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Chemoselective sulfide oxidation mediated by bridged flavinium organocatalysts

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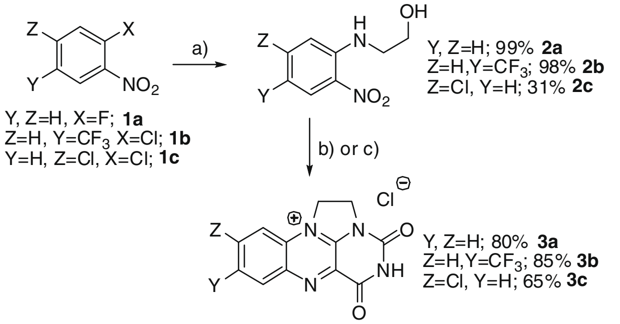
ABSTRACT

The chemoselective oxidation of sulfides to sulfoxides, catalysed by bridged, tetracyclic flavinium catalysts is presented. The flavinium catalysts are easily prepared via a telescoped three-step process. A range of sulfoxides is accessed in excellent yield and chemoselectivity.

The development of clean synthetic technologies which obviate the use of transition metal catalysts by using small organic molecules is of significant contemporary importance.[1] Furthermore, catalysts which mimic biological processes are often desirable as high levels of moisture and oxygen tolerance are exhibited, often leading to enhanced practical utility. Flavin and flavinium catalysts are one such class of biomimetic catalyst receiving attention.[2] In particular, they have been shown to be useful for the activation of the “green oxidant” hydrogen peroxide,[3] allowing oxidation of sulfides to sulfoxides.[4] Previously reported systems have been shown to be efficient catalysts, however their main drawback has been their often laborious synthesis,[5] difficulty of storage[6] and high molecular weights.[7] By contrast, it has been reported by Sayre that N^1,N^{10}-ethylene-bridged flavinium salts **3a–c** (Scheme 1) offer improved stability in a number of flavin-mediated transformations.[8] However, their catalytic activity towards the important transformation of sulfide oxidation to sulfoxide has yet to be examined.[9] We hereby report our initial findings concerning the use of these flavinium catalysts in sulfide oxidation.

Flavinium catalysts **3a–c** were initially prepared according to the previously reported procedure. However, in an attempt to improve the practicality and isolated yield of the flavinium catalyst, we discovered that the four individual synthetic steps can be telescoped obviating intermediate purification prior to a final recrystallisation (Scheme 1).

The catalytic efficiency of flaviniums **3a–c** with respect to sulfoxidation has been assessed through a series of NMR experiments. The oxidation of *p*-tolyl methyl sulfide using catalysts **3a–c** was monitored by ^{1}H NMR in CD_3OD.[10] Two sets of experiments were conducted, initially to ascertain the most efficient catalyst, and secondly to determine the rate enhancement achieved for each flavinium relative to the background reaction. To achieve this, *pseudo* first-order conditions were adopted, by using an excess of H_2O_2 (1.75 equiv) and running the experiments for 20 min or before the oxidations reached 20% conversion, allowing for a direct comparison with previously reported kinetic studies (Fig. 1).[4b,d]



Scheme 1. Preparation of bridged flavinium organocatalysts. Reagents and conditions: (a) 2-Aminoethanol (3 equiv), K_2CO_3 (1.2 equiv), EtOH, reflux, 5 h; (b) for **2a**/**2b**; HCO_2NH_4 (5 equiv), Pd/C (10% wt), MeOH, 0 °C to rt, 1 h; then alloxane monohydrate (1 equiv), $B(OH)_3$ (1.01 equiv), AcOH, 50 °C, dark, 18 h; then $SOCl_2$, 50 °C, dark, 18 h; (c) for **2c**; Sn (3 equiv), HCl (concd), H_2O, 100 °C, 0.5 h; then alloxane monohydrate (1 equiv), $B(OH)_3$ (1.01 equiv), AcOH, 50 °C, dark, 18 h; then $SOCl_2$, 50 °C, dark, 18 h.

