Eco-friendly construction of highly functionalized chromenopyridinones by an organocatalyzed solid-state melt reaction and their optical properties

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Sanjay Paul and Yong Rok Lee*

The library construction of highly functionalized and diverse chromenopyridinones was achieved by three-component reactions of various 4-hydroxycoumarins with ammonium acetate and 3-formylchromones under L-proline catalyzed solid-state melt conditions. The advantages of this protocol include the use of an inexpensive organocatalyst, avoidance of toxic organic solvents, environmentally benign conditions, easy work-up procedure and good to excellent product yields. The optical properties of these π-expanded varieties of synthesized chromenopyridinone derivatives were also examined. A chromeno[4,3-*b*]pyridine nucleus bearing an electron donating group exhibited strong emission in the blue-green region of the visible spectrum.

Introduction

The chromenopyridinone framework bearing two main cores of a chromene and a pyridine ring is found widely in biologically interesting and active molecules.[1] The chromenopyridinone-containing molecules possess a range of biological activities, such as anti-inflammatory,[2] antibacterial,[3] antifungal,[4] anticancer,[5] and α-adrenergenic antagonists.[6] They have been used for the treatment of bronchitis and asthma[7] and as a building block for the synthesis of fluorescent pH sensors.[8] Among these, chromeno[4,3-*b*]pyridine **1** exhibited potent tumor growth and metastasis inhibitory activities by targeting topoisomerases[9] and chromeno[4,3-*b*]pyridinone **2** exhibited potent anticancer activity (Fig. 1).[10] Compound **3** bearing a chromeno[4,3-*b*]pyridine ring possesses antibacterial and antimicrobial activity.[11] Schumanniophytine (**4**) and isoschumanniophytine (**5**), which were isolated from the rootbark of *Schumanniophyton magnificum*, have potential antiviral activities.[12]

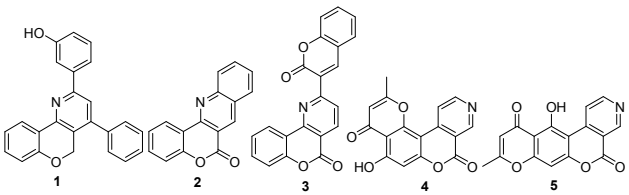
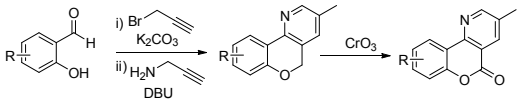


Fig. 1 Bioactive and naturally occurring molecules bearing chromenopyridinone moiety

School of Chemical Engineering, Yeungnam University, Gyeongsan 712-749, Republic of Korea
E-mail: yrlee@yu.ac.kr; Fax: +82-53-810-4631; Tel: +82-53-810-2529
†Electronic Supplementary Information (ESI) available: Spectroscopic data, ^{1}H NMR and ^{13}C NMR Spectra of synthesized compounds. See DOI: 10.1039/x0xx00000x

Owing to the importance of these compounds, several methods for the synthesis of chromeno[4,3-*b*]pyridines and chromeno[4,3-*b*]pyridinones have been reported. The representative approach for chromeno[4,3-*b*]pyridines includes an intramolecular Diels-Alder reaction of pyrimidines followed by a retro Diels-Alder reaction,[13] the $AuCl_3$-catalyzed [3+2+1] cycloaddition of an aldehyde with an aldimine of a glycine ester bearing a terminal triple bond,[14] and intramolecular Diels-Alder cycloaddition of 2-azadienes.[15] Other synthetic approaches for chromeno[4,3-*b*]pyridinones have been reported, such as the Suzuki-Miyaura cross coupling of bromo arylcarboxylates with o-hydroxyarylboronic acids[16] and by Cu(I)-mediated C-O lactone formation of 2-halobiarylcarboxylates.[17] Recently, a facile and efficient synthetic approach for chromeno[4,3-*b*]pyridinones was described in three steps via the intramolecular heterocyclization of O-propargylated aromatic hydroxyaldehydes as a key-step (Scheme 1).[18]

