ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 10295

Received 7th July 2014,
Accepted 18th July 2014

DOI: 10.1039/c4cc05216a

www.rsc.org/chemcomm

Flavin-catalyzed aerobic oxidation of sulfides and thiols with formic acid/triethylamine†

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An efficient and practical catalytic method for the aerobic oxidative transformation of sulfides into sulfoxides, and thiols into disulfides with formic acid/TEA in the presence of a new, readily available, and stable flavin catalyst 5d is described.

Sulfoxides are important intermediates in the synthesis of biologically important compounds;[1] therefore, chemoselective, environmentally benign catalytic oxidation of sulfides under mild conditions without overoxidation is much needed. Although the transition-metal-catalyzed aerobic oxidation of sulfides has been well documented, the aerobic oxidation of sulfides by organocatalysts is limited to a few cases.[2] Over the last decade, compounds containing disulfide bonds have been used in various fields, including their application as biologically active compounds. There is still a need for an improved, general, versatile, efficient, and green methodology for the synthesis of disulfides from thiols.[3]

We wish to report that oxidation reactions of sulfides and thiols with molecular oxygen can be performed with high efficiency using a new flavin catalyst **5d** in the presence of formic acid and triethylamine (TEA) (Scheme 1). These methods are very useful, because formic acid is an inexpensive and key compound that is obtained by catalytic hydrogenation of CO_2 as an attractive option of reuse of CO_2.[4] Moreover, catalyst **5d** is stable and can be readily obtained from commercially available riboflavin (vitamin B_2).

Simulation of the functions of enzymes using simple organocatalysts may lead to the discovery of biomimetic, catalytic oxidation reactions.[5,6] Flavoenzymes are responsible for the oxidation of substrates *via* the activation of molecular oxygen and transfer of one oxygen to the substrate. The catalytic cycle of flavin adenine dinuleotide-containing monooxygenase (FADMO) using simplified

Scheme 1 Flavin-catalyzed oxidation of sulfides and thiols with molecular oxygen.

5-ethyl-3-methyllumiflavin is shown in Scheme 2. 4a-Hydroperoxyflavin (FlEtOOH, **1**) participate in the monooxygenation of a substrate (S), to give an oxidized product (SO) and 4a-hydroxyflavin (FlEtOH, **2**), which undergoes dehydration to give oxidized flavin ($FlEt^+$, **3**). $FlEt^+$ (**3**) is reduced by the hydrogen donor ZH (NADPH) to give reduced flavin (FlEtH, **4**), which undergoes a reaction with molecular oxygen to generate FlEtOOH (**1**), to complete the catalytic cycle.

In 1989, based on the kinetic study of the reactivity of 4a-hydroxyflavin using the stopped-flow technique, the first catalytic oxidation with hydrogen peroxide was reported.[7] Thus, the oxidation of sulfides and secondary amines by hydrogen peroxide proceeds in the presence of the $FlEt^+ClO_4$ (**5a**) catalyst with high efficiency;[7] then, various flavin-catalyzed oxidation reactions with hydrogen peroxide have been reported for secondary amines,[7] tertiary amines,[8] sulfides,[8b–10] ketones,[11] and aryl aldehydes[12,13] under mild conditions (Scheme 2). Asymmetric flavin-catalyzed oxidation of sulfides[5a,10e,14] with hydrogen peroxide, and asymmetric Baeyer–Villiger oxidation reactions[15] have also been reported using the advantage of the easy design of chiral flavin catalysts.

The next challenge was the attainment of more environmentally benign flavin-catalyzed oxidation with molecular oxygen under mild conditions as shown in Scheme 3. Flavin-catalyzed oxidation with molecular oxygen requires a reducing reagent (ZH), which may correspond to NADPH. We reported the first aerobic oxidation reaction using hydrazine hydrate in 2,2,2-trifluoroethanol as a reducing reagent. The aerobic catalytic oxidation of sulfides and secondary amines can be performed

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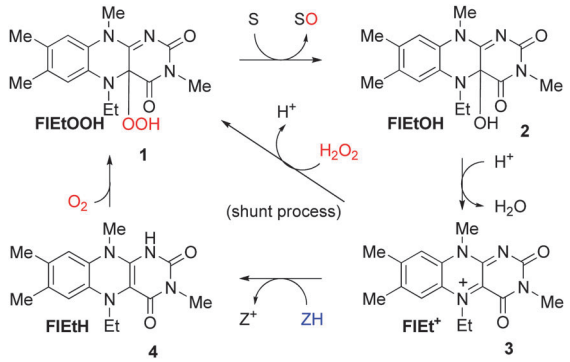
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc05216a



