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Sequential Energy Transfer Catalysis: A Cascade Synthesis of Angularly-Fused Dihydrocoumarins

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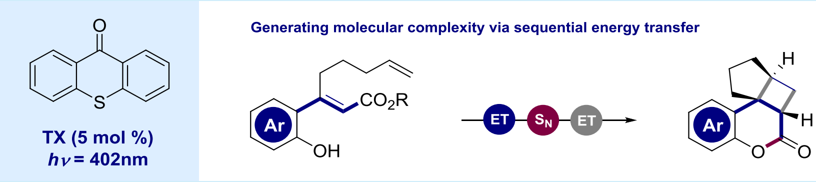
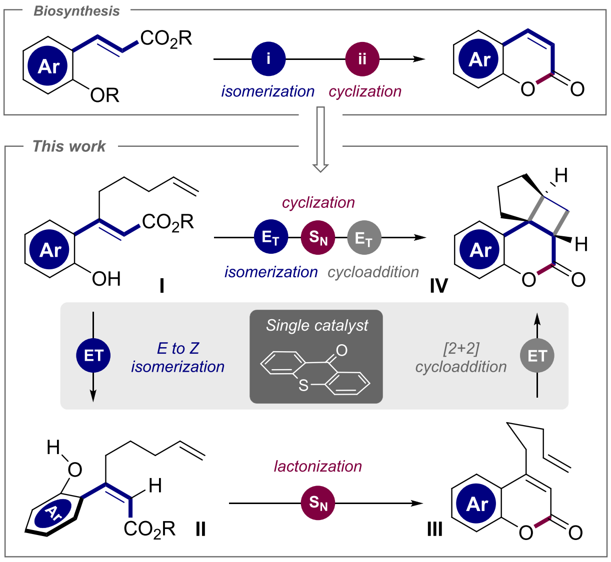
Supporting Information



ABSTRACT: An operationally simple one-pot protocol has been developed to enable the conversion of diversely substituted cinnamic acid derivatives into angularly-fused dihydrocoumarins (up to 94%). Inspired by coumarin biosynthesis, this reaction cascade harnesses photochemical *E* → *Z* alkene isomerization enabled by energy transfer catalysis using inexpensive thioxanthen-9-one (TX) under irradiation at 402 nm. Subsequent lactonization generates the heterocyclic core prior to a second photosensitization event to induce a [2 + 2] cycloaddition, again mediated by TX. The tetracyclic products are generated efficiently, and proof of the structure was established by X-ray crystallography. Mechanistic investigations, including structural probes and NMR reaction monitoring, support the postulated order of events. The study underscores the synthetic value of inexpensive small-molecule organic photocatalysts in the generation of structural complexity via sequential π-bond activation.

The functional versatility and structural tenacity of coumarins has led to their privileged status in biomedicine and materials science[1] and continues to fuel the development of innovative strategies to facilitate their construction.[2] In addition to the venerable Pechmann condensation,[3] the contemporary repertoire of synthetic approaches includes transition metal[4] and Lewis acid[5] catalyzed processes, variations of the Knoevenagel reaction,[6] and photochemical strategies.[7] In this diverse arsenal, bioinspired strategies that translate the conceptual simplicity of coumarin biosynthesis to a laboratory paradigm remain elusive. Inherent to this process is a geometrical *E* → *Z* isomerization of coumaric acid glycosides,[8] which facilitates rapid lactonization to generate the heterocyclic core (Scheme 1, top).[9] Given the renaissance of contra-thermodynamic alkene isomerization enabled by selective energy transfer catalysis,[10] mechanistic constructs that emulate the first two steps of coumarin biosynthesis[9a] might also be extended to generate structural complexity. This laboratory recently reported the direct photocatalytic conversion of simple cinnamic acids to coumarins to enable a sequential selective energy transfer−single electron transfer cascade (Scheme 1, center).[11] However, efforts to induce a subsequent energy transfer event under the auspices of flavin catalysis were unsuccessful. By re-engineering the transformation to more accurately reflect the biosynthetic precursor, the photoinduced SET step would be circumvented,[12] thereby potentially allowing two sequential energy transfer events to be coupled (Scheme 1, bottom). It was envisaged that appropriately substituted cinnamic acid precursors would respond to sequential energy transfer activation to generate additional complexity with high atom economy.[13]

