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ARTICLE

Green synthesis of polyhydroquinolines catalyzed by silica-supported ionic liquid Si–[SbSipim][PF_6]

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Silica-supported ionic liquid Si–[SbSipim][PF_6] as a catalyst was used first in the synthesis of polyhydroquinolines. The catalyst exhibits high catalytic activity in the reaction, and can be easily recovered and reused without significant loss of its activity for six runs. This green method offers several advantages, including high yield, short reaction time, simple work-up procedure, ease of separation, and recyclability of the catalyst.

KEYWORDS

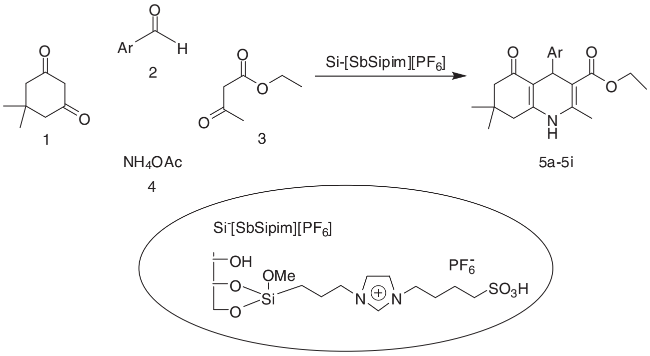
ionic liquid, multicomponent reaction, recyclable, silica-supported

1 | INTRODUCTION

Polyhydroquinolines and their derivatives are an important class of organic heterocyclic compounds due to their applications in pharmaceutical and chemical industries. They are very well known for their wide range of biological activities including antiulcer,[1] antihypertensive, analgesic, and hypnotic.[2] They are also very well known for the most important classes of drugs for the treatment of angina pectoris, hypertension, and other cardiovascular diseases.[3,4] The Hantzsch reaction for the synthesis of polyhydroquinolines involves one-pot condensation of an aldehyde with β-ketoester and NH_3 in AcOH or in alcohol under reflux for several hours.[5–11] This reaction has subsequently been promoted by employing different catalysts, such as nano-CuO, ZnO,[12,13] nano-Fe_3O_4@SiO_2,[14] Ni nanoparticles,[15] lewis acid,[16] $Mg(ClO_4)_2$ or $Yb(OTf)_3$,[17,18] and ionic liquid.[19] In recent years, supported ionic liquid catalysts (SILCs) have been an attractive research area.[20,21] This reaction has subsequently been carried out by employing different catalysts such as silica-supported acids,[22] silica-functionalized sulfonic acid coated with ionic liquid,[23] and ionic liquid-supported nanoporous silica.[24] However, the synthesis of polyhydroquinolines using efficient and reusable catalysts under green conditions is still the need of the day. As a part of our program to explore the potential applications of functional ionic liquids, we now report silica-supported ionic liquid (Si–[SbSipim][PF_6]) as the catalyst for the synthesis of polyhydroquinolines. To the best of our knowledge, the use of silica-supported ionic liquid for the synthesis of polyhydroquinolines has not been studied yet.

2 | RESULTS AND DISCUSSION

In continuation of our work [25] on the development of useful synthetic methodologies, we observed that polyhydroquinolines can conveniently be synthesized by a multicomponent reaction of an aldehyde, ethyl acetoacetate, 5, 5-dimethyl-1, 3-cyclohexanedione, and $AcONH_4$ in the presence of Silica-supported ionic liquid Si–[SbSipim][PF_6] in ethanol under reflux with 8 mol% of Si–[SbSipim][PF_6] (Scheme 1). The acid exchange capacity of Si–[SbSipim][PF_6] measured by potentiometric titration with NaOH was 1.0 mmol/g. The sulfonic acid-functional ionic liquid had been bound to a surface of silica by covalent bonds and avoided any loss of ionic liquid after the reaction. Thermogravimetric (TG) experiments were carried out in N_2 at a scan rate of 100 mL/min. The heating rate employed was



