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Supported and liquid phase task specific ionic liquids for base catalysed Knoevenagel reactions

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Abstract

A series of Hünig's base tethered ammonium ionic liquids have been used to catalyse the Knoevenagel condensation of aldehydes/ketones with malononitrile and ethyl cyanoacetate. The reactions were performed under homogeneous and under biphasic, liquid–liquid and liquid–silica supported ionic liquid, conditions with the biphasic systems employing cyclohexene as the second phase. By increasing the distance between the ammonium head group and Hünig's base the activity of the catalyst was found to increase. Higher activity, in general, was found under homogeneous reaction conditions; however, the recyclability of the catalyst was improved by supporting the BIL under biphasic conditions.

Keywords: Supported; Task specific; Ionic liquids; Basic; Knoevenagel

1. Introduction

Base catalysed transformations are frequently used both on small scale as well as large scale in organic synthesis for example in aldol [1], Knoevenagel [2], Henry [3] and Michael [4] reactions. To catalyse these process organic amines, alkali alkoxides, and alkali hydroxides are commonly used as a homogeneous phase with the reagents. Although effective, these reagents are difficult to separate and, in many cases, are not recycled. To alleviate this problem, solid basic catalysts have been developed utilizing either inorganic solid materials, such as base metal oxides and carbonates, or by supporting organic bases, for example amines, on inorganic or polymeric supports. This approach has attracted intense interest and has been reviewed extensively [5]. Effective heterogeneous base catalysis have been found for aldol [6], Knoevenagel [7], Henry [8] and Michael [9] reactions and, in many, cases the solid base is recyclable.

Within the family of base catalysed reactions for fine chemical synthesis, the Knoevenagel condensation is widely employed to synthesize intermediates of fine chemicals. This reaction allows the formation of a C=C double bond from carbonyl compounds and active methylene groups (Scheme 1). For example, the condensation of carbonyl compounds and methylene malonic esters produce several important key industrial products which include nitriles used in anionic polymerization, α,β-unsaturated ester intermediates employed in the synthesis of several therapeutic drugs, for example niphendipine and nitrendipine [10], and pharmacological products, for example calcium channel blockers and antihypertensives may also be produced using this reaction [11]. A wide range of bases can be employed for this condensation; however, alkali metal hydroxides and pyridine as well as other amines such as ethylenediamine and piperidine are the most studied [12]. A wide range of solid catalysts and solid-supported catalysts have also been applied to this reaction such as anion-exchange resins [13], KF [14], magnesium and aluminum oxides, [15] alkali-exchanged and alkali-encapsulated zeolites [16], hydrotalcites [17], amino group-immobilized silica materials [18], clays [19], alkali and alkaline earth carbonates [20], nitridated aluminosilicates and aluminophosphates [21], and porous silicate quaternary ammonium composites [22].

Recently, ionic liquid technology has been utilized to enable base catalysed reactions to occur allowing the base to be recycled and, in some cases, showing higher selectivities compared with

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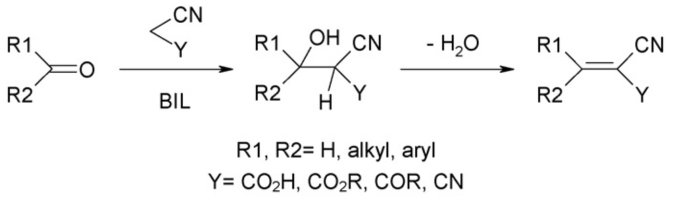

Scheme 1. Base-catalysed Knoevenagel condensation reaction.

Table 1
Textural characteristics of silica and silica with basic ionic liquids

Sample	S_{BET} (m^2 g^{-1})	Pore diameter (nm)
SiO_2 (pH = 4)	287	16
BIL1/SiO_2	139	17
BIL2/SiO_2	149	17
BIL3/SiO_2	142	17

