Facile access to 2-aryl-3-nitro-2*H*-chromenes and 2,3,4-trisubstituted chromanes

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Abstract

Using salicylaldehydes and *β*-nitrostyrenes as starting materials, 2-aryl-3-nitro-2*H*-chromenes were prepared in good yields (up to 83%) through the combination of 30 mol% of pyrrolidine-benzoic acid catalyzed tandem oxa-Michael-Henry reactions in refluxing ethanol. Additionally, the Michael reactions of 2-aryl-3-nitro-2*H*-chromenes with acetone were also performed by the same catalytic combination in brine to give 2,3,4-trisubstituted chromanes up to 86% yield with excellent stereoselectivities. The structures of 2-aryl-3-nitro-2*H*-chromenes and 2,3,4-trisubstituted chromanes are confirmed by X-ray single crystal diffraction analysis. The reductive amination of a suitable 2,3,4-trisubstituted chromane with Zn/HOAc affords a fused tricyclic amine in 92% yield.

Keywords: 2-aryl-3-nitro-2*H*-chromene, 2,3,4-trisubstituted chromane, tandem oxa-Michael-Henry reaction, reductive amination, X-ray diffraction analysis

Introduction

2-Aryl-3-nitro-2*H*-chromenes and 2,3,4-trisubstituted chromanes are not only important building blocks in organic synthesis but also key intermediates for pharmaceutics.[1-3] Due to their versatile transformations in synthetic chemistry, a simple and efficient preparation of these valuable bulding blocks has drawn much attention from synthetic chemists.[4-6] The tandem oxa-Michael-Henry reaction of salicylaldehyde with β-nitrostyrenes is considered to be the most straightforward for preparation of 2-aryl-3-nitro-2*H*-chromenes. Several reports describe construction of 2-aryl-3-nitro-2*H*-chromenes in good yields using 1,4-diazabicyclo[2.2.2]octane (DABCO),[7,8] L-pipecolinic acid[9] or C_2-symmetric pyrrolidine-triazoles[10] as catalysts. The preparation of optically active 2-aryl-3-nitro-2*H*-chromenes through asymmetric tandem oxa-Michael-Henry reactions has also been realized recently, with chiral pyrrolidine derivatives,[11,12] or cinchona alkaloid-derived bifunctional thioureas[13] as catalysts under mild conditions,

respectively. Kinetic resolution of racemic 2-aryl-3-nitro-2*H*-chromenes can also be used to provide their enantioriched forms.[14,15] However, long reaction times (up to 7 days), high catalyst-loadings (up to 50 mol%) and toxic solvents (usually in toluene) are involved in some of the aforementioned processes. Therefore, a practical and efficient synthesis of 2-aryl-3-nitro-2*H*-chromenes in good yields under mild conditions is still needed. 2,3,4-Trisubstituted chromanes are usually obtained through nucleophilic additions of activated 2*H*-chromenes with 1,3-dicarbonyl compounds,[16,17] pyrrole[18] or indole.[19] The activation of all reagents by the combination of two catalysts to afford a single chemical transformation is emerging as a powerful synthetic strategy in recent decades, and it was also highlighted by MacMillan and co-workers.[20] In 2007, Córdova and colleagues[21] developed a novel and efficient one-pot synthesis of 2-aryl-3-formyl-2*H*-chromenes from salicylaldehydes and cinnamic aldehydes using the combination of pyrrolidine and benzoic acid as catalyst.

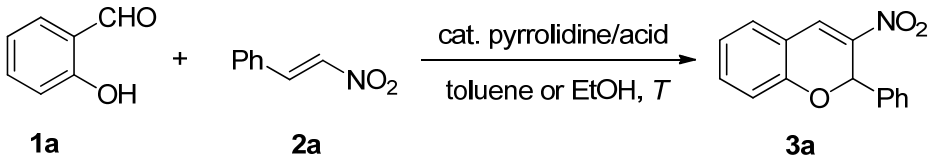
Herein we report a facile access to 2-aryl-3-nitro-2*H*-chromenes through tandem oxa-Michael-Henry reactions of various salicylaldehydes and β-nitrostyrenes using the combination of pyrrolidine and benzoic acid as catalyst, and the Michael additions of 2-aryl-3-nitro-2*H*-chromenes with acetone are firstly performed under the same catalytic combination in brine to provide multi-substituted chromanes in good yields. The structures of 2-aryl-3-nitro-2*H*-chromenes and 2,3,4-trisubstituted chromanes were confirmed by X-ray single crystal diffraction analysis. Additionally, the reductive amination of a 2,3,4-trisubstituted chromane was also investigated and provided a fused tricyclic amine in high yield.

