Oxidative Ring Expansion of Cyclobutanols: Access to Functionalized 1,2-Dioxanes.

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**ABSTRACT:** Cyclobutanols undergo an oxidative ring expansion into 1,2-dioxanols by using Co(acac)₂ and triplet oxygen (³O₂) as radical promoters. The formation of an alkoxy radical drives to the regioselective break of the strained ring with stabilization of a new radical on the most substituted side. The radical 1,4-traps then oxygen to form 1,2-dioxanols. The reaction is particularly effective on secondary cyclobutanols but can work also on tertiary alcohols. Further acetylation generates peroxyxycarbenium species under catalytic Lewis acid conditions, which react with neutral nucleophiles. Many original 1,2-dioxanes, which would be difficult to prepare by another method, were then obtained with a preferred 3,6-cis-configuration. This method provides an interesting access to the total synthesis of many natural endoperoxides.

1,2-Dioxanes are a particular example of endoperoxides, which can be found in many natural products. They are mainly isolated from various sponges but also from other marine species, plants, and fungi. Most of natural dioxanes display anti-parasitic, antifungal, or cytotoxic activities. Although hundreds of these natural substances were reported with more or less variety in their structures, relatively few works were driven towards their total synthesis. (Figure 1).

Many of these synthetic studies were targeting natural products isolated from marine species, and more specifically marine sponges. Indeed, sponges are known to be a tremendous pool for endoperoxides, and 1,2-dioxanes represent a large part of them. Nevertheless, other natural products with a 1,2-dioxane scaffold, produced by other marine species, fungi or plants, were studied for their total synthesis. Indeed, synthetic works toward mycaperoxide B, ² 9,10-dihydro-plakortin, ³ peroxycarboxane A,² peroxycarboxane A & D, ³ gracilooether A, ⁴ dichar- noxide C, ⁵ plakortolide E, ⁶ ¹⁰ talaperoxides and other derivatives of the chamigrane family, ¹¹ isooxacarboxylics, ¹² yingzahosu A ¹³,¹⁴ & C, ¹⁵,¹⁶ and steenkrin B ¹⁷ were accomplished using different strategies to build the key 1,2-dioxane ring. ¹⁸

These last years, our group was involved in a scientific program towards the total synthesis of mycangimycin, a polyunsaturated fatty acid containing an uncommon disubstituted 1,2-dioxolane ring. ¹⁹ Our strategy was to build the endoperoxide through an oxidative ring expansion of a cyclopropanol to a 1,2-dioxolan-3-ol. ²⁰,²¹ We discovered that the corresponding acetate...
can react with various silylated nucleophiles through either Sakurai or Mukaiyama reactions, catalyzed by strong Lewis acids such as TiCl₄ or SnCl₄ in quasi-stoichiometric amounts. The process was further improved by the use of milder catalysts, such as Sc(OTf)₃ or InCl₃/TMSCl in catalytic amount, which allows to run the reactions at room temperature with an expanded reagent scope (Scheme 1).

**Scheme 1.** Oxidative ring expansion of strained cycloalkyl alcohols and further functionalization of the endoperoxycetals.

**Previous work:**

O₂

1 mol%, Mn(acac)₂ or Co(acac)₂

30-60 min, rt, THF

Conditions A: SnCl₄ or TiCl₄, 40 °C, CH₂Cl₂

Conditions B: Sc(OTf)₃ or InCl₃/TMSCl, 5 mol%, rt, CH₂Cl₂

This work:

O₂

Metal salt

1) A₂O₃, Yb(OTf)₃

2) Conditions A or B

Conditions: Sc(OTf)₃ or InCl₃/TMSCl, 5 mol%, rt, CH₂Cl₂

On the basis of this work, we were wondering if we could apply this strategy to the synthesis of functionalized 1,2-dioxanes. Indeed, Dussault earlier reported the nucleophilic substitution on 6-membered endoperoxycetal rings on 1,2-dioxene derivatives in some pioneering studies. In contrast, oxidative ring expansion of cyclobutanols under radical conditions was relatively unknown, and the difference of kinetics between cyclopropoxy and cyclobutoxy radicals, by analogy with the cyclopropymethyl radicals and cyclobutymethyl radicals, might not allow the expected transformation in our favor. Nevertheless, a few examples of ring opening of cyclobutoxy radicals were reported in the literature, driving to the formation of 1,4-diketones under oxidative conditions, or to 4-substituted ketone derivatives when the radical is trapped with some good radical acceptors. It is also important to note that during the total synthesis of gracilone A, the last key step included a radical transformation of a particularly strained cyclobutane ring into a 1,2 dioxane (Scheme 1).

To study the oxidative ring expansion of cyclobutanols into 1,2-dioxolan-3-ols, the desired starting materials were first prepared. For this purpose, we found that the most general route was based on a Wittig olefination of ketones or aldehydes through a cyclopropylyl ylide. Further epoxidation with m-CPBA provided unstable spiro-epoxycyclopropanes, which were converted into cyclobutanones through a pinacol rearrangement promoted by acid catalysis. On one hand, further reduction with NaBH₄ gave cyclobutanols as a mixture of diastereoisomers. Tertiary alcohols were also synthesized, on the other hand, by addition of an organolithium or organomagnesium reagent onto cyclobutanones (Scheme 2).

