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An efficient and eco-friendly synthesis of 1,4-dihydro-1,8-naphthyridine-3-carbonitrile derivatives in aqueous media

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ABSTRACT

A green protocol for the synthesis of pharmacologically interesting scaffolds 1,4-dihydro-1,8-naphthyridine-3-carbonitrile derivatives has been developed through one-pot condensation of aromatic aldehyde, malononitrile and 2-amino pyridine using DAHP (Diammmonium hydrogen phosphate) in aqueous ethanol (water 10 mL and ethanol 5 mL) at 85 °C. This efficient and eco-friendly procedure offers various prominent advantages such as mild reaction conditions, excellent yields and easy workup.

Keywords: Multicomponent reaction, 1,4-dihydro-1,8-naphthyridine-3-carbonitrile, DAHP, 2-amino pyridine.

INTRODUCTION

Nitrogen containing heterocyclic compounds found very extensively in nature and are necessary to life. Among the *N*-based heterocycles, pyridine is one of the most important scaffolds constitute the largest portion of chemical articles, which are part of many natural products, biologically active compounds and fine chemicals [1-2].

Naphthyridine derivatives are one of the most significant classes of compounds due to their widespread occurrence as key structural subunits in numerous natural products that exhibit many interesting biological activities. The 1,8-naphthyridine derivatives posses a prominent place in the field

of medicinal chemistry [3] as the presence of two nitrogen atom in the aromatic ring make appropriate linkage sites through hydrogen bonding with microbes. In medicinal chemistry field, many 1,8-naphthyridines are used as antibacterial [4], anti-inflammatory [5], antihypertensive [6] and anticancer activities [7].

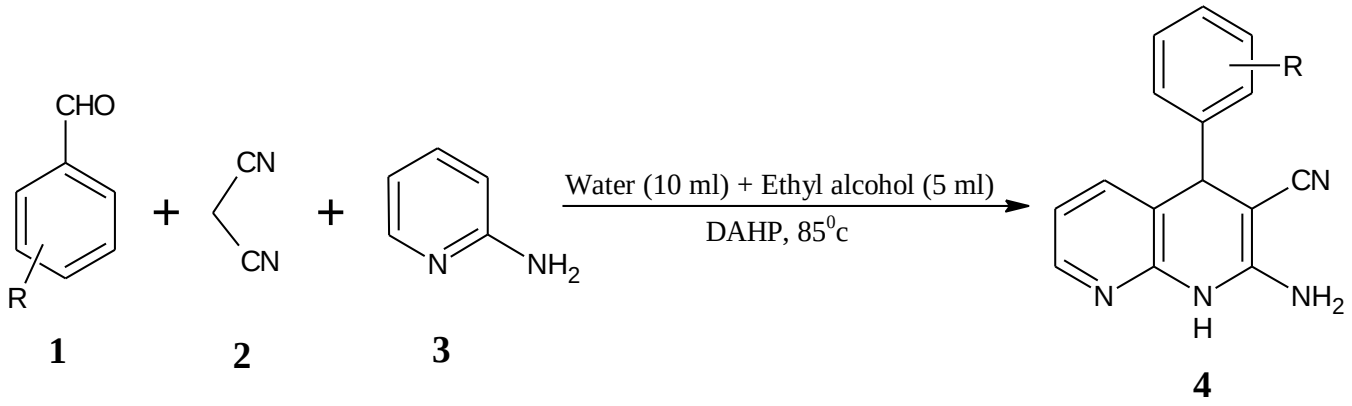
From the wide-ranging literature survey, it has been noted that, various methods are described by number of researchers for synthesis of 1,8-naphthyridines by using different catalyst and solvents such as 85 % H_3PO_3 at 95 °C [8], in ethanol at reflux condition [9], bleaching earth clay (pH 12.5) at 70-80 °C in PEG-400 [10], refluxion in THF [11], bismuth(III) nitrate pentahydrate [$Bi(NO_3)_3.5H_2O$] under solvent-free microwave irradiation [12], Furthermore, Koller *et al.* [13] has reported the synthesis of 7-ethyl-1,8-naphthyridin-2-amine by reaction of 2,6-Pyridinediamine with 1,1-dimethoxybutan-2-one and Mohamed *et al.* [14] have synthesized some 4-hydroxy-1,8-naphthyridin-2(1H)-one derivatives at high temperature.

