# *P*-TSA Catalyzed Facile and Efficient Synthesis of Polyhydroquinoline Derivatives through Hantzsch Multi-Component Condensation

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**A facile and efficient synthetic route to polyhydroquinolines has been developed *via* four-component condensation reactions of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of *p*-toluenesulfonic acid (*p*-TSA) catalyst in ethanol at ambient temperature through Hantzsch reaction. Simple work-up procedure, environmentally friendly, inexpensive and non-toxic catalyst, shorter reaction times along with excellent product yields are the significant features of this practical method.**

**Key words** *p*-toluenesulfonic acid; polyhydroquinoline; one-pot conversion; multi-component condensation

Compounds containing the 4-substituted 1,4-dihydropyridine (DHP) nucleus comprise a large family of medicinally important compounds. They can cure the disordered heart ratio as a chain-cutting agent of factor IV channel, possess the calcium channel agonist-antagonist modulation activities[1—3] and also behave as neuroprotectants, cerebral antiischaemic agents and chemosensitizers.[4,5] A recent computational analysis of the comprehensive medicinal chemistry database found that the DHP framework to be among the most prolific chemotypes found. Thus, the synthesis of 4-substituted 1,4-dihydro-pyridines (1,4-DHPs) is of continuing interest.

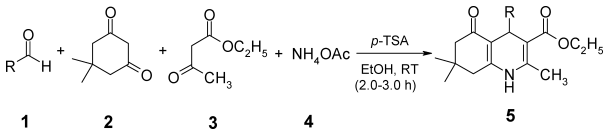
Recently, several methods have been reported comprising the use of microwave,[6] iodotrimethylsilane (TMSI),[7] ionic liquids,[8,9] metal triflates,[10] HY-zeolite,[11] $HClO_4$–$SiO_2$,[12] organocatalysts[13] and polymers[14,15] for the synthesis of 1,4-DHPs. However, the use of high temperatures, expensive metal precursors, catalysts that are harmful to environment, and longer reaction times limit the use of these methods. Therefore, there is a scope to find potential alternate procedures for the synthesis of 1,4-DHPs especially that are in high demand and having advantages such as low cost, non-toxic and environmentally benign.

In recent years, *p*-toluenesulfonic acid (*p*-TSA) has been used for many synthetic organic transformations[16—22] including the synthesis of ZDO947, in which it has been used as a dehydrating reagent.[23] The most characteristic feature of *p*-TSA is that its catalytic amount is only enough to complete reactions in many cases. Additionally, many advantages such as low cost, eco-friendly nature, ease of handling, non-toxicity and high reactivity make *p*-TSA a potent catalyst in the synthetic transformations. These facts inspired us to use *p*-TSA catalyst for the synthesis of polyhydroquinolines. Moreover, no report has been made so far about the use of *p*-TSA as a catalyst in the Hantzsch condensation. Herein, we report the studies of a facile Hantzsch condensation for the synthesis of polyhydroquinoline derivatives by one-pot four-component condensation of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate using a catalytic amount of *p*-TSA at ambient temperature. This method not only preserves the simplicity, but also consistently gives the corresponding products in good to excellent yields.

Thus, we have treated a variety of substituted aldehydes **1**, dimedone **2**, ethyl acetoacetate **3**, and ammonium acetate **4**, in the presence of *p*-TSA catalyst to form the corresponding polyhydroquinolines **5**. Excellent yields of polyhydroquinolines were obtained by carrying out the reaction in ethanol solvent at room temperature for 2—3 h (Chart 1).

The scope and generality of this four-component coupling one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction is illustrated with different aldehydes (Table 1). This method has the ability to tolerate a variety of functional groups such as hydroxyl, methoxy, methyl, nitro, halides, olefins *etc.*, under the reaction conditions. Both, the electron-rich and electron-deficient aldehydes as well as heterocyclic aldehyde (furfural) worked well, leading to high yields of product. The structures of all the products were established from their spectral data.

