Efficient Synthesis of 3-Aminoimidazo[1,2-*a*] Pyridines Using Silica-Supported Perchloric Acid ($HClO_4$-SiO_2) as a Novel Heterogenous Catalyst

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Abstract: One pot three-component reaction of 2-amino pyridines, aldehydes and isocyanides in the presence of silica-supported perchloric acid ($HClO_4$-SiO_2), produces 3-aminoimidazo[1,2-*a*] pyridines in excellent yields. The reaction time is short and work up of reaction is very easy. New compounds were identified by IR, ^{1}H NMR, ^{13}C NMR and Mass spectrum.

Keywords: 3-Aminoimidazo[1,2-*a*] pyridine, isocyanide, multi-component reaction, silica-supported perchloric acid ($HClO_4$-SiO_2).

INTRODUCTION

Heterocyclic compounds are particularly interested in all branches of chemistry especially in medicinal chemistry. These classes of compounds are widely distributed in nature and are essential to life. Extensive researches have been done to discover new heterocyclic compounds and develop novel methods. The imidazo[1,2-*a*]annulanes bearing pyridine, pyrazine and pyrimidine core constitute are an important heterocycles which they show broadly biologically activities such as anticytomegalo-zoster and antivaricella-zoster virus [1], antifungal, antibacterial [2, 3], anti-inflammatory [4], antiviral, antiulcer [5] and calcium channel blocker activities [6]. Among new studies in 2007, Gudmundsson described synthetic approach of novel imidazo[1,2-*a*] pyridines and their anti-HSV activity [7, 8].

In recent years, considerable efforts have been devoted to introduce new routes for the synthesis of imidazo[1,2-*a*]pyridines and other analogs. An earlier method for the synthesis of imidazo[1,2-*a*]pyridine is coupling of α-halocarbonyl compound with 2-amino pyridine. Although, this reaction has been used for imidazo[1,2-*a*]annulated pyrazines and pyrimidines, but has restricted for generation of a diverse library of this heterocycles. Another one-pot method is coupling of 2-amino annulated heterocycle, sodium cyanide and formaldehyde which have limitation for desired diversification in the molecules. These protocols because of their restrictions could not be introduced as a good general method.

RESULTS AND DISCUSSION

In recent years, significant isocyanide-based multi-component reactions (ISMCRs) have been reported [9-11]. Multi-component reactions are important tools for the rapid and efficient synthesis of a wide variety of organic molecules. In the usual organic chemistry, only a few MCRs are known and each reaction produces compounds with similar skeleton and only different substituent, whereas in the chemistry of the isocyanides, a much greater variation of MCRs is known and more different educts and products can participate than the conventional reactions. Three-component reaction of 2-amino pyridine, aldehyde and isocyanide was performed in different situations and their results were published in the literature. Some of these needs long time [for instance, reaction in the presence of protic acid (AcOH, $HClO_4$)] [12] whereas reactions which were performed in the presence of Lewis acid ($Sc(OTf)_3$) [13] had complicated work up procedure. Other synthetic routes for three condensation reaction in the condition of solid acid (montmorillonite clay K10 [14], ($Sc(OTf)_3$) [13], solid support {using isonitrile resin [3], resin bound aldehydes [15] or immobilized acid [16]}; catalyst-free, in water [17]; synthesis in ionic liquid medium [18], application of TMSCN as a non-classical isonitrile equivalent [19], were recently reported. Table **1**, shows differences in situation and condition, time of reaction, simplicity of work up and finally yields of reactions that recently reported. In spite of these interesting and suitable methods [13-24], there is a need to develop a facile route that can be easily used as a general and efficient synthetic approach.

On the basis of information of Table **1**, our procedure is a fast, simple and has easily worked up procedure that we can suggest as a general and efficient method for the synthesis of imidazo[1,2-*a*]pyridines derivatives.

Here, we wish to report a three component condensation of aldehyde **1**, 2-aminopyridine **2** and isocyanide **3** in the presence of silica-supported perchloric acid as catalyst (Scheme **1**).

