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AN EFFICIENT AND MULTI-COMPONENT SYNTHESIS OF 5-IMINO-3,5-DIHYDRO-2*H*-CHROMENO[3,4-*c*]PYRIDIN-2-ONE DERIVATIVES

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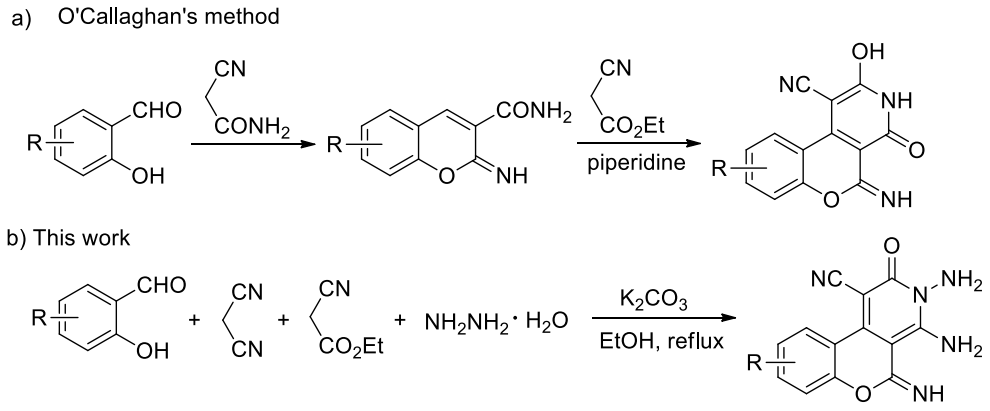
Abstract – A facile and efficient one-pot procedure for the synthesis of 5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one derivatives via a four-component reaction of salicylaldehyde, malononitrile, ethyl cyanoacetate and hydrazine hydrate under mild conditions in excellent yield is described. The structures of fused molecules have been unambiguously confirmed by their spectroscopic techniques as well as by single crystal X-ray analysis.

The chromene moiety appears as an important structural component in both biologically active and natural compounds.[1] Functionalized chromenes have been played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.[2] Recently, structures containing the chromene and pyridine skeleton are rapidly gaining importance in synthetic and natural product chemistry. Chromenopyridine derivatives have been found to possess wide spectrum pharmacological activities, including antibacterial,[3] anti-inflammatory,[4] antimicrobial,[5] anti-proliferative,[6] hypotensive,[7] anti-histaminic,[8] antirheumatic,[9] anti-asthmatic,[10] and anticancer[11] activities. Only few synthetic approaches to chromenopyridines employing different reaction conditions and using salicylaldehyde as starting material have been previously described in literatures.[12]

The development of a simple and efficient reaction protocol for the synthesis of heterocyclic compound libraries of medicinal motifs is an attractive area of research in both academia and the pharmaceutical industry. One of the most promising approaches to this type of efficiency relies on the use of multi-component reactions (MCRs), which are promising and powerful tools in organic, combinatorial, and medicinal chemistry, because of their atom economy, high complexity and diversity of products, multiple

bond formation efficiency, and environmental friendliness.[13] In the past decade, there have been tremendous developments in three- and four-component reaction methods and significant efforts continue to be made to develop new MCRs.[14] These features make MCRs suitable for the easy construction of complex heterocyclic scaffolds from readily available starting materials.[15] In recent years, some MCRs have been used for the constructions of chromenopyridine[16] skeleton. O'Callaghan has developed the synthesis of 2-imino-5-hydroxy-3,4-dihydrochromeno[3,4-*c*]pyridin-3-one by two step using salicylaldehyde, cyanoacetamide and ethyl cyanoacetate (Scheme 1, a). As part of our current studies on the development of MCRs method for the synthesis of functionalized heterocycles,[18] we now describe a simple and efficient synthesis of novel 5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one derivatives via a four-component reaction (Scheme 1, b). The attractive features of this newly developed MCRs include a novel strategy for the construction of 5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one, which were easily achieved without the need for multistep operation.

