Journal of Molecular Liquids 178 (2013) 113–121

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Liquids

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

Synthesis, characterization and application of ionic liquid 1,3-disulfonic acid imidazolium hydrogen sulfate as an efficient catalyst for the preparation of hexahydroquinolines

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ARTICLE INFO

Article history:
Received 23 March 2012
Received in revised form 15 October 2012
Accepted 25 October 2012
Available online 10 December 2012

Keywords:
Brønsted acidic ionic liquid
1,3-Disulfonic acid imidazolium hydrogen sulfate {[Dsim]HSO_4}
Hexahydroquinoline
Self-assembly

ABSTRACT

In this work, novel Brønsted acidic ionic liquid 1,3-disulfonic acid imidazolium hydrogen sulfate {[Dsim]HSO_4} is synthesized, and characterized by studying its FT-IR, ^{1}H NMR, ^{13}C NMR, mass, TG, DTG and XRD spectra. This ionic liquid, with three acidic functional groups, is utilized as a highly efficient, homogeneous and reusable catalyst for the preparation of hexahydroquinolines via one-pot multi-component condensation of arylaldehydes, dimedone (5,5-dimethylcyclohexane-1,3-dione), β-ketoesters and ammonium acetate under solvent-free conditions. The catalyst can form dual hydrogen-bond using its SO_3H groups which this subject can direct to its assembly and efficiency.

1. Introduction

Ionic liquids (ILs) have attracted a rising interest in the last decades from chemists because of their unique properties including non-flammability, non-volatility, wide liquid-state temperature range, high thermal and chemical stability, large electrochemical window and favorable salvation behavior [1,2]. These compounds have been extensively applied in electrochemistry [3], spectroscopy, extraction and separation processes [1], and as a solvent, a catalyst and a reagent in organic synthesis [1,2,4–10]. Among the different kinds of ILs, Brønsted acidic ones have offered a possibility for the development of environmental friendly acid catalysts for organic transformations, because of combining the advantages of liquid and solid acids, their operational simplicity, efficacy and selectivity coupled with their green natures [11–18].

A one-pot process is a promising plan of the novel organic synthesis in which a sequence of reactions without isolating intermediates is performed. In this kind, proceeding with studies on the synthesis of compounds by one-pot multi-component reactions (MCRs) have been of ongoing interest, since MCRs preferably are facile, fast, and efficient with a minimal workup [19–21]. Moreover, in these types of reactions, complex molecules can be assembled under mild conditions, often regio- and stereoselectively [22]. MCRs have also proven to be a valuable asset in medicinal chemistry, drug design, and drug discovery because of their simplicity, efficiency, and high selectivity. Such protocols can reduce the number of steps and present advantages, such as low energy consumption and little to no waste production, leading to desired environmentally friendly processes [23].

The one-pot multi-component symmetrical 1,4-dihydropyridines (1,4-DHPs) yielding Hantzsch reaction was first established by Hantzsch in 1881, and has attracted considerable attention over the years because of its efficiency to yield bioactive dihydropyridines [24]; therefore, current literature reveals that the synthesis of 1,4-dihydropyridines is an important goal in organic synthesis for the reason that 1,4-DHPs exhibit a variety of biological properties such as a vasodilator, a bronchodilator, an antiatherosclerotic, an antitumor, a geroprotective, and a hepatoprotective, as well as their antidiabetic activities [25–28]. 1,4-DHPs are used as the most popular drug as calcium channel blockers and also possess the disordered heart ratio as a chain cutting agent of factor IV channel [29–31].

Photochemical decomposition of drugs may lead to a decrease in their therapeutic effectiveness or even to the appearance of toxic products. Sometimes, intake of photochemically changed drugs may induce hypersensitivity to light resulting possibly in phototoxic and photoallergic effects [32,33]. The long list of photosensitive drugs includes,

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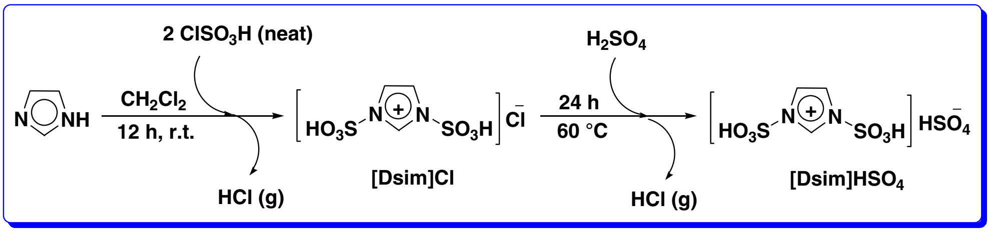
http://dx.doi.org/10.1016/j.molliq.2012.10.045



Scheme 1. The synthesis of 1,3-disulfonic acid imidazolium hydrogen sulfate {[Dsim]HSO_4}.

DHP derivatives that have been synthesized [34,35]. According to literature data, one of the methods to decrease the photosensitivity of these compounds was their modification leading to new groups, e.g., hexahydroquinoline derivatives (HHQs) which were synthesized according to the modified Hantzsch synthesis via the one-pot multi-component condensation reaction between arylaldehydes, dimedone (5,5-dimethylcyclohexane-1,3-dione), β-ketoesters and ammonium acetate, by Safak and coworkers [36,37]. The HHQ derivatives are structurally similar to the DHP derivatives used for many years in medical therapy, e.g., their common element is the presence of the dihydropyridine ring that on illumination is easily oxidized to the aromatic pyridine ring [38,39]. Moreover, some other methods and catalysts have been developed for the preparation of HHQs [40–48].

