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A novel method for the synthesis of aryl trihalomethyl sulfones and their derivatization: the search for new sulfone fungicides

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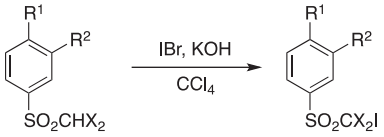
ABSTRACT

A novel method for the preparation of bioactive aryl trihalomethyl sulfones is reported. An iodination reaction with iodine bromide is applied for the synthesis of difluoroiodomethyl aryl sulfones. A series of difluoroiodomethylsulfonyl group bearing derivatives is afforded, including nitroanilines and benzimidazoles. Biological studies show high fungicidal activity for a number of the synthesized sulfones.

Many iodine-containing aryl halomethyl sulfones show high fungicidal activity against certain plant pathogens and are the subject of a number of reports, mainly patents.[1–4] Diiodomethyl *p*-tolyl sulfone was proposed as a veterinary medicine for the treatment of fungal diseases in domestic animals.[2] Moreover, many other *para*-substituted aryl diiodomethyl sulfones exhibit fungicidal activity toward pathogenic fungi.[3,4] In the context of applications in organic synthesis, difluoroiodomethyl phenyl sulfone has been utilized as a reagent in the radical (phenylsulfonyl)difluoromethylation of terminal alkenes.[5]

A known method for the preparation of aryl iodomethyl sulfones containing no other halogen in the halomethylsulfonyl group is based on the iodination of arylsulfonylacetic acids with molecular iodine in alkaline solution.[6] The major disadvantage of this method is that it is necessary to prepare an appropriate starting arylsulfonylacetic acid, most often via a multistep synthesis. There are only a few methods for the preparation of aryl trihalomethyl sulfones which also contain halogens other than iodine. Aryl iododifluoromethyl sulfones were synthesized by coupling the mercury salts of arylsulfinyldifluoroacetic acids with iodine followed by oxidation with MCPBA.[7] Difluoroiodomethyl phenyl sulfone was obtained from the reaction of difluoromethyl phenyl sulfone with iodine and potassium *tert*-butoxide in DMF at low (−30 to −20 °C) temperature.[8] Alternatively, it was obtained by treatment of difluoro(trimethylsilyl)methyl phenyl sulfone with copper(I) iodide and cesium fluoride in DMF (−30 °C, then 0 °C).[9]

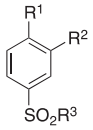


1 - 5

R^1 = H or Cl; R^2 = H or NO_2; X = F or Cl

Scheme 1. Iodination of the starting aryl halomethyl sulfones with iodine bromide (the substituents are identified in Table 1).

Table 1
Iodine-containing aryl trihalomethyl sulfones **1**–**5**



Entry	Product	R^1	R^2	R^3 (substrate)	R^3 (product)	Yield[a] (%)
1	**1**	H	H	CHF_2	CF_2I	92
2	**2**	Cl	H	$CHCl_2$	CCl_2I	82
3	**3**	Cl	H	CHF_2	CF_2I	94
4	**4**	Cl	NO_2	CHF_2	CF_2I	74
5	**5**	Cl	H	CH_2F	CFI_2	66

[a] Isolated yield.

