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COMMUNICATION

Visible-Light Promoted Oxidative Cyclization of Cinnamic Acid Derivatives using xanthone as the photocatalyst

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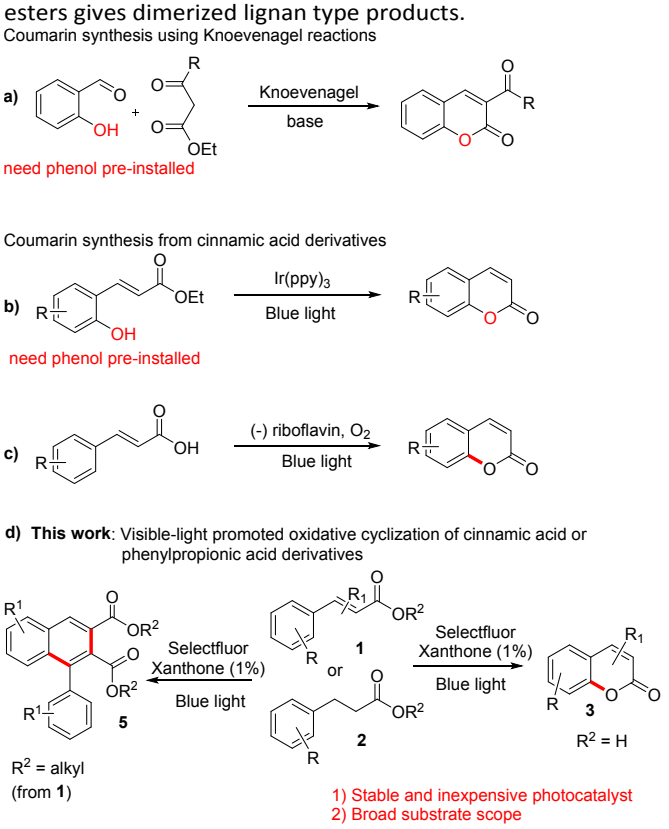
We have developed an efficient photocatalytic synthesis of coumarin derivatives via a tandem double bond isomerization/oxidative cyclization of cinnamic acids. Inexpensive and stable xanthone was used as the photocatalyst, and readily available Selectfluor was used as the oxidant. This method tolerates a wide range of functional groups and offers excellent chemical yields in general. Besides, the photocatalytic oxidative cyclization of cinnamic acid esters gives dimerized lignan type products.

Coumarin derivatives are frequently found in pharmaceuticals and biologically active natural products with antitumor[1-4], anti-HIV[5-7], antioxidant[8], antibacterial[9, 10], and anti-inflammatory[11-14] activities. They also have been used as organic electroluminescent materials.[15] Therefore, considerable efforts have been put into the synthesis of coumarin derivatives.[8, 13, 16-37] The classic method to prepare coumarin derivatives is the Knoevenagel reaction[22, 38], which involves condensation of β-ketoesters and *ortho*-aldehyde phenols (Scheme 1a). Many of these methods need harsh conditions such as high temperatures.[15, 17] What is more important, these reactions are based on aromatic aldehydes with phenol group pre-installed as the starting material.

Cinnamic acid derivatives are readily available; therefore, the synthesis of coumarins from cinnamic acid derivatives will be an attractive method. However, the synthesis of coumarins from cinnamic acid is challenging because common cinnamic acid derivatives exist as *E*-configuration. Typically, E to Z isomerization of the double bond requires high temperature or strong Lewis acids. Recently, Horaguchi and coworkers[39] described the cyclization of (E)-o-hydroxycinnamate via photo-catalyzed double bond E/Z isomerization-lactonization precess[40-42] (Scheme 1b). However, this method also needs a pre-installed phenol group. Along this line, oxidative cyclization of cinnamic acid derivatives will be a more straightforward route for coumarin synthesis without the need for a pre-installed phenol group. Gilmour and coworkers[43] reported an efficient (-)riboflavin catalyzed oxidative cyclization of cinnamic acids using oxygen as the oxidant (Scheme 1c). However, (-)riboflavin is structurally complex and may undergo photodegradation. Aromatic ketones such as xanthone are usually inexpensive and are also highly stable towards photodegradation. Herein we report an efficient photocatalytic synthesis of coumarin derivatives via a tandem double bond isomerization/oxidative cyclization of cinnamic acids catalyzed by xanthone (Scheme 1d). In addition, saturated 3-arylpropanoic acids are also suitable substrates, and the photocatalytic oxidative cyclization of cinnamic acid esters gives dimerized lignan type products.