In this work, we report the synthesis of Brønsted acidic ionic liquid 1,3-disulfonic acid imidazolium hydrogen sulfate {[Dsim]HSO_4}, from available and inexpensive starting materials, for the first time (Scheme 1), and its full characterization by using FT-IR, ^1H NMR, ^{13}C NMR, TG (thermal gravimetric), DTG (derivative thermal gravimetric) and XRD spectra. Afterward, we use this ionic liquid as a highly efficient, homogeneous and recyclable catalyst for the preparation of hexahydroquinolines via the one-pot multi-component condensation of dimedone (5,5-dimethylcyclohexane-1,3-dione), arylaldehydes, β-ketoesters and ammonium acetate under solvent-free conditions (Scheme 2).

Molecular self-assembly including intramolecular and intermolecular, is the process by which molecules adopt a defined arrangement without guidance or management from an outside source. Most often the term molecular self-assembly refers to intermolecular self-assembly, and assembly of molecules is directed through noncovalent interactions (such as hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π–π interactions and electrostatic) as well as electromagnetic interactions [49–52]. The specific structure of [Dsim]HSO_4 as a three functional Brønsted acidic ionic liquid with dual hydrogen-bond donors for any of these functional groups, can give it the ability to produce a molecular self-assembly through hydrogen bonds (Figs. 1 and 2). On the basis of the structure of [Dsim]HSO_4, it can act as an efficient catalyst in reactions which need the use of acidic catalysts to accelerate the rate of reaction.

2. Experimental

2.1. General

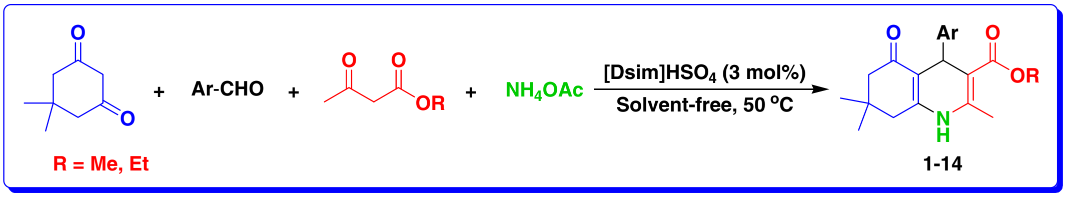
All chemicals were purchased from Merck, Aldrich or Fluka Chemical Companies. All known compounds were identified by a comparison of their melting points and NMR data with those reported in the literature. The ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) were run on Bruker Avance DPX FT-NMR spectrometers. Mass spectra were obtained with a Shimadzu GC–MS-QP 1100 EX model. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.2. Procedure for the preparation of ionic liquid 1,3-disulfonic acid imidazolium hydrogen sulfate [Dsim]HSO_4 (Scheme 1)

To a round-bottomed flask (100 mL) containing imidazole (0.340 g, 5 mmol) in dry CH_2Cl_2 (50 mL), was added chlorosulfonic acid (1.1885 g, 10.2 mmol) dropwise over a period of 20 min at room temperature. After the addition was completed, the reaction mixture was stirred for 12 h under pressure of nitrogen gas, let it stand for 5 min, and the CH_2Cl_2 was decanted. The residue was washed with dry CH_2Cl_2 (3 × 50 mL) and dried under vacuum to give 1,3-disulfonic acid imidazolium chloride {[Dsim]Cl} as a viscous pale yellow oil in 95% yield [16]. Then, sulfuric acid (99.99%) (0.49 g, 5 mmol) was added dropwise to [Dsim]Cl (1.63 g, 5 mmol) over a period of 5 min at room temperature under pressure of nitrogen gas (to remove the produced HCl during the reaction). The resulting mixture was stirred for 24 h at 60 °C under continuous flow of nitrogen gas to give [Dsim]HSO_4 as a viscous yellow oil in 99% yield. IR (Nujol): 624, 1031, 1053, 1085, 1285, 1324, 3100–3400 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.22 (s, 2H), 8.44 (s, 1H), 11.95 (s, 1H), 13.55 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 119.5, 134.0; MS: *m/z* 326 (M^+).

2.3. General procedure for the synthesis of hexahydroquinolines (Scheme 2)

To a mixture of dimedone (0.28 g, 2 mmol), arylaldehyde (2 mmol), β-ketoester (2 mmol) and ammonium acetate (0.185 g, 2.4 mmol) in a test tube, was added [Dsim]HSO_4 (0.02 g, 0.06 mmol), and the resulting mixture was firstly stirred magnetically, and after solidification of the reaction mixture with a small rod, at 50 °C. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature, ethyl acetate (20 mL) was added, stirred and refluxed for 3 min, and decanted (the product is soluble in hot ethyl acetate; however, [Dsim]HSO_4 is not soluble in this solvent). The viscous oil residue was washed with hot ethyl acetate (10 mL) to give the pure recycled catalyst. The decanted solutions were then combined, washed with water (20 mL) and dried. The solvent was evaporated and the crude product was purified by recrystallization from ethanol (95%) or column chromatography eluted with *n*-hexane/ethyl acetate (4/1). In this work, [Dsim]HSO_4 was recycled and reused for three times without significant loss of its catalytic activity.



Scheme 2. The one-pot multi-component preparation of hexahydroquinolines catalyzed by [Dsim]HSO_4.