



A new strategy for the synthesis of benzoxanthenes catalyzed by proline triflate in water

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ABSTRACT

Catalyzed by proline triflate, benzoxanthenes were obtained in good yields from the condensation of naphthols, aldehydes, and 1,3-dicarbonyl compounds in water. A possible mechanism of this reaction is proposed.

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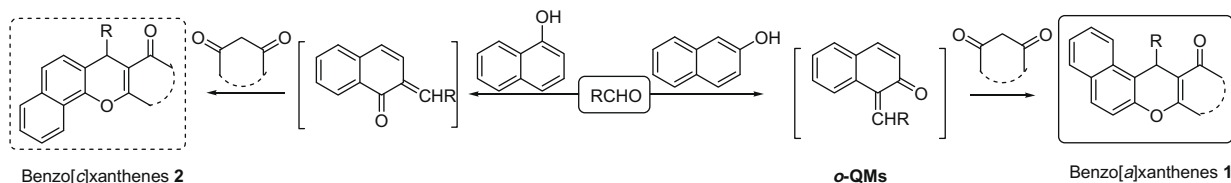
Xanthenes are one of the most widely distributed classes of natural compounds. Most of these derivatives are biologically active, such as possessing antiplasmodial¹ and anti-inflammatory² activities, and being utilized as antagonists for drug-resistant leukemia lines.³ Besides, these heterocyclic molecules have been widely used as dyes,⁴ pH-sensitive fluorescent materials⁵ as well as in laser technologies.⁶ Therefore, the synthesis of various xanthenes derivatives is of great importance.

Classical methods reported for the synthesis of xanthenes include: (1) annulation reaction of aryne with salicylates⁷ or salicylaldehyde;⁸ (2) palladium-catalyzed cyclization of polycyclic aryltriflate esters;⁹ (3) addition reaction of *ortho*-quinone methides (*o*-QMs) with certain nucleophiles.¹⁰ In comparison with other routes to synthesize xanthenes, the one that employs *o*-QMs has long been believed to be the most efficient.

Recently, Das et al.¹¹ have synthesized benzo[*a*]xanthenes **1** from β -naphthol, aldehydes, and 1,3-dicarbonyl compounds catalyzed by

NaHSO₄·SiO₂. Singh¹² and Khurana¹³ further explored *p*-toluenesulfonic acid as a catalyst for the synthesis of these compounds. Unfortunately, the current methods have not been extended to the use of simple α -naphthol to form the corresponding benzo[*c*]xanthenes **2**. The above studies illustrated the electron density at the β -position of the α -naphthol is not sufficient for the formation of the corresponding *o*-QMs under these acid catalysis conditions (Scheme 1). Therefore, the synthesis of xanthene from α -naphthol remains a challenge. In continuation of our previous work on the synthesis of benzoxanthenes,¹⁴ we were interested in developing an efficient catalyst for the preparation of new benzo[*c*]xanthenes **2** starting from α -naphthol.

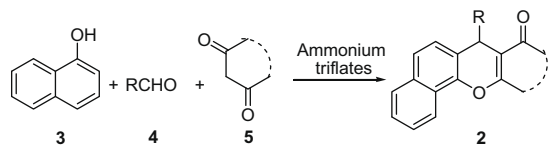
Ammonium triflate has been used as a mild and efficient catalyst in organic synthesis.¹⁵ Recently, ammonium triflate has shown the prospect to be used as a substitute for conventional acidic catalytic materials. We thus focused on the application of such catalyst in catalyzing the one-pot condensation reaction of



Scheme 1. Routes to synthesize benzoxanthenes by reaction of naphthol, aldehydes, and 1,3-dicarbonyl compounds.

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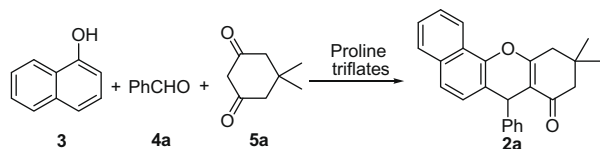
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Scheme 2. Reaction of α -naphthol, aldehyde, and 1,3-dicarbonyl compounds catalyzed by ammonium triflates.

Table 1

The condensation reaction catalyzed by proline triflate^a



Entry	Solvent	Temp (°C)	Time (h)	Yield ^b (%)
1	CH ₃ CH ₂ OH	Reflux	7.0	22
2	CH ₂ Cl ₂	Reflux	5.0	70
3	ClCH ₂ CH ₂ Cl	Reflux	4.5	57
4	CH ₃ CN	Reflux	6.0	28
5	THF	Reflux	7.0	<10
6	DMF	80	10.0	<10
7	Et ₂ O	Reflux	7.0	36
8	H ₂ O	80	6.5, 5.0 ^c	69, 79 ^c

^a All reactions were run with the molar ratio of **3**:**4a**:**5a**: proline triflate = 1:1:1:0.1.

^b Isolated yields based on **3**.

^c The reaction was carried out under reflux temperature.