This reaction was carried out at 70-90 ºC in a short time and excellent yield (Table **2**). New products (**4d**, **4f**, **4g**, **4h**, **4i**, **4j**, **4l**, **4n**, **4o**) were identified by IR, ^{1}H NMR, ^{13}C NMR and Mass spectrum. The melting point and spectral data of

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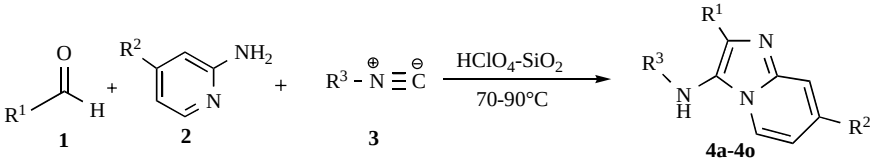
Table 1. Comparable Situation and Condition of Reported Procedures

Entry	solvent	catalyst	time	yield	Work up	conditions	Reference
1	-	Montmorillonite clay k10	3 min	56-86	easy	microwave	14
2	MeOH	Sc(OT*f*)$_3$	10 min	65-93	difficult	microwave	21
3	water	-	7 h	85-97	easy	70°c	18
4	1,4-dioxane	$ZnCl_2$	1h	14-78	difficult	microwave	22
5	1,4-dioxane	$ZnCl_2$	5h	9-75	difficult	Reflux	22
6	1,4- dioxane	Montmorillonite clay k10	1h	20-59	difficult	microwave	22
7	1,4-dioxane	Montmorillonite clay k10	5h	26-73	difficult	Reflux	20
8	Ionic liquid	b[mim]Br	3h	70-98	easy	r.t	19
9	MeOH	PTSA	2h	86-97	easy	r.t	23
10	MeOH	SSA	3h	77-99	easy	r.t	24
11	CH_2Cl_2-MeOH	Sc(OT*f*)$_3$	72h		difficult	r.t	25



1 **2** **3** **4a-4o**

Scheme 1. Three component reaction of isocyanide, 2-amino pyridine and aldehyde.

Table 2. Different Products and Yields of Reaction

Time(min)	Yield(%)	R^3	R^2	R^1	Product
80	80	Cyclohexyl	H	Ph	**4a**
165	70	Cyclohexyl	H	4-$CH_3C_6H_4$	**4b**
190	81	Cyclohexyl	H	4-$CH_3OC_6H_4$	**4c**
40	80	Cyclohexyl	H	4-FC_6H_4	**4d**
240	67	Cyclohexyl	H	4-ClC_6H_4	**4e**
45	78	Cyclohexyl	Me	4-FC_6H_4	**4f**
30	79	Cyclohexyl	H	4-BrC_6H_4	**4g**
60	65	Cyclohexyl	Me	4-$CH_3C_6H_4$	**4h**
60	74	Cyclohexyl	Me	ph	**4i**
60	75	Cyclohexyl	Me	4-$CH_3OC_6H_4$	**4j**
300	86	*tert*-butyl	H	ph	**4k**
225	85	*tert*-butyl	H	4-ClC_6H_4	**4l**
220	83	*tert*-butyl	H	4-$CH_3OC_6H_4$	**4m**
290	77	*tert*-butyl	H	4-$CH_3C_6H_4$	**4n**
60	78	*tert*-butyl	H	4-F-C_6H_4	**4o**

other known products were consistent with characterization reported earlier.

CONCLUSIONS

In conclusion, we have introduced simple, efficient and environmentally friendly method for the synthesis of 3-amino imidazo[1,2-*a*]pyridines *via* condensation of an aldehyde, 2-amino pyridine and isocyanide in the presence of silica-supported perchloric acid as a catalyst, in good to execllent yield and in a short time.

