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COMMUNICATION

Visible-Light-Induced Cascade Reaction of Etherification/C-C Cyclization: Efficient Synthesis of Dibenzo[b,d]oxepin-7(6*H*)-ones

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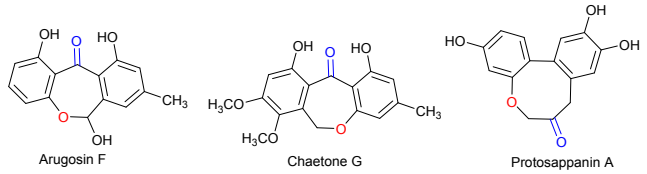
A visible-light-induced palladium-catalyzed cascade reaction was developed by etherification/C-C coupling cyclization of α-bromoacetophenones with phenols. A series of dibenzo[b,d]oxepin-7(6*H*)-one derivatives were efficiently synthesized by using this method in good yields. Furthermore, this method was applied to the synthesis of Protosappanin A. The protocol has such advantages as simple reaction conditions, wide range of substrates and high reaction efficiency.

The benzoheterocyclic fragments are widely found in important core skeletons of many natural products,[1] which are often used as lead compounds in drug designing and synthesis because of a variety of biological activities.[2] Dibenzoxepinone and dibenzoxocinone fragment structural motifs are widely used in drug active molecules, such as Arugosin F (for antifungal),[3] Chaetone G (for antitumor)[4] and Protosappanin A (a natural product for anti-HIV-1)[5] (**Scheme 1**), in which dibenzo[b,d]oxepinone motifs are important intermediates for the synthesis of Protosappanin A.[6] In view of the its wide application, synthesis of dibenzo[b,d]oxepinones is of great significance.



Scheme 1 Representative dibenzoxheterclic ketone structure.

Over the past years, various methods were reported about constructing dibenzo[b,d]oxepin-7(6*H*)-one skeleton. In 2015, our group[7] reported that the Friedel-Crafts acylation of 2-arylphenoxyacetic acids occurred under different conditions to afford selectively compounds dibenzo[b,d]oxepinones and arylcoumaranones in high regioselectivities(**Scheme 2a**). However, these methods still have many disadvantages, such as excessive synthetic steps, lower productivity and atom utilization. In order to solve the above issues, our group has improved preparation method of dibenzo[b,d]oxepin-7(6*H*)-ones by palladium-catalyzed ortho C-H activation/C-C cyclization under microwave irradiation[8] (**Scheme 2b**). However, in order to further improve the reaction efficiency, it is very challenging to develop a new synthetic method of dibenzo[b,d]oxepin-7(6*H*)-one skeleton.

In recent years, transition metal-catalyzed C-H functionalization has received widespread attention due to its high atomic economy.[9] In addition, the rapid development of C-C cyclization reaction has become an increasingly important method for C-C bond formation,[10] which could synthesize various polycyclic compounds and natural products.[11] Cheng[12] reported a palladium-catalyzed intramolecular oxidative cyclization of diaryl ketones for the synthesis of fluorenones. Lan and You[13] reported a palladium-catalyzed intramolecular oxidative coupling of (hetero)aryl carboxylic esters. At the same time, DDQ (2, 3-dichloro-5,6-dicyano-p-benzoquinone) is an inexpensive and readily available oxidizing reagent. Deng[14] and Liu[15] groups reported some DDQ-mediated oxidative coupling reaction, DDQ could promote the production of methylene radicals in this type of reaction. And some studies demonstrated that visible-light photoactivation is a powerful tool for organic synthetic reactions, especially those reactions that are generally difficult by common approaches.[16] Therefore, we attempted to use DDQ as an oxidant and introduced light to promote the synthesis of dibenzo[b,d]oxepin-7(6*H*)-ones in the reaction.

On the other hand, the cascade reaction is a powerful and ideal strategy for efficient and rapid synthesis of complex molecular structures,[17] because it can sequentially form two or more chemical bonds in a single step reaction without protection/deprotection and separation of intermediates.

