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ARTICLE

CBr_4 Promoted Intramolecular Aerobic Oxidative Dehydrogenative Arylation of Aldehydes: Applied in the Synthesis of Xanthones and Fluorenones

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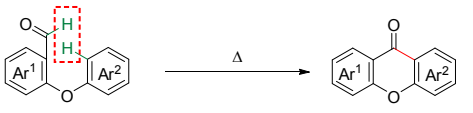
A simple and practical carbon tetrabromide promoted intramolecular aerobic oxidative dehydrogenative coupling reaction has been developed to provide a straightforward ring closure protocol of 2-aryloxybenzaldehydes to furnish xanthones. The reaction was performed under metal-, additive- and solvent-free conditions with good tolerance of functional groups. The present method is also applicable to the synthesis of fluorenones by using 2-arylbenzaldehydes as substrates. Preliminary Studies of the reaction mechanism indicated that the reaction may proceed through a radical pathway.

Introduction

Xanthones, an important type of oxygen-containing heterocyclic compounds, are the core structures of many natural products and pharmaceuticals; they are also versatile synthetic blocks in organic synthesis.[1] Therefore, the construction of xanthone skeletons is of great importance and synthetically attractive.[2] Traditionally and most frequently, the Friedel-Crafts acylation of arenes is a prevailing reaction for accessing aryl ketones. However, the Friedel-Crafts ring closures of 2-aryloxybenzoic acids or derivatives to construct xanthone derivatives are usually limited to electron-rich arenes or require multiple steps.[3]

Since 2004, the cross-dehydrogenative coupling (CDC) reaction, which means the direct coupling of two different C–H bonds, has become a growing and attractive field in organic synthesis.[4] Recently, Li et al developed a straightforward strategy to the preparation of xanthones via an intramolecular oxidative CDC reaction of 2-aryloxybenzaldehydes using $RhCl_3$ as the catalyst and *tert*-Butyl hydroperoxide (TBHP) as the oxidant.[5] Later on, two more catalytic systems, $FeCp_2$/TBHP[6] and TBAB/TBHP[7] have been achieved in this transformation. In general, theses catalytic systems were complicated and stoichiometric amounts of chemical oxidant TBHP which is potentially explosive were required. On the contrary, O_2 is one of the most environmentally benign and sustainable oxidants.[8] Therefore, the development of new oxidative dehydrogenative ring closure reaction of 2-aryloxybenzaldehydes to form xanthones under simpler aerobic conditions is highly desired.

Scheme 1. Xanthones formation from 2-aryloxybenzaldehydes



	metal	non-metal	oxidant	solvent
ref 5:	$RhCl_3$	PPh_3	TBHP	PhCl
ref 6:	$FeCp_2$	-	TBHP	MeCN
ref 7:	-	TBAB	TBHP	H_2O
this work:	**-**	CBr_4	O_2	**-**

Since 2015, we have for the first time discovered that carbon tetrabromide (CBr_4) showed good reactivity for CDC reactions.[9] We found that CBr_4 could efficiently promote the oxidative coupling of isochromans with aromatic ketones, the dehydrogenative C-H functionalization of *N*-aryl tetrahydroisoquinolines with nucleophiles such as indoles, ketones and phosphites, the dehydrogenative Povarov/aromatization tandem reaction of glycine derivatives with alkenes, the double-oxidative dehydrogenative cyclization/acidic ring opening/aromatization tandem reaction of glycine derivatives with dioxane, and the oxidative C–N bond formation of 2-aminopyridines or 2-aminopyrimidines with β-keto esters or 1,3-diones.

As part of our continuing interest in CBr_4 assisted transformations, herein, we developed a new and facile CBr_4-promoted intramolecular oxidative dehydrogenative protocol to construct xanthones (and also fluorenones) from 2-aryloxybenzaldehydes (and 2-arylbenzaldehydes) under aerobic solvent-free conditions.

