HETEROCYCLES, Vol. 102, No. 6, 2021, pp. 1194 - 1209. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 17th March, 2021, Accepted, 31st March, 2021, Published online, 12th April, 2021
DOI: 10.3987/COM-21-14459

A ONE-POT APPROACH TO CONSTRUCT 3-(2-METHOXYPYRIDIN-3-YL)-4*H*-CHROMEN-4-ONES *VIA* MEINWALD REARRANGEMENT/INTRAMOLECULAR DEMETHYLATION ANNULATION OF EPOXIDES

Min-Qi Hu,[a] Ying Zhang,[a] Kai-Li Dai,[a] Li-Fang Yu,[a] Ting Liu,[a] Jie Tang,[a,b] and Fan Yang[a]*

[a]Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai, 200062, PR China; E-mail: fyang@chem.ecnu.edu.cn; Tel.: +86-21-6223-2764
[b]Shanghai Greenchem & Biotech Co., Ltd., Shanghai, 200062, PR China.

Abstract – A convenient and practical approach for construction of 3-(2-methoxypyridin-3-yl)-4*H*-chromen-4-ones has been successfully developed by a one-pot Meinwald rearrangement/intramolecular demethylation annulation reaction sequence with easily accessible epoxides as the starting material. The synthetic protocol is of excellent functional group compatibility under mild reaction conditions, and 3-(2-methoxypyridin-3-yl)-4*H*-chromen-4-ones were obtained in high yields. Moreover, further derivation successfully furnished more complicated derivatives by Suzuki-Miyaura cross-coupling reaction which may provide a promising potential application in exploring biological activity of 3-aryl-4*H*-chromen-4-ones.

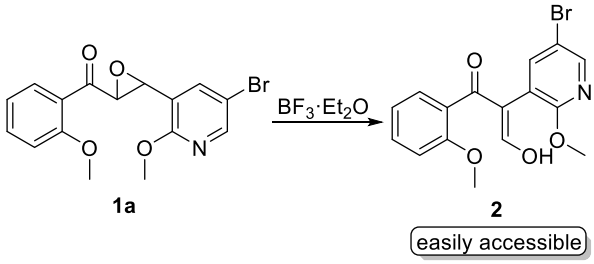
Chromones (4*H*-chromen-4-ones) are a class of heterocyclic compounds with the benzo-γ-pyrone skeleton. Among the substitution positions of chromone, the performance of 3-position substitution is the most prominent. The 3-phenyl substituted chromones are isoflavones, which exhibit attractive pharmacological activities.[1] In addition, it has been found that 3-position aromatic heterocyclic substituted chromones exhibit antianaphylaxis and antitumor activities.[2] Moreover, 3-pyridin-3-yl substituted chromones are also active as melanin-concentrating hormone receptor 1 (MCH1R) antagonists and selective cyclooxygenase-2 (COX-2) inhibitors.[3]

Compared with isoflavones, 3-pyridin-3-yl substituted chromones sometimes exhibit more attractive pharmacological activities. Due to the promising biological activities and applications, some synthetic strategies for the construction of valuable 3-aryl-4*H*-chromen-4-ones have been developed in recent years. The palladium-catalyzed Suzuki-Miyaura cross-coupling reactions from 3-halochromone and arylboronic acid were found to be efficient,[4] which involves enamine formation, ring closure, halogenation, and finally Suzuki-Miyaura cross-coupling reaction. Knochel and co-workers reported a metalation/cross-coupling sequence of 4*H*-chromen-4-one, which afforded the corresponding 3-(pyridin-3-yl)-4*H*-chromen-4-one with a yield of 77%.[5] Semenov and co-workers attempted intramolecular Ullmann type cyclization with arylbromo substituent with β-ketoaldehyde to construct the skeleton of 3-aryl-4*H*-chromen-4-ones with a yield of 24%-49%.[6]

Considering that the complicated steps and strict conditions led to a lower yield of the aromatic heterocyclic substituted products, some attempts to avoid the use of metal catalyst and improve the yield have been made in our group. Herein, we report a one-pot Meinwald rearrangement/intramolecular demethylation annulation protocol with easily accessible mixture of stereoisomers of epoxides, phenyl(3-(pyridin-3-yl)oxiran-2-yl)methanones, as the starting material which provides a straightforward protocol for the preparation of 3-(pyridin-3-yl)-4*H*-chromen-4-one derivatives in good yields.

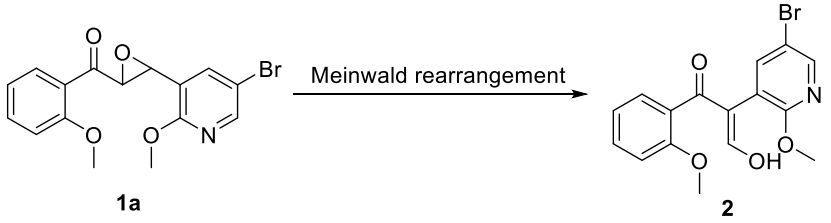
Tandem Meinwald rearrangement/intramolecular cycloaddition of chalcone epoxides to construct functionalized tetrahydrofurans or bridged oxa-[n.2.1] skeletons have been reported,[7] and Meinwald rearrangement of chalcone epoxides to form 3-oxo-2,3-diphenylpropanal has been well known. On the basis of the previous work in our group,[8] we envisioned that the molecular skeleton of 3-(pyridin-3-yl)-4*H*-chromen-4-one could be constructed by the demethylation/annulation of 3-(2-methoxyphenyl)-3-oxo-2-(pyridin-3-yl)propanal derivatives.

Lewis acid-catalyzed Meinwald rearrangement of epoxide was investigated.[9] However, Meinwald rearrangement reaction is difficult to carry out maybe due to the pyridine moiety could capture the Lewis acid to form pyridinium salt which acted as an electron-withdrawing group. Thus, a methoxy group was introduced as an activating group. Moreover, a bromine atom was introduced for further functionalization. While introducing a methoxy group at the 2-position of pyridine group, the reaction proceeded well and the product was determined as an enol form by ^{1}H NMR, ^{13}C NMR and IR spectra (Scheme 1). (3-(5-Bromo-2-methoxypyridin-3-yl)oxiran-2-yl)(2-methoxyphenyl)methanone (1a) was used as a template substrate to optimize the rearrangement reaction conditions (Table 1).