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EXPERIMENTAL

General

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a AGILENT TECHNOLOGY(HP)-5973 mass spectrometer operating at an ionization potential of 70 eV(EI). ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in $CDCl_3$. All starting materials were purchased from Fluka and Merck and used without purification. Silica-supported perchloric acid was prepared on the basis of procedure was used by Khan's group [25].

Typical Procedure for Preparation of N-Cyclohexyl -2-(4-fluorophenyl)H-imidazo[1,2-a]pyridine-3-amine (4d)

A mixture of *p*-fluoro benzaldehyde **1** (1 mmol), 2-amino pyridine **2** (1 mmol), cyclohexyl isocyanide **3** (1 mmol) and 0.2 g silica-supported perchloric acid was stirred in a tube at 70-90°C. Completion of reaction was monitored by TLC. Time needed for completion was about 45 minutes. At the end of the reaction time, mixture was cooled to room temperature. Then dichloromethane was added to reaction mixture and silica was filtered off. Finally, the solvent was removed under reduced pressure and the curde product was purified by crystallization in *n*-hexane to give **4d** as a colorless crystal. Yield: 80%; m.p. 166-171 °C; Anal. calcd for $C_{19}H_{20}FN_3$ (309.37): C, 73.76; H, 6.52; N, 13.58. Found: C, 73.65; H, 6.50; N, 13.67; IR (KBr, cm^{-1}): 3231 (N-H), 1633, 1605 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, δ/ppm): 1.14-1.83 (10H, m, 5CH_2 of cyclohexyl), 2.93 (1H, m, CH-NH), 3.09 (1H, d, J = 4.5 Hz, NH), 6.80 (1H, t, J = 6.8 Hz, CH of pyridine), 7.11 (1H, dd, J = 6.8, J = 9.0 Hz, CH of pyridine), 7.17 (2H, dd, J = 5.7 and J = 8.5 Hz, 2CH of ph), 7.56 (1H, d, J = 9.0 , CH of pyridine), 8.05 (2H, dd, J = 5.7 and J = 8.5 Hz, 2CH of ph), 8.10 (1H, d, J = 6.8, CH of pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ/ppm): 24.79, 25.69, 34.19 (5CH_2 of cyclohexyl), 56.82 (CH-NH), 111.84, 115.28, 115.57 (3CH-Ar), 117.23, 122.72, 124.30 (3C-Ar), 128.78, 128.88 (3CH-Ar), 160.63, 163.92 (2C-Ar); MS (*m/z*, (relative abundance, %)): 309 (M^+, 52), 227 (33), 226 (100), 200 (15), 199 (97), 78 (59.

N-cyclohexyl-2-(4-fluorophenyl)-7-methyl H-imidazo[1,2-a]pyridine-3-amine (4f)

Yield: 78%; m.p. 156-158 °C; Anal. calcd for $C_{20}H_{22}FN_3$ (323.41): C, 74.28; H, 6.86; N, 12.99. Found: C, 74.15; H, 6.80; N, 13.18; IR (KBr, cm^{-1}): 3227 (N-H), 1645, 1606 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, δ/ppm): 1.13-1.70 (10H, m, 5CH_2 of cyclohexyl), 2.40 (3H, s, CH_3), 2.92 (1H, m, C*H*-NH), 3.05 (1H, d, J = 4.4 Hz, NH), 6.64 (1H, d, J = 7.0 Hz, CH of pyridine), 7.13 (2H, d, J = 8.8 Hz, 2CH of ph), 7.32 (1H, s, CH of pyridine), 7.98 (1H, d, J = 7.0 Hz, CH of pyridine), 8.06 (2H, d, J = 8.8, 2CH of ph)**;** ^{13}C NMR (75.5 MHz, $CDCl_3$, δ/ppm): 21.32 (CH_3), 23.9, 24.9, 34.0 (5 CH_2 of cyclohexyl), 55.4 (CH-NH), 116, 117.1 (2CH-Ar), 122.3 (C-Ar), 124, 124.3, 129.2 (3 CH-Ar), 128.7, 135.1, 144.4, 151.1, 162 (5C-Ar); MS (*m/z*, (relative abundance, %)): 323 (M^+, 50), 241 (26), 240 (100), 213 (90), 78 (45).

