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Hantzsch synthesis of polyhydroquinolines - A simple, efficient and neat protocol

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A variety of polyhydroquinolines have been synthesized under eco-benign conditions. The reaction proceeds smoothly without any catalyst at room temperature in short reaction time. The yields and purity are excellent.

Keywords: Hantzsch, polyhydroquinolines, catalyst free, solvent free condition, room temperature

1,4-Dihydro pyridyl compounds are important class of pyridine derivatives which possess a wide spectrum of biological activities[1-4]. 1,4-Dihydropyridine derivatives are used in the treatment of congestive heart failure[5] since they act as a dual cardioselective calcium channel agonist (GPLA)/smooth muscle selective calcium channel antagonist (GPILSM). Furthermore, 4-phenyl substituted 3,5-dibenzoyl-1,4-dihydropyridines show cytotoxic activity against human oral squamous carcinoma (HSC-2) cells[6].

Though many classical methods[7] are available for the synthesis of 1,4-dihydro pyridines, many of these classical methods require high temperature, prolonged reaction time and drastic reaction conditions and the yields are unsatisfactory due to the occurrence of several side reactions. The expensive Lewis acid like $Yb(OTf)_3$ (ref.8) are also found to be effective in the Hantzsch polyhydroquinoline synthesis.

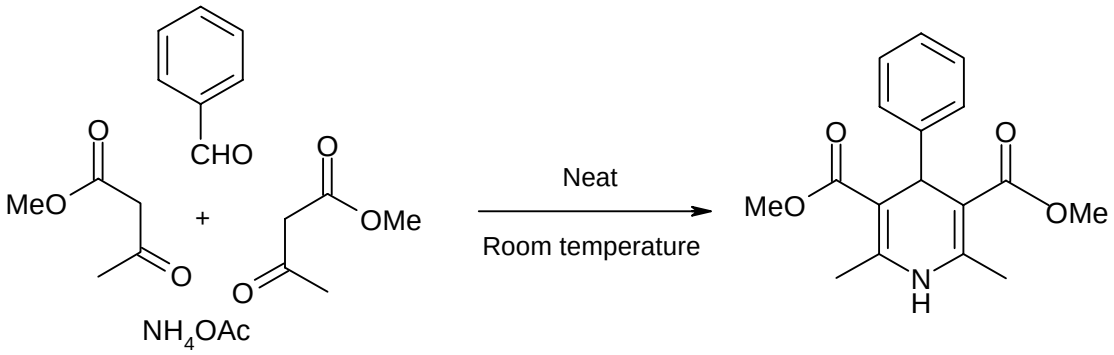
In order to avoid the toxic and chronic effects of organic solvents, the solvent free microwave assisted synthesis and ionic-liquid promoted synthesis of polyhydroquinoline derivatives are reported by Tu *et al.*[9] and Zhao-Qin Jiang *et al.*[10] respectively, but the microwave assisted synthesis are not applicable to large scale production and the ionic-liquid promoted reactions which are carried out on an industrial scale due to the difficulties involved in the preparation of ionic-liquids and cost effect. Since polyhydroquinolines are increasingly useful and important class of organic compounds, the development of simple, eco-benign, room temperature and high yielding protocol is desirable.

In continuation of the interest in solvent free reactions[11], a simple, efficient and solvent free synthesis of dihydroquinolines without using any catalyst at RT is reported. Thus, the treatment of aldehyde and β-keto ester and/or dimedone with ammonium acetate under mechanical stirring leads to the formation of various dihydroquinolines (**Scheme I**, **Table I**) and (**Scheme II** and **Table II**) in excellent yield and in short reaction time. The main advantage of this solvent free, RT protocol is that it is operable on large scale, and it proceeds even when all of the precursors are solids. Unlike earlier reports the current protocol does not require heating of the reaction mixture, use of catalysts or the use of toxic solvents like acetonitrile to produce polyhydroquinolines.

Experimental Section

A typical procedure for polyhydroquinolines, 1a-h

To a stirred mixture of benzaldehyde (0.318 g, 3 mmole) and methyl acetoacetate (0.696 g, 6 mmole), was added ammonium acetate (0.231 g, 3 mmole) and stirred, the reaction-mixture became homogeneous viscous liquid. The progress of the reaction was monitered by TLC. After completion of the reaction, a small amount of ethanol was added (otherwise the reaction mixture is sticky) and the reaction mass stirred for 5 min. Then, ice-cold water was added and the solid thus obtained was filtered. The crude product was purified by recrystallization from ethanol:water (95:5).



