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# *p*-Toluene Sulfonic Acid Catalyzed One-Pot Synthesis of Unsymmetrical 1,4-Dihydropyridines Derivatives *via* Hantzsch Reaction

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A simple, inexpensive and efficient one-pot synthesis of a series of unsymmetrical 1,4-dihydropyridines derivatives using *p*-toluene sulfonic acid as catalyst at room temperature was achieved in excellent yields from the four-component Hantzsch condensation reactions of various aromatic aldehydes, 1,3-cyclohexanedione, methyl acetoacetate (or ethyl acetoacetate) and ammonium acetate in a little methanol (or ethanol). The procedure possesses the advantages of short reaction time, high yields, an environmental friendly procedure as well as easy isolation of products.

**Key Words: 1,4-Dihydropyridine, *p*-Toluene sulfonic acid, Hantzsch condensation reaction.**

## INTRODUCTION

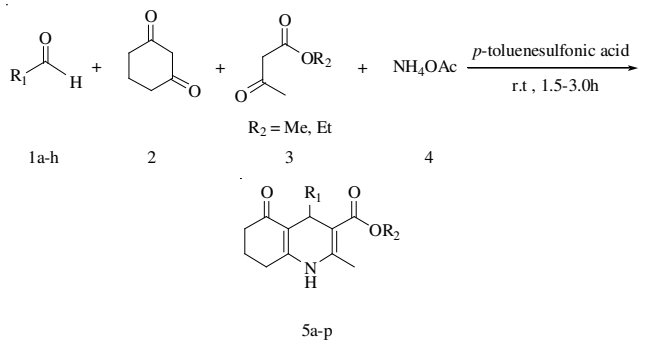
1,4-Dihydropyridines (1,4-DHPs) and their derivatives have received considerable attention due to their significant pharmacological and biological properties[1]. Cardiovascular agents such as nifedipine, nicardipine, amlodipine and other related derivatives are dihydropyridyl compounds, which are effective for the treatment of hypertension, angina, pectoris and infarction[2]. Moreover, 1,4-dihydropyridines have been widely used as calcium channel modulation[3] and the quinoline derivatives exhibit a wide range of biological activities such as antimalarial[4], anti HIV[5], antiplasmodial[6], antiinflammatory[7], antibacterial[8], antiproliferative and anticancer effects[9]. Current literatures have revealed that 1,4-dihydropyridines even possess other medicinal applications including neuroprotective and platet antiaggregation activity[10]. 1,4-Dihydropyridines are also good precursors of the corresponding substituted pyridine derivatives and constitute useful reductants for imines and α,β-unsaturated compounds in organic synthesis[11,12]. The interesting properties of 1,4-dihydropyridines have attracted many organic chemists to synthesize these heterocyclic derivatives.

The 1,4-dihydropyridines were first synthesized by Hantzsch in 1882 from a one-pot, three-component condensation of aldehyde, 1,3-dicarbonyl compounds and ammonia either in acetic acid or in refluxing alcohol for several hours[13]. However, this method suffers from several drawbacks associated with longer reaction times, excess of organic solvent, unsatisfactory yields and drastic reaction conditions. Recently, many efficient methods for preparing 1,4-dihydropyridines has been developed including the use of microwave[14], ionic liquid[15], refluxing at high temperature[16], iodine[17], TMSCl-NaI[18], ceric ammonium nitrate[19], Montmorillonite K10[20], $SiO_2/HClO_4$[21], nanoparticle and metal triflates[22]. But there are still some limitations for the synthesis of 1,4-dihydropyridines in terms of the use of high temperatures, expensive metal precursors, relatively longer reaction times and difficult isolation of products.

In recent years, *p*-toluene sulfonic acid (PTSA) as catalyst has been extensively used for many organic synthetic transformations[23]. Especially, it makes the reaction possess many advantages such as low cost, eco-friendly nature, ease of handling, non-toxicity, excellent product yields and high reactivity. These features encouraged us to explore a cheaper, environmentally friendly and high active *p*-toluene sulfonic acid catalyst for the synthesis of 1,4-dihydropyridines and their derivatives. Herein, we wish to report a facile and efficient unsymmetrical Hantzsch condensation reactions of aldehydes, 1,3-cyclohexanedione, methyl acetoacetate (or ethyl acetoacetate) and ammonium acetate in the presence of a catalytic amount *p*-toluene sulfonic acid to gives the corresponding 1,4-dihydropyridine derivatives in excellent yields at room temperature (**Scheme-I**).