2-(4-bromophenyl)-N-cyclohexylH-imidazo[1,2-a] pyridine-3-amine (4g)

Yield: 79%; m.p. 175-177 °C; Anal.calcd for $C_{19}H_{20}BrN_3$ (370.11): C, 61.63; H, 5.44; N, 11.35. Found: C, 61.42; H, 5.37; N, 11.36; IR (KBr, cm^{-1}): 3230 (N-H), 1659, 1631 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, δ/ppm): 1.14-1.26 (10H, m, 5CH_2 of cyclohexyl), 2.94 (1H, m, C*H*-NH), 3.05 (1H, d, J = 4.5 Hz, NH), 6.80 (1H, t, J = 6.8 Hz , CH of pyridine) 7.15 (1H, dd, J = 6.8 and J = 8.2 Hz, CH of pyridine), 7.53 (1H, d, J = 8.2, CH of pyridine), 7.57 (2H, d, J = 8.5 Hz , 2CH of ph), 7.97 (2H, d, J = 8.5 Hz , 2CH of ph), 8.08 (1H, d, J = 6.8 Hz, CH of pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ/ppm): 24.80, 25.68, 34.21 (CH_2 of cyclohexyl), 56.87 (CH-NH), 111.80, 117.42 (2CH-Ar), 121.27 (C-Ar), 122.67, 124.26 (2 CH-Ar), 125.31 (C-Ar), 128.58, 131.5 (2CH-Ar), 133.38, 141.60, 146.12 (3C-Ar); MS (*m/z*, (relative abundance, %)): 371 (M^+, 42), 369 (M^+, 40), 289 (24), 288 (73), 287 (24), 286 (68), 261 (53), 259 (51), 79 (20), 78 (100).

N-cyclohexyl-7-methyl-2-p-tolyl H-imidazo[1,2-a]pyridine-3-amine (4h)

Yield: 65%; m.p. 186-187 °C; Anal. calcd for $C_{21}H_{25}N_3$: C, 78.96; H, 7.89; N, 13.55%. Found: C, 78.99; H, 7.67; N, 13.78%; IR (KBr, cm^{-1}): 3227 (N-H), 1673, 1642 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, δ/ppm): 1.13-1.57 (10H, m, 5CH_2 of cyclohexyl), 2.39 (6H, s, 2CH_3), 2.93 (1H, m, C*H*-NH), 3.16 (1H, d, J = 4.7 Hz, NH), 6.65 (1H, d, J = 7.0 Hz, CH of pyridine) ,7.24 (2H, d, J = 8.4 Hz, 2CH of ph), 7.35 (1H, s, CH of pyridine), 7.90 (2H, d, J = 8.4 Hz , 2CH of ph), 8.02 (1 H, d, J = 7.0 Hz ,CH of pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ/ppm): 21.29 (2CH_3), 24.40, 25.04, 34.11 (5CH_2 of cyclohexyl), 56.37 (CH-NH), 112.03 (C-Ar), 114.28, 117.6 (2CH-Ar), 122.0 (C-Ar), 124.4, 127.4, 130.2 (3CH-Ar), 135.1, 138.4, 144.4, 146.8, 151.1 (5C-Ar); MS (*m/z*, (relative abundance, %)): 319 (M^+,35), 236 (65), 209 (100), 92 (30), 78 (52).

