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Research Paper

A Convenient One-Pot Synthesis of 2-Amino-4-Phenyl-1,8-Naphthyridine-3-Carbonitrile Derivatives

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Abstract: A simple, efficient and one-pot procedure has been described for the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives. A mixture of 2-amino pyridine, malononitrile and aromatic aldehydes were reacted in presence of catalytic amount of 3-nitrophenylboronic acid as catalyst at room temperature to produce 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitriles. The mild reaction condition, short reaction time, high yield and simple experimental operation are the salient future of this method.

Introduction

Naphthyridine derivatives 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 [2a], anti-inflammatory [2b], antihypertensive [2c] and anticancer activities [2d]. 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]. 1, 8-Naphthyridines are also prepared by the condensation of ethanolic 2-amino-3-formylpyridines in the presence of strong base such as piperidine with active methylene compounds, aldehydes, acyclic and cyclic ketones or diketones [12]. Thus due to immense biological significance, various protocols was reported for synthesis

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of naphthyridine derivatives utilizing different type of reagents [13-16].

In recent years, Multi component reactions (MCRs) have gained significant attention from the organic area due to their advantages over conventional multistep synthesis. MCRs are more environmentally benign and atom economic as they avoid time-consuming and protection-deprotection steps. In this regard, the developments of new MCRs are most important in the fields of organic and medicinal chemistry.

The phenylboronic acid particularly those with electron-withdrawing substituent on aromatic ring work as an efficient Lewis acid catalyst. Recently phenylboronic acid has been effectively used as a catalyst in organic transformation as mild Lewis acid for several synthetic protocol such as amidation of carboxylic acids, asymmetric Diels-Alder cycloadditions and enantioselective allylation reactions [17], synthesis of 3,4-dihydropyrimidinones [18] and synthesis of 1,4-dihydropyridines [19].

As a continuation of our interest in the development of MCRs using organoboron compounds as a catalyst [20], 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 3-nitrophenylboronic acid as a catalyst at ambient temperature condition (**Scheme 1**).

Materials and Methods

Experimental

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 $F_{254,}$ Merck grade was used for thin layer chromatography to determine progress of reaction. The column chromatography was carried out over silica gel (80–120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ solvent.

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

2-Aminopyridine (10 mmol), aromatic aldehyde (15 mmol) and malononitrile (10 mmol) were mixed in methanol (15 ml). Catalytic amount of 3-nitrophenylboronic acid (20 mole %) was added. Reaction mixture was stirred at room temperature for appropriate time (Table 2). The progress of reaction was monitored by thin layer chromatography (pet ether: ethyl acetate 9:1). 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. 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-(4-chlorophenyl)-1,8-naphthyridine-3-carbonitrile (4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.40 (s, 2H), 7.40-7.62 (m,4H), 8.15-8.35 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 92.1, 114.2, 116.8, 125.6, 133.2, 136.1, 139.3, 142.8, 151.5, 156.1, 164.1; Mass GC-MS (m/z): 281.56 [M+], Elem. Anal for $C_{15}H_9ClN_4$: C, 64.18; H, 3.23; Cl, 12.63; N, 19.96 Found C, 64.25; H, 3.32; Cl, 12.56; N, 19.84.

Synthesis of 2-Amino-4-(2-chlorophenyl)-1,8-naphthyridine-3-carbonitrile (4b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.36 (s, 2H), 7.25-7.42 (m,4H), 8.10-8.28 (m, 3H); ^{13}C

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NMR (300 MHz, $CDCl_3$): δ 91.2, 112.1, 118.4, 124.2, 130.6, 136.1, 138.4, 140.2, 151.1, 157.6, 165.2; Mass GC-MS (m/z): 280.71 [M+], Elem. Anal for $C_{15}H_9ClN_4$: C, 64.18; H, 3.23; Cl, 12.63; N, 19.96 Found C, 64.21; H, 3.25; Cl, 12.58; N, 19.88.

Synthesis of 2-Amino-4-(4-methylphenyl)-1,8-naphthyridine-3-carbonitrile (4c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.10 (s, 2H), 6.85 (d, 2H), 7.01-7.20 (m, 3H), 7.64 (d,1H), 8.12 (d, 1H), ^{13}C-NMR (CDCl3): δ 110.2, 114.4, 120.1, 124.4, 126.1, 128.2, 131.1, 133.9, 136.2, 141.2, 144.8, 146.5, 150.2, 153.1, 159.4, 166.8; Mass GC-MS (m/z): 260.51 [M+]; Elem. Anal for $C_{16}H_{12}N_4$: C; 73.83, H; 4.65, N; 21.52. Found: C; 73.81, H; 4.66, N; 21.50.

