

# The development of an environmentally benign sulfide oxidation procedure and its assessment by green chemistry metrics

Claudio Omar Kinen, Laura Isabel Rossi\* and Rita Hoyos de Rossi\*

Received 12th September 2008, Accepted 24th October 2008

First published as an Advance Article on the web 21st November 2008

DOI: 10.1039/b815986f

Different Iron (III) species were used as catalysts in sulfoxidation reactions giving excellent yields and high chemoselectivity. Among the iron (III) species, the best one was a solid  $\beta$ -cyclodextrin-FeBr<sub>3</sub> complex. Sulfoxidation takes place with high chemoselectivity in the presence of other groups such as isothiocyanate. Good results were obtained when these reactions were analyzed using green chemistry metrics.

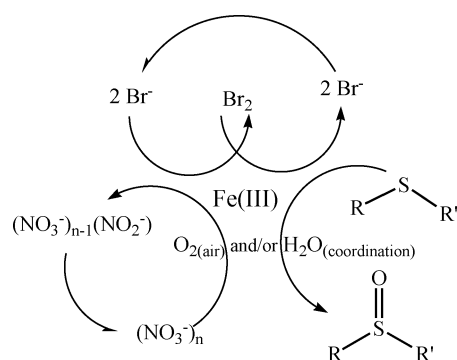
## Introduction

Sulfoxides and other organosulfur compounds are important synthetic intermediates in organic chemistry<sup>1</sup> and are valuable in the preparation of biologically and pharmaceutically relevant materials.<sup>2</sup> One of the oxidation reactions found in pharmaceutical research and production is that of a sulfide to a sulfoxide, which is achieved with a very wide variety of reagents.<sup>3</sup> When there are several different functional groups present in a molecule as in esomeprazole,<sup>4</sup> a sulfoxide-containing drug, chemoselective transformations are of great significance. This has often been difficult in sulfoxidation chemistry because oxidations of other functional groups can take place simultaneously.<sup>5</sup> Furthermore, sulfoxides can undergo overoxidation to sulfones and therefore it is important that the catalyst has a low reactivity towards the sulfoxides.<sup>6</sup>

In view of the general and continuous interest in the oxidation of sulfides<sup>7</sup> and particularly in the development of synthetic methods for the selective conversion of sulfides into sulfoxides,<sup>8</sup> we are currently involved in the study of reaction methodologies to achieve chemoselective sulfoxidation reactions.<sup>9</sup>

From a study of different combinations of metallic bromides and/or metallic nitrates it was concluded that combinations of iron salts formed an excellent catalytic system for the oxidation of sulfides to sulfoxides (Scheme 1).<sup>10</sup> Electrochemical studies in the presence of iron salts lead one to propose that the reaction occurs within the coordination sphere of the metal where the substrate is activated to be oxidized by the bromine generated from the Fe<sup>III</sup> bromide and the nitric acid. The water molecules and/or the oxygen present in the system subsequently oxygenated the substrate. Selectivity fails whenever this metal was absent.<sup>11</sup>

In a previous paper,<sup>12</sup> we have reported on the synthesis, characterization and catalytic activity of several cyclodextrins-FeBr<sub>3</sub> (CD-Fe) complexes. We found that cyclodextrin complexes have a very good catalytic activity in sulfoxidation



**Scheme 1** Redox mediators in catalytic and selective oxidation of sulfide.

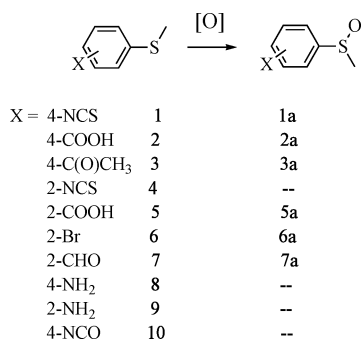
reactions and it was shown that several sulfides give sulfoxides with excellent yields in the presence of a catalytic amount of [Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O] as oxidant. Furthermore, these complexes can be re-used several times. These reactions were performed by recycling the solid CD-Fe complexes while the substrate, iron(III) nitrate and the organic solvent were renewed.<sup>12b</sup>

Based on previous studies using catalysts containing FeBr<sub>3</sub> stabilized by complexation with DMSO or with different cyclodextrins we considered it of interest to explore the scope of their use in the chemoselective synthesis of sulfoxides. Complexes with cyclodextrins are of particular interest because of the possibility of inducing enantiomeric excess.

We report here that substrates such as 4-(methylthio)-phenylisothiocyanate **1**; 4-(methylthio)benzoic acid **2**; 4-(methylthio)acetophenone, **3**; 2-(methylthio)benzoic acid **5**; 2-(methylthio)bromo benzene **6** and 2-(methylthio) benzaldehyde **7** are oxidized with very high chemoselectivity and in excellent yields (Scheme 2). It should be noted that highly oxidizable functions such as isothiocyanate or aldehyde remain unchanged under the reaction conditions used.

