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Ionic liquid supported nanoporous silica (SBA-IL) as an efficient and heterogeneous catalyst in the domino synthesis of polyhydroquinoline derivatives

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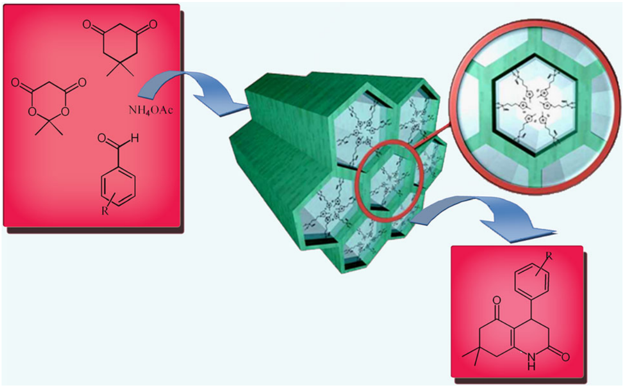
Abstract A simple, efficient, and environmentally benign protocol for the synthesis of polyhydroquinoline derivatives was developed using a bio-compatible, heterogeneous, and recoverable mesoporous ionic liquid supported nanoporous silica as a nano-catalyst. The polyhydroquinoline derivatives were obtained by the four-component reaction of aldehyde, Meldrum's acid, dimedone, and ammonium acetate in excellent yields.

Graphical Abstract



Keywords Four component reaction · SBA-IL · Polyhydroquinoline derivatives · Nanoporous · Heterogeneous catalyst

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Introduction

The application of ionic liquids (ILs) as "green" alternatives has become increasingly important in recent years. ILs have the potential to exhibit low human toxicities and eco-toxicities [1, 2]. In addition, ILs are nonvolatile, stable, and can be reused [3, 4]. ILs as a solvent were found to produce unique selectivities and reactivities. Because of these singularities, these materials have become promising alternatives to volatile organic solvents. Immobilization of ILs on the solid supports by covalent bonds between silanol groups and the anion or the cation of the ILs transfers the catalytic properties of the liquids to a solid catalyst known as "immobilised" or "heterogenised" liquids [5, 6]. Supported ILs as heterogeneous catalysts led to more improvements in efficiency than homogenous ILs because of their easy handling, separation, and reusability in addition to simple work-up procedure and reducing waste products [5, 7, 8].

1,4-Dihydropyridines (1,4-DHPs) are compounds known for their pharmacological activity as calcium channel modulators [9]. After this discovery, many works have been directed towards the synthesis of novel 1,4-DHPs acting as calcium antagonists [10, 11]. 1,4-DHPs possess a variety of biological activities, such as vasodilator, bronchodilator, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic properties [12–15]. Investigation of a new method for the synthesis of DHPs is mandatory because the previous methods have some drawbacks such as long reaction time, low yields, and using harmful solvents. In connection with our research interest in the development of novel methods for the preparation of various biologically important heterocyclic compounds [16–18], herein we would like to report the application of SBA-ILs as a new nano-catalyst to prepare the 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline derivatives. The previous studies revealed that this method is the first report using a heterogeneous catalyst system for the synthesis of octahydroquinoline compounds.

Experimental

Materials

Surface area was measured using the Brunnauer–Emmett–Teller (BET) method; pore size distributions were calculated from the nitrogen isotherms using the Barret–Joyner–Halenda (BJH) method. IR spectra were recorded from KBr and NaCl disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an Electrothermal 9200 apparatus. The ^{1}H NMR (500 MHz) was run on a Bruker DPX at 400 MHz using TMS as an internal standard (DMSO-d_6 solution). GC-MS analysis was performed on a GC-Mass model 5973 Network Mass Selective Detector, GC 6890 Agilent. Calcinations were carried out in a box furnace under conditions of flowing air.

Preparation of ionic liquid supported nanoporous silica (SBA-IL)

Synthesis of the mesoporous silica SBA-15

In a typical synthesis, pluronic 123 (90 g) was dissolved in 2700 g of an aqueous HCl 2 mol l^{-1} and stirred for 3 h. Then 191.75 g of tetraethylorthosilicate was added to the homogeneous solution. This gel was continuously stirred at 313 K for 24 h, and then the solid product was filtered, washed with distilled water, and dried in air at room temperature; silica was washed with boiling ethanol using a Soxhlet apparatus for 192 h, followed by drying at room temperature to removal ethanol. The material was calcined in air at 873 K for 6 h to decompose the triblock copolymer and to obtain a white powder SBA-15. IR (NaCl): $v_{\max}/\mathrm{cm}^{-1} = 3434$ (O–H stretch), 1086 (Si–O–Si asymmetric stretch), 814 (Si–O–Si symmetric stretch).

