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Synthesis of 2-Amino-3,5-dicarbonitrile-6-thiopyridines Using Silica-bonded *N*-Propyldiethylenetriamine as a Heterogeneous Solid Base Catalyst

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Silica-bonded *N*-propyldiethylenetriamine (7) is employed as a recyclable heterogeneous solid base catalyst for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines through *pseudo* four-component condensation reaction between aromatic aldehydes, malononitrile, and 2-amino-thiophenol in refluxing ethanol. Silica-bonded *N*-propyldiethylenetriamine showed much the same efficiency when used in consecutive reaction runs.

Keywords: 2-Amino-3,5-dicarbonitrile-6-thiopyridines, Heterogeneous catalysts, Solid bases, Synthesis, Multi-component reactions

INTRODUCTION

Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of their ability to synthesize small drug-like molecules with several degrees of structural diversity. MCRs have performed quantitative revolutions in molecular architecting, access to multifunctional molecules, and combinatorial chemistry in recent years [1-3].

The pyridine ring systems represent a major class of heterocycles and their analogues exhibit diverse biological and physiological activities [4]. In particular, 2-amino-3,5-dicarbonitrile-6-thio-pyridines serve as 'privileged scaffold' due to their potential therapeutic applications [5-18]. These structures represent such a class of medicinally significant compounds, libraries of which demonstrate activity against a wide range of biological targets (Fig. 1). For example, compounds 1 and 2 displays efficacy as selective human adenosine receptor modulators [5,6], relevant for treatment of a range of conditions, and compound 3 as anti-prion agents [7].

Compound 4 showed varying degrees of efficacy as an anti-proliferative agent [18]. Compounds 5 and 6 were reported to inhibit PrPSc accumulation in scrapie-infected mouse neuroblastoma cells (ScN2a) and modulate androgen receptor function [17]. In addition, 2-amino-3,5-dicarbonitrile-6-thio-pyridines skeleton is often used as anti-prion [7,12,13], anti-hepatitis B virus [14], anti-bacterial [15] and anti-cancer [8] agents. Recently, some of these compounds have been recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, cancer [16] and Creutzfeldt-Jacob disease [7,12,17].

Many synthetic methods have been developed for the construction of 2-amino-6-thiopyridine-3,5-dicarbonitrile derivatives. Among these reported methods, three-component condensation reaction between aldehydes, malononitrile, and thiophenols catalyzed by Lewis/Brønsted bases is the most common approach. The reported Lewis/Brønsted base catalysts include DBU [19], Et_3N [20,21], piperidine [22,23], KF/alumina [24,25], K_2CO_3/$KMnO_4$ [26], *etc*. Besides bases, Lewis acids, Brønsted acids, nanoparticles, and ionic liquids, such as $ZnCl_2$ [27], boric acid [28], silica nanoparticles [29], nano MgO [30], $ZrOCl_2$ [31], [bmim]OH [32], [bmim]Br [33], Zn(II) and Cd(II) metal-organic frameworks (MOFs) [34], 2-hydroxyethylammonium acetate [35], K_2CO_3 in PEG-400 [36], and phosphotungstic acid [37], are also occasionally

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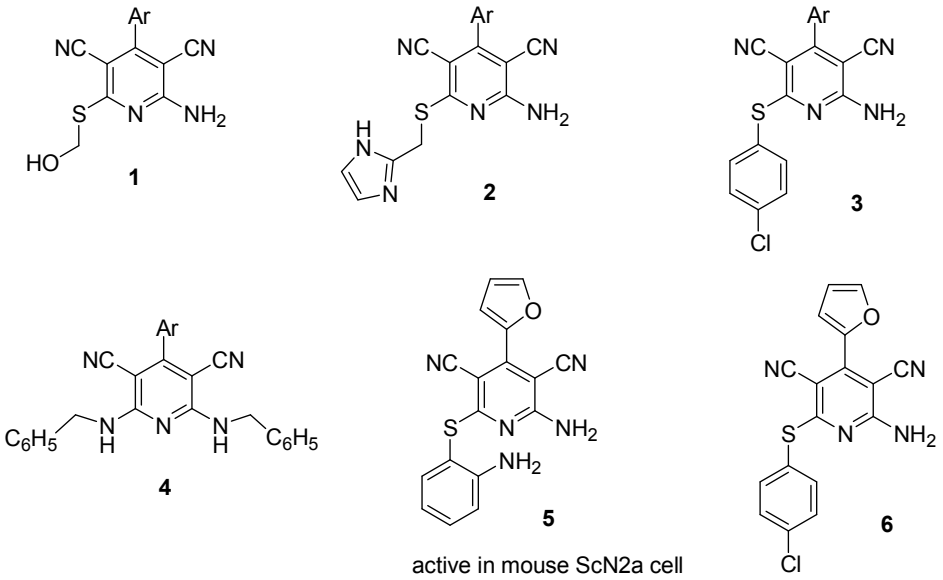


