

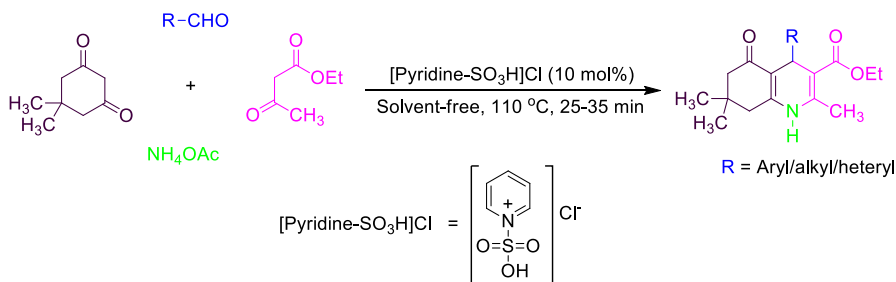
Polyhydroquinolines: 1-sulfonypyridinium chloride catalyzed an efficient one-pot multicomponent synthesis via Hantzsch condensation under solvent-free conditions

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Abstract A simple and highly efficient method has been developed for the construction of polyhydroquinoline derivatives via one-pot, four-component Hantzsch condensation of various aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate in the presence of an ionic liquid, 1-sulfonypyridinium chloride, as a catalyst under solvent-free conditions. This methodology has an advantage of high yields, short reaction times, a clean reaction profile, and reusability of the catalyst.

Graphical Abstract



Keywords Hantzsch condensation · Polyhydroquinolines · Multicomponent reaction · Solvent-free conditions · 1-Sulfonypyridiniumchloride

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Introduction

Multicomponent reactions (MCRs) are efficient synthetic tools for the construction of chemically and biological active compounds. They have unique advantages such as the generation of highly diverse and complex products from readily available substrates in a single synthetic operation without isolation of intermediates, and with maximum selectivity in minimal time, high atom economy, and high purity with excellent yields [1–3]. Nowadays, ionic liquid catalyzed reactions have gained considerable attention because of their interesting properties like high thermal stability, non-flammability, an ability to dissolve a wide range of materials, eco-friendly nature, and reusability, all contributing to carrying out reactions more effectively [4, 5]. Moreover, reactions under solvent-free conditions are also increasingly attractive to researchers due to the fact that without solvent, reactions usually need shorter reaction times, simpler reactors, and require simple and efficient workup procedures [6, 7].

1,4-Dihydropyridine (1,4-DHP) derivatives are well known as calcium channel modulators and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases (e.g. amlodipine, nifedipine, nimodipine, nicardipine, and efonidipine, etc.; Fig. 1) [8–11]. Thus, in recent years an increasing interest has been focused on their syntheses. 1,4-DHPs were also found to possess antiviral [12], antioxidant [13], antitumour [14], anti-inflammatory [15], antimalarial [16], antibacterial [17], and antitubercular [18] activities. They also act as NADH coenzymes for the reduction of carbonyl compounds and their derivatives [19], as neuroprotectants, with platelet anti-aggregatory activity and cerebral anti-ischemic activity in the treatment of Alzheimer's disease, and as chemosensitizers in tumor therapy [20].

In view of their pharmacological activities, numerous methods have been reported for the synthesis of structurally related polyhydroquinoline derivatives. The classical method involves the condensation of an aldehyde with ethyl acetoacetate

