Novel One-Pot Synthesis of Xanthones via Sequential Fluoride Ion-Promoted Fries-Type Rearrangement and Nucleophilic Aromatic Substitution

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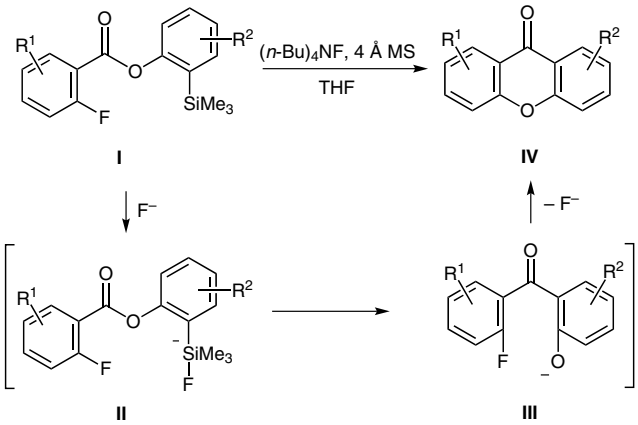
Abstract: A novel and efficient synthesis of xanthones is described. 2-(Trimethylsilyl)phenyl 2-fluorobenzoate derivatives undergo Fries-type rearrangement and intramolecular S_NAr reaction in a one-pot sequential manner under fluoride ion-promoted mild conditions. The method provides efficient access to xanthones that have significant steric congestion around the C9 carbonyl, which are not readily available by conventional methods.

Key words: xanthone, Fries-type rearrangement, nucleophilic aromatic substitution, fluoride ion

Xanthones are secondary metabolites occurring in a variety of higher plant families, fungi, lichens, and bacteria.[1] Because of their diverse biological and pharmacological properties, such as antimicrobial,[2] anti-inflammatory,[3] antioxidative,[4] antimalarial,[5] anticancer,[6] and enzyme inhibitory activities,[7] a large number of synthetic approaches to xanthones have been reported.[8] Among those classical methods are intramolecular ether formation of 2-hydroxybenzophenone derivatives possessing a leaving group at the C2′ position by nucleophilic aromatic substitution (S_NAr) and the cyclization of diaryl ether derivatives by intramolecular acylation. The former approach is most commonly applied, although problems often arise from steric congestion by the substituents and functional group incompatibility in the cyclization and/or the preparation of the precursor benzophenones. Recently published approaches include direct formation of the xanthone framework by the reaction of arynes with salicylates,[9] the palladium-catalyzed annulation of 1,2-dihaloarenes and salicyladehydes,[10] and the Diels–Alder reaction of 2-vinylchromones.[11] In the light of the structural diversity of xanthone derivatives of biological interests, further investigations are needed to devise new syntheses that could be adopted, in particular, to multiply substituted derivatives in a regiocontrolled manner with high tolerance of functional groups and substitution patterns.

Herein, we wish to report a novel one-pot synthesis of xanthones from phenyl benzoate derivatives promoted by fluoride ion (Scheme 1). Upon treatment with tetrabutylammonium fluoride (TBAF) in the presence of 4 Å molecular sieves, 2-(trimethylsilyl)phenyl 2-fluorobenzoate **I** undergoes Fries-type rearrangement via silicate **II** to generate benzophenone **III**, possessing phenoxide and fluorine moieties at the C2 and C2′ positions, which immediately cyclizes into xanthone **IV** through an intramolecular S_NAr reaction.[12–14]



Scheme 1 Fluoride ion promoted one-pot synthesis of xanthone

The key features of this new method include (1) ready availability of the substrate esters **I** from the corresponding carboxylic acids and phenols, (2) mild conditions promoted by fluoride ion, (3) capability to produce sterically congested benzophenone intermediates **III** and then the corresponding xanthones **IV**, which are not readily accessible by conventional methods.

