Greener Preparation of 5-Ethyl-4a-hydroxyisoalloxazine and Its Use for Catalytic Aerobic Oxygenations

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Dedication ((optional))

Abstract: Isoalloxazine ring systems are found in flavin cofactors in nature, and the simulation of their redox catalyses is an important task for developing sustainable catalytic oxidation reactions. Although 5-ethyl-4a-hydroxyisoalloxazines are among the most promising candidates as catalyst for such purposes, the use of them for laboratorial as well as industrial synthetic chemistry has so far been quite limited presumably due to the lack of their preparation methods readily, safely, and inexpensively available. In this communication, we introduce an environmentally benign and practical preparation of 5-ethyl-4a-hydroxy-3,7,8,10-tetramethylisoalloxazine (**1Et^{OH}**) from 3,7,8,10-tetramethylisoalloxazine (**1**), in which conventional synthetic requirements, including (i) operations under inert conditions, (ii) risky or expensive chemicals, and (iii) isolation of labile intermediates, have all been dissolved. In addition, we have presented that **1Et^{OH}** could be an effective catalyst for Baeyer-Villiger oxidation as well as sulfoxidation with molecular oxygen (O_2) as a terminal oxidant under suitable conditions, which is the first report on aerobic oxygenations catalyzed by 5-alkyl-4a-hydroxyisoalloxazines.

Introduction

5-Ethyl-4a-hydroxy-3,7,8,10-tetramethylisoalloxazine (**1Et^{OH}**, Figure 1, upper left) is a crystalline pseudobase, which has been occasionally used as a structural mimic of flavin cofactors not only for understanding the redox function of native flavin-dependent enzymes but also for developing artificial flavin-catalyzed oxidation reactions.[1] The dissociation constant of **1Et^{OH}** (pK_{R+} = 3.9)[1l] explains that it is rather stable under neutral conditions but readily undergoes reversible dehydration in the presence of an acid (HX) to produce the corresponding conjugate acid, 5-ethyl-3,7,8,10-tetramethylisoalloxazinium salt (**1Et^{+}X^{-}**, Scheme 1, upper right), and water (H_2O) (Figure 1a). Besides the hydration of **1Et^{+}X^{-}**, **1Et^{OH}** can be produced from its 4a-hydroperoxy analogue, 5-ethyl-4a-hydroperoxy-3,7,8,10-tetramethyl-isoalloxazine (**1Et^{OOH}**, Figure 1, lower left), as a result of a well-established flavin enzyme-mimetic oxygenation process (Figure 1d). For example, **1Et^{OOH}** can donate an oxygen atom to substrates (Sub) at a rate approximately 10^4 times faster than hydrogen peroxide (H_2O_2) to give oxidized products (SubO) and **1Et^{OH}**.[1b] On the other hand, **1Et^{+}X^{-}** can be readily converted into **1Et^{OOH}** by either reduction with a sacrificial reducing agent (Red-H_2, Scheme 1b), providing 5-ethyl-3,7,8,10-tetramethyl-1,5-dihydroisoalloxazine (**1HEt**, Figure 1, lower right), followed by oxidation with molecular oxygen (O_2, Figure 1c), or just addition of H_2O_2 (Figure 1e). Based on these facts, the biomimetic oxygenation with **1Et^{OOH}** can be evolved into a catalytic reaction, as first demonstrated by Murahashi[1h] and us[2a] with H_2O_2 and O_2 as a terminal oxidant, respectively, by means of an isoalloxazinium salt, **1Et^{+}ClO$_4^{-}$**, as a catalyst.

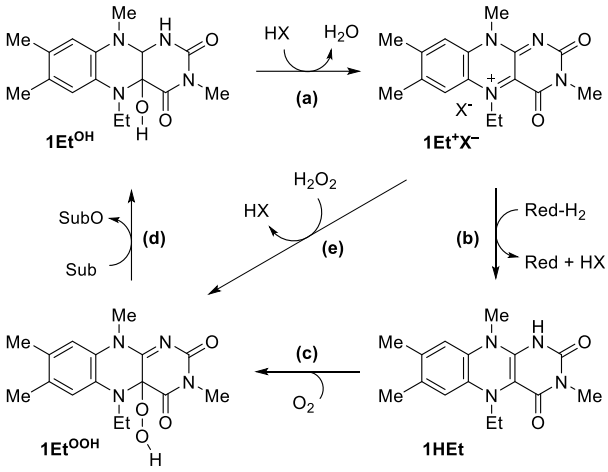

Figure 1. Catalytic cycle concerning 5-ethylated 3,7,8,10-tetramethy-lisoalloxazines.

