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An efficient and selective aerobic oxidation of sulfides to sulfoxides catalyzed by $Fe(NO_3)_3$–$FeBr_3$

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Abstract—The binary system $Fe(NO_3)_3$–$FeBr_3$ is a very efficient catalyst for the selective air-oxidation of sulfides to sulfoxides. Since the oxidation is selective, it may be applied to any type of dialkyl and alkyl aryl sulfide, as well as to substrates of biological interest. It develops in mild conditions, giving a high yield in the presence of different functional groups on the sulfide. Other binary systems such as $Fe(NO_3)_3$–$FeBr_2$ and $Cu(NO_3)_2$–$CuBr_2$ are also effective catalysts for sulfoxidation. In contrast to previous oxygenation methods, this oxidation requires neither an aldehyde nor a transition metal complex.

The oxidation of sulfides to sulfoxides has been the aim of considerable research due to the importance of sulfoxides as useful intermediates in organic synthesis and the key roles some of them play in the activation of enzymes.[1] Many oxidants are available to perform this key transformation.[2] Unfortunately one or more equivalents, often hazardous or toxic oxidizing agents, are usually required. Otherwise overoxidation of sulfides resulting in sulfone formation and undesired reactions of other functional groups are common problems, particularly when preparing biologically relevant sulfoxides. From an economical and environmental standpoint, catalytic oxidation processes are thus extremely valuable, and those involving dioxygen are particularly attractive. Dioxygen is an inexpensive, non-toxic and easily available oxidant about which many studies have been made for its eventual use in oxidation reactions.[3] At high dioxygen pressure and elevated temperatures, a selective oxidation of sulfides to sulfoxides can be achieved with high selectivity in the absence of any catalyst.[4] In addition, the high pressure oxygenation is catalyzed by Ce(IV)[5] or Ru(II)[6] complexes. Thus, most of the reported methods for the oxidation of sulfides to sulfoxides using dioxygen require rather high reaction temperatures, high pressure of dioxygen, or long reaction times.[7] Relatively few catalytic systems using less pressure or atmospheric dioxygen have been reported for this oxygenation.[8] Recently, new methods including dioxygen oxidation catalyzed by either a palladium complex,[9] or a complex of Ru(III),[10] and dioxygen and aldehydes,[11] have been developed. Although the direct use of air under mild conditions is more desirable, not many examples have been reported, instead most of them are based on homogeneous catalysts.[12] Thus, catalytic systems that use dioxygen from the air as secondary oxidant are greatly sought after. On the other hand, clay-supported metallic nitrates have been widely used as reagents in organic synthesis, particularly in the field of oxidation and nitration.[13] The reactivity of Fe(III) and Cu (II) montmorillonite-supported metal nitrates (*Clayfen* and *Claycop*) towards organic substrates has been extensively studied.[14] *Clayfen* is unstable, but may be stored for a few days under pentane and the preparation of the compound also needs some caution.[13a,b] Several methods for the oxidation of sulfides with metal nitrates have been reported.[12a,15] Such systems include hydrated Fe(III) and Cu(II) nitrates under solvent free conditions,[16] and microwave thermolysis with *Clayfen*.[17] In all cases the metal nitrates are used as reagent. Iron is an abundant, cheap and non-toxic metal. In a previous work, we reported the selective oxidation of sulfides with nitric acid catalyzed by $FeBr_3$ and $[(FeBr_3)_2(DMSO)_3]$.[18] Mechanistic studies by electrochemical methods demonstrated that the high selectivity exhibited was controlled by the transition metal, that the role of nitric acid was to oxidize bromides into bromine, and that this couple was the redox mediator in sulfide oxidation.[19]

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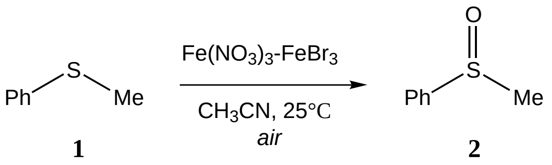
Taking these results into account, and considering that the use of an easy handling medium is much more desirable than nitric acid, we decided to examine the ability of $Fe(NO_3)_3{\cdot}9H_2O$ in the presence of $FeBr_3$ to accomplish this oxidation. We have reported here some of our recent results on a binary catalyst, $Fe(NO_3)_3$–$FeBr_3$, a selective and efficient catalytic system for the oxidation of sulfides with air under mild conditions. To the best of our knowledge, this is the first time that the $Fe(NO_3)_3{\cdot}9H_2O$ was used in a catalytic amount to carry out oxidation. The advantage of this method is that it does no demand a metal complex or any cooxidant, such as an aldehyde.[11]

The catalytic oxidation reaction of sulfides takes place at room temperature, in CH_3CN, under air in the presence of $Fe(NO_3)_3{\cdot}9H_2O$ (0.1 mmol%) and $FeBr_3$ (0.05 mmol%) as catalysts (Eq. (1)).



