RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2014, **4**, 13708

An organocatalyst from renewable materials for the synthesis of coumarins and chromenes: three-component reaction and multigram scale synthesis†

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Received 23rd January 2014
Accepted 21st February 2014

DOI: 10.1039/c4ra00673a

www.rsc.org/advances

A new concept of catalysts which are prepared from renewable materials is demonstrated. It is known that amino acids (*e.g.*, proline and hydroxyproline) are robust organocatalysts for several reactions. Bovine tendons which are proteins rich in hydroxyproline and proline were used as a source of amino acids. An acid hydrolysate of tendons (a TH catalyst) could catalyze two reactions: (i) the synthesis of coumarins and chromenes under solvent-free conditions and (ii) the synthesis of densely functionalized 4*H*-chromenes *via* a three-component reaction. Moreover, an economical and easily accessible TH catalyst is applicable in a multigram scale synthesis of coumarins and chromenes, as well as in the three-component reaction for chromene synthesis. A catalytic activity of hydroxyproline for the synthesis of 4*H*-chromenes *via* the three-component reaction was also discovered. The present work demonstrates not only the green catalysts from renewable materials, but also an environmentally benign preparation of coumarins and chromenes.

Introduction

The benzopyran chemical class, formed from the fusion of a benzene ring and a pyran ring with various levels of saturation and oxidation, appears in many natural products.[1] 1-Benzopyran skeletons including coumarin **1** and 4*H*-chromene **2** (Fig. 1) are important scaffolds in many drugs and bioactive natural products.

Coumarins (2*H*-chromen-2-one derivatives) possess many biological activities including anticoagulant, anticancer, enzyme inhibition, vasorelaxant, antimicrobial, antioxidant, and anti-inflammatory, and anti-HIV activities.[2–12] In addition to the biological properties, they have been used in food additives, cosmetics, optical brightener, and fluorescent and laser dyes.[13] 4*H*-Chromene moiety is present in many bioactive compounds and drug leads.[14–18] The examples of drugs currently used are warfarin **3a** and cromoglicic acid **3b** as anticoagulants and anti-asthmatic agents, respectively (Fig. 2). Because of their important use in pharmaceuticals, there are many synthetic methods towards the synthesis of these privileged structures.

Several synthetic routes have been reported for the synthesis of coumarins.[19–21] Whereas, chromene derivatives were synthesized by various methods, for example, DBU-catalyzed reaction between salicylic aldehydes and ethyl 2-methylbuta-2,3-dienoate;[22] tandem benzylation and cyclization by $FeCl_3$;[23] Cu(I)-catalyzed domino reactions;[24] and triazine functionalized ordered mesoporous organosilica as an organocatalyst.[25]

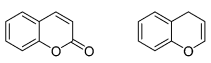

Fig. 1 Structure of coumarin **1** and 4*H*-chromene **2**.

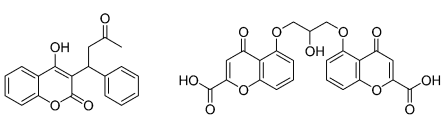

Fig. 2 Structure of warfarin **3a** cromoglicic acid **3b**.

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† Electronic supplementary information (ESI) available. CCDC 952576–952579. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra00673a

However, these procedures are not green methods since metals and hazardous solvents are used in the synthesis. Recently, green methods were developed for the synthesis of chromene and coumarin, for example, four-component catalyst-free reaction in water[26] and biocatalytic domino reaction with the enzyme alkaline protease.[27] However, the development of new methods and catalysts, which provide economical and environmentally friendly routes, is still required for both coumarin and chromene syntheses.

Among various organocatalysts, amino acids play an important role in asymmetric organocatalysis. L-Proline and derivatives have been extensively used as efficient organocatalysts,[28,29] and they are employed in several asymmetric organic syntheses.[30] L-Proline and other amino acids have been demonstrated to be powerful catalysts for various reactions, *i.e.*, aldol reactions, Mannich reactions, Michael reaction, and α-functionalizations of carbonyl compounds.[31] Utilization of renewable materials for fine and industrial chemicals is one of the important topics in green chemistry,[32–36] because renewable resources provide not only the reduction of environmental impacts, but also economical feasibility and sustainable productions. Normally, tendons are composed of various collagen fibers, which are proteins rich in hydroxyproline and proline;[37–39] both amino acids are known as robust organocatalysts.[28–31,40] In the present work, we demonstrate a new concept of catalysts which are prepared from renewable materials. We used bovine tendons as a source of amino acids, and found that a tendon hydrolysate (TH) served as an excellent organocatalyst, catalyzing the synthesis of coumarins and 4*H*-chromenes under solvent-free conditions. The TH catalyst also efficiently catalyzed the three-component reactions for the construction of densely functionalized 4*H*-chromenes, recently reported by Gu and coworkers.[41] Moreover, the cheap and easily accessible TH catalyst was applicable in a multigram scale synthesis of coumarins and chromenes, as well as in a multigram scale chromene synthesis *via* the three-component reactions.

Results and discussion

The TH catalyst was simply prepared from the acid hydrolysis of bovine tendons. The hydrolysate obtained from acid hydrolysis was neutralized by base, and then extracted with MeOH to give the TH catalyst. The reaction between salicylaldehyde (**4a**) methyl acetoacetate (**5**) catalyzed by the TH catalyst under solvent-free condition (at 55 °C) was initially investigated; this reaction gave coumarin **6a** and two diastereomers of chromene **7a** as products (Fig. 3). We also found that methyl acetoacetate provided better yields of products than that of ethyl acetoacetate. To ensure that the reaction was not catalyzed by the residue of base or acid which was probably present in the prepared catalyst, portions of the TH catalyst were dissolved in water, and pH of solutions were found to be at 6.5–7.2, confirming that the reaction was not due to the activity of base or acid.

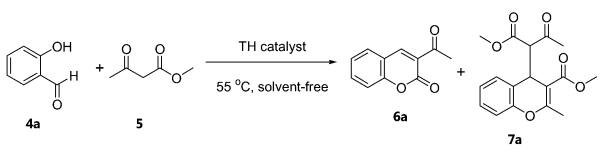


Fig. 3 Reaction of salicylaldehyde (**4a**) and methyl acetoacetate (**5**) catalyzed by the TH catalyst.

Next, we investigated the influence of the molar ratio of substrates (salicylaldehyde **4a** to methyl acetoacetate **5**) on the product ratios of coumarin (**6a**) to chromene (**7a**). As shown in Table 1, increasing the molar ratio of methyl acetoacetate (**5**) gave a slightly increase in chromene (**7a**) production. We next investigated the effect of temperature for the reaction, and the reactions were conducted at room temperature (26–28 °C), 55 °C, and 80 °C. It was found that the times used for the reaction at room temperature, 55 °C, and 80 °C were 96 h, 29 h, and 19 h, respectively (the yields were >96% as indicated by ^{1}H NMR spectrum). Although increasing temperature could shorten the time for the reactions, performing the reaction at 55 °C was more reasonable, in term of the reduction of energy consumption, than that at 80 °C. We therefore decided to carry out the reaction at 55 °C for further experiments.

Next, we investigated the reaction of methyl acetoacetate (**5**) and a variety of salicylaldehyde derivatives (**4**), using the molar ratio 1 : 3 of salicylaldehyde derivatives (**4**) to methyl acetoacetate (**5**) with 20% of the TH catalyst (at 55 °C). As shown in Table 2, both coumarins and chromenes were obtained in low to moderate yields (3–54%). Unsubstituted salicylaldehyde and those bearing electron-donating groups (Table 2, entries 1–4 and 8) favored the formation of chromenes (**7a**, **7b**, **7c**, **7d**, and **7h**) with respect to coumarins (**6a**, **6b**, **6c**, **6d**, and **6h**). In contrast, salicylaldehyde bearing an electron-withdrawing group (Table 2, entries 5 and 6) provided coumarins (**6e** and **6f**) more than chromenes (**7e** and **7f**). 5-Nitrosalicylaldehyde and 2-hydroxy-1-naphthaldehyde did not provide chromenes (**7i** and **7k**), therefore only coumarins (**6i** and **6k**) were obtained (Table 2, entries 9 and 11). This could be because the nitro group increases the acidity of the hydroxyl group, which is likely to be deprotonated, and thus reducing the electrophilicity of the aldehyde group. It was found that 4-(diethylamino)salicylaldehyde (**4j**) did not give both coumarin (**6j**) and chromene (**7j**) (Table 2, entry 10). This could be because a diethylamino group of **4j** probably makes an aldehyde group less reactive *via para*-donating electron from a nitrogen atom.