N-Cyclohexyl-7-methyl-2-phenylH-imidazo[1,2-a]pyridine-3-amine (4i)

Yield: 74%; m.p. 168-171 °C; Anal.calcd for $C_{20}H_{23}N_3$ (305.24): C, 78.65; H, 7.59; N, 13.76. Found: C, 78.67; H, 7.76; N, 13.58; IR (KBr, cm^{-1}): 3240 (N-H), 1643, 1604 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, δ/ppm): 1.14-1.83 (10H, m, 5CH_2 of cyclohexyl), 2.40 (3H, s, CH_3), 2.95 (1H, m, C*H*-NH), 3.13 (1H, d, J = 4.7 Hz, NH), 6.63 (1H, d, J = 7.0 Hz, CH of pyridine), 7.31 (2H, m, 2CH of ph), 7.42 (1H, s, CH of pyridine), 7.45 (1H, m, CH of ph), 8.01 (2H, m, 2CH of ph), 8.04 (1H, d, J = 7.0, CH of pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ/ppm): 21.32 (CH_3), 24.8, 25.7, 34.1 (CH_2 of cyclohexyl), 57.0 (C*H*-NH), 114.4 (CH-Ar), 115.6 (C-Ar), 117.6, 122.0 (2CH-Ar), 122.3 (C-Ar), 124.3, 127.2, 128.5 (3CH-Ar), 144.4, 147.5, 151.1 (3C-Ar). MS (*m/z*, (relative abundance, %)): 305 (M^+, 60), 223 (29), 222 (100), 196 (16), 195 (90), 92 (60), 65 (21).

N-Cyclohexyl-2-(4-methoxyphenyl)-7-methylHimidazo[1, 2a]pyridine-3-amin (4j)

Yield: 75%; m.p. 190-192 °C; Anal.calcd for $C_{21}H_{25}N_3O$ (335.23): C, 75.19; H, 7.51; N, 12.53. Found: C, 75.05; H, 7.28; N, 12.50; IR (KBr, cm^{-1}): 3227 (N-H), 1673, 1642 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, δ/ppm): 1.14-1.83 (10H,

m, $5CH_2$ of cyclohexyl), 2.40 (6H, s, $2CH_3$), 2.94 (1H, m, C*H*-NH), 3.09 (1H, d, *J* = 4.6 Hz, NH), 6.62 (1H, d, *J* = 7.0 Hz , CH of pyridine), 7.25 (2H, d, *J* = 8.0 Hz, 2CH of ph), 7.33 (1H, s, CH of pyridine), 7.93 (2H, d, *J* = 8.0 Hz , 2CH of ph), 8.0 (1H, d, *J* = 7.0 Hz, CH of pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$, *δ*/ppm): 21.29 ($2CH_3$), 24.80, 25.74, 34.13 ($5CH_2$ of cyclohexyl), 56.97 (C*H*-NH), 112.03 (C-Ar), 114.28 (CH-Ar), 114.68, 115.52, 119.60 (3C-Ar), 122.0 (CH-Ar), 124.1 (C-Ar), 124.9, 126.82, 129.23 (3CH-Ar), 136.9 (C-Ar); MS (*m/z*, (relative abundance, %)): 335 (M^+, 1), 319 (97), 252 (10), 237 (24), 236 (100), 225 (16), 209 (82), 117 (98), 92 (36).

N-tert-butyl-2-(4-chlorophenyl) H-imidazo[1,2-a]pyridine-3-amine (4l)

Yield: 85%; m.p. 146-148 °C; Anal.calcd for $C_{17}H_{18}ClN_3$ (299.78): C, 68.11; H, 6.05; N, 14.02. Found: C, 67.87; H, 5.93; N, 14.08; IR (KBr, cm^{-1}): 3284 (N-H), 1654, 1632 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, *δ*/ppm): 1.04 (9H, s, $C(CH_3)_3$), 3.07 (1H, s, NH), 6.80 (1H, t, *J* = 6.7 Hz, CH of pyridine), 7.17 (1H, dd, *J* = 6.7 and *J* = 9.0 Hz, CH of pyridine), 7.40 (2H, d, *J* = 8.4 Hz, 2CH of ph), 7.55 (1H, d, *J* = 9.0, CH of pyridine), 7.92 (2H, d, *J* = 8.4 Hz, 2CH of ph), 8.21 (1H, d, *J* = 6.7 Hz, CH of pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$, *δ*/ppm): 30.33 ($C(CH_3)_3$), 56.53 ($C(CH_3)_3$), 111.82, 116.9, 122.45, 123.48 (4CH–Ar), 124.86 (C-Ar), 128.48 (CH-Ar), 128.93 (C-Ar), 129.30 (CH-Ar), 130.13, 133.28, 140.01 (3C-Ar).); MS (*m/z*, (relative abundance, %)): 301 (M^+, 14), 299 (M^+, 42), 245 (34), 244 (46), 243 (90), 242 (87), 217 (37), 215 (100), 149 (38), 78 (94).