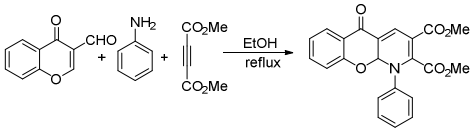


Scheme 1 Reported method for chromenopyridinones

Recently, multicomponent reactions (MCRs) have been widely used as a green and powerful tool in organic synthesis.[19] Although several methods for the synthesis of chromeno[4,3-*b*]pyridines and chromeno[4,3-*b*]pyridinones have been developed, more environmentally benign and efficient approaches are desirable. In this regard, organocatalysts are suitable for the construction of a wide variety of structurally diverse heterocyclic molecules because of the mild reaction conditions, environmental benignity, atom

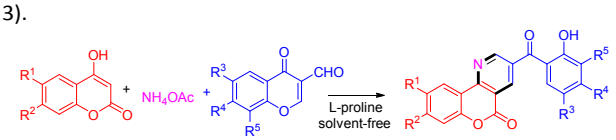
economy, and functional group tolerance.[20] In addition, a solid-state melt reaction (SSMR) is an economically attractive and environmentally acceptable synthetic tool for the construction of a wide range of structurally diverse heterocyclic motifs without using toxic, flammable, expensive, and hazardous organic solvents.[21]

Recently, the catalyst-free three-component reaction of 3-formylchromone, amine and dimethyl acetylenedicarboxylate in refluxing ethanol was developed to afford chromenopyridine in linear form (Scheme 2).[22] To the best of the authors' knowledge, there are no reports of the L-proline-catalyzed three-component condensation of 4-hydroxycoumarins, ammonium acetate and 3-formylchromones to furnish chromenopyridinone derivatives in an angular form under solid-state melt reaction conditions.



Scheme 2 Reported method for chromenopyridones by three-component reaction using 3-formylchromone

As part of an ongoing investigation into the synthesis of heterocycles,[23] this paper reports the L-proline-catalyzed construction of highly functionalized and diverse chromenopyridinones via a three-component reaction of 4-hydroxycoumarins with ammonium acetate and 3-formylchromones under a solid-state melt reaction (Scheme 3).

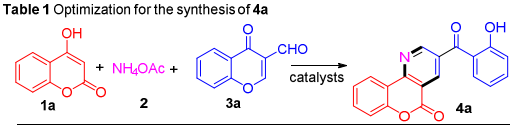


Scheme 3 Our protocol for the synthesis of diverse chromenopyridinones by three-component reaction

Results and discussion

To develop an efficient and an environmentally benign protocol for the construction of chromenopyridinone scaffold, a three-component reaction of 4-hydroxycoumarin (**1a**), ammonium acetate (**2**) and 3-formylchromone (**3a**) was first examined. The results are depicted in Table 1. A reaction of **1a** (1.0 mmol) with **2** (2.0 mmol) and **3a** (1.0 mmol) in the absence of any catalyst at 130 °C for 12 h afforded product **4a** in 20% yield (entry 1, Table 1). To optimize the reaction conditions, further reactions were carried out applying several Lewis acid and Brønsted acid catalysts. For example, the treatment of **1a** with **2** and **3a** in the presence of Lewis acid catalysts, such as 15 mol.% of $Cu(OTf)_2$, $FeCl_3$ and $In(OTf)_3$ under solvent-free conditions afforded the desired product **4a** in 30, 38 and 27% yield, respectively (entries 2-4, Table 1). With 15 mol.% of *p*-TsOH and AcOH as Brønsted acids, the yield was increased to 68 and 70%, respectively (entries 5-6, Table 1). Interestingly, with L-proline (15 mol.%), compound **4a** was isolated in 91% yield (entry 7, Table 1). Increasing (20 mol.%) or decreasing (10 mol.%) catalyst loading did not improve the product yield (entries 8-9, Table 1).

