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

Abdolkarim Zare [a,*], Fereshteh Abi [a], Ahmad Reza Moosavi-Zare [b], Mohammad Hassan Beyzavi [c], Mohammad Ali Zolfigol [d,*]

[a] Department of Chemistry, Payame Noor University, PO Box 19395-4697 Tehran, Iran
[b] Department of Chemistry, University of Sayyed Jamaleddin Asadabadi, Asadabad, 6541835583, Iran
[c] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
[d] Faculty of Chemistry, Bu-Ali Sina University, Hamedan, 6517838683, Iran

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].

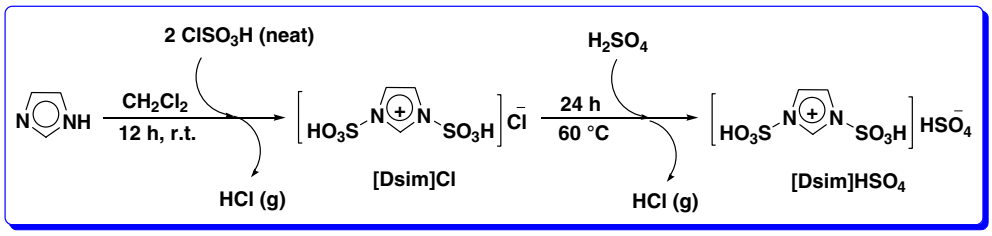
A one-pot process is a promising plan of the novel organic synthesis in which a sequence of reactions without isolating intermediates is performed. In this kind, proceeding with studies on the synthesis of compounds by one-pot multi-component reactions (MCRs) have been of ongoing interest, since MCRs 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,

* Corresponding authors. Fax: +98 771 5559489.
E-mail addresses: abdolkarimzare@yahoo.com (A. Zare), mzolfigol@yahoo.com (M.A. Zolfigol).

0167-7322/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
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, ^{1}H 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

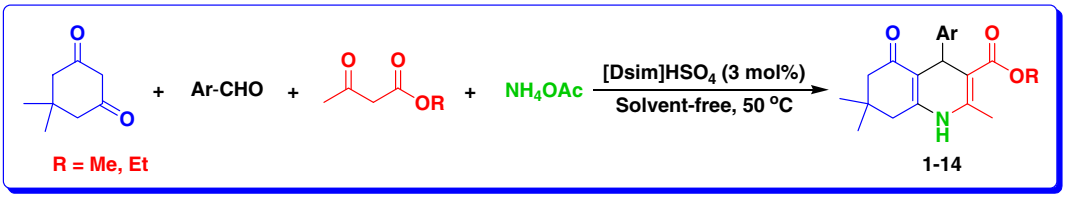
All chemicals were purchased from Merck, Aldrich or Fluka Chemical Companies. All known compounds were identified by a comparison of their melting points and NMR data with those reported in the literature. The ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) were run on Bruker Avance DPX FT-NMR 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}; ^{1}H 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.

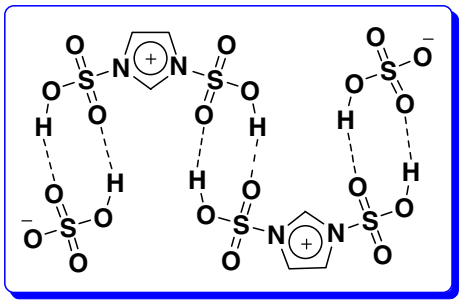


Fig. 1. Molecular self-assembly of [Dsim]HSO_4 by hydrogen bonds.

2.4. Selected spectral data of the products

Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**1**): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.85 (s, 3H), 1.00 (s, 3H), 1.13 (t, J=7.0 Hz, 3H), 2.01–2.20 (m, 2H), 2.29 (s, 3H), 2.38–2.50 (m, 2H), 3.97 (q, J=7.0 Hz, 2H), 4.82 (s, 1H), 7.05 (m, 1H), 7.18 (t, J=6.7 Hz, 2H), 7.21 (t, J=6.5 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 14.5, 18.8, 26.8, 29.5, 32.6, 36.5, 50.6, 59.6, 103.4, 109.9, 113.5, 126.9, 128.8, 130.5, 146.0, 150.3, 167.0, 194.7.

Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**2**): ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.92 (s, 3H), 1.10 (s, 3H), 1.19 (t, J=7.1 Hz, 3H), 2.16 (d, J=16.4 Hz, 2H), 2.24–2.29 (Distorted AB system, 2H), 2.41 (s, 3H), 4.07 (q, J=7.1 Hz, 2H), 5.18 (s, 1H), 6.68 (s, 1H), 7.51 (d, J=8.5 Hz, 2H), 8.09 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 14.6, 19.8, 27.5, 29.8, 33.1, 37.7, 41.3, 51.0, 60.5, 105.3, 111.4, 123.7, 129.4, 145.0, 146.6, 149.6, 154.9, 167.3, 195.9.

Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**4**): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.85 (s, 3H), 1.00 (s, 3H), 1.14 (t, J=7.0 Hz, 3H), 1.96 (d, J=16.0 Hz, 1H), 2.15 (d, J=16.1 Hz, 1H), 2.27 (s, 3H), 2.37–2.49 (m, 2H), 3.66 (s, 3H), 3.97 (q, J=7.0 Hz, 2H), 4.79 (s, 1H), 6.73 (d, J=8.3 Hz, 2H), 7.05 (d, J=8.3 Hz, 2H), 8.99 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 14.6, 18.7, 26.9, 29.6, 32.6, 35.4, 50.6, 55.3, 59.4, 104.4, 110.7, 113.5, 128.8, 140.5, 145.1, 149.7, 157.7, 167.4, 194.7.

Ethyl 2,7,7-trimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5**): ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.96 (s, 3H), 1.08 (s, 3H), 1.24 (t, J=7.1 Hz, 3H), 2.15–2.31 (m, 7H), 2.35 (s, 3H), 4.09 (q, J=7.1 Hz, 2H), 5.04 (s, 1H), 6.76 (s, 1H), 7.02 (d, J=7.8 Hz, 2H), 7.21 (d, J=7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 14.7, 19.7, 21.5, 27.6, 29.8, 33.1, 36.6, 41.3, 51.2, 60.2, 106.6, 112.4, 128.3, 129.0, 135.8, 143.9, 144.7, 149.3, 167.9, 196.1.

Ethyl 4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**6**): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.86 (s, 3H), 1.00 (s, 3H), 1.14 (t, J=7.0 Hz, 3H), 1.96 (d, J=16.0 Hz, 1H), 2.15 (d, J=16.1 Hz, 1H), 2.26 (s, 3H), 2.36–2.49 (m, 2H), 3.96 (q, J=7.0 Hz, 2H), 4.74 (s, 1H), 6.56 (d, J=8.1 Hz, 2H), 6.93 (d, J=8.1 Hz, 2H), 8.94 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 14.6, 18.7, 26.9, 29.6, 32.6, 35.3, 50.8, 59.4, 104.6, 110.8, 114.9, 128.8, 138.9, 144.8, 149.6, 155.7, 167.5, 194.7.

Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**7**): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.83 (s, 3H), 0.99 (s, 3H), 1.10 (t, J=6.9 Hz, 3H), 1.96 (d, J=16.0 Hz, 1H), 2.16 (d, J=16.1 Hz, 1H), 2.29 (s, 3H), 2.38–2.49 (m, 2H), 3.97 (q, J=7.0 Hz, 2H), 4.84 (s, 1H), 7.11 (d, J=7.2 Hz, 2H), 7.37 (d, J=7.2 Hz, 2H), 9.09 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 14.6, 18.8, 26.9, 29.5, 32.6, 36.2, 50.6, 59.5, 103.5, 110.1, 119.1, 130.2, 131.0, 145.8, 147.4, 150.0, 167.1, 194.7.

Methyl4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**12**): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.84 (s, 3H), 0.99 (s, 3H), 1.97 (d, J=16.0 Hz, 1H), 2.15 (d, J=16.1 Hz, 1H), 2.28 (s, 3H), 2.37–2.49 (m, 2H), 3.52 (s, 3H), 3.66 (s, 3H), 4.81 (s, 1H), 6.73 (d, J=7.4 Hz, 2H), 7.05 (d, J=7.4 Hz, 2H), 9.02 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 18.7, 26.9, 29.6, 32.6, 35.2, 50.7, 51.1, 55.3, 104.0, 110.7, 113.6, 128.7, 140.3, 145.4, 149.7, 157.7, 167.9, 194.7.

Methyl4-(3-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**14**): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.83 (s, 3H), 1.00 (s, 3H), 1.99 (d, J=16.0 Hz, 1H), 2.18 (d, J=16.1 Hz, 1H), 2.30 (s, 3H), 2.39–2.49 (m, 2H), 3.53 (s, 3H), 4.85 (s, 1H), 7.14–7.16 (m, 2H), 7.25–7.27 (m, 2H), 9.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 18.8, 26.8, 29.5, 32.6, 36.3, 103.1, 109.9, 121.6, 126.8, 129.1, 130.5, 130.6, 146.3, 150.3, 150.5, 167.5, 194.7; MS: m/z 404 (M^+).

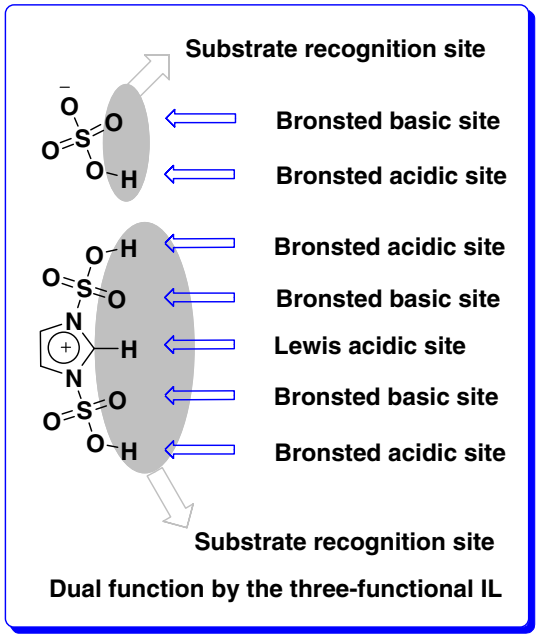


Fig. 2. The structure of [Dsim]HSO_4.

