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$FeCl_3$ and ether mediated direct intramolecular acylation of esters and their application in efficient preparation of xanthone and chromone derivatives†

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The direct intramolecular acylation of esters was developed by using the combined system of $FeCl_3$ with Cl_2CHOCH_3. This unique cooperative system offered a new and efficient approach to biologically important xanthone and chromone derivatives with regioselectivity. Examples were reported, and control experiments were carried out to examine the effect of the benzyl esters and Cl_2CHOCH_3.

Introduction

Diaryl and aryl alkyl ketones are important intermediates which are used to prepare various pharmaceuticals, natural products, agrochemicals and other functional materials.[1] Traditionally they are synthesized by many methods, and Friedel–Crafts acylation may be the most common approach.[2] However, the Friedel–Crafts acylation suffers from poor regioselectivity, use of an over-stoichiometric amount of a Lewis acid catalyst and poor functional group tolerance.[2b,3] Besides, *ortho* direct acylations have already reached an impressive performance level (Scheme 1, entry a).[4,5] Effective ways of directing acyl substituents to the *ortho* position with a functional group[6g] are oxidative couplings of arylmethyl amines[6a] or benzylic alcohols,[6c] decarboxylative couplings of α-oxoacids,[6d–f] or carbonylative processes[6h] (Scheme 1, entry a). The acylation by using aldehydes,[6b,7b,c,d,g] ketones,[7e] toluenes[7f] *etc.* are also reported (Scheme 1, entries a and d).[7] Compared to these acylation reagents, benzyl ester as a new intramolecular acylation reagents would be an important complement to these reported methods.

The xanthone and chromone substructures are of great significance in natural products and more and more different compounds have been identified. Due to the various biological and pharmaceutical activities of these derivatives, these structural scaffolds attract interests across chemistry, biology and medicine, and have even been described as "privileged structure".[8,9b] Many synthetic strategies leading to xanthone derivatives have been widely explored in the past years.[7b–d,9c,e,f] However, some methods suffers from some drawbacks, such as high reaction temperatures,[7b] using of strong acids (Scheme 1, entry b), low yields,[9e] high cost of the metal[7b] and its air/moisture sensitivity. Consequently, the development of a complement reaction that proceeds under very mild and simple conditions is desirable.

Results and discussion

Gross formylation reaction utilizing dichloromethyl methyl ether (Cl_2CHOCH_3) as a formylating reagent for benzenes[10,11] has been applied to the synthesis of natural products[12] Initially, we wanted to prepare the *ortho*-formylation product of benzyl 3-phenoxypropanoate **3a** through the Gross formylation (Scheme 2). However, the formylation product **5a** was not observed, and to our surprise, an unexpected product **4a** was detected and isolated (Scheme 2).

The initial serendipitous discovery suggested us a new and facile way to synthesize xanthone derivatives rather than any reported methods. We took the reaction to prepare **2a**, by treating benzyl 2-phenoxybenzoate (**1a**) with Cl_2CHOCH_3 and $SnCl_4$ in dichloromethane at room temperature as the model. Firstly, we commenced a systematic screening of the reaction conditions, and the results were summarized in Table 1. As shown in the table, we found that $SnCl_4$ and $FeCl_3$ gave the best results (Table 1, entries 1 and 4) while other catalysts including $AlCl_3$ and $TiCl_4$ showed less or no efficiency in terms of chemical yields (Table 1, entries 2 and 3). Because iron is inexpensive,

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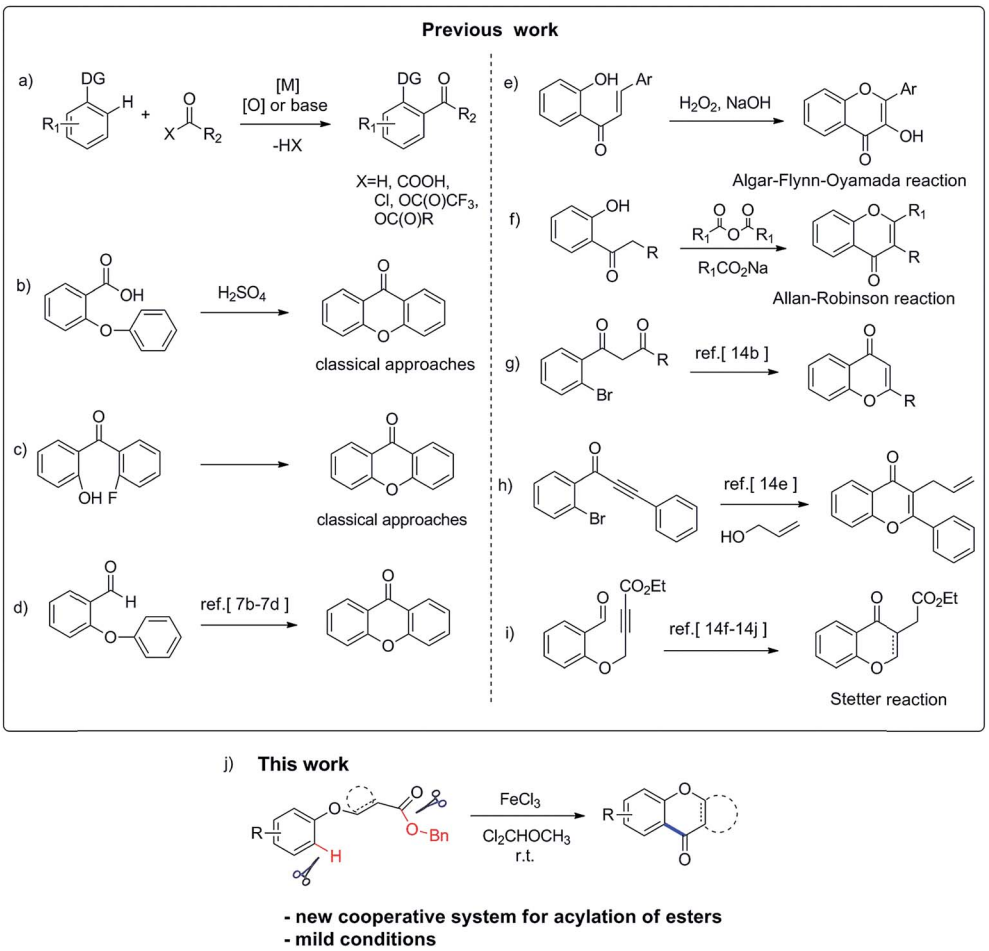
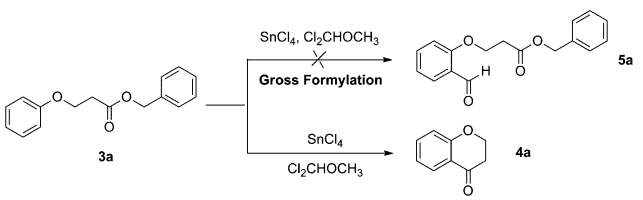
† Electronic supplementary information (ESI) available: ^1H and ^{13}C spectra and spectral data and crystallographic information for **2a**, **4a** and **4d** are available for all compounds. CCDC 982623, 982620 and 982630. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra10174j



Scheme 1 (a–i) Previous work on direct acylation and xanthone, chromone derivatives formation, DG = directing group, Tf = trifluoromethanesulfonyl. (j) This work.

