Iron-catalyzed one-pot reactions of *o*-aryloxybenzaldehydes to xanthenes

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An efficient one-pot procedure for the synthesis of multisubstituted xanthone derivatives using Fe-catalyzed reactions of 2-aryloxybenzaldehydes followed by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation has been developed. This method offers a convenient high-yield route to xanthenes from easily accessible starting materials.

iron catalysis, xanthenes, oxidation reaction, one-pot process

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The xanthone nucleus is the core structure in a large number of natural products and synthetic compounds that exhibit interesting anti-tumor, and anti-inflammatory activities [1–3]. There are a number of known methods for their synthesis [4–13]. The reported procedures generally involve the reaction of a diaryl ether or a benzophenone intermediate [2], and typically require harsh reaction conditions and/or the use of strong acids or expensive metals. Recently, syntheses of xanthenes by trapping of arynes with phenol derivatives have been reported [14,15]. The development of sustainable, environmentally benign C–C bond-forming processes is very attractive in modern organic chemistry. Iron-catalyzed reactions have received considerable attention [16–19] because iron catalysts are cheap, non-toxic and easy to synthesize. We are interested in developing new Fe-catalyzed synthetic methods for C–C or C–X bond formation [20–25]. In this paper, we report the Fe-catalyzed synthesis of xanthenes from 2-aryloxybenzaldehydes (eq. (1)).

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We started our investigation with the reaction of 2-(4-methoxyphenoxy) benzaldehyde (**1a**) in toluene at 120°C, using 20 mol% of FeCl₃ as the catalyst. However, after 12 h, only trace amounts of products were detected (Table 1, entry 1). Increasing the amount of FeCl₃ to 1.0 equiv resulted in formation of xanthone **2a** and xanthene **3a** in yields of 42% and 31%, respectively (Table 1, entry 2). 2.0 equiv of FeCl₃ offered similar results as that of 1.0 equiv (Table 1, entry 3). Other solvents such as DMF, THF, DMSO, NMP resulted in no reaction (Table 1, entries 4–7). CH₃CN and 1,4-dioxane as solvents also produced **2a** and **3a** in good yields after 12 h (Table 1, entries 8 and 9). When DCE was used as the solvent, the combined yield of **2a** and **3a** was around 90% (Table 1, entry 10). Both **2a** and **3a** could be produced by the disproportionation of the corresponding xanthol, and it is possible to convert the xanthol to a xanthone by oxidation. In order to obtain **2a** as the sole product, several oxidants were tested (Table 1, entries 11–15). To our delight, when 1.0 equiv of DDQ was employed, the desired xanthone **2a** was produced in 94% yield (Table 1, entry 11). Other catalysts such as CuCl and Cu₂O failed to accomplish the reaction (Table 1, entries 16 and 17). It was clear that the optimized reaction conditions for xanthone formation were 20 mol% FeCl₃ as the catalyst with addition

Table 1 Optimization of reaction conditions for the synthesis of **2a**

Entry	Cat. (mol%)	Sol.	<i>T</i> (°C)	Time (h)	Yield (%) ^{a)}	
					3a	2a
1	FeCl ₃ (20)	Toluene	120	12		Trace
2	FeCl ₃ (100)	Toluene	120	12	31	42
3	FeCl ₃ (200)	Toluene	120	1	37	44
4	FeCl ₃ (100)	DMF	135	7		NR ^{b)}
5	FeCl ₃ (100)	THF	70	5		NR ^{b)}
6	FeCl ₃ (100)	DMSO	130	11		NR ^{b)}
7	FeCl ₃ (100)	NMP	130	10		NR ^{b)}
8	FeCl ₃ (100)	CH ₃ CN	80	12	38	38
9	FeCl ₃ (100)	Dioxane	120	12	18	22
10	FeCl ₃ (100)	DCE	100	5	38	50
11	FeCl ₃ ·6H ₂ O (20)	DCE	100	62	–	94
12	FeCl ₃ ·6H ₂ O (50)	DCE	100	24	–	91
13	FeCl ₃ ·6H ₂ O (20)	DCE	100	62	–	36
14	FeCl ₃ ·6H ₂ O (20)	DCE	100	62	–	10
15	–	DCE	100	62		Trace
16	CuCl (2)	DCE	100	62		Trace
17	Cu ₂ O (5)	DCE	100	62		Trace

a) Isolated yield; b) no reaction.

of 1.0 equiv of DDQ, in DCE at 100°C.

