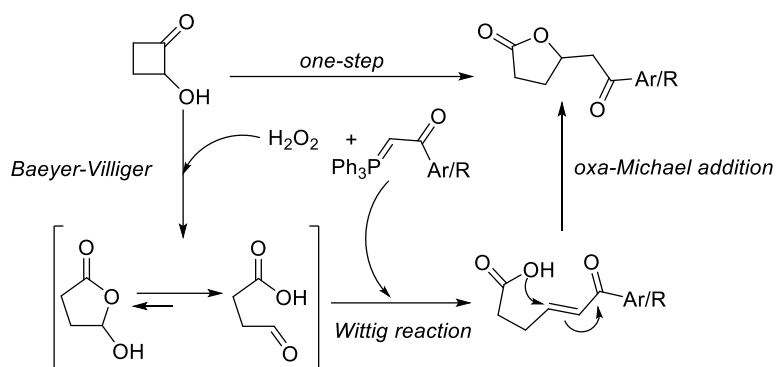


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Tandem Baeyer–Villiger/Wittig/oxa-Michael addition: one-step to 5-substituted γ -lactones

Stefano Barranco, Federico Cuccu, Pierluigi Caboni and Angelo Frongia*





Tandem Baeyer–Villiger/Wittig/oxa-Michael addition: one-step to 5-substituted γ -lactones

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ABSTRACT

The results reported in this study provide a practical protocol for the construction, in one single step of synthetically important γ -lactones in good yields starting from α -hydroxy cyclobutanone, H_2O_2 and several stabilized phosphonium ylides. Our synthetic strategy relies on a tandem Baeyer–Villiger oxidation/Wittig reaction/oxa-Michael addition.

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Baeyer–Villiger

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Introduction

γ -Lactones represent an important class of organic compounds which have received considerable attention due to their diverse and interesting biological activities. [1] Several synthetic methods have been reported in the literature for their efficient preparation. [1–8] Among them numerous elegant achievements have been made in the synthesis of 5-(2-oxoalkyl) γ -lactones, including transition-metal catalyzed C–H functionalizations [9–11] and organocatalyzed intramolecular oxa-Michael cyclization cascades. [12–16] Furthermore, tandem oxidation/oxa-Michael addition reaction of 2-alkenylbenzaldehydes [17] and the intramolecular one-pot oxa-Michael reaction of peroxy hemiacetals followed by Kornblum DeLaMare fragmentation [18] have also recently been developed.

Over the last few years, our group has explored the reactivity of α -hydroxy cyclobutanones with electrophiles [19–20] and nucleophiles [21–23] leading to the enantioselective synthesis of other functionalized cyclobutanone derivatives. Hence, further transformations useful for constructing diverse functionalized heterocycles [24–27] and cyclopropane carboxaldehydes [27–29] have also been developed. Continuing with our interest in exploiting new reactivities of α -hydroxy cyclobutanone and bearing in mind that 5-hydroxydihydrofuran-2(3H)-

ones could be used efficiently as substrates in Wittig olefination reactions with stabilized phosphonium ylides (Scheme 1a), [15–16] we wondered whether it was possible to generate γ -lactol **3** (in mixture with its corresponding acyclic oxoacid) in situ from α -hydroxy cyclobutanone **1** and H_2O_2 (via a Baeyer–Villiger reaction), and trap it to undergo a tandem Wittig/oxa-Michael addition reaction to access γ -lactones such as **5** (Scheme 1c).

It is worth mentioning that γ -lactol **3** is unstable and its synthesis usually requires tedious multistep procedures (Wermuth-protocol) and/or employ relatively harsh reaction conditions (Scheme 1b). [30–37] On the other hand, tandem- and one-pot reactions incorporating Wittig reagents represent a commonly used strategy in organic synthesis to prepare diverse synthetically useful compounds. [38–39] In particular, oxidation processes carried out in the presence of a Wittig reagent turned out to be an efficient solution to the difficulties of handling carbonyl intermediates labile and/or difficult to isolate. [40–46] Accordingly, the development of new efficient and versatile tandem oxidative procedures is desirable.

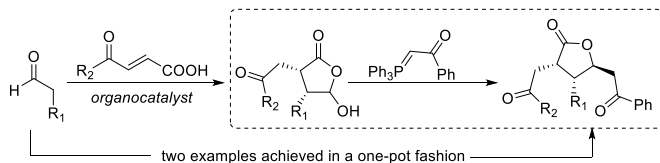
Results and discussion

We began our exploration by examining the reaction with α -hydroxy cyclobutanone **1**, phosphonium ylide **2a** and