(1)

Other reaction solvents such as AcOEt or methylene chloride rendered lower yields, and methanol or benzene were not useful for this reaction. For our early experiments we selected methyl phenyl sulfide (**1**) as the model substrate, and the results are presented in Table 1. A typical experiment was run with a 1 mmol of the substrate, but the reaction could be scaled up to 20 mmol without any change in the reaction products. An excellent result for the oxidation reaction was obtained using **1** at room temperature, which afforded the methyl phenyl sulfoxide (**2**) with total selectivity in 98% conversion and 92% isolated yield within 1 hour (entry 1, Table 1). The binary catalyst was found to be very selective, no further oxidation to sulfones was evidenced.

In order to improve the efficiency of this catalytic system we investigated different ratios between the metallic salt and the metal bromide. The best results were found when the relation between the salts $Fe(NO_3)_3$:$FeBr_3$ was 1:0.5. When a molar ratio substrate:$Fe(NO_3)_3$:$FeBr_3$ 1:0.05:0.025 was used as catalyst, the reaction was completed in 4.5 hours (entry 2, Table 1). The use of a lesser amount of catalyst took a longer time to react. No improved rates could be observed at higher temperatures. When $Fe(NO_3)_3$ was used as catalyst alone, the conversion of substrate was only about 26% (entry 3, Table 1), as expected according to previous data reporting this nitrate as an oxidation regent.[12a,15–17] However, the presence of $FeBr_3$ enhanced the rate of oxidation, and turned the system into a catalytic one, provided that the reaction was carried out with a substrate:NO_3^- 1:0.3 molar ratio. Attempted oxidation with only $FeBr_3$ under the same conditions resulted in no reaction, and **1** remained unchanged (entry 4, Table 1). Under a dioxygen atmosphere the reaction proceeded in the same way as in air (entry 5, Table 1). Otherwise, under a nitrogen atmosphere, only 25% of the sulfide **1** was oxidized to **2** and the remaining **1** was recovered (entry 6, Table 1). Controls showed that under nitrogen atmosphere the oxidation with $Fe(NO_3)_3$ took place in the same way as in air (26%). Therefore, the catalytic oxidation reactions with the binary catalyst $Fe(NO_3)_3$–$FeBr_3$ system, apparently need dioxygen for oxidation to take place. It is interesting to note that the reaction does not require a high pressure of dioxygen, in fact, it can be run at room pressure with air. This is an important issue and a great advantage from a safe handling viewpoint. The aerobic oxidation can also be successfully carried out

Table 1. Catalytic air oxidation of methyl phenyl sulfide (**1**) to methyl phenyl sulfoxide (**2**) at room temperature[a]

Entry	Catalyst (% mmol)	Time (h)	Conditions	Yield of **2**[b] (%)
1	$Fe(NO_3)_3$[c]–$FeBr_3$	1	Air	98
2	$Fe(NO_3)_3$–$FeBr_3$[d]	4.50	Air	99
3	$Fe(NO_3)_3$	1.50	Air	26
4	$FeBr_3$	1.50	Air	N.R.[e]
5	$Fe(NO_3)_3$–$FeBr_3$	1	O_2[f]	98
6	$Fe(NO_3)_3$–$FeBr_3$	1	N_2[f]	25
7	$Fe(NO_3)_3$–$[(FeBr_3)_2(DMSO)_3]$	5	Air	96
8	$Fe(NO_3)_3$–KBr	1.50	Air	20
9	$Fe(NO_3)_3$–$FeCl_3$	1.50	Air	21
10	$Fe(NO_3)_3$–$FeBr_2$	4	Air	89
11	$Zn(NO_3)_2$[g]–$ZnBr_2$	3	Air	N.R.[e]
12	$Cu(NO_3)_2$[h]–$CuBr_2$	3	Air	82

[a] Reaction carried out with 1 mmol in an open system at room temperature, with molar ratio substrate:$Fe(NO_3)_3$:$FeBr_3$ 1:0.1:0.05 mmol, in 5 mL of CH_3CN.

[b] Determined by GC.