## EXPERIMENTAL

Melting points were determined on $X_4$ melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in KBr discs on Nicolet 6700 FT-IR spectrophotometer.




**Scheme-I:** Synthetic route for unsymmetrical 1,4-dihydropyridine derivatives

$^1$H and $^{13}$H NMR spectra were recorded on Varian Inova-300 MHz or Varian Inova-400 MHz spectrometer using TMS as internal standard and DMSO as a solvent. Mass spectra were obtained on Shimadzu SIL-10A Auto Injector LCMS spectrometer. TLC was carried out on $GF_{254}$ silica gel plates.

**General procedure for the preparation of 1,4-dihydropyridines derivatives (5a-p):** To a stirred mixture of 1,3-cyclohexanedione (2 mmol), methyl acetoacetate or ethyl acetoacetate (2 mmol) and *p*-toluene sulfonic acid (10 mol %) in methanol or ethanol (2 mL), aldehyde (2 mmol) and ammonium acetate (3 mmol) were added at ambient temperature. The reaction mixture was then stirred at room temperature until the reaction completed (monitored by TLC). The reaction mixture treated with saturated $NaHCO_3$ solution and the resulting yellow solid product was filtered to afford the crude product. The crude product was recrystallized from ethanol to obtain pure compounds **5a-p**.

**Methyl 2-methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3279, 3213 (-NH), 3071, 2943, 1695 (-C=O), 1608 (-C=C), 1557, 1482, 1380, 1287, 1225, 1181, 1139, 1074, 985, 720; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.15 (s, 1H, NH), 7.19-7.13 (m, 4H, Ar-H), 7.08-7.03 (m, 1H, Ar-H), 4.93 (s, 1H, $C_4$-H), 3.52 (s, 3H, $OCH_3$), 2.49 (d, *J* = 4.8 Hz, 2H, $C_6$-H), 2.29 (s, 3H, $CH_3$), 2.20 (t, *J* = 5.2 Hz, 2H, $C_8$-H), 1.91-1.86 (m, 1H, $C_7$-H), 1.78-1.69 (m, 1H, $C_7$-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.6, 167.3, 151.3, 147.6, 145.2, 127.8, 127.2, 125.6, 111.1, 103.1, 50.6, 36.7, 35.3, 26.1, 20.7, 18.2; EI-MS: m/z (%) = 298 ([M + H]$^+$, 100).

**Methyl 4-(4-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3- carboxylate (5b):** Pale yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3271, 3186 (-NH), 3069, 2944, 1701 (-C=O), 1652 (-C=C), 1604, 1504, 1487, 1383, 1222, 1178, 1137, 1031, 986, 829; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.10 (s, 1H, NH), 7.04 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.74 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.85 (s, 1H, $C_4$-H), 3.66 (s, 3H, $ArOCH_3$), 3.52 (s, 3H, $OCH_3$), 2.50-2.45 (m, 2H, $C_6$-H), 2.28 (s, 3H, $CH_3$), 2.21-2.15 (m, 2H, $C_8$-H), 1.92-1.86 (m, 1H, $C_7$-H), 1.78-1.69 (m, 1H, $C_7$-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.6, 167.4, 157.3, 151.0, 144.8, 139.9, 128.1, 113.2, 111.4, 103.4, 54.8, 50.5, 36.7, 34.4, 26.0, 20.8, 18.2; EI-MS: m/z (%) = 328 ([M + H]$^+$, 100).

**Methyl 2-methyl-5-oxo-4-(2-phenylethenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5c):** Yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3280, 3211 (-NH), 3080, 3021, 2947, 1698 (-C=O), 1629 (-C=C), 1606, 1483, 1383, 1289, 1228, 1184, 1140, 1077, 752, 698; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.13 (s, 1H, NH), 7.30-7.23 (m, 4H, Ar-H), 7.16 (t, *J* = 7.2 Hz, 1H, Ar-H), 6.12-6.02 (m, 2H, =CH), 4.53 (d, 1H, *J* = 4.8 Hz, $C_4$-H), 3.63 (s, 3H, $OCH_3$), 2.50-2.45 (m, 2H, $C_6$-H), 2.29-2.22 (m, 5H, $CH_3$, $C_8$-H), 1.97-1.84 (m, 2H, $C_7$-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.6, 167.2, 152.0, 146.0, 137.0, 132.4, 128.4, 127.1, 126.8, 125.9, 108.7, 100.8, 50.7, 36.7, 32.4, 26.1, 20.9, 18.2; EI-MS: m/z (%) = 324 ([M + 1]$^+$, 21), 220(100).