Fig. 1. Structure of some bio-active compounds containing 2-amino-pyridine-3,5-dicarbonitriles.

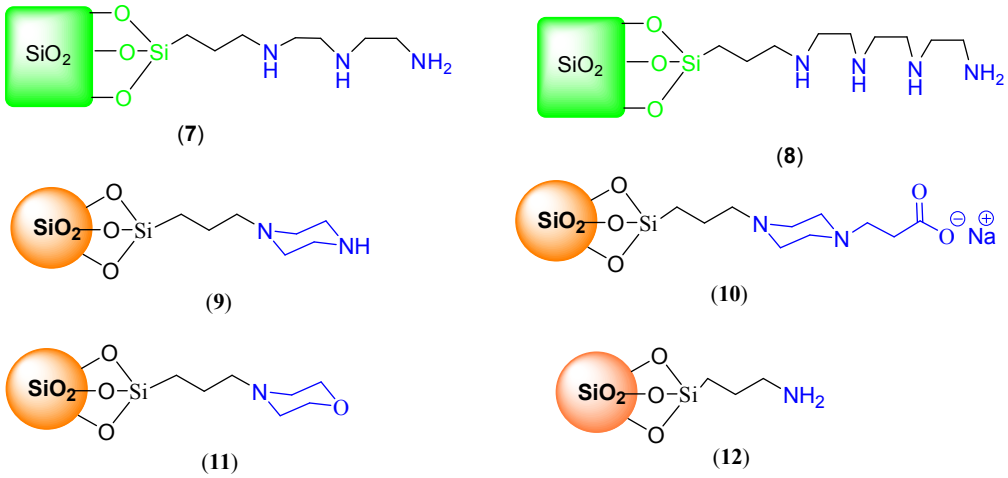


Fig. 2. The structure of silica-bonded amines.

used.

Several types of propyl amine functionalized silica, hydrotalcites, and basic zeolites (microporous and mesoporous) have been synthesized and applied as an alternative to traditional amines in base catalyzing chemical transformations [38-48].

Recently, we prepared some silica immobilized amines such as; silica-bonded *N*-propyldiethylenetriamine (7) [43], silica-bonded *N*-propyltriethylenetetramine (8) [44], silica-bonded *N*-propylpiperazine (9) [49,50], silica-bonded *N*-propylpiperazine sodium *N*-propionate (10) [49,50], silica-bonded *N*-propylmorpholine (11) [51] and 3-silicapropyl amine (12) [52], and investigated their applications as heterogeneous solid bases in organic reactions [49-54] or using as ligand for stabilizing Pd nano particles [51,55-57] (Fig. 2).

EXPERIMENTAL

General

Chemicals were purchased from Merck and Aldrich chemical companies. For recorded ^{1}H NMR spectra we were using Bruker Ultrashield (400 MHz) in pure deuterated $CDCl_3$ or DMSO-d_6 solvent with tetramethylsilane (TMS) as internal standard. Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel Poly Gram SILG/UV254 plates. All the products are known compounds and were characterized by comparison of their IR, ^{1}H NMR and ^{13}C NMR spectroscopic data and their melting points with reported values [24-37]. Solid bases 7-12 [43,44,49-52] were prepared according to our previously reported procedure.

