MICROWAVE-ASSISTED IONIC LIQUID CATALYZED ONE-POT SYNTHESIS OF HEXAHYDROQUINOLINE DERIVATIVES

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Ionic liquid catalyzed one-pot synthesis of hexahydroquinoline derivatives using substituted aryl aldehydes, dimedone, malononitrile and ammonium acetate has been described under microwave irradiation. The protocol has been utilized mild reaction conditions, excellent yield, shorter reaction time and simple workup procedure. The synthesized derivatives were obtained in 80-95% yields and were characterized by IR, ^{1}H NMR, and mass spectra.

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INTRODUCTION

Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where all or most of the atoms contribute to the newly created product. In chemistry, a one-pot synthesis is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor.

Organic synthesis in an ionic liquid medium is a lucrative research area considering its cost, safety and significance to environmentally benign process development .[1-4] Ionic liquid (IL) is a salt in the liquid state. In some contexts, the term has been restricted to salts whose melting point is below some arbitrary temperature. While ordinary liquids such as water and gasoline are predominantly made of electrically neutral molecules, ionic liquids are primarily made of ions and short-lived ion pairs. These substances are variously called liquid electrolytes, ionic melts, ionic fluids, fused salts and liquid salts.[5-7]

Hexahydroquinoline has a broad spectrum of biological properties and it is well known structural scaffold of several natural products and artificial drugs.[8] These are used due to their antibacterial and antifungal activity,[9] anticancer activity,[10] insecticidal activity,[11] and as antimicrobial,[12] anti-inflammatory agents,[13] antioxidant,[14] anti-anaphylactic and diuretic agent.

Several related approaches have been documented in the literature for the synthesis of 5-quinolinones, which generally involve the cyclocondensation of aldehyde, dimedone, an active methylene compound, and ammonium acetate.[15-19] Microwave irradiation and solvent-free medium have been used as activation conditions, as well as various catalysts, such as nano-ZrO_2-SO_3H, [20] Fe_3O_4-TiO_2, [21] nano MgO,[22] and nano Fe_3O_4.[23] Pasha M.A. *et al*. reported synthetic strategy for obtaining 2-amino-4-aryl-7, 7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles from aryl aldehydes, dimedone, malononitrile, and ammonium acetate using K_2CO_3 as a base in water with ultrasound treatment.[24] Jonnalagadda S.B. reported synthetic strategy by using TEA (triethylamine) as a base with microwave irradiation.[25]

The literature survey also reveals that the published protocols suffer from one or several drawbacks, such as prolonged reaction time, harsh conditions, complicated preparation of the catalyst, reduced yield and lack of generality.

In the present study, we have developed an elegant, efficient, easy and direct procedure for the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile and its nine derivatives under microwave irradiation using aryl aldehydes, dimedone, malononitrile and ammonium acetate and a catalytic amount of N-methylpyridinium tosylate (NMPyTs) ionic liquid.[26] The effect of catalyst and the green technique gives the excellent yield of the product under the aspect of environmentally benign processes. This methodology has numerous and significant advantages, such as atom economy, the use of a green solvent, mild catalyst-free conditions, short reaction time as well as a more comfortable workup procedure when compared with the conventional methods.

EXPERIMENTAL

All the chemicals and synthetic grade reagents were procured from Sigma Aldrich India and Merck chemicals. They were used without further purification. Melting points were recorded in open capillaries using a Buchi melting-point B-540 apparatus. ^{1}H NMR spectra were obtained on a Bruker instrument (400 MHz) and chemical shifts are reported in δppm. Mass spectra were measured using high-resolution ESI–MS (DFS) Thermo spectrometers (70 eV). Microwave irradiation was carried out in a Microwave Oven, Model No. MS2043DB DB1QILN (2450 MHz, 1050 W) equipped with Erlenmeyer flask.

MATERIAL AND METHODS

Synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile and its derivatives (5a-e)

A mixture of substituted aryl aldehydes **1** (0.01 mol), dimedone **2** (0.01 mol), malononitrile **3** (0.01 mol), ammonium acetate **4** (0.01 mol) and catalytic amount of N-methylpyridinium tosylate (NMPyTs) as a ionic liquid were irradiated in microwave oven in an Erlenmeyer flask and irradiated until completion of the reaction. Reaction was monitored by TLC (ethyl acetate-hexane, 2:8). The reaction mixture was poured in crushed ice and filtered. The crude product was collected and recrystallized in ethanol and dried. The entire product was characterized by physical constant and spectroscopic techniques and compared with the standard method.