Unsubstituted catalyst **3a** was seen to attain 50% conversion within 3.5 h. The 7-CF_3 system **3b** offered an improvement in rate with 50% conversion obtained within 2.5 h. However, the 8-Cl catalyst **3c** offered a distinct improvement and reached 50% conversion within 50 min. Determination of the initial k_{obs} showed a significant increase in reactivity versus the background. The rate of reaction increased from Ph derivative **3a** (6.8×10^{-5} Ms^{-1}), to the 7-CF_3 **3b** (1.2×10^{-4} Ms^{-1}) to a maximum with the 8-Cl derivative **3c** (2.3×10^{-4} Ms^{-1}). The k_{obs} value calculated for catalyst **3c** is of a similar magnitude to that reported for non-bridged flavinium catalysts under comparable conditions.[4a,7] The background rate of this reaction (4.0×10^{-5} Ms^{-1}) was still a cause for concern, even with the pleasing results obtained from the 8-Cl derivative

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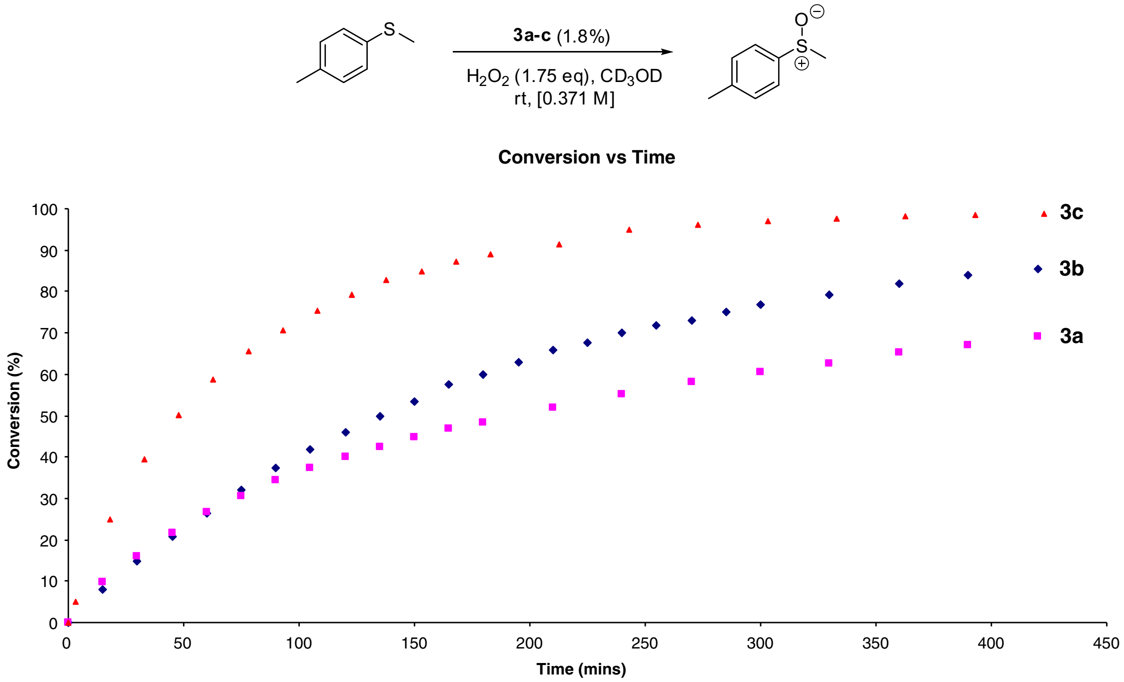


Figure 1. Comparison of various flaviniums for the oxidation of *p*-tolyl methyl sulfide with hydrogen peroxide.

3c (Fig. 2). It is currently unclear exactly why the presence of the 8-Cl group in flavinium **3c** improves the rate as observed.

With the increase in the rate of oxidation offered by flavinium catalyst **3c** being muted due to the relatively high background reaction, a solvent screen was undertaken in an attempt to reduce the background reaction. It was found that aprotic solvents such as CH_2Cl_2, MeCN and DMF led to a reduction in magnitude of the background reaction (Table 1).

