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A highly efficient, one-pot synthesis of benzo[*b*]fluoren-10-ones

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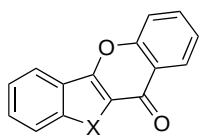
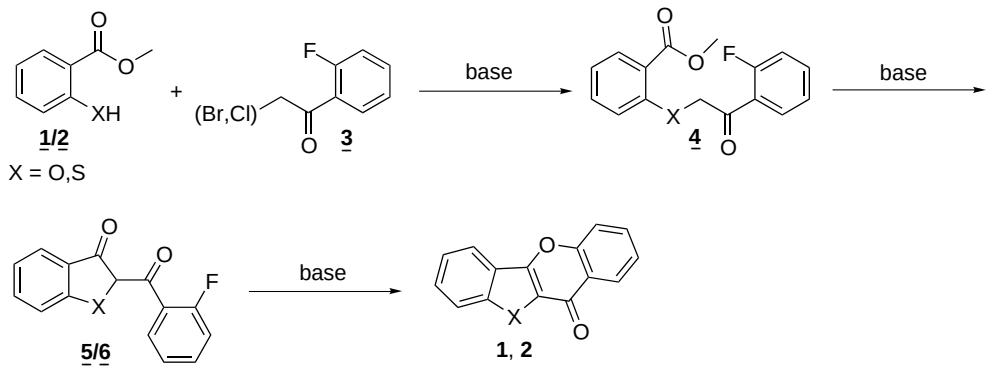
Abstract—5,11-Dioxa- and 5-oxa-11-thiabenzo[*b*]fluoren-10-ones were prepared via a one-pot procedure initiated by the reaction of salicylates or thiasalicylates with *ortho* fluoro-α-bromoacetophenones in the presence of cesium carbonate. The reactions proceeded in good yield and the final products were obtained without chromatography. The reaction presumably proceeds via a sequential intermolecular alkylation, intramolecular acylation sequence concluded by an intramolecular, *ipso*-fluoro substitution.

The rapid assembly of 'drug-like' core templates is fundamental to the discovery phase of many medicinal chemistry programs. Provided that the syntheses of these core templates will allow for their ready functionalization, a meaningful SAR study can be efficiently conducted. In addition to ready assembly and core functionalization, the core template should have relatively low molecular weight and log *P*.[1,2] This will allow room for the molecule to 'grow' as functionalization is incorporated, thus allowing the targeting of the many essential criteria of drug candidates including selectivity, potency, and efficacy. We identified 5,11-dioxa- **1** and 5-oxa-11-thiabenzo[*b*]fluoren-10-ones **2** as attractive molecular scaffolds for our medicinal chemistry program since both platforms are relatively novel in the patent literature, compatible with our pharmacophore model and have relatively low starting molecular weights and calculated log *P* values (**1**, Mw 236, Clog *P* 2.4 and **2**, Mw 252, Clog *P* 3.8).



1 X = O
2 X = S

There have been a few reports of the synthesis of the ring systems 5,11-dioxa- **1** and 5-oxa-11-thiabenzo[*b*]fluoren-10-ones **2** in the chemical literature.[3–7] For example, Newman and co-workers reported that 3-chloroflavones with a 2′-hydroxy function can be induced to cyclize to 5,11-dioxabenzo[*b*]fluoren-10-ones



Scheme 1. Proposed mechanistic scheme for 'one-pot' conversion of salicylate or thiosalicylate to benzo[*b*]fluoren-10-ones.

