

## Hantzsch 반응을 통한 1,4-Dihydropyridine계 화합물의 PEG-Promoted One-Pot 합성

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## PEG-Promoted One-Pot Synthesis of 1,4-Dihydropyridine Derivatives Via Hantzsch Reaction in H<sub>2</sub>O

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주제어: 1,4-디히드로피리딘 (1,4-DHPs), 녹색 화학, 녹색 용매, 이온성 액체 (ILs), 폴리에틸렌글리콜 (PEG), Hantzsch 반응  
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### INTRODUCTION

1,4-Dihydropyridines (1,4-DHPs) are well known as Ca<sup>2+</sup> channel blockers, and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases.<sup>1</sup> Dihydropyridines have been classically synthesized using the Hantzsch synthesis described in 1882, which is one-pot condensation of aldehydes with ethyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol.<sup>2</sup> However, this method involves long reaction time, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally gives low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-DHPs and there were several efficient methods developed for the synthesis of 1,4-dihydropyridines, comprising the use of microwave,<sup>3</sup> ionic liquid,<sup>4</sup> solvent-free,<sup>5</sup> TMSCl-NaI,<sup>6</sup> solar energy,<sup>7</sup> and so on.

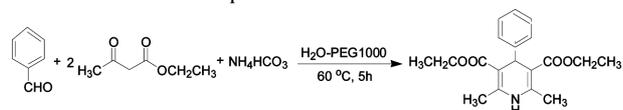
Green chemistry is a major issue of modern chemistry currently. The use of environmentally benign solvent instead of traditional organic solvents is the important and efficient strategy in green chemistry. Water is a promising green solvent for use in chemistry because it is cheap, readily available, and nontoxic. There is increasing recognition that organic reactions carried out in water may offer advantages over those in organic solvents.<sup>8-11</sup> However, the poor solubility of reactants in water is the main obstacle to the

use of water as reaction solvent.<sup>12</sup> In previous studies, many additives, such as ionic liquid (ILs), poly(ethylene glycol) (PEG), and sodium dodecyl sulfate (SDS) have been successfully applied in cross-coupling reaction of arylboronic acid with carboxylic derivative as useful promoters.<sup>13-15</sup> As a part of our program aiming at developing selective and environmental friendly methodologies for the preparation of fine chemicals and in continuation of our interest in PEG or ionic liquid promoted organic reactions, in this paper, we report on the evaluation of Hantzsch's dihydropyridine synthesis in the H<sub>2</sub>O-PEG system. The method is straightforward and the 1,4-dihydropyridines can be synthesized under mild reaction conditions in high yields in short reaction times.

### RESULTS AND DISCUSSION

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of DHPs, we employed the condensation reaction of benzaldehyde, ethyl acetoacetate and NH<sub>4</sub>HCO<sub>3</sub> as the model reaction. The reactions were carried out in H<sub>2</sub>O at 60 °C for 5 h in the presence of PEG, an inexpensive and eco-friendly catalyst. The separation of the products was easily performed by the extraction with ethyl ether.

As can be seen from Table 1, the Hantzsch reaction was less active in the pure H<sub>2</sub>O under the reaction conditions

**Table 1.** Effect of the amount of PEG1000 on the Hantzsch condensation reaction in aqueous media


| Entry | PEG1000 : H <sub>2</sub> O (g) | PEG (mol%) | Yield (%) <sup>b</sup> |
|-------|--------------------------------|------------|------------------------|
| 1     | 0 : 3.0                        | 0          | 82.6                   |
| 2     | 0.1 : 2.9                      | 0.03       | 86.0                   |
| 3     | 0.3 : 2.7                      | 0.1        | 92.3                   |
| 4     | 0.5 : 2.5                      | 0.18       | 89.7                   |
| 5     | 1.0 : 2.0                      | 0.5        | 86.6                   |
| 6     | 1.5 : 1.5                      | 0.94       | 85.4                   |
| 7     | 2.0 : 1.0                      | 2.0        | 82.6                   |
| 8     | 3.0 : 0                        | 100        | 71.4                   |
| 9     | 0.3 : 2.7 <sup>c</sup>         | 0.1        | 92.9                   |

<sup>a</sup>Reaction condition: ArCHO (0.106 g, 1.0 mmol), ethyl acetoacetate (0.260 g, 2.0 mmol), NH<sub>4</sub>HCO<sub>3</sub> (0.119 g, 1.5 mmol), 60 °C, 5 h.

