

An efficient and eco-friendly synthesis of 1,4-dihydropyridines via Hantzsch reaction in Glycine-HCl buffer as solvent and bio-catalyst

Ali Reza Molla Ebrahimlo^{*}, Mounes Hanafroush and Roya Attari

Department of Chemistry, Islamic Azad University, Khoy Branch, P.O. Box 58168–44799, Khoy, Iran

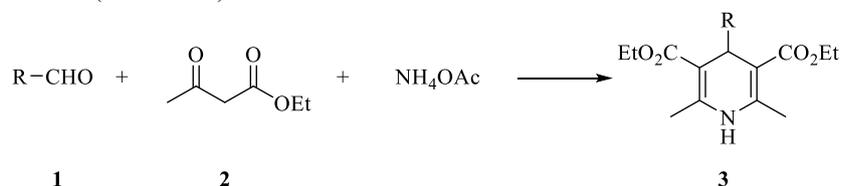
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Abstract: A green and efficient procedure was established to synthesize 1,4-dihydropyridines via one-pot Hantzsch reactions in buffering conditions without the use of organic solvent. In this method, Glycine-HCl buffer solution was used as solvent and catalyst reaction; therefore, using this method has several benefits including high yields, an environmentally friendly procedure, short reaction times, and a simple work-up procedure. All the compounds were characterized by TLC, FT-IR, ¹H NMR and elemental studies.

Keywords: Hantzsch reaction; 1,4-dihydropyridines; glycine-HCl buffer; green procedure. ©2019 ACG Publication. All right reserved.

1. Introduction

1,4-Dihydropyridines (1,4-DHPs) are an significant class of bioactive molecules, well known for their role as calcium channel modulators and used widely for the treatment of hypertension¹⁻³. The derivatives of 1,4-DHPs have shown a variety of biological activities such as vasodilator, bronchodilator, antitumor, hepatoprotective and geroprotective activity^{4,5}. Commercial drugs such as Nifedipine which are a prototype of the 1,4-DHP structure has been used extensively in both antianginal and antihypertensive treatment⁶. Hantzsch reported the first synthesis of dihydropyridine in 1882 in the course of developing his beneficial synthetic method for pyridine⁷. This reaction produces 1,4-dihydropyridines, as isolable intermediates, that can then be oxidized to pyridines. The Hantzsch synthesis of dihydropyridines has been revisited by many chemists over the years. This synthesis allows the efficient preparation of 1,4-dihydropyridines (**3**) through a one-pot multicomponent condensation reaction of an aldehyde (**1**), ethylacetoacetate (**2**) and ammonium acetate performed at 80°C under solvent-free conditions⁷ (Scheme 1).



Scheme 1. Hantzsch's synthesis of dihydropyridine (**3**)

* Correspondin author: E-Mail: E-mail: mollaebrahimilo@yahoo.com

A number of modified methods have been reported in the literature for this condensation which involve the use of various catalysts such as ionic liquids⁸ TMSI⁸, Yb(OTf)₃⁸, CAN¹¹, silica gel/NaHSO₄¹² and Sc(OTf)₃¹³. In addition to the aforementioned catalysts, nanocatalysts such as Ni nanoparticles¹⁴, Ru/Al₂O₃ nanocatalyst¹⁵, magnesium oxide nanotubes (NT)¹⁶, nano Fe₃O₄¹⁷⁻¹⁹ have shown the exclusive application and properties. Also enzymes were used as catalysts for Hantzsch 1,4-DHP synthesis. *Candida antarctica* lipase B (CAL-B) catalysed three-component Hantzsch-type reaction of aldehyde, acetamide, and 1,3-dicarbonyl compounds which also used as solvent was reported by Wang et al²⁰. Likewise urease was found to be an efficient biocompatible catalyst for synthesis of 1,4-DHPs in water via urea/ammonium-based Hantzsch reaction²¹. Recently, the progress of modified Hantzsch reactions in aqueous medium, solvent-, and/or catalyst-free synthesis has attracted the consideration of chemists because they are environmentally benign processes^{22,23}. Considering the importance of Hantzsch reaction and the diverse applications of 1,4-DHPs and the limitation with the previous synthetic routes and our earlier interest in green procedures of one-pot multicomponent reactions, here, we report an efficient and green procedure for the Hantzsch reaction by one-pot cyclocondensation of aldehydes, ammonium salts, and β -keto esters under organic solvent-free conditions.

2. Experimental

2.1. Chemical material and apparatus

All substrates were obtained from Merck of the highest quality and were used without further purification. ¹HNMR spectra were recorded with a Bruker UltraShield spectrometer at 400 MHz. The spectra were measured in CDCl₃, using TMS as the internal standard. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) FT-infrared spectrometer, using KBr disks. Agilent 1200 Series HPLC System was used for the unreacted reactant determination.

