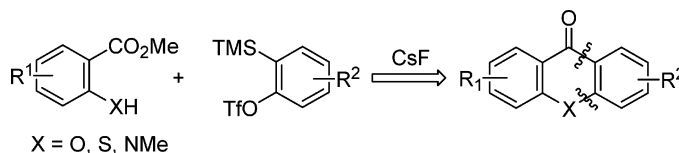# Synthesis of Xanthones, Thioxanthones, and Acridones by the Coupling of Arynes and Substituted Benzoates

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The reaction of silylaryl triflates, CsF, and *ortho*-heteroatom-substituted benzoates affords a general and efficient way to prepare biologically interesting xanthones, thioxanthones, and acridones. This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the benzoate with an aryne and a subsequent intramolecular electrophilic cyclization.

Introduction

Xanthones are secondary metabolites found in higher plant families, fungi, and lichens.[1] This class of compounds exhibits interesting pharmaceutical properties; specifically, antibacterial, anti-inflammatory, anticancer, and antiviral activities have been observed.[2] Some xanthone-containing plants, for example,

X = O   Xanthones
X = S   Thioxanthones
X = NR   Acridones
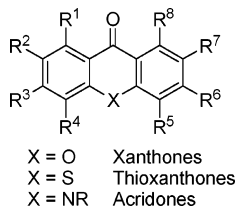
Cratoxylum cochinchinense (Lour.) Blume, have been used as traditional medicines to treat fever, coughing, diarrhea, itching, ulcers, and abdominal complaints.[3] Thioxanthone derivatives also exhibit interesting anticancer activities.[4] Xanthones are usually synthesized through the intermediacy of benzophenones or diaryl ethers under harsh reaction conditions and/or in the presence of strong acids or toxic metals.[5] Acridones are naturally occurring compounds exhibiting a variety of biological activities. They are important antileishmanial, antifungal, antitumor, and DNA-intercalating anticancer drugs.[6] Acridones are usually prepared by the acid-induced ring closure of *N*-phenyl anthranilic acids, which are usually obtained from Ullmann condensation of anilines with *ortho*-halogen-substituted benzoic acids. However, harsh reaction conditions and tedious workup procedures are generally required.[7] An efficient and general synthesis of each of these heterocycles is thus highly desirable.

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SCHEME 1. Aryne Insertion Reactions
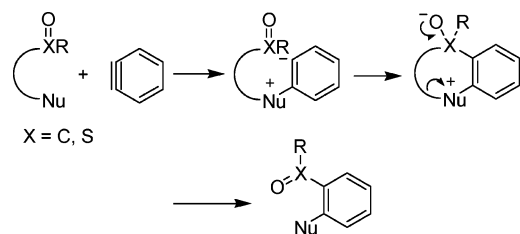
Benzyne, a highly reactive intermediate, was first proposed by Wittig in 1942,[8] and the structure was confirmed by Roberts in 1956 using ^{14}C isotope labeling.[9] Since then, many methods have been developed to generate benzynes, for example, the base-promoted elimination of hydrogen halide from aryl halides,[10] the elimination of *o*-dihaloaromatics with lithium amalgam or magnesium,[11] or the recently reported decomposition of 2-magnesiated aryl sulfonates.[12] In 1983, Kobayashi first reported a novel way to generate arynes from silylaryl triflate precursors in the presence of CsF.[13] Later, nucleophiles bearing neighboring electrophiles, such as ureas,[14] trifluoroacetanilides and sulfinamides,[15] and β-keto esters[16] were shown to react with these aryne precursors to afford the C−N bond or C−C bond insertion products (Scheme 1). These nucleophiles first undergo intermolecular nucleophilic attack on the aryne. Subsequent intramolecular electrophilic cyclization, followed by fragmentation, affords the final insertion product.

