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Cascade Nucleophilic Addition–Cyclic Michael Addition of Arynes and Phenols/Anilines Bearing Ortho α,β-Unsaturated Groups: Facile Synthesis of 9-Functionalized Xanthenes/Acridines

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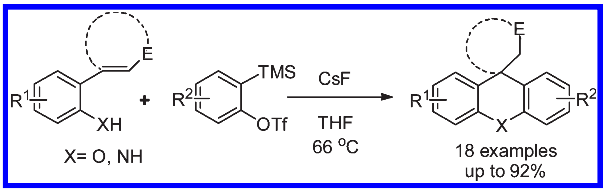

A facile synthesis of xanthenes and acridines based on a cascade nucleophilic addition–cyclic Michael addition process of arynes and phenols/anilines substituted with α,β-unsaturated groups at the ortho positions is described. The reaction has also been successfully extended to the synthesis of 9-spiro-xanthene and acridine derivatives with potential biochemical interest.

Xanthenes and acridines are of biochemical and pharmaceutical importance.[1] A class of fluorescent dyes including fluoresceins, rhodamines, etc., which have a xanthene nucleus, exhibit essentiality in labeling proteins,[2] riboses,[3] and cell processes.[4] Some xanthenes are good protein[5] or peptide[6] receptor antagonists and potentially useful as *anti*-Alzheimer drugs.[7] Recently, xanthene derivatives were referred to photocatalysts in metal-free hydrogenations[8] and ligands in transition metal catalysis.[9] The unit of acridines also frequently shows up in many useful dyes which could bond to RNA.[10] Moreover, acridine derivatives such as AcrHRs are haptens of catalytic antibody 9D9[11] and play particular roles in biocatalysis[12] and organic chemistry.[13] Acridines are potential drugs due to their trypanocidal activities.[14] It is notable that although substituents at the 9 positions of xanthenes and acridines are essential linkers to attach biomolecules in these examples, the linking modes were rather limited. This is probably because of the fact that the existing strategies to afford 9-functionalized xanthenes or acridines are rare, most of which often include at least a Fiedel–Craft cyclization reaction[15] to construct the heterocyclic nucleus and subsequent manipulation at the 9 positions of these compounds.[16] So it is still desirable to develop

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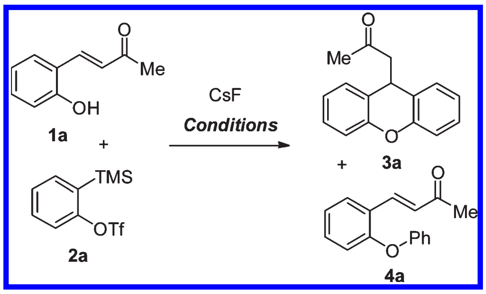
more efficient and facile methods to access 9-functionalized xanthene and acridine derivatives.

Since the innovation with the in situ generation of aryne from silylaryl triflates induced by fluoride anion,[17] research on aryne chemistry sprang up again. Due to their low-lying LUMO, arynes are highly apt to accept nucleophilic attacks.[18] Many cascade reactions triggered by nucleophilic additions to arynes have been developed.[19] Recently, the scaffolds of xanthene and acridine were constructed from a cascade nucleophilic addition−electrophilic cyclizing reaction of Nu-E bifunctional reagents and arynes. As the intramolecular Nu-E reagents, salicylaldehydes, *o*-hydroxylphenyl ketones,[20] salicylates, and their nitrogen- or sulfur-containing analogues participated well in these processes.[21] During our study on aryne chemistry,[22] we envisioned that 9-functionalized xanthenes or acridines may be obtained via a cascade nucleophilic addition−cyclic Michael addition process if the electrophilic countpart in the Nu-E reagents is replaced by α,*β*-unsaturated Michael acceptors, which seems difficult due to the limited examples of aryl carbanions participating in Michael addition.[23] Herein, we wish to report our results on this facile annulation using arynes and phenols/anilines bearing ortho-substituted α,*β*-unsaturated groups.