General Procedure for the Synthesis of 2-Amino-3,5-dicarbonitrile-6-thio-pyridines

A mixture of aromatic aldehyde (1 mmol), malononitrile (2 mmol), 2-amino-thiophenol (1 mmol), catalyst 7 (0.1 g, 5 × 10^{-7} mmol of OH^-) [43], in refluxing ethanol (5 ml) for the time specified in Table 2 (the progress of the reaction was monitored by TLC). After completion, warm ethanol (10 ml) was added and filtered. The remaining was washed with warm ethanol (2 × 5 ml) to separate catalyst. After cooling the organic phase the crude was precipitated and filtered to obtain products. For further purification the crude was recrystallized from ethanol (95%). The recovered catalyst was dried and reused for the subsequent runs.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(4-chloro-phenyl)-pyridine-3,5-dicarbonitrile (13a). M.p.: 230-232 °C (Lit. [28] 234-236 °C); IR (KBr): 3419, 3325, 3214, 2214, 1634, 1538, 1427, 1094, 1029, 874, 804 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 4.27 (s, 2H), 5.64 (s, 2H), 6.82-6.87 (m, 2H), 7.32-7.36 (m, 1H), 7.39-7.42 (m, 1H), 7.50-7.52 (m, 2H), 7.56-7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 87.1, 96.1, 109.9, 115.1, 115.8, 118.9, 129.5, 129.8, 129.9, 131.5, 132.3, 137.5, 137.9, 149.5, 159.4.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(3-chloro-phenyl)-pyridine-3,5-dicarbonitrile (13b). M.p.: 162-164 °C; IR (KBr): 3455, 3389, 3218, 2215, 1635, 1538, 1472, 1257, 1472, 1257, 1030, 874, 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.07 (s, 2H), 5.71 (s, 2H), 6.82-6.87 (m, 2H), 7.31-7.36 (m, 1H), 7.40-7.43 (m, 2H), 7.51-7.58 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 87.4, 96.1, 114.6, 114.8, 115.8, 118.9, 126.7, 128.5, 130.5, 131.1, 132.4, 134.8, 135.1, 137.9, 149.5, 156.9, 159.3, 168.6.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(4-bromo-phenyl)-pyridine-3,5-dicarbonitrile (13c). M.p.: 236-238 °C; IR (KBr): 3409, 3347, 3220, 2213, 1632, 1536, 1409, 1260, 1024, 876, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.27 (s, 2H), 5.66 (s, 2H), 6.82-6.87 (m, 2H), 7.32-7.36 (m, 1H), 7.40-7.45 (m, 3H), 7.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 86.7, 93.8, 107.9, 115.6, 115.9, 116.0, 116.9, 124.6, 131.1, 132.2, 132.3, 133.8, 137.7, 151.6, 160.0, 167.3.