Synthesis of N-methyl-N′-propyltrimethoxysilylimidazolium chloride

A mixture of *N*-methyl-*N*′-propyltrimidazole (6.57 g, 80 mmol) and 3-(chloropropyl)trimethoxysilane (15.89 g, 80 mmol) were stirred in a dry 100 ml flask under inert atmosphere (Ar) at 95 °C for 24 h. After cooling at room temperature, the resulting liquid product was extracted with ether. The final compound was obtained as a yellow liquid. IR (NaCl): $v_{\max}/\mathrm{cm}^{-1} = 1568$ (C=C, C=N), 1457 (C–H asymmetric stretch), 1373 (C–H symmetric stretch), 625 (mono 4-substituted imidazole).

Synthesis of imidazolium functionalized material

Reaction was carried out under inert atmosphere (Ar) in a flask that was equipped with a reflux condenser and a magnetic stirrer. 2.0 g of mesoporous SBA-15 silica was warmed under vacuum for 2 h to remove the adsorbed water. Dried toluene (100 ml) was added to the calcined and activated SBA-15 and stirred for 30 min. Then *N*-methyl-*N*′-propyltrimethoxysilyl-imidazolium chloride (5.61 g) was added to the resulting mixture. This mixture was stirred for 48 h under inert atmosphere (Ar). Then, toluene was removed and the functionalized silica was washed with boiling dichloromethane using a Soxhlet apparatus for 48 h, followed by drying under vacuum to remove dichloromethane.

General procedure in the domino synthesis of 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline derivatives

The SBA-IL (0.02 g) was activated in vacuum at 100 °C and then after cooling to room temperature, dimedone **7** (1.5 mmol) and ammonium acetate **8** (2.4 mmol) were added to it. In solvent-free conditions, the whole reaction mixture was heated at 90 °C for 30 min. After completion of the first step and without any work-up, Meldrum's acid **10** (1.5 mmol) and aldehyde **11a–i** (1.5 mmol) were added to the reaction mixture, as reported in Table 2, at 90 °C.

The completion of two steps of the reaction was indicated by TLC, the resulting solid product was dissolved in hot ethanol, filtered to remove the unsolvable catalyst, and the filtrate was cooled to afford the pure product. The spectroscopic and analytical data for new compounds are presented in the following section.

*4-(2′-Methoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (**12h**)*

IR(KBr): $\upsilon_{max} = 3260$ (NH), 2959, 1711(C=O), 1614 (C=O), 1464, 1379, 1282, 1149, 1024, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 9.16 (brs, 1H, NH), 7.18 (t.d, $J = 7.8$ Hz, 1H, Ar–H), 7.00 (d, $J = 7.5$ Hz, 1H, Ar–H), 6.85 (d.d, $J = 8.2$ Hz, 1H, Ar–H), 6.81 (t.d, $J = 7.4$ Hz, 1H, Ar–H) 4.59 (d, $J = 8.8$ Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 2.86 (dd, $J = 16.8$, 9.0 Hz, 1H, CH), 2.73 (d, $J = 16.7$ Hz, 1H, CH), 2.42 (q, $J = 17.3$, 16.0 Hz, 2H, CH_2), 2.28 (d, $J = 3.15$ Hz, 2H, CH_2), 1.08 (s, 3H, CH_3), 1.06 (s, 3H, CH_3) ppm; MS (EI): *m/z*: 299 (100 %), 268, 240, 215, 192.