Green chemistry was introduced with the aim to overcome health and environmental problems at the source by developing cleaner chemical processes for the chemical industry through the design of innovative and environmentally benign chemical reactions.<sup>13–15</sup> We have analyzed the results in terms of reported green metric parameters and we demonstrate that the

Instituto de Investigaciones en Fisicoquímica de Córdoba (INFIQC), Facultad de Ciencias Químicas, Departamento de Química Orgánica, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000, Córdoba, Argentina. E-mail: lauraras@fcq.unc.edu.ar, ritah@fcq.unc.edu.ar



Scheme 2

methodology proposed for the oxidation of sulfides fulfill several of the green chemistry principles since the oxidant is oxygen from the air, the reactions are highly selective producing a minimum amount of waste and the catalyst is a non-contaminating metal.

## Results and discussion

Compound **1**, 4-(methylthio)phenylisothiocyanate, was oxidized with high yield and chemoselectivity using FeBr<sub>3</sub> free or in the form of complexes. As can be observed in Table 1, we have obtained 4-(methylsulfinyl) phenylisothiocyanate **1a** with excellent yields using FeBr<sub>3</sub>, the β-CD complex or the DMSO complex. Although all the reactions gave almost quantitative yield, the amount of isolated product is not the same because the work-up is in some cases more complicated than in others. No efforts were done to optimize the isolation procedures. The best reaction conditions are those involving the β-CD complex as catalyst and Fe(NO<sub>3</sub>)<sub>3</sub> in catalytic amount as oxidation promoter, Table 1 entry 3, because the catalyst is easily eliminated from the system by filtration and can be reused. The FeBr<sub>3</sub> and its DMSO complex are completely soluble in the reaction system and difficult to separate from the reaction products without an important loss of the product of interest and consequently a decrease in the isolated product. For this reason, although FeBr<sub>3</sub> appears as a more efficient catalyst since less reaction time is required, its use is not recommended

because complete elimination of the catalyst from the product could not be achieved without significant loss of the product of interest. Entries 2 and 4 in Table 1 show that without the catalyst the yield is very low or there is no reaction. Decreasing the amount of the nitrate (compare entries 1 and 3 in Table 1) did not result in a significant change in the yield of **1a**. When HNO<sub>3</sub> was used the product of interest was obtained with very good yield, Table 1 entry 7. It is remarkable that functions such as the isothiocyanate group, that can react with nucleophiles and with electrophiles or can isomerize to thiocyanate,<sup>16</sup> survive under the reaction conditions and remain unchanged. This is very important because isothiocyanates are useful intermediates in organic synthesis,<sup>17</sup> and they are also interesting for their biological activities.<sup>18</sup>

The sulfoxidation reaction was also very efficient in the presence of *ortho* and *para* carboxylic acid groups since 4-(methylthio)benzoic acid **2** and 2-(methylthio)benzoic acid **5** gave the expected products. The results are summarized in Table 2.

Excellent yield of 4-(methylsulfinyl)benzoic acid **2a** was obtained in most of the used conditions, Table 2 entries 1, 3 and 5. Nevertheless, in the absence of a catalyst, Table 2 entries 2 and 4, the sulfoxidation did not take place. The *ortho* derivative is significantly more reactive than the *para* derivative under all conditions and it is even reactive in the absence of the catalyst (compare runs 2 with 7 and 4 with 9 in Table 2).

Under the same reaction conditions used for **1** and **2**, 4-(methylthio)acetophenone **3** was oxidized on the sulfur almost quantitatively, although somewhat more slowly, compare for instance run 1 in Table 3 with run 1 in Table 2.

In order to determine the importance of the group position, we carried out the reaction with 2-(methylthio)phenyl isothiocyanate **4** (Table 1, entries 9–13), with 2-(methylthio) benzoic acid **5** (Table 2, entries 7–10), with 2-(methylthio) bromobenzene **6** (Table 4, entries 1–3) and with 2-(methylthio)benzaldehyde **7** (Table 4, entries 4–6).

For substituents –COOH, Br and –COH the reactivity of the *o*-substituted compounds is significantly higher than that of the *p*-substituted derivatives.<sup>12b,19</sup> Contrasting with that, in the case

Table 1 Oxidation reactions of *x*-(methylthio)phenylisothiocyanate to *x*-(methylsulfinyl)phenylisothiocyanate<sup>a</sup>