[c] $Fe(NO_3)_3$ corresponds to $Fe(NO_3)_3{\cdot}9H_2O$.

[d] Reaction carried out with a molar ratio substrate:$Fe(NO_3)_3$:$FeBr_3$ 1:0.05:0.025.

[e] N.R: Reaction did not occur.

[f] Under an O_2 or N_2 atmosphere (1 atm).

[g] $Zn(NO_3)_2$ corresponds to $Zn(NO_3)_2{\cdot}6H_2O$.

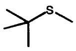
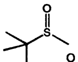
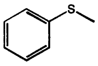
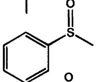
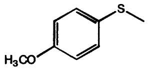
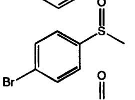
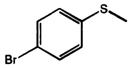
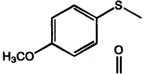
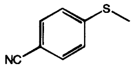
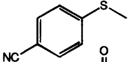
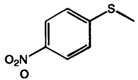
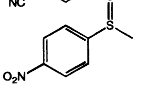
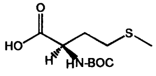
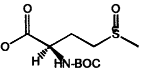
[h] $Cu(NO_3)_2$ corresponds to $Cu(NO_3)_2{\cdot}2.5H_2O$

with the complex $[(FeBr_3)_2(DMSO)_3]$ (entry 7, Table 1). This complex was synthesized as previously reported.[18b] The main advantage of the use of this coordination compound is its high stability unlike anhydrous $FeBr_3$, which facilitates storage and handling. The only reports on the applications of coordination compounds of DMSO to iron or other transition metal halides in organic reactions are the bromination of diphenyl sulfide;[20] the sulfide oxidations catalyzed with $RuX_2(DMSO)_4$, X = Cl, Br;[21] and the oxidation of sulfides by nitric acid catalyzed by $[(FeBr_3)_2(DMSO)_3]$.[18,19] The fact that the aerobic oxidation of **1** took longer to be completed than those performed with $FeBr_3$ (entry 7, Table 1), could be explained if the organic sulfide should coordinate to the metal prior to oxidation and displace a DMSO ligand before coordination, as previously reported.[6,18,21] The catalytic reaction proceeded hardly varying from $FeBr_3$ to KBr (entry 8, Table 1). The observed sulfoxide may be due to the oxidation reaction with $Fe(NO_3)_3$ as a reagent. Evidently, the importance of the metal center shows that the oxidation of the substrate is related to the Fe(III) center of the halide salt, and that the catalytic oxidation fails when this metal is absent. This is further supported by the results of the reaction carried out with $Fe(NO_3)_3$–$[(FeBr_3)_2(DMSO)_3]$, as previously discussed, the presence of a ligand delayed oxidation, which means that the metal center was less available for the coordination of the substrate. From all these findings, we may infer that in a special manner Fe(III) controls oxidation.

On the other hand, keeping all other conditions constant, the $Fe(NO_3)_3$–$FeBr_3$ catalyst was replaced by $Fe(NO_3)_3$–$FeCl_3$. This system had very little catalytic activity, even though it has Fe(III) (entry 9, Table 1). Although, there was practically no reaction with KBr, the last result confirmed the catalytic role of the bromide together with the Fe(III). This is also in agreement with the result found in the oxidation of sulfides with nitric acid in a biphasic system catalyzed by $FeBr_3$ and $FeCl_3$[19] or by tetrabromoaurate(III) and tetrachloroaurate,[22] whereas in the oxidation involving chlorides lower yields were obtained. Furthermore, $FeBr_2$ can also accomplish oxidation effectively (entry 10, Table 1), and may truly be regarded as a good alternative for this catalytic system. The catalytic activity of various transition metal nitrates and bromides was also examined. With the $Zn(NO_3)_2{\cdot}6H_2O$–$ZnBr_2$ system, the oxidation of **1** did not occur (entry 11, Table 1). However, sulfoxide **2** was obtained more efficiently, but still not as efficiently as in the iron catalytic system, with $Cu(NO_3)_2{\cdot}2.5H_2O$–$CuBr_2$ (entry 12, Table 1).

