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1,3-Carbothiolation of 4-(Trifluoromethyl)-*p*-Quinols: A New Access to Functionalized (Trifluoromethyl)arenes

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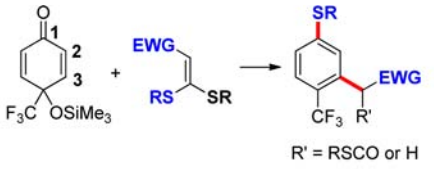
ABSTRACT



***meta*-difunctionalization; single operation; high yields**

A new strategy, the *1,3-carbothiolation/aromatization*, for the synthesis of functionalized (trifluoromethyl)arenes has been developed that enables the regioselective introduction of two different functional groups onto an "aromatic ring" in the *meta*-position to each other in a single step.

Organofluorine compounds have received increasing interest because of their higher bioavailability compared to that of the corresponding nonfluorinated analogues.[1,2] Thus, over the past two decades, (trifluoromethyl)trimethylsilane ($TMSCF_3$)[3] has been widely applied since its first synthetic application as a nucleophilic trifluoromethylating reagent.[3b]

Different from numerous methods for the synthesis of trifluoromethylated arenes that rely on substitution of a preexisting aromatic ring,[4] in 1989, Stahly and Bell described the monotrifluoromethylation of *p*-quinones to give 4-(trifluoromethyl)-*p*-quinols[5a] as precursors of (trifluoromethyl)-arenes.[5] More recently, Hu and co-workers revealed an unprecedented *vicinal trifluoromethylation/iodination* of arynes, which can introduce CF_3 and I groups onto an aromatic ring in a single step.[6] Herein, a new reaction, the *1,3-carbothiolation/aromatization* of 4-CF_3-*p*-quinol derivatives **1** (Figure 1), is described (Scheme 1). This reaction allows the regioselective introduction of two different functional groups onto an aromatic ring in the *meta*-position to each other (*meta-double functionalization*) and therefore enables the construction of functionalized CF_3-arenes[4−6] in a single operation with readily available **1** as the nonaromatic precursors and ketene dithioacetals **2** (Figure 1). The latter are versatile intermediates in organic synthesis,[7] both as carbon and sulfur nucleophiles.[7a,8a,8b]

In the present research, the model reaction of 4-(trifluoromethyl)-*p*-quinol silyl ether **1a** with 3,3-bis-(methylthio)-1-phenylprop-2-en-1-one **2a** (Figure 1) was first investigated using $CuBr_2$, $Cu(OAc)_2$, $SnCl_4 \cdot 5H_2O$, $SnCl_4$, $AlCl_3$, TfOH (triflic acid), $Pd(OAc)_2$, $BF_3 \cdot Et_2O$,

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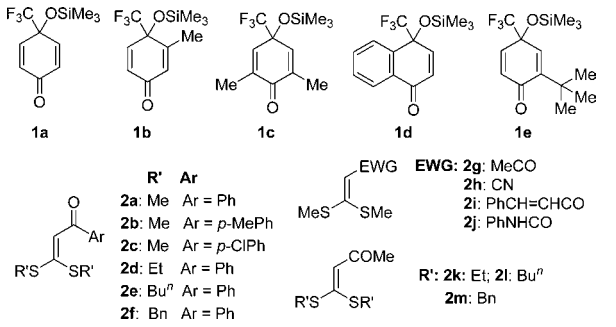

Figure 1. Selected 4-(trifluoromethyl)-*p*-quinols and ketene dithioacetals.

and $In(OTf)_3$ as the catalysts, respectively.[7,8] After careful screening of the reaction conditions (for details, see the Supporting Information), it was found that, when catalyzed by $In(OTf)_3$, a mixture of (trifluoromethyl)arenes **3aa**/**3′aa** (in the tautomeric keto−enol form) were obtained in 95% overall yields by reaction in DCE (1,2-dichloroethane, Scheme 1), whereas, in the presence of TMSCl (trimethylsilyl chloride) and catalyzed by $In(OTf)_3$, (trifluoromethyl)arene **4aa** was produced in 92% yield (Scheme 1). However, under identical conditions for 6 h but promoted only by TMSCl (2.0 equiv), no reaction occurred for reaction of **1a** with **2a** (Table S1, entry 14, Supporting Information), and no transformation of **3aa**/**3′aa** to **4aa** was observed. These results indicate that TMSCl can accelerate the reaction.

