DOI: 10.1002/adsc.201601057

Advanced Synthesis & Catalysis

Efficient Synthesis of Anthraquinones from Diaryl Carboxylic Acids via Palladium(II)-Catalyzed and Visible Light-Mediated Transformations

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Received: September 23, 2016; Published online: ■■ ■■, 0000

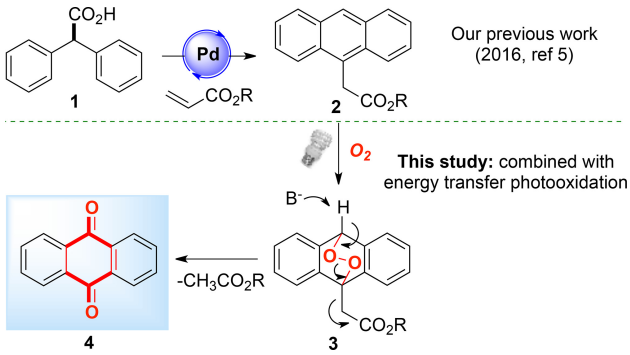
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201601057

Abstract: Irradiation of 9-ester-substituted anthracenes with visible light results in the formation of endoperoxides in the absence of a photocatalyst, which further undergo base-assisted fragmentation to afford anthraquinones. The excited state species of anthracene generated by energy transfer, interacts with $^3O_2$ to afford $^1O_2$ by energy transfer and undergoes cycloaddition with $^1O_2$. By employing palladium(II)-catalyzed and visible light-mediated transformations, we have developed an efficient synthetic protocol for accessing diverse anthraquinones from readily available diaryl carboxylic acids. The optimal result was obtained with palladium(II) acetate, Ac-Ile-OH, benzoquinone and potassium carbonate in tert-amyl alcohol under O_2 at 90 °C with irradiation from a 30 W fluorescent light bulb.

Keywords: Palladium; visible light; anthraquinone; singlet oxygen; photooxidation

The anthraquinone moiety is an important constituent of numerous naturally occurring and synthetic compounds.[1] Moreover, anthraquinones have been extensively investigated as a result of their broad range of biological activities.[2] Consequently, synthetic approaches to anthraquinone skeletons through efficient bond formation is a topic of intensive research, in which a number of synthetic approaches to synthesize this family of compounds have been developed using various catalytic systems.[3,4] Despite the important contributions thus far, most methods suffer from drawbacks such as multiple steps, harsh reaction conditions or regioselectivity issues. In this context, a more straightforward approach for synthesizing structurally diverse anthraquinones, without requiring the pre-functionalization of the starting materials appears to be very attractive.

We envisioned that the 9-ester-substituted anthracenes **2** generated in situ, as a result of the tandem reactions,[5] could be further utilized for spontaneously generating transannular endoperoxides **3** via a visible light-induced photooxidation process.[6] Subsequently, the generated endoperoxide intermediates **3** might further undergo a base-assisted fragmentation pathway to form anthraquinones **4** with removal of the ethyl acetate leaving group.[7,8] The combinations of Pd(II)-catalyzed tandem reactions and visible light-induced photooxidation to synthesize diverse anthraquinones in one synthetic operation can be highly desirable by reducing synthesis time, costs and undesired waste. In this context, we were intrigued in exploring a more challenging one-pot, multi-step synthetic protocol that would enable the facile synthesis of an anthraquinone scaffold starting from diaryl carboxylic acids employing Pd(II)-catalyzed and visible light-induced transformations (Scheme 1).



Scheme 1. Synthetic approach to the anthraquinone scaffold via Pd(II)-catalyzed and visible light-induced transformations.

