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Protic pyridinium ionic liquid as a green and highly efficient catalyst for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation in water

Mahmood Tajbakhsh [a], Heshmatollah Alinezhad [a], Mohammad Norouzi [a,b,*], Saeed Baghery [c], Maryam Akbari [b]

[a] Department of Chemistry, Mazandaran University, Babolsar, Iran
[b] Department of Chemistry, Payame Noor University, P.O. Box 19395-3697, Tehran, Iran
[c] Young Researchers Club, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran

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ABSTRACT

The four-component Hantzsch condensation reaction of dimedone, ethyl acetoacetate, ammonium acetate and various aromatic and aliphatic aldehydes in the presence of 2-methylpyridinium trifluoromethanesulfonate ([2-MPyH]OTf) as a green and highly efficient catalyst in water affords polyhydroquinoline derivatives in good to excellent yields. This reaction has been carried out in the presence of 1 mol% of [2-MPyH]OTf at room temperature. The described novel synthesis method proposes several advantages of short reaction times, high yields, mild condition, high melting point, simplicity and easy workup compared to the traditional method of synthesis.

1. Introduction

4-Substituted 1,4-dihydropyridine (1,4-DHP) nucleus is a fertile source of biologically important molecules possessing various important pharmacological properties such as antihypertensive, anti-therosclerotic, hepto-protective, anti-mutagenic, vasodilator, bronchodilator, anti-tumor, geroprotective and anti-diabetic agents. Thus, these compounds are analogues of NADH coenzymes, which have been investigated for their calcium channel activity and the heterocyclic rings are found in variety of bioactive compounds [1–6]. In 1882, Arthur Hantzsch reported first synthesis of symmetrically substituted 1,4-dihydropyridines by the one-pot, four component condensation of two molecules of ethylacetoacetate, aromatic aldehyde and ammonia [7]. The standard Hantzsch procedure does not need the intervention of any additive or reagent and the reaction was originally conducted either in acetic acid or at reflux in alcohol for rather long periods, resulting in low or modest yields of condensation products. Replacement of ammonia by ammonium acetate allowed the efficient synthesis of Hantzsch compounds in aqueous medium as well as under solvent free conditions [8,9].

Realizing the importance of polyhydroquinoline derivatives in the synthesis of various drug sources, we reported many characteristic methods such as conventional heating [10,11], *L*-proline [12], various catalysts such as ammonium nitrate (CAN) [13], silica perchloric acid ($HClO_4$–SiO_2) [14], trimethylsilyl chloride [15], nickel nanoparticle [16], FeF_3 [17], $K_7[PW_{11}CoO_{40}]$ [18], *p*-TSA [19], solar heat [20], hafnium (IV) [21], SBA-Pr-SO_3H [22], Bakers' yeast [23], iron (III) trifluoroacetate [24].

Ionic liquids are salts consisting of ions, which exist in the liquid state at ambient temperatures [25]. They show reasonably high ionic conductivities. Although the first ionic liquid, ethylammonium nitrate (m.p 12 °C) was reported as early as 1914 [26], ionic liquids have found great interest only recently. Ionic liquids are usually characterized by a wide electrochemical window of stability, a reasonable ionic conductivity (similar to most non-aqueous electrolytes). ILs typically consist of organic nitrogen-containing heterocyclic cations and inorganic anions [25]. Nevertheless, in the last few years they have become more attractive in other fields such as catalysis [27], formation of metal nanostructures [28], analytical chemistry [29] including sensors [30] and for electrochemical biosensors [31]. Due to their high polarities, the ionic liquids are expected to be very suitable solvents for the reactions between organo-soluble and water soluble reagents. Utility of the ionic liquids as solvents for various organic reactions [32,33] and polymerization reactions [34–36] has been studied. Generally, ILs are defined as those fused salts with a melting point less than 100 °C, with salts with higher melting points referred to as molten salts. The

* Corresponding author. Tel.: +98 191 3257681; fax: +98 191 3257680.
E-mail addresses: mnorouzi346@yahoo.com, mnorouzi346@pnu.ac.ir (M. Norouzi).

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Brønsted acidic AILs have been incorporated within the organic synthesis section, since that is the principal application of that compounds [37].

However, some of reported methods in the synthesis of polyhydroquinoline derivatives have one or more disadvantages such as moisture sensitive, or highly toxic in environment and unpleasant experimental procedure and reagents which are expensive. A mild and efficient catalyst for the synthesis of polyhydroquinoline is very desirable. Performing organic reactions in aqueous media has attracted much attention because of wonderful water properties. It would be significantly safe, cheap, non-toxic and environmentally friendly compared to organic solvents [38].

