

# L-Proline as an Efficient Organo-Catalyst for the Synthesis of Polyhydroquinoline Via Multicomponent Hantzsch Reaction

Nandkishor N. Karade<sup>\*,a</sup>, Vishnu H. Budhewar<sup>a</sup>, Sandeep V. Shinde<sup>b</sup> and Wamanrao N. Jadhav<sup>b</sup>

<sup>a</sup>School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431606, Maharashtra, India

<sup>b</sup>Dnyanopasak College, Parbhani-431401, Maharashtra, India

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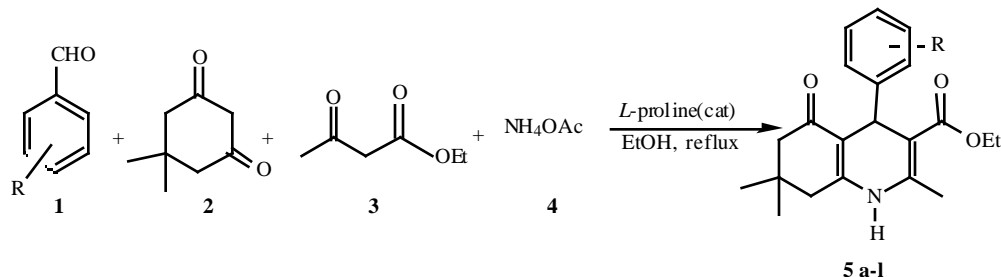
**Abstract:** L-Proline has been found as an effective catalyst for the one pot synthesis of polyhydroquinoline derivatives via four component Hantzsch reaction. This method provides several advantages such as being environmentally benign, possessing high yields with increased variations of the substituents in the product and preparative simplicity.

**Keywords:** Hantzsch reaction, multi-component reactions, L-proline, polyhydroquinoline, –dicarbonyl compound, aldehyde.

## 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 vasodilator, antihypertensive, bronchodilator, antithrombotic, hepto-protective, antitumor, antimutagenic, geroprotective and antidiabetic agents [1]. DHPs have found commercial utility as calcium channel blockers as exemplified by therapeutic agents such as Nifedine, Nitrendipine and Nimodipine [2]. Furthermore, DHP has

rather long periods, resulting in low or modest yields of condensation products. The great biological importance of the 1,4-dihydropyridine nucleus has over the years prompted the development of new improved methodologies, including solid phase synthesis [5] and activation with a catalyst such as Me<sub>3</sub>SiI, molecular sieves and pyridine [6]. Replacement of ammonia by ammonium acetate allowed the efficient synthesis of Hantzsch compounds in aqueous medium as well as under solvent free conditions [7]. Significant rate and yield enhancements were also reported for Hantzsch reaction



Scheme 1.

been meticulously used as a reducing agent for the direct reductive amination of aldehydes and ketones [3]. Consequently, the discovery of a milder and more practical route for the synthesis of such dihydropyridines continues to attract the attention of researcher.

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 [4]. 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

carried out under microwave irradiation [8]. The utilization of cyclic 1,3-diketone in Hantzsch reaction for the synthesis of polyhydroquinoline is recently demonstrated by using molecular iodine [9], HClO<sub>4</sub>-SiO<sub>2</sub> [10] and expensive metal triflates, Yb(OTf)<sub>3</sub> [11]. Each of the above methods for Hantzsch reaction has its own merits, while some of the methods are plagued by the limitations of poor yield, longer reaction time, difficult work-up and effluent pollution. Moreover, there are relatively limited number of reports on the synthesis of polyhydroquinoline derivatives compared to the synthesis of simple 4-substituted 1,4-dihydropyridine nucleus. Consequently, there is scope for further work towards increased variations of the substituents in the product, mild conditions and better yields.