Scheme 1. Literature background.

We selected the oxidative cyclization of cinnamic acid **1a** as our model reaction (Table 1). More detailed optimization

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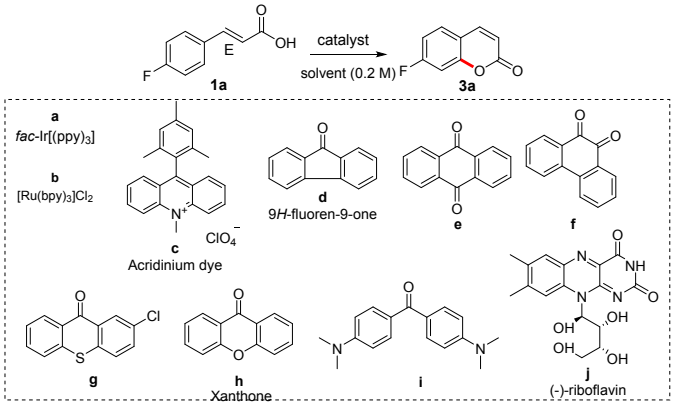
information was shown in Tables S1-6 in Supporting information. First, we screened various photocatalysts. Widely used photocatalysts[44-46] such as *fac*-Ir[(ppy)$_3$] and [Ru(bpy)$_3$]Cl$_2$, and (-)-riboflavin only gave trace amount of product (Table 1, entry 1) under 400 nm LED irradiation and using Selectfluor (F-TEDA-BF$_4$) as the oxidant. Acridinium dye was moderately effective (Table 1, entry 2). Aromatic ketones are effective photocatalyst in this reaction (Table 1, entries 4-6), and among diverse ketone catalysts, xanthone gave the best result (70% at 0.2 mmol-scale, Table 1, entry 6). In general, the solvent of light-induced reaction in current use is mostly acetonitrile, which may elongate the lifetime of triplet excited states or stabilize radical intermediates.[47-50] However, we found acetonitrile and other common solvents used in photochemistry (e.g., DMF, THF, dioxane) were not suitable (Table 1, entries 7-8). DCM was moderately effective (Table 1, entry 9). We found that 1.0 equivalent F-TEDA-BF$_4$ was enough for the reaction. To our delight, the reaction gave an even better yield (75%) when conducted at a larger scale (1 mmol). In the last, there was no reaction without photocatalyst (Table 1, entry 11). We also investigated the effects of oxidants and wavelengths. Other oxidants such as $K_2S_2O_8$, O_2 were less effective, and the reaction worked best using 400 nm and 365 nm lights (see SI for more information).

