Strontium triflate catalyzed one-pot condensation of β-naphthol, aldehydes and cyclic 1,3-dicarbonyl compounds

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ABSTRACT

An efficient one-pot condensation of β-naphthol, aldehydes, and cyclic 1,3-dicarbonyl compounds has been achieved with strontium triflate as a catalyst, thus a variety of 8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one or 8,9-dihydrobenzo-[*f*]cyclopenta[*b*]chromen-10(11*H*)-one derivatives were prepared in good yields.

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Xanthenes and benzoxanthenes have attracted considerable interest because they possess various biological activities such as anti-inflammatory,[1] antiviral,[2] and antibacterial.[3] Some of them have been used as antagonists for paralyzing the action of zoxazolamine[4] and in photodynamic therapy.[5] Moreover, these compounds can be used as dyes,[6] pH-sensitive fluorescent materials for the visualization of biomolecular assemblies[7] and in laser technologies.[8] Therefore, the synthesis of xanthene derivatives (Fig. 1) is of great importance.

Recently, rare earth metal triflates, a new type of Lewis acid, were widely used in organic synthesis due to their low toxicity, high stability, ease of handling, water tolerance, and recoverability from water.[9] In our previous studies, we have successfully applied metal triflates into several reactions.[10] Very recently, we reported the reaction of β-naphthol, aldehydes, and amides forming amidoalkyl naphthols[11] and condensation of β-naphthol and aromatic aldehydes affording dibenzoxanthenes.[12] In continuation with the investigation, we found that one-pot condensation of β-naphthol, aldehydes, and cyclic 1,3-dicarbonyl compounds could be

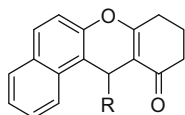**Figure 1.** Xanthenes.

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achieved in the presence of strontium triflate, thus tetrahydrobenzo[*a*]xanthen-11-one derivatives **5** and dihydrobenzo[*f*]cyclopenta[*b*] chromen-10-one derivatives **6** were obtained in good yields. To the best of our knowledge, only a few methods were reported on the synthesis of tetrahydrobenzo[*a*]xanthen-11-one derivatives,[13] and no reports are available at all on the synthesis of dihydrobenzo[*f*]cyclopenta[*b*]chromen-10-one derivatives.

Initially, we investigated the condensation reaction of β-naphthol, benzaldehyde, and 5,5-dimethylcyclohexane-1,3-dione using different catalysts at reflux temperature, and the results are listed in Table 1 (Scheme 1). It was found that metal triflates showed better catalytic activity among these catalysts. Most excitingly, when Sr(OTf)$_2$ was used, the reaction proceeded very smoothly and gave the product **5a** in 85% yield (Table 1, entry 9). Moreover, we found that the yields were obviously affected by the amount of Sr(OTf)$_2$ loaded. When 1 mol %, 5 mol %, 10 mol %, and 15 mol % of Sr(OTf)$_2$ were used, the yields were 25%, 75%, 85%, and 86%, respectively (Table 1, entries 9–12). Therefore, 10 mol % of Sr(OTf)$_2$ was sufficient and excessive amount of catalyst did not increase the yields significantly (Table 1, entries 9). The catalytic activity of the recycled Sr(OTf)$_2$ was also examined. Sr(OTf)$_2$ could be reused five times for the reaction without noticeable loss of activity (Table 1, entry 9). In addition, no product was detected in the absence of the catalyst. The above results showed that Sr(OTf)$_2$ was essential in the reaction, and the best results were obtained when the reaction was carried out with 10 mol % of Sr(OTf)$_2$ in 1,2-dichloroethane at 80 °C (Table 1, entry 9).

Then, we examined the above reaction in various solvents (Table 2). The results indicate that different solvents affected the

Table 1
Lewis acids catalyzed one-pot condensation of β-naphthol, benzaldehyde, and 5,5-dimethylcyclohexane-1,3-dione[a]

Entry	Catayst	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	La(OTf)$_3$	10	5	31
2	Y(OTf)$_3$	10	5	35
3	ZnCl$_2$	10	5	35
4	AlCl$_3$	10	5	49
5	Yb(OTf)$_3$	10	5	51
6	Zn(OTf)$_2$	10	5	73
7	Mg(OTf)$_2$	10	5	75
8	Cu(OTf)$_2$	10	5	80
9[c]	Sr(OTf)$_2$	10	5	85, 87, 85, 85, 84
10	Sr(OTf)$_2$	1	5	25
11	Sr(OTf)$_2$	5	5	75
12	Sr(OTf)$_2$	15	5	86