<sup>b</sup>Isolated yield. <sup>c</sup>Isolated yield under N<sub>2</sub>.

and only 82.6% of the expected product was obtained (Table 1, entry 1). To improve the yield and optimize the reaction conditions, PEG1000 as catalyst was added and found that the addition of incremental amounts of PEG1000 led to a very rapid increase in the activity. A maximum (92.3%) was obtained when the ratio of PEG1000 and H<sub>2</sub>O was 0.3 : 2.7 g (Table 1, entry 3). Further addition of PEG1000 led to a decrease of the yield (Table 1, entries 3-7). On the other hand, lower yield (71.4%) was obtained when using neat PEG1000 as the solvent (Table 1, entry 8). The reaction under nitrogen presented the similar yields of desired product (Table 1, entry 9). It was found that catalytic amount (0.1 mol%) of PEG1000 was sufficient to catalyze the reaction effectively (Table 1).

The effect of various PEG on the condensation reaction was screened and the results were presented in Table 2. PEG400, PEG600 delivered a moderate yield, while PEG6000, PEG10000 exhibited good efficiency on the Hantzsch reaction (Table 2, entries 1, 2, 6, 7). Among the PEG species tested, PEG1000 and PEG2000 showed better efficiency (Table 1, entries 3 and 4), and the best yield of desired product was obtained using PEG1000. Therefore PEG1000 was used as the source of PEG throughout the studies. In addition, the yields of the reaction were found to be dependent on the nitrogen source (Table 2), and a number of N-sources were tested, including liq. NH<sub>3</sub>, (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>, NH<sub>4</sub>HCO<sub>3</sub> and NH<sub>4</sub>OAc. Liquid ammonia was used generally in classical Hantzsch reaction. However, it was found to be not a desired N-source without N<sub>2</sub> due to its strong volatility (Table 2, entry 10). Ammonium carbonate (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> yield good yield of DHP for ben-

**Table 2.** Effect of different PEG and the source of N on the Hantzsch condensation reaction

| Entry | PEG (0.1 mol%) | N-source   | Yield (%) |
|-------|----------------|--|-----------|
| 1     | PEG400         | NH <sub>4</sub> HCO <sub>3</sub> (1.5 eq)                | 78.1      |
| 2     | PEG600         | NH <sub>4</sub> HCO <sub>3</sub> (1.5 eq)                | 80.0      |
| 3     | PEG1000        | NH <sub>4</sub> HCO <sub>3</sub> (1.5 eq)                | 92.3      |
| 4     | PEG2000        | NH <sub>4</sub> HCO <sub>3</sub> (1.5 eq)                | 90.1      |
| 5     | PEG4000        | NH <sub>4</sub> HCO <sub>3</sub> (1.5 eq)                | 80.2      |
| 6     | PEG6000        | NH <sub>4</sub> HCO <sub>3</sub> (1.5 eq)                | 74.9      |
| 7     | PEG10000       | NH <sub>4</sub> HCO <sub>3</sub> (1.5 eq)                | 69.5      |
| 8     | PEG1000        | NH <sub>4</sub> HCO <sub>3</sub> (1.0 eq)                | 88.2      |
| 9     | PEG1000        | NH <sub>4</sub> HCO <sub>3</sub> (2.0 eq)                | 92.4      |
| 10    | PEG1000        | Liq NH <sub>3</sub> (1.5 eq)                             | 50.1      |
| 11    | PEG1000        | (NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub> (1.5 eq) | 85.3      |
| 12    | PEG1000        | NH <sub>4</sub> OAc (1.5 eq)                             | 90.9      |

Reaction condition: ArCHO (0.106 g, 1.0 mmol), ethyl acetoacetate (0.260 g, 2.0 mmol), H<sub>2</sub>O (2.7 g), PEG (0.1 mol%), 60 °C, 5 h.

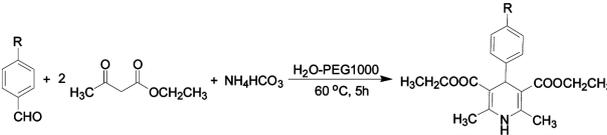
zaldehyde (85.3%) (Table 2, entry 11). NH<sub>4</sub>HCO<sub>3</sub> and NH<sub>4</sub>OAc (Table 2, entry 12) were better N-sources and NH<sub>4</sub>HCO<sub>3</sub> showed maximum yield (92.3%) in 5 h with smaller by-products (Table 2, entry 3). This could be due to differential rates of release of ammonium ions. Increasing the concentration of ammonium acetate caused a significant increase in the yield of DHP, and 1.5 eq. NH<sub>4</sub>HCO<sub>3</sub> was chosen as the nitrogen source (Table 2, entries 3, 8, 9).

