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SHORT COMMUNICATION

A new one-pot three-component synthesis of 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile derivatives

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Abstract In this study, a three-component one-pot synthesis of new 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles derived from 2-amino-1,1,3-tricyanopropene, salicylic aldehydes and secondary cyclic amines is reported. The reaction is conducted in ethanol at ambient temperature in good-to-excellent yields.

Keywords Chromeno[2,3-*b*]pyridine · 2-Amino-1,1,3-tricyanopropene · Multicomponent coupling reaction · One-pot reaction · Catalyst-free reaction

Introduction

Multicomponent reactions (MCRs) are always resource effective and environmentally acceptable and thus greener as compared to multi-step reactions [1]. They offer significant advantages over conventional linear step syntheses by way of reducing time, saving money, energy and raw-materials thus resulting in both economical and environmental benefits [1]. Multicomponent coupling reactions (MCCRs) are highly efficient strategies to achieve the rapid assembly of complex products, especially sequential carbon–carbon and carbon–heteroatom bond-forming reactions in the area of heterocycles and natural products [1].

Chromenopyridines have been reported to have antiproliferative [2], cancer chemopreventive [3], antibacterial [4, 5], antimyopic [6], hypotensive [7] and antiasthmatic activities [8]. For example, chromeno[2,3-*b*]pyridine has reported to inhibit mitogen activated protein kinase-activated protein kinase 2 and attenuate the production of pro-inflammatory cytokine TNF-α [9]. Amlexanox is another approved drug with chromeno[2,3-*b*]pyridine framework which is a commonly prescribed antiallergic and topical antiulcer agent [10].

A few methods have been reported for the synthesis of chromeno[2,3-*b*]pyridine derivatives by a MCR of malononitrile with aldehydes and thiols in the presence of triethylamine as a catalyst under reflux conditions in ethanol [9–12]. As a consequence, the search for new methodologies and development of new synthetic routes proceeding more efficiently without using catalyst and activation still remains an active area of research in chromenopyridines now.

Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. All the products are new compounds, which were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra and Mass Spectroscopy.

Typical procedure for the synthesis of 2,4-diamino-5-(piperidin-1-yl)-5H-chromeno[2,3-*b*]pyridine-3-carbonitrile (**4a**)

A solution of salicylaldehyde (0.122 g, 1 mmol), piperidine (0.094 g, 1.1 mmol) and ATCP (0.132 g, 1 mmol) was stirred for 2 h in 5 mL of ethanol at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 5/1), the solid product was filtered off and washed with further water to give **4a** as pure yellowish-white solid.

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Compounds characterization data

2,4-Diamino-5-(piperidin-1-yl)-5*H*-chromeno[2,3-*b*] pyridine-3-carbonitrile (**4a**)

Yellowish-white solid: mp 234–236 °C. IR (KBr) cm^{-1}: 3466, 3368, 3310, 3173, 2931, 2849, 2814, 2782, 2209, 1645, 1609, 1566, 1485, 1464, 1402. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.16–1.20 (2H, m, CH_2), 1.32–1.35 (4H, m, $2CH_2$), 2.20–2.22 (4H, m, $2CH_2-N$), 4.87 (1H, s, CH–N), 6.50 (4H, br s, $2NH_2$), 7.08–7.30 (4H, m, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.7, 26.4, 48.9, 55.8, 71.3 (CH_2), 88.7 (CH–N), 116.5 (C–Ar), 117.0 (CN), 118.1, 123.4, 129.1, 130.0, 152.3, 158.7, 160.2, 160.9 (C-Ar). MS m/z: 237 (M^+ − 84, 100), 171 (25), 84 (30), 56 (15).

2,4-Diamino-7-bromo-5-(piperidin-1-yl)-5*H*-chromeno[2,3-*b*] pyridine-3-carbonitrile (**4b**)

Yellowish-white solid: mp 248–250 °C. IR (KBr) cm^{-1}: 3425, 3330, 3284, 3190, 2935, 2784, 2204, 1635, 1614, 1562, 1477, 1411. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.18–122 (2H, m, CH_2), 1.32–1.36 (4H, m, $2CH_2$), 2.17–2.20 (4H, m, $2CH_2-N$), 4.89 (1H, s, CH–N), 6.53 (4H, br s, $2NH_2$), 7.01 (1H, d, J = 8.8, H–Ar), 7.37 (1H, br, H–Ar), 7.50 (1H, d, J = 8.6, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.7, 26.4, 48.9, 55.5, 55.7, 71.4 (CH_2), 88.9 (CH–N), 101.4, 110.0, 110.3 (C–Ar), 116.0 (CN), 130.7, 153.2, 158.7, 159.8, 160.2, 160.8 (C–Ar). MS m/z: 380 (M^+–19, ^{81}Br, 4), 378 (M^+–21, ^{79}Br, 3), 317 (100), 315 (90), 301 (9), 299 (10), 273 (20), 67 (20), 39 (15).

