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Letter

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Transition-Metal-Free Photoinduced Intramolecular Annulation of 2,3-Di(hetero)arylchromen-4-one

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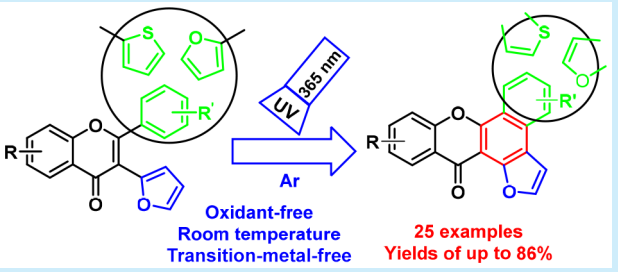
Supporting Information

ABSTRACT: An efficient transition-metal-free photoinduced intracyclization of 4*H*-chromen-4-ones in EtOH−H_2O (7:1, v/v) at ambient temperature for the construction of complicated fused-ring heteroaromatics is established. The reaction proceeds smoothly without requiring any catalysts/additives.

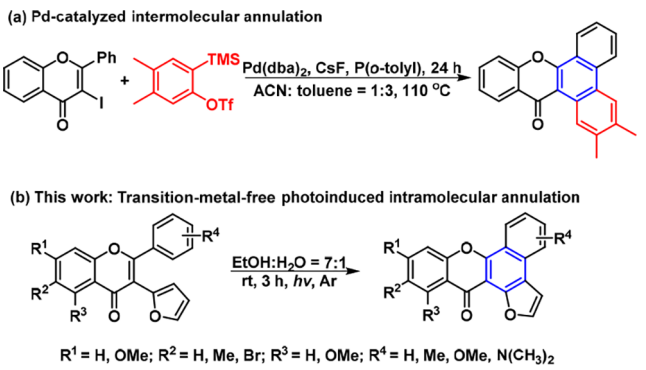


Polycyclic heteroaromatics (PHAs) have been extensively studied in various research areas during the past decade, and various synthetic methods have been developed.[1] Traditionally, one of the most versatile and frequently used approaches in PHA chemistry is transition-metal-catalyzed annulation, which not only closes the ring but also installs expected functional groups. Recently, however, alternative approaches have begun to compete with the classical protocol. Such approaches include C−H activation and dehydrogenative functionalization, which is based on only one activated component (e.g., halides or Ts, among others) or on two C−H bonds from both components. Although methods in PHA chemistry have dramatically improved, the need for transition metals, which are crucial for annulation, remains the major drawback that limits the applications of these approaches. Thus, it is important to continue developing better synthetic methods.

Recently, photocatalyzed organic reactions have drawn greatly increased attention due to their sustainability and cost efficiency compared with reactions that use transition metal catalysts.[2] The photocatalyzed formation of C−C or C−heteroatom bonds in the presence of transition metals has been well developed and reviewed.[2,3] Although a few examples of light-promoted intramolecular annulation that proceeds smoothly requiring oxidant O_2 or I_2 have been reported,[4] the application of photoinduced oxidative annulation in chromone (benzopyran-4-one) substrates remains unaddressed.

Benzopyran-4-one based natural products, such as chromones, chromanones, flavones, isoflavones, and 2-styrylchromones, exhibit a wide range of biological activities.[5] Many chemical modification approaches for the synthesis of novel derivatives have been developed to satisfy growing biological and medicinal requirements.[5b,6] Benzo[*c*]furo[2,3-*a*]xanthen analogs, which are polycyclic derivatives of benzopyran-4-one, have not previously been explored. Current methods for the synthesis of benzo[*c*]furo[2,3-*a*]xanthen derivatives require the presence of transition metals and a high reaction temperature; these requirements limit the application of these approaches (Scheme 1a).[7]

Scheme 1. Intermolecular and Intramolecular Annulation



Given our interest in the development of direct C−H functionalization[8] and photoinduced annulation[9] as well as the existence of limited literature reports on dehydrogenative annulation, which was thought to require transition metals[10] and/or oxidative additives,[11,12] in this letter, we report an efficient transition-metal-free photoinduced intramolecular dehydrogenative annulation of 4*H*-chromen-4-ones for the synthesis of benzo[*c*]furo[2,3-*a*]xanthenone derivatives that does not require catalysts or additives (Scheme 1b).