2-Amino-6-(2-amino-phenylsulfanyl)-4-*p*-tolyl-pyridine-3,5-dicarbonitrile (13d). M.p.: 210-212 °C (Lit. [28] 208-210 °C); IR (KBr): 3421, 3322, 3212, 2215, 1630 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.25 (s, 3H, CH_3), 4.32 (brs, 2H, NH_2), 6.26 (brs, 2H, NH_2), 6.55 (t, 1H, ^3J = 5.0 Hz, Ar), 6.65 (d, 1H, ^3J = 8.1 Hz, Ar), 7.06 (dt, 1H, ^3J = 7.7 Hz, ^4J = 1.3 Hz, Ar), 7.14-7.18 (m, 3H, Ar), 7.23 (d, 2H, ^3J = 8.1 Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$ & two drops of DMSO-d_6): δ (ppm) 21.8, 87.5, 95.4, 110.2, 115.8, 115.8, 116.1, 118.5, 128.7, 129.9, 130.9, 132.3, 137.9, 141.3, 150.4, 158.8, 160.2, 168.0.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(4-methoxy-phenyl)-pyridine-3,5-dicarbonitrile (13e). M.p.: 229-231 °C (Lit. [28] 230-232 °C); IR (KBr): 3426, 3324, 3210, 2214, 1620 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.90 (s, 3H), 4.45 (s, 2H), 5.29 (s, 2H), 7.40 (d, 2H, ^3J =7.6 Hz), 7.54 (d, 2H, ^3J =7.6 Hz), 7.65-7.67 (m, 1H), 8.03-8.05 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 43.9, 87.0, 94.1, 107.9, 115.6, 115.8, 116.1, 116.3, 116.5, 116.9, 130.9, 131.5, 132.2, 137.7, 151.7, 157.9, 160.1.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(4-ethoxy-phenyl)-pyridine-3,5-dicarbonitrile (13f). M.p.: 201-204 °C; IR (KBr): 3425, 3323, 3211, 2215, 1620 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.15 (t, 3H, ^3J = 7.2 Hz), 3.58-3.64 (m, 2H), 4.65 (s, 2H), 5.59 (s, 2H), 6.82-6.87 (m, 2H), 7.33 (m, 2H), 7.53-7.55 (m, 3H), 7.74 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 23.1, 65.7, 86.7, 93.8, 108.0, 115.5, 115.8, 116.0, 116.3, 124.5, 131.1, 132.2, 132.3, 133.8, 137.6, 151.6, 157.8, 160.1.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(3-nitro-phenyl)-pyridine-3,5-dicarbonitrile (13g). M.p.: 191-192 °C; IR (KBr): 3424, 3321, 3212, 2214, 1621 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 4.27 (s, 2H), 5.51 (s, 2H), 7.15 (m, 1H), 7.20-7.24 (t, 2H, J = 8.8 Hz), 7.33 (m, 1H), 7.35 (s, 1H), 7.68 (s, 1H), 8.01-8.13 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 86.7, 93.8, 107.0, 115.6, 115.9, 116.8, 116.9, 124.1, 131.6, 132.2, 132.3, 133.6, 137.7, 151.8, 157.8, 160.3, 167.1.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(4-nitro-phenyl)-pyridine-3,5-dicarbonitrile (13h). M.p.: 207-209 °C, (Lit. [28] 206-208 °C); IR (KBr): 3426, 3320, 3214, 2215, 1622 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 4.59 (s, 2H), 5.57 (s, 2H), 6.82-6.88 (m, 2H), 7.33-7.34 (m, 1H), 7.45-7.49 (m, 3H), 7.75-7.77 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 88.86, 97.2, 111.1, 117.1, 125.8, 128.1, 129.7, 130.3, 130.4, 133.0, 133.8, 140.0, 140.3, 155.5, 158.0, 160.2.

2-Amino-6-(2-amino-phenylsulfanyl)-4-(4-cyano-phenyl)-pyridine-3,5-dicarbonitrile (13i). M.p.: 245-246 °C; IR (KBr): 3428, 3321, 3210, 2214, 1619 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.93 (s, 2H), 5.30 (s, 2H), 7.08 (d, 2H, ^3J = 8.0 Hz), 7.55 (m, 2H), 7.65-7.67 (m, 2H), 8.01 (d, 2H, ^3J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 86.7, 93.9, 107.9, 115.5, 115.8, 116.0, 116.9, 124.5, 131.0, 132.2, 133.8, 137.6, 146.2, 151.6, 157.8, 160.0.

2-Amino-4-phenyl-6-*p*-tolylsulfanyl)-pyridine-3,5-dicarbonitrile (13j). M.p.: 216-218 °C, (Lit. [25] 218-220 °C); IR (KBr): 3450, 3322, 3208, 2214, 1618, 1547, 1524, 1490, 1264, 808, 704 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.43 (s, 3H), 5.37 (s, 2H), 7.24 (d, 2H, ^3J = 8.2 Hz), 7.43 (d, 2H, ^3J = 8.2 Hz), 7.51-7.58 (m, 5H).^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 20.8, 86.9, 93.1, 114.9, 115.2, 123.4, 128.3, 128.6, 130.0, 130.2, 133.9, 134.8, 139.5, 158.5, 159.6, 166.5.

