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Cascade Oxa-Michael–Henry Reaction of Salicylaldehydes with Nitrostyrenes via Ball Milling: A Solvent-Free Synthesis of 3-Nitro-2*H*-chromenes

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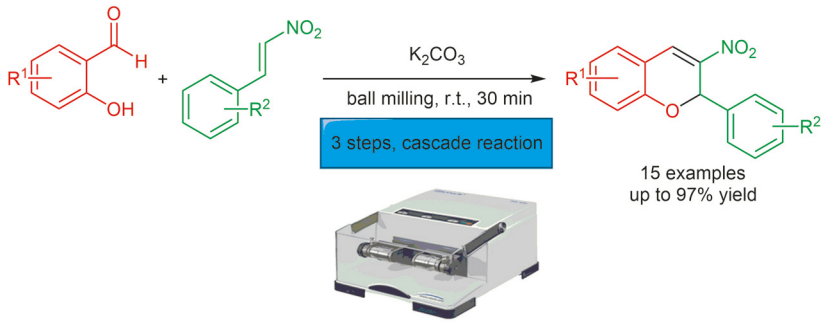

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Abstract Cascade oxa-Michael–Henry reactions of salicylaldehyde derivatives with β-nitrostyrenes catalyzed by potassium carbonate via solvent-free ball milling are demonstrated. The corresponding 3-nitro-2*H*-chromene products were obtained in moderate to excellent yields. This method offers significant advantages, particularly in terms of high yields, short reaction times and mild conditions.

Key words solvent-free, ball milling, cascade, oxa-Michael–Henry reaction, 3-nitro-2*H*-chromenes

3-Nitro-2*H*-chromenes represent important nitro-bearing heterocyclic compounds.[1] Studies of these derivatives have been extensively reported in recent years, mainly due to the fact that these compounds prove to be easily accessible and feature high biological activities.[2] Several methods are known to be suitable for the synthesis of 3-nitro-2*H*-chromenes;[3,4] among them, the cascade reaction of salicylaldehydes or their corresponding imines[5] with unsaturated nitro compounds is probably the most widely used approach. The corresponding products are formed according to an oxa-Michael/Henry/dehydration sequence, with often tedious workup requirements.[6] Many of these procedures are catalyzed by a variety of bases[7–9] in an organic solvent (e.g., toluene, CH_2Cl_2, $CHCl_3$, DMSO). However, solvents may be toxic and harmful to the environment. Furthermore, long reaction times (4–6 days) and/or harsh reaction conditions (100 °C in an inert gas atmosphere) are often required for these reactions to proceed. In contrast to the traditional synthetic procedures in solution, Yan and co-workers reported the reaction of salicylaldehydes with β-nitrostyrenes catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) in the absence of a solvent. Unfortunately, a large excess of the salicylaldehyde (4–10 equiv) was required for these reactions to succeed, and the reactions were generally more efficient when aqueous salicylaldehyde was used.[10] Therefore, a method with both mild reaction conditions and high efficiency would prove highly beneficial.

In the last decade, the ball-milling technique has emerged as a powerful tool, offering a new, environmentally friendly and cost-effective strategy in organic synthesis.[11] This particular method tends to provide high reaction yields and shorter reaction times, without the need for solvents.[12,13]

Significant progress has been made in the use of mechanical milling techniques in synthetic chemistry.[11,14] Some recent examples of mechanical ball-milling techniques in organic synthesis include C–H bond functionalization of acetanilides,[15] C–N coupling of arylsulfonamides and carbodiimides,[16] and the formation of 2-substituted 1*H*-indoles[17] and 1*H*-pyrazoles.[18] The first mechanochemically induced cascade reaction was reported by Kaupp and co-workers in 1999.[19] Here, the reaction of *trans*-1,2-dibenzoylethene with primary or secondary enamine esters or enamine ketones in a ball mill afforded the corresponding pyrrole or indole products in nearly quantitative yields. Studies describing mechanochemically induced cascade reactions can be frequently found in the literature.[20] However, to the best of our knowledge, milling techniques for the cascade reaction of salicylaldehydes with β-nitrostyrenes have not been reported as yet. We now present the mechanochemical activation of cascade oxa-Michael–Henry reactions as a novel, as well as 'green', protocol for the production of bioactive heterocyclic 3-nitro-2*H*-chromenes.

Previous studies have used different bases to carry out this type of cascade reaction in solution.[21] For this reason, we initially investigated the influence of the base on the cascade oxa-Michael–Henry reaction. Reactions were conducted in a ball-milling apparatus at a rotational frequency of 15 Hz at room temperature for a total of three hours [6 ×

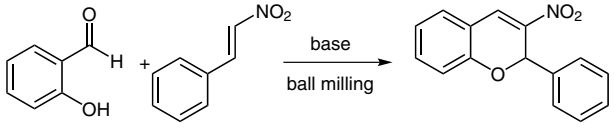
(30 minutes + 5 minute break)]. Silicon dioxide was chosen as the milling auxiliary, and the reaction progress was continuously monitored by thin-layer chromatography.