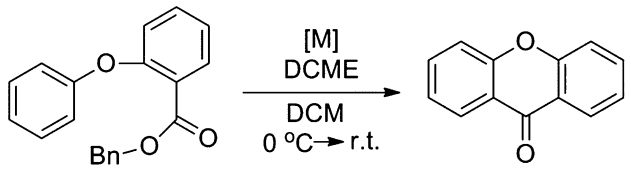


Scheme 2 Discovery of an intramolecular acylation of ester.

environmentally friendly and it's a one of the most abundant metals on Earth, $FeCl_3$ was chosen as the catalyst. Control experiments were performed to prove the necessity of the coexistence of the catalyst $FeCl_3$ and the promoter Cl_2CHOCH_3. The experimental results showed that no reaction took place without either $FeCl_3$ or 1,1-dichlorodimethyl (Table 1, entries 5 and 6). The DCME loading was decreased from 3.0 to 0.2 equiv., and a comparable reaction efficiency was shown (*i.e.*, 64%, 69%, 73%, 56%, 38%, 7%, Table 1, entries 7–12). From the amount of $FeCl_3$, it could be found that 0.6 equiv. of $FeCl_3$ was the best choice (Table 1, entries 13–18). Unsurprisingly, decreasing yields was observed when the $FeCl_3$ and DCME loadings were decreased from 0.8 to 0.5 equiv. (Table 1, entries 19 and 20). Thus, the optimized conditions were established to be as follows: $FeCl_3$ (0.6 equiv.), Cl_2CHOCH_3 (1.0 equiv.), DCM as the solvent and stirring at 0 °C to room temperature.

With the optimized conditions in hand, the scope of the reaction was investigated and the results were listed in Table 2. The acylation could tolerate various functional groups such as OCH_3, NO_2, CO_2CH_3, Br and Cl, affording the desired products in good yields. Substrates with electron-donating or electron-withdrawing groups such as methoxyl, *tert*-butyl, phenyl, CF_3, Cl, Br and CO_2CH_3 *etc.* were smoothly to give the desired products at room temperature in excellent yields (Table 2, entries 1–19). Surprisingly, treatment of compound **1** bearing the strong electron-withdrawing group CF_3, NO_2 afforded **2k**, **2o** and **2q** in excellent yields (Table 2, entries 11, 15 and 18). Multi-substituted substrates also reacted well in this acylation (Table 2, entries 8, 9 and 18). In addition, the acylation showed regioselectivity for the substrate containing a *meta*-substituent in the benzene ring, and the reaction could occur at the less sterically hindered *ortho*-C–H bond of the ester (Table 2, entry 19). The molecular structure of the acylated product (**2a**) was unambiguously determined by the single crystal X-ray diffraction study (Fig. 1).[13]

Table 1 Optimization of the reaction conditions[a]



1a 2a

Entry	M (equiv.)	DCME[b] (equiv.)	Time[c] (min)	Yield[d] (%)
1	$SnCl_4$ (1.0)	1.0	5	93
2	$AlCl_3$ (1.0)	1.0	15	9
3	$TiCl_4$ (1.0)	1.0	180	0
4	$FeCl_3$ (1.0)	1.0	8	87
5	$FeCl_3$ (0.0)	1.0	180	0
6	$FeCl_3$ (1.0)	0.0	180	0
7	$FeCl_3$ (1.0)	3.0	60	64
8	$FeCl_3$ (1.0)	2.0	60	69
9	$FeCl_3$ (1.0)	0.8	60	73
10	$FeCl_3$ (1.0)	0.6	60	56
11	$FeCl_3$ (1.0)	0.4	60	38
12	$FeCl_3$ (1.0)	0.2	60	7
13	$FeCl_3$ (3.0)	1.0	60	78
14	$FeCl_3$ (2.0)	1.0	60	74
15	$FeCl_3$ (0.8)	1.0	10	86
16	$FeCl_3$ (0.6)	1.0	10	88
17	$FeCl_3$ (0.4)	1.0	60	63
18	$FeCl_3$ (0.2)	1.0	60	34
19	$FeCl_3$ (0.8)	0.8	60	69
20	$FeCl_3$ (0.5)	0.5	60	37

[a] Reaction were conducted in DCM (dichloromethane) solvents at 0 °C to room temperature for 5–180 minutes. [b] DCME = dichloromethyl methyl ether, Bn = benzyl. [c] Time = reaction time to complete conversion (TLC). [d] Yields of pure, isolated products (characterized by MS and ^{1}H and ^{13}C NMR).

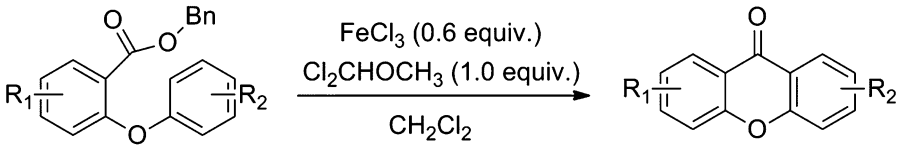
Motivated by these results, we next sought to expand the scope of the system to intramolecular acylation of benzyl esters to form chromone derivatives. Some methods for the synthesis of chromone derivatives have been developed, but they depend on the availability of the requisite 1-(2-hydroxyphenyl)ethanone or *o*-halogen aryl ketone derivatives (Scheme 1, entries e–i).[14] Some of the starting materials are difficult to prepare, and phenols are naturally abundant and they can be readily converted to relative phenol derivatives that are isolated by filtration without further purification.[15] Therefore, it is desirable to develop a mild and efficient approach to chromones using simple materials (such as phenol derivatives). It was pleased to see that under the optimized reaction conditions, the dihydrochromone products **4a** and **4b** were obtained smoothly in high yields (Table 3, entries 20 and 21). Furthermore, phenol derivatives with both electron-donating and electron-withdrawing groups were well tolerated providing the desired flavones in excellent yields (Table 3, entries 22–26). On the other hand, the chromone products **4h**, **4i** and **4j** were also obtained in 84%, 37% and 48% yields, respectively (Table 3, entries 27–29). Moreover, the acylation took place at a sterically less hindered side (Table 3, entry 29). The molecular structure of the representative products **4a** and **4d** were determined by X-ray crystallography (Fig. 1).[13]

