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Trifluoromethylation

Traceless Solid-Phase Synthesis of Trifluoromethylarenes**

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Fluorine-containing drugs have played a major role over the past decade and currently make up 20% of all pharmaceuticals and 30% of all agrochemicals on the world market.[1] Since Fried et al. demonstrated the enhanced properties of a fluorinated hydrocortisone derivative more than fifty years ago, many studies have shown that the metabolism and pharmacokinetics of active compounds can be improved by introducing fluorine atoms.[2,3] Fluorinated compounds also play an important role in materials chemistry.[4] Apart from single fluorine atoms, trifluoromethyl groups—especially at aromatic positions—are the most common and important fluorine-containing units used in the design of new potential bioactive structures. Well-known examples include the antidepressant Fluoxetine and the arthritis drug Celecoxib as well as Sorafenib and Flutamide used for the treatment of kidney and prostate cancer, respectively (Figure 1). One example of a crop-protecting agent bearing CF_3 units is the herbicide Fomesafen.

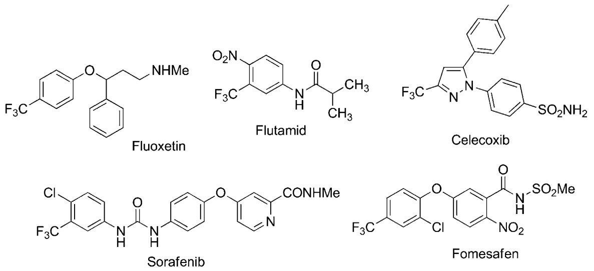
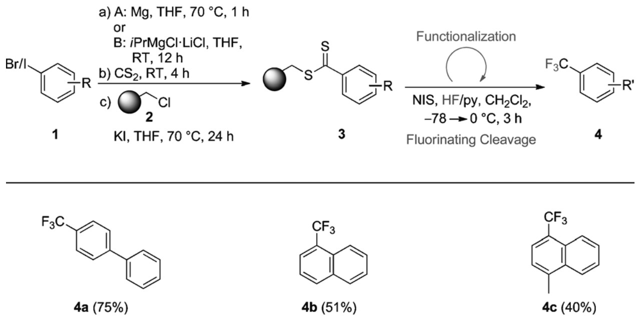


Figure 1. Structures of important drugs containing CF_3 moieties.

Herein, we report the first method for the traceless solid-phase synthesis of trifluoromethylarenes.[5] The procedure requires common and cheap trifluoromethylarene building blocks and uses conventional reagents that are available with various functional groups. The introduction of fluorine moieties is often accompanied with a drastic decrease of reactivity for subsequent transformations as a result of the altered electron density in the molecules, especially on aromatic systems. In this context, the main advantage of our strategy is that fluorination is the final synthetic step. Since the target structures are released from the solid support under simultaneous fluorination, the method is also suitable for the synthesis of radio-labeled compounds.[6]

We first developed a robust route for the anchoring of commercially available haloarenes **1** (Scheme 1). Dithioesters are well-suited precursor structures since every C—S bond can be transformed easily into the corresponding C—F bond by oxidative desulfuration–fluorination.[7] Transformation of haloarenes **1** to the corresponding Grignard reagents and subsequent reaction with an excess of carbon disulfide and Merrifield resin (cross-linked, loading 0.97 $\mathrm{mmol\,g^{-1}}$) in the presence of potassium iodide resulted in deep-reddish dithioester resins **3**. The immobilization was monitored using ^{13}C gel-phase NMR spectroscopy and was quantified precisely by sulfur elemental analysis.[8] A loading efficiency of over 90% was accomplished in all cases.



Scheme 1. Synthesis of trifluoromethylarenes **4** through fluorinating cleavage. Yields of purified compounds over two steps.

