ELECTRON DEFICIENT FLAVIN AS CATALYST FOR BAEYER-VILLIGER REACTION: OXIDATION OF CYCLOBUTANONES TO γ-LACTONES USING HYDROGEN PEROXIDE

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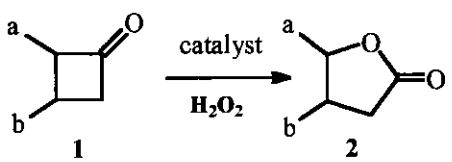
Abstract- The use of an electron deficient isoalloxazine derivative as coenzyme model for the Baeyer-Villiger oxidation is described. This allows, in the presence of hydrogen peroxide, the catalytic oxidation of cyclobutanones into the corresponding γ-lactones with good to excellent yields.

The Baeyer-Villiger (BV) oxidation of ketones to esters or lactones is a well known reaction in organic synthesis. This is, in general, carried out using stoichiometric quantities of various oxidants[1] although catalytic processes have also been achieved.[2] Approaches allowing enantioselective BV reactions have been described up to now.[2c-e] On the other hand, during the recent years, several studies have been devoted to enzymatically catalyzed BV oxidations.[3] Thus, the use of microbial whole-cell cultures[4] as well as of purified enzymes,[5] proved to be a very efficient way to achieve the synthesis of various lactones in enantiomerically purer form.



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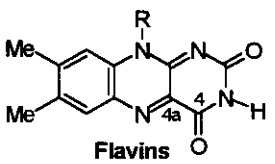
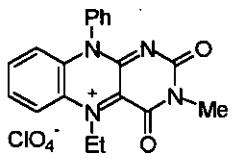
It has been well documented that a flavin moiety must be implied as a coenzyme during the enzymatic oxidation of various ketones, sulfites, amines and other types of organic molecules.[6] Following the pioneering work by Bruice,[7a] Shinkai[7b] and others,[7c-d] we described in our previous paper the first example of BV-type oxidation of ketones (**1**) to lactones (**2**), using a flavin entity (**3**) as a catalyst.[8] However, this

catalyst showed a reactivity limited to the only cyclobutanones. With the aim of increasing the scope and efficiency of our flavin models, we present here the first example of the successful use of electron deficient isoalloxazine derivatives as catalysts in the BV oxidation of ketones.



Flavins



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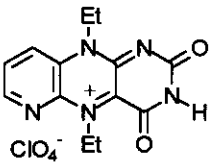

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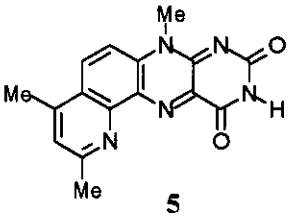

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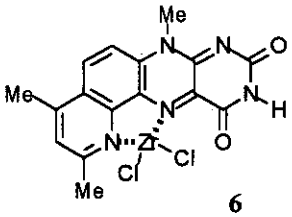

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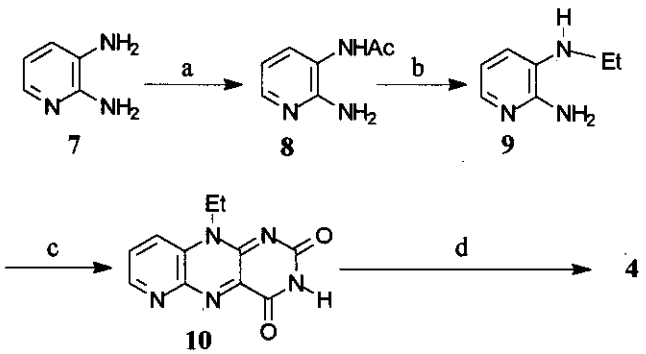
As already showed by Bruice,[7a,9] the oxidizing power of this kind of compound is correlated to the acidity of C(4a). Indeed electron deficient flavins were shown to be better oxidizing agent than normal flavins.[9a] We synthesized the two flavin analogues (**4**) and (**5**) (Scheme 1), containing a nitrogen atom in the aromatic ring. Indeed, this type of derivatives, as well as their complex with metals like zirconium (**6**),[10] have been showed to present increased acidity at C(4a),[11] suggesting a higher catalytic ability.