**Methyl 4-(4-chlorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5d):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3268, 3177 (-NH), 3063, 2950, 1701 (-C=O), 1657 (-C=C), 1605, 1491, 1381, 1223, 1181, 1137, 1114, 991; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.20 (s, 1H, NH), 7.24 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.15 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.90 (s, 1H, $C_4$-H), 3.52 (s, 3H, $OCH_3$), 2.49-2.38 (m, 2H, $C_6$-H), 2.30 (s, 3H, $CH_3$), 2.25-2.11 (m, 2H, $C_8$-H), 1.91-1.81 (m, 1H, $C_7$-H), 1.77-1.70 (m, 1H, $C_7$-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.6, 167.1, 151.4, 146.5, 145.5, 130.2, 129.0, 127.8, 127.1, 110.8, 102.6, 50.6, 36.6, 35.1, 26.0, 20.7, 18.2; EI-MS: m/z (%) = 332 ([M + H]$^+$, 100).

**Methyl 4-(4-bromophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5e):** Pale yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3268, 3177 (-NH), 3058, 3021, 2969, 2948, 1700 (-C=O), 1659 (-C=C), 1605, 1492, 1429, 1382, 1301, 1223, 1181, 1137, 1113, 1073, 993, 832; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.21 (s, 1H, NH), 7.37 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.10 (d, *J* = 8.0 Hz, 2H, Ar-H), 4.89 (s, 1H, $C_4$-H), 3.53 (s, 3H, $OCH_3$), 2.49- 2.46 (m, 2H, $C_6$-H), 2.30 (s, 3H, $CH_3$), 2.27-2.15 (m, 2H, $C_8$-H), 1.92-1.88 (m, 1H, $C_7$-H), 1.77-1.73 (m, 1H, $C_7$-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.6, 167.1, 151.4, 146.9, 145.5, 130.8, 129.4, 118.7, 110.7, 102.6, 50.6, 36.6, 35.2, 26.0, 20.7, 18.2; EI-MS: m/z (%) = 377 ([M + H]$^+$, 100).

**Methyl 2-methyl-4-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5f):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3276, 3209 (-NH), 3077, 2954, 1699 (-C=O), 1647 (-C=C), 1608, 1488, 1377, 1292, 1228, 1176, 1109, 1072, 991, 775; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.11 (s, 1H, NH), 7.02 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.0 Hz, 2H, Ar-H), 4.88 (s, 1H, $C_4$-H), 3.52 (s, 3H, $OCH_3$), 2.50-2.45 (m, 2H, $C_6$-H), 2.28(s, 3H, $CH_3$), 2.20-2.17 (m, 5H, $ArCH_3$, $C_8$-H), 1.91-1.85 (m, 1H, $C_7$-H), 1.77-1.66 (m, 1H, $C_7$-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 195.0, 167.8, 151.6, 145.4, 145.2, 134.9, 128.9, 127.5, 111.7, 103.7, 51.0, 37.1, 35.4, 26.5, 21.2, 20.9, 18.6; EI-MS: m/z (%) = 312 ([M + H]$^+$, 100).

**Methyl 2-methyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5g):** Pale yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3293, 3217(-NH), 3080, 2948, 1708 (-C=O), 1650 (-C=C), 1607, 1524, 1483, 1380, 1352, 1227, 1186, 1138, 1079, 831; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.32 (s, 1H, NH), 8.08 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.42 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.04 (s, 1H, $C_4$-H), 3.54 (s, 3H, $OCH_3$), 2.53-2.50 (m, 2H, $C_6$-H), 2.34 (s, 3H, $CH_3$), 2.25-2.16 (m, 2H, $C_8$-H), 1.94-1.89 (m, 1H, $C_7$-H), 1.79-1.71 (m, 1H, $C_7$-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.5, 166.9, 154.9, 151.9, 146.2, 145.6, 128.5, 123.2, 110.1, 101.9, 50.7, 36.5, 36.1, 26.0, 20.6, 18.2; EI-MS: m/z (%) = 344 ([M + H + 1]$^+$, 100).