In view of the current thrust in the utilization of 1,3-diketones in multi-component reactions [12], there is merit in developing a truly catalytic method for the formation of

\*Address correspondence to this author at the School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431606, Maharashtra, India; Fax: +91-02462-229245; E-mail: nmkarade@rediffmail.com

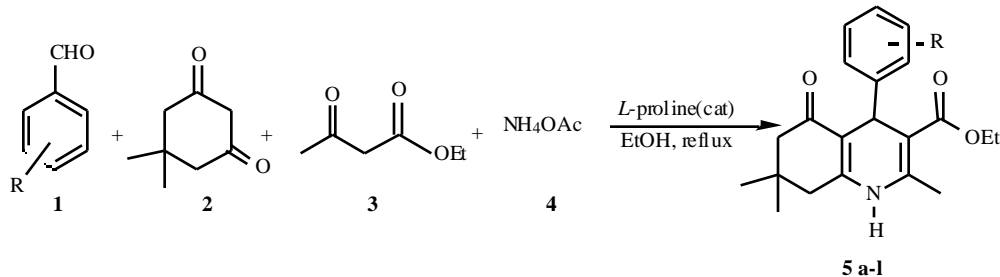
polyhydroquinoline via Hantzsch reaction. Proline is an efficient bi-functional abundant chiral organo-catalyst which is inexpensive and available in both enantiomeric forms [13]. These two functional groups can both act as acid or base and can also facilitate chemical transformations in concert, similar to enzymatic catalysis. It has been extensively used in the synthesis of various heterocycles [14] as well as in aldol, Mannich and Michael reactions [15]. As the mechanism of multi-component Hantzsch reaction originally involves aldol related reactions such as Knoevenagel condensation and Michael addition, the use of *L*-proline for the same reaction will be an useful and attractive modification for the same. Herein, we report first time the use of *L*-proline as an organo-catalyst for the multicomponent Hantzsch reaction under benign reaction conditions. Our results demonstrate that *L*-proline is a very effective, environmentally friendly catalyst for the four component condensations of dimedone, ethylacetoacetate, aromatic aldehyde and ammonium acetate to form polyhydroquinoline in excellent yields (Scheme 1).

## RESULTS AND DISCUSSION

In a typical experimental procedure, a mixture of dimedone (3 mmol), benzaldehyde (3 mmol), ethyl acetoacetate (3 mmol) and ammonium acetate (6 mmol) in ethanol was refluxed in the presence of *L*-proline (10 mol %) for 6 hrs. After cooling the reaction mixture at room

