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An environmentally-friendly one-pot synthesis of 4-sulfonyl benzoic acids

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ABSTRACT

This Letter reports an environmentally-friendly one-pot S_NAr reaction of thiols to 4-halobenzoic acid methyl esters to provide 4-substituted sulfone benzoic acids and picolinic acids after bleach-mediated oxidative workup. These acid intermediates were synthesized on gram scale, are perfect partners for library synthesis, and have good physical chemical properties useful for drug discovery.

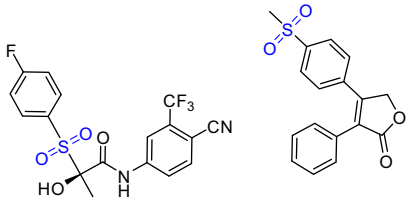
Introduction

Aryl sulfones are an important moiety in drug discovery. Sulfones are generally stable toward heat, acids, bases, oxidation, and reduction and often improve the crystallinity of drug products.[1] AstraZeneca's androgen receptor inhibitor Bicalutamide (Casodex®) (**1**) and Merck's Cox-2 inhibitor Rofecoxib (Vioxx®) (**2**) are two examples of drugs containing aryl sulfones (Fig. 1). Sulfones are strong H-bond acceptors and are classical bioisosteres[2] of carbonyl containing compounds.

There have been several reviews which have detailed the many methods used to prepare non-complex aryl sulfones.[1,3] These methods include alkylation of sulfinic acid salts,[4] sulfonylation of simple arenes via Friedel Crafts-type chemistry,[5] palladium-catalyzed addition of an organostanane to an arylsulfonyl chloride,[6] and palladium catalyzed cross-coupling chemistry of aryl halides with organo thiols.[7–10]

Another common method to prepare aryl sulfones has been through a two-step method. First, a thiol reacts with an aryl halide or pseudohalide through nucleophilic aromatic substitution (S_NAr) followed by oxidation using a variety of oxidants in a second step to form an aryl sulfone. Common oxidants include MCPBA, H_2O_2,[11] $KMnO_4$,[12] RuO_4,[13] and oxone.[14]

Despite the well-known S_NAr literature for preparing arylthioethers,[15] and the simple oxidative conversion to aryl sulfones, less than 100 functionalized 4-substituted benzoic acids are commercially available from reliable vendors. This has been verified as some of these building blocks were needed for an in-house library effort and were synthesized based on lack of commercial availability. The in situ bleach oxidation was very nice in that the foul smelling mercaptan products and excess thiolates that were employed in the reaction were oxidized in situ to alleviate the foul odor. In addition, bleach is very inexpensive and is characterized as an environmentally-friendly oxidant[16] due to its extremely fast dissociation in water and offers low environmental harm to the community. This Letter reports the first one-pot S_NAr reaction of thiols to 4-halobenzoic acid methyl esters to provide 4-substituted sulfone benzoic acids after bleach oxidative workup. These acid intermediates are perfect partners for library synthesis and have good physical chemical properties for drug discovery.



Bicalutamide (**1**) Rofecoxib (**2**)

Figure 1. Commercial sulfone containing drugs.

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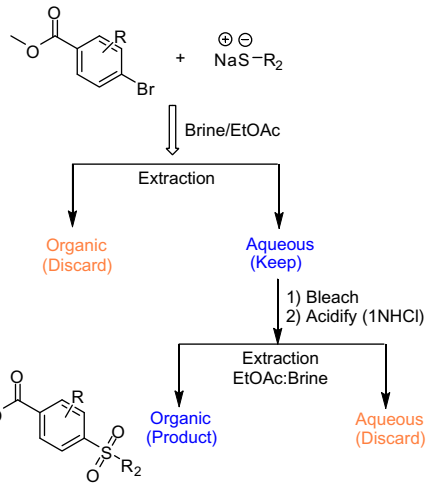
Results and discussions