**Methyl 2-methyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5h):** Pale yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3285, 3206 (-NH), 3071, 2945, 1698 (-C=O), 1646 (-C=C), 1607, 1527, 1480, 1381, 1346, 1291, 1223, 1183, 1078, 716; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.32 (s, 1H, NH), 7.95 (d, $J$ = 7.5 Hz, 2H, Ar-H), 7.58 (d, $J$ = 7.5 Hz, 1H, Ar-H), 7.49 (t, $J$ = 7.5 Hz, 1H, Ar-H), 5.00 (s, 1H, $C_4$-H), 3.51 (s, 3H, $OCH_3$), 2.48-2.41 (m, 2H, $C_6$-H), 2.30 (s, 3H, $CH_3$), 2.26-2.16 (m, 2H, $C_8$-H), 1.92-1.82 (m, 1H, $C_7$-H), 1.79-1.64 (m, 1H, $C_7$-H); EI-MS: m/z (%) = 343 ([M + H]$^+$, 100).

**Ethyl 2-methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5i):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3268 (-NH), 2975, 1690 (-C=O), 1639 (-C=C), 1607, 1479, 1380, 1285, 1224, 1181, 1090, 1050, 881, 694; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.10 (s, 1H, NH), 7.16-7.11 (m, 5H, Ar-H), 4.89 (s, 1H, $C_4$-H), 3.96 (q, $J$ = 6.9 Hz, 2H, $OCH_2$), 2.41-2.33 (m, 2H, $C_6$-H), 2.26 (s, 3H, $CH_3$), 2.18-2.13 (m, 2H, $C_8$-H), 1.92-1.82 (m, 2H, $C_7$-H), 1.10 (t, $J$ = 6.9 Hz, 3H, $OCH_2CH_3$); EI-MS: m/z (%) = 312 ([M + H]$^+$, 100).

**Ethyl-4-(4-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5j):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3283, 3220 (-NH), 3075, 2975, 1691 (-C=O), 1625 (-C=C), 1607, 1510, 1482, 1380, 1286, 1223, 1183, 1138, 1073, 826; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.05 (s, 1H, NH), 7.03 (d, $J$ = 8.4 Hz, 2H, Ar-H), 6.72 (d, $J$ = 8.4 Hz, 2H, Ar-H), 4.81 (s, 1H, $C_4$-H), 3.96 (q, $J$ = 7.2 Hz, 2H, $OCH_2$), 3.65 (s, 3H, $OCH_3$), 2.43-2.36 (m, 2H, $C_6$-H), 2.25 (s, 3H, $CH_3$), 2.19-2.11 (m, 2H, $C_8$-H), 1.93-1.83 (m, 1H, $C_7$-H), 1.79-1.66 (m, 1H, $C_7$-H), 1.11 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$); EI-MS: m/z (%) = 342([M + H]$^+$, 18), 234 (100).

**Ethyl 2-methyl-5-oxo-4-(2-phenylethenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5k):** Pale yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3283, 3214 (-NH), 3077, 3029, 2978, 1693 (-C=O), 1646 (-C=C), 1605, 1482, 1382, 1287, 1226, 1182, 1139, 1077, 1060, 963, 761; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.09 (s, 1H, NH), 7.29-7.23 (m, 4H, Ar-H), 7.18-7.14 (m, 1H, Ar-H), 6.06 (t, $J$ = 2.0 Hz, 2H, =CH), 4.51 (s, 1H, $C_4$-H), 4.16-4.02 (m, 2H, $OCH_2$), 2.51-2.44 (m, 2H, $C_6$-H), 2.32-2.24 (m, 5H, $CH_3$, $C_8$-H), 1.97-1.90 (m, 2H, $C_7$-H), 1.20 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.6, 166.7, 152.0, 145.7, 137.1, 132.4, 128.4, 127.2, 126.8, 125.8, 108.6, 101.1, 59.0, 36.7, 32.5, 26.1, 20.9, 18.2, 14.2; EI-MS: m/z (%) = 338 ([M + 1]$^+$, 5), 234(100).

**Ethyl 4-(4-chlorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5l):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3284, 3214 (-NH), 3077, 2955, 1698 (-C=O), 1643 (-C=C), 1625, 1607, 1481, 1381, 1284, 1224, 1181, 1137, 1073, 824; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.17 (s, 1H, NH), 7.24 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.16 (d, $J$ = 8.4 Hz, 2H, Ar-H), 4.89 (s, 1H, $C_4$-H), 4.01-3.95 (m, 2H, $OCH_2$), 2.51-2.46 (m, 2H, $C_6$-H), 2.30 (s, 3H, $CH_3$), 2.26-2.14 (m, 2H, $C_8$-H), 1.92-1.86 (m, 1H, $C_7$-H), 1.77-1.70 (m, 1H, $C_7$-H), 1.11 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.5, 166.6, 151.4, 146.6, 145.2, 130.1, 129.2, 127.6, 110.7, 103.0, 59.0, 36.6, 35.3, 26.0, 20.7, 18.2, 14.0; EI-MS: m/z (%) = 346([M + H]$^+$, 100).