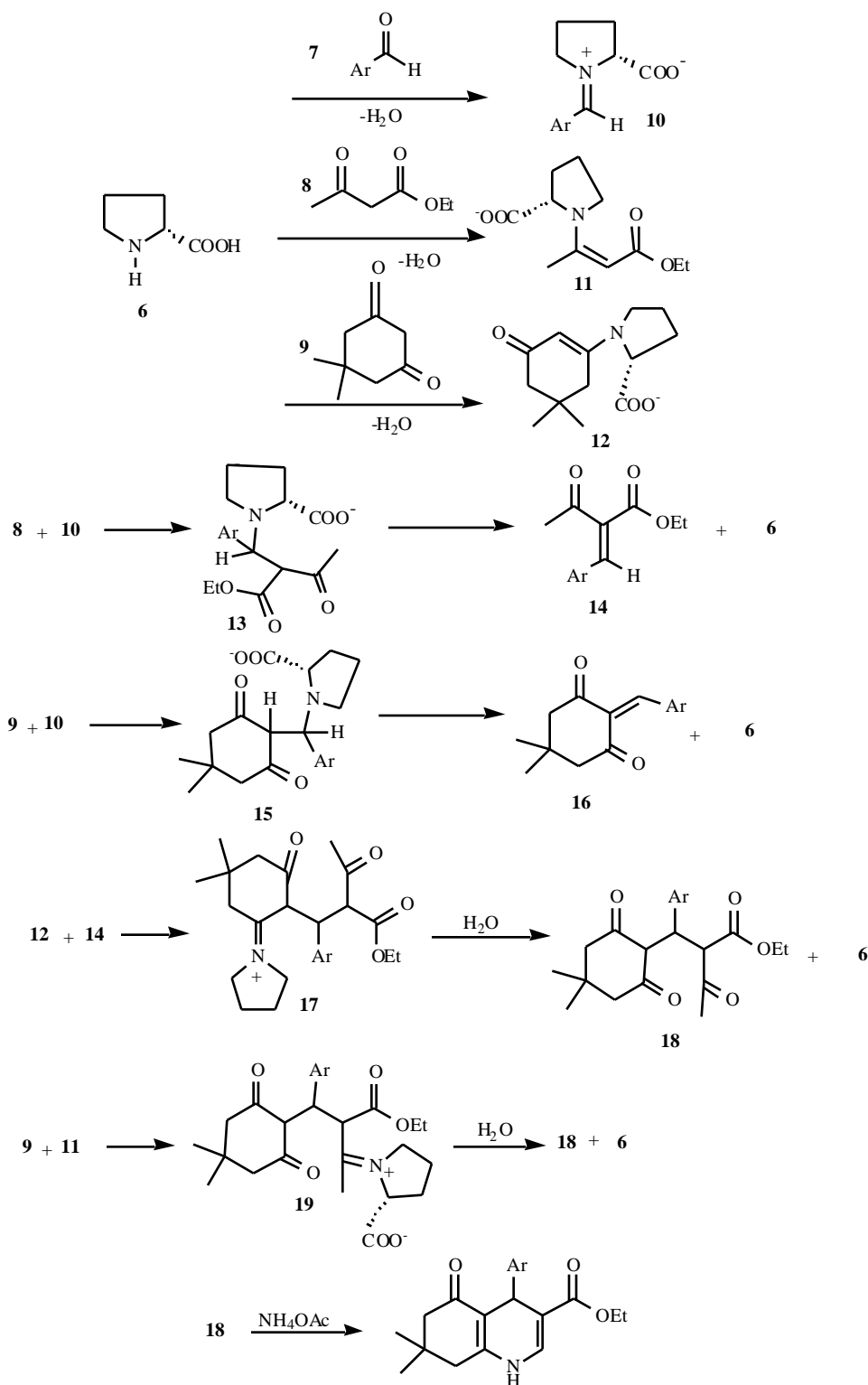
temperature, it was then poured into crushed ice and the solid product, which separated, was filtered and recrystallized from ethanol to get yellow colored crystalline polyhydroquinoline **5a** in 92 % yield. The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields of polyhydroquinoline. For example, the formation of **5a** did not proceed in absence of the catalyst *L*-proline even after refluxing the above same reaction mixture for 24 hrs, instead, the intermediate product such as 2-benzylidene-5,5-dimethylcyclohexane-1,3-dione, due to Knoevenagel condensation was exclusively formed in 73 % yield. While using *L*-proline (5 mol %) as catalyst, the reaction gave yellow color product in 73 % yield in four hours. By changing the amount of the catalyst from 2.5 mol % to 5 mol %, 7.5 mol %, and 10 mol %, the reaction resulted in the formation of **5a** in 86, 89, 91 and 92 % yield respectively. Thus the use of just 10 mol % of *L*-proline was therefore, chosen as a quantitative catalyst to push the reaction forward with maximum yield of the product and 6-7 hour as reaction time. Increase in the quantity of the catalyst has not resulted in any enhancement of the yield of **5a**. These results encouraged us to extend this method to synthesize other substituted polyhydroquinoline (Table 1). All yields are those of isolated products after purification and are comparable to the best overall yields previously reported for the appropriate polyhydroquinoline products. The structures of the products were confirmed from melting point and spectroscopic data [18].

**Table 1.** *L*-Proline Catalyzed Synthesis of Polyhydroquinoline Derivatives Through Hantzsch Reaction



Entry	1	Ar	Time (h)	Product	Yield (%) <sup>a</sup>	Mp. (°C) found	Mp. (°C) (Lit)
1	1a	C <sub>6</sub> H <sub>5</sub>	6	5a	92	202-205	202-204 [11]
2	1b	4-MeOC <sub>6</sub> H <sub>4</sub>	7	5b	86	252-254	257-259 [11]
3	1c	3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	7	5c	87	197-199	199-200 [17]
4	1d	4-HOC <sub>6</sub> H <sub>4</sub>	6	5d	90	234-237	232-234 [11]
5	1e	4-HO-3-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	7	5e	87	208-210	210-212 [15]
6	1f	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	6	5f	88	228-230	229-230 [10]
7	1g	4-ClC <sub>6</sub> H <sub>4</sub>	6	5g	87	232-234	230-232 [9]
8	1h	4-BrC <sub>6</sub> H <sub>4</sub>	6	5h	81	251-253	253-255 [11]
9	1i	4-MeC <sub>6</sub> H <sub>4</sub>	6	5i	83	258-260	260-261 [11]
10	1j	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	6	5j	91	241-243	242-244 [16]
11	1k	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	6	5k	84	176-179	177-178 [17]
12	1l	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	7	5l	81	208-211	206-208 [17]

<sup>a</sup>Isolated yields after crystallization.