Having established an effective catalytic system for the xanthone-forming reactions, we next synthesized a variety of *o*-aryloxybenzaldehyde derivatives to explore the scope of the cyclization-oxidation reaction under the optimized conditions. Representative results are shown in Table 2 (spectroscopic data see supporting information). The reaction was applicable to various *o*-aryloxybenzaldehydes. *o*-Aryloxybenzaldehyde **1b** with an electron-donating (*-p*-Me) aryl group cyclized smoothly to give the xanthone **2b** in 94% yield (Table 2, entry 2). The unsubstituted *o*-aryloxybenzaldehyde **1c** afforded **2c** in 85% yield (Table 2, entry 3), and **1d**, with an electron-withdrawing (*-p*-Cl) aryl group, gave **2f** in 71% yield (Table 2, entry 4). 2,4-Dichloro-substituted **1e** afforded **2e** in medium yield (Table 2, entry 5). Substituents could also be present on the aromatic ring bearing the formyl group, for example, **1g** and **1h**, and the corresponding xanthenes **2g** and **2h** were obtained in high yields under the standard conditions, respectively (Table 2, entries 6,7). When **1i** with a 2-naphthyl group was subjected to the optimal reaction conditions, the desired tetracyclic product was produced in 95% yield (Table 2, entry 9). The substrate scope of the reaction could also be extended to other *o*-substituted benzaldehydes, such

as phenylthiobenzaldehyde and biphenyl-2-carbaldehyde. It is interesting to note when 2-(phenylthio)benzaldehyde (**1j**) was employed, the corresponding thioxanthone **2j** was obtained in 55% yield (Table 2, entry 10). Biphenyl-2-carbaldehyde (**1k**) furnished fluorenone (**2k**) in 70% yield (Table 2, entry 11). These results may further broaden the substrate scope of these reactions.

Based on the above observations and the reported results [13,15], a plausible reaction mechanism is proposed in Scheme 1. Intramolecular Friedel-Crafts reaction of **1** to produce **4**, proton transfer to form xanthol **5**, and then oxidation to give the desired xanthone **2**.

In summary, we have reported an efficient iron-catalyzed cascade cyclization-oxidation process for conversion of 2-aryloxybenzaldehydes to xanthone derivatives. The reactions proceed to afford xanthone derivatives in good to high yields, using FeCl₃·6H₂O as the catalyst and DDQ as the oxidant in DCE. Further investigations of this novel iron-catalyzed procedure to extend the scope of synthetic applications are in progress.

Typical procedure for the iron-catalyzed formation of xanthone (**2a**): FeCl₃·6H₂O (54 mg, 20 mol%), 2-(4-methoxyphenoxy)benzaldehyde (**1a**) (228 mg, 1.0 mmol), DDQ (227 mg, 1.0 mmol), and DCE (5 mL) were added to a

Table 2 Synthesis of xanthenes from *o*-aryloxybenzaldehydes

Entry	Substrate	Time (h)	Product	Yields (%) ^{a)}
1	(1a)	62	(2a)	94
2	(1b)	50	(2b)	94
3	(1c)	62	(2c)	85
4	(1d)	80	(2d)	71
5	(1e)	70	(2e)	40
6	(1f)	62	(2f)	93
7	(1g)	36	(2g)	95
8	(1h)	62	(2h)	86
9	(1i)	62	(2i)	95
10	(1j)	64	(2j)	55 ^{b)}
11	(1k)	8	(2k)	70

a) Isolated yield; b) 50 mol% of FeCl₃ · 6H₂O was used. **Scheme 1** Proposed reaction mechanism.

Schlenk tube under nitrogen. The resulting solution was stirred at 100°C for 62 h. Then the reaction was quenched with distilled water and filtered with celite. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over MgSO₄. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica-gel column to give **2a** as a white solid in 94% isolated yield. ¹H NMR (400 MHz, CDCl₃, Me₄Si) δ 3.82 (s, 3H), 7.21–7.38(m, 4H), 7.59–7.60 (m, 2H), 8.24 (dd, *J* = 8.6, 1.2 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃, Me₄Si) δ 55.79, 105.81, 117.91, 119.34, 121.19,

122.05, 123.66, 124.81, 126.63, 134.52, 150.97, 155.98, 155.11, 177.06.

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Supporting Information

Experimental details and spectroscopic characterization of all new compounds.

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