The successful construction of CF_3-bearing aryl sulfides **3aa**/**3′aa** and **4aa** significantly extends the synthetic utility of the readily available 4-(trifluoromethyl)-*p*-quinol derivatives[5] and adds a new entry to the chemo- and regioselective construction of polyfunctionalized arenes from readily available nonaromatic precursors.[4−6,9] Therefore, the scope of the *meta*-double-functionalization of 4-CF_3-*p*-quinol derivatives **1** with ketene dithioacetals **2** was next examined. As a result, under optimal conditions (Scheme 1, for products **3aa**/**3′aa** and **4aa**), a series of functionalized CF_3-arenes was prepared, and the results are summarized in Scheme 1.

According to the experimental results (Scheme 1), methyl aryl sulfides **3aa**/**3′aa**−**3ac**/**3′ac** with phenacyl substituents on the aryl ring were obtained in excellent yields from reactions of **1a** with **2a**−**c**, respectively. Similarly, alkyl aryl sulfides **3ad**/**3′ad** and **3af**/**3′af** with ethylthio and benzylthio groups were prepared in high yields from reactions of **1a** with **2d** and **2f**. Similarly, sulfides **3′ag** and **3′ak**−**3′am** were prepared in high yield from the reactions of **1a** with the corresponding α-acetyl ketene dithioacetals **2g** and **2k**−**m** having two methyl, ethyl, benzyl, or *n*-butyl groups on the ketene dithioacetyl moiety. It was noted that the reaction of **1a** with α-cinnamoyl ketene dithioacetal **2i** showed a good tolerance for the cinnamoyl group giving **3′ai** in high yield. Moreover, all reactions were completed within 0.4−2.4 h except for the reaction of **1a** with α-cyano ketene dithioacetal **2h**, which led to *p*-quinol and 4-hydroxy-4-(trifluoromethyl)cyclohexa-2,5-dienone in 70% yield, instead of **3ah**. Thus, the desired sulfide **3ah** was prepared under identical conditions as above but catalyzed by $SnCl_4 \cdot 5H_2O$. In products **3**/**3′**, **3′ag**, **3′ai**, and **3′ak**−**3′am** exist primarily in their enol forms, whereas others, except for **3ah**, in the tautomeric keto−enol forms.[10]

All of the functionalized (trifluoromethyl)arenes **3**/**3′** show that an (alkylthiocarbonyl)methyl and an alkylthio group can be introduced into the *ortho* and *para* positions of the electron-deficient (trifluoromethyl)benzene ring. This efficient domino sequence comprises a fundamentally new way to synthesize (trifluoromethyl)arenes having high structural complexity.[1,4−6] Fortunately, the scope of the synthesis of functionalized (trifluoromethyl)arenes **4** under optimized conditions (Scheme 1, for products **4aa**) gave further powerful support for the efficiency of the double functionalization/aromatization reaction.

The corresponding functionalized (trifluoromethyl)-arenes **4aa**−**ag**, **4ai**, **4aj**, **4ba**, **4ca**, **4da**, **4dg**, **4ea**, and **4ak**−**am** were synthesized in high-to-excellent yields (except for **4ea** in 40% yield due to the steric hindrance of the bulky *t*-Bu group) under similar reaction conditions as the synthesis of **3** but in the presence of TMSCl (Scheme 1). Similar to the preparation of **3ah**, **4ah** was obtained in high yield under identical conditions but catalyzed by $SnCl_4 \cdot 5H_2O$ in the absence of TMSCl. For the formation of CF_3-arenes **4**, the electron-donating alkyl substituents on the *p*-quinol ring of substrates **1b**, **1c**, and **1e** did not affect the regioselectivity of the reaction (Scheme 1). In addition, 4-(trifluoromethyl)-4-(trimethylsilyloxy)naphthalen-1(4*H*)-one **1d** was also proved to be the suitable substrate (Scheme 1, products **4da** and **4dg**). Clearly, our new method based on the tandem 1,3-carbothiolation/aromatization sequence is flexible and opens up new possibilities for the construction of valuable polyfunctionalized arenes.