Entry	<i>x</i> -	Oxidant (%)	Catalyst <sup>b</sup>	Time <sup>c</sup>	% Substrate <sup>d</sup>	% Yield <sup>e</sup>
1	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	β-CD-Fe	3.0	0	93
2	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	—	3.6	75 <sup>f</sup>	25 <sup>f</sup>
3	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (5)	β-CD-Fe	6.0	0	96
4	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (5)	—	6.0	87 <sup>f</sup>	13 <sup>f</sup>
5	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	FeBr <sub>3</sub>	2.5	0	90
6	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	DMSO-Fe	5.5	0	95
7	4-	HNO <sub>3</sub> (13)	FeBr <sub>3</sub>	2.5	0	100
8	4-	HNO <sub>3</sub> (13)	—	5.5	50 <sup>f</sup>	50 <sup>f</sup>
9	2-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	β-CD-Fe	20.0	62	38 <sup>g</sup>
10	2-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	—	20.0	100	N.R. <sup>h</sup>
11	2-	HNO <sub>3</sub> (13)	FeBr <sub>3</sub>	20.0	100	N.R.
12	2-	HNO <sub>3</sub> (13)	—	8.5	100	N.R.
13	2-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	DMSO-Fe	20.0	70	30 <sup>g</sup>

<sup>a</sup> Solvent acetonitrile, oxidant Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O or nitric acid, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. <sup>b</sup> Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr<sub>3</sub>; DMSO-Fe = (FeBr<sub>3</sub>)<sub>2</sub>(DMSO)<sub>3</sub>. <sup>c</sup> Reaction time in hours. <sup>d</sup> Percent substrate recovered. <sup>e</sup> Percent yield of oxidation products after isolation and purification. <sup>f</sup> Percent yield of product and/or substrate determined by <sup>1</sup>H NMR analysis of the raw reaction products. <sup>g</sup> Unidentified products, percent conversion of substrate. <sup>h</sup> N.R. = no reaction.

**Table 2** Oxidation reaction of *x*-(methylthio)benzoic acid to *x*-(methylsulfinyl)benzoic acid<sup>a</sup>

Entry	<i>x</i> -	Oxidant (%)	Catalyst <sup>b</sup>	Time <sup>c</sup>	% Substrate <sup>d</sup>	% Yield <sup>e</sup>
1	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	β-CD-Fe	4.0	0	100
2	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	—	19.0	100	N.R. <sup>f</sup>
3	4-	HNO <sub>3</sub> (13)	FeBr <sub>3</sub>	2.5	0	100
4	4-	HNO <sub>3</sub> (13)	—	22.0	100	N.R.
5	4-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	DMSO-Fe	2.0	0	95
6	2-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	β-CD-Fe	2.0	0	100
7	2-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	—	20.0	30	70
8	2-	HNO <sub>3</sub> (13)	FeBr <sub>3</sub>	1.0	0	100
9	2-	HNO <sub>3</sub> (13)	—	20.0	66	44 <sup>g</sup>
10	2-	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	DMSO-Fe	1.5	0	93

<sup>a</sup> Solvent acetonitrile, oxidant Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. <sup>b</sup> Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr<sub>3</sub>; DMSO-Fe = (FeBr<sub>3</sub>)<sub>2</sub>(DMSO)<sub>3</sub>. <sup>c</sup> Reaction time in hours. <sup>d</sup> Percent substrate recovered. <sup>e</sup> Percent yield of oxidation products after isolation and purification. <sup>f</sup> N.R. = no reaction. <sup>g</sup> Percent yield of product and/or substrate determined by <sup>1</sup>H NMR analysis of the raw reaction products.

**Table 3** Oxidation reaction of 4-(methylthio)acetophenone to 4-(methylsulfinyl)acetophenone<sup>a</sup>

Entry	Oxidant (%)	Catalyst <sup>b</sup>	Time <sup>c</sup>	% Substrate <sup>d</sup>	% Yield <sup>e</sup>
1	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	β-CD-Fe	6.0	0	100
2	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	—	22.5	92 <sup>f</sup>	8 <sup>f</sup>
3	HNO <sub>3</sub> (13)	FeBr <sub>3</sub>	2.5	0	100
4	HNO <sub>3</sub> (13)	—	22.5	78 <sup>f</sup>	22 <sup>f</sup>
5	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	DMSO-Fe	3.0	0	95

<sup>a</sup> Solvent acetonitrile, oxidant Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. <sup>b</sup> Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr<sub>3</sub>; DMSO-Fe = (FeBr<sub>3</sub>)<sub>2</sub>(DMSO)<sub>3</sub>. <sup>c</sup> Reaction time in hours. <sup>d</sup> Percent substrate recovered. <sup>e</sup> Percent yield of oxidation products after isolation and purification. <sup>f</sup> Percent yield of product and/or substrate determined by <sup>1</sup>H NMR analysis of the raw reaction products.

