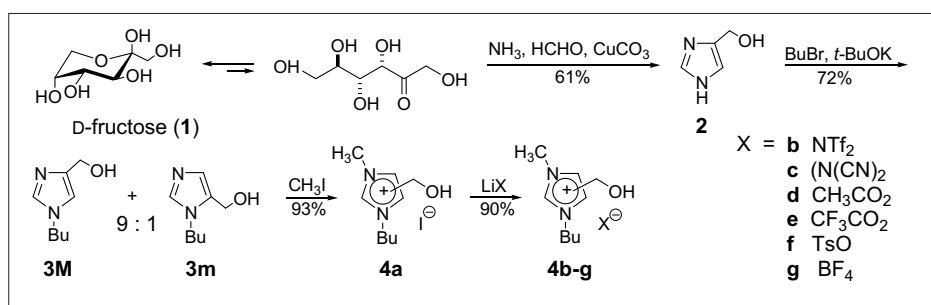
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Synthesis of Ionic Liquids from Carbohydrates

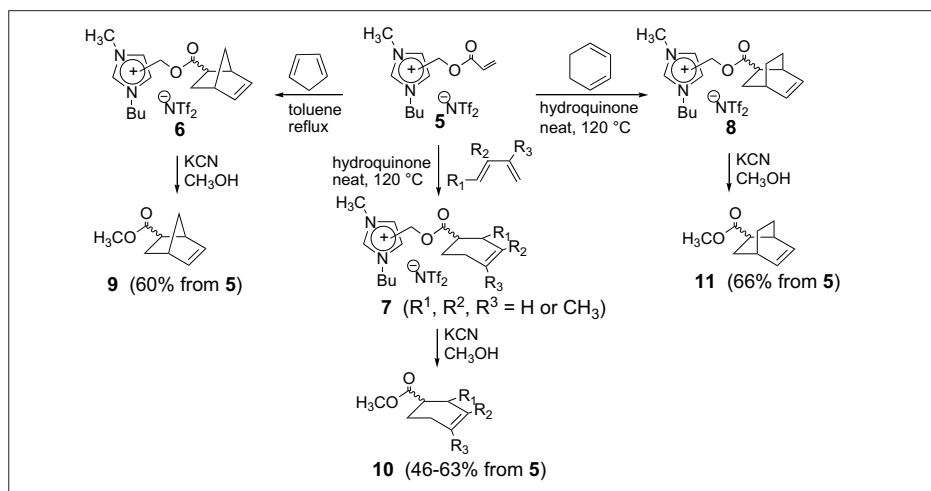
Ionic liquids, like their molecular (*i.e.* non-ionic) analogues, are almost invariably prepared from simple building blocks, both aromatic (imidazole, pyridine, *etc.*) and aliphatic (amines, alcohols, *etc.*), which are derived from fossil gas and oil, whereas only a limited number of ionic liquids have been prepared from renewable sources.^[5] For instance, anions were synthesized from naturally occurring hydroxy acids^[6] or proteinogenic amino acids,^[7] and cations were obtained from amino alcohols,^[8] hydroxy acids,^[9] amino acids,^[7] and terpenes.^[10] Surprisingly, the most available and inexpensive raw material, *i.e.* carbohydrates, has been hardly exploited in the synthesis of new or known ionic liquids.^[11]

In 2003 Handy and coworkers^[12] described the first synthesis of ionic liquids from naturally occurring sugars. They exploited the transformation of D-fructose (**1**) into monosubstituted imidazoles developed more than fifty years ago by Trotter and Darby,^[13] to prepare **2** in 61% yield (Scheme 1). The authors made some modifications to the original procedure, such as the replacement of H₂S by thioacetamide to remove the copper salts as CuS and the use of column chromatography purification instead of the precipitation as perchlorate salt for the isolation of the hydroxymethylimidazole **2**. The latter compound was alkylated with butyl bromide to give an inseparable 9:1 mixture of **3M** and **3m**, which were methylated and then submitted to anion metathesis. Seven ILs (**4a–g**) were thus prepared and their physical properties were investigated. In particular, it was found that the least viscous ILs of the collection, *i.e.* the triflimide (**4b**) and dicyanimide anion bearing ILs (**4c**), showed opposite solubility behaviors. Then, the ionic liquid **4b** was employed as solvent for model Heck reactions of methyl acrylate with simple aryl iodides in the presence of palladium acetate, the solvent and catalyst being recycled 4–5 times without affecting the efficiency of the reaction. Finally, the kinetics of the reaction of methyl acrylate with iodobenzene in **4b** and butyl-methyl-imidazolium triflimide [bmim][NTf₂] and tetrafluoroborate [bmim][BF₄] were compared. The Heck reaction carried out in **4b** was slower than those performed in the standard, non-protic [bmim] series ionic liquids.