As common Grignard conditions based on elemental magnesium (Scheme 1, method A, used for nonfunctionalized arenes) are not compatible with many functional groups, we developed an alternative protocol (Scheme 1, method B) using Knochel's *i*PrMgCl·LiCl reagent which proved to be compatible with ethers, carbonyls, nitriles, acetals, and competitive halide functionalities.[9]

After screening experimental conditions, we found that a protocol using a mixture of *N*-iodosuccinimide (NIS) and HF/pyridine (Olah's reagent) is most suitable for the fluorinating cleavage of the dithioester linker to give the corresponding trifluoromethylarenes. When 1,3-dibromo-5,5-dimethylhydantoin (DBH) was used as an alternative additive, *ortho* bromination of electron-rich aromatic rings could be observed.[7]

The immobilized haloarenes were subsequently modified by different transformations to demonstrate the robustness of

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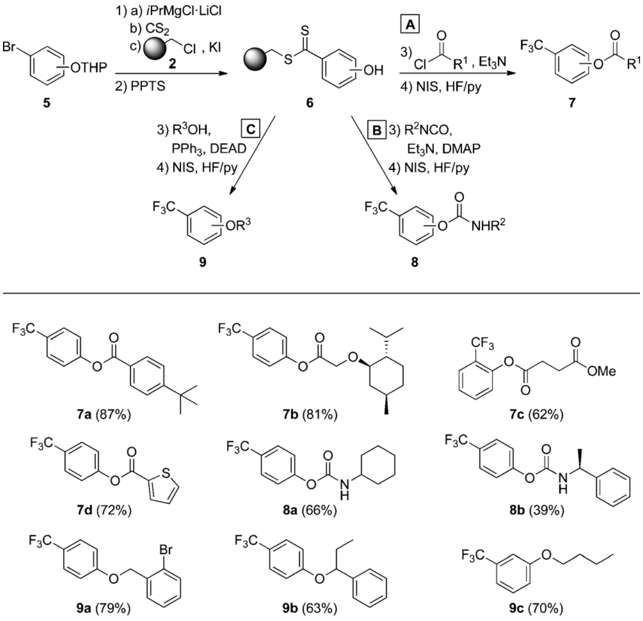
the novel dithioester linker system (Scheme 2). After facile removal of protecting groups like THP ethers (using pyridinium *p*-toluenesulfonate (PPTS)) and TBDMS ethers (using 1 M TBAF solution in THF), the resulting bromophenols **6** were treated with different acid chlorides (Scheme 2, path A) and isocyanates (Scheme 2, path B) to give the corresponding esters and carbamates on bead, respectively. Cleavage from the resins gave the trifluoromethylated compounds **7** and **8** in yields up to 87 % over four steps (based on the initial loading of Merrifield resin).

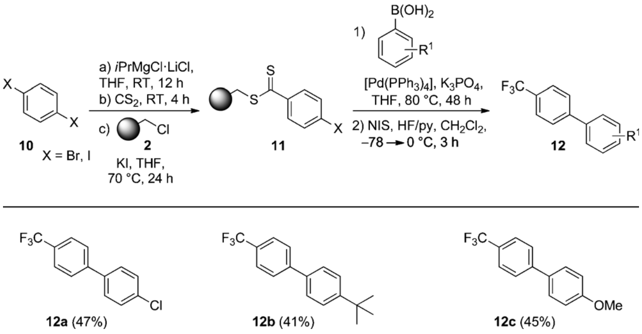


Scheme 2. Modification of immobilized phenols and fluorinating cleavage: 1) a) dioxane/THF, RT, 12 h; b) RT, 4 h; c) THF, 70 °C, 24 h; 2) toluene, 80 °C, 16 h; 3) **A**: CH_2Cl_2, RT, 12 h; **B**: THF, 70 °C, 48 h; **C**: THF, 70 °C, 24 h; 4) **A**,**B**,**C**: CH_2Cl_2, −78→0 °C, 3 h. Yields of purified compounds over four steps.

Etherification under Mitsunobu conditions on bead (Scheme 2, path C) followed by fluorinating cleavage gave rise to trifluormethylated phenyl ethers **9** in very good yields up to 79 % over four steps. Notably, the crude products already showed high purities (> 90 %) and contained only small amounts of succinimide as a byproduct, which could be removed easily by flash filtration.

Importantly, formation of mono-Grignard reagents was possible with dibromo- and diiodoarenes **10** (X = Br, I), giving access to aryl halides resins **11** (Scheme 3). These underwent coupling reactions to give biaryls with different aryl boronic acids. Cleavage of the functionalized resins gave the trifluoromethylated biphenyls **12** in good yields of 41–47 % over three steps.

Palladium-catalyzed reactions on solid supports are established and have already been demonstrated by a number of Suzuki coupling reactions.[10] However, to our knowledge, we describe herein the first Suzuki reactions with retention of dithioester moieties in general.[11,12]



Scheme 3. Pd-catalyzed cross-coupling and fluorinating cleavage. Yields of purified compounds over three steps.