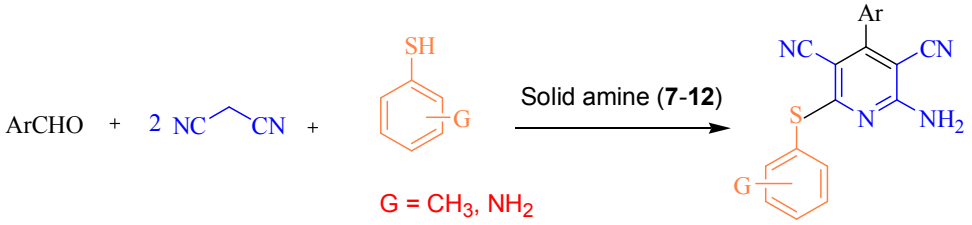
RESULTS AND DISCUSSION

In continuation our research on the design and application silica functionalized solid acids and bases as heterogeneous catalysts in organic transformations [43,44,49-57], we describe the application of silica-bonded amines (7-12) in the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives *via pseudo* four-component condensation reaction of aromatic aldehydes, malononitrile, thiophenols in refluxing ethanol (Scheme 1).

To this end, the reaction between 4-chloro-benzaldehyde (1 mmol), malononitrile (2 mmol), and 2-aminothiophenol (1 mmol) was selected as a model reaction to establish the feasibility of the strategy and optimize the reaction conditions. As shown in Table 1, the catalytic effect of solid bases 7-12 was studied as heterogeneous base catalysts. All of these silica immobilized amines were accomplished this *pseudo* four-component condensation reaction in refluxing ethanol.

The model reaction was converted into corresponding product in a higher yield using solid amine 7 as catalyst (Table 1, entry 4). The lower amounts of 7 (0.05 and 0,07 g) was converted the model reaction in longer reaction time and lower yield (Table 1, entries 2 and 3) and using higher amounts of the catalyst (0.15 g) did not improve the result to an appreciable extent (Table 1, entry 5). The model reaction was treated in solvents such as methanol, dichloromethane, chloroform, water, and acetonitrile in the presence of 7 (0.1 g) at reflux conditions (Table 1, entries 6-10). The condensation reaction under solvent-free conditions at 100 °C gave corresponding product in 85% yield after 50 min (Table 1, entry 11). So, the optimum conditions was aromatic aldehyde (1 mmol), malononitrile (2 mmol), thiophenol (1 mmol), and 7 (0.1 g) in refluxing ethanol.

To explore the generality and efficiency of the current protocol, malononitrile and 2-aminothiophenol were reacted with different aromatic aldehyde derivatives and the corresponding products were obtained in high yields. Results indicate that both electron-donating and electron-withdrawing substituents on the benzaldehyde ring were well tolerated under optimized conditions. As it is clear in Table 2, the reactions of benzaldehyde having substituents such as 4-Me-, 4-OMe- and 4-OEt- with malononitrile and 2-aminothiophenol were proceeded efficiently to generate the 2-amino-3,5-dicarbonitrile-6-thiopyridine derivates in high yields. Also, benzaldehyde substituted halogens (such as 4-Cl-, 3-Cl- and 4-Br-) and electron-withdrawing groups (such as 3-NO_2-, 4-NO_2-, 4-CN-) converted into the corresponding products after 30 to 45 min in high yields (Table 2, entries 1-3 and 7-9). In addition, the reaction of malononitrle, benzaldehyde and 4-methyl-thiophenol gave the corresponding product in high yields (Table 2, entry 10).