Scheme 1

Table 1. Optimization of Meinwald rearrangement reaction conditions[a]



Entry	Lewis acids/mol%	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$BF_3·Et_2O$/100	DCM	0	1	75
2	BBr_3/100	DCM	0	4	34
3	$AlCl_3$/100	DCM	25	4	39
4	$BF_3·Et_2O$/50	DCM	0	1	55
5	$BF_3·Et_2O$/10	DCM	0	1	28
6	$BF_3·Et_2O$/100	DCM	25	1	70
7	$BF_3·Et_2O$/10	DCM	25	1	47
8	$BF_3·Et_2O$/100	DCM	reflux	1	58
9	$BF_3·Et_2O$/100	DCM	0	4	78
10	$BF_3·Et_2O$/50	DCM	0	4	78
11	$BF_3·Et_2O$/30	DCM	0	4	66
12	$BF_3·Et_2O$/10	DCM	0	4	33
13	$BF_3·Et_2O$/100	DCM	0	8	94
14	$BF_3·Et_2O$/30	DCM	0	8	94
15	$BF_3·Et_2O$/10	DCM	0	8	74
16	$BF_3·Et_2O$/50	toluene	0	4	trace
17	$BF_3·Et_2O$/50	toluene	25	16	trace
18	$BF_3·Et_2O$/50	THF	0	4	trace

19	$BF_3·Et_2O$/50	THF	25	16	50
20	$BF_3·Et_2O$/50	THF	50	4	trace

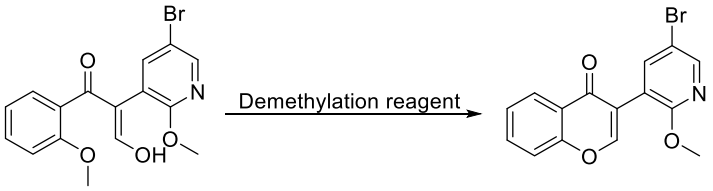
[a] Reaction conditions: 0.5 mmol of **1a**, 10 mL of solvent. [b] Isolated yields.

The formation of β-ketoaldehydes by Lewis acid–catalyzed rearrangement of chalcone epoxides has been developed, and 1~2 equiv of $BF_3·Et_2O$ was used in the previous reports.[9e] For comparison, BBr_3 and $AlCl_3$ was employed respectively, the result showed that the reaction system was complicated and the yield was lower for the produced by-products (Table 1, entries 2-3). As expected, using $BF_3·Et_2O$ as the demethylation reagents led to less by-products and higher yield (Table 1, entry 1). Then we tried to reduce the amount of $BF_3·Et_2O$ from 100 mol% to 10 mol% at 0 ºC, but the isolated yield was significantly dropped due to an incomplete rearrangement reaction after 1 h (Table 1, entries 4-5). Then, the temperature was increased and the reaction time was prolonged to improve the yield (Table 1, entries 6-15). Unfortunately, when the temperature was increased from 0 ºC to reflux, the by-products formed (Table 1, entries 6-8). While extending the reaction time from 1 h to 8 h at 0 ºC, 94% yield was obtained while using catalytic amount of $BF_3·Et_2O$ (30 mol%, Table 1, entries 14). Continue to lower the amount of $BF_3·Et_2O$, the yield was decreased (Table 1, entries 15). The influence of solvent on the rearrangement reaction was also preliminarily tested and the reactions were sluggish and gave lower yields in toluene or THF due to the incomplete reaction of rearrangement (Table 1, entries 16-19). When the temperature was increased to 50 ºC, few products were observed and most of the epoxides were converted into by-products (Table 1, entry 20). Therefore, the optimum reaction conditions for the rearrangement were established, that is, the reaction was carried out at 0 ºC for 8 h in dichloromethane with 30 mol% $BF_3·Et_2O$ as the catalyst.

To construct the skeleton of 3-(pyridin-3-yl)-4*H*-chromen-4-one, compound **2** was selected as a model substrate to examine its behavior under different demethylation conditions (Table 2). Different demethylation reagent systems were screened for conversion of **2** to final product 3-(5-bromo-2-methoxypyridin-3-yl)-4*H*-chromen-4-one (**3a**). Initially, the demethylation/annulation reaction sequence of **2** was carried out in the presence of $AlCl_3$ or LiCl. However, no reaction took place, or only a trace amount of **3a** was obtained (Table 2, entries 1-3). Then 48% HBr, TMSI (TMS = trimethylsilyl) and BBr_3 were employed as the demethylation reagents. To our delight, the products were obtained with moderate yields (Table 2, entries 4-6). Compared with 48% HBr and TMSI, using BBr_3 as the demethylation reagents led to less by-products and higher yield which was found to be the best choice (Table 2, entries 4-6). Further investigation was conducted, and it seems that temperature is also a crucial factor for the reaction. The reaction couldn't proceed smoothly at either 0 ºC or reflux temperature (Table 2, entries 7-8). However, prolonging the reaction time at 25 ºC couldn't improve the yield (Table 2, entry

9). When the amount of BBr_3 is increased from 2.5 to 4 and 5 equiv, the desired product was afforded in a yield of 77% and 82%, respectively (Table 2, entries 10-11). In addition, prolonging the reaction time in the presence of 5 equiv BBr_3 led to the by-products which caused a slight decrease of the yield (Table 2, entry 12). Thus, the optimized condition for the demethylation/annulation reaction was established as employing 5 equiv of BBr_3 in dichloromethane at 25 ºC for 12 h.

Table 2. Optimization of reaction conditions for the conversion of **2** into **3a**[a]



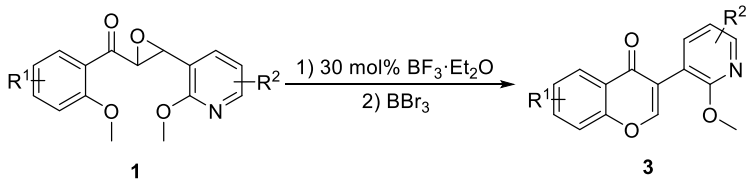
2 **3a**

Entry	Reagents	Equiv	Solvent	Temp(ºC)	Time(h)	Yield (%)[b]
1	$AlCl_3$	2.5	DCM	reflux	24	trace
2	LiCl	2.5	DMF	25	4	n.r.[c]
3	LiCl	2.5	DMF	reflux	12	n.r.
4	48% HBr	10	AcOH	25	12	53
5	TMSI	3	MeCN	25	4	45
6	BBr_3	2.5	DCM	25	12	55
7	BBr_3	2.5	DCM	0	24	trace
8	BBr_3	2.5	DCM	reflux	4	45
9	BBr_3	2.5	DCM	25	24	52
10	BBr_3	4	DCM	25	12	77
11	BBr_3	5	DCM	25	12	82
12	BBr_3	5	DCM	25	24	62

[a] Reaction conditions: 0.5 mmol of reactant, 10 mL of solvent. [b] Isolated yields. [c] n.r.: no reaction.

