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Reaction of Benzyne with Salicylaldehydes: General Synthesis of Xanthenes, Xanthones, and Xanthols

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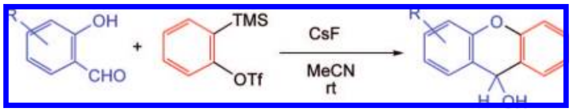
ABSTRACT



The reaction of salicylaldehydes with benzyne prepared from *o*-trimethylsilyphenyl triflate and CsF gave xanthenes and xanthones. When the reaction was carried out under basic conditions, 9-hydroxyxanthenes (xanthols) were obtained in good yields.

Arynes are highly reactive intermediates that have found numerous applications in organic synthesis.[1,2] Our ongoing interest in the exploration of reactive benzyne with thio- and selenocarbonyl compounds for the synthesis of functionalized S- and Se-heterocycles has led to our investigation of the synthesis of benzothietes, benzothianes, and benzoselenates.[3] Although reactions of aldehydes with benzyne to give C=O bond insertion products (ca. 20%) were reported in the early seventies,[4] Yoshida et al. reported the formation of 9-arylxanthenes by a novel insertion reaction of benzyne derived from *o*-trimethylsilylphenyl triflate (**1**) with aromatic aldehydes (22−70%).[5] Larock and Zhao have reported the reaction of arynes with benzoates, which afforded xanthones and thioxanthones, and acridones (35−81%).[6]

The reaction of benzyne derived from benzenediazonium carboxylate with *N*,*N*-dimethylformamide was reported by Yaroslavsky, in which the product was only salicylaldehyde (**2a**) in 32% yield.[7] These interesting observations raise the question whether salicylaldehydes will react with benzyne to give xanthene derivatives, which constitute functionalized molecules as dyes, natural products, and pharmaceuticals.[8] Herein, we report our preliminary results on the annulation of arynes by salicylaldehydes.

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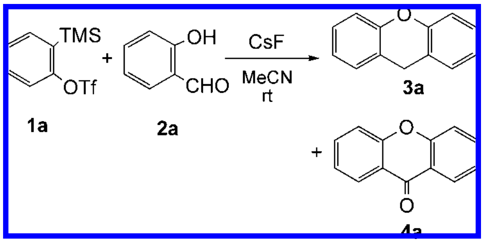
We started our investigation using commercially available *o*-trimethylsilylphenyl triflate **1a** and salicylaldehyde **2a**. Treatment of **1a** with **2a** in the presence of CsF at room temperature for 13 h resulted in the formation of xanthene **3** and xanthone **4** in 42% and 46% yields, respectively. When the reaction was carried out with Bu$_4$NF instead of CsF, the yields of **3** and **4** were only 10% and 12%, respectively. When benzenediazonium carboxylate was added to a solution of **2a** at reflux, complex mixtures were produced. The results are shown in Table 1.

Table 1. Reaction Optimization

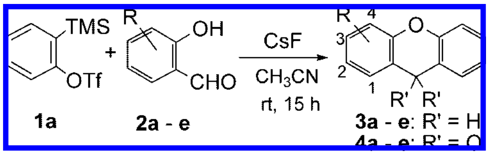


entry	additive	temp (°C)	time (h)	solvent	**3a** (%)	**4a** (%)
1[a]		reflux	5	THF		
2	TBAF	rt	15	CH$_3$CN	10	12
3	CsF	rt	14	CH$_3$CN	42	46
4	KF[b]	rt	19	CH$_3$CN	40	46

[a] Benzenediazonium carboxylate was used as a benzyne precursor. [b] 18-Crown ether (2 equiv) was also added.

Since salicylaldehyde **2** could react with benzyne at room temperature, we investigated the reaction of several substituted salicylaldehydes with triflate **1a** in the presence of CsF. As shown in Table 2, xanthenes **3** and xanthones **4** were obtained in moderate yields.

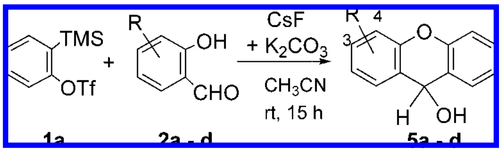
Table 2. Reaction of **1a** with **2** in the Presence of CsF



R	**3**	yield (%)	**4**	yield (%)
H	**3a**	42	**4a**	46
4-MeO	**3b**	42	**4b**	47
4-Me	**3c**	43	**4c**	46
4-*tert*-Bu	**3d**	21	**4d**	26
2-Cl	**3e**	40	**4e**	42

It is known that phenol derivatives react with benzyne to afford the corresponding diaryl ethers.[9] Intramolecular trapping of benzynes by phenols to give xanthenes was reported by Knight and Little.[10] However, to the best of our knowledge, there is no report on the reaction of benzyne with **2a**. As acidic and metal-catalyzed disproportionation of 9-hydroxyxanthene **5a** was already reported,[11] we investigated the present reaction under basic conditions to isolate **5**. When CsF was added to a suspension of triflate **1a**, salicylaldehydes **2a**−**d**, and K$_2$CO$_3$ in acetonitrile, compounds **5a**−**d** were obtained in good yields (Table 3).