Results and Discussion

Initially, the tandem oxa-Michael-Henry reaction of salicylaldehyde **1a** with β-nitrostyrene **2a** was selected as a model reaction (Table 1). It was found that there is no transformation when benzoic acid was used as the sole catalyst, and pyrrolidine was used as sole catalyst to give 2-phenyl-3-nitro-2*H*-chromene **3a** in 32% yield (entry 1). The catalytic combination of pyrrolidine and benzoic acid can provide **3a** in 74% yield in toluene at 80 °C (entry 2). From an environmental viewpoint, ethanol was investigated as solvent instead of toluene. To our delight, **3a** was obtained in 76% yield in refluxing ethanol. Then, combinations of pyrrolidine with various acids were screened (entries 3-8). Interestingly, when salicylic acid was used as co-catalyst, **3a** was isolated in low yield (41%, entry 4), thus it seems that the hydroxyl group for one hydrogen-bonding donor in salicylic acid is not helpful to this tandem reaction. The combinations of pyrrolidine with the other acids such as acetic acid (HOAc, entry 5), trifluoroacetic acid (TFA, entry 6) and *para*-toluenesulfonic acid (PTSA, entry 7) respectively resulted in no reaction under the comparable conditions. Chiral phosphoric acids (CPAs) based on the BINOL-skeleton have been widely used as efficient catalysts for many enantioselective transformations.[22] Due to the scarcity of direct enantioselective synthesis of chiral 2-aryl-3-nitro-2*H*-chromenes, we have used a BINOL-based chiral phosphoric acid as a co-catalyst with pyrrolidine in the tandem oxa-Michael-Henry reaction of salicylaldehyde with β-nitrostyrene

(entry 8) hopefully to give enantioriched **3a**. Unfortunately, this catalytic combination proved to be useless. The catalyst-loading was also investigated and it was found that the lower catalyst-loadings resulted in lower yields (entry 3 *vs* entries 9 and 10).

Table 1. Optimization of conditions for oxa-Michael-Henry reaction



1a **2a** **3a**

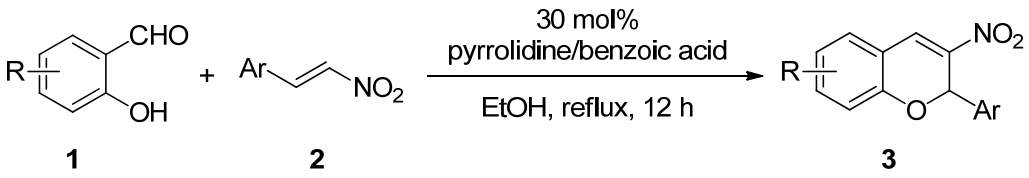
Entry[a]	Co-catalyst	Solvent	*T*(°C)	Yield (%)[c]
1	none	toluene	80	32
2	benzoic acid (30 mol%)	toluene	80	74
3	benzoic acid (30 mol%)	EtOH	reflux	76
4	salicylic acid (30 mol%)	EtOH	reflux	41
5	HOAc (30 mol%)	EtOH	reflux	0
6	TFA (30 mol%)	EtOH	reflux	0
7	PTSA (30 mol%)	EtOH	reflux	0
8	CPA[b] (30 mol%)	EtOH	reflux	0
9[d]	benzoic acid (20 mol%)	EtOH	reflux	49
10[e]	benzoic acid (10 mol%)	EtOH	reflux	22

[a]1.1 mmol of salicylaldehyde, 1.0 mmol of β-nitrostyrene and 0.30 mmol of pyrrolidine were used in 2.0 mL of solvent for entries 1 to 8, and the reaction time was within 12 hours; [b]CPA = (*S*)-(+)-1,1'-binaphthyl-2,2'-diylhydrogen phosphate; [c]Isolated yield based on β-nitrostyrene **2a**. [d]The use of pyrrolidine was also decreased to 20 mol%; [e]The use of pyrrolidine was also decreased to 10 mol%.