Table 1 shows the results of the cascade reaction of salicylaldehyde (**1a**) with β-nitrostyrene (**2a**) using different additives. It should be noted that none of the desired product **3aa** was formed when no base was added (Table 1, entry 1). Presumably, 4-(dimethylamino)pyridine offers improved activity characteristics for this type of cascade reaction relative to other organic bases (e.g., DABCO, Et_3N, DIPEA; Table 1, entries 3–5 and 11). Interestingly, the reaction proceeded quickly when potassium carbonate was used as an additive, resulting in the best obtained yield of 25% among all bases examined at 20 mol% (Table 1, entry 7). In contrast, an adverse effect on the reaction was observed when hydrated potassium carbonate was used, resulting in a slight product loss (Table 1, entry 6). Strong bases (e.g., NaOH, DBU) resulted in a significant decrease in the yields obtained (Table 1, entries 8 and 9). Furthermore, weak bases such as L-proline and pyridine exhibited a low efficiency for catalyzing the reaction (Table 1, entries 2 and 12). The use of cesium carbonate resulted in a similar product yield as the reaction catalyzed by hydrated potassium carbonate (Table 1, entry 10).

Unfortunately, all observed yields still proved to be inadequate at this point. Therefore, we focused our attention on determining the influence of the potassium carbonate concentration on the product yield. As a consequence, we used potassium carbonate in stoichiometric amounts instead of catalytic amounts. The results obtained clearly show that there is a significant increase in the reaction rate and the product yield (Table 1, entries 13–16); when an increased amount (0.75 equiv) of potassium carbonate was used, the product **3aa** was formed in 68% yield (Table 1, entry 14). Increasing the amount of potassium carbonate to 1.5 equivalents, however, did not significantly improve the yield further (Table 1, entry 15).

Various other reaction conditions were investigated in an effort to further improve the product yield. Interestingly, increasing the ratio of **1a**/**2a** from 1.0 in the initial experiments to 1.3 and 1.5 resulted in higher observed yields of **3aa** of 76% and 78%, respectively (Table 2, entries 1 and 2). Improving the rotational frequency from 15 Hz to 20 Hz also led to an increased product yield, along with a 2-hour decrease in the reaction time (Table 2, entries 1 and 3). The best result of 85% yield of **3aa** was obtained at a rotational frequency of 25 Hz within 30 minutes (Table 2, entry 4). Decreased yields were observed when the reaction was performed at a higher rotational frequency (e.g., 30 Hz; Table 2, entry 5). This latter finding is most likely due to product and/or substrate degradation resulting from the increased amount of energy per impact. Furthermore, the formation of various side products was observed. It is worth noting that the amount of base (0.5–1.5 equiv) proved to have no significant influence on the product yields, as the reaction time was increased until the starting material was completely consumed (Table 2, entries 4, 6 and 7). On the other hand, if the substrates could not be mixed in an efficient manner, such as when silicon dioxide was not added, a poor product yield and partial polymerization of β-nitrostyrene was observed (Table 2, entry 8). However, the addition of a relatively large amount of silicon dioxide resulted in a drastic yield decrease, most likely due to diluted reagent concentrations (Table 2, entry 9). As a consequence, the optimal reaction conditions with respect to ball-milling time, base loading and ratio of reagents are as follows: milling frequency = 25 Hz for 30 minutes, reagent ratio (**1a**/**2a**/K_2CO_3) = 1.3:1.0:0.75.

Table 1 Cascade Oxa-Michael–Henry Reaction of **1a** with **2a** Using Different Additives[a]

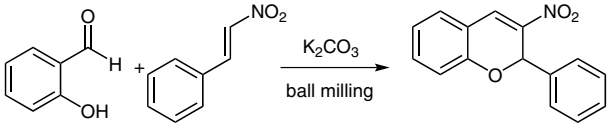


1a **2a** **3aa**

Entry	Additive	Amount (mol%)	Yield[b] (%) of **3aa**
1	–	–	0
2	L-proline	20	5
3	DMAP	20	16
4	DABCO	20	14
5	Et_3N	20	10
6	$K_2CO_3·1.5H_2O$	20	20
7	K_2CO_3	20	25
8	NaOH	20	17
9	DBU	20	18
10	Cs_2CO_3	20	22
11	DIPEA	20	12
12	pyridine	20	7
13	K_2CO_3	50	65
14[c]	K_2CO_3	75	68
15[c]	K_2CO_3	150	69
16[c]	NaOH	150	53

[a] Reaction conditions: salicylaldehyde (**1a**; 0.2 mmol, 1.0 equiv), β-nitrostyrene (**2a**; 0.2 mmol, 1.0 equiv), SiO_2 (500 mg); ball-milling conditions: [6 × (30 min + 5 min break)] at 15 Hz.
[b] Isolated yields, obtained via chromatographic purification on silica gel.
[c] Ball-milling conditions: [4 × (30 min + 5 min break)] at 15 Hz.