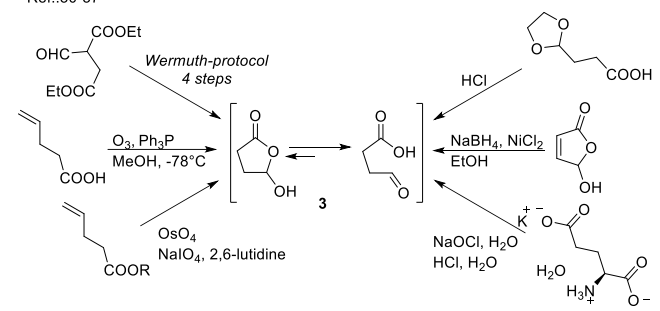
H₂O₂ (30% aqueous v/v solution) in DMF at room temperature (entry 1). The proposed tandem reaction occurred with complete consumption of the starting materials and 5-(2-oxo-2-phenylethyl) dihydrofuran-2(3H)-one **5a** was obtained in a high conversion (80%) after 48 h along with 6% of the by-product **6a** (coming from a hydrogen peroxide-induced oxidative dimerization of phosphonium ylide **2a**) [47] and a minor amount of intermediate **4a** (14%).

Scheme 1. Research background (top and middle panel) and the present work (bottom panel).

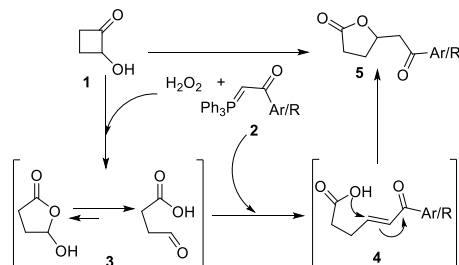
a) Michael/cyclization cascade followed by tandem Wittig/oxa-Michael addition (previous work): two-step strategy
Ref.: 15-16



b) synthetic methods reported in literature for the generation of γ -lactol **3**
Ref.:30-37



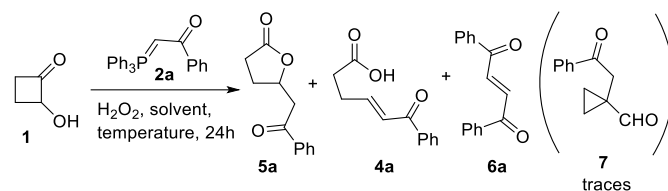
c) tandem Baeyer-Villiger/Wittig/oxa-Michael addition (present work): one-step strategy



Pleasingly, the reaction time was shortened to 24h increasing the reaction temperature to 30°C (79% conversion; entry 2). Further enhancing the temperature to 40°C afforded **5a** with a comparable conversion (81%; entry 3). Next, the solvents were briefly investigated and MeCN (entry 4) was found to give a slightly higher conversion (89%) and 70% of isolated yield. The use of other solvents such as toluene, CH₂Cl₂, 1,4-dioxane, 2-Me-THF and CHCl₃ were suitable (entries 5-9), however MeCN remained the preferred choice. Interestingly, in every case examined only trace amount of cyclopropanated 1,4-dicarbonyl **7**, coming from a tandem Wittig reaction–ring contraction process were detected. [28] To get insight into the reaction mechanism for the formation of compound **5a**, a controlled experiment was performed (Scheme 2). We observed the formation of γ -lactol **3** (a mixture of aldehyde: cyclic hemiacetal forms at a ratio of 64:36% was detected according to the ¹H NMR

spectrum) reacting **1** with H₂O₂ in CDCl₃ at 40°C after 24 h at room temperature and its subsequent transformation into the corresponding lactone **5a** (82%), along with 18% of intermediate **4a**, following the addition of phosphonium ylide **2a**.

Table 1. Screening of the reaction conditions^a

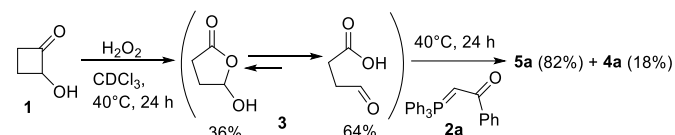


entry	solvent	temp. °C	ratio 5a : 4a : 6a ^b
1	DMF	RT	80:14:6 ^c
2	DMF	30	79:17:4
3	DMF	40	81:11:8
4	CH ₃ CN	40	89:5:6 (70%) ^d
5	Toluene	40	74:14:12
6	1,4-Dioxane	40	65:23:12
7	2-Me-THF	40	78:17:5
8	CHCl ₃	40	70:16:14
9	CH ₂ Cl ₂	reflux	81:10:9

