

*Short communication*

# An Efficient Procedure for the Synthesis of Hantzsch 1,4-Dihydropyridines Under Mild Conditions

Arash Ghorbani-Choghamarani,<sup>\*,a</sup> Mohammad Ali Zolfigol,<sup>\*,b</sup> Peyman Salehi,<sup>c</sup> Ezat Ghaemi,<sup>b</sup> Elaheh Madrakian,<sup>b</sup> Hossein Nasr-Isfahani<sup>d</sup> and Mozhjgan Shahamirian<sup>b</sup>

*a* Department of Chemistry, Faculty of Science, Ilam University, P.O. Box, 69315516, Ilam, Iran

*b* Faculty of Chemistry, Bu-Ali Sina University, P.O. Box 6517838683, Hamadan, Iran

*c* Department of Phytochemistry, Aromatic and Medicinal Plants and Drug Research Institute, Shahid Beheshti University, Evin, Tehran 1983963113, Iran

*d* College of Chemistry, Shahrood University of Technology, Shahrood, Iran

\* Corresponding author: E-mail: arashghch58@yahoo.com (A. Ghorbani-Choghamarani) zolfi@basu.ac.ir. (M. A. Zolfigol)

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## Abstract

A simple and efficient one-pot synthesis of 1,4-dihydropyridine derivatives was achieved via condensation of methyl acetoacetate or ethyl propiolate with various alkyl and aryl aldehydes and ammonium acetate at 80 °C under solvent free conditions with good to excellent yields.

**Keywords:** 1,4-Dihydropyridines, ethyl propiolate, methyl acetoacetate, ammonium acetate, solvent-free conditions

## 1. Introduction

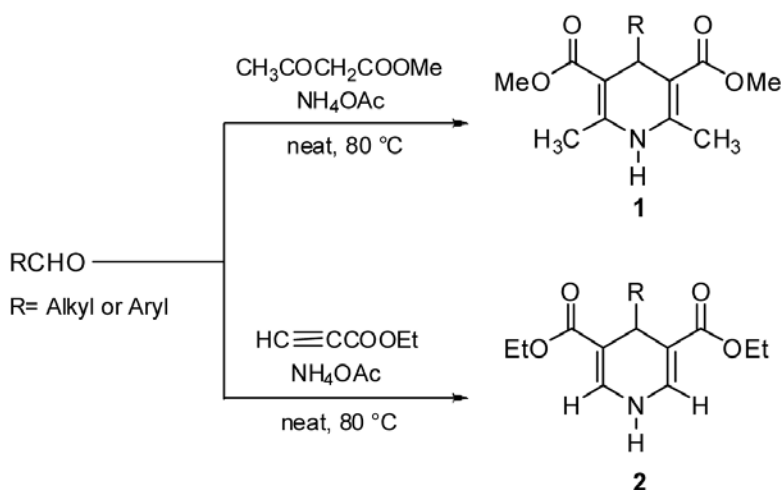
Hantzsch 1,4-dihydropyridines are well-known compounds as the most important calcium channel modulators.<sup>1–5</sup> 1,4-Dihydropyridines and their derivatives are important class of bioactive molecules in the field of drug and pharmaceuticals.<sup>6</sup> For example, Amlodipine besylate, Nifedipine and related dihydropyridines are Ca<sup>2+</sup> channel blockers, and are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertension. Recent studies have revealed that 1,4-dihydropyridines exhibit several other medicinal applications including neuroprotectant and platelet anti-aggregator activity in addition to acting as cerebral antiischemic agents in the treatment of Alzheimer's disease and as a chemosensitizer in tumor therapy.<sup>7–10</sup> Additionally, dihydropyridines are often produced in a synthetic sequence, and oxidized to pyridines.<sup>11–18</sup> Recently, much effort has been devoted to developing more efficient met-

hods for the synthesis of 1,4-dihydropyridines.<sup>19–25</sup> The classical method for the synthesis of these compounds is the Hantzsch reaction involving a multicomponent condensation of an aldehyde with a 1,3-dicarbonyl compound and NH<sub>3</sub>.<sup>26</sup> Recently Tripathi et al. reported an efficient method for the synthesis of glycosyl 1,4-dihydropyridines using tetrabutyl ammonium hydrogen sulfate as a catalyst,<sup>27</sup> where enamines of  $\beta$ -keto compounds are as intermediates in this strategy.<sup>28</sup>

## 2. Results and Discussion

The development of efficient and versatile procedures for the preparation of 1,4-dihydropyridines is an active research area aiming at further improvements towards milder reaction conditions and improved yields.<sup>29</sup> In continuation of our previous work on the synthesis of dihydropyridines,<sup>30,31</sup> we disclose a new synthetic protocol for

the synthesis of two different classes of 1,4-dihydropyridine derivatives under mild and green reaction conditions as outlined in Scheme 1.