**Scheme 2.** Mechanism of polyhydroquinoline formation.

It follows from Table 1 that the yields of all the products are good to excellent and a variety of functionalities such as nitro, halide, ether and hydroxy can be accommodated in polyhydroquinoline derivatives. Aromatic aldehydes carrying electron withdrawing substituents reacted in shorter reaction time with excellent yields to give polyhydroquinoline compared to the presence of electron donating groups in aromatic aldehydes.

The tentative mechanism for the formation of polyhydroquinoline is shown in Scheme 2. There is evidence in the literature that *L*-proline can catalyse aldol related reactions such as Knoevenagel condensation as well as Michael additions [15]. In this Hantzsch reaction, *L*-proline is supposed to facilitate the Knoevenagel condensation for the formation of 14 and 16 and the Michael addition for the formation of 1,5-dicarbonyl intermediate 18.

Finally, **18** undergoes cyclodehydration with ammonium acetate to form polyhydroquinoline product.

## CONCLUSION

In summary, the use of inexpensive *L*-proline in a catalytic quantity is a general practical alternative to existing procedures for multicomponent Hantzsch synthesis of polyhydroquinoline derivatives. The procedure offers several advantages including increased variations of substituent in the product with high yields, operational simplicity, minimum environmental effects and above all, the ease in purification of products simply by crystallization.

## ACKNOWLEDGEMENT

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## EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. <sup>1</sup>HNMR spectra were recorded at 400 MHz in CDCl<sub>3</sub> using TMS as internal standard. *L*-Proline was purchased from Aldrich Chemicals Limited and used as received without any activation.

## General Procedure for the Synthesis of Polyhydroquinoline

A mixture of dimedone (2 mmol), aromatic aldehyde (2 mmol), ethylacetoacetate (2 mmol), ammonium acetate (4 mmol) and *L*-proline (10 mol%) was refluxed in ethanol (15 ml) for the time as mentioned in Table 1. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into crushed ice and the solid product, which separated was filtered and recrystallized from ethanol to get pure yellow coloured crystalline polyhydroquinoline derivative **5a-l**.