Recently, we communicated a novel annulation reaction utilizing readily accessible salicylates and silylaryl triflates plus CsF, which affords an efficient one-step synthesis of biologically interesting xanthones and thioxanthones (eq 1).[17] This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the benzoate and aryne and a subsequent intramolecular electrophilic cyclization. A fragmentation step, which is inevitable in the insertion examples, is not involved in this annulation process because the intermediate obtained from the cyclization is a stable six-membered ring system. Herein, we provide a full account of this efficient synthesis of xanthones and thioxanthones; plus, we also wish to report an extension of this coupling-cyclization strategy for the synthesis of biologically interesting acridones.
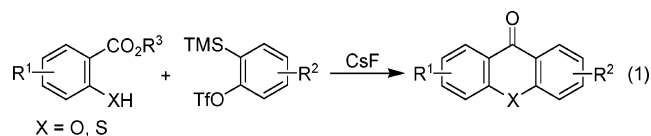

Results and Discussion

Optimization Studies. The reaction of methyl salicylate (**1a**) and the commercially available aryne precursor *o*-(trimethyl-

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TABLE 1. Optimization Studies

entry	fluoride source	solvent	temp (°C)	time (h)	% yield (3a:4a)[a]
1	4 CsF	MeCN	rt	12	80 (40:60)
2	4 CsF	acetone	rt	4	75 (38:62)
3	4 CsF	CH$_2$Cl$_2$	rt	24	trace
4	4 CsF	THF	rt	24	20 (5:95)
5	4 CsF	toluene	100	48	trace
6	4 CsF	MeNO$_2$	rt	24	−
7	4 CsF	THF	65	24	82 (8:92)
8	4 CsF	THF	90	12	80 (14:86)
9	4 CsF	THF	50	24	30 (6:94)
10	4 CsF	DME	65	24	70 (25:75)
11	4 TBAF	THF	65	3	60 (83:17)
12	2 CsF	THF	65	24	65 (8:92)

[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 to 1.1. The ratio of **3a** to **4a**, in parentheses, has been determined by GC−MS analysis.

SCHEME 2
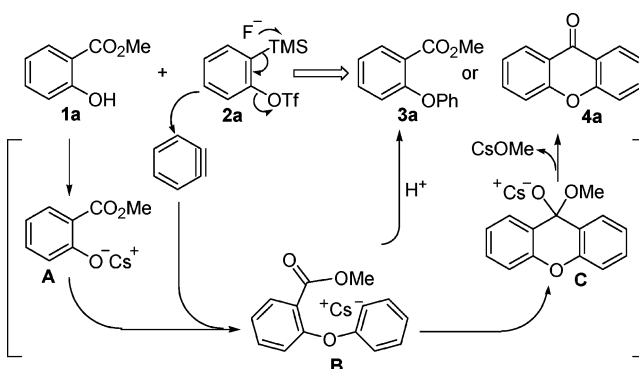
silyl)phenyl triflate (**2a**) was first conducted in the presence of 4 equiv of CsF in 5 mL of MeCN. After a 12 h reaction at room temperature, an 80% combined yield of methyl 2-phenoxybenzoate (**3a**) and xanthone (**4a**) was obtained in a 40:60 ratio (Table 1, entry 1). Presumably, this reaction proceeds through the key intermediate, **B**, generated by nucleophilic coupling of the aryne and the aryloxide, **A** (Scheme 2). The carbanion, **B**, can either undergo H abstraction to afford benzoate (**3a**) or intramolecular electrophilic cyclization to generate the xanthone (**4a**). The major problem here is the proton abstraction process, which could be suppressed by adjusting the reaction conditions, for example, using different solvents and concentrations. Thus, we next conducted the coupling-cyclization reaction in acetone, and a 75% yield of diaryl ether (**3a**) and xanthone (**4a**) was obtained in a 38:62 ratio (entry 2), which suggests that a less polar solvent should be examined. We then performed the reaction in CH$_2$Cl$_2$. However, only a trace of the xanthone (**4a**) was observed by GC−MS analysis after 24 h (entry 3). When THF was used as the solvent at room temperature, after 24 h of reaction, a 20% yield of products **3a** and **4a** was obtained, and a lot of the starting materials, **1a** and **2a**, was observed by GC−MS analysis. However, the ratio of **3a** to **4a** was 5:95, suggesting that proton abstraction has been almost completely suppressed (entry 4). When this reaction was conducted in toluene, only a trace of the product was evident by GC−MS analysis (entry 5). MeNO$_2$ also turned out to be an unsuitable solvent for this reaction (entry 6). At this point,