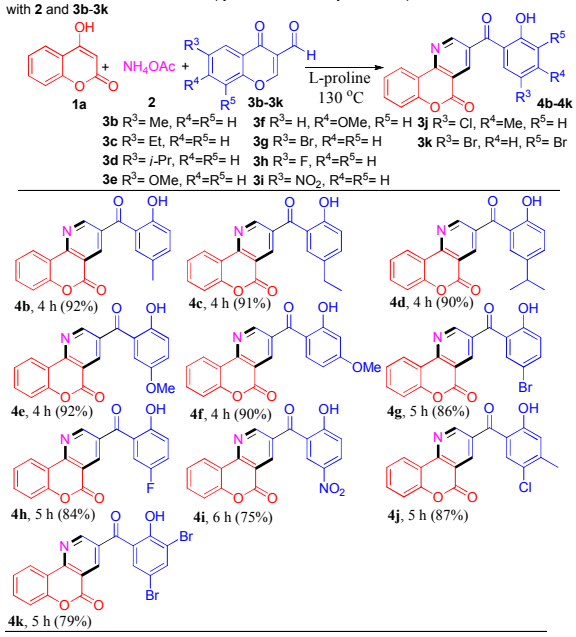
Table 1 Optimization for the synthesis of **4a**



entry	catalyst (mol%)	solvent	temperature (°C)	time	yield (%)
1	-	-	130	12	20
2	$Cu(OTf)_2$ (15)	-	130	8	30
3	$FeCl_3$ (15)	-	130	8	38
4	$In(OTf)_3$ (15)	-	130	8	27
5	*p*-TsOH (15)	-	130	6	68
6	AcOH (15)	-	130	6	70
7	**L-proline (15)**	**-**	**130**	**4**	**91**
8	L-proline (20)	-	130	4	90
9	L-proline (10)	-	130	4	80
10	L-proline (15)	toluene	reflux	10	10
11	L-proline (15)	CH_3CN	reflux	10	27
12	L-proline (15)	MeOH	reflux	5	83
13	L-proline (15)	EtOH	reflux	5	85
14	L-proline (15)	DMF	100	8	65
15	L-proline (15)	DMSO	100	8	60

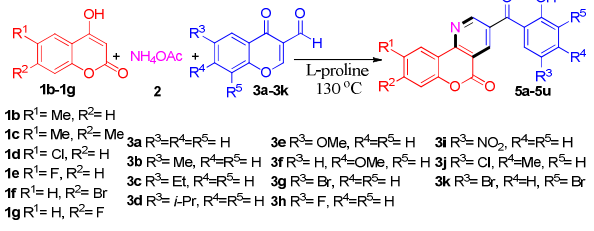
Additional reactions were examined in several solvents to identify the catalytic activity of L-proline. The use of toluene and acetonitrile was found to be ineffective (entries 10-11, Table 1) and more polar solvents, such as MeOH, EtOH, DMF, and DMSO, provided product **4a** in 83, 85, 65, and 60% yield, respectively (entries 12-15, Table 1). This showed that the use of solvents did not improve the reaction yield compared to the solvent-free conditions (Table 1, entries 7, 10-15). Compound **4a** was isolated by recrystallization from hot ethanol without column chromatography after washing with cold ethanol. The structure of **4a** was determined by spectroscopic analysis. In its ^{1}H NMR spectrum, a broad singlet peak of the OH group was observed at δ 11.71 ppm and two characteristic protons on the pyridine ring appeared as two doublets at δ 9.27 ppm (J = 2.1 Hz) and δ 8.86 ppm (J = 2.1 Hz), respectively. The structure of **4a** was confirmed further by its ^{13}C NMR. The peaks at 197.3 and 163.4 ppm clearly indicated the presence of two carbonyl groups due to a keto and ester group in the molecule.