2,4-Diamino-8-methoxy-5-(piperidin-1-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**4c**)

Yellowish-white solid: mp 243–245 °C. IR (KBr) cm^{-1}: 3453, 3330, 3284, 3180, 2953, 2784, 2199, 1635, 1565, 1503, 1403. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.00–1.05 (2H, m, CH_2), 1.24–1.26 (4H, m, $2CH_2$), 2.12–2.16 (4H, m, 2 CH_2–N), 3.75 (3H, s, OCH_3), 4.81 (1H, s, CH–N), 6.48 (4H, br s, $2NH_2$), 6.66–7.14 (3H, m, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.7, 26.4, 48.9, 55.5 (CH_2), 55.7 (OCH_3), 71.4 (CH_2), 88.9 (CH–N), 101.4, 110.0, 110.3 (C–Ar), 116.0 (CN), 130.7, 153.2, 158.7, 159.8, 160.2, 160.8 (C–Ar). MS m/z: 330 (M^+–21, 6), 305 (2), 267 (100), 224 (15).

2,4-Diamino-9-methoxy-5-(piperidin-1-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**4d**)

Yellowish-white solid: mp 240–242 °C. IR (KBr) cm^{-1}: 3435, 3303, 3161, 2897, 2814, 2784, 2206, 1619, 1589, 1562, 1484, 1464, 1402. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.02–1.06 (2H, m, CH_2), 1.24–1.27 (4H, m, $2CH_2$), 2.20–2.24 (4H, m, $2CH_2$–N), 3.80 (3H, s, OCH_3), 4.86 (1H, s, CH–N), 6.48 (4H, br s, $2NH_2$), 6.78–7.05 (3H, m, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 24.7, 26.4, 48.9, 55.5 (CH_2), 55.7 (OCH_3), 71.37 (CH_2), 88.9 (CH–N), 101.4, 110.0, 110.3 (C–Ar), 117.0 (CN), 130.7, 153.2, 158.7, 159.8, 160.2, 160.8 (C–Ar). MS m/z: 352 ($M^+ + 1$, 30), 298 (100), 269 (84), 208 (15), 98 (18), 81 (22), 67 (20), 55 (50), 41 (55).

2,4-Diamino-5-morpholino-5*H*-chromeno[2,3-*b*] pyridine-3-carbonitrile (**4e**)

Yellowish-white solid: mp 243–245 °C. IR (KBr) cm^{-1}: 3472, 3350, 3310, 3170, 2963, 2849, 2814, 2794, 2210, 1645, 1605, 1567, 1489, 1464, 1402. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.20–2.24 (4H, m, $2CH_2$–N), 3.32–3.36 (4H, m, $2OCH_2$), 4.93 (1H, s, CH–N), 6.47 (2H, br s, NH_2), 6.56 (2H, br s, NH_2), 7.13–7.33 (4H, m, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 48.0, 55.1 (CH_2–N), 66.8, 71.2 (OCH_2), 87.9 (CH–N), 116.5 (C–Ar), 117.0 (CN), 117.7, 123.5, 129.3, 130.1, 152.4, 158.5, 160.4, 161.2 (C–Ar). MS m/z: 324 ($M^+ + 1$, 10), 298 (100), 269 (38), 208 (20), 98 (15), 81 (12), 67 (42), 55 (36), 41 (40).