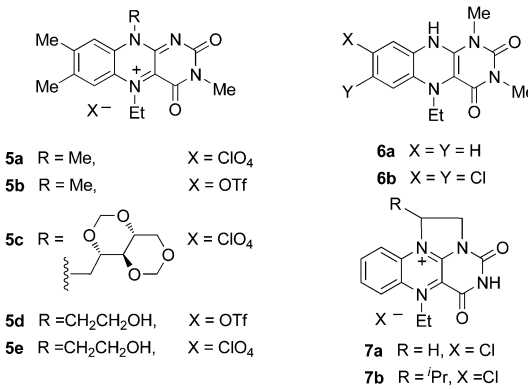
Scheme 2 Catalytic cycle of flavin-catalyzed oxidation.

Scheme 3 Flavin-catalyzed oxidation reactions with H_2O_2 and molecular oxygen.

at room temperature.[16] Aerobic flavin-catalyzed Baeyer–Villiger oxidation was performed using zinc dust as a reducing reagent.[17] Recently, aerobic oxidation of sulfides and aryl aldehydes was also carried out using ascorbic acid[18] and Hantzsch ester as reducing reagents.[19] These aerobic flavin-catalyzed oxidation reactions are not practical and not suitable for large-scale production, because the reducing reagents are specific and cannot be obtained at a reasonable cost. 2,2,2-Trifluoroethanol is very expensive and not environmentally friendly solvent.

We reinvestigated flavin catalysts to discover stable, efficient, and readily available catalysts. There are three types of flavin catalysts, as shown in Scheme 4; *i.e.*, flavinium ion catalysts (**5**),[7,15] such as **5a**[7] and **5c**,[17] flavin catalysts (**6**),[9] such as **6a** and **6b**, and bridged flavin catalysts (**7**),[10] such as **7a**[10a] and **7b**.[10b]

Since we reported the high efficiency of the flavinium perchlorate catalyst ($FlEt^+ClO_4$) (**5a**),[7] the ClO_4 anion has been used as a counter ion; however, it is desirable to use a safer counter ion in large-scale preparation. We confirmed that the efficiency of catalysts bearing other counter ions (OTf, BF_4, and PF_6)



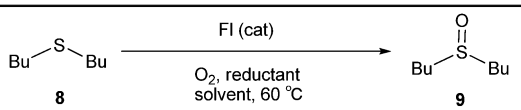
Scheme 4 Structures of representative flavin catalysts.

was not very different compared with that of **5a** by examining the aerobic oxidation of sulfides by hydrazine hydrate in trifluoroethanol (see Table S1, ESI†). Therefore, we decided to use OTf as a safer and more convenient counter ion.

A flavin catalyst was prepared simply and easily from commercially available riboflavin (vitamin B_2). Thus, the oxidation of riboflavin with sodium periodate in water, treatment with $NaBH_4$, and *N*-methylation gave 10-(2-hydroxylethyl)-3,7,8-trimethylisoalloxazine. A mixture of this compound, Pd–C, conc HCl, and acetaldehyde was allowed to react, and subsequent treatment with $NaNO_2$ and HOTf/NaOTf gave 5-ethyl-10-(2-hydroxylethyl)-3,7,8-trimethylisoallozazium triflate (**5d**). This compound is stable and can be stored in the refrigerator (−10 °C) for half a year. Similarly, **5e** was prepared after treatment with $NaNO_2$ and $HClO_4/NaClO_4$. It was found that compounds **5a**, **5d**, and **5e** are excellent catalysts for the aerobic oxidation of sulfides (see Table S1, ESI†), therefore, we selected **5d** for further oxidation reactions. The hydroxyl group did not retard any catalytic activity.

