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Scandium triflate: An efficient and versatile catalyst for one-pot four-component synthesis of 2-amino-3-cyanopyridine derivatives

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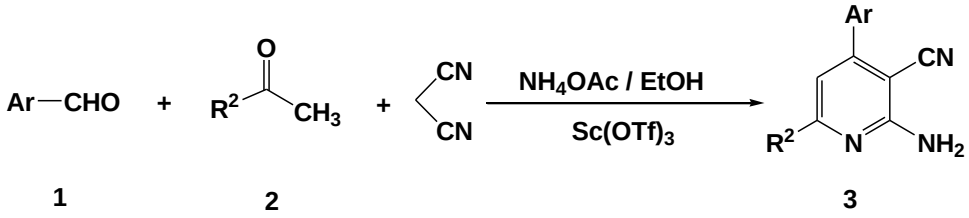
ABSTRACT

One-pot multi-component condensation of aldehydes, ketones, malononitrile and ammonium acetate catalyzed by Scandium triflate [$Sc(OTf)_3$] in ethanol has been accomplished for the synthesis of a series of 2-amino-3-cyanopyridine derivatives. This method is facile, rapid, efficient and environment friendly. The novelty of this present work is that the products do not need column purification. Reaction proceeds within 45 min, and the products are obtained in good to very high yields. The reaction works under mild and gentle conditions; is environmentally benign, involves safe isolation procedures and the catalyst is inexpensive.



Key words: Scandium triflate; 2-amino-3-cyanopyridines; aromatic aldehydes; ketones; malononitrile; ammonium acetate.

1. Introduction

In the mainstream of current interest, the rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. One approach to address this challenge involves the development of one-pot multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials. In addition to the intrinsic atom economy and selectivity underlying such reactions, simpler procedures and equipment, time and energy savings, as well as environmental friendliness have all led to a sizable effort to design and implement MCRs in both academia and chemical industries. [1−4]

The pyridine ring system is an important structural unit of many natural and biologically interesting compounds, which possess various pharmacological activities. [5] In recent years, 2-amino-3-cyanopyridine derivatives have been identified as novel IKK-b inhibitors [6], potent HIV-1 integrase inhibitor [7] and A2 Aadenosine receptor antagonists. [8] Including these kind of cyanopyridine derivatives, several pyridine

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analogues have been reported for various pharmacological properties such as: antimicrobial [9], antiviral [10], antibacterial [11], antifungal [12], herbicidal [13], anti-inflammatory [14], antihypertensive [15] and antitumour activity [16]. This class of intermediates are very useful for preparing a variety of heterocyclic compounds also. The synthesis of 2-amino-3-cyanopyridines has been reported, and most common procedures need multiple steps [17], long reaction time, toxic benzene as solvent [18], high temperature or microwave assistance [19,20] or ultrasonic irradiation [21,22]. Recently, Wang and Khaksar's group reported the synthesis 2-amino-3-cyanopyridines using Ytterbium perfluorooctanoate [23] and 2,2,2-trifluroethanol [24] as catalysts. Some 2-amino,3-cyanopyridine derivatives have been prepared by using various, versatile and eco-friendly synthetic protocols to obtain these valuable compounds in good yields [25,26]. Other catalysts used for this purpose are: hexadecyldimethyl benzyl ammonium bromide [27], triethyl amine [28], DMF [29] and acetic acid [30]. The reported methods suffer from several drawbacks such as: prolonged reaction time, low yields, harsh reaction conditions, critical isolation procedures and use of expensive catalysts.

Metal triflates are unique Lewis acids which are currently of great research interest. [31,32] Firstly, metal triflates are air, water and thermally stable, less toxic, easily recoverable and reusable. In addition, metal triflates are active in the coexistence of many substrates containing nitrogen, oxygen, phosphorous and sulfur atoms. Due to these advantages, they are widely used in organic synthesis. [33]

2. Results and Discussion

In continuation of our interest in green chemistry, we, herein, report a green, simple and practical method for the synthesis of 2-amino-3-cyanopyridine derivatives from substituted aromatic aldehydes, ketones, malononitrile and ammonium acetate catalyzed by $Sc(OTf)_3$ in ethanol as a solvent.

