Chemical Engineering Journal 240 (2014) 228–234

Contents lists available at ScienceDirect

Chemical Engineering Journal

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

Short oligo ethylene glycolic tailor-made ionic liquids as highly efficient and reusable catalyst for one-pot synthesis of 1,5-benzodiazepine derivatives under solvent free condition

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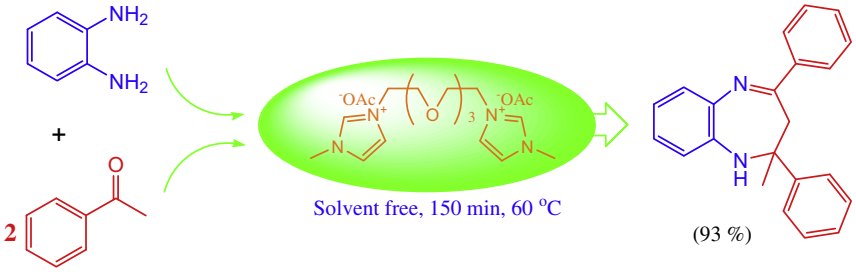
HIGHLIGHTS

- Tailor made short oligo ethylene glycolic dicationic RTILs were synthesized.
- *N*-methyl imidazolium cations and acetate moieties as anions were used.
- RTILs characterized by various methods & evaluated catalytic activity.
- Catalytic activity of RTILs was tested for benzodiazepine synthesis.
- Effects of different solvent system on catalyst were also determined.

GRAPHICAL ABSTRACT

Short oligo ethylene glycolic tailor-made ionic liquids as highly efficient and reusable catalyst for one-pot synthesis of 1,5-benzodiazepine derivatives under solvent free condition.



ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 11 November 2013
Accepted 23 November 2013
Available online 27 November 2013

Keywords:
Dicationic ionic liquids
Imidazolium salt
Benzodiazepine
Solvent free reactions
Homogeneous catalyst

ABSTRACT

Dicationic room temperature ionic liquids (RTILs) based on 1-methylimidazolium salts with varying their linkage chain between the cations were synthesized, characterized, and evaluated their catalytic activity for the synthesis of 1,5-benzodiazepine derivatives under solvent free mild reaction condition. On screening, all new synthesized imidazolium based dicationic RTILs showed efficient yields and selectivity of respective benzodiazepine. Especially, 5 wt% of tetraethylene glycol-bis (3-methylimidazolium) diacetate ([tetraEG(mim)$_2$][OAc]$_2$) was found to be the best dicationic RTIL as catalyst for this reaction. All these reactions were preceded very well under relatively mild reaction condition without addition of any co-catalyst and solvent. The present RTILs catalytic system compared with several homogeneous, heterogeneous catalysts. Moreover, effects of different solvent system on benzodiazepine reactions with these RTILs were also determined.

1. Introduction

With their unique set of properties not attainable with any other material, ionic liquids (ILs) have gained overwhelming interest over the past few years. Low volatility, chemical and thermal stability, reusability and eco-friendliness are the key properties to develop green and sustainable chemical processes. Therefore, ILs have been used as green reaction media and structure directing agents [1–4]. The low vapour pressure of ILs makes them potential substituent for highly volatile organic solvents thus reducing the amount of pollution caused by solvent evaporation. Especially, imidazolium based ILs played important role in various organic reactions as a catalyst or alternative for conventional solvents [5–14].

Room temperature dicationic ILs have been widely used in various fields of science and in biological activities such as antiviral, antifungal and anticancer activities [1–4,15–17]. Tailor-made

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http://dx.doi.org/10.1016/j.cej.2013.11.046

dicationic ILs explored their opportunity to design unique structure with respect to cation, anion and length of linker chain in between two cations to achieve significant properties according to specific chemical tasks [18–24]. Indeed, pyrrolidinium and imidazolium based dicationic ILs have been showed superior favorable range of physicochemical properties [1–4,25]. Imidazolium rings accompanying via alkyl, aryl, fluoroalkyl, and alkoxy chains were used as an linker with halogenated anions have been showed to possess good thermal stability (>300 °C), volatility properties, promising catalytic activity, and effective reaction media for different varieties of organic reactions [1–4,26–28]. Structurally tailored imidazolium based dicationic ILs have been also successfully applied in the field of zeolite synthesis, biomass conversion, cellulose dissolution processes, and in various organic transformations [25,29–31]. However, halogenated dicationic ILs are expensive to synthesize, antagonistic properties, and complex procedures are environmentally unsafe [1–6]. These drawbacks provoked us to develop more special imidazolium based dicationic RTILs from commercially accessible sources and environmentally benign with high yielding process considering the diversity of dicationic RTILs. Recently, we reported short oligo ethylene glycol functionalized imidazolium based dicationic RTILs as a catalyst for azidation reaction and in dehydration of fructose and sucrose into 5-hydroxymethylfurfural (HMF) [32–34]. In continuation of this work, new development of structurally altered dicationic RTILs and their use as catalyst in synthesis of 1,5-benzodiazepine under solvent free condition is drawing more attention in our laboratory.