After further systematic optimization of the reaction conditions, the tandem oxa-Michael-Henry reactions between various substituted salicylaldehydes **1** and β-nitrostyrenes **2** were explored (Table 2). All salicylaldehydes, regardless of possessing an electron-withdrawing or -donating group, reacted smoothly with β-nitrostyrenes (entries 1-9) to afford 2-phenyl-3-nitro-2*H*-chromenes **3a-i** in moderate to good yields, and the reactions between the salicylaldehydes with electron-withdrawing group and **2a** gave the corresponding products in higher yields than those salicylaldehydes with electron-donating groups under the same conditions (entries 4 and 5 *vs* entries 6, 7 and 9). The substitutents on the β-nitrostyrenes seem to have slight effect on the yields (entry 1 *vs* entries 2, 3 and 8). Single crystals of **3i** were grown from CH_2Cl_2, suitable for X-ray diffraction analysis, and the X-ray structure of **3i** is shown in Figure 1. In order to show the reliability of this synthetic strategy, the tandem reaction between **1a** and **2a** in ethanol was

performed on a gram scale (10 mmol), and **3a** was isolated in 72% yield (1.87 g) after a simple column chromatographic purification.

Table 2. The oxa-Michael reactions between salicylaldehydes **1** and β-nitrostyrenes **2**



1 **2** **3**

Entry[a]	R	Ar	Product	Yield (%)[b]
1	H	Ph	**3a**	76
2	H	4-ClC_6H_4	**3b**	74
3	H	4-$MeOC_6H_4$	**3c**	76
4	3-OMe	Ph	**3d**	75
5	4-OMe	Ph	**3e**	73
6	5-Cl	Ph	**3f**	82
7	5-Br	Ph	**3g**	79
8	H	4-BrC_6H_4	**3h**	80
9	3,5-dichloro	Ph	**3i**	83

[a]All the reactions were performed with 1.1 mmol of salicylaldehyde, 1.0 mmol of β-nitrostyrene, 0.30 mmol of pyrrolidine and 0.30 mmol of benzoic acid in 2.0 mL of EtOH; [b]Isolated yield based on β-nitrostyrene.

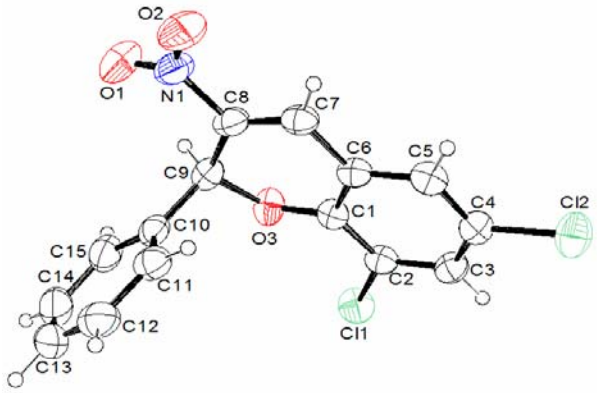
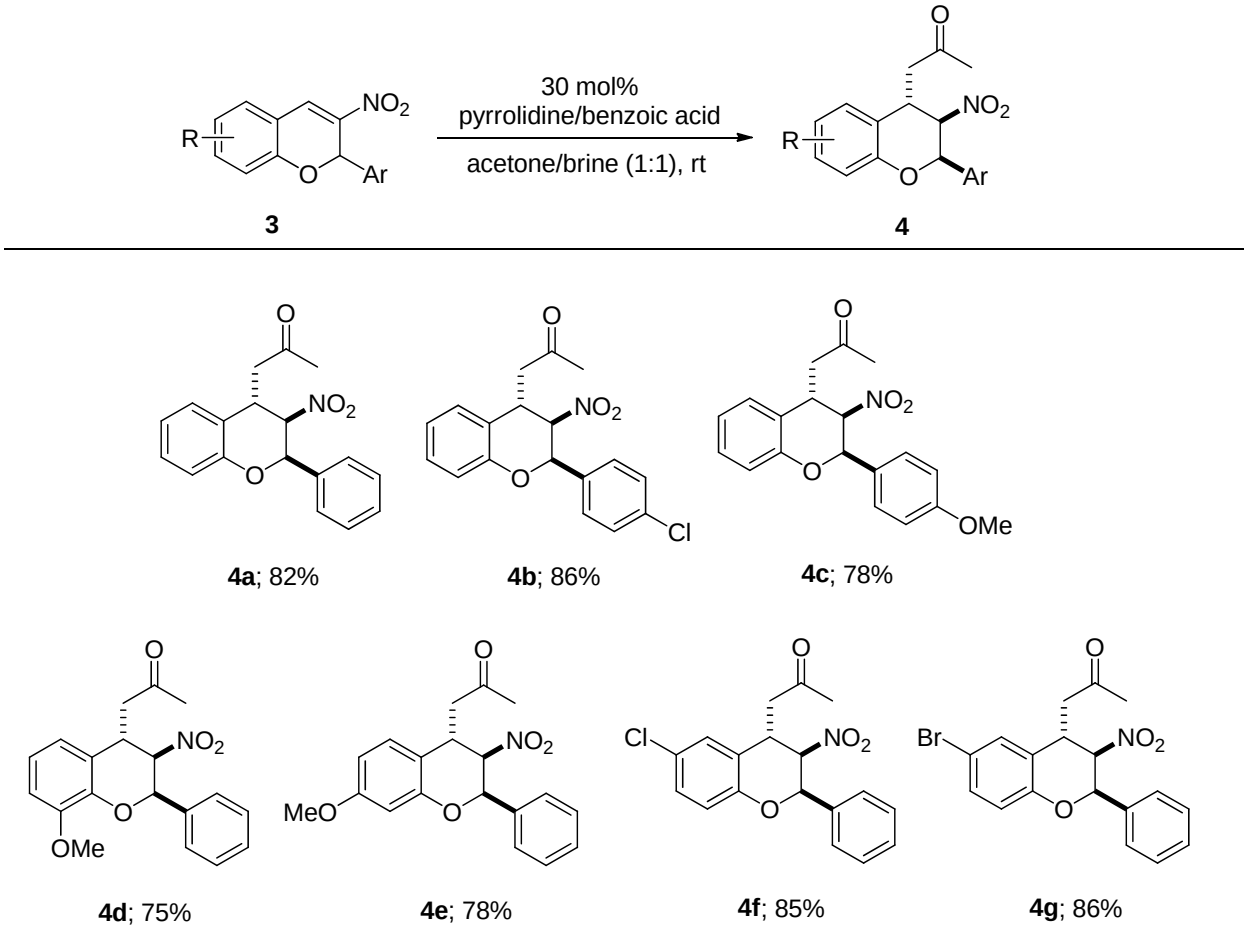