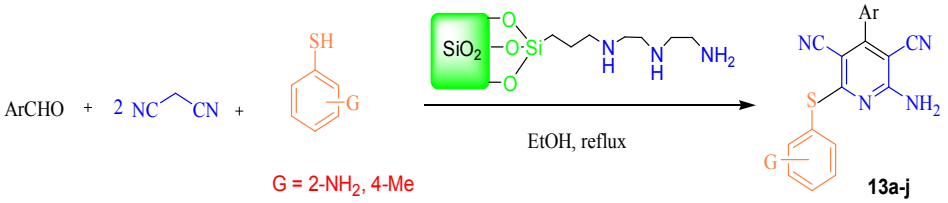
Scheme 1. Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

Table 1. Investigation the Effect of Catalysts and Solvents on the Reaction of 4-Chloro-benzaldehyde, Malononitrile and 2-Amino-thiophenol in Different Conditions[a]

Entry	Catalyst	Catalyst loading (g)	Solvent	Time (min)	Yield (%)[b]
1	-	-	Ethanol	24 h	-
2	7	0.05	Ethanol	60	60
3	7	0.07	Ethanol	45	70
4	7	0.1	Ethanol	30	90
5	7	0.15	Ethanol	30	90
6	7	0.1	Methanol	30	90
7	7	0.1	Dichloromethane	60	70
8	7	0.1	Chloroform	50	65
9	7	0.1	Water	80	-
10	7	0.1	Acetonitrile	60	65
11	7	0.1	Solvent-free/100 °C	50	85
12	8	0.1	Ethanol	35	90
13	9	0.1	Ethanol	60	80
14	10	0.1	Ethanol	50	87
15	11	0.1	Ethanol	40	75
16	12	0.1	Ethanol	50	75

[a]Reaction conditions; aromatic aldehyde (1 mmol), malononitrile (2 mmol), and 2-amino-thiophenol in 5 ml of solvent under reflux conditions. [b]Isolated yield.

Table 2. Synthesis of 2-Amino-3,5-dicarbonitrile-6-thio-pyridines Using 7 as Catalyst in Refluxing Ethanol

