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Organocatalytic Synthesis of Lactones via an Oxidation of Alkenoic-acids

Ierasia Triandafillidi,[a] Marianna Raftopoulou,[a] Anatoli Savvidou[a] and Christoforos G. Kokotos*[a]

Abstract: Along the lines of modern sustainable oxidation, a green and mild organocatalytic synthetic procedure for the synthesis of hydroxy-lactones from alkenoic-acids is described. The reaction includes activation of H_2O_2 by an organocatalyst (2,2,2-trifluoromethylacetophenone), followed by the oxidation of an olefinic group to the corresponding epoxide and intramolecular lactonization affording a variety of substituted *γ*- or *δ*-lactones with multiple substitution patterns in good to high yields. The product can be obtained with enough purity after simple extractions, when conversion is quantitative. Attempts to render the process asymmetric met with limited success.

Introduction

Lactones are important structural motifs, which are frequently encountered in natural products, pharmaceuticals, including antibiotic and antitumor agents, agrochemicals, flavor components, material and polymer production (Figure 1).[1-3] Furthermore, lactones are versatile building blocks for the synthesis of biologically important compounds with antimicrobial activity, such as (+)-tanikolide and (-)-malyngolide.[4] *γ*-Lactones are useful intermediates for the synthesis of compounds presenting inhibitory activity against HIV reverse transcriptase.[5] Additionally, DAG-lactones are very important compounds as protein kinase C (PKC) ligands and antitumor agents. [6]

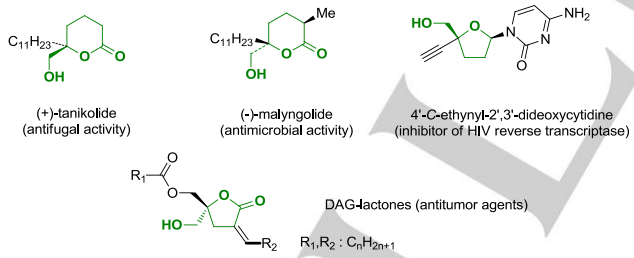

Figure 1. Useful molecules bearing the lactone motif.

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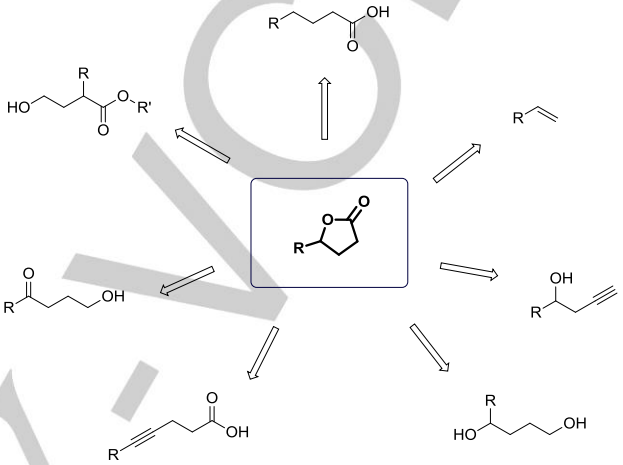
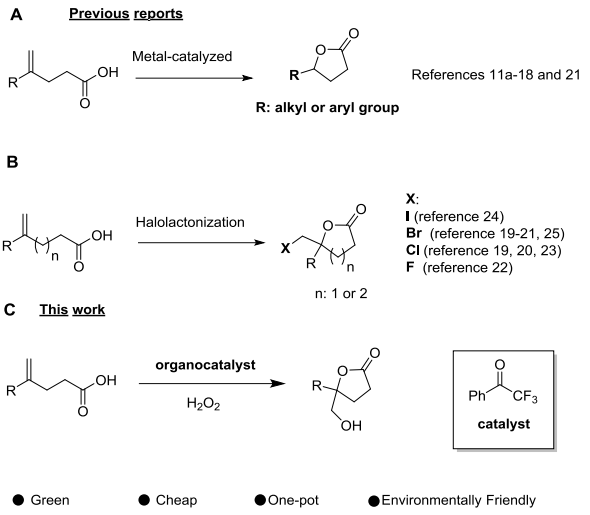


Scheme 1. Various retrosynthetic approaches for the synthesis of lactones found in literature.