Table 2 Further Optimization of the Cascade Oxa-Michael–Henry Reaction of **1a** with **2a**[a]



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

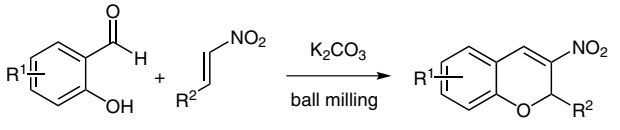
Entry	Time (h)	Rotational frequency (Hz)	Reagent ratios (**1a**/**2a**/K_2CO_3)	Yield[b] (%) of **3aa**
1	3	15	1.3:1:0.75	76
2	3	15	1.5:1:0.75	78
3	1	20	1.3:1:0.75	81
4	0.5	25	1.3:1:0.75	85
5	0.5	30	1.3:1:0.75	74
6	2	25	1.3:1:0.5	82
7	0.5	25	1.3:1:1.5	84
8[c]	0.5	25	1.3:1:0.75	70
9[d]	0.5	25	1.3:1:0.75	61

[a] Reaction conditions: 0.20-mmol scale, using SiO_2 (500 mg); ball-milling conditions: 5-min break between each 30-min interval.
[b] Isolated yields, obtained via chromatographic purification on silica gel.
[c] SiO_2 was not added.
[d] SiO_2 (2 g) was added.

Having established the optimal reaction conditions, we subsequently investigated a range of different salicylaldehyde derivatives **1** and β-nitrostyrenes **2** in an effort to evaluate the scope of this cascade process. The corresponding results are summarized in Table 3.

The reactivity of this reaction type was shown to be mainly determined by the electronic properties and the positions of the substituents on the phenyl ring of the nitroalkene moiety (Table 3, entries 1–9). In general, electron-deficient nitroalkene derivatives exhibit a higher reactivity than electron-rich species (Table 3, entries 2, 4 and 5 vs entry 9). Electron-withdrawing functional groups such as nitro and bromo at the 2-position on the phenyl ring of the β-nitrostyrene species result in the formation of the desired products **3ab** and **3ad** in 94% and 97% yield, respectively (Table 3, entries 2 and 4). β-Nitrostyrenes bearing two electron-withdrawing groups on the phenyl ring can also provide the corresponding products in excellent yields, namely 85% and 83% for **3af** and **3ag**, respectively (Table 3, entries 6 and 7). Overall, salicylaldehyde derivatives bearing an electron-deficient or electron-rich aryl group undergo the cascade oxa-Michael–Henry reaction with β-nitrostyrene efficiently, resulting in the formation of the corresponding 3-nitro-2*H*-chromenes in good yields (Table 3, entries 10–15). Here, the use of 5-bromosalicylaldehyde (**1b**) provided the best product yield of 86% (**3bj**; Table 3, entry 10).

Table 3 Cascade Oxa-Michael–Henry Reaction of Salicylaldehyde Derivatives **1** with β-Nitrostyrenes **2**[a]



1 **2** **3aa–gj**

Entry	R^1 (Substrate **1**)	R^2 (Substrate **2**)	Product **3**	Yield[b] (%)
1	H (**1a**)	Ph (**2a**)	**3aa**	85
2	H (**1a**)	2-$O_2NC_6H_4$ (**2b**)	**3ab**	94
3	H (**1a**)	3-$O_2NC_6H_4$ (**2c**)	**3ac**	71
4	H (**1a**)	2-BrC_6H_4 (**2d**)	**3ad**	97
5	H (**1a**)	3-BrC_6H_4 (**2e**)	**3ae**	91
6	H (**1a**)	2,4-$Cl_2C_6H_3$ (**2f**)	**3af**	85
7	H (**1a**)	2-Cl-5-$NO_2C_6H_3$ (**2g**)	**3ag**	83
8	H (**1a**)	2-FC_6H_4 (**2h**)	**3ah**	74
9	H (**1a**)	3-$MeOC_6H_4$ (**2i**)	**3ai**	70
10	5-Br (**1b**)	Ph (**2j**)	**3bj**	86
11	5-CF_3 (**1c**)	Ph (**2j**)	**3cj**	60
12	4-Br (**1d**)	Ph (**2j**)	**3dj**	64
13	4-Cl (**1e**)	Ph (**2j**)	**3ej**	67
14	5-CO_2Me (**1f**)	Ph (**2j**)	**3fj**	60
15	5-Me (**1g**)	Ph (**2j**)	**3gj**	64

[a] Reaction conditions: salicylaldehyde **1** (0.26 mmol, 1.3 equiv), β-nitrostyrene **2** (0.2 mmol, 1.3 equiv), K_2CO_3 (0.15 mmol, 0.75 equiv), SiO_2 (500 mg); ball-milling conditions: 30 min at 25 Hz.
[b] Isolated yields obtained via chromatography on silica gel, without any aqueous workup.

In order to demonstrate the reliability and reproducibility of this synthetic approach, the cascade reaction of salicylaldehyde (**1a**) and β-nitrostyrene (**2a**) was performed on a gram scale (10 mmol). In doing so, compound **3aa** could be isolated in 80% yield (2.02 g) upon a simple column chromatographic purification. Celite® and sodium chloride were also tested as grinding aids in an effort to further optimize the reaction conditions, resulting in a product yield of **3aa** of 73% and 79%, respectively; however, these isolated yields remain lower than the 85% yield obtained with silicon dioxide as the grinding aid.

