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DIRECT SYNTHESIS OF δ-LACTONES FROM 2-(3-LITHIOPROPYL)-1,3-DIOXOLANE AND CARBONYL COMPOUNDS+

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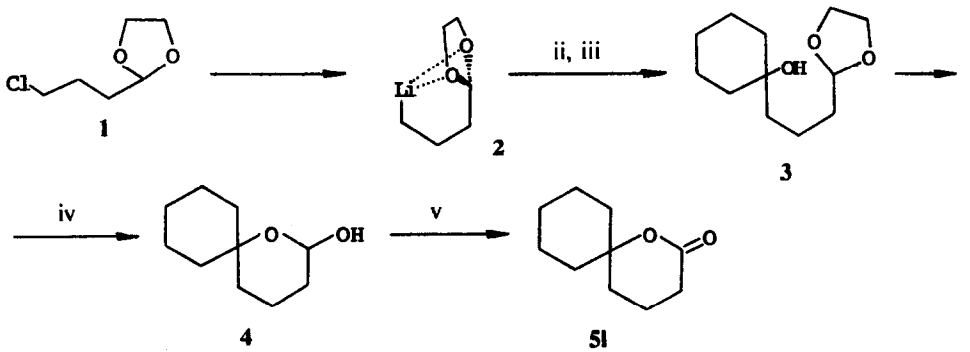
Summary: The reaction of 2-(3-lithiopropyl)-1,3-dioxolane (**2**), prepared *in situ* by lithiation of the chloroacetal **1** with lithium naphthalenide at -78°C, with aldehydes and ketones followed by hydrolysis with hydrochloric acid and final oxidation with PCC or Jones reagent yields the corresponding δ-lactones **5**.

Lactonic functionality is fairly common among natural products and in a variety of biologically active molecules, the corresponding δ-lactones occurring preferentially in products from animal origin.[1] Thus, many δ-lactones are significant as insect pheromones[2] and therefore a lot of synthetic effort has been done to prepare these type of molecules.[3] However, general synthetic routes to δ-lactones are relatively scarce[4] and most methods involve strongly basic conditions.[5]

On the other hand, we have described[6] the preparation at the first time of the naked masked lithium bishomoenolate **2** by lithiation of the corresponding chlorinated precursor **1** with lithium naphthalenide at -78°C and its reactivity with electrophilic reagents. Thus, the reaction with cyclohexanone yields the regioselectively protected bifunctional product **3**, which is easily hydrolysed in acid medium to the corresponding hemiacetal **4** in practically quantitative yield (Scheme 1). At this point, and for the above mentioned reasons,[4] we decided to study the transformation of compounds of the type **4** into the corresponding δ-lactones **5**.



Scheme 1. *Reagents*: i, $Li^+C_{10}H_8^-$, -78°C; ii, $(CH_2)_2CO$, -78 to 20°C; iii, H_2O; iv, 2 N HCl-THF; v, CrO_3-H_2SO_4-Me_2CO.

+Dedicated to Prof. A. G. González on occasion of his 73th birthday.

Table. Preparation of δ-lactones **5.**

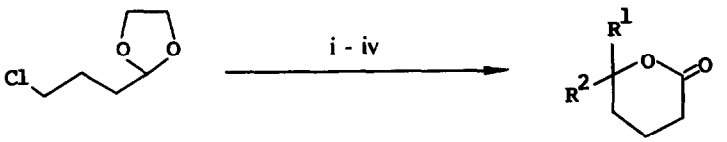
Entry	Carbonyl compound R^1R^2CO		δ-Lactone[a]		
	R^1	R^2	No.	Yield (%)[b]	R_f[c]
1	H	*i*-Pr	**5a**	60	0.48
2	H	*n*-C_5H_{11}	**5b**	45	0.44
3	Me	Me	**5c**	51	0.53
4	Me	Et	**5d**	62	0.44
5	Me	*i*-Bu	**5e**	47	0.39
6	Me	*t*-Bu	**5f**	44	0.39
7	Me	Ph	**5g**	30	0.39[d]
8	Et	Et	**5h**	36	0.39
9	Et	Ph	**5i**	34	0.28[d]
10	*n*-Pr	Ph	**5j**	33	0.29[d]
11		-$(CH_2)_4$-	**5k**	56	0.48
12		-$(CH_2)_5$-	**5l**	49 (85)[e]	0.51
13		-$(CH_2)_7$-	**5m**	60	0.46

[a]All products were > 95 % pure (g.l.c. and n.m.r.) and gave satisfactory spectral data (i.r., ^1H and ^{13}C-n.m.r., and mass spectra). [b]Overall isolated yield based on the starting chloroacetal **1**, after flash chromatography (silica gel, hexane/ethyl acetate). [c]Silica gel, hexane/ethyl acetate: 3/2. [d]Silica gel, hexane/ethyl acetate: 4/1. [e]Isolated yield based on compound **4**.