Under solvent free conditions, the reaction proceeded quickly but the obtained yellow solid contained many other by products. We then studied the reaction using different solvents. In each case, the reactants were mixed together with 10 mol% *p*-TSA, stirred with 5 ml solvent. The polar solvents such as ethanol and acetonitrile were found much bet-




1 2 3 4 5

Chart 1

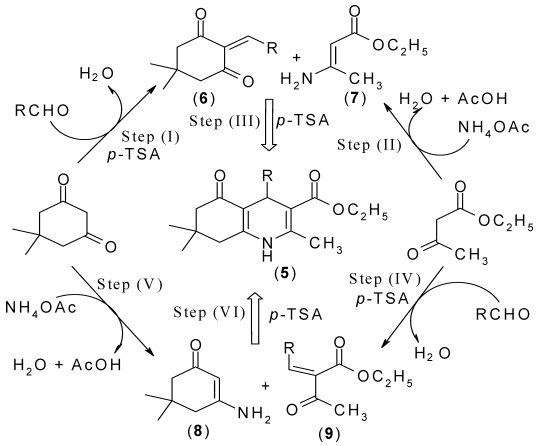



Chart 2

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Table 1. *p*-TSA Catalyzed Synthesis of Polyhydroquinoline Derivatives

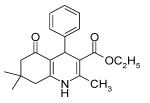
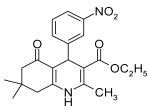
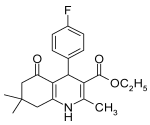
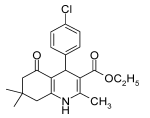
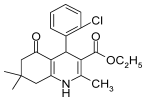
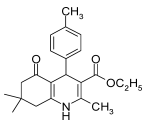
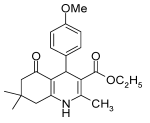
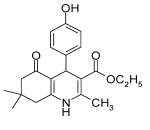
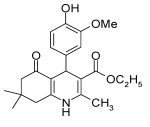
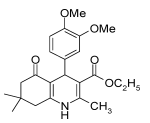
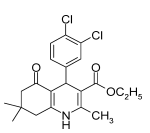
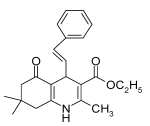
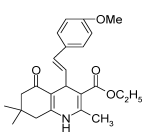
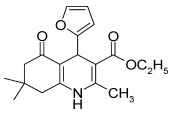
| Entry | Aldehyde | Product | Time (h) | Yield (%)[a] | Product characterization data |
|---|---|---|---|---|---|
| **5a** |  |  | 2.0 | 93 | mp 202—204 °C (lit. 203—204 °C[14]). IR (KBr) $cm^{-1}$: 3287, 3077, 2964, 1696, 1610. $^1$H-NMR ($CDCl_3$) $\delta$: 0.93 (3H, s), 1.06 (3H, s), 1.20 (3H, t, $J$=7.1 Hz), 2.12—2.28 (4H, m), 2.34 (3H, s), 4.05 (2H, q, $J$=7.1 Hz), 5.06 (1H, s), 6.63 (1H, s), 7.07—7.12 (1H, m), 7.17—7.22 (2H, m), 7.27—7.32 (2H, m). |
| **5b** |  |  | 2.0 | 85 | mp 178—180 °C (lit. 178—179 °C[14]). IR (KBr) $cm^{-1}$: 3285, 3210, 3080, 2960, 1705, 1605, 1530. $^1$H-NMR ($CDCl_3$) $\delta$: 0.93 (3H, s), 1.08 (3H, s), 1.21 (3H, t, $J$=7.1 Hz), 2.12—2.41 (7H, m), 3.68 (2H, q, $J$=7.1 Hz), 5.15 (1H, s), 6.86 (1H, s), 7.35 (1H, t, $J$=7.9 Hz), 7.72 (1H, d, $J$=7.9 Hz), 7.96 (1H, m), 7.98 (1H, m). |