SCHEME 1 Green one-pot route for the synthesis of polyhydroquinolines

TABLE 1 Effect of catalysts and solvents on model reaction

Entry[a]	Solvent	T (°C)	Catalyst (g)	Time (hr)	Yield[b] (%)
1	Solvent-free	Reflux	0.5	2	25
2	Acetonitrile	Reflux	0.5	2	65
3	Water	Reflux	0.5	2	18
4	Ethanol	Reflux	0.5	2	86
5	Ethanol	60	0.5	2	78
6	Ethanol	30	0.5	2	40
7	Ethanol	Reflux	0.4	2	86
8	Ethanol	Reflux	0.3	2	74
9	Ethanol	Reflux	0.6	2	86

[a] Reaction conditions: benzaldehyde (5.0 mmol), 5, 5-dimethyl-1, 3-ethylacetoacetate (5.0 mmol), ammonium acetate (5.0 mmol), and Si–[SbSipim][PF_6] (0.4 g) as catalysts.

[b] Isolated yield.

10°C/min. We investigated the thermostability of Si–[SbSipim][PF_6] via Thermogravimetric analysis (TGA) measurement. The TGA curve measured for the catalyst revealed the weight loss process with a thermal decomposition temperature (T) in the 0–700°C range (Figure 1). As shown in Figure 1, a mass loss begins at 250°C, which is attributed to the dehydration of Si–[SbSipim][PF_6]. Therefore, Si–[SbSipim][PF_6] retained a high thermostability before 250°C. This provides the basis for our later catalytic experiments.

The catalytic Si–[SbSipim][PF_6] has been systematically studied in the rapid and efficient preparation of polyhydroquinolines through a multicomponent reaction. A four-component coupling reaction of benzaldehyde, 5, 5-dimethyl-1,3-cyclohexanedione, ethyl acetoacetate, and ammonium acetate as a modeling reaction was examined. As can be seen from the results in Table 1, the use of benzaldehyde (5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (5 mmol), ethyl acetoacetate (5 mmol), and ammonium acetate (5 mmol) in the presence of Si–[SbSipim][PF_6] (0.4 g) in ethanol under reflux was the best condition. Aromatic aldehydes with various substituents carrying either electron-donating or electron-withdrawing groups reacted successfully with 1, 3-dicarbonyl compounds to afford the corresponding products in excellent yields (Table 2).

The recyclability of the Si–[SbSipim][PF_6] was investigated through the syntheses of 5a as modeling reaction. After completion of the reaction, monitored by TLC, the catalyst was filtered and washed with ethanol, dried and reused five times. The average chemical yield for six consecutive runs was 86% to 83%. The yield did not drop significantly until the eighth consecutive runs, which clearly demonstrates the practical recyclability of this catalyst (Figure 2).

The mechanism for the formation of polyhydroquinolines in the presence of [SbSipim][PF_6] was hypothesized, which can act as an acid catalyst. As can be seen, the interaction between [SbSipim][PF_6] and lone pair electrons of oxygen in the carbonyl bond causes the formation of corresponding Knoevenagel product **5** as well as enamine product **6**. In the following, Michael addition and cyclohydration to furnish the desired products **7** occurred between **5** and **6** under [SbSipim][PF_6] (Scheme 2).