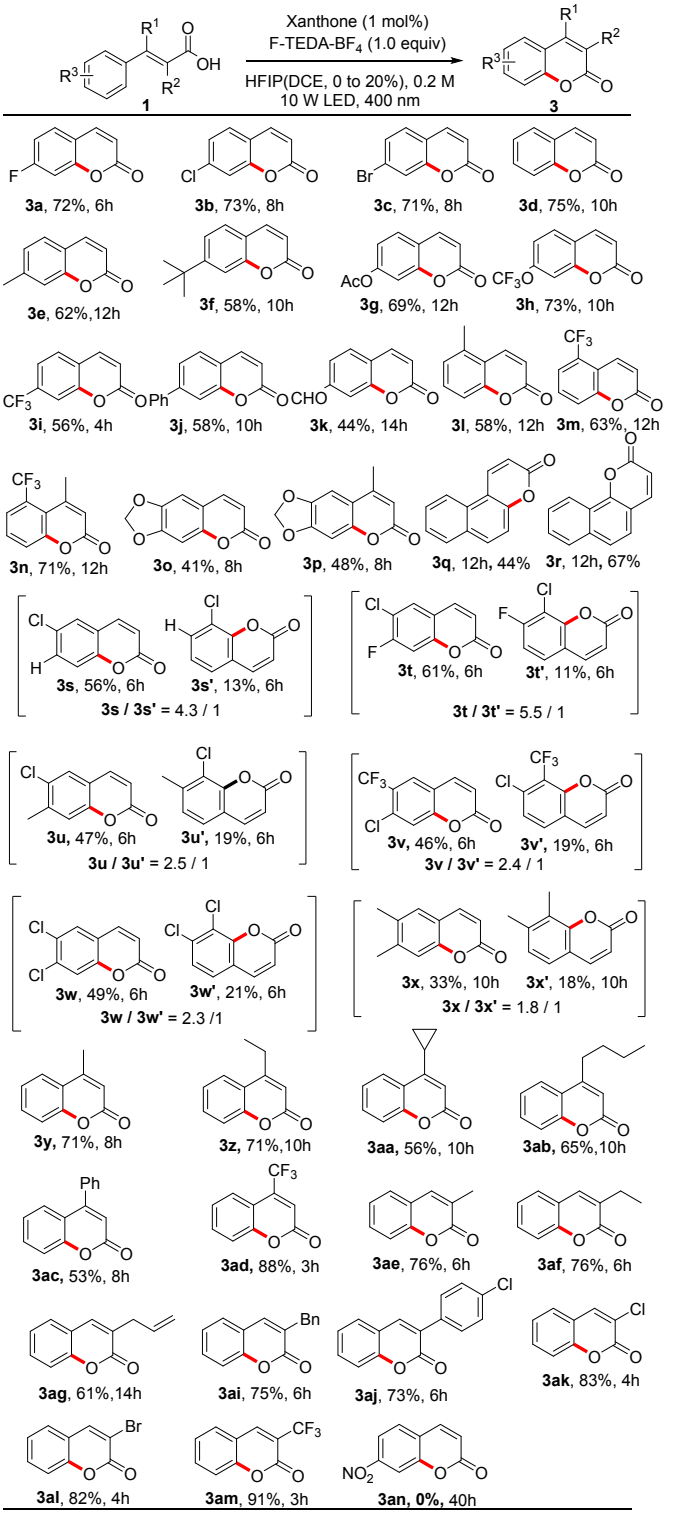
Table 1. Optimization of reaction conditions.[a]



Entry	Photo-catalyst	Solvent	Selectfluor (equiv)	Yield[b]/%
1	**a**, **b**, **d**, **f** or **j**	HFIP	1.5	< 5[c]
2	**c**	HFIP	1.5	57
3	**e**	HFIP	1.5	30[c]
4	**g**	HFIP	1.5	68
5	**i**	HFIP	1.5	14
6	h	HFIP	1.5	70
7	**h**	CH_3CN or DMF	1.5	0
8	**h**	Dioxane or THF	1.5	<1
9	**h**	DCM	1.5	54
10	**h**	HFIP	1.0	72 (75[d])
11	-	HFIP	1.5	0[c]

[a] Conditions: **1a** (0.2 mmol), photocatalyst (1 mol%), solvent and F-TEDA-BF$_4$ as indicated, rt, 400 nm 10W LEDs, N_2, 20 -24 h. [b] Yield of isolated products. [c] Conversions determined by GC-MS. [d] Conducted at 1.0 mmol scale.

Table 2. Oxidative cyclization of cinnamic acids.[a]



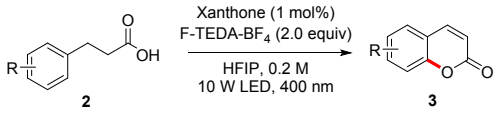
[a] Conditions: **1** (0.2 mmol), xanthone (1 mol%), HFIP (DCE, 0 to 20%, 1.0 mL), F-TEDA-BF$_4$ (1.0 equiv), rt, 400 nm 10W LEDs, N_2.