**Table 4** Oxidation reaction of 2-(methylthio)bromobenzene **6** and 2-(methylthio)benzaldehyde **7**<sup>a</sup>

Entry	Substrate	Oxidant (%)	Catalyst <sup>b</sup>	Time <sup>c</sup>	% Substrate <sup>d</sup>	% Yield <sup>e</sup>
1	<b>6</b>	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	β-CD-Fe	3.0	0	92
2	<b>6</b>	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	—	3.0	100 <sup>f</sup>	N.R. <sup>g</sup>
3	<b>6</b>	HNO <sub>3</sub> (13)	FeBr <sub>3</sub>	2.0	0	100 <sup>h</sup>
4	<b>7</b>	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	β-CD-Fe	3.0	0	100
5	<b>7</b>	Fe(NO <sub>3</sub> ) <sub>3</sub> (10)	—	3.0	95 <sup>f</sup>	5 <sup>f</sup>
6	<b>7</b>	HNO <sub>3</sub> (13)	FeBr <sub>3</sub>	6.7	0	100 <sup>h</sup>

<sup>a</sup> Solvent acetonitrile, oxidant Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. <sup>b</sup> Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr<sub>3</sub>. <sup>c</sup> Reaction time in hours. <sup>d</sup> Percent substrate recovered. <sup>e</sup> Percent yield of oxidation products after isolation and purification. <sup>f</sup> Percent yield of product and/or substrate determined by <sup>1</sup>H NMR analysis of the raw reaction products. <sup>g</sup> N.R. = no reaction. <sup>h</sup> Without purification.

of the isothiocyanate derivatives the *p*-substituted compound reacts very well but the *o*-substituted derivatives do not react at all or give other products (see Table 1, runs 9–13). Mechanistic studies are currently being done in our laboratory in order to understand the substituent effect.

In previous work, we reported that substrates such as 4-(methylthio) benzaldehyde; 4-(methylthio)benzylalcohol; 2-(methylthio)benzothiazole; 2-(benzylthio)benzothiazole were oxidized with very high chemoselectivity and in excellent yields.<sup>19</sup> It should be noted that highly oxidizable functions such as benzaldehyde, benzylic alcohol, benzylic methylene and heterocyclic sulfur or nitrogen atoms remained unchanged under the reaction conditions.

Compounds 4-(methylthio)aniline **8**, 2-(methylthio)aniline **9** and 4-(methylthio)phenylisocyanate **10** were not completely consumed after 50 hours, and a complex mixture of products

was obtained. We think that the reason for this is that the amino group reacts faster than the sulfur group with nitrogen oxides formed in the reaction medium and consumes irreversibly those species which are needed to initiate the oxidation process. These reactions are currently under investigation in our laboratory and will be a matter for future publications.

The reaction conditions used in the present work meets several green chemistry principles since a catalytic amount of oxidant is used, in fact the real oxidant is oxygen,<sup>20</sup> the catalyst is a non-contaminating metal and the reactions are carried out at room temperature under normal pressure.

The definitions of green chemistry related terms,<sup>21</sup> as well as the green metrics are frequently revised in modern literature.<sup>22</sup> It is generally agreed that metrics must be clearly defined, simple, measurable and objective rather than subjective. Some of the most commonly used metric are the environmental factor based

on molecular weight ( $E_{mw}$ ), atom economy ( $AE$ ), mass intensity ( $MI$ ), reaction mass efficiency ( $RME$ ), the environmental impact factor based on mass ( $E_m$ ) and the carbon efficiency ( $CE$ ).<sup>23</sup> The reactions reported here meet several of the green chemistry principles with very satisfactory green metrics.

Atom economy ( $AE$ ), mass intensity ( $MI$ ), reaction mass efficiency ( $RME$ ) and the carbon efficiency ( $CE$ ) have been proposed in the last decade as a measure of environmental sustainability in terms of minimisation theoretical waste amount.<sup>22b</sup>  $AE$  was introduced by Trost<sup>24</sup> and is a theoretical measure of the chemical and environmental efficiency of a chemical reaction based on stoichiometric equation; it does not consider solvents, possible excess of reagents, formation of unwanted products, *etc.*  $MI$  takes into account the yield, stoichiometry, the solvent and the reactant used in the reaction.  $RME$  is a more sophisticated measure of *greenness* which allows for the effect of yield and the excess or catalytic amount of reactants used, but it does not account for solvent use. Finally,  $CE$  is the percentage of carbon in the reactants that remain in the final product, this parameter is not very important here because the oxidation does not involve carbon, it mainly reflects the yield of the reactions. In an ideal situation %  $AE \approx 100$ ,  $MI \approx 1$ , %  $RME \approx 100$ , %  $CE \approx 100$ .

In Table 5 the green metrics calculated for our reaction mixtures are summarized. The results show that our reactions have an excellent  $CE$ ; which in this case is equal to the yield because all carbon atoms of the reactant are present in the product. In the same direction, the high yields, the catalytic amounts of oxidant and the use of catalyst produce very good values of  $RME$ . On the other hand, the  $MI$  values obtained are acceptable since not much solvent is used. It is important to remark that this reaction can be carried out with much less solvent than the amount used which results in a significant improvement of the  $MI$  parameter. In fact, we carry out one reaction using substrate 4-(methylthio)benzaldehyde and only 0.6 mL of solvent and the product was obtained with excellent yield and the  $MI$  value was 4.04. Since 4-(methylthio)benzaldehyde is liquid at room

temperature, the reaction was also done without any solvent and the yield obtained was excellent. The  $MI$  value was 1.2 in this case, thus very close to the ideal value. The reason why we used more solvent in all the other reactions is because that was needed to take samples and determine the time needed for completion.