Thus, (trifluoromethyl)arenes **3** and **4**, which also share structural features of aryl sulfides, α-aryl ketones, α-aryl nitriles, and related structural motif,[11−14] are obtained selectively under controllable conditions with or without the addition of TMSCl. In addition, products **3** also have the β-ketothioester motif, allowing straightforward access, in principle, to a series of functional groups such as ketones,

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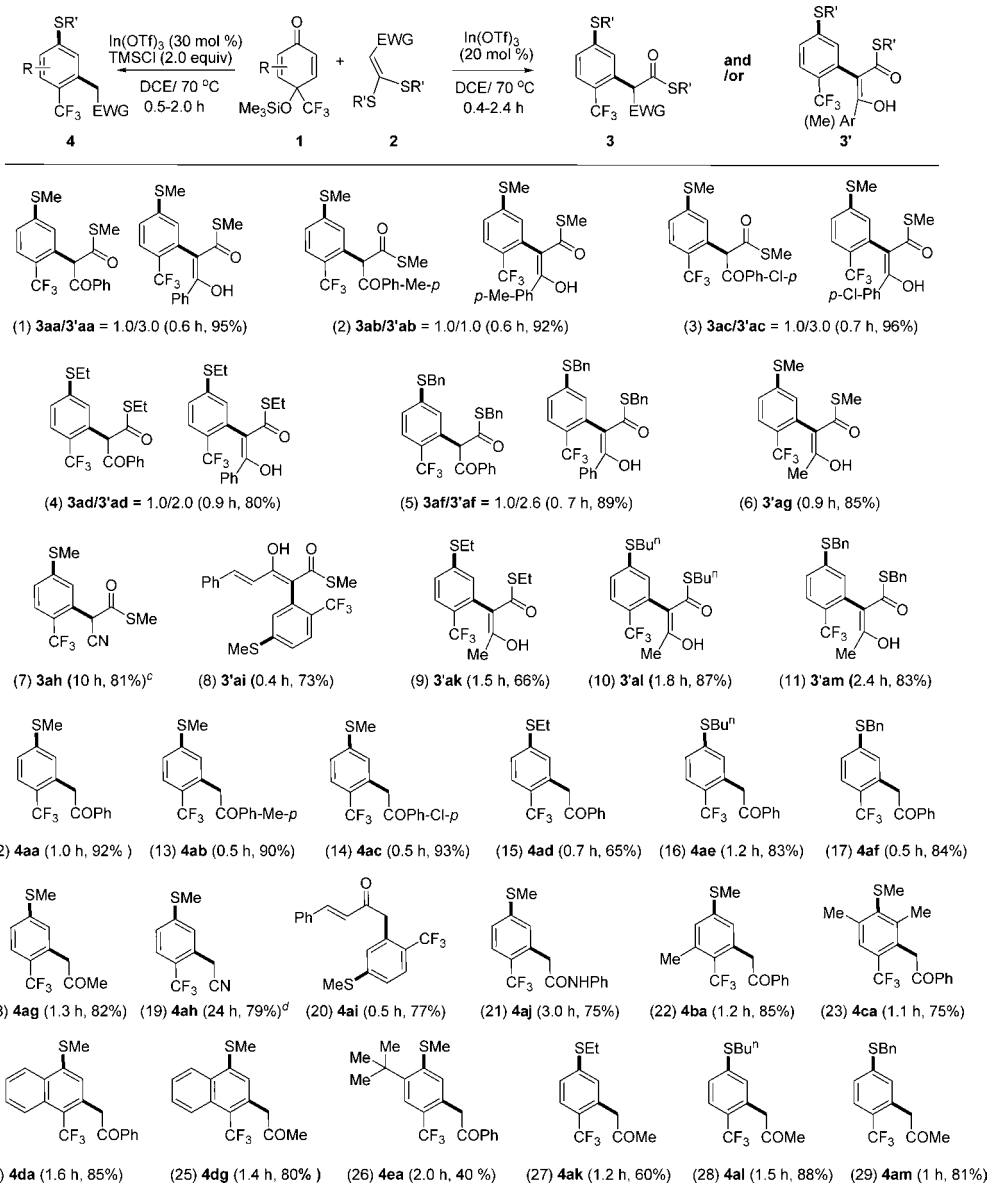
Scheme 1. Synthesis of Functionalized (Trifluoromethyl)arenes[a,b]



[a] Conditions for **3**/**3**′: **1** (0.60 mmol), **2** (0.50 mmol), $In(OTf)_3$ (20 mol %), DCE (2 mL), 70 °C, 0.4−2.4 h. [b] Conditions for **4**: **1** (0.60 mmol), **2** (0.50 mmol), $In(OTf)_3$, (30 mol %), TMSCl (2.0 equiv), DCE (2 mL), 70 °C, 0.5−2.0 h. [c] Catalyzed by $SnCl_4 \cdot 5H_2O$ (30 mol %) and reacted for 10 h. [d] Catalyzed by $SnCl_4 \cdot 5H_2O$ (30 mol %) in THF (2.0 mL) in the absence of TMSCl and reacted for 24 h.

