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Article

Four-component one-pot synthesis of unsymmetrical polyhydroquinoline derivatives using 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate as a catalyst

Nader Ghaffari Khaligh^{a,b,*}^a Department of Chemistry, Qaemshahr Branch, Islamic Azad University, Qaemshahr, 47651-61964, Iran^b Research House of Professor Reza, Education Guilan, District 1, Rasht, 41569-17139, Iran

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ABSTRACT

3-Methyl-1-sulfonic acid imidazolium hydrogen sulfate has been used as an efficient, halogen-free, and reusable Brönsted acidic ionic liquid catalyst for the synthesis of ethyl-4-aryl/heteryl-hexahydro-trimehtyl-5-oxoquinoline-3-carboxylates via the one-pot condensation of dimedone with aryl/heteryl aldehydes, ethyl acetoacetate, and ammonium acetate under solvent-free conditions. This method has the advantage of being clean and simple, as well as providing the desired product in high yield over a short reaction time. Furthermore, the catalyst could be recycled and reused four times without any discernible reduction in activity.

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1. Introduction

N-containing heterocycles such as quinoline and its derivatives are found in a wide range of natural products, including alkaloids. Quinoline in particular has been reported to exhibit a variety of different pharmacological and biological properties [1], including anti-asthmatic, anti-inflammatory, antimalarial, anticancer, and anthelmintic activity [2–7]. Compounds belonging to this structural class have also been used as dyes and intermediates in organic synthesis [8–15], as well as ligands for the preparation of OLED phosphorescent complexes [16] and the preparation of nano and mesostructures with enhanced electronic and photonic properties [17,18].

4-Substituted-1,4-dihydropyridines (1,4-DHPs) have received considerable attention in chemistry because of their occurrence in a wide range of clinically validated therapeutic agents such as amlodipine, felodipine, isradipine, lacidipine, nifedipine, and nicardipine [19–23]. Compounds of this type

have also been used in a number of other therapeutic applications where they have exhibited neuroprotectant and platelet anti-aggregatory activity, as well as being used as cerebral anti-ischemic agents in the treatment of Alzheimer's disease and chemo-sensitizers in tumor therapy [24,25]. Several procedures have been reported for the preparation of polyhydroquinolines, including the use of microwave irradiation [26], sonication [27], and a variety of different catalysts [28–36].

Ionic liquids possess a range of important and unique properties such as low volatility, nonflammability, high thermal stability, negligible vapor pressure, and the ability to dissolve a broad spectrum of materials [37]. Task-specific ionic liquids (TSILs) have been used as excellent alternatives to organic solvents, as well as environmentally benign catalysts and reagents for research in both academia and industry [38]. Brönsted acidic ionic liquids were originally synthesized to replace mineral liquid acids such as H₂SO₄ and HCl in chemical procedures [39]. The introduction of Brönsted-acidic functional

* Corresponding author. Tel: +98-2166431738; Fax: +98-2166934046; E-mail: ngkhaligh@guilan.ac.ir, ngkhaligh@gmail.com

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groups to the cations or anions of ionic liquids, especially SO_3H and SO_4H functional groups, leads to an obvious increase in their acidity and water solubility [40–42]. Furthermore, the polar nature of these functional groups makes their application under solvent-free conditions particularly attractive. TSILs have attracted considerable attention in terms of their application to catalytic reactions, because the TSIL and product exist in two different phases, which makes it easy for the product to be isolated and the TSIL to be recycled. Ionic liquids have been used extensively as catalysts under solvent-free conditions for the four-component synthesis of polyhydroquinoline derivatives using a Hantzsch reaction. In 2004, Ji et al. [31] performed a four-component Hantzsch reaction and reported that the use of the ionic liquid $[\text{HMIm}]\text{BF}_4$ under solvent-free conditions shortened the reaction time to a few minutes at 90 °C and increased the yields up to 96%. Ionic liquids typically consist of halogen-containing anions, which have limited their overall utility from a “green chemistry” perspective, and research towards the development of greener ionic liquids using halogen-free anions such as phosphate or sulfate anion has been reported in the literature, together with studies pertaining to the effect of different anions on the toxicology of these liquids [43–48].