Scheme 1. Cascade Route to Angularly-Fused Dihydrocoumarins via Sequential Energy Transfer Catalysis



To validate the notion of sequential energy transfer in enabling a bioinspired coumarin synthesis, substrate **I** bearing a

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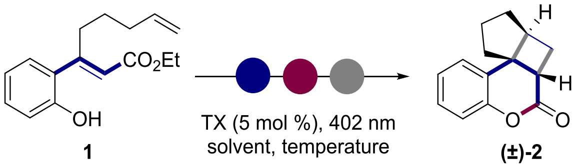
pendent alkene unit was conceived. Efficient photosensitized *E* → *Z* isomerization would generate *cis*-cinnamic acid **II** with concomitant lactonization (**III**). Since the terminal alkene is predisposed to undergo a [2 + 2] cycloaddition with the coumarin core via a second energy transfer process,[14] the angularly fused dihydrocoumarin scaffold **IV** would result. This would validate the conceptual framework of using sequential energy transfer events to generate structural complexity. Collectively, this bioinspired cascade[15] would enable angularly fused coumarins such as **4** to be generated using a single photocatalyst. In identifying a suitable photosensitizer to enable successive activation via energy transfer, (−)-riboflavin was considered.[16] Previous studies from this laboratory have demonstrated that photoexcited (−)-riboflavin effectively isomerizes activated alkenes embedded in the cinnamoyl motif.[17] Although isomerization and in situ cyclization were observed, the [2 + 2] cycloaddition presented a challenge (see Table 1, entry 6). Given the high triplet energy of coumarin (E_T = 261 kJ/mol)[18] it was reasoned that thioxanthen-9-one (E_T = 265 kJ/mol)[19] would be a prudent replacement for (−)-riboflavin (E_T = 209 kJ/mol).[18]

Initially, the conversion of substrate **1** to tetracycle (±)-**2** was investigated using TX under irradiation at 402 nm using a violet LED (Table 1). Reactions were performed at 50 °C under an inert atmosphere to mitigate any effects of oxygen on the efficiency of the energy transfer process. Gratifyingly, the initial reaction in acetonitrile at 50 °C furnished the expected product (±)-**2** in 91% yield (entry 1). Reducing the reaction time had a detrimental effect on the yield (entry 2), as did lowering the temperature to 20 °C (entry 3). Changes to the reaction medium were tolerated, albeit with slight reductions in yield (81 and 86%; entries 4 and 5).

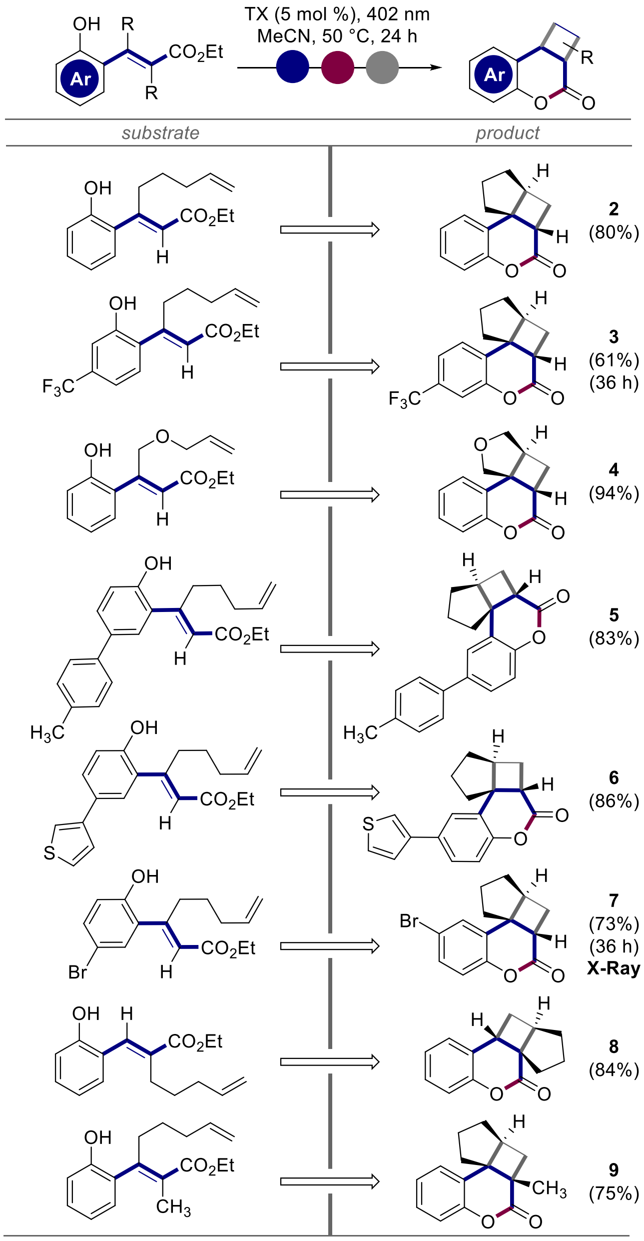
Table 1. Reaction Optimization Using TX[a]