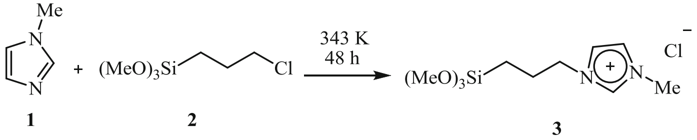
*4-(2′,3′-Dichloro)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (**12i**)*

IR(KBr): $\upsilon_{max} = 3250$ (NH), 2958, 1719(C=O), 1615 (C=O), 1464, 1374, 1280, 1147, 1042, 784 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 10.26 (brs, 1H, NH), 7.53 (t, $J = 7.4$ Hz, 1H, ArH), 7. 29 (d, $J = 7.8$ Hz, 1H, ArH), 6.95 (d, $J = 7.6$ Hz, 1H, Ar–H), 4.52 (d, $J = 8.6$ Hz, 1H, CH), 3.07 (dd, $J = 16.7$, 8.9 Hz, 1H, CH), 2.50 (m, $J = 17.5$, 10.5, 1.5 Hz, 2H,CH_2), 2.32 (d, $J = 16.4$ Hz, 1H, CH), 2.20 (q, $J = 15.9$, 9.6 Hz, 2H, CH_2), 1.08 (s, 3H, CH_3), 1.06 (s, 3H, CH_3) ppm; MS(EI): *m/z*: 304 (M^{+2}), 303 (M^{+1}), 302 (100 %), 260, 246, 204.

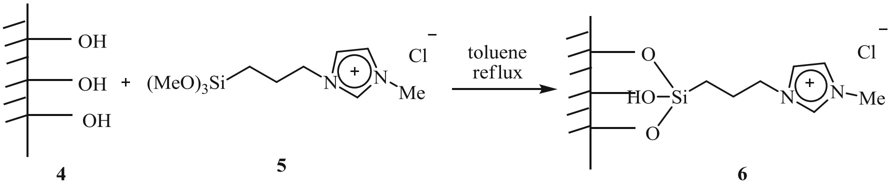
Result and discussion

Preparation of ionic liquid supported nanoporous silica (SBA-IL)

Ionic liquid supported SBA-15 material was synthesized by following the procedure reported in the literature [19–22]. The *N*-methyl-*N*′-propyltrimethoxysilylimidazolium chloride **3** was prepared as follows. A mixture of *N*-methyl-*N*′-propyltrimidazole **1** and 3-(chloropropyl)trimethoxysilane **2** was stirred under inert atmosphere (Ar) at 70 °C. The final compound was obtained as a yellow liquid (Scheme 1).



Scheme 1 Synthesis of *N*-methyl-*N*′-propyl trimethoxysilylimidazolium chloride



Scheme 2 Preparation of functionlized SBA-15 (SBA-IL)

Fig. 1 N_2 adsorption–desorption isotherms of *a* SBA-15, *b* SBA-IL (*inset*) BJH pore size distribution curves

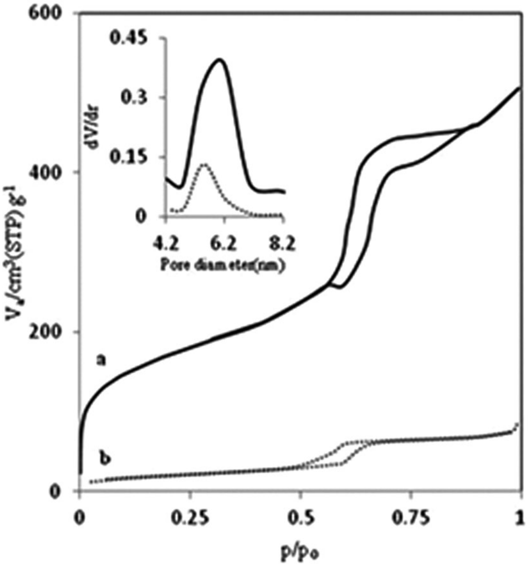


Table 1 The pore diameters (D_{BJH}), BET surface area (S_{BET}) and the total pore volumes (V_{total}) from nitrogen adsorption–desorption for the SBA-15, SBA-IL

Molecular sieves	D_{BJH} (nm)	S_{BET} (m^2/g)	V_{total} (cm^3/g)
SBA-15	6.2	587	0.780
SBA-IL	5.5	71	0.128

Subsequently, *N*-methyl-*N′*-propyltrimethoxysilyl-imidazolium chloride **5** was added to calcined and activated solid mesoporous SBA-15 silica **4** to produce the functionalized SBA-15 silica **6** (Scheme 2). The surface of the catalyst was analyzed by different methods such as BET, BJH methods, and FT-IR which were demonstrated that the organic groups were immobilized into the pores.

