Tetrahedron Letters 50 (2009) 4389–4393

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Silica-sulfuric acid: a highly efficient catalyst for the synthesis of imidazo[1,2-*a*]pyridines using trimethysilyl cyanide or cyanohydrins

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ARTICLE INFO

Article history:
Received 14 March 2009
Revised 12 May 2009
Accepted 22 May 2009
Available online 27 May 2009

Keywords:
Multicomponent condensation
Cyanohydrins
Imidazopyridines
Catalyst
Cyanides

ABSTRACT

This Letter describes a novel synthetic approach towards imidazo[1,2-*a*]pyridines via a three-component condensation using trimethylsilyl cyanide (TMSCN) or cyanohydrins as the source of CN^- ions and silica-sulfuric acid as the catalyst.

Imidazo[1,2-*a*] annulated nitrogen heterocycles containing pyridine, pyrazine or pyrimidine fragments constitute a class of biologically active compounds that are potent antibacterial agents,[1] inhibitors of gastric acid secretion,[2] calcium channel blockers[3] and which also exhibit cytoprotective properties.[4] The isocyanide-based multi-component condensation (MCC) reported simultaneously by Blackburn,[5] Bienayme and Bouzid[6] and Groebke et al.[7] represents an effective synthetic pathway towards these compounds. Since, several groups have reported modifications of the protocol, including the use of Montmorillonite K-10 clay as a catalyst[8] and microwave acceleration.[9] However, the main disadvantage of this approach is the use of pungent isonitriles. A more recent Letter[10] describes the discovery of a unique application of TMSCN as a non-classic isonitrile equivalent; however, microwave irradiation was required. An attractive protocol has recently been reported[11] which uses an ionic liquid as a promoter for the one-pot, three-component condensation of 2-aminoazines, aldehydes and TMSCN. However, all our attempts to reproduce this process were unsuccessful. In our hands, the yields of the target products did not exceed 12%, while isolation required column chromatography. This communication details the application of TMSCN or acetone–cyanohydrin as functional isonitrile equivalents in the MCR catalyzed by silica-sulfuric acid,[12] leading to the target imidazo[1,2-*a*]pyridines. The current study was aimed at elaborating a synthetic protocol towards imidazo[1,2-*a*](di)azines avoiding the use of (i) isonitriles as starting materials; (ii) costly catalysts, for example, scandium triflate; (iii) special instrumentation, for example, microwave reactors; and (iv) column chromatography.

The method should be applicable to routine parallel solution-phase synthesis followed by a simple isolation procedure. Thus, we turned our attention to the use of the H_2SO_4/SiO_2 catalytic system (silica-sulfuric acid).[13] TMSCN or the cyanohydrin of acetone or acetaldehyde was used instead of isonitriles.

Aminoimidazo(di)azines **1**–**10** were synthesized from the appropriate aminoazines, aldehydes and cyano-substituted compounds, via condensation catalyzed by silica-sulfuric acid.

We presume that the reaction starts with the formation of cyanohydrins from the aldehydes and TMSCN or 2-hydroxy-2-methylpropanenitrile, followed by Strecker reaction with the corresponding 2-aminoazine to form the intermediate aminonitrile **A**. Acid-catalyzed cyclization of **A**, followed by a [1,3] proton-shift in intermediate **B** yields the amino imidazo(di)azines **1a**, **2a**, **3** and **4**. (Scheme 1, Table 1). In some cases (Table 1, entries 1, 2 and 5) further modification of the primary amino group occurred and the corresponding Schiff bases were also isolated. The 3-aminoimidazopyridines and the corresponding Schiff bases could be separated easily due to their different solubilities in hexane. The structure of compound **1b** was additionally confirmed by the alternative 'classical' synthesis of its reduced derivative **14**.[14] (Scheme 2).