3-Methyl-1-sulfonic acid imidazolium hydrogen sulfate $[(\text{MSAIm})\text{HSO}_4]$, which consists of a sulfonic acid group with an imidazolium cation and hydrogen sulfate anion, was recently synthesized as a halogen-free acidic ionic liquid, and investigated as a catalyst for the protection of hydroxyl groups [49] and the synthesis of coumarins *via* the Pechmann reaction [50]. In the current study, we have developed and optimized a $(\text{MSAIm})\text{HSO}_4$ -catalyzed process for the synthesis of ethyl-4-aryl-hexahydro-trimehtyl-5-oxoquinoline-3-carboxylate derivatives, which could exhibit good dye properties, as well as interesting biological and pharmaceutical activity.

2. Experimental

2.1. General

All the chemicals were purchased from Fluka AG, Merck, and Synthetic Chemicals Ltd. The reactions were monitored by TLC using silica TLC plates and the product purities were determined by GC-MS on an Agilent GC-Mass-6890 instrument under ionization conditions of 70 eV. Fourier transform infrared (FT-IR) spectra were recorded on a Perkin-Elmer 781 FT-IR spectrometer and a Bruker Equinox 55 system. The FT-IR spectra of solid samples were recorded as KBr disks, whereas the spectra of liquid samples were recorded neat in the range of 4000–400 cm^{-1} . ^1H NMR spectra were recorded on a Bruker Avance 400 MHz instrument using deuterated DMSO or chloroform containing TMS as an internal reference standard. Mass spectra were recorded on a PEsCiex model API 3000 instrument. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points (m.p.) were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.2. Typical procedure for the preparation of the

ethyl-4-aryl-hexahydro-trimehtyl-5-oxoquinoline-3-carboxylate derivatives (4)

The $(\text{MSAIm})\text{HSO}_4$ catalyst (10 mg, 3.8 mol%) was added to a mixture of dimedone (1 mmol), ethyl acetoacetate (1 mmol), aryl/heteryl aldehyde (1 mmol) and ammonium acetate (1 mmol), and the resulting mixture was stirred for an appropriate time period at 50 °C under solvent-free conditions. When the reaction mixture existed as a solid, the material was placed in a porcelain dish and ground with a mortar at 50 °C. Upon completion of the reaction, as determined by TLC, the mixture was cooled to room temperature. The reaction product was subsequently extracted with ethyl acetate (EtOAc , 3×5 mL) and the $(\text{MSAIm})\text{HSO}_4$ catalyst was recovered. The Brönsted acidic ionic liquid was immiscible with EtOAc , and could therefore be conveniently separated from the products via a simple phase separation. The recovered catalyst was washed with EtOAc (2×5 mL) before being dried at ambient temperature and reused in the next run. The combined EtOAc extracts were evaporated under reduced pressure to give the crude products as solids, which were crystallized from ethanol to afford the pure polyhydroquinoline derivatives.

2.3. Spectral data of new products

Ethyl-4-(3-ethoxy-4-hydroxyphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**4q**). White solid; m.p. = 195–197 °C; FT-IR (KBr): ν_{max} = 3282, 3203, 3077, 2958, 1689, 1615, 1511, 1488, 1215 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 0.87 (s, 3H), 1.01 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 6.8 Hz, 3H), 1.98 (d, J = 16 Hz, 1H), 2.16 (d, J = 16.4 Hz, 1H), 2.25–2.43 (m, 5H), 3.85–3.91 (m, 2H), 3.96–4.01 (m, 2H), 4.73 (s, 1H), 6.48–6.51 (m, 1H), 6.57 (d, J = 8 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 8.53 (s, 1H), 8.98 (s, 1H) ppm; MS (ESI) m/z = 400 $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_5$: C 69.15%, H 7.32%, N 3.51%; Found: C 69.27%, H 7.64%, N 3.42%.

Ethyl-4-(5-bromo-2-hydroxyphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**4r**). Pale yellow solid; m.p. = 226–228 °C; FT-IR (KBr): ν_{max} = 3318, 3253, 3093, 2962, 1654, 1606, 1590, 1489, 1230, 619 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 0.84 (s, 3H), 1.01–1.06 (m, 6H), 2.05 (d, J = 16.4 Hz, 1H), 2.23 (d, J = 16.4 Hz, 1H), 2.25–2.43 (m, 5H), 3.87–3.97 (m, 2H), 4.89 (s, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 7.07–7.10 (m, 1H), 9.28 (s, 1H), 9.58 (s, 1H) ppm; MS (ESI) m/z = 435 $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{21}\text{H}_{24}\text{BrNO}_4$: C 58.07%, H 5.57%, N 3.22%; Found: C 58.26%, H 5.34%, N 3.41%.