Nitrogen adsorption–desorption

The textural properties of SBA-15 and SBA-IL were evaluated by the nitrogen adsorption–desorption isotherms (Fig. 1). The samples exhibit a typical irreversible

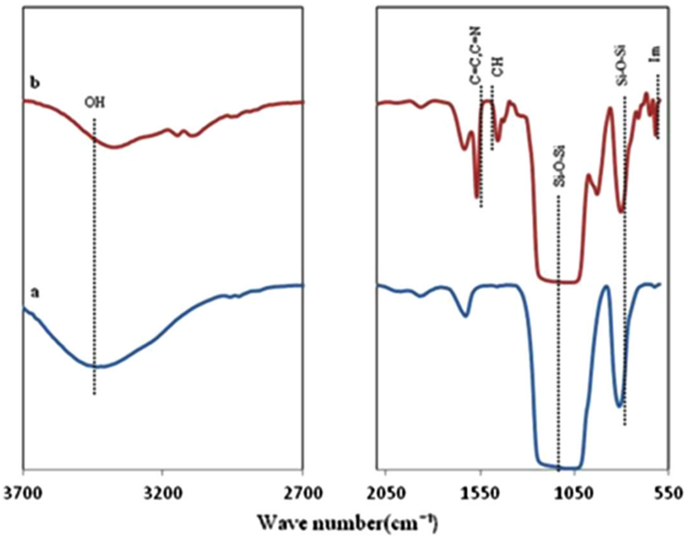
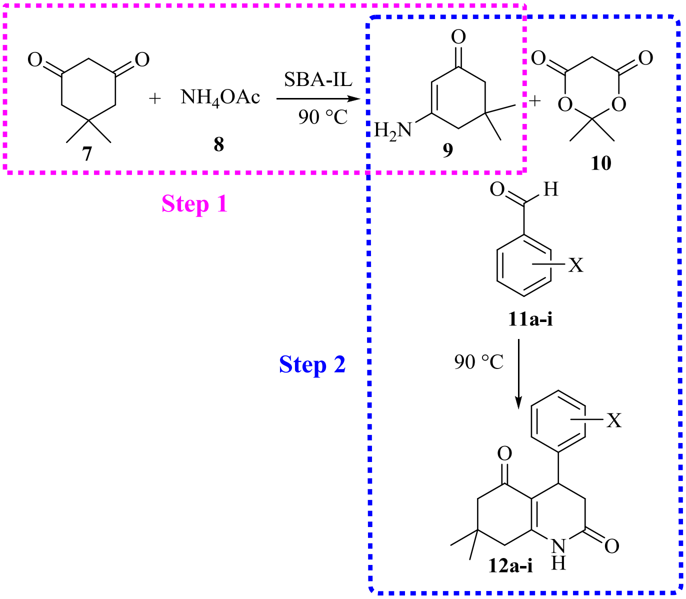


Fig. 2 FT-IR spectra of *a* SBA-15 *b* SBA-IL



Scheme 3 Synthesis of 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline derivatives **12a–i** in two steps

type IV nitrogen adsorption isotherm with an H1 hysteresis loop as defined by IUPAC [23]. There is a shift of the hysteresis position toward low relative pressures and a slight decreasing trend in overall nitrogen adsorption volume as the loading of imidazole. The pore size distribution can be calculated from the BJH method based on the desorption branch of the N_2 adsorption isotherm. In a typical BJH plot from modified SBA-15 with imidazole, a narrow pore size distribution is observed. The uniformity of the mesopores in SBA-IL is comparable to the SBA-15, indicating that the integrity of the original inorganic wall structure of the SBA-15, is retained. In comparison with SBA-15, decrement in the pore diameter value by about 0.7 nm is observed for SBA-IL. The textural parameters, specific surface areas (BET method), pore diameters (BJH method), and total pore volumes are given in Table 1, which shows a trend of decreasing in surface area, pore volume and pore diameter caused by functionalization inside the channels of SBA-15.