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot reaction [39]. We would like to report a highly efficient and green four-component Hantzsch condensation in the presence of 2-methylpyridinium trifluoromethanesulfonate ([2-MPyH]OTf) [40] as an ionic liquid catalyst in water using various aromatic and aliphatic aldehyde, dimedone, ethyl acetoacetate and ammonium acetate to produce the polyhydroquinoline derivatives in good to excellent yields.

2. Experimental

2.1. General procedure for the synthesis of [2-MPyH]OTf as an ionic liquid catalyst

The ionic liquid [2-MPyH]OTf as a catalyst was synthesized according to literature [40]. A white solid was formed in high purity and then the physical data (IR, NMR) of this known ionic liquid were found to be identical. Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (s, 3H), 7.26–7.67 (m, 2H), 8.29–8.36 (m, 1H), 8.84 (d, J = 5.9 Hz, 1H), 17.21 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 146.8, 141.5, 128.1, 125.2, 120.9, 20.3; IR (KBr, cm^{-1}) 2983, 1631, 1365, 1223, 1070, 957, 887, 579.

2.2. General procedure for the synthesis of polyhydroquinoline derivatives

A mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1 mmol) was added to [2-MPyH]OTf catalyst (1 mol%) in water (2 mL), and the reaction mixture was stirred at room temperature for an appropriate time. Completion of the reactions was monitored by TLC (*n*-hexan/ethyl acetate 4:1). After completion of the reaction, the resulting solid crude product was filtered and then recrystallized from ethanol–water to obtain pure product. The formation of products was related by comparing the melting points, IR and NMR data with authentic samples and literature data.

2.3. Spectral data for the synthesis of polyhydroquinoline derivatives

Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 1—ntry 3): Yield: 97%; M.p 233–235 °C (Ref. [43] 230–232 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 3H, —CH_3), 0.93 (s, 3H, —CH_3), 1.11 (t, 3H, J = 7.3 Hz, —CH_3), 2.04 (dd, 2H, —CH_2—), 2.12 (dd, 2H, —CH_2—), 2.26 (s, 3H, —CH_3), 3.95 (q, 2H, J = 7.2 Hz, —OCH_2—), 4.93 (s, 1H, —CH—), 7.07 (d, 2H, J = 9.1 Hz, Ar—H), 7.15 (d, 2H, J = 9.2 Hz, Ar—H), 7.91 (brs, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 18.8, 26.7, 29.3, 31.7, 35.3, 41.1, 50.4, 59.8, 75.9, 103.1, 110.8, 127.1, 128.6, 130.7, 144.3, 150.2, 164.9, 193.9; IR (KBr, cm^{-1}) 3270, 3195, 3070, 2945, 1670, 1604, 1475, 1367, 1227, 1105, 857.

Ethyl 4-(3,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 1—entry 11): Yield: 96%; M.p 202–204 °C (Ref. [44] 198–199 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 3H, – CH_3), 1.04 (s, 3H, —CH_3), 1.25 (t, 3H, J = 7.3 Hz, —CH_3), 1.92–2.15 (dd, 2H, —CH_2—), 2.21–2.35 (dd, 2H, —CH_2—), 2.27 (s, 3H, —CH_3), 3.57 (s, 3H, —OCH_3), 3.73 (s, 3H, —OCH_3), 4.03 (q, 2H, J = 7.2 Hz, —OCH_2—), 4.71 (s, 1H, —CH—), 6.45–6.73 (m, 3H, Ar—H), 8.19 (brs, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 26.5, 27.2, 28.3, 33.4, 38.6, 47.5, 52.1, 58.1, 105.3, 107.3, 111.3, 114.9, 121.1, 135.3, 147.4, 147.9, 153.2, 155.1, 167.7, 195.1; IR (KBr, cm^{-1}) 3396, 3280, 3067, 2959, 1687, 1550, 1475, 1263, 1223, 850.

Ethyl 2,7,7-trimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 1—entry 14): Yield: 96%; M.p 262–264 °C (Ref. [41] 260–261 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 3H, —CH_3), 1.07 (s, 3H, —CH_3), 1.17 (t, 3H, J = 7.2 Hz, —CH_3), 1.98 (s, 3H, —CH_3), 2.03 (dd, 2H, —CH_2—), 2.21 (dd, 2H, —CH_2—), 2.41 (s, 3H, —CH_3), 4.06 (q, 2H, J = 7.1 Hz, —OCH_2—), 5.15 (s, 1H, —CH—), 7.43 (d, 2H, J = 9.2 Hz, Ar—H), 8.13 (d, 2H, J = 9.2 Hz, Ar—H), 8.22 (brs, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 18.5, 23.1, 27.1, 27.8, 33.9, 37.6, 40.7, 51.3, 61.9, 77.5, 104.4, 111.9, 121.2, 127.1, 146.5, 150.3, 154.3, 167.2, 193.5; IR (KBr, cm^{-1}) 3270, 3180, 3075, 2967, 1661, 1615, 1557, 1480, 1359, 1270, 1150, 875.