According to reports published previously,[22] the suggested reaction mechanism for this sequence involves oxa-Michael/Henry/dehydration steps. The synthesis proceeds via cascade nucleophilic additions and a Henry condensation. In the presence of base, a nucleophilic phenolate anion is believed to attack the β-nitroalkene species, resulting in the formation of the corresponding intermediates. The latter may undergo an intramolecular condensation reaction to form the 4-hydroxy-3-nitrochromane derivatives. A subsequent dehydration process would then afford the target compounds **3aa**–**gj**.

In summary, we have developed a general procedure for the production of 3-nitro-2*H*-chromene derivatives via the cascade oxa-Michael–Henry reaction of salicylaldehyde derivatives with β-nitrostyrenes promoted by potassium carbonate and solvent-free ball milling with product yields up to 97%. This method, which has significant advantages in terms of high yields, short reaction times and mild conditions, may prove useful in the green and efficient synthesis of bioactive heterocyclic 3-nitro-2*H*-chromene derivatives. Further studies to support this hypothesis are currently underway in our laboratory.

Ethyl acetate, light petroleum ether and dichloromethane were distilled prior to use. All other solvents, reagents and chemicals were used as obtained from commercial sources. Flash column chromatography was performed with 100–200 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer, and TMS was used as a reference. ^{1}H NMR spectroscopic data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants in hertz (Hz), integration, assignment. ^{13}C NMR spectroscopic data are reported in ppm. IR spectra were recorded on a Bruker Tensor 27 spectrometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were measured on a Shimadzu LCMS-IT-TOF spectrometer (APCI). All melting points were determined using a digital melting point apparatus and are uncorrected. The starting β-nitrostyrene and salicylaldehyde derivatives were prepared according to literature procedures.[23,24]

3-Nitro-2*H*-chromenes 3aa–3gj; General Procedure

Reactions were conducted in a ball-milling apparatus (Retsch MM400 Mixer Mill, Retsch GmbH, Haan, Germany; volume of stainless steel vial: 10 mL; diameter of stainless steel balls: 10.0 mm). In a typical experiment, a salicylaldehyde **1** (0.26 mmol, 1.3 equiv), a β-nitrostyrene **2** (0.2 mmol, 1 equiv) and K_2CO_3 (0.15 mmol, 0.75 equiv) were ball-milled with 500 mg SiO_2 for 30 min [2 × (15 min + 5 min break)] at 25 Hz. The reaction mixture was then transferred directly onto a flash column, without any additional workup step, and was subjected to chromatographic purification on silica gel [eluent(s) given below] to afford the corresponding 3-nitro-2*H*-chromene **3aa**–**gj**.

3-Nitro-2-phenyl-2*H*-chromene (3aa)

Eluent: hexane–EtOAc, 1000:1; yield: 43 mg (85%); yellow solid; mp 93.0 °C.

R_f = 0.2 (hexane–EtOAc, 60:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, CH=), 7.41–7.28 (m, 7 H_{arom}), 7.00 (t, *J* = 7.5 Hz, 1 H_{arom}), 6.87 (d, *J* = 8.7 Hz, 1 H_{arom}), 6.59 (s, 1 H, CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.57, 141.17, 136.79, 134.35, 130.47, 129.50, 129.33, 128.87, 127.05, 122.56, 117.95, 117.30, 74.27.

The ^{1}H NMR and ^{13}C NMR data for this compound are in accordance with the literature data.[9]

HRMS (APCI$^-$–TOF): *m*/*z* [M]$^-$ calcd for $C_{15}H_{11}NO_3$: 253.0739; found: 253.0738.

3-Nitro-2-(2-nitrophenyl)-2*H*-chromene (3ab)

Eluent: PE–EtOAc, 20:1; yield: 56 mg (94%); yellow solid; mp 143.0–144.0 °C.

R_f = 0.25 (PE–EtOAc, 7:1).

IR (KBr): 1648, 1604, 1534, 1517, 1456, 1335, 1119, 764 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (s, 1 H, CH=), 7.93 (d, *J* = 9.1 Hz, 1 H_{arom}), 7.53–7.44 (m, 2 H_{arom}), 7.42 (s, 1 H, CH), 7.37–7.24 (m, 3 H_{arom}), 7.01 (t, *J* = 7.5 Hz, 1 H_{arom}), 6.82 (d, *J* = 8.2 Hz, 1 H_{arom}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.00, 148.71, 139.49, 134.78, 132.95, 130.96, 130.51 (d, *J* = 6.3 Hz), 130.31, 128.01, 125.41, 123.15, 117.53 (d, *J* = 13.2 Hz), 68.90.

HRMS (APCI$^-$–TOF): *m*/*z* [M]$^-$ calcd for $C_{15}H_{10}N_2O_5$: 298.0590; found: 298.0589.

3-Nitro-2-(3-nitrophenyl)-2*H*-chromene (3ac)

Eluent: PE–EtOAc, 20:1; yield: 42 mg (71%); yellow solid; mp 146.5–147.5 °C.

R_f = 0.4 (PE–EtOAc, 7:1).