3. Results and discussion

The structure of Brønsted acidic ionic liquid 1,3-disulfonic acid imidazolium hydrogen sulfate was identified by studying its FT-IR, ^{1}H NMR, ^{13}C NMR, mass, TG, DTG and XRD spectra. The full details of FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectra were reported in the Experimental section.

In this section, we study FT-IR, ^{1}H NMR, mass, TG, DTG and XRD spectra of the ionic liquid:

The IR spectrum of [Dsim]HSO_4 showed a broad peak at 3100–3400 cm^{-1} related to the OH of the SO_3H groups. Moreover, two peaks observed in 1085 cm^{-1} and 1285 cm^{-1} correspond to the vibrational modes of N–SO_2 bond.

The ^{1}H NMR spectrum of [Dsim]HSO_4 showed two peaks related to the two types of the acidic hydrogens (SO_3H) in 13.55 and 11.95 ppm. To prove that this peak corresponds to the hydrogen of SO_3H in the compound, we also ran the ^{1}H NMR spectra of the starting materials for the preparation of the ionic liquid (i.e., [Dsim]Cl and H_2SO_4) in DMSO-d_6 wherein the peaks of the acidic hydrogens of [Dsim]Cl and H_2SO_4 were observed in 13.34, and 12.54 ppm, respectively. The difference between the peaks of the acidic hydrogens in the compounds confirmed that the peaks observed in 13.55

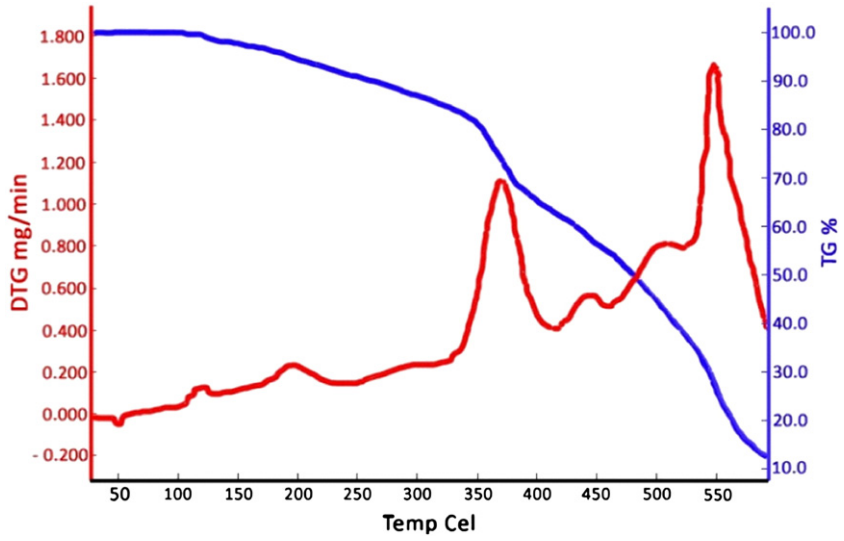


Fig. 3. TG and DTG diagrams of the ionic liquid.

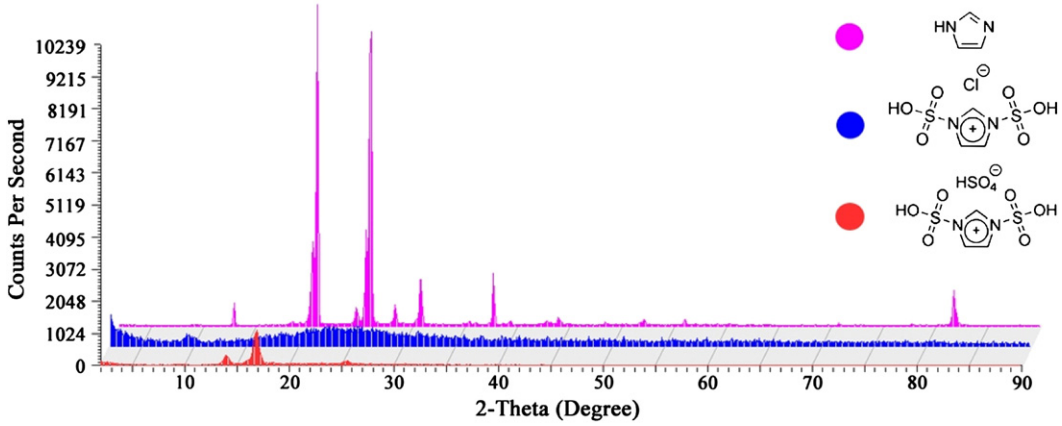


Fig. 4. The XRD patterns of imidazole, [Dsim]Cl and [Dsim]HSO_4.

and 11.95 ppm of the ^{1}H NMR spectra of [Dsim]HSO_4 is correctly related to the hydrogen of the SO_3H groups of this compound.