Figure 1. The X-ray structure of chromene **3i**.

With **3a-i** in hand, the Michael reactions between acetone and 2-aryl-3-nitro-2*H*-chromenes were also performed. At first, **3a** was not isolated from the reaction mixture and acetone was directly added to the mixture hopefully to give the 2,3,4-trisubstituted chromane **4a**, but the

reaction was complex. When pure **3a** was used as substrate in acetone, the Michael adduct **4a** was obtained in 35% yield after one day using pyrrolidine-benzoic acid as catalyst. Encouraged by this positive result, we continued to search for optimal conditions for this reaction. Many examples of Michael additions in aqueous media have been reported to provide Michael adducts in both excellent yields and enantioselectivities.[23-26] When the Michael reaction of **3a** and acetone was performed in water, **4a** was isolated in 52% yield after flash column chromatography purification. The best result was obtained by using a mixture of brine and acetone as reaction medium, and **4a** was produced in 82% yield with excellent stereoselectivity (>99%, based on its ^{1}H NMR spectrum) within eight hours. Under these optimum conditions, the Michael reactions of chromenes **3** and acetone in brine were performed to provide 2,3,4-trisubstituted chromanes **4** in good to high yields (Scheme 1). To our delight, a single crystal of **4f** was grown from CH_2Cl_2, suitable for X-ray diffraction analysis, and the X-ray structure of **4f** is shown in Figure 2. The X-ray structure of **4f** shows that the 2-aryl and 3-nitro groups are arranged in a *cis*-configuration on the pyran ring.



Scheme 1. Synthesis of 2,3,4-trisubstituted chromanes **4** in brine.