In the case of 2-hydroxypropanenitrile (Scheme 3) Strecker reaction leads to 3-amino-2-methylimidazopyridines, which can

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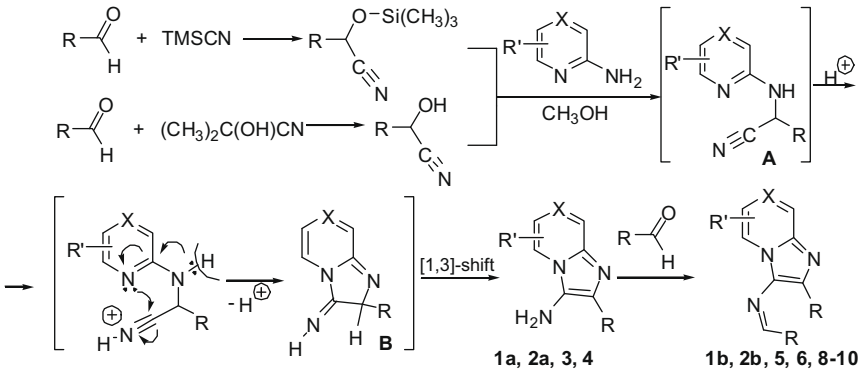
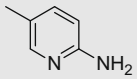
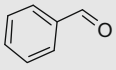
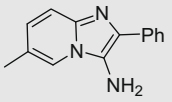
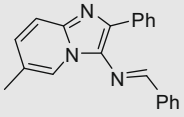
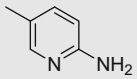
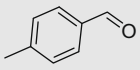
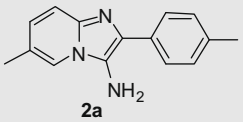
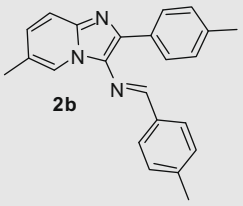
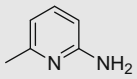
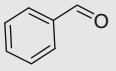
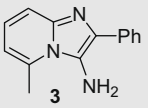
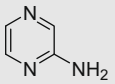
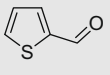
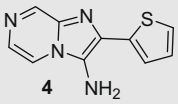
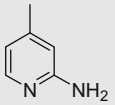
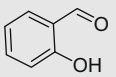
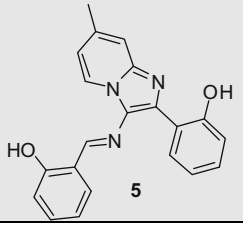
doi:10.1016/j.tetlet.2009.05.080

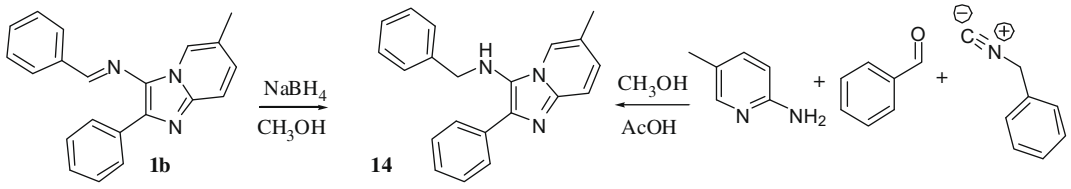


Scheme 1. Three-component condensation via Strecker reaction.

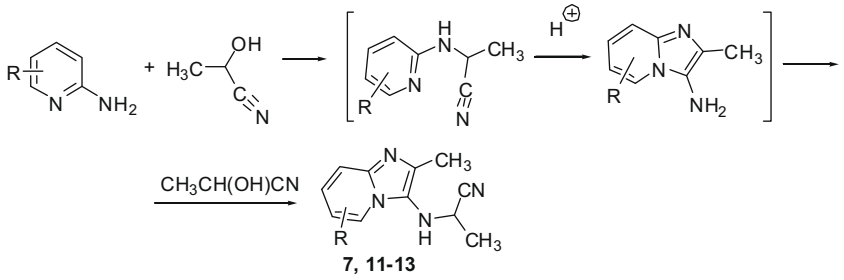
Table 1
Products of condensation and yields via method A using TMSCN

Entry	Amidine	Aldehyde	Product	Yield[a] (%)	Mp (°C)
1[b]			 **1a**	55	190
			 **1b**	15	110
2			 **2a**	49	187
			 **2b**	21	135
3			 **3**	38	184
4[15]			 **4**	53	130–132
5[c]			 **5**	47	210–211

[a] Isolated yield.
[b] Compound **1a** was isolated and described previously;[11] however, the data given therein differ from ours.
[c] When a 2:1 ratio of salicylic aldehyde 2-amino-4-picoline was used, the yield of product was 83%.