Ethyl-4-(3,5-dibromo-2-hydroxyphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**4s**). Pale yellow solid; m.p. = 277–279 °C; FT-IR (KBr): ν_{max} = 3287, 3212, 3073, 2957, 1635, 1614, 1577, 1485, 1225, 667 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 0.94 (s, 3H), 1.01–1.05 (m, 6H), 2.13 (d, J = 16 Hz, 1H), 2.28–2.44 (m, 6H), 3.88–3.95 (m, 2H), 4.82 (s, 1H), 6.88–6.91 (m, 1H), 7.48–7.50 (m, 1H), 9.56 (s, 1H), 9.86 (s, 1H) ppm; MS (ESI) m/z = 513 $[\text{M}]^+$; Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{Br}_2\text{NO}_4$: C 49.15%, H 4.52%, N 2.73%; Found: C 49.26%, H 4.71%, N 2.60%.

Ethyl-4-(5-chloro-2-hydroxyphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**4t**). Pale yellow solid; m.p. = 208–210 °C; FT-IR (KBr): $\nu_{\max}$ = 3317, 3253, 3096, 2961, 1654, 1608, 1591, 1490, 1230, 643 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 0.84 (s, 3H), 1.01–1.05 (m, 6H), 2.06 (d, J = 16 Hz, 1H), 2.22–2.44 (m, 6H), 3.89–3.94 (m, 2H), 4.91 (s, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.96–6.99 (m, 1H), 9.30 (s, 1H), 9.58 (s, 1H) ppm; MS (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 64.53%, H 6.33%; N 3.72%.

3. Results and discussion

The condensation of dimedone (**1**) with 4-chlorobenzaldehyde (**2c**), ethyl acetoacetate (**3**), and ammonium acetate was selected as a model reaction, and several different reaction parameters, including the amount of $(\text{MSAIm})\text{HSO}_4$ (i.e., 5, 10, and 20 mg), different types of solvent (i.e., CH_2Cl_2 , CH_3CN , MeOH, EtOH, and H_2O) and solvent-free conditions, and various reaction temperatures (i.e., room temperature, reflux for solvents, 50–100 °C for solvent-free conditions) were evaluated to optimize the reaction conditions (Table 1).

When the model reaction was carried out in ethanol at reflux in the presence of 20 mg $(\text{MSAIm})\text{HSO}_4$, the desired product **4c** was obtained in 72% yield within 1 h. Pleasingly, when the reaction was conducted under solvent-free conditions at 50 °C in the presence of 10 mg of $(\text{MSAIm})\text{HSO}_4$, **4c** was formed in 92% yield within 17 min (Scheme 1), with the solvent-free conditions effectively facilitating the condensation reactions involved in the Hantzsch reaction to a much greater extent. These results suggested that the microenvironment of the solvent-free system was different to that of the solution-based system, resulting in the observed improvement in the yield of the Hantzsch condensation reaction [51].

To evaluate the scope of this transformation over the $(\text{MSAIm})\text{HSO}_4$ catalyst, we evaluated the conversion of a variety of different aryl/heteryl aldehydes to the corresponding ethyl-4-aryl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate derivatives (**4a–4x**) under the optimized conditions (Table 2). Aryl aldehydes bearing electron-donating or electron-withdrawing substituents reacted smoothly to afford the corresponding polyhydroquinolines in good to high yields over short reaction time (Table 2, entries 1–21). The position and electronic properties of the substituent on aromatic aldehyde had a significant impact on the yield of the polyhydroquinoline and the reaction time. For example, aryl aldehydes bearing electron-donating substituents required longer

Table 1

Optimization of the reaction conditions for the synthesis of ethyl-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylates in the presence of $(\text{MSAIm})\text{HSO}_4$.

Entry	Solvent	Amount of $(\text{MSAIm})\text{HSO}_4$ (mg)	Temperature (°C)	Time (min)	Yield* (%)
1	CH_2Cl_2	20	r.t.	60	14
2	CH_2Cl_2	20	reflux	60	32
3	CH_3CN	20	r.t.	60	34
4	CH_3CN	20	reflux	60	52
5	CH_3OH	20	r.t.	60	39
6	CH_3OH	20	reflux	60	60
7	$\text{C}_2\text{H}_5\text{OH}$	20	r.t.	60	48
8	$\text{C}_2\text{H}_5\text{OH}$	20	reflux	60	72
9	H_2O	20	r.t.	60	32
10	H_2O	20	reflux	60	68
11	solvent-free	20	r.t.	60	72
12	solvent-free	20	50	15	92
13	solvent-free	10	50	17	92
14	solvent-free	5	50	20	87
15	solvent-free	10	80	15	92
16	solvent-free	10	100	20	83

Reaction conditions: dimedone 1 mmol, 4-chlorobenzaldehyde 1 mmol, ethyl acetoacetate 1 mmol, ammonium acetate 1 mmol.