Synthesis of 2-Amino-4-(4-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (4d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.60 (s, 3H), 5.69 (s, 2H), 6.79-7.10 (m, 3H), 7.55-8.10 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 58.1, 91.8, 116.3, 118.2, 119.8, 123.1, 129.9, 135.4, 149.5, 156.1, 164.3; Mass GC-MS (m/z): 277.21 [M+]; Elem. Anal for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28; O, 5.79 Found: C, 69.81; H, 4.32; N, 20.38; O, 5.56.

Synthesis of 2-amino-4-(4-hydroxy-3-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile (4e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.60 (s, 3H), 5.69 (s, 2H), 6.21 (s, 1H), 6.74 (d, 1H), 6.76 (d, 1H), 7.21 (d, 1H), 8.02-8.10 (m, 3H),^{13}C NMR (300 MHz, $CDCl_3$): δ 57.6, 91.2, 116.2, 118.2, 119.4, 122.2, 125.8, 129.1, 133.2, 135.5, 139.4, 141.8, 147.1, 149.7, 155.8, 165.1 Mass GC-MS (m/z): 293.16 [M+]; Elem. Anal for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17; O, 10.95 Found: C, 65.78; H, 4.12; N, 19.18; O, 10.97.

Synthesis of 2-amino-4-(3,4-dimethoxyphenyl)-1,8-naphthyridine-3-carbonitrile (4f): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 6H), 5.68 (s, 2H), 6.72 (d, 1H), 6.74 (d, 1H) 7.21-7.50 (m, 4H), ^{13}C NMR (300 MHz, $CDCl_3$): δ 57.2, 90.6, 116.1, 118.6, 119.1, 123.1, 126.3, 129.9, 133.1, 135.8, 139.2, 142.1, 147.4, 149.5, 156.1, 164.3; Mass GC-MS (m/z): 306.34 [M+]; Elem. Anal for $C_{17}H_{14}N_4O_2$**:** C, 66.66; H, 4.61; N, 18.29; O, 10.45. Found: C, 66.68; H, 4.64; N, 18.27; O, 10.48.

Synthesis of 2-Amino-4-phenyl-1,8-naphthyridine-3-carbonitrile (4g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.05 (s, 2H), 6.55 (d, 1H), 6.72 (d, 1H), 7.25-7.54 (m, 4H), 8.12 (d, 1H); ^{13}C-NMR (CDCl3): δ 118.2, 120.4, 124.6, 126.2, 127.4, 128.5, 129.1, 132.0, 136.4, 139.8, 143.1, 154.2, 158.2, 170.1, 171.4; Mass GC-MS (m/z): 247.66 [M+]; Elem. Anal for $C_{15}H_{10}N_4$: C, 73.16, H; 4.09, N; 22.75. Found: C; 73.13, H; 4.08, N; 22.73.

Synthesis of 2-amino-4-(3-nitrophenyl)-1,8-naphthyridine-3-carbonitrile (4h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.48 (s, 2H), 7.44-7.68 (m,4H), 8.14-8.31 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 90.3, 113.9, 115.9, 118.2, 122.4, 124.8, 129.1, 134.2, 136.1, 139.5, 142.3, 147.2, 149.1, 151.7, 156.1, 165.3; Mass GC-MS (m/z): 291.41 [M+]; Elem. Anal for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.04; O, 10.99. Found: C, 69.86; H, 3.14; N, 24.03; O, 10.97.

Synthesis of 2-amino-4-(4-nitrophenyl)-1,8-naphthyridine-3-carbonitrile (4i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.46 (s, 2H), 7.42-7.65 (m,4H), 8.11-8.30 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 90.1, 114.2, 116.8, 118.6, 122.2, 125.6, 128.5, 133.2, 136.1, 139.3, 142.8, 147.4, 148.2, 151.5, 156.1, 164.1; Mass GC-MS (m/z): 291.32 [M+]; Elem. Anal for $C_{15}H_9N_5O_2$**:** C, 61.85;

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H, 3.11; N, 24.04; O, 10.99. Found: C, 61.82; H, 3.13; N, 24.07; O, 10.96.

Synthesis of 2-amino-4-(4-cyanophenyl)-1,8-naphthyridine-3-carbonitrile (4j): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82 (s, 2H), 6.84 (d, 2H), 7.04-7.18 (m, 3H), 7.62 (d,1H), 8.10 (d, 1H),**;** ^{13}C NMR (300 MHz, $CDCl_3$): δ 91.5, 112.6, 114.2, 116.3, 118.2, 119.8, 123.1, 126.2, 127.6, 129.9, 135.4, 149.5, 153.2, 156.1, 159.4 164.3; Mass GC-MS (m/z): 271.25 [M+]; Elem. Anal for $C_{16}H_9N_5$: C, 70.84; H, 3.34; N, 25.82 Found: C, 70.86; H, 3.31; N, 25.83.

Result and Discussion

In general experimental procedure, a mixture of 2-aminopyridine **(1)**, aromatic aldehyde **(2a-j)** and malononitrile **(3)** was stirred in methanol in the presence of catalytic amount of 3-nitrophenylboronic acid at room temperature to obtain desired products **(4a-j)** with good to moderate yield. To the best of our knowledge, this is the first approach in which organoboron compound is used as catalyst for the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives.