[a] Reaction conditions: β-naphthol (1.0 mmol), benzaldehyde(1.0 mmol), and 5,5-dimethylcyclohexane-1,3-dione (1.1 mmol), 1,2-dichloroethane as solvent, 80 °C.
[b] Isolated yield.
[c] Catalyst was reused five times.
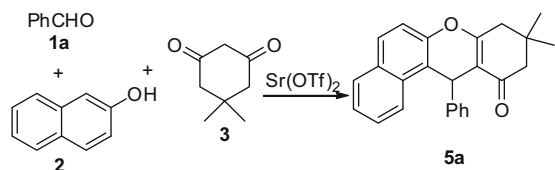
Scheme 1. Reaction of β-naphthol, benzaldehyde, and 5,5-dimethylcyclohexane-1,3-dione.

efficiency of the reaction. Acetonitrile, ethanol, nitromethane, and chloroform afforded low yields (Table 2, entries 3–6), while when water and tetrahydrofuran were used as solvents, no products were detected (Table 2, entries 1 and 2). The use of solvents such as [bpy]BF$_4$, DMF, and toluene could improve the yields (Table 2, entries 8–10). Especially, the reaction could be carried out under solvent-free condition and gave moderate yield (Table 2, entry 7). Finally, when 1,2-dichloroethane was used, the yield increased to

Table 2
Solvent effect on the reaction of β-naphthol, benzaldehyde, and 5,5-dimethylcyclohexane-1,3-dione catalyzed by Sr(OTf)$_2$

Entry	Solvent	Temperature	Time (h)	Yield[a] (%)
1	Water	80 °C	5	–
2	THF	Reflux	5	–
3	CH$_3$CN	Reflux	5	<5
4	CH$_3$CH$_2$OH	Reflux	5	<10
5	CH$_3$NO$_2$	80 °C	5	30
6	CHCl$_3$	Reflux	5	42
7	None	80 °C	5	56
8	[bpy]BF$_4$	80 °C	5	60
9	DMF	80 °C	5	69
10	Toluene	80 °C	5	55
11	ClCH$_2$CH$_2$Cl	80 °C	5	85

[a] Isolated yield.

85% (Table 2, entry 11) better than any other solvents examined here.

In addition, two by-products were characterized. One was aryl-14H-dibenzo[a,j]xanthene **7a**, the other was trace adduct of dinaphthalenol, both of which were formed from the condensation of 2 equiv of β-naphthol and 1 equiv of benzaldehyde (Scheme 2). The side reactions were also observed in our previous work.[12] However, the corresponding of **5a** and **7a** were the major products when Sr(OTf)$_2$ was employed as the catalyst, hence, showing good chemoselectivity (Scheme 2).

In order to study the generality of this procedure, a series of aldehydes and cyclic 1,3-dicarbonyl compounds were applied. The results are shown in Table 3.

In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. It could also be concluded that the aldehydes bearing electron-withdrawing groups required shorter time and gave higher yields (Table 3).
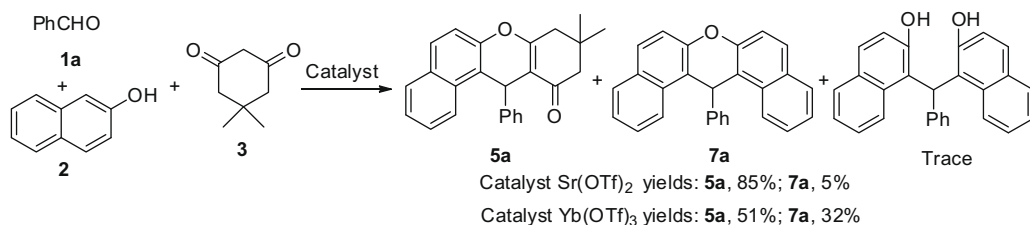
With the successful condensation of aromatic aldehydes, β-naphthol, and 5,5-dimethylcyclohexane-1,3-dione **3**, we further studied the reaction of aromatic aldehydes, β-naphthol, and cyclopentane-1,3-dione **4** under similar conditions. It was found that the corresponding tetrahydrobenzo[a]xanthen-11-one **5** and dihydrobenzo[f]cyclopenta-[b]chromen-10-one **6** could also be obtained in good yields (Scheme 3 and Table 3).

