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Biomimetic Flavin-Catalyzed Aldehyde Oxidation

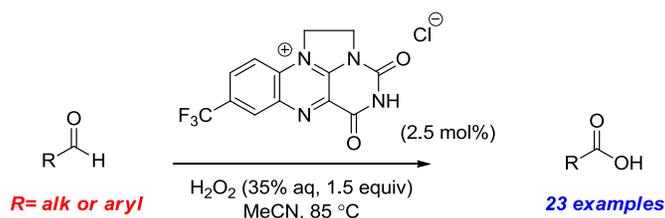
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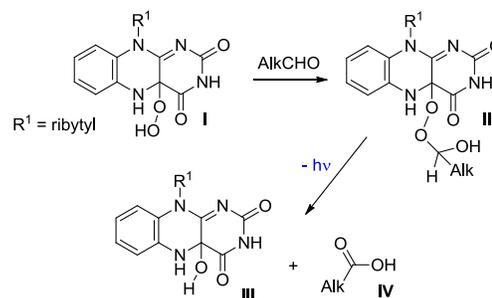
ABSTRACT



The oxidation of alkyl and aryl aldehydes to their corresponding carboxylic acids has been achieved through the action of a biomimetic bridged flavin catalyst. The reaction uses readily available 35% aqueous hydrogen peroxide and is operationally simple. The oxidation is a green and sustainable reaction, obviating chlorinated solvents with minimal byproducts.

Bacterial bioluminescence has attracted significant interest, with flavoenzyme monooxygenases now known to mediate light production.¹ Extensive mechanistic studies have identified that an enzyme-bound flavin hydroperoxide **I** undergoes nucleophilic addition to a fatty aldehyde electrophile, forming peroxy-hemiacetal **II**. It is the collapse of **II** to hydroxy flavin **III** and the fatty carboxylic acid that effects the ejection of a photon. Arguably, most studies have concentrated on the mechanism of luminescence as opposed to the synthetic potential of a “green” flavin-catalysed aldehyde oxidation.²

Scheme 1. Flavoenzymatic Bacterial Bioluminescence Mediated by Aldehyde Oxidation



The molecular understanding of flavin monooxygenase chemistry has, to a large extent, been elucidated through the study of simplified small-molecule flavin models. For instance, flavinium perchlorate salt **1** has been key in demonstrating that many oxygen transfer reactions mediated by flavin monooxygenases do so *via* flavin

(1) For a general overview of flavoenzyme biochemistry, see: *Flavins and Flavoproteins*; Bray, R. C., Engel, P.C., Mayhew, S. E., Eds.; DeGruyter: Berlin, 1984.

(2) Industrially relevant, clean oxidation protocols in non-chlorinated solvents has been identified as reactions desirable for further development, see: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

hydroperoxide intermediates, as modeled by hydroperoxide **2**. Indeed, Bruce has been successful in demonstrating chemoluminescence with **2** and benzaldehyde. However, this was only accomplished on an analytical scale, with benzoic acid only recovered in a 2% yield.³

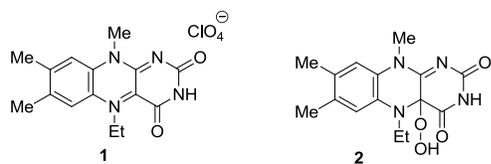


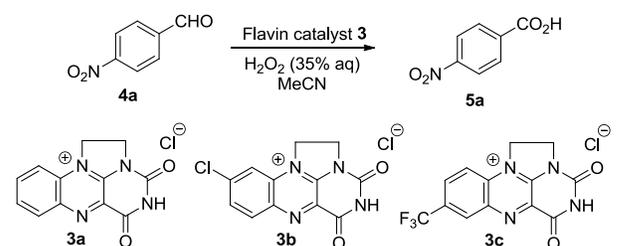
Figure 1. Flavins and Hydroperoxides Relevant to this Study