FT-IR measurements

Figure 2 shows FT-IR spectra of SBA-15and SBA-IL. In the FT-IR spectrum of the SBA-15 silica the band at 3434 cm^{-1} can be assigned to the stretching vibration of OH groups. The bands at 814 and 1086 cm^{-1} are attributed to Si–O–Si symmetric and asymmetric stretching vibrations, respectively [24]. After grafting *N*-methyl-*N′*-propyltrimethoxysilylimidazolium chloride on the surface of SBA-15, the intensity of the band at 3434 cm^{-1} is decreased. Meanwhile, the SBA-IL showed the new

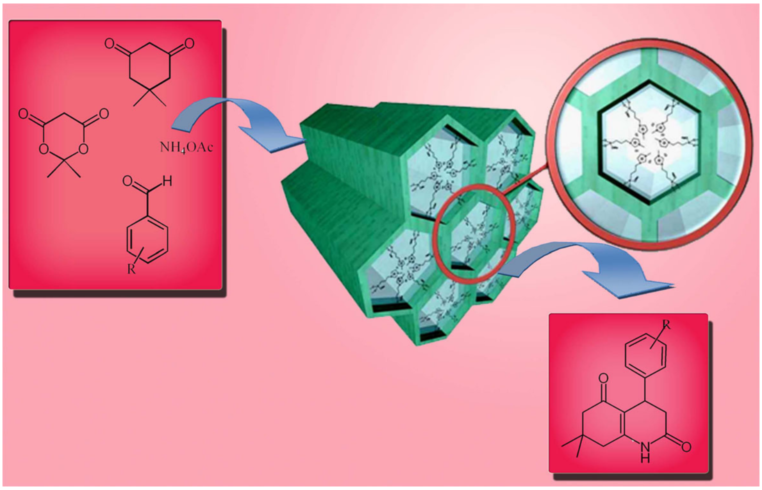


Fig. 3 SBA-IL as a nanoreactor

Table 2 Synthesis of **12b** in different solvents

Entry	Solvent	Time	Yield[a] (%)
1	EtOH	1.5 h	50
2	MeCN	3.5 h	50
3	H_2O	No reaction	–
4	–	45 min	90

[a] Isolated yields

Table 3 Synthesis of 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines **12a–i**

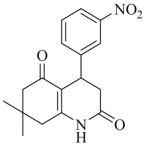
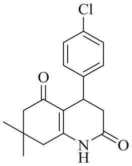
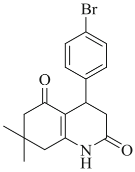
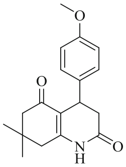
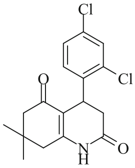
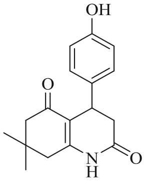
Entry	X	Product	Time (min)	Yield[a] (%)	Mp (°C)	Mp (l)
1	3-NO_2	 **12a**	60	85	202–207	193–194 [25]
2	4-Cl	 **12b**	45	90	189–191	188–190 [26]
3	4-Br	 **12c**	65	83	202–205	196–197 [26]
4	4-OMe	 **12d**	60	80	218–220	218–220 [27]
5	2,4-Cl	 **12e**	70	85	200–202	180–182 [27]
6	4-OH	 **12f**	140	83	>300	>300 [28]

Table 3 continued

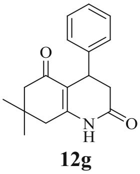
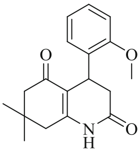
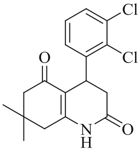
Entry	X	Product	Time (min)	Yield[a] (%)	Mp (°C)	Mp (l)
7	H	 **12g**	70	80	226–228	217–219 [25]
8	2-OMe	 **12h**	60	87	188–190	New
9	2,3-Cl	 **12i**	40	93	248–250	New

