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Oxidation of Substituted Spiro[bicyclo[n.1.0]alkane-2,2'-[1,3]dioxolanes]. Formation of Substituted Lactones.

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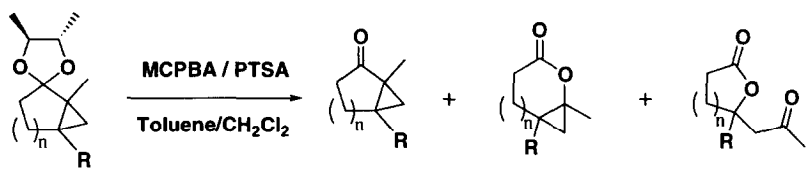
Abstract: 5-(Aryl)-1,4',5'-trimethylspiro[bicyclo[3.1.0]hexane-2,2'-[1,3]dioxolanes] are transformed to substituted ketolactones by treatment with *m*-chloroperbenzoic acid in the presence of *p*-toluenesulfonic acid.

Keywords: lactones; ketals; oxidation; cyclopropanes.

Ketals can be transformed into lactones by treatment with peracids in acidic conditions. [1] We have found that treatment of compounds of type **1** [2] with *m*-chloroperbenzoic acid (MCPBA) [3] in the presence of *p*-toluenesulfonic acid (PTSA) can lead to lactones of type **3** or **4** depending on the nature of substituent R and on the ring size of the spiroketal. Ketones of type **2** can also be isolated as minor products.



$\mathbf{1}_{A\text{-}E}$ $\mathbf{2}_{A\text{-}E}$ $\mathbf{3}_{A\text{-}E}$ $\mathbf{4}_{A\text{-}E}$

When $\mathbf{1}_A$ was treated with MCPBA (2.5 eq) in the presence of PTSA (1.0 eq) lactone $\mathbf{3}_A$ was obtained with high regioselectivity and in good yield (62%); ketone $\mathbf{2}_A$ was also isolated as a minor product (17%). Treatment of $\mathbf{1}_B$ in the same conditions led to ketone $\mathbf{2}_B$ (30% yield) and lactone $\mathbf{3}_B$ (40% yield) with no trace of lactone $\mathbf{4}_B$.[4] On the contrary, when $\mathbf{1}_C$, $\mathbf{1}_D$, and $\mathbf{1}_E$ were treated for several days with MCPBA (2.5 eq) and PTSA (1.0 eq), only traces of lactones $\mathbf{3}_C$-$\mathbf{3}_D$ were detected by GC/MS and ketolactones $\mathbf{4}_C$, $\mathbf{4}_D$ and $\mathbf{4}_E$ were respectively isolated as major products (~ 40% yield). Ketones $\mathbf{2}_C$-$\mathbf{2}_E$ were also formed as side-products and were isolated in low yields (1% - 25%). The results are summarized in the Table.

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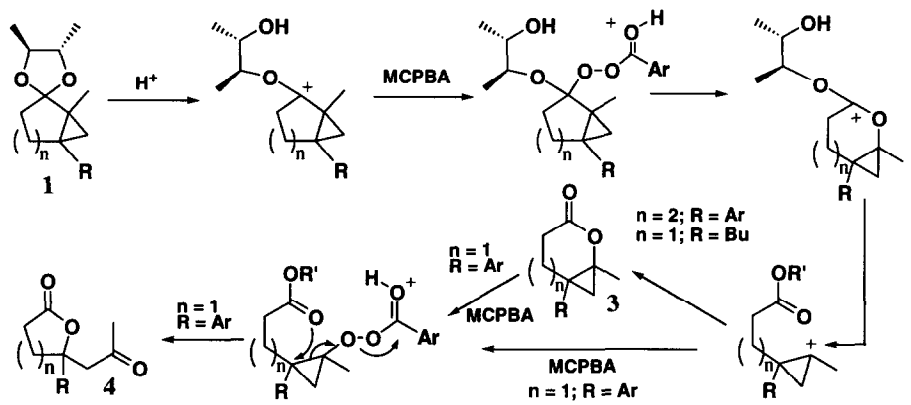
Table: Oxidation of lactones $\mathbf{1_A}$ – $\mathbf{1_E}$ by MCPBA/PTSA [a]

Starting material 1	time	Products (yield % [b]) 2	3	4
$\mathbf{1_A}$ n = 1 ; R = butyl	12 h	(17)	(62)	(-)
$\mathbf{1_B}$ n = 2 ; R = *p*-methoxyphenyl	7 d	(30)	(40)	(-)
$\mathbf{1_C}$ n = 1 ; R = phenyl	7 d	(20)	(-)	(41)
$\mathbf{1_D}$ n = 1 ; R = *p*-tolyl	3 h	(24)	(70)	(-)
	7 d	(10)	(-)	(35)
$\mathbf{1_E}$ n = 1 ; R = *p*-methoxyphenyl	7 d	(traces)	(-)	(40)

[a] The reactions were performed at rt in toluene/CH_2Cl_2 (1/1) at 0.1 M in $\mathbf{1_A}$-$\mathbf{1_E}$; MCPBA (2.5 eq) ; PTSA (1.0 eq). [b] Isolated products, after purification by flash-chromatography.

Variation of the aromatic substituent in ketals $\mathbf{1_C}$-$\mathbf{1_E}$ suggests that the yield of ketolactone $\mathbf{4_C}$-$\mathbf{4_E}$ (~ 40%) is almost unaffected by increasing electron density in the cyclopropane. When ketals $\mathbf{1_C}$-$\mathbf{1_E}$ were treated for several days with an excess of MCPBA or with MCPBA in the presence of $NaHCO_3$, they were recovered in 70% yield and ketones $\mathbf{2_C}$-$\mathbf{2_E}$ were isolated (5 – 10%). No lactones $\mathbf{3_C}$-$\mathbf{3_E}$ or $\mathbf{4_C}$-$\mathbf{4_E}$ were then detected. We have to point out that treatment of ketones $\mathbf{2_C}$-$\mathbf{2_E}$ with MCPBA and PTSA led only to degradation. Treatment of lactone $\mathbf{3_D}$ with MCPBA (1.2 eq) and PTSA (1.0 eq) (7 days) furnished ketolactone $\mathbf{4_D}$ (40%). When lactone $\mathbf{3_D}$ was treated either with MCPBA alone or with PTSA alone, only traces of ketolactone $\mathbf{4_D}$ were detected (~ 4 %) and the starting lactone was recovered. Therefore, it appears that the transformation of ketals $\mathbf{1_C}$-$\mathbf{1_E}$ to ketolactones $\mathbf{4_C}$-$\mathbf{4_E}$ implies the protonation of the ketal by PTSA. (Scheme)



By applying a simple procedure, 5-(aryl)-1,4',5'-trimethylspiro[bicyclo[3.1.0]hexane-2,2'-[1,3]dioxolanes] can thus be transformed easily into γ-disubstituted γ-lactones (aryl, acetonyl) in moderate yields.

References and notes

1. Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* **1997**, *38*, 6019-6022 and references therein.
2. Compounds of type **1** were prepared by treatment of the corresponding ketone with (±)-2,3-butanediol.
3. Commercially available from ACROS (70-75%).
4. The presence of lactone $\mathbf{4_B}$ was not detected in the crude reaction mixture by GC/MS or in the ^{1}H NMR spectra.