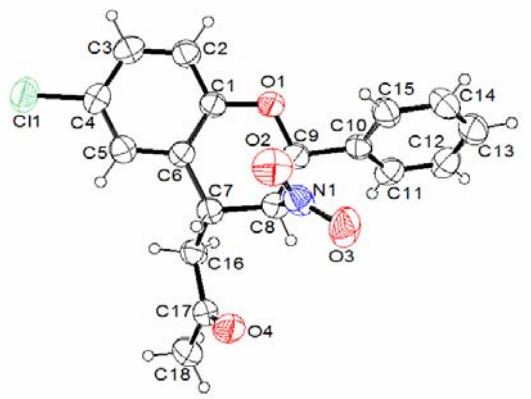
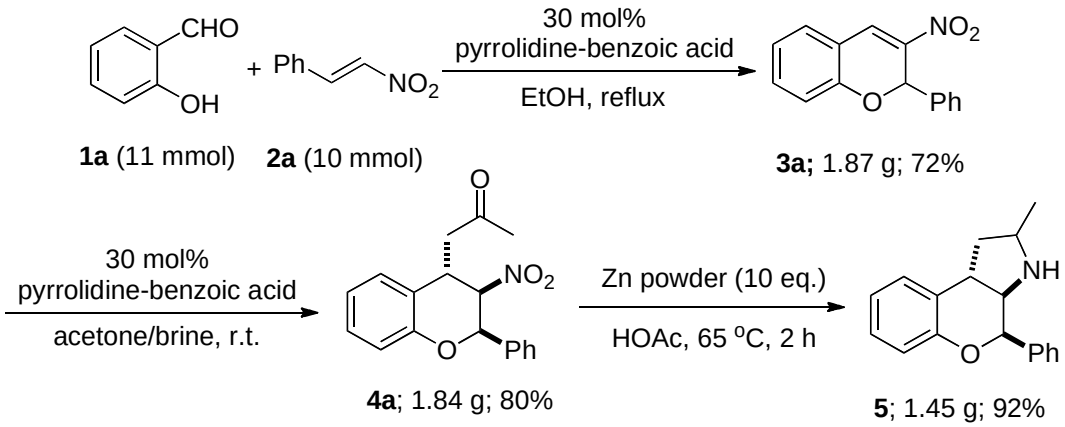


Figure 2. The X-ray structure of chromane **4f**.

Because 2,3,4-trisubstituted chromanes **4** possess aryl, nitro- and carbonyl groups, they can serve as useful synthetic intermediates for some fused ring derivatives of possible biological interest. So we performed a further transformation of **4a** to furnish tricyclic compound **5** through the reductive amination[27] of **4a** with Zn/AcOH (Scheme 2). Tricyclic amine **5** was obtained in high yield (92%).



Scheme 2. The reductive amination of **4a** to tricyclic compound **5**.

Conclusions

A facile synthesis of 2-aryl-3-nitro-2*H*-chromenes has been realized by using the combination of pyrrolidine and benzoic acid catalyzed tandem oxa-Michael-Henry reactions in refluxing ethanol. This catalytic strategy has also shown good reliability in the Michael reactions between 2-aryl-3-nitro-2*H*-chromenes and acetone in brine to provide 2,3,4-trisubstituted chromanes in good yields and excellent stereoselectivities. The structures of chromenes and chromanes were

confirmed by X-ray diffraction analysis of a typical examples of each type. Additionally, the reductive amination of 2,3,4-trisubstituted chromane was performed smoothly to afford a fused tricyclic amine in high yield. The investigation of enantioselective synthesis of functional chromanes by various organocatalysts is ongoing in our laboratory.

Experimental

General. Melting points are uncorrected and expressed in °C by MRS-2 Melting point apparatus from Shanghai Apparatus Co., Ltd. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, MeOD or DMSO-d_6 solution on a Bruker AV-400 or AV-500 spectrometer using TMS as an internal reference. Coupling constant (*J*) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High-resolution mass spectra were performed on a Bruker micrOTOF-Q II Mass Spectrometer with ES ionization (ESI). All commercially available reagents were used as received, ethanol (AR, 99.5%) and acetone (AR, 99.5%) was used as solvent or reagent in the preparation of chromenes **3** and chromanes **4**, respectively. Thin-layer chromatography on silica (with GF254) was used to monitor all reactions. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. All reactions involving air- or moisture-sensitive species were performed in oven-dried Schlenk tubes under an inert atmosphere.

Typical procedure for the preparation of chromenes 3

To a salicylaldehyde **1a** (1.1 mmol), β-nitrostyrene **2a** (1.0 mmol), pyrrolidine (0.30 mmol) and benzoic acid (0.30 mmol) in 2.0 mL of anhydrous EtOH were heated at reflux for 12 h under an inert atmosphere. The reaction was monitored by thin-layer chromatography (eluent: *n*-hexane/EtOAc 50:1, V/V). After the reaction finished, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (eluent: *n*-hexane/EtOAc 50:1, V/V) to provide pure chromene **3a** as yellow crystals. Chromenes **3a-i** are known compounds.

