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# Benzyl (Phenyl) $\gamma$- and $\delta$-lactones via Photoinduced Tandem Ar−C, C−O Bond Formation

Stefano Protti, Maurizio Fagnoni,* and Angelo Albini

*Department of Organic Chemistry, The University, V. Taramelli 10, 27100 Pavia, Italy*

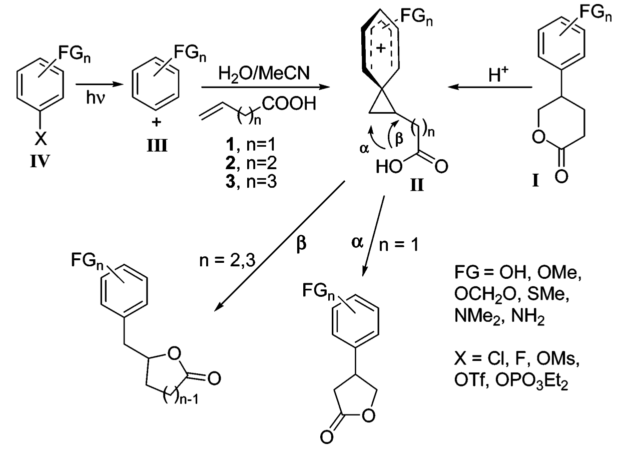
Received April 19, 2006; E-mail: fagnoni@unipv.it

The $\gamma$-lactone moiety is present in many biologically active natural compounds.[1] In particular, some benzyl- and aryl-substituted $\gamma$-lactones have shown cancer preventive and anti-inflammatory activity[2a] or are used as intermediates for the synthesis of antibiotic antitumor agents.[2b] This notwithstanding, the synthesis of such derivatives has received only sparse attention. Thus, aryl $\gamma$-lactones have been obtained by Baeyer−Villiger reaction of aryl cyclobutanones,[3] or by reaction of 2-phenyloxirane with the malonate anion,[4] while benzyl lactones have been formed by arylation of a substituted epoxide by means of an aryl cyanocuprate.[2b] The arylation of unsaturated lactones has been exploited in the Rh(I)-catalyzed conjugate addition of aryl boronic acids[5a] or of aryltrimethylstannanes.[5b] Recently, it has been reported that aryl $\delta$-lactones (I, Scheme 1) rearrange to benzyl $\gamma$-lactones under acidic conditions[6] via a phenonium ion (II). We reasoned that generating directly the phenonium ion by addition of a phenyl cation (III) onto an unsaturated acid would offer a novel entry to these lactones via tandem formation of an aryl−C and a C−O bond. There is hardly a precedent for this strategy.[7] However, we recently showed that phenyl cations (III) are smoothly generated by photoheterolysis of electron-rich aromatic chlorides, fluorides, or esters (IV)[8] and add to alkenes forming phenonium ions. We first tested this idea by generating phenyl cations in the presence of some terminal alkenoic acids, namely, 3-butenoic (**1**), 4-pentenoic (**2**), and 5-hexenoic (**3**) acid. Electron-donating substituted phenyl halides and esters **6**−**13** were used as precursors of the cations. Because photoheterolysis is favored by polar (protic) solvents, the irradiation (310 nm, 254 nm for **13**)[9a] was carried out in acetonitrile−water 5:1.[9b]

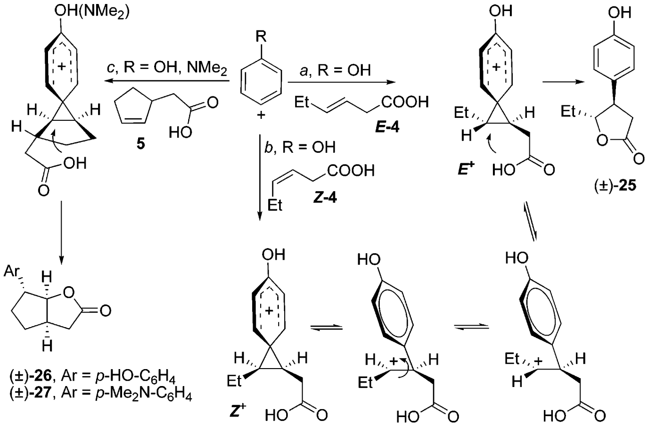
Indeed, irradiation of 4-chlorophenol (**6**) in the presence of **1** under these conditions (see Supporting Information for details) gave the desired phenyl-$\gamma$-lactone **14** in a moderate yield (52%, Table 1), arising via path α, Scheme 1. On the other hand, irradiation of aniline **7a** and anisole **10a** under the same conditions gave only a 30% of the corresponding lactone (not reported in the Table).