CH_2Cl_2 was found to be the most effective at suppressing the background reaction with only 5% conversion after 5 h in the absence of catalyst, with the catalysed reaction giving 71% conversion after this time (Table 1, entries 7 and 8). Due to the non-homogeneous nature, these initial results were difficult to reproduce. This lack of reproducibility led us to examine MeCN and we now found the background reaction limited to 25% conversion after 5 h, with the catalysed reaction showing 70% conversion after this time. However, when applied to other sulfide substrates, these conditions provided variable and non-reproducible reaction rates, again attributed to reaction non-homogeneity. With a view to assessing substrate scope, MeOH was ultimately employed as the solvent

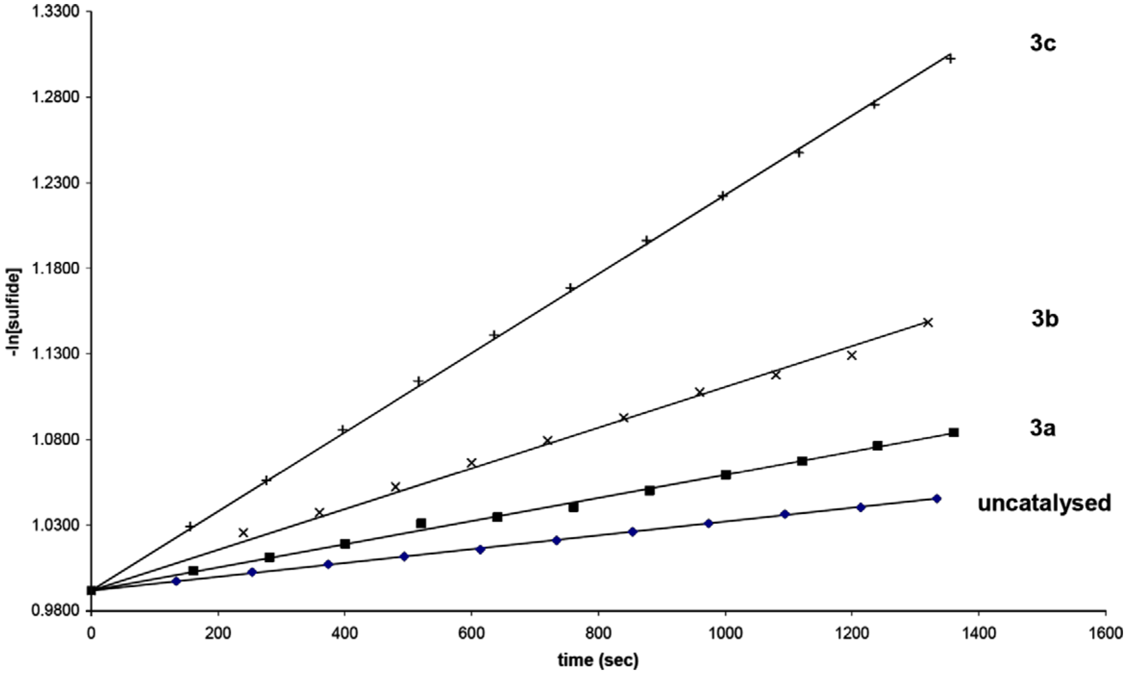
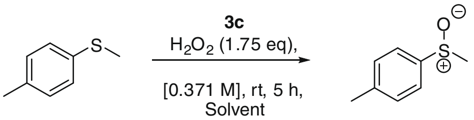


Figure 2. *Pseudo* first-order kinetic plot for the oxidation of *p*-tolyl methyl sulfide with flavinium catalysts **3a–c**.

