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An efficient and one-pot green synthesis of novel 6-oxo-7-aryl-6,7-dihydrochromenopyrano[2,3-*b*]pyridine derivatives

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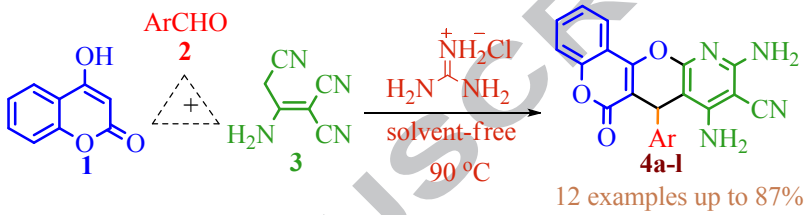

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An efficient and one-pot green synthesis of novel 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*]pyridine derivatives

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ABSTRACT

A simple and efficient protocol has been developed for the construction of novel 6-oxo-7-aryl-6,7-dihydrochromenopyrano[2,3-*b*]pyridine derivatives using one-pot, three-component cyclocondensation of 4-hydroxycoumarin, various aromatic aldehydes and 2-aminoprop-1-ene-1,1,3-tricarbonitrile using 10 mol % guanidine hydrochloride as the organocatalyst under solvent-free conditions at 90 °C for the first time. The significant features of this protocol are operational simplicity, provide good to high yields, avoidance of toxic solvents, straightforward work-up, no column chromatographic purification and atom-economy which is considered to be relatively environmentally benign.

The chromene skeleton is considered as one of the most important heterocyclic ring systems in organic synthetically chemistry and is implanted in many edible fruits and vegetables.[1] These compounds have occupied an important place in drug research because of their various biological and pharmacological activities such as antioxidant, antileishmanial, antibacterial, antifungal, hypotensive, anticoagulant, antiviral, diuretic, antiallergenic, and antitumor activities.[2] Other properties such as laser dyes,[3] optical brighteners,[4] fluorescence markers,[5] pigments,[6] cosmetics, and potent biodegradable agrochemicals[7] are well known for decades. Recently, there have been many methods reported for the preparation of chromenes and their derivatives such as dihydropyrano[3,2-*c*]chromenes by three-component condensations of 4-hydroxycoumarin, aldehydes and malononitrile in the presence of different catalysts such as basic ionic liquid,[8] thiourea dioxide,[9] ammonium acetate,[10] potassium phthalimide,[11] Fe_3O_4 nanoparticles,[12] $Mg(ClO_4)_2$,[13] Na_2SO_4,[14] iron ore pellet,[15] potassium phthalimide-*N*-oxyl (POPINO),[16] tetragonal ZrO_2 nanoparticle (t-ZrO_2 NP),[17] potassium sodium tartrate,[18] nano-Al_2O_3,[19] Ni@Imine-Li^+-MMT[20] and nano-SiO_2.[21]

2-Aminoprop-1-ene-1,1,3-tricarbonitrile has attracted a great deal of interest due to its wide applications in the field of pharmaceuticals.[22] The title reagent had great applicability in heterocyclic synthesis since it was used for the synthesis of pyridines, pyrimidines, pyridazines, thiophenes, thiazoles and their analogs.[23,24] It should be noted that this compound in the synthesis of chromene derivatives has been less widely used, and few articles have been reported so far in literature.[25,26] Recently, we have reported an efficient tandem reaction approach to the synthesis of 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridines from 2,3-dihydroxynaphthalene, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and aldehydes using 10 mol % guanidine hydrochloride as the catalyst under solvent-free conditions.[27] Thus, in view of the importance of chromenes for diverse therapeutic activity and in continuation to our endeavor of developing methodologies aimed at synthesis of polyfunctionalized heterocyclic moieties,[28] we considered it necessary to develop a general rapid, high yielding, environmentally benign and easy synthetic protocol for a variety of chromene derivatives.

