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AN EXPEDIENT ONE-POT SYNTHESIS OF BENZO-1,8-NAPHTHYRIDINES UNDER AMBIENT TEMPERATURE CONDITION

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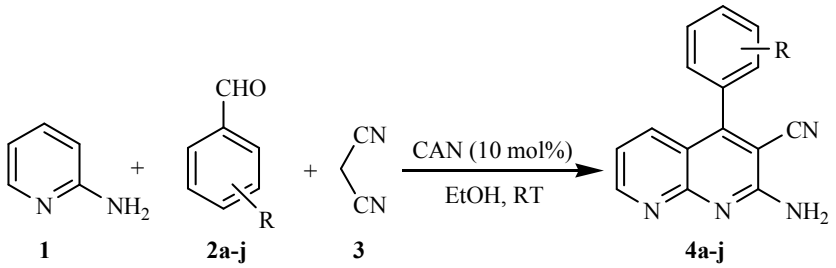
Abstract: A convenient catalyst ceric ammonium nitrate was employed for the synthesis of benzo-1,8-naphthyridines via a one-pot reaction of aromatic aldehydes, 2-amino pyridine and malononitrile in solvent ethanol under ambient temperature condition. The present protocol offers some of the agreeable features such as mild reaction conditions, environmentally benign, non-toxicity of reagent, easy experimental workup and excellent yields of desired products.

Keywords: One-pot synthesis, Ceric ammonium nitrate, Benzo-1,8-naphthyridiene, 2-Amino pyridine, Malononitrile.

Introduction

Among the nitrogen heterocycles, naphthyridines describe the important class of heterocycles that fascinate the attention of researcher from synthetic and medicinal chemistry because of their extensive range of biological activities as well as their function as essential binding units in the molecular design of synthetic receptors.[i] The highly functionalized derivatives of naphthyridine find application in the medicinal field as anti-inflammatory,[ii] anticancer,[iii] antitumor,[iv] antiplatelet,[v]local anaesthetic[vi] and anticonvulsant activities.[vii] The naphthrydines are observed to be potent against anxiolytic, bactericides, fungicides, herbicides and advantageous synthetic blocks in the synthesis of numerous natural products.[viii-ix] This moiety has been employed in the antibiotics for the diagnostics and chemotherapy of transferable diseases of humans including AIDS.[x] As a heterocyclic moiety, 1,8-naphthyridine also justify particular attention as in its molecule, the arrangement of the nitrogen atoms is optimal for chelation of various metal cations, together with lanthanide ions.[xi] The literature survey shows the synthesis of 1,8-naphthyridines concerning the condensation of carbonyl compounds with 2-aminopyridine having an active methylene group[xii-xiii] or with β-ketoesters.[xiv] Thus owing to huge biological consequence, several methods were employed for synthesis of naphthyridine derivatives using various kinds of reagents.[xv-xviii] Though, there are some disadvantages related with these methodologies including long conversion times, low yields, use of toxic and flammable solvents and incompatibility with other functional groups.

As interest in the development of MCRs, herein we report an effective ceric ammonium nitrate (CAN) catalyzed one-pot synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitriles starting from 2-aminopyridine, malononitrile and aromatic aldehydes at ambient temperature condition (**Scheme 1**).



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

Scheme 1: One-pot synthesis of benzo-1,8-naphthyridines

Results and Discussion

In extension of our interest in synthesis of heterocycles[xix-xxv] herein we depict the synthesis of benzo-1,8-naphthyridines using a green catalyst ceric ammonium nitrate. The synthesis of benzo-1,8-naphthyridines was accomplished by a one-pot three-component reaction of 2-amino pyridine, aromatic aldehydes and malononitrile utilizing ceric ammonium nitrate as catalyst in solvent ethyl alcohol under ambient temperature condition. In the initial stage of study, we focused on screening of suitable solvent and catalyst loading for the model reaction of 2-amino pyridine, 4-chlorobenzaldehyde and malononitrile under ambient temperature condition.