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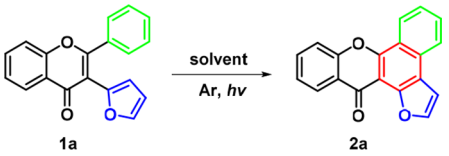
The substrate 3-(furan-2-yl)-2-phenyl-4*H*-chromen-4-one (**1a**) was synthesized using an approach described in a literature report.[13] The photoinduced intramolecular dehydrogenative annulation of compound **1a** was carried out by exciting the cinnamoyl group ($\pi-\pi^*$ band) at $h\nu$ = 365 nm [absorption spectrum of **1a** is shown in Figure 4 in the Supporting Information (SI)] at ambient temperature under a dry argon atmosphere. Various parameters, such as solvent, concentration, and irradiation time, were screened. Experimental data are presented in Table 1. The irradiation of **1a** in CH_2Cl_2 (100 mL) with a high-pressure mercury lamp (500 W) at ambient temperature under an argon atmosphere for 3 h afforded **2a** with a yield of 28% (Table 1, entry 1). Yields of **2a** decreased dramatically in acetone and acetonitrile (7−16%, entries 2−3), whereas a similar yield of **2a** was obtained in ethanol (36%, entry 4). Interestingly, the yield of **2a** was significantly affected by the presence of H_2O (entries 5−7). The optimal yield was obtained when EtOH−H_2O (7:1, v/v) was utilized as the reaction solvent (60%, entry 6). Notably, lower or higher reaction concentrations decreased cyclization yields (entries 6, 8−9).

Table 1. Optimization of the Intramolecular Cyclization[a]



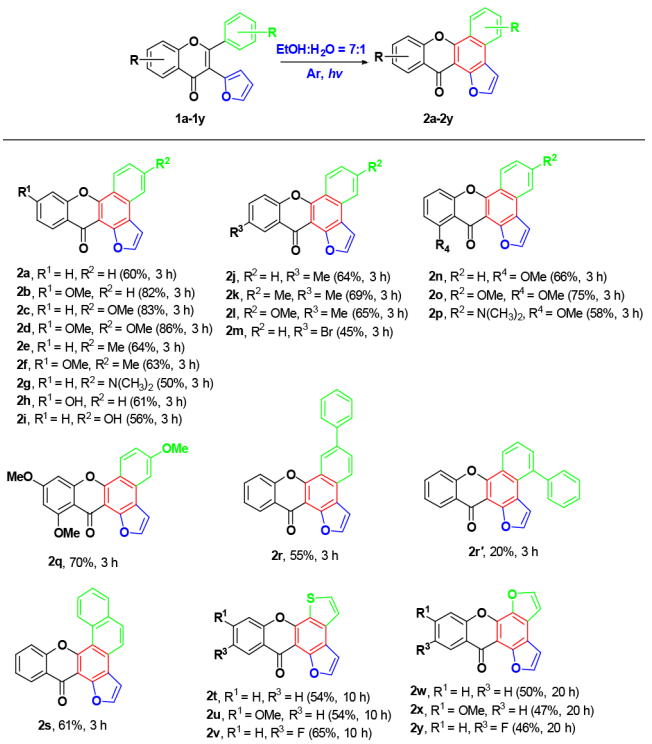
entry	concn (mM)	solvent (v/v)	time (h)	conv (%)[b]	yield (%)[b]
1	5	CH_2Cl_2	3	41	28
2	5	Me_2CO	3	31	7
3	5	MeCN	3	52	16
4	5	EtOH	3	73	36
5	5	EtOH−H_2O (9:1)	3	76	43
6	**5**	**EtOH−H_2O** (7:1)	**3**	**88**	**60**
7	5	EtOH−H_2O (4:1)	3	81	40
8	1	EtOH−H_2O (7:1)	3	100	38
9	10	EtOH−H_2O (7:1)	3	57	43
10	5	EtOH−H_2O (7:1)	1	37	30
11	5	EtOH−H_2O (7:1)	2	66	52
12	5	EtOH−H_2O (7:1)	4	92	48
13	5	EtOH−H_2O (7:1)	6	98	50
14	5	EtOH−H_2O (7:1)	3	83	36[c]

[a]On the 0.5 mmol scale, **1a** in various solvents (100 mL, 5 mM) was irradiated with a 500 W high-pressure mercury lamp at ambient temperature. [b]Isolated yield. [c]On the 0.5 mmol scale, **1a** in EtOH−H_2O (7:1, v/v, 100 mL, 5 mM) was irradiated with a 500 W high-pressure mercury lamp in the open air at ambient temperature.