**Ethyl 4-(4-bromophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5m):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3285, 3217 (-NH), 3075, 2978, 1698 (-C=O), 1646 (-C=C), 1625, 1606, 1483, 1381, 1285, 1223, 1182, 1137, 1074, 826, 710; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.18 (s, 1H, NH), 7.37 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.10 (d, $J$ = 8.4 Hz, 2H, Ar-H), 4.86 (s, 1H, $C_4$-H), 3.97 (q, $J$ = 7.2 Hz, 2H, $OCH_2$), 2.51-2.46 (m, 2H, $C_6$-H), 2.29 (s, 3H, $CH_3$), 2.24-2.12 (m, 2H, $C_8$-H), 1.92-1.86 (m, 1H, $C_7$-H), 1.79-1.69 (m, 1H, $C_7$-H), 1.11 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.6, 166.6, 151.5, 147.1, 145.3, 130.6, 129.7, 118.7, 110.7, 102.9, 59.0, 36.6, 35.4, 26.0, 20.7, 18.2, 14.1; EI-MS: m/z (%) = 390 ([M + H]$^+$, 98), 392 ([M + H + 2]$^+$, 100); 393 ([M + H + 3]$^+$, 18).

**Ethyl 2-methyl-4-(4-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5n):** White crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3283, 3212 (-NH), 3077, 2954, 1696 (-C=O), 1646 (-C=C), 1606, 1481, 1380, 1284, 1223, 1182, 1137, 1072, 971, 716; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.08 (s, 1H, NH), 7.02 (d, $J$ = 8.0 Hz, 2H, Ar-H), 6.96 (d, $J$ = 8.0 Hz, 2H, Ar-H), 4.85 (s, 1H, $C_4$-H), 3.97 (q, $J$ = 7.2 Hz, 2H, $OCH_2$), 2.50-2.45 (m, 2H, $C_6$-H), 2.27 (s, 3H, $CH_3$), 2.19-2.15 (m, 5H, $ArCH_3$, $C_8$-H), 1.91-1.86 (m, 1H, $C_7$-H), 1.78-1.67 (m, 1H, $C_7$-H), 1.12 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.5, 166.9, 151.1, 144.9, 144.6, 134.5, 128.3, 127.2, 111.2, 103.6, 58.9, 36.7, 35.1, 26.1, 20.8, 20.5, 18.2, 14.1; EI-MS: m/z (%) = 326 ([M + H]$^+$, 100).

**Ethyl 2-methyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5o):** Pale yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3296, 3217 (-NH), 3080, 2945, 1701 (-C=O), 1652 (-C=C), 1605, 1517, 1481, 1379, 1347, 1224, 1184, 1071, 857; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.29 (s, 1H, NH), 8.09 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.43 (d, $J$ = 8.4 Hz, 2H, Ar-H), 5.03 (s, 1H, $C_4$-H), 3.96 (q, $J$ = 7.2 Hz, 2H, $OCH_2$), 2.51-2.39 (m, 2H, $C_6$-H), 2.33 (s, 3H, $CH_3$), 2.29-2.15 (m, 2H, $C_8$-H), 1.94-1.88(m, 1H, $C_7$-H), 1.78-1.73 (m, 1H, $C_7$-H), 1.11 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 194.5, 166.4, 155.1, 151.9, 146.0, 145.6, 128.8, 128.6, 123.1, 110.1, 102.2, 59.1, 36.5, 36.3, 26.0, 20.6, 18.2, 14.0; EI-MS: m/z (%) = 357 ([M + H]$^+$, 100).