On the basis of the established optimal reaction conditions for both Meinwald rearrangement and the intramolecular demethylation annulation, a one-pot method for transformation of epoxides to **3a** via Meinwald rearrangement/intramolecular demethylation annulation without isolating the intermediate **2** was carried out. As expected, the reaction proceeded successfully and the final product was obtained in good yield. To examine the scope of the construction method, a series of derivatives were prepared through this one-pot synthetic strategy (Table 3).

Table 3. The one-pot Meinwald rearrangement/intramolecular demethylation annulation of epoxide derivatives[a]



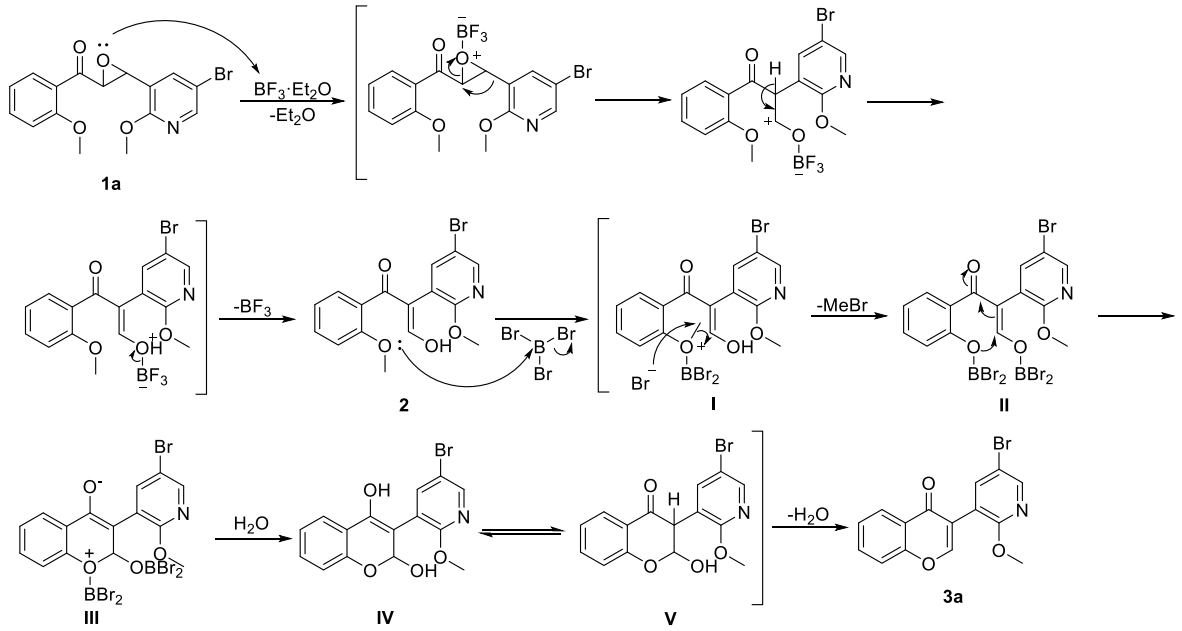
1 3

Entry	3	R^1	R^2	Yield (%)[b]
1	**3a**	H	5-Br	82
2	**3b**	H	5-F	77
3	**3c**	H	H	78
4	**3d**	H	5-cyclopropyl	74
5	**3e**	H	4-I	77
6	**3f**	H	6-OMe	78
7	**3g**	7-F	H	84
8	**3h**	6-F	H	70
9	**3i**	6-Me	H	69
10	**3j**	5-Cl	H	87
11	**3k**	8-NO_2	H	74
12	**3l**	6-Me, 7-Me	H	78

[a] Reaction conditions: 0.5 mmol of **1**, 10 mL of DCM, 0.3 equiv of $BF_3{\cdot}Et_2O$, 0 °C, 8 h; then 5 equiv of BBr_3, 25 °C, 12 h. [b] Total isolated yields.

As can be seen from Table 3, the variation of R^1 and R^2 groups had little influence on the reaction yields (Table 3, **3a-3l**). The substrates with either electron-rich or electron-deficient substituent on pyridyl ring or phenyl ring afforded the corresponding substituted derivatives in good yield (69%-87%, Table 3). Chloro and fluoro substitution at 5-, 7-position were benefit to the reaction, and 84% and 87% yields were obtained (Table 3, **3j**, **3g**). 8-Nitro substituted substrate also gave the corresponding product with a satisfactory yield (74%, Table 3, **3k**) which could be convert to a series of interesting derivatives for new drug candidate discovery. The one-pot Meinwald rearrangement/intramolecular demethylation annulation protocol has good functional group compatibility.

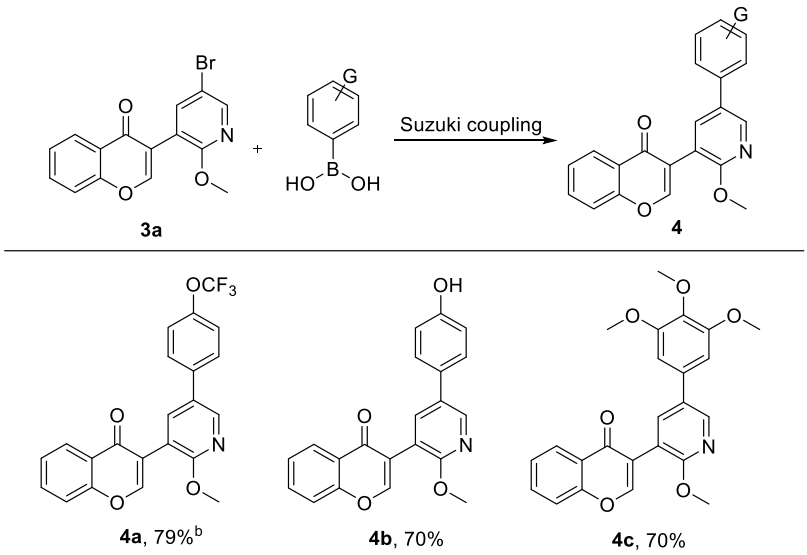
According to our experimental results and reported literature,[8b,8c] a possible reaction mechanism is proposed (Scheme 2), which includes: i) The epoxide undergoes smooth Meinwald rearrangement reaction with $BF_3{\cdot}Et_2O$ to afford an enol form intermediate **2**. ii) Treating **2** with BBr_3 leads to the formation of intermediate **I**. Demethylation of **I** leads to the formation of **II**, which is possibly converted into **III** through a subsequent annulation reaction. The hydrolysis of **III** can give **IV**, which is the tautomeric form of **V**. Subsequently, dehydration reaction of **V** forms the desired **3a**.