Scheme I

2,6-Dimethyl-3,5-dicarbomethoxy-4-(phenyl)-1,4-dihydropyridine, 1a

1a: m.p. 197ºC; FT-IR (KBr): 3322, 1676, 1633, 1595, 1529, 1102, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.23 (s, 6H), 3.50 (s, 6H), 4.86 (s, 1H), 7.06 (t, 1H, *J* = 7.6Hz), 7.11 (d, 2H, *J* = 6.9Hz), 7.16 (t, 2H, *J* = 7.6Hz), 8.86 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.7, 51.1, 102.0, 126.4, 127.5, 128.5, 146.2, 148.3, 167.9; MS: *m/z* 301(M^+); Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.71; H, 6.28; N, 4.42%.

2,6-Dimethyl-3,5-dicarbomethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine, 1b

1b: m.p. 152-54ºC; FT-IR (KBr): 3320, 1669, 1628, 1590, 1529, 1102, 847 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.16 (s, 6H), 3.76 (s, 6H), 5.01 (s, 1H), 7.40 (d, 1H, *J* = 8.7Hz), 7.66 (d, 1H, *J* = 7.5Hz), 8.02 (d, 1H, *J* = 7.5Hz), 8.13 (s, 1H), 8.82 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5, 41.3, 50.7, 103.2, 121.3, 123.1, 128.6, 134.5, 145.0, 148.1, 150.0, 167.2; MS: *m/z* 346 (M^+); Anal. Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.83; H, 5.39; N, 8.15%.

2,6-Dimethyl-3,5-dicarbomethoxy-4-(2-nitrophenyl)-1,4-dihydropyridine, 1c

1c: m.p. 146-48ºC; FT-IR (KBr): 3329, 1652, 1619, 1597, 1521, 1102, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.18 (s, 6H), 3.62 (s, 6H), 5.45 (s, 1H), 7.40 (d, 1H, *J* = 8.7Hz), 7.66 (d, 1H, *J* = 7.5Hz), 7.69-8.02 (m, 2H), 9.20 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6, 41.6, 50.8, 102.2, 122.4, 123.5, 128.6, 135.5, 146.0, 148.1, 151.0, 166.2; MS: *m/z* 346 (M^+); Anal. Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.82; H, 5.37; N, 8.18%.

2,6-Dimethyl-3,5-dicarboethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine, 1d

1d: m.p. 163-64ºC; FT-IR (KBr): 3328, 1674, 1633, 1590, 1529, 1105, 857 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, 6H), 2.36 (s, 6H), 4.10 (q, 4H, *J* = 7.8Hz), 5.10 (s, 1H), 7.38 (d, 1H, *J* = 8.7Hz), 7.66 (d, 1H, *J* = 7.5Hz), 8.02 (d, 1H, *J* = 7.5Hz), 8.13 (s, 1H), 9.17 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 19.5, 40.0, 60.0, 103.2, 121.3, 123.1, 128.6, 134.5, 145.0, 148.1, 150.0, 167.2; MS: *m/z* 374 (M^+); Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.81; H, 5.88; N, 7.62%.

