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ARTICLE

One-pot synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyranes and pyridopyrimidines under mild conditions

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1,8-Diazabicyclo[5.4.0]undec-7-ene immobilized on silica (SB-DBU)Cl as a reusable and heterogeneous catalyst was applied for the one-pot, three-component synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles and pyridopyrimidines, under solvent-free conditions. The reaction was carried out at room temperature, and pure products were obtained in high yields and short reaction times (3–7 min). This work introduced an environmentally benign procedure for the synthesis of these classes of biological active compounds.

KEYWORDS

ambient conditions, kojic acid, pyridopyrimidines

1 | INTRODUCTION

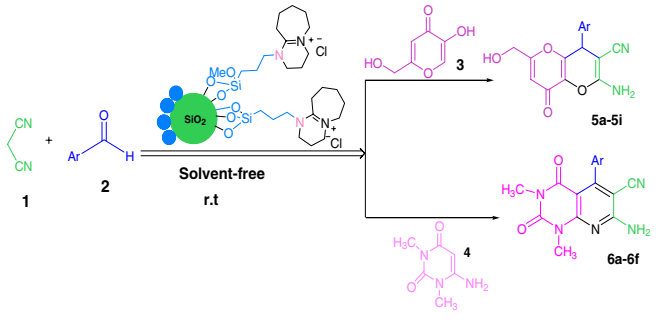
Multicomponent reactions (MCRs) are one of the most dominant approaches for the green synthesis of organic compounds. They are atom economic and efficient, and they show a high bond-forming index.[1] Therefore, MCRs have been considered a suitable and green alternative to sequential multistep synthesis.[2–6] However, not all MCRs are actually green if 1 or more of the 12 green chemistry principles[7] are violated, such as utilization of nonrecoverable catalysts, poisonous solvents, pollutants chemical reagents, etc.[8–10]

Polysubstituted 2-amino-4*H*-dihydropyrano-pyranes are important biologically active compounds that have profound medical applications.[11,12] Furthermore, pyridopyrimidine derivatives have attracted significant attention due to their various biological activities, including antitumor,[13] antimicrobial,[14] antileishmanial,[15] and calcium channel antagonist[16] activities. In this regard, many MCRs have been reported for the synthesis of polysubstituted 2-amino-4*H*-pyran-3-carbonitrile and pyridopyrimidine derivatives.[17–20] However, most of these methods suffer from disadvantages such as long reaction times, use of toxic solvents, and nonreusable catalysts.

In continuation of our developments for the synthesis of organic compounds using MCRs,[21–23] herein, we report a green and practical method for the preparation of 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles via a three-component reaction of aromatic aldehyde, malononitrile, and kojic acid in the presence of (SB-DBU)Cl as a catalyst (Scheme 1). We also report the synthesis of corresponding pyridopyrimidine derivatives by the replacing 6-amino1, 3-dimethyl uracil for kojic acid in the mentioned reaction (Scheme 1).

2 | RESULTS AND DISCUSSION

To find the optimum conditions, the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), and kojic acid (1 mmol) was selected as a model under solvent-free conditions. Various amounts of (SB-DBU)Cl as a catalyst were investigated in this reaction at room temperature. The results are



SCHEME 1 Preparation of 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles (5a–5i) and pyridopyrimidines (6a–6f)

summarized in Table 1. As shown as Table 1, the best result was obtained at 0.10 g of the catalyst at room temperature.

Using this optimization, we applied a wide variety of aryl aldehydes containing electron-withdrawing and electron-donating groups to afford the corresponding 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles in high yields (Table 2, Entries 1–8).

In such a previous method, we used various aromatic aldehydes in the reaction of 6-amino1,3-dimethyl, malononitrile, and aldehydes to obtain the desired substituted pyridopyrimidines (Table 2, Entries 9–14).

According to literature,[24,25] the plausible mechanism for the synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles was described in Scheme 2. (SB-DBU)Cl catalyzed the Knoevenagel reaction from aryl aldehyde (1) and malononitrile (2). Afterward, kojic acid (5) was reacted with Knoevenagel product (4) via 1,4-Michael addition, followed by cyclization, to give compound (9). Compound 9 was converted to the final product 10 after proton transfer and tautomerization (Scheme 2).

To demonstrate the importance of this research, we compared the results of the present method with the other reported works in the literature[24–28] (Table 3). The results show that our protocol is the most efficient with respect to the reaction time and yield.

Finally, reusability of the catalyst was investigated. For this purpose, the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), and kojic acid (1 mmol) was considered a model in the presence of (SB-DBU)Cl (0.1 g) as a catalyst at room temperature. After completion of the reactions, the catalyst was separated by simple filtration, washed with ethanol, and dried in the oven at 65°C. The recovered catalyst was reused for at least four runs without any significant loss of its activity (Figure 1).

