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Iron-Catalyzed, Microwave-Promoted, One-Pot Synthesis of 9-Substituted Xanthenes by a Cascade Benzylation−Cyclization Process

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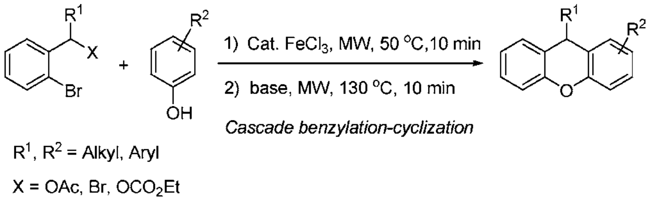
ABSTRACT



An efficient iron-catalyzed, microwave-promoted cascade benzylation−cyclization of phenols is reported. Benzyl acetates, benzyl bromides, and benzyl carbonates are suitable benzylating reagents. The reactions proceed to afford both 9-aryl and 9-alkyl xanthene derivatives in good to high yields using $FeCl_3$ as the catalyst under MW irradiation conditions.

Direct C−H functionalization catalyzed by transition metals has become an important topic in organometallic chemistry. This method represents one of the most effective and atom-economical routes for C−C bond-forming reactions. The catalysts employed in these processes are usually expensive metals such as Ru, Rh, Pt, Pd, Au, etc.[1,2] In recent years, the development of sustainable, environmentally friendly, and low-cost C−C bond-forming protocols attracted much attention in synthetic organic chemistry. As a result, several excellent works concerning direct C−C bond-forming reactions catalyzed or mediated by iron have been reported, for example, the benzylation of arenes and heteroarenes,[3] the arylation of 2-arylpyridines,[4] and the direct functionalization of a C−H bond adjacent to a heteroatom,[5] as a result of the unique properties of iron catalysts, such as low price, less toxicity, and ease of synthesis. Our group[6] and others[7] reported the iron-catalyzed C−H activation of terminal alkynes. During the course of our ongoing study on the development of transition-metal-mediated heterocycle-forming protocols,[8] we found that xanthenes could be efficiently prepared using iron catalyst under microwave irradiation conditions.

Xanthenes are important classes of compounds as they are useful biologically active molecules;[9] they can also be used as dyes and fluorescent materials.[10] There have been various

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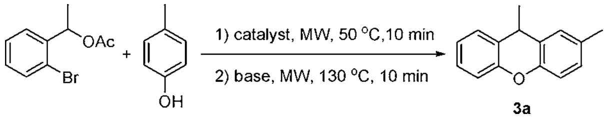
procedures for the synthesis of xanthenes;[8f,11−14] elegant examples include: inter- or intramolecular trapping of arynes by phenols or aldehydes,[11] Pd-catalyzed cyclization of polycyclic aryltriflate esters,[12] Yb-catalyzed reaction of β-naphthol and aldehydes,[13] and the reaction of 2-tetralone and salicylaldehydes under acidic conditions.[14a] Although these methods are efficient for the synthesis of xanthenes, the application scope is limited to the synthesis of either 9-aryl- or 9-alkyl-substituted xanthenes. Therefore, the development of a general procedure for the synthesis of both 9-aryl- and 9-alkyl-substituted xanthenes is highly desired. In addition, the advantages of microwave-assisted synthesis have been widely recognized,[15] such as dramatically reducing reaction times, less or no toxic waste generation and higher yields. Herein we would like to present our results of the iron-catalyzed, microwave-promoted cascade benzylation−cyclization of phenols for the synthesis of 9-substituted xanthenes.

We started our investigation with 1-(2-bromophenyl)ethyl acetate (**1a**), which was synthesized according to the reported method.[16] The reaction of **1a** with 4-methyl phenol (**2a**) was selected as a model reaction to screen the experimental conditions. Selected results are summarized in Table 1. First, the reaction was carried out using 5 mol % of $FeCl_3$ as catalyst under microwave irradiation at 50 °C. We were happy to see that the benzylation reaction was completed in 10 min. After the mixture cooled to room temperature, DMF and Cs_2CO_3 (5.0 equiv) were added. The resulting reaction mixture was kept for another 10 min under microwave irradiation at 130 °C, and the desired xanthene **3a** was formed in 75% yield (Table 1, entry 1). Controlled experiments without the microwave irradiation afforded xanthene **3a** in only 46% yield (Table 1, entry 2). Less Cs_2CO_3 (4.0 equiv) gave much lower yield of the product (Table 1, entry 3). When 10 mol % of $FeCl_3$ was used, the product yield was similar to that of 5 mol % (Table 1, entry 4). Two mole percent of $FeCl_3$ resulted in trace amount of the desired product (Table 1, entry 6). Switching to other bases such as K_2CO_3, KOH, and ${}^tBuOK$ gave only benzylation product or very low yields of the xanthene (Table 1, entries 7−9). It is interesting to note when solvents such as DCM or DMF were used from the benzylation step, there was almost no formation of xanthene **3a** (Table 1, entries 10 and 11). In the presence of catalytic amounts of various acids ($BF_3{\cdot}Et_2O$, HCl, $TsOH{\cdot}H_2O$) the desired product **3a** was obtained in low yields (Table 1, entries 12−14). It was clear that the optimized reaction condition was to use 5 mol % of $FeCl_3$ as the catalyst under microwave irradiation, followed by the addition of Cs_2CO_3 as the base and DMF as the solvent for the subsequent cyclization.