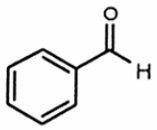
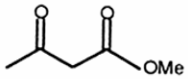
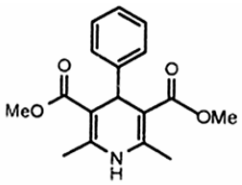
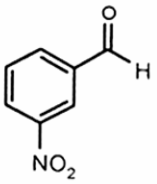
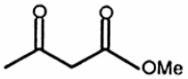
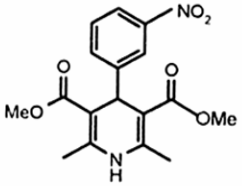
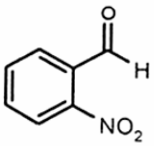
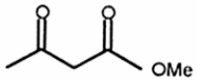
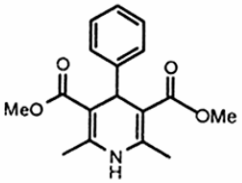
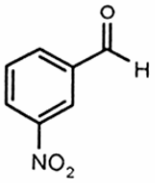
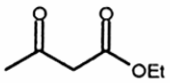
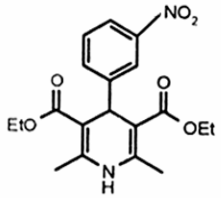
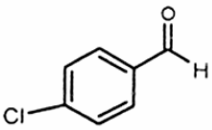
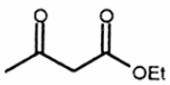
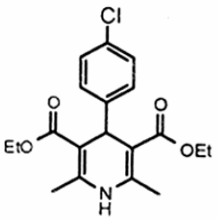
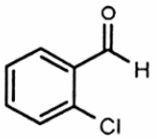
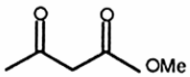
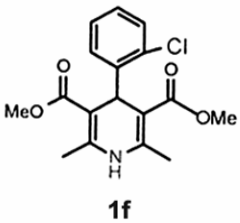
2,6-Dimethyl-3,5-dicarboethoxy-4-(4-chlorophenyl)-1,4-dihydropyridine, 1e

1e: m.p. 156-58ºC; FT-IR (KBr): 3322, 1679, 1628, 1592, 1519, 1112, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, 6H), 2.31 (s, 6H), 4.08 (q, 4H, *J* = 7.7Hz), 4.96 (s, 1H), 7.26 (m, 4H), 8.84 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 19.5, 39.2, 59.8, 103.7, 127.9, 129.4, 132.3, 144.2, 146.4, 167.5; MS: *m/z* 363 (M^+), 365 (M+2); Anal. Calcd. for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; N, 3.85. Found: C, 62.87; H, 6.18; N, 3.67%.

2,6-Dimethyl-3,5-dicarbomethoxy-4-(2-chlorophenyl)-1,4-dihydropyridine, 1f

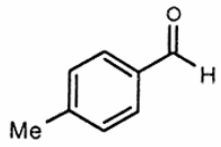
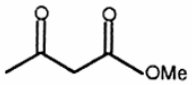
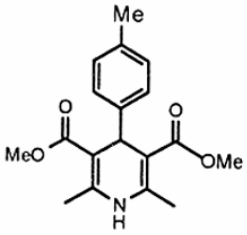
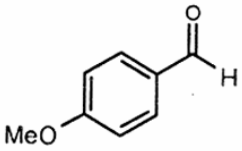
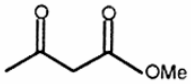
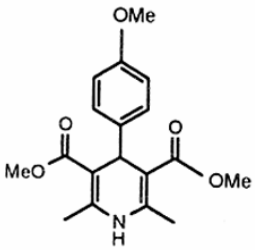
1f: m.p. 143-45ºC; FT-IR (KBr): 3313, 1658, 1622, 1591, 1521, 1122, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 6H), 3.70 (s, 6H), 5.13 (s, 1H), 7.40-8.02 (m, 4H), 8.86 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8, 41.3, 51.1, 103.7, 123.3, 124.1, 128.2, 129.5, 145.0, 148.1, 150.0, 167.2; MS: *m/z* 335 (M^+), 337 (M+2); Anal. Calcd. for $C_{17}H_{18}ClNO_4$: C, 60.81; H, 5.40; N, 4.17. Found: C, 60.96; H, 5.33; N, 4.32%.

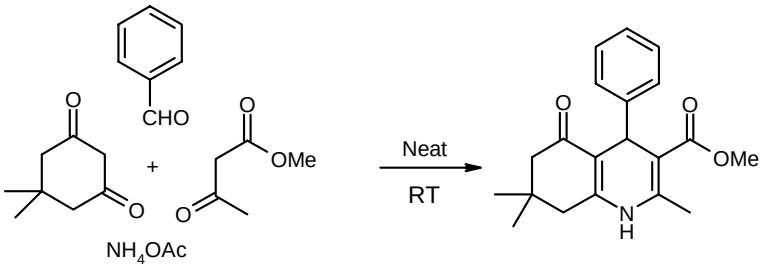
Table 1—Synthesis of dihydroquinolines

Entry	Aldehyde	Dicarbonyl compd	Product	Time (min)	Yield[a] (%)
1			 **1a**	10	95
2			 **1b**	10	93
3			 **1c**	10	90
4			 **1d**	10	90
5			 **1e**	12	96
6			 **1f**	10	90