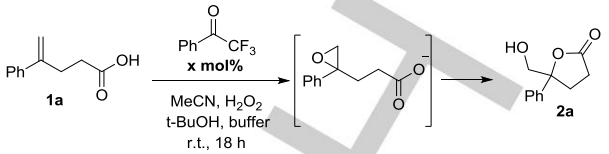
Since lactones constitute a repeatedly occurring scaffold in nature, a plethora of synthetic methods to access lactones has been reported utilizing as starting materials a variety of functional groups, such as carboxylic acids,[7] terminal alkenes[8] or alkynes,[9] diols[10] or chains that contain some functional groups (Scheme 1).[11] Despite the utility of all these pathways, the intramolecular lactonization of alkenoic acids is among the most common approaches employed and it still constitutes a challenge for the scientific community. Olefins are among the most diverse building blocks in organic synthesis and their utility derives from the wide variety of functionalization reactions that can participate in. There have been published numerous reports, taking advantage of metal-catalyzed processes using zinc,[12] palladium,[13] silver,[14] copper,[15] gold,[16] vanadium[17] or cobalt[18] (Scheme 2, **A**). Despite the widespread popularity of these reactions, the toxicity of metals and high levels of inorganic waste make their application harmful for the environment and to be adopted by chemical industry. Organocatalytic halolactonizations have attracted much attention from the viewpoint of “green” chemistry. Therefore, a variety of organocatalysts have been developed, such as alkyl-[19] or amino-thiocarbamate,[20] catalysts based on iodine,[7,21] phosphite,[22] substituted imidazoles,[23] squaramides,[24] peptides[25] or other (Scheme 2, **B**).[26] However, most of them require cryogenic conditions that limit applications in industry. Also, in most cases, the developed methodologies can harness only *γ*- or *δ*-lactones with specific substitution pattern. Although Organocatalysis has presented elegant contributions for the epoxidation of alkenes,[27] it is quite surprising, that there is



Scheme 2. Synthetic methods for the synthesis of lactones from alkenoic acids.

limited knowledge on the use of hydrogen peroxide as the oxidant for such a tandem epoxidation-lactonization. Very recently, we have reported a cheap, sustainable and environmentally friendly protocol for various oxidations employing H_2O_2 as the oxidant. This procedure has the advantage that its only by-product is water, while 2,2,2-trifluoroacetophenone was employed as the organocatalyst to activate hydrogen peroxide, which by itself is quite poor to perform oxidations.[28] We had previously employed this protocol in the synthesis of tetrahydrofurans,[28e] isoxazolines[28g] and pyrrolidines.[28h] We envisaged we could extend this organocatalytic oxidative protocol via the introduction of an one-pot procedure for the isolation of substituted lactones starting from alkenoic acids. Once the intermediate epoxide is formed, an intramolecular ring opening reaction would afford the desired cyclized compound bearing a hydroxy moiety (Scheme 2, **C**).

Table 1. Organocatalytic synthesis of lactone **2a** from alkenoic acid **1a**.[a]



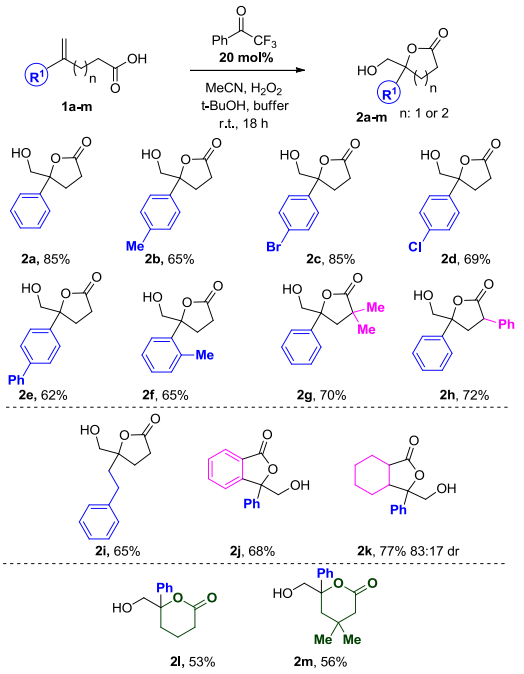
Entry	Catalyst (mol%)	MeCN/H_2O_2 (equiv.)	Solvent	Yield[b] (%)
1	10	5	t-BuOH	50
2	0	5	t-BuOH	traces
3	10	8	t-BuOH	56
4	10	12	t-BuOH	62
5	10	16	t-BuOH	75
6	5	16	t-BuOH	65
7	20	12	t-BuOH	73
8	**20**	**16**	**t-BuOH**	**85**
9	20	16	EtOAc	75
10	20	16	$CHCl_3$	52
11	20	16	MeCN	76
12	20	16	MeOH	64
13	20	16	CH_2Cl_2	45

[a] All reactions were carried out with **1a** (0.30 mmol), 2,2,2-trifluoro-1-phenylethanone (x mol%), solvent (0.3 mL), aqueous buffer solution (0.3 mL, 0.6M K_2CO_3 – 4 x 10^{-4} M EDTA disodium salt), acetonitrile and 30% aqueous H_2O_2. The reaction mixture was left stirring for 18 hours. [b] Isolated yield.