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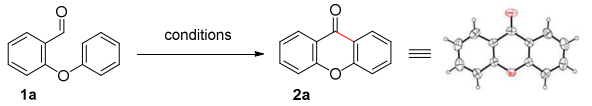
Results and Discussion

We started our study with the reaction of 2-phenoxybenzaldehyde **1a** in the presence of 1.2 equiv. of CBr_4 in various solvents under oxygen atmosphere (O_2 balloon) (Scheme 2, entries 1–6). The best result for xanthone **2a** construction (60%) was obtained under solvent-free conditions. The structure of **2a** was identified by X-ray crystallographic analysis.[10] The use of solvents was found to be less or no productive. Recently, there is an increasing attention in solvent-free reactions because this strategy leads to an economical technology with the increment of safety, the simpleness of work-up, and the reduction of cost. The use of other halogen reagents such as NBS, NCS, NIS, DBDMH instead of CBr_4, was found to be less effective (Scheme 2, entries 7–10). $BrCH_2CH_2Br$, $CHBr_3$ and CH_2Br_2 were inactive for this transformation (Scheme 2, entries 11–13). On decreasing the loading of promoter from 1.2 equiv. to 0.2 equiv., the yield was decreased a little (from 60% to 52%) with much longer reaction times (Scheme 2, entries 14–18). Then, temperature effect was investigated too. Increasing or decreasing the temperature of the reaction did not lead to any further improvements in the yield (Scheme 2, entries 19, 20). The control experiment showed that no reaction was observed in absence of O_2 (under an argon atmosphere) (Scheme 2, entry 22). Finally, only a trace amount of product was formed in the absence of any promoter (Scheme 2, entry 23). Therefore, the optimal reaction conditions were at 140°C, under oxygen atmosphere using 1.2 equiv. of CBr_4 without any solvent for 20 minutes (Scheme 2, entry 6).

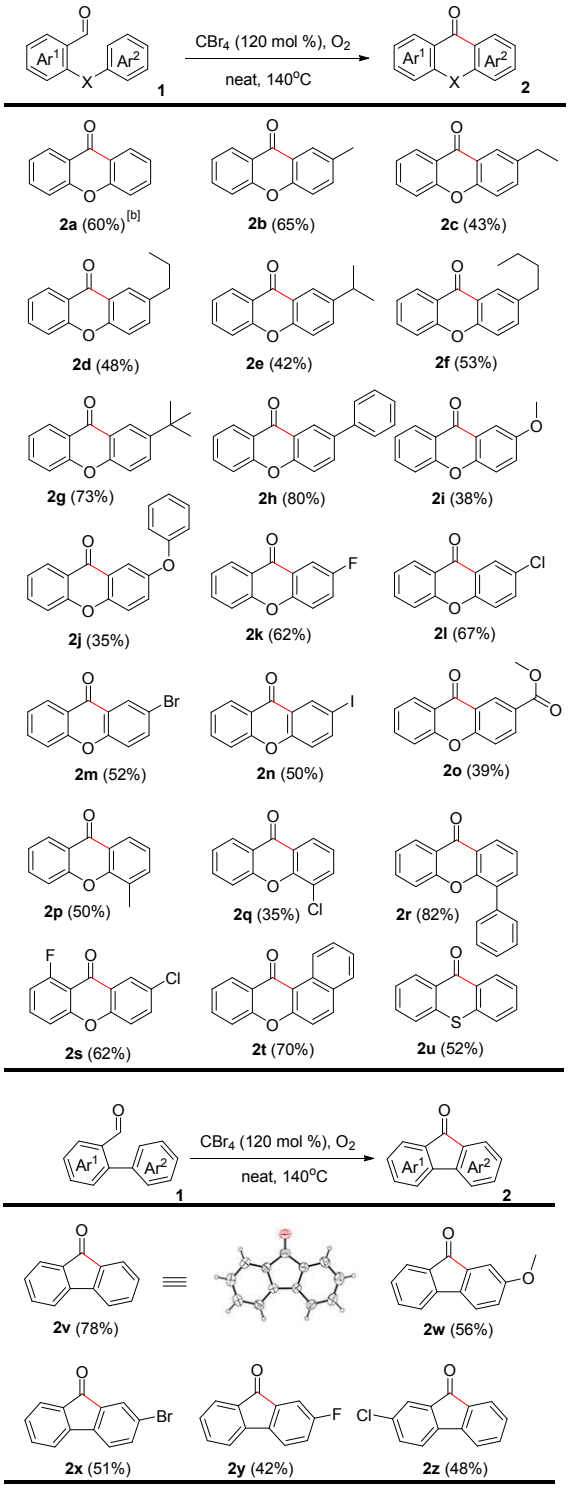
Scheme 2. Screening of Reaction Conditions[a]