In order to explore the mechanism of the reaction, the following control experiments were performed under the standard reaction conditions (Scheme 3). The studies showed that the *ortho*-hydrogen from benzyl ester was required for the reaction under no alkaline environment. We attempted the reaction of intramolecular *o*-acylation of **a**, **b** and **c**, respectively (Scheme 3, entries A1, A2 and A3). But the reaction did not work, which suggested that the reaction may not proceed *via* traditional Friedel–Crafts ways, and the benzyl ester was the first required structural factor for the reaction to occur. When the benzyl 3-phenoxypropanoate **3a** was replaced by compound **d**, the reaction didn't occur too (Scheme 3, entry A4), which implies that the benzyl group might participate in the intermediate process (Scheme 4, entry C1). Furthermore, compound **e** was reacted for 40 minutes at the same conditions, leading to the desired product **4a** in 60% yield (Scheme 3, entry A5). This result together with experiment A4 suggested that the *ortho*-hydrogen from benzyl group was another key role in the acylation. When the base K_2CO_3 (1.0 equiv.) was added to the standard reaction conditions, the reaction did not occur (Scheme 3, entry A6), which implies that the reaction did not proceed under the alkaline environment.

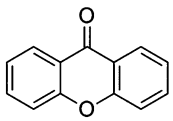
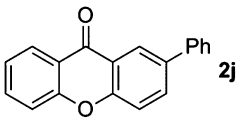
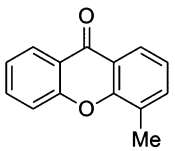
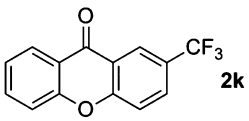
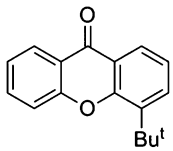
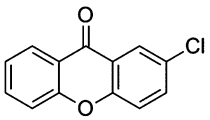
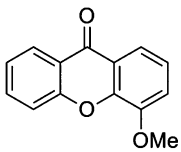
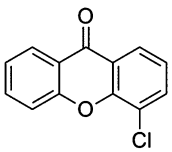
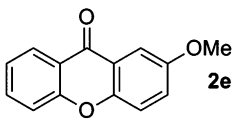
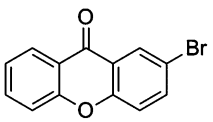
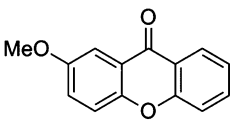
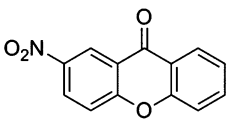
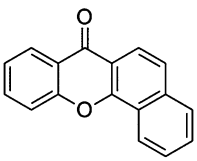
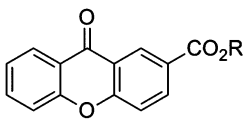
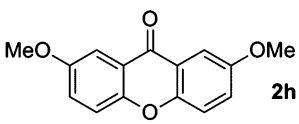
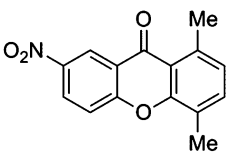
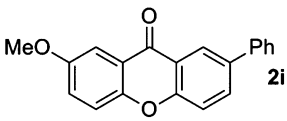
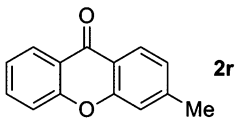
To further probe the interaction of the substrate, Lewis acid and DCME, we monitored the interaction of any two of those reagents in CD_2Cl_2 by on-line ^{1}H NMR spectroscopic studies (the paramagnetism of $FeCl_3$ made the characterisation by NMR spectroscopy impossible, so $SnCl_4$ was used instead, for that it had almost the same catalytic ability as $FeCl_3$). There were no changes of the signals of the benzyl 3-phenoxypropanoate **3a** and dichloromethyl methyl ether through comparison with an authentic sample (Fig. 2, entries B1 *vs.* B2; B3 *vs.* B4; B3 *vs.* B5 and B2 *vs.* B5). The results suggested that none of any two of the three regents formed an intermediate first and then reacted with the third one to obtain 4-chromanone **4a**, but all regents were required to react simultaneously to afford 4-chromanone **4a**. For the function of Cl_2CHOCH_3, the ^{1}H NMR spectrum of Cl_2CHOCH_3, $SnCl_4$ and **3a** (benzyl 3-phenoxypropanoate) in CD_2Cl_2 at room temperature gave important proof in the formation of intermediate **A**. The on-line NMR tracking displayed two new signals, a [δ: 8.13 (s, 1H)] and b [δ: 3.79 (s, 3H)], once the reaction take placed (Fig. 2, entry B6). The integral of signals a (s, 1H) and b (s, 3H) could be attributed to the protons of methyne and methyl from Cl_2CHOCH_3, It clearly indicated that intermediate **A** was formed *via* Cl_2CHOCH_3, $SnCl_4$ and **3a**. For the effect of the Sn atom, the signal of CH_3 (δ: 3.79) from intermediate **A** had a downfield shift comparing with the normal CH_3 (δ: 3.72) from Cl_2CHOCH_3. From this result, it may be concluded that the use of $SnCl_4$ and Cl_2CHOCH_3 cooperatively activated benzyl esters to form intermediate by enhancing the electrophilicity of benzyl ester.

On the basis of the control and on-line NMR experimental results, we propose a cooperative mechanism, where the Fe(III) enhances electrophilicity of benzyl ester along with dichloromethyl methyl ether, and the HCl activates benzene to facilitate nucleophilic addition (Scheme 4, entry C1). The $FeCl_3$

Table 2 The combined system for direct intramolecular acylation of esters[a]



1 2

Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **2a**	88	10	 **2j**	63
2	 **2b**	86	11	 **2k**	77
3	 **2c**	73	12	 **2l**	71
4	 **2d**	75	13	 **2m**	82
5	 **2e**	87	14	 **2n**	69
6	 **2f**	66	15	 **2o**	90
7	 **2g**	84	16, 17	 **2p-1**: R = Me **2p-2**: R = Bn	73 85
8	 **2h**	74	18	 **2q**	92
9	 **2i**	65	19	 **2r**	78

[a] Standard reaction conditions: benzyl 2-aryloxybenzoate derivatives (1.0 equiv.), $FeCl_3$ (0.6 equiv.), Cl_2CHOCH_3 (1.0 equiv.), DCM, 0 °C to room temperature, 5–180 min. [b] Yields of pure, isolated products (characterized by MS and ^1H and ^{13}C NMR).