Table 2 Construction of chromenopyridinones **4b-4k** by multi-component reaction of **1a** with **2** and **3b-3k**



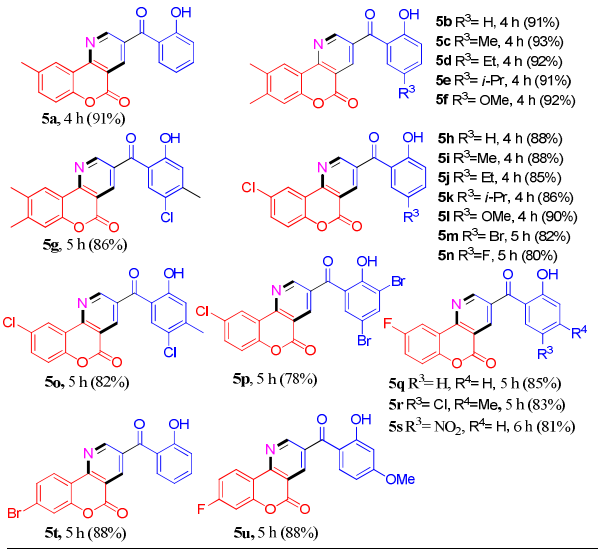
Under the optimized conditions, the scope of this three-component reaction was further explored employing different 3-formylchromones **3b**-**3k** (Table 2). Reactions of **1a** with **2** and **3b**-**3f** bearing electron-donating groups, such as 6-methyl, 6-ethyl, 6-isopropyl, 6-methoxy, and 7-methoxy at 130 °C for 4 h provided the desired products **4b**-**4f** in 90-92% yield. Treatment with **3g**-**3i** bearing electron-withdrawing groups, such as 6-bromo, 6-fluoro and 6-nitro for 5-6 h afforded the products **4g**-**4i** in 75-86% yield. A combination of **1a** with **2** and **3j** bearing an electron donating and an electron-withdrawing group on the benzene ring afforded the desired product **4j** (87%), whereas that with **3k** bearing two electron-withdrawing groups provided **4k** in 79% yield.

Table 3 Construction of chromenopyridinones **5a-5u** by multi-component reaction of **1b-1g** with **2** and **3a-3k**



1b R^1= Me, R^2= H
1c R^1= Me, R^2= Me
1d R^1= Cl, R^2= H
1e R^1= F, R^2= H
1f R^1= H, R^2= Br
1g R^1= H, R^2= F

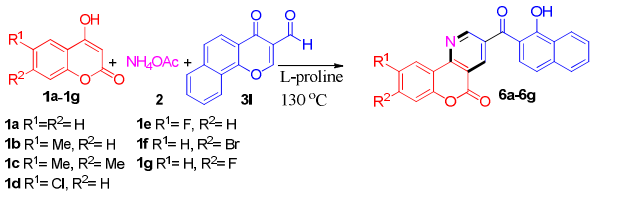
3a R^3=R^4=R^5= H
3b R^3= Me, R^4=R^5= H
3c R^3= Et, R^4=R^5= H
3d R^3= *i*-Pr, R^4=R^5= H
3e R^3= OMe, R^4=R^5= H
3f R^3= H, R^4=OMe, R^5= H
3g R^3= Br, R^4=R^5= H
3h R^3= F, R^4=R^5= H
3i R^3= NO_2, R^4=R^5= H
3j R^3= Cl, R^4=Me, R^5= H
3k R^3= Br, R^4=H, R^5= Br