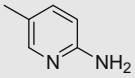
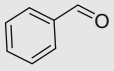
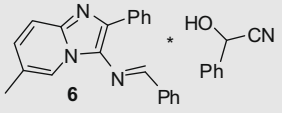
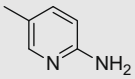
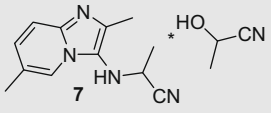
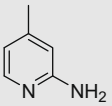
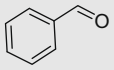
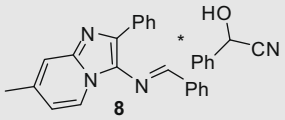
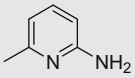
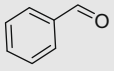
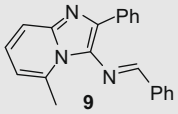
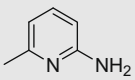
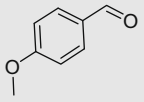
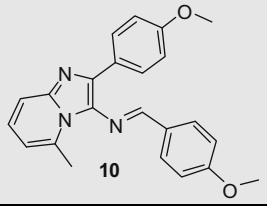


Scheme 2. 'Classical' synthesis of **14**.



Scheme 3. Condensation with 2-hydroxypropanenitrile.

Table 2
Products of condensation and yields via method B using $(CH_3)_2C(OH)CN$

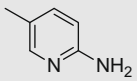
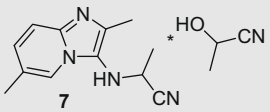
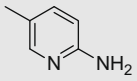
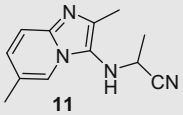
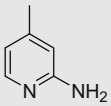
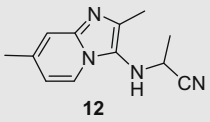
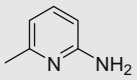
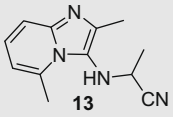
Entry	Amidine	Aldehyde	Product	Yield[a] (%)	Mp (°C)
1[16]			 **6**	70	65
2		CH_3CHO	 **7**	16	Oil
3			 **8**	67	80–82
4			 **9**	61	135
5			 **10**	74	175

[a] Isolated yield.

react with the excess of 2-hydroxypropanenitrile giving substituted imidazopyridines **7** and **11–13**.

The use of TMSCN seems to be more appropriate in order to synthesize primary amines, that is, **1a**, **2a**, **3** and **4** (Table 1). At the same time, 2-hydroxy-2-methylpropanenitrile can be used if further modifications of the NH_2 group are required. The use of 2-hydroxy-2-methylpropanenitrile as the CN source via formation of the aldehyde cyanohydrin (Scheme 1) required a fivefold molar excess of the aldehyde in order to proceed effectively. This caused further derivatization of the NH_2 group, yielding the corresponding Schiff bases (**6**, **8**, **9** and **10**) or aminonitrile **7**, in the case of acetaldehyde (Table 2, entry 2). In some cases (Table 2, entries 1–3), the target products were isolated as Schiff base complexes with cyanohydrins (ratio, 1:1, according to ^1H NMR analysis). After treatment of the complexes with aqueous ammonia, the free Schiff bases were isolated. The low yield (16%) of **7** encouraged us to explore the use of acetaldehyde cyanohydrin as the CN-source (Scheme 3) in the condensation reaction. The reactions proceeded smoothly,

Table 3
Products of condensation and yields via method C using $CH_3CH(OH)CN$

Entry	Amidine	Product	Yield[a] (%)	Mp (°C)
1		 **7**	48	Oil
2[b],[17]		 **11**	80	135
3		 **12**	46	137
4		 **13**	51	120

[a] Isolated yield.
[b] Yield after treatment of complex **11** with aqueous NH_3.