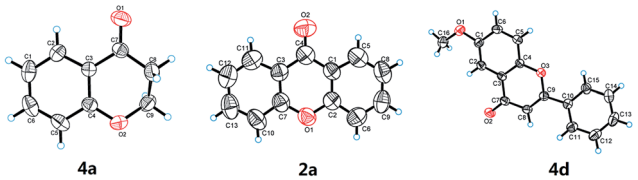
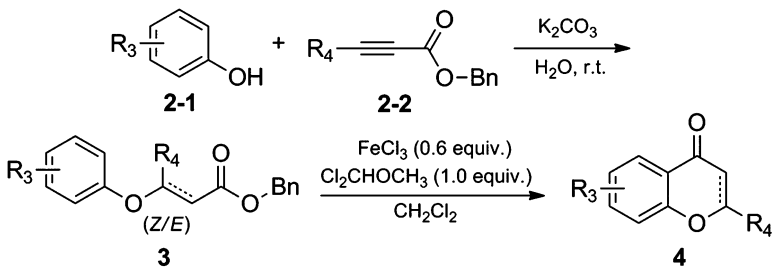


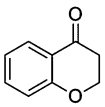
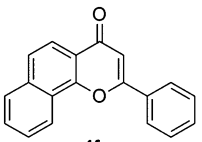
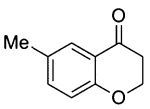
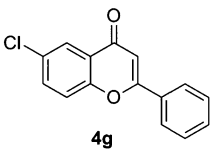
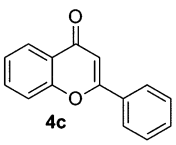
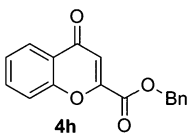
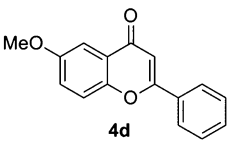
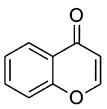
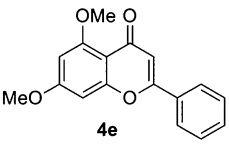
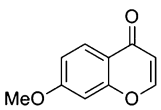
Fig. 1 Crystal structures of **4a**, **2a** and **4d**.

catalyzed reaction of **3a** with Cl_2CHOCH_3 would take place to generate a coordination intermediate **A-1** through Gross reaction process. The intramolecular acylation of **B** would produce adduct **4a** by path one or path two ways. Byproduct was isolated as a mixture of the free aldehyde (**I**) and the ring-closed hemiacetal (**II**) after aqueous work up. The ^1H NMR spectrum of compounds **I** and **II** was shown in ESI,† according to that of literature ref. 27 On comparison, we attempted the reaction of compound **f** (Scheme 4, entry C2) with $FeCl_3$ in the absence of Cl_2CHOCH_3, and the reaction did not work, which suggested **A-1** may be the important intermediate which promoted the formation of the target molecules instead of the compound **f.**

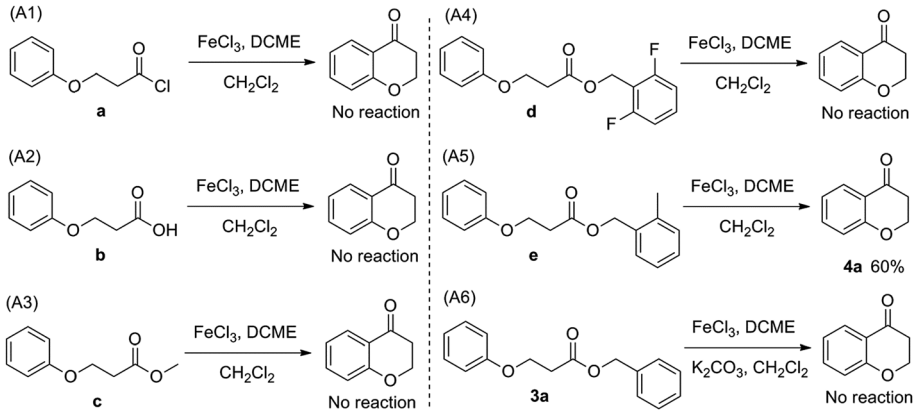
In summary, a new strategy for the direct intramolecular acylation of esters using iron and ether was developed. The present combined system can be applied to the synthesis of structurally diverse substituted xanthone and chromone derivatives with regioselectivity under very mild conditions. Mechanistic studies revealed that $FeCl_3$ and Cl_2CHOCH_3 cooperatively activated benzyl esters to form intermediate that played a key

Table 3 The combined system for direct intramolecular acylation of esters[a]

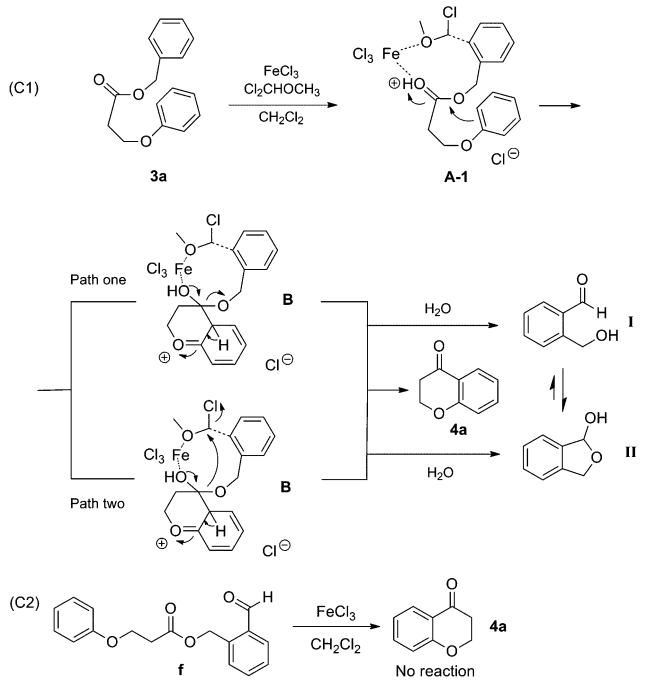


Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
20	 **4a**	87	25	 **4f**	74
21	 **4b**	77	26	 **4g**	43
22	 **4c**	83	27	 **4h**	84
23	 **4d**	75	28	 **4i**	37
24	 **4e**	57	29	 **4j**	48

[a] Standard reaction conditions: (*Z*/*E*)-benzyl 3-phenoxyacrylate derivatives (1.0 equiv.), $FeCl_3$ (0.6 equiv.), Cl_2CHOCH_3 (1.0 equiv.), DCM, 0 °C to room temperature, 5–180 minutes. [b] Yields of pure, isolated products (characterized by MS and ^1H and ^{13}C NMR).



Scheme 3 Investigation of the reaction mechanism (DCME = dichloromethyl methyl ether).



Scheme 4 A proposed mechanism.

role in the acylation of esters. The advantage of such a simple combination of a Lewis acid with ether is that it provides a new protocol for the intramolecular acylation of the ester under mild conditions and the effect of benzyl esters and Cl_2CHOCH_3 was examined.