Satisfactory results were obtained in the arylation of 4-pentenoic acid (**2**). Thus, when using 4-chlorophenol, lactone **15** was formed in nearly quantitative yield and with complete regioselectivity (in this case path $\beta$ was followed, see Scheme 1). This result fostered a more extensive exploration of the reaction, which showed that benzyl $\gamma$-lactones were consistently the only products. Phenyl chlorides could be substituted by other halides or esters. Thus, aminobenzyl lactone **16** was formed in more than 70% yield when starting both from 4-chloro- (**7a**)[11] and from 4-fluoro-*N*,*N*-dimethylaniline (**7b**, same irradiation time, 6 h) and in a lower yield (50%) from phosphate **7c**. Analogously, aminobenzyl lactone **17** was prepared by irradiating both 4-chloro and 4-fluoroaniline.

***Scheme 1.*** Photochemical Synthesis of Benzyl(phenyl) Lactones



***Scheme 2.*** Possible Pathways in the Reaction between Phenyl Cations and Unsaturated Acids **4** and **5**



Further derivatives bearing *O*- or *S*-bonded electron-donating groups in position 4 reacted similarly. In particular, the photolysis of 4-chloroanisole **10a** or of the triflate or phosphate esters (**10b**,**c**) afforded dihydrofuranone **19** in moderate to excellent yield (48 to 87%). 4-Chloro-1,2-benzodioxole and 4-chlorothioanisole gave lactones **20** and **21**, respectively (>50% yield). Interestingly, a phenyl cation could be generated and trapped also when using an alkyl-substituted phenyl halide. Thus, lactone **22** was formed from 4-butylchlorobenzene (**13**) and **2** upon 254 nm irradiation. Furthermore, we recently demonstrated that *ortho*-substituted phenyl cations were obtained just as the *para*-analogues,[13] and this suggested a further extension of the study. Thus, 2-chlorophenol (**9**) was irradiated in the presence of acid **2** and found to give lactone **18**. Noteworthy, the alternative cyclization of the phenolic OH group onto the phenonium ion did not take place.[14] As for the hexenoic acid **3**, this gave, regioselectively, the hydroxyphenyl and aminophenyl tetrahydropyranones **23** and **24** (following again path $\beta$ in Scheme 1). In these cases the yields were slightly lower with respect to the previous cases (53 and 37%).

In the second part of our work, we explored the scope and the selectivity of the reaction by using nonterminal alkenoic acids. Irradiation of 4-chlorophenol in the presence of (*E*)-3-hexenoic acid

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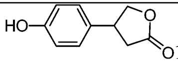
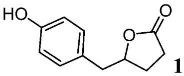
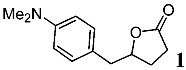
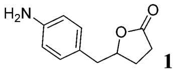
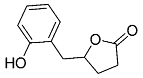
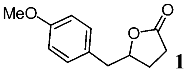
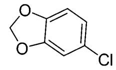
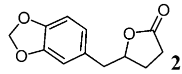
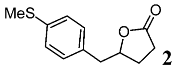
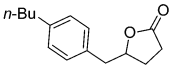
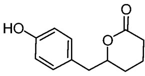
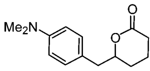
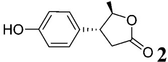
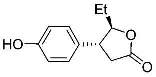
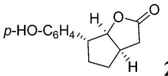
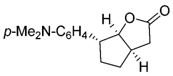
***Table 1.*** Photoinduced Synthesis of Phenyl(benzyl) Lactones[10]

| reagents | *t* (h) | product | yield[a] (%) |
|---|---|---|---|
| **1**, *p*-HO-$C_6H_4$-Cl (**6**) | 14 |  **14** | 52 |
| **2**, **6** | 14 |  **15** | 95 |
| **2**, *p*-$Me_2N$-$C_6H_4$-Cl (**7a**) | 6 |  **16** | 78 |
| **2**, *p*-$Me_2N$-$C_6H_4$-F (**7b**) | 6 | **16** | 70 |
| **2**, *p*-$Me_2N$-$C_6H_4$-$PO_4Et_2$ (**7c**) | 6 | **16** | 50 |
| **2**, *p*-$H_2N$-$C_6H_4$-Cl (**8a**) | 4 |  **17** | 68 |
| **2**, *p*-$H_2N$-$C_6H_4$-F (**8b**) | 6 | **17** | 48 |
| **2**, *o*-HO-$C_6H_4$-Cl (**9**) | 24 |  **18** | 56[b] |
| **2**, *p*-MeO-$C_6H_4$-Cl (**10a**) | 14 |  **19** | 72 |
| **2**, *p*-MeO-$C_6H_4$-OTf (**10b**) | 36 | **19** | 87[b] |
| **2**, *p*-MeO-$C_6H_4$-$PO_4Et_2$ (**10c**) | 36 | **19** | 48 |
| **2**,  **11** | 14 |  **20** | 51 |
| **2**, *p*-MeS-$C_6H_4$-Cl (**12**) | 14 |  **21** | 57 |
| **2**, *p*-$C_4H_9$-$C_6H_4$-Cl (**13**) | 8 |  **22** | 57[c] |
| **3**, **6** | 14 |  **23** | 53 |
| **3**, **7a** | 6 |  **24** | 37 |
| ***E*-4**, **6** | 24 |  **25** | 54 |
| ***Z*-4**, **6** | 24 |  **25** | 67 |
| **5**, **6**[d] | 36 |  **26** | 61[e] |
| **5**, **7a**[d] | 6 |  **27** | 61[f] |

[a] Isolated yields. [b] 0.9 M acetone added. [c] Irradiation at 254 nm. [d] Halide 0.025 M. [e] Phenol (6%) as a byproduct. [f] *N*,*N*-Dimethylaniline (9%) also formed.