Scheme 1. *Reagent and conditions:* **a.** acetic anhydride, THF, 0 °C to rt. **b.** $LiAlH_4$, THF, 0 °C to reflux. **c.** alloxane, AcOH, 70 °C. **d.** see ref. 12.

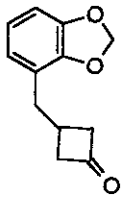
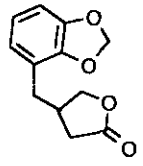
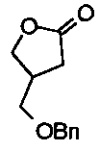
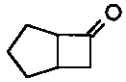
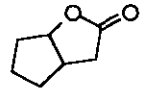
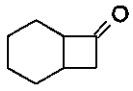
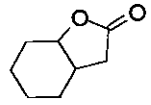
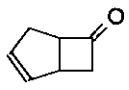
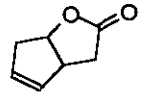
Compound (**4**) was synthesized as indicated in Scheme 1. Starting from the commercially available diaminopyridine (**7**) we made the amide (**8**) which was reduced to the amine (**9**), which upon reaction with alloxane, afforded the flavin derivative (**10**). Following the procedure described by Mager[12] we transformed **10** into its perchlorate salt (**4**). On the other hand, **5** and **6** were obtained as already showed

by Shinkai.[11]

The model substrates to be oxidized were the cyclobutanones (**1a-e**), and the results obtained using catalysts (**4**) are reported in Table 1.

The best experimental conditions appeared to be the ones already described in our previous work.[8] In all cases the system was heterogeneous: indeed, similarly to **3**, the flavin derivatives (**4**, **5** and **6**) were only partially soluble in all the solvents tested. Our first results showed that the new compound (**4**) was more reactive than the flavin catalyst (**3**). Indeed, using the same experimental conditions as those described for **3** (see below), **4** achieved oxidation of ketones (**1**) to lactones (**2**) about three times faster than **3**. Unfortunately, the flavin catalyst (**5**) and its complex (**6**) had no catalytic activity.

Table 1. Oxidation of cyclobutanones (**1a-e**) by **4** at room temperature in the presence of H_2O_2.

Entry	Substrate	Time(h)	Entry	Product	Yield%*
1a		2	**2a**		80
1b		2	**2b**		90
1c		1	**2c**		84
1d		1	**2d**		86
1e		1	**2e**		84

* Yield of product recovered after purification (see experimental part)

The oxidations performed using 2-methyl-2-propanol as a solvent, 2 equiv of hydrogen peroxide and 5% amount of catalyst resulted in the formation of the corresponding lactones in good yields (see Table). In all

cases, only the expected regioisomer was formed, contrary to what we had observed previously in the case of biocatalyzed reactions.[4] No products resulting from either over oxidation or transesterification with the solvent were observed, even when excess of hydrogen peroxide was used. Blank experiments conducted in the absence of catalyst showed that the corresponding lactone was only formed in small quantity (≤ 5%). Bicyclobutanones (**1c-e**) were the most reactive and led to high yield of the corresponding lactones (**2c-e**). Interestingly, although **4** was a better catalyst than **3**, the double bond of substrate (**1e**) was not oxidized, even over long reaction periods. However, cyclohexanones, cyclopentanones and linear ketones remained unreactive. The chemical-physical data of the various lactones (**2**) were consistent with the ones described previously.[4a]

At the light of the previous work by Bruice[7a] and Shinkai,[7b,13] and as we already proposed,[8] the mechanism suggested to explain these oxidations involves the formation of a peroxide intermediate by action of hydrogen peroxide on the flavin moiety, similarly to the scheme proposed for enzymatic BV oxidations.[6] This hydroperoxide intermediate would then react with ketones (**1**), affording the corresponding lactones (**2**) and the corresponding hydroxyflavin which, over dehydration, leads back to the catalyst.

It should be mentioned that the new catalyst (**4**) is indeed more powerful than **3**. Although **4** is not strong enough to accomplish the BV oxidation of other types of ketones, this is an additional demonstration to the fact that the acidity of C(4a) plays an important role in the reactivity of such flavin derivatives.

In conclusion, these results describe the synthesis and use of a more efficient flavin derivative as catalyst for the BV oxid ation of ketones. This reaction can be run in a very simple fashion at room temperature using hydrogen peroxide as a cheap oxidant.