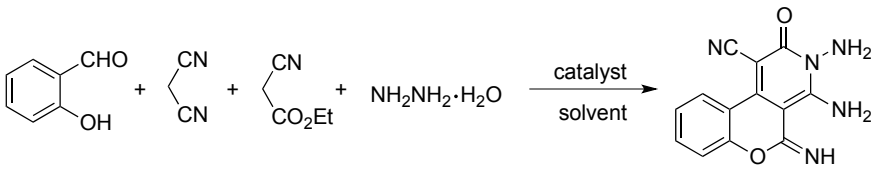


Scheme 1. The synthetic methods for 2-iminochromeno[3,4-*c*]pyridine derivatives

Initially, for optimization of the reaction conditions, a representative reaction of salicylaldehyde (**1a**), malononitrile (**2**), ethyl cyanoacetate (**3**) and hydrazine hydrate (**4**), which presumably affords the 5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one derivatives (**5a**), was performed under various conditions. The effect of catalysts, solvents and reaction temperatures were evaluated for this transformation, and the results are summarized in Table 1. It was found that when the four-component reaction was carried out in ethanol at refluxing temperature for 40 min without any catalyst, the desired product **5a** was obtained in 34% yield (Table 1, entry 1). To improve the yield, several catalysts were evaluated, i. e., sodium hydroxide, cesium carbonate, potassium carbonate, piperidine, and sodium ethoxide (Table 1, entries 2-6). The results showed that when potassium carbonate was used as the catalyst, the yield of product **5a** was increased to 70% (Tabale 1, entry 4). So the best catalyst for this reaction was potassium carbonate. Then various solvents were evaluated to determine the impact of the solvent on the yield. Of all the solvents tested, such as, ethanol, chloroform, dioxane, water, toluene, and

DMF, ethanol gave the best results (Table 1, entries 4 and 7-11). We also evaluated the amount of potassium carbonate required for this reaction. The results from Table 1 (entries 4 and 12-14) showed that 10 mol% potassium carbonate is sufficient to initiate the reaction. Higher loading of the catalyst had no significant influence on the reaction yield. To find the optimum reaction temperature, the reaction was carried out at room temperature, 40 °C, 60 °C, and refluxing temperature, resulting in the isolation of **5a** in a trace amount, 18%, 58%, and 70% yields (Table 1, entries 4 and 15-17), respectively. Based on all these experiments, the optimum reaction conditions were identified as using ethanol as solvent at refluxing temperature for 40 min catalyzed by 10 mol% potassium carbonate.

Table 1. Optimization of the reaction conditions for the synthesis of compound **5a**

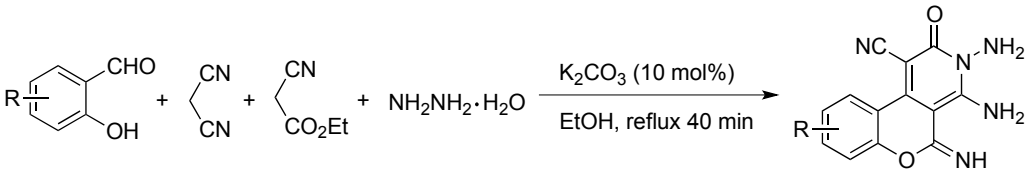


1a **2** **3** **4** **5a**

Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (min)	Isolated Yield (%)
1	EtOH	no	reflux	40	34
2	EtOH	NaOH (10)	reflux	40	trace
3	EtOH	Cs_2CO_3 (10)	reflux	40	68
4	EtOH	K_2CO_3 (10)	reflux	40	70
5	EtOH	piperidine (10)	reflux	40	54
6	EtOH	EtONa (10)	reflux	40	trace
7	$CHCl_3$	K_2CO_3 (10)	reflux	40	trace
8	dioxane	K_2CO_3 (10)	reflux	40	trace
9	H_2O	K_2CO_3 (10)	reflux	40	45
10	toluene	K_2CO_3 (10)	reflux	40	trace
11	DMF	K_2CO_3 (10)	reflux	40	37
12	EtOH	K_2CO_3 (5)	reflux	40	64
13	EtOH	K_2CO_3 (15)	reflux	40	70
14	EtOH	K_2CO_3 (20)	reflux	40	70
15	EtOH	K_2CO_3 (10)	25	40	trace
16	EtOH	K_2CO_3 (10)	40	40	18
17	EtOH	K_2CO_3 (10)	60	40	58

The optimized reaction conditions were then tested for library construction with eight salicylaldehydes **1a-h**. The corresponding 5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one derivatives **5a-h** were obtained in good yields at refluxing temperature in ethanol catalyzed by potassium carbonate. The results are summarized in Table 2. It was found that salicylaldehydes bearing either electron-withdrawing or electron-donating groups were tolerated under the reaction conditions, leading to the final products in satisfactory yields (66-91%). Moreover, the pure products can be simply obtained by washing the crude products with cold ethanol. It is indicated that this synthetic method was confirmed to follow the GAP (group-assisted-purification) chemistry process,[19] which can avoid the traditional recrystallization or chromatography purifications.