| **5c** |  |  | 2.5 | 91 | mp 184—186 °C (lit. 185—186 °C[14]). IR (KBr) $cm^{-1}$: 3290, 2960, 1695, 1610, 1490, 1380, 1220, 1025, 764. $^1$H-NMR ($CDCl_3$) $\delta$: 0.93 (3H, s), 1.08 (3H, s), 1.19 (3H, t, $J$=7.3 Hz), 2.12—2.26 (4H, m), 2.37 (3H, s), 4.06 (2H, q, $J$=7.3 Hz), 5.02 (1H, s), 5.81 (1H, s), 6.86—6.90 (2H, m), 7.22—7.28 (2H, m). |
| **5d** |  |  | 2.0 | 90 | mp 244—246 °C (lit. 245—246 °C[14]). IR (KBr) $cm^{-1}$: 3275, 3200, 3075, 2965, 1705, 1650, 1605. $^1$H-NMR ($CDCl_3$) $\delta$: 0.94 (3H, s), 1.08 (3H, s), 1.19 (3H, t, $J$=7.1 Hz), 2.12—2.35 (4H, m), 2.36 (3H, s), 4.05 (2H, q, $J$=7.1 Hz), 5.03 (1H, s), 6.46 (1H, s), 7.15—7.20 (2H, m), 7.25—7.27 (2H, m). |
| **5e** |  |  | 2.5 | 89 | mp 206—208 °C (lit. 207—208 °C[14]). IR (KBr) $cm^{-1}$: 3062, 2955, 1720, 1640, 1610, 1468, 1385, 1228, 1020, 745. $^1$H-NMR ($CDCl_3$) $\delta$: 0.94 (3H, s), 1.06 (3H, s), 1.20 (3H, t, $J$=7.2 Hz), 2.02—2.20 (4H, m), 2.39 (3H, s), 4.05 (2H, q, $J$=7.2 Hz), 4.61 (1H, s), 7.11—7.30 (4H, m), 7.61 (1H, s). |
| **5f** |  |  | 2.0 | 92 | mp 260—262 °C (lit. 261—262 °C[14]). IR (KBr) $cm^{-1}$: 3275, 3080, 2960, 1700, 1650. $^1$H-NMR ($CDCl_3$) $\delta$: 0.95 (3H, s), 1.08 (3H, s), 1.21 (3H, t, $J$=7.1 Hz), 2.12—2.27 (7H, m), 2.33 (3H, s), 4.05 (2H, q, $J$=7.1 Hz), 5.02 (1H, s), 6.65 (1H, s), 7.00 (2H, d, $J$=7.9 Hz), 7.18 (2H, d, $J$=7.9 Hz). |
| **5g** |  |  | 2.0 | 93 | mp 255—257 °C (lit. 256—257 °C[12]). IR (KBr) $cm^{-1}$: 3275, 2957, 1705, 1647, 1605, 1497, 1382, 1217, 1032, 766. $^1$H-NMR ($CDCl_3$+DMSO-$d_6$) $\delta$: 0.93 (3H, s), 1.08 (3H, s), 1.22 (3H, t, $J$=7.2 Hz), 2.02—2.11 (4H, m), 2.31 (3H, s), 3.73 (3H, s), 4.01 (2H, q, $J$=7.2 Hz), 4.81 (1H, s), 6.64 (2H, d, $J$=7.3 Hz), 7.11 (2H, d, $J$=7.3 Hz), 8.64 (1H, s). |
| **5h** |  |  | 3.0 | 87 | mp 232—234 °C (lit. 233—234 °C[12]). IR (KBr) $cm^{-1}$: 3390, 2955, 1700, 1645, 1590, 1480, 1385, 1220, 782. $^1$H-NMR ($CDCl_3$) $\delta$: 0.93 (3H, s), 1.07 (3H, s), 1.19 (3H, t, $J$=7.2 Hz), 2.09—2.19 (3H, m), 2.20—2.34 (4H, m), 4.06 (2H, q, $J$=7.6 Hz), 4.98 (1H, s), 5.61, (1H, s), 6.65 (2H, d, $J$=8.9 Hz), 7.17 (2H, d, $J$=8.4 Hz). |
