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Phenylboronic Acid Promoted an Efficient One-pot Synthesis of 2-Amino-4-Phenyl-1,8-Naphthyridine-3-Carbonitriles

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Abstract: A convenient one-pot synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives has been developed using phenylboronic acid as catalyst at room temperature. The short reaction time, mild reaction condition and high yield are the features of this method.

Keywords: 2-Amino-4-phenyl-1,8-naphthyridine-3-carbonitriles, aromatic aldehydes, 2-aminopyridine, phenylboronic acid.

Introduction

Multi-component reactions because of their productivity, simplicity of execution and usually high yields of products have concerned significant attention from the point of view of combinatorial chemistry [1-3]. In addition, there has been an intense interest in the selection of different catalysts for the development of new MCRs methods.

Further, the synthesis of 1,8-naphthyridines and their derivatives is of high interest in organic chemistry due to their wide range of biological activities such as chemotherapeutic agents and anti-infectives. Some 1,8-naphthyridines have been reported to act as growth regulators, fungicides, bactericides, herbicides, insecticides, and nemathocides [4-8]. Because of the significance of these compounds in medicinal chemistry, several methods have been described [9-15]. However, there are several disadvantages associated with these methodologies including low yields, long conversion times, use of toxic solvents. Thus, herein we describe a mild and efficient one-pot synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives starting from 2-aminopyridine, malononitrile and aromatic aldehydes using phenylboronic acid as a catalyst at ambient temperature condition (**Scheme 1).**

Experimental

All solvents were utilized as commercial anhydrous grade without further purification. Melting points were determined in open capillary tube and are uncorrected.

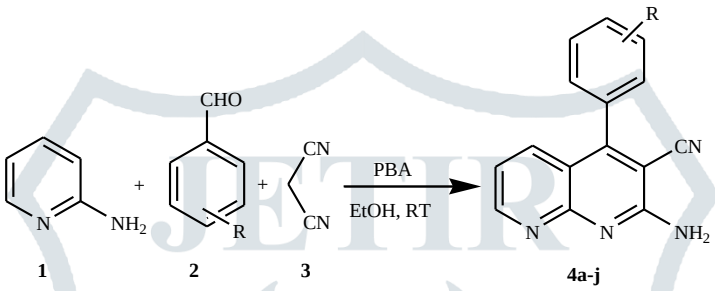
General procedure for the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives (4a-j):

2-Aminopyridine (1 mmol), aromatic aldehyde (1.5 mmol) and malononitrile (1 mmol) were mixed in

ethanol (15 ml). Catalytic amount of phenylboronic acid (0.1 mmol) was added. Reaction mixture was stirred at room temperature for appropriate time (Table 1). The progress of reaction was monitored by thin layer chromatography (pet ether: ethyl acetate 8:2). After the completion of reaction, reaction mixture was poured in crushed ice. Obtained precipitate was filtered and washed with hot water to obtain crude product.

2-Amino-4-(4-nitrophenyl)-1,8-naphthyridine-3-carbonitrile (4d): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 (s, 2H), 7.38-7.52 (m, 4H), 8.02-8.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 91.1, 112.0, 115.8, 119.0, 121.6, 126.0, 128.2, 131.0, 135.8, 138.0, 142.1, 146.4, 149.2, 152.1, 156.0, 164.2; Mass GC-MS (m/z): 291.36 [M^+].

2-Amino-4-(4-cyanophenyl)-1,8-naphthyridine-3-carbonitrile (4j): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.31 (s, 2H), 7.44-7.60 (m, 4H), 7.66-7.78 (m, 3H)**;** ^{13}C NMR (75 MHz, $CDCl_3$): δ 92.0, 113.2, 115.3, 117.8, 120.0, 121.1, 123,4, 125.8, 127.1, 130.2, 134.8, 148.6, 155.0, 158.1, 160.3 165.2; Mass GC-MS (m/z): 270.95 [M^+].



Scheme 1

Results and discussion

In initial investigation, a model reaction of 4-chloro benzaldehyde, 2-amino pyridine and malononitrile was carried out in different solvent using 10 mol % of catalyst phenylboronic acid at room temperature condition. In solvent acetonitrile, the reaction was completed in 4 hours and 56 % product yield was observed (Table 1, entry 1). The reaction in solvent dichloromethane, reaction offered only 26 % product yield in 6.30 hours (Table 1, entry 2). The product yield in the solvent ethanol was observed in satisfactory amount 88% (Table 1, entry 3). Again we studied effect of methanol solvent which gave 68 % product yield in 3 hours (Table 1, entry 4). The study reveals best results in solvent ethanol. Further we have studied the effect of catalyst amount by increasing up to 20 % mol but there is no any improvement in the yield and reaction time (Table 1, entry 5 & 6). So we continue our research using 10 mol % catalyst in solvent ethanol considering best reaction condition.

Table 1: Effect of solvent and catalyst amount on Synthesis of 2-Amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives

Sr. No.	Phenylboronic acid (mol %)	Solvent	Reaction time (hrs)	Yield[a] (%)
1	10	CH_3CN	4.00	56
2	10	DCM	6.30	26
3	10	EtOH	2.00	88
4	10	MeOH	3.00	68
5	15	EtOH	2.00	86
6	20	EtOH	2.30	87

[a]Isolated Yield

Table2: Synthesis of 2-Amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives

Entry	R	Product	Reaction time. (hrs)	M. P. (°C)	Yield[a] (%)
1	4-Cl	4-a	2.00	164-166	88
2	3-NO_2	4-b	2.00	171-173	89
3	4-OH	4-c	2.30	157-159	84
4	4-NO_2	4-d	2.30	174-176	85
5	-H	4-e	3.00	153-155	82
6	4-OCH_3	4-f	2.00	162-164	86
7	4-OH, 3-OCH_3	4-g	2.30	170-172	88
8	4-CN	4-h	3.00	141-143	84
9	3,4-$(OCH_3)_2$	4-i	2.30	181-183	86
10	2-Cl	4-j	2.00	168-169	89

[a]Isolated Yield

With this optimized condition, we have employed several aromatic aldehydes. Effect of substituent showed very little difference in yield and reaction time (entry 1-10, Table 2).

Conclusion:

Our results demonstrate that phenylboronic acid play important role in terms of reaction rate and yield of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives. This method offers several advantages such as mild reaction conditions, short reaction time, easy work up and excellent yield.

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