Table 2. The synthesis of 5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one derivatives **5**



1 **2** **3** **4** **5**

Entry	Compound	R	Isolated Yield (%)
1	**5a**	H	70
2	**5b**	7-MeO	88
3	**5c**	8-MeO	80
4	**5d**	9-F	89
5	**5e**	9-Cl	91
6	**5f**	9-Br	90
7	**5g**	7,9-Cl_2	70
8	**5h**	7,9-Br_2	66

The structures of the products synthesized in the current study were identified using IR, ^{1}H NMR, and ^{13}C NMR spectroscopies, and HRMS analysis. The structure of compound **5a** was confirmed using single-crystal X-ray diffraction analysis.[20] The crystal structure of compound **5a** was shown in Figure 1.

Based on the references,[21] the proposed mechanism for the formation of compound **5** is shown in Scheme 2. The intermediate **A** was formed by the Knoevenagel condensation of salicylaldehydes (**1**) with malononitrile (**2**) catalyzed by K_2CO_3. The intermediate **A** was then transformation to intermediate **B** by the intramolecular cyclization. Then the Michael addition of intermediate B with ethyl cyanoacetate (**3**) catalyzed by K_2CO_3 was taken placed, and the intermediate C was formed. The intermediate **D** was

formed by the reaction of intermediate **C** with hydrazine hydrate (**4**). The desired product **5** was obtained by intramolecular cyclization, tautomerization and oxidation in air from the intermediate **D**.

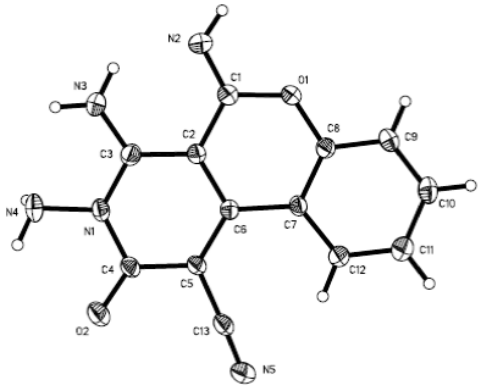
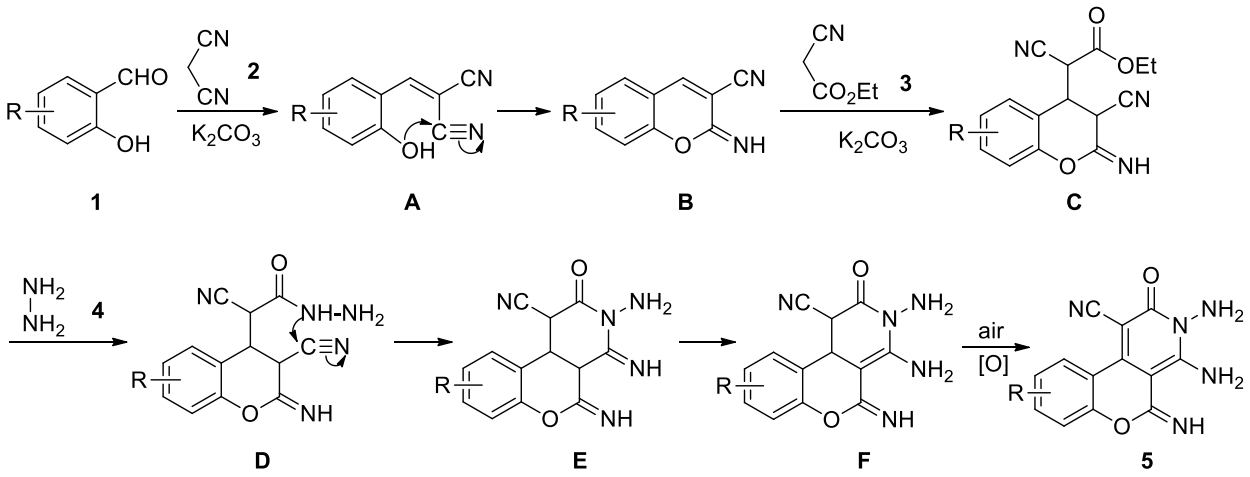