We initiated our studies with the synthesis of ester **5a** as a model substrate (Scheme 2). 2-Fluoro-5-methoxybenzoic acid (**3**) was converted into the acid chloride by the standard procedure and then reacted with the phenolate anion of 2-(trimethylsilyl)phenol (**2**), which was obtained from 2-iodophenol through an O-silylation/retro-Brook rearrangement sequence,[15] to afford the desired ester **5a**. In a similar manner, esters **5b**–**h** were prepared in good to high yield (see Table 2).

With a series of substrate esters, we first subjected ester **5a** to a commercial THF solution of TBAF (1.5 equiv) at 25 °C, only leading to hydrolysis of ester to give, after the

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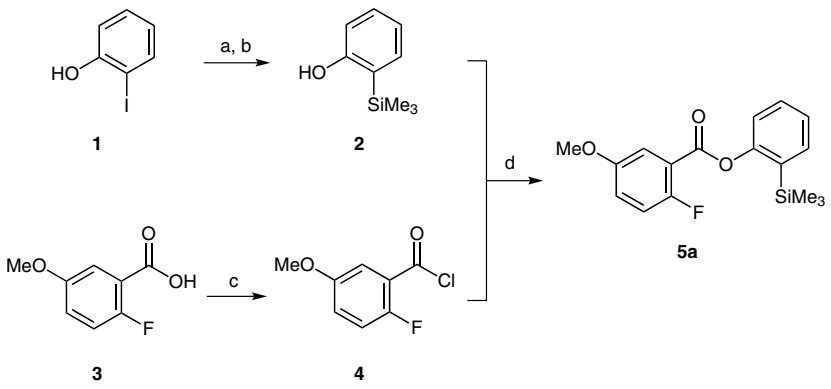


Scheme 2 Preparation of ester **5a**. *Reagents and conditions*: (a) HMDS, THF, reflux, 2 h; (b) *t*-BuLi, THF, –78 °C, 30 min, 99% (2 steps); (c) $SOCl_2$, DMF (cat.), $CHCl_3$, reflux, 5.5 h; (d) **2**, NaH, THF, 0 °C, 10 min; then **4**, 0 to 25 °C, 1 h, 94%.

two-hour reaction, compounds **2** and **3** in 30–40% yields with recovery of the starting material. To our delight, however, the situation changed by the combined use of TBAF with 4 Å molecular sieves (Scheme 3). A solution of TBAF in THF was admixed with powdered and freshly dried 4 Å molecular sieves at 25 °C, to which was added ester **5a**. The starting material was gradually consumed at 25 °C, and the reaction went to completion in one hour to afford the desired xanthone **6a** as a single product. Notably, none of the other possible compounds, such as the proto-desilylation product **7** or benzophenone **8**, were detected by TLC-monitoring of the reaction course.

With this successful result, we next attempted to reduce the amount of TBAF used, since the reaction could, in principle, proceed under fluoride-ion catalysis (Table 1). Indeed, the use of 0.5 or 0.25 equivalent of TBAF led to a fairly clean reaction, giving xanthone **6a** in reasonable yields, although the starting material was not completely consumed even after prolonged reaction time. The yield of the xanthone drastically decreased with 0.1 equivalent of TBAF.

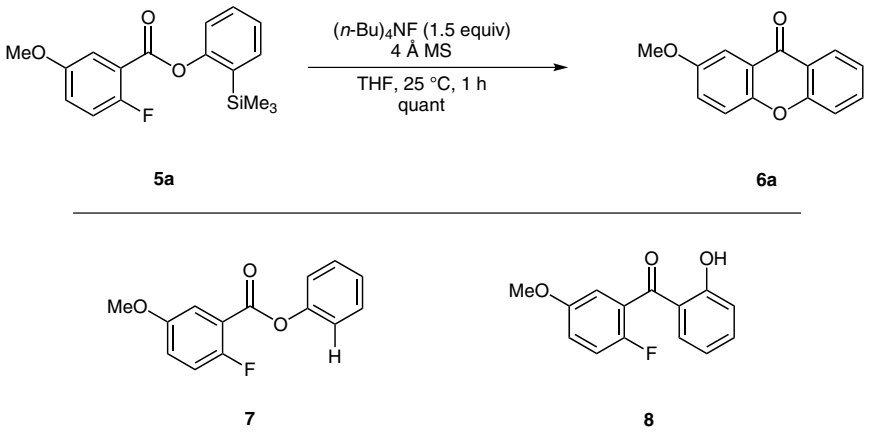
Further extensive screening of fluoride sources, solvents, and drying agents eventually showed the protocol detailed above [i.e., TBAF (0.5–1.0 equiv), 4 Å molecular sieves, THF, r.t.] to be optimal for the reaction.[16]