Although the above pioneering works[1h, 2a] have been followed by a number of researches on the development of biomimetic oxidation reactions catalyzed by a flavin molecule, often using flavinium salts including isoalloxazinium salts such as **1Et^{+}X^{-}** and their structural analogues (alloxazinium salts),[3] they have rarely been used for practical applications despite their considerable merits such as unique reactivity and selectivity and environmentally friendliness compared with conventional metal-based oxidation techniques.[4] We have supposed that this is due to operational risk and complexity in the catalyst preparation. For example, many isoalloxazinium salts are used as an explosive perchlorate salt,[3] e.g. **1Et^{+}ClO$_4^{-}$**, which are generally prepared with careful operation under an inert atmosphere, purification steps with intricate experimental techniques, and a large excess of hazardous reagents such as $NaNO_2$ and $NaClO_4$ (Figure 2a),[2b, 1j] although the explosive risk can be avoided by using other non-coordinating salts rather expensive, e.g. NaOTf.[1n, 5] As a solution

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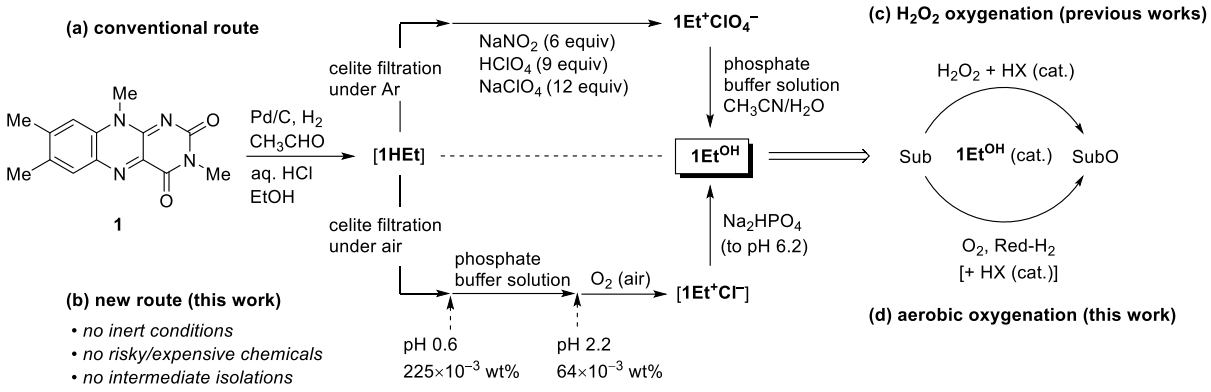


Figure 2. Conventional route (a) and new route (b) for the preparation of **1Et^{OH}** and its application as a catalyst for H_2O_2 oxygenation (c) and aerobic oxygenation (d).

strategy of these issues, we recentlly introduced a safe, simple, inexpensive, and environmentally benign alternative method for preparing isoalloxazinium salt catalysts.[6] For example, **1Et$^+$X$^-$** could be generated from **1HEt** by oxidation with O_2 in air (instead of $NaNO_2$) and purified through anion exchange with a sulfonic acid cation exchange resin (instead of $HClO_4$ and $NaClO_4$) to isolate it as a resin-immobilized variant. On the other hand, an alternative solution would be to start the catalytic cycles (Figure 1) from one of the neutral intermediates (**1Et^{OH}**, **1Et^{OOH}**, **1HEt**) in combination with an acid co-catalyst (HX), and particularly promising is **1Et^{OH}** since it is rather stable compared with the others; indeed, the dehydration of **1Et^{OH}** (Figure 1a) is recognized to be a rate-limiting step in the catalysis with H_2O_2.[1h] Nevertheless, to our knowledge, such 5-ethyl-4a-hydroxyisoalloxazine pseudobases have been used only for mechanistic or kinetic studies of flavin catalyses so far,[1] which is presumably because their preparation has involved the isolation of the corresponding isoalloxazinium salts as the precursor after all. For example, **1Et^{OH}** is generally prepared by the treatment of an isolated **1Et$^+$ClO$_4^-$** with a neutral phosphate buffer solution in CH_3CN/H_2O mixture (Figure 2a). Thus, the development of an alternative method for preparing isoalloxazine pseudobases, which is free from any risky and expensive material, and the study of their utility as an oxidation catalyst is highly valuable. In this communication, we show a novel and highly practical protocol for the synthesis of **1Et^{OH}** (Figure 2b) and unveil its catalytic performance in aerobic oxygenation reactions (Figure 2d).