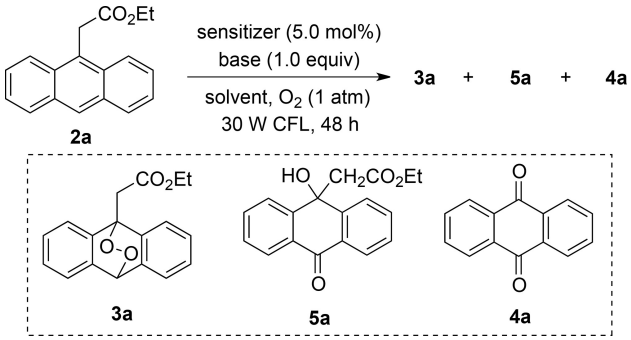
To test the feasibility of this approach, we initially explored converting ethyl 2-(anthracen-9-yl)acetate **2a** into anthraquinone **4a** with the visible light-induced photooxidation process.[7–9] The photooxidation mechanism of acenes was proposed to go through a photoinduced electron transfer redox process and radical coupling with superoxide.[9c–e] An alternative reaction pathway involves formation of singlet oxygen ($^1O_2$) by the sensitizer,[10,11] which reacts with acenes to afford endoperoxides. The photooxidation of anthracene initiated by energy transfer rather than an electron transfer mechanism represents a more attractive option, without inducing undesired radical associated reactions of photochemically sensitive functional groups in the overall reaction process. In an energy transfer pathway, singlet oxygen sensitization typically requires a triplet sensitizer rather than a photoredox catalyst.[11]

Upon irradiation of ethyl 2-(anthracen-9-yl)acetate **2a** with a household fluorescent light bulb in the presence of a sensitizer, such as methylene blue or tetraphenylporphyrin, which are known to generate $^1O_2$ by energy transfer, endoperoxide intermediate **3a** was obtained (entries 1 and 2). It was found out that the use of base promoted the formation of anthraquinone **4a** at the elevated temperature (entry 3). Further screening studies revealed that the optimal result could be obtained at 90 °C, and the sensitizer is not actually required in this process. These observations suggest that the energy barrier between $^3O_2$ and $^1O_2$ (22.5 kcal/mol) is presumably fulfilled with the anthracene chromophore,[11b,12] which generates $^1O_2$ via triplet sensitization and undergoes cycloaddition with anthracene. Indeed, the addition of methylene blue or tetraphenylporphyrin was less effective in the formation of anthraquinone presumably as a result of competitive decomposition. Among the bases screened, KOAc (1.0 equiv.) was most effective in this process, and anthraquinone was obtained with the 71% isolated yield (entry 8). No reaction occurred in the absence of either light or oxygen (see the Supporting Information).

After successfully achieving the visible light-mediated transformation of 9-ester-substituted anthracene **2a** into anthraquinone **4a**, we next explored the prospects of the proposed one-pot sequence of mechanistically different events using diphenyl carboxylic acid (**1a**), which can be easily obtained from the arylation of ethyl acetate,[13] with ethyl acrylate as model substrates (Table 2). Although KOAc was most effective in the photooxidation process (Table 1), K_2CO_3 proved to be the most efficient base for the overall reactions, especially at the stage of formation of anthracene.[5] After much experimentation employing a Pd-catalytic system under visible light, we were pleased to find that the desired anthraquinone **4a** was formed in 23% yield (entry 2), proving that the tandem process was indeed operating. A control experiment in the absence of a light source was carried out, and the anthraquinone product was not obtained (entry 1). Interestingly, changing the light source, 30 W CFL to 23 or 45 W CFL, diminished the reaction efficiency (entries 2, 6 and 8). Again, no beneficial effects were observed in the presence of a sensitizer, including methylene blue, tetraphenylporphyrin, and $Ru(bpy)_3(PF_6)_2$ (entries 3, 4, and 5). Further screening studies revealed that the optimal result could be obtained with $Pd(OAc)_2$ (10 mol%), Ac-Ile-OH (10 mol%), benzoquinone (10 mol%) and K_2CO_3 (1 equiv.) in ^{t}AmylOH under O_2 (balloon) and light from a 30 W fluorescent light bulb to generate anthraquinone **4a** in a 52% yield (entry 6). A slightly higher product yield was obtained when the solutions were extracted after 24 h and carried forward to the subsequent transformation (entry 9).