We first studied the oxidation of compound **4** with different reagents such as MCPBA,[7] MMPP,[8] PCC,[9] or Fetizon reagent.[10] In every case, surprisingly, the reaction failed recovering the starting material. However, the use of Jones reagent[11] worked very well giving the expected lactone **5l** in 85 % isolated yield (Scheme 1 and Table, entry 12).

We then considered the possibility of carrying out the reaction of obtaining δ-lactones **5** without isolation of the intermediates of the type **3** and **4**. Thus, the lithiation of 2-(3-chloropropyl)-1,3-dioxolane **1** with lithium naphthalenide at -78°C yielded the intermediate **2**,[6] which was treated in situ with different ketones R^1R^2CO followed by hydrolysis with 2 N hydrochloric acid and final oxidation with the Jones reagent, giving the expected lactones **5c-m** (Scheme 2 and Table, entries 3-13). When the same process was carried out using aldehydes (R^2CHO) as electrophiles the corresponding lactones **5** were not isolated; thus, for instance, in the case of the benzaldehyde derivative, 5-phenyl-5-oxopentanoic acid (35%; R_f=0.20[12]) was the only reaction product isolated, arisen from the total oxidation of both the secondary alcohol and the aldehyde functionalities. This problem was overcome -after trying the other above mentioned oxidants- by using PCC[9] in the final step of the *in situ* method, so the corresponding δ-lactones **5a,b** were isolated (Scheme 2 and Table, entries 1 and 2).

In some cases, mainly when the carbonyl compounds is a phenone (Table, entries 7,9, and 10), the low overall yields obtained can be explained due to the competition of an enolization process which leads to 2-propyl-1,3-dioxolane -Li/H interchange in **2**- instead of the corresponding compound of the type **3** (Scheme 1).

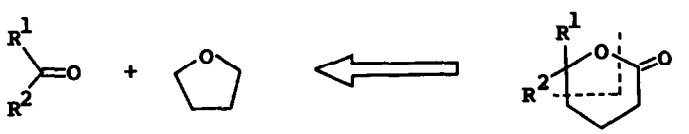


1 **5**

Scheme 2. *Reagents*: i,Li$^+$C$_{10}$H$_8^-$, -78°C; ii, R^{1}R^{2}CO, -78 to 20°C; iii, 2 N HCl-THF; iv, CrO_3-H_2SO_4-Me_2CO.

From the results described in this communication we find specially interesting the products derived from aldehydes because there are important biologically active substances having this skeleton.[13] Thus, for instance, compound **5b** is a constituent of massory bark (*Cryptocarya massoica*);[14] work is now in progress in order to prepare other interesting compounds of this type.[15] On the other hand, spirolactones of the type **5k-m** are also key structural features of many natural products.[16] Finally, it is noteworthy that δ-lactones are, in general, interesting synthetic materials for other types of functionalities.[17]

In conclusion, we have demonstrated that the chloroacetal **1** and carbonyl compounds can be adequate precursors for δ-lactones; considering that the starting material **1** is easily available from tetrahydrofuran (tandem opening with hydrogen chloride followed by PCC oxidation and final ketalization) the whole synthetic operation is that shows the Scheme 3.



Scheme 3.

Typical procedure: To a tetrahydrofuran solution of the intermediate **2**[6] (2.5 mmol) was added the corresponding carbonyl compound (2.5 mmol) at -78°C and it was stirred overnight allowing the temperature to rise to 20°C. The resulting mixture was hydrolyzed with water (5 ml), neutralized with 2 N hydrochloric acid, extracted with ether (2x5 ml) and the organic layer dried over anhydrous sodium sulfate. Solvents were evaporated (15 torr), to the resulting residue was added tetrahydrofuran (5 ml) and 2 N hydrochloric acid (5 ml) and it was stirred for 2 h. The resulting solution was extracted with ether (2x10 ml), the organic layer dried over anhydrous sodium sulfate and evaporated (15 torr). The resulting residue was oxidized with PCC[9] (for **5a,b**) or the Jones reagent[11] (for **5c-m**) following the literature procedures.[18]

References and Notes

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