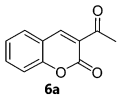
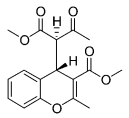
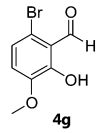
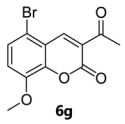
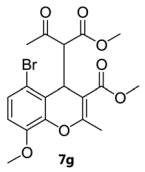
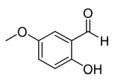
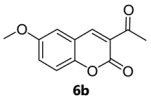
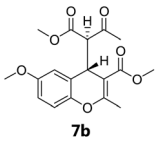
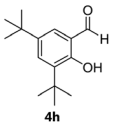
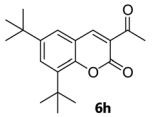
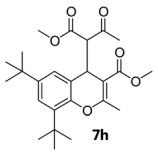
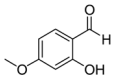
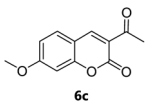
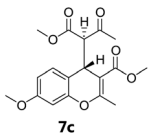
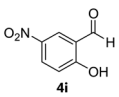
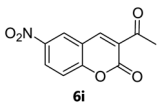
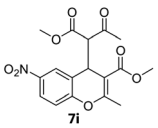
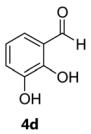
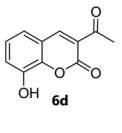
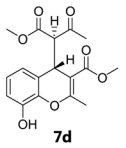
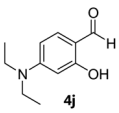
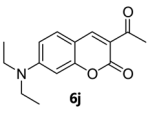
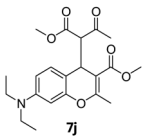
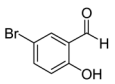
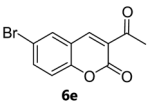
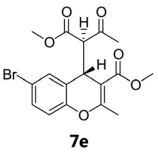
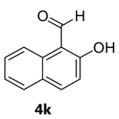
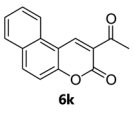
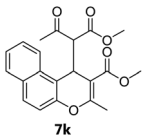
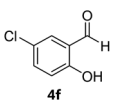
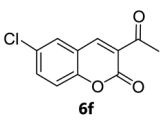
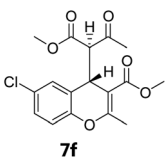
As mentioned earlier, this reaction gave two diastereomers of chromene products with the ratio of *ca.* 1.5–2.0 to 1 for the

Table 1 Effects of the molar ratio of **4a** : **5** on the yield of **6a** and **7a**[a]

Entry	**4a** : **5**	Time (h)	**6a** : **7a**[b]
1	1 : 1	65	15 : 8
2	1 : 3	65	3 : 4
3	1 : 5	65	7 : 11
4	1 : 7	65	1 : 2

[a] Reactions were performed using salicylaldehyde (50 mg, 0.41 mmol) and 20% (by weight) of the TH catalyst. [b] The ratio of **6a** : **7a** was determined by ^{1}H NMR spectrum.

Table 2 Synthesis of coumarins and chromenes from salicylaldehyde derivatives (**4**) and methyl acetoacetate (**5**) using the TH catalyst[a]

Entry	4	Coumarin (% yield)	Chromene[f] (% yield)	Time (h)	Entry	4	Coumarin (% yield)	Chromene[f] (% yield)	Time (h)
1	 4a	 6a 23%[e]	 7a 38%[h,d]	29	7	 4g	 6g 40%[b]	 7g 17%[i,e]	72
2	 4b	 6b 28%[c]	 7b 46%[h,d]	25	8	 4h	 6h 3%[e]	 7h 21%[i,e]	72
3	 4c	 6c 14%[c]	 7c 26%[h,b]	72	9	 4i	 6i 41%[b]	 7i 0%	24
4	 4d	 6d 28%[c]	 7d 42%[h,d]	25	10	 4j	 6j Trace amount	 7j 0%	72[g]
5	 4e	 6e 54%[b]	 7e 31%[h,d]	72	11	 4k	 6k 42%[c]	 7k 0%	36
6	 4f	 6f 39%[b]	 7f 33%[h,d]	72					

[a] Reactions contained *ca.* 4.09 mmol of salicylaldehyde derivatives (**4**), *ca.* 12.28 mmol of **5**, and 20% of the TH catalyst (at 55 °C). [b] Yield of the product that was precipitated and obtained without chromatographic separation. [c] Yield from product precipitation and chromatographic separation. [d] Yield from crystallization and chromatographic separation. [e] Yield from chromatographic separation. [f] Before crystallization, the ratios of *ca.* 1.5–2.0 to 1 for the major diastereomer to minor diastereomer were observed. [g] Substrate was recovered. [h] Yield of the major diastereomer of chromene. [i] Yield of two diastereomers of chromene.

major diastereomer to minor diastereomer. ^{1}H NMR spectrum (ESI, Fig. 1S†) of the two diastereomers (0.429 g) of chromene **7b** indicated the ratio of 2 to 1 (a major isomer to a minor isomer). However, after crystallization from EtOH–CH_2Cl_2, a large amount (0.397 g) of the major diastereomer of chromene **7b** was obtained, leaving only 0.029 g of the filtrate containing the two chromene diastereomers at the ratio of 5 : 3 (ESI, Fig. 2S†). This result suggested that only the major diastereomer could be crystallizable, and that the minor diastereomer was converted to the major diastereomer during crystallization. As shown in Table 2 (entries 1–6), large amounts of the major diastereomer of chromenes **7a–f** (26–46% yield) were obtained after crystallization. It should be noted that chromenes **7g** and **7h** could not be crystallized, and unfortunately they could not be separated by chromatographic techniques; therefore, percentage yields of chromenes **7g** and **7h** were of a mixture of the two diastereomers (Table 2, entries 7 and 8).

The structure of a major diastereomer of chromene **7a** was elucidated by analysis of spectroscopic data; extensive analysis of 2D NMR data established a planar structure of **7a**. Fortunately, appropriate crystals of the major diastereomer of chromenes **7a**, **7b**, **7e**, and **7f** were obtained, and they were subjected

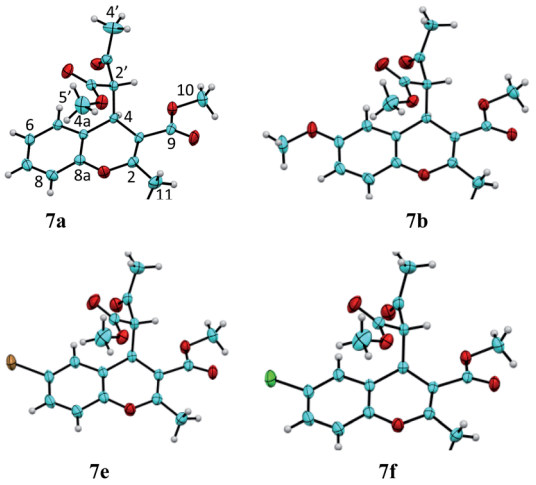


Fig. 4 ORTEP plots (30% probability level) of chromenes **7a**, **7b**, **7e**, and **7f** (color codes: C = cyan, O = red, Br = orange, Cl = green, H = white).