Benzodiazepines represent a significant class of biologically active nitrogen-containing compounds which exhibit a number of important biological or pharmacological properties, such as anticonvulsant, antianxiety, analgesic, hypnotic, antiinflammatory, antidepressive, anti-ulcerative, antiallergic, antihistaminic, and antipyretic [35–39]. In addition, diazepines and their derivatives are used for the preparation of number of fused ring compounds such as oxazino, triazolo, or furano-benzodiazepines [40]. Derivatives of benzodiazepines are also used as dyes for acrylic fibers in photography for their distinct electron mobility have been developed as layer materials for electron transformation [41]. However, their wide applications in pharmacological, industrial, and in synthetic applications, the preparation of benzodiazepines have received attention and various methods for their synthesis are reported in the literature [35–41]. Including, condensation reaction of *o*-phenylenediamine with α–β unsaturated carbonyl compounds, β-haloketones or ketones in presence of BF_3-diethyl ether, $NaBH_4$, polyphosphoric acid or SiO_2, MgO and $POCl_3$, Yb-$(OTf)_3$ [42–48]. Recently, Al_2O_3/P_2O_5 and acetic acid under microwave irradiation were also showed substantial activity in synthesis of benzodiazepines [49,50]. In addition, ionic liquids were also displayed promising results in synthesis of diazepines as a catalyst or solvent [51,52].

However, many of these reaction methods have several limitations such as drastic reaction conditions, tedious work-up procedures, low to adequate yields, expensive reagents and solvent, existence of several side reaction products and relatively long reaction period. Furthermore, the main drawback of most of the existing methods is that, the catalysts are devastated in work- up procedure and could not be recovered or reused easily. Therefore, there is essential need for homogeneous catalyst for the synthesis of benzodiazepines in high yield with significant selectivity in environmental benign reaction condition. Recent developments in organic reactions lead to new eco-benign reaction procedures that save utilization of energy and preserve green reaction procedure. Solvent free organic reactions show various advantages over traditional reactions in organic solvents, such reactions are reducing the load of organic solvent disposal and improve the rate of organic reactions [40]. Therefore, the development of an environmental benign homogeneous catalytic system which is more efficient, highly selective, and less expensive for the synthesis of 1,5-benzodiazepines under solvent free condition is enormously desirable.

Herein, we disclose the imidazolium based dicationic RTILs were functionalized with short oligo ethylene glycol chains as linker in between two imidazolium cations with acetate (CH_3COO^-) groups as anion moiety. These new synthesized and characterized dicationic RTILs were applied in catalytic amount for the synthesis of benzodiazepine derivatives in solvent free condition. Moreover, influence of amount of catalyst, various solvents, and comparison with other homogeneous and heterogeneous catalyst in diazepine reactions were investigated as well as various substituted derivatives were prepared by using synthesized dicationic RTIL as catalyst.

2. Experimental

2.1. Material

N-methylimidazole (99.0%), tetraethylene glycol (99.0%), triethylene glycol (99.0%), diethylene glycol (99.0%), triethyl amine (99.0%), methane sulfonyl chloride (99.0%), sodium acetate (99.0%) sodium sulphate (99.0%), dimethyl sulfoxide (DMSO) (99.9%), and all substrate for 1,5-benzodiazepine derivatives were purchased from Sigma Aldrich. Reagents were used as received without further purification. All solvents were purchased from commercial sources and were distilled from relevant agents prior to use. TLC analysis was performed on silica-gel Poly Gram SIL G/UV 254 plates to monitor the reactions.

2.2. Procedure for synthesis of mesylate anion RTILs

All short oligo ethylene glycol dimesylate precursors and mesylate anions containing RTILs (Scheme 1) were synthesized and characterized according our previous method and detail characterization data were also mentioned in our previous reported method [32].

2.3. Procedure for synthesis of acetate anion RTILs

2.3.1. Tetraethylene glycol-bis (3-methylimidazolium) diacetate ([tetraEG(mim)$_2$][OAc]$_2$) (1)

A mixture of tetraethylene glycol-bis (3-methylimidazolium) dimesylate ([tetraEG(mim)$_2$][OMs]$_2$) (1.0 mmol) RTIL and sodium acetate NaOAc (2.0 mmol) in acetonitrile was stirred magnetically for 5 days in a single necked round bottom flask at room temperature. After completion of reaction, the reaction mixture was filtered by using Whatman filter paper. The solid NaOMs salt could be easily separated by using simple filtration process by using Whatman filter paper. The residue was washed three times by acetonitrile and filtrate was collected, solvent was evaporated from the filtrate under reduced pressure on rotary evaporator and afforded thick oily liquid. The thick oily liquid (RTIL) was washed three times with ethyl acetate to remove unreacted starting materials and resulting quaternized tetraethylene glycol-bis (3-methylimidazolium) diacetate ([tetraEG(mim)$_2$][OAc]$_2$) (**1**): Yield 76%; oily liquid; ^{1}H NMR (400 MHz, DMSO): δ 9.20 (s, 2 × H), 7.53 (s, 2 × H), 7.51 (s, 2 × H), 4.32 (t, *J* = 4.8 Hz, 2 × 2H), 3.84 (s, 2 × 3H), 3.70 (t, 2 × 2H), 3.59 (t, 2 × 2H); 3.49 (s, 2 × 2H); 2.31 (s, 2 × 3H), ^{13}C NMR (100 MHz, DMSO): δ 170.80, 137.45, 123.08, 123.06, 68.46, 63.50, 48.94, 39.26, 33.13, 21.04. FT-IR (500–4000 cm^{-1}): 3097 [υ(Ar—H)]; 2931, 2849 [υ(C—H)]; 1733 [υ(C=O)]; 1612 [υ(C=N)]; 1569, 1448, 1427 [υ(C=C)]; 1190, 1038; [υ(C—O)]; 1157. MS-ESI: *m/z* [M—OAc]$^+$ calcd: 383.23; found: 383.19. Elem. Anal. Calc. (%)