(***E*-4**) gave exclusively (*E*)-arylethyllactone **25** (Table 1). As a matter of fact, the process was fully stereoselective, because **25** was likewise obtained by using ***Z*-4** in the place of ***E*-4**.

The selectivity results from the facile ring closure by backside attack in ion $\boldsymbol{E}^+$ (path a), a process that is sterically hindered in isomeric ion $\boldsymbol{Z}^+$ from ***Z*-4**, where preliminary bond rotation is required (see Scheme 2).[15] The analogy between this finding and the selectivity observed in the solvolysis of phenethyl derivatives, at the time the basis for the phenonium ion proposal, is apparent.[16]

With 2-cyclopentenacetic acid **5**, arylation and ring closure likewise took place with full regio- and stereoselectivity, affording hexahydrocyclopenta[*b*]furan-2-ones **26** (from **6**) and **27** (from **7a**; Table 1 and Scheme 2). In these compounds, three stereogenic centers were simultaneously generated and the phenyl group laid on the same side of the hydrogens of the *cis* ring junction, again due to the backside attack in the ring-closure step. To the best of our knowledge, only a single synthesis of a bicyclic aryllactone has been previously reported and was based on a nickel-catalyzed phenylation reaction (via trifluoroarylsilanes) of the corresponding iodide as the final step.[17]

In conclusion, the electrophilic addition of a phenyl cation onto alkenoic acids occurs efficiently and is followed by an intramolecular attack by the carboxylic group. This tandem reaction has no close precedent and results in the one-step synthesis of 4- (or, respectively, 5-) benzyl $\gamma$- and $\delta$-lactones from 4-pentenoic and 5-hexenoic acids, as well as (although in a lower yield) of 4-phenyl-$\gamma$-lactones from 3-butenoic acids. Such compounds are otherwise obtained in several steps by thermal reactions. The photoinduced method avoids the use of expensive and labile metal catalysts, of a high temperature,[14b] or of anhydrous conditions (actually water favors the initial heterolytic step), making this an experimentally convenient procedure. Furthermore, the intermediacy of a phenonium ion imparts a strict stereoselectivity to the reaction, supporting the synthetic significance of the proposed method.

**Supporting Information Available:** Experimental details and $^1$H and $^{13}$C NMR spectra of compounds **14**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Nagumo, S.; Ishii, Y.; Kakimoto, Y.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 5333−5337.

(7) A related process is the Pd-catalyzed reaction of aryl bromides with $\gamma$-hydroxy alkenes, see: Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620−1621.

(8) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713−721.

(9) (a) Chlorides **9**, **10b**, and **13** did not significantly absorb at >300 nm. Acetone sensitization was effective for **9** and **10b**. (b) A convenient medium such as 2,2,2-trifluoroethanol could not be used in this case because it formed the corresponding trifluoroethyl esters and precluded the formation of the lactones.

(10) General procedure: A solution of the carboxylic acid **1**−**5** (15 mmol, 0.5 M) and halides or esters **6**−**12** (1.5 mmol, 0.05 M) in MeCN−water 5:1 (30 mL) was irradiated at 310 nm (unless when otherwise stated). The photolyzed mixture was neutralized and extracted with $CH_2Cl_2$, and the residue was purified by column chromatography.

(11) The same reaction carried out in acetonitrile gave 5-(4-(dimethylamino)-benzyl)-dihydro-furan-2-one in about the same yield (70%, see ref 12).

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(13) Dichiarante, V.; Fagnoni, M.; Mella, M.; Albini, A. *Chem.*−*Eur. J.* **2006**, *12*, 3905−3915.

(14) (a) The formation of an oxonium ion has been invoked in related cases. See: (b) Nagumo, S.; Ono, M.; Kakimoto, Y.-I.; Furukawa, T.; Hisano, T.; Mizukami, M.; Kawahara, N. Akita, H. *J. Org. Chem.* **2002**, *67*, 6618−6622. (c) Manner, J. A.; Cook, J. A., Jr.; Ramsey, B. G. *J. Org. Chem.* **1974**, *39*, 1199−1203.

(15) The orthogonal staggered and planar perpendicular open-chain forms of these cations are known to equilibrate with negligible activation energy, see: Hehre, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 5919−5920.

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