EXPERIMENTAL

General Methods. All reactions involving anhydrous conditions were conducted in flame-dried glassware under a positive atmosphere of oxygen-free nitrogen. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl and distilled under nitrogen immediately prior to use. All the chemicals were purchased from Aldrich and used without further purification. Melting points were recorded on a Buchi 510 apparatus and are uncorrected. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were recorded on a Bruker AC 250, chemical shifts (δ) are given in ppm referring to tetramethylsilane used as internal standard and coupling constants (J) are in hertz. IR spectra were recorded on a Perkin Elmer 1600 from KBr. Absorption maxima are given in waves numbers (cm^{-1}). Separations by flash-chromatography were performed using silica gel 60H (Merck).

3-Acetamido-2-aminopyridine (8). To a solution of 2,3-diaminopyridine (7) (1.1 g, 10 mmol) and triethylamine (2 mL, 15 mmol) in 50 mL of THF at 0 °C, a solution of Ac_2O (1 mL, 10 mmol) in 20 mL of THF was added dropwise and the mixture was stirred at 0 °C for 30 min. The reaction was left to warm-up at room temperature and after 2 h the solvent was evaporated. The residue was solubilized in 200 mL of EtOAc and washed twice with 50 mL of saturated aqueous $NaHCO_3$ solution. The organic layers were separated, combined, dried over $MgSO_4$ and concentrated to give 980 mg (65%) of **8** after flash chromatography as a white solid; mp 88-89 °C (ether); IR: 3552, 3054, 2987, 1685, 1611, 1421, 1270; ^{1}H NMR (CD_3OD): 2.30 (s, 3H), 6.81 (dd, 1H, J = 7.6, J = 5.1), 7.69 (dd, 1H, J = 7.6, J = 1.6), 7.97 (dd, 1H, J = 5.1, J = 1.6); ^{13}C NMR (CD_3OD): 23.5 (q), 114.7 (d), 120.5 (s), 135.8 (d), 146.8 (d), 155.8 (s), 172.9 (s); *Anal.* Calcd for $C_6H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.74; H, 6.13; N, 27.94.

2-Amino-3-ethylaminopyridine (9). To a suspension of $LiAlH_4$ (800 mg, 20 mmol) in 10 mL of dry THF at 0 °C, a solution of **8** (800 mg, 5.2 mmol) in 30 mL of dry THF was added dropwise, the mixture was stirred at 0 °C for 30 min and then refluxed for 3 h. The reaction was quenched at 0 °C with 5 mL of water, filtered and the residue was washed several times with a total amount of 100 mL of EtOAc. All the organic filtrates were collected and washed twice with 50 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$ and concentrated. After flash chromatography 640 mg (90%) of **9** as an undistillable oil were obtained; IR: 3357, 2971, 1617, 1578, 1458, 1219; ^{1}H NMR ($CDCl_3$): 1.13 (t, 3H, J = 7.1), 3.00 (q, 2H, J = 7.1), 3.49 (br, 1H), 4.54 (br, 2H), 6.57 (dd, 1H, J = 7.7, J = 5), 6.65 (dd, 1H, J = 7.7, J = 1.6), 7.47 (dd, 1H, J = 5, J = 1.6); ^{13}C NMR ($CDCl_3$): 14.7 (q), 38.5 (t), 115.6 (d), 116.5 (d), 132.4 (s), 136.0 (d), 149.1 (s); *Anal.* Calcd for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.68. Found: C, 61.49; H, 8.30; N, 30.39.

7-Aza-10-ethylisoalloxazine (10).[14] A suspension of **9** (640 mg, 4.7 mmol) and alloxane monohydrate (1.5 g, 9.5 mmol) in 30 mL of AcOH was stirred at 70 °C for 3 h. The solvent was evaporated and the residue was washed thoroughly with hot EtOH which gave a single spot on TLC. This afforded 680 mg (60%) of **10** as a yellow solid; mp 305-306 °C (with decomp); ^{1}H NMR (DMSO-d_6): 1.30 (t, 3H, J = 7), 4.61 (q, 2H, J = 7), 7.91 (dd, 1H, J = 8.7, J = 4.2), 8.49 (d, 1H, J = 8.7), 8.88 (d, 1H, J = 4.2), 11.52 (s, 1H); IR: 3154, 3071, 1712, 1682, 1591, 1543, 1514, 1467,1407, 1267, 1165, 827; *Anal.* Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.08; H, 3.91; N, 28.61.