3-Nitro-2-phenyl-2*H*-chromene (3a).[8] R_f (*n*-hexane/EtOAc 50:1): 0.43, yellow crystals, mp 93–94 °C (Lit. 88–89 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.38–7.25 (m, 7H), 7.01–6.99 (m, 1H), 6.87–6.85 (m, 1H), 6.56 (s, 1H).

2-(4-Chlorophenyl)-3-nitro-2*H*-chromene (3b).[8] R_f (*n*-hexane/EtOAc 50:1): 0.45; yellow crystals, mp 141.0–141.5 °C (Lit. 133–134 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.34–7.25 (m, 6H), 7.02–6.99 (m, 1H), 6.87–6.85 (m, 1H), 6.54 (s, 1H).

2-(4-Methoxyphenyl)-3-nitro-2*H*-chromene (3c).[8] R_f (*n*-hexane/EtOAc 50:1): 0.50; yellow crystals, mp 159–160 °C (Lit. 154–155 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.32–7.25 (m, 4H), 7.02–6.99 (m, 1H), 6.84–6.81 (m, 3H), 6.52 (s, 1H), 3.75 (s, 3H).

8-Methoxy-3-nitro-2-phenyl-2*H*-chromene (3d).[12,28] R_f (*n*-hexane/EtOAc 50:1): 0.50; yellow crystals, mp 123–124 °C (Lit. 120 °C for racemic, 125 °C for *R*-form). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.40–7.38 (m, 2H), 7.31–7.28 (m, 3H), 6.94 (s, 3H), 6.66 (s, 1H), 3.80 (s, 3H).

7-Methoxy-3-nitro-2-phenyl-2*H*-chromene (3e).[12,29] R_f (*n*-hexane/EtOAc 50:1): 0.50; yellow crystals, mp 143–145 °C (Lit. 140–141 °C for racemic, 147 °C for *R*-form). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.38–7.36 (m, 2H), 7.32–7.31 (m, 3H), 7.25–7.22 (m, 1H), 6.56–6.54 (m, 2H), 6.39 (s, 1H), 3.77 (s, 3H).

6-Chloro-3-nitro-2-phenyl-2*H*-chromene(3f).[9,28,] R_f (*n*-hexane/EtOAc 50:1): 0.50; yellow crystals, mp 113–114 °C (Lit. 116 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.36–7.23 (m, 7H), 6.81–6.79 (m, 1H), 6.57 (s, 1H).

6-Bromo-3-nitro-2-phenyl-2*H*-chromene (3g).[9,28] R_f (*n*-hexane/EtOAc 50:1): 0.50; yellow crystals, mp 124–125 °C (Lit. 122 °C for racemic, 127-128 °C for *R*-form). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.44–7.25 (m, 7H), 6.76–6.74 (m, 1H), 6.57 (s, 1H).

2-(4-Bromophenyl)-3-nitro-2*H*-chromene (3h).[13] R_f (*n*-hexane/EtOAc 50:1): 0.50; yellow crystals, mp 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.45–7.22 (m, 6H), 7.03–6.99 (m, 1H), 6.87–6.85 (m, 1H), 6.53 (s, 1H).

6,8-Dichloro-3-nitro-2-phenyl-2*H*-chromene (3i).[9,11] R_f (*n*-hexane/EtOAc 50:1): 0.50; yellow crystals, mp 143.0–143.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.50 (m, 1H), 7.36–7.32 (m, 2H), 7.11 (m, 2H), 7.03–6.99 (m, 2H), 6.83–6.81 (m, 1H).

Typical procedure for the synthesis of chromanes 4

Chromene **3a** (1.0 mmol), pyrrolidine (0.30 mmol) and benzoic acid (0.30 mmol) in the mixed medium of acetone (1.0 mL) and brine (1.0 mL) was stirred for 8 h at rt. When the reaction finished, the mixture was diluted by the addition of EtOAc (15 mL), and washed by water (5 mL) and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified on a flash column chromatography (eluent: *n*-hexane/EtOAc 3:1, V/V) to afford pure chromane **4a** as a white powder.