The same year, Handy and Okello^[14] reported on another application of their fructose-derived ionic liquid **4b**. In fact, they exploited the hydroxymethyl group of **4b** to prepare a series of supported Diels-Alder adducts. Usually, the support is made of cross-linked polystyrene



Scheme 1.



Scheme 2.

and is easily separated from the reaction medium by filtration. On the other hand, this kind of support can limit the reaction conditions and features a rather low loading (less than 2 mmol/g). Moreover, the recently developed polyethyleneglycol (PEG)-based supports, whose solubility can be modulated by an appropriate choice of solvent, display an even lower loading (less than 1 mmol/g). On the contrary, taking into account the low molecular weight of **4b**, it was anticipated that this ionic liquid would allow high loadings (>2 mmol/g). The latter feature, together with the solubility properties of **4b** (*i.e.* miscibility with H₂O and CH₃OH, immiscibility with apolar solvents), were the main reasons for its use as a new soluble support. To this aim, the acrylate **5** (Scheme 2) was prepared in almost quantitative yield by reaction of **4b** with acryloyl chloride in the presence of triethylamine. Optimized acylation conditions were required in order to avoid the formation of polymeric material derived by the deprotonation at the C(2) position of the imidazolium moiety. Then, the ester **5** was submitted to standard thermal cycloaddition with cyclopentadiene, cyclohexadiene, and butadiene derivatives to afford the corresponding Diels-Alder adducts **6–8** in good yields (Scheme 2). These supported cycloadducts were then treated

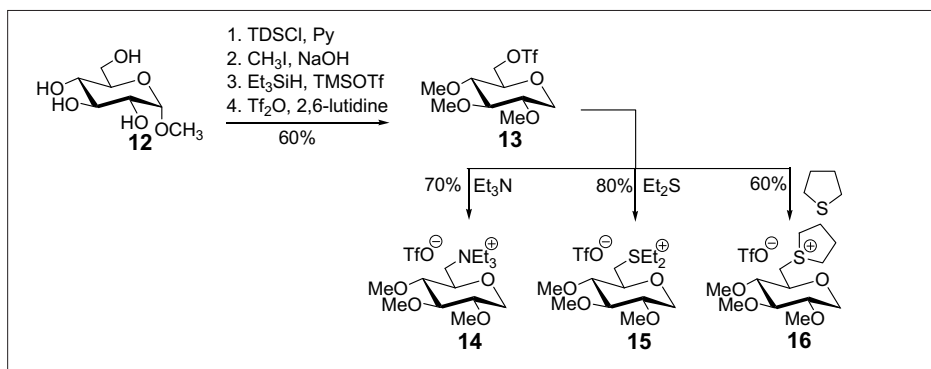
with a base (LiOH, NaOH) in a mixture of water and alcohol to give the expected free acid derivatives. However, for the ionic liquid **4b** milder reaction conditions were required to cleave the Diels-Alder product from the ionic liquid support. Handy and Okello found that the best method was the cyanide-mediated transesterification that gave the corresponding methyl esters **9–11** and allowed the recovery of **4b** in at least 90% yield. It was also demonstrated that the recovered **4b** could be used for further supported syntheses.

In the synthetic approach described above,^[12] the chirality of the starting monosaccharide was not retained in the target ionic liquids and the latter products were isolated as mixtures of achiral regioisomers. The first chiral ILs derived from sugars were described by Poletti and coworkers.^[15] They envisaged the preparation of such ionic liquids because these compounds can act as solvents for asymmetric syntheses, as chiral phases for gas chromatography, and as NMR shift reagents for the determination of the enantiomeric composition of pharmaceutically active products. Moreover, the use of carbohydrates as starting material leads to suitably protected polyoxygenated ionic liquids endowed with high coordination ability, particularly useful for the metal-catalyzed reactions.