Despite, the potential utility of these strategies, they exhibit various drawbacks such as harsh reaction conditions, use of toxic organic solvents, expensive catalyst, hazardous catalyst, unsatisfactory yields and cumbersome experimental procedures. Therefore, development of clean and efficient procedure for the synthesis of 1,8-naphthyridines is required.

RESULTS AND DISCUSSIONS

All these literature facts attracted us to develop convenient, efficient and green procedure for the synthesis of 1,8-naphthyridines. Owing to this approach, we have described highly efficient one-pot multicomponent and green protocol for the synthesis of 2-amino-4-phenyl-1,4-dihydro-1,8-naphthyridine-3-carbonitrile derivatives by reaction of aromatic aldehyde **1,** malononitrile **2** and 2-amino pyridine **3** using DAHP (Diammmonium hydrogen phosphate) in aqueous ethanol (water 10 mL and ethanol 5 mL) at 85 °C (Scheme 1).

In trial case, reaction of 4-nitro benzaldehyde **1** (1 mmol) and malononitrile **2** (1 mmol) in 10 mL water with 10 mol % DAHP (Diammmonium hydrogen phosphate) were heated at 85 °C for 5 hour. The progress of the reaction was monitored by TLC. After 5 h heating, the product **4** was obtained in only 50 % yield along with intermediate Knoevenagel condensate and unreacted starting materials (Table 1, entry 1). To investigate ideal reaction condition, when we carried out the reaction in aqueous ethanol (Water 10 mL & ethanol 5 mL) using DAHP (10 mol %), the desired product 2-amino-4-(4-nitrophenyl)-1,4-dihydro-1,8-naphthyridine-3-carbonitrile **4** was achieved in high yield (92 %) after 2 h heating (Table 1, entry 2).



1 **2** **3** **4**

Scheme 1: Synthesis of 2-amino-4-phenyl-1,4-dihydro-1,8-naphthyridine-3-carbonitrile

Table 1 Solvent and catalyst optimization for the synthesis of **4** [a]

Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	Water	DAHP (10)	5	50
2	**Water 10 mL & ethanol 5 mL**	**DAHP (10)**	**2**	**92**
3	Ethanol	DAHP (10)	3	90
4	Water 10 mL & ethanol 5 mL	No catalyst	10	- [c]
5	Water 10 mL & ethanol 5 mL	DABCO	5	66
6	Water 10 mL & ethanol 5 mL	Acetic acid	6	60
8	Water 10 mL & ethanol 5 mL	ZnO nanoparticles	5	30

[a] Reactions of 4-nitrobenzaldehyde **1** (1 mmol), malononitrile **2** (1 mmol) and 2-aminopyridine **3** (1 mmol) were carried out at 85 °C.
[b] Isolated yield, [c] Reaction failed to occur, Bold values indicate optimized reaction conditions.

Table 2 Synthesis of 2-amino-4-phenyl-1,4-dihydro-1,8-naphthyridine-3-carbonitrile derivatives in aqueous media at room temperature [a]

Entry	Aldehyde[1]	Product[4]	Time (h)	Yield [b] (%)
1	4-nitro benzaldehyde	4a	2	92
2	4-chloro benzaldehyde	4a	2	91
3	benzaldehyde	4c	2.5	90
4	4-methyl benzaldehyde	4d	2.5	89
5	4-methoxy benzaldehyde	4e	2.5	88