**Scheme 2.** Preparation of 2-substituted cyclobutanols and 6a-e.

A first investigation of the oxidative ring expansion of cyclobutanols was conducted on cyclobutanol 5a. This substrate was particularly interesting to start the study with, as a driving force of the C-C bond cleavage would be the stabilization of the new radical into the intermediate opened product, and a benzene substituent could play perfectly this role.

**Table 1.** Screening of conditions for oxidative ring expansion of cyclobutanol 5a into 1,2-dioxane 7a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal salt</th>
<th>(mol%)</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mn(acac)₂</td>
<td>1</td>
<td>rt, 48h</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Mn(acac)₂</td>
<td>5</td>
<td>rt, 48h</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Co(acac)₂</td>
<td>1</td>
<td>rt, 24h</td>
<td>THF</td>
<td>23⁺</td>
</tr>
<tr>
<td>4</td>
<td>Co(acac)₂</td>
<td>5</td>
<td>rt, 48h</td>
<td>THF</td>
<td>84⁺</td>
</tr>
<tr>
<td>5</td>
<td>Co(acac)₂</td>
<td>5</td>
<td>rt, 48h</td>
<td>MeCN</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>Co(acac)₂</td>
<td>5</td>
<td>40 °C, 8h</td>
<td>MeCN</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>Co(acac)₂</td>
<td>100</td>
<td>rt</td>
<td>MeCN</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>Co(acac)₂</td>
<td>5</td>
<td>rt, 48h</td>
<td>MeCN</td>
<td>traces</td>
</tr>
</tbody>
</table>

*Isolated yield as a 60:40 mixture of diastereomers. Yield was overestimated due to THF peroxides byproducts contamination.

By using reported conditions for the oxidative ring expansion of cyclopropanols, it was observed that cyclobutanol 5a did not react in presence of Mn(acac)₂ (Table 1, entries 1 and 2). Gratifyingly, Co(acac)₂ proved to promote strained cycle cleavage and be able to deliver a small amount of desired product over 48 h (Table 1, entry 3). Almost full conversion was attained with more cobalt salt (Table 1, entry 4), but yield was overestimated due to a large production of THF peroxide byproducts, which contaminated the desired product. These side-products were not observed, in contrast, on the ring expansion of cyclopropanols because of the fast scission process. To overcome this problem we switched THF for MeCN, which seemed inert to oxidation and allowed the transformation to occur, providing dioxane 7a in 61% yield after 48 h (Table 1, entry 5).
Increasing the temperature to 40 °C could decrease significantly the reaction time to 8 h improving the overall process (Table 1, entry 6). Using stoichiometric amount of cobalt(II) salt did not improve significantly the kinetic of the reaction, but lowered the yield due to the appearance of some degradations (Table 1, entry 7). Co(II) salt was essential to this reaction since starting directly from a source of Co(III) proved to be unproductive (Table 1, entry 8).

Oxidative ring expansion was then applied to other cyclobutanols 5b-f and 6a-e. Secondary alcohols 5b-f are, in general, best substrates for such a transformation. Indeed, the reaction works well, with 2,2-disubstituted cyclobutanols 5b-d and 5f, affording isolated yields above 60%. Mono-substituted cyclobutanol 7e were also able to undergo an oxidative ring extension but required a longer reaction time (up to 48 h). We also observed no reaction at room temperature with this last substrates; meaning heating is a mandatory in that case. Tertiary alcohols 6a-e were also examined, and first trials were disappointing. Mono-substituted cyclobutanols 6a and 6e gave unsatisfactory results: no conversion into dioxane 8e was observed from 6e. Isolation of diketone 9a and hydroxyketone 10a in 36% and 24% yield, respectively, from cyclobutanol 6a was experienced in place of dioxanol 8a. Isolation of these two unexpected products means the reaction was probably working but compound 8a might undergo a Kornblum-DeLamare rearrangement to form 9a in one hand, because the benzyl position facilitates an elimination process. In the other hand, hydroxyketone 10a might have been produced from 1,2-dioxan 8a by homolytic cleavage of the peroxide bond, but the exact pathway is for the while unclear. In contrast, it was found that 2,2-disubstituted cyclobutanols 5b-d and 5f were better substrates for an oxidative ring expansion. However the kinetic of this process was slower compared to secondary alcohols derivatives 6b-d, affording the desired products in lower yields with sometimes recovery of unreacted starting materials. This observation was unexpected and might be attributed to steric hindrance for the formation of the cyclobutoxy radical rather than a decrease of the kinetic of the cyclobutoxy radical scission. (Scheme 3).