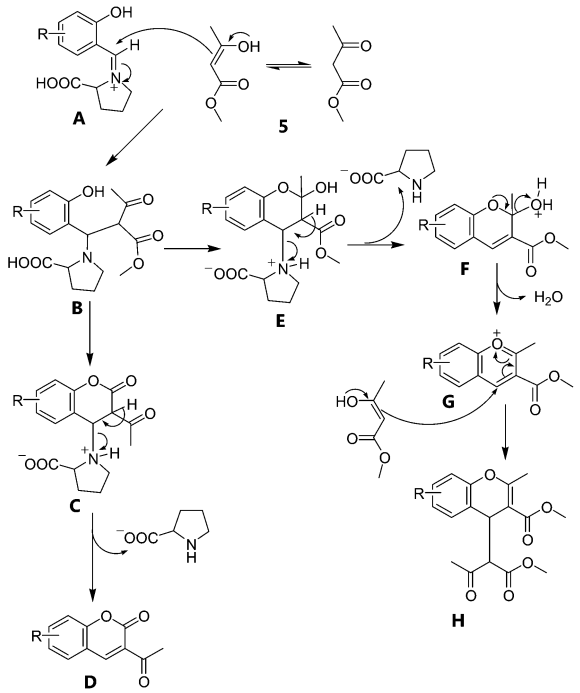


Fig. 5 A proposed mechanism for the formation of coumarin and chromene.

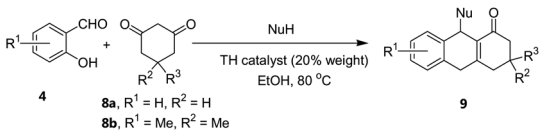
to a single crystal X-ray analysis, which conclusively disclosed the relative configuration of *S** and *R** for the positions 4 and 2′, respectively (Fig. 4). We proposed that the isomerization between the two chromene diastereomers proceeds *via* an enol intermediate (ESI, Fig. 3S†). It is worth mentioning that this is the first report on the preparation of a single 4*S*,2′*R*-diastereomer of chromenes (*e.g.* **7a–f**), particularly under environmentally benign conditions.

Tendons are proteins rich in hydroxyproline and proline amino acids.[37–39] The fact that both proline and hydroxyproline are robust organocatalysts,[28–31,40] we therefore propose that the two amino acids in the TH catalyst are possibly responsible for the catalytic activity. Analysis of an amino acid content in the TH catalyst revealed that, among 20 natural amino acids, the percentage of proline and hydroxyproline were 15.89% and 13.12%, respectively (ESI, Table 2S†), which were relatively high as compared to other amino acids, except glycine (19.23%). To prove our hypothesis, we then used L-proline (20% mol) as a catalyst for the reaction entries 1, 2, and 5 (Table 2). Indeed, we found that L-proline gave the same coumarins and chromenes as that obtained from the TH catalyst; respective yields of coumarins **6a**, **6b**, and **6e** were 29%, 28%, and 50%, while those of chromenes **7a**, **7b**, and **7e** were 40%, 18%, and 24%, respectively. However, hydroxyproline (20% mol) did not catalyze such reaction, possibly due to the insolubility of hydroxyproline in solvent-free conditions (its precipitate was observed). This result conclusively indicated that hydroxyproline did not involve in the reaction under solvent-free conditions. We then performed the reaction in EtOH : H_2O (9 : 1), in which hydroxyproline could be completely dissolved; the reaction proceeded under this condition, giving respective yields of 23%, 14%, and 24% for coumarins **6a**, **6b**, and **6e** and 9%, 17%, and 8% for chromenes **7a**, **7b**, and **7e**. Therefore, hydroxyproline also had a catalytic activity for the formation of chromenes and coumarins under a relatively polar condition that could dissolve hydroxyproline, but not under solvent-free conditions as shown in Table 2. A proposed mechanism for the formation of coumarin and chromene catalyzed by amino acids is shown in Fig. 5. The reaction starts with a condensation of an aldehyde and a catalyst (represented as L-proline), giving rise to an iminium intermediate **A**, which subsequently reacts with methyl acetoacetate (**5**), to give the intermediate **B**. Lactonization of **B** leads to the formation of the intermediate **C**. A release of a catalyst from the intermediate **C** gives rise to a coumarin **D**. Alternatively, a phenolic group of the intermediate **B** intramolecularly attacks a carbonyl to give the intermediate **E**; a release of a catalyst from the intermediate **E** yields the intermediate **F**. Loss of water assisted by lone pair electrons on oxygen gives the oxonium intermediate **G**, which in turn reacts with methyl acetoacetate (**5**) to give a chromene **H** (Fig. 5).

Table 3 Multigram scale synthesis of coumarin **6a** and chromene **7a**

Entry	Weight of **4a** (g)	Ratio of **4a** : **5**	Temperature (°C)	Time (h)	Yield of **6a** (g) (%)	Yield of **7a** (g) (%)
1	10.0	1 : 3	55	72	4.3 (28%)	8.6 (33%)
2	10.6	1 : 7	55	72	6.8 (41%)	10.4 (37%)
3	10.4	1 : 7	80	15	4.8 (30%)	9.9 (36%)

Table 4 Three-component reaction of salicylaldehyde derivatives (**4**), dimedone derivatives (**8**), and nucleophiles (NuH) by the TH catalyst



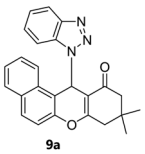
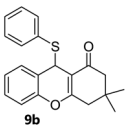
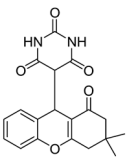
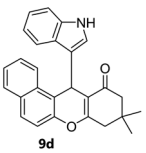
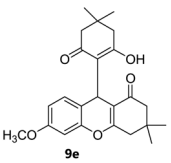
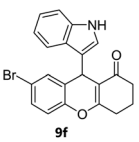
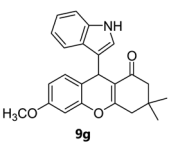
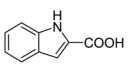
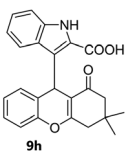
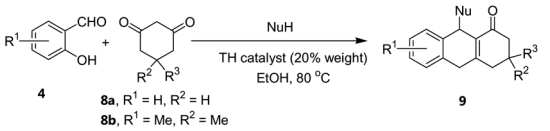
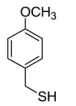
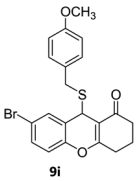
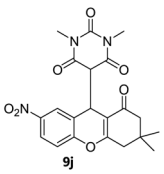
Entry	NuH	Product	Time (h)	Yield (%)
1		 **9a**	24	67
2		 **9b**	24	79
3		 **9c**	24	56
4		 **9d**	24	95
5		 **9e**	24	76
6		 **9f**	24	43
7		 **9g**	16	66
8		 **9h**	16	73

Table 4 (*Contd.*)



Entry	NuH	Product	Time (h)	Yield (%)
9		 **9i**	16	73
10		 **9j**	4	70

Since the TH catalyst is inexpensive, we performed multigram scale synthesis of coumarin **6a** and chromene **7a** with three separated (solvent-free) conditions (Table 3). With *ca.* 10 g of a substrate **4a**, respective yields of 28–41% and 33–37% for coumarin **6a** and chromene **7a** were obtained (Table 3), indicating that a practical multigram scale synthesis of coumarins and chromenes is feasible with the TH catalyst. The TH catalyst is a green catalyst derived from renewable materials (bovine tendons), and the solvent-free conditions employed for this multigram scale synthesis is also environmentally friendly.

Next we used the TH catalyst for the synthesis of densely functionalized 4*H*-chromenes *via* a three-component reaction. Gu *et al.* reported the elegant green chemistry route for the synthesis of densely functionalized 4*H*-chromenes *via* a three-component reaction of salicylaldehydes, 1,3-cyclohexanediones, and nucleophiles, employing L-proline as catalyst, and some products could be easily isolated by filtration, avoiding the use of chromatographic separations.[41] We followed Gu method for the synthesis of 4*H*-chromenes, using our TH catalyst. As shown in Table 4, the reaction of salicylaldehyde derivatives (**4**), dimedone derivatives (**8**), and nucleophiles (NuH) gave chromenes (**9a–j**) with yields of 43–95%. It should be noted that chromene products (**9a–j**) were obtained by filtration and washing with ethanol (without chromatographic separations). Chromenes **9a–c** were previously synthesized by Gu and coworkers with respective yields of 98, 88, and 87%,[41] however, these chromenes (**9a–c**) obtained from the present work (by the TH catalyst) were 67, 79, 56%, respectively (Table 4, entries 1–3). It should be noted that Gu and coworkers cooled the reaction mixture to 0 °C before filtration and washing with ethanol,[41] however, in the present work, this process was performed at room temperature (26–28 °C). This may be the reason that the yields of **9a–c** were lower than Gu method.[41] Compounds **9d–j**

were new chromenes (Table 4, entries 4–10) obtained from the TH catalyst with yields ≥ 70%, except **9f** (43%) and **9g** (66%). Although chromene products were simply obtained by filtration and washing with ethanol, we observed that the derivatives that are relatively polar (*e.g.*, **9c** and **9f**, Table 4, entries 3 and 6) had substantial yield losses from ethanol washing. Whereas non-polar products (*e.g.*, **9d**) did not have much yield losses from ethanol washing, and thus providing good yield (95%).