Table 1 Optimization of the Amount of TBAF

Entry	TBAF (equiv)	Time (h)	Yield (%)[a]
1	1.5	1.0	100
2	1.0	1.5	100
3	0.5	6.0	86[b]
4	0.25	10	84[b]
5	0.10	24	7[b]

[a] Isolated yield.
[b] The starting material was recovered in 2, 4 and 81% in entries 3, 4 and 5, respectively.

Examples of the substrate scope are summarized in Table 2, in which each reaction was carried out with 1 equivalent of TBAF.[17] As shown in entry 2, ester **5b** gave 1-methoxyxanthone (**6b**) in 69% yield. It is worth noting for comparison that 2-methoxybenzoate derivative **9** underwent the Fries-type rearrangement to give benzophenone **10** under similar conditions, but not the subsequent intramolecular substitution of the methoxy group even after prolonged reaction time (Scheme 4).[18] Moreover, 2,6-dimethoxybenzoate derivative **11** only gave the proto-desilylation product **13**, revealing that steric congestion

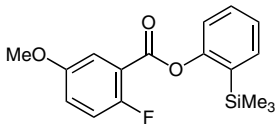
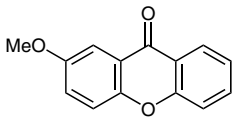
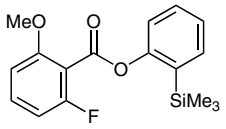
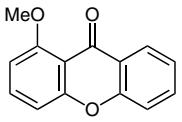
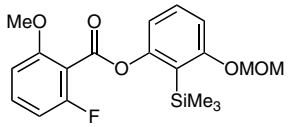
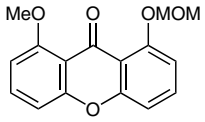
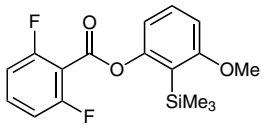
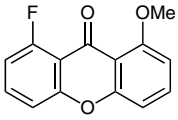
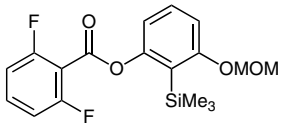
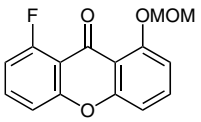
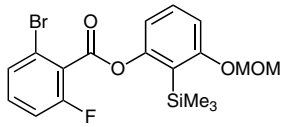
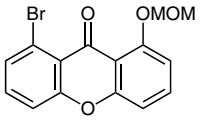
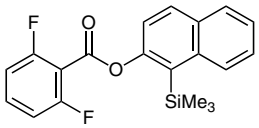
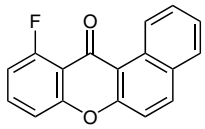
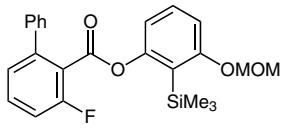
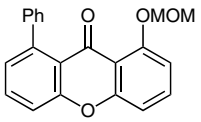


Scheme 3 Xanthone formation from ester **5a**; compounds **7** and **8** were not observed