## Experimental

The  $^1\text{H}$  NMR spectra were carried out in a 400 MHz Bruker Avance II spectrometer. The chromatograms were carried out in a GC-14B Shimadzu chromatograph and mass spectra in MS-GC CQ5050 Shimadzu GC-Mass Spectrometer.

The solvents used,  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  and  $\text{FeBr}_3$ , were analytical grade commercially available samples and used as received. Cyclodextrin- $\text{FeBr}_3$  and DMSO- $\text{FeBr}_3$  complexes were prepared as described in previous papers.<sup>12a,25</sup> Substrates 4-(methylthio)phenylisothiocyanate **1**; 4-(methylthio)benzoic acid **2**; 4-(methylthio)acetophenone, **3**; 2-(methylthio)phenyl isothiocyanate **4**; 2-(methylthio)benzoic acid **5**; 2-(methylthio) bromobenzene **6**; 2-(methylthio)benzaldehyde **7**; 4-(methylthio)aniline **8**, 2-(methylthio)aniline **9** and 4-(methylthio)phenylisocyanate **10** were obtained from commercial suppliers. The products were characterized by the  $^1\text{H}$  NMR spectra and/or by MS-GC.

## General procedure

All reactions were carried out in a closed reaction tube, 165 mL, with magnetic stirring at room temperature. The volume of the reaction vessel is important because it must have enough oxygen for the oxidation reaction. The molar ratios substrate : catalyst : nitrate were 1.00 : 0.05 : 0.10 or 0.13. In a typical procedure, the substrate (1 mmol) was dissolved in acetonitrile (2.6 mL) and the iron complex (0.05 mmol) and the iron (III) nitrate (0.10 mmol) or nitric acid (0.13 mmol) were added.

**Table 5** Green metrics calculated for the sulfoxidation reactions<sup>a</sup>

Substrate	% Yield (Table;Entry)	MI <sup>b</sup>	% RME	% CE	% AE
1	93 (1;1)	12.46 <sup>c</sup>	77.20 <sup>c</sup>	93	92.50
1	96 (1;3)	11.94 <sup>c</sup>	87.08 <sup>c</sup>	96	92.50
1	90 (1;5)	12.93	70.34	90	92.50
1	95 (1;6)	12.39	67.17	95	92.50
1	100 (1;7)	11.50	87.81	100	92.50
2	100 (2;1)	12.31 <sup>c</sup>	82.01 <sup>c</sup>	100	92.01
2	100 (2;3)	12.24	87.05	100	92.01
2	95 (2;5)	13.28	65.91	95	92.01
3	100 (3;1)	12.43 <sup>c</sup>	81.85 <sup>c</sup>	100	91.93
3	100 (3;3)	12.37	86.93	100	91.93
3	95 (3;5)	13.33	65.59	95	91.93
5	100 (2;6)	12.31 <sup>c</sup>	82.01 <sup>c</sup>	100	92.01
5	100 (2;8)	12.24	87.05	100	92.01
5	93 (2;10)	13.48	64.42	93	92.01
6	92 (4;1)	11.42 <sup>c</sup>	77.69 <sup>c</sup>	92	93.19
6	100 (4;3)	10.45	88.88	100	93.19
7	100 (4;4)	13.39 <sup>c</sup>	80.63 <sup>c</sup>	100	91.31
7	100 (4;6)	13.31	85.99	100	91.31

<sup>a</sup> MI: mass intensity; % RME: percentage reaction mass efficiency; % CE: percentage carbon efficiency; % AE: percentage atom economy. <sup>b</sup> The solvent used in the purification step was not considered in the calculations. <sup>c</sup> The amount of catalyst was not used in the calculations because it is recoverable by filtration and it can be reused.<sup>12b</sup>

The reactions were analyzed from time to time by thin layer chromatography or by GC in order to determine the time of the total consumption of the substrate. Under the same reaction conditions, the total reaction time depended on the sulfide. The reactions with cyclodextrin complexes are heterogeneous since complexes are solid, not soluble in this system. Once the reaction was over, diverse isolation and/or purification methods were used. In all cases 10 mL of CH<sub>2</sub>Cl<sub>2</sub> were added, the solution was filtered and the solid washed several times with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated and washed with distilled water (3 × 10 mL) to remove any inorganic residue. Then, it was dried with MgSO<sub>4</sub> and the solvent was evaporated and recovered for further use. The residue was analysed by different chromatographic and spectroscopic methods. In some cases after filtration, the products were purified by column chromatography on silica gel 60 (70–230 mesh ASTM). All reactions were conducted in duplicate. In no case were sulfones detected.

### Reactants and products characterization

**4-(Methylthio)phenylisothiocyanate 1.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.48 (3H, s, -CH<sub>3</sub>) and 7.10–7.22 (4H, m, ArH).  $m/z$  181(M<sup>+</sup>, 100%), 166(91), 135(12), 122(20), 108(35), 90(8), 69(8), 50(10).