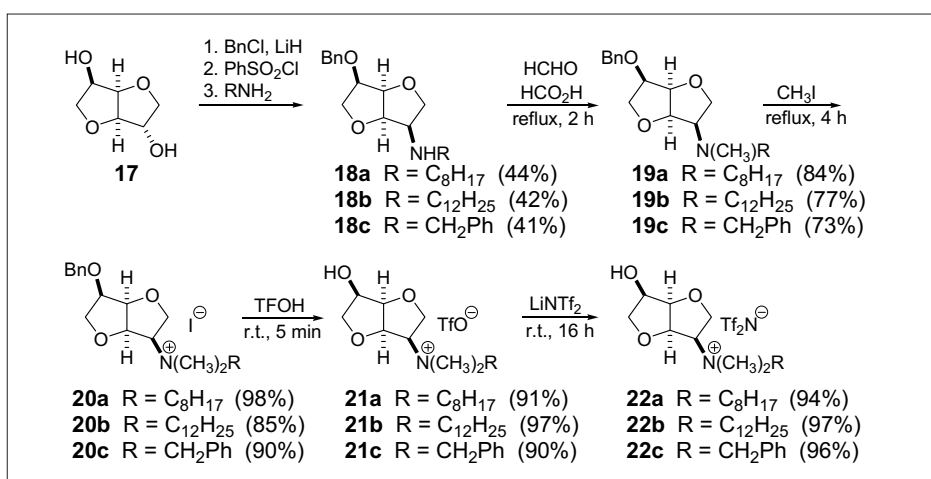
The key intermediate **13**, a tetra-substituted tetrahydropyran derivative, was obtained from commercially available methyl D-glucopyranoside **12** via a four-step reaction sequence (Scheme 3). First the primary hydroxyl group was protected as hexyldimethylsilyl (TDS) ether, then, the other OH groups were methylated under standard conditions. The resulting glycoside was deoxygenated at the anomeric position by treatment with a Lewis acid (trimethylsilyl triflate) and a hydride donor (triethylsilane). This treatment cleaved also the silyl ether protecting group affording the corresponding alcohol in 60% overall yield. The latter compound was converted into the triflate **13**, which was submitted to the subsequent nucleophilic substitutions to give the tetraalkylammonium salt **14** (70%) and the sulfonium salts **15** (80%) and **16** (60%).

Although these compounds were all well soluble in H₂O and scarcely soluble in Et₂O and CH₂Cl₂, their physico-chemical properties were quite different. First of all, **14** and **16** were solid at room temperature while **15** was a liquid. The thermogravimetric analysis demonstrated that **14**, **15**, and **16** did not decompose at temperatures higher than 200 °C, the most thermally stable being the tetraalkylammonium salt **14**. Finally, the three chiral ionic liquids were carefully analyzed by ESI mass spectrometry to assess their ion-pairing behaviors. This investigation revealed that **14** and **15** had a higher ion-pairing than that displayed by **16**, but much lower than that observed for a model imidazolium-based ionic liquid bearing the same anionic counterpart (*i.e.* a triflate ion). Therefore, the cationic moiety of **14** and **15** should interact efficiently with all kinds of dissolved catalyst.

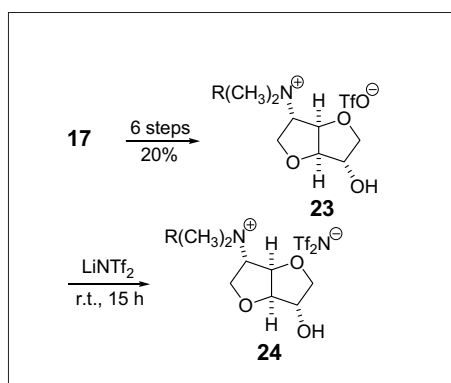
In the same year, a family of new chiral ionic liquids was obtained by Nguyen Van Buu and Vo-Thanh^[16] starting from commercially available isosorbide (1,4:3,6-dianhydro-D-glucitol, **17**), a bicyclic compound obtained in large scale by dehydration of D-sorbitol (Scheme 4). The first step of the synthesis of the new ionic liquids involved the selective protection of the C(3)-OH to give a mono-benzyl ether. Then, the exo OH group at position 6 was quantitatively activated as benzenesulfonate and treated with an excess of three primary amines to afford the corresponding secondary amino derivatives **18a–c** in good yield. The latter compounds were transformed into the tertiary amines **19a–c** by reaction with formaldehyde in formic acid (Eschweiler-Clark reaction). The quaternization of the nitrogen atom, followed by cleavage of the benzyl ether under strong acidic conditions, led to the ionic liquids **21a–c**. It should be noted that the treatment of



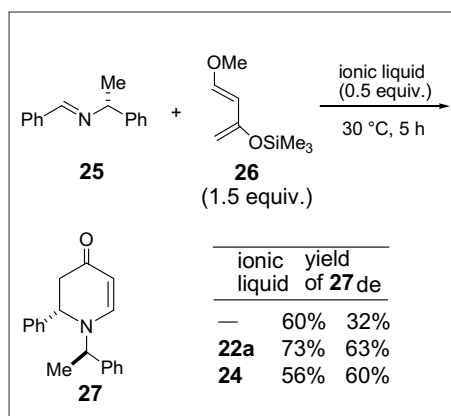
Scheme 3.