—Contd

Table 1—Synthesis of dihydroquinolines—*Contd*

Entry	Aldehyde	Dicarbonyl compd	Product	Time (min)	Yield[a] (%)
7			 **1g**	10	92
8			 **1h**	10	90



Scheme II

2,6-Dimethyl-3,5-dicarbomethoxy-4-(4-methylphenyl)-1,4-dihydropyridine, 1g

1g: m.p. 162-64ºC; FT-IR (KBr): 3317, 1667, 1622, 1592, 1519, 1114, 848 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.14 (s, 6H), 2.52 (s, 3H), 3.68 (s, 6H), 5.18 (s, 1H), 7.32 (d, 2H, *J* = 8.7Hz), 8.00 (d, 2H, *J* = 8.7Hz), 8.80 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8, 25.3, 43.4, 50.2, 103.8, 123.3, 124.1, 145.0, 146.1, 150.0, 168.2; MS: *m/z* 315 (M^+); Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.65; H, 6.64; N, 4.61%.

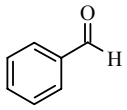
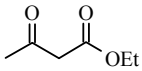
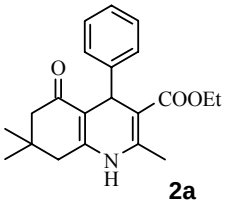
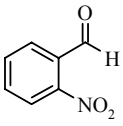
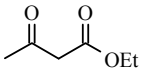
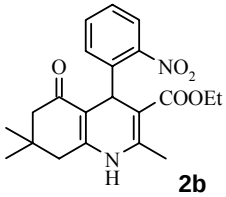
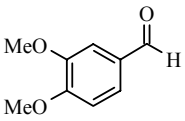
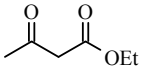
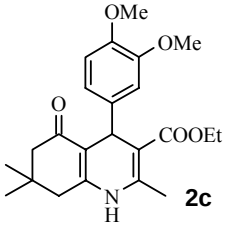
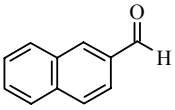
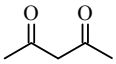
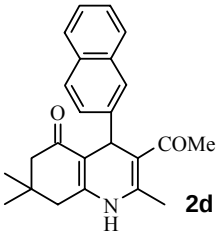
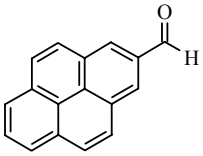
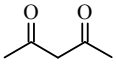
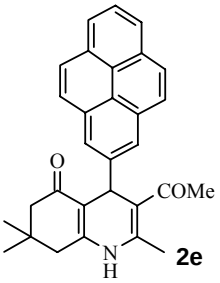
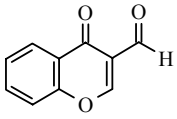
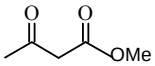
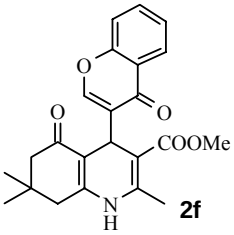
2,6-Dimethyl-3,5-dicarbomethoxy-4-(4-methoxyphenyl)-1,4-dihydropyridine, 1h

1h: m.p. 141-43ºC; FT-IR (KBr): 3329, 1651, 1591, 1512, 1122, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.17 (s, 6H), 3.68 (s, 6H), 3.80 (s, 3H), 4.98 (s, 1H), 7.21 (d, 2H, *J* = 8.8Hz), 7.62 (d, 2H, *J* = 8.9Hz), 8.45 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.1, 41.0, 44.6, 50.2, 103.8, 123.3, 124.1, 145.0, 146.1, 150.0, 168.2; MS: *m/z* 331 (M^+); Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.37; H, 6.22; N, 4.39%.