Figure 1. Crystal structure of compound **5a**



Scheme 2. The proposed mechanism for the formation of compound **5**

In summary, we have developed a simple and efficient protocol for the construction of 5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one derivatives via a novel four-component reaction of salicylaldehydes, malononitrile, ethyl cyanoacetate and hydrazine hydrate catalyzed by potassium carbonate. This protocol has the advantages of mild reaction conditions, short reaction times, convenient operation, high yields, and environmental friendliness.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR and ^{13}C NMR were determined on Agilent Invoa-400 MHz spectrometer in DMSO-d_6 solutions. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal

standard TMS. HRMS analyses were carried out using Bruker MicrOTOF-Q II instrument. X-Ray diffraction analysis was carried out on a Smart-1000 diffractometer.

Starting Materials. All chemicals used in this study were commercially available.

Typical experimental procedure for the synthesis of 5-amino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one derivatives 5. A mixture of salicylaldehydes **1** (1 mmol), malononitrile **2** (1 mmol), ethyl cyanoacetate **3** (1 mmol), hydrazine hydrate **4** (1 mmol), K_2CO_3 (0.1 mmol) and EtOH (2 mL) was stirred at 80 ºC for 40 min. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The precipitate was collected and washed with a little cold EtOH to give the pure products **5**.

1-Cyano-3,4-diamino-5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5a: Yellow solid; mp >300 °C; IR (KBr) 3348, 2932, 2210, 1677, 1503, 1352, 1267, 1214, 1160, 1106, 1037, 987, 917, 863, 811, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H, NH), 7.32-7.30 (m, 1H, ArH), 7.18-7.15 (m, ArH), 6.99-6.89 (m, 2H, ArH), 5.64 (s, 2H, NH_2), 3.43 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 158.2, 156.6, 154.0, 131.3, 129.2, 122.1, 119.0, 116.5, 116.2, 115.6, 87.6, 75.5; HRMS Calculated for $C_{13}H_8N_5O_2$: $[M-H]^+$ 266.0678, found: 266.0680.

1-Cyano-3,4-diamino-5-imino-7-methoxy-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5b: Yellow solid; mp >300 °C; IR (KBr) 3399, 3259, 2839, 2209, 1720, 1607, 1546, 1501, 1353, 1272, 1221, 1092, 1011, 917, 876, 762, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H, NH), 7.05 (d, J = 8.4 Hz, 1H, ArH), 6.90-6.55 (m, 2H, ArH), 5.60 (s, 2H, NH_2), 3.85 (s, 3H, CH_3O), 3.43 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 158.0, 156.7, 147.9, 143.3, 122.4, 120.5, 119.4, 116.5, 115.6, 113.0, 87.5, 75.6, 56.0; HRMS Calculated for $C_{14}H_{10}N_5O_3$: $[M-H]^+$ 296.0784, found: 296.0761.

1-Cyano-3,4-diamino-5-imino-8-methoxy-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5c: Yellow solid; mp >300 °C; IR (KBr) 3391, 3260, 2845, 2208, 1727, 1611, 1546, 1521, 1370, 1277, 1166, 1134, 1026, 948, 855, 774 cm^{-1}; ^1H NMR (400 MHz DMSO-d_6) δ 8.62 (s, 1H, NH), 7.06 (d, J = 7.6 Hz, 1H, ArH), 6.89 (t, J = 7.6 Hz, 1H, ArH), 6.75 (d, J = 7.6 Hz, 1H, ArH), 5.64 (s, 2H, NH_2), 3.85 (s, 3H, CH_3O), 3.36 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 157.9, 156.5, 147.8, 143.2, 122.3, 120.4, 119.2, 116.4, 115.5, 113.0, 87.5, 75.5, 55.9; HRMS Calculated for $C_{14}H_{10}N_5O_3$: $[M-H]^+$ 296.0784, found: 296.0762.