Apart from the chromene synthesis reported by Gu and coworkers,[41] there were other works recently reported for the synthesis of densely functionalized 4*H*-chromenes using ZnO nanoparticles,[42] tetrabutylammonium fluoride,[43] L-proline,[44] and iron(III) chloride and triphenylphosphine[45] as catalysts. The TH catalyst is much cheaper than those catalysts previously employed for such chromene synthesis,[41–45] and we therefore used the TH catalyst for multigram scale synthesis of chromenes. As shown in Fig. 6, a scale of *ca.* 10 g salicylaldehyde derivatives was used with 20% of the TH catalyst. After stirring the reaction mixture at 80 °C for 15–18 h, chromene products (**9k–p**) were simply obtained by filtration and washing with ethanol, giving yields of 56, 91, 74, 85, 96, and 97%, respectively (Fig. 6). This result indicates that the economical and green TH catalyst is applicable in the multigram scale synthesis of chromenes; the products were easily obtained without chromatographic separations.

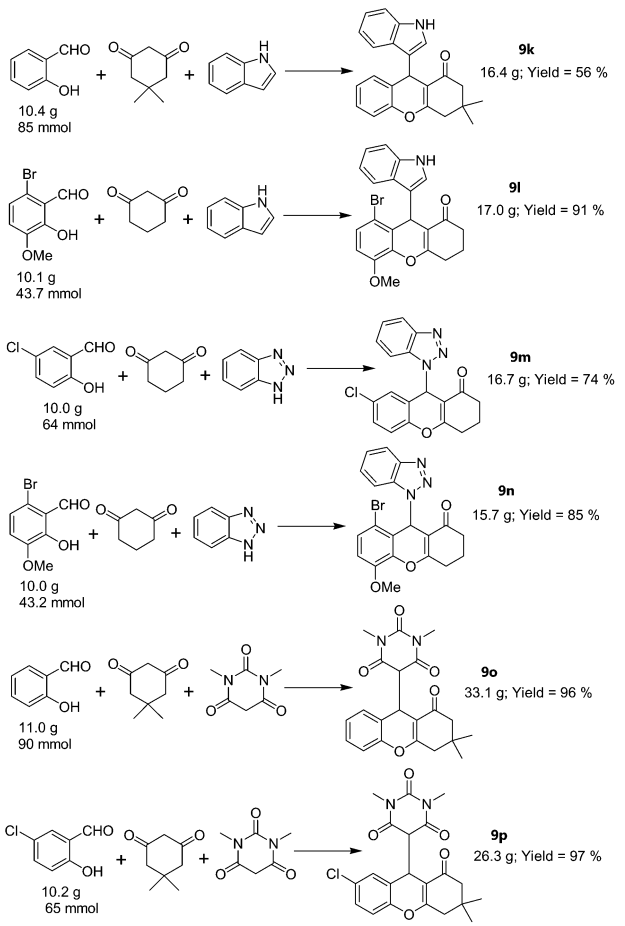


Fig. 6 Multigram scale synthesis of chromenes **9k–p**.

Since hydroxyproline was also present in the TH catalyst (ESI, Table 2S†), we then performed the three-component reaction for the synthesis of 4*H*-chromenes **9n** and **9p** using hydroxyproline as a catalyst. Surprisingly, quantitative yields of the chromenes **9n** (99.5%) and **9p** (99.8%) were obtained from the reaction; this result indicated that hydroxyproline in the TH catalyst should also involve in the formation of chromenes. This is the first report on a catalytic activity of hydroxyproline for the synthesis of 4*H*-chromenes *via* the three-component reaction.

Overall, the present study highlights a feasible eco-friendly multigram scale synthesis of coumarins and chromenes with a green catalyst from renewable materials, bovine tendons. It should be noted that bovine tendons are used as food ingredients in some countries in Asia, but they are waste from meat industry in Western countries. The multigram scale synthesis of coumarins and/or chromenes reported here could be performed under solvent-free conditions (Table 3) or without chromatographic separations of the products (Fig. 6). Therefore, both the catalyst and the synthetic method are green and friendly to the environment.

Conclusions

The economical, easily accessible, and environmentally friendly TH catalyst was prepared from the acid hydrolysis of bovine tendons which are renewable materials. The TH catalyst catalyzed the synthesis of coumarins and chromenes (*e.g.*, **7a–h**) under the solvent-free conditions, and it also catalyzed the synthesis of densely functionalized 4*H*-chromenes *via* the three-component reaction. Moreover, the TH catalyst is applicable in the multigram scale synthesis of coumarins and chromenes, as well as in the three-component reaction for the construction of the 4*H*-chromenes. A multigram scale preparation of chromenes with a single 4*S*,2′*R*-diastereomer was demonstrated for the first time. Proline, not hydroxyproline, in the TH catalyst possibly catalyzes the formation of coumarins and chromenes under solvent-free conditions. In addition to proline, hydroxyproline was also found to catalyze the three-component reaction for the synthesis of 4*H*-chromenes. To the best of our knowledge, this is the first report on the green catalyst prepared from renewable materials.

Experimental section

Instruments

Melting points were measured on Buchi 535 Melting Point Apparatus and reported without correction. UV-Vis spectra were obtained from Shimadzu UV-1700 PharmaSpec Spectrophotometer. FTIR data were obtained using a universal attenuated total reflectance (UATR) attachment on a Perkin-Elmer Spectrum One spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 NMR instrument (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) and a Bruker AVANCE 400 NMR spectrometer (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C). APCI TOF MS spectra were obtained from a Bruker MicroTOF$_{LC}$ spectrometer.

Preparation of the TH catalyst

Two batches of the TH catalyst were prepared, and the TH catalysts from both batches had the same catalytic properties. Amino acid content in the TH catalyst is in Table 2S (ESI).†

The first batch. Bovine tendon (135 g) was hydrolyzed in 110 mL of 6 M HCl. A mixture was stirred and refluxed for 12 h; pH of the mixture was adjusted to 7 with saturated NaOH. The mixture was dried by a rotary evaporator, vacuum-dried, and then dissolved in methanol. The methanol soluble part was collected and dried to yield 7 g of the TH catalyst.

The second batch. Bovine tendon (256 g) was hydrolyzed in 90 mL of 6 M HCl. The mixture was stirred and refluxed for 18 h, and its pH was adjusted to 7 with saturated NaOH. The mixture was dried by a rotary evaporator, vacuum-dried, and extracted with 100 mL of MeOH (eleven times, a total volume of 1100 mL). The MeOH extracts were combined and dried, giving 24 g of the TH catalyst.

General procedure for the synthesis of coumarins and chromenes using the TH catalyst

A mixture of a salicylaldehyde derivative (500 mg, 1 equiv.) and methyl acetoacetate (3 equiv.) was added the TH catalyst (20% by weight of a salicylaldehyde derivative). The reaction was stirred at 55 °C, and the progress of a reaction was monitored by TLC. After the reaction was complete (the time for each reaction is indicated in Table 2), if coumarin product precipitated, it was collected by filtration. However, if the coumarin product did not precipitate, the reaction mixture was left at room temperature, in order to crystallize chromene product. In case that both chromene and coumarin did not crystallize or precipitate, the reaction mixture was subjected to chromatographic separations (*i.e.*, Sephadex LH-20 column chromatography (CC), silica gel CC, and preparative TLC). In some cases, chromene or coumarin in the fractions obtained from chromatographic separations were recrystallized from EtOH–CH_2Cl_2.

