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Synthesis of 3-Trifluoromethylbenzo[*b*]furans from Phenols via Direct *Ortho* Functionalization by Extended Pummerer Reaction

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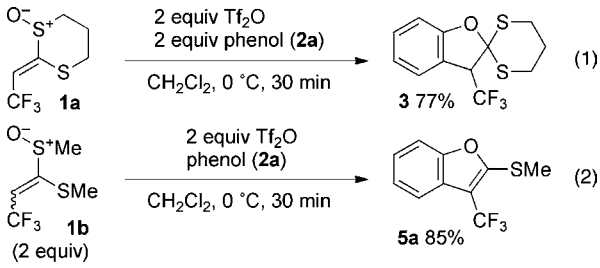
Abstract: A concise and diversity-oriented route to trifluoromethylbenzo[*b*]furans has been devised. A variety of phenols are directly converted to the corresponding 2-methylthio-3-trifluoromethylbenzo[*b*]furans by new triflic-anhydride-mediated extended Pummerer annulation reactions with trifluoromethylketene dithioacetal monoxide. The methylthio group of the products undergoes further transformations, which increase the diversity of available trifluoromethylbenzo[*b*]furans.

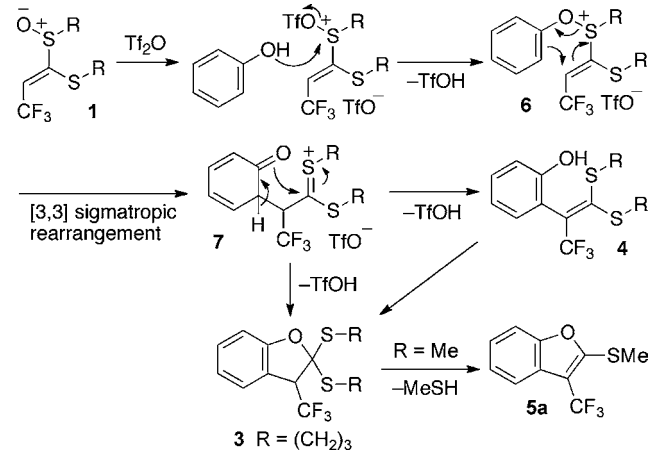
Trifluoromethyl-substituted aromatics display interesting properties and are widely used in the fields of pharmaceutical, agricultural, and material sciences.[1] However, the synthesis of such compounds is not trivial because of the unusual chemical behavior of a trifluoromethyl group. It is hence important to develop new methods for introducing a trifluoromethyl group into aromatic rings.[2]

Quite recently, we have developed 2-(2,2,2-trifluoroethylidene)-1,3-dithiane 1-oxide (**1a**) as a new trifluoromethylketene equivalent.[3] The reagent exhibited distinct reactivity toward allylsilanes[3a] and ketones[3b] under Pummerer conditions and provided a facile route to difficult-to-synthesize α-trifluoromethyl carbonyl compounds. We next envisioned that phenols would be good substrates for our extended Pummerer chemistry,[3−5] which would represent a rare example of selective direct *ortho* vinylation of phenols[6] (vide infra) under mild conditions.

Treatment of a mixture of phenol (**2a**) and **1a** with trifluoromethanesulfonic anhydride (Tf_2O) in dichloromethane at 0 °C unexpectedly provided trifluoromethyl-substituted dihydrobenzo[*b*]-furan **3** in 77% yield (eq 1), instead of affording the corresponding *o*-vinylphenol derivative **4** (Scheme 1). To our surprise, replacement of **1a** with acyclic **1b**[7] in the extended Pummerer reaction resulted in the direct and efficient formation of 2-methylthio-3-trifluoromethylbenzo[*b*]furan (**5a**) (eq 2). Although 3-trifluoromethylbenzo[*b*]furans are important in pharmaceutical as well as material sciences, the precedent synthesis of 3-trifluoromethylbenzo[*b*]furans required tedious multistep transformations[8] or the use of *o*-iodophenols[9] or 3-bromobenzo[*b*]furans[10] as starting materials.