Table 1. Optimization of Reaction Conditions for the One-Pot Synthesis of **3a**



entry	catalyst (mol %)	base (equiv)	yield (%)[a]
1	$FeCl_3$ (5)	Cs_2CO_3 (5.0)	75
2	$FeCl_3$ (5)	Cs_2CO_3 (5.0)	46[b]
3	$FeCl_3$ (5)	Cs_2CO_3 (4.0)	39
4	$FeCl_3$ (10)	Cs_2CO_3 (5.0)	72
5	$FeCl_3$ (10)	Cs_2CO_3 (4.0)	39
6	$FeCl_3$ (2)	Cs_2CO_3 (5.0)	trace
7	$FeCl_3$ (10)	K2CO3 (5.0)	*c*
8	$FeCl_3$ (10)	KOH (5.0)	trace
9	$FeCl_3$ (10)	${}_tBuOK$ (5.0)	*c*
10	$FeCl_3$ (10)	Cs_2CO_3 (5.0)	*c,d*
11	$FeCl_3$ (10)	Cs_2CO_3 (5.0)	*e*
12	$BF_3{\cdot}Et_2O$ (5)	Cs_2CO_3 (5.0)	*f*
13	HCl (5)	Cs_2CO_3 (5.0)	trace
14	$TsOH{\cdot}H_2O$ (5)	Cs_2CO_3 (5.0)	10

[a] Yields were determined by GC after hydrolysis, and unless otherwise noted, the benzylation reaction was carried out under solvent-free conditions. [b] Reactions were carried out without the MW irradiation: benzylation at 50 °C for 1 h, then cyclization at 130 °C for 9 h. [c] Only benzylation product was obtained. [d] Reactions were carried out in DCM. [e] Reactions were carried out in DMF, and a trace amount of benzylation product was detected. [f] The reaction system was complicated.

Having established an effective catalytic system for the one-pot synthesis of xanthenes, we next examined the reaction of a variety of benzyl acetates and phenols to explore the scope of the cascade benzylation−cyclization reaction under the optimized conditions. The representative results are shown in Table 2. The reaction was applicable to various benzyl acetates and phenols. Acetates with an alkyl group at the benzylic position reacted smoothly with various phenols to afford 9-alky-substituted xanthenes. For example,

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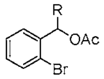
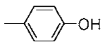
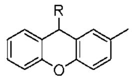
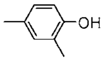
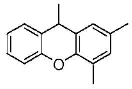
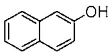
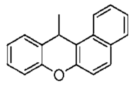
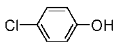
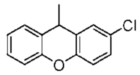
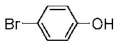
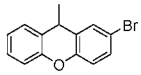
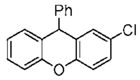
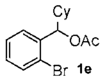
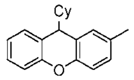
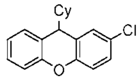
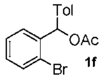
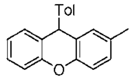
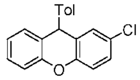
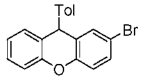
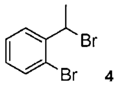
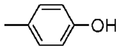
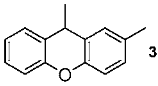
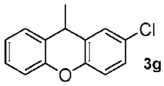
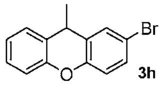
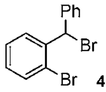
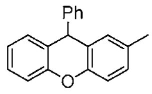
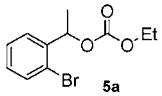
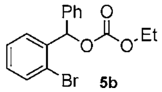
Table 2. Synthesis of Xanthenes from the Reaction of Phenols and Benzyl Acetates

entry	acetate	phenol	product	yield [a]
				