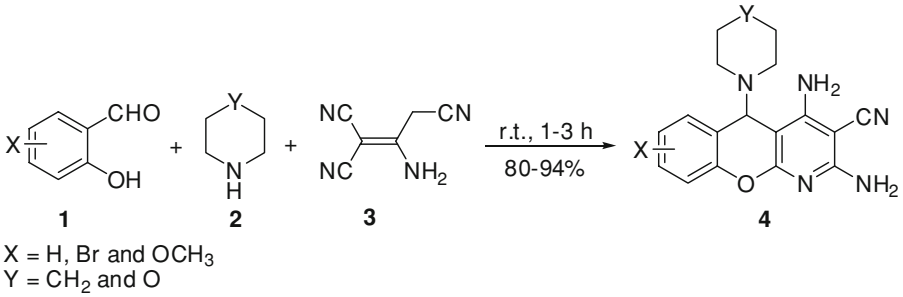
2,4-Diamino-7-bromo-5-morpholino-5*H*-chromeno [2,3-*b*] pyridine-3-carbonitrile (**4f**)

Yellowish-white solid: mp 258–260 °C. IR (KBr) cm^{-1}: 3444, 3330, 3310, 3190, 2963, 2944, 2849, 2831, 2794, 2200, 1645, 1616, 1564, 1489, 1478, 1409. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.16–2.20 (4H, m, $2CH_2$–N), 3.40–2.44 (4H, m, 2 OCH_2), 4.93 (1H, s, CH–N), 6.56 (2H, br s, NH_2), 6.62 (2H, br s, NH_2), 7.12 (1H, d, J = 8.6, H–Ar), 7.36 (1H, br s, H–Ar), 7.52 (1H, d, J = 7.1, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 47.9, 54.8 (CH_2–N), 66.8, 71.4 (OCH_2), 87.3 (CH–N), 115.0 (C–Ar), 116.9 (CN), 118.9, 120.0, 132.1, 151.7, 158.5, 160.4, 160.8 (C–Ar). MS m/z: 380 (M^+–21, ^{81}Br, 5), 378 (M^+–23, ^{79}Br, 4), 355 (4), 353 (4), 315 (100), 313 (100), 237 (10), 87 (30), 57 (60), 30 (33).

2,4-Diamino-8-methoxy-5-morpholino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (**4g**)

Yellowish-white solid: mp 238–240 °C. IR (KBr) cm^{-1}: 3463, 3359, 3310, 3171, 2953, 2831, 2814, 2794, 2201, 1626, 1601, 1562, 1503, 1404. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.17–2.20 (4H, m, $2CH_2$–N), 3.40-2.43 (4H, m, $2OCH_2$), 3.75 (3H, s, OCH_3), 4.87 (1H, s, CH–N), 6.51 (2H, br s, NH_2), 6.57 (2H, br s, NH_2), 6.67–7.16 (3H, m, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 48.0, 54.8 (CH_2–N), 55.8 (OCH_3), 66.9, 71.3 (OCH_2), 88.2 (CH–N), 101.4, 109.9, 110.1 (C–Ar), 117.0 (CN), 130.8, 153.4, 158.5, 156.0, 160.3,

Scheme 1 Synthesis of chromeno[2,3-*b*]pyridines **4a–h**



161.1 (C–Ar). MS *m*/*z*: 354 ($M^+ + 1$, 14), 298 (100), 269 (26), 208 (20), 98 (36), 81 (18), 67 (30), 55 (44), 41 (60).

2,4-Diamino-5-(pyrrolidin-1-yl)-5*H*-chromeno[2,3-*b*] pyridine-3-carbonitrile (**4h**)

Yellowish-white solid: mp 225–227 °C. IR (KBr) cm^{-1}: 3465, 3366, 3310, 3175, 2931, 2849, 2782, 2209, 1645, 1609, 1564, 1485, 1464, 1402. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 1.15–1.35 (4H, m, $2CH_2$), 2.25–2.45 (4H, m, $2CH_2$–N), 4.88 (1H, s, CH–N), 6.52 (4H, br s, $2NH_2$), 7.05–7.35 (4H, m, H–Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 26.4, 48.5, 55.6, 68.4 (CH_2), 88.6 (CH–N), 116.4 (C–Ar), 117.2 (CN), 118.1, 123.4, 129.3, 130.0, 152.3, 158.5, 160.2, 161.5 (C–Ar). MS *m*/*z*: 307 (M^+, 10), 237 (100), 171 (25), 84 (30), 56 (15).

Results and discussion

In our continuing interest in MCRs [13–19], herein, we wish to report a MCCR which affords a new class of 2,4-diamino-5*H*-chromeno[2,3-*b*] pyridine-3-carbonitrile derivatives **4a–h** *via* the one-pot three-component reaction of salicylic aldehydes **1**, secondary cyclic amines **2** and 2-amino-1,1,3-tricyanopropene (ATCP) **3** in ethanol at room temperature in good to excellent yields (Scheme 1).