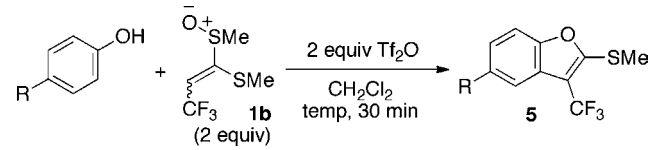
Scheme 1. Plausible Mechanism



A plausible mechanism is shown in Scheme 1. After Tf_2O activates **1**,[11] nucleophilic attack of the phenolic hydroxy group at the cationic sulfur would take place to yield intermediate **6**. Sulfonium **6** would then undergo rapid [3,3] sigmatropic rearrangement to form a carbon−carbon bond at the *ortho* position of phenol. Direct cyclization of **7**[12] or stepwise cyclization via **4** would afford dihydrobenzo[*b*]furan. When acyclic **1b** was used, elimination of methanethiol occurred in the presence of triflic acid to yield **5a**.

The scope of *para*-substituted phenols is summarized in Table 1. The reactions of less nucleophilic phenols required a temperature as high as 40 °C to achieve high efficiency (entries 4−7). In contrast, *p*-methoxyphenol proved to be too reactive to be converted to the corresponding benzo[*b*]furan (entry 2), and the triflate of *p*-methoxyphenol was obtained as the major byproduct. Alternatively, (pinacolato)boryl-substituted phenol reacted to afford **5d** (entry 3), serving as a *p*-methoxyphenol equivalent.

Table 1. Scope of *Para*-Substituted Phenols



entry	R	temp/°C	5	yield /%
1	*n*Bu	0	**5b**	89
2	OMe	−40	**5c**	0
3	B(pinacolato)	0	**5d**	64
4	CN	40	**5e**	73
5	CF_3	40	**5f**	70
6	Br	40	**5g**	76
7	CO_2Et	40	**5h**	72

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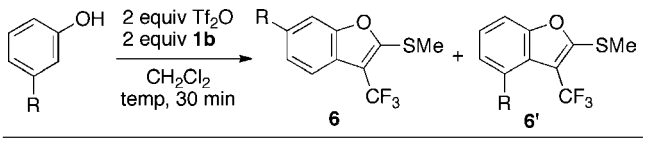
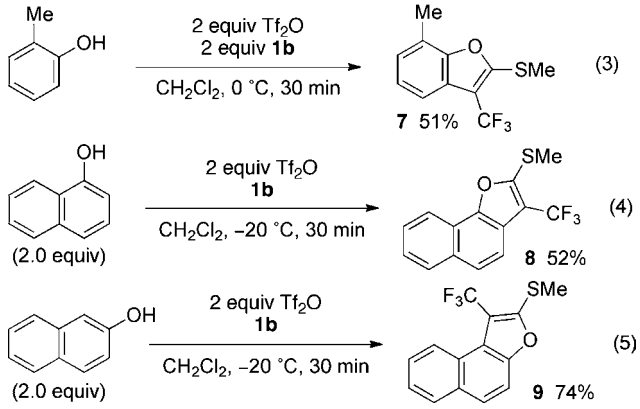
Table 2. Reactions of *Meta*-Substituted Phenols



entry	R	temp/°C	yield /%	6/6′
1	Me	0	70	**6a**/**6a′** = 67:33
2	*t*Bu	0	76	**6b**/**6b′** > 99:1
3	OMe	−20	57	**6c**/**6c′** > 99:1
4	CF_3	40	55	**6d**/**6d′** > 99:1

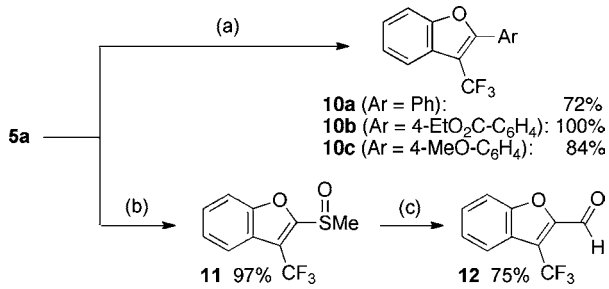
The reaction of *m*-cresol afforded a 67:33 mixture of regioisomers in favor of the sterically less demanding isomer **6a** (Table 2, entry 1). *tert*-Butyl and trifluoromethyl groups are large enough to control the regioselectivity, and **6b** and **6d** were exclusively obtained (entries 2 and 4). Since a *m*-methoxy group has a weaker influence on the reactivity of the hydroxy group than a *p*-methoxy group, the reaction of *m*-methoxyphenol at −20 °C proceeded to yield **6c** in good yield (entry 3).