Experimental section

All reactions were carried out under dry conditions unless otherwise stated. All work-up and purification procedures were carried out with reagent-grade solvents. Reaction progress was monitored using analytical thin layer chromatography (TLC) on precoated silica gel GF254 (Qingdao Haiyang Chemical Plant, Qingdao, China) plates and the spots were detected under UV light (254 nm). Melting point was measured on an XT-4 micromelting point instrument and uncorrected. ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were measured on a Bruker ACF-500 spectrometer at 25 °C and referenced to TMS. Chemical shifts were reported in ppm (δ) using the residual solvent line as internal standard ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm; DMSO: ^{1}H = 2.5, 3.3 ppm, ^{13}C = 40.09 ppm). Splitting patterns were designated as s, singlet; d, doublet; t, triplet; m, multiplet. High resolution mass spectra (HRMS) were obtained with a Mariner ESI-TOF spectrometer (HRESIMS). Column chromatography was performed on silica gel (90–150 μm; Qingdao Marine Chemical Inc.).

General procedure for the synthesis of xanthone and chromone derivatives

Phenol derivatives (0.188 g, 2 mmol) was dissolved in aqueous solution of K_2CO_3 (0.276 g, 2 mmol) and benzyl 3-phenylpropiolate derivatives (0.284 g, 1 mmol) was added. The reaction mixture was stirred vigorously at room temperature. A turbid solution was formed which by consumption of phenol derivatives (monitored by TLC) in 5 min, the reaction mixture became clear and (*Z*/*E*)-benzyl 3-phenoxy-3-phenylacrylate (**3**) existed as solid in water. The product was isolated by filtration without further purification.

To a cold (0 °C), magnetically stirred solution of benzyl 2-aryloxybenzoate derivatives (**1**) or (*Z*/*E*)-benzyl 3-phenoxy-3-phenylacrylate (**3**) (for example 1.5 mmol) with 1,1-dichlorodimethyl ether (1.0 equiv.) in anhydrous dichloromethane (50 ml) and the corresponding $FeCl_3$ (0.6 equiv.) was added dropwise in one portion under an atmosphere of nitrogen. The resulting mixture was warmed to room temperature, and the reaction mixture was stirred at room temperature until the completion of the reaction. Then the reaction mixture was poured into ice-cooled 10% aqueous HCl, and the aqueous layer was extracted with dichloromethane. The combined organic extract was dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (SiO_2; petroleum ether/ethyl acetate).

Xanthone (2a).[7b] Isolated yield: 88% (colourless solid, 2.63 g, eluent: petroleum ether/EtOAc 40 : 1) m.p. 172–173 °C; ^{1}H NMR

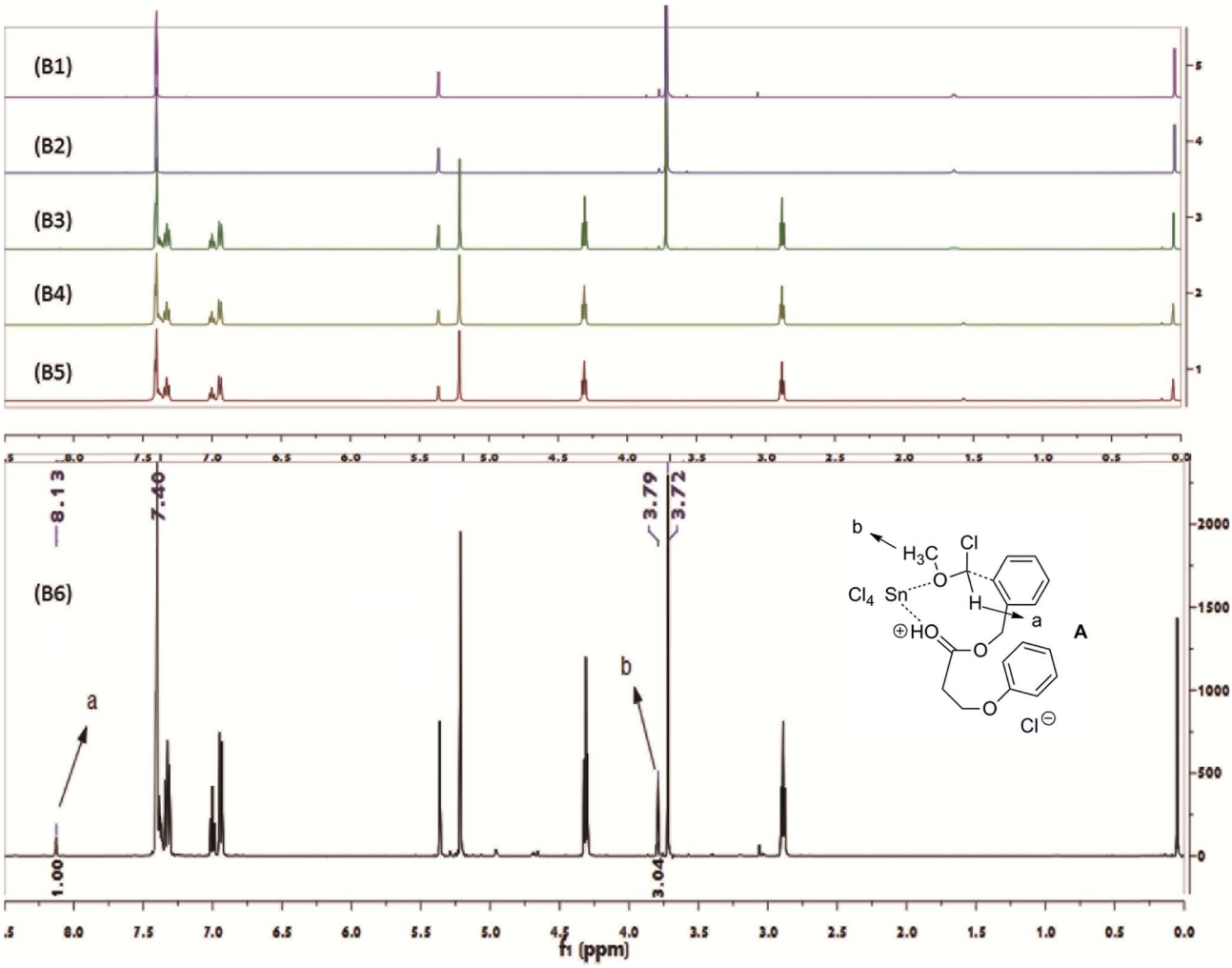


Fig. 2 ^{1}H NMR spectra in CD_2Cl_2; (B1) Cl_2CHOCH_3, (B2) Cl_2CHOCH_3 (1.0 equiv.) and $SnCl_4$ (1.0 equiv.), (B3) benzyl 3-phenoxypropanoate (**3a**, 1.0 equiv.) and Cl_2CHOCH_3 (1.0 equiv.), (B4) benzyl 3-phenoxypropanoate (**3a**, 1.0 equiv.), (B5) benzyl 3-phenoxypropanoate (**3a**, 1.0 equiv.) and $SnCl_4$ (1.0 equiv.). (B6) Benzyl 3-phenoxypropanoate (**3a**, 1.0 equiv.), Cl_2CHOCH_3 (1.0 equiv.) and $SnCl_4$ (1.0 equiv.).