Scheme 4.



Scheme 5.



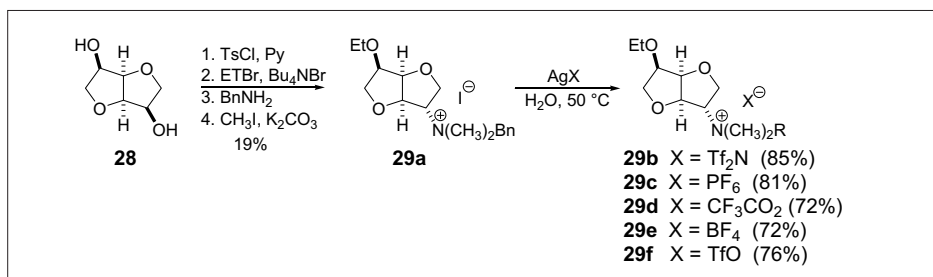
Scheme 6.

20a–c with TFOH caused also the iodide to triflate anion exchange. Moreover, the bistriflimide derivatives **22a–c** were efficiently obtained by reaction of **21a–c** with LiNTf₂. All the salts shown in Scheme 4 were viscous liquids with the exception of **21a** which was a solid.

Exploiting the above-mentioned strategy, the two diastereomeric salts **23** and **24** were prepared from the 6-*O*-benzylated derivative of isosorbide **17** (Scheme 5).

Then, the potential for asymmetric induction of some of these chiral ionic liquids was investigated. The aza Diels-Alder cycloaddition between the chiral imine **25** and the Danishefsky's diene **26** was chosen as the model asymmetric reaction (Scheme 6). As already pointed out in previous studies,^[17] the presence of both an ammonium ion moiety and a free hydroxy function was crucial for the efficient chirality transfer. In fact, when the aza Diels-Alder reaction was carried out in the presence of compounds lacking the OH group or the ammonium ion, poor results were observed. On the other hand, the ionic liquids **22a** and **24** afforded **27** in moderate yields and diastereoselectivities (Scheme 6). Moreover, nearly the same results were obtained by recycling **22a** three times.

A closely related approach was followed by Parmar and Malhotra and co-



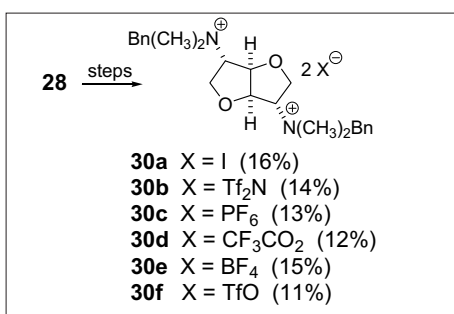
Scheme 7.

workers^[18] to prepare a family of tetraalkylammonium-based chiral ionic liquids starting from commercial isomannide (1,4:3,6-dianhydro-D-mannitol, **28**), prepared on large scale by acid-catalyzed double dehydration of D-mannitol (Scheme 7). It is worth noting that, for synthetic purposes, the isomannide presents an important advantage with respect to isosorbide as starting material. Since the former bicyclic diol is a molecule with C₂-axial symmetry, the protection of the OH groups gives a single monoprotected product together with small amounts of the sterically disfavored diprotected derivative. Under similar reaction conditions, the protection of the isosorbide OH functions is expected to afford a mixture of two mono- and one diprotected derivatives. Isomannide **28** was monotosylated in moderate yield and the other hydroxyl group was transformed into an ethyl ether function under phase-transfer conditions (Scheme 7). The bis-protected compound was treated with benzylamine to afford the corresponding amino derivative showing a total inversion of configuration at