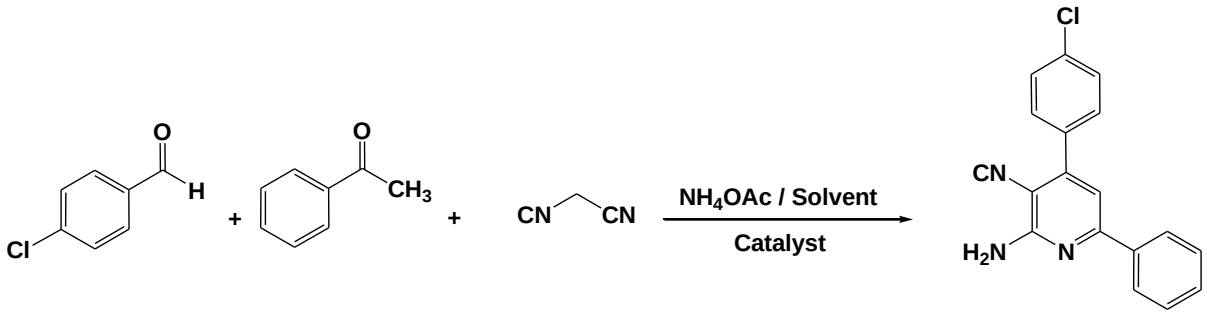
The present protocol is not only simple and high-yielding but also decreases environmental pollution. At the onset of this work, we have investigated a variety of reaction conditions with the model reaction using metal chlorides and metal triflates as catalysts, and the results of this study are presented in the **Table 1**. As can be seen, $Sc(OTf)_3$ gave maximum yield of 88% in just 45 min (entry 8).

Table 1: Synthesis of 2-amino-4-(4′-chloro-phenyl)-6-phenylnicotinonitrile (**3i**) using various catalysts.

Entry	Catalyst	Amount (mol %)	Time	Yield of **3i** (%)
1	$NiCl_2$	20	6h	40
2	$ZnCl_2$	20	6h	60
3	$CdCl_2$	20	6h	45
4	$SnCl_2$	20	6h	45
5	$YbCl_3$	5	6h	60
6	$Yb(OTf)_3$	5	6h	75
7	$La(OTf)_3$	5	6h	60
8	$Sc(OTf)_3$	5	45 min	88
9	None	-	6h	30

Reaction condition: Acetophenone (2 mmol), 4-chlorobenzaldehyde (2 mmol), malanonitrile (2 mmol) and ammonium acetate (3 mmol) in ethanol (10 mL)

Encouraged by this result, a systematic study was carried out to find the best molar concentration of Scandium (III) triflate for the synthesis of 2-amino-4-(4′-chlorophenyl)-6-phenylnicotinonitrile (**3i**, **Scheme 1**). The one-pot four-component reaction of acetophenone (2 mmol), 4-chlorobenzaldehyde (2 mmol), malanonitrile (2 mmol) and ammonium acetate (3 mmol) was carried out either in the absence of catalyst or in the presence of various solvents under different conditions. As shown in **Table 2**, the best yield was achieved when 5 mol% $Sc(OTf)_3$ was used in ethanol as solvent (entry 6).

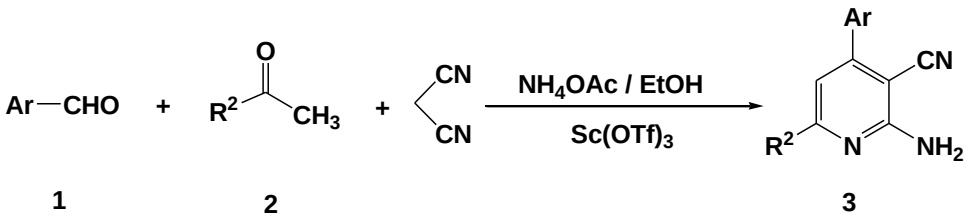


Scheme 1: Synthesis of 2-amino-4-(4′-chlorophenyl)-6-phenylnicotinonitrile (**3i**)

Table 2: Synthesis of 2-amino-4-(4′-chlorophenyl)-6-phenylnicotinonitrile (**3i**) under different reaction conditions.