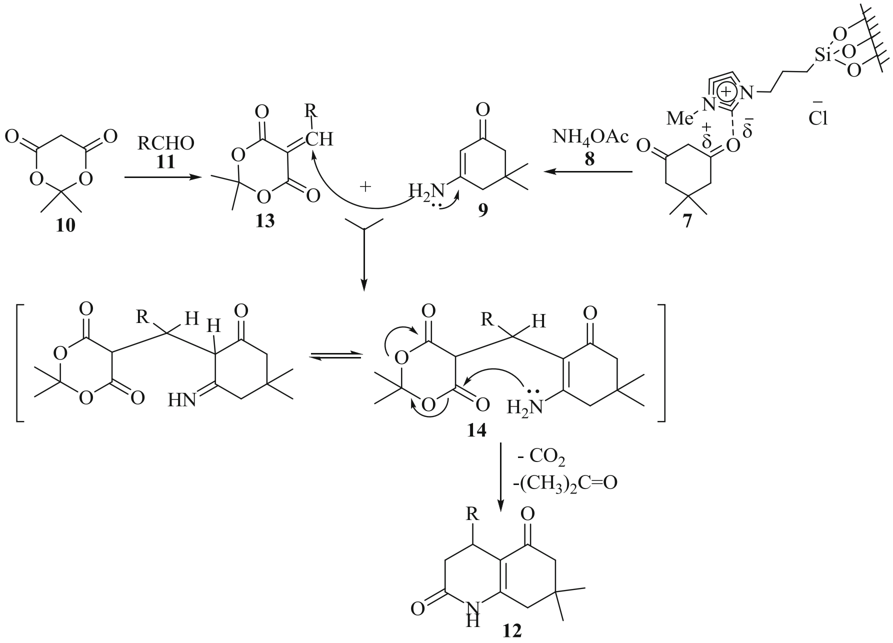
Table 4 Comparison of different conditions in the synthesis of **12g**

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%)	Lit.
1	–	AcOH	Reflux	30	60	[27]
2	–	–	MW	3 min	72.4	[26]
3	–	[bmim][BF4]	Heating (80 °C)	4	89	[25]
4	SBA-IL	–	Heating (90 °C)	1.16	80	This work

adsorption bands at 1568 (C=C, C=N), 1457 (C–H asymmetric stretch), 1373 (C–H symmetric stretch), 625 (mono 4-subistituted imidazole).

In this paper, SBA-IL as an efficient nanoreactor catalyzed the four-component reaction of dimedone **7**, ammonium acetate **8**, Meldrum's acid **10**, and various aromatic aldehydes **11a–i** (Scheme 3; Fig. 3).

For optimizing the conditions of the reaction in the synthesis of 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines, dimedone **7**, ammonium acetate **8**, Meldrum's acid **10**, and 4-chlorobenzaldehyde **11b** were selected as a model of reaction in the presence of SBA-IL. Initially, different solvents such as EtOH, MeCN, H_2O, and solvent-free condition were applied as shown in Table 2. The results indicated that the solvent-free condition gave a higher yield and shorter reaction time than other solvents, and among the different solvents water was found to be the worst solvent at 100 °C (Table 2, entry 3). To investigate the effect of immobilization on the silica surface, a further reaction with pure silica used as support was performed, but the reaction proceeded slowly, and after 5 h the product was obtained in 60 % yield.



Scheme 4 Plausible mechanism of the reaction

The scope and generality of this method were illustrated with respect to various aromatic aldehydes. The results were good in terms of yields (80–93 %) and short reaction time (40–140 min) as shown in Table 3.

The efficiency of various catalysts in synthesis of polyhydroquinoline derivatives was compared in Table 4. The best yield and short reaction time is attributed to the high efficiency of the nano-catalyst of SBA-IL.

A possible mechanism for this SBA-IL-catalyzed transformation is depicted in Scheme 4. In the first step, dimedone **7** and ammonium acetate 2 gave intermediate **9** via a condensation reaction. In this step, the SBA-IL could activate the methylene group of dimedone. The intermediate **13** is obtained by the condensation of Meldrum's acid **10** and aldehyde **11**. After that, the reaction of intermediate **13** and **9** led to adduct product **14** through Michael addition. Finally, intramolecular cyclodehydration of the intermediate **14** released acetone and carbon dioxide and gave target compound **12**.

Conclusion

In this study, we have demonstrated the successful incorporation of heterogeneous and mesoporous ionic liquid supported nanoporous silica (SBA-IL) in a four-component process. In this procedure, polyhydroquinoline derivatives were synthesized in excellent yields, mild and green reaction conditions, short reaction times, and easy work-up process.