With the optimized conditions in hand, the scope of the reaction was evaluated (Table 2). Functional groups such as Me (**3e**), *t*-Bu (**3f**), OAc (**3g**), and OCF_3 (**3h**) were all well

tolerated. However, for highly electron-rich substrates, relatively lower yields were observed (**3o**, **3p**), which may due to these substrates were partially oxidized by Selectfluor. Naphthyl derived coumarin **3r** could also be accessed regio-selectively in 67% yield. Relatively lower yields were observed for cinnamic acids bearing electron-withdrawing functional groups (CF_3-, CHO-) (**3i, 3k**), and no reaction took place in the presence of a highly electron-withdrawing group (-NO_2) (**3an**). While *ortho*- or *para*-substituted cinnamic acids gave the single regio-isomer, *meta*- substituted cinnamic acids usually gave a mixture of regio-isomers (Table 2, **3s**-**3x**).

Our protocol also worked well for cinnamic acids with substituents at the double bond. For cinnamic acids with β-substituents such as Me (**3y**, 71%) to Et (**3z**, 71%), *n*-Bu (**3ab**, 65%), cyclopropyl (**3aa**, 56%), phenyl (**3ac**, 53%) and CF_3 (**3ad**, 88%) were all suitable starting materials. It should be noted that **3ac** contains the core structure of important lipoxygenase inhibitors.[51] Cinnamic acids with β-substituents such as Me (**3ae**, 76%) Et (**3af**, 76%), Bn (**3ai,** 75%), halogen (**3ak** in 83%, **3al** in 82%) and CF_3 (**3am,** 91%) all worked well.

Table 3. Synthesis of coumarins from 3-arylpropanoic acids.[a]



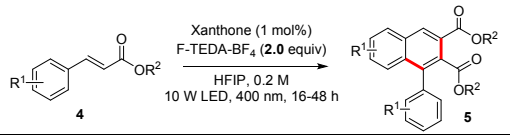
Substrates (**2**)	Yields% (**3**)	Substrates (**2**)	Yields% (**3**)
2a	**3a,** 24 h, 52%	**2f**	**3ae**, 40 h, 0%
2b	**3b,** 40 h, 36%	**2g**	**3y**, 40 h, 0%
2c	**3d,** 48 h, 41%	**2h**	**3d,** 40 h, 67%
2d	**3h,** 60 h, 24%	**2i**	**3ac**, 48 h, 0%
2e	**3i,** 60 h, 12%		

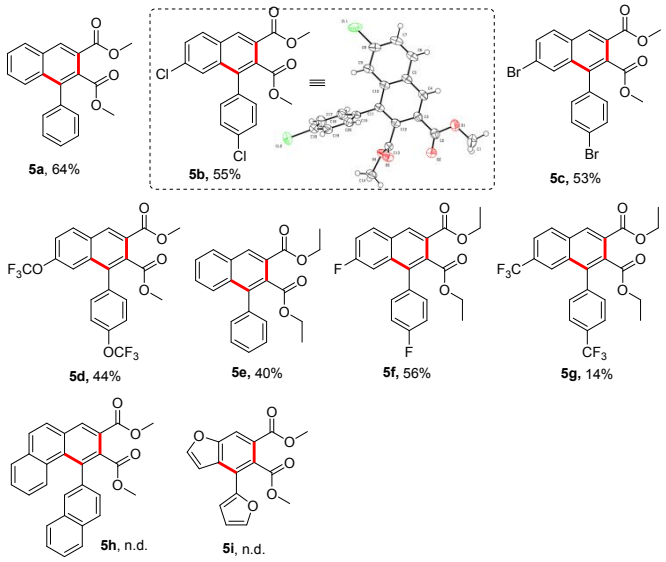
[a] Conditions: **2** (0.2 mmol), xanthone (1 mol%), HFIP (1.0 mL), F-TEDA-BF_4 (2.0 equiv), rt, 400 nm LED, N_2.

Because 3-arylpropanoic acids could be converted to cinnamic acid in the presence of oxidants, we proposed that 3-arylpropanoic acids could be converted to coumarins using our protocol. Indeed, 3-arylpropanoic acid gave coumarin products, albeit lower yields were observed (Table 3, **2a** – **2e**). However, no desired product formation was observed starting from α- or β-alkyl-substituted 3-arylpropanoic acids (**2f** – **2i**). Interestingly, the α-OH substituted 3-phenylbutanoic acid (**2h**) furnished hydroxyl eliminated coumarins **3d** in 67% yield instead of α-OH substituted coumarins.