With this optimistic result in hand, we further investigated the best reaction conditions by observe the effect of temperature and reaction time. The increase of temperature from 40 °C, 60 °C to 80 °C has a positive effect on the Hantzsch reaction (Table 3, entries 1-3), but the by-product of reaction increased at 80 °C. The high temperature (100 °C, 110 °C) led to the decreasing of the yields (Table 3, entries 4, 5). The yield of Hantzsch reaction was found

**Table 3.** Effect of time and temperature on the Hantzsch condensation reaction

| Entry | Time(h) | T (°C) | Yield (%) |
|-------|---------|--------|-----------|
| 1     | 5       | 40     | 79.3      |
| 2     | 5       | 60     | 92.3      |
| 3     | 5       | 80     | 92.8      |
| 4     | 5       | 100    | 86.6      |
| 5     | 5       | 110    | 69.1      |
| 6     | 2       | 60     | 58.7      |
| 7     | 4       | 60     | 87.2      |
| 8     | 6       | 60     | 93.0      |
| 9     | 8       | 60     | 79.3      |
| 10    | 10      | 60     | 68.9      |

Reaction condition: ArCHO (0.106 g, 1.0 mmol), ethyl acetoacetate (0.260 g, 2.0 mmol), NH<sub>4</sub>HCO<sub>3</sub> (0.119 g, 1.5 mmol), H<sub>2</sub>O (2.7 g), PEG1000 (0.1 mol%).

**Table 4.** Hantzsch reactions of aldehydes with ethyl acetoacetate, and ammonia


| Entry | R                 | Yield (%) |
|-------|-------------------|-----------|
| 1     | OCH <sub>3</sub>  | 88.0      |
| 2     | CH <sub>3</sub>   | 89.7      |
| 3     | OH                | 85.7      |
| 4     | H                 | 92.3      |
| 5     | F                 | 91.9      |
| 6     | Cl                | 90.3      |
| 7     | COCH <sub>3</sub> | 92.8      |
| 8     | CF <sub>3</sub>   | 94.4      |

Reaction condition: Aldehyde (0.106 g, 1.0 mmol), ethyl acetoacetate (0.260 g, 2.0 mmol), NH<sub>4</sub>HCO<sub>3</sub> (0.119 g, 1.5 mmol), H<sub>2</sub>O (2.7 g), PEG1000 (0.1 mol%).

to be a dependency on the reaction time. A prolongation of reaction time to 6 h led to a slight increase in yield of desired product (Table 3, entry 8), whereas longer time up to 8 h and 10 h lead to the occurrence of new by-product. After certain optimization work on the reaction, the optimal reaction conditions for this three-component reaction utilized catalytic amount of PEG1000 (0.1 mol%) in water at 60 °C for 5 h.

The scope and limitations of this condensation reaction were studied as shown in Table 4. Under the standard reaction conditions, the reaction between various aryl aldehydes, ethyl acetoacetate and NH<sub>4</sub>HCO<sub>3</sub> in the presence of catalytic amount of PEG1000 in aqueous medium at 60 °C underwent smoothly and delivered good yields (Table 4). It is worth note that the aqueous system was tolerated to a broad range of functional groups, such as Me, OMe, OH, F, Cl, COMe and CF<sub>3</sub>. Moderate yields were obtained for the electron-rich aryl aldehydes (Table 4, entries 1-3). The electron-deficient aryl aldehydes showed an excellent reactivity and furnished the products in high yields in short reaction times in the H<sub>2</sub>O-PEG system (Table 4, entries 7, 8). F and Cl led to the slight effect on the reactivity (Table 4, entries 5, 6).

## EXPERIMENTAL SECTION

### General

Starting materials and solvents were purchased from common commercial sources and were used without additional purification. <sup>1</sup>H NMR spectra were recorded at 400 MHz, using TMS as internal standard. Mass spectroscopy

data of the product of Hantzsch reaction was collected on a MS-EI instrument.

### Typical experimental procedure for the synthesis of 1,4-dihydropyridines in H<sub>2</sub>O-PEG1000

In a 50 mL round-bottom flask, aryl aldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol) and NH<sub>4</sub>HCO<sub>3</sub> (1.5 mmol) were stirred in presence of PEG (0.1 mol%) in H<sub>2</sub>O at 60 °C for the indicated time. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction solution was cooled to room temperature. The resulted suspension was extracted with diethyl ether (5 mL) with four times, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to give crude product. The pure product was obtained by crystallization from EtOH.

## CONCLUSIONS

In conclusion, we have successfully developed a simple, economical and environmentally benign synthesis of 1,4-dihydropyridine derivatives from the reaction of different aryl aldehydes, ethyl acetoacetate and ammonium acetate at 60 °C using PEG as catalyst. The catalytic activity of PEG1000 is remarkable for the synthesis of 1,4-DHPs. Further investigations into the scope of such reactions are underway.

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