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TABLE 2. Synthesis of Xanthones[a]

entry	salicylate		aryne	product(s)		% yield	entry	salicylate	aryne	product(s)		% yield
	X						11		1k	2a		4k	52
1	H	1a	2a	4a		75	12	1l	2a		4a	81
2	3-OMe	1b	2a	4b		59	13	1m	2a		4a	0
3	4-OMe	1c	2a	4c		62[b]	14	1n	2a		4l	73
4	5-OMe	1d	2a	4d		69	15	1o	2a		4m	46[c]
5	6-OMe	1e	2a	4e		35	16	1p	2a		4n	0
6	5-COMe	1f	2a	4f		58	17	1a	2b		4e	62[b]
7	5-F	1g	2a	4g		83	18	1a	2c		4o	57[b]
8	5-Br	1h	2a	4h		75	19	1a	2d		4p	51[b]
9	5-Ph	1i	2a	4i		64	20	1a	2e	4j 4q		59[b] (1:1)
10	5-Me	1j	2a	4j		71	21	1a	2f		4r	45[b]

[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), unless otherwise stated. [b] The reaction was conducted in 5 mL of THF at 90 °C. [c] The yield has been determined by GC analysis due to the impurities in the product.
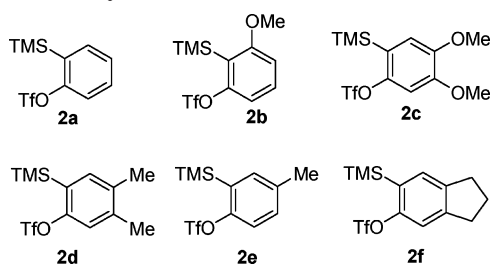
THF seemed to be the best solvent, at least as far as the reaction selectivity was concerned. The same reaction was then carried out at 65 °C in THF for 24 h. A 75% yield of xanthone (**4a**) was isolated by flash chromatography, and GC–MS analysis indicated only a trace of the diaryl ether **3a** was obtained (entry 7). Further investigation indicated that a reaction temperature of 90 or 50 °C reduces the amount of xanthone product (entries 8 and 9). When DME was used as the solvent, the reaction afforded only a 70% yield of two isomers formed in a 25:75 ratio (entry 10).

The effect of the fluoride source has also been examined in this process. When tetrabutylammonium fluoride (TBAF) was used as the fluoride source, the reaction proceeded much faster.

After 3 h, all of the starting materials were consumed and the proton abstraction product (**3a**) predominated (entry 11). A 65% yield of an 8:92 ratio of **3a** and **4a** was obtained when this reaction was carried out in the presence of 2 equiv of CsF (entry 12). In conclusion, the optimal reaction conditions for this one-step synthesis of xanthone utilize 4 equiv of CsF in THF solvent at 65 °C for 24 h (entry 7).

Synthesis of Xanthones. Employing our optimal reaction conditions, we have investigated the reaction scope and limitations of this process. These results are summarized in Table 2. We first examined the effect of a methoxy substituent on the salicylate ring to determine which position on the salicylate ring affords the best yield of xanthone. Thus, salicylates **1b, 1c, 1d,**

SCHEME 3. Aryne Precursors

SCHEME 4. Diversification of Halogen-Substituted Xanthones[a]

[a] Conditions: (i) 5% Pd(PPh$_3$)$_4$, 1 Na$_2$CO$_3$, 1:4 MeOH/toluene, 80 °C, 12 h; (ii) 5% Pd(OAc)$_2$, 2 NaHCO$_3$, 1 TBAC, DMF, 100 °C, 24 h.

