An efficient one-pot multicomponent synthesis of 1,4-dihydropyridines catalyzed by guanidine hydrochloride

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Abstract. Guanidine hydrochloride has been successfully used in one-pot three component assembly of aromatic aldehyde, ethyl acetoacetate and ammonium acetate to produce 1,4-dihydropyridines. Optimization of reaction conditions revealed that 10 mol% guanidine at room temperature for 4 h in ethanol is the best condition for synthesis of compound $4a$ in 85% yield. Furthermore, compound $4b$ was synthesized and obtained in 62%.

Keywords: 1,4-dihydropyridine, guanidine HCl, multicomponent.

1. Introduction
In the recent decades, nitrogen-containing heterocyclic compounds especially with five- and six-membered ring have displayed powerful pharmacological activities [1]. This fact has influencing the development of new reaction protocols to produce diversity-oriented products through an effective synthetic scheme [2]. Multicomponent reactions (MCRs) are one of the most useful tools in organic synthesis that provide quick access to heterocyclic frameworks [3]. They have attractive features such as high atom economy, time and energy efficiency, practical and environmentally friendly [4,5]. Up to now, many organic reactions have been performed using MCRs strategy, such as Biginelli condensation [6], Kabachnik-Field reaction [7], Knoevenagel-induced domino reaction [8] and 1,3-dipolar cycloaddition based MCRs [9-12]. Therefore, the usefulness of MCRs has enamored a considerable interest from synthetic chemists.

1,4-Dihydropyridine derivatives (DHPs) are widely known to show various biological significances [13]. They have shown antimicrobial [14], antidiabetic [15], anticancer [16] and anti-inflammatory [17] activities. Successful development of 1,4-DHPs has been proven by the availability of some commercial drugs containing 1,4-DHP moieties for treatment of hypertension and cardiovascular diseases, such as nifedipine, felodipine and amlodipine [18]. Because of their widespread of biological activities, numerous strategies have been improved from the classical Hantzsch condensation, such as using microwave irradiation [19], trichloroisocyanuric acid in water media [20], visible light in ethanol [21] and melamine trisulfonic acid [22]. However, some of the reported methods suffer from low product yields, use of excessive or harmful organic solvents, or long reaction time requirement. In continuation of our effort to develop more efficient synthetic protocols for MCRs, herein we reported the use of catalytic amount of guanidine HCl in 1,4-DHPs synthesis.

2. Materials and methods

2.1. General
All chemicals were bought from commercial suppliers, such as Sigma Aldrich and Merck. Thin-Layer Chromatography (TLC) analysis was performed on silica gel Si-Gel 60 F$_254$ coated on alumina sheet.
Table 1. Optimization of reaction conditions\textsuperscript{a} in 1,4-DHP synthesis

| Entry | Catalyst (mol\%) | T (°C) | Time (h) | Solvent     | Yield\textsuperscript{b} (%) |
|-------|------------------|--------|----------|-------------|-----------------------------|
| 1     | -                | rt     | 3        | Ethanol     | 38                          |
| 2     | 2.5              | rt     | 3        | Ethanol     | 58                          |
| 3     | 5                | rt     | 3        | Ethanol     | 61                          |
| 4     | 10               | rt     | 3        | Ethanol     | 77                          |
| 5     | 20               | rt     | 3        | Ethanol     | 68                          |
| 6     | 10               | 50     | 3        | Ethanol     | 79                          |
| 7     | 10               | 60     | 3        | Ethanol     | 76                          |
| 8     | 10               | 70     | 3        | Ethanol     | 56                          |
| 9     | 10               | rt     | 0.5      | Ethanol     | 45                          |
| 10    | 10               | rt     | 1        | Ethanol     | 48                          |
| 11    | 10               | rt     | 2        | Ethanol     | 47                          |
| 12    | 10               | rt     | 4        | Ethanol     | 85                          |
| 13    | 10               | rt     | 3        | Water       | 11                          |
| 14    | 10               | rt     | 3        | -           | 51                          |

\textsuperscript{a}Cinnamaldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1 mmol)

\textsuperscript{b}Isolated Yield

Maximum absorption of products was measured on Shimadzu 2450 UV-Vis spectrophotometer. Fourier Transform Infrared (FTIR) spectra were recorded on Shimadzu Prestige-21 spectrophotometer. Confirmation of organic product was done by Gas Chromatography and Mass Spectrometry (GC-MS).

2.2. Synthesis of 1,4-dihydropyridines using guanidine HCl
In 20 mL round-bottom flask, cinnamaldehyde (1a, 1 mmol), ethyl acetoacetate (2, 2 mmol), ammonium acetate (3, 1 mmol) in ethanol (2 mL) were stirred along with guanidine hydrochloride (2.5 mol %) at room temperature for 3 h. Solvent was volatilized, then crude result was refined through crystallization from hot ethanol to afford (E)-diethyl-2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (4a) in 48 % yield (table 1, entry 2). To obtain optimized conditions, temperature, time, solvent, and catalyst amount were varied. Compound 4b was also synthesized using benzaldehyde instead of cinnamaldehyde under optimized protocol.

3. Results and discussion
The results of optimization of reaction conditions are given in table 1. Optimization of reaction conditions was performed using cinnamaldehyde, ethyl acetoacetate and ammonium acetate as substrates and subjected for one-pot three component reaction. For control experiment, we conducted the synthesis in the absence of guanidine hydrochloric acid as catalyst. As expected, low yield (38 %) was obtained (table 1, entry 1). Then, the reaction was attempted with the presence of 2.5 to 20 mol% of catalyst in ethanol at room temperature.

The desired product reached 77 % when 10 mol% of catalyst used. Unfortunately, using 20 mol% of catalyst was ineffective with yield of product of 68 % only. It is noteworthy that increasing temperature did not give better yield. When the reaction was allowed to stir for longer time (4h) at room temperature in ethanol in the presence of 10 mol% catalyst, compound 4a was isolated in 85 %. To our delight, this is the best result among the screened conditions. We have also synthesized
Figure 1. FT-IR spectra of compound 4a and 4b

Figure 2. Mass spectra of compound 4a and 4b
compound 4b using benzaldehyde, ethyl acetooacetate and ammonium acetate under the best conditions. The yield of this product was found to be 62%.

FTIR spectra of compound 4a and 4b are depicted in figure 1. These compounds have similar absorption characteristics. A sharp peak appeared at 3347 cm⁻¹ indicates the presence of secondary amine group. Several absorptions around 3017–3030 cm⁻¹ are due to olefinic and aromatic C-H having sp hybridization. The band around 2850–2950 cm⁻¹ is corresponding to C-H sp² stretching vibration. Meanwhile, sharp absorption at around 1639–1687 cm⁻¹ is caused by the stretching vibration of C=O as well as C=C bond. Compound 4a and compound 4b have maximum absorption at 353 and 354 nm, respectively.

Confirmation of product structure was done by gas chromatography-mass spectrometry (figure 2). Compound 4a with relative molecular formula of C₇H₇NO₂ is appeared as single peak in GC chromatogram (retention time of 13.94 min); and has m/z value of 355.3 after analysis by mass spectrometer. Compound 4b has m/z value of 329.1, appropriate with molecular formula of C₇H₆NO₂.

4. Conclusions
This work highlighted the use of guanidine as an organic basic catalyst for an efficient synthesis of 1,4-dihydropyridines by the method of multicomponent reaction. Easy work-up and mild condition are the advantages of this method. Compound 4a and 4b were obtained in 85% and 62% yield, respectively.

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