Scheme 2. Possible reaction pathway

In addition, it is noteworthy that the obtained halide products are useful intermediates for further functionalization to give a variety of derivatives (Table 3, **3a**). To expand the utilization of the method, we tried to further synthesize more complicated derivatives based on substrate **3a** by Suzuki-Miyaura cross-coupling reaction. Phenyl ‑substituted derivatives **4a**, **4b** and **4c** were obtained by treating **3a** with the corresponding phenylboronic acids under the catalysis of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (Table 4).

Table 4. Functionalization of the product **3a** by Suzuki-Miyaura cross-coupling reaction[a]



[a] Reaction conditions: 0.5 mmol of **3a**, 1.2 equiv of the corresponding phenylboronic acid, 1 mL of 2 M K_2CO_3, 4 mL of DMF, 0.05 equiv of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 80 ºC, 8 h. [b] Isolated yields.

In summary, an efficient method for synthesis of 3-(2-methoxypyridin-3-yl)-4*H*-chromen-4-one derivatives has been developed by a one-pot Meinwald rearrangement/intramolecular demethylation annulation protocol in good yields under mild reaction conditions. This method avoids the use of metal catalysts and is of satisfactory functional groups compatibility. In addition, the products with different substituents could be further functionalized easily to afford series of derivatives which may apply for the new drug candidate discovery.

EXPERIMENTAL

General methods

Commercial reagents and solvents were purchased by commercial suppliers and used without further purification. All non-aqueous reactions were under a nitrogen atmosphere and all non-aqueous reaction vessels were oven-dried. Flash column chromatography was performed using Qingdao Ocean silica gel (200–300) with the indicated eluents. All final compounds were characterized by their NMR and HRMS spectra, unless stated otherwise. ^{1}H NMR spectra were recorded at a spectrometer frequency of 400 MHz, and ^{13}C NMR spectra at 100 MHz on Bruker Avance 400. Chemical shifts are reported in δ (ppm) using signals of tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra (HRMS) were measured on a Bruker ESI-TOF high-resolution mass spectrometer. Melting points (mp) were uncorrected and were recorded on a Büchi B-54 melting point apparatus. IR spectra were recorded on an FT-IR spectrometer and were reported in cm^{-1}.

General procedure for synthesis of epoxides

The 1-(2-methoxyphenyl)ethan-1-one derivative (10 mmol) and 2-methoxynicotinaldehyde derivative (10 mmol) were dissolved in MeOH (30 mL) followed by the addition of aqueous solution of potassium hydroxide (20%, 20 mmol) at 0 °C and stirred at room temperature for 4 h and monitored by TLC. Upon completion, the solution was cooled to 0 °C again and hydrogen peroxide (50 mmol) was added dropwise. The solution was stirred at room temperature for another 4 h. The resulting precipitate was isolated by suction filtration and washed with H_2O (10 mL), MeOH (5 mL) and H_2O (10 mL) sequentially to give the corresponding epoxide.

(3-(5-Bromo-2-methoxypyridin-3-yl)oxiran-2-yl)(2-methoxyphenyl)methanone (1a). White solid (96% yield), mp 175 °C–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.65 (s, 1H), 7.58–7.50 (m, 1H), 7.10–7.02 (m, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.22–4.17 (m, 2H), 3.95 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 160.0, 158.5, 146.0, 135.6, 134.0, 129.8, 124.8, 120.6, 120.1, 111.0, 110.6, 62.5, 54.6, 53.4, 52.9. HRMS (ESI) *m/z*: calcd for $C_{16}H_{15}BrNO_4$ $[M+H]^+$: 364.0179, found: 364.0154.

(3-(5-Fluoro-2-methoxypyridin-3-yl)oxiran-2-yl)(2-methoxyphenyl)methanone (1b). White solid (95% yield), mp 202 °C–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 3.0 Hz, 1H), 7.83 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.57–7.50 (m, 1H), 7.34 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.09–7.03 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.24–4.21 (m, 1H), 4.18 (d, *J* = 1.9 Hz, 1H), 3.95 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 158.6, 157.3 (d, *J* =0.7 Hz), 154.6 (d, *J* = 246.5 Hz), 134.0, 131.8 (d, *J* = 26.1 Hz), 129.8, 124.8, 121.2 (d, *J* = 22.6 Hz), 120.1, 120.0 (d, *J* = 4.1 Hz), 110.6, 62.7, 54.5, 53.4, 52.9. HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}FNNaO_4$ $[M+Na]^+$: 326.0799, found: 326.0808.

(2-Methoxyphenyl)(3-(2-methoxypyridin-3-yl)oxiran-2-yl)methanone (1c). White solid (90% yield), mp 156 °C–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.81 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.56–7.48 (m, 2H), 7.06–7.00 (m, 1H), 6.96–6.88 (m, 2H), 4.24 (d, *J* = 1.7 Hz, 1H), 4.20 (d, *J* = 1.9 Hz, 1H), 3.96 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 161.2, 158.5, 145.5, 133.8, 133.1, 129.7, 125.0, 120.0, 118.6, 115.8, 110.6, 62.7, 54.5, 54.0, 52.4. HRMS (ESI) *m/z*: calcd for $C_{16}H_{15}NNaO_4$ $[M+Na]^+$: 308.0893, found: 308.0905.