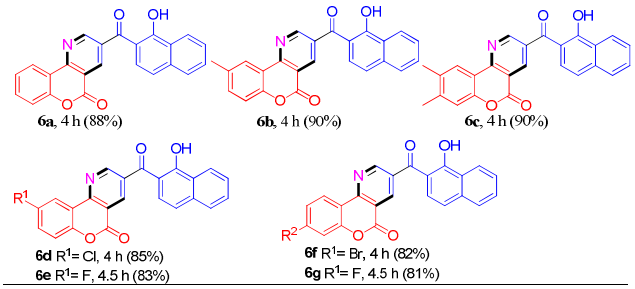
5b R^3= H, 4 h (91%)
5c R^3=Me, 4 h (93%)
5d R^3= Et, 4 h (92%)
5e R^3= *i*-Pr, 4 h (91%)
5f R^3= OMe, 4 h (92%)
5h R^3= H, 4 h (88%)
5i R^3=Me, 4 h (88%)
5j R^3= Et, 4 h (85%)
5k R^3= *i*-Pr, 4 h (86%)
5l R^3= OMe, 4 h (90%)
5m R^3= Br, 5 h (82%)
5n R^3=F, 5 h (80%)
5q R^3= H, R^4= H, 5 h (85%)
5r R^3= Cl, R^4=Me, 5 h (83%)
5s R^3= NO_2, R^4= H, 6 h (81%)

Reactions with substituted 4-hydroxycoumarins were examined to further demonstrate the versatility of this protocol after exploring the efficacy of various 3-formylchromones (Table 3). A reaction of **1b** bearing a methyl group as the electron-donating group on the coumarin ring with **2** and **3a** at 130 °C for 4 h provided the desired product **5a** in 91% yield. Similarly, the treatment of **1c** bearing two methyl groups with **2** and **3a**-**3e** or **3j** afforded the corresponding products **5b**–**5g** in 86-93% yield. A combination of **1d** bearing a chloro group as an electron-withdrawing group with **2** and **3a**-**3e**, **3g**, **3h**, or **3j**-**3k** resulted in the corresponding products **5h**-**5p** in 78-90% yield. Using 6-fluoro-4-hydroxycoumarin (**1e**), 7-bromo-4-hydroxycoumarin (**1f**) and 7-fluoro-4-hydroxycoumarin (**1g**), the desired products **5q**-**5u** were obtained in 81-88% yield.

Table 4 Construction of chromenopyridinones **6a-6g** by multi-component reaction of **1b-1g** with **2** and **3l**

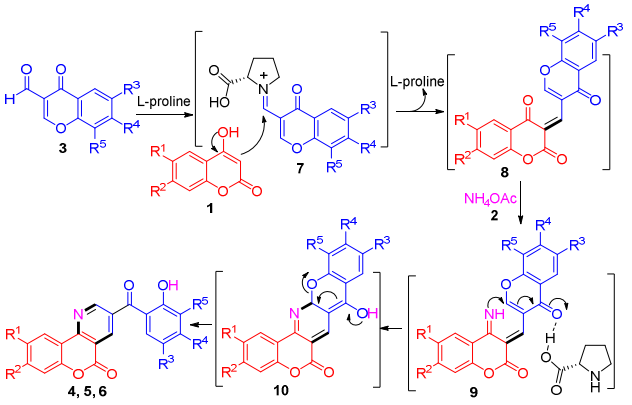


1a R^1=R^2= H
1b R^1= Me, R^2= H
1c R^1= Me, R^2= Me
1d R^1= Cl, R^2= H
1e R^1= F, R^2= H
1f R^1= H, R^2= Br
1g R^1= H, R^2= F



6d R^1= Cl, 4 h (85%)
6e R^1= F, 4.5 h (83%)
6f R^1= Br, 4 h (82%)
6g R^1= F, 4.5 h (81%)

Considering the general applicability of this reaction using various substituted 4-hydroxycoumarins and 3-formylchromones, the potential use of benzo[h]chromene-3-carbaldehyde to afford the complex and diverse chromenopyridinone derivatives was next examined (Table 4). A combination of **1a**-**1g** with **2** and **3l** at 130 °C for 4-4.5 h afforded the corresponding chromenopyridinones **6a-6g** in 81-90% yield.



Scheme 4 Possible mechanism for the formation of **4**, **5**, and **6**

Encouraged by the efficiency of the developed protocol, when the reaction was further carried out in 10 mmol scale, the desired product **4a** was formed in 91% yield. This result demonstrates that our method for the synthesis of chromenopyridinones is viable for large-scale preparation.