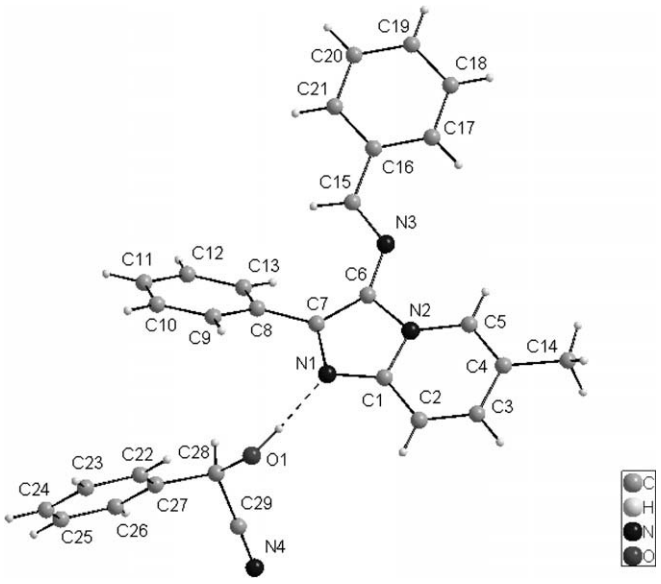


Figure 1. X-ray structure of complex **6**.

providing the target aminonitriles **7**, **11**, **12** and **13** in good preparative yields (Table 3).

To determine whether this approach can be applied to other 2-aminoazines, we studied the condensation of 2-aminopyrazine, thiophene-2-carboxaldehyde and trimethylsilyl cyanide. The corresponding imidazo[1,2-*a*]pyrazine **4** was obtained in 53% yield, (Table 1, entry 4).

Deep-red crystals of the complex of mandelic acid nitrile and *N*-benzylidene-6-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-amine **6** were used for X-ray analysis (Fig. 1). A suitable monocrystal of compound **6** was obtained by recrystallization from methanol by slow evaporation at room temperature.[18] The benzylideneamino and imidazolopyridine fragments are located in the same plane while the C7-phenyl ring is partially withdrawn from conjugation forming a torsion angle of 42.6°.

In conclusion, we have reported a method for the synthesis of 3-aminoimidazoles using silica-sulfuric acid as a catalyst for the condensation of aminoazines and cyano-substituted compounds, via the Strecker reaction. Further experiments aimed at exploring the scope and limitations of this procedure and its optimization are underway and will be reported in due course.

General procedure. Method A. To a stirred mixture of aminoazine (3 mmol) in methanol (5 mL), aldehyde (3 mmol), TMSCN (3.3 mmol) and silica-sulfuric acid (0.4 g) were added. Stirring was continued for 3–5 d at room temperature (TLC monitoring). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The remaining residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ (10%), dried and evaporated. The Schiff base was extracted with hot hexane. The obtained residue was recrystallized from hexane to give the 3-aminoimidazole.

Method B. Aminoazine (3 mmol) was added to a stirred mixture of aldehyde (15 mmol), 2-hydroxy-2-methylpropanenitrile (15 mmol) and silica-sulfuric acid (0.4 g). Stirring was continued for 2–3 d at room temperature (TLC monitoring). The catalyst was removed by filtration, the filtrate was diluted with isopropanol and left at 0 °C to give a complex of the cyanohydrin with imidazo[1,2-*a*]pyridine. Treatment of the complex with aqueous NH_3 (5%) produced the free Schiff base.

Method C. Aminoazine (3 mmol) was added to a stirred mixture of 2-hydroxypropanenitrile (30 mmol) and silica-sulfuric acid (0.4 g). Stirring was continued at room temperature for 2–3 d (TLC monitoring). The catalyst was removed by filtration and washed with CH_2Cl_2 (30 mL). The filtrate was washed with brine (3×50 mL), followed by aqueous NH_3 (5%, 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was triturated in isopropanol/hexane mixture.