In initial investigation, a model reaction of 2-aminopyridine, 4-chlorobenzaldehyde and malononitrile was carried out in different solvent using 10 mole % of 3-nitrophenylboronic acid at room temperature and reflux condition. In the solvent dichloromethane, only trace amount of product was obtained after 8 hours of stirring (entry 1, Table 1). We observed in our course of investigation, phenylboronic acid as catalyst worked well in polar solvents [20], so we performed same reaction in the solvent acetonitrile at room temperature. We were glad to note that reaction completed in 1.2 hours, but yield was not so impressive (entry 2, Table 1). We subjected reaction to reflux, however there was not significant increase in the yield of the product and taking more time for completion of reaction (entry 3, Table 1). Then, we used solvent ethanol and continued same reaction at room temperature which gave 71 % yield and under reflux condition gave almost similar yield 72 % (entry 4 and 5 respectively, Table 1). Reaction shown much better performance in solvent methanol, reaction completed in just 1 hour to obtain yield of 79 % (entry 6, Table 1). However under reflux condition reaction showed adverse effect on the time for completion and obtained yield 74 % (entry 7, Table 1).

We found methanol to be the suitable solvent for reaction to synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives but reaction yield was not meeting our expectations. Further, to optimize reaction condition, we increased catalyst concentration to 15 mole % which gave 82 % yield as per our anticipation (entry 8, Table 1). With this delightful result catalyst concentration was increased to 20 mole %, reaction completed in 40 minutes and we obtained excellent yield 91 % (entry 9, Table 1). Further increasing catalyst concentration was not showing improved performance.

Optimized protocol was extended to other aromatic aldehydes having different substituents. Effect of substituent showed very little difference in yield, but time required for completion of reaction was more in case of electron withdrawing substituent. Aromatic aldehyde having electron donating group were found to be more reactive (entry 1-10, Table 2).

Conclusion

Our results demonstrate that 3-nitrophenylboronic acid play significant role

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in success of the reaction in terms of reaction rate and yield of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives. This method suggests several advantages such as mild reaction conditions, short reaction time, high yield and simple experimental operation. The products obtained were isolated in satisfactory yields by conventional work up.

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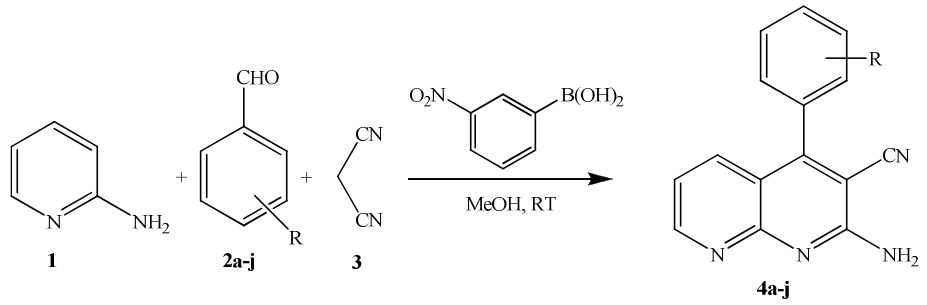

Scheme 1

Table 1: Effect of catalyst concentration, solvent and temperature on synthesis of 2-amino-4-(4-chlorophenyl)-1,8-naphthyridine-3-carbonitrile

Entry	3-Nitrophenylboronic acid (mole %)	Solvent	Temperature	Time (h)	Yield (%)[a]
1	10	DCM	RT	8	-
2	10	CH_3CN	RT	1.2	52
3	10	CH_3CN	Reflux	2.0	58
4	10	EtOH	RT	1.2	71
5	10	EtOH	Reflux	1.2	72
6	10	MeOH	RT	1.0	79
7	10	MeOH	Reflux	1.2	74
8	15	MeOH	RT	1.0	82
9	**20**	**MeOH**	**RT**	**0.40**	**91**
10	25	MeOH	RT	1.0	68

[a]Isolated yield.

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

Entry	R	Product	Time (h)	Mp (°C)	Yield (%)[a]
1	4-Cl	**4a**	0.40	165-166[8]	91
2	2-Cl	**4b**	0.45	168-170	88
3	4-CH_3	**4c**	0.50	168-170[8]	85
4	4-OCH_3	**4d**	0.40	162-164[8]	90

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5	3-OCH_3,4-OH	**4e**	0.50	170-172	88
6	3,4-$(OCH_3)_2$	**4f**	0.45	182-184	89
7	H	**4g**	1.0	155-156[8]	82
8	3-NO_2	**4h**	1.0	172-176	86
9	4-NO_2	**4i**	0.55	175-178	83
10	4-CN	**4j**	1.0	140-141	87

[a]Isolated yield.

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