We started the investigation using 1 equiv of 4-(2-hydroxyphenyl)but-3-(*E*)-en-2-one **1a**, 1.5 equiv of aryne precursor 2-(trimethylsilyl)phenyl triflate **2a**, and 3.0 equiv of CsF in MeCN. After the reaction was stirred for 36 h at room temperature, the product 1-(9*H*-xanthen-9-yl)propan-2-one **3a** was obtained in a yield of 29%, and the arylation product 4-(2-phenoxyphenyl)but-3-(*E*)-en-2-one **4a** was also isolated in 58% yield with 5% of **1a** being recovered (Table 1, entry 1). Increasing the amount of CsF to 4.0 equiv, the starting materials were completely consumed in a shorter time, but the yield of **3a** was only slightly improved to 31% (Table 1, entry 2). Gratifyingly, when we used THF as solvent, the formation of **4a** was reduced to 5.6%, and the yield of **3a** was improved to 84%, although a prolonged reaction time of 6 days was required at room temperature (Table 1, entry 3). Furthermore, the reaction conducted under reflux at 66 °C could furnished **3a** in a yield of 92% within 36 h (Table 1, entry 5). Therefore, the optimized conditions for the cascade reaction utilized 1.0 equiv of **1a**, 1.5 equiv of **2a**, and 4 equiv of CsF in THF at 66 °C.

With the optimal experimental conditions in hand, various ortho α,*β*-unsaturated phenols **1** and arynes were employed in the cascade nucleophilic addition−cyclic Michael addition reactions, and a variety of xanthenes were obtained in moderate to good yields (Table 2). First, to introduce substituents into the aromatic scaffolds of xanthenes, 5-halo-substrates **1b** and **1c** and 3,5-dialkyl substrate **1d** were tested to react with unsubstituted aryne precursor **2a**. The incorporated halogen atoms were well tolerated, and the reactions afforded the products **3b** and **3c** in 91% and 84% yields, respectively (Table 2, entries 2 and 3). However, probably due to the steric repulsive interaction of the *tert*-butyl group appended at the 3-position in **1d**, a decreased yield of **3d** was observed (Table 2, entry 4). Next, we examined the reactions of aryne and substrates **1** containing other unsaturated groups at the ortho position. As the EWG of Michael acceptors, not only the acyl group, but also the benzoyl, methoxycarbonyl, and cyano groups

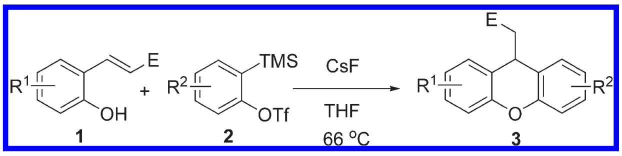
TABLE 1. Optimization Experiments on the Synthesis of Xanthene 3a[a]



entry	equiv of CsF	solvent	T (°C)	time (h)	yield (%)[b] 3a	4a
1[c]	3	MeCN	rt	36	29	58
2	4	MeCN	rt	24	31	61
3	4	THF	rt	144	84	5.6
4	4	THF	40	72	89	6.3
5	**4**	**THF**	**66**	**36**	**92**	**7.0**

[a]The reactions were carried out with **1a** (0.6 mmol), **2a** (0.9 mmol), and a specified amount of CsF in 20 mL of solvent. [b]The reactions were monitored by TLC. Isolated yields based on 1 equiv of **1a**. [c]0.05 equiv of **1a** was recovered.

TABLE 2. Synthesis of Xanthenes 3[a]



entry	1	E	R[1]	2	R[2]	product	yield (%)[b]
1	**1a**	MeCO	H	**2a**	H	**3a**	92
2	**1b**	MeCO	5-Br	**2a**	H	**3b**	91
3	**1c**	MeCO	5-Cl	**2a**	H	**3c**	84
4	**1d**	MeCO	3,5-t-Bu_2	**2a**	H	**3d**	64
5	**1e**	C_6H_5CO	H	**2a**	H	**3e**	72
6	**1f**	MeO_2C	H	**2a**	H	**3f**	64
7	**1g**	CN	H	**2a**	H	**3g**	73
8[c]	**1a**	MeCO	H	**2b**	4,5-Me_2	**3h**	77
9[d]	**1a**	MeCO	H	**2c**	4-F	**3ia** + **3ib**	47 + 23

[a]Unless otherwise specified, the reactions were conducted with **1** (0.6 mmol), **2** (0.9 mmol), and CsF (2.4 mmol) in 20 mL of THF at 66 °C for 36 h. [b]The reactions were monitored by TLC. Isolated yields based on **1**. [c]A reaction time of 96 h was needed. [d]A reaction time of 54 h was needed.

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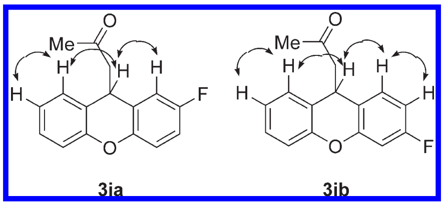
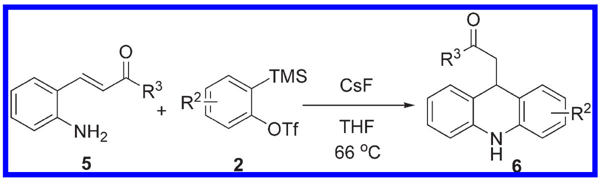


FIGURE 1. NOE experiments on **3ia** and **3ib**.