(500 MHz, DMSO) δ 8.21 (dd, J = 8.0, 1.5 Hz, 2H), 7.89 (td, J = 8.0, 1.0 Hz, 2H), 7.69 (dd, J = 7.5, 1.5 Hz, 2H), 7.50 (td, J = 7.5, 1.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO) δ 176.5, 156.1, 136.1, 126.5, 124.9, 121.7, 118.7; HRMS (ESI) m/z = 219.0417 calcd for $C_{13}H_8NaO_2$ [M + Na]$^+$, found: 219.0415.

4-Methyl-9*H*-xanthen-9-one (2b).[9e] Isolated yield: 86% (colourless solid, 1.82 g, eluent: petroleum ether/EtOAc 30 : 1) m.p. 124–125 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.22 (dd, J = 7.9, 1.5 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.94–7.89 (m, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 8.4 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 176.8, 156.0, 154.5, 136.6, 135.96, 127.7, 126.4, 124.9, 124.3, 124.1, 121.5, 121.4, 118.9, 15.8; HRMS (ESI) m/z = 233.0573 calcd for $C_{14}H_{10}NaO_2$ [M + Na]$^+$, found: 233.0571.

4-(*tert*-Butyl)-9*H*-xanthen-9-one (2c).[7b] Isolated yield: 73% (colourless solid, 125 mg, eluent: petroleum ether/EtOAc 40 : 1) m.p. 110–112 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.23 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 7.1 Hz, 1H), 7.95–7.91 (t, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.56–7.51 (m, 1H), 7.45 (t, J = 7.1 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, DMSO) δ 176.8, 155.5, 154.8, 139.0, 136.1, 132.8, 126.3, 125.0, 124.7, 124.4, 122.3, 121.1, 118.7, 35.5, 30.4; HRMS (ESI) m/z = 275.1043 calcd for $C_{17}H_{16}NaO_2$ [M + Na]$^+$, found: 275.1047.

4-Methoxy-9*H*-xanthen-9-one (2d).[9e] Isolated yield: 75% (colourless solid, 102 mg, eluent: petroleum ether/EtOAc 40 : 1) m.p. 175–176 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.20 (dd, J = 8.0, 2.0 Hz, 1H), 7.88 (m, 1H), 7.72 (m, 2H), 7.51 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 176.5, 155.9, 149.0, 146.3, 136.0, 126.40, 125.0, 124.5, 122.4, 121.5, 118.9, 117.0, 117.0, 56.8; HRMS (ESI) m/z = 249.0522 calcd for $C_{14}H_{10}NaO_3$ [M + Na]$^+$, found: 249.0521.

2-Methoxy-9*H*-xanthen-9-one (2e or 2f).[7b] Isolated yield: 87% and 66% (colourless solid, 89 mg and 77 mg, eluent: petroleum ether/EtOAc 45 : 1) m.p. 130–131 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.23 (dd, J = 8.0, 1.6 Hz, 1H), 7.92–7.88 (m, 1H), 7.69 (dd, J = 8.7, 4.1 Hz, 2H), 7.60 (d, J = 8.7 Hz, 1H), 7.53–7.49 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 176.3, 156.3, 156.1, 150.9, 135.9, 126.5, 125.2, 124.7, 122.1, 121.0, 120.3, 118.7, 106.4, 56.3;

HRMS (ESI) m/z = 249.0522 calcd for $C_{14}H_{10}NaO_3$ $[M + Na]^+$, found: 249.0525.

7*H*-Benzo[*c*]xanthen-7-one (2g).[7b] Isolated yield: 84% (colourless solid, 142 mg, eluent: petroleum ether/EtOAc 40 : 1) m.p. 159–160 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.77 (d, J = 7.7 Hz, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.17 (m, 2H), 8.00–7.94 (m, 3H), 7.92–7.84 (m, 2H), 7.60 (m, 1H); ^{13}C NMR (125 MHz, DMSO) δ 176.2, 155.8, 153.5, 136.6, 135.7, 130.6, 128.8, 128.0, 126.3, 125.4, 124.8, 124.0, 123.2, 122.3, 121.3, 119.0, 117.5; HRMS (ESI) m/z = 269.0573 calcd for $C_{17}H_{10}NaO_2$ $[M + Na]^+$, found: 269.0571.

2,7-Dimethoxy-9*H*-xanthen-9-one (2h).[7a] Isolated yield: 74% (colourless solid, 113 mg, eluent: petroleum ether/EtOAc 40 : 1) m.p. 174–176 °C; ^{1}H NMR (500 MHz, DMSO) δ 7.67 (d, J = 9.1 Hz, 2H), 7.60 (d, J = 3.2 Hz, 2H), 7.51 (dd, J = 9.1, 3.2 Hz, 2H), 3.91 (s, 6H); ^{13}C NMR (125 MHz, DMSO) δ 176.0, 156.2, 150.8, 125.1, 121.4, 120.3, 106.1, 56.3; HRMS (ESI) m/z = 257.0808 calcd for $C_{15}H_{13}O_4$ $[M + H]^+$, found: 257.0806.

2-Methoxy-7-phenyl-9*H*-xanthen-9-one (2i). Isolated yield: 65% (colourless solid, 144 mg, eluent: petroleum ether/EtOAc 35 : 1) m.p. 165–166 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.42 (d, J = 2.4 Hz, 1H), 8.21 (dd, J = 8.8, 2.4 Hz, 1H), 7.80 (m, 3H), 7.71 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.58–7.51 (m, 3H), 7.45 (t, J = 7.9 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 176.3, 156.4, 155.5, 150.8, 139.1, 136.6, 134.3, 129.7, 128.3, 127.3, 125.2, 123.6, 122.0, 121.2, 120.4, 119.5, 106.4, 56.3; HRMS (ESI) m/z = 325.0835 calcd for $C_{20}H_{14}NaO_3$ $[M + Na]^+$, found: 325.0836.

2-Phenyl-9*H*-xanthen-9-one (2j).[7d] Isolated yield: 63% (colourless solid, 218 mg, eluent: petroleum ether/EtOAc 35 : 1) m.p. 159–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 2.0 Hz, 1H), 8.38 (dd, J = 7.5, 1.5 Hz, 1H), 7.98 (dd, J = 9.0, 2.5 Hz, 1H), 7.75 (td, J = 7.5, 2.0 Hz, 1H), 7.69 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 156.4, 155.8, 139.6, 137.3, 135.0, 133.8, 129.2, 127.9, 127.3, 127.0, 124.8, 124.2, 122.2, 122.1, 118.7, 118.2; HRMS (ESI) m/z = 273.0910 calcd for $C_{19}H_{13}O_2$ $[M + H]^+$, found: 273.0911.