Although *o*-cresol reacted smoothly (eq 3), the reaction of 2,6-dimethylphenol afforded a complex reaction mixture. Naphthols were good substrates (eqs 4 and 5), and notably, regioselective cyclization of 2-naphthol took place to furnish **9**[13] in high yield.



The methylthio groups at the 2 positions of the products would undergo a number of transformations. For instance, palladium-catalyzed arylation of **5a**[14] with arylzinc iodide-lithium chloride complexes[15] provided 2-aryl-3-trifluoromethylbenzo[*b*]furans (**10a**−**c**) in high yield (Scheme 2). Oxidation of **5a** by *m*CPBA provided sulfoxide **11**. Aryl sulfoxide **11** underwent efficient sulfoxide-magnesium exchange with isopropylmagnesium chloride-lithium chloride.[16] The benzofurylmagnesium was trapped with DMF to yield the formylated product. Thus, products **5**−**9** would serve as both 3-trifluoromethylbenzo[*b*]furyl cation and anion equivalents.

Scheme 2. Transformations of Methylthio Group[a]



[a] Conditions: (a) 2.5−10 mol% $PdCl_2$(dppf), 2−3 equiv of ArZnI·LiCl, MeCN, 60 °C, 1−3 h. (b) 1.2 equiv of *m*CPBA, CH_2Cl_2, 0 °C, 30 min. (c) 2.0 equiv of *i*PrMgCl·LiCl/THF, toluene, −78 °C, 10 min then 2.5 equiv of DMF, −78 to 25 °C, 2 h.

The optical properties of **10a**−**c** were investigated in methanol by UV−vis absorption and fluorescence spectroscopy (Table 3). Compounds **10a**−**c** have similar strong absorbance peaks around 300 nm and exhibit bright blue fluorescence. Especially, ethoxycarbonyl-substituted **10b** shows the highest fluorescence quantum yield of 0.54. The synthesis of other fluorescent trifluoromethylated benzofurans is now under investigation.

Table 3. Optical Properties of **10a**−**c** in Methanol

10	λ_{max} (nm)/ε ($M^{-1}\cdot cm^{-1}$)	λ_{em} (nm)	Φ_F
10a	290/1.9 $\times 10^4$	344, 361	0.28
10b	303/2.3 $\times 10^4$	382	0.54
10c	298/2.4 $\times 10^4$	359	0.29

In summary, we have found a straightforward synthesis of 3-trifluoromethylbenzo[*b*]furans from phenols and acyclic **1b** with the aid of Tf_2O. A wide range of phenols participate in the annulation reaction. Further transformations of the methylthio group of the products will bring diversity to highly substituted trifluoromethylbenzo[*b*]furans.

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Supporting Information Available: Experimental details and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The highly electron-withdrawing trifluoromethyl group plays an important role, suppressing the formation of the corresponding dicationic intermediate from the activated **1** by elimination of TfO^-. Although a methyl or phenyl group could not replace the trifluoromethyl group of **1b**, substitution of the trifluoromethyl group with a heptadecafluorooctyl group successfully

led to the formation of 2-methylthio-3-heptadecafluorooctylbenzo[*b*]furan (**5a′**) in 85% yield.
(12) The methylthio group of **1b** would be important to precisely control the reactivity of the cationic intermediate **7**. Replacing the methylthio group of **1b** with a phenyl or methoxyphenyl group, which can stabilize cationic intermediates, failed to afford the corresponding 2-arylbenzofurans.
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