We report in this paper, an efficient and one-pot synthesis of a variety of chromene derivatives namely 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*]pyridines **4**, catalyzed by guanidine hydrochloride as organocatalyst. In order to find the most appropriate reaction conditions and to evaluate the catalytic efficiency of guanidinium chloride, a model study was conducted to determine the best conditions for the synthesis of 8,10-diamino-6-oxo-7-phenyl-6,7-dihydrochromeno[3',4':5,6] pyrano[2,3-b]pyridine-9-carbonitrile (**4a**) (Table 1). The solvents H_2O, CH_3CN, EtOH, 1,4-dioxane, THF, and solvent-free conditions in the presence of 10 mol % guanidinium chloride catalyst were tested (Table 1, entries 1-8). As can be seen in Table 1, the reaction was found to proceed slowly in the protic solvents under reflux and a low yield of the product observed after 150 min (Table 1, entries 1-2). Also, it was revealed that the reaction did not proceed in the presence of the catalyst when the reaction was carried out in refluxing aprotic solvents such as CH_3CN, THF and 1,4-dioxane for 150 min (Table 1, entries 3-5). In the next step, the model reaction was also examined under solvent-free conditions in the presence of the 10 mol% catalyst. The reaction was conducted at a range of temperatures, including 70, 90 and 120 °C. It was found that, by increasing temperature from 70 °C to 90 °C the yield of the product was improved (Table 1, entries 6-7). It should be noted that by increasing reaction time at 90 °C showed no significant change in the yield of the reaction. The yield also decreased by increasing temperature from 90 °C to 120 °C (Table 1, entry 8). We also evaluated the quantity of catalyst required for the synthesis of compound **4a** at 90 °C. Catalyst loadings in the range of 5–20 mol% were tested (Table 1, entries 7, 9-11). A low yield of the product was observed in the presence of the 5 mol% catalyst. Loading of the catalyst from 10 to 20 mol% did not improve yields to a greater extent. Thus,

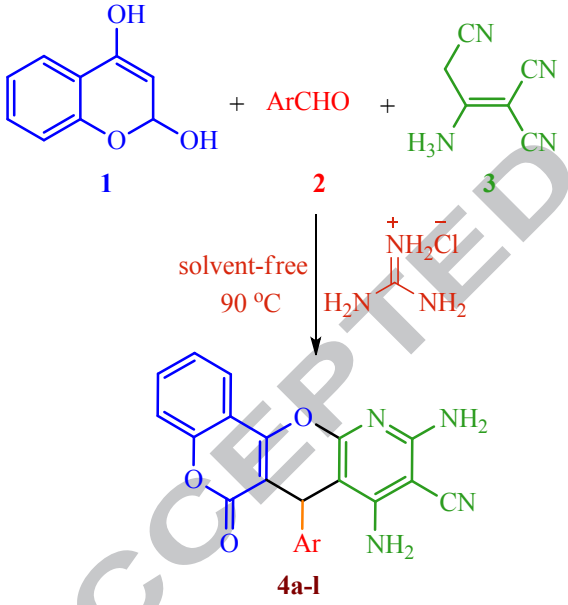
loading of 10 mol% guanidine hydrochloride under solvent-free conditions was sufficient to push the reaction forward (Table 1, entry 7).

Table 1. Optimization of reaction conditions for the synthesis of **4a**[a]

Entry	Amount of catalyst	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	10 mol%	H_2O	reflux	150	30
2	10 mol%	EtOH	reflux	150	25
3	10 mol%	CH_3CN	reflux	150	-
4	10 mol%	1,4-dioxane	reflux	150	-
5	10 mol%	THF	reflux	150	-
6	10 mol%	-	70	90	70
7	**10 mol%**	**-**	**90**	**60**	**82**
8	10 mol%	-	120	60	73
9	5 mol%	-	90	60	65
10	15 mol%	-	90	60	83
11	20 mol%	-	90	60	83

[a]Reaction conditions: 4-hydroxycoumarin (1.0 mmol), benzaldehyde (1.0 mmol), and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (1.0 mmol), solvent 5 mL.
[b]Isolated yields.

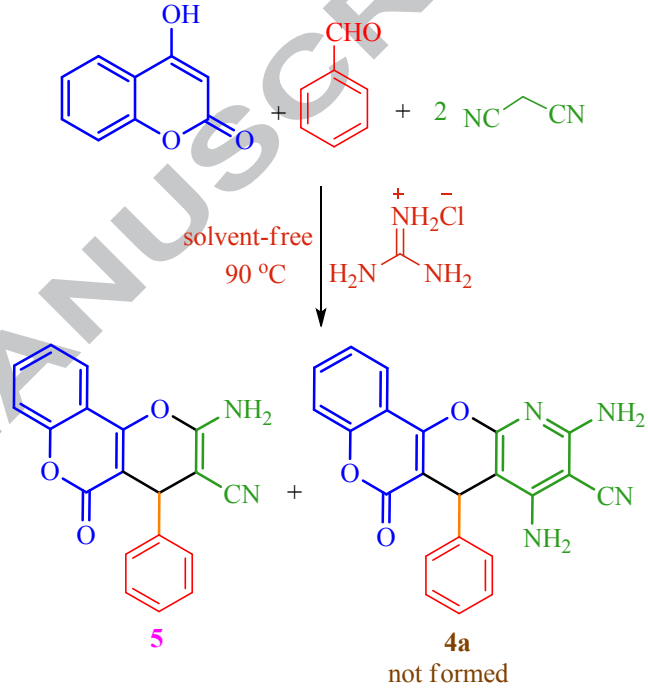
Using the optimized conditions (solvent-free, 10 mol% catalyst, 90 °C), a series of products **4a–l** were synthesized with this simple reaction procedure (Scheme 1).[29] The reaction time and percentage yield for each of the products are presented in Figure 1.