Results and Discussion

In general, **1Et$^+$X$^-$**, the precursor of **1Et^{OH}**, is derived from 3,7,8,10-tetramethylisoalloxazine (**1**) through the reductive conversion of **1** into **1HEt** followed by the oxidative conversion of **1HEt** into **1Et$^+$X$^-$**. Our previous study has demonstrated that the latter oxidation process takes place efficiently just under air in the absence of any oxidizing agent except for O_2 by adjusting the pH from <1 (required for the former process) to 1.5–3, because of shifts of the position of equilibrium between **1Et$^+$X$^-$** and **1Et^{OH}** to the side of **1Et^{OH}**.[6] This finding led us to explore whether **1Et^{OH}** could be extracted directly from the crude mixture as a solid by further pH adjustment. Therefore, first of all, we prepared an aqueous solution of **1Et$^+$X$^-$** according to the following procedure that had previously been optimized.[6] The preparation of **1HEt** from **1** was carried out using acetaldehyde and hydrogen gas in the presence of Pd/C under acidic aqueous-alcoholic conditions for 48 h (Figure 2, left). The reaction mixture was filtered through a pad of Celite under air, and the concentration of the filtrate was adjusted at 25 × 10^{-3} wt% with respect to **1**-related species by using deionized water to make its pH value around 1.8, which was further stirred under air for 2 hours to fully convert all *N*5-ethylated species into **1Et$^+$X$^-$** (Figure 3, purple line). The resulting acidic aqueous solution was then used for testing different pH conditions that might trigger precipitation of **1Et^{OH}**. Several batches having pH values ranging from 3.0 to 7.8 were prepared with the addition of sodium hydrogen phosphate (Na_2HPO_4) and their UV/Vis spectra were measured, which showed that **1Et^{OH}** could be predominant in the equilibrium at pH 5.9–7.8 [Figure 3, yellow (pH 3.9); green (pH 5.9); for others, see supporting information]. A small amount of green precipitate was observed only from the solutions having pH between 5 to 7 when these solutions were kept standing overnight at room temperature. One of the solutions (pH 6.3) was concentrated under reduced pressure roughly until half of the volume to accelerate the precipitation and further kept standing at 4 °C for another 53 h. However, the degree of precipitation was not apparently improved, and what was more disappointing, the precipitate was identified as 4a-spirohydantoin,

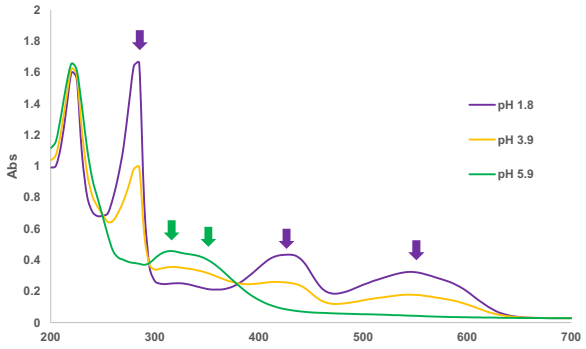


Figure 3. Absorption spectra for the **1Et$^+$X$^-$** solution (pH 1.8, purple) prepared according to our previous procedure[6] and its variations at pH 3.9 (yellow) and pH 5.9 (green). The spectrum at pH 5.9 is in good agreement with that of **1Et^{OH}** published.[1g]

a known rearrangement product of **1Et^{OH}**,[1a] by ^{1}H NMR spectroscopy after its isolation by filtration (23% yield). This result shows that the above aqueous solution of **1Et$^+$X$^-$** (25×10^{-3} wt%, pH 1.8) prepared according to the previously optimized protocol[6] cannot be used for the present purpose, probably due to the very low concentration.