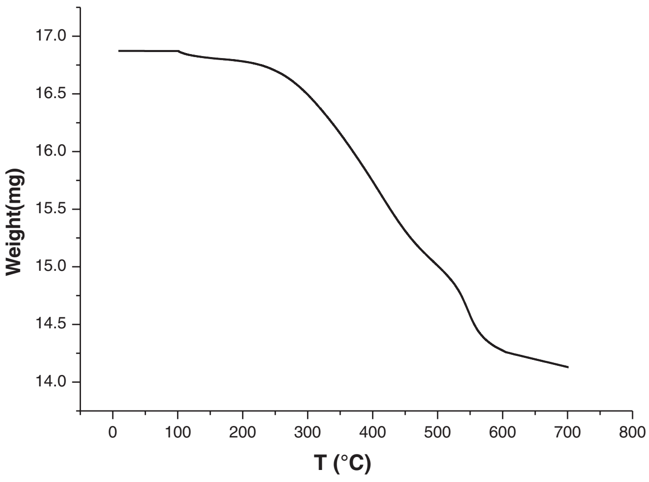


FIGURE 1 TGA of Si–[SbSipim][PF_6]

TABLE 2 Formation of polyhydroquinolines using Si–[SbSipim][PF_6] ionic liquid as a catalyst

Product[a]	R	t/hr	Yield[b] /%	M.p./(°C) Found	M.p./(°C) Reported
5a	C_6H_5	2	86	228.9–229.0	228–229 [26]
5b	2-Cl-C_6H_4	2	88	210.8–211.0	210–212 [27]
5c	3-Br-C_6H_4	2	87	203.7–204.2	201–204 [28]
5d	3-NO_2	1	86	179.1–179.4	177–178 [29]
5e	4-CH_3-C_6H_4	1	84	294.9–295.3	297–298 [30]
5f	4-OCH_3-C_6H_4	2	85	258.5–258.8	260–262 [26]
5g	4-$N(CH_3)_2$-C_6H_4	1	84	230.5–230.9	230–232 [29]
5h	2,4-diCl-C_6H_3	1	85	217.7–217.9	216–218 [26]
5i	α-Naphthyl	1	80	201.4–201.5	201–204 [31]

[a] Reaction conditions: aldehyde (5.0 mmol), 5, 5-dimethyl-1, 3-ethylacetoacetate (5.0 mmol), ammonium acetate (5.0 mmol), and Si–[SbSipim][PF_6] (0.4 g), ethanol as a solvent, reflux.

[b] Isolated yield.

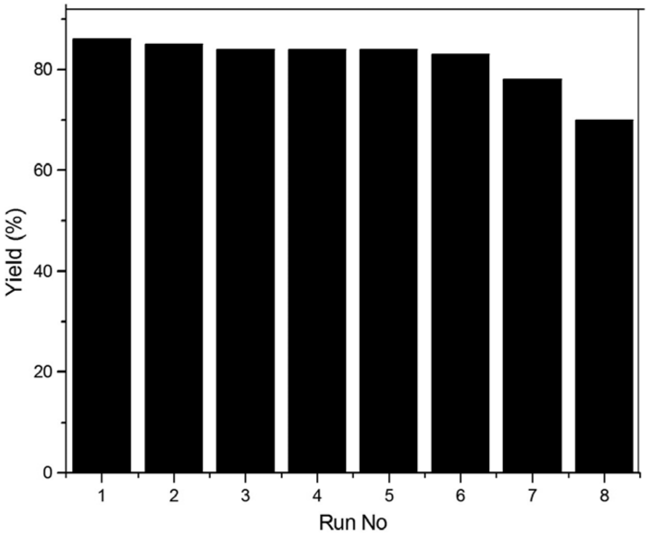


FIGURE 2 Recycling of Si–[SbSipim][PF_6]

3 | EXPERIMENTAL

3.1 | Chemicals and instrumentation

Melting points were measured on a WRS-IB digital melting point instrument. ^1H NMR was recorded on an AVANG 500 MHz spectrometer with TMS as an internal standard. The ionic liquid Si–[SbSipim][PF_6] was synthesized according to the procedure reported in previous literature.[32]