The mass spectrum of the compound gave the correct molecular ion peak in 326 *m/z*.

Thermal gravimetric (TG) and derivative thermal gravimetric (DTG) analyses of 1,3-disulfonic acid imidazolium hydrogen sulfate were studied in a range of temperature between 25 and 600 °C (Fig. 3). The TG and DTG of the catalyst showed two weight losses; the first strong loss weight was observed after 350 °C, and the second strong weight loss appears after 540 °C. Therefore, the molecular decomposition of the ionic liquid occurred after 350 °C.

In another study, the XRD patterns of imidazole, [Dsim]Cl and [Dsim]HSO_4 in a domain of 0–90° were compared (Fig. 4). As Fig. 4 indicates, the XRD pattern of imidazole was revealed in $2\theta \approx 13°$, 20°, 24°, 26°, 28°, 31°, 38° and 81°. The XRD pattern of [Dsim]Cl showed a broad maximum that was assigned to an amorphous peak in $2\theta \approx 16–38°$. Finally, the XRD pattern of [Dsim]HSO_4 appeared in $2\theta \approx 14°$, 17° and 25°. These results showed that the arrangement in [Dsim]HSO_4 is more than that of in [Dsim]Cl due to an increase of the acidic functional groups with dual hydrogen-bond donors for any of these functional groups, and its molecular self-assembly (Figs. 1 and 2).

To confirm that 1,3-disulfonic acid imidazolium chloride {[Dsim]Cl} was completely converted to [Dsim]HSO_4, a solution of $AgNO_3$ in distilled water was added to a solution of the ionic liquid in distilled water. The absence of AgCl precipitate indicated a complete conversion of the [Dsim]Cl to [Dsim]HSO_4 [13,18].

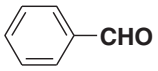
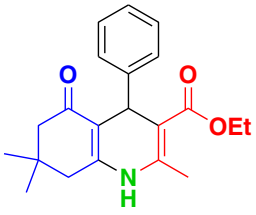
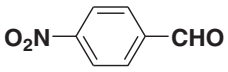
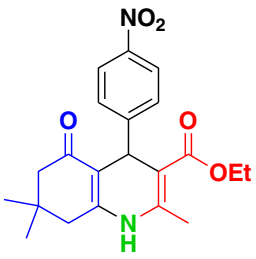
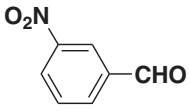
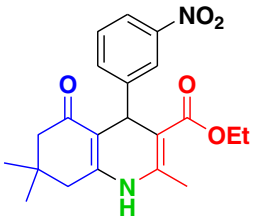
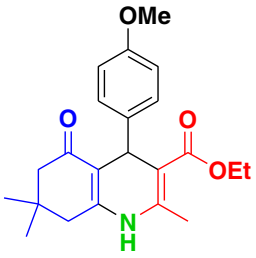
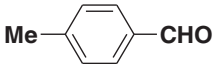
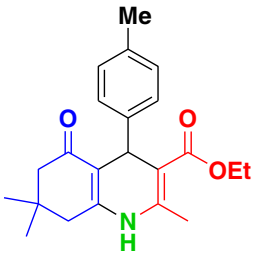
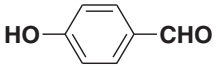
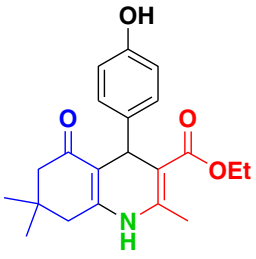
After the full characterization of [Dsim]HSO_4, we examined its catalytic activity to promote the synthesis of hexahydroquinolines. For this purpose, as a model reaction, a mixture of dimedone (2 mmol), 4-methylbenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (2.4 mmol) was stirred in the presence of different amounts of [Dsim]HSO_4 at a range of 40 to 55 °C in the absence of a solvent; the respective results are summarized in Table 1. As it can be seen

Table 1
Effect of the catalyst amount and temperature on the reaction between dimedone, 4-methylbenzaldehyde, ethyl acetoacetate and ammonium acetate.

Entry	Catalyst	Catalyst amount (mol%)	Temp. (°C)	Time (min)	Yield[a] (%)
1	[Dsim]HSO_4	2	50	35	93
2	[Dsim]HSO_4	3	50	25	96
3	[Dsim]HSO_4	5	50	25	87
4	[Dsim]HSO_4	3	40	60	79
5	[Dsim]HSO_4	3	55	25	96
6	H_2SO_4	3	50	25	63
7	[Dsim]Cl	3	50	25	72

