A Four-Component Cascade Synthesis of Hexahydroquinoline Derivatives at Room Temperature

Rajat Kumar R., Siva Senthil Kumar B*
Sri Ramakrishna Mission Vidyalaya College of Arts and Science, SRKV Post, Coimbatore 6410120.

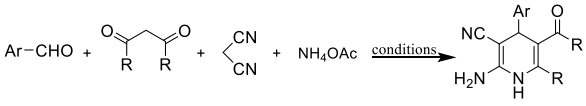
***Abstract*-A sustainable four-component cascade synthesis of hexahydroquinoline derivatives has been developed under mild and environmentally benign conditions. The protocol employs an ethanol–water solvent system at room temperature without the need for catalysts or additives, making the method simple, efficient, and operationally convenient. The reaction proceeds smoothly with a different aldehyde, affording the desired products in good to excellent yields within short reaction times. Compared to traditional approaches, this strategy eliminates harsh reaction conditions, minimizes waste, and aligns with green chemistry principles.**

***Index Terms*— Cascade synthesis, Hantzsch type reaction, Hexahydroquinolines, Multicomponent reactions (MCR), Green solvents.**

I. INTRODUCTION

Nitrogen-based heterocycles have a long and rich history, with extensive applications that make a significant impact on synthetic, medicinal, and industrial chemistry. [1-4] A wide range of natural products, pharmaceuticals, and advanced materials contain heterocyclic frameworks, which are indispensable to humankind. [5] Amon the nitrogen heterocycles, 1,4-dihydropyridines derivatives, constitute an important class of compounds with broad biological activities. [6-7] They exhibit diverse pharmacological properties, including antitumor, calcium channel blocking, antitubercular, analgesic, antithrombotic, anti-inflammatory, anticonvulsant, and antimalarial activities, which has made them highly attractive to researchers (Figure 1).[8-13]

From a green chemistry perspective, the development of efficient multi-component reactions (MCRs) has gained remarkable attention.[14-15] One-pot MCRs are energy-efficient processes that eliminate multiple synthetic steps, enhance productivity, and provide access to molecules with high structural diversity. As tandem reactions, MCRs offer a powerful strategy for building molecular complexity from simple starting materials, while simultaneously avoiding the isolation of unstable intermediates. The first 1,4-dihydropyridines were synthesized through the classical Hantzsch reaction, a multicomponent condensation of aldehydes with ethyl acetoacetate and ammonia in acetic acid or under reflux in ethanol.[16] Over the years, this reaction has been further advanced using a variety of catalysts and conditions, including Lewis/Brønsted acids, ionic liquids, and nanoparticles. [17-22] Catalyst-free approaches have also been explored, often requiring elevated temperatures. Notably, Ganesh U. Chaturbhuj reported a catalyst-free one-pot synthesis of 2-amino-4*H*-chromenes employing ammonium carbonate as an ammonia source. Despite these advancements, there remains significant scope for improvement and modifications, particularly in developing operationally simple methods that minimize reaction time and avoid the use of catalysts. In this work, we present a catalyst-free, mild, and straightforward method for the efficient synthesis of 1,4-dihydropyridine scaffolds from aromatic aldehydes, diketones, malononitrile and ammonium acetate.



Conditions:

Previous works:

a) Sourav et.al., sulphonated rice husk, 60-80 ^{o}C, solvent free
b) D. Patil et.al., H_2O, 100 ^{o}C
c) James L Donelson et.al., $Sc(OTf)_3$, EtOH, RT
d) Mehdi Abaszadeh et.al., Ionic liquid, H_2O/EtOH, Reflux
e) Manoj B. Gawande et. al., Fe-Cu nano catalyst, EtOH, rt