2.2. Chemistry

2.2.1. Preparation of glycine buffers

For preparation of glycine buffers were used of solutions of Glycine (0.2M), HCl (0.2M) and NaOH (0.2M). (See supporting information).

2.2.2. General procedure for the one-pot Hantzsch reaction in buffer solution

A mixture of aldehyde (1 mmol), alkyl acetoacetate (2 mmol) and anhydrous ammonium carbonate (1 mmol) was stirred in buffer solution (pH=2.2, 3 mL) at 50–65 °C. After completion of the reaction (TLC monitoring), the mixture was diluted with cold H₂O (5 mL) and filtered to remove the precipitated product which was further purified by recrystallization from EtOH/H₂O.

3. Results and Discussion

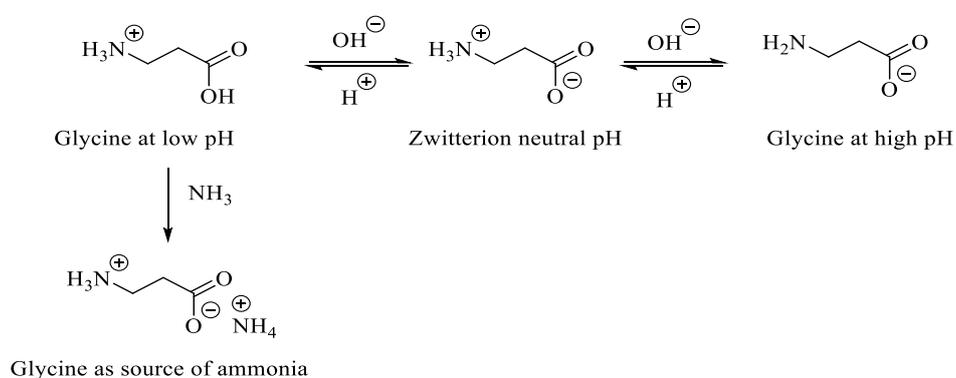
Tamaddon and co-worker reported²⁴ the synthesis of 1,4-dihydropyridines using ammonium carbonate with high yield at long reaction times. Also, Kumar and co-worker presented²⁵ catalytic efficiency of glycine nitrate (GlyNO₃) ionic liquid under microwave (MW) irradiation for the synthesis of symmetrical and unsymmetrical 1,4-DHPs, in which the yield of the reaction in the water was very low. We herein introduce a convenient, inexpensive and efficient synthetic method in glycine-HCl buffer as a solvent and biocatalyst. So, to optimize the pH of glycine buffer, in initial experiments, benzaldehyde, ethyl acetoacetate, and ammonium carbonate (molar ratio was 1:2:1) were used as model reactants in the different pH (Table 1). As shown in Table 1, generally, in alkaline buffers offered less efficiency and lower yields (entries 1 and 2), but the reaction proceeded in a considerably high yield under acidic buffer conditions due to glycine and low pH.

Table 1. Effect of different pH buffer on one-pot Hantzsch reaction.

Entry	Buffer pH	Time (Min)	Temperature (°C)	Yield (%) ^d
1	10 ^a	60	55-60	30
2	9 ^a	45	55-60	54
3	6 ^b	30	55-60	65
4	3.6 ^c	15	55-60	65
5	3 ^c	15	55-60	85
6	2.2 ^c	10	55-60	97

^aGlycine-NaOH buffer; ^bGlycine solution; ^cGlycine-HCl buffer; ^dIsolated yield

As regards, ammonium carbonate is decomposed into water and ammonia by heat and ammonia is released from the reaction medium, As a result, efficiency decreases. In our method, ammonia is absorbed by glycine in low pH, thus preventing the release of ammonia. Therefore, in the open system and at high temperature, the amount of ammonia in the solution remains constant (Scheme 2).

**Scheme 2.** Behavior of glycine with changing pH

Less leaks of the ammonia of this procedure are not only facilitated for the Hantzsch reaction but also has the potential application for others with easy decomposition and/or malodorous reactants such as ammonium salts, including NH_3 . From the results of Table 1, it could easily be seen that entry 6 has high yielding compared other entries. The reaction temperature might range from 0 to 90 °C, below the boiling point of water. Therefore, the effect of temperature on the reaction was investigated. The results listed in Table 2 showed that the reaction temperature does not have much effect on the efficiency and reaction time. So, the reaction temperature was 50-65 °C, and this open system would not only prevent the loss of the ammonium salts and environmental pollution but also proved satisfactory with respect to reaction time and yield of the desired 1,4-DHPs.