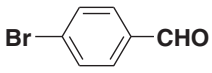
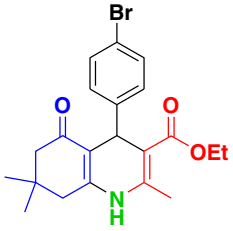
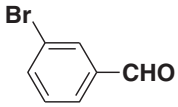
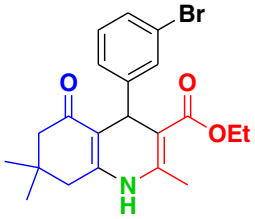
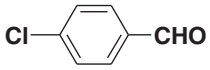
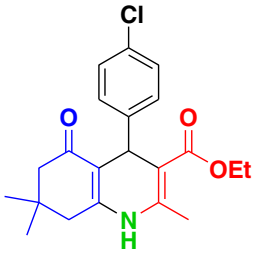
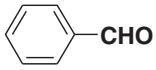
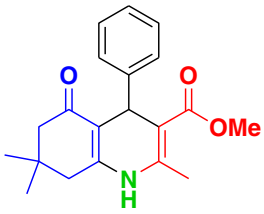
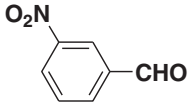
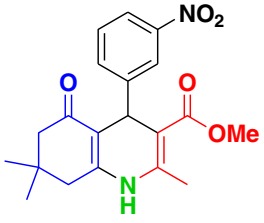
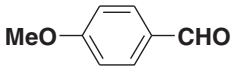
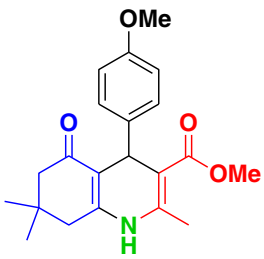
[a] Isolated yield.

Table 2
The solvent-free synthesis of HHQs from dimedone, arylaldehydes, β-ketoesters and ammonium acetate catalyzed by $[Dsim]HSO_4$ at 50 °C.

Aldehyde	Product	Time (min)	Yield[a] (%)	M.p. °C (Lit.)
	 (1)	35	94	206–208 (203–205) [40]
	 (2)	35	93	247–249 (242–244) [44]
	 (3)	38	89	178–180 (177–178) [42]
	 (4)	36	89	255–257 (257–259) [43]
	 (5)	25	96	256–258 (260–261) [43]
	 (6)	28	94	234–236 (232–234) [43]

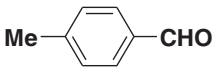
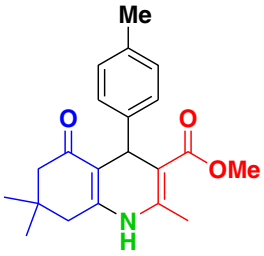
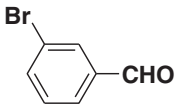
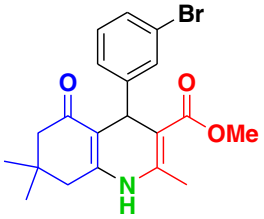
(continued on next page)

Table 2 (*continued*)

Aldehyde	Product	Time (min)	Yield[a] (%)	M.p. °C (Lit.)
	 (7)	30	91	255–256 (255–257) [40]
	 (8)	32	88	230–232 (235–237) [40]
	 (9)	25	89	244–246 (245–246) [42]
	 (10)	40	91	260–262 (258–260) [47]
	 (11)	30	88	229–231 (222–223) [53]
	 (12)	32	91	257–259 (256–257) [53]

in Table 1, 3 mol% of the ionic liquid was sufficient to catalyze the reaction efficiently at 50 °C; in these conditions, the corresponding HHQ was obtained in 96% within 25 min (Table 1, entry 2). Moreover, to prove that the reaction of [Dsim]Cl with H_2SO_4 was completely progressed to give [Dsim]HSO_4; the model reaction was also examined in the presence of 3 mol% of [Dsim]Cl or H_2SO_4 (Table 1, entries 6 and

Table 2 (*continued*)

Aldehyde	Product	Time (min)	Yield[a] (%)	M.p. °C (Lit.)
	 (13)	35	92	281–283 (285–288) [47]
	 (14)	25	89	221–223

[a] Isolated yield.

7). As it is shown in Table 1, these catalysts afforded the products in lower yields compared with [Dsim]HSO_4. These results also showed that [Dsim]Cl and H_2SO_4 were completely converted to [Dsim]HSO_4, and this ionic liquid was the real catalyst of the reaction.

To assess the efficacy and the generality of the new catalyst, dimedone was reacted with different arylaldehydes (benzaldehyde as well as arylaldehyde possessing electron-withdrawing groups, electron-donating groups and halogens), β-ketoesters (ethyl and methyl acetoacetate) and ammonium acetate under the optimized reaction conditions; the results are displayed in Table 2. As it is clear from Table 2, all reactions proceeded efficiently to afford the corresponding hexahydroquinolines in high yields and in short reaction times. Thus, our new ionic liquid, [Dsim]HSO_4, was a highly efficient and general catalyst for the synthesis of a reaction that needs an acidic catalyst to promote, i.e., the synthesis of HHQs.