Scheme 1. Synthesis of 6-oxo-7-aryl-6,7-dihydrochromenopyrano [2,3-*b*]pyridine derivatives **4**

The results indicated that this guanidine hydrochloride catalyzed three-component reaction worked well for a wide range of aryl aldehydes possessing various functional groups including electron-donating and electron-withdrawing substituents. In all cases, the reaction proceeded smoothly to produce the corresponding product in good to high yield. However, when some aliphatic aldehydes such as acetaldehyde and propionaldehyde were used in this protocol under the above optimized conditions, unfortunately, the expected products could not be obtained. It should be noted that the purification of the title compounds is very easy. After cooling the reaction mixture to room temperature, CH_3CN was added to the mixture and the solid products were formed, which can be easily separated by simple filtering. The crude product was stirred for 5 min in boiling CH_3CN and the resulting precipitate was filtered and the pure product was obtained.

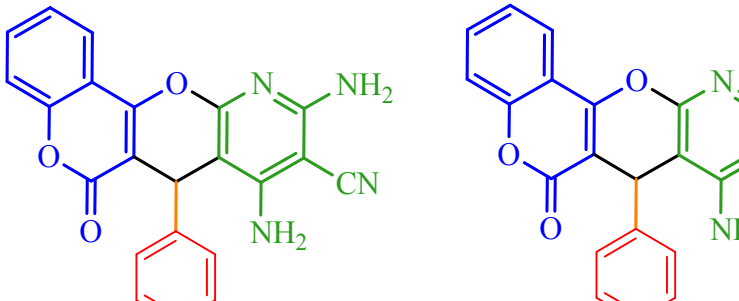
Encouraged by the successful cyclocondensation of 4-hydroxycoumarin, various aromatic aldehydes and 2-aminoprop-1-ene-1,1,3-tricarbonitrile under solvent-free conditions to give 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*]pyridine derivatives, we next attempted on the formation of the product **4a** by executing the reaction of 4-hydroxycoumarin (1.0 mmol) and benzaldehyde (1.0 mmol) with double molar ratios of malononitrile under similar reaction conditions. The result showed that the product 2-amino-4-phenyl-5-oxo-4H,5H-pyrano-[3,2-c]chromene-3-carbonitrile (**5**) was obtained as only product instead of expected target product **4a** (Scheme 2).



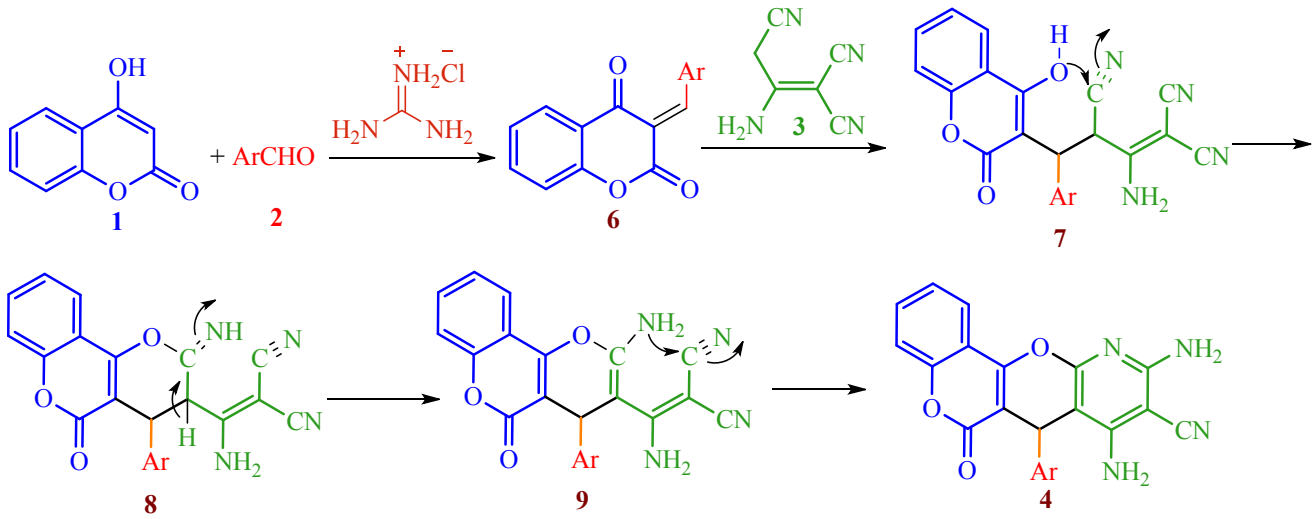
Scheme 2. Synthesis of pyrano-[3,2-*c*]chromene **5**