Table 2

The condensation reaction catalyzed by different catalysts^a

Entry	Cat. (10 mol %)	Temp (°C)	Time (h)	Yield ^b (%) 2a : 6a : 7a
1	Proline triflate	Reflux	5	79:5:3
2	DPAT	Reflux	5	45:12:9
3	DCAT	Reflux	5	35:10:12
4	Sr(OTf) ₂	Reflux	5	ND ^c
5	Proline triflate	0	22	25:9:9
6	Proline triflate	rt	15	23:12:9

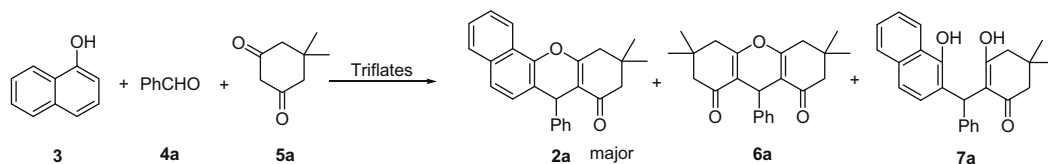
^a All reactions were run with **3** (1.0 mmol), **4a** (1.0 mmol), **5a** (1.0 mmol), and catalyst (0.1 mmol) in H₂O (2 mL).

^b Isolated yields based on **3**.

^c No desired product was detected.

α -naphthol **3**, aldehyde **4**, and 1,3-dicarbonyl compounds **5** so as to prepare benzo[c]xanthene **2** (Scheme 2).

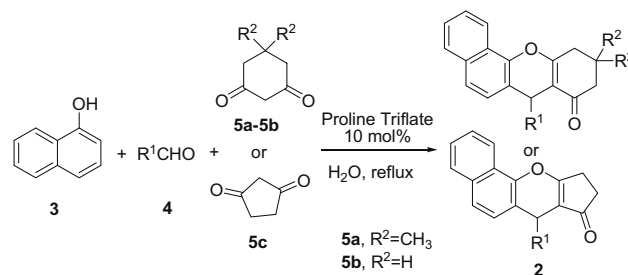
Initially, we investigated the condensation reaction of α -naphthol **3**, benzaldehyde **4a**, and 5,5-dimethylcyclohexane-1,3-dione **5a** using 10 mol% of proline triflate in different solvents. It is encouraging to find **2a** could be isolated with this catalyst albeit in low to moderate yields. The results are listed in Table 1. Tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF) afforded **2a** in not more than 10% yield (Table 1, entries 5 and 6), and other polar solvents such as ethanol and acetonitrile proved inefficient, either (Table 1, entries 1 and 4). Use of 1,2-dichloroethane and



Scheme 3. The condensation reaction of aldehyde, α -naphthol, and 1,3-dicarbonyl compound.

Table 3

Reaction of α -naphthol **3**, benzaldehyde **4**, and 1,3-dicarbonyl compounds **5** catalyzed by proline triflate^a



Entry	R ¹	Compounds 5	Product 2	Time (h)	Yield ^b (%)
1	C ₆ H ₅	5a	2a	5.0	79
2	<i>p</i> -ClC ₆ H ₄	5a	2b	5.0	76
3	<i>m</i> -OCH ₃ C ₆ H ₄	5a	2c	4.0	77
4	<i>m</i> -NO ₂ C ₆ H ₄	5a	2d	5.5	72
5	PhCH=CH	5a	2e	6.5	64
6	2-Thiophene	5a	2f	9.0	70
7	CH ₃ CH ₂	5a	2g	15.0	<5, 70 ^c
8	Cyclohexyl	5a	2h	15.0	<5
9	C ₆ H ₅	5b	2i	5.0	78
10	<i>m</i> -OHC ₆ H ₄	5b	2j	4.5	68
11	C ₆ H ₅	5c	2k	5.0	80
12	<i>m</i> -OHC ₆ H ₄	5c	2l	5.0	71

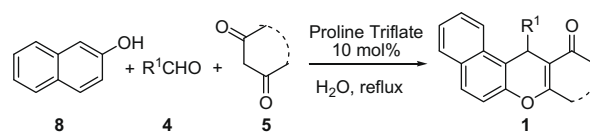
^a All reactions were run with **3** (1.0 mmol), **4** (1.0 mmol), and **5** (1.0 mmol) in the presence of proline triflate (0.1 mmol) in H₂O (2 mL) at reflux temperature.

^b Isolated yields based on **3**.

^c The major product obtained was 1,8-dioxo-dodecahydroxanthene **6g**, which was formed from the condensation of one aldehyde and two cyclic 1,3-dicarbonyl compounds.

Table 4

Reaction for synthesizing benzo[a]xanthenes^a



Entry	R ¹	Compounds 5	Product 1	Time (h)	Yield ^b (%)
1	C ₆ H ₅	5a	1a	3.0	85
2	<i>p</i> -ClC ₆ H ₄	5a	1b	3.0	82
3	<i>m</i> -OCH ₃ C ₆ H ₄	5a	1c	2.5	88
4	2-Thiophene	5a	1d	4.0	79
5	<i>m</i> -OCH ₃ C ₆ H ₄	5b	1e	3.0	84
6	C ₆ H ₅	5c	1f	3.0	83

^a All reactions were run with **8** (1.0 mmol), **4** (1.0 mmol), and **5** (1.0 mmol) in the presence of proline triflate (0.1 mmol) in H₂O (2 mL) at reflux temperature.

^b Isolated yields based on **8**.

dichloromethane afforded **2a** in better yields (Table 1, entry 4). However, the best results came from the use of water as a solvent (Table 1, entry 8).

It should be mentioned that besides **2a**, a noticeable amount of **6a**¹⁶ and **7a** was also obtained (Scheme 3). To minimize the formation of **6a** and **7a**, further optimization of the reaction by using different catalysts and reaction temperature was undertaken (Table

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