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One-Pot Synthesis of Xanthones and Thioxanthones by the Tandem Coupling–Cyclization of Arynes and Salicylates

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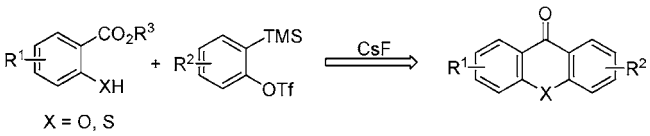
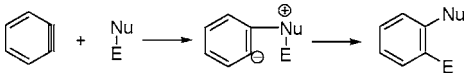
ABSTRACT



The reaction of silylaryl triflates, CsF, and salicylates affords a general and efficient way to prepare biologically interesting xanthones and thioxanthones. This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling and subsequent intramolecular electrophilic cyclization.

The xanthone ring is the core structure of a wide variety of naturally occurring and manmade compounds that exhibit extraordinary anti-inflammatory and anti-cancer activity.[1] Some xanthone-containing plant extracts are directly used in traditional medicines.[2] Analogous thioxanthone derivatives are also potential anti-cancer drugs.[3] Standard syntheses of the xanthone skeleton typically involve multistep procedures, which generally involve the intermediacy of a benzophenone or a diaryl ether, plus harsh reaction conditions, and/or strong acids or toxic metals are often employed.[3c,4] A mild approach to highly reactive arynes from silylaryl triflates was first reported by Kobayashi in 1983.[5] Recently, the reaction of these aryne precursors with CsF and nucleophiles bearing neighboring electrophiles has been shown to afford overall aryne insertion products (Scheme 1). In particular, nitrogen

Scheme 1



(ureas)[6] and carbon (ketoesters)[7] nucleophiles have been employed in this transformation, which presumably proceeds through a tandem intermolecular nucleophilic coupling, followed by intramolecular electrophilic cyclization, resulting in an overall insertion process. To the best of our knowledge, protic nucleophiles, such as phenols and thiols, have not been examined in this type of tandem process utilizing aryne precursors, although the insertion of arynes into the OH bond of phenols has been reported by our group.[8] We now wish

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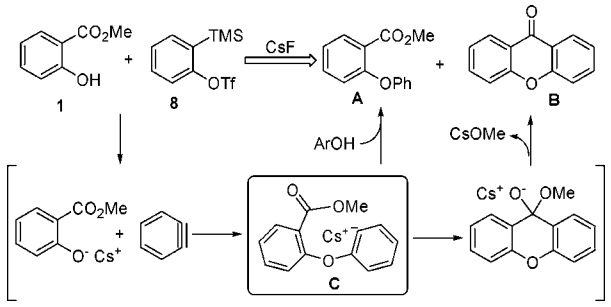
Scheme 2. Synthesis of Xanthones



to report a novel annulation reaction utilizing readily accessible salicylates and silylaryl triflates plus CsF, which appears to proceed through just such a tandem process and affords an efficient one-pot synthesis of biologically interesting xanthones and thioxanthones under very mild reaction conditions (Scheme 2).

A plausible mechanism for this synthetically useful xanthone synthesis is illustrated in Scheme 2. The key intermediate **C** generated from nucleophilic coupling of the aryne and the aryl oxide apparently undergoes intramolecular electrophilic cyclization to afford the desired xanthone **B**. However, H abstraction by **C** could also lead to the diaryl ether **A**. Since aromatic carbanions are usually generated in aprotic environments by organolithium reagents, the survival of intermediate **C** in the presence of protic substrates appears to be fairly challenging.

We first examined the reaction of methyl salicylate and the commercially available aryne precursor *o*-(trimethylsilyl)-phenyl triflate (**8**) in the presence of 4 equiv of CsF in 5 mL of MeCN. After 12 h reaction at room temperature, an 80% yield of a 2:3 mixture of methyl 2-phenoxybenzoate **A** and xanthone **B** was obtained, as shown in Table 1, entry 1.

Table 1. Optimization Studies[a]

entry	fluoride source	solvent	*T* (°C)	time (h)	% yield (**A**/**B**)[b]
1	4CsF	MeCN	rt	12	80 (2:3)
2	4CsF	acetone	rt	4	75 (3:5)
3	4CsF	CH_2Cl_2	rt	24	trace
4	4CsF	THF	rt	24	20 (1:20)
5	4CsF	THF	65	24	82 (1:11)
6	4CsF	THF	90	12	80 (1:6)
7	4TBAF	THF	65	3	60 (5:1)
8	2CsF	THF	65	24	65 (1:11)

[a] All reactions were conducted on a 0.25 mmol scale in 5 mL of solvent (sealed vial). The ratio of methyl salicylate to aryne precursor is 1:1.1.[b] The yield reported and the ratio of **A** to **B** in parentheses are determined by GC−MS analysis.

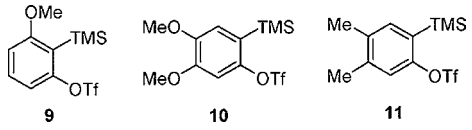
Although the proton abstraction process appears to be fairly competitive, we still felt that we might be able to suppress it by adjusting the reaction conditions, for example, using different solvents and concentrations to promote intramolecular cyclization over intermolecular proton abstraction.