(3-(4-Cyclopropyl-2-methoxypyridin-3-yl)oxiran-2-yl)(2-methoxyphenyl)methanone (1d). White solid (81% yield), mp 138 °C–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.55–7.49 (m, 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.07–7.02 (m, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 4.22 (d, *J* = 1.9 Hz, 1H), 4.17 (d, *J* = 1.9 Hz, 1H), 3.94 (s, 3H), 3.67 (s, 3H), 1.84 (tt, *J* = 8.4, 5.1 Hz, 1H), 0.97–0.92 (m, 2H), 0.66–0.61 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 159.6, 158.5, 143.3, 133.8, 131.1, 130.7, 129.7, 125.0, 120.0, 118.0, 110.5, 62.7, 54.5, 54.2, 52.4, 11.2, 7.1(2C). HRMS (ESI) *m/z*: calcd for $C_{19}H_{19}NNaO_4$ $[M+Na]^+$: 348.1206, found: 348.1222.

(3-(4-Iodo-2-methoxypyridin-3-yl)oxiran-2-yl)(2-methoxyphenyl)methanone (1e). White solid (89% yield), mp >220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, *J* = 5.0 Hz, 1H), 7.66-7.60 (m, 2H), 7.52 (d, *J* = 5.1 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.13-7.07 (m, 1H), 4.77-4.73 (m, 1H), 4.02-3.98 (m, 1H), 3.83-3.77 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.6, 161.5, 159.3, 147.4, 135.3, 130.2, 128.5, 126.5, 121.2, 121.1, 113.0, 112.0, 59.8, 59.3, 56.4, 54.2. HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}INNaO_4$ $[M+Na]^+$: 433.9860, found: 433.9861.

(3-(2,6-Dimethoxypyridin-3-yl)oxiran-2-yl)(2-methoxyphenyl)methanone (1f). White solid (92% yield), mp 175 °C–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.54–7.49 (m, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.07–7.02 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.32 (d, *J* = 8.1 Hz, 1H), 4.30–4.28 (m, 1H), 4.22–4.20 (m, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 162.0, 160.3, 158.5, 136.3, 133.7, 129.7, 125.1, 119.9, 110.5, 108.7, 100.0, 62.3, 54.6, 54.3, 52.7, 52.3. HRMS (ESI) *m/z*: calcd for $C_{17}H_{17}NNaO_5$ $[M+Na]^+$: 338.0999, found: 338.1017.

(4-Fluoro-2-methoxyphenyl)(3-(2-methoxypyridin-3-yl)oxiran-2-yl)methanone (1g). White solid (99% yield), mp 159 °C–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 5.0 Hz, 1H), 7.92–7.86 (m, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 6.97–6.89 (m, 1H), 6.79–6.73 (m, 1H), 6.65 (d, *J* = 10.5 Hz, 1H), 4.23 (s, 1H), 4.17 (s, 1H), 3.98 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 167.0 (d, *J* = 255.3 Hz), 162.2, 161.5 (d, *J* = 10.8 Hz), 146.6, 134.1, 133.0 (d, *J* = 11.3 Hz), 122.3 (d, *J* = 2.9 Hz), 119.5, 116.9, 108.3 (d, *J* = 21.8 Hz), 99.7 (d, *J* = 25.9 Hz), 63.7, 55.9, 55.0, 53.5. HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}FNNaO_4$ $[M+Na]^+$: 326.0799, found: 326.0807.

(5-Fluoro-2-methoxyphenyl)(3-(2-methoxypyridin-3-yl)oxiran-2-yl)methanone (1h). White solid (94% yield), mp 155 °C–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 3.6 Hz, 1H), 7.58–7.52 (m, 2H), 7.25–7.21 (m, 1H), 6.95–6.89 (m, 2H), 4.25 (d, *J* = 1.8 Hz, 1H), 4.21 (d, *J* = 1.9 Hz, 1H), 3.98 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5 (d, *J* = 1.7 Hz), 162.2, 156.9 (d, *J* = 242.0 Hz), 155.8 (d, *J* = 1.9 Hz), 146.6, 134.1, 126.7 (d, *J* = 6.2 Hz), 121.3 (d, *J* = 23.5 Hz), 119.4, 116.9, 116.7 (d, *J* = 24.3 Hz), 113.0 (d, *J* = 7.4 Hz), 63.6, 56.1, 55.2, 53.5. HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}FNNaO_4$ $[M+Na]^+$: 326.0799, found: 326.0793.

(2-Methoxy-5-methylphenyl)(3-(2-methoxypyridin-3-yl)oxiran-2-yl)methanone (1i). White solid (93% yield), mp 134 °C–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 4.7 Hz, 1H), 7.64 (s, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.94–6.89 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.26–4.24 (s, 1H), 4.23–4.21 (m, 1H), 3.97 (m, 3H), 3.64 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 161.2, 156.7, 145.5, 134.5, 133.1, 129.7, 129.3, 124.5, 118.6, 115.9, 110.6, 62.7, 54.6, 54.0, 52.4, 19.2. HRMS (ESI) *m/z*: calcd for $C_{17}H_{17}NNaO_4$ $[M+Na]^+$: 322.1050, found: 322.1042.

(2-Chloro-6-methoxyphenyl)(3-(2-methoxypyridin-3-yl)oxiran-2-yl)methanone (1j). White solid (89% yield), mp >220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 3.2 Hz, 1H), 7.46 (d, *J* = 6.8 Hz, 1H),

7.35–7.29 (m, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.90–6.84 (m, 2H), 4.30 (d, *J* = 1.9 Hz, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 3.76 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 161.1, 156.9, 145.7, 133.0, 130.7, 130.5, 125.3, 120.9, 117.6, 115.7, 108.4, 61.9, 55.1, 53.8, 52.5. HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}ClNNaO_4$ $[M+Na]^+$: 342.0504, found: 342.0519.

(2-Methoxy-3-nitrophenyl)(3-(2-methoxypyridin-3-yl)oxiran-2-yl)methanone (1k). White solid (87% yield), mp >220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.0, 1.9 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.96 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.53 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.39–7.33 (m, 1H), 6.93 (dd, *J* = 7.3, 5.1 Hz, 1H), 4.39 (d, *J* = 1.8 Hz, 1H), 4.22 (d, *J* = 1.8 Hz, 1H), 3.97 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.9, 162.2, 152.4, 147.5, 144.2, 135.6, 134.9, 133.1, 129.8, 125.3, 118.4, 117.7, 64.5, 61.3, 55.2, 53.9. HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}N_2NaO_6$ $[M+Na]^+$: 353.0744, found: 353.0749.