| **5i** |  |  | 2.0 | 89 | mp 211—212 °C (lit. 211—212 °C[14]). IR (KBr) $cm^{-1}$: 3390, 2955, 1700, 1645, 1590, 1480, 1385, 1220, 1030, 782. $^1$H-NMR ($CDCl_3$) $\delta$: 0.95 (3H, s), 1.09 (3H, s), 1.24 (3H, t, $J$=7.2 Hz), 2.02—2.20 (4H, m), 2.30 (3H, s), 3.81 (3H, s), 4.06 (2H, q, $J$=7.2 Hz), 4.81 (1H, s), 6.61 (2H, s), 6.83 (1H, s), 7.69 (1H, s), 8.50 (1H, s). |
| **5j** |  |  | 2.0 | 88 | mp 197—199 °C (lit. 198—199 °C[14]). IR (KBr) $cm^{-1}$: 3240, 2955, 1694, 1645, 1610, 1490, 1380, 1217, 1027, 753. $^1$H-NMR ($CDCl_3$) $\delta$: 0.95 (3H, s), 1.08 (3H, s), 1.21 ( 3H, t, $J$=7.3 Hz), 2.19—2.35 (4H, m), 2.38 (3H, s), 3.82 (3H, s), 3.84 (3H, s), 4.07 (2H, q, $J$=7.3 Hz), 5.03 (1H, s), 5.92 (1H, s), 6.69 (1H, d, $J$=8.30 Hz), 6.77 (1H, dd, $J$=1.96, 8.30 Hz), 6.93 (1H, d, $J$=1.96 Hz). |
| **5k** |  |  | 2.0 | 86 | mp 214—216 °C (lit. 213—215 °C[15]). IR (KBr) $cm^{-1}$: 3282, 3080, 2960, 1710, 1650, 1600, 1490. $^1$H-NMR ($CDCl_3$) $\delta$: 0.83 (3H, s), 1.08 (3H, s), 1.22 (3H, t, $J$=7.1 Hz), 2.13—2.39 (7H, m), 4.04 (2H, q, $J$=7.1 Hz), 5.03 (1H, s), 6.42 (1H, s), 7.18 (1H, m), 7.18 (1H, m), 7.35 (1H, d, $J$=2.0 Hz). |
| **5l** |  |  | 3.0 | 90 | mp 204—206 °C (lit. 204—206 °C[12]). IR (KBr) $cm^{-1}$: 3300, 2965, 1675, 1602, 1483. $^1$H-NMR ($CDCl_3$) $\delta$: 1.09 (3H, s), 1.11 (3H, s), 1.24—1.31 (3H, m), 2.28 (3H, t, $J$=7.3 Hz), 2.33—2.37 (4H, m), 4.11—4.20 (2H, m), 4.70 (1H, d, $J$=7.0 Hz), 5.75 (1H, s), 6.21 (2H, d, $J$=7.1 Hz), 7.22—7.30 (5H, m). |
| **5m** |  |  | 2.5 | 91 | mp 199—201 °C (lit. 198—200 °C[15]). IR (KBr) $cm^{-1}$: 3302, 2963, 1674, 1603, 1484. $^1$H-NMR ($CDCl_3$) $\delta$: 1.09 (3H, s), 1.13 (3H, s), 1.26 (3H, t, $J$=7.1 Hz), 2.18—2.33 (4H, m), 2.38 (3H, s), 3.77 (3H, s), 4.13—4.27 (2H, m), 4.72 (1H, d, $J$=6.1 Hz), 6.17 (1H, dd, $J$=6.1, 16.2 Hz), 6.46 (1H, s), 6.59 (1H, d, $J$=16.2 Hz), 6.79—6.89 (2H, m), 7.11—7.17 (1H, m), 7.38 (1H, d, $J$=1.3 Hz). |