2-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5a)

IR(KBr cm^{-1}); 3398, 3317, 3258, 2933, 2165, 1657, 1624, 1490; ^{1}H NMR (400 MHz, DMSO-d_6) :δ 0.98(s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.93-2.13 (dd, 2H, J=15 Hz, CH_2), 2.33-2.55 (dd, 2H, J=17.5, CH_2), 4.39 (s, 1H, CH), 5.90 (s, 2H, NH_2), 6.95-7.30 (m, 5H, Ar-H), 7.25-7.50 (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.2, 28.3, 30.4, 42.2, 53.8, 59.0, 111.7, 113.3, 120.9, 124.2, 126.2, 129.4, 131.4, 143.5, 149.0, 163.2, 198.2 .; ESI-MS(*m/z*): 294.3 $[M+H]^+$

2-Amino-4-(4-methylphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5b)

IR(KBr cm^{-1}); 3390, 3312, 3248, 2923, 2175, 1670, 1610, 1488.; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95(s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.95-2.18 (dd, 2H, J=15 Hz, CH_2), 2.35-2.45 (dd, 2H, J=17.5, CH_2), 4.45 (s, 1H, CH), 5.94 (s, 2H, NH_2), 6.92-7.30 (dd , 2H Ar-H), 6.90-7.00, (dd , 2H Ar-H), 7.15-8.5, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.9, 28.5, 30.5, 42.1, 52.4, 58.0, 111.2, 120.9, 124.9, 127.2, 129.4, 130.4, 145.5, 150.0, 162.2, 199.0; ESI-MS(*m/z*); 307$[M+H]^+$

2-Amino-4-(4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5c)

IR(KBr cm^{-1}); 3375, 3310, 3170, 2960, 2675, 1660, 1490, 1378; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.90-2.10,3.70-3.80 (s, 3H, -OCH_3) (dd, 2H, J=15 Hz, CH_2), 2.30-2.40 (dd, 2H, J=17.0, CH_2), 4.40 (s, 1H, CH), 5.95 (s, 2H, NH_2), 6.60-7.00, (dd , 2H Ar-H), 6.60-7.00, (dd, 2H, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.2, 31.9, 37.5, 45.1, 55.4, 60.0, 111.0, 121.9, 124.9, 128.2, 130.4, 131.4, 150.5, 153.0, 166.2, 198.0; ESI-MS(*m/z*); 324$[M+H]^+$

2-Amino-4-(4-hydroxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5d)

IR(KBr cm^{-1}); 3425, 3314, 3174, 2970, 2680, 1676, 1493, 1380.; ^{1}H NMR (400 MHz, DMSO-d_6) :δ 0.91(s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.90-2.86 (dd, 2H, J=15 Hz, CH_2), 2.70-2.90 (dd, 2H, J=17.0, CH_2), 4.45 (s, 1H, CH), 5.97 (s, 2H, NH_2), 6.60-7.00, (dd , 2H Ar-H), 6.60-7.00, (dd , 2H, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.5, 32.3, 38.1, 43.2,51.3, 57.0, 111.9,115.4,117.7, 130.9, 134.2, 150.5, 161.0, 198.4; ESI-MS(*m/z*); 309.3$[M+H]^+$

2-Amino-4-(2-fluorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5e)

IR(KBr cm^{-1}); 3488, 3343, 3129, 2970, 2687, 1686, 1490, 1390,740; ^{1}H NMR (400 MHz, DMSO-d_6) :δ 0.95(s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.92-2.96 (dd, 2H, J=15 Hz, CH_2), 2.70-2.95 (dd, 2H, J=17.0, CH_2), 4.55 (s, 1H, CH), 5.87 (s, 2H, NH_2), 6.60-7.00, (m , 4H, Ar-H), 7.15-8.5, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.5, 32.3, 38.1, 43.2,51.3, 57.0, 111.9,115.4,117.7, 130.9, 134.2, 150.5, 161.0, 198.4; ESI-MS(*m/z*); 311.3$[M+H]^+$

2-Amino-4-(2-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5f)

IR(KBr cm^{-1}); 3445, 3330, 3133, 2924, 2667, 1690, 1440, 1388,724.; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (s, 3H, CH_3), 1.10 (s, 3H CH_3), 1.93-2.95 (dd, 2H, J=15 Hz, CH_2), 2.70-2.95 (dd, 2H, J=17.0, CH_2), 4.65 (s, 1H, CH), 5.97 (s, 2H, NH_2), 6.60-7.00, (m, 4H, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.2, 31.3, 39.1, 43.3, 51.5, 57.0, 111.5, 115.4, 117.7, 130.9, 134.2, 150.5, 161.0, 197.4; ESI-MS(*m/z*); 327.8$[M+H]^+$

2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5g)

IR(KBr cm^{-1}); 3495, 3321 and 3223, 2174, 1690, 1440, 1330, 745; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.93-2.30 (dd, 2H, J=15 Hz, CH_2), 2.40-2.95 (dd, 2H, J=17.0, CH_2), 4.35 (s, 1H, CH), 5.78 (s, 2H, NH_2), 7.31, (d, 2H, J=8.0 Hz, Ar-H), 7.15, (d, 2H, J=8.0 Hz, Ar-H), 7.15-8.5, (br, s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.2, 31.3, 38.4, 43.3, 51.5, 57.3, 111.6, 115.4, 117.7, 130.9, 134.2, 150.5, 161.0, 197.4.; ESI-MS(*m/z*); 327 $[M+H]^+$