**4-(Methylsulfinyl)phenylisothiocyanate 1a.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.73 (3H, s, -CH<sub>3</sub>) and 7.35–7.67 (4H, m, ArH).  $m/z$  197(M<sup>+</sup>, 23%), 182(100), 166(51), 150(22), 134(15), 108(21), 90(8), 69(6), 50(12).

**4-(Methylthio)benzoic acid 2.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.54 (3H, s, -CH<sub>3</sub>) and 7.31–7.94 (4H, m, ArH).  $m/z$  168(M<sup>+</sup>, 100%), 151(43), 135(7), 123(12), 108(5), 105(5), 69(11), 45(20).

**4-(Methylsulfinyl)benzoic acid 2a.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.84 (3H, s, -CH<sub>3</sub>) and 7.76–8.20 (4H, m, Ar).  $m/z$  184(M<sup>+</sup>, 2%), 168(27), 153(21), 152(100), 151(82), 123(20), 108(11), 97(12), 77(19), 65(12), 45(28).

**4-(Methylthio)acetophenone 3.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.52 (3H, s, -CH<sub>3</sub>), 2.57 (3H, s, -CH<sub>3</sub>) and 7.25–7.88(4H, m; ArH).  $m/z$  166(M<sup>+</sup>, 77%), 151(100), 123(31), 108(17), 79(21), 45(37).

**4-(Methylsulfinyl)acetophenone 3a.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.61 (3H, s, -CH<sub>3</sub>), 2.73 (3H, s, -CH<sub>3</sub>) and 7.48–8.06 (4H, m; ArH).<sup>26</sup>  $m/z$  182(M<sup>+</sup>, 59%), 167(100), 162(42), 153(10), 152(81), 151(80), 139(20), 123(19), 121(15), 108(12), 91(7), 76(18), 63(13), 45(24), 43(31).

**2-(Methylthio)phenylisothiocyanate 4.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.51 (3H, s, -CH<sub>3</sub>) and 7.12–7.30 (4H, m, ArH).

**2-(Methylthio)benzoic acid 5.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.50 (3H, s, -CH<sub>3</sub>) and 7.20–8.16 (4H, m, ArH).  $m/z$  168(M<sup>+</sup>, 100%), 153(47), 135(20), 122(60), 121(53), 108(13), 105(23), 97(11), 69(18), 45(40).

**2-(Methylsulfinyl)benzoic acid 5a.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.90 (3H, s, -CH<sub>3</sub>) and 7.59–8.10 (4H, m, ArH).  $m/z$  166(27%), 136(100), 121(1), 108(42), 92(3), 82(9), 69(15), 50(6).

**2-(Methylthio)bromobenzene 6.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.43 (3H, s, -CH<sub>3</sub>) and 6.81–7.69 (4H, m; ArH).

**2-(Methylsulfinyl)bromobenzene 6a.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.83 (3H, s, -CH<sub>3</sub>) and 7.37–7.98 (4H, m, ArH).<sup>27</sup>

**2-(Methylthio)benzaldehyde 7.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.45 (3H, s, -CH<sub>3</sub>), 7.25–7.77 (4H, m, ArH) and 10.91 (1H, s, CHO).

**2-(Methylsulfinyl)benzaldehyde 7a.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.75 (3H, s, -CH<sub>3</sub>), 7.67–8.26 (4H, m, ArH) and 9.98 (1H, s, CHO).  $m/z$  168(M<sup>+</sup>, 28%), 153(28), 152(100), 123(18), 109(10).

**4-(Methylthio)aniline 8.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.43 (3H, s, -CH<sub>3</sub>) and 6.63–7.21 (4H, m, ArH).

**2-(Methylthio)aniline 9.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.39 (3H, s, -CH<sub>3</sub>) and 6.74–7.45 (4H, m, ArH).

**4-(Methylthio)phenylisocyanate 10.**  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.48 (3H, s, -CH<sub>3</sub>) and 7.02–7.22 (4H, m, ArH).

### Green metric calculations

The green metrics were calculated using the procedures reported in the literature.<sup>22b</sup> They are defined as follows:

$$\text{Mass intensity (MI)} = \frac{\text{Total mass used in a process or process step (g)}}{\text{Mass of product (g)}}$$

$$\text{Reaction mass efficiency (RME)} = \frac{\sum \text{mass of products}}{\sum \text{mass of reactants}} \times 100$$

$$\text{Carbon efficiency (CE)} = \frac{\text{N}^{\circ} \text{ of moles of product} \times \text{N}^{\circ} \text{ of carbons in product}}{\sum (\text{N}^{\circ} \text{ of moles of reactant} \times \text{N}^{\circ} \text{ of carbons in reactant})} \times 100$$

$$\text{Atom economy (AE)} = \frac{\text{molecular weight of product}}{\sum \text{molecular weight of reactant}} \times 100$$