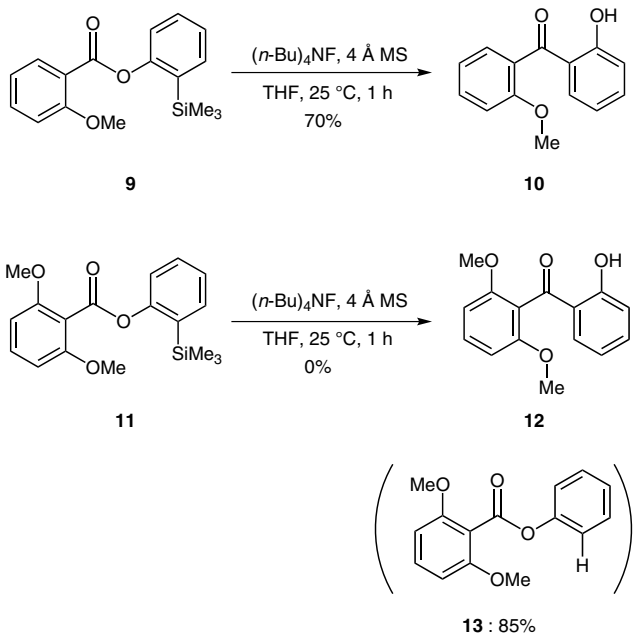
by two methoxy groups hindered the C–C bond formation from the silicate.

These results demonstrate the advantage of employing a fluorine as the *ortho* substituent of the ester moiety; due to its sterically less demanding and strongly electron-withdrawing nature,[12] it not only serves as an effective leaving group in the S_NAr process to enable the one-pot formation

Table 2 One-Pot Synthesis of Xanthones[a]

Entry	Ester **5**	Yield of **5** (%)[b]	Xanthone **6**	Time (min)	Yield of **6** (%)[c]
1	 **5a**	94	 **6a**	60	quant
2	 **5b**	78	 **6b**	60	69[d,e]
3	 **5c**	68	 **6c**	60	68[d]
4	 **5d**	76	 **6d**	15	97
5	 **5e**	85	 **6e**	10	96
6	 **5f**	98	 **6f**	60	74
7	 **5g**	81	 **6g**	10	93
8	 **5h**	76	 **6h**	60	30

[a] The reactions were carried out by using 1 equiv of TBAF in the presence of 4 Å MS in THF at 25 °C.
[b] Yields from the corresponding phenols.
[c] Isolated yields of chromatographically pure materials.
[d] The corresponding proto-desilylation product was obtained in 10% yield.
[e] See the literature.[17]



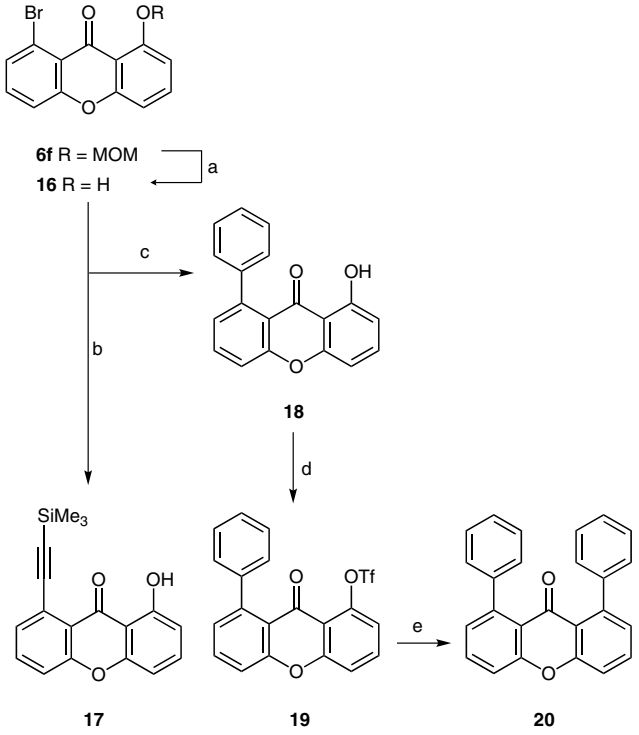
Scheme 4 The reactions of 2-methoxybenzoate **9** and 2,6-dimethoxybenzoate **11**

of the xanthone framework but also does not encumber the C–C bond formation process.