IR (KBr): 1646, 1604, 1534, 1514, 1459, 1344, 1325, 1121 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.53 (s, 1 H, CH=), 8.27 (s, 1 H_{arom}), 8.24 (d, *J* = 10.4 Hz, 1 H_{arom}), 7.87 (d, *J* = 8.9 Hz, 1 H_{arom}), 7.71–7.66 (m, 2 H_{arom}), 7.42 (t, *J* = 7.8 Hz, 1 H_{arom}), 7.11 (t, *J* = 7.5 Hz, 1 H_{arom}), 6.94 (d, *J* = 8.2 Hz, 1 H_{arom}), 6.90 (s, 1 H, CH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 152.79, 148.54, 140.20, 139.18, 135.29, 133.96, 131.93, 131.32, 131.22, 124.84, 123.45, 122.36, 118.36, 117.24, 72.67.

HRMS (APCI$^-$–TOF): *m*/*z* [M]$^-$ calcd for $C_{15}H_{10}N_2O_5$: 298.0590; found: 298.0584.

2-(2-Bromophenyl)-3-nitro-2*H*-chromene (3ad)

Eluent: PE–EtOAc, 300:1; yield: 64 mg (97%); yellow solid; mp 115.5–116.5 °C.

R_f = 0.25 (PE–EtOAc, 100:1).

IR (KBr): 1647, 1603, 1511, 1456, 1334, 1222, 1120, 762, 573 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, CH=), 7.67 (d, *J* = 6.6 Hz, 1 H_{arom}), 7.35 (dd, *J* = 7.6, 1.6 Hz, 1 H_{arom}), 7.33–7.28 (m, 1 H_{arom}), 7.22–7.16 (m, 3 H_{arom}), 7.03 (s, 1 H, CH), 7.01 (t, *J* = 7.5 Hz, 1 H_{arom}), 6.83 (d, *J* = 8.2 Hz, 1 H_{arom}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.09, 140.31, 134.86, 134.50, 134.00, 131.15, 130.38, 130.28, 128.08, 127.81, 124.29, 122.69, 117.73, 117.51, 73.13.

HRMS (APCI$^-$–TOF): *m*/*z* [M]$^-$ calcd for $C_{15}H_{10}BrNO_3$: 330.9844; found: 330.9842.

2-(3-Bromophenyl)-3-nitro-2*H*-chromene (3ae)

Eluent: hexane–CH_2Cl_2, 20:1; yield: 60 mg (91%); yellow solid; mp 114.5–115.5 °C.

R_f = 0.1 (hexane–CH_2Cl_2, 80:1).

IR (KBr): 1647, 1602, 1510, 1457, 1334, 1222, 1119, 762 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, CH=), 7.67 (dd, *J* = 8.0, 1.7 Hz, 1 H_{arom}), 7.35 (dd, *J* = 7.6, 1.6 Hz, 1 H_{arom}), 7.31 (m, 1 H_{arom}), 7.22–7.15 (m, 3 H_{arom}), 7.04 (s, 1 H, CH), 7.01 (t, *J* = 8.0 Hz, 1 H_{arom}), 6.83 (d, *J* = 8.2 Hz, 1 H_{arom}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.10, 140.30, 134.87, 134.51, 134.00, 131.16, 130.39, 130.28, 128.09, 127.82, 124.29, 122.70, 117.74, 117.51, 73.14.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{15}H_{10}BrNO_3$: 330.9844; found: 330.9844.

2-(2,4-Dichlorophenyl)-3-nitro-2*H*-chromene (3af)

Eluent: PE–EtOAc, 200:1; yield: 55 mg (85%); yellow solid; mp 155.0–156.0 °C.

R_f = 0.2 (PE–EtOAc, 100:1).

IR (KBr): 1649, 1605, 1506, 1457, 1333, 1223, 1071, 759 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.52 (s, 1 H, CH=), 7.80 (s, 1 H_{arom}), 7.66 (d, *J* = 9.1 Hz, 1 H_{arom}), 7.38 (dd, *J* = 17.7, 8.8 Hz, 2 H_{arom}), 7.30 (d, *J* = 8.4 Hz, 1 H_{arom}), 7.09 (t, *J* = 7.4 Hz, 1 H_{arom}), 6.95 (s, 1 H, CH), 6.85 (d, *J* = 8.2 Hz, 1 H_{arom}).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 152.53, 139.59, 135.67, 135.19, 134.33, 132.79, 131.90, 131.70, 130.49, 130.06, 128.48, 123.35, 118.26, 117.15, 70.31.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{15}H_9Cl_2NO_3$: 320.9959; found: 320.9959.

2-(2-Chloro-5-nitrophenyl)-3-nitro-2*H*-chromene (3ag)

Eluent: hexane–EtOAc, 90:1; yield: 55 mg (83%); yellow solid; mp 206.0–207.0 °C.

R_f = 0.2 (hexane–EtOAc, 30:1).