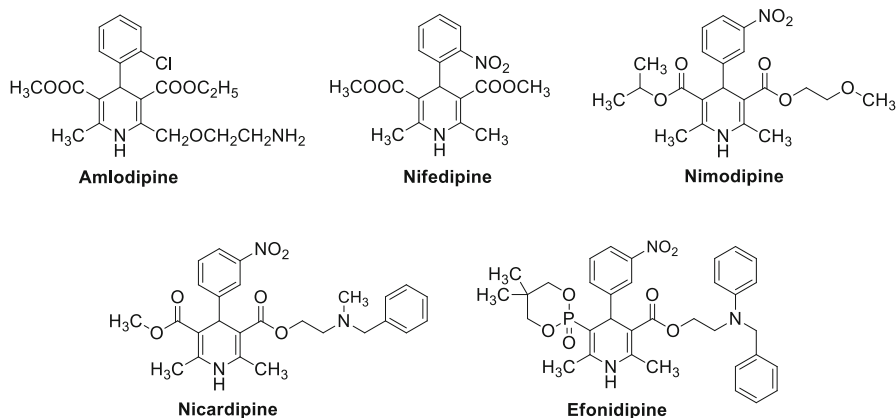


Fig. 1 Examples of dihydropyridine calcium channel blocker

and ammonia in acetic acid or in refluxing alcohol [21–23]. However, these methods suffer from several drawbacks such as long reaction times, use of large quantities of volatile organic solvents, low yields, and harsh reaction conditions. Thus, chemists have developed more competent methods including conventional heating [24], microwave irradiation [25], ultrasound irradiation [26], and also using various catalytic systems such as ionic liquids [27], L-proline [28], magnetic Fe₃O₄ nanoparticles [29], molecular iodine [30], Sc(OTf)₃ [31], HClO₄–SiO₂ [32], PPA–SiO₂ [33], PTSA [34], FeF₃ [35], CAN [36], P(4-VPH)HSO₄ [37], cellulose sulphuric acid [38], cross-linked poly(AMPS-co-AA) [39] and 1,3-bromo/chloro-5,5-dimethylhydantoin [40]. However, most of these methods have one or several drawbacks such as low yields, long reaction times, tedious workup procedures, and the use of expensive and large quantities of reagents. Thus, to overcome these limitations and in continuation of our previous studies on the development of eco-friendly methodologies [41], we herein report the synthesis of polyhydroquinoline derivatives utilizing an efficient, eco-friendly, and reusable ionic liquid, 1-sulfoypyridinium chloride [pyridine–SO₃H]Cl, as a catalyst under solvent-free conditions.

Experimental

Materials and methods

All the solvents and chemicals were purchased from Aldrich/Merck/Fisher and used without further purification. The melting points were determined on a Buchi melting point apparatus and are uncorrected. The progress of the reaction as well as the purity of the compounds were checked using *F*₂₅₄ silica-gel pre-coated TLC plates with hexane and ethyl acetate as eluent. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer using KBr pellets. ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer and mass spectra were obtained using a Jeol JMSD-400 spectrometer. Elemental analyses were performed on a Carlo-Erba model EA1108 analytical unit.

General procedure for the synthesis of Hantzsch polyhydroquinolines (5a–m)

Ionic liquid, [pyridine–SO₃H]Cl (10 mol%, 0.1 mmol, 19.56 mg) was added to a mixture of dimedone (1 mmol, 140.18 mg), aldehyde (1 mmol), ethyl acetoacetate (1 mmol, 127.46 μL), and ammonium acetate (3 mmol, 231.25 mg), and heated at 110 °C under neat conditions for an appropriate time, as described in Table 1. After completion of the reaction shown by TLC, the mixture was diluted with water and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure, and then purified by recrystallization from ethanol to obtain the pure polyhydroquinoline derivatives. The recovered catalyst was washed with ethyl acetate, dried under vacuum at 90 °C for about 2.5 h, and reused for consecutive reactions.

Table 1 Optimizing the reaction conditions

	Entry	Amount of IL (mol%)	Temp. (°C)	Time (min)	Yield (%) ^a
<i>Reaction conditions</i> Dimedone (1 mmol), benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and ammonium acetate (3 mmol) under solvent-free conditions	1	–	RT	180	–
	2	–	60	120	Trace
	3	–	110	120	32
	4	–	140	120	35
	5	5	RT	60	36
	6	5	60	60	68
	7	5	110	30	82
	8	5	140	30	82
	9	10	110	25	93
	10	15	110	25	91

^a Isolated yields

Spectral data of representative compounds

Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5b) White solid; IR (KBr, ν_{\max} , cm^{-1}): 3285, 2962, 1701, 1606, 1510, 1382, 1231, 1023, 765; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 0.94 (s, 3H), 1.07 (s, 3H), 1.24 (t, 3H, $J = 7.2$ Hz), 2.21–2.24 (m, 3H), 2.35–2.41 (m, 4H), 4.09 (q, 2H, $J = 7.2$ Hz), 5.07 (s, 1H), 5.92 (s, 1H), 7.30 (d, 2H, $J = 8.0$ Hz), 7.39 (d, 2H, $J = 8.0$ Hz); Mass (ESI) m/z : 417 (M^+); Anal. Calcd. for $\text{C}_{21}\text{H}_{24}\text{BrNO}_3$: C, 60.29; H, 5.78; N, 3.35. Found: C, 60.36; H, 5.71; N, 3.42.