After determining the optimal procedure, we set up a series of experiments to investigate the scope of substrates, as summarized in Table 3. We were pleased to observe that diaryl carboxylic acids possessing methyl, *t*-butyl, methoxy, fluoro, chloro, trimethylsilyl

Table 1. Studies for photooxidation of 9-ester-substituted anthracene[a)]



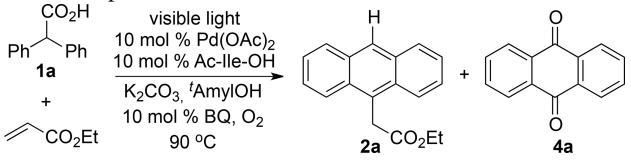
entry	base	sensitizer	solvent	Tem. (°C)	yield (%)[b)] 3a	5a	4a
1	–	MB	1,2-DCE	rt	67	4	7
2	–	MB	^{t}AmylOH	rt	61	2	2
3	K_2CO_3	MB	^{t}AmylOH	70	0	0	41
4	K_2CO_3	MB	^{t}AmylOH	90	0	0	57
5	K_2CO_3	TPP	^{t}AmylOH	90	0	0	58
6	K_2CO_3	$Ru(bpy)_3(PF_6)_2$	^{t}AmylOH	90	0	0	56
7	K_2CO_3	–	^{t}AmylOH	90	0	0	68
8	KOAc	–	^{t}AmylOH	90	0	3	71
9[c)]	K_2CO_3	–	^{t}AmylOH	90	0	0	53
10	Cs_2CO_3	–	^{t}AmylOH	90	0	0	62

[a)] **2a** (0.20 mmol, 1.0 equiv.), base (1.0 equiv.), sensitizer (5.0 mol%) in solvent (0.17 M) at 90 °C under O_2 (1 atm) for 48 h with irradiation from a 30 W compact fluorescent light bulb.

[b)] ^{1}H NMR yield using an internal standard.

[c)] K_2CO_3 (2.0 equiv.), was used. MB = Methylene blue, TPP = tetraphenylporphyrin.

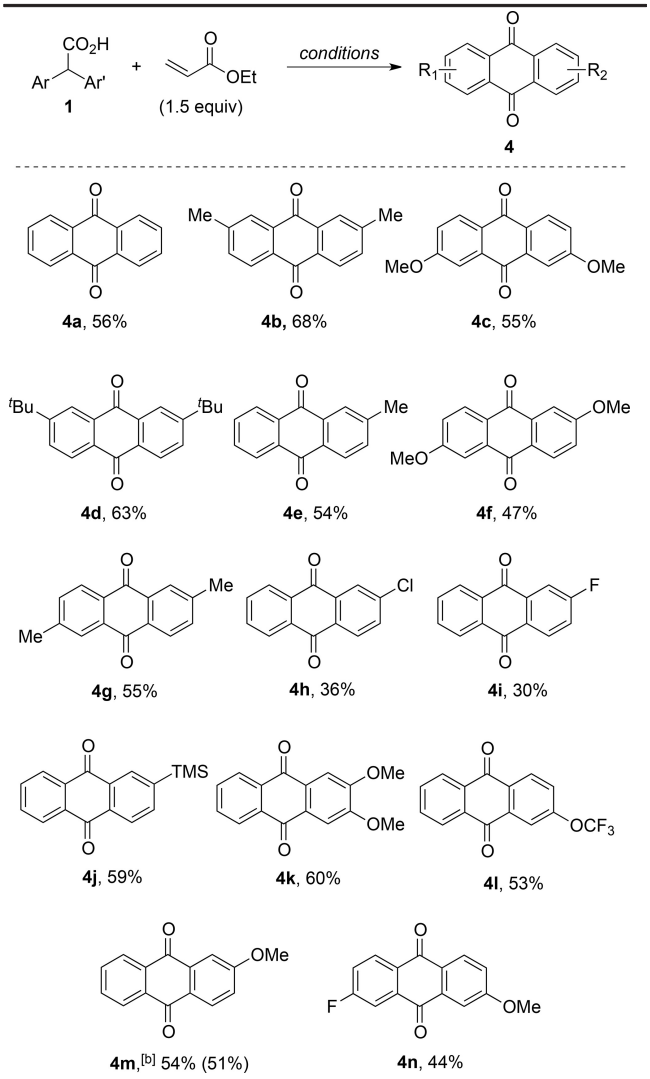
Table 2. Optimization of the reaction conditions[a)]