Many oxidation reactions mediated by flavin-hydroperoxide intermediates do so with electrophilic behaviour, i.e. oxygen is transferred to a nucleophile with representative examples being oxygen transfer to sulfides, 3° amines and phosphines to form sulfoxides, *N*-oxides and phosphine oxides respectively.⁴ However, there are examples of synthetically useful flavin-catalysed reactions which operate through a nucleophilic flavin hydroperoxide.^{5,6} Key amongst these oxidations are flavin-catalysed Baeyer-Villiger reactions which use H₂O₂ as terminal oxidant. Accordingly, we felt there to be scope to examine a biomimetic oxidation of aldehydes. We and others have further examined the synthetic utility of Sayre's ethylene-bridged flavin catalysts (**3a-c**, Table 1)⁷ in oxidative⁸ and reductive transformations.⁹ These catalysts are readily prepared in three steps, without recourse to intermediate purification and therefore offer themselves as thermally stable and versatile organocatalysts.

We initially chose to examine the flavin-catalysed oxidation of 4-nitrobenzaldehyde **4a** to 4-nitrobenzoic acid **5a** mediated by aqueous hydrogen peroxide. Reasonable oxidation with catalyst **3a** was only observed

when heating to 85 °C in acetonitrile as solvent (entries 1-3).¹⁰ There is some sensitivity to the exact structure of the catalyst with 7-CF₃-substituted catalyst **3c** offering improvement over **3a** and **3b** (entries 3-5). Increasing the reaction time also was beneficial (entry 6). Intriguingly, we have observed that the reaction offers an improved reaction as gauged by an improved final conversion after 3 hours when catalyst loading was lowered to 2.5 and 1 mol% (entries 7-8). Full conversion can be achieved by conveniently raising the loading of oxidant and allowing the reaction to proceed to a longer duration (entry 11). Finally, minimal background reaction is observed, confirming both a catalytic role but also the presence of minimal background oxidation mediated solely by H₂O₂ (entry 12).

Table 1. Biomimetic oxidation of 4-nitrobenzaldehyde **4a**.



Entry	3 (mol%)	H ₂ O ₂ (equiv)	Temp (°C)	Time (h)	Conv (%) ^a
1	a (5)	1.25	23	1	0
2	a (5)	1.25	50	1	0
3	a (5)	1.25	85	1	49
4	b (5)	1.25	85	1	54
5	c (5)	1.25	85	1	60
6	c (5)	1.25	85	3	66
7	c (2.5)	1.25	85	3	79
8	c (1)	1.25	85	3	76
9	c (1)	1.5	85	3	85
10	c (2.5)	1.5	85	3	96 ^b
11	c (2.5)	5	85	17	100
12	-	1.25	85	3	6

^aNMR conversion; assayed by relevant ¹H NMR integrals. ^bIsolated yield = 89%.

(3) (a) Kemal, C.; Bruce, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 7064. (b) Shepherd, P. T.; Bruce, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7774. (c) Bruce, T. C.; Noar, J. B.; Ball, S. S.; Venkataram, U. V. *J. Am. Chem. Soc.* **1983**, *105*, 2452.

(4) For a review of the synthetic chemistry of flavin hydroperoxides, see: Galalcha, F. G. *Chem. Rev.* **2007**, *107*, 3338.

(5) For examples of flavin-catalyzed Baeyer-Villiger, see: (a) Mazzini, C.; Lebreton, J.; Furstoss, R. *Heterocycles*, **1997**, *45*, 1161. (b) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 8. (c) Imada, Y.; Iida, H.; Murahashi, S.-I.; Naota, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1704. (d) Murahashi, S.-I.; Ono, Imada, S., *Y. Angew. Chem., Int. Ed.* **2002**, *41*, 2366.

(6) For a recent example of a flavin-catalyzed Dakin oxidation, see: Chen, S.; Hossain, M. S.; Foss Jr, F. W. *Org. Lett.* **2012**, DOI: 10.1021/ol3010326.