Results and Discussion

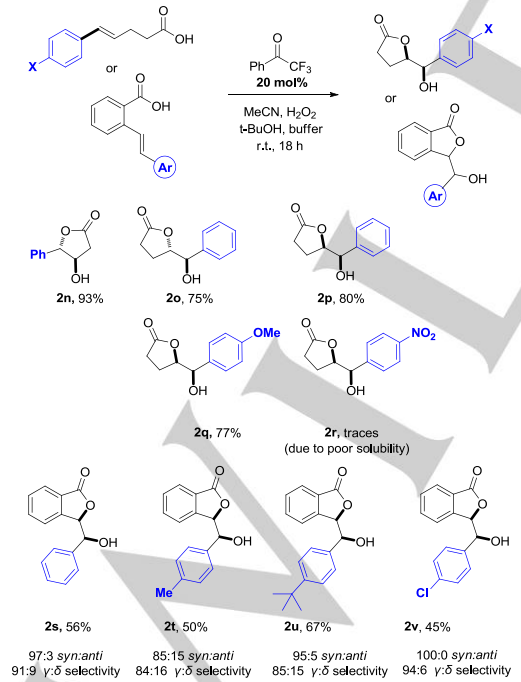
Initially, we began our investigation with the use of alkenoic acid **1a**, employing our optimized reaction conditions for the epoxidation of terminal alkenes. Utilizing 10 mol% of 2,2,2,-trifluoroacetophenone as the organocatalyst and 5 equiv. of MeCN and H_2O_2, lactone **2a** could be obtained, albeit in moderate yield (Table 1, entry 1). It has to be highlighted that if the catalyst is omitted, no reaction is taking place and lactone **2a** is not being formed (Table 1, entry 2). Increasing the amount of MeCN and hydrogen peroxide had as a consequence an upsurge in the yield of the product (Table 1, entries 1 and 2-5). Next the catalyst loading was studied, leading to the identification of the optimum reaction conditions (Table 1, entries 6-8). It has to be noted that full conversion was observed and no chromatographic purification is required in this last case, since the product can be isolated in excellent yield (85%) in high purity (>95%) after simple extractions. Alternatively, filtration through a short silica plug can lead to the isolation of pure lactone **2a**. The acetamide byproduct, which is also produced, can be removed by simple aqueous extractions. A variety of solvents were then tested affording lactone **2a** in lower yields (Table 1, entries 9-13).

Once the optimum reaction conditions were found, the substrate scope of the reaction was sought (Scheme 3 and 4). Initially, the substitution pattern on the aromatic group was studied, leading to *γ*-lactones bearing a tetrasubstituted carbon atom. In all cases, the desired lactones **2a-f** were obtained in high yield. Thus, the substitution pattern (*ortho*- or *para*-subsitution, as well as electron donating or electron withdrawing groups) does not affect the outcome of the reaction. Addition of alkyl moieties on the alkyl backbone between the alkene and the carboxylic acid does not alter the efficiency of the reaction, since products **2g** and **2h** were obtained in high yield. Thus, polysubstituted *γ*-lactones can be synthesized efficiently. Replacing the aromatic group with an aliphatic chain poses no problem for our methodology and lactone **2i** was isolated in high yield. In an attempt to further



Scheme 3. Synthetic scope for the synthesis of lactones.

expand the substrate scope, polysubstituted alkenoic acids were employed. In all cases, the desired polysubstituted lactones **2j** and **2k** were obtained in high yields. Moving from *γ*-lactones to *δ*-lactones, which is usually not a trivial task, seems possible employing our procedure. Six-membered ring lactones **2l** and **2m** were obtained from the corresponding alkenoic acids, albeit

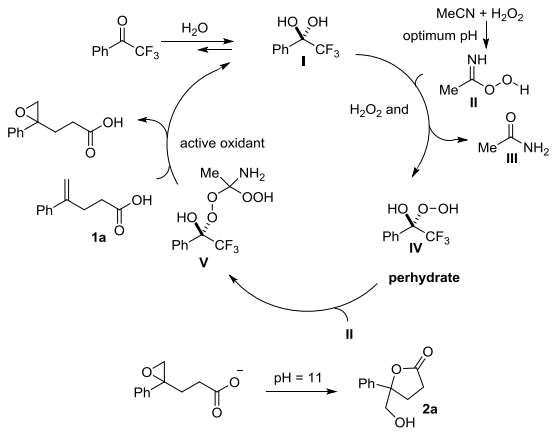


Scheme 4. Substrate scope for the synthesis of lactones.

in slightly lower yields. In all the above cases, Baldwin's empirical rules for ring closure are followed, since products **2a-2k** are synthesized via a 5-*exo-tet* ring closure, which is favored, while a forbidden 6-*endo-tet* would have led to the six-membered ring lactone. Similarly, a favorable 6-*exo-tet* ring cyclization is followed for products **2l** and **2k**.