Based on the reported condensation of 1,3-dicarbonyl compound with enals and ammonium acetate, the formation of **4, 5** and **6** can be explained, as shown in Scheme 4.[24] The 4-hydroxycoumarin (**1**) first attacks the iminium ion **7**, which was formed from **3** in the presence of L-proline to furnish the intermediate **8** via Knoevenagel-type condensation.[25] Imine formation by NH_4OAc (**2**) followed by the cyclization of **9** in the presence of L-proline produced another intermediate **10**,

which affords the final product (**4**, **5** and **6**) through double bond migration by the attack of an OH group and subsequent C-O bond cleavage. In the proposed reaction mechanism, it is demonstrated that only one equivalent of NH_4OAc is required. At elevated temperature, one equivalent of NH_4OAc did not complete the reaction due to expulsion of NH_3. Therefore, two equivalents of NH_4OAc were used for the complete conversion of the reactant to the product.

The synthesis of a coumarin core containing heterocyclic scaffold is a very attractive field of research not only due to their pharmacological importance but also their applications in photonics.[26] The π-expanded versions of coumarin derivatives are used widely as fluorescent probes, optical brighteners and also as organic light emitting diodes (OLEDs).[27] Only a few reports of the synthesis of chromeno[4,3-*b*]pyridine derivatives have been published but the optical properties of these compounds were not examined. Therefore, after synthesizing the chromeno[4,3-*b*]pyridine derivatives, the absorption and emission spectra of several synthetic compounds in MeOH were screened (Fig. 2).

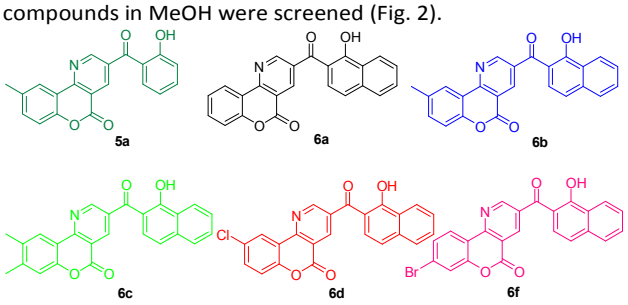


Fig. 2 Structure of the compounds screened for absorption and emission spectra

The synthesized compounds **6b** and **6c** emitted strong fluorescence in the blue-green region (450-550 nm) (Fig. 3). The fluorescence intensity of compound **6b** was greater than that of compound **6c**.

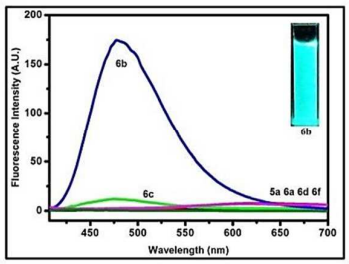


Fig. 3 Emission spectra of compound **5a**, **6a**, **6b**, **6c**, **6d** and **6f** in MeOH

The incorporation of a suitable electron donating substituent at the 6 and 7 position of the coumarin ring boosts intramolecular charge transfer (ICT). Very few coumarin cores containing fluorescent probes that contain electron donating substituents at the 6 position of the coumarin ring have been reported. Importantly, compound **6b**, which showed excellent fluorescence intensity (Fig. 3) contains methyl group at the 6 position of the coumarin ring.

The effect of polar and nonpolar solvents on the fluorescence intensity of compound **6b** was also screened (Fig. 4). The maximum fluorescence intensity was observed in MeOH and the intensity was moderate in DMSO. On the other hand, the fluorescence intensity is much lower in nonpolar solvents.