(2-Methoxy-4,5-dimethylphenyl)(3-(2-methoxypyridin-3-yl)oxiran-2-yl)methanone (1l). White solid (95% yield), mp 150 °C–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.62 (s, 1H), 7.55 (dd, *J* = 7.3, 1.9 Hz, 1H), 6.91 (dd, *J* = 7.3, 5.0 Hz, 1H), 6.72 (s, 1H), 4.26–4.21 (m, 2H), 3.96 (s, 3H), 3.61 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 161.2, 157.0, 145.4, 143.9, 133.1, 130.3, 128.2, 122.2, 118.8, 115.8, 111.9, 62.8, 54.5, 53.9, 52.4, 19.6, 17.6. HRMS (ESI) *m/z*: calcd for $C_{18}H_{19}NNaO_4$ $[M+Na]^+$: 336.1206, found: 336.1229.

Synthesis of 2-(5-bromo-2-methoxypyridin-3-yl)-3-hydroxy-1-(2-methoxyphenyl)prop-2-en-1-one (2)

1a (0.5 mmol) was dissolved in DCM (10 mL) followed by the addition of $BF_3{\cdot}Et_2O$ (0.15 mmol) and stirred at 0 °C for 8 h. Upon completion, ice water (20 mL) was added to the reaction system and organics were extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford crude mixture. The crude mixture was then purified by flash column chromatography in a mixture of petroleum ether and EtOAc to yield the pure product **2**. Yellow oil (94% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.43 (s, 1H), 8.34 (s, 1H), 8.00 (s, 1H), 7.36–7.27 (m, 3H), 6.97–6.91 (m, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 3.70 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.5, 179.9, 159.6, 154.5, 145.0, 140.4, 131.2, 128.4, 124.7, 112.0, 119.4, 110.9, 109.8, 109.8, 53.9, 52.5. HRMS (ESI) *m/z*: calcd for $C_{16}H_{14}BrNNaO_4$ $[M+Na]^+$: 385.9998, found: 386.0007. FT-IR: 3423, 3067, 2946, 2842, 1734, 1639, 1606, 1558, 1484, 1465, 1399, 1370, 1296, 1244, 1193, 1112, 1027, 957, 905, 754, 713, 643, 536.

General one-pot procedure for synthesis of 3-(2-methoxypyridin-3-yl)-4*H*-chromen-4-ones from epoxides

Epoxide (0.5 mmol) was dissolved in DCM (10 mL) followed by the addition of $BF_3{\cdot}Et_2O$ (0.15 mmol) and stirred at 0 °C for 8 h. Then BBr_3 (1 M in DCM, 2.5 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at 25 °C for another 12 h. Upon completion, saturated aqueous solution of bicarbonate

solution (10 mL) was added and the mixture was stirred for 1 h. The mixture was diluted with H_2O (40 mL) and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. The crude mixture was then purified by flash column chromatography in a mixture of petroleum ether and EtOAc to yield the pure product.

3-(5-Bromo-2-methoxypyridin-3-yl)-4*H*-chromen-4-one (3a). White solid (82% yield), mp 183 °C–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.0 Hz, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 7.93 (s, 1H), 7.73–7.67 (m, 1H), 7.52–7.42 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 160.2, 156.1, 155.5, 147.1, 142.5, 133.9, 126.3, 125.5, 124.4, 119.3, 118.1, 116.6, 111.5, 54.1. HRMS (ESI) *m/z*: calcd for $C_{15}H_{11}BrNO_3$ $[M+H]^+$: 331.9917, found: 311.9915.

3-(5-Fluoro-2-methoxypyridin-3-yl)-4*H*-chromen-4-one (3b). White solid (77% yield), mp 198 °C–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.23 (s, 1H), 8.00 (d, *J* = 3.0 Hz, 1H), 7.72–7.66 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.46–7.40 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 156.2, 155.0, 154.8, 154.0 (d, *J* = 246.2 Hz), 132.8, 131.6 (d, *J* = 25.6 Hz), 127.2 (d, *J* = 22.0 Hz), 125.3, 124.4, 123.4, 117.9 (d, *J* = 1.0 Hz), 117.1, 114.5 (d, *J* = 5.0 Hz), 53.1. HRMS (ESI) *m/z*: calcd for $C_{15}H_{10}FNNaO_3$ $[M+Na]^+$: 294.0537, found: 294.0546.

3-(2-Methoxypyridin-3-yl)-4*H*-chromen-4-one (3c). White solid (78% yield), mp 145 °C–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.19 (dd, *J* = 5.0, 2.0 Hz, 1H), 8.13 (s, 1H), 7.77 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.71–7.65 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.45–7.40 (m, 1H), 6.98 (dd, *J* = 7.3, 5.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 160.3, 155.1, 154.1, 145.7, 139.3, 132.6, 125.3, 124.3, 123.4, 119.4, 117.1, 115.6, 113.9, 52.7. HRMS (ESI) *m/z*: calcd for $C_{15}H_{11}NNaO_3$ $[M+Na]^+$: 276.0631, found: 276.0643.

3-(5-Cyclopropyl-2-methoxypyridin-3-yl)-4*H*-chromen-4-one (3d). White solid (74% yield), mp 131 °C–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.11 (s, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 7.72–7.65 (m, 1H), 7.51–7.46 (m, 2H), 7.46–7.40 (m, 1H), 3.91 (s, 3H), 1.91-1.85 (m, 1H), 0.97–0.91 (m, 2H), 0.70–0.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 159.7, 156.2, 155.2, 144.6, 138.3, 133.6, 131.7, 126.3, 125.3, 124.5, 120.5, 118.1, 114.2, 53.7, 12.2, 8.0 (2C). HRMS (ESI) *m/z*: calcd for $C_{18}H_{15}NNaO_3$ $[M+Na]^+$: 316.0944, found: 316.0960.

3-(4-Iodo-2-methoxypyridin-3-yl)-4*H*-chromen-4-one (3e). White solid (77% yield), mp 173 °C–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.85 (s, 1H), 7.83 (d, *J* = 5.4 Hz, 1H), 7.75–7.68 (m, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.47–7.42 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 162.0, 156.5, 155.3, 147.2, 133.8, 127.3, 126.5, 125.4, 124.5, 124.2, 121.1, 118.3, 114.5, 54.3. HRMS (ESI) *m/z*: calcd for $C_{15}H_{10}INNaO_3$ $[M+Na]^+$: 401.9598, found: 401.9599.