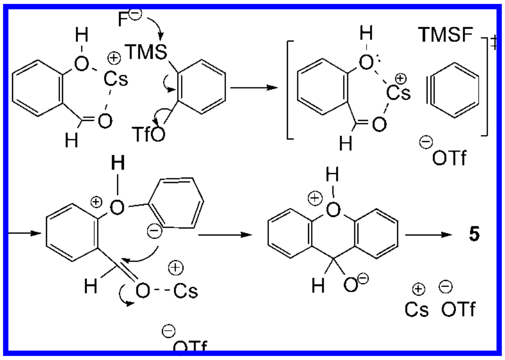
Table 3. Reaction of **1a** with **2** in the Presence of CsF and K$_2$CO$_3$



5	R	yield (%)
5a	H	91
5b′	4-MeO	86
5b′	3-MeO	88
5c	4-Me	52
5d	4-*t*-Bu	85

Since benzenediazonium carboxylate did not afford the corresponding adduct and TBAF as a fluoride source afforded low yields of xanthene and xanthone, the cesium cation plays an important role in the present reaction. Thus, the reaction might proceed as follows: salicylaldehyde solvates CsF to acetonitrile to give Cs-complexed salicylaldehyde, which reacted with adjacent triflate **1a** to afford benzyne. Reactive benzyne further reacted with the salicylaldehyde to give the 9-hydroxyxanthene **5**, which disproportionated to give xanthene **3** and xanthone **4** (Scheme 1).

Scheme 1. Reaction Mechanism



The substituted triflate **1b** also reacted with benzyne to afford 9-hydroxyxanthene **5f** in 83% yield (Scheme 2).

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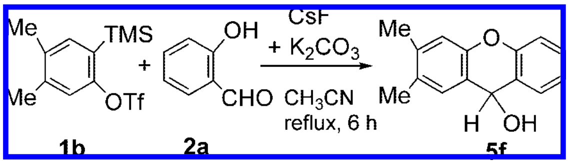
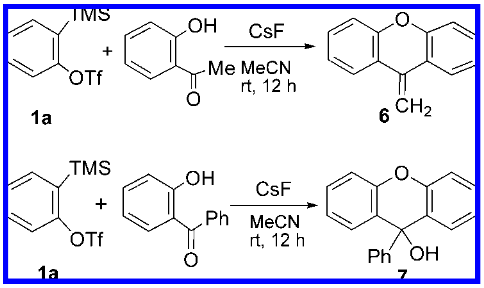
Scheme 2. Reaction of **1b** with Salicylaldehyde **2a**



We applied the present method to the reaction with 2-hydroxyphenyl ketone derivatives in the hope that 9-substituted 9-hydroxylxantenes would be obtained. When a solution of 2-hydroxyacetophenone and **1a** was treated with CsF in acetonitrile at room temperature for 12 h, 9-methylenexanthene (**6**) was obtained in 86% yield. Initially formed 9-hydroxy-9-methylxanthene was dehydrated to give **6**. When 2-hydroxybenzophenone was used as a substrate, 9-hydroxy-9-phenylxanthene (**7**) was obtained in 82% yield (Scheme 3).

Scheme 3. Reaction of **1a** with Phenones



The present method provides a novel approach to the synthesis of 9-hydroxyxanthenes, xanthones, and xanthenes by reaction of benzyne with salicylaldehyde and its derivatives. Further studies on the synthetic application of this procedure are underway.

Supporting Information Available: Experimental details of xanthenes, xanthone, 9-hydroxylxanthenes, and 9-methylenexanthene including full ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **General Procedure.** To a suspension of triflate **1** (1.5 mmol), salicylaldehyde **2** (1.0 mmol), and K_2CO_3 (3.0 mmol) in 5 mL of acetonitrile was added CsF (3.0 mmol). The reaction mixture was stirred at room temperature for 15 h, and the reaction mixture was poured into aqueous Na_2CO_3 and extracted with ether. The combined organic layers were dried over sodium sulfate, evaporated, and purified by alumina chromatography to give **5**.