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Synthesis of Spirocyclic Bislactones Substituent Effects on the Regioselectivity of the Baeyer-Villiger of 1,3-Diketones

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Abstract : The Baeyer-Villiger oxidation of substituted spirocyclic lactones and 1,3-diketones led to spirocyclic bislactones with a good regioselectivity.

Keywords : Baeyer-Villiger, lactones, spirocyclic compounds, substituent effect.

The Baeyer-Villiger oxidation of ketones is an important reaction that has been used in synthesis [1]-[3]. In many instances and when there are no specific steric effect [4]-[9], the regioselectivity of the oxygen atom insertion can be predicted by considering the differential ability of the two concurrent migrating alkyl groups to stabilize a carbenium ion. The substituent effects on the regioselectivity of the Baeyer-Villiger oxidation has been studied intensively in the case of 7-oxabicyclo[2.2.1]heptan-2-ones [10]. Ether or alcohol α or β to the carbonyl aids migration during peracid reaction. In the case of 1,3-diketone [11]-[12] the treatment of these compounds by a peracid led to complex reaction mixtures where α-hydroxylation [13], cleavage of both acyl groups [14] and molecular rearrangement [15] can occur.

Here, we report that spirocyclic 1,3-diketones of type **A** [16] and spirocyclic ketolactones of type **B** can be oxidized regioselectively and with high diastereoselectivity with *m*-chloroperbenzoic acid (*m*-cpba) to produce the corresponding spirocyclic bislactone **C** as the major compound . The results are summarized in the Table.

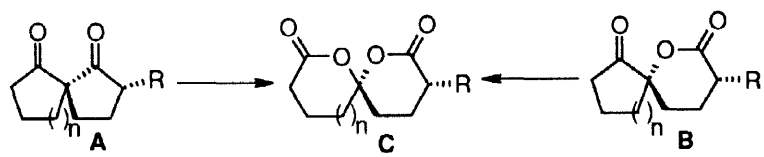

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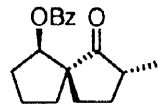
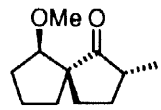
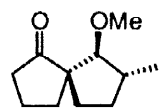
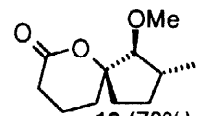
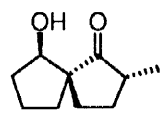
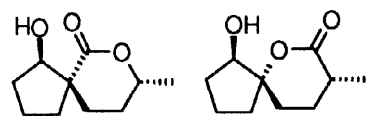
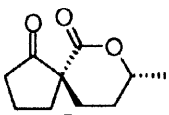
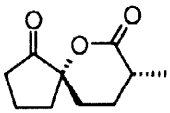
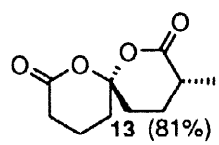
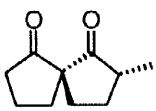
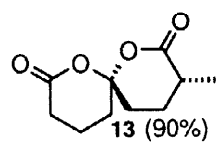
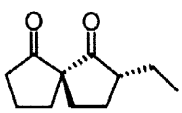
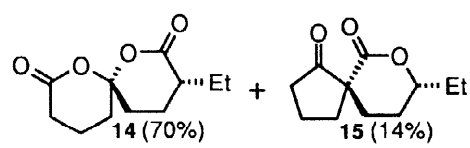
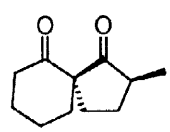
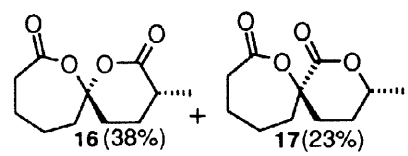
Table : Oxidation of spirocyclic compounds [16] with peracids

Starting material[1]	Solvent	Conditions	Time	Product (isolated yield %)
 **1**	CH_2Cl_2 CH_2Cl_2 CH_2Cl_2	*m*-cpba MMPP UHP	7 d 7 d 7 d	– – –
 **2**	CH_2Cl_2	*m*-cpba	7 d	–
 **3**	CH_2Cl_2	*m*-cpba	3 d	 **10** (70%)
 **4**	CH_2Cl_2	*m*-cpba	24 h	 **11** (22%) **12** (6%)
 **5**	CH_2Cl_2	*m*-cpba	24 h	–
 **6**	CH_2Cl_2	*m*-cpba	24 h	 **13** (81%)
 **7**	CH_2Cl_2	*m*-cpba	24 h	 **13** (90%)
 **8**	CH_2Cl_2	*m*-cpba	24 h	 **14** (70%) + **15** (14%)
 **9**	CH_2Cl_2	*m*-cpba	24 h	 **16** (38%) + **17** (23%)

Spirocyclic monoketones **1** and **2** refused to undergo Baeyer-Villiger oxidation with *m*-cpba, with magnesium monoperoxyphthalate (MMPP) [17]-[19] and with urea hydrogen

[1] All compounds are racemic.