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- Spectral data for selected compounds:  
**Ethyl 1, 4, 5, 6, 7, 8 – hexahydro – 4 – (4-methoxyphenyl) – 7, 7 – dimethyl – 5 – oxoquinoline-3-carboxylate (5b)**: Yellow solid, M. p. 252-254 °C (Lit.<sup>10</sup> mp: 257-259 °C); IR (KBr, cm<sup>-1</sup>): 3305, 3040, 2964, 1687, 1614, 1498, 1371, 1207, 757; <sup>1</sup>HNMR (CDCl<sub>3</sub>, ppm): 0.95 (3H, s, CH<sub>3</sub>), 1.08 (3H, s, CH<sub>3</sub>), 1.21 (3H, t, J = 7.2 Hz, CH<sub>2</sub>), 2.21 (3H, s, CH<sub>3</sub>), 2.33-2.38 (4H, m, 2CH<sub>2</sub>), 3.74 (3H, s, OCH<sub>3</sub>), 4.06 (2H, q, J = 7.2 Hz, CH<sub>2</sub>), 5.00 (1H, s, ArCH), 6.43 (1H, br., s, NH), 6.73 (2H, d, J = 8.1 Hz, Ar-H), 7.21 (2H, d, J = 8.2 Hz, Ar-H); Elemental Analysis: Found (%): C, 71.58; H, 7.33; N, 3.87. Calcd. For C<sub>22</sub>H<sub>27</sub>O<sub>4</sub>N: C, 71.54; H, 7.31; N, 3.79.  
**Ethyl 1, 4, 5, 6, 7, 8 – hexahydro – 4 – (3, 4, 5 – trimethoxyphenyl) – 7, 7-dimethyl – 5-oxoquinoline-3-carboxylate (5c)**: Yellow solid, M. p. 197 – 199 °C (Lit mp. 199-200<sup>16</sup>); IR (KBr, cm<sup>-1</sup>): 3293, 3031, 2958, 1687, 1612, 1486, 1377, 1219, 1115, 751; <sup>1</sup>HNMR (CDCl<sub>3</sub>), ppm): 1.04, (3H, s, CH<sub>3</sub>), 1.18 (3H, s, CH<sub>3</sub>) 1.30 (3H, t, J = 7.1 Hz, CH<sub>2</sub>), 2.23 (3H, s, CH<sub>3</sub>), 2.35-2.46 (4H, m, 2CH<sub>2</sub>), 3.68-3.87 (9H, m, 3OCH<sub>3</sub>), 4.17 (2H, q, J = 7.1 Hz, CH<sub>2</sub>), 5.09 (1H, s, ArCH), 5.99 (1H, s, br. NH), 6.59 (2H, s, Ar-H); Elemental analysis: Found (%): C, 72.47; H, 7.69; N, 3.64. Calcd. For C<sub>24</sub>H<sub>31</sub>O<sub>6</sub>N: C, 72.54; H, 7.80; N, 3.52.  
**Ethyl 1, 4, 5, 6, 7, 8 – hexahydro – 4 – (4- N, N – dimethylamino-phenyl) – 7, 7-dimethyl – 5 – oxoquinoline-3-carboxylate (5f)**: Yellow solid, M. p. 232-234 °C (Lit.<sup>9</sup> mp. 230-232); IR (KBr, cm<sup>-1</sup>): 3287, 3018, 2964, 1602, 1510, 1377, 1207, 751; <sup>1</sup>HNMR (CDCl<sub>3</sub>), ppm): 1.00 (3H, s, CH<sub>3</sub>), 1.12 (3H, s, CH<sub>3</sub>), 1.25 (3H, t, J = 7.1 Hz, CH<sub>2</sub>), 2.17 (3H, s, CH<sub>3</sub>), 2.30-2.42 (4H, m, 2CH<sub>2</sub>), 4.13 (2H, q, J = 7.1 Hz, CH<sub>2</sub>), 5.11 (1H, s, ArCH), 6.00 (1H, br., s, NH), 7.12 (2H, d, J = 8.2 Hz, ArH), 7.23 (2H, d, J = 8.3 Hz, ArH); Elemental analysis: Found (%): C, 72.17; H, 7.81; N, 7.26; Calcd. For C<sub>23</sub>H<sub>30</sub>O<sub>3</sub>N<sub>2</sub>: C, 72.25; H, 7.85; N, 7.32.  
**Ethyl 1, 4, 5, 6, 7, 8 – hexahydro – 4 – (4-methoxyphenyl)-7, 7-dimethyl-5-oxoquinoline-3-carboxylate (5i)**: Yellow solid, M. p. 241-243 °C (Lit. mp 242-244<sup>15</sup>); IR (KBr, cm<sup>-1</sup>): 3287, 3031, 2958, 1644, 1596, 1480, 1334, 1213, 757; <sup>1</sup>HNMR (CDCl<sub>3</sub>), ppm): 0.97 (3H, s, CH<sub>3</sub>), 1.13 (3H, s, CH<sub>3</sub>), 1.24 (3H, t, J = 7.1 Hz, CH<sub>2</sub>), 2.18 (3H, s, CH<sub>3</sub>), 2.37-2.50 (4H, m, 2CH<sub>2</sub>), 4.16 (2H, q, J = 7.1 Hz, CH<sub>2</sub>), 5.25 (1H, s, ArCH), 6.00 (1H, br., s, NH), 7.56 (2H, d, J = 8.7 Hz, ArH), 8.15 (2H, d, J = 8.2 Hz ArH); Elemental analysis: Found (%): C, 74.73; H, 7.61; N, 3.89. Calcd. For C<sub>22</sub>H<sub>27</sub>O<sub>3</sub>N: C, 74.78; H, 7.64; N, 3.96.