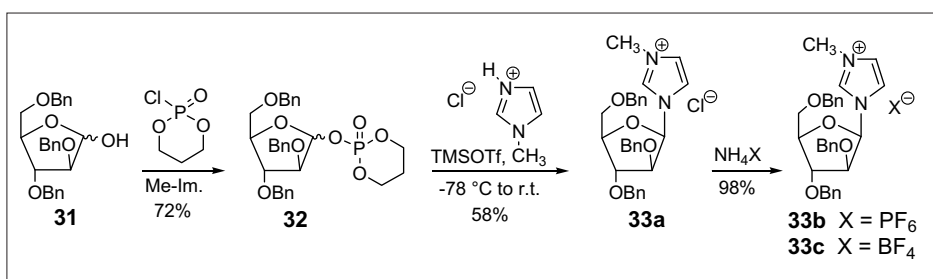
the endocyclic carbon bearing the nitrogen atom. Therefore, by means of the latter reaction the original isomannide unit was converted into an isosorbide moiety. The secondary amine was then directly quaternized by treatment with iodomethane and potassium carbonate to give **29a** that was submitted to the anion metathesis using different silver salts in aqueous solutions. Thus, other five tetraalkylammonium salts **29b–f** were prepared and their physical properties were compared. Only two of these compounds (**29b** and **29d**) were liquids at room temperature, the others were solids with melting points ranging from 80 °C (**29f**) to 170 °C (**29a**). This behavior was not unexpected since it is well known that salts bearing weakly coordinating anions, such as the bistriflimide, trifluoroacetate, and triflate ions, have low melting points. Then the chiral recognition ability of all the above-mentioned salts was investigated by NMR spectroscopy.^[18]

Parmar and Malhotra and coworkers described also the preparation of bis-tetraalkylammonium ionic liquids **30a–f** starting from isomannide **28** (Scheme 8).^[19] All the bis-ammonium derivatives were solid at room temperature, although their melting points exhibited large variation (from 60 °C for **30b** to 251 °C for **30c**).

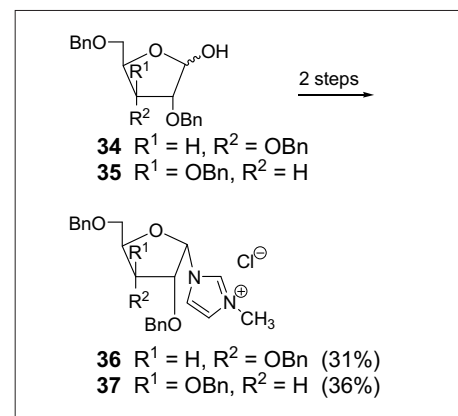
In 2008, the research group of Singh reported the synthesis of imidazolium-based ionic liquids in which the chiral moiety was constituted of a pentofuranoside unit.^[20] The 2,3,5-tri-*O*-benzyl-D-arabinofuranose **31**, easily prepared from commercial D-arabinose in 75% yield



Scheme 8.



Scheme 9.



Scheme 10.

following known procedures, was transformed into the phosphate **32** by reaction with propane-1,3-diylidioxophosphoryl chloride in the presence of 1-methylimidazole (Scheme 9). The mixture of anomeric phosphates was then treated with 1-methylimidazolium chloride and trimethylsilyl triflate to give the ionic liquid **33a** as pure β-D anomer. The latter compound was submitted to the anion metathesis to afford other chiral ionic liquids (**33b–c**) in nearly quantitative yields. The same reaction sequence was repeated using commercially available L-arabinose as starting material in order to obtain the enantiomers of the ionic liquids shown in Scheme 9.

The use of 2,3,5-tri-*O*-benzyl-D-ribofuranose **34** or xylofuranose **35** instead of arabinofuranose **31** as starting material, allowed the straightforward synthesis of two diastereomeric methylimidazolium-based ionic liquids, **36** and **37**, respectively, although only as chloride salts (Scheme 10). The new ILs were stable compounds as proved by the recovery after the use as solvents in presence of organozinc and organomagnesium reagents. Unfortunately, when **33b** was employed as co-solvent for the addition of methylmagnesium chloride to various aromatic aldehydes, the formed chiral alcohols were recovered in almost quantitative yield as racemic mixtures.

Conclusion

In order to develop more environmentally compatible chemical syntheses, the replacement of traditional organic solvents with ionic liquids has attracted considerable attention. However, the 'green' behaviors of these alternative solvents are not fully evident because most ILs are still prepared starting from non-renewable raw material. Therefore, the efficient synthesis, at meaningful scale and reasonable price, of sugar-derived ionic

liquids should contribute to their more widespread utilization.

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