Finally, the irradiation time was also optimized; in particular, 3 h of irradiation clearly resulted in the best photoinduced cyclization (entries 6, 10−13). It is important to note that lower yields were observed due to the decomposition of **2a** upon prolonged irradiation (entries 12 and 13). Furthermore, when the cyclization was performed in the presence oxygen (open air), **2a** was obtained in 36% yield (entry 14). Thus, the irradiation of 5 mM **1a** in EtOH−H_2O (7:1, v/v) at ambient temperature for 3 h was determined to be the optimal approach. The quantum yield of photochemical conversion of 3-(furan-2-yl)-2-phenyl-4*H*-chromen-4-one into 13*H*-benzo[*c*]furo[2,3-*a*]xanthen-13-one is approximately 0.121 in EtOH−H_2O (7:1, v/v) (SI).

With optimized conditions determined for the intramolecular annulation, we proceeded to explore the generality and functional group tolerance of this annulation with various substrates (Scheme 2). In general, substrates with electron-donating groups (e.g., Me, OMe, and OH) at the R^1, R^2, R^3, or R^4 position produced better yields than the substrate bearing an electron-withdrawing group (Br). Notably, the presence of a free hydroxyl group and amine could also be tolerated, although slightly reduced yields were obtained (50%−61%). With respect to regioselectivity, substrate **1r** yielded **2r** and **2r′** as a mixture of regioisomers with partial selectivity that could readily be explained by steric hindrance. Thus, **2r** was obtained as a major regioisomer (55%). Interestingly, only one regioisomer was isolated in 61% yield for the 2-naphthalene substrate **1s**. Both 2-(fur-2-yl)- and 2-(thiophen-2-yl)-substituted chromone derivatives afforded the corresponding annulation products in moderate yields (46%−65%). However, much longer irradiation times were required (10−20 h), likely due to the lower activity of the C3−H of the heteroaromatics relative to the original substrate.

Scheme 2. Examination of Substrate Scope[a]



[a]All reactions were performed on a 0.5 mmol scale of **1** at ambient temperature in EtOH/H_2O (100 mL, 7:1, v/v) with the isolated yields listed.

The structure of **2** was established via (a) ^{1}H NMR, ^{13}C NMR, HRMS, UV, and IR and (b) the X-ray structure of **2a**. The absorption and fluorescence spectra of **2a** are shown Figures 2 and 3 in the SI. Due to the formation of a conjugated system, the $\pi-\pi^*$ band absorption for **2a** is red-shifted, which decreased the probability of photoexcitation upon irradiation at 365 nm.

The molecular structure of **2a** is presented in Figure 1.[14] The 13*H*-benzo[*c*]furo[2,3-*a*]xanthen-13-ones moiety includes

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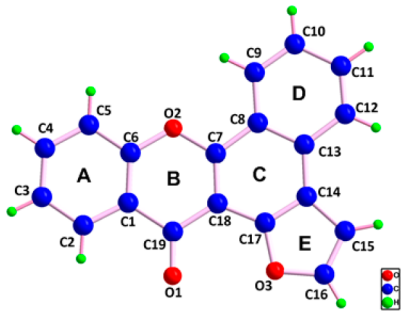
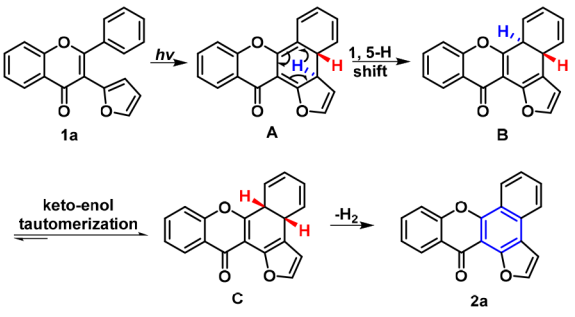


Figure 1. X-ray crystal structure of **2a**.