Because high-loaded Merrifield resin can be used and most of the transformations are quantitative, the method is very suitable for the combinatorial synthesis of libraries with trifluoromethylarenes. The advantage lies in the fluorination in the final cleavage step, and therefore the negative influence of the electronic structure of a CF_3 substituent is circumvented. Based on the same principle the development of a xanthogenate linker[7a] for the synthesis of trifluormethyl ethers should be possible.

Experimental Section

3a: Representative synthesis for the immobilization of aryl halides with elemental magnesium: A dry three-neck flask with a Dimroth condenser and a dropping funnel was charded with magnesium turnings (170 mg, 7.00 mmol, 7.00 equiv) suspended in anhydrous THF (1.70 mL) under an argon atmosphere. The dropping funnel was charged with a solution of 4-bromobiphenyl (**1a**; 1.67 g, 5.00 mmol, 5.00 equiv) in anhydrous THF. The reaction was started by continuous addition of the solution to the suspension (when necessary three drops of dibromoethane were added). The reaction mixture was stirred for 1 h at 70 °C, then cooled to 40 °C and carbon disulfide (1.90 g, 25.0 mmol, 25.0 equiv) was added. After 2 h of stirring at 40 °C, the red solution was transferred into a vial and Merrifield resin (1.03 g, 1.00 mmol, 1.00 equiv) and potassium iodide (330 mg, 2.00 mmol, 2.00 equiv) were added. The vial was flushed with argon and sealed, and the mixture was shaken overnight at 70 °C. The red suspension was then transferred to a separation funnel, methylene chloride (20 mL) was added, and the insoluble, inorganic compounds were removed. Finally, the resin was filtered off, washed, and dried under high vacuum to yield the red resin **3a** (1.20 g; conversion: 95 %).

10a: Representative synthesis for the immobilization of functionalized aryl halides using Knochel's *i*PrMgCl·LiCl reagent. A solution of *i*PrMgCl·LiCl (1.3 M in THF; 6.50 mL, 5.00 mmol, 5.00 equiv) in a 9:1 mixture of anhydrous THF and dioxane (10 mL) was stirred overnight in a Schlenk flask under an argon atmosphere. The colorless precipitate was filtered off under argon and the filtrate added dropwise to a solution of 1,4-dibromobenzene (1.18 g, 5.00 mmol, 5.00 equiv) in THF. The mixture was stirred overnight at ambient temperature, and carbon disulfide (2.28 g, 30.0 mmol, 20.0 equiv) was added. After 4 h of stirring at the same temperature, the red solution was transferred into a vial and Merrifield resin (1.03 g, 1.00 mmol, 1.00 equiv) and potassium iodide (320 mg, 2.00 mmol, 2.00 equiv) were added. The vial was flushed with argon and sealed, and the mixture was shaken overnight at 70 °C. The red suspension was then transferred to a separation funnel, methylene chloride (20 mL) was added, and the insoluble, inorganic compounds were removed. Finally the resin was filtered off, washed, and dried under high vacuum to yield the red resin **10a** (1.23 g; conversion: 99%).

4a: Representative synthesis for the fluorinating cleavage of the dithioester linker: All cleavage reactions were performed under argon atmosphere in 100 mL Teflon-coated flasks. *N*-Iodosuccinimide (505 mg, 2.25 mmol, 5.00 equiv) was suspended in anhydrous methylene chloride (10 mL). After the reaction mixture had been cooled to −78°C, HF (70% in pyridine; 0.45 mL (18.0 mmol, 40.0 equiv) was added, and the mixture was stirred for 10 min. Then resin **3a** (550 mg, 0.450 mmol, 1.00 equiv) was allowed to swell in the twofold volume of anhydrous dichloromethane before it was transferred into the flask. The reaction mixture was stirred for 3 h and allowed to warm up to 0°C. Methylene chloride (20 mL) was added, followed by 5% aq. $NaHSO_3$ solution (10 mL). After the red color had disappeared, the pH was adjusted to 10 by addition of a 20:1 mixture of a saturated $NaHCO_3$ solution and a 1 M NaOH solution. The resin was filtered off, the layers were separated, and the aqueous phase was extracted two times with methylene chloride. The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude product, which was purified by flash column chromatography on silica gel (cyclohexane/ethyl acetate, 10:1, $R_f = 0.70$) to yield a colorless solid (72.0 mg, 0.324 mmol, 72% yield over two steps).

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