Tetrahedron Letters 51 (2010) 2434–2437

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Jianjun Li, Lingmei Lu, Weike Su *

Key Laboratory of Pharmaceutical Engineering of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, PR China

ARTICLE INFO

Article history:
Received 6 January 2010
Revised 20 February 2010
Accepted 24 February 2010
Available online 1 March 2010

Keywords:
Benzoxanthenes
Proline triflate
Condensation reaction
Naphthol

ABSTRACT

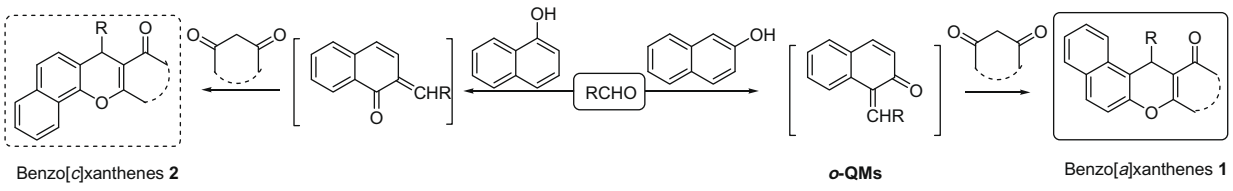
Catalyzed by proline triflate, benzoxanthenes were obtained in good yields from the condensation of naphthols, aldehydes, and 1,3-dicarbonyl compounds in water. A possible mechanism of this reaction is proposed.

Xanthenes are one of the most widely distributed classes of natural compounds. Most of these derivatives are biologically active, such as possessing antiplasmodial[1] and anti-inflammatory[2] 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 materials[5] as well as in laser technologies.[6] Therefore, the synthesis of various xanthene derivatives is of great importance.

Classical methods reported for the synthesis of xanthenes include: (1) annulation reaction of aryne with salicylates[7] 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 $NaHSO_4{\cdot}SiO_2$. Singh[12] and Khurana[13] 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.

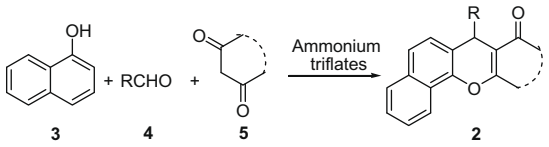
Ammonium triflate has been used as a mild and efficient catalyst in organic synthesis.[15] Recently, ammonium triflate has shown the prospect to be used as a substitute for conventional acidic catalytic materials. We thus focused on the application of such catalyst in catalyzing the one-pot condensation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



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

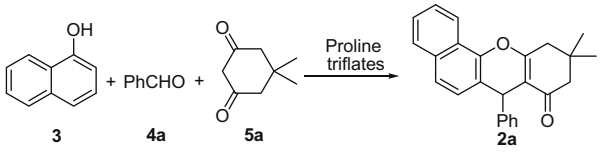
* Corresponding author. Tel./fax: +86 (571) 88320752.
E-mail address: pharmlab@zjut.edu.cn (W. Su).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.149



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_3CH_2OH	Reflux	7.0	22
2	CH_2Cl_2	Reflux	5.0	70
3	$ClCH_2CH_2Cl$	Reflux	4.5	57
4	CH_3CN	Reflux	6.0	28
5	THF	Reflux	7.0	<10
6	DMF	80	10.0	<10
7	Et_2O	Reflux	7.0	36
8	H_2O	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

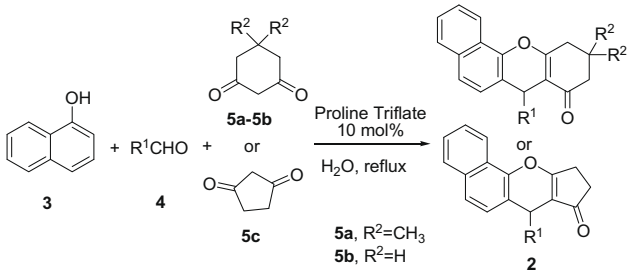
[a] All reactions were run with **3** (1.0 mmol), **4a** (1.0 mmol), **5a** (1.0 mmol), and catalyst (0.1 mmol) in H_2O (2 mL).
[b] Isolated yields based on **3**.
[c] No desired product was detected.