A series of sulfides was then reacted with this remarkably simple procedure and the results are presented in Table 2. As shown, both aliphatic and aromatic sulfides were oxygenated and most of the reactions proceeded nearly quantitatively. All the reactions occurred with complete selectivity for sulfoxide formation, no overoxidation products such as sulfones were detected in the reaction mixtures. The products could be readily isolated. The only purification step consisted of a filtration through a silica gel column leading to the products in excellent yields and purities. A simple dialkyl sulfide, such as *tert*-butyl methyl sulfide was efficiently oxidized (entry 1, Table 2). Besides, aryl methyl sulfides were selectively converted to sulfoxides almost quantitatively (entries 2–6, Table 2). Interesting results were obtained in the oxidation of the amino acid *N*-(*tert*-butoxycarbonyl)-L-methionine. The presence of amide and carboxylic groups did not interfere with the oxidation process of the sulfide (entry 7, Table 2). Sulfoxide was obtained in good yields and in a 1:1 mixture

Table 2. Selective air oxidation of sulfides to sulfoxides using $Fe(NO_3)_3$–$FeBr_3$ as catalyst[a]

Entry	Substrate	Time (h)	Product[b]	Conversion[c] (%)	Isolated yield[d] (%)
1		1.50		89	82
2		1		98	92
3	 H_3CO	1.50	 Br	96	90
4	 Br	1.25	 H_3CO	99	90
5	 NC	1.50	 NC	99	92
6	 O_2N	2	 O_2N	98	91
7	 HO, H, HN-BOC	3	 HO, H, HN-BOC	92	87

[a] Reaction carried out with 1 mmol of 1 in 5 mL of CH_3CN in an open system at room temperature, with molar ratio substrate:$Fe(NO_3)_3$:$FeBr_3$ 1:0.1:0.05 mmol.

[b] Spectral data were in agreement with the proposed structure and with literature data

[c] Determined by GC.

[d] Yields were calculated on the starting sulfide and given on the pure isolated products.

[e] Two diastereoisomers with a different configuration at the sulfur atom were obtained in 1:1 ratio.

of the two diastereoisomers with a different configuration at the sulfur atom.[23] The use of this catalytic system has raised some questions about the nature of all active species in the catalytic cycle. In a system like this, which contained NO_3^- and $FeBr_3$, it is assumed that NO_2 is generated in situ, as proposed in a related system.[12a] There are few examples of the direct use of NO_2 as an oxidation reagent in sulfoxidations.[2a,8c] Since the reaction mixture became light brown, it is possible that it might play a role in this oxidation, and thus the system $Fe(NO_3)_3$–$FeBr_3$ could be a source of NO_2. However, we also had to take into account the participation of other species in our system. Mechanistic studies of the selective oxidation of sulfides with nitric acid catalyzed by $FeBr_3$ and $[(FeBr_3)_2(DMSO)_3]$, demonstrated that the selectivity of the reaction was due to the activation of sulfides by coordination to the metal center, that the role of nitric acid was to oxidize bromides into bromine, and that this couple was the redox mediator in sulfide oxidation.[19] In our system the catalytic role of the bromides and the control of the oxidation by Fe(III) was also demonstrated. Furthermore, the oxidation potential of the nitrates is too low for an efficient oxidation of chloride into chlorine.[19] This fact may account for the low yields obtained from the oxidations by the $Fe(NO_3)_3$–$FeCl_3$ system. Thus, in the catalytic cycle of our system an oxidation where the active oxidant could be the bromide and bromine couple as redox mediator and the sulfides were activated by coordination to the metal, for oxygenation, should be kept in mind.

In conclusion, during the course of our ongoing study on the Fe(III)-catalyzed oxidation, we found that the $Fe(NO_3)_3$–$FeBr_3$ catalytic system was very effective for the selective *air*-oxidation of several types of sulfides to sulfoxides and it also succeeded with substrates of biological interest. The reaction proceeded under very mild conditions and in a simple procedure to the oxidation and isolation. Unlike previous oxygenation methods, this one requires neither an aldehyde nor a transition metal complex. Two types of active species may be considered in the metal-catalyzed oxidation, either oxidation by NO_2, or oxidation by the bromides/bromine couple controlled by Fe(III).

General procedure. Oxidation reactions catalyzed by $Fe(NO_3)_3$–$FeBr_3$. A typical experiment was carried out in an open reaction tube provided with a condenser. To the mixture of $Fe(NO_3)_3 \cdot 9H_2O$ (0.1 mmol) and $FeBr_3$ (0.05 mmol) in 5 mL of CH_3CN was added methyl phenyl sulfide (1 mmol). The reaction mixture was stirred under aerial conditions at room temperature. The reaction progress was followed by GC and TLC. When the reaction was complete, CH_2Cl_2 were added to the reaction mixture and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was chromatographed on a silica gel (70–270 mesh ASTM) column, eluting with ethyl acetate/hexanes using various ratios. All products were identified and found to be identical to authentic samples.

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