Multigram scale synthesis of coumarin **6a** and chromene **7a** was performed with *ca.* 10 g of salicylaldehyde **4a**, using 20% of the TH catalyst. The ratio of substrates **4a** and **5**, time, and temperature for the reaction were indicated in Table 3. After the reaction was complete, it was added an equal volume of CH_2Cl_2 and H_2O; compounds **6a** and **7a** were in the CH_2Cl_2 layer, while the TH catalyst was in the H_2O layer. The CH_2Cl_2 layer was left at room temperature, and chromene **7a** crystallized from the mixture, followed by coumarin **6a**. Finally, a mother liquid was separated by Sephadex LH-20 CC (eluted with MeOH); fractions were left at room temperature, and **6a** or **7a** individually crystallized from the fractions.

Synthesis of coumarin 6a and chromene 7a

Both **6a** and **7a** were prepared according to the general procedure. The crude reaction mixture was left at room temperature, and the major diastereomer of chromene **7a** crystallized from the mixture. After removing crystals of **7a**, the reaction mixture was then washed with water to remove a catalyst, dried under vacuum, and further purified by Sephadex LH-20 CC (eluted with 100% MeOH), followed by silica gel preparative TLC (developed with 20% EtOAc in hexane) to obtain coumarin **6a** and a mixture of the two diastereomers of chromene **7a**. The mixture of the two diastereomers of chromene **7a** was dissolved in a mixture of EtOH–CH_2Cl_2 (2 : 1) and left at room temperature, and the major diastereomer of chromene **7a** again crystallized from a solution.

(*S)-Methyl 4-((*R**)-1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7a).** Colorless crystals; mp 119–122 °C; UV (MeOH) λ_{max} (log ε) 268 (3.68); IR (UATR) ν_{max}: 3002, 2952, 2840, 1713, 1640, 1584, 1488, 1459, 1434, 1381, 1356, 1291, 1218, 1188, 1154, 1106, 1064, 990, 947, 822, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 2.44 (s, 3H), 3.44 (s, 3H), 3.65 (d, $J = 4.5$ Hz, 1H), 3.76 (s, 3H), 4.76 (d, $J = 4.5$ Hz, 1H), 6.98 (dd, $J = 1.0$ Hz, 8.1 Hz, 1H), 7.05 (td, $J = 1.2$ Hz, 7.5 Hz, 1H), 7.19 (td, $J = 1.1$ Hz, 8.0 Hz, 1H) 7.29 (dd, $J = 1.5$ Hz, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.7, 29.5, 34.6, 51.5, 51.9, 66.1, 103.4, 115.8, 121.4, 124.3, 128.2, 129.1, 151.2, 163.9, 167.1, 168.9, 201.6; APCI-TOF MS: calcd for $C_{17}H_{18}NaO_6$, *m*/*z* 341.0996 $(M + Na)^+$, found 341.1000.

Synthesis of coumarin 6b and chromene 7b

Compounds **6b** and **7b** were prepared according to the general procedure. Coumarin **6b** precipitated from the reaction mixture. After removing coumarin **6b**, the reaction mixture was washed with water to remove a catalyst, dried under vacuum, and further purified by Sephadex LH-20 CC (eluted with 100% MeOH) to obtain additional amounts of coumarin **6b** and the mixture of two diastereomers of chromene **7b**. The mixture of two diastereomers of chromene **7b** was dissolved in a mixture of EtOH–CH_2Cl_2 (2 : 1) and left at room temperature, and the major diastereomer of chromene **7b** crystallized from a solution.

(*S)-Methyl 6-methoxy-4-((*R**)-1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7b).** Yellow crystals; mp 97–98 °C; UV (MeOH) λ_{max} (log ε) 279 (3.83); IR (UATR) ν_{max}: 2997, 2952, 2838, 1713, 1636, 1601, 1496, 1433, 1380, 1351, 1283, 1244, 1204, 1155, 1106, 1068, 1034, 992, 947, 870, 814, 774, 721, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 2.38 (s, 3H), 3.41 (s, 3H), 3.62 (d, $J = 6$ Hz, 1H), 3.71 (s, 6H), 4.69 (d, $J = 3$ Hz, 1H), 6.68 (dd, $J = 3$ Hz, 9 Hz, 1H), 6.80 (d, $J = 3$ Hz, 1H), 6.86 (d, $J = 9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.3, 29.0, 34.4, 51.0, 51.6, 55.0, 65.7, 102.1, 112.6, 114.0, 116.1, 121.7, 144.9, 155.7, 163.8, 166.7, 168.6, 201.3; ESI-TOF MS: calcd for $C_{18}H_{20}NaO_7$, *m*/*z* 371.1101 $(M + Na)^+$, found 371.1106.

Synthesis of coumarin 6c and chromene 7c

Compounds **6c** and **7c** were prepared according to the general procedure. The major diastereomer of chromene **7c** precipitated from the reaction mixture. After removing precipitate of **7c**, the resulting mixture was left at room temperature, and coumarin **6c** was precipitated. After removing coumarin **6c**, the reaction mixture was purified by Sephadex LH-20 CC, eluted with 100% MeOH, to obtain fractions that contained coumarin **6c**, and these fractions were combined. A combined fraction containing **6c** was dried by a rotary evaporator, and dissolved in EtOH–CH_2Cl_2; coumarin **6c** crystallized from EtOH–CH_2Cl_2.

(*S)-Methyl 7-methoxy-4-((*R**)-1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7c).** White solid; UV (MeOH) λ_{max} (log ε) 271 (3.75), 222 (4.21); IR (UATR) ν_{max}: 3003, 2952, 2841, 1705, 1638, 1583, 1508, 1437, 1385, 1358, 1337, 1288, 1260, 1243, 1206, 1189, 1157, 1140, 1069, 1035, 1005, 952, 849, 805, 778, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 2.43 (s, 3H), 3.47 (s, 3H), 3.64 (d, $J = 3$ Hz, 1H), 3.76–3.77 (s, 6H), 4.70 (d, $J = 3$ Hz, 1H), 6.54 (d, $J = 3$ Hz, 1H), 6.80 (d, $J = 3$ Hz, 1H), 6.63 (d, $J = 9$ Hz, 1H), 7.19 (d, $J = 6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.8, 29.6, 34.2, 51.6, 52.1, 55.4, 66.1, 101.1, 103.8, 110.8, 113.3, 129.8, 152.1, 159.6, 164.0, 167.3, 169.2, 202.0; ESI-TOF MS: calcd for $C_{18}H_{20}NaO_7$, *m*/*z* 371.1101 $(M + Na)^+$, found 371.1109.

Synthesis of coumarin 6d and chromene 7d

Compounds **6d** and **7d** were prepared according to the general procedure. Coumarin **6d** precipitated from the reaction mixture. After removing coumarin **6d**, the reaction mixture was left at room temperature, and the major diastereomer of chromene **7d** crystallized from the mixture. After removing crystals of **7d**, the reaction mixture was washed with water to remove a catalyst, dried under vacuum, and further purified by Sephadex LH-20 CC (eluted with 100% MeOH), followed by silica gel CC (eluted with 20% EtOAc in petroleum ether) to obtain additional amounts of coumarin **6d** and a mixture of two chromene diastereomers **7d**. The mixture of the two chromene diastereomers **7d** was dissolved in EtOH–CH_2Cl_2 (2 : 1) and left at room temperature; the major diastereomer of chromene **7d** crystallized from EtOH–CH_2Cl_2.

(*S)-Methyl 8-hydroxy-4-((*R**)-1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7d).** Colorless crystals; mp 124–126 °C; UV (MeOH) λ_{max} (log ε) 286 (3.62), 267 (3.65), 205 (4.20); IR (UATR) ν_{max}: 3420, 3002, 2953, 2845, 1712, 1641, 1617, 1598, 1480, 1435, 1382, 1356, 1211, 1160, 1084, 995, 843, 781, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 2.49 (s, 3H), 3.47 (s, 3H), 3.64 (d, $J = 4.9$ Hz, 1H), 3.78 (s, 3H), 4.76 (d, $J = 4.8$ Hz, 1H), 5.44 (s, 1H), 6.79–6.86 (m, 2H), 6.92–6.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 29.5, 34.7, 51.6, 52.1, 66.0, 104.2, 114.6, 119.9, 122.1, 124.5, 139.1, 143.5, 163.3, 167.1, 168.9, 201.7; ESI-TOF MS: calcd for $C_{17}H_{18}NaO_7$, *m*/*z* 357.0944 $(M + Na)^+$, found 357.0952.