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 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

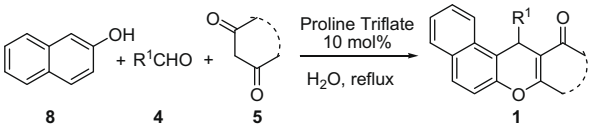
Table 3
Reaction of α-naphthol **3**, benzaldehyde **4**, and 1,3-dicarbonyl compounds **5** catalyzed by proline triflate[a]



Entry	R^1	Compounds **5**	Product **2**	Time (h)	Yield[b] (%)
1	C_6H_5	**5a**	**2a**	5.0	79
2	*p*-ClC_6H_4	**5a**	**2b**	5.0	76
3	*m*-$OCH_3C_6H_4$	**5a**	**2c**	4.0	77
4	*m*-$NO_2C_6H_4$	**5a**	**2d**	5.5	72
5	PhCH=CH	**5a**	**2e**	6.5	64
6	2-Thiophene	**5a**	**2f**	9.0	70
7	CH_3CH_2	**5a**	**2g**	15.0	<5, 70[c]
8	Cyclohexyl	**5a**	**2h**	15.0	<5
9	C_6H_5	**5b**	**2i**	5.0	78
10	*m*-OHC_6H_4	**5b**	**2j**	4.5	68
11	C_6H_5	**5c**	**2k**	5.0	80
12	*m*-OHC_6H_4	**5c**	**2l**	5.0	71

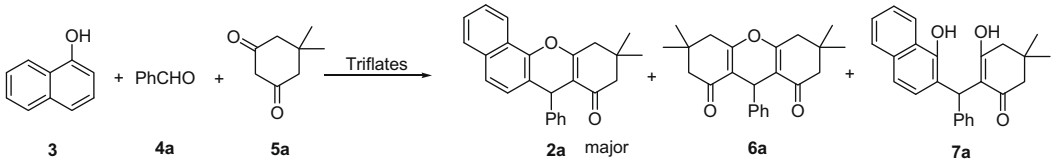
[a] All reactions were run with **3** (1.0 mmol), **4** (1.0 mmol), and **5** (1.0 mmol) in the presence of proline triflate (0.1 mmol) in H_2O (2 mL) at reflux temperature.
[b] Isolated yields based on **3**.
[c] The major product obtained was 1,8-dioxo-dodecahydroxanthene **6g**, which was formed from the condensation of one aldehyde and two cyclic 1,3-dicarbonyl compounds.

Table 4
Reaction for synthesizing benzo[*a*]xanthenes[a]

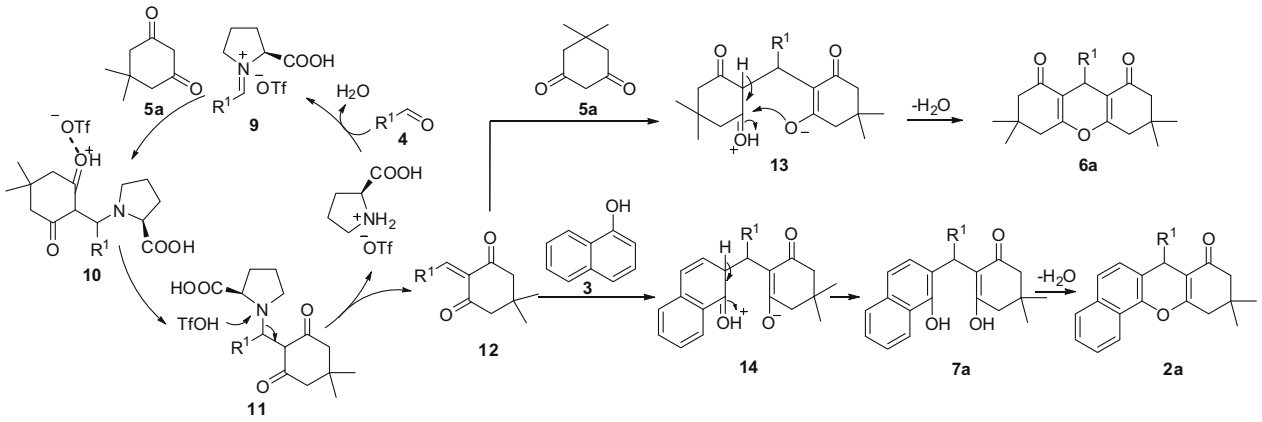


Entry	R^1	Compounds **5**	Product **1**	Time (h)	Yield[b] (%)
1	C_6H_5	**5a**	**1a**	3.0	85
2	*p*-ClC_6H_4	**5a**	**1b**	3.0	82
3	*m*-$OCH_3C_6H_4$	**5a**	**1c**	2.5	88
4	2-Thiophene	**5a**	**1d**	4.0	79
5	*m*-$OCH_3C_6H_4$	**5b**	**1e**	3.0	84
6	C_6H_5	**5c**	**1f**	3.0	83

[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 H_2O (2 mL) at reflux temperature.
[b] Isolated yields based on **8**.