We then attempted to convert **1HEt** into **1Et$^+$X$^-$** at a higher concentration with O_2 from the air as an oxidant in an appropriate buffer solution. Previously, the use of sodium bicarbonate ($NaHCO_3$) was tested for this purpose, in which the desired reaction was actually promoted but undesired decomposition products were observed when the pH was increased to 2.7 probably due to locally enhanced pH.[6] Thus we adopted a milder manner for this study, which was successfully optimized as follows (Figure 2b). The starting mixture of **1HEt** (225×10^{-3} wt%, pH 0.6), obtained through the above-mentioned reductive ethylation of **1** followed by the celite filtration, was diluted 3.5 times with a phosphate buffer solution (pH 6.86), and the resulting solution (64×10^{-3} wt%, pH 2.2) was stirred under air. The desired conversion to **1Et$^+$Cl$^-$** was efficiently promoted and completed within an hour without observable decomposition, which was monitored by UV/Vis spectroscopy as before.[6] With this relatively concentrated solution containing **1Et$^+$Cl$^-$** in hand, we retried its derivatization to **1Et^{OH}** and finally found that the addition of Na_2HPO_4 until reaching pH 6.2 followed by vigorous stirring at ambient temperature for 2 h could give rise to rapid precipitation of **1Et^{OH}**, yellowish green solid, characterized by NMR and UV/Vis spectroscopy as well as elemental analysis (Figure 2b). We emphasize that the present protocol can provide **1Et^{OH}** from **1** with an acceptable total yield and is highly reproducible irrespective of scale (47% and 49% yields, respectively, when 0.3 mmol and 15 mmol of **1** were used).

Catalytic activities of 5-ethyl-4a-hydroxyisoalloxazines including **1Et^{OH}** in H_2O_2 oxidations have been reported (Figure 2c),[1n] while those in aerobic oxidations have remained unexplored (Figure 2d). We thus sought to examine the utility of **1Et^{OH}** as a catalyst for aerobic oxygenation reactions in this study. First, the Baeyer-Villiger oxidation of (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one (**2**) was carried out under conditions that were previously developed by us for the reaction catalyzed by 5-ethyl-3-methyl-2',4':3',5'-di-*O*-methyleneriboflavinium perchlorate (DMRFlEt$^+$ClO$_4^-$).[7] In the presence of 2 mol% of **1Et^{OH}**, 2 mol% of *p*-toluenesulfonic acid monohydrate (TsOH·H_2O), 1 atm of O_2, and 3 equivalents of zinc dust as a reductant in a mixed solvent of ethyl acetate, acetonitrile, and H_2O (8:1:1), the desired oxidations proceeded efficiently at 60 °C with quantitative conversion of **2** in 4 h to afford the corresponding normal *cis*-lactone **3** and abnormal *cis*-lactone **4** as a mixture in 43% yield and 46% yield, respectively, without undesired oxidations to epoxides (Figure 4). The reactivity, chemoselectivity, and unique regiodivergent behaviour were similar to those of DMRFlEt$^+$ClO$_4^-$[7] as well as flavoenzymes.[8] The absence of TsOH·H_2O as a co-catalyst resulted in large decrease in catalytic activity (25% conv.) under identical conditions, which was within our anticipation because the dissociation of **1Et^{OH}** in catalysis must be disfavoured (Figure 1a). The use of 1.5 equivalents of zinc dust or the reaction at 50 °C also decrease in catalytic activities (see supporting information).