1-(3-Nitro-2-phenylchroman-4-yl)propan-2-one (4a).[30] Yield: 82%, white powder, mp 170.5–171.5 °C (Lit. 185–186 °C). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.51–7.49 (m, 2H), 7.42–7.36 (m, 4H), 7.23–7.20 (m, 1H), 7.04–6.98 (m, 2H), 5.54 (s, 1H), 5.27 (s, 1H), 3.97–3.94 (dd, J_1 7.0 Hz, J_2 2.5 Hz, 1H), 3.39–3.33 (dd, J_1 10.3 Hz, J_2 8.7 Hz, 1H), 3.28–3.24 (dd, J_1 15.65 Hz, J_2 3.35 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 205.9, 154.8, 137.3, 129.9, 129.3, 129.2, 128.6, 126.7, 123.6, 122.7, 171.6, 87.8, 73.7, 50.4, 34.7. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{18}NNaO_4$ $[M+Na]^+$: 334.1055; Found: 334.1056.

1-(2-(4-Chlorophenyl)-3-nitrochroman-4-yl)propan-2-one (4b). Yield: 82%, white powder, mp 178.5–179.7 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.54–7.52 (m, 2H), 7.46–7.44 (m, 2H), 7.37–7.36 (m, 1H), 7.23–7.20 (m, 1H), 7.04–6.98 (m, 2H), 5.58–5.57 (m, 1H), 5.30–5.29 (m, 1H), 3.98–3.96 (m, 1H), 3.38–3.32 (dd, J_1 10.3 Hz, J_2 8.7 Hz, 1H), 3.29–3.23 (dd, J_1 15.45 Hz, J_2 3.5 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 205.9, 154.5, 136.3, 134.6,

129.9, 129.3, 128.6, 128.5, 123.6, 122.9, 117.6, 87.6, 73.1, 50.2, 34.5. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{17}ClNNaO_4$ $[M+Na]^+$: 368.0666; Found: 368.0663.

1-(2-(4-Methoxyphenyl)-3-nitrochroman-4-yl)propan-2-one (4c). Yield: 78%, white powder, mp 172.8–174.3 °C. ^{1}H NMR (acetone-d_6, 500 MHz): δ 7.39–7.34 (m, 3H), 7.2–7.19 (m, 1H), 7.02–6.94 (m, 4H), 5.47 (m, 1H), 5.21 (m, 1H), 3.94–3.91 (dd, J_1 6.5 Hz, J_2 3.5 Hz, 1H), 3.80 (s, 3H), 3.36–3.30 (dd, J_1 10.25 Hz, J_2 8.75 Hz, 1H), 3.26–3.21 (dd, J_1 15.4 Hz, J_2 3.6 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 205.9, 160.8, 154.9, 129.9, 129.1, 128.5, 128.0, 123.6, 122.7, 117.6, 114.6, 87.9, 73.5, 55.5, 50.4, 34.6. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{19}NNaO_5$ $[M+Na]^+$: 364.1161; Found 364.1161

1-(8-Methoxy-3-nitro-2-phenylchroman-4-yl)propan-2-one (4d). Yield: 76%, white powder, mp 159.5–161.0 °C. ^{1}H NMR (acetone-d_6, 500 MHz): δ 7.40–7.39 (m, 2H), 7.37–7.35 (m, 3H), 6.97–6.87 (m, 3H), 5.49 (m, 1H), 5.27 (m, 1H), 3.95–3.93 (dd, J_1 6.75 Hz, J_2 3.5 Hz, 1H), 3.83 (s, 3H), 3.37–3.32 (dd, J_1 10.3 Hz, J_2 8.7 Hz, 1H), 3.28–3.23 (dd, J_1 15.4 Hz, J_2 3.6 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 205.9, 149.4, 144.6, 137.4, 129.2, 129.1, 126.8, 124.2, 122.3, 121.3, 111.0, 87.7, 73.7, 56.2, 50.4, 34.7. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{20}NNaO_5$ $[M+Na]^+$: 364.1161; Found 364.1164.

