Flavin-Catalyzed Baeyer−Villiger Reaction of Ketones: Oxidation of Cyclobutanones to γ Lactones Using Hydrogen Peroxide

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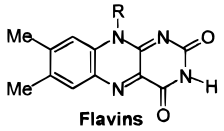
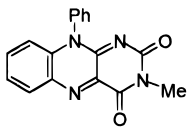
The Baeyer−Villiger (BV) oxidation of ketones to lactones is a well-known reaction in organic synthesis. This is, in general, carried out using stoichiometric quantities of various oxidants,[1] although catalytic processes have also been achieved.[2] Only two approaches allowing enantioselective BV reactions have been described up to now, but they lead only to lactones showing modest ees.[2c,d] On the other hand, during 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 enantiopure form. 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] In the frame of our work concerning these biocatalyzed BV transformations, we were interested in investigating the possible use of isoalloxazine derivatives as enzyme models for achieving such type of reactions. Many studies have been performed in this field;[7] however, to our best knowledge, there are no successful examples relating the use of such catalysts in the BV oxidation of ketones. Following the pioneering work by Bruice,[7a] Shinkai[7b] and others,[7c,d] we report here the first example of the BV-type oxidation of ketones to lactones, achieved using a flavin entity as a catalyst.

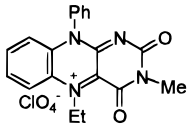
As we already mentioned, the use of molecules like **1** or **2** as catalysts has been well documented in the literature.[7] Moreover, as described by Bruice,[7a] the catalytic activity of this kind of compound was shown to be increased by alkylation of the N(5) position. Thus, the flavin **1** as well as its N(5) alkylated derivative **2** were tested. Their synthesis was achieved according to the synthetic schemes described by Shinkai[8] and by Mager[9] for similar products. The model substrates to be oxidized



Flavins



(1)



(2)

were the cyclobutanones **3** (see Table 1), a choice which results from our previous experience on such biocatalyzed BV reactions[4] and from our current interest in the use of chiral γ-lactones as building blocks for the synthesis of biologically active molecules like, for instance, pheromones or flavor compounds.[10]

In order to find the proper experimental conditions for optimum reactivity, several parameters (nature of the catalyst, catalyst ratio, temperature, proportion of hydrogen peroxide) including the use of various solvents allowing good solubility of the catalyst and of the substrate were examined. Our first results showed that the nonalkylated isoalloxazine **1** was inactive, even when used in stoichiometric amount. The use of **2**, however, led to much more interesting results and catalyzed the BV oxidation of ketones **3** in various conditions. Running the oxidation in the presence of benzene, toluene, acetonitrile, tetrahydrofuran, or ethyl ether only led to poor (if any) yields of lactone **4**. Different alcohols, i.e., methanol, ethanol, 2-propanol, and 2-methyl-2-propanol were also tested and led to much better results. In all cases the system was heterogeneous: indeed, the catalyst **2** was only partially soluble into all the tested solvents. The best experimental conditions appeared to be the use of a 5% proportion of catalyst **2**, at room temperature, using 2-methyl-2-propanol as a solvent in the presence of 2 equiv of hydrogen peroxide added all in one shot. The use of a smaller proportion of catalyst did afford unreproducible results. We also noticed that when molecular oxygen was used as the oxidant (atmospheric pressure) only small proportions (5−10% by GC) of lactones were formed and that, contrary to what was observed previously,[11] these reactions were not influenced by light. Thus, the oxidations performed using these optimized conditions, resulted in the formation of the corresponding lactones in 45−90% yields after 3−24 h reaction, depending on the structure of the substrate.[12] No products resulting from either overoxidation or transesterification with the solvent were observed.

However, in the absence of catalyst, the corresponding lactone was shown to be also formed, but only in small proportions. Only in the case of **3c** was a noticeable spontaneous lactone formation observed. Thus, the reaction was run in 2-propanol instead of 2-methyl-2-propanol

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(11) Shinkai, S.; Yamaguchi, T.; Manabe, O.; Toda, F. *J. Chem. Soc., Chem. Commun.* **1988**, 1399.