A typical procedure for polyhydroquinolines, 2a-f

To a stirred mixture of benzaldehyde (0.318 g, 3 mmole), dimedone (0.420 g, 3 mmole) and ethyl acetoacetate (0.390 g, 3 mmole), was added ammonium acetate (0.231 g, 3 mmole). After the addition of ammonium acetate, the reaction-mixture became a free homogeneous viscous liquid. The progress of the reaction was monitered by TLC. After completion of the reaction, a small amount of ethanol

Table II—Synthesis of dihydroquinolines

Energy	Aldehyde	Dicarbonyl compds	Products	Time (min)	Yield (%)
1			 **2a**	30	90
2			 **2b**	2	9
3			 **2c**	60	90
4			 **2d**	80	90
5			 **2e**	120	85
6			 **2f**	90	93

[a] Isolated yield after column chromatography

was added, (otherwise the reaction mixture is sticky) and the reaction mass stirred for 5 min. Then, ice-cold water was added and the solid thus obtained was filtered. The crude product was purified by recrystallization from ethanol:water (95:5).

Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 2a

2a: m.p. 220-22ºC; FT-IR (KBr): 3322, 1697, 1676, 1633, 1595, 1529 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.04 (s, 3H), 1.18 (t, 3H, *J* = 6.9 Hz), 2.11-2.29 (m, 4H), 2.32 (m, 3H), 4.05 (q, 2H, *J* = 6.9Hz), 5.03 (s, 1H), 6.65 (s, 1H, NH), 7.07 (t, 1H, *J* = 7.6Hz), 7.17 (t, 2H, *J* = 7.6Hz), 7.29 (d, 2H, *J* = 7.6Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.30, 19.36, 27.21, 29.55, 32.76, 36.68, 40.97, 50.85, 59.91, 106.05, 112.03, 126.12, 127.96, 128.09, 143.83, 147.20, 148.91, 167.62, 195.86; MS: *m/z* 339 (M^+); Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.43; H, 7.15; N, 4.19%.

Ethyl 2,7,7-trimethyl-5-oxo-4-(2-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 2b

2b: m.p. 218-20ºC; FT-IR (KBr): 3312, 1671, 1634, 1575, 1529, 1102, 851 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.71 (s, 3H), 0.93-0.96 (s, 6H), 1.85 (d, 1H, *J* = 16.0Hz), 2.07 (d, 1H, *J* = 16.0Hz), 2.21 (d, 1H, *J* = 16.8Hz), 2.26 (s, 3H), 2.36 (d, 1H, *J* = 16.8Hz), 3.87 (q, 2H, *J* = 6.4Hz), 5.61 (s, 1H), 7.25 (t, 1H, *J* = 7.6Hz), 7.38 (d, 1H, *J* = 6.8Hz), 7.52 (t, 1H, *J* = 6.9Hz), 7.68 (d, 1H, *J* = 8.4Hz), 9.15 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.39, 18.82, 26.82, 26.84, 29.40, 32.33, 32.55, 50.55, 59.57, 103.58, 110.34, 124.11, 127.36, 131.17, 133.36, 142.46, 146.42, 148.18, 150.27, 167.12, 194.52; MS: *m/z* 384 (M^+); Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.49; H, 6.15; N, 7.19%.

Ethyl 2,7,7-trimethyl-5-oxo-4-(3,4-dimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 2c

2c: m.p. 165-66ºC; FT-IR (KBr): 3352, 1678, 1653, 1585, 1529, 831 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.85 (s, 3H), 0.98 (s, 3H), 1.12 (t, 3H, *J* = 6.8Hz), 1.87 (d, 1H, *J* = 16.0Hz), 2.04 (d, 1H, *J* = 16.0Hz), 2.15 (d, 1H, *J* = 16.8Hz), 2.23 (s, 3H), 2.33 (d, 1H, *J* = 16.8Hz), 3.58 (s, 3H), 3.65 (s, 3H), 3.96 (q, 2H, *J* = 6.6Hz), 5.79 (s, 1H), 6.8-7.1 (m, 3H), 9.15 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.40, 18.92, 26.12, 26.74, 29.42, 31.98, 32.56, 50.67, 50.80, 55.91, 59.55, 102.58, 110.48, 124.13, 126.89, 131.28, 133.48, 142.96, 146.78, 149.18, 152.21, 169.12, 195.62; MS: *m/z* 399 (M^+); Anal. Calcd. for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.19; H, 7.18; N, 3.65%.