1-(7-Methoxy-3-nitro-2-phenylchroman-4-yl)propan-2-one (4e). Yield: 78%, white powder, mp 171.5–172.5 °C. ^{1}H NMR (acetone-d_6, 500 MHz): δ 7.50–7.48 (m, 2H), 7.42–7.36 (m, 3H), 7.25–7.23 (d, *J* 8.55 Hz, 1H), 6.64–6.61 (dd, J_1 6.0 Hz, J_2 2.55 Hz, 1H), 6.56–6.55 (d, *J* 2.5 Hz, 1H), 5.52–5.51 (m, 1H), 5.25-5.24 (m, 1H), 3.89–3.86 (dd, J_1 6.45 Hz, J_2 3.65 Hz, 1H), 3.79 (s, 3H), 3.33–3.27 (dd, J_1 10.15 Hz, J_2 8.85 Hz, 1H), 3.24–3.19 (dd, J_1 10.15 Hz, J_2 8.85 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 206.0, 160.4, 155.6, 137.3, 130.5, 129.3, 129.2, 126.7, 115.4, 110.0, 102.2, 87.9, 73.8, 55.6, 50.4, 34.2. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{20}NNaO_5$ $[M+Na]^+$: 364.1161; Found 364.1165.

1-(6-Chloro-3-nitro-2-phenylchroman-4-yl)propan-2-one (4f). Yield: 84%, white powder, mp 162.5–163.8 °C. ^{1}H NMR (acetone-d_6, 500 MHz): δ 7.49–7.35 (m, 6H), 7.24–7.23 (m, 1H), 7.03–7.01 (d, *J* 8.75 Hz, 1H), 5.58–5.57 (d, *J* 1.85 Hz, 1H), 5.29–5.28 (m, 1H), 3.98–3.95 (dd, J_1 6.3 Hz, J_2 3.7 Hz, 1H), 3.42–3.37 (q, *J* 10.0 Hz, 1H), 3.33–3.29 (dd, J_1 15.3 Hz, J_2 3.8 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 205.7, 153.6, 136.9, 129.6, 129.4, 129.2, 128.6, 127.0, 125.7, 119.3, 87.4, 73.9, 50.1, 34.7. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{16}ClNNaO_4$ $[M+Na]^+$: 368.0666; Found 368.0662.

1-(6-Bromo-3-nitro-2-phenylchroman-4-yl)propan-2-one (4g). Yield: 86%, white powder, mp 148.0–149.5 °C. ^{1}H NMR (acetone-d_6, 500 MHz): δ 7.59 (s, 1H), 7.49–7.48 (m, 2H), 7.43–7.35 (m, 4H), 6.98–6.96 (d, *J* 8.7 Hz, 1H), 5.59–5.58 (m, 1H), 5.29–5.28 (m, 1H), 3.98–3.95 (dd, J_1 6.2 Hz, J_2 3.75 Hz, 1H), 3.42–3.36 (q, *J* 10 Hz, 1H), 3.34–3.29 (dd, J_1 15.25 Hz, J_2 3.8 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 205.7, 154.1, 136.9, 132.6, 131.5, 129.4, 129.3, 126.7, 126.3, 119.7, 114.3, 87.4, 73.8, 50.1, 34.6. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{17}BrNNaO_4$ $[M+Na]^+$: 412.0160; Found 412.0163.

Procedure for conversion of chromane 4a into 5

Chromane **4a** (1.84 g, 5.9 mmol) was suspended in 30 mL of HOAc and heated to 55 ^{o}C, Zn powder (3.90 g, 60 mmol) was added to the above suspension in four portions. The reaction mixture was heated to 65 ^{o}C and stirred for 2 h under n inert atmosphere (monitored by TLC). When the reaction finished, the solvent HOAc was evaporated under reduced pressure to yield dark-brown oily residue which was diluted by the addition of CH_2Cl_2 (60 mL), and this solution washed with cold saturated $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified on a flash column chromatography (eluent: *n*-hexane/EtOAc/Et_3N 1:1:0.01, V/V) to afford pure tricyclic compound **5** as a light yellow powder (1.45 g, 92%).

(3a,9b)-2-methyl-4-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*b*]pyrrole (5). Yield: 92%, light yellow powder, mp 123.6–125.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.19 (m, 7H), 7.04–6.88 (m, 3H), 6.12–6.11 (d, *J* 5.2 Hz, 1H), 4.04–4.00 (m, *J* 2.4 Hz, 1H), 2.83–2.75 (m, *J* 7.2 Hz, 2H), 2.46–2.37 (m, J_1 14.0 Hz, J_2 4.0 Hz, 1H), 2.07-2.06 (d, *J* 2.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.2, 153.9, 138.8, 128.2, 128.0, 127.4, 126.3, 126.1, 125.0, 120.3, 116.1, 78.7, 74.4, 40.7, 37.8, 21.0. HRMS (ESI) *m*/*z* Calcd for $C_{18}H_{20}NO$ $[M+H]^+$: 266.1545; Found 266.1554.

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