Ethyl 4-(5-chloro-2-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5f) Pale yellow solid; (KBr, ν_{\max} , cm^{-1}): 3317, 3253, 3096, 2961, 1654, 1608, 1591, 1490, 1368, 1230, 1122, 819, 643; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.84 (s, 3H), 1.01–1.05 (m, 6H), 2.06 (d, $J = 16.0$ Hz, 1H), 2.21–2.45 (m, 6H), 3.88–3.95 (m, 2H), 4.91 (s, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.96–6.98 (m, 1H), 9.30 (s, 1H), 9.58 (s, 1H); Mass (ESI) m/z : 390 ($\text{M}+\text{H}^+$); Anal. Calcd. for $\text{C}_{21}\text{H}_{24}\text{ClNO}_4$: C, 64.69; H, 6.20; N, 3.59. Found: C, 64.58; H, 6.32; N, 3.76.

Ethyl 2,7,7-trimethyl-5-oxo-4-styryl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5i) White solid; IR (KBr, ν_{\max} , cm^{-1}): 3312, 2962, 1674, 1601, 1482; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 1.08 (s, 3H), 1.12 (s, 3H), 1.24–1.32 (m, 3H), 2.27 (t, 3H, $J = 7.3$ Hz), 2.32–2.36 (m, 4H), 4.11–4.20 (m, 2H), 4.71 (d, 1H, $J = 7.0$ Hz), 5.74 (s, 1H), 6.22 (d, 2H, $J = 7.1$ Hz), 7.22–7.31 (m, 5H). Mass (ESI) m/z : 366 ($\text{M}+\text{H}^+$); Anal. Calcd. For $\text{C}_{23}\text{H}_{27}\text{NO}_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.72; H, 7.33; N, 3.91.

Ethyl 2,7,7-trimethyl-5-oxo-4-propyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5j) White solid; IR (KBr, ν_{\max} , cm^{-1}): 3283, 3206, 3082, 2963, 1703, 1606, 1494, 1379, 1279, 1213, 843; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 0.83 (t, 3H, $J = 6.9$ Hz), 1.09 (s, 6H), 1.18–1.22 (m, 2H), 1.29 (t, 3H, $J = 6.9$ Hz), 1.33–1.40 (m, 2H), 2.22 (d, $J = 17.2$ Hz, 2H), 2.30 (s, 3H), 2.37 (d, $J = 17.2$ Hz, 2H), 4.02 (t,

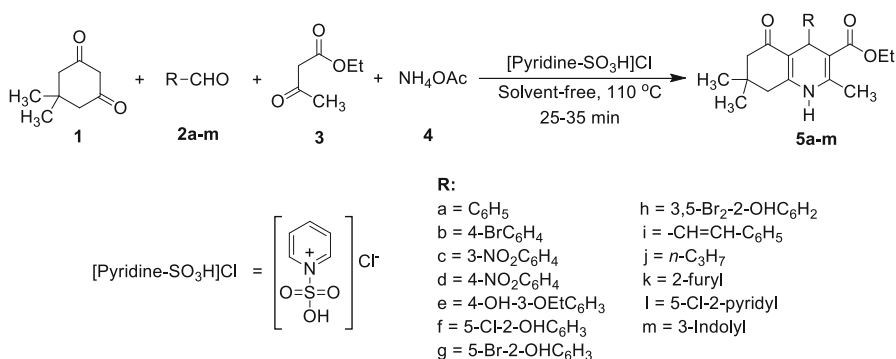
1H, $J = 5.5$ Hz), 4.10–4.22 (m, 2H), 6.32 (s, 1H); Mass (ESI) m/z : 306 (M+H)⁺; Anal. Calcd. For C₁₈H₂₇NO₃: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.92; H, 8.70; N, 4.66.