Keywords: 5,11-dioxabenzo[*b*]fluoren-10-one; 5-oxa-11-thiabenzo[*b*]fluoren-10-one; one-pot; cesium carbonate.
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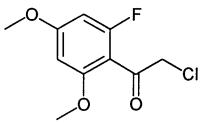
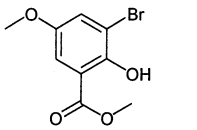
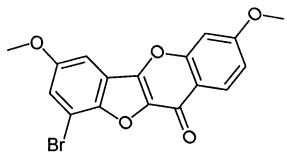
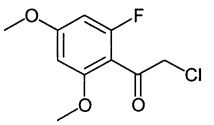
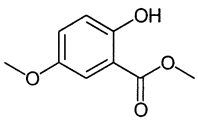
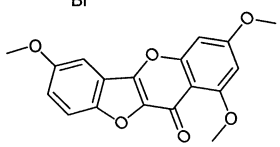
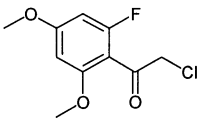
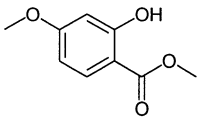
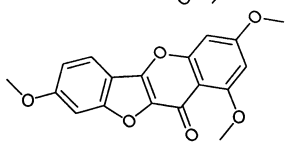
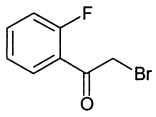
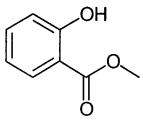
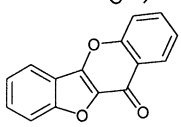
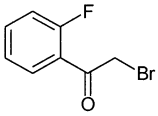
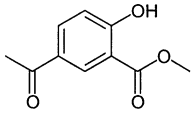
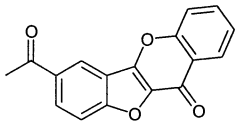
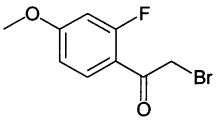
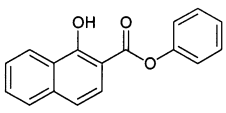
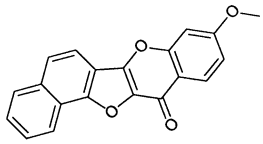
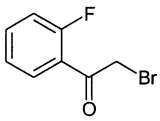
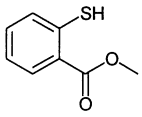
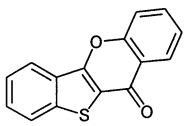
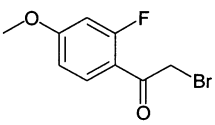
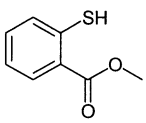
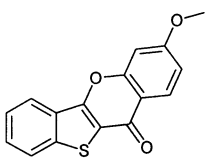
in the presence of potassium *t*-butoxide.[2] Since the 3-chloroflavone is the penultimate intermediate, it follows that the utility of this reaction will depend on the ease of its preparation. In the Newman example, the 3-chloroflavone used required two linear steps from a 3,4-dichlorocoumarin which in turn must be prepared from additional steps.[8] Other routes described have similar limitations in that they require multiple steps as well as require starting materials or reaction conditions that limit the ultimate utility of the reaction.

Unlike the previously reported procedures which required multiple linear steps, we envisioned the convergent, simultaneously executed sequence wherein two readily available segments are brought together (fluoro-α-haloacetophenone and salicylate or thiasalicylate) in the presence of base, and the ordered sequence of events shown in Scheme 1 occurs. In the first step, a salicylate **1**/**2** is deprotonated with base and the resulting anion reacts with the α-haloacetophenone **3** to form substituted adduct **4**. Subsequent deprotonation of ketone **4** allows for the intramolecular acylation of an α-carbanion enolate to give the benzofuran-3-one **5** or benzothiophene 3-one **6** which is deprotonated, setting up the final ring closure step, an intramolecular *ipso*-fluoro substitution via the enolate oxygen to render **1** or **2**.

After some initial experimentation with bases (NaH, K_2CO_3), we tried cesium carbonate as the base component in order to maximize the intermediate anion reactivity by minimizing any ion-pairing effect. Additionally, we decided to use DMF as the solvent to further increase the anion nucleophilic reactivity, base solubility as well as allow for higher reaction temperature (reactions typically required 100°C for about 1 h). We found this combination of base and solvent to be quite effective and, as shown in Table 1, allowed for different substituents and patterns of substituents to be located on either of the reacting fragments. In no case

Table 1. Some examples 5,11-dioxa- and 5-oxa-11-thiabenzo[*b*]fluorenones prepared via the one-pot method

Entry	halo-Ketone	Salicylate	Product	Yield %
1				65
2				47
3				50
4				54
5				47
6				53
7				66
8				56

were we required to perform chromatography to obtain the pure final products, the reactions were simply worked up and the desired tetracycles were obtained by triturating the crude mixture with methanol (or in many cases, simply adding water to the cooled reaction mixture then filtering and washing the crude product with methanol).[9] Unfortunately, attempts to make nitrogen containing analogues (X = N) using this procedure were unsuccessful.

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9. Procedure for preparation of 7-methoxy-5-oxa-11-thiabenzo[*b*]fluoren-10-one (entry 8 of Table 1): A mixture of 2-bromo-1-(2-fluoro-4-methoxyphenyl)ethanone (bromoketone from entry 8) (1.3 g, 5.3 mmol), 2-mercapto-benzoic acid methyl ester (thiosalicylate from entry 8) (0.9 g, 5.3 mmol) and Cs_2CO_3 (3.0 g, 9 mmol) in DMF (130 mL) was heated at 90°C for 2 h. The reaction mixture was poured into water and extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. The crude product obtained was triturated with MeOH to yield the desired product as a white crystalline solid (0.84g, 56%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (d, 1H, J = 8.8 Hz), 8.15 (dd, 1H, J = 7.2 Hz, 1.2 Hz), 7.91 (dd, 1H, J = 7.6 Hz, 1.0 Hz), 7.61–7.50 (m, 2H), 7.07 (d, 1H, 1H, J = 2.3 Hz), 7.04 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 3.97 (s, 3H); MS (eI) m/z 282; CHN calcd for C, 68.07; H, 3.57; N, 0.00; found C, 68.01; H, 3.28; N, −0.03.