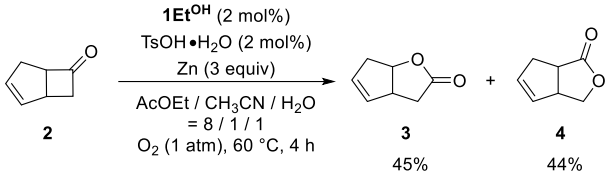
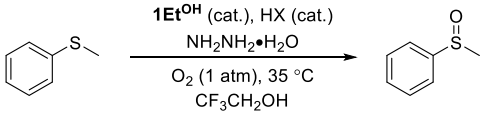


Figure 4. Aerobic Baeyer-Villiger oxidation of **2** with **1Et^{OH}**.

We then turned our attention to aerobic sulfoxidations, which were explored under conditions also originally developed by us with **1Et$^+$ClO$_4^-$**.[2] The oxidation of thioanisole (**5a**, 1.0 M) was performed using 1 equivalent of hydrazine monohydrate ($NH_2NH_2 \cdot H_2O$) as a sacrificial reductant in the presence of 1 mol% of **1Et^{OH}**, 1 mol% of TsOH·H_2O, and 1 atm of O_2 in 2,2,2-trifluoroethanol (TFE) at 35 °C for 7 h to give methyl phenyl sulfoxide (**6a**) in 73% conversion (Table 1, entry 1), which was as efficient as the reaction catalyzed by **1Et$^+$ClO$_4^-$** (80% conv., see supporting information). Unexpectedly, the use of $HClO_4$ [p*K*a = –10 (H_2O)] instead of TsOH·H_2O [p*K*a = –2.8 (H_2O)] as a co-catalyst under otherwise identical conditions resulted in considerable decrease in catalytic activity despite its much higher acidity (entry 2). Although other acids with a range of p*K*a values were also tested, a clear correlation between their acidity and the catalytic activity was not found (see supporting information), unlike with H_2O_2

Table 1. Optimizing reaction conditions for aerobic oxidation of **5a** catalyzed by **1Et^{OH}**.



5a **6a**

Entry	Conc. of **5a** [M]	Loading of **1Et^{OH}** [mol%]	HX (loading [mol%])	Amount of $NH_2NH_2 \cdot H_2O$ (equiv)	Time (h)	Conv. (%)[a]
1	1	1	TsOH•H_2O (1)	1	7	73
2	1	1	$HClO_4$ (1)	1	7	33
3	1	1	none	1	7	66
4	0.5	5	none	1	4	65
5	0.5	5	none	1.2	4	77
6	0.5	5	none	1.5	4	98
7	0.5	5	none	0.5	12	36
8	1	1	none	1.5	4	39
9	1	2.5	none	1.5	4	97
10[b]	1	2.5	none	1.5	4	98

[a] Determined by GLC analysis.
[b] Reaction was performed by using **1Et^{OH}** stored for 6 months under N_2 in a refrigerator.

sulfoxidation.[1n] Interestingly, an acceptable level of reaction efficiency was observed even in the absence of any HX co-catalyst (entry 3), which led us to optimize such acid-free conditions for the present reaction. A similar moderate conversion was obtained with a shorter reaction time by increasing the catalyst loading from 1 mol% to 5 mol% at a lower concentration ([**5a**] = 0.5 M), although the improvement of efficiency was not as significant as we expected (entry 4). On the other hand, the equivalents of $NH_2NH_2 \cdot H_2O$ greatly influenced (entry 4–7), and a nearly quantitative conversion was attained when 1.5 equivalents of $NH_2NH_2 \cdot H_2O$ was used (entry 6). Returning to the initial concentration ([**5a**] = 1.0 M) allowed for lowering the catalyst loading to 2.5 mol% while keeping the highest level of catalytic activity (entry 9), although 1 mol% was too low to be efficient (entry 8). It should be noted that **1Et^{OH}** retained its catalytic activity after 6 months during which it was stored under nitrogen in a refrigerator (entry 10). The reaction may take place basically according to the catalytic cycle for aerobic oxidation with NH_2NH_2 as a reductant, previously proposed by us,[2] but without the involvement of HX, which has so far been considered to be important for the efficient catalysis. It is plausible that **1Et^{OH}** undergoes an S_N1 type substitution with NH_2NH_2 even in the absence of HX to give the corresponding adduct **1Et^{NHNH2}** via transient generation of **1Et^{+}HO^{-}**, and the shift of their equilibrium is continuously driven to the side of **1Et^{NHNH2}** due to the following irreversible formation of **1HEt** and diimide (NH=NH), enabling the catalytic cycle (Figure 5). The formation of **1HEt** in the proposed catalysis was supported by ^{1}H NMR measurement of **1Et^{OH}** in the presence of NH_2NH_2 under anaerobic conditions (see supporting information). Given that the conversion of **5a** was less than half with 0.5 equivalents of NH_2NH_2 (Table 1, entry 7), the resulting NH=NH might hardly act as a reductant presumably due to its nucleophilicity much poorer than that of NH_2NH_2, which could also explain why an acid co-catalyst was required for the afore-mentioned Baeyer-Villiger oxidation by means of zinc as a non-nucleophilic reductant (Figure 3).