entry	[hal]	loading	solvent	temperature	atmosphere	time	yield [%][b]
1	CBr_4	1.2 equiv.	**DMSO**	140°C	O_2	20 min	-
2	CBr_4	1.2 equiv.	**1,4-dioxane**	140°C	O_2	20 min	-
3	CBr_4	1.2 equiv.	**diglyme**	140°C	O_2	20 min	-
4	CBr_4	1.2equiv.	**DMF**	140°C	O_2	20 min	37
5	CBr_4	1.2 equiv.	**anisole**	140°C	O_2	20 min	trace
6	**CBr_4**	1.2 equiv.	**Neat**	140°C	O_2	20 min	60
7	**NBS**	1.2 equiv.	Neat	140°C	O_2	20 min	34
8	**NCS**	1.2 equiv.	Neat	140°C	O_2	20 min	10
9	**NIS**	1.2 equiv.	Neat	140°C	O_2	20 min	8
10	**DBDMH**	1.2 equiv.	Neat	140°C	O_2	20 min	42
11	**DBE**	1.2 equiv.	Neat	140°C	O_2	20 min	-
12	**$CHBr_3$**	1.2 equiv.	Neat	140°C	O_2	20 min	-
13	**CH_2Br_2**	1.2 equiv.	Neat	140°C	O_2	20 min	-
14	CBr_4	**0.1 equiv.**	Neat	140°C	O_2	12 h	33
15	CBr_4	**0.2 equiv.**	Neat	140°C	O_2	6 h	52
16	CBr_4	**0.5 equiv.**	Neat	140°C	O_2	3 h	54
17	CBr_4	**1 equiv.**	Neat	140°C	O_2	20 min	58
18	CBr_4	**1.5 equiv.**	Neat	140°C	O_2	20 min	46
19	CBr_4	1.2 equiv.	Neat	**120°C**	O_2	3 h	49
20	CBr_4	1.2 equiv.	Neat	**160°C**	O_2	10 min	40
21	CBr_4	1.2 equiv.	Neat	140°C	**air**	20 min	50
22	CBr_4	1.2 equiv.	Neat	140°C	**Ar**	20 min	0
23	**-**	-	-	140°C	O_2	20 min	trace

[a] The amount of substrate **1a**: 1 mmol. [b] Yield of the isolated product. NCS = *N*-Chlorosuccinimide. NBS = *N*-Bromosuccinimide. NIS = *N*-Iodosuccinimide. DBDMH = 1,3-dibromo-5,5-dimethylhydantoin. DBE = dibromoethane.

Scheme 3. CBr_4 mediated synthesis of xanthones and fluorenones[a]



[a] Reaction conditions: **1** (1 mmol), CBr_4 (1.2 mmol), O_2 balloon, 140°C, 0.33-8 h. [b] Yield of the isolated product.

We then examined the substrate scope of this CBr_4 promoted intramolecular arylation reactions of aldehydes under the optimized conditions. The structures of the obtained aromatic

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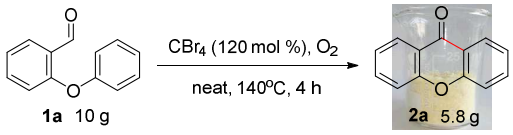
polycyclic ketones and the yields are depicted in Scheme 3. The effect of substituents on the arene ring undergoing the cyclization was first examined. Both electron-donating groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *tert*-butyl, phenyl, methoxy and phenoxy and electron-withdrawing groups such as halogen atoms and carboxylate at the *para*-position were well tolerated, and xanthones **2b-2o** were isolated in 35-80% yields. The introduction of halogen atoms into this fused ring system makes this methodology more useful for the further transformations. Moreover, the reaction of substrates bearing a substituent at the *ortho* position of the aryloxy group also proceeded well (Scheme 3, **2p-2r**). We further showed that the *ortho*-formyl biphenylether with both arene rings carry substituents provided the corresponding products in good yield (Scheme 3, **2s**). The reaction of 2-(naphthalen-2-yloxy) benzaldehyde yielded tetracyclic compound **2t** in high yield. In addition, this protocol can facilitate the preparation of thioxanthones too (Scheme 3, **2u**).

Encouraged by these promising results, to develop a more general and useful method, we further applied the optimized reaction conditions to construct fluorenones which are found in a lot of naturally occurring molecules exhibiting promising biological activities[11] using 2-arylbenzaldehydes as the test substrates. As shown in Scheme 3, to our delight, *ortho*-formyl biphenyls with electron-donating substituents and with electron-withdrawing substituents were all well tolerated under the standard reaction conditions (Scheme 3, **2v-2z**). The structure of fluorenone **2v** was also identified by X-ray crystallographic analysis.[12]

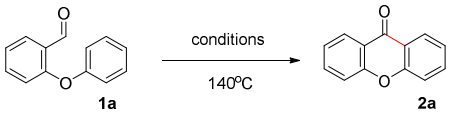
To demonstrate the practicability of the present methodology, as shown in Scheme 4, we carried out the reaction starting from 10 g of 2-phenoxybenzaldehyde **1a** and the isolated yield of the corresponding product **2a** was 58 %. That is to say, here we present a convenient and scalable synthetic route to xanthone motifs.