This work:

f) Ethanol/H_2O, RT

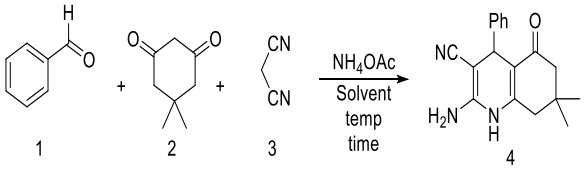
Scheme 1. Previous Works

II. RESULTS AND DISCUSSION

To evaluate the hypothesis, the reaction conditions for the synthesis of dihydropyridine derivatives were systematically optimized using a model reaction

composed of benzaldehyde (1 mmol), dimedone (1.2 mmol), malononitrile (2 mmol) and ammonium acetate (1.5 mmol), with isolated yields recorded for each solvent system. Pure solvents such as water (entry 1) and ethanol (entry 2) provided yields of 81% and 83%, respectively, within a short reaction time. Other organic solvents, including acetonitrile, 1,4-dioxane, DMSO, DMF, and THF (entries 3–7), resulted in moderate to good yields, but generally required longer reaction times for complete consumption of reactants. The highest yield (90%) was observed with a mixture of ethanol and water in a 2:1 ratio at room temperature (entry 8), indicating a synergistic effect between these solvents that enhances the condensation reaction. Adjusting the ethanol-to-water ratio to 1:1 maintained a high yield (86%, entry 9), whereas increasing the temperature to 60°C was not advantageous, reducing the yield to 82% (entry 10). Therefore, the optimized conditions ethanol/water (2:1) at room temperature were selected to further investigate the substrate scope of this protocol (entry 8).

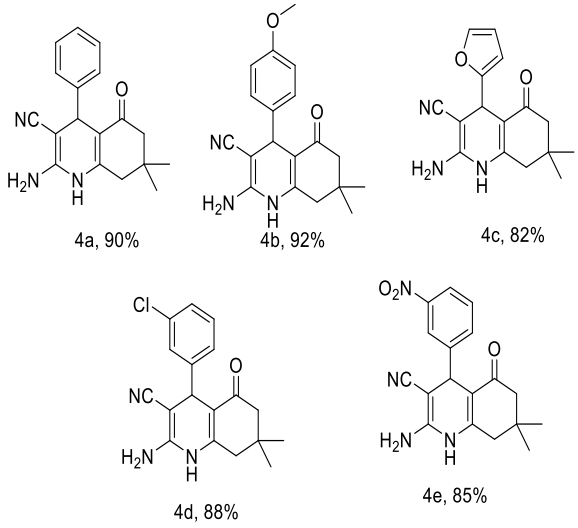
Table 1: Optimization studies



Entry	Solvent	Temp (°C)	Time (min)	Yield [b] (%)
1	H_2O	rt	25	71
2	Ethanol	rt	20	83
3	Acetonitrile	rt	30	77
4	1, 4 dioxane	rt	360	65
5	DMSO	rt	120	75
6	DMF	rt	150	69
7	THF	rt	360	40
8	EtOH/H_2O (2:1)	rt	15	90
9	EtOH/H_2O (1:1)	rt	15	86
10	EtOH/H_2O (2:1)	60	15	82