Table 2. Coupling−Cyclization of Arynes and Salicylates

entry	salicylate	aryne precursor	product	% yield[a]
1	R = H **1**	**8**	**12**	75
2	R = OMe **2**	**8**	**13**	69
3	R = COMe **3**	**8**	**14**	58
4	R = F **4**	**8**	**15**	83
5	**5**	**8**	**12**	81
6	**6**	**8**	**16**	73
7	**1**	**9**	**17**	62[b]
8	**1**	**10**	**18**	57[b]
9	**1**	**11**	**19**	51[b]
10	**7**	**8**	**20**	64[c]
11	**7**	**9**	**21**	45[d]

[a] All reactions were conducted on a 0.25 mmol scale in the presence of 4 equiv of CsF and 1.1 equiv of silylaryl triflate in 5 mL of THF at 65 °C for 24 h (sealed vial). [b] The reaction was conducted in 5 mL of THF at 90 °C. [c] The reaction was conducted in 10 mL of THF at 65 °C under argon. [d] The reaction was conducted in 10 mL of THF at 90 °C under argon.

We next conducted the coupling−cyclization reaction in acetone, and a 75% yield of the diaryl ether **A** and the xanthone **B** was obtained in a 3:5 ratio (entry 2), which demonstrates the important role of solvent in this reaction. We then performed the reaction in CH_2Cl_2. However, only a trace of the xanthone was observed by GC−MS analysis (entry 3). When THF was used as the solvent at room temperature, a 20% yield of products **A** and **B** was obtained with large amounts of starting materials remaining. GC−MS analysis indicated that the ratio of **A** to **B** was 1:20, which suggested that proton abstraction was largely suppressed in this solvent (entry 4). When this same reaction was carried out at 65 °C for 24 h (entry 5), all of the starting materials were consumed and a 75% yield of xanthone **B** was isolated; only a trace of the diaryl ether **A** was evident



9 10 11

Figure 1. Aryne precursors.

by GC−MS analysis. The phenol or the HF generated by this process should be less acidic in THF than MeCN or acetone, which presumably helps to retard the proton abstraction process. Further investigation indicated that a reaction temperature of 90 °C (sealed vial) reduces the amount of xanthone, although it does shorten the reaction time considerably (entry 6). We also investigated the effect of the fluoride source on this tandem process. When tetrabutylammonium fluoride (TBAF) was employed in this reaction, the reaction was complete in 3 h, but the proton abstraction product **A** predominates (entry 7). A reaction carried out using only 2 equiv of CsF afforded only a 65% yield of a 1:11 ratio of **A** and **B** (entry 8). In conclusion, the optimal reaction conditions for this one-pot synthesis of xanthone utilizes 4 equiv of CsF in THF solvent at 65 °C for 24 h (entry 5).

Employing our optimal reaction conditions, we have investigated the reaction scope and limitations. These results are shown in Table 2. We first examined methyl salicylates bearing various functional groups. When methyl 5-methoxysalicylate (**2**) was employed, a 69% yield of xanthone **13** was obtained (entry 2). However, when methyl 5-acetylsalicylate (**3**) was used as the starting material, only a 58% yield of the substituted xanthone **14** was isolated by flash chromatography (entry 3). The coupling−cyclization reaction of methyl 5-fluorosalicylate (**4**) and aryne precursor **8** afforded an 83% yield of the xanthone **15** (entry 4). It appears that both moderate electron-donating and electron-withdrawing groups work fairly well in this tandem process. Since a phenoxy group is a better leaving group than a methoxy group, phenyl salicylate (**5**) has been employed in this reaction and an 81% yield of xanthone **12** was obtained (entry 5). Interestingly, the cross coupling of methyl 1-hydroxy-2-naphthoate (**6**) with silylaryl triflate **8** afforded a 73% yield of the xanthone **16** (entry 6).

We have also examined the behavior of the aryne precursors **9**, **10**, and **11** (Figure 1) in this reaction.[6,10] Aryne precursor **9** afforded a 62% yield of a single isomeric methoxyxanthone **17** after 24 h at 90 °C (entry 7). The regioselectivity of this reaction is presumably controlled by steric and electronic effects during the course of the nucleophilic coupling. When the dimethoxysilylaryl triflate **10** was allowed to react with methyl salicylate under the same reaction conditions, a 57% yield of the xanthone **18** was isolated (entry 8). Finally, the reaction of aryne precursor **11** with methyl salicylate afforded a 51% yield of the xanthone **19** (entry 9). With all of these substituted triflates, a higher reaction temperature is necessary.

At this stage, we envisioned that the analogous thiol nucleophiles could also be employed in this tandem process. Indeed, when methyl thiosalicylate (**7**) and 1.1 equiv of benzyne precursor (**8**) were treated with 4 equiv of CsF in 10 mL of THF at 65 C for 24 h, a 64% yield of thioxanthone (**20**) was isolated (entry 10). However, the reaction must be carried out under argon in order to prevent the oxidative homocoupling of the thiol to a disulfide, which is known to proceed smoothly in the presence of CsF on a Celite solid support in air.[9] The reaction of this thiol and benzyne precursor **9** under the same reaction conditions afforded a 45% yield of the desired thioxanthone **21** (entry 11).

In conclusion, we have demonstrated that protic nucleophiles, such as phenols and thiols, can be used in annulation reactions with silylaryl triflate aryne precursors through tandem nucleophilic coupling and electrophilic cyclization. This reaction affords a general one-pot approach to biologically interesting xanthone and thioxanthone derivatives under very mild reaction conditions. Efforts to extend this protocol to other heteroatom compounds and further mechanistic studies are underway.

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Supporting Information Available: Preparation and characterization of the xanthones and thioxanthones in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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