Aerobic oxidation of thiols to disulfides using iron metal–organic frameworks as solid redox catalysts[†]

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Aerobic oxidation of thiols to disulfides has been carried out using iron metal-organic frameworks (MOFs) as solid redox catalysts with very high yield and selectivity in acetonitrile under mild reaction conditions.

Catalytic oxidation using oxygen as the terminal oxidant is a hot topic in modern organic synthesis due to the environmental advantages.¹ The key point in aerobic oxidations is to develop a highly selective catalyst able to promote at high substrate conversion the formation of a single product among all the possible oxidation products. While considerable progress has been made in aerobic oxidation using noble metal nanoparticles such as Pt and Au,² it would still be desirable to develop catalysts based on less expensive metals. In this regard, novel metal-organic frameworks^{3,4} (MOFs) have appeared as promising heterogeneous catalysts^{5,6} for oxidations using organic peroxides⁷ and even molecular oxygen.⁸ In the present work, we describe that commercially available Fe(BTC) (BTC: 1,3,5-benzenetricarboxylate) is a suitable, reusable redox catalyst to perform selectively the aerobic oxidation of thiols to disulfides. Fe(BTC) is constituted by the trimers of iron octahedra sharing a common vertex μ_3 -O linked by the benzene-1,3,5-tricarboxylate moieties in such a way that this leads to two types of mesoporous cages of free apertures of 25 and 29 Å, accessible through microporous windows of 5.5 and 8.6 Å.

Oxidation of thiols to disulfides has important applications in the preparation of biomolecules as well as ligands for metal nanoparticles and has received considerable attention.^{9–12} The problem of thiol oxidation is the large variety of oxidation products that can possibly be formed. Besides disulfides, sulfones, sulfoxides and sulfonic acids are also typical products formed in thiol oxidation. The target is to develop a selective process for the transformation of thiols into disulfides avoiding over oxidation to oxygenated sulfur products.

In the first stage of our work, thiophenol (1) was selected as the substrate. Aerobic oxidation of 1 to the corresponding disulfide 2 in the absence of catalyst resulted in low conversion and with Fe(BTC) (840 m² g⁻¹ BET specific surface area, used as received) as the solid redox catalyst moderate to high conversion was achieved at room temperature and at 70 °C under air in acetonitrile as solvent. Acetonitrile (58% conversion) as

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solvent gives higher initial rate measured at 15 min than ethanol (51% conversion). Increasing the temperature from 40 to 70 °C with Fe(BTC) as catalyst in acetonitrile as solvent resulted in a very high conversion of 1 in 1 h. On the other hand, aerobic oxidation of 1 with Fe(BTC) in ethanol exhibited similar activity of acetonitrile but toluene showed only moderate conversion of 1. Further, we also wanted to study the effect of added base (pyridine) on the Lewis acid nature of Fe(BTC) but the influence of the presence of pyridine on this conversion and selectivity of the aerobic oxidation of 1 into 2 was negligible. This result suggests that Fe(BTC) acts as a redox catalytic system. In order to understand the nature of the active site, we did a control experiment with iron nitrate as homogeneous catalyst for the aerobic oxidation of 1 to 2. As it can be seen in Fig. 1, although the initial reaction rate is similar in both systems, Fe(BTC) exhibited long term better activity than iron nitrate due to the deactivation of the latter catalyst. Therefore, the well defined, crystalline, microporous structure of Fe(BTC) acts as a single site heterogeneous redox catalyst for the aerobic oxidation of 1 to 2 and maintains the catalytic activity during the reaction (in contrast to dissolved iron nitrate).

Other MOFs namely $Cu_3(BTC)_2$ and $Al_2(BDC)_3$ (BDC: 1,4benzenedicarboxylate) showed poor catalytic activity for this aerobic oxidation and the conversion achieved is 28 and 4%, respectively. Particularly, $Cu_3(BTC)_2$ exhibited poor stability under the present experimental conditions as evidenced from its colour change (Fig. 2) and the variation of the diffraction pattern observed from optical spectroscopy and XRD. Even EPR spectroscopy shows disappearance of the Cu^{2+} signal (see ESI[†]).