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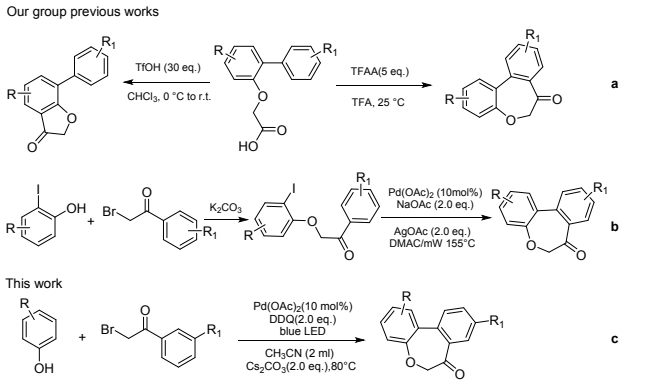
Moreover, this process can improve the reaction efficiency, raise atom utilization, and reduce environmental pollution. Herein, we designed a novel method for the synthesis of dibenzo[b,d]oxepin-7(6*H*)-ones via visible-light-induced Pd(II)-catalyzed cascade reaction of etherification/C-C coupling cyclization of α-bromoacetophenones with phenols (**Scheme 2c**).



Scheme 2 The methods of synthesizing dibenzo[b,d]oxepin-7(6*H*)-ones.

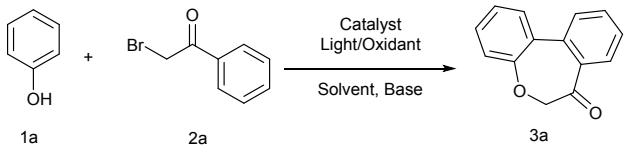
Firstly, the method for synthesis of dibenzo[b,d]oxepin-7(6*H*)-ones via the cascade reaction of etherification/C-C coupling cyclization was investigated. Phenol (**1a**) and α-bromoacetophenone (**2a**) were chosen as model substrates to examine reaction conditions such as catalysts, oxidants, solvents, temperature and base under the 25W blue LED. The experimental results were shown in **Table 1**.

The catalysts such as Pd(0), Pd(II), Ru(0), Ru(III) and Rh(II) were firstly screened as a kind of critical factor in the reaction in acetonitrile (CH_3CN) at 80 °C. $Pd(PPh_3)_4$, $Pd(PPh)_3Cl_2$ and $Pd(OAc)_2$ were used as catalysts to give the yields of 22%, 26% and 35%, respectively (**Table 1**, entries 1-3). $[Cp^*RhCl_2]_2$ and $Ru(PPh_3)_3$ as the catalysts exhibited low catalytic activity to give the yields of 10% and 6%, respectively (**Table 1**, entries 4-5). Using $RuCl_3$ as a catalyst or $Pd(OAc)_2$ (no light) as a catalyst, the reaction did not occur (**Table 1**, entries 6-7).

The effect of different oxidants such as $Cu(OAc)_2$, $Cu(OTf)_2$, AgOAc, $K_2S_2O_8$ and DDQ were screened. $Cu(OAc)_2$ and $Cu(OTf)_2$ gave the yields of 21% and 23%, respectively (**Table 1**, entries 8-9). AgOAc and $K_2S_2O_8$ gave the yields of 18% and 16%, respectively (**Table 1**, entries 10-11). With DDQ as the oxidant, the yield could reach 52% (**Table 1**, entry 12), but the reaction only gave isolated yields of 35% and 50% at 70 °C and 90 °C, respectively (**Table 1**, entries 12d and 12e). After the introduction of light, the yield was significantly increased to 86% (**Table 1**, entry 13). This indicated that the reaction may be a free radical reaction, and DDQ could more easily undergo single electron transfer to generate radicals under visible light irradiation. The reaction gave isolated yields of 70% and 86% (**Table 1**, entries 13d and 13e) at 70 °C and 90 °C. When the amount of $Pd(OAc)_2$ was reduced to 5 mol%, the reaction only gave a yield of 65% (**Table 1**, entry 13f).