Several solvents were screened to check the efficiency of ceric ammonium nitrate (10 mol%), as shown in table 1, it is notable to reveal that the polar-protic solvents ethyl alcohol and methyl alcohol afforded enhanced yield than the non-polar solvents (Table 1, entry 1 & 2 respectively) and the delightful result was observed in the solvent ethyl alcohol. Moreover the model reaction in solvents acetonitrile afforded 62 % yield (Table 1, entry 3). In the non-polar solvent chloroform and dichloromethane, desired product was obtained in lower yields with enhanced reaction time (Table 1, entry 4 & 5 respectively). Consequently we continued our research in the solvent ethyl alcohol.

Subsequently, we studied the influence of catalyst concentration on the model reaction. It was observed that amount of the catalyst plays a major role in determining the desired product yield. On diminishing catalyst concentration to 5 mol%, reaction afforded lower yield 70% with elongated reaction time (Table 1, entry 6). By increasing the molar concentration of ceric ammonium nitrate from 10 to 15mol% in ethanol, it was observed that at a 15 and 20 mol% catalyst loading, no yield improvements were obtained (Table 1, entry 7 and 8 respectively). However, at 10 mol% catalyst loading higher yield (90%) of desired product were observed. Consequently, we selected 10 mol% of ceric ammonium nitrate and ethyl alcohol the optimum conditions for the synthesis of benzo-1,8-naphthyridine compounds at room temperature.

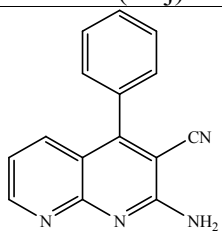
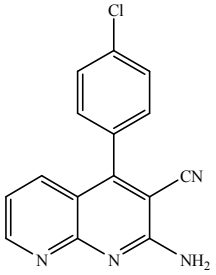
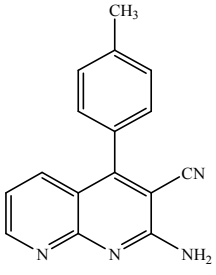
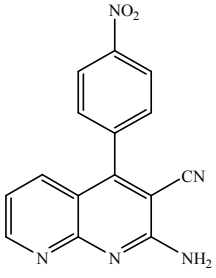
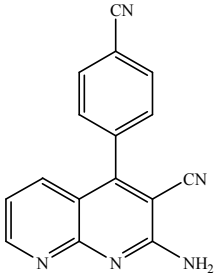
Table 1. Screening of the solvent and catalyst concentration on synthesis of 2-amino-4-(4-chlorophenyl)-1,8-naphthyridine-3-carbonitrile[a]

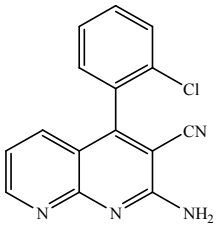
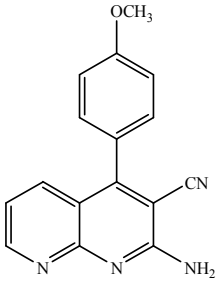
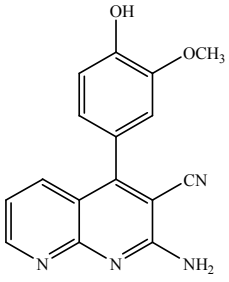
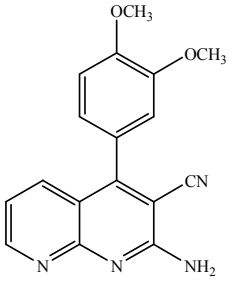
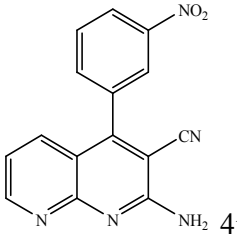
Entry	Solvent	Ceric Ammonium Nitrate (mole %)	Time(h)	Yield[b] (%)
1	EtOH	10	1.00	90
2	MeOH	10	2.00	72
3	CH_3CN	10	4.50	62
4	$CHCl_3$	10	7.50	32
5	DCM	10	9.00	28

6	EtOH	5	2.00	70
7	EtOH	15	1.20	88
8	EtOH	20	1.00	90

[a]Conditions: 2-Aminopyridine (10 mmol), 4-chlorobenzaldehyde (15 mmol), malononitrile (10 mmol), solvent (15 ml), ceric ammonium nitrate (mol %) at room temperature. Reaction was monitored by thin layer chromatography. [b]Isolated yield.