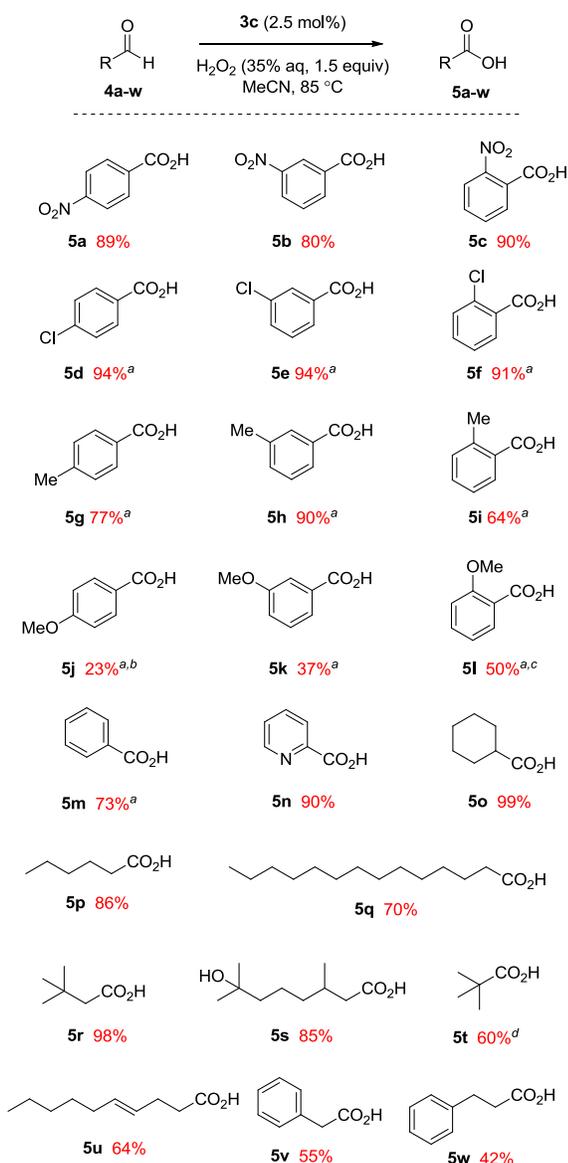
(7) (a) Li, W.-S.; Zhang, N.; Sayre, L. M. *Tetrahedron* **2001**, 4507. (b) Li, W.-S.; Sayre, L. M. *Tetrahedron* **2001**, *57*, 4523.

(8) (a) Marsh, B. J.; Carbery, D. R. *Tetrahedron Lett.* **2010**, *51*, 2362. (b) Žurek, J.; Cibulka, R.; Dvořáková, H.; Svoboda, J. *Tetrahedron Lett.* **2010**, *51*, 1083. (c) Jurok, R.; Cibulka, R.; Dvořáková, H.; Hampl, F.; Hodačová, J. *Eur. J. Org. Chem.* **2010**, 5217.

(9) Marsh, B. J.; Heath, E. L.; Carbery, D. R. *Chem. Commun.* **2011**, 280.

Having developed an effective oxidation protocol, as optimised on **4a**, we looked to examine the scope with other aromatic aldehydes (Scheme 2). This protocol works well with electron deficient aryl aldehydes, as seen with regioisomeric nitro- and chlorobenzaldehydes **4a-f**. The heteroaromatic substrate picolinaldehyde **4n** also demonstrates this point. In contrast, decreasing levels of aldehyde electrophilicity result in a more sluggish oxidation as seen with the regioisomeric anisaldehydes **4j-l** (Scheme 2). The presence of the strong-electron donating groups in *ortho*- and *para*-positions led to the formation of phenol byproducts, consistent with a competitive Dakin oxidation.

(10) See Supporting Information for full reaction optimisation.