IR (KBr): 1649, 1607, 1558, 1509, 1498, 1336, 1304, 1271, 1244 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.62 (s, 1 H, CH=), 8.25 (dd, *J* = 8.8, 2.7 Hz, 1 H_{arom}), 7.99–7.93 (m, 2 H_{arom}), 7.71 (d, *J* = 7.5 Hz, 1 H_{arom}), 7.41 (t, *J* = 7.8 Hz, 1 H_{arom}), 7.12 (t, *J* = 7.4 Hz, 1 H_{arom}), 7.08 (s, 1 H, CH), 6.87 (d, *J* = 8.2 Hz, 1 H_{arom}).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 152.35, 147.18, 140.07, 139.14, 135.46, 135.27, 132.56, 132.00, 131.92, 126.74, 123.65, 123.18, 117.98, 117.15, 70.51.

HRMS (APCI⁻–TOF): *m*/*z* [M – NO_2]⁻ calcd for $C_{15}H_9ClNO_3$: 286.0271; found: 286.0271.

2-(2-Fluorophenyl)-3-nitro-2*H*-chromene (3ah)

Eluent: PE–EtOAc, 2000:1; yield: 40 mg (74%); yellow solid; mp 141.5–142.5 °C.

R_f = 0.3 (PE–EtOAc, 100:1).

IR (KBr): 1650, 1605, 1512, 1457, 1325, 1219, 1120, 1070, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.12 (s, 1 H, CH=), 7.36–7.30 (m, 3 H_{arom}), 7.20 (t, *J* = 7.5 Hz, 1 H_{arom}), 7.13 (m, 1 H_{arom}), 7.06–6.98 (m, 2 H_{arom}), 6.93 (s, 1 H, CH), 6.83 (d, *J* = 8.2 Hz, 1 H_{arom}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.42, 159.43, 153.30, 139.74, 134.46, 131.56 (d, *J* = 8.4 Hz), 130.25 (d, *J* = 45.8 Hz), 128.22 (d, *J* = 2.8 Hz), 124.31 (d, *J* = 3.6 Hz), 123.69 (d, *J* = 13.7 Hz), 122.65, 117.66, 117.26, 116.31 (d, *J* = 21.7 Hz), 68.31.

HRMS (APCI⁻–TOF): *m*/*z* [M – NO_2]⁻ calcd for $C_{15}H_{10}FO$: 225.0716; found: 225.0725.

2-(3-Methoxyphenyl)-3-nitro-2*H*-chromene (3ai)

Eluent: PE–EtOAc, 170:1; yield: 40 mg (70%); yellow solid; mp 64.0–65.0 °C.

R_f = 0.3 (PE–EtOAc, 60:1).

IR (KBr): 2925, 2854, 1645, 1606, 1510, 1454, 1379, 1326, 1283 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (s, 1 H, CH=), 7.31 (t, *J* = 6.5 Hz, 2 H_{arom}), 7.22 (t, *J* = 7.9 Hz, 1 H_{arom}), 7.04–6.82 (m, 5 H_{arom}), 6.55 (s, 1 H, CH), 3.75 (s, 3 H, OCH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.85, 153.56, 141.08, 138.23, 134.32, 130.46, 129.92, 129.31, 122.57, 119.21, 117.93, 117.27, 114.62, 113.06, 74.11, 55.25.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{16}H_{13}NO_4$: 283.0845; found: 283.0845.

6-Bromo-3-nitro-2-phenyl-2*H*-chromene (3bj)

Eluent: hexane–Et_2O, 160:1; yield: 57 mg (86%); yellow solid; mp 136.5–137.5 °C.

R_f = 0.3 (hexane–Et_2O, 80:1).

IR (KBr): 1649, 1592, 1521, 1337, 1320, 1063 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, CH=), 7.39–7.29 (m, 5 H_{arom}), 7.18 (d, *J* = 8.1 Hz, 1 H_{arom}), 7.14 (dd, *J* = 8.1, 1.7 Hz, 1 H_{arom}), 7.05 (d, *J* = 1.2 Hz, 1 H_{arom}), 6.57 (s, 1 H, CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.90, 141.17, 136.24, 131.09, 129.76, 128.99, 128.41, 128.10, 127.06, 125.98, 120.73, 116.94, 74.59.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{15}H_{10}BrNO_3$: 330.9844; found: 330.9840.

3-Nitro-2-phenyl-6-(trifluoromethyl)-2*H*-chromene (3cj)

Eluent: 100% PE; yield: 40 mg (60%); yellow solid; mp 112.0 °C.

R_f = 0.15 (PE).

IR (KBr): 1656, 1620, 1520, 1337, 1302, 1193, 1160, 1121, 1058 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1 H, CH=), 7.60 (s, 1 H_{arom}), 7.56 (d, *J* = 9.9 Hz, 1 H_{arom}), 7.42–7.30 (m, 5 H_{arom}), 6.96 (d, *J* = 8.6 Hz, 1 H_{arom}), 6.64 (s, 1 H, CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.81, 142.09, 136.15, 130.91 (d, *J* = 3.5 Hz), 129.93, 129.09, 127.76, 127.49, 127.46, 127.05, 125.53–124.46 (m), 122.53, 117.82 (d, *J* = 18.0 Hz), 74.88.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{16}H_{10}F_3NO_3$: 321.0613; found: 321.0615.

7-Bromo-3-nitro-2-phenyl-2*H*-chromene (3dj)

Eluent: 100% PE; yield: 42 mg (64%); yellow solid; mp 133.0–134.0 °C.