The reaction of methyl 4-bromobenzoate (**3**) with sodium isopropylthiolate (**4**) was used to optimize this process. A solvent screen was performed to find the best reaction conditions in our system. We found that 1.1 equiv of the isopropylthiolate in DMF at 65 °C cleanly provided methyl 4-(isopropylthio) benzoate in 3 h, but 2.5 equiv of the isopropylthiolate was needed to cleanly provide 4-(isopropylthio) benzoic acid (**5**). Such thiolate mediated ester deprotections are well known.[17] Performing the same reaction on 4-bromobenzoic acid resulted in no conversion to product. This showed that this reaction proceeds through a two-step mechanism where first, the S_NAr reaction takes place, followed by deprotection of the methyl ester to the carboxylate. Suitable solvents for the S_NAr reaction were typical polar aprotic solvents such as DMF, DMSO, DMA, and NMP. Unsuitable solvents that showed no reaction and recovered starting material were THF, dioxane, acetonitrile, diglyme, dichloroethane, and methanol. Water or 1 N sodium hydroxide only resulted in conversion of the starting material methyl ester to the corresponding carboxylic acid (Table 1). The use of polar aprotic solvents is necessary to avoid the bivalent reactivity of thio anions (i.e., as nucleophiles and as reductants through radical pathways).[18]

After performing an S_NAr reaction with a thiolate, a common work-up after extraction is to add bleach to the waste to oxidize any remaining thiol and eliminate the foul odor of the thiol employed in the reaction. Instead, we envisioned that perhaps we could use this work-up for the extracted product to oxidize the thio ether during work-up and provide the sulfone product without the need for purification. We began by performing the reaction of methyl 4-bromobenzoate with 2.5 equiv of sodium isopropylthiolate in DMF. After 3 h, the reaction was quenched with brine and extracted with ethyl acetate. The ethyl acetate layer was washed with brine three times to remove all of the carboxylate product. The ethyl acetate layer was discarded. The aqueous layer was then treated with commercial bleach and stirred for 10 min. Complete oxidation of the thio ether to the sulfone was seen by LCMS. Acidification of the mixture to pH 1 using 1 N HCl followed by extraction with ethyl acetate and concentration provided 4-(isopropylsulfonyl)benzoic acid as a white solid without the need for purification (Scheme 1).[19]

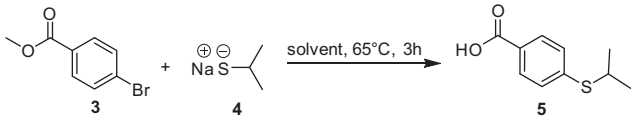


Scheme 1. Flow chart for S_NAr-oxidation protocol.

In order to test the ability of different commercial and in situ prepared sodium thiolates in the S_NAr reaction, a few reactions were performed using methyl 4-bromobenzoate. Isopropylthiolate, the more sterically hindered *t*-butyl thiolate, and isobutyl thiolate worked efficiently to provide the desired sulfone carboxylic acids in respectable yields. As expected, the in situ prepared pyrimidine-2-thiolate did not undergo the S_NAr reaction due to the poor nucleophilicity of the pyrimidine thiolate (Table 2).

In order to evaluate the utility of this methodology, substrates were chosen based on varying substitution pattern and electronics of the benzoate, functional group compatibility, and reactivity with different thiolates (Table 3). Both electron rich and electron deficient aryl halides had no effect on the S_NAr reaction and led to good

Table 1
Solvent screen for optimizing S_NAr reaction conditions

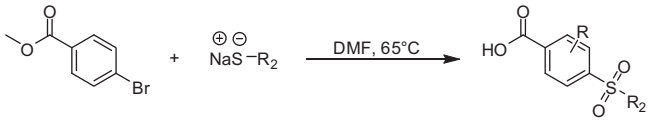


3 4 5

Entry	Equivalents (4)	Solvent	Conversion[c] (%)
1	1.1	DMF	100[a]
2	2.5	DMF	100
3	2.5	DMSO	100
4	2.5	THF	0
5	2.5	Dioxane	0
6	2.5	Toluene	0
7	2.5	Water	0[b]
8	2.5	1 N NaOH	0[b]
9	2.5	Diglyme	0
10	2.5	DMA	100
11	2.5	NMP	100
12	2.5	DCE	Trace
13	2.5	MeOH	100
14	2.5	ACN	100

[a] Methyl ester product formed.
[b] Carboxylic acid of starting material formed.
[c] Conversion percent determined by Sciex LCMS (1–99% ACN/H_2O) averaging the 220 nm and 254 nm trace.