N-tert-butyl-2-p-tolyl H-imidazo[1,2-a]pyridine-3-amine (4n)

Yield: 77%; m.p. 149-150 °C; Anal.calcd for $C_{18}H_{21}N_3$ (279.37): C, 77.38; H, 7.57; N, 15.04. Found: C, 77.32; H, 7.75; N, 15.17; IR (KBr, cm^{-1}): 3316 (N-H), 1656, 1632 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, *δ*/ppm): 1.04 (9 H, s, $C(CH_3)_3$), 2.39 (3H, s, CH_3), 3.12 (1H, s, NH) , 6.77 (1 H, t, *J* = 6.8 Hz, CH of pyridine), 7.13 (1H, dd, *J* = 6.8 and *J* = 9.0 Hz, CH of pyridine), 7.24 (2H, d, *J* = 8.1 Hz, 2CH of ph), 7.55 (1H, d, *J* = 9.0 Hz, CH of pyridine), 7.81 (2H, d, *J* = 8.1 Hz, 2CH of ph) , 8.23 (1H, d, *J* = 6.8 Hz, CH of pyridine). ^{13}C NMR (75.5 MHz, $CDCl_3$, *δ*/ppm): 21.30 (CH_3), 30.27 ($C(CH_3)_3$), 56.43 ($C(CH_3)_3$), 111.25, 117.11 (2CH–Ar), 123.22 (C-Ar), 123.43, 123.98, 127.94, 128.99 (4CH-Ar), 132.11, 137.06, 139.33, 141.82 (4C-Ar); MS (*m/z*, (relative abundance, %)): 279 (M^+, 39), 223 (54), 222 (81), 196 (20), 195 (100), 78 (49).

N-tert-butyl-2-(4-fluorophenyl) H-imidazo[1,2-a]pyridine-3-amine (4o)

Yield: 78%; m.p. 158-160 °C; Anal. calcd for $C_{17}H_{18}FN_3$ (283.33): C, 72.06; H, 6.40; N, 14.83. Found: C, 71.66; H, 6.45; N, 14.63; IR (KBr, cm^{-1}): 3286 (N-H), 1632, 1605 (Ar); ^{1}H NMR (300.1 MHz, $CDCl_3$, *δ*/ppm): 1.05 (9H, s, $C(CH_3)_3$), 3.05 (1H, s, NH), 6.80 (1H, t, *J* = 6.8 Hz, CH of pyridine), 7.13 (1H, dd, *J* = 6.8 and *J* = 9.0 Hz, CH of pyridine), 7.17(2H, dd, *J* = 5.7 and *J* = 8.5 Hz, 2CH of ph), 7.55 (1H, d, *J* = 9.1 Hz, CH of pyridine), 7.92 (2H, dd, *J* = 5.7 and *J* = 8.5 Hz, 2CH of ph), 8.22 (1H, d, *J* = 6.8 Hz, CH of pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$, *δ*/ppm): 30.32 ($C(CH_3)_3$), 56.42 ($C(CH_3)_3$), 111.58, 115.09, 115.38, 117.14 (4CH-Ar), 123.20, 123.42, 124.42 (3C-Ar), 129.75, 129.86 (2CH-Ar), 160.63, 163.89 (2C-Ar).); MS (*m/z*, (relative abundance, %)): 283 (M^+, 37), 227 (74), 226 (78), 199 (100), 79 (28), 78 (94).

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