TABLE 3. Synthesis of Acridines 6[a]



entry	5	R^3	2	R^2	product	yield (%)[b]
1	**5a**	C_6H_5	**2a**	H	**6a**	54
2	**5b**	4-ClC_6H_4	**2a**	H	**6b**	55
3	**5c**	3-MeOC_6H_4	**2a**	H	**6c**	52
4	**5d**	Me	**2a**	H	**6d**	53
5[c]	**5b**	4-ClC_6H_4	**2b**	4,5-Me_2	**6e**	43
6[d]	**5b**	4-ClC_6H_4	**2d**	6-Me	**6fa** + **6fb**	47 + 6.2

[a]Unless otherwise specified, the reactions were conducted with **5** (0.6 mmol), **2** (0.9 mmol), and CsF (2.4 mmol) in 20 mL of THF at 66 °C for 36 h. [b]The reactions were monitored by TLC. Isolated yields based on **5**. [c]A reaction time of 120 h was needed. [d]A reaction time of 168 h was needed.

have all been well tolerated in the reactions, and moderate to good yields of products were obtained (Table 2, entries 5−7).

When symmetric aryne precursor 4,5-dimethyl-2-(trimethylsilyl)phenyl triflate **2b** was employed to react with **1a**, the reaction gave the expected product **3h** in 77% yield. Nevertheless, regioisomers **3ia** and **3ib** were isolated in 47% and 23% yields when asymmetrical aryne precursor 4-fluoro-2-(trimethylsilyl)phenyl triflate **2c** was used. The regiochemistry of compounds **3ia** and **3ib** was identified by NOE experiments (Figure 1). This result could be rationalized by the electric effects in the step of nucleophilic addition to aryne with a fluoro group.[24]

We then applied this method to prepare acridines. Utilizing unsubstituted aryne precursor **2a** and **5a** under optimal condition, the reaction proceeded smoothly at 66 °C to give the derived product **6a** in 54% yield (Table 3, entry 1). As the EWG of Michael acceptors of substrates **5**, halogen or alkoxy group substituted phenyl carbonyls and alkyl carbonyl were tolerated by the procedure, which furnished corresponding products **6b**, **6c**, and **6d** in moderate yields (Table 3, entries 2, 3, and 4).

Comparing with the reaction of unsubstituted aryne precursor **2a**, the reaction of symmetrically substituted aryne precursor **2b** and **5b** gave a slightly lower yield (Table 3, entry 5). When unsymmetrical aryne precursor 6-methyl-2-(trimethylsilyl)phenyl triflate **2d** was applied in

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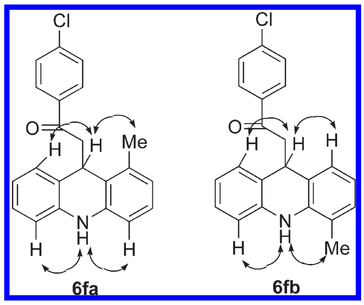
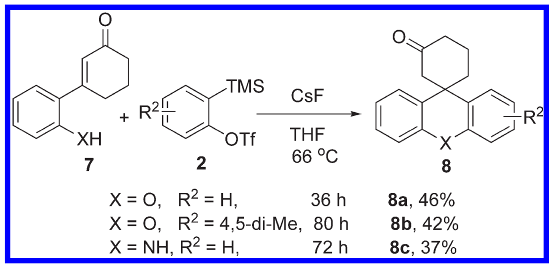


FIGURE 2. NOE experiments on **6fa** and **6fb**.

SCHEME 1. Synthesis of 9-Spiro Xanthenes and Acridines 8[a,b]



[a]The reactions were conducted with **7** (0.6 mmol), **2** (0.9 mmol), and CsF (2.4 mmol) in 20 mL of THF at 66 °C. [b]The reactions were monitored by TLC. Isolated yields based on **7**.

the reaction, a 47% yield of sterically favored product **6fa** and only a 6.2% yield of unfavored **6fb** were obtained. This regioselectivity, determined by NOE experiments (Figure 2), might result from the steric effect of the methyl group in **2d** during the nucleophilic addition step.[24]

In addition, we extended this methodology to synthesize 9-spiro xanthenes and acridines. Under the established conditions, the targeted products **8a**, **8b**, and **8c** could be obtained smoothly in moderate yields (Scheme 1), which were difficult to prepare in traditional methods[25] and might be potentially worthy as drugs.[25d]

In conclusion, we have developed a useful methodology to synthesize 9-functionalized xanthenes and acridines of potential biochemical interest via cascade intermolecular nucleophilic addition and intramolecular cyclic Michael addition cyclization. Variations of this cascade reaction to synthesize other meaningful structures are expected.