Heterogeneity of the reaction was established by the hot filtration test. After achieving about 39% conversion of 1, Fe(BTC) was removed from the reaction mixture by hot



Fig. 1 Time conversion plot for the aerobic oxidation of thiophenol with (a) iron nitrate and (b) Fe(BTC) as catalysts.

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Fig. 2 Visual changes observed in the reaction of thiophenol with $Cu_3(BTC)_2$ in acetonitrile. (a) $Cu_3(BTC)_2$ in acetonitrile; (b) thiophenol (0.250 mL) with $Cu_3(BTC)_2$ in acetonitrile at 0 min; (c) 1 min; (d) 10 min and (e) 60 min.



Fig. 3 (a) Oxidation of thiophenol with Fe(BTC) as catalyst in acetonitrile and (b) time conversion plot after removing the catalyst at 39% conversion of thiophenol.

filtration and the resultant liquid was allowed to continue further for additional time (Fig. 3). It was noticed that the percentage conversion was slightly increased to 51% after 1 h and this additional 12% must be due to homogeneous catalysis caused by some iron species leached from the solid to the solution. In fact, ICP analysis of the filtrate showed 3.4 ppm of iron, corresponding to less than 0.05% of the initial Fe present in the catalyst.

Then we extended our studies towards reusability of Fe(BTC) for this aerobic oxidation. It was reused for two consecutive runs without much loss in its activity (entry 8, Table 1). Fig. 4 presents the XRD pattern of the fresh and two times used Fe(BTC) and it is very clear that the crystalline nature is preserved during the catalysis. Clearly Fe(BTC) is much more stable than $Cu_3(BTC)_2$ for this particular reaction condition. In contrast to the XRD presented in Fig. 4 for the case of thiophenol, XRD of Fe(BTC) isolated after the reaction with thiobenzoic acid and 1,5-pentanedithiol shows that the catalyst is destroyed during the course of reaction in the presence of these two substrates.

After identifying the optimum conditions to achieve better conversion with very high selectivity for the aerobic oxidation of **1**, we wanted to extend the scope of Fe(BTC) with aromatic thiols having different substituents and some aliphatic thiols. The results are presented in Table 2. As expected, aromatic thiols with different substituents in *ortho* and *para* positions resulted also in very good yields of the corresponding disulfides with very high selectivities. In several cases, disulfide was obtained as pure crystals by filtration of the catalyst and

Table 1 Aerobic oxidation of thiophenol to diphenyldisulfide catalyzed by various catalysts^a

$ \begin{array}{c} \text{SH} \\ \text{MOFs} \\ \text{Solvent, Oxygen} \end{array} $						
Entry	Catalyst	Solvent	$T/^{\circ}\mathrm{C}$	Conversion ^b (%)		
	_	Acetonitrile	70	7		
2	Fe(BTC)	Acetonitrile	RT	44^c		
;	Fe(BTC)	Acetonitrile	70	87^c		
Ļ	Fe(BTC)	Acetonitrile	40	63		
5	Fe(BTC)	Acetonitrile	60	73		
, ,	Fe(BTC)	Acetonitrile	70	98 (91)		
,	Fe(BTC)	Acetonitrile	70	$94,^{d} 92^{e}$		
;	Fe(BTC)	Acetonitrile	70	$99^{g}(90)^{f}$		
)	Fe(NO ₃) ₃ .9H ₂ O	Acetonitrile	70	57 ^g		
0	Fe(BTC)	Ethanol	70	99 (91)		
1	Fe(BTC)	Toluene	70	53		
2	Cu ₃ (BTC) ₂	Acetonitrile	70	28		
3	$Al_2(BDC)_3^f$	Acetonitrile	70	4		

^{*a*} Reaction conditions: thiophenol (2.22 mmol), catalyst (100 mg), solvent (4 mL), 1 h, oxygen atmosphere. ^{*b*} Determined by GC using nitrobenzene as internal standard. Values in the parentheses correspond to the isolated yield. ^{*c*} Under air atmosphere. ^{*d*} First reuse. ^{*e*} Second reuse. ^{*f*} With 25 mg of pyridine. ^{*g*} With 160 mg of Fe(NO₃)₃·9H₂O.