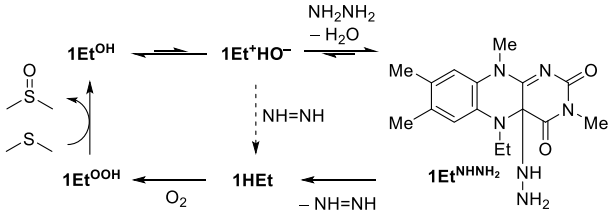
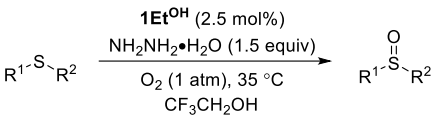
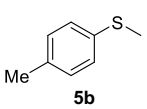
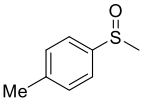
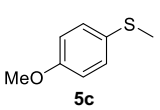
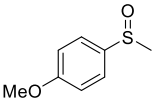
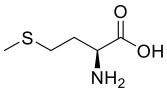
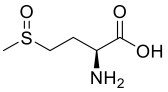


Figure 5. Plausible reaction mechanism for the **1Et^{OH}**-catalyzed aerobic sulfoxidation under acid-free conditions.

The optimum acid-free reaction conditions with **1Et^{OH}** (Table 1, entry 9) were successfully applied to aerobic oxidations of various sulfides (Table 2). In addition to **5a**, 4-methylthioanisole (**5b**), 4-methoxythioanisole (**5c**), and dioctyl sulfide (**5d**) were tolerated and all the corresponding sulfoxides (**6a**–**6d**) were isolated through a chromatographic purification in high yields (Table 2, entries 1–4). L-Methionine (**5e**) could also be oxidized into biologically and synthetically important L-methionine sulfoxide (**6e**),[9] which was readily isolated in 95% yield only by filtration and washing with general solvents (entry 5).

Table 2. Aerobic sulfoxidation catalyzed by **1Et^{OH}** under acid-free conditions.[a]



Entry	Substrate	Product	Yield (%)[b]
1	**5a**	**6a**	80
2	 **5b**	 **6b**	93
3	 **5c**	 **6c**	89
4	$(n\text{-}C_8H_{17})_2S$ **5d**	$(n\text{-}C_8H_{17})_2S{=}O$ **6d**	96
5	 **5e**	 **6e**	95

[a] Reactions were performed with 1 mmol of sulfide and 1.5 mmol of $NH_2NH_2 \cdot H_2O$ in 1 mL of TFE in the presence of 2.5 mol% of **1Et^{OH}** under 1 atm of O_2 at 35 °C for 4 h.
[b] Isolated yields.

Conclusions

In conclusion, first, we have developed a facile and green approach for the preparation of **1Et^{OH}**, which no longer requires any inert condition, risky or expensive chemical, and intermediate isolation, by applying our original method for the synthesis of its precursor, **1Et^{+}X^{-}**, using O_2 as an oxidant from the air.[6] Second, we have for the first time studied the utility of **1Et^{OH}** as a catalyst for aerobic oxygenations, also based on our original protocols for those with conventional isoalloxazinium salt catalysts such as **1Et^{+}ClO$_4^{-}$**.[2,7] The aerobic Baeyer-Villiger oxidation and sulfoxidation by means of zinc and hydrazine as effective sacrificial reductants, respectively, were demonstrated to be efficiently catalyzed by **1Et^{OH}** in the presence of TsOH as a readily available co-catalyst, and most notably, the latter was feasible with high efficiency even under acid-free conditions. We believe that this study makes the use of flavin-based catalysts much easier and expands their applications both in laboratory and in industry.