**Ethyl 2-methyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5p):** Pale yellow crystals, IR (KBr, $\nu_{max}$, $cm^{-1}$): 3293, 3217 (-NH), 3080, 2945, 1703 (-C=O), 1651 (-C=C), 1607, 1526, 1482, 1382, 1344, 1285, 1123, 1179, 1080, 714, 680; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.31 (s, 1H, NH), 8.00-7.97 (m, 2H, Ar-H), 7.62 (d, $J$ = 8.0 Hz, 1H, Ar-H), 7.52 (d, $J$ = 8.0 Hz, 1H, Ar-H), 5.03 (s, 1H, $C_4$-H), 4.03-3.94 (m, 2H, $OCH_2$), 2.57-2.51 (m, 2H, $C_6$-H), 2.34 (s, 3H, $CH_3$), 2.30-2.15 (m, 2H, $C_8$-H), 1.95-1.89 (m, 1H, $C_7$-H), 1.81-1.73 (m, 1H, $C_7$-H), 1.12 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 194.6, 166.4, 151.9, 149.8, 147.4, 146.0, 134.2, 129.4, 121.9, 120.8, 110.3, 102.5, 59.1, 36.5, 36.1, 26.0, 20.7, 18.2, 13.9; EI-MS: m/z (%) = 357 ([M + H]$^+$, 100).

## RESULTS AND DISCUSSION

In an initial experiment, the mixture of benzaldehyde (**1a**), 1,3-cyclohexanedione (**2**), methyl acetoacetate (**3**) and ammonium acetate (**4**) in small amount of methanol were stirred at room temperature. After 6 h, only 39 % of product **5a** was obtained after recrystallization of the crude product from ethanol (entry 1, Table-1).

To detect whether the use of catalyst *p*-toluene sulfonic acid was efficient or not and to optimize the reaction conditions, *p*-toluene sulfonic acid was used in catalytic amount (5 mol %) and the reaction was carried out under similar conditions. The speed of the reaction was obviously accelerated, but the yield of the corresponding product **5a** was still unsatisfactory (entry 2, Table-1). Subsequently, we also investigated the reaction results catalyzed by the different amounts of *p*-toluene sulfonic acid from 5-30 %. Fortunately, a significant improvement in the yield (96 %) after only 1.5 h was observed using 10 % *p*-toluene sulfonic acid (entry 3, Table-1).

TABLE-1
OPTIMIZING THE REACTION CONDITIONS*

| Entry | *p*-Toluene sulfonic acid (mol %) | Time (h) | Yield (%)** |
|---|---|---|---|
| 1 | 0 | 6 | 39 |
| 2 | 5 | 3.5 | 71 |
| 3 | 10 | 1.5 | 96 |
| 4 | 20 | 1.5 | 89 |
| 5 | 30 | 1.5 | 75 |

*Ratio of benzaldehyde: 1,3-cyclohexanedione: methyl acetoacetate: ammonium acetate was 1:1:1:1.5. **Crude isolated yields.

Based on these results, we then selected the optimized reaction conditions to determine the scope of Hantzsch reaction catalyzed by *p*-toluene sulfonic acid. A wide range of substituted aromatic aldehydes with 1,3-cyclohexanedione, methyl acetoacetate and ammonium acetate could be converted successfully to the corresponding products in excellent yields (entry 1-8, Table-2). Different substituents on the aromatic aldehydes including either electrondonating groups (such as alkoxyl groups) or electron-withdrawing groups (such as nitro or chloro groups) did not detrimentally affect the yields of the product.

In order to examined the effect on the reaction of different 1,3-dicarbonyl compound containing active methylene such as ethyl acetoacetate, different substituted benzaldehydes were carried out with 1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate in the presence of *p*-toluene sulfonic acid, The results has not shown much difference in the product yields (entry 9-16, Table-2). All used aromatic aldehydes can afford the corresponding products in excellent yields. The increased reaction times with all substituted benzaldehydes may be due to the less reactivity of ethyl acetoacetate in comparison to methyl acetoacetate.

## Conclusion

In summary, we have developed a simple, cheaper and efficient method to synthesize a variety of unsymmetrical 4-substituted-1,4-dihydropyridines from the Hantzsch condensation reactions of various aromatic aldehydes, 1,3-cyclohexanedione, active methylene 1,3-dicarbonyl compounds and ammonium acetate in the presence of a catalytic amount *p*-toluene sulfonic acid (10 mol %) at room temperature. The procedure offers several advantages including high yields, a short reaction time, milder conditions, an environmental friendly procedure as well as easy isolation of products, which makes it a useful process for the synthesis of 1,4-dihydropyridines derivatives.