entry	sensitizer	light source	time	yield (%)[b)] 2a	4a
1	–	–	24 h	77	0
2	–	23 W CFL	48 h	47	23
3	MB	30 W CFL	48 h	5	4
4	TPP	30 W CFL	48 h	21	44
5	$Ru(bpy)_3(PF_6)_2$	30 W CFL	48 h	39	27
6	**–**	**30 W CFL**	**48 h**	**22**	**52**
7	–	30 W CFL	72 h	21	45
8	–	45 W CFL	48 h	35	36
9[c)]	**–**	**30 W CFL**	**48 h**	**5**	**57**

[a)] Condition A: **1a** (0.20 mmol, 1.0 equiv.), ethyl acrylate (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), Ac-Ile-OH (10 mol%), benzoquinone (10 mol%), K_2CO_3 (1.0 equiv.), sensitizer (5.0 mol%) in ^{t}AmylOH (0.17 M) at 90 °C under O_2 for 48 h with irradiation using a compact fluorescent light bulb.
[b)] ^{1}H NMR yield using an internal standard.
[c)] Conditions B: The above reaction mixture was stirred for 24 h at 90 °C. After workup, reaction mixture was subjected to K_2CO_3 (1.0 equiv.) in ^{t}AmylOH (1.2 ml) at 90 °C under O_2 (1 atm) with irradiation using a 30 W CFL bulb (24 h).

Table 3. Substrate scope studies[a)] .

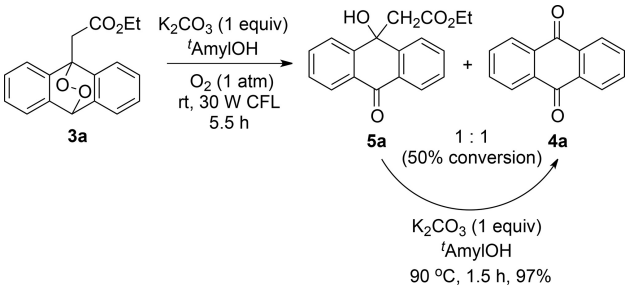


Condition A or B, Condition A: **1a** (0.20 mmol, 1.0 equiv.), ethyl acrylate (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), Ac-Ile-OH (10 mol%), benzoquinone (10 mol%), K_2CO_3 (1.0 equiv.) in ^{t}AmylOH (0.17 M) at 90 °C under O_2 for 48–60 h with irradiation using a 30 W CFL bulb. Conditions B: The above reaction mixture was stirred for 24 h at 90 °C. After workup, reaction mixture was subjected to K_2CO_3 (1.0 equiv.) in ^{t}AmylOH (1.2 ml) at 90 °C under O_2 (1 atm) with irradiation using a 30 W CFL bulb (24-30 h).
[b)] 54% from 4-methoxydiphenyl acetic acid and 51% from 3-methoxydiphenylacetic acid. Yields of isolated products.

or trifluoromethoxy groups reacted with ethyl acrylate to afford the desired anthraquinones under the reaction conditions. Notably, the chloro and trimethylsilyl functional groups were compatible under these reaction conditions to provide the desired products (**4h, 4j**), thus enabling further manipulation at this position. In a similar fashion, starting materials bearing both a symmetrical- and unsymmetrical substitution pattern were suitable substrates to obtain the corresponding products. The utility of the present method was further broadened by reactions with disubstituted substrates to obtain the dimethoxy-substituted product **4k.** When the conversion of anthracenes into anthraquinones was not completed, the reaction solutions were extracted and carried forward to next with the addition of K_2CO_3 in ^{t}AmylOH (condition B). Due to C_2 symmetrical property of anthraquinone, starting materials bearing 3- or 4-substituents were converted into the same anthraquinone products. For example, 2-methoxyanthraquinone (**4m**) was prepared from both starting materials possessing *meta*- or *para*-substituents in comparable yields (54% and 51%, respectively).