Table 1. (Continued)

| Entry | Aldehyde | Product | Time (h) | Yield (%)[a] | Product characterization data |
|---|---|---|---|---|---|
| **5n** |  |  | 2.0 | 91 | mp 245—247 °C (lit. 246—248 °C[14]). IR (KBr) $cm^{-1}$: 3288, 3078, 2969, 1687, 1602, 1493, 1034, 941, 877, 826. $^1$H-NMR ($CDCl_3$) $\delta$: 1.03 (3H, s), 1.12 (3H, s), 1.26 (3H, t, $J$=6.9 Hz), 2.21—2.27 (3H, m), 2.35—2.38 (4H, m), 4.10—4.18 (2H, m), 5.25 (1H, s), 5.80 (1H, s), 6.02 (1H, s), 6.20 (1H, s), 7.17 (1H, s). |

*a*) The yields refer to isolated products.

ter solvents than the non-polar solvents like toluene, dichloromethane, cyclohexane *etc*. Obviously, the results could be interpreted with the much better solubility of the catalyst and the reagents in the polar solvents. Among ethanol and acetonitrile, ethanol stands out as the solvent of choice, with its fast conversion, high yield and low toxicity.

We also carried out the reactions without any catalyst, but the polyhydroquinoline derivatives were isolated in poor yields (15—20%), and the major product isolated was a dimedone aldehyde adduct. The use of just 10 mol% of *p*-TSA in stirring ethanol is sufficient to push the reaction forward. Higher amounts of *p*-TSA did not lead to significant improvement in the yield of polyhydroquinolines. In stirring ethanol at room temperature the reaction was complete within 2—3 h. Upon refluxing in ethanol the reaction rate accelerated and the reaction was complete within 1 h, but the yield did not increase. The use of smaller amounts of *p*-TSA (2 mol% or 5 mol%) took longer time for completion of the reaction.

A tentative mechanism to rationalize the product formation is shown in Chart 2. Polyhydroquinoline **5** may be formed either through steps I—III or through steps IV—VI. The role of *p*-TSA comes in steps I and IV, where it catalyzes the Knoevenagel type coupling of aldehydes with active methylene compounds and in steps III and VI, where it catalyzes the Michael type addition of intermediates **6**, **7** and **8**, **9** to give product **5**. The isolated products **5** were racemic mixtures and not atropisomers.

In conclusion, we have developed a facile and efficient method for the synthesis of a variety of polyhydroquinoline derivatives *via* an improved Hantzsch reaction catalyzed by *p*-TSA. The reaction conditions are mild and the reaction gives excellent yields of the products at room temperature. This method does not involve the use of toxic solvents thus it is an environmentally friendly process.

## Experimental

**General** Melting points were determined on a Kofler hot-stage apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer, FT-IR spectrometer using KBr discs. $^1$H-NMR spectra were obtained on a Varian Gemini-200 MHz NMR spectrometer in $CDCl_3$ or a $CDCl_3$+DMSO-$d_6$ using TMS as internal standard. TLC was carried out on $GF_{254}$ silica gel plates. Commercially available chemicals (BDH and Fluka) were used without further purification.

**Typical Procedure** To a stirred mixture of dimedone (1 mmol), ethyl acetoacetate (1 mmol) and *p*-TSA (10 mol%) in ethanol (5 ml), aldehyde (1 mmol) and ammonium acetate (1 mmol) were added at ambient temperature. The reaction mixture was stirred at room temperature until the reaction completed (monitored by TLC). The resulting yellow solid product was filtered, treated with water followed by brine solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness to afford the crude product. The crude product was subjected to column chromatography over silica gel using 30% EtOAc in hexane as eluent to obtain pure polyhydroquinolines.

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