entry	*t* [h]	*T* [°C]	solvent	yield [%][b]
1	24	50	MeCN	91
2	14	50	MeCN	77
3	24	20	MeCN	28
4	24	50	MeOH	81
5	24	50	$PhCF_3$	86
6[c]	24	50	MeCN	<5 (67)[d]

[a] Reactions were carried out on a 0.05 mmol scale in 1 mL of degassed solvent under an argon atmosphere with irradiation at 402 nm. [b] NMR yields using 1,3,5-trimethoxybenzene as the internal standard. [c] (−)-Riboflavin (5 mol %) was used instead of TX. [d] Only the lactonized product was observed (e.g., **III** in Scheme 1).

Scheme 2. Exploration of the Substrate Scope[a]

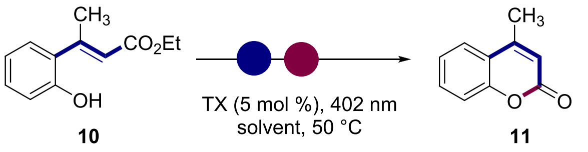


[a] Reactions were carried out on a 0.1 mmol scale in 2 mL of degassed MeCN under Ar with irradiation at 402 nm for 24 h. Isolated yields are shown.

For the purposes of scope expansion, a series of structurally modified substrates were prepared and exposed to TX (5 mol %) in acetonitrile (50 °C) under irradiation at 402 nm (Scheme 2). This one-pot protocol enabled the formation of parent coumarin **2** in 80% yield. The trifluoromethyl substrate required 36 h to reach completion to generate compound **3** in 61% yield, and the most efficient example in the study arose from the introduction of an ether side chain (**4**; 94%). The *π*-extended examples **5** and **6** were furnished in respectable yields of 83% and 86%, respectively, and the bromo derivative **7** provides a building block for subsequent derivatization. Switching the pendent alkene from the *β*- to the *α*-position allowed the isomeric coumarin scaffold **8** to be accessed. Finally, *α*,*β*-disubstitution was tolerated, as exemplified by scaffold **9** (75%). The relative stereochemistry of the racemic products was established by detailed ^{1}H NMR analysis, and it was possible to grow crystals of **7** that were suitable for X-ray crystallographic analysis (CCDC 1960689; see the inset at the bottom of Scheme 2 and the Supporting Information).

A process of reaction deconstruction was then conducted to independently investigate the two energy transfer processes. To that end, the starting material was simplified and the alkenyl side chain was truncated to explore the isomerization/lactonization (Table 2, **10** → **11**). Control reactions confirmed

Table 2. Study of the Isomerization/Lactonization Step[a]

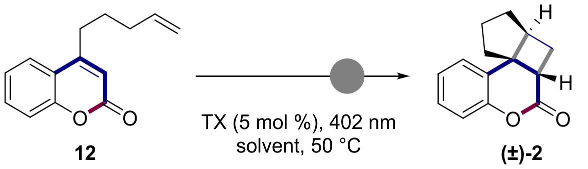


entry	variation	t [h]	conv. [%]	yield [%][b]
1	no light	24	<5	0 (0)
2	no TX	24	<5	0 (0)
3	MeCN	14	86	66 (12)
4	MeCN	24	>95	53 (30)
5	MeOH	24	>95	0 (71)
6	$PhCF_3$	24	>95	0 (79)

[a] Reactions were carried out on 0.1 mmol scale in 2 mL of degassed solvent under Ar with irradiation at 402 nm. [b] NMR yields using 1,3,5-trimethoxybenzene as the internal standard. Values in parentheses are the yields of the coumarin dimer.