Identification of **4a–l** was carried out on the basis of ^{1}H-NMR, ^{13}C-NMR, FT-IR, mass spectra and elemental analysis. It is very important to mention here that in the Mass spectra of these compounds showed the base peak at m/z = 305 which is related to the general fragmentation pattern in these compounds include loss of the phenyl derivatives. This fragmentation also confirms the structure of the synthesized compounds.

The proposed mechanism for the preparation of 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*]pyridines is depicted in Scheme 3. As is shown, nucleophilic attack of 4-hydroxycoumarin to the activated aldehyde (by guanidine hydrochloride), followed by H_2O elimination provides intermediate **6**. Next, the Michael addition of 2-aminoprop-1-ene-1,1,3-tricarbonitrile (activated by guanidine hydrochloride) to intermediate **6** provides the intermediate **7** which then undergoes tautomerization and subsequent intramolecular cyclization twice, to afford final the corresponding 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*]pyridines **4**.



In summary, we demonstrated a simple and direct route for the one-pot green synthesis of novel 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*]pyridines from easily available substrates using guanidinium chloride as organocatalyst. The reactions were carried out under solvent-free conditions at 90 ^{o}C produced the corresponding products in good to high yields. The notable advantages of this work are simple workup, avoidance of



Scheme 3. Proposed mechanism for the guanidinium chloride catalyzed synthesis of 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*] pyridines **4**

toxic solvents, no column chromatographic purification which is considered to be relatively environmentally benign.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version.

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29. General procedure for the synthesis of 6-oxo-7-aryl-6,7-dihydrochromeno pyrano[2,3-*b*]pyridines 4: In a 25 mL round bottom flask, a mixture of 4-hydroxycomarin (1.0 mmol), aldehyde (1.0 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (1.0 mmol) and guanidine hydrochloride (10 mol %) were taken, and the mixture was stirred at 90 °C in an oil bath for appropriate amount of time as indicated in Figure 1. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and CH_3CN (5 mL) was added and then a precipitate was allowed to form. The precipitate was filtered, washed with CH_3CN and dried. The crude product was stirred for 5 min in boiling CH_3CN and the resulting precipitate was filtered. The product 4 thus obtained was found to be pure upon ^1H and ^{13}C-

NMR, mass spectra, elemental analyses, and TLC examination.

8,10-Diamino-6-oxo-7-phenyl-6,7-dihydrochromeno[3',4':5,6]pyrano[2,3-b]pyridine-9-carbonitrile (4a): Light brown powder; m.p. = 340 °C (dec.); IR (KBr, cm^{-1}): 3440, 3340, 3239, 3043, 2846, 2210, 1716, 1654, 1612, 1562, 1481, 1369, 1268, 1187, 1049; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.92 (s, 1H, methine-H), 6.38 (s, 2H, NH_2), 6.47 (s, 2H, NH_2), 6.87-7.00 (m, 3H, Ar-H), 7.12-7.22 (m, 4H, Ar-H), 7.39-7.45 (m, 1H, Ar-H),7.63 (d, 1H, *J* = 7.8 Hz, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): 72.45, 90.78, 105.99, 114.04, 116.38, 116.97, 117.00, 122.84, 125.25, 127.37, 128.64, 133.14, 143.23, 152.52, 154.99, 157.33, 157.49, 160.13, 160.39, 160.87; MS m/z (%): 382 $(M)^+$, 306, 305 (100), 277, 252, 239, 223, 211, 185, 169, 157, 140, 121, 105, 93, 92, 91, 77; Anal. calcd. for $C_{22}H_{14}N_4O_3$: C, 69.11; H, 3.66; N, 14.66. Found: C, 69.17; H, 3.59; N, 14.71.

Highlightes

- One-pot synthesis of 6-oxo-7-aryl-6,7-dihydrochromenopyrano[2,3-*b*]pyridines was described.
- Guanidine hydrochloride as the organocatalyst was used.
- Aromatic aldehydes containing various functional groups are well tolerated in the reaction.
- Double heterocyclization was carried out in the reaction.