2-(Trifluoromethyl)-9*H*-xanthen-9-one (2k).[7b] Isolated yield: 77% (colourless solid, 77 mg, eluent: petroleum ether/EtOAc 50 : 1) m.p. 118–119 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.45 (s, 1H), 8.24 (t, J = 7.5 Hz, 2H), 7.99–7.92 (m, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 175.8, 158.1, 156.1, 136.7, 132.1, 132.1, 126.6, 125.6, 124.0, 124.0, 121.7, 121.6, 120.6, 118.9; HRMS (ESI) m/z = 265.0471 calcd for $C_{14}H_8F_3O_2$ $[M + H]^+$, found: 265.0473.

2-Chloro-9*H*-xanthen-9-one (2l).[7b] Isolated yield: 71% (colourless solid, 92 mg, eluent: petroleum ether/EtOAc 40 : 1) m.p. 174–175 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.21 (dd, J = 7.9, 2.6 Hz, 1H), 8.13 (d, J = 2.6 Hz, 1H), 7.93 (m, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 175.6, 156.1, 154.7, 136.5, 135.8, 129.2, 126.5, 125.3, 125.2, 122.7, 121.3, 121.3, 118.8; HRMS (ESI) m/z = 253.0027 calcd for $C_{13}H_7ClNaO_2$ $[M + Na]^+$, found: 253.0026.

4-Chloro-9*H*-xanthen-9-one (2m).[7b] Isolated yield: 82% (colourless solid, 78 mg, eluent: petroleum ether/EtOAc 30 : 1) m.p. 135–136 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.24 (dd, J = 7.9, 1.5 Hz, 1H), 8.19 (dd, J = 8.0, 1.5 Hz, 1H), 8.09 (dd, J = 7.5, 1.5 Hz, 1H), 7.98–7.93 (m, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 176.1, 155.8, 151.6, 136.5, 135.9, 126.6, 125.6, 125.5, 125.1, 123.2, 122.2, 121.4, 118.8; HRMS (ESI) m/z = 231.0207 calcd for $C_{13}H_8ClO_2$ $[M + H]^+$, found: 231.0212.

2-Bromo-9*H*-xanthen-9-one (2n).[7b] Isolated yield: 69% (light yellow solid, 98 mg, eluent: petroleum ether/EtOAc 50 : 1) m.p. 176 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.27 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 8.05 (dd, J = 8.9, 2.4 Hz, 1H), 7.95–7.92 (m, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 175.5, 156.0, 155.1, 138.5, 136.4, 128.5, 126.5, 125.2, 123.2, 121.4, 121.4, 118.8, 116.9; HRMS (ESI) m/z = 296.9522 calcd for $C_{13}H_7BrNaO_2$ $[M + Na]^+$, found: 296.9524.

2-Nitro-9*H*-xanthen-9-one (2o).[16] Isolated yield: 90% (colourless solid, 158 mg, eluent: petroleum ether/EtOAc 25 : 1) m.p. 157–158 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.88 (d, J = 3.0 Hz, 1H), 8.63 (dd, J = 9.5, 3.0 Hz, 1H), 8.23 (dd, J = 8.0, 1.5 Hz, 1H), 7.96 (m, 1H), 7.92 (d, J = 9.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 175.2, 158.8, 155.4, 143.4, 136.4, 129.4, 126.0, 125.4, 122.0, 121.1, 120.8, 120.3, 118.4; HRMS (ESI) m/z = 264.0267 calcd for $C_{13}H_7NNaO_4$ $[M + Na]^+$, found: 264.0263.

Methyl 9-oxo-9*H*-xanthene-2-carboxylate (2p-1).[16] Isolated yield: 73% (colourless solid, 67 mg, eluent: petroleum ether/EtOAc 20 : 1) m.p. 218–219 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.77 (d, J = 2.2 Hz, 1H), 8.38 (dd, J = 8.8, 2.2 Hz, 1H), 8.25 (dd, J = 7.9, 1.5 Hz, 1H), 7.97–7.94 (m, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 176.2, 165.6, 158.8, 156.1, 136.6, 135.8, 128.3, 126.6, 126.1, 125.5, 121.6, 121.5, 119.7, 118.9, 53.0; HRMS (ESI) m/z = 277.0471 calcd for $C_{15}H_{10}NaO_4$ $[M + Na]^+$, found: 277.0473.

Benzyl 9-oxo-9*H*-xanthene-2-carboxylate (2p-2). Isolated yield: 85% (colourless solid, 97 mg, eluent: petroleum ether/EtOAc 30 : 1) m.p. 122–123 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.77 (d, J = 2.1 Hz, 1H), 8.40 (dd, J = 8.8, 2.1 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.94 (t, J = 7.9 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.58–7.51 (m, 3H), 7.46 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 8.4 Hz, 1H), 5.44 (s, 2H); ^{13}C NMR (125 MHz, DMSO) δ 176.1, 164.9, 158.8, 156.0, 136.6, 136.4, 135.9, 129.1, 128.8, 128.6, 128.4, 126.6, 126.0, 125.5, 121.6, 121.5, 119.7, 118.9, 67.1; HRMS (ESI) m/z = 331.0965 calcd for $C_{21}H_{15}O_4$ $[M + H]^+$, found: 331.0962.

1,4-Dimethyl-7-nitro-9*H*-xanthen-9-one (2q). Isolated yield: 92% (colourless solid, 145 mg, eluent: petroleum ether/EtOAc 25 : 1) m.p. 215–216 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (d, J = 3.0 Hz, 1H), 8.52 (dd, J = 9.0, 3.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 2.89 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 158.4, 155.5, 143.9, 139.9, 135.8, 128.6, 127.4, 125.1, 123.7, 122.6, 119.8, 119.2, 23.0, 15.9; HRMS (ESI) m/z = 270.0761 calcd for $C_{15}H_{12}NO_4$ $[M + H]^+$, found: 270.0764.

3-Methyl-9*H*-xanthen-9-one (2r).[7c] Isolated yield: 78% (colourless solid, 71 mg, eluent: petroleum ether/EtOAc 50 : 1) m.p. 93–94 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.21 (dd, J = 7.9, 1.6

Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.91–7.87 (m, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.53–7.47 (m, 2H), 7.33 (d, J = 8.1 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 176.2, 156.2, 156.1, 147.3, 135.8, 126.4, 126.3, 126.3, 124.8, 121.7, 119.5, 118.6, 118.3, 21.9; HRMS (ESI) m/z = 233.0573 calcd for $C_{14}H_{10}NaO_2$ $[M + Na]^+$, found: 233.0569.

Chroman-4-one (4a).[17] Isolated yield: 87% (colourless solid, 1.29 g, eluent: petroleum ether/EtOAc 5 : 1) m.p. 38–39 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.5, 1.7 Hz, 1H), 7.46 (m, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.54–4.51 (m, 2H), 2.82–2.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 162.0, 136.0, 127.3, 121.5, 121.5, 118.0, 67.1, 37.9; HRMS (ESI) m/z = 149.0597 calcd for $C_9H_9O_2$ $[M + H]^+$, found: 149.0596.