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



Scheme 4. Proposed mechanism for the condensation reaction of aldehydes, α-naphthol, and 1,3-dicarbonyl compounds.

2). Other ammonium triflates such as diphenylammonium triflate (DPAT) and dicyclohexylammonium triflate (DCAT) did not give improved yields and selectivity (Table 2, entries 2 and 3). It should be noted that $Sr(OTf)_2$, which was effective for the synthesis of benzo[*a*]xanthene,[14] did not promote the reaction at all under similar conditions (Table 2, entry 4). On the other hand, decreasing temperature favored the formation of **6a** and **7a**. Therefore, although better conditions were not found, it is reasonable to support that the proline triflate has higher activity and selectivity in this condensation reaction (Table 2, entry 1). Control experiment without proline triflate showed that only the starting materials were recovered.

To demonstrate the generality of this method, the scope of the reaction was investigated under the optimized conditions (10 mol % proline triflate in H_2O at reflux temperature), and the results are summarized in Table 3.

Gratifyingly, all the aromatic aldehydes employed here gave good yields of **2**. As shown in Table 3, electron-neutral, -rich, and -poor aromatic aldehydes were all compatible with this condition. It could also be concluded that the reaction rate of aromatic aldehydes with electron-donating groups is faster than those with electron-withdrawing groups. Furthermore, α,β-unsaturated aldehydes and heteroaromatic aldehydes also afforded good yields (Table 3, entries 5 and 6). However, the reaction failed with aliphatic aldehydes such as propionaldehyde and cyclohexanecarbaldehyde (Table 3, entries 7 and 8). In these cases, 1,8-dioxo-dodecahydroxanthene **6g** was the exclusive product.

On the basis of the above-mentioned results, this process was then extended to other cyclic 1,3-dicarbonyl compounds, such as cyclohexane-1,3-dione and cyclopentane-1,3-dione. As summarized in Table 3, good yields of the corresponding tetrahydrobenzo[*c*]xanthen-8-one derivatives and dihydrobenzo[*h*]cyclopenta[*b*]chromen-8-one derivatives were obtained regardless of structural variations in the cyclic 1,3-dicarbonyl compounds.

Encouraged by this success, we attempted to synthesize benzo[*a*]xanthenes **1** from β-naphthol, aldehydes and 1,3-dicarbonyl compounds under similar conditions (Table 4). Good yields were obtained for all cases, all the aldehydes and 1,3-dicarbonyl compounds gave the corresponding benzo[*a*]xanthenes as the major products. By contrast, the reaction between phenol, aldehyde, and 1,3-dicarbonyl compounds resulted in no target product under the same reaction conditions.

With the above-mentioned results in hand, a plausible mechanism of this condensation reaction was proposed in Scheme 4. The first step was the condensation of the aldehyde **4** with the catalyst to form an iminium ion **9**.[17] Iminium ion was then attacked by the 1,3-dicarbonyl compound to give intermediate **12**. Subsequently, *ortho* C-alkylation of α-naphthol with intermediate **12** produced **7a**. Title product **2a** was obtained by loss of a molecule of H_2O. Otherwise, the intermediate may react with 1,3-dicarbonyl compound via a conjugate addition to form 4*H*-pyran derivatives **6a**. The latter pathway has been proved by the reaction between aldehyde **4** and 1,3-dicarbonyl compound **5a**, where only **6a** was obtained in the absence of α-naphthol under the same condition.

In summary, we have developed an efficient synthesis of benzo[*c*]xanthene derivatives[18] via a one-pot condensation of α-naphthol, aldehydes, and cyclic 1,3-dicarbonyl compounds in the present of proline triflate. Further applications of proline triflate on the extension of this protocol are ongoing in our laboratory.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (No. 20806073), Technology Projects of Zhejiang (No. 2008C11046), the Opening Foundation of Zhejiang Provincial Top Key Pharmaceutical Discipline for financial support. We also thank professor Xiaoxia Wang of Zhejiang Normal University for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.149.