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## REFERENCES

1. (a) F. Bossert and W. Vater, *Med. Res. Rev*., **9**, 291 (1989); (b) S. Shinkai and T.C. Bruice, *J. Am. Chem. Soc*., **94**, 8258 (1972); (c) K. Masami, S. Anamik, G. Harsukh, M. Noboru, S. Hiroshi, V. Andreas and M. Joseph, *Bioorg. Med. Chem*., **10**, 1051 (2002); (d) S. Margarita, V. Yamila, I. Beatriz, M. Roberto, A. Amaury, O. Estael, S. Carlos, K. Nour and M. Nazario, *Tetrahedron*, **59**, 9179 (2003); (e) D. Auzerall and F.H. Westheimer, *J. Am. Chem. Soc*., **77**, 2261 (1955); (f) N. Edrakia, A.R. Mehdipoura, M. Khoshneviszadeha and R. Miri, *Drug Discov. Today*, **14**, 1058 (2009); (g) A. Hilgeroth, M. Wiese and A. Billich, *J. Med. Chem*., **42**, 4729 (1999).
2. (a) F.H.H. Leenen, *J. Hypertens*., **16**, S9 (1998); (b) S. Goldmann and J. Stoltefuss, *Angew. Chem. Int. Ed. Engl*., **30**, 1559 (1991).

TABLE-2
*p*-TOLUENESULFONIC ACID-CATALYZED SYNTHESIS OF UNSYMMETRICAL 1,4-DIHYDROPYRIDINES DERIVATIVES *VIA* HANTZSCH CONDENSATION REACTION

| Entry | $R_1$ | $R_2$ | Time (h) | Product | Yield (%)* | m.p. (ºC)** (found) | m.p. (ºC) (reported)[Lit] |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | Me | 1.5 | **5a** | 96 | 219-221 | 222-224[19] |
| 2 | 4-$CH_3O$-$C_6H_5$ | Me | 2.0 | **5b** | 90 | 208-211 | – |
| 3 | $C_6H_5CH$=CH | Me | 1.5 | **5c** | 93 | 217-220 | – |
| 4 | 4-Cl-$C_6H_5$ | Me | 2.0 | **5d** | 93 | 221-223 | – |
| 5 | 4-Br-$C_6H_5$ | Me | 2.0 | **5e** | 92 | 223-235 | – |
| 6 | 4-$CH_3$-$C_6H_5$ | Me | 1.5 | **5f** | 92 | 241-244 | – |
| 7 | 4-$NO_2$-$C_6H_5$ | Me | 2.0 | **5g** | 95 | 219-221 | – |
| 8 | 3-$NO_2$-$C_6H_5$ | Me | 2.0 | **5h** | 91 | 230-233 | – |
| 9 | $C_6H_5$ | Et | 3.0 | **5i** | 89 | 241-244 | 240-241[19] |
| 10 | 4-$CH_3O$-$C_6H_5$ | Et | 2.5 | **5j** | 91 | 196-198 | 193-195[19] |
| 11 | $C_6H_5CH$=CH | Et | 2.0 | **5k** | 92 | 219-221 | – |
| 12 | 4-Cl-$C_6H_5$ | Et | 2.5 | **5l** | 93 | 237-239 | 234-235[19] |
| 13 | 4-Br-$C_6H_5$ | Et | 2.5 | **5m** | 91 | 260-263 | – |
| 14 | 4-$CH_3$-$C_6H_5$ | Et | 3.0 | **5n** | 92 | 244-246 | 241-242[19] |
| 15 | 4-$NO_2$-$C_6H_5$ | Et | 3.0 | **5o** | 93 | 201-203 | 204-205[19] |
| 16 | 3-$NO_2$-$C_6H_5$ | Et | 3.0 | **5p** | 90 | 203-205 | 198-200[19] |

*Crude isolated yields. **After recrystallization.