An important property of ionic liquids or supported ionic liquids on solids is their recyclability or regenerability [5,15,16,54,55]. Thus, recyclability of the ionic liquid [Dsim]HSO_4 was investigated. For this purpose, the reaction of dimedone (2 mmol), 3-nitrobenzaldehyde (2 mmol), methyl acetoacetate (2 mmol) and ammonium acetate (2.4 mmol) was performed in the presence of [Dsim]HSO_4 (3 mol%) at 50 °C. After completion of the reaction, 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, the catalyst is not soluble in this solvent). The viscous oil residue was washed with hot ethyl acetate (10 mL) and dried to give the pure recycled catalyst. The recycled catalyst was used for the next run of the reaction. Catalytic activity of [Dsim]HSO_4 was restored within the limits of the experimental errors for three successive recycle runs (see Table 3).

Table 3
The condensation of dimedone with 3-nitrobenzaldehyde, methyl acetoacetate and ammonium acetate using recycled [Dsim]HSO_4.

Run	Time (min)	Yield[a] (%)
1	30	88
2	33	87
3	35	85
4	40	83

[a] Isolated yield.

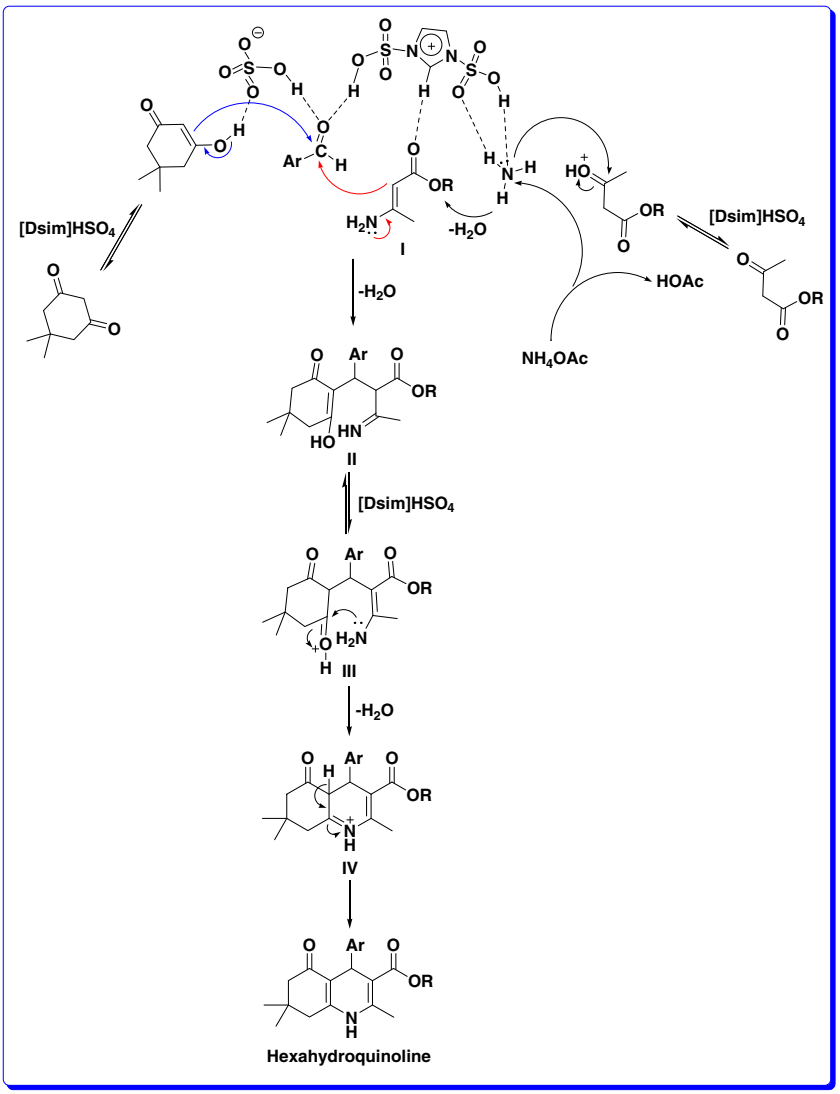
In a proposed mechanism (Scheme 3), we suggest that at first dimedone is converted to its enol form by using [Dsim]HSO_4. On the other hand, the activated β-ketoester (by the catalyst) and ammonia (resulted from ammonium acetate) gives enamine **I**. Afterward, the enol and enamine **I** react with the activated aldehyde (by [Dsim]HSO_4) to afford intermediate **II** and one molecule H_2O. **II** is converted to **III** by tautomerization, and intermediate **III** affords **IV** by intramolecular nucleophilic attack of the NH_2 group to the activated carbonyl group and then removes one molecule H_2O. Finally, hexahydroquinonine forms by tautomerization of **IV**. In fact, the catalyst not only activates carbonyls to accept nucleophilic attack, and amine as well as enamine groups for nucleophilic attack by its three SO_3H groups, it also can collect and arrange the starting materials by dual hydrogen-bonding. For these reasons, a small amount of the catalyst (3 mol%) was sufficient to promote the reaction efficiently. It should be mentioned that in the steps in which [Dsim]HSO_4 gives a proton to activate carbonyl groups, the proton is transferred to the catalyst in another step. The mechanism is confirmed by the literature [40,42,44].