4-(5-Chloro-pyridin-2-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester (**5l**) Pale yellow solid; IR (KBr, ν_{\max} , cm⁻¹): 3321, 3250, 3090, 1595, 1242, 1070; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 0.86 (s, 3H), 1.01–1.06 (m, 6H), 2.06 (d, 1H, $J = 16.4$ Hz), 2.25 (d, 1H, $J = 16.3$ Hz), 2.29–2.46 (m, 5H), 3.89–3.99 (m, 2H), 5.06 (s, 1H), 5.92 (s, 1H), 7.14 (d, 2H, $J = 8.7$ Hz), 7.29 (s, 1H); Mass (ESI) m/z : 375 (M+H)⁺; Anal. Calcd. For C₂₀H₂₃ClN₂O₃: C, 64.08; H, 6.18; N, 7.47. Found: C, 64.18; H, 6.01; N, 7.56.

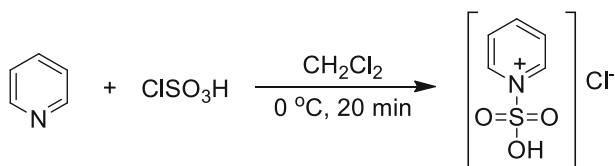
Results and discussion

Polyhydroquinoline derivatives (**5a–m**) were synthesized via Hantzsch multicomponent condensation of various aryl/alkyl/heteryl aldehydes (**2a–m**) with dimedone (**1**), ethyl acetoacetate (**3**), and ammonium acetate (**4**) under neat conditions at 110 °C in the presence of an eco-friendly ionic liquid, [pyridine–SO₃H]Cl, as a catalyst with excellent yields. The schematic representation is shown in Scheme 1. The ionic liquid [pyridine–SO₃H]Cl was prepared according to the published procedure [42] from readily available starting materials, as shown in Scheme 2.

We initially investigated the reaction of benzaldehyde (**2a**) with dimedone (**1**), ethyl acetoacetate (**3**), and ammonium acetate (**4**) as a model reaction in the absence as well as in the presence of an ionic liquid (5, 10 and 15 mol%) at different temperatures ranging from room temperature to 140 °C under solvent-free conditions. The observations are as follows: Without catalyst at room temperature the formation of product (**5a**) was not observed; as the temperature increases to 140 °C, only 35 % of the product was observed (Table 1, entries 1–4). In the presence of 5 mol% of catalyst, at room temperature only 36 % of the product was formed; as the temperature increased to 110 °C the yield of the product dramatically increased to 82 %, however, further increments of temperature up to 140 °C did not



Scheme 1 1-Sulfonypyridinium chloride catalyzed Hantzsch polyhydroquinoline synthesis



Scheme 2 Synthesis of ionic liquid, 1-sulfonylpyridinium chloride

show any affect on product yield and reaction time (Table 1, entries 5–8). To achieve better yields, the above reaction was conducted with 10 and 15 mol % of the catalyst, and observed the maximum yield (93 %) in shorter reaction times (25 min) with 10 mol % of the catalyst. We also observed that as the amount of the catalyst increased to 15 mol % the yield slightly decreased due to the formation of unidentified impurities. Thus, the optimum condition is 10 mol% of the catalyst at 110 °C under solvent-free conditions.

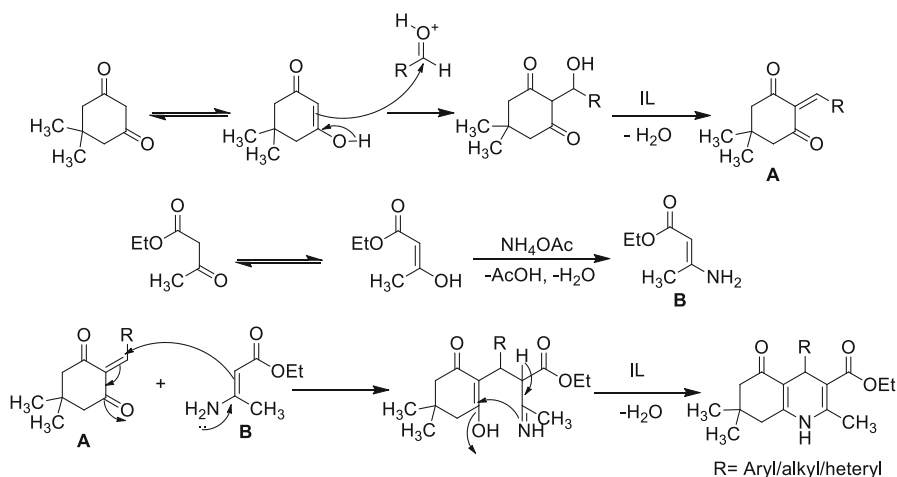
With the optimized conditions in hand, we proceeded to examine the scope of the reaction using a variety of different aromatic, aliphatic, and hetero aromatic aldehydes (Scheme 1), and obtained the desired polyhydroquinoline derivatives (**5a–m**) with excellent yields and in shorter reaction times (Table 2). After completion of the reaction, the catalyst was recovered by evaporating the aqueous layer, washed with warm ethyl acetate, dried under vacuum and at 90 °C for about 2.5 h, and reused for subsequent reactions for additional four cycles. In this process,