* GC-MS yield.

whereas the use of a *para*- NO_2 group led to an increase in the rate of the reaction, with the corresponding product with 96% yield in only 15 min (Table 2, entries 8 and 10). These results demonstrated that aldehydes bearing electron-withdrawing groups (i.e., $-\text{NO}_2$ and halogens) were more active towards the reaction than those bearing electron-donating groups (i.e., $\text{CH}_3\text{O}-$ and $\text{HO}-$). The use of aldehydes bearing substituents at the *ortho*-position of their phenyl ring gave lower yields of the products than those bearing the same substituents at the *para*-position, most likely because of steric hindrance (Table 2, entries 3, 10, 11, and 14). The use of aliphatic aldehydes as substrates for the reaction was unsuccessful, and analysis of the reaction mixtures by TLC and GC-MS revealed numerous byproducts. It is noteworthy that when the model reaction was conducted in the absence of catalyst under the optimized conditions for 1 h, the yield of the product was low (22%). The structure of the new products were established on the basis of their spectral properties (i.e., IR, ^1H NMR, and MS), melting points, and elemental analysis. The known products were characterized on the basis of their physical data (i.e., m.p., IR,

Scheme 1. Synthesis of ethyl-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**4c**) in the presence of $(\text{MSAIm})\text{HSO}_4$.

Table 2Synthesis of ethyl-4-aryl/heteryl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylates in the presence of (MSAIm)HSO₄.

Entry	Substrate (2)	Product (4)	Time (min)	Yield ^a (%)	m.p. (°C)		Ref.
					Found	Reported	
1	C ₆ H ₅ -CHO	4a	18	92	202–204	202–204	[28]
2	4-F-C ₆ H ₄ -CHO	4b	17	92	182–184	184–186	[28]
3	4-Cl-C ₆ H ₄ -CHO	4c	17 (17,17,18,18) ^b	95 (95,94,94,93) ^b	240–242	241–243	[29]
4	4-Br-C ₆ H ₄ -CHO	4d	17	94	250–252	253–255	[28]
5	4-CH ₃ -C ₆ H ₄ -CHO	4e	20	92	261–263	260–261	[28]
6	4-(CH ₃) ₂ C-C ₆ H ₄ -CHO	4f	20	90	175–177	179–180	[30]
7	4-CH ₃ O-C ₆ H ₄ -CHO	4g	22	89	255–257	257–259	[28]
8	4-HO-C ₆ H ₄ -CHO	4h	25	86	230–232	232–234	[28]
9	4-(CH ₃) ₂ N-C ₆ H ₄ -CHO	4i	22	87	231–233	229–231	[28]
10	4-NO ₂ -C ₆ H ₄ -CHO	4j	15	96	240–242	240–242	[31]
11	2-Cl-C ₆ H ₄ -CHO	4k	20	90	202–204	208–210	[31]
12	2,4-Cl ₂ -C ₆ H ₃ -CHO	4l	20	92	242–244	241–244	[28]
13	3,4-(CH ₃ O) ₂ -C ₆ H ₃ -CHO	4m	25	88	196–198	198–200	[32]
14	2-NO ₂ -C ₆ H ₄ -CHO	4n	17	90	207–209	207–208	[32]
15	3-NO ₂ -C ₆ H ₄ -CHO	4o	17	94	182–184	182–184	[29]
16	3-CH ₃ O-4-HO-C ₆ H ₃ -CHO	4p	23	84	215–217	219–221	[30]
17	2-C ₂ H ₅ O-4-HO-C ₆ H ₃ -CHO	4q	25	82	197–199	—	—
18	2-HO-5-Br-C ₆ H ₃ -CHO	4r	25	84	228–230	—	—
19	2-HO-(3,5-Br ₂)-C ₆ H ₃ -CHO	4s	25	86	280–282	—	—
20	2-HO-5-Cl-C ₆ H ₃ -CHO	4t	25	85	210–212	—	—
21	Cinnamaldehyde	4x	18	92	200–202	204–206	[28]
22	Furfural	4u	27	86	242–244	246–248	[28]
23	3-Nicotinaldehyde	4v	25	80	69–71	66–67	[28]
24	2-Thienylaldehyde	4w	30	78	236–238	238–240	[28]

Reaction conditions: dimedone 1 mmol, aryl/heteryl aldehyde 1 mmol, ethyl acetoacetate 1 mmol, ammonium acetate 1 mmol, (MSAIm)HSO₄ 10 mg, 50 °C, solvent-free.