Entry	Solvent (10 mL)	$Sc(OTf)_3$ (mol%)	Time (h)	Temp (°C)	Isolated yield (%)
1	Dichloromethane	5	12	30	20
2	Acetonitrile	5	12	26	20
3	Acetonitrile	5	1	Reflux	80
4	Methanol	5	12	26	Trace
5	Methanol	5	1.5	Reflux	85
6	Ethanol	5	0.5	Reflux	88
7	Ethanol	0	4	Reflux	30
8	Ethanol	1	4	Reflux	50
9	Ethanol	2	4	Reflux	55

Reaction condition: Acetophenone (2 mmol), 4-chlorobenzaldehyde (2 mmol), malononitrile (2 mmol) and ammonium acetate (3 mmol)



Scheme 2: Synthesis of 2-amino-3-cyanopyridines catalyzed by $Sc(OTf)_3$

We, then, extended the methodology to a variety of aromatic aldehydes, substituted aromatic ketones and malononitrile in the presence of ammonium acetate which are summarized in **Table 3** and shown in **Scheme 2**. This method is effective for the preparation of 2-amino-3-cyanopyridines (**3a−k**) from both electron-rich as well as electron-deficient aromatic aldehydes. The different functional groups on aryl group at different positions did not show any significant effect on the formation of 2-amino-3-cyanopyridines (**3**).

Table 3: Synthesis of 2-amino-3-cyanopyridines catalyzed by $Sc(OTf)_3$.

Entry	Ar	R^2	Product[a]	Time (min)	Yield (%)[b]	m.p (°C)	
						Found	Reported [ref][c]
1	C_6H_5	C_6H_5	**3a**	40	83	186-187	186-187 [23]
2	4-ClC_6H_4	2,4-$Cl_2C_6H_3$	**3b**	45	84	198	198-199 [19]
3	4-ClC_6H_4	4-$CH_3OC_6H_4$	**3c**	35	85	195-196	195-196 [19]
4	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**3d**	30	82	160	159-160 [23]
5	4-$CH_3OC_6H_4$	2,4-$Cl_2C_6H_3$	**3e**	40	86	185-186	184-185 [19]
6	2-ClC_6H_4	C_6H_5	**3f**	35	80	192-193	193-196 [24]
7	4-$CH_3C_6H_4$	C_6H_5	**3g**	40	88	176-177	175-176 [24]
8	4-ClC_6H_4	C_6H_5	**3h**	25	88	235	233-235 [25]
9	4-ClC_6H_4	4-FC_6H_4	**3i**	25	80	218-219	219-220 [19]
10	4-$CH_3OC_6H_4$	C_6H_5	**3j**	35	80	181-182	180-182 [19]
11	4-ClC_6H_4	CH_3	**3k**	40	85	171-173	172-173 [19]

[a]All are known products, characterized by IR, ^1H & ^{13}C-NMR and LC-Mass spectral and elemental analysis; and by comparison of their physical properties with those of authentic samples; [b] Isolated yield; [c] melting points are consistent with the reported values [19-25].

3. Experimental

All aromatic aldehydes, aryl ketones, malononitrile, ammonium acetate and $Sc(OTf)_3$ were commercial products and were used without further purification; except aldehydes which were distilled before use. Reported yields refer to yield of the isolated products. IR and ^1H & ^{13}C-NMR spectra were recorded on Nicolet 400D FT-IR and Bruker AMX (400 & 100 MHz) spectrophotometers respectively. The IR spectra were taken as KBr pellets, LC-MS was performed on an Agilent Technologies 1200 series instrument and melting points were determined on a Buchi melting point apparatus.

3.1 ***Typical procedure for the preparation of 2-amino-3-cyanopyridines*** **(3)*:***
A mixture of ketone (2 mmol), aromatic aldehyde (2 mmol), malononitrile (2 mmol), ammonium acetate (3 mmol) and $Sc(OTf)_3$ (5 mol%) in ethanol (10 mL) was stirred at reflux for the appropriate time (**Table 3**), after the completion of the reaction [monitored by thin-layer chromatography (TLC)], the reaction mixture was filtered and the solid was washed with cold ethanol (2 mL). The crude products were purified by recrystallization using 95% aq. ethanol.