On the basis of the above results, this process was then extended to heterocyclic and aliphatic aldehydes. Thiophene-2-carbaldehyde, propionaldehyde, and pivalaldehyde afforded the corresponding products (**5f**, **5g**, **5h**) in 70%, 75%, and 73% yields, respectively (Table 3, entries 6–8). Compared with aromatic aldehydes, heterocyclic or aliphatic aldehydes afforded relatively lower yields of the corresponding **5** (Table 3).

A tentative mechanism for the formation of derivatives **5** is proposed in Scheme 4. By referring to the literature,[14] we supposed that the reaction may proceed via the ortho-quinone methides intermediate **8**, which was formed by the nucleophilic addition of β-naphthol to aldehyde catalyzed with Sr(OTf)$_2$. Subsequent

Table 3
Synthesis of xanthenes in the presence of Sr(OTf)$_2$[15]

Entry	R^1	R^2	Product	Time (h)	Yield[a] (%)
1	C$_6$H$_5$	CH$_3$	**5a**	5	85
2	3-CH$_3$-4-CH$_3$–C$_6$H$_3$	CH$_3$	**5b**	6	82
3	p-(OCH$_3$)C$_6$H$_4$	CH$_3$	**5c**	6	78
4	p-(Cl)C$_6$H$_4$	CH$_3$	**5d**	5	88
5	m-(NO$_2$)C$_6$H$_4$	CH$_3$	**5e**	5	86
6	CH$_3$CH$_2$	CH$_3$	**5f**	7	70
7	CH$_3$C(CH$_3$)$_2$	CH$_3$	**5g**	7	75
8	2-Thiophene	CH$_3$	**5h**	7	73
9	3-CH$_3$-4-CH$_3$–C$_6$H$_3$	H	**5i**	6	81
10	C$_6$H$_5$	H	**5j**	5	85
11	p-(Cl)C$_6$H$_4$	H	**5k**	5	86
12	3-CH$_3$-4-CH$_3$–C$_6$H$_3$	–	**6a**	6	82
13	C$_6$H$_5$	–	**6b**	5	86
14	p-(Cl)C$_6$H$_4$	–	**6c**	5	89

[a] Isolated yield.

Catalyst Sr(OTf)$_2$ yields: **5a**, 85%; **7a**, 5%

Catalyst Yb(OTf)$_3$ yields: **5a**, 51%; **7a**, 32%

Scheme 2. The condensation reaction catalyzed with different catalyst.
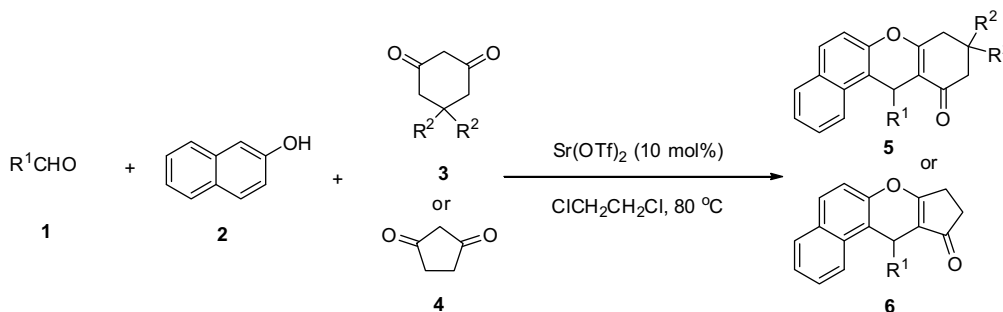
Scheme 3. Sr(OTf)$_2$ catalyzed condensation of β-naphthol, aldehydes, and cyclic 1,3-dicarbonyl compounds.
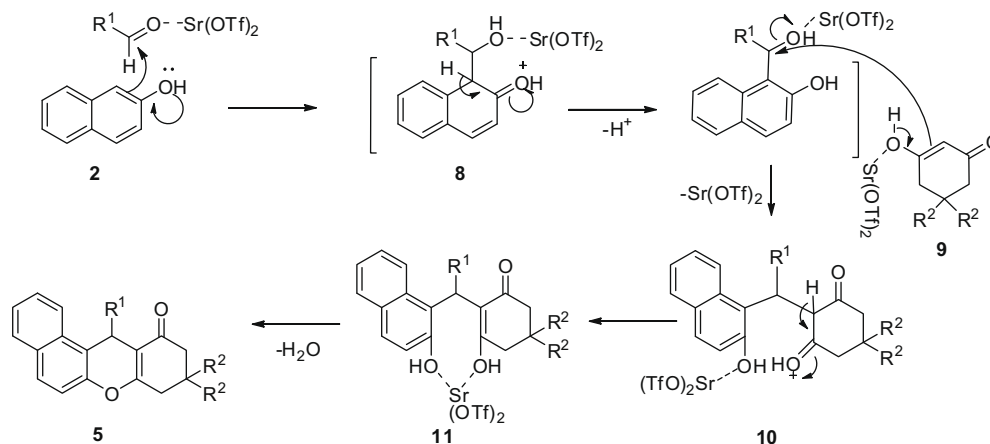
Scheme 4. Proposed mechanism for the condensation reaction of aldehydes, β-naphthol and 1,3-dicarbonyl compounds.