Different solvents such as 1,4-dioxane, dimethylsulfoxide (DMSO), *N*, *N*-dimethylformamide (DMF) and toluene (PhMe) were also investigated. These solvents gave lower yields of 62%, 38%, 35% and 41%, respectively (**Table 1**, entries 14-17).

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

Entry	Catalyst	light[b]/oxidant	Solvent	Base	%[c]
1	$Pd(PPh_3)_4$	Y/-	CH_3CN	Cs_2CO_3	22
2	$Pd(PPh)_3Cl_2$	Y/-	CH_3CN	Cs_2CO_3	26
3	$Pd(OAc)_2$	Y/-	CH_3CN	Cs_2CO_3	35
4	$[Cp^*RhCl_2]_2$	Y/-	CH_3CN	Cs_2CO_3	10
5	$Ru(PPh_3)_3$	Y/-	CH_3CN	Cs_2CO_3	6
6	$RuCl_3$	Y/-	CH_3CN	Cs_2CO_3	-
7	$Pd(OAc)_2$	N/-	CH_3CN	Cs_2CO_3	-
8	$Pd(OAc)_2$	N/$Cu(OAc)_2$	CH_3CN	Cs_2CO_3	21
9	$Pd(OAc)_2$	N/$Cu(OTf)_2$	CH_3CN	Cs_2CO_3	23
10	$Pd(OAc)_2$	N/AgOAc	CH_3CN	Cs_2CO_3	18
11	$Pd(OAc)_2$	N/$K_2S_2O_8$	CH_3CN	Cs_2CO_3	16
12	$Pd(OAc)_2$	N/DDQ	CH_3CN	Cs_2CO_3	35[d] , 52, 50[e]
13	$Pd(OAc)_2$	Y/DDQ	CH_3CN	Cs_2CO_3	70[d], 86, 86[e], 65[f]
14	$Pd(OAc)_2$	Y/DDQ	dioxane	Cs_2CO_3	62
15	$Pd(OAc)_2$	Y/DDQ	DMSO	Cs_2CO_3	38
16	$Pd(OAc)_2$	Y/DDQ	DMF	Cs_2CO_3	35
17	$Pd(OAc)_2$	Y/DDQ	PhMe	Cs_2CO_3	41
18	$Pd(OAc)_2$	Y/DDQ	CH_3CN	Et_3N	33
19	$Pd(OAc)_2$	Y/DDQ	CH_3CN	Pyridine	26
20	$Pd(OAc)_2$	Y/DDQ	CH_3CN	K_2CO_3	60
21	$Pd(OAc)_2$	Y/DDQ	CH_3CN	Na_2CO_3	46

[a] Reaction conditions: **1a** (0.45 mmol), **2a** (0.47 mmol), catalyst (10 mol%), oxidant (2.0 eq.), base (2.0 eq.) and solvent 2 ml at 80 °C, the reaction completed (monitored by TLC). [b] Y = with the 25W blue LED, N = in the dark. [c] Isolated yields after silica gel column chromatography. [d] Yield at 70°C. [e] Yield at 90°C. [f] Yield of 5 mol% $Pd(OAc)_2$.

Simultaneously, the base also plays a vital role in the reaction. When organic bases were selected including Et_3N and pyridine (**Table 1**, entries 18-19), the reaction progressed in poor yields. This may result from oxidation from DDQ. Conversely, inorganic bases were found to be more helpful in the reaction. In particular, the use of Cs_2CO_3 improved the reaction process to give a good yield of 86% (**Table 1**, entries 13, and 20-21).

Based on the above research, optimized conditions of the cascade reaction were 10 mol% $Pd(OAc)_2$ as the catalyst, 2.0 equiv of DDQ as oxidant and 2.0 equiv of Cs_2CO_3 as base, CH_3CN as solvent, and irradiation with 25W blue LED at 80 °C.

