Chemical Engineering Journal 308 (2017) 664–668

Contents lists available at ScienceDirect

Chemical Engineering Journal

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

Task-specific hexaethylene glycol bridged di-cationic ionic liquids as catalysts for nucleophilic fluorination using potassium fluoride

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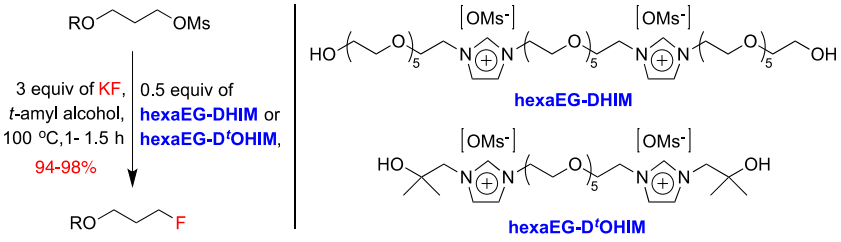
HIGHLIGHTS

- Di-cationic ionic liquids (DCILs) enhanced the reactivity of KF efficiently.
- hexaEG-DHIM and hexaEG-D^{t}OHIM DCILs were used as catalysts for S_N2 fluorination.
- KF/hexaEG-DHIM/*t*-alcohol combination showed excellent selectivity in the fluorination.
- Tailor-made DCILs were well-designed for nucleophilic fluorination.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 19 May 2016
Received in revised form 21 September 2016
Accepted 23 September 2016
Available online 24 September 2016

Keywords:
Di-cationic ionic liquid
Nucleophilic fluorination
Organic catalyst
Alkali metal fluorides
Potassium fluoride

ABSTRACT

A tailor-made di-cationic ionic liquid (DCIL), hexaethylene glycol (hexaEG) bridged bis(2-hydroxy-2-methyl-*n*-propylimidazolium) dimesylate (hexaEG-D^{t}OHIM), was prepared in 94% yield. We investigated the catalytic activity of hexaEG-D^{t}OHIM and hexaEG-bridged bis(3-hexaEGyl imidazolium) dimesylate (hexaEG-DHIM) in nucleophilic fluorination using an alkali metal fluoride (MF) and compared their activities with a variety of mono-cationic ILs. In this reaction, these two task-specific DCILs exhibited much higher catalytic activity than mono-cationic ILs. Moreover, the hexaEG functionalized IL (e.g. hexaEG-DHIM) more effectively enhanced the reactivity of KF compared with the *t*-alcohol functionalized IL (e.g. hexaEG-D^{t}OHIM). In particular, the combination of KF/hexaEG-DHIM in *t*-alcohol media provided excellent chemoselectivity and high chemical yields in the fluorination reaction of base sensitive substrates such as 1-(2-mesyloxyethyl)naphthalene. This protocol was shown to be generally applicable to fluorination reactions with a variety of substrates.

1. Introduction

Ionic liquids (ILs) consisting of bulky organic cations paired with their counter anions have been extensively investigated for various chemical applications as a result of their intrinsic physical and chemical properties [1,2]. Moreover, task-specific ILs, prepared by structural modifications of either the cation or anion component to meet specific needs, have received considerable attention in the chemical engineering area of solvent engineering [3–5]. Recently, a variety of multicationic ionic liquids (MCILs), such as di-, tri-, and polycationic ILs, have been developed to amplify their favorable properties with multiple combinations of cations, anions, and linkers for adapting to a specific chemical task compared with monocationic ILs [6,7].

