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Short Research Article

Synthesis of aryl [^{35}S]sulfones: Friedel–Crafts sulfonylation of aryl ethers with high specific activity [^{35}S]methanesulfonyl chloride†

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Abstract: Lewis acid-assisted sulfonylation of anisole with [^{35}S]methanesulfonyl chloride afforded high specific activity aryl [^{35}S]sulfones. Demethylation and treatment with triflic anhydride gave the versatile [^{35}S]triflate **1** in good overall yields. The [^{35}S]sulfone triflate could be further functionalized by catalyzed aminations, Stille couplings, and cyanation. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: [^{35}S]methanesulfonyl chloride; aryl [^{35}S]sulfones; [^{35}S]sulfone triflate

Introduction

High specific activity ^{35}S-labeled radioligands (> 900 Ci/mmol) have previously been limited primarily to alkyl and aryl [^{35}S]sulfonamides.[1] These tools have proven to be very useful in biological applications, including receptor occupancy and binding, and offer some advantages over ^{3}H and ^{125}I-labeled radioligands.[2] While we have been able to broaden the scope of accessible [^{35}S]sulfonamide radioligands by varying the alkyl group and using functionalized aromatics,[3] we sought to expand the range of our high specific activity ^{35}S-chemistry to include aryl [^{35}S]sulfone-containing radioligands. It has been reported that methanesulfonyl chloride can be added to aryl compounds in a Friedel-type addition using bismuth or indium catalyst.[4] Herein, we report the Lewis acid-assisted sulfonylation of anisole with [^{35}S]methanesulfonyl chloride to afford high specific activity (> 900 Ci/mmol) aryl [^{35}S]sulfones. Separation of regioisomers, followed by demethylation, and treatment with triflic anhydride gave the versatile [^{35}S]triflate (A) which could be further functionalized by catalyzed aminations, Stille couplings, and cyanation.

Results and discussion

Our initial attempts were directed toward ^{35}S-sulfonylation of bromobenzene and toluene with high specific activity [^{35}S]methanesulfonyl chloride. When no methyl [^{35}S]sulfone was observed with bromobenzene or toluene under the described conditions,[4] we were forced to reconsider the suitability of the aryl group.

Subsequent ^{35}S-sulfonylation of a more electron-rich arene, anisole, provided moderate yields of the desired isomeric methyl [^{35}S]sulfones as shown in Scheme 1. A concentrated solution of [^{35}S]methanesulfonyl chloride in dichloromethane, anisole, and appropriate catalyst were warmed to 80°C for 4–6 h. The resulting *ortho*- and *para*-isomers of the methoxy [^{35}S]methyl sulfones were purified and separated by preparative HPLC.

Demethylation with boron tribromide[5] cleanly gave the [^{35}S]phenol in quantitative yield. Treatment of the phenol with triflic anhydride[6] under biphasic conditions (toluene, aqueous potassium phosphate) afforded clean [^{35}S]sulfone triflate **1** in 95% yield (scheme 2). The [^{35}S]sulfone triflate was stable in toluene and could be used as a stock solution in subsequent reactions without further purification.

The [^{35}S]sulfone triflate **1** proved to be quite a versatile intermediate and could be further functionalized

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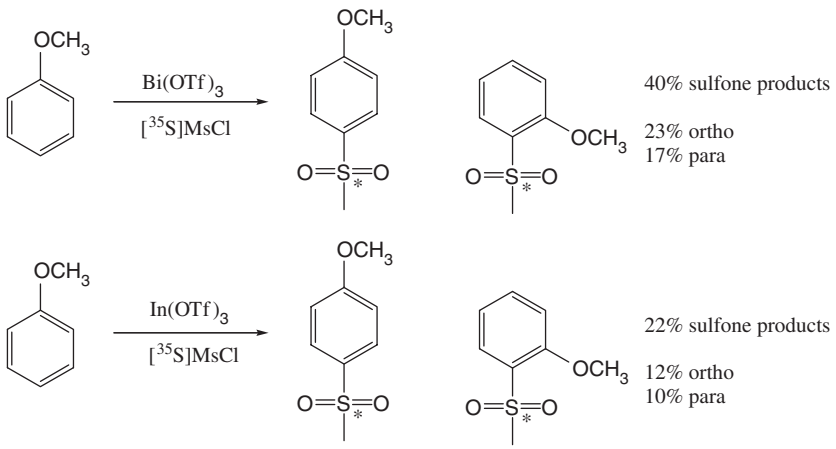
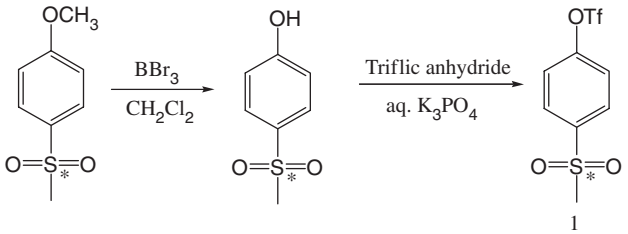
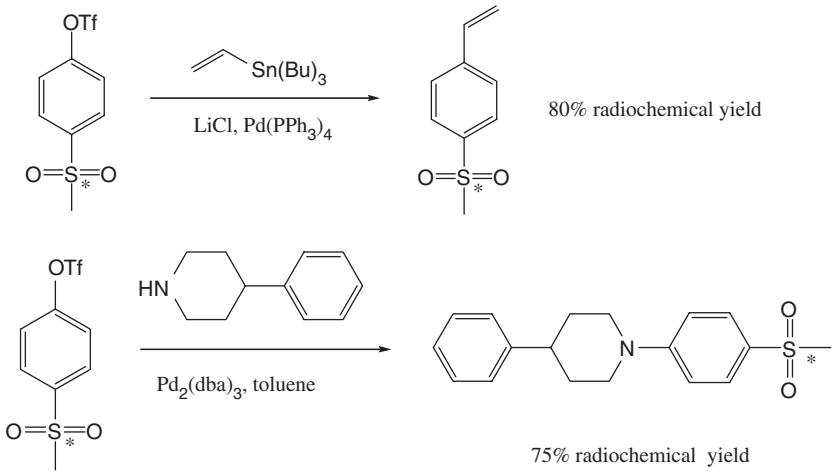


Scheme 1



Scheme 2



Scheme 3

through several standard triflate reactions, including aminations[7] and Stille-type couplings[8] of which a few examples are shown in Scheme 3.

Conclusion

We have developed a methodology to provide a high specific activity methyl [^{35}S] sulfone triflate from [^{35}S]methanesulfonyl chloride which is stable and functionalizable through amine couplings and carbon–carbon bond forming reactions. The sequence of reactions is robust, providing clean products even with many equivalents of reagents and further enhances our efforts to provide a range of structurally different ^{35}S-radioligands for biological applications.

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