Table 2
S_NAr-oxidation reaction of thiolates with methyl 4-bromobenzoate



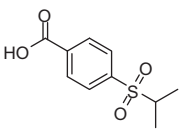
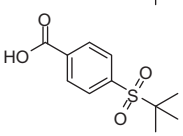
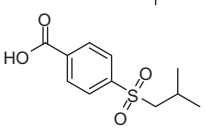
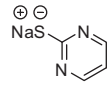
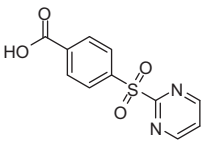
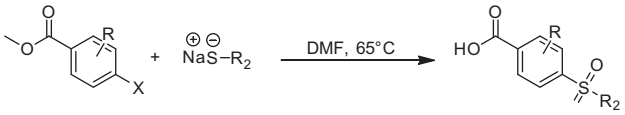
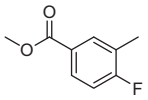
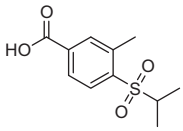
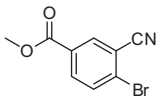
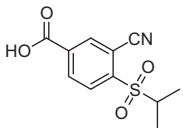
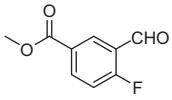
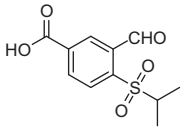
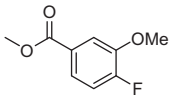
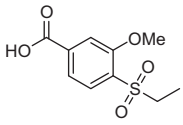
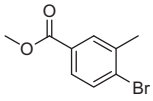
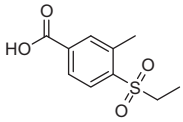
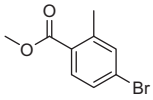
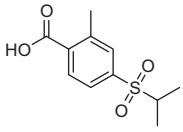
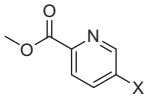
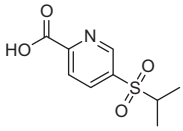
Entry	Thiol/thiolate	Product	Yield (%)
1			82
2			79
3			70
4			NR

Table 3
Preparation of 4-sulfone benzoic and picolinic acids references



Entry	Aryl halide	Thiol/thiolate	Product	Yield (%)
1				81
2				99
3				40
4				60
5				86
6				0
7	 [a]X=Br [b]X=NO_2			86[a] 51[b]

[a] 4-Br picolinic ester
[b] 4-NO_2 picolinic ester

yields of the corresponding sulfones (entries 1, 2, & 5). Somewhat reactive functionalities such as aldehydes and methoxy groups in the presence of isopropyl and ethyl thiolate were tolerated but resulted in lower yields (entries 3 & 4). As expected, *ortho* substitution was not tolerated (entry 6) due to changing the electronics of the ring and the conjugation into the ester resulting in only recovery of the carboxylic acid. In the literature, there are no reports of thiol additions to electron rich *ortho* benzoic acid esters. All examples use transition metals such as palladium or copper for this transformation.[20] This methodology also works very well for picolinic acids (entry 7). 4-Bromo-picolinic acid methyl ester was cleanly converted to the isopropyl sulfone in excellent yield (entry 7[a]). It is noteworthy that other electron withdrawing groups such as nitro can act as pseudo halides and react with thiolates to provide the S_NAr product but in lower yields (entry 7[b]).

In brief, we have successfully developed an environmentally friendly one-pot synthesis of 4-substituted sulfone benzoic acids and picolinic acids. In general, these building blocks are prepared from simple commercially available starting materials and can be isolated without the need for purification. This methodology has been employed on multi-gram scale to prepare these simple building blocks and was used in a drug discovery effort.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.092.

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19. *Representative procedure:* 4-Isopropylsulfonyl benzoic acid (Table 2, entry 1). To a 100 mL rbf were added methyl 4-fluorobenzoate (1.075 g, 5 mmol), DMF (20 mL), and sodium propane-2-thiolate (1.227 g, 12.5 mmol) and the reaction was heated for 3 h at 65 °C. The reaction was found to be complete by LCMS analysis. The reaction was removed from the oil bath and was allowed to cool to rt. The reaction was quenched with brine and allowed to stir for 20 min. The reaction mixture was then extracted with EtOAc 3 times and the aqueous layer was collected in a 1 L Erlenmeyer flask. The aqueous layer was then treated with 100 mL of commercial bleach and the reaction mixture immediately turned colorless and transparent. The reaction mixture was then allowed to stir for 10 min. The reaction was then treated with 1 N HCl until the reaction was pH 1. The reaction was then extracted with EtOAc 3 times and the organic layers were then washed with brine 3 times to remove any trace DMF. The organic layer was then dried over sodium sulfate and the solvent was removed to provide 4-isopropylsulfonyl benzoic acid (931 mg, 81.6%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.28–8.22 (m, 2H), 8.03–7.96 (m, 2H), 3.38 (dt, J = 13.7, 6.8 Hz, 1H), 1.26 (d, J = 6.8 Hz, 6H).
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