The scope of substrates was further investigated by the above optimized synthetic process. A series of dibenzo[b,d]oxepin-7(6*H*)-one derivatives were successfully synthesized by this method and were shown in **Table 2**. Under

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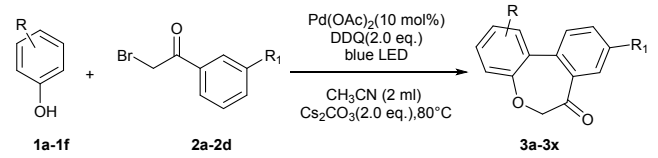
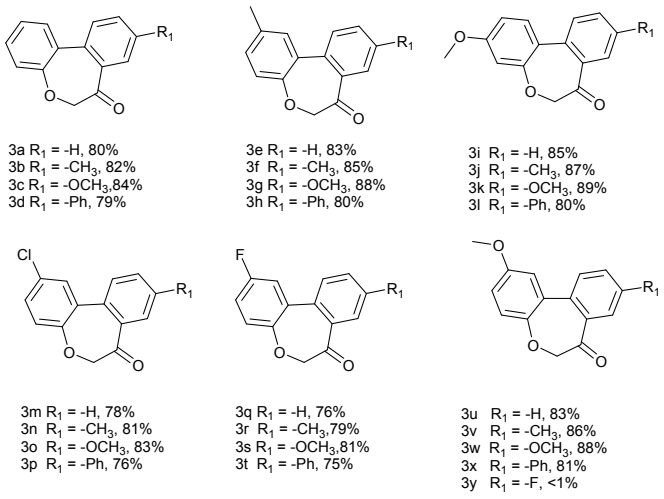
the optimized reaction conditions, phenols and α-bromoacetophenones with different electron-donating and electron-withdrawing groups were catalyzed to undergo the cascade reaction of etherification/C-C coupling cyclization smoothly to afford the corresponding dibenzo[b,d]oxepin-7(6*H*)-one derivatives **3** in good yields.

Table 2 Substrates scope of the cascade reaction [a].



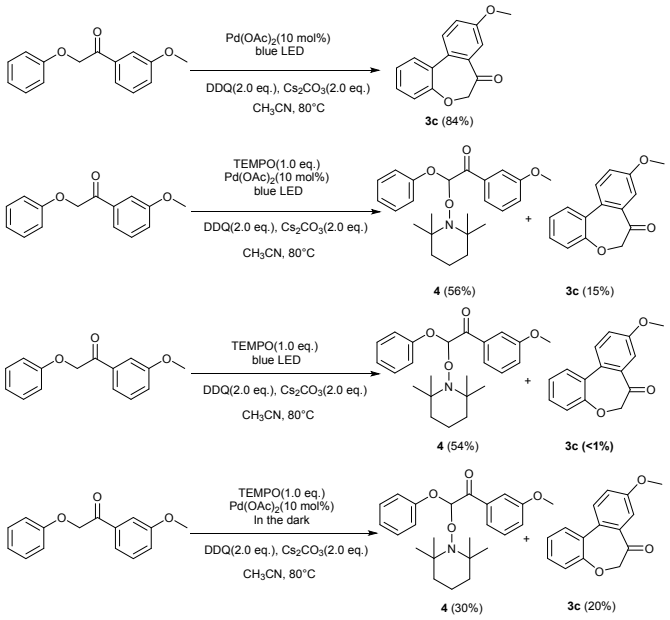


[a] Reaction conditions: **1a**-**1f** (0.45 mmol), **2a**-**2d** (0.47 mmol), 10 mol% $Pd(OAc)_2$, DDQ (2.0 eq.), Cs_2CO_3 (2.0 eq.), CH_3CN 2 ml, 25W blue LED at 80 °C. After 10 h, the reaction completed (monitored by TLC), isolated yield by flash column chromatography.