Synthesis of coumarin 6e and chromene 7e

Compounds **6e** and **7e** were prepared according to the general procedure. Coumarin **6e** precipitated from the reaction mixture. After removing coumarin **6e**, the reaction mixture was left at room temperature, and the major diastereomer of chromene **7e** crystallized from the mixture. After removing crystals of **7e**, the reaction mixture was then washed with water to remove a catalyst, dried under vacuum, and further purified by silica gel preparative TLC (developed with 25% EtOAc in petroleum ether) to obtain the mixture of two chromene diastereomers **7e**. The mixture of the two chromene diastereomers **7e** was dissolved in EtOH–CH_2Cl_2 and left at room temperature; the major diastereomer of chromene **7e** crystallized from EtOH–CH_2Cl_2.

(*S)-Methyl 6-bromo-4-((*R**)-1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7e).** Colorless crystals; mp 119–120 °C; UV (MeOH) λ_{max} (log ε) 272 (3.73); IR (UATR) ν_{max}: 3003, 2953, 2922, 1714, 1645, 1578, 1480, 1435, 1382, 1344, 1279, 1221, 1189, 1161, 1116, 1069, 993, 894, 826, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 2.43 (s, 3H), 3.48 (s, 3H), 3.64 (d, $J = 3$ Hz, 1H), 3.77 (s, 3H), 4.72 (d, $J = 3$ Hz, 1H), 6.87 (d, $J = 9$ Hz, 1H), 6.29 (m, 1H), 7.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.7, 29.5, 34.3, 51.7, 52.2, 65.9, 103.3, 116.7, 117.6, 123.6, 131.2, 131.9, 150.5, 163.9, 166.9, 168.8, 201.24; ESI-TOF MS: calcd for $C_{17}H_{17}BrNaO_6$, *m*/*z* 419.0101 $(M + Na)^+$, found 419.0093.

Synthesis of coumarin 6f and chromene 7f

Compounds **6f** and **7f** were prepared according to the general procedure. Coumarin **6f** precipitated from the reaction mixture. After removing coumarin **6f**, the reaction mixture was left at room temperature, and the major diastereomer of chromene **7f** crystallized from the mixture. After removing crystals of **7f**, the reaction mixture was washed with water to remove a catalyst, dried under vacuum, and purified by silica gel preparative TLC (developed with 25% EtOAc in petroleum ether) to obtain a mixture of the two diastereomers of **7f**. The mixture of two chromene diastereomers **7f** was dissolved in EtOH–CH_2Cl_2 and left at room temperature; the major diastereomer of chromene **7f** crystallized from EtOH–CH_2Cl_2.

(*S)-Methyl 6-chloro-4-((*R**)-1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7f).** Colorless crystals; mp 111–113 °C; UV (MeOH) λ_{max} (log ε) 271 (3.48); IR (UATR) ν_{max}: 3003, 2953, 2841, 1716, 1694, 1643, 1582, 1483, 1435, 1381, 1351, 1281, 1223, 1190, 1158, 1116, 1069, 992, 950, 887, 820, 775, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 2.43 (s, 3H), 3.48 (s, 3H), 3.64 (d, $J = 4.4$ Hz, 1H), 3.77 (s, 3H), 4.72 (d, $J = 4.2$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 7.16 (dd, $J = 2.5$ Hz, 8.7 Hz, 1H), 7.32 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 29.5, 34.4, 51.6, 52.1, 65.9, 103.2, 117.1, 123.1, 128.2, 129.0, 129.2, 150.0, 163.9, 166.9, 168.8, 201.3; ESI-TOF MS: calcd for $C_{17}H_{17}ClNaO_6$, *m*/*z* 375.0606 $(M + Na)^+$, found 375.0603.

Synthesis of coumarin 6g and chromene 7g

Compounds **6g** and **7g** were prepared according to the general procedure. Coumarin **6g** precipitated from the reaction mixture. After removing coumarin **6g**, the reaction mixture was washed with water to remove a catalyst, dried under vacuum, and purified by preparative TLC (50% EtOAc in petroleum ether) to obtain the mixture of two diastereomers of chromene **7g**.

3-Acetyl-5-bromo-8-methoxy-2*H*-chromen-2-one (6g). Yellow solid; UV (MeOH) λ_{max} (log ε) 320 (3.80), 259 (3.62), 213 (4.08); IR (UATR) ν_{max}: 3084, 2942, 1733, 1686, 1592, 1563, 1466, 1437, 1358, 1328, 1264, 1227, 1202, 1152, 1095, 953, 924, 832, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.74 (s, 3H), 3.97 (s, 3H), 7.04 (d, $J = 9$ Hz, 1H), 7.47 (d, $J = 6$ Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.5, 56.5, 113.9, 116.1, 118.5, 125.3, 128.2, 145.7, 146.5, 146.6, 158.0, 195.0; ESI-TOF MS: calcd for $C_{12}H_9BrNaO_4$, *m*/*z* 318.9576 $(M + Na)^+$, found 318.9587.

Methyl 5-bromo-8-methoxy-4-(1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7g). Yellow viscous oil; UV (MeOH) λ_{max} (log ε) 292 (3.82), 265 (4.01), 202 (4.61); IR

(UATR) ν_{max}: 2997, 2951, 2841, 2172, 1717, 1644, 1602, 1578, 1477, 1435, 1382, 1357, 1312, 1237, 1210, 1155, 1096, 1062, 883, 800 cm^{-1}; The major diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 2.51 (s, 3H), 3.54 (s, 3H), 3.73 (s, 3H), 3.86 (s, 3H), 3.95 (d, J = 3 Hz, 1H), 4.81 (d, J = 3 Hz, 1H), 6.71–6.75 (m, 1H), 7.27–7.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.4, 30.0, 36.2, 51.3, 52.0, 56.2, 62.3, 101.5, 111.9, 112.4, 122.4, 127.4, 127.8, 147.3, 163.7, 167.1, 167.8, 201.1; The minor diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ: 2.11 (s, 3H), 2.47 (s, 3H), 3.66 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 3.94–3.97 (m, 1H), 4.85 (d, J = 3 Hz, 1H), 6.71–6.75 (m, 1H), 7.27–7.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.1, 30.1, 36.8, 51.7, 52.3, 56.3, 62.4, 103.8, 111.4, 112.4, 122.4, 127.4, 127.8, 147.2, 162.9, 167.1, 168.2, 201.2; ESI-TOF MS: calcd for $C_{18}H_{19}BrNaO_7$, m/z 449.0206 $(M + Na)^+$, found 449.0215.

Synthesis of coumarin 6h and chromene 7h

Compounds **6h** and **7h** were prepared according to the general procedure. The reaction mixture was washed with water to remove a catalyst, dried under vacuum, and purified by Sephadex LH-20 CC (eluted with 100% MeOH) to obtain the mixture of two chromene diastereomers **7h** and the fractions that contained coumarin **6h**. The fractions containing **6h** were combined and purified again by preparative TLC (40% hexane in CH_2Cl_2) to give coumarin **6h**.

Methyl 6,8-di-*tert*-butyl-4-(1-methoxy-1,3-dioxobutan-2-yl)-2-methyl-4*H*-chromene-3-carboxylate (7h). Yellow viscous oil; UV (MeOH) λ_{max} (log ε) 276 (3.83); IR (UATR) ν_{max}: 2954, 2870, 1716, 1643, 1598, 1435, 1380, 1361, 1274, 1246, 1213, 1199, 1170, 1074, 994, 883, 832, 774 cm^{-1}; The major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28–1.29 (s, 9H), 1.42 (s, 9H), 2.21 (s, 3H), 2.50 (s, 3H), 3.45 (s, 3H), 3.55 (d, J = 6.1 Hz, 1H), 3.75 (s, 3H), 4.72 (m, 1H) 7.15 (m, 1H), 7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.5, 29.4, 30.0, 30.4 (3C), 31.4 (3C), 34.8, 36.1, 51.4, 52.0, 66.4, 103.8, 121.6, 122.4, 123.9, 127.3, 136.1, 146.3, 163.9, 167.1, 169.0, 201.7; the minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28–1.29 (s, 9H), 1.42 (s, 9H), 1.78 (s, 3H), 2.49 (s, 3H), 3.64 (d, J = 6.5 Hz, 1H) 3.71 (s, 3H), 3.77 (s, 3H), 4.72 (m, 1H) 7.15 (m, 1H), 7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.3, 29.5, 29.7, 30.0 (3C), 31.4 (3C), 34.5, 36.7, 51.4, 52.2, 64.9, 104.2, 121.8, 122.5, 123.7, 127.2, 136.4, 146.6, 163.4, 167.1, 168.6, 202.3; ESI-TOF MS: calcd for $C_{25}H_{34}NaO_6$, m/z 453.2248 $(M + Na)^+$, found 453.2261.