Experimental Section

Gram-Scale Preparation of 1Et^{OH}

A mixture of **1** (4.1 g, 15 mmol), Pd/C (5%; 6.4 g, 3 mmol), and acetaldehyde (34 mL, 0.6 mol) in degassed ethanol (300 mL), HCl (conc.; 25 mL) and degassed water (300 mL) was stirred at room temperature for 48 h under hydrogen (1 atm). The mixture was filtered through a pad of Celite (7 g) under air by using H_2O for rinsing. The reddish-brown colored filtrate (2.0 kg, 225 × 10^{-3} wt%) was poured into a phosphate buffer solution (pH 6.86, 7.0 L) over 2 min and stirred under air for 60 min at room

temperature. To the resulting deep purple mixture (64 × 10^{-3} wt%, pH 2.77) was added Na_2HPO_4 until reaching pH 6, which was further vigorously stirred at room temperature for 90 min to induce solid precipitation. The precipitate was then collected by filtration, washed with H_2O, and dried under reduced pressure to afford 2.3 g of **1Et^{OH}** as yellowish green solid (49%): UV/Vis (CH_3CN): λ_{max} (ε) = 346 (8400), 316 (6000), 282 nm (6000); IR (ATR): ν = 1716, 1645, 1550, 1318, 1281, 1160, 1086, 1047, 1014, 900, 772; ^{1}H NMR (500 MHz, CD_3CN) δ = 1.03 (t, *J* = 6.8 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 3.37–3.51 (m, 2H, -CH_2-), 3.60 (s, 3H, CH_3), 4.62 (s, 1H, OH), 7.03 (s, 1H, ArH), 7.14 (s, 1H, ArH); ^{13}C NMR (125 MHz, CD_3CN) δ=14.1, 19.3, 19.5, 28.5, 33.0, 45.3, 75.3, 121.8, 129.5, 131.3, 131.8, 134.7, 155.7, 158.9, 167.3; Elemental analysis: Calcd for C16H20N4O3: C 60.75; H 6.37; N 17.71. Found: C 60.50; H 6.36; N 17.56.

General Procedure for Aerobic Oxidation of Sulfides 5a–5d Catalyzed by 1Et^{OH} Under Acid-Free Conditions

A mixture of sulfide (1 mmol), **1Et^{OH}** (0.025 mmol), and $NH_2NH_2{\cdot}H_2O$ (75 mg, 1.5 mmol) in TFE (1 mL) was stirred at 35 ˚C for 4 h under an atmosphere of oxygen. To the resulting mixture was added a saturated Na_2SO_3 aqueous solution (200 μL). After stirring for 10 min at ambient temperature, the mixture was treated with HCl (conc., 100 μL) and concentrated under reduced pressure. The resulting residue was extracted with diethyl ether, and the combined organic layers were concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel using a mixture of EtOAc:hexane as the eluent.

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Keywords: isoalloxazine; flavin • environmentally benign • oxygenation • aerobic oxidation

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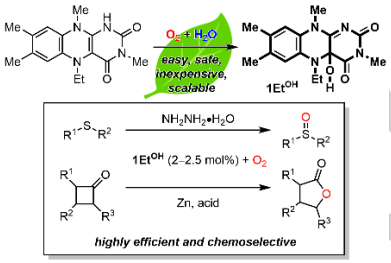
Entry for the Table of Contents

Layout 1:

COMMUNICATION

A novel preparation of 5-ethyl-4a-hydroxyisoalloxazine, an artificial flavin pseudobase, and its utility as a catalyst for biomimetic aerobic oxygenations including Baeyer-Villiger oxidation and sulfoxidation are described. The present method for preparing the catalyst does not involve operations under inert conditions, risky or expensive chemicals, and isolation of labile intermediates, which have been required for the conventional catalyst preparation.



Flavin Catalysts*

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Greener Preparation of 5-Ethyl-4a-hydroxyisoalloxazine and Its Use for Catalytic Aerobic Oxygenations