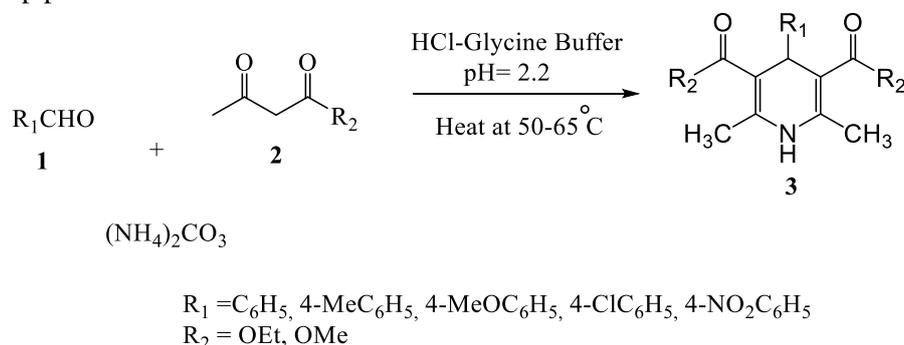
Table 2. Effect of reaction temperature on Hantzsch reaction in pH=2.2

Entry	Time (Min)	Temperature (°C)	Yield (%) ^a
1	10	45-50	96
2	10	50-65	97
3	10	65-70	94
4	10	70-75	94
5	10	75-80	93
6	10	85-90	93

^aIsolated yield

After the completion of the reaction, 1,4-DHPs were isolated by simple filtration. The filtrate containing the excess unreacted reactant (ranged from 2% to 5% determined by HPLC) was used in the next cycle without further treatment. The Hantzsch reactions of various aromatic aldehydes with ethyl- or methyl acetoacetate and Ammonium carbonate were performed based on the optimized conditions to yield respective 1,4-DHPs (Scheme 3), and the results are presented in Table 3. In all cases, good yields

ranging from 75% to 98%. Aromatic aldehydes possessing either electron-donating or electron-withdrawing substituents afforded good yields of 1,4-DHPs in high purity. An important feature of this method is the reuse of the buffer solution for other reactions. Therefore, this procedure has the advantages such as high yields, an environmentally friendly procedure, short reaction times, and a simple work-up procedure.



Scheme 3. Synthesis of 1,4-dihydropyridines in Glycine-HCl buffer (pH=2.2)

Table 3. Glycine-HCl buffer (pH=2.2) catalyst and organic solvents-free synthesis of 1,4-dihydropyridines

Entry	R ₁	R ₂	Compound	Time (min)	Yield (%) ^a	Mp(°C)found (reported)
1	C ₆ H ₅	OEt	3a	10	97	154-157(156-157) ²⁶
2	4-MeC ₆ H ₅	OEt	3b	15	85	134-136(136-137) ²⁷
3	4-MeOC ₆ H ₅	OEt	3c	30	78	159-162(158-160) ²⁸
4	4-ClC ₆ H ₅	OEt	3d	10	98	144-145(145-146) ²⁶
5	4-NO ₂ C ₆ H ₅	OEt	3e	10	98	129-131(128-130) ²⁹
6	C ₆ H ₅	OMe	3f	10	93	194-196(196-198) ²⁸
7	4-MeC ₆ H ₅	OMe	3g	20	75	174-176 (175-177) ²⁸
8	4-MeOC ₆ H ₅	OMe	3h	30	75	186-189(188-191) ³⁰
9	4-ClC ₆ H ₅	OMe	3i	10	80	194-197(196-198) ³⁰
10	4-NO ₂ C ₆ H ₅	OMe	3j	10	87	195-198(196-198) ³⁰

^aIsolated yield

4. Conclusion

We have developed a rapid, convenient and clean method for synthesis of DHPs under buffering conditions. Notable features of the reported novel methodology are: (a) high efficiency; (b) easy work-up; (c) shorter reaction times; (d) elimination of the use of toxic reagents, organic solvents and inorganic catalysts; and (e) recyclable performance, which has the potential application for the green synthesis.

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Supporting Information

Supporting information accompanies this paper <http://www.acgpubs.org/journal/organic-communications>

ORCID Ali Reza Molla Ebrahimlo: [0000-0002-4473-0107](https://orcid.org/0000-0002-4473-0107)Mounes Hanaforoush: [0000-0002-2367-9971](https://orcid.org/0000-0002-2367-9971)Roya Attari: [0000-0002-5889-6976](https://orcid.org/0000-0002-5889-6976)

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