Fig. 4 Powder XRD pattern: (a) fresh Fe(BTC), (b) two times reused for the aerobic oxidation of thiophenol, and after the reaction with (c) thiobenzoic acid and (d) 1,5-pentanedithiol.

cooling of the solvent. Further, pyridine and pyrimidine based thiols have also resulted in good yields of their disulfides, this being consistent with the lack of influence of pyridine in the oxidation. Cyclohexyl and 1-hexanethiol have also exhibited good yields towards their disulfides without any other byproducts. On the other hand, benzyl thiol exhibited moderate yield after 20 h. Finally, we wanted to study the stability of Fe(BTC) with some thioacids. For instance, when the reaction was performed between thioacetic acid and Fe(BTC), the corresponding disulfide was detected with 55% yield. On the other hand, thiobenzoic acid produces decomposition of the Fe(BTC) (Fig. 4) and the solid also turned out to be black from its original colour.

Further, we also tested the reactivity of 3-mercaptopropyl trimethoxysilane using Fe(BTC) as catalyst, but no disulfide was detected in this case too. Finally, we wanted to study the coupling of dithiols and the reaction of 1,5-pentanedithiol

		SS	२		
	$\frac{1}{CH_3CN, 70^{\circ}C} R^{-1}S^{-1}S^{-1}$				
Entry	R	Time/h	$\operatorname{Yield}^{b}(\%)$		
1	C ₆ H ₅	1	91		
2	$4-Cl-C_6H_4$	1	80		
3	$4-\text{Me-C}_6\text{H}_4$	3	82		
4	4-OMe-C ₆ H ₄	2.5	85		
5	$2-NH_2-C_6H_4$	2.5	87		
6	2-Pyridyl	1	81		
7	2-Pyrimidyl	2	72		
8	$C_6H_5CH_2$	20	61		
9	C_6H_{11}	10	72		
10	C_6H_{13}	6	73		
11	CH ₃ CO	7	55		
12	$C_6 H_5 CO^c$	2			
13	$H_2NCH_2CH_2^c$	2	_		

Table 2 Aerobic oxidation of various thiols catalyzed by $Fe(BTC)^{a}$

^{*a*} Reaction conditions: thiols (0.250 g, 2.22 mmol), Fe(BTC) 100 mg, acetonitrile (4 mL), oxygen purged. ^{*b*} Determined by GC. ^{*c*} Decomposition of catalyst was noticed.



Scheme 1 Aerobic oxidation of 1,5-pentanedithiol with Fe(BTC).

resulted in two products as shown in Scheme 1. Interestingly, under the present experimental conditions, no polymeric products were noticed and the reaction was completed in 1 h, although the stability of Fe(BTC) was seriously compromised (Fig. 4).

Based on the observed results, we propose that the reaction of 1 with Fe(BTC) generates thiyl radical that undergoes selfcoupling giving the desired disulfide 2. On the other hand, partially reduced iron is oxidized back to its native state by molecular oxygen as given in Scheme 2.

In summary, aerobic oxidation of thiols to disulfides can be performed using Fe(BTC) as the redox and reusable catalyst in acetonitrile medium under mild reaction conditions. Aromatic disulfides crystallize from acetonitrile after filtration of Fe(BTC) and cooling. The advantages of using Fe(BTC) solid



Scheme 2 Proposed mechanism for the aerobic oxidation of 1 to 2 using Fe(BTC) as redox catalyst.

redox catalyst was further demonstrated by performing the same reaction with homogeneous iron nitrate as catalyst. Fe(BTC) exhibited much better stability over $Cu_3(BTC)_2$ although the occurrence of some leaching and a strong influence of the substrate on Fe(BTC) stability were observed. The present protocol utilizes molecular oxygen as the only oxidant and iron being the most environmentally benign non-toxic metal and hence the present protocol may contribute to the development of greener and cleaner chemistry.

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