We looked for an efficient and practical method to achieve aerobic oxidation of sulfides using flavin as an organocatalyst. We focused on formic acid as a reducing reagent instead of hydrazine in 2,2,2-trifluoroethanol, because formic acid is a key compound in the construction of low-carbon society and is an excellent hydrogen source for catalytic-transfer hydrogenation reactions.[20] Our initial study targeted aerobic oxidation of dibutyl sulfide (**8**) using the flavin catalyst **5d**. The representative results of the aerobic oxidation of **8** with formic acid are summarized in Table 1. The catalytic oxidation of **8** in the presence of formic acid alone did not give the corresponding sulfoxide **9** (Table 1, entry 1); however, aerobic oxidation took place with formic acid in the presence of the corresponding

Table 1 Flavin-catalyzed aerobic oxidation of dibutyl sulfide[a]



Entry	Cat.	Reductant	Ratio	Equiv.	Solvent	Time (h)	Yield[b] (%)
1	**5d**	HCO_2H	—	50	—	14	Trace
2	**5d**	HCO_2H/HCO_2Na	4 : 1	50	—	21	79
3	**5d**	HCO_2H/HCO_2Na	8 : 1	50	—	7	59
4	**5d**	HCO_2H/HCO_2NH_4	8 : 1	50	—	14	74
5	**5d**	HCO_2H/TEA	5 : 2	50	—	7	95
6	**5d**	HCO_2H/TEA	8 : 1	50	—	7	99
7	**5d**	HCO_2H/TEA	8 : 1	3.12	MeCN[c]	24	(94)
8	**5d**	HCO_2H/TEA	8 : 1	6.25	MeCN[c]	7	99
9	**5d**	HCO_2H/TEA	8 : 1	12.5	MeCN	7	99 98[d]
10	**5d**	HCO_2H/TEA	8 : 1	12.5	DMA	7	99
11	**5d**	HCO_2H/TEA	8 : 1	12.5	DME	7	99
12	**5d**	HCO_2H/TEA	8 : 1	12.5	DMF	7	99
13	**5e**	HCO_2H/TEA	8 : 1	12.5	MeCN	7	88
14	**5b**	HCO_2H/TEA	8 : 1	12.5	MeCN	7	99
15	**5a**	HCO_2H/TEA	8 : 1	12.5	MeCN	7	99

[a] Unless otherwise noted, the reactions were carried out using dibutyl sulfide (0.5 mmol) in a solvent (0.4 mL) in the presence of catalyst (5 mol%) at 60 °C under molecular oxygen (1 atm, balloon). [b] Yields of dibutyl sulfide were determined by ^1H NMR or HPLC (parentheses). [c] The amount of solvent used was 0.8 mL. [d] Isolated yield.

salts, such as HCO_2Na and HCO_2NH_4, to give the sulfoxides with a yield of 59–79% (entries 2–4). The screening of the combination of formic acid with a base revealed that HCO_2H/triethylamine (TEA) gave excellent results (entries 5 and 6).

We examined the HCO_2H/TEA ratio and found that a ratio of 8/1 gave a higher yield compared with a ratio of 5/2 (entries 5 and 6).

The amount of HCO_2H and reaction time influenced the conversions (entries 7–9). Regarding the solvent, MeCN, DMA, DME and DMF were used similarly (entries 9–12). The oxidation of **8** in the presence of the flavin catalyst **5d** (5 mol%) in MeCN under molecular oxygen (1 atm, balloon) with HCO_2H/TEA (8 : 1) at 60 °C gave **9** with a yield of 99%. The isolated yield of **9** was over 98% (entry 9). As no overoxidation product was detected, it was not necessary to control reaction conditions to avoid overoxidation. We examined the catalytic activity of the related flavin catalysts. The catalytic activity of **5e** was slightly lower than that of **5d** (entry 13). Catalysts **5a**[7] and **5b**[17] exhibited high catalytic activity, as did catalyst **5d** (entries 14 and 15).

To demonstrate the generality and the scope of this methodology, a variety of sulfides bearing various functional groups were oxidized. Representative results are shown in Table 2. As expected, electron-rich sulfides (entries 1–6) were oxidized faster than electron-deficient sulfides (entry 7). The oxidation proceeds smoothly, when tertiary amine (entry 8) and olefin (entry 9) (allylsulfide **10**) are present. Disulfide **11** was converted to the corresponding monosulfoxide selectively (entry 10).

The reaction mechanism can be rationalized by assuming the following pathway. The oxidation of sulfides with FlEtOOH occurs electrophilically to give sulfoxides and FlEtOH, which undergoes a pseudo first order reaction to give $FlEt^+$ and water.[7,16] The reaction of $FlEt^+$ with $HCOO^-$ would give FlEtH, together with carbon dioxide. FlEtH thus formed would undergo reaction with molecular oxygen to form FlEtOOH and complete the catalytic cycle.