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References

1. S. Stolte, M. Matzke, J. Arning, A. Boschen, W.-R. Pitner, U. Welz-Biermann, B. Jastorff, J. Ranke, Green Chem. **9**, 1170 (2007). doi:10.1039/B711119C
2. J. Ranke, S. Stolte, R. Störmann, J. Arning, B. Jastorff, Chem. Rev. **107**, 2183 (2007). doi:10.1021/cr050942s
3. V.I. Pârvulescu, C. Hardacre, Chem. Rev. **107**, 2615 (2007). doi:10.1021/cr050948h
4. A.M. da Costa Lopes, K.G. João, D.F. Rubik, E. Bogel-Łukasik, L.C. Duarte, J. Andreaus, R. Bogel-Łukasik, Bioresour. Technol. **142**, 198 (2013). doi:10.1016/j.biortech.2013.05.032
5. M. Valkenberg, W. Hölderich, Green Chem. **4**, 88 (2002). doi:10.1039/b107946h
6. C.P. Mehnert, Chem. A Eur. J. **11**, 50 (2005). doi:10.1002/chem.200400683
7. D.J. Macquarrie, Chem. Commun. (1997). doi:10.1039/A700261K
8. C. Paun, J. Barklie, P. Goodrich, H.Q.N. Gunaratne, A. McKeown, V.I. Pârvulescu, C. Hardacre, J. Mol. Catal. A: Chem. **269**, 64 (2007). doi:10.1016/j.molcata.2007.01.002
9. R. Janis, P. Silver, D. Triggle, Adv. Drug Res. **16**, 309 (1987)
10. R.A. Janis, D.J. Triggle, J. Med. Chem. **26**, 775 (1983). doi:10.1021/jm00360a001
11. F. Bossert, W. Vater, Med. Res. Rev. **9**, 291 (1989). doi:10.1002/med.2610090304
12. T. Godfraid, R. Miller, M. Wibo, Pharmocol. Rev. **38**, 321 (1986)
13. A. Sausins, G. Duburs, Heterocycles **27**, 291 (1988). doi:10.3987/REV-87-371
14. P. Mager, R. Coburn, A. Solo, D. Triggle, H. Rothe, Drug Des. Discov. **8**, 273 (1992)
15. R. Mannhold, B. Jablonka, W. Voigt, K. Schönafinger, E. Schraven, Eur. J. Med. Chem. **27**, 229 (1992). doi:10.1016/0223-5234(92)90006-m
16. G. Mohammadi Ziarani, S. Asadi, A. Badiei, S. Mousavi, P. Gholamzadeh, Res. Chem. Intermed. **41**, 637 (2015). doi:10.1007/s11164-013-1217-x
17. P. Gholamzadeh, G. Mohammadi Ziarani, A. Badiei, Z. Bahrami, Eur. J. Org. Chem. **3**, 279 (2012). doi:10.5155/eurjchem.3.3.279-282.630
18. G. Mohammadi Ziarani, A. Badiei, A. Abbasi, Z. Farahani, Chin. J. Chem. **27**, 1537 (2009). doi:10.1002/cjoc.200990259
19. A. Badiei, H. Goldooz, G. Mohammadi Ziarani, Appl. Surf. Sci. **257**, 4912 (2011). doi:10.1016/j.apsusc.2010.12.146
20. S. Hamoudi, A. El-Nemr, K. Belkacemi, J. Colloid Interface Sci. **343**, 615 (2010). doi:10.1016/j.jcis.2009.11.070
21. T. Sasaki, C. Zhong, M. Tada, Y. Iwasawa, Chem. Commun. (2005). doi:10.1039/B500349K
22. D. Zhao, Q. Huo, J. Feng, B.F. Chmelka, G.D. Stucky, J. Am. Chem. Soc. **120**, 6024 (1998). doi:10.1021/ja974025i
23. K. Sing, D. Everett, R. Haul, L. Moscou, R. Peirotti, J. Rouquerol, Pure Appl. Chem. **57**, 603 (1985)
24. G. Socrates, *Infrared and Raman Characteristic Group Frequencies* (Wiley, London, 2004)
25. X.S. Fan, Y.Z. Li, X.Y. Zhang, G.R. Qu, J.J. Wang, X.Y. Hu, Heteroat. Chem. **17**, 382 (2006). doi:10.1002/hc.20221
26. S. Tu, Q. Wei, H. Ma, D. Shi, Y. Gao, G. Cui, Synth. Commun. **31**, 2657 (2001). doi:10.1081/scc-100105393
27. M. Suárez, E. Ochoa, Y. Verdecia, B. Pita, L. Morán, N. Martín, M. Quinteiro, C. Seoane, J. Soto, H. Novoa, N. Blaton, O.M. Peters, Tetrahedron **55**, 875 (1999). doi:10.1016/s0040-4020(98)01078-3
28. J. Svetlik, V. Hanus, J. Bella, Synth. Commun. **23**, 631 (1993). doi:10.1080/00397919308009821