6-Methylchroman-4-one (4b).[18] Isolated yield: 77% (colourless solid, 190 mg, eluent: petroleum ether/EtOAc 7 : 1) m.p. 32–33 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 8.4, 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.51–4.49 (m, 2H), 2.80–2.77 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 160.1, 137.2, 131.0, 126.9, 121.2, 117.8, 67.2, 38.0, 20.5; HRMS (ESI) m/z = 163.0597 calcd for $C_{10}H_{11}O_2$ $[M + H]^+$, found: 163.0596.

2-Phenyl-4*H*-chromen-4-one (4c).[19] Isolated yield: 83% (colourless solid, 183 mg, eluent: petroleum ether/EtOAc 1 : 1) m.p. 98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, J = 8.4, 1.5 Hz, 1H), 7.93 (dd, J = 7.5, 2.0 Hz, 2H), 7.74–7.67 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.54 (m, 3H), 7.42 (t, J = 7.5 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 163.6, 156.5, 133.9, 132.0, 131.7, 129.2, 126.5, 125.9, 125.4, 124.2, 118.2, 107.8; HRMS (ESI) m/z = 223.0754 calcd for $C_{15}H_{11}O_2$ $[M + H]^+$, found: 223.0753.

6-Methoxy-2-phenyl-4*H*-chromen-4-one (4d).[20] Isolated yield: 75% (colourless solid, 220 mg, eluent: petroleum ether/EtOAc 6 : 1) m.p. 192–193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.4, 2.2 Hz, 2H), 7.61 (d, J = 3.1 Hz, 1H), 7.55–7.52 (m, 3H), 7.51 (s, 1H), 7.30 (dd, J = 9.1, 3.1 Hz, 1H), 6.83 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 163.4, 157.2, 151.3, 132.2, 131.6, 129.2, 126.4, 124.8, 124.0, 119.7, 107.1, 105.1, 56.1; HRMS (ESI) m/z = 253.0859 calcd for $C_{16}H_{13}O_3$ $[M + H]^+$, found: 253.0860.

5,7-Dimethoxy-2-phenyl-4*H*-chromen-4-one (4e).[21] Isolated yield: 57% (colourless solid, 144 mg, eluent: petroleum ether/EtOAc 1 : 2) m.p. 145–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.85 (m, 2H), 7.54–7.46 (m, 3H), 6.76 (s, 1H), 6.59 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 164.3, 161.2, 160.9, 160.1, 131.8, 131.3, 129.1, 126.1, 109.5, 109.2, 96.4, 93.1, 56.6, 55.9; HRMS (ESI) m/z = 283.0965 calcd for $C_{17}H_{15}O_4$ $[M + H]^+$, found: 283.0963.

2-Phenyl-4*H*-benzo[*h*]chromen-4-one (4f).[22] Isolated yield: 74% (colourless solid, 73 mg, eluent: petroleum ether/EtOAc 1 : 1) m.p. 158–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64–8.57 (m, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.03 (dd, J = 6.7, 3.0 Hz, 2H), 7.97–7.91 (m, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.75–7.68 (m, 2H), 7.63–7.54 (m, 3H), 6.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.0, 153.8, 136.3, 132.2, 131.8, 129.5, 129.4, 128.4, 127.4, 126.5, 125.6, 124.4, 122.5, 121.0, 120.4, 109.0; HRMS (ESI) m/z = 273.0910 calcd for $C_{19}H_{13}O_2$ $[M + H]^+$, found: 273.0911.

6-Chloro-2-phenyl-4*H*-chromen-4-one (4g).[23] Isolated yield: 43% (colourless solid, 66 mg, eluent: petroleum ether/EtOAc 3 : 1) m.p. 187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 2.6 Hz, 1H), 7.90 (dd, J = 8.0, 1.4 Hz, 2H), 7.62 (dd, J = 8.9, 2.6 Hz, 1H), 7.57–7.48 (m, 4H), 6.81 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 163.8, 154.7, 134.0, 132.0, 131.6, 131.3, 129.2, 126.4, 125.3, 125.1, 119.9, 107.6; HRMS (ESI) m/z = 257.0364 calcd for $C_{15}H_{10}ClO_2$ $[M + H]^+$, found: 257.0365.

Benzyl 4-oxo-4*H*-chromene-2-carboxylate (4h).[24] Isolated yield: 84% (colourless solid, 94 mg, eluent: petroleum ether/EtOAc 1 : 2) m.p. 106–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, J = 8.0, 1.5 Hz, 1H), 7.77–7.70 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.41 (m, 6H), 7.14 (s, 1H), 5.43 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 160.5, 156.2, 152.2, 134.89, 134.6, 129.1, 129.0, 128.7, 126.1, 125.9, 124.7, 119.0, 115.2, 68.6; HRMS (ESI) m/z = 281.0808 calcd for $C_{17}H_{13}O_4$ $[M + H]^+$, found: 281.0806.

4*H*-Chromen-4-one (4i).[25] Isolated yield: 37% (colourless solid, 137 mg, eluent: petroleum ether/EtOAc 1 : 1) m.p. 57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (dd, J = 8.0, 1.4 Hz, 1H), 7.84 (d, J = 6.0 Hz, 1H), 7.70–7.62 (m, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 6.33 (d, J = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 156.7, 155.4, 133.8, 126.0, 125.3, 125.1, 118.3, 113.1; HRMS (ESI) m/z = 147.0441 calcd for $C_9H_7O_2$ $[M + H]^+$, found: 147.0440.

7-Methoxy-4*H*-chromen-4-one (4j).[26] Isolated yield: 48% (colourless solid, 119 mg, eluent: petroleum ether/EtOAc 1 : 4) m.p. 105–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 6.0 Hz, 1H), 6.92 (dd, J = 8.9, 2.4 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 6.23 (d, J = 6.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 164.2, 158.3, 154.9, 127.2, 118.8, 114.5, 113.0, 100.5, 55.8; HRMS (ESI) m/z = 177.0546 calcd for $C_{10}H_9O_3$ $[M + H]^+$, found: 177.0545.

2-(Hydroxymethyl)benzaldehyde (I and II).[27] Colorless liquid; product was isolated as a mixture of the ring-closed hemiacetal and the free aldehyde: ^{1}H NMR (500 MHz, $CDCl_3$) for (I) δ 4.78 (s, 2H), 7.80 (d, J = 8.4 Hz, 1H), 10.02 (s, 1H); for (II) δ 4.95 (d, J = 12.7 Hz, 1H), 5.18 (d, J = 12.7 Hz, 1H), 6.42 (d, J = 1.7 Hz, 1H).

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