



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



Maciej D. Korzyński, Krzysztof M. Borys, Justyna Białek, Zbigniew Ochal\*

Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

## ARTICLE INFO

### Article history:

Received 17 September 2013

Revised 5 November 2013

Accepted 5 December 2013

Available online 12 December 2013

### Keywords:

Diiododimethyl sulfone

Iodine bromide

$S_NAr$  reaction

Sulfone fungicides

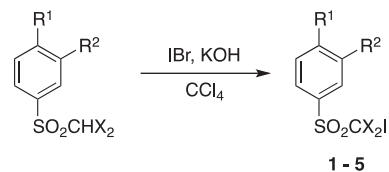
## ABSTRACT

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 diiododimethyl aryl sulfones. A series of diiododimethylsulfonyl group bearing derivatives is afforded, including nitroanilines and benzimidazoles. Biological studies show high fungicidal activity for a number of the synthesized sulfones.

© 2013 Elsevier Ltd. All rights reserved.

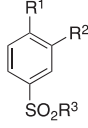
Many iodine-containing aryl halomethyl sulfones show high fungicidal activity against certain plant pathogens and are the subject of a number of reports, mainly patents.<sup>1–4</sup> Diiodomethyl *p*-tolyl sulfone was proposed as a veterinary medicine for the treatment of fungal diseases in domestic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

A known method for the preparation of aryl iodoethyl sulfones containing no other halogen in the halomethylsulfonyl group is based on the iodination of arylsulfonylacetic acids with molecular iodine in alkaline solution.<sup>6</sup> 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 iodoethyl sulfones were synthesized by coupling the mercury salts of arylsulfonyldifluoroacetic acids with iodine followed by oxidation with MCPBA.<sup>7</sup> Diiododimethyl 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.<sup>8</sup> 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).<sup>9</sup>



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

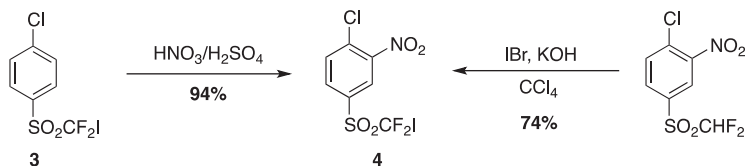
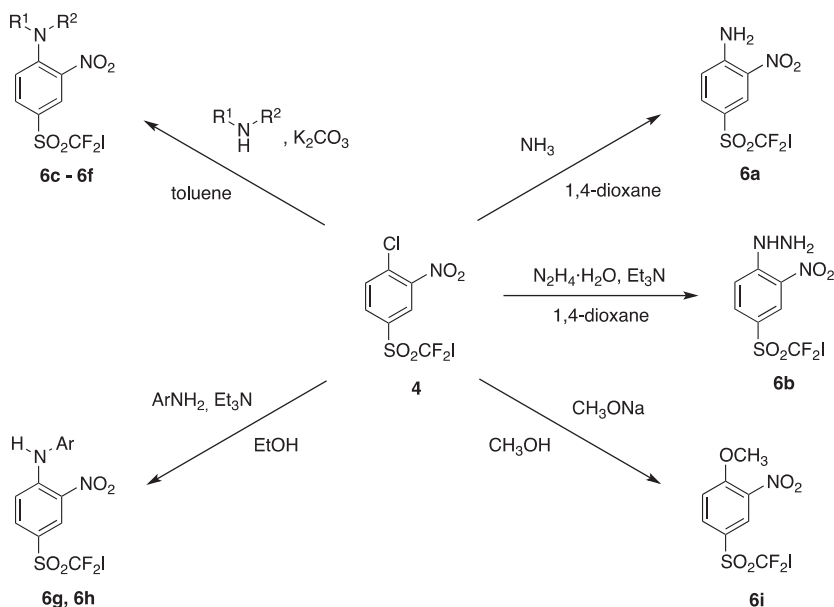
**Table 1**  
Iodine-containing aryl trihalomethyl sulfones 1–5

Entry	Product			$R^3$ (substrate)	$R^3$ (product)	Yield <sup>a</sup> (%)
		$R^1$	$R^2$			
1	<b>1</b>	H	H	CHF <sub>2</sub>	CF <sub>2</sub> I	92
2	<b>2</b>	Cl	H	CHCl <sub>2</sub>	CCl <sub>2</sub> I	82
3	<b>3</b>	Cl	H	CHF <sub>2</sub>	CF <sub>2</sub> I	94
4	<b>4</b>	Cl	NO <sub>2</sub>	CHF <sub>2</sub>	CF <sub>2</sub> I	74
5	<b>5</b>	Cl	H	CHF <sub>2</sub>	CF <sub>2</sub> I	66

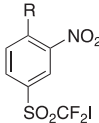


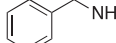
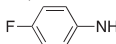
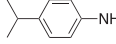
<sup>a</sup> Isolated yield.