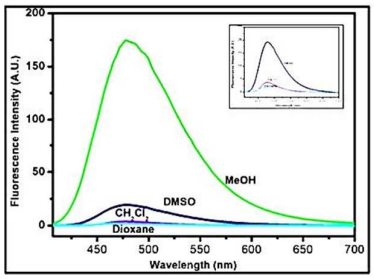


Fig. 4 Emission spectra of compound **6b** in MeOH, DMSO, CH_2Cl_2, and dioxane

The fluorescence intensity of compounds **5a**, **6a**, **6b**, **6c**, **6d** and **6f** was compared to elucidate the intramolecular charge transfer mechanism[28] of the chromeno[4,3-*b*]pyridine derivatives. From the structure of the compounds screened (Fig. 2) and fluorescence intensity (Fig. 3), the electron donating group at the 6 and or 7 position on chromeno[4,3-*b*]pyridine ring and naphthol ring are significant structural features that are essential for ICT, leading to the strong fluorescence emission.

The $-CH_3$ group stabilizes the intermediates (**I**, **II** and **III**) by the hyperconjugation (Scheme 5). Interestingly, compound **6c** showed less fluorescence emission compared to compound **6b**. This might be due to the lack of planarity of the two $-CH_3$ groups (steric hindrance) causing less hyperconjugative stability of the intermediates (Scheme 5).

Scheme 5 Plausible resonance structures for intramolecular charge transfer (ICT)

The intramolecular charge transfer mechanism of the chromeno[4,3-*b*]pyridine derivative was also supported by the solvent dependence of the fluorescence intensity. The dipolar intermediates (Scheme 5) were more stabilized in polar solvents compared to nonpolar solvents (Fig. 4).

Conclusions

A simple, mild and convenient L-proline catalyzed solid-state melt reaction for one-pot three-component condensation to afford highly substituted chromenopyridinone derivatives was reported. The features of this developed protocol were mild reaction condition, solvent-free, use of inexpensive non transition-metal catalyst, higher product yield, and simple column-free purification procedure. This solid-state melt reaction provides an excellent choice for the construction of a variety of chromenopyridinone derivatives for biological evaluations in the development of new medicines and sensors.

Experimental Section

General procedure for the synthesis of chromenopyridinone derivatives 4a-4k, 5a-5u, and 6a-6g

A mixture of 4-hydroxycoumarin (1.0 mmol), ammonium acetate (2.0 mmol) and 3-formylchromone (1.0 mmol) was heated to 130 ^{o}C in the presence of L-proline (15 mol.%) for 4-5 h (TLC). After completion of the reaction (TLC), ethanol (5 mL) was added to the reaction mixture and the yellow solid separated was filtered and washed with ethanol (10 mL). The products were finally recrystallized from hot ethanol (20 mL) to afford the pure product.

General procedure for the large scale synthesis of chromenopyridinone 4a

A mixture of 4-hydroxycoumarin (**1a**) (1.621 g, 10.0 mmol), ammonium acetate (**2**) (1.542 g, 20.0 mmol) and 3-formylchromone (**3a**) (1.742 g, 10.0 mmol) was heated to 130 ^{o}C in the presence of L-proline (15 mol.%) for 4 h (TLC). Solid product was precipitated by adding 50 mL of ethanol in cold reaction mixture. The yellow solid was collected by filtration and washed with ethanol (30 mL) to afford **4a** (2.887 g, 91%).

Optical Measurements

1mM solution of the compounds (**5a, 6a, 6b, 6c, 6d** and **6f**) in MeOH, DMSO, CH_2Cl_2, and dioxane were used to assay the optical properties. OPTIZEN 3220UV UV-Visible spectrophotometer and Hitachi-7000 F fluorescence spectrometer were used for acquiring the absorption and emission spectral data. All solutions were prepared in spectroscopic grade solvents without further purification. Quartz cells (10 mm) were used. Excitation wavelengths were 335 nm (for compound **6b**) and 390 nm (for compound **5a**, **6a, 6c, 6d** and **6f**) respectively.

Acknowledgements

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Graphical Abstract

Diverse chromenopyridinone derivatives were synthesized under organocatalytic solid-state melt conditions. The optical properties of these π-expanded chromenopyridine derivatives were examined.