4. Conclusions

In summary, we have introduced Brønsted acidic ionic liquid [Dsim]HSO_4 as a novel, highly efficient, general and homogeneous catalyst for the one-pot multi-component reaction between dimedone, aromatic aldehydes, β-ketoesters and ammonium acetate leading to hexahydroquinolones. The promising points for the presented protocols are efficiency, generality, high yields of the products, short reaction times, cleaner reaction profile, simplicity, low cost, ease of preparation and recycling of the catalyst.

Acknowledgments

The authors gratefully acknowledge the financial support of this work from the Research Affairs Office of Payame Noor University and Bu-Ali Sina University (grant number 32-1716 entitled development of chemical methods, reagents and molecules), and the Center of Excellence in Development of Chemical Method (CEDCM), Hamedan, I.R. Iran.



Scheme 3. The proposed mechanism for the synthesis of hexahydroquinolines promoted by [Dsim]HSO_4.

References

[1] J. Pavlinac, M. Zupan, K.K. Laali, S. Stavber, Tetrahedron 65 (2009) 5625–5662.
[2] H. Olivier-Bourbigou, L. Magna, D. Morvan, Applied Catalysis A: General 373 (2010) 1–56.
[3] P. Hapiot, C. Lagrost, Chemical Reviews 108 (2008) 2238–2264.
[4] P. Wasserscheid, T. Welton, Ionic Liquids in Synthesis, Wiley-VCH, Weinheim, 2008.
[5] A. Hasaninejad, A. Zare, M. Shekouhy, J. Ameri Rad, Journal of Combinatorial Chemistry 12 (2010) 844–849.
[6] A. Zare, A. Parhami, A.R. Moosavi-Zare, A. Hasaninejad, A. Khalafi-Nezhad, M.H. Beyzavi, Canadian Journal of Chemistry 87 (2009) 416–421.
[7] M. Eichmann, W. Keim, M. Haumann, B.U. Melcher, P. Wasserscheid, Journal of Molecular Catalysis A: Chemical 314 (2009) 42–48.
[8] Y.J. Kim, R.S. Varma, Tetrahedron Letters 46 (2005) 1467–1469.
[9] E. Öchsner, M.J. Schneider, C. Meyer, M. Haumann, P. Wasserscheid, Applied Catalysis A: General 399 (2011) 35–41.
[10] R.G. Kalkhambkar, K.K. Laali, Tetrahedron Letters 52 (2011) 1733–1737.
[11] H.R. Shaterian, M. Ranjbar, Journal of Molecular Liquids 160 (2011) 40–49.
[12] P.P. Salvi, A.M. Mandhare, A.S. Sartape, D.K. Pawar, S.H. Han, S.S. Kolekar, Comptes Rendus Chimie 14 (2011) 883–886.
[13] N. Ghaffari Khaligh, Journal of Molecular Catalysis A: Chemical 349 (2011) 63–70.
[14] H.R. Shaterian, M. Ranjbar, K. Azizi, Journal of Molecular Liquids 162 (2011) 95–99.
[15] A. Zare, A.R. Moosavi-Zare, M. Merajoddin, M.A. Zolfigol, T. Hekmat-Zadeh, A. Hasaninejad, A. Khazaei, M. Mokhlesi, V. Khakyzadeh, F. Derakhshan-Panah, M.H. Beyzavi, E. Rostami, A. Arghoon, R. Roohandeh, Journal of Molecular Liquids 167 (2012) 69–77.
[16] M.A. Zolfigol, A. Khazaei, A.R. Moosavi-Zare, A. Zare, V. Khakyzadeh, Applied Catalysis A: General 400 (2011) 70–81.
[17] M.A. Zolfigol, A. Khazaei, A.R. Moosavi-Zare, A. Zare, Organic Preparations and Procedures International 42 (2010) 95–102.
[18] M.A. Zolfigol, A. Khazaei, A.R. Moosavi-Zare, A. Zare, H.G. Kruger, Z. Asgari, V. Khakyzadeh, M. Kazem-Rostami, The Journal of Organic Chemistry 77 (2012) 3640–3464.
[19] P.J. Edwards, B. Allart, M.J.I. Andrews, J.A. Clasev, C. Menet, Current Opinion in Drug Discovery & Development 9 (2006) 425–444.
[20] V. Polshettiwar, R.S. Varma, Pure and Applied Chemistry 80 (2008) 777–790.
[21] A. Hasaninejad, M. Shekouhy, N. Golzar, A. Zare, M.M. Doroodmand, Applied Catalysis A: General 402 (2011) 11–22.
[22] B.B. Touré, D.G. Hall, Chemical Reviews 109 (2009) 4439–4486.
[23] A. Dömling, I. Ugi, Angewandte Chemie International Edition 39 (2000) 3168–3210.
[24] A. Hantzsch, Chemische Berichte 14 (1881) 1637–1638.
[25] T. Godfaid, R. Miller, M. Wibo, Pharmacological Reviews 38 (1986) 321–416.
[26] A. Sausins, G. Duburs, Heterocycles 27 (1988) 269–289.
[27] P.P. Mager, R.A. Coburn, A.J. Solo, D.J. Trigle, H. Rothe, Drug Design and Discovery 8 (1992) 273–289.
[28] R. Mannhold, B. Jablonka, W. Voigdt, K. Schoenafinger, K. Schravan, European Journal of Medicinal Chemistry 27 (1992) 229–235.
[29] M. Kawase, A. Shah, H. Gaveriya, N. Motohashi, H. Sakagami, A. Varga, Molnar, Journal of Bioorganic and Medicinal Chemistry 10 (2002) 1051–1055.
[30] R. Shan, C. Velazque, E.E. Knaus, Journal of Medicinal Chemistry 47 (2004) 254–261.
[31] Y. Sawada, H. Kayakiri, Y. Abe, T. Mizutani, N. Inamura, M. Asano, C. Hatori, I. Aramori, T. Oku, H. Tanaka, Journal of Medicinal Chemistry 47 (2004) 2853–2863.
[32] B.D. Glass, M.E. Brown, P.M. Drummond, in: A. Albini, E. Fasani (Eds.), Drugs: Photochemistry and Photostability, The Royal Society of Chemistry, Cambridge, 1998, pp. 134–149.
[33] G.M.J. Beijersbergen van Henegouwen, in: B. Testa, U.A. Meyer (Eds.), Advances in Drug Research, vol. 29, Academic Press, London, 1997, pp. 79–170.
[34] K. Görlitzer, H.J. Baltrusch, E. Gossnitzer, W. Wendelin, Pharmazie 55 (2000) 35–41.
[35] H. De Vries, G.M.J. Beijersbergen van Henegouwen, Photochemistry and Photobiology 62 (1995) 959–963.