aldehydes, esters, amides and α-hydroxy-*β*-ketothioesters upon a single transformation.[15,16] Fortunately, the chemoselective oxidation of **4ag**, **4dg**, and **4am** to the corresponding aryl aldehydes **5** was also successful (Scheme 2).[17]

On the basis of the above results (Scheme 1), a mechanism for the formation of **3** and **4** is proposed (Scheme 3, with **3aa** and **4aa** as an example). The overall process involves (1) hydrolysis of ketene dithioacetal **2a** to release methanethiol under acidic conditions in the presence of water (moisture);[7a,e,18] (2) formation of complex **I** from **1a**, $In(OTf)_3$ and methanethiol;[8a] (3) addition of methanethiol

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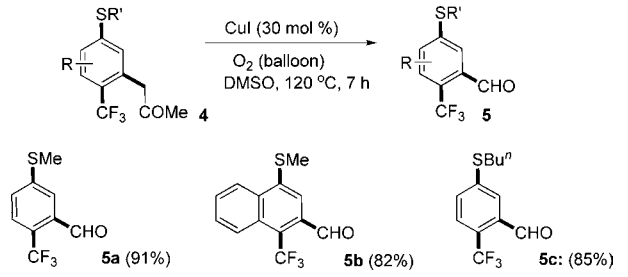
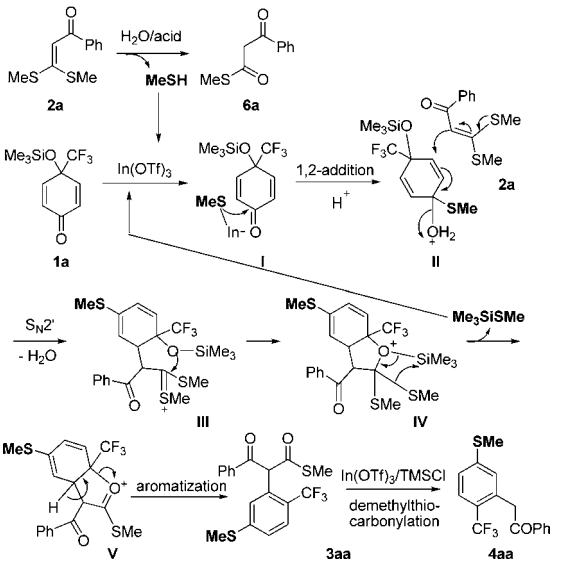
Scheme 2. Synthesis of (Trifluoromethyl)aryl Aldehydes **5**



Scheme 3. Proposed Mechanism for Formation of **3** and **4**



at the carbonyl group of **I** in a pseudointramolecular manner to give intermediate **II**;[8a,14,19] (4) attack of the nucleophilic α-C of **2a** at **II** in a S_N2' manner,[7a,b,8a,20] along with the release of water to produce thionium **III**; and finally, (5) further transformation involving intramolecular thiophilic attack of the silyloxy oxygen (**III** to **IV**),[21] elimination of trimethyl(methylthio)silane (**IV** to **V**) and subsequent aromatization to give **3aa** or further to give **4aa** in the assistance of TMSCl.

Clearly, the above transformation would benefit from reincorporation of the ketene dithioacetals **2** into the products in the form of an efficient recycling of the alkylthiol and trimethyl(methylthio)silane generated in situ to enable further transformations. Accordingly, the synthesis of functionalized CF_3-arenes described in this study represents a new carbothiolation reaction,[22,23] the catalytic intermolecular 1,3-carbothiolation, through *meta*-double functionalization of the nonaromatic precursors. Significantly, the 1,3-carbothiolation enables two different functional groups to be introduced into the aromatic ring in the *ortho* and *para* positions to an electron-withdrawing trifluoromethyl group, which has been a tough challenge in chemistry.

In summary, a new strategy for the synthesis of functionalized trifluoromethyl arenes with readily available 4-(trifluoromethyl)-*p*-quinol derivatives as the nonaromatic precursors has been developed. The reactions can be carried out under mild reaction conditions to afford a series of (trifluoromethyl)arenes with important structural features, including aryl sulfides, α-arylated carbonyl and nitrile compounds, and *β*-ketothioesters in good to excellent yields in most cases in a single operation via a tandem 1,3-carbothiolation/aromatization sequence. Further investigations to demonstrate the utility of the intermolecular 1,3-carbothiolation reaction are in progress.

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Supporting Information Available. Experimental procedures and analytical and spectral data for all the new compounds. CCDC 906801 (**3′aa**) and CCDC 896680 (**4aa**). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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