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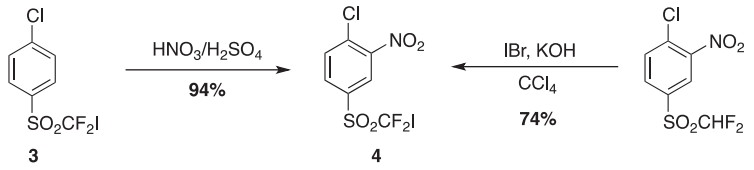
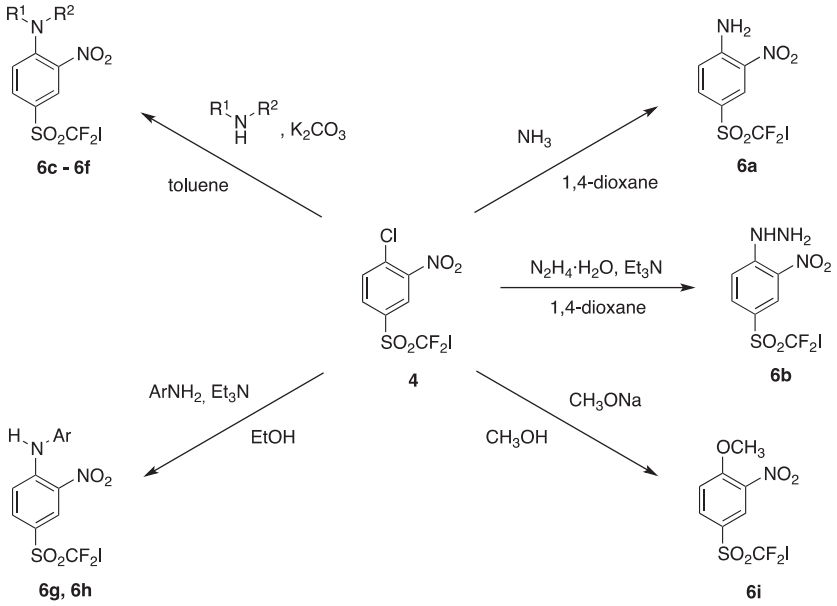
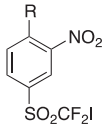


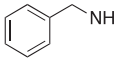
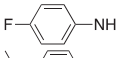
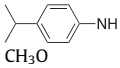
Scheme 2. Methods for the preparation of nitro derivative **4**.



Scheme 3. S_NAr transformations of sulfone **4**.

Table 2
Iodine-containing nitroaryl trihalomethyl sulfones **6a–6i**



Entry	Product	R	Yield[a] (%)
1	**6a**	NH_2	92
2	**6b**	$NHNH_2$	89
3	**6c**	CH_3NH	86
4	**6d**		87
5	**6e**		95
6	**6f**		92
7	**6g**		87
8	**6h**		92
9	**6i**	CH_3O	87

[a] Isolated yield.

Herein we report a novel method for the synthesis of difluoroiodomethyl aryl sulfones, which makes use of simple substrates. The synthetic procedure is easy to execute, occurs at room or slightly elevated temperature, and the isolation of the product is straightforward. Further functionalization of the nitro-substituted product afforded a series of difluoromethyl sulfone derivatives, including nitroanilines and benzimidazoles (compounds previously shown to exhibit increased biological activity when combined with a halomethylsulfonyl group).[10,11] The products were then investigated in terms of their fungicidal activity. As a result, several promising new leads for the development of sulfone-based biocidal agents were obtained.

Our research revealed that a convenient method for the preparation of aryl trihalomethyl sulfones containing one or two iodine atoms involved iodination with commercially available iodine bromide. The reactions were carried out with potassium hydroxide in carbon tetrachloride within the temperature range of 20–60 °C (Scheme 1 and Table 1).

Notably, in the reaction of 4-chlorophenyl fluoromethyl sulfone with iodine bromide a diiodo derivative was formed, and no monoiodinated derivative was observed, despite utilizing iodine bromide in less than stoichiometric quantity.

The substrates: 4-chlorophenyl difluoromethyl sulfone, 4-chlorophenyl fluoromethyl sulfone, and 4-chlorophenyl dichloromethyl sulfone were obtained according to our previous work.[12] Application of potassium *tert*-butoxide as a base resulted in similar or lower yields, except for the iodination of chlorophenyl 4-fluoromethyl sulfone in which the product **5** was obtained in 12% higher yield (78% yield with *t*-BuOK compared to 66% yield with KOH). The desired products were obtained in very good yields (82–92%).

Analogous reactions carried out with iodine chloride afforded sulfone **3** in yields ranging from 18% to 26%. With 4-chlorophenyl dichloromethyl sulfone and 4-chlorophenyl fluoromethyl sulfone, no products were obtained in the reactions with ICl; instead the starting substrates were isolated from the reaction mixture.

Bearing in mind the interesting fungicidal activity of aryl iodomethyl sulfones, we decided to undertake further synthetic transformations of compound **4** to give derivatives with potentially