3.1.1 ***2-Amino-4,6-diphenylnicotinonitrile*** (**3a**): Yield: 83%; White solid; m.p. 186–187 °C; IR (KBr): ν 3461, 3301, 3176, 2202, 1637, 1546, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 2H), 7.48 (m, 8H), 7.32 (s, 1H), 7.12 (s, 2H) ppm; ^{13}CNMR (100 MHz $CDCl_3$): 158.7, 155.2, 151.3, 138.9, 135.4, 127.6, 125.8, 123.1, 122.7, 121.9, 120.8, 119.7, 107.4, 84.5 ppm; ESI-HRMS $[M+H]^+$ m/z Found: 271.1152. $C_{18}H_{13}N_3$ Calcd: 271.1138.

3.1.2 ***4-(4′-Chlorophenyl)-6-(2′′,4′′-dichlorophenyl)-2-amino-3-cyanopyridine*** (**3b**): Yield: 84%; Colorless solid; m.p. 198 °C; IR (KBr): ν 3462, 3307, 3185, 2202 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 7.55–7.76 (7H, m, ArH), 7.19 (2H, s, NH_2), 6.95 (1H, s, CH) ppm; Anal. Calcd for $C_{18}H_{10}Cl_3N_3$ (373.14): C, 57.71; H, 2.69; N, 11.22. Found (374): C, 57.48; H, 2.83; N, 11.56.

3.1.3 ***4-(4′-Chlorophenyl)-6-(4′′-methoxyphenyl)-2-amino-3-cyanopyridine*** (**3c**): Yield: 85%; Colorless crystals; m.p. 195–196 °C; IR (KBr): ν 3454, 3361, 3232, 2201 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 8.12 (2H, d, J=8.4 Hz), 7.70 (2H, d, *J* = 8.4 Hz,), 7.63 (2H, d, *J* = 8.4 Hz), 7.23 (1H, s) 7.04 (2H, d, *J* = 8.4 Hz) 6.99 (2H, s) 3.83 (3H, s) ppm; Anal. Calcd for $C_{19}H_{14}ClN_3O$ (335.17): C, 67.96; H, 4.20; N, 12.51. Found (335): C, 67.58; H, 4.58; N, 12.20.

3.1.4 ***4-(4′-Methoxyphenyl)-6-(4′′-methoxyphenyl)-2-amino-3-cyanopyridine*** (**3d**): Yield: 82%; Colorless crystals; m.p. 160 °C; IR (KBr): ν 3458, 3361, 3232, 2201 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 8.10 (2H, d, *J* = 8.4 Hz), 7.64 (2H, d, *J* = 8.4 Hz), 7.19 (1H, s), 7.11 (2H, d, *J* = 8.4 Hz), 7.03 (2H, d, *J* = 8.4 Hz), 6.88 (2H, s), 3.84 (3H, s), 3.82 (3H, s) ppm; Anal. Calcd for $C_{20}H_{17}N_3O_2$ (332): C, 72.49; H, 5.17; N, 12.68. Found (331): C, 72.73; H, 4.85; N, 12.94.

3.1.4 ***4-(4′-Methoxyphenyl)-6-(2′′,4′′-dichlorophenyl)-2-amino-3-cyanopyridine*** (**3e**): Yield: 86%; Colourless crystals; m.p. 185–186 °C; IR (KBr): ν 3467, 3364, 3309, 2201 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 7.08–7.75 (9H, m), 6.19 (1H, s) ppm; Anal. Calcd for $C_{19}H_{13}Cl_2N_3O$ (370): C, 61.64; H, 3.54; N, 11.35. Found (369): C, 61.25; H, 3.90; N, 11.03.

3.1.5 ***2-Amino-4-(2′-chlorophenyl)-6-phenylnicotinonitrile*** (**3f**): Yield: 80%; Colorless solid; ^1H NMR (400 MHz, $CDCl_3$): δ 5.48 (br s, 2H), 7.07 (s, 1H), 7.48–7.60 (m, 7H), 7.92–7.94 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 92.1, 115.6, 120.1, 124.3, 125.6, 126.1, 128.1, 129.8, 133.8, 134.1, 135.6, 136.5, 138.5, 155.3, 160.2, 166.1 ppm; Anal. Calcd for $C_{18}H_{12}ClN_3$ (305). Found: C, 70.71; H, 3.96; N 13.74.