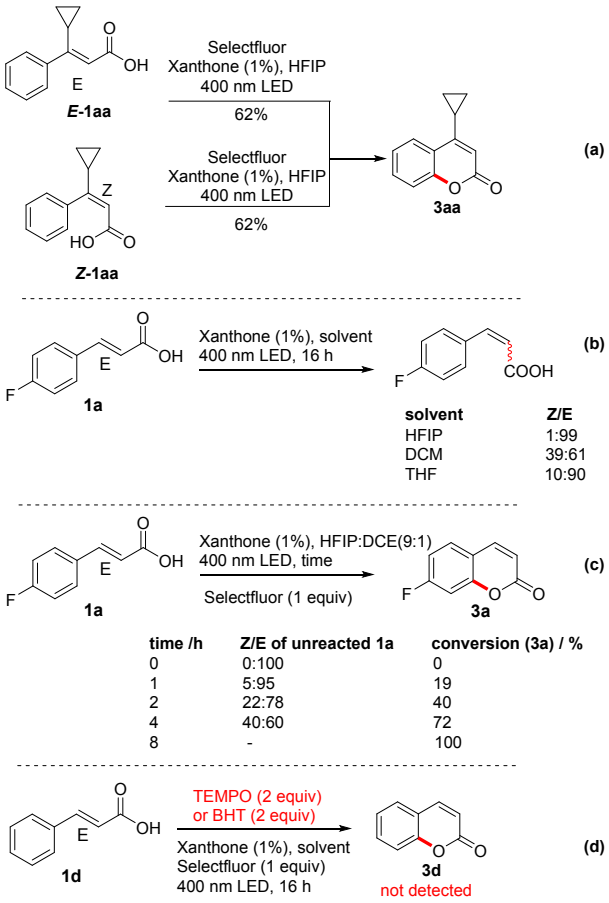
We also investigated the reactivity of cinnamic acid esters under our standard conditions (Table 4). Instead of coumarin products, this reaction gave dimeric lignans products in moderate yields (Table 4). The single-crystal X-ray diffraction further confirmed the structure assignments of our obtained products (see the ORTEP drawings of **5b.**[52] Functional groups such as halogens, OCF_3 were tolerated with moderate yields, electron-rich CF_3 cut down the reaction efficiency. Interestingly, replacing the benzene ring with naphthalene or furan invalidates the reaction. The possible reason is that these highly electron-rich aromatics did not tolerate Selectfluor, which is a strong oxidant.

Table 4. Oxidative dimerization of cinnamic acid esters.[a]





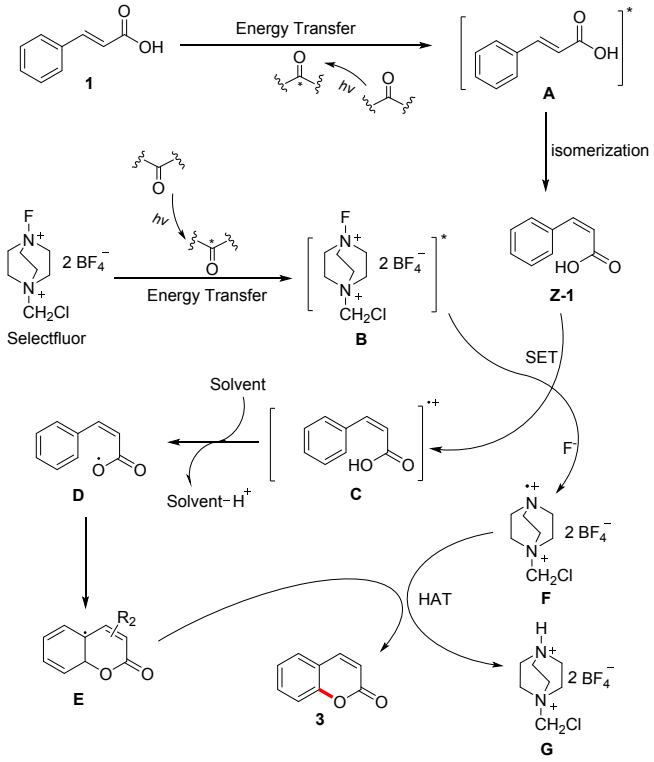
[a] Conditions: **4** (0.2 mmol), xanthone (1 mol%), HFIP (1.0 mL), F-TEDA-BF_4 (2.0 equiv), rt, 400 nm 10W LEDs, N_2, 16 h.