and **1e** were employed, and 35−69% yields of substituted xanthones **4b**−**4e** were obtained (entries 2−5). Having an electron-donating methoxy group in the 5 position of the salicylate ring gave the highest yield (entry 4). The yields of xanthones from the 3- and 4-methoxy starting materials were only slightly lower, but the 6-methoxy isomer gave a much lower yield. When methyl 5-acetylsalicylate (**1f**) with an electron-withdrawing group in the 5 position was used as the starting material, a 58% yield of xanthone **4f** was isolated by flash chromatography (entry 6). On the other hand, the reaction of methyl 5-fluorosalicylate (**1g**) and aryne precursor **2a** affords an 83% yield of xanthone **4g** (entry 7). The reaction of methyl 5-bromosalicylate (**1h**) with aryne **2a** affords a 75% yield of the product **4h** (entry 8). The phenyl- and methyl-substituted salicylates, **1i** and **1j**, afforded 64 and 71% yields of the corresponding xanthone products, respectively (entries 9 and 10). When methyl 5-hydroxysalicylate (**1k**) is allowed to react with 2.5 equiv of aryne precursor **2a**, the O-arylated xanthone product **4k** was isolated in a 52% yield (entry 11). We have previously reported the facile arylation of phenols by these same aryne precursors.[18] From these results with 5-substituted salicylates, there is no obvious correlation between the electronic properties of the substituent and the yield. Phenyl salicylate (**1l**) has been employed in this reaction, and an 81% yield of xanthone **4a** was obtained (entry 12). Assuming that 2-hydroxybenzoic acid would first form the corresponding phenyl ester **1l**,[18] which should then afford the corresponding xanthone (**4a**), we treated 2 equiv of benzyne precursor **2a** and 2-hydroxybenzoic acid (**1m**) in the usual fashion. Unfortunately, none of the desired product was observed for reasons we do not really understand at this time (entry 13). Interestingly, the cross-coupling of methyl 1-hydroxy-2-naphthoate (**1n**) with silylaryl triflate **2a** affords a 73% yield of xanthone **4l**, but the reaction using methyl 2-hydroxy-3-naphthoate (**1o**) only generates a 48% yield of the product **4m** (entries 14 and 15). This latter reaction produced several side products which have not been identified. The annulation of **1p**, which contains a pyridine ring, afforded none of the xanthone product under our optimal conditions (entry 16). Again, we are uncertain why this latter reaction failed.

After investigating the effect of varying the salicylate structure, we examined the reaction efficiency using different aryne precursors (Scheme 3). A 62% yield of a single isomeric methoxyxanthone **4e** was obtained from the reaction of methyl salicylate **1a** with aryne precursor **2b** after 24 h at 90 °C (entry 17). Note that a somewhat higher temperature was required to get a good yield. The regioselectivity of this reaction is due to the steric and electronic effects in the step involving nucleophilic attack on the aryne, which has been seen in several previous reactions involving this aryne.[18] When the dimethoxysilylaryl
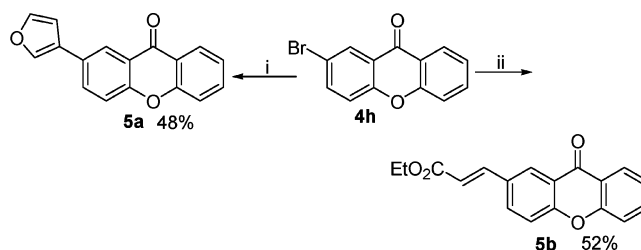
triflate **2c** was employed, a 57% yield of xanthone **4o** was isolated (entry 18). Again a higher temperature was required. The reaction of aryne precursor **2d** with methyl salicylate (**1a**) afforded a 51% yield of xanthone **4p** (entry 19). When aryne precursor **2e** was employed, a 59% yield of two isomeric xanthones, **4j** and **4q**, was obtained in a 1:1 ratio (entry 20). This is consistent with the intermediacy of an unsymmetrical methyl-substituted benzyne. Aryne precursor **2f** afforded a 45% yield of a single xanthone product **4r** (entry 21).