^a Isolated yield following chromatographic purification.

^b Recycled Brønsted acidic ionic liquid catalyst was used.

and ¹H NMR) and through a comparison with authentic samples.

The recyclability of the (MSAIm)HSO₄ catalyst represents one of the key advantages of the current method, and the catalyst could be recycled at least five times without any significant impact on the yield of ethyl-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate under the optimized conditions (Table 2, entry 3). Upon completion of the reaction, the product was extracted and new substrates were added to the reaction vessel. The progress of the reaction was monitored by TLC under the optimized conditions and this process was repeated for five runs. The results showed that there was no discernible decrease in the activity of catalyst, with yields in the range of 93% to 95% across all five runs, and an average reaction time of approximately 18 min.

A possible mechanism has been proposed for this reaction, as shown in Scheme 2. Dimedone (**1**), aldehyde (**2**), and ethylacetoacetate (**3**) would be activated by the Brønsted acidic ionic liquid catalyst. Dimedone or ethyl acetoacetate would be converted to its enol form by the Brønsted acidic ionic liquid and a Knoevenagel type coupling would then take place with the activated aldehyde to afford intermediate (**I**) or (**III**). In contrast, the activated ethyl acetoacetate or activated dimedone could react with ammonium acetate to give enamine (**II**) or (**IV**). It is noteworthy that the ionic liquid would effectively provide a proton to activate the carbonyl groups of the starting material and that this proton would ultimately be transferred back to the ionic liquid in another step. Subsequent Michael addition of enamine (**II**) to intermediate (**I**) or enamine (**IV**) to

intermediate (**III**) followed by sequential cyclization and dehydration reactions would afford the polyhydroquinoline product (**4**) [29]. In multicomponent reactions of this type, the elimination of H₂O is critical, and the observed increase in the reaction rate may have occurred as a consequence of an increase in the rate of the absorption of H₂O by the ionic liquid or the elimination of H₂O at the high temperature of reaction.

The possible leaching of H₂SO₄ from the matrix was studied under the optimized reaction conditions. No leaching was observed under the optimized conditions. After eight recycled runs, the catalyst retained about 92% of its initial activity (data not shown).

A comparison of our results with several other results reported in the literatures for the same transformation has been provided in Table 3 to highlight the merits of the current method. It is clear that the reaction time and yields achieved with our newly developed procedure are similar to or higher than those described in the literatures. When the Hantzsch reaction was carried out in the presence of 10 mol% guanidine HCl (organocatalyst) in ethanol at room temperature, compounds **4c**, **4x**, **4u**, and **4v** were formed in yields of 95%, 90%, 78%, and 75%, respectively, after 3 h [54]. Furthermore, when 10 mol% L-proline was used as a catalyst for the same transformation, compounds **4c**, **4e**, and **4i** were formed in 91%, 94%, and 96% yields, respectively, after 30 min [29]. In contrast to both of these reports, the use of the current method gave compounds **4c**, **4e**, **4i**, **4x**, **4u**, and **4v** in yields of 95%, 92%, 87%, 92%, 86%, and 80% within 17, 20, 22, 18, 27, and 25 min, respectively.

Scheme 2. A possible mechanism for the synthesis of polyhydroquinoline in the presence of (MSAIm)HSO₄ under solvent-free conditions.

Table 3

Comparison of the use of different catalysts for the preparation of ethyl-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate.