\* Corresponding author. Tel.: +48 22 234 73 27; fax: +48 22 628 27 41.

E-mail address: [zbigniew.ochal.pw@gmail.com](mailto:zbigniew.ochal.pw@gmail.com) (Z. Ochal).

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 <sup>a</sup> (%)
1	<b>6a</b>	NH <sub>2</sub>	92
2	<b>6b</b>	NHNH <sub>2</sub>	89
3	<b>6c</b>	CH <sub>3</sub> NH	86
4	<b>6d</b>		87
5	<b>6e</b>		95
6	<b>6f</b>		92
7	<b>6g</b>		87
8	<b>6h</b>		92
9	<b>6i</b>	CH <sub>3</sub> O	87

<sup>a</sup> Isolated yield.

Herein we report a novel method for the synthesis of difluoriodomethyl 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).<sup>10,11</sup> 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.

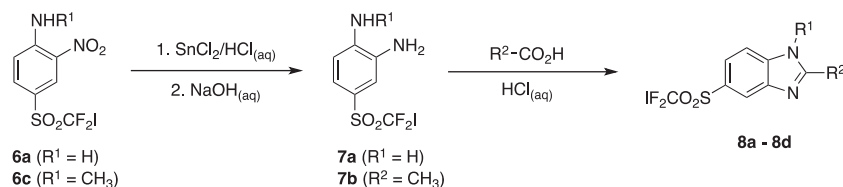
Our research revealed that a convenient method for the preparation of aryl trihalomethyl sulfones containing one or two iodine atoms involved iodination with commercially available iodine bromide. The reactions were carried out with potassium hydroxide in carbon tetrachloride within the temperature range 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.<sup>12</sup> 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 iodo-methyl sulfones, we decided to undertake further synthetic transformations of compound **4** to give derivatives with potentially



**Scheme 4.** Preparation of benzimidazoles **8a–8d** (the substituents are identified in Table 3).

**Table 3**  
Benzimidazole derivatives **8a–8d**

Entry	Product	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>a</sup> (%)
1	<b>8a</b>	H	CH <sub>3</sub>	65
2	<b>8b</b>	H	CF <sub>3</sub>	72
3	<b>8c</b>	CH <sub>3</sub>	CH <sub>3</sub>	65
4	<b>8d</b>	CH <sub>3</sub>	CF <sub>3</sub>	70

<sup>a</sup> Isolated yields over two steps (starting from the nitroaniline substrate).

higher biological activity. In the first step, a nitro derivative was synthesized in two different ways: the first was via nitration of 4-chlorophenyl difluoriodomethyl sulfone, and the second involved the reaction of 4-chloro-3-nitrophenyl difluoromethyl sulfone with iodine bromide (Scheme 2).

Both the nitration and iodination of the sulfones occurred in satisfactory yields (94% and 74%, respectively). Sulfone **4** was then used as a substrate for aromatic nucleophilic substitution reactions with ammonia, hydrazine, and primary and secondary amines (Scheme 3). In the reaction with sodium methoxide, the chlorine atom underwent substitution with a methoxy group. The substitution products were obtained in good to excellent yields (Table 2).

The 2-nitroanilines **6a** and **6c** were converted into benzimidazole derivatives in a two-step synthesis (Scheme 4). The first step

consisted of the reduction of the nitro group using stannous chloride in concentrated hydrochloric acid, followed by work-up with aqueous sodium hydroxide (hydrolysis of the resulting chlorostannic acid–diamine complexes). The so-obtained crude nitroanilines **7a** and **7b** were used directly in the next step. The formation of the benzimidazole scaffolds was carried out according to the Phillips method,<sup>13,14</sup> based on the treatment of an aromatic diamine with a carboxylic acid and aqueous hydrochloric acid. 2-Substituted benzimidazoles **8a–8d** were obtained in good yields over the two steps (Table 3).

The synthesized compounds were tested for their fungicidal activity (Table 4), which was investigated by inhibition of mycelium growth on agar medium, caused by the tested compounds and compared with the control (untreated mycelium).

The highest fungicidal activity was exhibited by sulfone **4**, which at both examined concentrations resulted in nearly total elimination of the five tested fungi. Substitution of the chlorine atom in sulfone **4** with an amine group (**6a**) resulted in lower fungicidal activity. Introduction of other substituents at the 1-position also lowered the fungicidal activity. Interesting activity was showed by benzimidazole derivatives **8b** and **8d** containing a trifluoromethyl group at their 2-position, being much more active than their 2-methyl-substituted analogues.