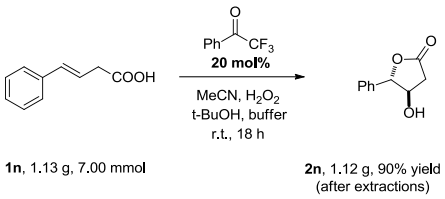
When the alkene is not 1,1-disubstituted but 1,2-disubstituted, like in the cases of Scheme 4, *γ*-lactones were isolated in excellent yield (**2n**-**2q**). Both *cis* and *trans* alkenes led to the corresponding cyclized product. Turning our attention to *trans*-disubstituted alkenoic acids, *γ*-lactones **2s-v** were obtained in good yield and in most cases with high diastereocontrol and almost full control on the cyclization towards the 5-membered ring. For compounds **2o-v**, the cyclization follows Baldwin's rules (5-*exo* vs 6-*endo*) leading to *γ*-lactones instead of *δ*-lactones. In an attempt to make this hydrogen peroxide-mediated process more attractive, we envisaged the use of Shi's catalyst to render the process asymmetric.[29] Unfortunately, the corresponding lactones were isolated in low enantioselectivity, which is in agreement with our latest finding that probably a dioxirane is not involved in our catalytic system.[28f]

To summarize the events that take place, a proposed reaction mechanism is shown in Scheme 5. Initially, the catalyst (2,2,2-trifluoroacetophenone) is converted to diol **I** in the presence of the aqueous buffer.[28f] When the appropriate pH is employed, MeCN reacts with H_2O_2 to afford **II**, which in conjunction with H_2O_2 oxidizes **I** to perhydrate **IV**. Another molecule of **II** reacts with **IV** affording the compound **V**. This could be or can be transformed into the active oxidant of the protocol, which epoxides alkenoic-acid **1a**. Then, and since the pH is adjusted to 11, the deprotonated carboxylate ring opens the epoxide, and a simultaneous cyclization occurs leading to lactone **2a**.



Scheme 5. Proposed reaction mechanism.

In order to provide a more industrial-friendly process, alkene **1n** was oxidized in a gram scale (Scheme 6). After the reaction was completed, lactone **2n** was isolated in high yield after simple extractions, bypassing the need for column chromatography.



Scheme 6. Gram scale reaction.

Conclusions

In conclusion, an effective organocatalytic synthetic protocol for the organocatalytic synthesis of hydroxy-lactones is described. Utilizing mild reaction conditions, a metal-free catalyst is employed to activate hydrogen peroxide leading to a green and highly sustainable process. When conversion of the starting material is full, the product can be isolated with enough purity (95%) by simple extractions. A variety of substitution patterns is well tolerated leading to either *γ*-lactones to *δ*-lactones in good to excellent yields. Finally, when further substitution is employed, polysubstituted lactones are obtained. An asymmetric variant was attempted leading to low enantioselectivities, strengthening our hypothesis for the reaction mechanism not involving a dioxirane intermediate. A gram scale reaction enhanced the industrial character of this method.

Experimental Section

Alkenoic-acid (0.30 mmol) was placed in a round bottom flask and dissolved in *tert*-butanol (0.3 mL). 2,2,2-Trifluoro-1-phenylethanone (10.4 mg, 0.06 mmol), aqueous buffer solution (0.3 mL, 0.6M K_2CO_3 – 4 x 10^{-4}M EDTA disodium salt), acetonitrile (0.24 mL, 4.80 mmol) and 30% aqueous H_2O_2 (0.48 mL, 4.80 mmol) were added consecutively. The reaction mixture was left stirring for 18 hours at room temperature. The crude product was quenched with HCl (1N) (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The mixture was purified using flash column chromatography (10%-40% EtOAc in Pet. Ether) to afford the desired product.

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Keywords: organocatalysis • oxidation • alkenoic-acid • lactones • green chemistry

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[29] For more details, see Supporting Information.

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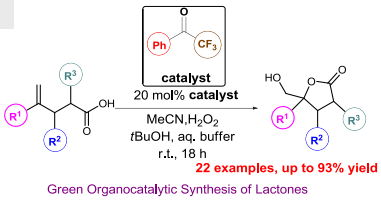
FULL PAPER

Organo-Lactones. A green organocatalytic method for the activation of hydrogen peroxide and the oxidation of alkenoic acids to lactones is described.



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