molecular solvents. For example, L-proline has been reported to act as a recyclable chiral base in ionic liquids in the chiral aldol condensations between propanone and a range of aromatic and aliphatic aldehydes [23]. In addition, Forsyth and co-workers have demonstrated that in ionic liquids based on $[NTf_2]^-$ and $[FAP]^-$ significantly higher selectivities are found at high conversion for aldol condensation of 4-*t*-butylbenzaldehyde and propanal to form 3-(4-*t*-butyl-phenyl)-2-methyl-propenal, using piperidine compared with either the industrial process or using piperidine in molecular solvents [24]. Ionic liquids have also been used in combination with solid supports. The Knoevenagel reaction has been performed in ionic liquids catalysed by hydrotalcite achieving excellent conversions after 1 h [25]. Shen et al., immobilized a functionalized imidazolium ionic liquid on to silica gel, producing a solvent free recyclable system for the Knoevenagel condensation and for the cycloadditon of CO_2 with propylene [26]. For each reaction conversions in excess of 90% were reported with a slight decrease upon recycle. Recently, guanidine based ionic liquids have been developed and employed as catalysts for the aldol [27], Henry [28], and Knoevenagel [29] reactions without any loss in catalytic activity after 15 runs. Amino-acids such as glycine and proline [30] have also been used as a promoter in imidazolium ionic liquids for the condensation of aliphatic and aromatic aldehydes with malononitrile and diethylmalonate at 35–55 °C leading to high conversions albeit over a period of 12–48 h.

Herein, we report the Knoevenagel reaction mediated by recyclable basic ionic liquid (BIL) using the methodology of task specific ionic liquids pioneered by Davis et al. [31]. The ionic liquids used are derivatives of the non-nucleophilic Hünig's base tethered to an alkyl ammonium side chain. The cations are shown in Fig. 1 and in each case the counter ion used was bis{(trifluoromethyl)sulfonyl}imide ($[NTf_2]^-$). These ionic liquids were employed as the solvent/catalyst, supported on silica suspended in an organic solvent and as a biphasic system with the BIL in catalytic amounts.

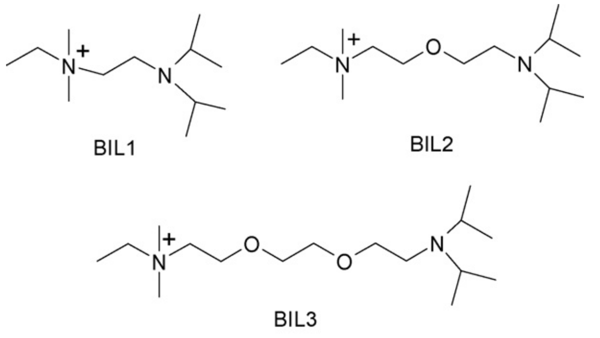

Fig. 1. Structure of the basic ionic liquids (BILs) used in this study.

2. Experimental

2.1. Materials

Unless otherwise stated all reagents (*ex* Aldrich) were used as received. 1-Butyl-1-methylpyrrolidinium bis{(trifluoromethyl)sulfonyl}imide ($[C_4mpyrr][NTf_2]$), 1-butyl-3-methylimidazoluim bis{(trifluoromethyl)sulfonyl}imide ($[C_4mim][NTf_2]$) and 1-butyl-2,3-dimethylimidazloiumium bis{(trifluoromethyl)sulfonyl}imide ($[C_4dmim][NTf_2]$) were prepared in house using standard literature methods [32]. The synthesis and the characteristics of the task specific basic ionic liquids BIL1, BIL2 and BIL3 have previously been reported [33]. In all cases, prior to reaction, the ionic liquids were dried under vacuum at 50 °C overnight. All ionic liquids contained <0.16 wt% water determined by Karl-Fischer analysis and <5 ppm halide by suppressed ion chromatography.

2.2. Preparation and characterisation of the silica supported BIL catalyst

In the case of the silica supported BILs, the catalysts were prepared by stirring 0.35 g of silica (DAVICAT, pH 4, 7 and 10, Davidson Catalysts) and 0.19 mmol of BIL dissolved in 3 cm^3 of methanol. The solvent was removed under vacuum and the BIL/silica was left to dry overnight under vacuum at 50 °C. The BET surface areas and the DRIFTS of the samples formed are shown in Table 1 and Fig. 2, respectively. As expected, after adsorption of the BIL, the BET surface area of the support decreased due to some pore blocking; this is also shown in the small increase in average pore diameter. The DRIFTS were taken on a Bruker Equinox 55 spectrometer, operating at a resolution of 4 cm^{-1} using the mirror as the background. A comparison of the DRIFT spectra from the silica and the silica supported BILs clearly shows additional bands at ~2970 cm^{-1}. These bands are also present in the pure BILs and are due to CH stretching vibrations, as found in other ionic liquid systems [34], indicating the presence of the BIL on the surface of the silica.

2.3. Homogeneous reaction procedure

Typically, malononitrile (0.138 g, 2.09 mmol) or ethyl cyanoacetate (0.235 g, 2.09 mmol) was added to 0.19 mmol of BIL either at room temperature or, in the case of malononitrile,