3.2 | General procedure for the synthesis of 5a–5i

The aldehyde (5 mmol), ethyl acetoacetate (5 mmol), cyclohexane-1,3-dione (5 mmol), $AcONH_4$ (5 mmol), Si–[SbSipim][PF_6] (0.4 g), and ethanol (5 cm^3) were added to a 50 mL round-bottom flask equipped with a magnetic stirring bar connected to a water-cooled condenser. The mixture was stirred at reflux for a certain period of time to complete the reaction (oil bath, monitored by TLC). After the reaction, the hot mixture was filtered to separate the catalyst. The catalyst was recovered by washing with ethanol and drying. The filtrate was cooled to ambient temperature and the resulting solid crude product was filtered and then recrystallized from 95% ethanol to obtain pure product polyhydroquinolines. All compounds were characterized by the ^1H NMR spectra were listed in the Supporting Information. Melting points are found to be almost identical with those that reported in the literature elsewhere.

3.2.1 | Ethyl 4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5b)

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.98 (s, 3H), 1.09 (s, 3H), 1.18–1.21 (t, J = 7 Hz, 3H), 2.16–2.23 (m, 3H), 2.33–2.36 (m, 4H), 4.02–4.10 (m, 2H), 5.40 (s, 1H), 5.82 (s, 1H), 7.03–7.06 (t, J = 7.5 Hz, 1H), 7.12–7.15 (t, J = 7.25 Hz, 1H), 7.25–7.26 (d, 1H), and 7.40–7.42 (d, 1H).

3.2.2 | Ethyl 4-(3-brominephenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5c)

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.98 (s, 3H), 1.11 (s, 3H), 1.21–1.24 (t, J = 7.25 Hz, 3H), 2.17–2.27 (m, 3H), 2.35–2.41 (m, 4H), 4.07–4.10 (m, 2H), 5.04 (s, 1H), 5.82 (s, 1H), 7.07–7.10 (t, J = 7.75 Hz, 1H), 7.24–7.26 (d, 1H), 7.28 (d, 1H), and 7.42 (s, 1H).

3.2.3 | Ethyl 4-(3-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5d)

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.957 (s, 3H), 1.12 (s, 3H), 1.20–1.23 (t, J = 2 Hz, 3H), 2.15–2.30 (m, 4H), 2.42–2.44 (m, 3H), 4.06–4.10 (m, 2H), 5.17 (s, 1H), 5.86 (s, 1H), 7.38–7.41 (t, J = 8 Hz, 1H), 7.74–7.76 (d, 1H), 7.99–8.01 (d, 1H), and 8.12 (s, 1H).

3.2.4 | Ethyl 4-(4-methylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5e)

Yellow solid; ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.97 (s, 3H), 1.09 (s, 3H), 1.22–1.25 (t, J = 7.25 Hz, 3H), 2.16–2.27 (m, 6H), 2.33–2.38 (m, 4H), 4.08–4.09 (m, 2H), 5.03 (s, 1H), 5.86 (s, 1H), 7.01–7.03 (d, 2H), and 7.19–7.21 (d, 2H).

3.2.5 | Ethyl 4-(4-methoxylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5f)

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.96 (s, 3H), 1.09 (s, 3H), 1.21–1.24 (t, 3H, J = 7.25 Hz), 2.16–2.26 (q, 3H), 2.33–2.38 (m, 4H), 3.78 (s, 3H), 4.06–4.10 (m, 2H), 5.01 (s, 1H), 5.77 (s, 1H), 6.79–6.75 (d, 2H), and 7.24–7.23 (d, 2H).

3.2.6 | Ethyl 4-(4-N, N -dimethylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5g)