Experimental Section

General Procedure for the Synthesis of 9-Substituted Xanthenes 3. Under an atmosphere of dry nitrogen, **1** (0.6 mmol) and 4.0 equiv of CsF (2.4 mmol) were added to an oven-dried Schlenk tube equipped with a stirring bar, then the tube was sealed with a rubber plug. After evacuating and backfilling the Schlenk with nitrogen for three cycles, 20 mL of anhydrous THF was added followed by the addition of 1.5 equiv of aryne precursor **2** (0.9 mmol) by syringes. The mixture was stirred at 66 °C. After complete consumption of the starting materials (monitored by TLC; a reaction time of 36 h was

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needed unless otherwise specified), the mixture was diluted with 20 mL of ethyl acetate and then filtered through a pad of silica gel to remove the insoluble substances. After the filtrates were concentrated in vacuo, the residue was purified by flash chromatography on silica gel to afford **3**.

1-(9*H*-Xanthen-9-yl)propan-2-one (3a): pale white solid, mp 99−101 °C (recrystallized from petroleum ether/ethyl acetate 100:1 v/v after purification by flash chromatography (eluent: petroleum ether/ethyl acetate 40:1 v/v)) (lit.[26] mp 103 °C); R_f 0.52 (TLC eluent: petroleum ether/ethyl acetate 10:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.04 (t, J = 7.6 Hz, 2H), 4.61 (t, J = 6.8 Hz, 1H), 2.80 (d, J = 6.8 Hz, 2H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 34.3, 54.3, 116.5, 123.4, 125.2, 127.8, 128.5, 152.1, 206.6; IR (neat) 2920, 1703, 1479, 1455, 1259, 752 cm^{-1}; GC-MS (70 eV, EI) m/z 238 [M]$^+$; HRMS (EI) m/z calcd for $C_{16}H_{14}O_2$ [M]$^+$ 238.0994, found 238.0991.

The following compounds **6** and **8** were prepared similarly.

2-(9,10-Dihydroacridin-9-yl)-1-phenylethanone (6a): yellowish solid, mp 168−170 °C (recrystallized from petroleum ether after purification by flash chromatography (eluent: petroleum ether/ethyl acetate 40:1 v/v)) (lit.[27] mp 169−171 °C); R_f 0.45 (TLC eluent: petroleum ether/ethyl acetate 10:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J=7.2 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 6.8 Hz, 2H), 7.24 (d, J = 7.2 Hz, 2H), 7.08 (td, J = 7.6, 1.2 Hz, 2H), 6.84 (td, J = 7.5, 1.0 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 6.20 (s, 1H), 4.82 (t, J = 7.2 Hz, 1H), 3.21 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.4, 47.5, 113.7, 121.1, 123.7, 127.2, 128.1, 128.3, 128.7, 132.8, 137.3, 139.8, 198.6; MS (70 eV, EI) m/z 299 [M]$^+$; HRMS (EI) m/z calcd for $C_{21}H_{17}NO$ [M]$^+$ 299.1310, found 299.1308.

Spiro[cyclohexane-1,9′-xanthen]-3-one (8a): pale white solid, mp 124−126 °C (recrystallized from petroleum ether/ethyl acetate 100:1 v/v after purification by flash chromatography (eluent: petroleum ether/ethyl acetate 40:1 v/v)); R_f 0.16 (TLC eluent: petroleum ether/ethyl acetate 10:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.24 (m, 4H), 7.18−7.15 (m, 2H), 7.10 (td, J = 7.6, 1.2 Hz, 2H), 3.10 (s, 2H), 2.49 (t, J = 6.8 Hz, 2H), 1.86−1.83 (m, 2H), 1.66−1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 39.3, 41.0, 42.4, 47.7, 116.9, 123.4, 125.2, 127.8, 129.6, 152.2, 211.9; IR (neat) 2973, 2896, 1651, 1453, 1380, 1271, 1086, 1046, 880 cm^{-1}; MS (70 eV, EI) m/z 264 [M]$^+$; HRMS (EI) m/z calcd for $C_{18}H_{16}O_2$ [M]$^+$ 264.1150, found 264.1148.

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Supporting Information Available: General experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) For a report of **3a**, see: Krohnke, F.; Dickore, K. *Chem. Ber*. **1959**, *92*, 46.

(27) For a report on the synthesis of **6a**, see: Sheppard, C. S.; Levine, R. *J. Heterocycl. Chem*. **1964**, *1*, 67.