An example of a typical calculation follows

4-(Methylthio)phenylisothiocyanate (0.181 g, 1 mmol, FW 181.28) reacts with the iron (III) nitrate nonahydrate (0.040 g, 0.10 mmol, FW 404.00) and molecular oxygen (0.016 g, 0.5 mmol, FW 32.0) in the presence of iron complex (0.068 g, 0.05 mmol, FW 1369.17) in acetonitrile (2.6 mL, 2.044 g) to give 4-(methylsulfinyl)phenylisothiocyanate (FW 197.28) isolated in 93% yield (0.93 mmol, 0.183 g). The amount of catalyst was not used in the calculations because it is recoverable by filtration and it can be reused. For *AE*, reagents in catalytic quantities and catalysts are not considered in the calculation.

$$\text{Mass intensity} = (0.181 + 0.040 + 2.044 + 0.016)/0.183 = 12.46 \text{ g/g}$$

$$\text{Reaction mass efficiency} = [0.183/(0.181 + 0.040 + 0.016)] \times 100 = 77.2\%$$

$$\text{Atom Economy} = (197.28/181.28 + 32.00) \times 100 = 92.5\%$$

$$\text{Carbon efficiency} = (0.93 \times 8)/(1 \times 8) = 93\%$$

## Conclusions

It can be concluded that FeBr<sub>3</sub> and its complexes with cyclodextrin or DMSO are excellent catalysts for chemoselective sulfoxidation reactions. The cyclodextrin complex is the best because it not only gave very good yields of products but it was easily handled under normal laboratory conditions. It could be easily isolated after the reaction and eventually re-used, this cannot be made with FeBr<sub>3</sub> or with its DMSO complex because they are soluble in the reaction media. Besides, the isolation of the reaction products was very simple when cyclodextrin complexes were used as catalyst. All these reactions are achieved in the presence of a catalytic amount of nitrate and the oxygen from the air is the oxidant agent. From the green chemistry point of view, the reactions reported here follow several of its principles and they have very good green metrics. It is also important to remark that the reactions take place a room temperature and under normal pressure.

In summary, we report herein a green and efficient method for the selective oxidation of sulfides to sulfoxides under very mild heterogeneous conditions with high yields and excellent chemoselectivity in the presence of other reactive groups such as *p*-isothiocyanate, *o*- and *p*-carboxylic acid, *p*-acetyl, *o*-bromo and *o*-aldehyde.

## Acknowledgements

This research was supported in part by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Agencia Nacional de Promoción Científica y Técnica (FONCYT), the Secretaría de Ciencia y Técnica (SECyT) of Universidad Nacional de Córdoba, Argentina. C.O.K. is a grateful recipient of a fellowship from CONICET.