peroxide (UHP) [19]-[20]. On the contrary, ketone **3** was oxidized with *m*-cpba and gave the spirocyclic lactone **10** in good yield (70%). The difference of reactivity between **1**, **2** and **3** is probably due to steric hindrance. In the case of compounds **1** and **2**, the benzyloxy or the methoxy group impedes the approach of the peracid on one face of the carbonyl group and the methyl group on the other face of the carbonyl group. In compound **3**, only one face of the carbonyl group is sterically hindered by the methoxy group and the peracid can attack on the other face. The treatment of the aldol **4** by *m*-cpba gave a 3.6:1 mixture of lactones **11** (22%) and **12** (6%). This regioselectivity of the Baeyer-Villiger reaction demonstrates that the α-hydroxy substituted alkyl group has a lower migratory aptitude than the secondary alkyl group. The fact that aldol **4** reacts with *m*-cpba and the corresponding ethers **1** and **2** do not, can be attributed to a differential steric effects or to a stabilizing effect of the peracid/ketone adduct intermediate by the free alcoholic moiety.

When spirocyclic lactone **5** was treated with *m*-cpba, no Baeyer-Villiger product was detected. On the contrary, β-diketone **7** reacted smoothly with *m*-cpba and furnished the spirocyclic bislactone **13** in good yield (90%). The reaction is highly regioselective as **13**[2] was the only spirocyclic bislactone formed (no other isomer was detected by ^{1}H NMR and ^{13}C NMR in the crude reaction mixture). Under similar conditions lactone **6**, which is an isomer of lactone **5**, provided the spirocyclic bislactone **13** in 81% yield. The regioselectivity of the reaction **6**→**13** was expected as the acyloxy substituted alkyl group is more electron rich than an alkyl group [21]-[25], it migrates faster. The absence of reaction with **5** can be attributed to the electron-withdrawing effect of the carboxylic moiety of the lactone that destabilizes the *m*-cpba-ketone adduct intermediate and therefore, retards the Baeyer-Villiger rearrangement. The Baeyer-Villiger oxidation of compound **7** led to **13** in 90% yield, showing that the carbonyl groups in **7**, contrary to the carboxyl group in **5**, does not retard the reaction.[3]

The oxidation of diketone **8** with *m*-cpba is less regioselective than the oxidation of **7** under the same conditions. In the case of **8**, the spirocyclic bislactone **14** (70%) and the monolactone **15** (14%) were isolated. The comparison of the reactivity of **7** and **8** shows that the presence of a better donating group (ethyl *versus* methyl) induced a poorer regioselectivity (100/0 *versus* 83/17). We have to point out that, as in the case of **5**, the bislactone resulting from the oxidation of **15** was not detected. The oxidation of the spirocyclic diketone **9** led to two bislactones **16** (38%) and **17** (23%) in a 1.6:1 ratio. As cyclohexanones are more reactive towards the oxidation than cyclopentanones [26], the first intermediate which is formed is

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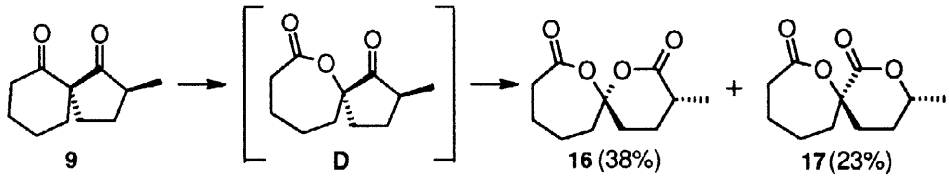
[2] IR (film): 2950, 1750, 1570 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (d, 3H, J = 7.0 Hz), 1.50-1.65 (m, 1H), 1.75-1.92 (m, 2H), 1.94-2.10 (m, 1H), 2.10-2.21 (m, 2H), 2.22-2.41 (m, 2H), 2.43-2.60 (m, 1H), 2.68-2.81 (m, 1H), 2.94 (b.sex, 1H, J = 7.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.7 (t), 16.7 (q), 23.0 (t), 28.7 (t), 31.2 (t), 32.4 (t), 32.9 (d), 105.9 (s), 168.9 (s), 173.2 (s). SM (70 eV) *m/z* 170 (M-CO, 2), 154 (M-COO, 12), 126 (44), 112 (73), 98 (22), 84 (100), 83 (90), 70 (17), 69 (15), 56 (38), 55 (46).

[3] When compound **7** was treated with 0.5 equiv. of *m*-cpba, the spirocyclic bislactone **13** was the only product formed.

probably the 7-membered ring lactone **D**. If the alkyl group can migrates as well as the acyloxy substituted alkyl group it is probably due to the fact that the acyl group of the 7-membered ring induces a steric hindrance as does the methyl group. However electronic effects seem preponderant as **16** is the major product.



We have shown that spirocyclic 1,3-diketones can be transformed to spirocyclic bislactones with good yields through Baeyer-Villiger reactions. The regioselectivity is sensitive to electronic as well as to steric factors. Spirocyclic bislactones were obtained with excellent regioselectivity and diastereoselectivity when one of the ketone of spirocyclic 1,3-diketones is α-substituted by an alkyl group.

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