R_f = 0.1 (PE).

IR (KBr): 1651, 1591, 1515, 1320, 1130, 1064, 821, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, CH=), 7.37–7.33 (m, 5 H_{arom}), 7.18 (d, *J* = 8.1 Hz, 1 H_{arom}), 7.14 (dd, *J* = 8.1, 1.8 Hz, 1 H_{arom}), 7.05 (d, *J* = 1.2 Hz, 1 H_{arom}), 6.57 (s, 1 H, CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.90, 141.16, 136.23, 131.09, 129.77, 129.00, 128.42, 128.10, 127.06, 125.98, 120.73, 116.94, 74.58.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{15}H_{10}BrNO_3$: 330.9844; found: 330.9846.

7-Chloro-3-nitro-2-phenyl-2*H*-chromene (3ej)

Eluent: PE–EtOAc, 400:1; yield: 38 mg (67%); yellow solid; mp 127.0 °C.

R_f = 0.16 (PE–EtOAc, 120:1).

IR (KBr): 1644, 1598, 1515, 1318, 1074, 824, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, CH=), 7.37–7.31 (m, 5 H_{arom}), 7.25 (d, *J* = 5.1 Hz, 1 H_{arom}), 6.98 (dd, *J* = 8.2, 1.9 Hz, 1 H_{arom}), 6.88 (d, *J* = 1.4 Hz, 1 H_{arom}), 6.57 (s, 1 H, CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.03, 141.06, 139.86, 136.27, 130.99, 129.75, 128.99, 128.36, 127.06, 123.09, 117.82, 116.57, 74.55.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{15}H_{10}ClNO_3$: 287.0349; found: 287.0351.

Methyl 3-Nitro-2-phenyl-2*H*-chromene-6-carboxylate (3fj)

Eluent: PE–CH_2Cl_2, 10:1; yield: 37 mg (60%); yellow solid; mp 174.0–175.0 °C.

R_f = 0.2 (PE–CH_2Cl_2, 3:1).

IR (KBr): 1721, 1655, 1611, 1520, 1444, 1323, 1268, 1206, 1134, 1069 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (s, 1 H, CH=), 8.05 (d, *J* = 2.1 Hz, 1 H_{arom}), 7.99 (dd, *J* = 8.6, 2.1 Hz, 1 H_{arom}), 7.38–7.32 (m, 5 H_{arom}), 6.90 (d, *J* = 8.6 Hz, 1 H_{arom}), 6.63 (s, 1 H, CH), 3.91 (s, 3 H, OCH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.70, 157.05, 141.64, 136.35, 135.52, 132.18, 129.83, 129.02, 128.35, 127.05, 124.68, 117.56, 117.26, 75.02, 52.29.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{17}H_{13}NO_5$: 311.0794; found: 311.0792.

6-Methyl-3-nitro-2-phenyl-2*H*-chromene (3gj)

Eluent: PE–EtOAc, 1000:1; yield: 34 mg (64%); yellow solid; mp 122.0 °C.

R_f = 0.15 (PE–EtOAc, 100:1).

IR (KBr): 2926, 2854, 1648, 1503, 1455, 1384, 1332, 1209, 1070, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, CH=), 7.37 (dd, *J* = 6.7, 3.0 Hz, 2 H_{arom}), 7.32 (d, *J* = 2.2 Hz, 2 H_{arom}), 7.31 (d, *J* = 1.6 Hz, 1 H_{arom}), 7.12 (t, *J* = 7.3 Hz, 2 H_{arom}), 6.77 (d, *J* = 8.9 Hz, 1 H_{arom}), 6.56 (s, 1 H, CH), 2.29 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.47, 141.20, 136.85, 135.16, 132.02, 130.53, 129.54, 129.40, 128.82, 127.02, 117.79, 117.05, 74.14, 20.41.

HRMS (APCI⁻–TOF): *m*/*z* [M]⁻ calcd for $C_{16}H_{13}NO_3$: 267.0895; found: 267.0891.

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References

(1) Fouqué, A.; Delalande, O.; Jean, M.; Castellano, R.; Josselin, E.; Malleter, M.; Shoji, K. F.; Hung, M. D.; Rampanarivo, H.; Collette, Y.; Weghe, P.; Legembre, P. *J. Med. Chem.* **2015**, *58*, 6559.

(2) (a) Xiao, G. Q.; Liang, B. X.; Chen, S. H.; Ou, T. M.; Bu, X. Z.; Yan, M. *Arch. Pharm. (Weinheim, Ger.)* **2012**, *345*, 767. (b) Galano, J. J.; Alías, M.; Pérez, R.; Velázquez-Campoy, A.; Hoffman, P. S.; Sancho, J. *J. Med. Chem.* **2013**, *56*, 6248. (c) Rahmani-Nezhad, S.; Safavi, M.; Pordeli, M.; Ardestani, S. K.; Khosravani, L.; Pourshojaei, Y.; Mahdavi, M.; Emami, S.; Foroumadi, A.; Shafiee, A. *Eur. J. Med. Chem.* **2014**, *86*, 562. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (e) Banskota, A. H.; Tezuka, Y.; Prasain, J. K.; Matsushige, K.; Saiki, I.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 896.