Considering the importance of biomolecules containing single or only a few fluorine atoms for a range of applications in biomedicinal fields including positron emission tomography (PET) [8,9], nucleophilic fluorination using alkali metal fluorides (MFs) is one of the most fundamental chemical transformations to form the C-F bond at a specific molecular site for preparation of low-fluorinated biomolecules [9–11]. Among MFs, the ready availabil-

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http://dx.doi.org/10.1016/j.cej.2016.09.118
1385-8947/

ity and thermal stability of potassium fluoride (KF) allow it to be widely used as a fluoride source for this type of reaction [10,11]. However, due to low reactivity and poor solubility caused by a tight ion pair interaction, nucleophilic displacement reactions using KF are typically carried out in the presence of phase transfer catalysts (PTCs) such as quaternary ammonium salts [12] or crown ether derivatives [13,14] in polar aprotic media such as CH_3CN, DMF, or DMSO [11,15]. It was reported that the use of imidazolium based ILs as co-solvents delivered good performance in nucleophilic fluorinations using KF due to the PTC effect provided by the imidazolium salt [16,17]. However, even though the fluoride sources, generated by PTCs in polar aprotic media, have high nucleophilicity, it is well-known that these "*naked*" fluoride sources often bring about side-reactions such as competing β-elimination and/or hydroxylation in the fluorination of base-sensitive substrates because of their strong basicity [10,14,18].

In significant recent advances, protic solvents such as *tert*-alcohols [19,20] and oligo-ethylene glycols (oligoEGs) [21,22] were shown to be excellent solvents for nucleophilic fluorinations using MFs. These protic solvents generate the active fluoride source from MFs by controlled hydrogen bonding between the protic solvent and fluoride, which has been called the "flexible" fluoride effect [20,23,24]. In the case of oligoEGs, their oxygen atoms can generate a freer (more reactive) fluoride from ion pairs by chelation with the metal cation [21]. However, *t*-alcohol solvents were not efficient in the same reaction using KF, and oligoEGs are not easily removed for purification due to their high boiling points [19,25]. For the synergistic effect of a protic solvent and IL in a single molecule, *t*-alcohol- or oligoethylene glycol-tethered mono-cationic ILs were developed for nucleophilic fluorination as shown in Fig. 1 [26,27]. These tailor-made ILs could act as multifunctional organic promoters (not solvents), to enhance the reactivity of MFs in the nucleophilic fluorination process compared with conventional ILs. Herein, we introduce more reactive tailor-made di-cationic ionic liquids (DCILs) functionalized with two *t*-alcohol or hexaethylene glycol (hexaEG) groups, that act as organic catalysts designed to enhance the reactivity of KF in nucleophilic fluorination reactions.

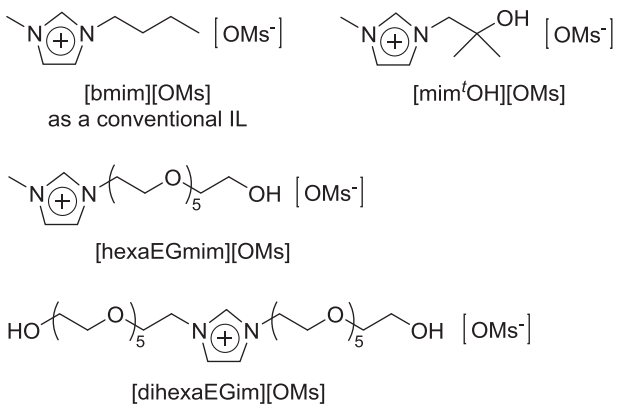

Fig. 1. Conventional and custom-made mono-cationic ionic liquids. bmim = 1-*n*-butyl-3-methylimidazolium; mim^{t}OH = 1-(2-hydroxy-2-methyl-*n*-propyl)-3-methylimidazolium; hexaEGmim = 1-hexaethylene glycol 3-methylimidazolium; dihexaEGim = 1,3-dihexaethylene glycol imidazolium cation; OMs = mesylate anion.

2. Experimental

2.1. Material

Unless otherwise noted, all reagents and solvents were commercially available. Reaction progress was followed by TLC on 0.25 mm silica gel 60 aluminium sheets containing F-254 indicator. Visualization on TLC was monitored by UV light. Flash chromatography was performed with 230–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 600 MHz spectrometer, and chemical shifts were reported in δ units (ppm) relative to tetramethylsilane. Low- and high-resolution electron impact (EI, 70 eV, JEOL JMS-700) spectra were obtained.