References and notes

1. Zelefack, F.; Guilet, D.; Fabre, N.; Bayet, C.; Chevalley, S.; Ngouela, S.; Lenta, B. N.; Valentin, A.; Tsamo, E.; Dijoux-Franca, M. G. *J. Nat. Prod.* **2009**, *72*, 954.
2. Poupelin, J. P.; Saint-Ruf, G.; Foussard-Blanpin, O.; Narcisse, G.; Uchida-Ernouf, G.; Lacroix, R. *Eur. J. Med. Chem.* **1978**, *13*, 67.
3. Nguyen, H. T.; Lallemand, M. C.; Boutefnouchet, S.; Michel, S.; Tillequin, F. *J. Nat. Prod.* **2009**, *72*, 527.
4. (a) Peters, A. T.; Bide, M. J. *Dyes Pigments* **1985**, *6*, 349; (b) Banerjee, A.; Mukherjee, A. K. *Stain Technol.* **1981**, *56*, 83.
5. (a) Liu, J.; Diwu, Z.; Leung, W. Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2903; (b) Knight, C. G.; Stephens, T. *Biochem. J.* **1989**, *258*, 683.
6. (a) Ahmad, M.; King, T. A.; Ko, D. K.; Cha, B. H.; Lee, J. *J. Phys. D: Appl. Phys.* **2002**, *35*, 1473; (b) Sirkencioglu, O.; Talinli, N.; Akar, A. *J. Chem. Res. Synop.* **1995**, 502.
7. Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.
8. Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169.
9. Wang, J. Q.; Harvey, R. G. *Tetrahedron* **2002**, *58*, 5927.
10. (a) Jha, A.; Beal, J. *Tetrahedron Lett.* **2004**, *45*, 8999; (b) Yoshida, H.; Wasahiko, W.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049.
11. Das, B.; Laxminarayana, K.; Krishnaiah, M.; Srinivas, Y. *Synlett* **2007**, 3107.
12. Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron* **2009**, *65*, 7129.
13. Khurana, J. M.; Magoo, D. *Tetrahedron Lett.* **2009**, *50*, 4777.
14. Li, J. J.; Tang, W. Y.; Lu, L. M.; Su, W. K. *Tetrahedron Lett.* **2008**, *49*, 7117.
15. (a) Wakatsugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249; (b) Funatomi, T.; Wakasugi, K.; Misaki, T.; Tanabe, Y. *Green Chem.* **2006**, *8*, 1022; (c) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*,

4168; (d) Iida, A.; Osada, J.; Nagase, R.; Misaki, T.; Tanabe, Y. *Org. Lett.* **2007**, *9*, 1859.
16. (a) Fang, D.; Gong, K.; Liu, Z. L. *Catal. Lett.* **2009**, *127*, 291; (b) Amalraj, J.; Palamari, J. P. Y.; Srinivasan, P. *Chem. J. Mol. Catal. A: Chem.* **2006**, *248*, 121.
17. (a) Seebach, D.; Groselj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2008**, *91*, 1999; (b) Groselj, U.; Schweizer, W. B.; Ebert, M. O.; Seebach, D. *Helv. Chim. Acta* **2009**, *92*, 1.
18. *Typical procedure for the preparation of compound* **2a**: To a mixture of α-naphthol (1.0 mmol) **3**, benzaldehyde (1.0 mmol) **4a**, and 5,5-dimethylcyclohexane-1,3-dione (1.0 mmol) **5a** was added proline triflate (0.1 mmol) in H_2O (2 mL). The progress of the reaction was monitored by TLC. The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:10) to provide 10,10-dimethyl-7-phenyl-10,11-dihydro-7*H*-benzo[*c*]xanthen-8(9*H*)-one **2a**. White solid; mp: 155.7–156.9 °C. IR (KBr): ν_{max} = 2958, 2935, 1650, 1628, 1370, 1253, 807 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.58–7.55 (m, 1H), 7.52–7.48 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.23–7.19 (m, 2H), 7.16–7.09 (m, 2H), 5.13 (s, 1H), 2.75 (d, *J* = 17.2 Hz, 1H), 2.68 (d, *J* = 17.2 Hz, 1H), 2.32 (d, *J* = 16.0 Hz, 1H), 2.26 (d, *J* = 16.0 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.0, 164.2, 145.8, 133.1, 128.4, 128.2 (CH × 2), 127.7 (CH × 2), 127.0 (CH × 2), 126.4 (CH × 3), 126.3, 124.6, 123.7, 121.0, 119.9, 113.6, 50.9, 41.5, 32.3, 29.2, 27.5. MS (ESI): *m*/*z* = 355 $[M+1]^+$. HRMS-ESI: calcd for $C_{25}H_{23}O_2$: 355.1698; found: 355.1680.