Table 1
Effect of solvent on suppression of the background reaction



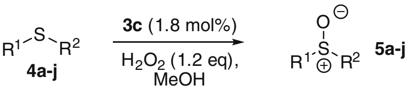
Entry	Solvent	Loading **3c** (mol %)	Conversion[a] (%)
1	MeOH	1.8	>99
2	MeOH	0	45
3	MeOH[b]	1.8	>99
4	MeOH[b]	0	25
5	MeCN	1.8	70
6	MeCN	0	25
7	CH_2Cl_2	1.8	71
8	CH_2Cl_2	0	5
9	DMF	1.8	25
10	DMF	0	8

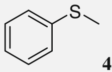
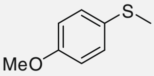
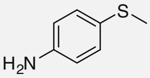
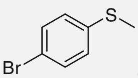
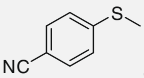
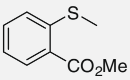
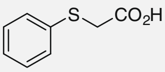
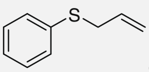
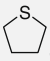
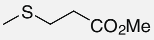
[a] Assessed by ^1H NMR spectroscopy of the crude reaction mixture.
[b] 1.2 equiv of H_2O_2.

after lowering the loading of H_2O_2 to 1.2 equiv (Table 1, entries 3 and 4). This change in protocol offered a pragmatic balance between solubility, reproducibility and background reaction suppression.

With optimal conditions at hand, a range of sulfides was examined to ascertain the generality of this sulfoxidation protocol (Table 2).[11] Pleasingly, all the substrates were oxidised cleanly to the corresponding sulfoxide, without any over-oxidation to sulfone observed for all substrates.

Table 2
Substrate scope



Entry	Substrate	Temp (°C)	Time (h)	Product	Yield (%)
1	 **4a**	25	3.5	**5a**	95
2	 **4b**	25	2	**5b**	99
3	 **4c**	25	0.5	**5c**	93
4	 **4d**	25	12	**5d**	94
5	 **4e**	25	3.5	**5e**	97
6	 **4f**	25	24	**5f**	92
7	 **4g**	25	12	**5g**	94
8	 **4h**	25	12	**5h**	91
9	 **4i**	25	1	**5i**	89
10	 **4j**	25	1	**5j**	93

It is noted that the electronic character of the sulfide plays an important role in the rate of the reaction. Alkyl and electron-rich aromatic sulfides were oxidised, in particular the amino thioanisole (Table 1, entry 3) was fully consumed within 30 min and tetrahydrothiophene (Table 1, entry 9) was fully consumed within 1 h. However, when electron-deficient aromatic systems were examined, increased reaction times were required, or in the case of the cyano thioanisole (Table 1, entry 5) elevated temperature to achieve full conversion.

In conclusion, bridged flaviniums **3a–c** are efficient catalysts for the chemoselective oxidation of sulfides to sulfoxides with no over-oxidation to sulfones observed using this protocol. The flavinium catalysts are simple to access via a telescoped procedure and are bench-stable. Further investigations are ongoing to improve the catalytic efficiency and to apply this procedure to different flavin-catalysed transformations.

Note added in proof: After submission of this Letter, the authors became aware of sulfide oxidation catalysed by structurally similar N^1,N^{10}-ethylene-bridged flavinium catalysts derived from valinol.[12]

Acknowledgements

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10. *NMR experimental procedure*: Flaviniums **3a–c** (1.8 mol %) and *p*-tolyl methyl sulfide (31 mg, 0.223 mmol) were dissolved in CD_3OD (600 µl, 0.371 M). The yellow solution was then treated with H_2O_2 (35% wt, 37 µl, 1.75 equiv) and shaken vigourously until the solution attained homogeneity. Spectra were recorded every 2 min for 20 min or until conversion had reached 20%.

Conversion was determined by making a comparison of the integrals for the S–Me and (O)S–Me signals from the sulfide and sulfoxide, respectively.

11. *Typical experimental procedure*: Flavinium **3c** (2.4 mg, 1.8 mol %) and *p*-tolyl methyl sulfide (61.5 mg, 0.446 mmol) were dissolved in MeOH (1.2 cm^3, 0.371 M). The yellow solution was treated with H_2O_2 (35% wt, 68 μl, 1.2 equiv) and stirred vigourously under air until TLC showed full consumption of the starting material. The solution was diluted with Et_2O (30 cm^3) and washed with H_2O (5 cm^3). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent removed in vacuo to give the desired product as a white solid (62 mg, 95%) without the need for further purification.
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