References and notes

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14. *N*-Benzyl-6-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-amine (**14**): *Method A*. To a stirred mixture of **1b** (0.1 g, 0.33 mmol) in ethanol (5 mL) at 40 °C was added $NaBH_4$ (0.015 g, 0.4 mmol). Stirring was continued (TLC monitoring). The solvent was evaporated under reduced pressure and CH_2Cl_2 (15 mL) was added. The resulting solution was washed with H_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **14** (0.07 g, 70%). *Method B*. Benzyl isocyanide (0.35 g, 3 mmol) was added to a stirred mixture of 2-amino-5-methylpyridine (0.31 g, 3 mmol), benzaldehyde (0.32 g, 3 mmol) and acetic acid (0.18 g, 3 mmol) in methanol (10 mL). Stirring was continued (TLC monitoring). The product **14** (0.71 g, 78%) precipitated from the reaction.
The samples of **14**, obtained by both methods after recrystallization from ethanol were identical and gave no melting point depression.
Compound **14**: White solid, mp 165–167 °C (ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 4.12 (d, 2H, J = 4.4 Hz, CH_2–NH), 5.18 (t, 1H, J = 4.4 Hz, NH), 6.98 (d, 1H, J = 8.8 Hz, CH-Ar), 7.18–7.48 (m, 9H, CH-Ar), 7.94 (s, 1H, CH-Ar), 8.12 (d, 2H, J = 7.3 Hz, CH-Ar) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ = 17.7, 51.3, 116.1, 120.2, 120.5, 126.3, 126.4, 126.7, 126.9, 128.1, 128.2, 128.3, 134.7, 139.5, 139.8 ppm. EI MS: m/z (%) = 313 (3) [M^+], 222 (23), 195 (32), 91 (100), 77 (6), 65 (93), 51 (22), 39 (45). Calcd for $C_{21}H_{19}N_3$ (313.41): C, 80.40; H, 6.06; N, 13.40. Found: C, 80.48; H, 5.97; N, 13.32.
15. 2-(2-Thienyl)imidazo[1,2-*a*]pyrazin-3-amine (4) was obtained by method **A**. Yellow solid, mp 130–132 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.73 (br s, 2H, NH_2), 7.22 (dd, 1H, J = 4.6 Hz, J = 5.3 Hz, 4-H-thienyl), 7.54 (d, 1H, J = 4.6 Hz, 3-H-thienyl), 7.75 (m, 2H, CH-Ar), 8.30 (d, 1H, J = 5.3 Hz, 5-H-thienyl), 8.92 (s, 1H, CH-Ar) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ = 115.1, 122.5, 125.0, 127.0, 128.5, 129.8, 131.3, 132.5, 135.7, 136.2 ppm. EI MS: m/z (%) = 216 (100) [M^+], 188 (27), 137 (6), 122 (12), 110 (30), 95 (5), 84 (23), 80 (53), 69 (5), 64 (29), 58 (5), 52 (36), 48 (9), 44 (21), 39 (17). Calcd for $C_{10}H_8N_4S$ (216.05): C, 55.55; H, 3.70; N, 25.92. Found: C, 55.30; H, 3.76; N, 25.67.
16. (*E*)-3-(Benzylideneamino)-6-methyl-2-phenylimidazo[1,2-*a*]pyridin-1-ium cyano(phenyl) methanolate (**6**) was obtained by method B. Deep-red crystals, mp 65 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.34 (s, 3H, CH_3), 3.35 (br s, 3H, CH_3), 5.72 (d, 1H, J = 7.3 Hz, *CH*–OH), 7.02 (br d, 1H, J = 7.3 Hz, CH–*OH*), 7.18 (d, 1H, J = 10.1 Hz, CH-Ar), 7.30–7.55 (m, 10H, CH-Ar), 7.87–7.97 (m, 3H, CH-Ar), 8.39 (s, 1H, CH-Ar), 8.87 (s, 1H, CH=N) ppm. Calcd for $C_{29}H_{24}N_4O$ (444.20): C, 78.36; H, 5.44; N, 12.60. Found: C, 78.42; H, 5.76; N, 12.31.
17. 2-[(2,6-Dimethylimidazo[1,2-*a*]pyridine-3-yl)amino]propanenitrile (**11**) was obtained by method C. White solid, mp 135 °C (methanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.52 (d, 3H, J = 7.2 Hz, CH–*CH*$_3$), 2.27 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.17 (q, 1H, J = 7.2 Hz, *CH*–CH_3), 5.56 (d, 1H, J = 8.5 Hz, NH), 6.98 (d, 1H, J = 9.2 Hz, CH-Ar), 7.27 (d, 1H, J = 9.2 Hz, CH-Ar), 7.93 (s, 1H, CH-Ar) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ = 13.0, 17.7, 19.3, 44.4, 115.5, 120.3, 120.4, 122.2, 123.1, 126.3, 135.1, 139.6 ppm. ESI MS m/z 215 (M^++1). Calcd for $C_{12}H_{14}N_4$ (214.11): C, 67.28; H, 6.54; N, 26.16. Found: C, 67.12; H, 6.42; N, 25.89.
18. Crystallographic data (excluding structure factors) for compound **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 712214. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.