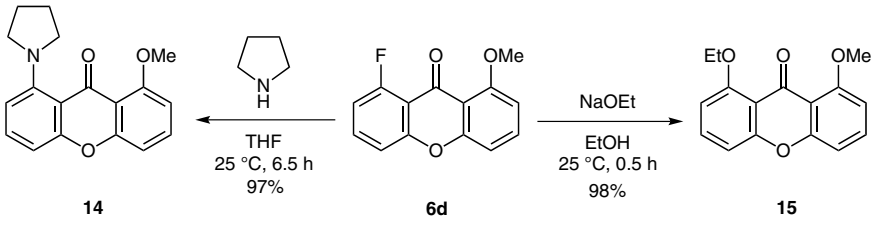
We then focused on the synthesis of 1,8-disubstituted xanthones, which demands the intermediacy of the severely congested *ortho*-tetrasubstituted benzophenone (Table 2, entries 3–8). The lack of an effective route to such xanthones is a major drawback of current xanthone syntheses, since most of the existing methods rely on the cyclization of the benzophenone derivatives, and the steric congestion makes the preparation of *ortho*-tetrasubstituted benzophenones troublesome.[19] Therefore, accessibility to 1,8-disubstituted xanthones would become a touchstone for evaluating the utility of the new method.

Gratifyingly, we found the reaction of **5c** proceeded smoothly to afford the desired 1-methoxy-8-(methoxymethoxy)xanthone (**6c**) in 68% yield, albeit accompanied by a small amount (10%) of the proto-desilylation product (entry 3). 2,6-Difluorobenzoates **5d** and **5e** reacted still more cleanly, thereby giving the corresponding xanthones **6d** and **6e** in excellent yields (entries 4 and 5). The reaction of 2-bromo-6-fluorobenzoate (**5f**) exclusively gave xanthone **6f** by involving the fluorine, rather than the bromine, in the ether bond formation, as expected from the general tendency of S_NAr reactions (entry 6). Benzo[*a*]xanthone **6g** was obtained by the reaction of naphthyl ester **5g** in high yield (entry 7), whereas the reaction of biphenylcarboxylate **5h** gave xanthone **6h**, possessing a phenyl group at the C8, only in low yield (entry 8).

Tolerance of a halogen substituent at the C1 (or C8) position (entries 4–7) is another notable feature of this method, since it would provide various opportunities for further transformation, as demonstrated in Scheme 5 and Scheme 6 (see Figure 1 for numbering). 1-Fluoroxanthone **6d** readily underwent S_NAr reactions with pyrrolidine and sodium ethoxide at room temperature. Introduction of a carbon substituent to the C1 position was effected by exploiting transition-metal catalyzed coupling of a 1-bromoxanthone derivative (Scheme 6). Phenyl and alkynyl xanthones **17** and **18** were successfully obtained from **16** by Sonogashira and Suzuki–Miyaura coupling, respectively.[20,21] Conversion of xanthone **18** into the corre-



Scheme 6 Transformations of 1-bromoxanthone **6f**. *Reagents and conditions*: (a) 4 M HCl (aq), THF, 25 °C, 24 h, quant; (b) 7.5 mol% $Pd(PPh_3)_4$, HC≡CSiMe$_3$, CuI, Et_3N, DMF, 70 °C, 1 h, 58%; (c) 10 mol% $Pd(PPh_3)_4$, $PhB(OH)_2$, $Ba(OH)_2 \cdot 8H_2O$, 1,2-dimethoxyethane (DME)/H_2O (4:1), reflux, 2 h, quant; (d) Tf_2O, pyridine, CH_2Cl_2, 25 °C, 17 h, 90%; (e) 17 mol% $Pd(PPh_3)_4$, $PhB(OH)_2$, K_3PO_4, 1,4-dioxane, 85 °C, 70 min, 72%.