Next, we applied this method to the aerobic catalytic oxidative transformation of thiols into disulfides. Generally, the aerobic oxidation of thiols is performed in the presence of a base or heavy-metal ions; however, metal-free conditions are often required in the synthesis of biologically active compounds and medicines.

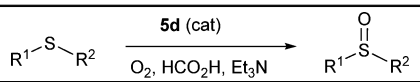
Flavin-promoted oxidation of thiols takes place under basic conditions *via* the nucleophilic attack of the thiolate at the C(4a) position, to form a covalent adduct, followed by the nucleophilic attack of the second thiol anion, to afford the corresponding disulfides, with very slow rates of oxidation.[21]

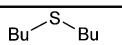
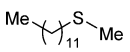
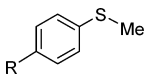
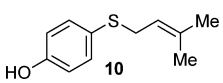
Flavin-catalyzed aerobic oxidation of thiols under the present acidic conditions gave the corresponding disulfides with excellent yields, as shown in Table 3. Aerobic oxidation tolerates various functional groups (entries 2–7). The oxidation of 2-mercapto pyridine (**12**) gave the corresponding disulfide with a yield of 83% (entry 5).

This method is highly useful for the direct synthesis of disulfides from *S*-protected thiols, because some thiols are very sensitive and difficult to handle from a synthetic perspective. Typically, the aerobic oxidation of *S*-[(acetylamino)methyl]-*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-l-cysteine (**13**)[22] in the presence of the flavin catalyst **5d** gave the corresponding *N*,*N*-bis[(9*H*-fluoren-9-ylmethoxy)carbonyl]-l-cysteine (**14**) selectively with an isolated yield of 84% without formation of the corresponding overoxidation products (Scheme 5). It is noteworthy that a control experiment performed in the absence of catalyst **5d** showed that compound **13** was recovered without any loss under the reaction conditions. The present method is highly useful for the synthesis of some complex disulfides to be used as drugs.

In conclusion, we have developed an efficient and practical catalytic method for the aerobic oxidative transformation of sulfides into sulfoxides, and thiols into disulfides with formic

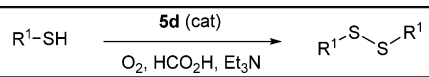
Table 2 Flavin-catalyzed aerobic oxidation of sulfides[a]

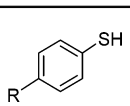
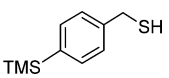
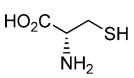


Entry	Substrate		Yield[b] (%)
1			98[c]
2			94
3		R = Me	95
4		R = OMe	99
5		R = OH	97
6		R = NHCOMe	98
7		R = Cl	76
8		R = $N(CH_3)_2$	85
9	 **10**		65[d]
10	 **11**		77

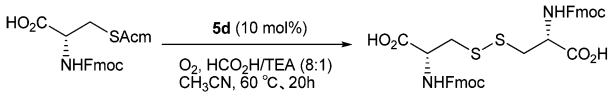
[a] The aerobic oxidation of sulfides (0.5 mmol) was carried out in the presence of a mixture of HCO_2H and Et_3N (8 : 1, 12.5 mmol) and **5d** (5 mol%) in MeCN (4 mL) under molecular oxygen (1 atm, balloon) at 60 °C for 24 h. [b] Isolated yield. [c] The reaction was run for 7 h. [d] The reaction was run for 16 h.

Table 3 Flavin-catalyzed aerobic oxidation of thiols[a]



Entry	Substrate		Yield[b] (%)
1		R = $C_{12}H_{25}$	93
2		R = ^{t}Bu	96
3		R = CO_2Me	93
4		R = CO_2H	95
5	 **12**		83
6			79
7			83

[a] The oxidation of thiols (0.5 mmol) was carried out in the presence of a mixture of HCO_2H and TEA (8 : 1, 12.5 mmol) and catalyst **5d** (5 mol%) in MeCN (0.4 mL) under molecular oxygen (1 atm, balloon) at 60 °C for 4 h. [b] Isolated yield.



13 14

Scheme 5 The aerobic flavin-catalyzed oxidation of Acm-protected cysteine.

acid/TEA in the presence of a new catalyst **5d**. This method offers several advantages, including the use of formic acid, which is sustainable and suitable for preparative synthesis. It will also provide a wide applicability of the principle of aerobic oxidation using a flavin catalyst.

T. Miyawaki passed away unexpectedly on October 15, 2013.

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