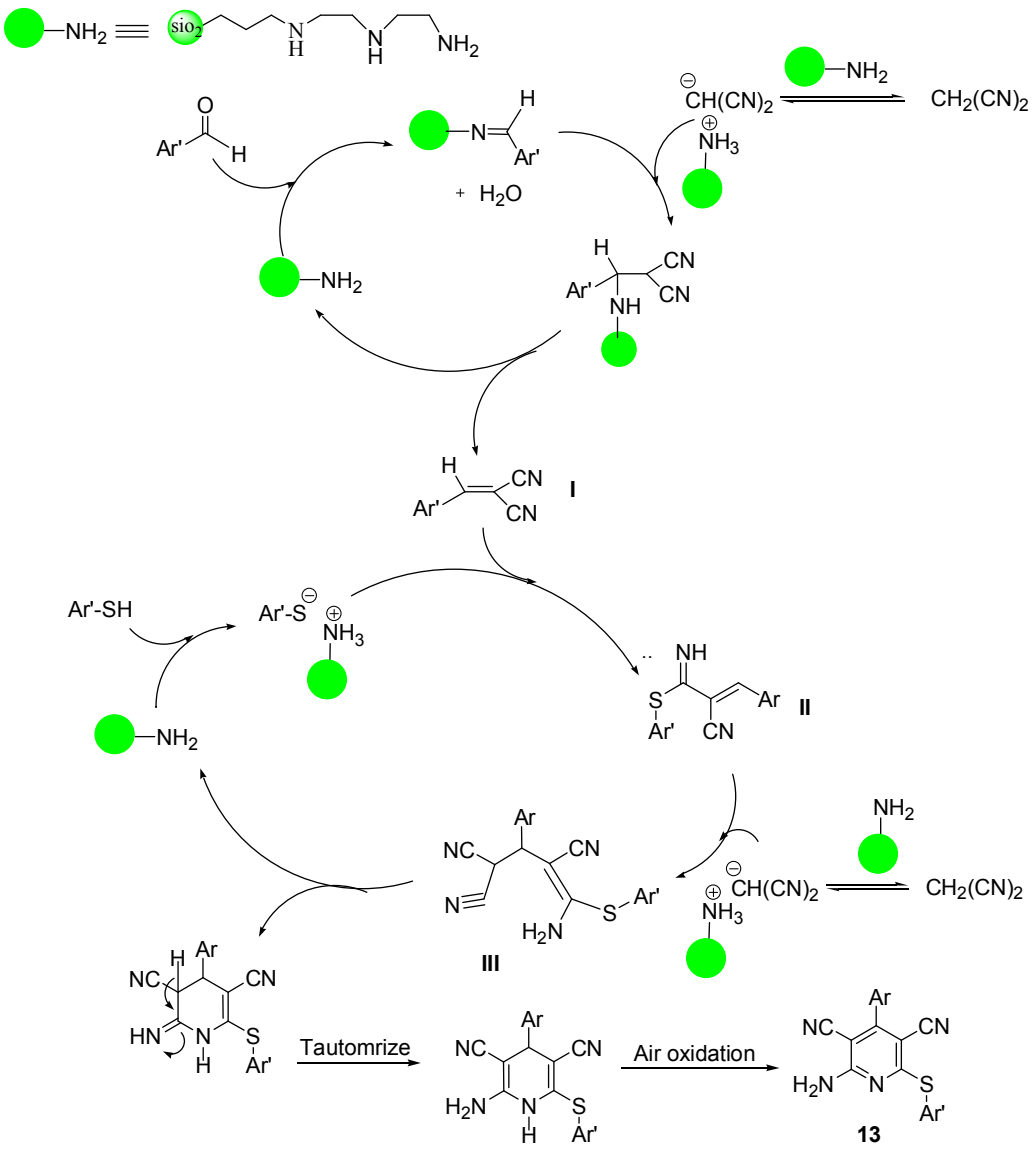


Entry	Ar	G	Product	Time (min)	Yeild (%)[a]	M.p. (°C)	Lit. M.p. (°C)
1	4-Cl-C_6H_4-	2-NH_2	13a	30	90	230-232	234-236 [28]
2	3-Cl-C_6H_4-	2-NH_2	13b	35	85	162-164	-
3	4-Br-C_6H_4-	2-NH_2	13c	40	80	236-238	-
4	4-Me-C_6H_4-	2-NH_2	13d	30	90	210-212	208-210 [28]
5	4-MeO-C_6H_4-	2-NH_2	13e	35	80	229-231	230-232 [28]
6	4-EtO-C_6H_4-	2-NH_2	13f	30	85	201-204	-
7	3-O_2N-C_6H_4-	2-NH_2	13g	40	80	191-192	-
8	4-O_2N-C_6H_4-	2-NH_2	13h	35	80	207-208	206-208 [28]
9	4-NC-C_6H_4-	2-NH_2	13i	45	75	245- 246	-
10	C_6H_5-	4-Me	13j	40	88	216-218	218-220 [25]

[a]Isolated yield.

A proposed mechanism for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines 13 was described in Scheme 2 [35,49]. The first step of the process involves the Knoevenagel condensation of an aldehyde with malononitrile to form the corresponding α-cyanocinnamonitrile (I). The solid base moiety of the catalyst (NH_2 or NH) activates the malononitrile and thiol, and its solid acid moiety (NH_3^+) activates the nitrile of the Knoevenagel product I. The reaction proceeds through thiolate addition to nitrile of the α-cyanocinnamonitrile (I) to form intermediate II which followed by Michael addition of the second molecule of malononitrile to produce intermediate III. Finally, intermediate III after cyclization and tautomrization produces dihydropyridine. Air oxidation of dihydropyridine adduct under the reaction conditions gives corresponding 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives (Scheme 2).

The possibility of recycling the catalyst 7 was examined using by the reaction of 4-chlorobenzaldehyde, malononitrile, and 2-aminothiophnol under the optimized conditions. Upon completion, the reaction mixture was filtered while hot. The remaining was washed with warm ethanol (2 × 5 ml). The separated catalyst was dried and reused as such for subsequent experiments under similar reaction conditions. The results showed that the catalyst could be effectively used for at least nine consecutive cycles without much appreciable loss in its catalytic activity (Fig. 3).



Scheme 2. Proposed mechanism for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

CONCLUSIONS

In conclusion, this work shows that silica-bonded amines as solid bases which can be prepared by simple operation from commercially available and relative cheap starting materials; efficiently catalyzed the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines. It could also be recovered and reused for several times without noticeable loss of reactivity.

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