**Scheme 3.** Diverse attempts towards the synthesis of 1,2-dioxan-6-ols 7b-g and 8a-e.

Although similar oxidation was reported in the literature, the exact mechanism has never been determined how are formed peroxo radical species. It seems plausible that Co(II)(acac)₂ is reacting with oxygen to form a superoxocobalt(III) radical. Indeed the reaction mixture, in presence of oxygen, turns rapidly from light brown color to intense green, which is a characteristic of Co(III) ions. These species seem then able to abstract an hydrogen from an hydroxy group to produce a new alkoxyradical, which can initiate the strained ring scission with stabilization of the radical at position 4. Regioselectivity in the carbon-carbon bond cleavage is dependant of the ability of the new site to stabilize the new radical species. Therefore, this driving force explains some differences of reactivity between mono- and disubstituted cyclobutanols. A molecule of O₂ is then trapped by the radical, making a new peroxyradical, which can evolve between the opened form and the closed one. One or the other form might abstract a hydrogen from a new cyclobutanol to propagate the reaction. In this case superoxocobalt(III) radical seems to work as an initiator of the reaction rather than a catalyst (Scheme 4).

**Scheme 4.** Possible mechanism of the cyclobutanol oxidative ring-expansion.

The so obtained 1,2-dioxanols 7a-g were then acylated using Yb(OTf)₃ as a Lewis acid catalyst to produce different acetate derivatives 11a-g. Further functionalization of these compounds was initiated with different silylated nucleophiles. The catalytic version of the nucleophilic substitution using Sc(OTf)₃ was chosen for this screening for a better convenience. The reaction of acetate 11e with allylTMS drove to compound 12 as a sole cis-product in 65% yield. In contrast, reaction of acetate 11e with TMS cyanide was less selective and gave product 13 with only a cis:trans 65:35 ratio, while Mukaiyama aldol reaction with a ketene TMS-thioethylacetal furnished 1,2-dioxane 14 with a quite good diastereoselectivity. The synthesis of allyl 1,2-dioxane 15 from 11a was achieved in poor yield due to an elimination process which might take place more easily at the benzylic position, and produced many degradation products. Sakurai reaction on acetate 11b produced compounds 16 and 17 with pretty good yields. Mukaiyama reaction on acetate 11b with silyl enol ether of acetophenone gave dioxane 18 in good yield, and a vinylogous process was also possible to produce 19 from TMS-siloxyfurane as a 2:1 mixture of diasteromers. Reduction of acetal 11d with triethylsilane furnished compound 20 in moderate yield. With unsymmetrical dialkylated dioxanes 11c and 11d, the diastereoselectivity is not as good as with mono-substituted compounds, but generally a major isomer is observed such as in the synthesis of 1,2-dioxanes 21-24. Carbamyl 7f proved to be unreactive under our used Lewis acid catalysis, due to Lewis base properties of the nitrogen function (Scheme 5).

The diastereoselectivity in this nucleophilic substitution leads to the 1,4-cis diasteromer as a major product, in an analogous manner to 4-substituted tetrahydropyranyl acetals. If we consider dioxanyl acetate 11e for example, reaction with a
Lewis acid drives to the formation of peroxyxcarbenium species, which adopt a half-chair like conformation.\cite{34} This species can evolve between conformations 27-\textit{eq} and 27-\textit{ax}, depending on whether the substituent is placed in axial or equatorial position. Because alkyl substituents prefer to adopt an equatorial position, the major reactive conformer must be 27-\textit{eq}. A nucleophilic substitution takes then place preferentially to the axial position of the peroxyxcarbenium species, which lead 27-\textit{eq} to compound 28-cis. In contrast, diastereoselectivity is poorer from 6,6-disubstituted-1,2-dioxanyl acetates, although 11c gave decent selectivity's due to the bulky tert-butyl group (75:25 and 85:15 selectivity for 23 and 24, respectively). (Scheme 6).

**Scheme 5.** Functionalization of 1,2-dioxanyl acetates 11a-g.

**Scheme 6.** Rationalization of the observed selectivity towards the 1,4 \textit{cis}-diastereoisomer in the nucleophilic substitution of 1,2-dioxanyl acetates.

In conclusion, we developed a new access to 1,2-dioxanes, by using an original approach involving an oxidative ring expansion of cyclobutanols under radical conditions. The oxidation is regioselective and its kinetic seems dependant of the ability of the substituents to stabilize an intermediate alkyl radical. The process seems to work particularly well with secondary alcohols even if specific examples of tertiary alcohols can also moderately work sometimes. Further functionalization was then achieved. For instance, the corresponding acetates 11a-g, by generating reactive peroxyxcarbenium species, react with neutral nucleophiles to afford expected 1,2-dioxanes, preferentially as the 1,4-\textit{cis} diastereoisomers. This new method is able to provide quickly functionalized 1,2-dioxanes, which would be difficult to obtain by another method. Indeed, it would be very valuable for the synthesis of new endoperoxides, but in particular for the total synthesis of natural marine products containing a 1,2-dioxane moiety such as mycaperoxides, stolonoxides, dihydroxylakortides, diacarnoxide C and many others, whose structures seem to correspond to potential targets for its use.

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