substitution of the oxygen atom, which was coordinated by strontium triflate, with cyclic 1,3-dicarbonyl compounds **9** afforded **11**. Then compounds **11** eliminated one molecule of H$_2$O and afforded title products **5**.

In summary, we have described an efficient and mild method for the preparation of 8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones and 8,9-dihydrobenzo-[*f*]cyclopenta[*b*]chromen-10(11*H*)-ones. This process is efficiently promoted by the strontium triflate. Unlike other existing methods, the advantages of this method include the use of recyclable catalyst, good chemoselectivity, high yields, simple workup procedure, and easy isolation. Further applications of strontium triflate on the extension of this protocol are ongoing in our group.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.129.

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15. *General procedure for the preparation of 8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives and 8,9-dihydrobenzo[f]cyclopenta[b]chromen-10(11H)-one derivatives*: To a mixture of β-naphthol (1.0 mmol), aldehyde (1.0 mmol), and cyclic 1,3-dicarbonyl compounds (1.1 mmol) was added strontium triflate (0.1 mmol) in 1,2-dichloroethane (2 mL). The mixture was stirred at 80 °C for the given time (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, water was added and the product was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (MgSO$_4$) and evaporated, and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to provide the pure product.Spectral data for selected products:
12-(3,4-dimethylphenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (**5b**). White crystals; mp 181–182 °C; yield: 82%. ^{1}H NMR (500 MHz,

CDCl$_3$): δ 8.04 (1H, d, J = 8.5 Hz, Ar-H), 7.77–7.72 (2H, m, Ar-H), 7.43–7.25 (3H, m, Ar-H), 7.10–7.03 (2H, m, Ar-H), 6.91 (1H, d, J = 8.0 Hz, Ar-H), 5.63 (1H, s, CH), 2.56 (2H, dd, J_1 = 2.5 Hz, J_2 = 17.5 Hz, CH$_2$), 2.27 (2H, dd, J_1 = 4.0 Hz, J_2 = 16.0 Hz, CH$_2$), 2.13 (3H, s, CH$_3$), 2.09 (3H, s, CH$_3$), 1.11 (3H, s, CH$_3$), 0.99 (3H, s, CH$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): 196.2, 163.8, 147.7, 142.3, 136.2, 134.4, 131.5, 129.7, 129.5, 128.7, 128.4 (CH × 2), 127.0, 125.9, 124.9, 123.8, 118.1, 117.1, 114.5, 51.0, 41.4, 34.3, 32.4, 29.2, 27.4, 20.0, 19.4. IR ν_{max} (KBr): 3125, 2958, 1650, 1593, 1398, 1371, 1237, 1226, 1172, cm^{-1}. MS (EI) m/z 382 (M$^+$, 40), 277 (100).

11-(3,4-dimethylphenyl)-8,9-dihydrobenzo[f]cyclopenta [b]chromen-10(11H)-one **(6a).** White crystals; mp 223–224 °C; yield: 82%. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.83–7.79 (3H, m, Ar-H), 7.40–7.36 (3H, m, Ar-H), 7.03–6.93 (3H, m, Ar-H), 5.50 (1H, s, CH), 2.79–2.75 (2H, m, CH$_2$), 2.50–2.47 (2H, m, CH$_2$), 2.13 (3H, s, CH$_3$), 2.12 (3H, s, CH$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): 202.5, 177.1, 149.2, 141.2, 136.6, 134.8, 131.9, 131.8, 129.7, 129.4, 129.3, 128.4, 127.1, 125.5, 125.1, 124.2, 119.2, 117.4, 116.5, 35.5, 33.8, 25.3, 19.9, 19.4. IR ν_{max} (KBr): 3407, 3131, 1709, 1670, 1591, 1396, 1237, cm^{-1}. MS (EI) m/z 340 (M$^+$, 10), 178 (22), 235 (100).