Synthesis of coumarin 6i and chromene 7i

Compound **6i** was prepared according to the general procedure. The reaction mixture was added ethanol to precipitate coumarin **6i**, and **6i** was then collected by filtration. Chromene **7i** was not obtained from this reaction.

Synthesis of coumarin 6j and chromene 7j

The synthesis was performed according to the general procedure. However, the reaction did not give coumarin **6j** and chromene **7j**.

Synthesis of coumarin 6k and chromene 7k

The synthesis was performed according to the general procedure. Coumarin **6k** precipitated from the reaction mixture. After removing coumarin **6k**, the resulting reaction mixture was then purified by silica gel preparative TLC (100% CH_2Cl_2) to obtain additional amounts of coumarin **6k**. Chromene **7k** was not formed from this reaction.

General procedure of three-component reactions of salicylaldehyde derivatives (4), 1,3-cyclohexanedione derivatives (8), and nucleophiles (NuH) by the TH catalyst

A mixture of salicylaldehyde derivatives (**4**) (1.0–1.7 mmol; 1 equiv.), 1,3-cyclohexanedione derivatives (**8**) (1 equiv.), NuH (1 equiv.) and the TH catalyst (20% by weight) in ethanol (3 mL) was stirred at 80 °C. The time for each reaction was indicated in Table 4. The reaction mixture was cooled to room temperature, and it was filtered and washed with ethanol to yield chromenes. Spectroscopic data of chromenes **9a–c**,[41] **9d**,[43] and **9e** (ref. 46) were identical to those reported in the literature.

Multigram scale synthesis of chromenes was performed in the same manner as that mentioned above. Amounts of *ca.* 10 g of salicylaldehyde derivatives (**4**), with 1 equivalent of 1,3-cyclohexanedione derivatives (**8**) and NuH, were used in the experiment; the reaction time was 15–18 h (Fig. 6). Spectroscopic data of chromene **9k** were in good agreement with those in the literature.[42,44,45]

7-Bromo-9-(1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (9f). White solid; UV (MeOH) λ_{max} (log ε) 280 (4.34) 221 (4.78); IR (UATR) ν_{max}: 3747, 3403, 3331, 3056, 2949, 2303, 1638, 1575, 1474, 1456, 1422, 1375, 1338, 1233, 1181, 1135, 1097, 1068, 997, 912, 816, 795, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.62–2.06 (m, 2H), 2.32–2.36 (m, 2H), 2.57–2.79 (m, 2H), 5.28 (s, 1H), 6.96–7.01 (m, 2H), 7.07–7.14 (m, 2H), 7.22–7.30 (m, 3H), 7.36 (d, J = 8 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.3, 27.7, 29.6, 37.0, 111.4, 113.6, 117.2, 118.0, 118.8, 119.5, 119.7, 121.7, 122.7, 125.5, 127.4, 130.5, 132.8, 136.5, 148.6, 165.7, 197.1; ESI-TOF MS: calcd for $C_{21}H_{16}BrNNaO_2$, m/z 416.0257 $(M + Na)^+$, found 416.0256.

9-(1*H*-Indol-3-yl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (9g). Orange solid; UV (MeOH) λ_{max} (log ε) 283 (4.09), 223 (4.65), 203 (4.59); IR (UATR) ν_{max}: 3408, 3336, 3050, 2958, 2869, 1637, 1582, 1542, 1505, 1456, 1421, 1374, 1336, 1284, 1264, 1190, 1167, 1145, 1112, 1096, 1035, 1013, 957, 838, 782, 738, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.95 (s, 3H), 1.10 (s, 3H), 2.17 (d, J = 16 Hz, 1H), 2.25 (d, J = 16 Hz, 1H), 2.51 (d, J = 18 Hz, 1H), 2.59 (d, J = 17 Hz, 1H), 3.76 (s, 3H), 5.25 (s, 1H), 6.56 (dd, J = 9, 3 Hz, 1H), 6.63 (d, J = 3 Hz, 1H), 6.98 (td, J = 8, 1 Hz, 1H), 7.05 (m, 2H), 7.15 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 8.02 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.6, 28.9, 29.0, 32.0, 41.5, 50.9, 55.4, 101.2, 111.2, 111.5, 113.0, 117.3, 119.0, 119.2, 120.5, 121.5, 122.3, 125.6, 130.6, 136.5, 150.0, 158.8, 164.1, 197.4; ESI-TOF MS: calcd for $C_{24}H_{23}NNaO_3$, m/z 396.1570 $(M + Na)^+$, found 396.1574.

3-(3,3-Dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)-1*H*-indole-2-carboxylic acid (9h). White solid; UV (MeOH) λ_{max} (log ε) 296 (3.77), 227 (4.01); IR (UATR) ν_{max}: 3261, 2937, 2877,

1676, 1644, 1579, 1547, 1485, 1446, 1417, 1376, 1350, 1319, 1289, 1257, 1227, 1201, 1183, 1143, 1199, 1034, 1015, 913, 875, 758, 736, 710, 682 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 0.87 (s, 3H), 1.05 (s, 3H), 1.98 (d, J = 16 Hz, 1H), 2.24 (d, J = 16 Hz, 1H), 2.60 (d, J = 18 Hz, 1H), 2.68 (d, J = 18 Hz, 1H), 6.25 (s, 1H), 6.87 (t, J = 7 Hz, 1H), 6.99 (td, J = 8, 3 Hz, 1H), 7.09–7.17 (m, 3H), 7.20–7.27 (m, 2H), 7.34 (d, J = 8 Hz, 1H), 11.50 (s, 1H), 13.18 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.8, 27.3, 28.8, 31.5, 40.5, 50.3, 111.5 (2C), 112.7, 116.2, 119.2, 119.9, 123.7, 124.0, 124.7, 124.9, 125.2, 127.7, 129.7, 136.1, 148.6, 163.6, 164.1196.0; ESI-TOF MS: calcd for $C_{24}H_{22}NO_4$, m/z 388.1543 $(M + H)^+$, found 388.1554.

7-Bromo-9-((4-methoxybenzyl)thio)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (9i). White crystals; mp 115–117 °C; UV (MeOH) λ_{max} (log ε) 279 (3.57), 205 (4.13); IR (UATR) ν_{max}: 2951, 2830, 1641,1608, 1574, 1509, 1474, 1411, 1374, 1301, 1233, 1170, 1133, 1033, 995, 908, 814, 734, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.81–2.02 (m, 2H), 2.27–2.49 (m, 4H), 3.57 (d, J = 14 Hz, 1H), 3.66 (d, J = 14 Hz, 1H), 3.79 (s, 3H), 4.94 (s, 1H), 6.80–6.89 (m, 3H), 7.17–7.20 (m, 3H), 7.28 (dd, J = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.9, 27.6, 34.7, 34.8, 36.8, 55.3, 111.8, 113.8 (2C), 117.5, 117.9, 124.8, 129.9 (2C), 130.2, 131.1, 132.5, 149.5, 158.6, 166.9, 196.2; ESI-TOF MS: calcd for $C_{21}H_{19}BrNaO_3S$, m/z 453.0131 $(M + Na)^+$, found 453.0133.