In conclusion, we have developed a novel, simple method for the synthesis of aryl difluoriodomethyl sulfones. The preparation of derivatives of these compounds, including nitroanilines and benzimidazoles, has broadened the scope for biological evaluation. The biological studies showed that some of the investigated species present high fungicidal activity and should therefore be fur-

**Table 4**  
Fungicidal activity of the most active compounds<sup>a</sup>

Entry	Test substrate	<i>A. alternata</i>	<i>B. cinerea</i>	<i>F. culmorum</i>	<i>P. cactorum</i>	<i>R. solani</i>
		100 µg/mL 10 mg/mL		200 µg/mL 20 µg/mL		
1	<b>4</b>	100 100	100 100	100 90	100 90	100 100
2	<b>5</b>	100 100	100 80	100 80	100 80	100 80
3	<b>6a</b>	100 100	80 80	100 80	100 80	100 100
4	<b>6b</b>	60 20	80 60	80 60	80 60	80 60
5	<b>6f</b>	60 20	80 60	50 20	50 30	40 0
6	<b>6g</b>	60 40	80 60	80 60	80 60	80 40
7	<b>6h</b>	50 20	80 60	80 50	50 20	40 0
8	<b>8b</b>	80 60	100 80	80 60	80 60	80 60
9	<b>8d</b>	60 20	80 60	80 60	80 60	80 60

<sup>a</sup> The results of biological evaluations as the values of percentage inhibition of colony growth of the fungus, derived from the following formula:  $I = 100(C - T)/C$ , where  $I$  = percentage inhibition of colony growth of the fungus,  $C$  = zone of growth of the fungus colony in mm in the control,  $T$  = zone of growth of the fungus colony in mm in the examined sample. The first row of the table contains the names of the utilized fungal pathogens, the second row shows the examined concentration(s) of the test compound in the sample.

ther investigated in terms of their application in crop protection against phytopathogenic fungi.

### Acknowledgements

This work was financially supported by the Polish State Committee for Scientific Research, Grant No. N N209 119937 and Warsaw University of Technology.

### Supplementary data

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.12.012>.

### References and notes

1. Malichenko, B. F.; Kornienko, R. A.; Yagupolskii, L. M. *Ukr. Khim. Zh.* **1968**, *34*, 486.
2. Smith, R. A. Topical Treatment of Fungal or Yeast Infections Using *p*-Tolyl Diiodomethyl Sulfone. U.S. Patent US 4185120, Jan 22, 1980; *Chem. Abstr.* **1980**, 92, 203585.
3. Crovetti, A. J. 4'-[(Diiodomethyl)Sulfonyl] Acetanilide. U.S. Patent US 3855253, Dec 17, 1974; *Chem. Abstr.* **1977**, 87, 584216.
4. Crovetti, A. J.; Germann, R. P.; Blank, A. Process for Producing Iodomethyl Sulfones. U.S. Patent US 3657353, Apr 18, 1972; *Chem. Abstr.* **1976**, 84, 135301.
5. Li, Y.; Liu, J.; Zhang, L.; Zhu, L.; Hu, J. *J. Org. Chem.* **2007**, *72*, 5824.
6. Ammo, T.; Yamagishi, M.; Kouchiwa, S.; Ukai, S.; Hayashi, H.; Tobari, Y. Novel Diiodomethyl Sulfones. Japanese Patent JP 43006609, Mar 12, 1968; *Chem. Abstr.* **1968**, 69, 496242.
7. Yagupolskii, L. V.; Matsnev, A. V. *Mendeleev Commun.* **2006**, *16*, 132.
8. Surya Prakash, G. K.; Hu, J.; Wang, Y.; Olah, G. A. *Org. Lett.* **2004**, *6*, 4315.
9. Zhu, J.; Wang, F.; Huang, W.; Zhao, Y.; Ye, W.; Hu, J. *Synlett* **2011**, 899.
10. Bakuniak, E.; Ptazkowska, J.; Zimińska, Z.; Ejmowski, Z.; Ochal, Z.; Tippe, A. Preparation of Trihalomethyl 3-Nitrophenyl Sulfones. Polish Patent PL 172321, Sep 30, 1997; *Chem. Abstr.* **1998**, 128, 62633.
11. Ochal, Z.; Mizerski, A.; Zalecki, S. Preparation of Novel Benzimidazole Derivatives as Herbicides. Polish Patent PL 194478, Jun 29, 2007; *Chem. Abstr.* **2008**, 148, 594265.
12. Borys, K. M.; Korzyński, M. D.; Ochal, Z. *Tetrahedron Lett.* **2012**, *53*, 6606.
13. Philips, M. A. *J. Chem. Soc.* **1928**, 2393.
14. Wright, J. B. *Chem. Rev.* **1951**, *48*, 397.