3-Acetyl-2,7,7-trimethyl-4-naphthyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one, 2d

2d: m.p. 247ºC; FT-IR (KBr): 3362, 1686, 1633, 1575, 1539, 1102 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.71 (s, 3H), 0.95 (s, 3H), 1.95 (d, 1H, *J* = 16.0Hz), 2.09 (m, 3H), 2.15 (d, 1H, *J* = 16.0Hz), 2.24 (d, 1H, *J* = 16.8Hz), 2.32 (m, 3H), 2.49 (d, 1H, *J* = 16.8Hz), 5.10 (s, 1H), 7.34 -7.41 (m, 3H), 7.58 (s, 1H), 7.72-7.78 (m, 3H), 9.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.72, 26.72, 29.69, 30.41, 32.64, 37.05, 50.81, 111.05, 112.86, 125.76, 125.82, 126.38, 127.15, 127.82, 128.25, 132.21, 133.33, 144.82, 145.05, 149.76, 194.88, 197.76; MS: *m/z* 359 (M^+); Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.29; H, 7.15; N, 4.05%.

3-Acetyl-2,7,7-trimethyl-4-pyren-4,6,7,8-tetrahydroquinolin-5(1*H*)-one, 2e

2e: m.p. 240-42ºC; FT-IR (KBr): 3352, 1675, 1639, 1595, 1529, 1102 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.74 (s, 3H), 0.97 (s, 3H), 1.80 (d, 1H, *J* = 16.0Hz), 2.13 (d, 1H, *J* = 16.0Hz), 2.33-2.35 (m, 4H), 3.27 (m, 3H), 5.91 (s, 1H), 7.91 (d, 1H, *J* = 8.4Hz), 7.97-8.01 (m, 2H), 8.05 (d, 1H, *J* = 9.2Hz), 8.13-8.21 (m, 4H), 8.86 (d, 2H, *J* = 9.9Hz), 9.22 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.86, 26.76, 29.75, 32.62, 50.68, 50.97, 105.52, 111.70, 123.99, 124.57, 124.85, 125.28, 125.92, 126.47, 126.65, 127.10, 127.37, 127.48, 127.74, 129.58, 131.03, 131.51, 144.22, 145.29, 167.95, 194.98; MS: *m/z* 434 (M^+); Anal. Calcd. for $C_{30}H_{27}NO_2$: C, 83.11; H, 6.28; N, 3.23. Found: C, 83.28; H, 6.24; N, 3.09%.

Methyl-2,7,7-trimethyl-5-oxo-4-(4-oxo-4*H*-chromene)-1,4,5,6,7,8 hexahydroquinoline -3-carboxylate, 2f

2f: m.p. 276-78ºC; FT-IR (KBr): 3340, 1690, 1672, 1676, 1633, 1595, 1529 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.78 (s, 3H), 0.97 (s, 3H), 1.89 (d, 1H, *J* = 16.0Hz), 2.09 (d, 1H, *J* = 16.0Hz), 2.20 (s, 3H), 2.22 (d, 1H, *J* = 16.8Hz), 2.32 (d, 1H, *J* = 16.8Hz), 3.49 (s, 3H), 4.68 (s, 1H), 7.36 (t, 1H, *J* = 7.6Hz), 7.50 (d, 1H, *J* = 8.4Hz), 7.67 (t, 1H, *J* = 8.4Hz), 7.94 (d, 1H, *J* = 6.8Hz), 8.06 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.99, 26.92, 29.68,

32.01, 32.54, 50.80, 51.07, 56.56, 100.20, 106.41, 118.66, 124.83, 125.45, 125.56, 125.85, 134.01, 147.07, 151.92, 155.07, 155.75, 167.90, 175.73, 194.72; MS: *m/z* 393 (M^+); Anal. Calcd. for $C_{23}H_{23}NO_5$: C, 70.22; H, 5.89. N, 3.26. Found: C, 70.19; H, 5.75; N, 3.19%.

Conclusion

A simple, efficient and eco-benign protocol for the Hantzsch synthesis of polyhydroquinolines is developed. The merits of the current protocol are: (a) the reaction is conducted under solvent free condition; (b) the reaction is carried out without using any catalyst; (c) the reaction proceeds at room temperature; (d) the use of hazardous strong acids like acetic acid are avoided; (e) the reaction-time is short; (f) work-up is simple; (g) operable on large scale; and (h) yields are excellent.

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