Ethyl 2,7,7-trimethyl-4-(4-trifluorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 1—entry 18): Yield: 98%; M.p 188–190 °C (Ref. [17] 188–190 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 3H, —CH_3), 1.12 (s, 3H, —CH_3), 1.27 (t, 3H, J = 7.5 Hz, —CH_3), 2.11 (dd, 2H, —CH_2—), 2.17 (dd, 2H, —CH_2—), 2.39 (s, 3H, —CH_3), 4.12 (q, 2H, J = 7.3 Hz, —OCH_2—), 5.19 (s, 1H, —CH—), 7.47 (d, 2H, J = 9.3 Hz, Ar—H), 8.01 (d, 2H, J = 9.4 Hz, Ar—H), 8.26 (brs, 1H, —NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 19.3, 27.6, 29.7, 32.9, 37.6, 54.7, 63.1, 105.4, 114.3, 123.9, 127.1, 129.6, 147.2, 152.3, 155.2, 168.1, 196.1; IR (KBr, cm^{-1}) 3287, 3157, 3065, 2978, 1670, 1610, 1557, 1480, 1345, 1270, 1201, 875.

Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 1—entry 21): Yield: 98%; M.p 242–244 °C (Ref. [10] 242–244 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (s, 3H, —CH_3), 1.06 (s, 3H, —CH_3), 1.15 (t, 3H, J = 7.3 Hz, —CH_3), 2.09 (dd, 2H, —CH_2—), 2.18 (dd, 2H, —CH_2—), 2.37 (s, 3H, —CH_3), 4.08 (q, 2H, J = 7.4 Hz, —OCH_2—), 5.13 (s, 1H, —CH—), 7.49 (d, 2H, J = 9.4 Hz, Ar—H), 8.11 (d, 2H, J = 9.4 Hz, Ar—H), 8.17

Table 1
Hantzsch condensation synthesis of polyhydroquinoline derivatives in the presence of [2-MPyH]OTf as a catalyst.

Entry	Aldehyde	M.p (°C)	Time (min)	Yield (%) [Ref.]
1	Benzaldehyde	203–205	8	95 [41]
2	2-Chlorobenzaldehyde	207–209	6	96 [15]
3	4-Chlorobenzaldehyde	233–235	5	97 [42]
4	2,4-Dichlorobenzaldehyde	241–243	5	97 [23]
5	3,4-Dichlorobenzaldehyde	201–203	7	96 [43]
6	4-Fluorobenzaldehyde	184–186	5	97 [13]
7	3-Hydroxybenzaldehyde	216–218	8	94 [16]
8	4-Hydroxybenzaldehyde	228–230	6	95 [41]
9	3-Methoxybenzaldehyde	201–203	7	96 [15]
10	4-Methoxybenzaldehyde	257–259	6	96 [41]
11	3,4-Dimethoxybenzaldehyde	202–204	6	96 [44]
12	4-Hydroxy-3-methoxybenzaldehyde	212–214	7	96 [45]
13	3,4,5-Trimethoxybenzaldehyde	193–195	6	97 [10]
14	4-Methylbenzaldehyde	262–264	7	96 [41]
15	2,5-Dimethylbenzaldehyde	246–248	6	96 [46]
16	4-Isopropylbenzaldehyde	182–184	7	96 [46]
17	4-Dimethylaminobenzaldehyde	233–235	4	97 [14]
18	4-Trifluoromethylbenzaldehyde	188–190	2	98 [17]
19	2-Nitrobenzaldehyde	204–206	2	97 [10]
20	3-Nitrobenzaldehyde	172–174	3	97 [10]
21	4-Nitrobenzaldehyde	242–244	1	98 [10]
22	4-Cyanobenzaldehyde	143–145	2	98 [17]
23	Cinnamaldehyde	203–205	10	93 [18]
24	Furan-2-carbaldehyde	245–247	8	95 [44]
25	Thiophene-2-carbaldehyde	223–225	10	95 [15]
26	Propionaldehyde	142–144	15	92 [41]
27	Butyraldehyde	147–149	15	92 [41]
28	Isobutyraldehyde	161–163	12	94 [41]