3.1.6 ***2-Amino-4-p-tolyl-6-phenylnicotinonitrile*** (**3g**): Yield: 88%; Colorless solid; mp: 176–177 °C; IR (KBr): ν 3463, 3293, 3168, 2202, 1631, 1575, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.35 (br s, 2H) , 7.21 (s, 1H), 7.32–7.99 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): d = 20.3, 91.2, 116.5, 120.1, 125.2, 125.7, 128.1, 129.2, 133.5, 133.8, 134.5, 136.5, 156.8, 162.3, 166.5 ppm; ESI-MS (%) 287 ($[M + 2]^+$, 8.3), 286 ($[M + 1]^+$, 28.8), 285, 233, 206, 149, 133, 111, 91, 69.

3.1.7 ***2-Amino-4-(4′-chlorophenyl)-6-phenylnicotinonitrile*** (**3h**): Yield: 88%; Colorless solid; m.p. 233–235 °C; IR (KBr): ν 3496, 3305, 3183, 2204, 1641, 1606, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (br s, 2H, NH2), 7.18 (s, 1H), 7.48–7.60 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 93.2, 116.3, 119.3, 125.2, 126.3, 127.5, 127.8, 132.2, 133.4, 134.5, 135.4, 154.3, 164.5, 166.2 ppm; ESI-MS (%) 307 ($[M + 2]^+$, 41.0), 306 ($[M + 1]^+$, 52.2), 305 ($[M^+]$, 100.0), 271, 227, 202, 140, 104, 83, 57.

3.1.8 ***4-(4′-Chlorophenyl)-6-(4′′-flurophenyl)-2-amino-3-cyanopyridine*** (**3i**): Yield: 80%; Colorless crystals; m.p. 218–219 °C; IR (KBr): ν 3483, 3350, 3217, 2214 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 8.20 (2H, d, *J* = 8.4 Hz), 7.72 (2H, d, *J* = 8.4 Hz), 7.64 (2H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 7.30 (1H, s), 7.06 (2H,

s) ppm; Anal. Calcd for $C_{18}H_{11}ClN_3F$ (324): C, 66.78; H, 3.42; N, 12.98. Found (323): C, 66.32; H, 3.08; N, 12.59.

3.1.9 ***4-(4'-Methoxyphenyl)-6-phenyl-2-amino-3-cyanopyridine*** (**3j**): Yield: 83%; Colorless crystals; m.p. 181–182 °C; IR (KBr): ν 3462, 3307, 3184, 2201 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 8.11–8.12 (2H, m), 7.66 (2H, d, J=8.4 Hz), 7.48–7.49 (3H, m), 7.25 (1H, s), 7.11 (2H, d, *J* = 8.4 Hz), 6.96 (2H, s), 3.85 (3H, s) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.4, 110.9, 114.4, 117.5, 127.3, 128.8, 129.1, 129.6, 130.1, 138.0, 154.7, 159.7, 160.4, 160.9 ppm; ESI-MS (%) 303 ($[M + 2]^+$, 14.5), 302 ($[M + 1]^+$, 62.8), 301 , 300 , 257, 239 , 134, 112, 83, 57; Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N,13.94. Found (301): C, 75.40; H, 5.38; N,13.68.

3.1.10 ***4-(4'-Chlorophenyl)-6-methyl-2-amino-3-cyanopyridine*** (**3k**): Yield: 85%; Colorless crystals; m.p. 171–173 °C; IR (KBr): ν 3402, 3313, 3170, 2213 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6): δ 7.60 (2H, d, *J* = 8.4 Hz), 7.58 (2H, d, *J* = 8.4 Hz), 6.89 (2H, s), 6.62 (1H, s), 2.36 (3H, s) ppm; Anal. Calcd for $C_{13}H_{10}ClN_3$ (244): C, 64.07; H, 4.14; N, 17.24. Found (243): C, 63.88; H, 3.98; N, 17.10.

4. Conclusions

In conclusion, we have described a mild and efficient method for the synthesis of 2-amino-3-cyanopyridines using $Sc(OTf)_3$ as a novel Lewis acid catalyst. The advantages of this method include good substrate generality, the use of inexpensive reagents, catalyst, mild conditions and operational ease.

5. Conflict of Interest

The authors declare no conflict of interest in publishing this work.

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