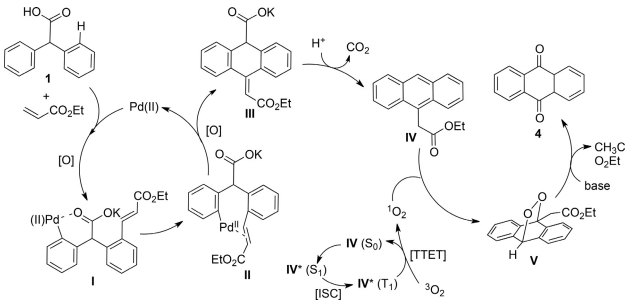
For more mechanistic insight, we studied each step of the anthracene photooxidation process. Irradiation of anthracene **2a** with a 30 W CFL in the absence of a base resulted in the formation of endoperoxide **3a**. Next, usage of K_2CO_3 led to the formation of intermediate **5a**.[8] At the elevated temperature (90 °C), the anthraquinone product **4a** was spontaneously generated by removal of ethyl acetate acting as a leaving group (Scheme 2).

Based on the observations, a plausible mechanism for the Pd(II)-catalyzed and visible light mediated process is shown in Scheme 3. The catalytic process



Scheme 2. Preliminary mechanistic studies.

can be initiated by Pd-catalyzed carboxyl-directed C–H activation of diphenyl carboxylic acid **1.** The resulting anthracene **IV** is then engaged in the second catalytic cycle, and its excited state species **IV*** is generated by energy transfer via visible light irradiation. The excited state species **IV*** interacts with $^3O_2$ to afford $^1O_2$ by energy transfer, and the anthracene substrate undergoes cycloaddition with $^1O_2$ to produce endoperoxide **V.** In the process, generation of $^1O_2$ via energy transfer from the incipient anthraquinone appears to be less feasible.[14] Finally, the base-assisted fragmentation of endoperoxide **V** yields anthraquinone **4.**



Scheme 3. Proposed mechanism for the synthesis of anthraquinone.

In summary, we developed an efficient protocol for the direct construction of anthraquinones from diaryl carboxylic acids via Pd-catalyzed and visible light-mediated transformations. The 9-ester-substituted anthracenes generated in situ during the reaction process, further underwent the visible light-mediated photooxidation without using a photocatalyst. This straightforward protocol offers a convenient and powerful synthetic tool for accessing anthraquinone derivatives that have high synthetic utility.

Experimental Section

General procedure

Procedure A: The mixture of diphenylacetic acid (**1**, 0.20 mmol, 1.0 equiv.), $Pd(OAc)_2$ (10 mol%), Ac-Ile-OH (10 mol%), K_2CO_3 (1.0 equiv.) was added in reaction tube. After the addition of ^{t}AmylOH, ethyl acrylate (1.5 equiv.), the reaction mixture was stirred at 90 °C under oxygen atmosphere with irradiation using 30 W CFL bulb. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was cooled down to room temperature and diluted with saturated aqueous NH_4Cl solution. The residue was extracted with CH_2Cl_2, and dried over Na_2SO_4. The crude mixture was concentrated under reduced pressure and purified by flash chromatography (CH_2Cl_2/hexanes) to obtain the desired product **4.**

Procedure B: The above reaction mixture was stirred for 24 h at 90 °C and the crude mixture was diluted with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The residue was concentrated under vacuum, which was subjected to K_2CO_3 (1 equiv.) in ^{t}AmylOH and stirred at 90 °C under oxygen atmosphere with irradiation using 30 W CFL bulb (24–30 h). After the reaction was completed, the crude mixture was purified by the procedure A.

Acknowledgements

This research was supported financially by Institute for Basic Science (*IBS–R010-G1*).

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UPDATES

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Adv. Synth. Catal. **2016**, *358*, 1–6

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