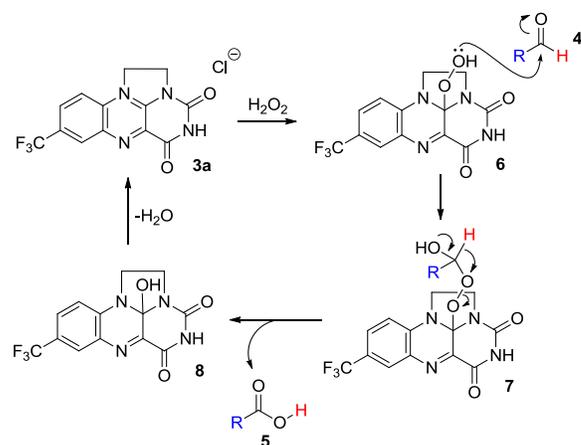
Scheme 2. Substrate Scope. ^aPerformed with 5 equiv H₂O₂. ^bDakin oxidation phenol observed in ¹H NMR of crude product (38%) ^cDakin oxidation phenol observed in ¹H NMR of crude product (31%) ^dtert-butanol observed in ¹H NMR of crude product (40%).

This flavin-catalysed reaction is also generally excellent for the oxidation of alkyl aldehydes, with high yields observed in many instances. Interestingly, diminished yields were observed with aldehydes bearing non-conjugated aryl groups (**4v-w**). It is unclear exactly why this is the case, however, ¹H NMR analysis of the crude reaction mixture of **5w** appears to support the presence of a stable peroxy hemiacetal. This observation suggests a slow formation of carboxylic acid in this instance.

The mechanism we propose for this flavin-catalysed oxidation is outlined in Scheme 3. Flavin-catalyst **3c** reacts with H₂O₂ to form hydroperoxide **6**. The C10^a

regioselectivity of peroxide addition is that proposed by Sayre as a result of extensive ¹³C NMR studies in the reaction of these bridged-flavins and benzylamine. This hydroperoxide now acts as a nucleophile, reacting with an aldehyde substrate to form peroxyhemiacetal **7**. This adduct now undergoes thermal collapse *via* 1,2-hydride migration with resultant *O-O* bond cleavage to form carboxylic acid **5** and hydrated flavin **8**. This flavin undergoes dehydration to regenerate catalyst **3**.

Scheme 3. Proposed Mechanism



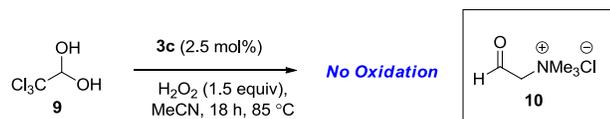
The nature of the aldehyde group is important. When this group is an electron rich aryl or a 3^o alkyl group, migration of these groups becomes competitive resulting in the formation of a formate ester which hydrolyses under the reaction conditions. Such a flavin-catalysed Dakin oxidation has very recently been reported.

It is noteworthy that chloral hydrate **9** does not undergo oxidation using this protocol (Scheme 4). This is supportive of the aldehyde acting as as an electrophile for a nucleophilic hydroperoxide. In this context, flavoenzyme choline oxidase has been extensively studied with respect to the oxidation of betaine aldehyde (**10** Scheme 4) to glycine betaine.^{11,12} This oxidation proceeds through the flavin co-factor acting as a hydride acceptor from an aldehyde hydrate, with this assertion also supported by the lack of enzymatic activity on the isosteric analogue **4r**. As noted already, **4r** acts as particularly good substrate in this reaction under our conditions, again suggesting the absence of an aldehyde hydrate mechanism.

(11) (a) Fan, F.; Germann, M. W.; Gadda, G. *Biochemistry* **2006**, *45*, 1979. (b) Fan, F.; Gadda, G. *J. Am. Chem. Soc.* **2005**, *127*, 2067.

(12) For a general discussion of oxygen activation in flaviprotein oxidases, see: Gadda, G. *Biochemistry*, **2012**, *51*, 2662.

Scheme 4. Attempted Oxidation of Chloral Hydrate.



In conclusion, ethylene-bridged flavin organocatalysts are competent catalysts for the activation of hydrogen peroxide in the oxidation of aldehydes to carboxylic acids. The oxidation does not require chlorinated solvents, and with low loadings of H_2O_2 , represents a clean oxidation protocol.

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