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"AN EXPEDIENT APPROACH FOR ONE-POT SYNTHESIS OF 1,8-NAPHTHYRIDINE DERIVATIVES"

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Abstract:

An efficient method has been described for the synthesis of 1,8-naphthyridine derivatives. A reaction of 2-amino pyridine, malononitrile and aromatic aldehydes was carried out in presence of lanthanum chloride as catalyst at room temperature to produce ,8-naphthyridines. The short reaction time, mild reaction condition and excellent yield are the remarkable features of this method.

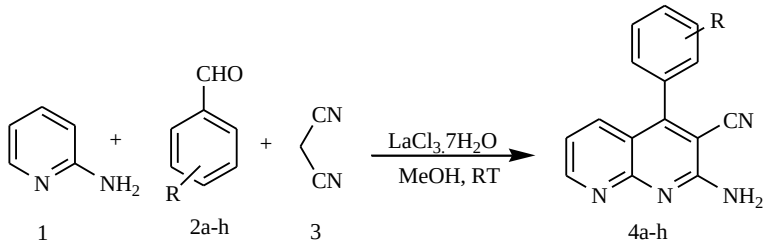
Keywords: *1,8-naphthyridines; 2-aminopyridine; aromatic aldehydes; malononitrile; lanthanum chloride.*

Introduction

Among the nitrogen heterocycles, naphthyridines represent an significant class of organic molecules that attract the interest of both synthetic and medicinal chemists due to their exceptionally wide spectrum of biological activities as well as their use as essential binding units in the molecular design of synthetic receptors [1]. In parallel to the growing interest in the synthesis of 1,8-naphthyridines to provide bioactive molecules, a large number of methods have reported that several of their derivatives possess antibacterial [2], antimycobacterial [3], antitumor [4], anti-inflammatory [5], analgesic [6], antiplatelet [7], local anaesthetic [8], anticonvulsant [9] and antihypertensive activity [10,11].

The literature survey reveals the synthesis of 1,8-naphthyridine derivatives involving the condensation of 2-aminopyridine with carbonyl compounds containing an activated methylene group [12-14]. Thus because of huge biological consequence, various methods were reported for synthesis of naphthyridine derivatives using different type of reagents [15-18].

Herein we describe an efficient method for synthesis of 1,8-naphthyridine derivatives by the reaction of 2-aminopyridine, malononitrile and aromatic aldehydes using lanthanum chloride as a catalyst at room temperature condition (**Scheme 1**).



Scheme 1

Experimental

All solvents were used 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.

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

A mixture of 2-aminopyridine (10 mmol), aromatic aldehyde (15 mmol) and malononitrile (10 mmol) was added in solvent methanol (15 ml). Lanthanum chloride (10 mol %) was added as catalyst. 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.

Synthesis of 2-Amino-4-phenyl-1,8-naphthyridine-3-carbonitrile (4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.89 (s, 2H), 6.62 (d, 1H), 6.93 (d, 1H), 7.45-7.62 (m, 4H), 8.20 (d, 1H); ^{13}C-NMR ($CDCl_3$): δ 115.2, 119.8, 125.3, 127.0, 127.9, 129.8, 130.1, 133.4, 138.1, 141.0, 145.4, 157.1, 160.5, 168.7, 173.2.

Synthesis of 2-Amino-4-(4-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (4e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 5.52 (s, 2H), 7.02-7.12 (m, 3H), 7.87-8.24 (m, 5H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 55.8, 94.2, 112.4, 119.3, 121.0, 125.2, 128.9, 133.8., 145.6, 154.2, 160.5.

Result and Discussion:

Initially, a model reaction of 2-aminopyridine, 3-nitrobenzaldehyde and malononitrile was carried out in different solvent using 10 mole % of catalyst at room temperature condition. In the solvent acetonitrile, 56% product yield was observed in 6 hours (Table 1, entry 1). Then, we used solvent DMF and DCM at room temperature which gave 48 % and 34 % product yield with extended reaction time (Table 1, entry 2 and 3 respectively). In solvent ethanol, reaction offered 75 % yield in 3.5 hours (Table1, entry 4). Reaction showed excellent results in solvent methanol, reaction afforded 87 % yield in reaction time 2.0 hours (Table 1, entry 5). 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	$LaCl_3.7H_2O$ (mol %)	Solvent	Temperature	Time (h)	Yield (%)[a]
1	10	CH_3CN	RT	6.00	56
2	10	DMF	RT	7.20	48
3	10	DCM	RT	8.00	34
4	10	EtOH	RT	3.50	75
5	10	MeOH	RT	2.00	87

[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**	3.50	154-155	80
2	3-NO_2	**4b**	2.00	170-172	87
3	4-Cl	**4c**	2.20	166-167	89
4	3,4-$(OCH_3)_2$	**4d**	2.40	180-182	88
5	4-OCH_3	**4e**	2.50	163-165	86

6	4-NO_2	**4f**	2.00	173-175	88
7	4-CH_3	**4g**	2.60	166-167	84
8	2-Cl	**4h**	2.50	170-172	89

[a]Isolated yield.

With the optimized method, we have used other aromatic aldehydes having different substituents. Result of substituent revealed short distinction in yield and reaction time (entry 1-8, Table 2).

Conclusion: In conclusion, our results demonstrate that lanthanum chloride is useful catalyst for the excellent yield of 1,8-naphthyridine derivatives. This method offers several advantages such as short reaction time, high yield and mild reaction conditions.

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