A CONVENIENT ONE-POT THREE COMPONENT SYNTHESIS OF 1,8-NAPHTHYRIDINE DERIVATIVES

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Abstract: An useful method has been developed for the synthesis of 1,8-naphthyridine derivatives by the reaction of aromatic aldehydes, 2-amino pyridine and malononitrile in presence of ammonium metavanadate as catalyst at room temperature. The mild reaction condition and excellent yield are the notable features of this method.

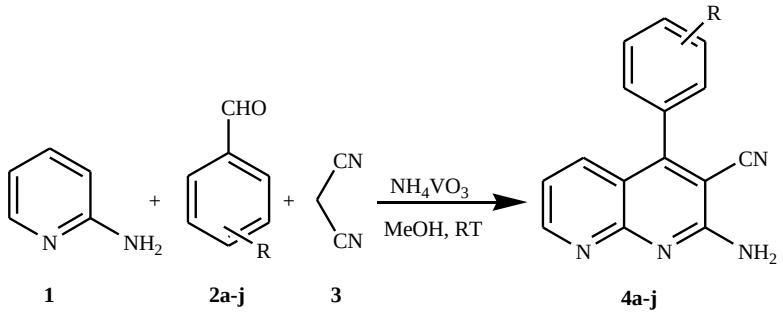
Keywords: 1,8-Naphthyridines, aromatic aldehydes, 2-aminopyridine, malononitrile, ammonium metavanadate.

Introduction

Naphthyridines are of significant class of organic molecules that catch the attention of researcher from synthetic and medicinal chemistry [1]. The highly functionalized derivatives of naphthyridine find application in the medicinal area as antibacterial, anti-inflammatory, antihypertensive and anticancer activities[2]. The naphthrydine derivatives are found to be potent against fungicides, bactericides, herbicides and insecticides as well as helpful synthetic blocks in the preparation of several natural products [3-5]. They have been used in the antibiotics for the diagnostics and chemotherapy of infectious diseases of humans including AIDS [6]. Also 1,8-naphthyridine derivatives have attracted significant attention as a backbone isolated from natural substances with various biological activities [7].

The review of literature reveals the synthesis of 1,8-naphthyridine derivatives involving the condensation of 2-aminopyridine with carbonyl compounds containing an activated methylene group [8-10] or with β-ketoesters [11]. Thus due to immense biological significance, various protocols were reported for synthesis of naphthyridine derivatives utilizing different type of reagents [12-15].

Herein we describe an useful method for synthesis of 1,8-naphthyridine derivatives by the reaction of 2-aminopyridine, aromatic aldehydes and malononitrile in presence of ammonium metavanadate as a catalyst at room temperature condition (**Scheme 1**).



1 **2a-j** **3** **4a-j**

Scheme 1

Experimental

All solvents were utilized as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (80-120 mesh). Melting points were determined in open capillary tube and are uncorrected.

Typical procedure for the synthesis of 1,8-naphthyridine derivatives (4a-j):

In 50 ml round bottom flask, a mixture of 2-aminopyridine (10 mmol), aromatic aldehyde (15 mmol) and malononitrile (10 mmol) was added in solvent methanol (15 ml). Catalytic amount of ammonium metavanadate (0.2mmol) was added. Reaction mixture was stirred at room temperature for appropriate time (Table 2). After the completion of reaction indicated by TLC, reaction mixture was poured in crushed ice. Obtained precipitate was filtered and washed with water to obtain crude product. The crude product was further purified by column chromatography on silica gel (60-120 mesh size) using 20 % ethyl acetate in petroleum ether as eluent to get pure product.

2-Amino-4-(4-chlorophenyl)-1,8-naphthyridine-3-carbonitrile (4a): ^{1}H NMR (300 MHz, $CDCl_3$):δ 5.34 (s, 2H), 7.29-7.38 (m, 3H), 8.01-8.19 (m,4); ^{13}C NMR (75 MHz, $CDCl_3$): _ 95.2, 112.5, 118.0, 123.8, 131.5, 134.9, 138.4, 144.0, 153.6, 159.1, 166.2.

Synthesis of 2-Amino-4-(4-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (4d): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 5.58 (s, 2H), 6.87-7.08 (m, 3H), 7.68-8.04 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 56.5, 93.0, 114.2, 119.5, 120.8, 124.6, 128.8, 133.9, 146.7, 154.2, 162.8.

Result and Discussion:

Firstly, a model reaction of 4-chloro benzaldehyde, 2-aminopyridine and malononitrile was carried out in different solvent using 10 mol % of catalyst ammonium metavanadate at room temperature condition. In solvent DMF, the reaction offered 51% product yield in 7 hours (Table 1, entry 1). The reaction in solvent acetonitrile and ethanol gave 57 % and 74% product yield (Table 1, entry 2 and 3 respectively). Reaction revealed admirable results in solvent methanol, reaction afforded 89% yield in reaction time 2.0 hours (Table 1, entry 4). We found methanol to be the suitable solvent for reaction to synthesis of 1,8-naphthyridine derivatives.

Table 1: Effect of solvent on synthesis of 1,8-naphthyridine derivatives

Entry	NH_4VO_3 (mol %)	Solvent	Time (h)	Yield (%)[a]
1	10	DMF	7.00	51
2	10	CH_3CN	6.30	57
3	10	EtOH	3.30	74
4	10	MeOH	2.00	89

[a]Isolated yield.

Table 2: One-pot Synthesis of 1,8-naphthyridine derivatives

Entry	R	Product	Time (h)	Mp (°C)	Yield (%)[a]
1	H	**4a**	3.00	154-155	81
2	4-OCH_3	**4b**	2.00	163-165	85
3	4-CH_3	**4c**	2.30	166-167	84
4	4-NO_2	**4d**	2.00	175-176	89
5	2-Cl	**4e**	2.30	168-169	87
6	3,4-$(OCH_3)_2$	**4f**	3.00	180-182	86
7	4-Cl	**4g**	2.00	166-167	89
8	3-NO_2	**4h**	2.30	172-173	88
9	4-OH	**4i**	3.30	158-160	86
10	3-OCH_3,4-OH	**4j**	4.00	170-171	87

[a]Isolated yield.

With this optimized condition, we have employed several aromatic aldehydes having different substituents. Result of substituent revealed short distinction in yield and reaction time (Entry 1-10, Table 2).

Conclusion:

In conclusion, our results reveals that ammonium metavanadate is an efficient catalyst for the excellent yield of corresponding 1,8-naphthyridine derivatives. This protocol affords several advantages such as high yield, short reaction time and mild reaction conditions.

Acknowledgement

We are grateful to Dr. S. S. Kadam, Principal, Dr. B. C. Khade, Head, Dnyanopasak College, Parbhani for offering required facilities to research work.

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