1-Cyano-3,4-diamino-9-fluoro-5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5d: Yellow solid; mp >300 °C; IR (KBr) 3328, 3280, 2954, 2211, 1673, 1587, 1497, 1349, 1226, 1195, 1222, 1032, 961, 916, 799, 773, 713 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H, NH), 7.18-7.09 (m, 2H,

ArH), 6.98-6.95 (m, 1H, ArH), 5.66 (s, 2H, NH_2), 3.43 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 156.9, 156.7, 155.0 (d, J = 234 Hz), 150.6, 122.8 (d, J = 8.0 Hz), 117.9 (d, J = 22 Hz), 117.4 (d, J = 8.0 Hz), 116.5, 115.8, 115.6, 87.5, 75.6; HRMS Calculated for $C_{13}H_7FN_5O_2$: $[M-H]^+$ 284.0584, found: 284.0579.

1-Cyano-3,4-diamino-9-chloro-5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5e: Yellow solid; mp >300 °C; IR (KBr) 3350, 2932, 2890, 2221, 1677, 1600, 1501, 1355, 1214, 1160, 1111, 1037, 917, 863, 833, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H, NH), 7.33 (d, J = 8.4 Hz, 1H, ArH), 7.25 (s, 1H, ArH), 6.97 (d, J = 8.8 Hz, 1H, ArH), 5.65 (s, 2H, NH_2), 3.49 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 156.8, 156.6, 153.7, 130.9, 128.5, 123.8, 122.0, 118.1, 116.4, 115.5, 87.4, 75.5; HRMS Calculated for $C_{13}H_7ClN_5O_2$: $[M-H]^+$ 300.0288, found: 300.0287.

1-Cyano-3,4-diamino-9-bromo-5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5f: Yellow solid; mp >300 °C; IR (KBr) 3459, 3288, 2957, 2212, 1692, 1563, 1501, 1477, 1399, 1347, 1269, 1180, 1122, 1077, 1034, 963, 916, 873, 824 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H, NH), 7.43 (d, J = 8.8 Hz, 1H, ArH), 6.35 (s, 1H, ArH), 6.93 (d, J = 8.8 Hz, 1H, ArH), 5.65 (s, 2H, NH_2), 3.52 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 156.8, 156.7, 154.1, 134.0, 131.4, 124.4, 118.6, 116.6, 115.7, 109.6, 87.5, 75.7; HRMS Calculated for $C_{13}H_7BrN_5O_2$: $[M-H]^+$ 343.9783, found: 343.9777.

1-Cyano-3,4-diamino-7,9-dichloro-5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5g: Yellow solid; mp >300 °C; IR (KBr) 3333, 2931, 2888, 2219, 1674, 1599, 1501, 1456, 1211, 1161, 1100, 927, 867, 830, 721 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H, NH), 7.65 (s, 1H, ArH), 7.32 (s, 1H, ArH), 5.71 (s, 2H, NH_2), 3.45 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 156.8, 155.7, 149.2, 130.8, 127.7, 125.9, 123.2, 122.7, 116.2, 115.3, 87.8, 75.6; HRMS Calculated for $C_{13}H_6Cl_2N_5O_2$: $[M-H]^+$ 333.9899, found: 333.9887.

1-Cyano-3,4-diamino-7,9-dibromo-5-imino-3,5-dihydro-2*H*-chromeno[3,4-*c*]pyridin-2-one 5h: Yellow solid; mp >300 °C; IR (KBr) 3311, 3060, 2203, 1737, 1676, 1491, 1343, 1245, 1177, 1143, 1037, 961, 911, 864, 803, 773, 729 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H, NH), 7.87 (s, 1H, ArH), 7.45 (s, 1H, ArH), 5.73 (s, 2H, NH_2), 3.41 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 159.2, 155.1, 150.1, 137.8, 133.5, 120.6, 112.8, 111.9, 110.9, 110.7, 87.8, 75.6; HRMS Calculated for $C_{13}H_6Br_2N_5O_2$: $[M-H]^+$ 421.8888, found: 421.8881.

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20. Crystal data for **5a**: $C_{13}H_9N_5O_2$, Monoclinic, space group $P2_1/n$, a = 7.0622(10) Å, b = 9.2415(13) Å, c = 17.120(2) Å, β = 97.9840(10)°, V = 1106.5(3) Å^3, Mr = 267.25, Z = 4, Dc = 1.604 Mg/m^3, λ = 0.71073 Å, μ(Mo Kα) = 0.115 mm^{-1}, $F(000)$ = 552, R = 0.0865, wR = 0.2472, largest diff. peak and hole: 0.348 and -0.383 e/ Å^3.
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