Scheme 1

A variety of 4-substituted 1,4-dihydro-2,6-dimethyl-3,5-bis(methoxycarbonyl)pyridines (**1**) were synthesized from a combination of methyl acetoacetate, different aldehydes and ammonium acetate under solvent-free conditions. Also various 4-substituted 1,4-dihydro-3,5-bis(ethoxycarbonyl)pyridines (**2**) were obtained by treatment of ethyl propiolate, different aldehydes and ammonium acetate under same conditions (Scheme 1 and Table 1). The reactions were completed within 15–165 minutes at 80 °C, and the crude products were obtained via precipitation in aqueous solution of  $\text{NaHCO}_3$ , followed by vigorous shaking and decanting of aqueous layer. The residue was

dissolved in dichloromethane, dried with  $\text{Na}_2\text{SO}_4$ , and after removal of dichloromethane, products were obtained with high yield and purity.

### 3. Experimental

#### 3.1. Synthesis of 1,4-dihydro-2,4,6-trimethyl-3,5-bis(methoxycarbonyl)pyridine (**1a**) as a Typical Procedure

Methyl acetoacetate (0.196 g, 2.5 mmol) was added to the stirring mixture of acetaldehyde (0.044 g, 1 mmol), and  $\text{NH}_4\text{OAc}$  (0.11 g, 1.5 mmol) at 80 °C for 60 min. Reaction completion was determined by TLC, using hexane and acetone (8:2) as eluent. After completion of the reaction  $\text{NaHCO}_3$  (20 ml, 10 %) was added to the reaction

Table 1. Synthesis of 1,4-dihydropyridine derivatives under mild and solvent-free conditions at 80 °C<sup>a</sup>

Entry	Product	R	Time (min)	Yield (%) <sup>b</sup>	Reference
1	<b>1a</b>	Me	60	97	32, 33
2	<b>1b</b>	Et	45	95	32
3	<b>1c</b>	<i>n</i> -Propyl	90	78	34
4	<b>1d</b>	Ph	120	84	32
5	<b>1e</b>	2-Thienyl	15	97	36
6	<b>1f</b>	2-Furyl	15	80	37
7	<b>1g</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	90	95	32, 37
8	<b>1h</b>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	45	95	35, 37
9	<b>1i</b>	4-Br-C <sub>6</sub> H <sub>4</sub>	90	94	35
10	<b>1j</b>	2-OMe-C <sub>6</sub> H <sub>4</sub>	120	95	38
11	<b>1k</b>	3-Pyridyl-C <sub>6</sub> H <sub>4</sub>	120	80	33
12	<b>2a</b>	4-Br-C <sub>6</sub> H <sub>4</sub>	90	83	39–42
13	<b>2b</b>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	165	70	39–42
14	<b>2c</b>	2-MeO-C <sub>6</sub> H <sub>4</sub>	50	76	39–42
15	<b>2d</b>	2-Furyl	60	85	39–42

<sup>a</sup> Molar ratio of reagents: a) methyl acetoacetate/aldehyde/ammonium acetate for entries 1–11: (2.5:1:1.5), b) ethyl propiolate/aldehyde/ammonium acetate for entries 12–14: (2:1:2), and c) for entry 15 (2:1:1.5). <sup>b</sup> Crude isolated yield.

mixture. The products were extracted with dichloromethane. Mixture was dried over  $\text{Na}_2\text{SO}_4$  (3 g) and filtered off. Dichloromethane was removed and 1,4-dihydro-2,4,6-trimethyl-3,5-bis(methoxycarbonyl)pyridine (**1a**) was obtained (0.259 g, 97%). The residue was recrystallized from mixture of ethanol and water (70:30), m.p.: 148–149 °C.<sup>32,33</sup> IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ) 3342 (N–H), 1682 (C=O);  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 0.99 (d, 3H, J = 8.1 Hz), 2.27 (s, 6H), 3.72 (s, 6H), 3.75 (q, 4H, J = 8.1 Hz), 5.85 (br, 1H).

IR ( $\nu$ ,  $\text{cm}^{-1}$ ) and  $^1\text{H}$  NMR ( $\delta$ , ppm) spectroscopic data of the reported products are as follows:

**1b**: m.p. 137–138 °C;<sup>32</sup> IR (KBr)  $\nu$  3359 (N–H), 1700 (C=O);  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  0.73 (t, 3H, J = 10.6 Hz), 1.28 (m, 2H), 2.29 (s, 6H), 3.71 (s, 6H), 3.89 (t, 1H, J = 6.4 Hz), 5.71 (br, 1H).