[36] C. Safak, L. Sahin, R. Sunal, Arzneimittel Forschung - Drug Research 40 (1990) 119–122.
[37] R. Simsek, U.B. Ismailoglu, C. Safak, I. Sahin-Erdemli, Farmaco 55 (2000) 665–668.
[38] J. Mielcarek, M. Stobiecki, R. Fránski, Journal of Pharmaceutical and Biomedical Analysis 24 (2000) 71–79.
[39] J. Mielcarek, A. Matłoka, R. Simsek, C. Safak, Archiv der Pharmazie 335 (2002) 77–82.
[40] S.-J. Song, Z.-X. Shan, Y. Jin, Synthetic Communications 40 (2010) 3067–3077.
[41] X.-L. Zhang, S.-R. Sheng, X.-L. Liu, X.-L. Liu, ARKIVOC XIII (2007) 79–86.
[42] A. Kumar, R.A. Maurya, Tetrahedron 63 (2007) 1946–1952.
[43] L.-M. Wang, J. Sheng, L. Zhang, J.-W. Han, Z.-Y. Fan, H. Tian, C.-T. Qian, Tetrahedron 61 (2005) 1539–1543.
[44] G. Mohammadi Ziarani, A.R. Badiei, Y. Khaniania, M. Haddadpour, Iranian Journal of Chemistry and Chemical Engineering 29 (2010) 1–10.
[45] K.K. Pasunooti, C.N. Jensen, H. Chai, M.L. Leow, D.-W. Zhang, X.-W. Liu, Journal of Combinatorial Chemistry 12 (2010) 577–581.
[46] R. Surasani, D. Kalita, A.V.D. Rao, K. Yarbagi, K.B. Chandrasekhar, Journal of Fluorine Chemistry 135 (2012) 91–96.
[47] M. Hong, C. Cai, W.-B. Yi, Journal of Fluorine Chemistry 131 (2010) 111–114.
[48] M. Saha, A.K. Pal, Tetrahedron Letters 52 (2011) 4872–4877.
[49] K. Ariga, J.P. Hill, M.V. Lee, A. Vinu, R. Charvet, S. Acharya, Science and Technology of Advanced Materials 9 (2008) 14109–14204.
[50] Y.-Q. Chen, X.-Z. Wang, X.-B. Shao, J.-L. Hou, X.-Z. Chen, X.-K. Jiang, Z.-T. Li, Tetrahedron 60 (2004) 10253–10260.
[51] N.K. Schwalb, F. Temps, Journal of Photochemistry and Photobiology A: Chemistry 208 (2009) 164–170.
[52] J. Zhu, J.-B. Lin, Y.-X. Xu, X.-K. Jiang, Z.-T. Li, Tetrahedron 62 (2006) 11933–11941.
[53] C.X. Yu, D.Q. Shi, Q.Y. Zhuang, S.J. Tu, Chinese Journal of Organic Chemistry 26 (2006) 263–267.
[54] Q. Zhang, H. Su, J. Luo, Y. Wei, Green Chemistry 14 (2012) 201–208.
[55] M.A. Zolfigol, V. Khakyzadeh, A.R. Moosavi-Zare, A. Zare, S.B. Azimi, Z. Asgari, A. Hasaninejad, Comptes Rendus Chimie 15 (2012) 719–736.