[a] Reactions of aldehyde **1** (1 mmol), malononitrile **2** (1 mmol) and 2-aminopyridine **3** (1 mmol) were carried out in aqueous ethanol using DAHP at 85 °C. [b] Isolated yield

For further study, this reaction was examined at 85 °C in different solvents with different catalysts resulted in trace or lower yields of **4** (Table 1). Also, the reaction was not performed in absence of catalyst even after prolonged reaction time (Table 1, entry 4). Accordingly, the reaction in aqueous ethanol (Water 10 mL & ethanol 5 mL) using 10 mol % DAHP at 85 °C temperature was selected as the optimal conditions (Table 1, entry 2). All reactions were successfully performed to afford a series of 2-amino-4-phenyl-1,4-dihydro-1,8-naphthyri-dine-3-carbonitrile derivatives with high to excellent yields. The structures of products **4** were assigned by their FTIR, ^{1}H NMR, HRMS spectroscopy and elemental analysis. This spectral data is in agreement with their proposed structures.

EXPERIMENTAL

The progress of reaction was monitored by TLC on Merck TLC silica gel 60 F_{254} plates. All the chemicals used in this process are purchased from Alfa Aesar, Aldrich, and Merck chemical companies and used without any purification. ^{1}H NMR spectra were recorded on 400 MHz Bruker spectrometer using DMSO-d_6 solvent. FT-IR spectra were determined on Thermo Fisher Scientific Nicolet iS-10 FT-IR Spectrometer. Mass spectra were obtained on Shimadzu Toshvin mass spectrometer.

General Experimental Procedure

A mixture of 4-nitrobenzaldehyde **1** (1 mmol) and malononitrile **2** (1 mmol)), 2-aminopyridine **3** (1 mmol) and 10 mole % DAHP in 10 mL water & 5 mL ethanol were heated in a round bottom at 85 °C for for the time specified in Table 2 . Reaction was monitored by TLC. The reaction mixture was cooled, precipitate obtained was then filtered, washed with cold water and finally product was recrystallized from ethanol to afford pure product **4**.

SPECTRAL DATA

2-amino-4-(4-nitrophenyl)-1,4-dihydro-1,8-naphthyridine-3-carbonitrile(4a):
Brown solid, Yield: 92 %, ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.71 (s, J=12 MHz, 1H, CH), 6.90 (d, 1H, NH), 7.55 (s, 2H, NH_2,), 7.69-7.76 (m, 4H, ArH), 8.18-8.23 (m, 3H, ArH); IR (KBr): 3342, 3197, 3083, 2920, 2221, 1662, 1613, 1518, 1460, 1339, 1347, 844, 773, 702 cm^{-1}; HRMS m/z (ESI) : 292.0837 [M-1]; Anal. Calcd for $C_{15}H_{11}N_5O_2$ (%): C (61.43), H (3.78), N (23.88); Found: C (61.56), H (3.82), N (23.84).

2-amino-4-(4-chlorophenyl)-1,4-dihydro-1,8-naphthyridine-3-carbonitrile (4b):
Brown solid, Yield: 91 %, ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.68 (s, J=12 MHz, 1H, CH), 6.90 (d, 1H, NH), 7.49 (s, 2H, NH_2,), 7.51-8.19 (m, 7H, ArH); IR (KBr): 3349, 3190, 3081, 2920, 2231, 1652, 1616, 1534, 1468, 1354, 864, 779, 708 cm^{-1}; HRMS m/z (ESI) : 281.0543 [M-1]; Anal. Calcd for $C_{15}H_{11}ClN_4$ (%): C (63.72), H (3.92), N (19.82); Found: C (63.79), H (3.98), N (19.86).

CONCLUSION

In conclusion, we have developed convenient and efficient procedure for the synthesis of 2-amino-4-phenyl-1,4-dihydro-1,8-naphthyridine-3-carbonitrile scaffolds using DAHP as a green catalyst in aqueous ethanol. The methodology offers several advantages such as greener reaction conditions, simple operation and excellent yields.

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