three benzene rings [**A** (C1−C6), **C** (C7, C8, C13, C14, C17, C18), and **D** (C8−C13)], one pyran ring **B** (C1, C6, O2, C7, C18, C19), and one furan ring **E** (C14−C17, O3). The average distance of atoms C1 to C19, O2, and O3 from the least-squares plane (C1−C19, O2, O3) was 0.0302 Å. This finding indicated that **2a** was essentially coplanar. In the crystal structure of **2a**, a dimer was formed via the nonconventional C−H···O intermolecular hydrogen bonds O1···H16#2−C16#2 [symmetry code #2 (1 − *x*, 2 − *y*, −*z*)] (Figure 1, SI). In addition, aromatic $\pi\cdots\pi$ stacking interactions exist in **2a**, linking xanthenone skeletons into a column along the *a* axis. Aromatic $\pi\cdots\pi$ stacking between the A and C, B and B, and C and A rings of two adjacent antiparallel xanthenone skeletons is observed. CgA−CgC#1 = 3.701 Å, CgB−CgB#1 = 3.665 Å, and CgC−CgA#1 = 3.701 Å, where CgA, CgB, and CgC are the centers of rings A, B, and C of the xanthenone skeleton at (*x*, *y*, *z*), respectively, and CgA#1, CgB#1, and CgC#1 are the centers of rings A, B, and C of the neighboring xanthenone skeleton at (−*x*, 1 − *y*, −*z*), respectively (Figure 1, SI).

Based on our experimental data and a literature report,[15] a plausible mechanism for the formation of **2a** was proposed; this mechanism is presented in Scheme 3. The proposed initial step

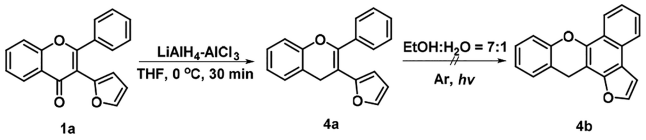
Scheme 3. Proposed Mechanism for the Formation of 2a



in the annulation is the irradiation of 3-(furan-2-yl)-2-phenyl-4*H*-chromen-4-one (**1a**) to produce intermediate **A**, followed by a thermal suprafacial [1,5]-H shift[16] to form intermediate **B**. The rearomatization of the furan ring is the force driving this [1,5]-sigmatropic shift. Subsequently, keto−enol isomerization of **B** leads to the formation of the more stable *syn*-isomer **C**. Similar transformations have previously been described for a number of structurally related compounds.[17] Polar protic solvent is beneficial to the process of keto−enol isomerization, which accounts for the higher yield of **2a** in EtOH−H_2O (7:1) compared to CH_2Cl_2, Me_2CO, and MeCN. Finally, the annulation product **2a** was generated by the *syn*-elimination of a hydrogen molecule (H_2) from intermediate **C** due to the restoration of aromaticity for the benzene ring and the entire conjugated system, which share a similar concept with a literature report for the restoration of aromaticity by elimination of the methane molecule.[15] Since the cyclization product **2a** was successfully obtained with the presence of oxygen (open air), we believe the photochemical cyclization proceeded through the S1 state.

Experiments were conducted to further establish the rationality of the proposed mechanism. In particular, the reduction of **1a** by $LiAlH_4$·$AlCl_3$ in THF at 0 °C for 30 min afforded **4a** with a yield of 54% (Scheme 4).[18] As expected, the

Scheme 4. Attempted Annulation of 4a under the Optimal Reaction Conditions



subjection of **4a** to the optimal reaction conditions (*hv*, rt, 7:1 EtOH/H_2O (v/v)) led to the recovery of the starting substrate due to the lack of keto−enol tautomerization. Thus, no dehydrogenative annulation product **4b** was detected.

In conclusion, we have developed a transition-metal-free photoinduced intramolecular dehydrogenative annulation of 2,3-di(hetero)arylchromen-4-one in EtOH−H_2O (7:1, v/v) at ambient temperature for the synthesis of 13*H*-benzo[*c*]furo-[2,3-*a*]xanthen-13-one derivatives. This atom-efficient protocol eliminates the use of a transition metal catalyst and proceeds smoothly without additives. In general, substrates bearing electron-donating groups, either in the chromone or at the C2 position of the aryl group, afforded annulation products in good yields. The failure of the annulation of **4a** further proves the rationality of the proposed mechanism and the importance of keto−enol tautomerization in the described mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01531.

Experimental procedures and detailed characterization data of all new compounds (PDF)

Crystallographic data for the compound **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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