5-(3,3-Dimethyl-7-nitro-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)-1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (9j). White solid; UV (MeOH) λ_{max} (log ε) 318 (3.94), 231 (4.23), 203 (4.51); IR (UATR) ν_{max}: 3744, 3070, 2960, 2869, 1747, 1675, 1651, 1584, 1526, 1446, 1422, 1381, 1343, 1287, 1235, 1209, 1194, 1147, 1127, 1089, 1031, 905, 840, 801, 749, 735, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.13 (s, 3H), 1.15 (s, 3H) 2.29 (d, J = 16 Hz, 1H), 2.37 (d, J = 16 Hz, 1H), 2.55 (s, 2H), 3.21 (s, 3H), 3.26 (s, 3H), 3.90 (d, J = 2 Hz, 1H), 4.97 (s, 1H), 7.17 (dd, J = 8.2 Hz, 1H), 8.1–8.2 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.9, 28.5, 28.6, 29.4, 32.1, 34.6, 41.3, 50.6, 55.4, 108.9, 117.7, 123.2, 124.4, 124.6, 144.5, 151.0, 154.6, 166.6, 166.7, 167.2, 197.5; ESI-TOF MS: calcd for $C_{21}H_{21}N_3NaO_7$, m/z 450.1272 $(M + Na)^+$, found 450.1262.

8-Bromo-9-(1*H*-indol-3-yl)-5-methoxy-2,3,4,9-tetrahydro-xanthen-1-one (9l). White solid; UV (EtOH) λ_{max} (log ε) 291 (4.36), 273 (4.40), 221 (4.96), 213 (4.96); IR (UATR) ν_{max}: 3338, 2319, 1644, 1573, 1471, 1428, 1372, 1311, 1217, 1182, 1135, 1092, 1062, 869, 800, 745 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.66–1.97 (m, 2H), 2.17–2.36 (m, 2H), 2.60–2.76 (m, 2H), 3.87 (s, 3H), 5.30 (s, 1H), 6.86–7.01 (m, 3H), 7.08 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 7.9 Hz, 1H), 10.90 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 19.9, 26.7, 29.5, 36.3, 55.9, 111.6, 111.9, 113.7, 114.3, 116.4, 118.3, 118.6, 120.5, 124.7, 125.2 (2C), 128.2, 136.0, 140.2, 147.1, 165.5, 195.9; ESI-TOF MS: calcd for $C_{22}H_{18}BrNNaO_3$, m/z 446.0362 $(M + Na)^+$, found 446.0363.

9-Benzotriazol-1-yl-7-chloro-2,3,4,9-tetrahydro-xanthen-1-one (9m). Yellow solid; UV (EtOH) λ_{max} (log ε) 265 (4.45); IR (UATR) ν_{max}: 3747, 2942, 1732, 1648, 1583, 1480, 1421, 1383, 1240, 1182, 1079, 1001, 823, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.03–2.17 (m, 2H), 2.39–2.44 (m, 2H), 2.73–2.97 (m, 2H), 7.02 (s, 1H), 7.18–7.31 (m, 3H), 7.36 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.1, 27.8, 36.4, 48.2, 109.3, 109.6, 118.7, 120.0, 120.9, 123.9, 127.6, 128.8, 130.3, 130.5, 132.3, 145.7, 148.6, 169.2, 196.0; ESI-TOF MS: calcd for $C_{19}H_{14}ClN_3NaO_2$, m/z 374.0667 $(M + Na)^+$, found 374.0658.

9-Benzotriazol-1-yl-8-bromo-5-methoxy-2,3,4,9-tetrahydro-xanthen-1-one (9n). White solid; UV (EtOH) λ_{max} (log ε) 293 (3.96), 264 (4.26), 207 (4.61); IR (UATR) ν_{max}: 2962, 2940, 2838, 1659, 1609, 1578, 1476, 1443, 1386, 1332, 1312, 1278, 1263, 1231, 1205, 1187, 1158, 1149, 1139, 1125, 1101, 1092, 1064, 1002, 941, 917, 873, 818, 802, 776, 764, 735, 743, 702, 657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.95–2.10 (m, 2H), 2.36–2.40 (m, 2H), 2.80–2.97 (m, 2H), 3.96 (s, 3H), 6.85 (d, J = 8.8 Hz, 1H), 7.11 (s, 1H), 7.28 (d, J = 8.9 Hz, 1H), 7.32 (td, J_t = 8.1 Hz, J_d = 0.7 Hz, 1H), 7.55 (td, J = 7.9 Hz, J_d = 0.7 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.0, 27.6, 36.4, 48.1, 56.4, 111.2, 111.7, 112.9, 114.1, 119.3, 120.4, 123.6, 127.2, 128.4, 133.5, 142.2, 144.8, 147.7, 168.8, 196.2; ESI-TOF MS: calcd for $C_{20}H_{16}BrN_3NaO_3$, m/z 448.0267 $(M + Na)^+$, found 448.0267.

5-(3,3-Dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)-1,3-dimethyl-pyrimidine-2,4,6-trione (9o). White solid; UV (EtOH) λ_{max} (log ε) 267 (3.30), 222 (3.38), 204 (3.50); IR (UATR) ν_{max}: 3749, 2957, 2886, 1746, 1675, 1643, 1582, 1457, 1421, 1387, 1319, 1289, 1230, 1185, 1114, 1034, 775, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.13 (s, 3H), 1.18 (s, 3H), 2.30 (d, J = 17.3 Hz, 1H), 2.36 (d, J = 16.3 Hz, 1H), 2.48 (d, J = 17.7 Hz, 1H), 2.56 (d, J = 17.6 Hz, 1H), 3.07 (s, 3H), 3.21 (s, 3H), 3.85 (d, J = 2.7 Hz, 1H), 4.87 (s, 1H), 7.03 (d, J = 8.22 Hz, 1H) 7.08–7.09 (m, 2H), 7.22–7.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.2, 28.1, 28.2, 29.2, 32.0, 36.3, 41.4, 50.5, 54.9, 108.8, 116.6, 120.5, 124.9, 127.9, 129.0, 150.4, 151.1, 166.9, 167.2, 168.0, 192.7; ESI-TOF MS: calcd for $C_{21}H_{22}N_2NaO_5$, m/z 405.1421 $(M + Na)^+$, found 405.1430.

5-(7-Chloro-3,3-dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)-1,3-dimethyl-pyrimidine-2,4,6-trione (9p). White solid; UV (EtOH) λ_{max} (log ε) 265 (4.24), 225 (4.31), 206 (4.42); IR (UATR) ν_{max}: 2959, 2876, 1734, 1677, 1645, 1449, 1420, 1382, 1287 1234, 1187, 1119, 1033, 827, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.12 (s, 3H), 1.14 (s, 3H), 2.28 (d, J = 15.9 Hz, 1H), 2.35 (d, J = 16.1 Hz, 1H), 2.47 (d, J = 18.5 Hz, 1H), 2.54 (d, J = 17.8 Hz, 1H), 3.16 (s, 3H), 3.24 (s, 3H), 3.85 (d, J = 2.5 Hz, 1H), 4.84 (s, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 7.21 (dd, J_a = 8.7 Hz, J_b = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.1, 28.3, 28.4, 29.3, 32.0, 35.5, 41.4, 50.5, 55.1, 108.5, 118.0, 122.9, 127.9, 129.0, 130.0, 148.9, 151.1, 166.8, 167.0, 167.8, 197.4; ESI-TOF MS: calcd for $C_{21}H_{21}ClN_2NaO_5$, m/z 439.1031 $(M + Na)^+$, found 439.1036.

Single crystal X-ray analysis

X-ray diffraction data for chromenes **7a**, **7b**, **7e**, and **7f** were collected at 296(2) K on a Bruker X8 APEX II KAPPA CCD diffractometer using graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). The structures were solved using SHELXS-97[47] and refined using full-matrix least squares on F^2 with SHELXL-97.[47] Final R-values and selected refinement details of **7a**, **7b**, **7e**, and **7f** are given in Table 1S (ESI).†

Acknowledgements

P. K. is supported by The Thailand Research Fund and the Center of Excellence on Environmental Health and Toxicology,

Science & Technology Postgraduate Education and Research Development Office (PERDO), Ministry of Education. T. A. acknowledges financial support by the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission, Ministry of Education. R. S. thanks the Ministry of Science and Technology for a student grant.

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