3 | EXPERIMENTAL

3.1 | Materials and measurements

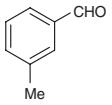
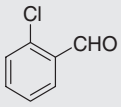
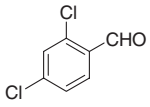
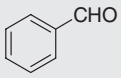
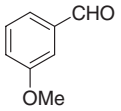
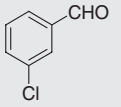
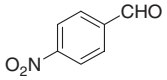
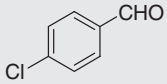
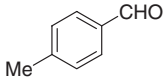
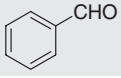
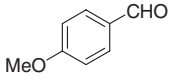
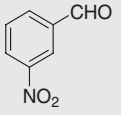
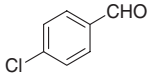
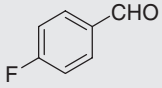
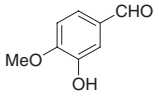
All reagents were purchased from Merck or Aldrich and used without further purification. All yields refer to isolated products after purification. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Advance DPX 400 MHz instrument. The spectra were measured in dimethyl sulfoxide-d_6 relative to tetramethylsilane. Infrared (IR) spectra were recorded using a JASCO FT-IR 460 Plus

TABLE 1 Optimization of the reaction conditions for the synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles under solvent-free and ambient conditions

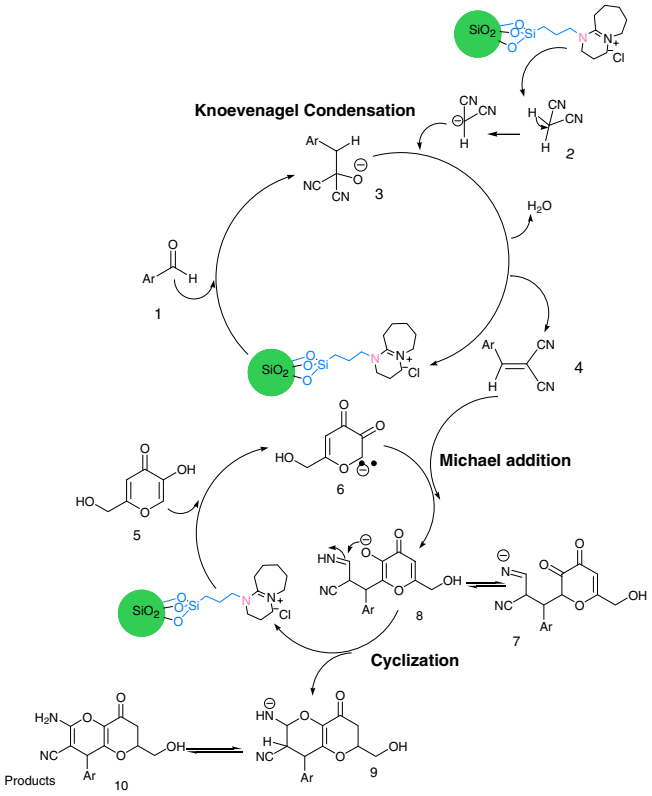
Entry	Catalyst (g)	Time (min)[b]	Yield (%)[a,b]
1	0.07	8	83
2	0.08	7	85
3	0.09	6	90
4	0.1	4	91
5	0.2	3	91
6	0.25	3	91

[a] Yields refer to the isolated pure products.
[b] Reaction of kojic acid (1 mmol), malononitril (1 mmol), and benzaldehyde (1 mmol).

TABLE 2 Preparation of 2-amino-4,8-dihydropyrano[3,2-b] pyrane-3-carbonitriles (5a–5h) and pyridopyrimidines (6a–6f)

Entry	Substrate	Time	Yield[a] (%)	Mp. [find] Mp. [literature]
1		3	98	218–220 219–221[24][5a]
2		5	90	211–215 210–213[24][5b]
3		5	93	242–243 240–242[24][5c]
4		4	96	217–219 220–222[24][5d]
5		3	94	220–223 225–227[20][5e]
6		5	92	237–239 238–240[25][5f]
7		4	90	231–233 230–232[25][5g]
8		5	95	233–236 235–237[25][5h]
9		3	97	220–222 221–223[25][5i]
10		7	87	263 268[26][6a]
11		3	89	270 272[26][6b]
12		4	90	289 284[26][6c]
13		3	89	288 291[26][6d]
14		3	91	279 276[26][6e]
15		6	86	271 276[26][6f]

[a] Yields refer to the isolated pure products.



SCHEME 2 The suggested mechanism for the preparation of 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles

spectrophotometer. Melting points were determined in open capillaries using a BUCHI 510 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica-gel Poly Gram SIL G/UV 254 plates. (SB-DBU)Cl was prepared according previous procedure.[29]

3.2 | General procedure for the preparation of 2-amino-4,8-dihydropyrano[3,2-b]pyrane-3-carbonitriles

A mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), kojic acid (1 mmol), and (SB-DBU)Cl (0.10 g) was stirred at room temperature. The completion of the reaction was monitored by TLC. After completion of reaction, the mixture was dissolved in hot ethanol, and the catalyst was filtered. The filtrated solution was concentrated, and the solid product was recrystallized in EtOH to give pure products.