(3) Wang, X. F.; Peng, L.; An, J.; Li, C.; Yang, Q. Q.; Lu, L. Q.; Gu, F. L.; Xiao, W. J. *Chem. Eur. J.* **2011**, *17*, 6484.

(4) (a) Hata, E.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3629. (b) Elomri, A.; Skaltsounis, A. L.; Michel, S.; Tillequin, F.; Koch, M.; Rolland, Y.; Pierré, A.; Atassi, G. *Chem. Pharm. Bull.* **1996**, *44*, 2165. (c) McHugh, D. J.; Wright, S. E. *Aust. J. Chem.* **1954**, *7*, 166.

(5) Zhang, Z.; Jakab, G.; Schreiner, P. R. *Synlett* **2011**, 1262.

(6) (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.

(7) (a) Sakakibara, T.; Koezuka, M.; Sudoh, R. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3095. (b) Deshpande, S. R.; Mathur, H. H.; Trivedi, G. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1983**, *22*, 166.

(8) Yin, G. H.; Zhang, R. C.; Li, L.; Tian, J.; Chen, L. G. *Eur. J. Org. Chem.* **2013**, *24*, 5431.

(9) Climent, M. J.; Iborra, S.; Sabater, M. J.; Vidal, J. D. *Appl. Catal. A: Gen.* **2014**, *481*, 27.

(10) Yan, M. C.; Jang, Y. J.; Yao, C. F. *Tetrahedron Lett.* **2001**, *42*, 2717.

(11) (a) Wang, G. W. *Chem. Soc. Rev.* **2013**, *42*, 7668. (b) Waddell, D. C.; Clark, T. D.; Mack, J. *Tetrahedron Lett.* **2012**, *53*, 4510. (c) Thorwirth, R.; Stolle, A.; Ondruschka, B. *Green Chem.* **2010**, *12*, 985.

(12) (a) Mack, J.; Fulmer, D.; Stofel, S.; Santos, N. *Green Chem.* **2007**, *9*, 1041. (b) Zhu, X.; Li, Z.; Jin, C.; Xu, L.; Wu, Q.; Su, W. *Green Chem.* **2009**, *11*, 163. (c) Thorwirth, R.; Stolle, A.; Ondruschka, B.; Wild, A.; Schubert, U. S. *Chem. Commun.* **2011**, *47*, 4370.

(13) (a) Schneider, F.; Szuppa, T.; Stolle, A.; Ondruschka, B.; Hopf, H. *Green Chem.* **2009**, *11*, 1894. (b) Fan, G. P.; Liu, Z.; Wang, G. W. *Green Chem.* **2013**, *15*, 1659.

(14) (a) Tullberg, E.; Schacher, F.; Peters, D.; Frejd, T. *Synthesis* **2006**, 1183. (b) Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K. *J. Am. Chem. Soc.* **2002**, *124*, 6244. (c) Bernhardt, F.; Trotzki, R.; Szuppa, T.; Stolle, A.; Ondruschka, B. *Beilstein J. Org. Chem.* **2010**, *6*, 1.

(15) Juribasić, M.; Užarević, K.; Gracin, D.; Ćurić, M. *Chem. Commun.* **2014**, *50*, 10287.

(16) Tan, D.; Mottillo, C.; Katsenis, A. D.; Štrukil, V.; Friščić, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 9321.

(17) Zille, M.; Stolle, A.; Wild, A.; Schubert, U. S. *RSC Adv.* **2014**, *4*, 13126.

(18) Paveglio, G. C.; Longhi, K.; Moreira, D. N.; München, T. S.; Tier, A. Z.; Gindri, I. M.; Bender, C. R.; Frizzo, C. P.; Zanatta, N.; Bonacorso, H. G.; Martins, M. A. P. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1895.

(19) Kaupp, G.; Schmeyers, J.; Kuse, A.; Atfeh, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 2896.

(20) For selected reviews on mechanochemically induced cascade reactions, see ref. 11a; for selected examples of mechanochemically induced cascade reactions, see ref. 12b and: (a) Kaupp, G.; Naimi-Jamal, M. R.; Schmeyers, J. *Chem. Eur. J.* **2002**, *8*, 594. (b) Mashkouri, S.; Naimi-Jamal, M. R. *Molecules* **2009**, *14*, 474. (c) Dong, Y.-W.; Wang, G.-W.; Wang, L. *Tetrahedron* **2008**, *64*, 10148. (d) Gérard, E. M. C.; Sahin, H.; Encinas, A.; Bräse, S. *Synlett* **2008**, 2702.

(21) Korotaev, V. Y.; Sosnovskikh, V. Y.; Barkov, A. Y. *Russ. Chem. Rev. (Engl. Transl.)* **2013**, *82*, 1081.

(22) Bhanja, C.; Jena, S.; Nayak, S.; Mohapatra, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1668.

(23) Worrall, D. E. *Org. Synth.* **1929**, *9*, 66.

(24) Jin, Z.; Yang, R.; Du, Y.; Tiwari, B.; Ganguly, R.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 3226.