Table 2 1-Sulfonylpyridinium chloride catalyzed synthesis of polyhydroquinolines (**5a–m**) under solvent-free conditions

Analog	Aldehyde	Time (min)	Yield (%) ^a	Melting points (°C)	
				Found	Reported [References]
5a	Benzaldehyde	25	93	202–204	203–204 [29]
5b	4-Bromo benzaldehyde	30	89	254–256	252–254 [33]
5c	3-Nitro benzaldehyde	35	91	178–180	177–178 [29]
5d	4-Nitro benzaldehyde	25	90	244–246	244–246 [33]
5e	3-Ethoxy-4-hydroxybenzaldehyde	35	91	198–200	196–198 [29]
5f	5-Chloro-2-hydroxybenzaldehyde	30	92	208–209	208–210 [37]
5g	5-Bromo-2-hydroxybenzaldehyde	35	92	225–227	226–228 [37]
5h	3,5-Dibromo-2-hydroxybenzaldehyde	35	90	278–280	277–279 [37]
5i	Cinnamaldehyde	30	92	206–207	206–207 [31]
5j	Butyraldehyde	35	91	150–151	150–152 [31]
5k	Furan-2-carbaldehyde	30	90	248–250	248–249 [31]
5l	5-Chloropicolininaldehyde	25	84	238–240	–
5m	1 <i>H</i> -Indole-3-carbaldehyde	25	91	169–170	–

Reaction conditions Dimedone (1 mmol), aldehyde (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (3 mmol), and [pyridine-SO₃H]Cl (10 mol%), neat conditions, 110 °C

^a Isolated yields after purification



Scheme 3 Plausible mechanism for the formation of polyhydroquinolines catalyzed by ionic liquid, [pyridine- SO_3H]Cl

we observed a slight decrease in its activity in terms of product yield. For example, the reaction of dimedone (**1**), benzaldehyde (**2a**) ethyl acetoacetate (**3**), and ammonium acetate (**4**) gave the desired product (**5a**) in 91, 89, 86, and 83 % yields over an additional four cycles. All the synthesized compounds were characterized by IR, 1H NMR and mass spectral data, as well as via elemental analyses studies, and the melting points of the known compounds were also compared with the literature values, where both were found to be in good agreement.

A plausible mechanism for the formation of polyhydroquinolines catalyzed by an ionic liquid, [pyridine- SO_3H]Cl is described in Scheme 3. The carbonyl oxygen of aldehyde is activated in the presence of [pyridine- SO_3H]Cl and readily reacts with the enolic form of dimedone, affording the corresponding chalcone type compound **A**. Intermediate **A** undergoes cyclization with ethyl-3-aminobut-2-enoate **B**, which is formed in situ by the reaction of ethyl acetoacetate with ammonium acetate followed by dehydration; this results in the corresponding polyhydroquinoline in excellent yields.

Conclusion

In conclusion, we have developed a simple, efficient, and eco-friendly protocol for the synthesis of polyhydroquinolines via Hantzsch multicomponent condensation of dimedone, aryl/alkyl/heteryl aldehydes, ethyl acetoacetate, and ammonium acetate utilizing 1-sulfonypyridinium chloride as a catalyst. This method offers several advantages including high yields, short reaction times, a simple workup procedure, reusability of the catalyst, and the ability to avoid use of hazardous organic solvents.

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