2.2. Procedure of hexaEG-bridged bis(2-hydroxy-2-methyl-n-propylimidazolium) dimesylate (hexaEG-D^{t}OHIM)

Hexaethylene glycol dimesylate (**2**) (0.66 g, 1.50 mmol) was added dropwise to the solution of 1-(2-hydroxy-2-methyl-*n*-propyl)imidazole (**1**) (0.43 g, 3.01 mmol) in CH_3CN (25 mL). The reaction mixture was stirred at 90 °C for 24 h, and then evaporated under reduced pressure to remove CH_3CN. The residue was washed repeatedly with diethyl ether (10 mL × 7) and dried under high vacuum for overnight at room temperature to afford 1.01 g (0.94 mmol, 94%) of hexaEG-D^{t}OHIM as a light yellow thick oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (s, 12H), 2.76 (s, 6H), 3.50–3.65 (m, 18H), 3.67–3.90 (m, 5H), 4.14–4.27 (m, 4H), 4,42–4.53 (m, 3H), 7.56 (S, 2H), 7.59 (s, 2H), 9.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.53, 39.78, 49.48, 59.41, 68.87, 68.93, 69.47, 70.36, 122.19, 124.10, 137.59; MS (FAB) *m*/*z* 623.6 (M-OMs)$^+$; HRMS (FAB TOF) *m*/*z* calcd for $C_{27}H_{51}O_{10}N_4S$ (M-OMs)$^+$ 623.3326, found 623.3327.

2.3. Typical procedure of nucleophilic fluorination in Table 1 (entry 5)

KF (174 mg, 3 mmol) was added to the mixture of 2-(3-methane sulfonyloxypropoxy)naphthalene (**3**, 281 mg, 1.0 mmol) and hexaEG-DHIM (551 mg, 0.5 mmol) in *tert*-amyl alcohol (4 mL) in a reaction vial. The reaction mixture was stirred over 1 h at 100 °C. The reaction time was determined by checking TLC. The reaction mixture was filtered and washed with diethyl ether, and the filtrate was evaporated under reduced pressure. Flash column chromatography (10% EtOAc/hexanes) of the filtrate afforded 194 mg (0.95 mmol, 95%) of 2-(3-fluoropropoxy)naphthalene (**4**) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14–2.39 (m, 2H), 4.24 (t, J = 6.2 Hz, 2H), 4.72 (dt, J = 46.8, 5.8 Hz, 2H), 7.16–7.22 (m, 2H), 7.34–7.53 (m, 2H), 7.76–7.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (d, J = 20.1 Hz), 63.6 (d, J = 25.3 Hz), 80.8 (d, J = 163.9 Hz), 106.8, 118.8, 123.6, 126.4, 126.7, 127.6, 129.1, 129.4, 134.6, 156.7; MS (EI) *m*/*z* 204 (M$^+$); HRMS (EI) *m*/*z* calcd for $C_{13}H_{13}FO$(M$^+$) 204.0950, found 204.0932. Registry No. provided by the author: 398-53-8.

3. Results and discussion

Fig. 2A shows the structure of hexaEG-bridged bis(3-hexaEGyl imidazolium) dimesylate (hexaEG-DHIM)DCIL. Recently, we reported that hexaEG-DHIM significantly enhanced the reactivity of water in hydroxylations in neat water media compared with conventional ILs [28]. Considering its structure, we supposed that hexaEG-DHIM might also more efficiently enhance the reactivity of KF. Thus, to investigate the activity and possible application of hexaEG-DHIM in nucleophilic fluorinations using KF, hexaEG-DHIM was prepared according to a previously reported procedure. Fig. 2B illustrates a simple procedure to synthesize hexaEG-bridged