1	R = Me **1a**	**2a**	R = Me **3a**	72%
2	R = H **1b**	**2a**	R = H **3b**	50%
3	R = Et **1c**	**2a**	R = Et **3c**	64%
4	R = Ph **1d**	**2a**	R = Ph **3d**	66%
5	**1a**	 **2b**	 **3e**	70%
6	**1a**	 **2c**	 **3f**	40%
7	**1a**	 **2d**	 **3g**	77%
8	**1a**	 **2e**	 **3h**	60%
9	**1d**	**2d**	 3i	71%
10[b]		**2a**	 3j	73%
11	**1e**	**2d**	 3k	40%
12		**2a**	 3l	75%
13	**1f**	**2d**	 **3m**	59%
14	**1f**	**2e**	 **3n**	38%

[a] Isolated yields. [b] Cy = cyclohexyl.

Table 3. Synthesis of Xanthenes from the Reaction of Phenols with Benzyl Bromides and Carbonates

entry	benzylating reagent	phenol	product	yield [a]
1		 **2a**	 **3a**	62%
2	**4a**	**2d**	 **3g**	73%
3	**4a**	**2e**	 **3h**	64%
4		**2a**	 **3d**	41%
5		**2a**	**3a**	60%
6	**5a**	**2d**	**3g**	67%
7	**5a**	**2e**	**3h**	61%
8		**2a**	**3d**	51%

[a] Isolated yields.

benzylating agents such as 1-(2-bromophenyl)ethyl acetate (**1a**), 2-bromobenzyl acetate (**1b**), and 1-(2-bromophenyl-)propyl acetate (**1c**) reacted with 4-methylphenol (**2a**) to give the corresponding 9-alkyl xanthene derivatives in good yields (Table 2, entries 1−3). When acetates with a cyclohexyl group at the benzylic position (**1e**) were used, the cyclized product was obtained in 73% yield (Table 2, entry 10). More interestingly, the reaction of **1e** and deactivated phenol **2d** could also proceed to give the desired xanthene in moderated yield (Table 2, entry 11). Acetates with an aryl group at the benzylic position were also suitable substrates. Reaction of (2-bromophenyl)(phenyl)methyl acetate (**1d**) and **2a** furnished the desired **3d** in 66% yield (Table 2, entry 4). Acetate bearing a *p*-tolyl group, **1f**, reacted with 4-methylphenol (**2a**) and halophenols **2d** and **2e** to afford the corresponding xanthenes in good yields (Table 2, entries 12−14). Phenols with various substitutes could also be employed in the xanthene forming reaction. 2,4-Dimethyl phenol (**2b**) reacted with **1a** smoothly to produce **3e** in 70% yield (Table 2, entry 5). Even deactivated phenols such as 4-chlorophenol (**2d**) and 4-bromophenol (**2e**) furnished the xanthenes in 77% (**3g**) and 60% (**3h**) yields, respectively (Table 2, entries 7 and 8). Likewise, the reaction of naphthalen-2-ol (**2c**) with **1a** led to the expected xanthene **3f** in 40% yield (Table 2, entry 6).

To further probe the scope and limitations of this process, we also examined other benzylating reagents under the optimized reaction conditions (Table 3). As shown in Table 3, in addition to benzyl acetates, benzyl bromides and benzyl carbonates are also suitable for the benzylation−cyclization reaction. Benzyl bromides with a methyl or a phenyl at the benzylic position reacted with phenols to give good yields of the desired xanthenes (Table 3, entries 1−4). When 1-(2-bromophenyl)ethyl ethyl carbonate (**5a**) was used, in all cases the corresponding products were obtained in good yields (60−67%, Table 3, entries 5−7). (2-Bromophenyl)(phenyl)methyl ethyl carbonate (**5b**) yielded the desired **3d** in 51% yield (Table 3, entry 8). When benzyl alcohol such as 1-(2-bromophenyl)ethanol was used as benzylating reagent, it reacted with 4-methyl phenol (**2a**) to afford the desired xanthene **3a** in only 29% yield.

In summary, we have reported an efficient iron-catalyzed, microwave-promoted cascade benzylation−cyclization of phenols and a variety of benzylating reagents such as benzyl acetates, benzyl bromides, and benzyl carbonates. The reactions proceed to afford both 9-aryl and 9-alkyl xanthene derivatives in good to high yields using $FeCl_3$ as the catalyst with the assistance of MW irradiation. Further application of this novel iron-catalyzed cascade benzylation−cyclization procedure to extend the scope of synthetic utility of the reaction are under progress in our group.

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Supporting Information Available: Experimental details and spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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