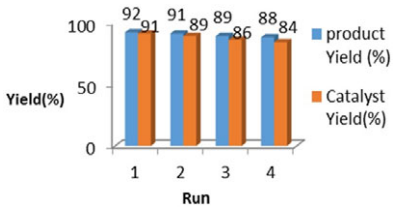


FIGURE 1 The reusability of the catalyst

3.3 | General procedure for the preparation of pyridopyrimidines

A mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), 6-amino1,3-dimethyl uracil (1 mmol), and (SB-DBU)Cl (0.1 g) was stirred at room temperature. The completion of the reaction was monitored by TLC. After completion of reaction, the mixture was dissolved in hot ethanol, and the catalyst was filtered. The filtrated solution was concentrated, and the solid product was recrystallized in EtOH to give pure products.

The structure of all known products was confirmed by comparing their physical properties with those of known samples in the literature.[24–28]

2-amino-4-(2-chlorophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxopyrano[3,2-b]pyran-3-carbonitrile (5b, Table 1 Entry 2): Mp. 211–215°C; IR (KBr) cm^{-1}:3,365, 3,190, 2,195, 1,646, 1,620, 1,591, 1,439, 1,409, 1,310, 1,256, 1,198, 1,046, 741. ^{1}H NMR (400 MHz, DMSO-d_6): 4.17 (m, 2H), 5.36 (s, 1H), 5.66 (t, 1H, J = 6.0 Hz), 6.30 (s, 1H), 7.23–7.433 (m, 4H), 7.91 (s, 2H) ppm; ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 59.3, 59.6, 111.8, 128.2, 129.3, 129.8, 130.6, 133.1, 136.4,141.1, 151.1, 160.3, 167.9 (6, 168.7, 170.0 ppm.

2-amino-4-(4-Nitrophenyl)-4,8-dihydro-6-(hydroxymethyl)-8-oxopyrano[3,2-b]pyran-3-carbonitrile (5g, Table 1 Entry 7): Mp. 230–232°C; IR (KBr) cm^{-1}:3,538, 3,452, 3,329, 2,195, 1,649, 1,591, 1,340. ^{1}H NMR (400 MHz, DMSO-d_6): 4.19 (m, 2H), 5.0 (s, 1H), 5.69 (t, 1H, J = 6.0 Hz), 6.33 (s, 1H), 7.55 (d, 2H, J = 8.8 Hz),7.95 (s, 2H), 8.20 (d, 2H, J = 8.8 Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 40.3, 59.5, 111.9, 124.3, 129.6, 136.6, 147.1, 150.6, 151.0, 160.1, 167.7, 168.7 ppm.

7-amino-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6c, Table 1 Entry 11): Mp. 289°C; IR (KBr) cm^{-1}:3,540, 3,385, 2,215, 1,706, 1,664, 1,630, 1,560, 1,531, 1,436, 1,348, 1,091,

TABLE 3 Comparison results of (SB-DBU)Cl for the preparation of 2-amino-4,8-dihydropyrano[3,2-b]pyranes as a catalyst with the other reported catalyst

Entry	Catalyst	Conditions[b]	Time (min)	Yield (%)[a]
1	(SB-DBU)Cl (0.10 g), this work	Solvent-free, r.t	3–7	89–98
2	Ultrasound irradiation[24]	H_2O, 50°C	5–25	5–25
3	MCM-41-SO_3H (30 mg)[25]	H_2O, 90°C	35–50	87–95
4	Nano-ZnO (0.03 g)[27]	EtOH, reflux	60–120	81–94
5	Imidazol (20 mol%)[28]	EtOH, reflux	60–90	83–89

[a] Yields refer to the isolated pure products.
[b] The reaction of kojic acid (1 mmol), malononitril (1 mmol), and aromatic aldehydes (1 mmol).

1,041. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.09 (3H, s), 3.52 (3H, s), 7.61–7.71 (4H, m), 8.07 (1H, s), 8.24 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1, 30.0, 89.1, 115.2, 122.8, 123.4, 129.7, 134.2, 139.0, 147.8, 151.1, 154.0, 156.8, 159.1, 160.7 ppm

4 | CONCLUSIONS

We have offered an environmentally friendly synthetic procedure for the synthesis of 2-amino-4,8-dihydropyrano [3,2-b]pyrane-3-carbonitriles and pyridopyrimidines using (SB-DBU)Cl as a heterogeneous catalyst. Mild reaction conditions, very easy workup, successful recycling system, use of nontoxic solvent, short reaction time (3–7 min), and high yields are worthy advantages of our work. This green approach may not only lead to an ecofriendly benign system but will also present a newer aspect of green chemistry for the synthesis of organic compounds.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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