The group R of the phenols could be an electron-donating group, or electron-withdrawing group. When electron-donating groups -Me were at the *para* position, the cascade reaction showed high reaction activities and afforded good yields of 80-88% (**Table 2**, entries **3e**-**3h**). Compared with the electron-donating groups, the electron-withdrawing groups such as -F and -Cl at the *para* position showed slightly low reaction activities and the yields of 75-83% (**Table 2**, entries **3m-3t**). When the electron-donating group -OMe was at the *meta* position, the cascade reaction also showed high reaction activities and the yields of 80%-89% (**Table 2**, entries **3i-3l**). When the electron-donating group -OMe was at the *para* position, it also could afford good yields (**Table 2**, 81%-88% for entries **3u-3x**).

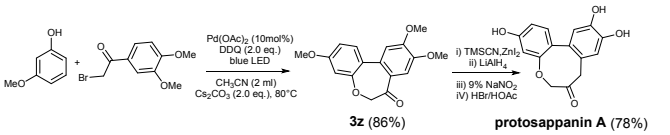
Another group R_1 on the α-bromoacetophenones could be -Me, -OMe, -Ph, -H and so on. When the electron-donating groups such as -OMe and -Me were at the *meta* position, the cyclization showed high reaction activities and afforded good yields of 79-89% (**Table 2**, entries **3b**, **3c**, **3f**, **3g**, **3j**, **3k**, **3n**, **3o**, **3r**, **3s**, **3v** and **3w**). The group -Ph was at the *meta* position, and the reaction activities and the yields slightly decreased to 75%-81% (**Table 2**, entries **3d**, **3h**, **3l**, **3p**, **3t** and **3x**). However, when the electron-withdrawing group -F at *meta* position, the reactivity is significantly reduced (**Table 2**, entry **3y**).

In order to understand the reaction mechanism (**Scheme 3**), 1-(4-methoxyphenyl)-2-phenoxyethan-1-one was synthesized by etherification between **1a** and **2c**. Then **3c** was synthesized under standard conditions in a yield of 84%.



Scheme 3 Mechanism research.

When one equivalent of 2, 2, 6, 6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction, 1-phenyl-2-(2-((2, 2, 6, 6-tetramethylpiperidin-1-yl)oxy)phenoxy)ethan-1-one **4** was isolated in 56% yield, and **3c** was obtained in a yield of 15%. And compound **4** was 54%, product **3c** was not obtained in the absence of $Pd(OAc)_2$. In addition, when the whole reaction system was in the dark, compound **4** was 30%, and product **3c** was isolated in 20% yield. The compound **4** radical intermediate was captured by the radical trap (TEMPO), it was confirmed that the 1-(4-methoxyphenyl)-2-phenoxyethan-1-one produced a methylene radical in this process. The process may be a cascade mechanism involving the palladacycle intermediates.[18, 19] However the exact mechanism is not clear at this moment.



Scheme 4 Application of the protocol to the synthesis of Protosappanin A.

To further demonstrate the synthetic utility of this protocol, we applied it to the synthesis of the Protosappanin A (**Scheme 4**). 3-Methoxyphenol and 2-bromo-1-(3,4-dimethoxyphenyl)ethan-1-one were selected to the optimized reaction conditions to obtain the compound **3z** (3,9,10-trimethoxy dibenzo[b,d]oxepin-7(6*H*)-one) with 86% yield. Then the Protosappanin A[8] was synthesized in four steps with a yield of 78%. Compared with previous methods, this protocol

has the advantages of readily available starting materials, concise steps and mild conditions.

Conclusion

In summary, a novel method to synthesize dibenzo[b,d] oxepin-7(6*H*)-one was developed via visible-light-induced cascade reaction of etherification/C-C coupling cyclization from α-bromoacetophenones and phenols. Twenty five desired products were obtained in moderate to good yields by this method. Furthermore, this protocol was applied to the synthesis of Protosappanin A. The protocol features are simple reaction conditions, readily available starting materials, broad substrate scope, and good tolerance of functional groups.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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