Scheme 5 Transformations of 1-fluoroxanthone **6d**

sponding triflate **19** allowed the introduction of a second phenyl moiety by the Suzuki–Miyaura coupling to give 1,8-diphenylxanthone (**20**) in 72% yield.

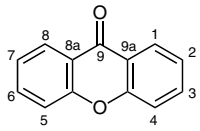


Figure 1 Xanthone numbering

In summary, a novel one-pot synthesis of xanthones has been demonstrated.[22] The reaction proceeds under mild conditions promoted by fluoride ion, and provides an efficient route to 1,8-disubstituted xanthone derivatives that are not readily accessible by conventional methods. Further studies including application to the synthesis of natural products with densely functionalized xanthone structures are under way.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) Recently, Larock and co-workers reported a xanthone synthesis involving a similar reaction pathway in which the aryl anion, formed by nucleophilic attack of a carboxylate anion of *o*-haloarenecarboxylic acid to aryne, undergoes Fries-type rearrangement and subsequent intramolecular S_NAr reaction. See: (a) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117. (b) Dubrovskiy, A. V.; Larock, R. C. *Tetrahedron* **2013**, *69*, 2789; Advantages of the present protocol over Larock's approach include the lower reaction temperature (25 versus 125 °C), the shorter reaction time, and accessibility to sterically congested xanthone derivatives.

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(16) (a) The following conditions were examined: TBAT ($[(n\text{-}Bu)_4N]^+[SiPh_3F_2]^-$), TASF ($[(Me_2N)_3S]^+[SiMe_3F_2]^-$), $Bn(Me)_3NF$, Me_4NF, $(n\text{-}Bu)_4NF\cdot(t\text{-}BuOH)_4$,[16b] C_6F_6/$(n\text{-}Bu)_4NCN$,[16c] CsF, KF, ZnF_2, and $LiBF_4$ as the fluoride ion source; Et_2O, 1,4-dioxane, DME, DMF, CH_2Cl_2, MeCN, and toluene as the solvent; molecular sieves 3A and 13X as the drying agent. The use of TBAT, TASF, $Bn(Me)_3NF$, or Me_4NF (1.5 equiv each) in the presence of 4 Å molecular sieves in THF gave xanthone **6a** in moderate yields (30–45%). Other combinations were still less effective. (b) Kim, D. W.; Jeong, H.-J.; Lim, S. T.; Sohn, M.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 8404. (c) Sun, H.; Dimagno, S. *J. Am. Chem. Soc.* **2005**, *127*, 2050.

(17) Since the use of a catalytic amount of TBAF in the reaction of **5b** led to unacceptable yield of 1-methoxyxanthone (**6b**) [60% with 0.5 equiv of TBAF (25 °C, 2 h); 38% with 0.2 equiv of TBAF (reflux, 24 h)], we opted to use 1 equiv of TBAF in the reactions used to obtain the congested xanthone possessing substituent(s) at C1 and/or C8.

(18) Treatment of benzophenone **10** with Cs_2CO_3 in DMF (80 °C, 5 h) cleanly effected the S_NAr reaction to give xanthone in 90% yield.

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(22) **One-Pot Synthesis of Xanthones; Typical Procedure (Table 2, Entry 4):** Powdered 4 Å molecular sieves (3.0 g) were placed in a two-necked, round-bottom flask, and dried by heating with a heat gun under vacuum. The flask was cooled to r.t. and filled with argon, then THF (9 mL) and TBAF (1.0 M in THF, 0.60 mL, 0.60 mmol) were added. After stirring for 1.5 h at 25 °C, a solution of ester **5d** (202 mg, 599 μmol) in THF (10 mL) was added and stirring was continued for 15 min. The reaction was quenched by the

addition of pH 7 phosphate buffer (0.1 M) at 0 °C, and molecular sieves were removed by filtration through a pad of Celite. The filtrate was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give xanthone **6d** (141 mg, 97%) as a white solid. Recrystallization from hexane–EtOAc gave **6d** as colorless needles.