## Notes and references

- (a) R. J. Cremling, *An Introduction to Organosulfur Chemistry*, John Wiley & Sons, England, 1996; (b) P. Page, *Organosulfur Chemistry: Synthetic and Stereochemical Aspects*, ACADEMIC PRESS, Great Britain, 1998, Vol. 2.
- (a) M. C. Carreño, *Chem. Rev.*, 1995, **95**, 1717; (b) I. Fernández and N. Khiar, *Chem. Rev.*, 2003, **103**, 3651.
- S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan and D. H. Brow Ripin, *Chem. Rev.*, 2006, **106**, 2943.
- H. Cotton, T. Elebring, M. Larsson, L. Li, H. Sörensen and S. Von Unge, *Tetrahedron: Asymmetry*, 2000, **11**, 3819.
- V. G. Shukla, P. D. Salgaonkar and K. G. Akamanchi, *J. Org. Chem.*, 2003, **68**, 5422.
- (a) M. M. Dell'Anna, P. Mastrorilli, C. F. Nobile, M. R. Taurino, V. Calò and A. Nacci, *J. Mol. Catal. A: Chem.*, 2000, **151**, 61; (b) N. S. Venkataramanan, G. Kuppuraj and S. Rajagopal, *Coord. Chem. Rev.*, 2005, **249**, 1249.
- (a) M. Hudlický, *Oxidations in Organic Chemistry*, ACS Monograph 186, American Chemical Society, Washington, DC, 1990; (b) E. G. Mata, *Phosphorus, Sulfur, Silicon Relat. Elem.*, 1996, **117**, 231; (c) G. P. Romanelli, D. O. Bennardi, V. Palermo, P. G. Vázquez and P. Tundo, *Lett. Org. Chem.*, 2007, **4**, 544.
- (a) P. Kowalski, K. Mitka, K. Ossowska and Z. Kolarska, *Tetrahedron*, 2005, **61**, 1933; (b) N. N. Mahamuni, P. R. Gogate and A. B. Pandit, *Ultrasonics Sonochem.*, 2007, **14**, 135; (c) Y. Yuan and Y. Bian, *Tetrahedron Lett.*, 2007, **48**, 8518; (d) A. Kumar and A. Kanksha, *Tetrahedron Lett.*, 2007, **48**, 7857; (e) A. G. Sathicq, G. P. Romanelli, V. Palermo, P. G. Vázquez and H. J. Thomas, *Tetrahedron Lett.*, 2008, **49**, 1441; (f) K. Matsumoto, T. Yamaguchi and T. Katsuki, *Chem. Commun.*, 2008, 1704.
- A reviewer has pointed out that oxidation reactions account for only 4% of the reactions carried out in the pharmaceutical industry (see J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337) however one of the reasons why oxidation reactions are not more frequently used is due to the fact that the procedures available are not clean or safe enough (see ref 2c). In 2006, the ACS GCI pharmaceutical Roundtable members identified oxidation/epoxidation reactions as an area in need of focused research to advance the principles of green chemistry and their application in the pharmaceutical industry (see D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, I. A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411).
- L. I. Rossi and S. E. Martín, *Appl. Catal. A: Gen.*, 2003, **250**, 271.
- A. R. Suárez, A. M. Baruzzi and L. I. Rossi, *J. Org. Chem.*, 1998, **63**, 5689.
- (a) L. I. Rossi and R. H. de Rossi, *J. Supramol. Chem.*, 2002, **2**, 509; (b) L. I. Rossi and R. H. de Rossi, *Appl. Catal. A: Gen.*, 2004, **267**, 267.
- (a) P. Tundo, P. Anastas, D. St. C. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff and W. Tumas, *Pure Appl. Chem.*, 2000, **72**, 1207; (b) P. Tundo, A. Perosa, F. Zecchini, *Methods and Reagents for Green Chemistry: An Introduction*. Wiley, 2007.
- (a) P. T. Anastas, L. B. Bartlett, M. M. Kirchoff and T. C. Williamson, *Catal. Today*, 2000, **55**, 11; (b) P. T. Anastas, M. M. Kirchoff and T. C. Williamson, *Appl. Catal. A: Gen.*, 2001, **221**, 3; (c) G. Centi and S. Perathoner, *Catal. Today*, 2003, **77**, 287.
- P. Tundo and F. Aricò, *Chemistry Inter.*, 2007, **29**, 4.
- (a) C. Karunakaran, S. K. T. Sheerin and P. N. Palanisamy, *J. Chem. Research (S)*, 2001, 398; (b) A. Lapprand, F. Boisson, F. Delolme, F. Méchin and J.-P. Pascault, *Polymer Degradation and Stability*, 2005, **90**, 363; (c) O. Vandenebelee-Trambouze, L. Mion, L. Garrelly and A. Commeyras, *Adv. Environ. Res.*, 2001, **6**, 45.
- (a) H. Miyake, Y. Nakao and M. Sasaki, *Tetrahedron*, 2007, **63**, 10433; (b) R. Wong and S. J. Dolman, *J. Org. Chem.*, 2007, **72**, 3969.
- (a) N. Juge, R. F. Mithena and M. Traka, *Cell. Mol. Life Sci.*, 2007, **64**, 1105; (b) N. Arranz, A. I. Haza, A. García, E. Delgado, J. Rafter and P. Morales, *Chem-Biological Inter.*, 2007, **169**, 63.
- C. O. Kinen, L. I. Rossi and R. H. de Rossi, *Appl. Catal. A: Gen.*, 2006, **312**, 120.
- We carried out experiments in closed systems of various volume and we determined that, in order to get 100% conversion, the volume of the container must be big enough to contain the number of moles of oxygen required for the oxidation.
- P. Glavic and R. Lukman, *J. Cleaner Production*, 2007, **15**, 1875.
- (a) A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1; (b) D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521; (c) J. Andraos, *Org. Process Res. Dev.*, 2005, **9**, 149; (d) J. Andraos, *Org. Process Res. Dev.*, 2005, **9**, 404; (e) J. Andraos, *Org. Process Res. Dev.*, 2006, **10**, 212.
- (a) M. Lombardo, K. Gianotti, S. Licciulli and C. Trombini, *Tetrahedron*, 2004, **60**, 11725; (b) P. J. Dunn, S. Galvin and K. Hettenbach, *Green Chem.*, 2004, **6**, 43; (c) M. A. Kuzemko, S. D. Van Amum and H. J. Niemezyk, *Org. Process Res. Dev.*, 2007, **11**, 470.
- B. M. Trost, *Science*, 1991, **254**, 1471.
- A. R. Suárez and L. I. Rossi, *Sulfur Lett.*, 1999, **23**, 89.
- V. G. Shukla, P. D. Salgaonkar and K. G. Akamanchi, *J. Org. Chem.*, 2003, **68**, 5422.
- (a) C. Imboden and P. Renaud, *Tetrahedron: Asymm.*, 1999, **10**, 1051; (b) J. Legros and C. Bolm, *Chem. Eur. J.*, 2005, **11**, 1086.