**1c**: m.p. 139–140 °C;<sup>34</sup> IR (KBr)  $\nu$  3362 (N–H), 1700 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  0.82 (m, 3H), 1.24 (m, 4H), 2.28 (s, 6H), 3.71 (s, 6H), 3.91 (t, 1H, J = 4.7 Hz), 5.78 (br, 1H).

**1d**: m.p. 196–197 °C;<sup>32</sup> IR (KBr)  $\nu$  3344 (N–H), 1699 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.31 (s, 6H), 3.64 (s, 6H), 5.00 (s, 1H), 5.87 (br, 1H), 7.22 (br, 5H).

**1e**: m.p. 198–199 °C;<sup>36</sup> IR (KBr)  $\nu$  3324 (N–H), 1678 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (s, 6H), 3.71 (s, 6H), 5.33 (s, 1H), 5.94 (br, 1H), 6.79 (m, 1H), 7.03 (m, 1H), 7.26 (m, 1H).

**1f**: m.p. 194–195 °C;<sup>37</sup> IR (KBr)  $\nu$  3347 (N–H), 1699 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.33 (s, 6H), 3.70 (s, 6H), 5.19 (s, 1H), 5.91 (br, 1H), 5.94 (m, 1H), 6.20 (m, 1H), 7.21 (m, 1H).

**1g**: m.p. 188–191 °C;<sup>32,37</sup> IR (KBr)  $\nu$  3350 (N–H), 1705 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.29 (s, 6H), 3.57 (s, 6H), 5.03 (s, 1H), 5.86 (br, 1H), 7.19–8.00 (m, 4H).

**1h**: m.p. 195–196 °C;<sup>35,37</sup> IR (KBr)  $\nu$  3310 (N–H), 1700 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (s, 6H), 3.64 (s, 6H), 5.11 (s, 1H), 6.16 (br, 1H), 7.48 (d, 2H, J = 8.1 Hz), 8.03 (d, 2H, J = 8.3 Hz).

**1i**: m.p. 200–201 °C;<sup>35</sup> IR (KBr)  $\nu$  3341 (N–H), 1657 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.32 (s, 6H), 3.64 (s, 6H), 4.95 (s, 1H), 5.79 (br, 1H), 7.15–7.40 (dd, 4H, J = 12.3, 14.3 Hz).

**1j**: IR (KBr)  $\nu$  3329 (N–H), 1695 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.27 (s, 6H), 3.60 (s, 6H), 3.79 (s, 3H), 5.27 (s, 1H), 5.82 (br, 1H), 6.85–7.09 (m, 4H).

**1k**: m.p. 248–249 °C;<sup>33</sup> IR (KBr)  $\nu$  3183 (N–H), 1694 (C=O);  $^1\text{H}$ -NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (s, 6H), 3.64 (s, 6H), 4.98 (s, 1H), 6.11 (br, 1H), 7.26 (m, 1H), 7.56 (m, 1H), 8.52 (m, 2H).

**2a**: IR (KBr)  $\nu$  3323 (N–H), 1668 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25 (t, 6H, J = 4.3 Hz), 4.08 (q, 4H, J = 4.2 Hz), 4.95 (s, 1H), 6.52–7.21 (m, 3H), 7.26–7.39 (m, 4H).

**2b**: IR (KBr)  $\nu$  3317 (N–H), 1681 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR

( $\text{CDCl}_3$ )  $\delta$  1.25 (t, 6H, J = 4.7 Hz), 4.07 (q, 4H, J = 4.8 Hz), 5.74 (s, 1H), 7.23–7.52 (m, 3H), 7.96 (d, 2H, J = 8.9 Hz), 8.23 (d, 2H, J = 8.9 Hz).

**2c**: IR (KBr)  $\nu$  3323 (N–H), 1682 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.14 (t, 6H, J = 5.1 Hz), 3.82 (q, 4H, J = 5.0 Hz), 3.98 (s, 3H), 5.25 (s, 1H), 6.85–7.25 (m, 7H).

**2d**: IR (KBr)  $\nu$  3311 (N–H), 1679 (C=O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.20 (t, 6H, J = 6.1 Hz), 4.09 (q, 4H, J = 6.4 Hz), 5.60–7.27 (m, 6H).

## 4. Conclusions

The cheapness and the availability of the starting materials, efficient work-up, and high yields make this method an attractive methodology. In addition, compatibility with various functional groups and environmentally friendly nature of the procedure should make the present method useful and important in addition to the known methodologies for the Hantzsch reaction.

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## Abstract

V prispevku je podana enostavna in učinkovita enostopenjska sinteza derivatov 1,4-dihidropiridina s kondenzacijo metil acetoacetata ali etil propiloata z različnimi alkil in aril aldehidi in amonijevim acetatom pri 80 °C, brez uporabe topila in dobrimi izkoristki.