Scheme 4. Scalability of the reaction to the multi-gram scale

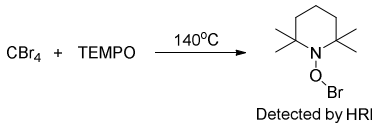


To get a better understanding on the mechanism of this CBr_4 promoted oxidative coupling reaction, a few control experiments were conducted. First of all, on decreasing the loading of CBr_4 from 1.2 equiv. to 0.2 equiv., the comparable yields of **2a** were obtained with prolonging of reaction time (Scheme 5, entries 1–4). Next, the reaction of **1a** in the absence of molecular oxygen (under argon atmosphere) furnished no desired product (Scheme 5, entries 5, 6). Moreover, 2,2,6,6-tetramethylpiperidin-1-yl hypobromite formed from the reaction of TEMPO and bromine radical could be detected by HRMS (Scheme 5, bottom). These results suggest that CBr_4 is the radical initiator and O_2 is the terminal oxidant for the reaction. In addition, the reactions in the presence of radical scavengers such as TEMPO or BHT did not occur (Scheme 5, entries 7–10), which signifies that the reaction probably proceeds through a radical pathway.

Scheme 5. Control experiments

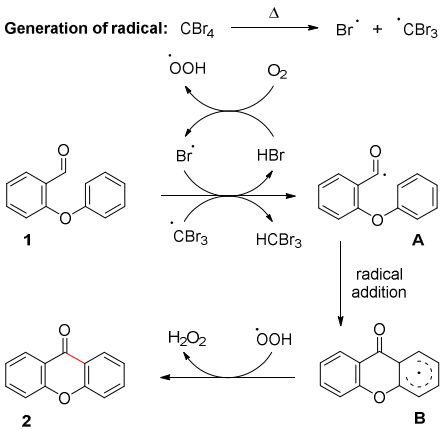


entry	promoter	Loading	atmosphere	inhibitor	time	yield
1	CBr_4	**1.2** equiv.	**O_2**	-	20 min	60%
2	CBr_4	**0.2** equiv.	**O_2**	-	12 h	52%
3	CBr_4	**1.2** equiv.	**air**	-	20 min	50%
4	CBr_4	**0.2** equiv.	**air**	-	12 h	46%
5	CBr_4	**1.2** equiv.	**Ar**	-	20 min	0%
6	CBr_4	**0.2** equiv.	**Ar**	-	12 h	0%
7	CBr_4	**1.2** equiv.	O_2	**TEMPO (5 equiv.)**	20 min	trace
8	CBr_4	**0.2** equiv.	O_2	**TEMPO (2 equiv.)**	12 h	trace
9	CBr_4	**1.2** equiv.	O_2	**BHT (2 equiv.)**	20 min	trace
10	CBr_4	**0.2** equiv.	O_2	**BHT (2 equiv.)**	12 h	trace



Although the mechanism of this CBr_4 initiated intramolecular CDC reaction is not fully clarified, on the basis of the preliminary results, a tentative mechanism was hypothesized as shown in Scheme 6. Initially, a homolytic cleavage of the C-Br bond of CBr_4 occurs upon heating to produce CBr_3 and Br radicals. Then, after abstraction of a hydrogen atom of substrate **1** by the Br radical (or CBr_3 radical), the carbonyl radical intermediate **A** is delivered. Subsequently, Intermediate **B** is generated by intramolecular radical addition of intermediate **A**. Finally, the previously formed OOH radical would act as the hydrogen-abstractor to provide the desired product **2**.

Scheme 6. Proposed mechanism



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Conclusion

In conclusion, we have for the first time demonstrated that CBr_4 is a highly effective promoter for the rapid synthesis of xanthones and fluorenones through the intramolecular oxidative dehydrogenative coupling of *ortho*-formyl biphenylethers and *ortho*-formyl biphenyls under aerobic and solvent-free conditions. The availability of the substrates, the use of simple non-metal reagent as promoter and O_2 as terminal oxidant, as well as the atom economy and the scalability make the process interesting for synthetic purposes and industrial applications. Experimental results suggest that the reaction proceeds through a radical pathway. Work to uncover further capabilities of CBr_4 is under way in our laboratories and the results will be reported in due course.

Experimental Section

Acknowledgements

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