Entry	Catalyst	Catalyst amount	Ammonium acetate (equiv.)	Solvent	Temperature (°C)	Time (min)	Isolated yield (%)	Ref.
1	MCM-41	1 mol%	1.5	—	90	15	90	[52]
2	Modified Mont. supported Nano-Ni ⁰	25 mg	1.5	—	r.t.	15	88	[53]
3	Guanidine hydrochloride	10 mol%	1	EtOH	r.t.	180	95	[54]
4	(PPA-SiO ₂)	30 mg	1	—	80	45	92	[55]
5	[Pyridine-SO ₃ H]Cl	3 mol%	1.2	—	50	10	92	[56]
6	Trifluoroethanol (TFE)	2 mL	1	TFE	70	180	95	[57]
7	Hf(NP ₂) ₄	1 mol%	1	C ₁₀ F ₁₈	60	120	96	[58]
8	FeF ₃	5 mol%	1	EtOH	75–80	60	92	[59]
9	Sc(OTf) ₃	5 mol%	1	EtOH	r.t.	240	89	[60]
10	K ₇ [PW ₁₁ CoO ₄₀]	30 mg	1	MeCN	reflux	30	85	[61]
11	[2-MPyH]OTf	1 mol%	1	H ₂ O	r.t.	5	97	[62]
12	Yb(OTf) ₃	5 mol%	1	EtOH	r.t.	240	95 ^a	[28]
13	CAN	5 mol%	1	EtOH	r.t.	35	88	[63]
14	L-Proline	10 mol%	1	—	r.t.	30	91	[29]
15	Bakers' yeast, D-glucose, phosphate buffer	200 mg, 300 mg, 5 mL (pH = 7)	1	—	r.t.	1440	79 ^b	[64]
16	Nano-Ni	10 mol%	1.5	—	microwave (540 W)	1	90	[65]
17	Nano-Pd	4 mol%	2	THF	reflux	240	87	[66]
18	—	—	1.5	EtOH	r.t.	360	84	[30]
19	HClO ₄ -SiO ₂	50 mg	1.5	—	90	10	95	[32]
20	[Dsim]HSO ₄	20 mg (3 mol%)	1.2	—	50	25	89	[67]
21	(MSAIm)HSO ₄	10 mg (3.4 mol%)	1	—	60	17	95	this work

Reaction conditions: dimerone 1 mmol, 4-chlorobenzaldehyde 1 mmol, ethyl acetoacetate 1 mmol.

^aData are for 4-bromobenzaldehyde.

^bData are for benzaldehyde.

Furthermore, the use of 3 mol% [pyridine-SO₃H]Cl as a catalyst for the procedure at 50 °C gave compounds **4c**, **4i**, **4g**, and **4h** in yields of 92%, 95%, 95%, and 94% with reaction time of 10, 8, 10, and 8 min, respectively [56], whereas the used of 3 mol% [2-MPyH]OTf as the catalyst at room temperature gave

the same compounds in 97, 98, 96 and 95% yields with reaction time of 5, 1, 6, and 6 min, respectively [62]. Pleasingly, the use of the current method under solvent-free conditions gave **4c**, **4i**, **4g**, and **4h** in 95%, 96%, 89%, and 86%, yields within 17, 15, 22, and 25 min, respectively.

Some of the reported methodologies suffer from one or more of the following disadvantages: (1) potential health hazards associated with the preparation of the catalysts (e.g., pyridine is flammable and has a flash point of 17 °C); (2) difficulty in handling the catalysts (e.g., triflates are moisture-sensitive); (3) high cost of the catalysts (e.g., triflates); (4) the requirement for halogenated solvents (e.g., C₁₀F₁₈); (5) difficulties associated with the preparation of the catalysts; (6) the lack of atom economy (i.e., the use of substrates and catalyst in excess); (7) the requirement for stringent reaction conditions and longer reaction time (4–24 h); and (8) in some cases the reported methodologies are not suitable for acid-sensitive substrates.

4. Conclusions

We have developed a facile and efficient method for the synthesis of polyhydroquinoline derivatives. There are several advantages associated with this newly developed procedure, including its simple experimental procedure, solvent-free conditions, use of an inexpensive and readily available catalyst, good to high yields, reusability of the catalyst and ease of product isolation/purification by non-aqueous work-up.

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Graphical Abstract

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Four-component one-pot synthesis of unsymmetrical polyhydroquinoline derivatives using 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate as a catalyst

Nader Ghaffari Khaligh*

Qaemshahr Branch, Islamic Azad University, Iran; Research House of Professor Reza, Education Guilan, Iran

One-pot condensation of dimedone with aryl/heteroaryl aldehydes, ethyl acetoacetate and ammonium acetate in the presence of 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate under solvent-free conditions. The catalyst could be recycled and reused at least four times without any significant loss in its activity. The structures of the new products were established from their spectral properties (IR, ¹H NMR, and MS), as well as their melting point and elemental analysis data. The known products were characterized by their physical data (m.p., IR, ¹H NMR) and through a comparison with the authentic samples.

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