the requirement of both light and photocatalyst for cyclization (entries 1 and 2). Inspection of the UV−vis spectrum of **10** indicates a lack of absorption at 402 nm (see the Supporting Information), thereby accounting for the exceptionally inefficient alkene isomerization observed. Exposing **10** to the reaction conditions reported above led to the formation of **11**, albeit with competing coumarin dimerization that proved to be solvent-dependent[20] (entries 3 and 4, yields given in parentheses). This is in line with the observation that TX induces both energy transfer events (Table 1). Switching the solvent from acetonitrile to methanol or trifluorotoluene (entries 5 and 6, respectively) led to exclusive formation of the dimer, which prompted a closer inspection of the cycloaddition event.

Table 3. Investigation of the [2 + 2] Cycloaddition with TX[a]

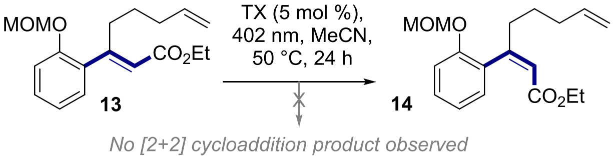


entry	variation	t [h]	conv. [%]	yield [%][b]
1	no light	24	<5	<5
2	no cat.	24	7	7
3	MeCN	24	>95	87
4	MeCN	1	>95	96
5	MeOH	1	>95	96
6	$PhCF_3$	1	>95	97

[a] Reactions were carried out on a 0.1 mmol scale in 2 mL of degassed solvent under Ar with irradiation at 402 nm. [b] NMR yields using 1,3,5-trimethoxybenzene as the internal standard.

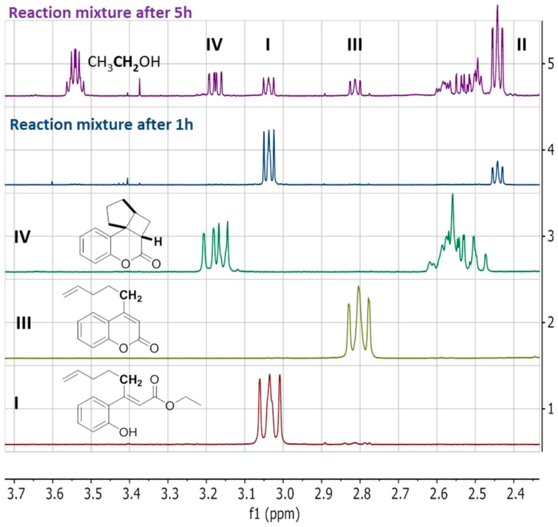
To that end, compound **12** was prepared, and the efficiency of the final step of the reaction cascade was interrogated (Table 3). Control reactions once again established the importance of the photon source and the TX photocatalyst for efficient cyclization (entries 1 and 2). Reducing the reaction time from 24 to 1 h improved the yield (entries 3 and 4), and the transformation was tolerant of changes in the solvent (entries 5 and 6). Finally, to provide experimental support for the postulated sequence of events involving isomerization, lactonization and finally cycloaddition, the MOM-protected substrate **13** was examined (Scheme 3).

Scheme 3. Probing the Order of Energy Transfer Events



This would prevent lactonization from occurring and thereby enable a competition between isomerization and [2 + 2] cycloaddition. Under the standard reaction conditions, only the Z-configured product **14** was generated, in line with the working hypothesis. Additional support for this order of events was obtained from the NMR time course shown in Scheme 4.

Scheme 4. NMR Time Course



From this analysis, it is possible to observe the initial isomerization after 1 h by virtue of the signals **I** (E, 3.04 ppm) and **II** (Z, 2.44 ppm). Moreover, the signal for the EtOH released during lactonization is visible at δ_H = 3.54 ppm.

In conclusion, an operationally simple one-pot conversion of cinnamic acids to angularly fused dihydrocoumarins is reported. This biomimetic strategy emulates the contra-thermodynamic alkene isomerization/lactonization sequence inherent to the natural product biosynthesis and extends the sequence to further photocycloaddition. Enabled by sequential energy transfer events using a single organic photocatalyst, this approach underscores the value of inexpensive small-molecule photosensitizers such as thioxanthen-9-one in generating structural complexity by π-bond activation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03882.

Experimental protocols and NMR and X-ray data (PDF)

Accession Codes

CCDC 1960689 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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