One of the major advantages of this methodology is that halogen atoms can be tolerated, which provides access to more structurally diverse xanthone skeletons via metal-catalyzed cross-coupling reactions. As illustrated in Scheme 4, the halogen-substituted xanthone product **4h** can be further modified by Heck[19] and Suzuki[20] reactions, affording interesting xanthone derivatives **5a** and **5b** for further biological examination.

Synthesis of Thioxanthones. Biologically interesting thioxanthone derivatives have also been prepared by this same methodology. All of the results are summarized in Table 3. Methyl thiosalicylate (**6a**) and 1.1 equiv of benzyne precursor **2a** were treated with 4 equiv of CsF in 5 mL of THF at 65 °C; after 24 h, a 35% yield of thioxanthone (**7a**) was isolated. The lower yield in this example is presumably due to oxidative homocoupling of the thiols since thiols are known to afford disulfides in the presence of CsF on a celite solid support in air.[21] In order to suppress this undesired homocoupling process, the same reaction was repeated under an Ar atmosphere, and a 55% yield of thioxanthone (**7a**) was obtained. Further optimization indicated that a 64% yield of product **7a** could be obtained under more dilute conditions, although a small amount of disulfide product and S-arylation product was present (Table 3, entry 1). The reaction of this thiol with benzyne precursor **2b** afforded a 45% yield of the desired thioxanthone **7b** (entry 2). When **2d** was employed as the aryne precursor in this reaction, a 40% yield of the product **7c** was isolated (entry 3). The reaction of **2e** afforded a 56% yield of two regioisomers, **7d** and **7e**, in a 1:1 ratio (entry 4). Finally, aryne precursor **2f**

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SCHEME 5. Plausible Mechanism for the Acridone Synthesis
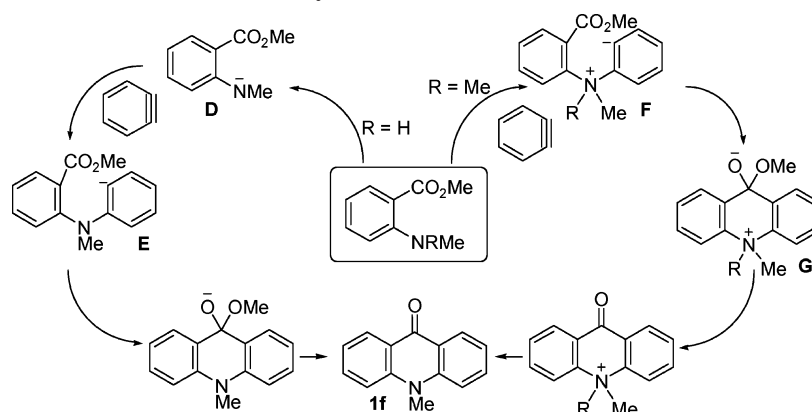
TABLE 3. Synthesis of Thioxanthones[a]

entry	thiosalicylate		aryne	product(s)		% yield
1		**6a**	**2a**		**7a**	64
2		**6a**	**2b**		**7b**	45[b]
3		**6a**	**2d**		**7c**	40[b]
4		**6a**	**2e**		**7d**	56[b,c] (1:1)
					7e	
5		**6a**	**2f**		**7f**	62[b]

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 10 mL of THF at 65 °C under Ar. *b* The reaction was conducted in 10 mL of THF at 90 °C under Ar (sealed tube). *c* The ratio in parentheses has been determined by ^{1}H NMR spectroscopy.

was allowed to react with thiosalicylate **6a**, and a 62% yield of thioxanthone **7f** was isolated by flash chromatography (entry 5).