3. (a) S.H. Yiu and E.E. Knaus, *Drug. Dev. Res*., **48**, 26 (1999); (b) A. DiStilo, S. Visentin, C. Cena, A.M. Gasco, G. Ermondi and A. Gasco, *J. Med. Chem*., **41**, 5393 (1998).
4. C. Portela, C.M.M. Afonso, M.M.M.M. Pinta and J. Ramos, *Bioorg. Med. Chem*., **12**, 3313 (2004).
5. X. Franck, A. Fournet, E. Prina, R. Mahieux, R. Hocquemiller and B. Figadere, *Bioorg. Med. Chem. Lett*., **14**, 3635 (2004).
6. P. Beagley, M.A.L. Blackie, K. Chibale, C. Clarkson, R. Meijboom, J.R. Moss, P. Smith and H. Su, *Dalton Trans*., 3046 (2003).
7. S.W. Elmore, M.J. Coghlan, D.D. Anderson, J.K. Pratt, B.E. Green, A.X. Wang, M.A. Stashko, C.W. Lin, C.M. Tyree, J.N. Miner, P.B. Jacobson, D.M. Wilcox and B.C. Lane, *J. Med. Chem*., **44**, 4481 (2001).
8. P. Narender, U. Srinivas, M. Ravinder, B.A. Rao, C. Ramesh, K. Harakishore, B. Gangadasu, U.S.N. Murthy and V.J. Rao, *Bioorg. Med. Chem*., **14**, 4600 (2006).
9. (a) P. Fossa, L. Mosti, G. Menozzi, C. Marzano, F. Baccichetti and F. Bordin, *Bioorg. Med. Chem*., **10**, 743 (2002); (b) A. Tsotinis, M. Vlachou, S. Zouroudis, A. Jeney, F. Timar, D.E. Thurston and C. Roussakis, *Lett. Drug Des. Discov*., **2**, 189 (2005).
10. (a) V. Klusa, *Drugs Future*, **20**, 135 (1995); (b) C.E. Sunkel, M.F.D. Casa-Juana, F.J. Cillero, J.G. Priego and P.M. Ortega, *J. Med. Chem*., **31**, 1886 (1988).
11. S.D. Sharma, P. Hazarika and D. Konwar, *Catal. Commun*., **9**, 709 (2008).
12. Z. Zhang, J. Gao, J.J. Xia and G.W. Wang, *Org. Biomol. Chem*., **3**, 1617 (2005).
13. A. Hantzsch, *J. Ann. Chem. Liebigs*, **215**, 1 (1882).
14. (a) M. Anniyappan, D. Muralidharan and P.T. Perumal, *Synth. Commun*., **32**, 659 (2002); (b) R. Alajarin, J.J. Vaquero, J. Navio and J. Alvarezbuila, *Synlett*, 297 (1992).
15. (a) H. Wu, Y. Wan, L.L. Lu, Y. Shen, L. Ye and F.R. Zhang, *Synth. Commun*., **38**, 666 (2008); (b) R. Sridhar and P.T. Perumal, *Tetrahedron*, **61**, 2465 (2005).
16. (a) J.J. Xia and G.W. Wang, *Synthesis*, 2379 (2005); (b) A. Dondoni, A. Massi, E. Minghini and V. Bertolasi, *Tetrahedron*, **60**, 2311 (2004).
17. M.A. Zolfigol, P. Salehi, A. Khorramabadi-Zad and M. Shayegh, *J. Mol. Catal. A: Chem*., **261**, 88 (2007).
18. G. Sabitha, G.S.K.K. Reddy, C.S. Reddy and J.S. Yadav, *Tetrahedron Lett*., **44**, 4129 (2003).
19. S.K. Ko and C.F. Yao, *Tetrahedron*, **62**, 7293 (2006).
20. J. Azizian, F. Hatamjafari and A.R. Karimi, *J. Heterocycl. Chem*., **43**, 1349 (2006).
21. M. Maheswara, V. Siddaiah, G.L.V. Damu and C.V. Rao, *Arkivoc*, 201 (2006).
22. (a) S.B. Sapkal, K.F. Shelke, B.B. Shingate and M.S. Shingare, *Tetrahedron Lett*., **50**, 1754 (2009); (b) L.M. Wang, J. Sheng, L. Zhang, J.W. Han, Z.Y. Fan, H. Tian and C.T. Qian, *Tetrahedron*, **61**, 1539 (2005).
23. (a) C.L. Peng, Y. Wang, L.Y. Liu, H.G. Wang, J.J. Zhao and Q. Zhu, *Eur. J. Org. Chem*., 818 (2010); (b) V. Anuradha, P.V. Srinivas, P. Aparna and J.M. Rao, *Tetrahedron Lett*., **47**, 4933 (2006); (c) T. Li, Y. Souma and Q. Xu, *Catal. Today*, **111**, 288 (2006); (d) C. Lim, G.N. Evenson, W.R. Perrault and B.A. Pearlman, *Tetrahedron Lett*., **47**, 6417 (2006); (e) B. Das, K.R. Reddy, Y. Srinivas and R.A. Kumar, *Can. J. Chem*., **85**, 479 (2007); (f) T.S. Jin, S.L. Zhang and T.S. Li, *Synth. Commun*., **32**, 1847 (2002); (g) A.R. Khosropour, M.M. Khodaei and H. Moghannian, *Synlett*, 0955 (2005).