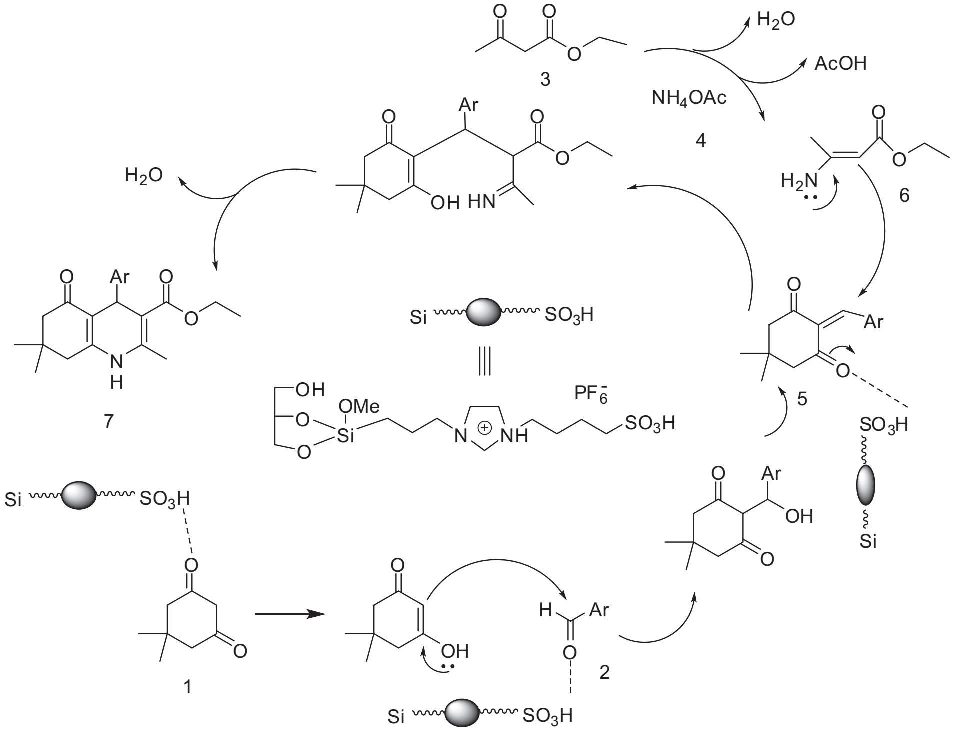
Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.09 (s, 3H), 1.23–1.26 (t, J = 7 Hz, 3H), 2.16–2.26 (m, 3H), 2.32–2.38 (m, 4H), 2.89 (s, 6H), 4.06–4.10 (m, 2H), 4.97 (s, 1H), 5.79 (s, 1H), 6.61–6.62 (m, 2H), and 7.17–7.18 (d, 2H).

3.2.7 | Ethyl 4-(2, 4- dichlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5h)

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.97 (s, 3H), 1.09 (s, 3H), 1.19–1.21 (t, 3H), 2.12–2.24 (m, 3H), 2.35 (m, 4H), 4.04–4.08 (m, 2H), 5.35 (s, 1H), 5.98 (s, 1H), 7.11–7.13 (d, 1H), 7.28 (s, 1H), and 7.34–7.35 (d, 1H).

3.2.8 | Ethyl 4-(α-naphthyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquin-oline-3-carboxylate (5i)

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (s, 6H), 1.08 (s, 3H), 2.09–2.10 (m, 1H), 2.18–2.23 (m, 2H), 2.32–2.36 (m, 1H), 2.41 (s, 3H), 3.77–3.94 (m, 2H), 5.84 (s, 1H), 5.93 (s, 1H), 7.33–7.36 (t, J = 7.5



SCHEME 2 Proposed mechanism for the formation of polyhydroquinolines

Hz, 1H), 7.42–7.45 (m, 2H), 7.55–7.58 (t, $J = 7.5$ Hz, 1H), 7.63–7.64 (d, 1H), 7.75–7.76 (d, 1H), and 8.82–8.88 (s, 1H).

4 | CONCLUSIONS

In summary, we have developed a convenient, efficient method for the synthesis of polyhydroquinolines via Si–[SbSipim][PF_6] as a highly efficient catalyst in alcohol under reflux. The catalytic system can combine the advantages of homogeneous and heterogeneous catalysts. The attractive features of this method are simple procedure, ease of separation, and recyclability of the catalyst.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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