Synthesis of Acridones. After we had a general and efficient synthesis of xanthones and thioxanthones in hand, we attempted to expand this methodology to the synthesis of acridones, a well-known class of antifungal, antitumor, and anticancer compounds.[6] Acridones have been prepared by the coupling of 3-halogeno-4-methoxybenzynes generated from 5-(3-halogeno-4-methoxyphenyl)thianthrenium perchlorates and LDA in THF at reflux with 2-aminobenzoate.[22] However, this protocol employs a fairly unusual aryne precursor, and it also suffers from the moisture-sensitive reagents and conditions. Methyl 2-aminobenzoate (**8a**) was first prepared and allowed to react with aryne precursor **2a**, and a 50% yield of the acridone product **9a** was obtained (Table 4, entry 1). Methyl 2-(*N*-methylamino)-benzoate (**8b**) was then allowed to react with aryne precursor **2a**. After 1 day of reaction, a 72% yield of acridone **9b** was

(22) Yoon, K.; Ha, S. M.; Kim, K. *J. Org. Chem.* **2005**, *70*, 5741.

TABLE 4. Synthesis of Acridones[a]

entry	benzoate			aryne	product(s)	% yield
	R[1]	R[2]	X			
1	H	H	H	**8a**	**2a**	**9a**	50
2	H	Me	H	**8b**	**2a**	**9b**	72
3	H	Ph	H	**8c**	**2a**	**9c**	7[b]
4	Me	Me	H	**8d**	**2a**	**9b**	65
5	H	Me	4-F	**8e**	**2a**	**9d**	48
6	H	Me	5-F	**8f**	**2a**	**9e**	71
7	H	Me	5-Br	**8g**	**2a**	**9f**	61
8	H	Me	H	**8b**	**2b**	**9g**	trace[c]
9	H	Me	H	**8b**	**2d**	**9h**	27[c]
10	H	Me	H	**8b**	**2e**	**9i**	51[c] (1:1)
						9j	
11	H	Me	H	**8b**	**2f**	**9k**	35[c]

a All reactions were conducted on a 0.25 mmol scale in the presence of 4 equiv of CsF and 1.1 equiv of the silylaryl triflate in 10 mL of THF at 65 °C. *b* The yield was determined by GC−MS analysis. *c* The reaction was conducted in 10 mL of THF at 90 °C (sealed tube). The ratio in parentheses has been determined by ^{1}H NMR spectroscopy.

isolated by flash chromatography (entry 2). However, the reaction employing methyl 2-(*N*-phenylamino)benzoate (**8c**) was very sluggish; after 2 days of reaction, only a 7% yield of the desired product **9c** was observed by GC−MS analysis. The low

yield is presumably due to the steric hindrance introduced by the presence of the phenyl substituent (entry 3). Interestingly, the reaction of methyl 2-(*N*,*N*-dimethylamino)benzoate (**8d**) affords a 65% yield of acridone product **9b**, which indicates that even tertiary amines can be successfully employed in this transformation (entry 4). Apparently the anticipated ammonium-containing product undergoes demethylation under the reaction conditions. Several halogen-substituted benzoates (**8e**–**8g**) have also been prepared from the corresponding acids and employed in this process (entries 5–7). Yields of 48–71% of the corresponding acridone products (**9d**–**9f**) have been obtained. We have not employed protecting groups on nitrogen since that could well lead to C–N insertion products.[14,15]

At this point, we examined the effect of the aryne structure on the yield of acridone. When silylaryl triflate **2b** was employed with benzoate **8b**, the reaction was very sluggish, and only a trace amount of the desired acridone product **9g** was observed by GC–MS analysis (entry 8). Aryne precursor **2d** afforded only a 27% yield of the product **9h**, and this reaction had to be run at 90 °C (entry 9). The reaction of aryne precursor **2e** with benzoate **8a** afforded a 51% yield of two isomeric acridones, **9i** and **9j**, in a 1:1 ratio (entry 10). A 35% yield of acridone product **9k** was obtained when aryne precursor **2f** was employed (entry 11). These last two reactions also had to be run at 90 °C.