3-(2,6-Dimethoxypyridin-3-yl)-4*H*-chromen-4-one (3f). Light yellow solid (78% yield), mp 190 °C–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.8 Hz, 1H), 8.09 (s, 1H), 7.74–7.63 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.44–7.38 (m, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 162.8, 160.0, 156.2, 154.9, 143.0, 133.5, 126.4, 125.1, 124.5, 120.5, 118.1, 105.5, 100.9, 53.6, 53.6. HRMS (ESI) *m/z*: calcd for $C_{16}H_{13}NNaO_4$ $[M+Na]^+$: 306.0737, found: 306.0755.

7-Fluoro-3-(2-methoxypyridin-3-yl)-4*H*-chromen-4-one (3g). White solid (84% yield), mp 205 °C–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33–8.27 (m, 1H), 8.20 (dd, *J* = 5.0, 1.9 Hz, 1H), 8.10 (s, 1H), 7.75 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.20–7.13 (m, 2H), 6.98 (dd, *J* = 7.3, 5.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 165.6 (d, *J* = 255.3 Hz), 161.3, 157.1 (d, *J* = 13.3 Hz), 155.2, 146.9, 140.4, 129.0 (d, *J* = 10.7 Hz), 121.3 (d, *J* = 2.4 Hz), 120.7, 116.7, 114.5, 114.2 (d, *J* = 22.8 Hz), 104.7 (d, *J* = 25.3 Hz), 53.8. HRMS (ESI) *m/z*: calcd for $C_{15}H_{10}FNNaO_3$ $[M+Na]^+$: 294.0537, found: 294.0554.

6-Fluoro-3-(2-methoxypyridin-3-yl)-4*H*-chromen-4-one (3h). White solid (70% yield), mp 148 °C–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 3.6 Hz, 1H), 8.13 (s, 1H), 7.90 (dd, *J* = 8.3, 3.0 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.52–7.47 (m, 1H), 7.45–7.36 (m, 1H), 6.97 (dd, J = 7.3, 5.0 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1 (d, *J* = 2.3 Hz), 161.3, 159.6 (d, *J* = 246.8 Hz), 155.3, 152.4 (d, *J* = 1.7 Hz), 146.9, 140.3, 125.6 (d, *J* = 7.3 Hz), 121.9 (d, *J* = 25.6 Hz), 120.3 (d, *J* = 8.1 Hz), 119.8, 116.7, 114.5, 111.1 (d, *J* = 23.7 Hz), 53.7. HRMS (ESI) *m/z*: calcd for $C_{15}H_{10}FNNaO_3$ $[M+Na]^+$: 294.0537, found: 294.0555.

3-(2-Methoxypyridin-3-yl)-6-methyl-4*H*-chromen-4-one (3i). Light yellow solid (69% yield), mp 132 °C–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 2.9 Hz, 1H), 8.10 (s, 1H), 8.06 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 6.98 (dd, J = 7.3, 5.0 Hz, 1H), 3.95 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 161.3, 155.0, 154.5, 146.5, 140.5, 135.3, 134.9, 125.6, 124.1, 120.2, 117.9, 116.7, 115.1, 53.8, 21.0. HRMS (ESI) *m/z*: calcd for $C_{16}H_{13}NNaO_3$ $[M+Na]^+$: 290.0788, found: 290.0798.

5-Chloro-3-(2-methoxypyridin-3-yl)-4*H*-chromen-4-one (3j). White solid (87% yield), mp 209 °C–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.1 Hz, 1H), 8.02 (s, 1H), 7.75 (d, *J* = 7.4 Hz, 1H), 7.56–7.50 (m, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.01–6.91 (m, 1H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 161.3, 157.8, 153.7, 146.8, 140.6, 134.0, 132.8, 128.3, 121.5, 121.4, 117.4, 116.6, 114.4, 53.7. HRMS (ESI) *m/z*: calcd for $C_{15}H_{10}ClNNaO_3$ $[M+Na]^+$: 310.0241, found: 310.0256.

3-(2-Methoxypyridin-3-yl)-8-nitro-4*H*-chromen-4-one (3k). Light yellow solid (84% yield), mp 189 °C–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.36 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.27–8.18 (m, 2H), 7.78 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.59–7.53 (m, 1H), 7.00 (dd, *J* = 7.3, 5.0 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 160.1, 154.0, 147.4, 146.3, 139.2, 137.8, 131.3, 128.8, 125.1,

123.4, 120.4, 115.7, 112.5, 52.8. HRMS (ESI) *m/z*: calcd for $C_{15}H_{11}N_2O_5$ $[M+H]^+$: 299.0662, found: 299.0662.

3-(2-Methoxypyridin-3-yl)-6,7-dimethyl-4*H*-chromen-4-one (3l). White solid (78% yield), mp 174 °C–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.1, 1.9 Hz, 1H), 8.07 (s, 1H), 8.01 (s, 1H), 7.78 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.28–7.26 (m, 1H), 6.98 (dd, *J* = 7.3, 5.0 Hz, 1H), 3.95 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 161.4, 154.8, 154.7, 146.5, 144.1, 140.4, 134.6, 125.9, 122.3, 120.1, 118.2, 116.7, 115.3, 53.8, 20.5, 19.4. HRMS (ESI) *m/z*: calcd for $C_{17}H_{15}NNaO_3$ $[M+Na]^+$: 304.0944, found: 304.0967.

General procedure for synthesis of 3-(2-methoxy-5-phenylpyridin-3-yl)-4*H*-chromen-4-ones

Compound **3a** (0.5 mmol), the corresponding arylboronic acid (0.6 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.025 mmol) were suspended in DMF (4 mL) in the presence of 2 M K_2CO_3 (1 mL) and stirred at 80 °C for 8 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. The crude mixture was then purified by flash column chromatography in a mixture of petroleum ether and EtOAc to yield the pure products.

3-(2-Methoxy-5-(4-(trifluoromethoxy)phenyl)pyridin-3-yl)-4*H*-chromen-4-one (4a). White solid (79% yield), mp 157 °C–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.5 Hz, 1H), 8.30 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J* = 2.5 Hz, 1H), 7.74–7.67 (m, 1H), 7.60–7.56 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.48–7.42 (m, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 159.9, 155.1, 154.4, 147.7 (q, *J* = 1.8 Hz), 143.6, 138.2, 135.4, 132.7, 127.8, 127.2 (2C), 125.3, 124.4, 123.4, 120.4 (2C),119.5 (q, *J* = 257.2 Hz), 118.9, 117.1, 113.8, 53.0. HRMS (ESI) *m/z*: calcd for $C_{22}H_{15}F_3NO_4$ $[M+H]^+$: 414.0948, found: 414.0918.