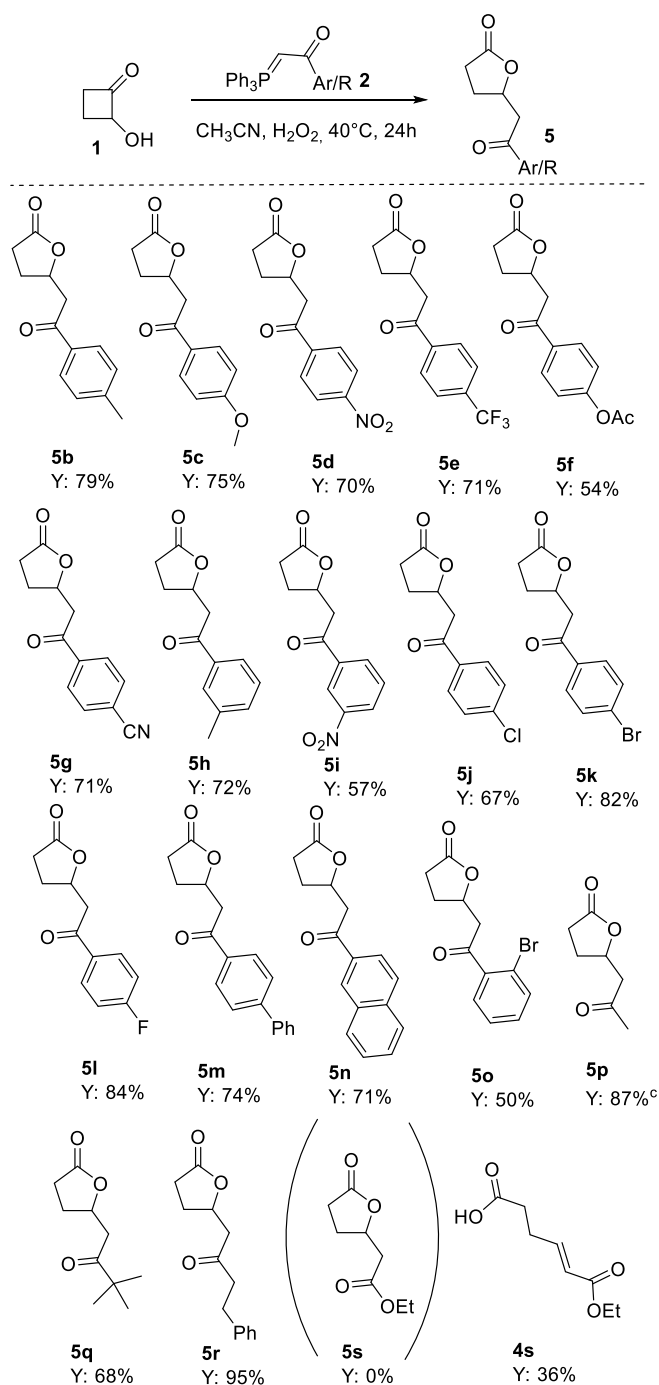
^aReaction conditions: **1** (0.423 mmol; 0.036 g), **2a** (0.423 mmol; 0.161 g), H₂O₂ 30% (0.465 mmol; 0.047 mL), solvent (0.32 mL). ^bDetermined by ¹H NMR. ^cReaction time of 48h. ^dIsolated yield of **5a** in parentheses.

This observation supports our working mechanistic hypothesis proposed in Scheme 1 involving the initial formation of a transient intermediate **3** which subsequently undergoes in a tandem Wittig/oxa-Michael addition reaction to form **5a**. The observed formation of **4a** during the reaction is also consistent with our proposal.

Scheme 2. Control experiment.



With the optimized conditions in hand, we next sought to evaluate the generality of this reaction using different substituted phosphonium ylides **2**. As summarized in Scheme 3, both electron-donating (Me and OMe) and electron-withdrawing (NO₂, CF₃, CN and OCOMe) substituents in the para or meta position of the aromatic ring of the phosphonium ylide were all compatible with the standard reaction conditions affording the corresponding products **5b-g** and **5h-i** in good to high yields (54-79%). Similarly, the reaction smoothly proceeded with halogens such as chloro, bromo and fluoro or phenyl at the para-position on the aromatic ring of the phosphonium ylide (**5j-m**: 67-84% yield) as well as with 1-naphthyl phosphonium ylide **2n** (**5n**: 71% yield). The presence of a bromo in ortho-position resulted in moderate yield (50%) of the corresponding lactone **5o**.

Scheme 3. Substrate scope.^{a,b}

^aReaction conditions: **1** (0.423 mmol; 0.036 g), **2** (0.423 mmol), H_2O_2 30% (0.465 mmol; 0.047 mL), CH_3CN (0.32 mL), 40°C , 24 h. ^bIsolated yield.

^cDetermined by crude ^1H NMR.

Finally, three representatives aliphatic phosphonium ylides such as **2p-r** could also be accommodated providing the corresponding derivative **5p-r** in good to high yields (68–95%). On the other hand, when ethyl 2-(triphenylphosphoranylidene) acetate, was employed, intermediate **4s** instead of γ -lactone **5s** was recovered from the reaction mixture (36% yield), most likely because of its less reactivity toward intramolecular oxa-conjugate cyclization.[48]

Conclusion

In conclusion, the results reported in this paper provide a new synthetic application of α -hydroxy cyclobutanone for the construction of important γ -lactones with moderate to good yields through a tandem sequence combining Baeyer-Villiger reaction and Wittig/oxa-Michael addition.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

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