A plausible mechanism for these aminobenzoate reactions is proposed in Scheme 5. The benzoate bearing an amino group presumably first undergoes nucleophilic attack on the aryne generated in situ from the silylaryl triflate. When R is a proton, the actual nucleophile involved could be either the neutral amine or the anionic intermediate **D** generated by hydrogen abstraction from the amine by CsF. However, when the tertiary amine **8d** is employed, although no proton is available for abstraction, this reaction still works well, suggesting that the neutral amine itself is nucleophilic enough for this transformation. Therefore, the reaction mechanism, which proceeds via intermediates **F** and **G**, seems more likely, although we cannot rule out possible anionic nucleophilic attack on the aryne, which proceeds via intermediates **D** and **E**. Subsequent intramolecular cyclization should afford the final acridone products.

Conclusions

A general one-pot synthesis of biologically interesting xanthones, thioxanthones, and acridones has been developed. This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the substituted benzoates and arynes and subsequent intramolecular electrophilic cyclization. The mild reaction conditions and generally high reaction efficiency provide advantages over previously reported multistep procedures. In general, this strategy tolerates both electron-donating and electron-withdrawing functionalities on the benzoate ring, but substituents on the aryne ring appear to lower the yields of the desired products.

Experimental Section

Representative Procedure for the Coupling-Cyclization of Arynes and Salicylates. CsF (1.0 mmol), the salicylate (0.25 mmol), and the silylaryl triflate (0.28 mmol) in 5 mL of anhydrous THF were stirred at 65 or 90 °C for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (25 mL), and washed with brine (25 mL). The aqueous layer was re-extracted with diethyl ether (2 × 25 mL). The organic layers were combined, dried (MgSO$_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel. **9*H*-Xanthen-9-one (4a)**: ^{1}H NMR (CDCl$_3$) δ 7.37 (t, J = 6.0 Hz, 2H), 7.48 (d, J = 6.4 Hz, 2H), 7.70–7.74 (m, 2H), 8.33 (dd, J = 6.0, 1.2 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 118.2, 122.1, 124.1, 126.9, 135.0, 156.4, 177.4; IR (CDCl$_3$) 2914, 2874, 1654, 1456 cm^{-1}; HRMS *m/z* 196.0527 (calcd for C$_{13}$H$_8$O$_2$, 196.0524).

Representative Procedure for the Coupling-Cyclization of Arynes and Thiosalicylates. CsF (1.0 mmol), the thiosalicylate (0.25 mmol), and the silylaryl triflate (0.28 mmol) were added to 10 mL of anhydrous THF, and the reaction vial was flushed with Ar. The whole reaction solution was then stirred at 65 or 90 °C for 24 h and worked up as described previously. **9*H*-Thioxanthen-9-one (7a)**: ^{1}H NMR (CDCl$_3$) δ 7.48 (td, J = 6.7, 1.5 Hz, 2H), 7.56–7.65 (m, 4H), 8.62 (dd, J = 7.4, 0.8 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 126.2, 126.5, 129.4, 130.1, 132.5, 137.5, 180.2; IR (CDCl$_3$) 2971, 2919, 1684, 1459 cm^{-1}; HRMS *m/z* 212.0299 (calcd for C$_{13}$H$_8$OS, 212.0296).

Representative Procedure for the Coupling-Cyclization of Arynes and 2-Aminobenzoates. CsF (1.0 mmol), the 2-aminobenzoate (0.25 mmol), and the silylaryl triflate (0.28 mmol) in 10 mL of anhydrous THF were stirred at 65 or 90 °C for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (25 mL), and washed with brine (25 mL). The aqueous layer was re-extracted with ethyl acetate (2 × 25 mL). The organic layers were combined, dried (MgSO$_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel. **10-Methyl-10*H*-acridin-9-one (9b)**: ^{1}H NMR (CDCl$_3$) δ 3.88 (s, 3H), 7.28 (t, J = 7.2 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.69–7.73 (m, 2H), 8.55 (dd, J = 8.0, 1.2 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 33.9, 115.0, 121.5, 122.7, 128.0, 134.0, 142.8, 178.3; IR (CDCl$_3$) 2917, 2850, 1637 cm^{-1}; HRMS *m/z* 209.0843 (calcd for C$_{14}$H$_{11}$NO, 209.0841).

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

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