2-Amino-4-(2-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5h)

IR(KBr cm^{-1}); 3450, 3340, 3163, 2944, 2677, 1650, 1420, 1382, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.93-2.95 (dd, 2H, J=15 Hz, CH_2), 2.70-2.95 (dd, 2H, J=17.0, CH_2), 4.65 (s, 1H, CH), 5.97 (s, 2H, NH_2), 6.60-7.00, (m , 4H, Ar-H), 7.15-8.5, (br, s 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.2, 31.3, 39.1, 43.3, 52.5, 59.0, 111.5, 114.4, 113.7, 130.3, 135.2, 150.5, 162.0, 199.4; ESI-MS(*m/z*); 372 $[M+H]^+$

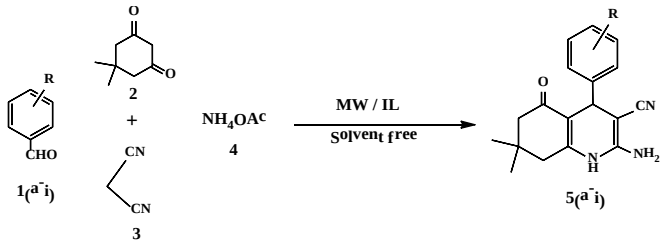
2-Amino-4-(4-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5i)

IR(KBr cm^{-1}); 3420, 3325, 3263, 2964, 2177, 1650, 1470, 1362, 670; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.94-2.95 (dd, 2H, J=15 Hz, CH_2), 2.75-2.90 (dd, 2H, J=17.0, CH_2), 4.75 (s, 1H, CH), 5.97 (s, 2H, NH_2), 6.60-7.00, (m , 4H Ar-H), 7.20-8.50, (br, s 1H,

NH); ^{13}C NMR (75 MHz, DMSO-d_6): 27.2, 31.4, 39.3, 43.4, 52.8, 59.2, 111.2, 114.3, 115.7, 132.3, 138.2, 155.5, 161.0, 198.9; ESI-MS(*m/z*); 372 $[M+H]^+$

RESULTS AND DISCUSSION

Here an attempt has been made to develop one-pot synthesis and a new synthetic protocol for selectively substituted hexahydroquinoline derivatives using dimedone, aryl aldehydes, malononitrile, and ammonium acetate in a catalytic amount of ionic liquid. To study of this green protocol and reaction leading to the desired product by using microwave irradiation (Scheme 1).



Scheme 1. Synthetic route for compound **5a-5i**

A literature survey reveals that all the derivatives in scheme consumed a long time (nearly 180 min and more) for the completion with relatively lower yield (60-98 %). The same transformation could be accomplished under microwave-assisted with shorter reaction time (3-8 min) with moderate to excellent yield (80-95 %) in (Table 1).

Table 1. Synthesis of hexahydroquinoline derivatives catalyzed by ionic liquid under microwave irradiation (120 °C/300 W).

Pro-duct	R	Time, min	Yield, %	Melting point, °C	
				Found	Reported[Ref]
5a	H	8	80	272	275-277[27]
5b	4-CH_3	5	84	298	294-295[27]
5c	4-OCH_3	4	87	290	289-293[27]
5d	4-OH	7	85	290	293-295[28]
5e	2-F	5	92	297	299-300[27]
5f	2-Cl	8	90	270	273-276[28]
5g	4-Cl	3	95	288	290-291[28]
5h	2-Br	5	88	280	285-287[28]
5i	4-Br	4	92	290	295-296[28]

Initially, the mixture of substituted aryl aldehydes, dimedone, malononitrile, ammonium acetate (0.01 mol each) was taken in an 50 mL vessel and subjected to microwave irradiation under neat conditions in the absence of catalyst and solvent, and the reaction was failed to get the product under this condition. The reaction was repeated in the presence of catalyst in the range of 2-10 mol %. We have optimized the amount of catalyst for the synthesis of (**5g**, Table 1) under microwave irradiation and excellent yield was obtained in only 3 minutes when 6 mol % catalysts are introduced (Table 2, entry 4).

Table 2. Optimization of catalyst concentration for the synthesis of (5 g) under M.W. Irradiation.

Entry	Catalyst mol %	Time, min	Yield,[a] %
1	No catalyst	15	-
2	2	7	76
3	4	5	89
4	6	3	95
5	8	4	85
6	10	6	70

[a]isolated yield

CONCLUSION

The microwave-assisted reaction is an efficient and beneficial protocol leading to the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile derivatives. The reaction is influenced under highly efficient, effortless, cheaply and recyclable homogenous catalyst (ionic liquid) for the one-pot multicomponent reaction of substituted aryl aldehydes, dimedone, malononitrile, and ammonium acetate under solvent-free condition. The advantages of the current protocol include its efficiency, high product yield, short reaction time and operational simplicity.

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