In a pilot experiment, ATCP, salicylaldehyde and piperidine were stirred in ethanol at room temperature to obtain yellowish-white solid product. The progress of the reaction was monitored by TLC. After 2 h, the reaction was completed and an aqueous workup afforded 2,4-diamino-5-(piperidin-1-yl)-5*H*-chromeno[2,3-*b*] pyridine-3-carbonitrile **4a** in 94% yield.

In view of the success of the above reaction, we explored the scope of this promising reaction by varying the structure of the salicylic aldehyde and amine component (Table 1). The reaction proceeds very fast and cleanly under mild conditions at room temperature and no undesirable side reactions were observed under these reaction conditions.

Regarding the substituents effects on the salicylic aldehyde ring, it should be mentioned that, a slight decrease in yield can be seen between entries 2 and 3 and also 6 and 7 in an electron withdrawing Br in comparison with an electron-donating OMe group. Similar decreasing in yields were observed when morpholine (entries 5–7) is used instead of piperidine (entries 1–4).

Table 1 Synthesis of chromeno[2,3-*b*]pyridines **4a–h** using ATCP in ethanol at room temperature

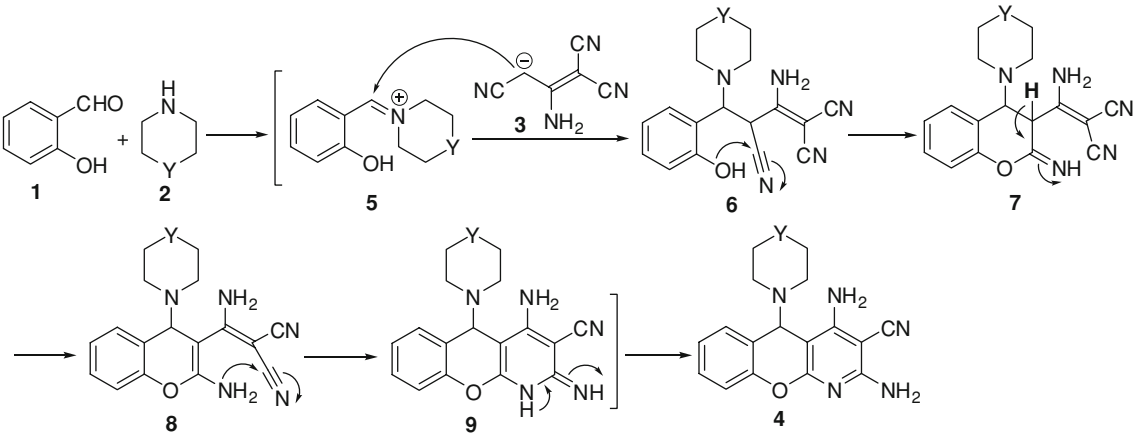
Entry	X	Y	Product	Time (h)	Yield[a] (%)
1	H	CH_2	**4a**	2	94
2	5-Br	CH_2	**4b**	2.5	94
3	4-OMe	CH_2	**4c**	1	88
4	3-OMe	CH_2	**4d**	3	90
5	H	O	**4e**	2	84
6	5-Br	O	**4f**	2.5	86
7	4-OMe	O	**4g**	1.5	82
8	H	–	**4h**	3	80

[a] Isolated yield

The possible mechanism for the formation of products **4a–h** is shown in Scheme 2. It is conceivable that the initial step is formation of the intermediate iminium ion **5**-from condensation of aldehyde **1** and amine **2**. Then, a nucleophilic attack by ATCP **3** gives **6**. After that, an intramolecular cyclization of **6** gives the intermediate **7** which undergoes a tautomerization to form intermediate **8**. The second intramolecular nucleophilic attack occurs by NH_2 group to form **9**. Finally, tautomerization and aromatization of **9** produces **4a–h**.

Conclusion

In summary, we have introduced a three-component condensation reaction leading to a new class of 2,4-diamino-5*H*-chromeno[2,3-*b*] pyridine-3-carbonitrile derivatives starting from simple and readily available precursors. This reaction can be regarded as a new approach for the preparation of synthetically and pharmaceutically relevant heterocyclic systems. This MCCR approach includes some important aspects such as high atom economy, mild reaction conditions, high yields and catalyst-free process involving no chromatography.



Scheme 2 Possible mechanism for the formation of products **4a–h**

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