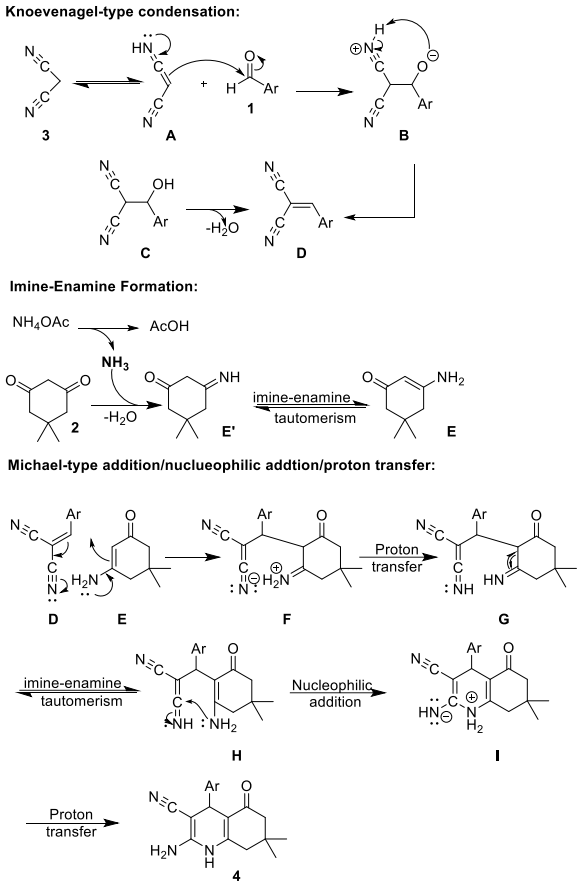
Optimization of reaction conditions: the reaction was performed using benzaldehyde 1 (1 mmol), malononitrile 2 (2 mmol), dimedone 3 (1.2 mmol), ammonium acetate (1.5 mmol), Isolated yield[b]

The substrate scope was systematically explored under optimized conditions and is summarized in Scheme 2. Employing malononitrile and dimedone as constant reactants, different aromatic aldehydes were evaluated. Benzaldehyde (**4a**) reacted efficiently, affording the desired product in a yield of 90%. The 4-methoxy-substituted benzaldehyde (**4b**) also underwent the transformation successfully, delivering a yield of 92%. Notably, furfuraldehyde proved to be a compatible heteroaromatic substrate (**4c**) under the established conditions with 82% yield. Aromatic aldehydes bearing electron-withdrawing substituents, such as chloro (**4d**) and nitro (**4e**) groups, participated well in the reaction, resulting in good yields (88% and 85%, respectively). These findings highlight the robustness of the protocol across a range of electronically varied substrates.



Scheme 2. Substrate Scope

A plausible mechanism for the synthesis of hexahydroquinoline (**4**) is outlined in Scheme XX, involving three discrete steps. In the initial step, arylidenemalononitrile (**D**) is generated through a Knoevenagel-type condensation between an aldehyde (**1**) and malononitrile (**2**). Concurrently, the second step features the formation of enaminone (**E**), which results from the reaction of dimedone (3) with ammonia, the latter being liberated in-situ from ammonium acetate. Subsequently, the intermediates (**D**) and (**E**) participate in a Michael-type addition, followed by nucleophilic attack and proton transfer, ultimately yielding the target compound (4).



Scheme 2. Plausible Reaction Mechanism

III. EXPERIMENTAL PROCEDURE

A 50 mL single-neck round-bottom flask was charged with benzaldehyde (106 mg, 1.0 mmol), malononitrile (132 mg, 2.0 mmol), dimedone (140 mg, 1.0 mmol), and ammonium acetate (115 mg, 1.5 mmol) in ethanol/water (2:1, 3 mL). The reaction mixture was stirred at room temperature under ambient atmospheric conditions. Progress of the reaction was monitored by thin-layer chromatography (TLC) using a 30% ethyl acetate/hexane solvent system. Upon completion, the reaction mixture was diluted with water and the resulting solid was collected by vacuum filtration. The crude product was washed 3-4 times with ethanol/water (1:1) and dried to afford the pure product as a solid.

IV. CONCLUSION

In this study, we have successfully developed an efficient one-pot multicomponent reaction protocol for the synthesis of hexahydroquinoline derivatives, employing benzaldehyde, malononitrile, dimedone, and ammonium acetate as substrates. This reaction was conducted in an eco-friendly ethanol/water solvent system under mild, room temperature conditions in open air, demonstrating an environmentally benign approach. Given the broad pharmacological, neuroscientific, agrochemical, and medicinal relevance of hexahydroquinoline derivatives, our green synthetic strategy provides a valuable platform for further exploration and application. Continued research into these versatile compounds could uncover novel functionalities and therapeutic potentials, advancing the fields of medicinal chemistry and biological probe development.

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