(12) A typical experiment was as follows: Ketone **3** (5 mmol) and the catalyst **2** (100 mg, 5 mol %) were dissolved in *t*-BuOH (10 mL), and 1 mL of 35% H_2O_2/water solution (10 mmol) was added *via* syringe. The mixture was stirred at room temperature for 3−24 h depending on the substrate. Evaporation of the solvent in vacuo and filtration on silica afforded the pure lactones **4** (up to 95% purity as checked by GC and by NMR).

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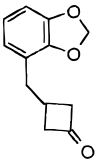
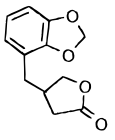
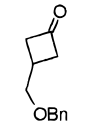
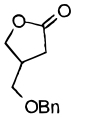
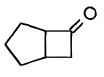
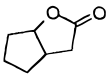
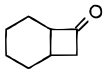
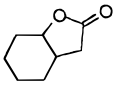
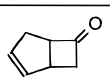
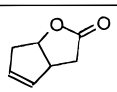
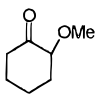
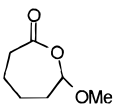
Table 1. Oxidation at Room Temperature of Various Cyclobutanones by 2 in the Presence of H_2O_2

Entry	Substrate	Time (h)	Entry	Product	Yield %[a]	Yield %[b]
3a		6	**4a**		90	< 5
3b		6	**4b**		93	< 5
3c		3	**4c**		85	< 5
3d		3	**4d**		83	< 5
3e		3 8[c]	**4e**		86 84[c]	20 <5[c]
3f		24	**4f**		45	< 5

[a] Isolated yield in the presence of catalyst **2**. [b] Without catalyst, GC yield. [c] Reaction performed using *i*-PrOH as a solvent at −5 °C.

in order to allow the reaction to be run at −5 °C. The results we have obtained are indicated in Table 1.

Bicyclobutanones **3c**−**e** were the most reactive and led to high yields of the corresponding lactones **4c**−**e**. In all cases, the expected regioisomer was formed, contrary to what we had observed previously in the case of biocatalyzed reactions.[4] Interestingly, the double bond of substrate **3e** was not oxidized, even over long reaction periods. Unfortunately, under such conditions, cyclohexanones, cyclopentanones, and linear ketones were less reactive and only α-alkoxycyclohexanones,[13,14] such as **3f**, gave good results. The lower yield observed in this case was presumably due to the extreme liability of the lactone **4f** during its isolation. The chemical−physical data of the various lactones **4** were consistent with the ones described previously.[4a,13]

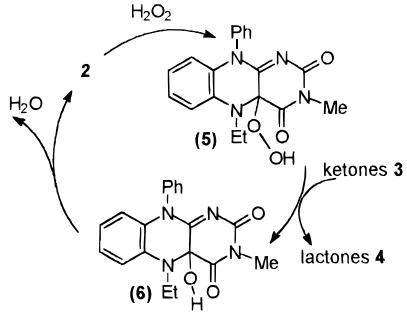


Figure 1. Proposed catalytic cycle for the BV oxidation of ketones **3**.

In light of the previous works of Bruice[7a] and Shinkai,[7b] the mechanism we propose to explain these oxidations is depicted in Figure 1. As outlined previously, hydrogen peroxide, in the presence of isoalloxazine **2**, presumably forms the peroxide **5** which has also been postulated to be the oxidizing species in enzymatic BV transformations.[6] Such an intermediate has also been isolated and fully characterized previously.[15] This peroxide intermediate will then react further on with ketones **3**, affording the corresponding lactones **4** and the hydroxyflavin **6** which, over dehydration, leads back to the catalyst **2**.

In conclusion, these results describe for the first time the possibility of using flavin derivatives as enzyme models for catalyzing the BV oxidation of ketones, a reaction which can be run in a very simple fashion at room temperature using hydrogen peroxide as a cheap oxidant. Moreover, the possibility to introduce some chiral moieties into such isoalloxazine catalysts opens the way to the design of chiral catalysts with the aim to perform enantioselective Baeyer−Villiger oxidations. Attempts to improve the range of reactivity of these flavin models as well as efforts to achieve asymmetric oxidations using some chiral isoalloxazines are underway in our laboratory.

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Supporting Information Available: Procedure and copies of spectra are included (5 pages).

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