3-(5-(4-Hydroxyphenyl)-2-methoxypyridin-3-yl)-4*H*-chromen-4-one (4b). White solid (70% yield), mp >220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.56 (s, 1H), 8.43 (d, *J* = 2.2 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 7.89–7.83 (m, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.57–7.49 (m, 3H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.0, 160.6, 157.6, 156.2, 156.1, 143.9, 138.8, 134.8, 129.8, 128.0 (2C), 127.9, 126.2, 125.9, 124.0, 121.1, 119.0, 116.3 (2C), 115.6, 54.0. HRMS (ESI) *m/z*: calcd for $C_{21}H_{16}NO_4$ $[M+H]^+$: 346.1074, found: 346.1056.

3-(2-Methoxy-5-(3,4,5-trimethoxyphenyl)pyridin-3-yl)-4*H*-chromen-4-one (4c). Light yellow solid (70% yield), mp 167 °C–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.5 Hz, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 8.18 (s, 1H), 7.95 (d, *J* = 2.5 Hz, 1H), 7.75–7.68 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.49–7.43 (m, 1H), 6.74 (s, 2H), 3.99 (s, 3H), 3.92 (s, 6H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 159.7, 155.2, 154.2, 152.6 (2C), 143.6, 138.2, 136.6, 132.8, 132.6, 129.4, 125.3, 124.4, 123.4, 119.4, 117.1, 113.7, 103.1 (2C), 60.0, 55.2 (2C), 53.0. HRMS (ESI) *m/z*: calcd for $C_{24}H_{22}NO_6$ $[M+H]^+$: 420.1442, found: 420.1452.

ACKNOWLEDGEMENTS

This research was financially supported by Shanghai Science and Technology Council (No. 20142201500), and National Development and Reform Commission (No. 115). We also thank the Laboratory of Organic Functional Molecules, Sino-French Institute of ECNU for support.

REFERENCES

1. L. Krizova, K. Dadakova, J. Kasparovska, and T. Kasparovsky, *Molecules*, 2019, **24**, 1076.
2. (a) A. Nohara, H. Kuriki, T. Saijo, H. Sugihara, M. Kanno, and Y. Sanno, *J. Med. Chem.*, 1977, **20**, 141; (b) P. H. Xiong, R. B. Wang, X. J. Zhang, E. Dela Torre, F. Leon, Q. Zhang, S. L. Zheng, G. D. Wang, and Q. H. Chen, *Anti-Cancer Agents Med. Chem.*, 2015, **15**, 1197.
3. (a) B. Dyck, L. Zhao, J. Tamiya, J. Pontillo, S. Hudson, B. Ching, C. E. Heise, J. Wen, C. Norton, A. Madan, D. Schwarz, W. Wade, and V. S. Goodfellow, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4237; (b) Y. H. Joo, J. K. Kim, S. H. Kang, M. S. Noh, J. Y. Ha, J. K. Choi, K. M. Lim, C. H. Lee, and S. Chung, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 413.
4. (a) C. R. Eisnor, R. A. Gossage, and P. N. Yadav, *Tetrahedron*, 2006, **62**, 3395; (b) N. Gavande, N. Karim, G. A. Johnston, J. R. Hanrahan, and M. Chebib, *ChemMedChem*, 2011, **6**, 1340; (c) A. Matin, N. Gavande, M. S. Kim, N. X. Yang, N. K. Salam, J. R. Hanrahan, R. H. Roubin, and D. E. Hibbs, *J. Med. Chem.*, 2009, **52**, 6835; (d) P. Mutai, E. Pavadai, I. Wiid, A. Ngwane, B. Baker, and K. Chibale, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2510; (e) C. Wu, Y. B. Tu, Z. Li, and Y. F. Li, *Bioorg. Chem.*, 2019, **88**, 102949.
5. L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, and P. Knochel, *J. Am. Chem. Soc.*, 2012, **134**, 13584.
6. (a) V. V. Semenov, D. V. Tsyganov, M. N. Semenova, R. N. Chuprov-Netochin, M. M. Raihstat, L. D. Konyushkin, P. B. Volynchuk, E. I. Marusich, V. V. Nazarenko, S. V. Leonov, and A. S. Kiselyov, *J. Nat. Prod.*, 2016, **79**, 1429; (b) D. V. Tsyganov, L. D. Konyushkin, M. N. Semenova, and V. V. Semenov, *Mendeleev Commun.*, 2016, **26**, 285.
7. (a) A. Kumar Pandey, A. Ghosh, and P. Banerjee, *Eur. J. Org. Chem.*, 2015, 2517; (b) W. Zhu, J. Ren, and Z. Wang, *Eur. J. Org. Chem.*, 2014, 3561.
8. (a) W. Luo, Z. Yu, W. Qiu, F. Yang, X. Liu, and J. Tang, *Tetrahedron*, 2011, **67**, 5289; (b) L. Ruan, M. Shi, S. Mao, L. Yu, F. Yang, and J. Tang, *Tetrahedron*, 2014, **70**, 1065; (c) S. Wang, C. Zhao, T. Liu, L. Yu, F. Yang, and J. Tang. *Tetrahedron*, 2016, **72**, 7025; (d) J. Zhang, J. Qiu, C. Xiao, L. Yu, F. Yang, and J. Tang, *Eur. J. Org. Chem.*, 2016, 3380.
9. (a) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.*, 1963, **85**, 582; (b) R. Kumar, J. Halder, and S. Nanda, *Tetrahedron*, 2017, **73**, 809; (c) R. Umeda, M. Muraki, Y. Nakamura, T. Tanaka,

K. Kamiguchi, and Y. Nishiyama, *Tetrahedron Lett.*, 2017, **58**, 2393; (d) D. Ma, C. B. Miao, and J. Sun, *J. Am. Chem. Soc.*, 2019, **141**, 13783; (e) C. Xu and J. Xu, *Org. Biomol. Chem.*, 2019, **18**, 127; (f) P. Mathew, D. Mathew, and C. V. Asokan, *Synth. Commun.*, 2007, **37**, 661.