7-Aza-5,10-diethylisoalloxazine perchlorate salt (4). Starting from 680 mg (2.8 mmol) of **10** and following the procedure already described by Mager,[12] 550 mg (50%) of **4** were obtained as a violet solid;

mp 214-216 °C (with decomp); IR: 3235, 3033, 1710, 1679, 1642, 1387, 786; *Anal.* Calcd for $C_{13}H_{14}N_5O_6Cl$: C, 41.97; H, 3.79; N, 18.82. Found: C, 42.12; H, 3.95; N, 18.49.

Typical experimental procedure for the BV oxidation of ketones (1) to lactones (2). Ketone (**1**) (5 mmol) and the catalyst (**4**) (90 mg, 5 mol%) were dissolved in *tert*-BuOH (10 mL) and 1 mL of 35% H_2O_2/water solution (10 mmol) was added *via* syringe. The mixture was stirred at rt for 1-2 h depending on the substrate. Evaporation of the solvent in vacuum and filtration on silica afforded the pure lactones (**2**) (up to 95% purity as checked by GC and by NMR).

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REFERENCES

1. G. R. Krow, *Org. React.*, 1993, **43**, p. 251.
2. (a) K. Kaneda, S. Ueno, T. Imanaka, Y. Nishhiyama, and Y. Ishii, *J. Org. Chem.*, 1994, **59**, 2915. (b) C. Bolm, G. Schlingloff, and K. Weickhardt, *Tetrahedron Lett.*, 1993, **34**, 3405. (c) *idem*, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1848. (d) *idem*, *J. Chem. Soc., Chem. Comm.*, 1995, 1247. (e) A. Gusso, C. Baccin, F. Pinna, and G. Strukul, *Organometallics*, 1994, **13**, 3442.
3. V. Alphand and R. Furstoss, "Enzyme Catalysis in Organic Synthesis," ed. by K. Drauz and H. Waldmann, VCH Publishers, 1995, pp. 745-772.
4. (a) V. Alphand and R. Furstoss, *J. Org. Chem.*, 1992, **57**, 1306. (b) F. Petit and R. Furstoss, *Tetrahedron: Asymmetry*, 1993, **4**, 1341.
5. R. Gagnon, G. Grognan, E. Groussain, S. Pedragosa-Moreau, P. F. Richardson, S. M. Roberts, P. W. H. Wan, A. Willetts, V. Alphand, J. Lebreton, and R. Furstoss, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2527.
6. C. T. Walsh and Y. -C. J. Chen, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 333.
7. (a) S. -R. Keum, D. H. Gregory, and T.C. Bruice, *J. Am. Chem. Soc.*, 1990, **112**, 2711 and references therein. (b) S. Shinkai, H. Nakao, I. Kuwahara, M. Miyamoto, T. Yamaguchi, and O. Manabe, *J. Chem. Soc., Perkin Trans. 1*, 1988, 313 and references therein. (c) A. Ohno, J. Kunitomo, T. Kawamoto, M. Tomishima, K. Bessho, and F. Yoneda, *Tetrahedron Lett.*, 1994, **35**, 9729 and

references therein. (d) J. -M. Kim, S. E. Hoegy, and P. S. Mariano, *J. Am. Chem. Soc.*, 1995, **117**, 100 and references therein.

8. C. Mazzini, J. Lebreton, and R. Furstoss, *J. Org. Chem.*, 1996, **61**, 8.
9. (a) T. C. Bruice, *J. Chem. Soc., Chem. Comm.*, 1983, 14. (b) R. L. Chan and T. C. Bruice, *J. Am. Chem. Soc.*, 1977, **99**, 6721.
10 S. Shinkai, H. Nakao, N. Honda, F. Muller and O. Manabe, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1825.
11 S. Shinkai, Y. Ishikawa, and O. Manabe, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1694.
12. H. I. X. Mager and S. -C. Tu, *Tetrahedron*, 1994, **50**, 5287.
13 S. Shinkai, T. Yamaguchi, O. Manabe, and F. Toda, *J. Chem. Soc., Chem. Comm.*, 1988, 1399.
14. For compound (**10**) it was not possible to record the ^{13}C NMR spectra.

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