Table 2: An Efficient one-pot synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitriles[a]

Entry	R	Products (4a-j)	Time (min)	Mp (°C)	Yield (%)[b]
1	H	 4a	2	155-157	81
2	4-Cl	 4b	1	165-167	90
3	4-CH_3	 4c	1.5	168-169	88
4	4-NO_2	 4d	3	175-177	84
5	4-CN	 4e	2.5	140-142	86

6	2-Cl	 4f	1.5	168-171	88
7	4-OCH_3	 4g	1	162-163	91
8	3-OCH_3,4-OH	 4h	2	170-171	87
9	3,4-$(OCH_3)_2$	 4i	2.5	182-183	89
10	3-NO_2	 4j	3	172-174	87

[a]Conditions: 2-Aminopyridine (10 mmol), aromatic aldehyde (15 mmol), malononitrile (10 mmol), EtOH (15 ml), ceric ammonium nitrate (10 mol %) at room temperature. Reaction was monitored by thin layer chromatography. [b]Isolated yield.

Optimistic by these results, we screened a variety of aromatic aldehydes and amines having electron-withdrawing as well as electron-donating substituents and in each case we observed good to excellent yields (Table 2, entry 1-10).

Experimental

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 F254, 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): In a round bottom flask, 2-aminopyridine (1 mmol), aromatic aldehyde (1.5 mmol) and malononitrile (1 mmol) in ethanol (15 ml) were mixed. Catalytic amount of ceric ammonium nitrate (10 mol %) 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 reaction completion (TLC monitoring using petroleum ether:ethyl acetate 8:2), the reaction mixture was diluted with 50mL of water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the resulting residue was purified by column chromatography using silica gel mesh 80-120 to afford pure product.

2-Amino-4-(4-chlorophenyl)-1,8-naphthyridine-3-carbonitrile(4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (s, 2H, NH_2), 7.22-7.42 (m, 3H, Ar-H), 8.05-8.26 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 90.1, 110.2, 115.4, 120.4, 124.5, 128.7, 131.2, 137.2, 143.2, 152.3, 156.2, 160.8, 164.1; GC-MS (m/z): 281 [M+].

2-Amino-4-(4-methylphenyl)-1,8-naphthyridine-3-carbonitrile(4c): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78(s, 3H, CH_3), 5.89 (s, 2H, NH_2), 6.75-6.99 (m, 3H, Ar-H), 7.21-7.51(m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 91.5, 114.2, 117.8, 120.4, 124.8, 129.2, 132.2, 136.1, 139.8, 147.2, 151.8, 160.3, 162.9; GC-MS (m/z): 260 [M+].

2-Amino-4-(4-methoxyphenyl)-1,8-naphthyridine-3-carbonitrile(4g): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 3H, OCH_3), 5.72 (s, 2H, NH_2), 6.68-7.03 (m, 4H, Ar-H), 7.28-7.52(m, 3H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.3, 90.2, 112.0, 114.8, 119.2, 122.0, 130.2, 134.1, 137.2, 148.6, 154.3, 158.2, 161.2, 163.5; GC-MS (m/z): 277 [M^+].

Conclusion

In conclusion, we have demonstrated an efficient and facile method for the synthesis of benzo-1,8-naphthyridines using ceric ammonium nitrate as catalyst under ambient temperature condition. The reaction proceeds smoothly at room temperature. The significant advantages of the present method include easy work-up, mild reaction conditions, wide range of substrate applicability, excellent yields of products and non-toxicity of the reagents.

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