Scheme 2. Control experiments.

To gain insights into the reaction mechanism, we conducted several control experiments (Scheme 2). First, both Z- and E-cinnamic acids (E-**1aa** and Z-**1aa**) gave a product with comparable chemical yields and reaction rates (Scheme 2a). When we irradiated E- cinnamic acid **1a** in the presence of xanthone, E/Z isomerization of double bond was observed (Scheme 2b). The isomerization was more efficient in THF and DCM than the isomerization in HFIP (see Table S3 for more information). However, the isomerization was significantly faster in the presence of Selectfluor (Scheme 2c). Because we observed a yellow color formation when xanthone and Selectfluor were mixed in HFIP (see Figure S1 in SI). This suggests that Selectfluor may participate in the photo-induced isomerization process as well. The radical trapping experiment (Scheme 2d) with excess TEMPO or BHT inhibited the formation of coumarins. We think our tandem reaction proceeds via a comparably fast E to Z isomerization and a slower (rate-determining) radical cyclization addition.

Our proposed mechanism was shown in Scheme 3. for the reaction from cinnamic acids (1) to coumarins (3). Firstly, triplet-triplet energy transfer from photo-excited triplet state of photosensitizer to **1** generates the intermediate **A**, following a productive photochemical isomerization to form the Z isomer **Z-1**. Similarly, Selectfluor also was excited by an energy transfer. Then, a Z carboxylic acid cation radical **C** was delivered via a single-electron-transfer (SET) process, with spontaneous formation of N-radical dication **F** and fluoride. Subsequently, the deprotonation of the cation radical **C** by the solvent yielded radical **D**, which could undergo radical addition to generate radical **E**. Lastly, **E** reacted with N-radical dication **F** to generate the final product **3** and **G**.



Scheme 3. Proposed mechanism.

In summary, we have developed a concise, one-pot protocol to synthesis new unnatural coumarins and lignans. This protocol is based on readily available cinnamic acids or 3-arylproponoic acids using stable and inexpensive organic photosensitizer - xanthone. Also, the mild, convenient reaction was successfully furnished the dimeric lignans in good regio-selectivity and moderate yields.

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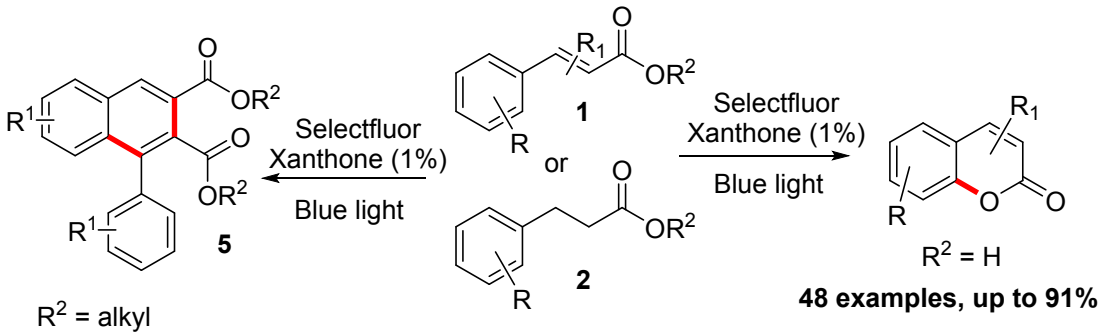

R^2 = alkyl
(from **1**)

9 examples, up to 64%

R^2 = H

48 examples, up to 91%

1) Stable and inexpensive photocatalyst
2) Broad substrate scope