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Reaction of Small-Size Cycloalkane Rings with RuO_4. Oxidative Scission of Ethyl 2,2-Dimethoxycyclopropane-1-carboxylates and Methyl 2,2,6,6-Tetramethoxybicyclo[2.2.0]hexane-1-carboxylates[1].

M. Liliana Graziano, Maria Lasalvia, Vincenzo Piccialli and Donato Sica*

Dipartimento di Chimica Organica e Biologica, Università degli Studi di Napoli "Federico II", Via Mezzocannone 16, 80134 Napoli, Italy.

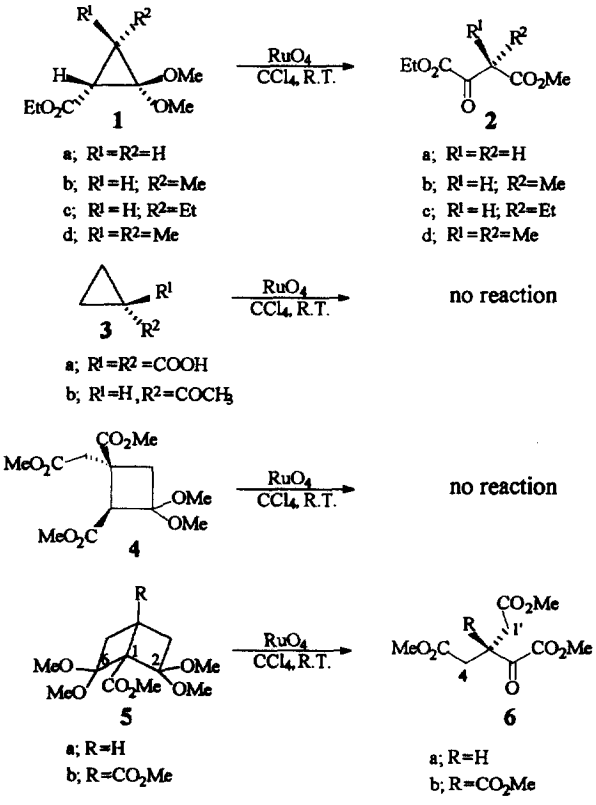
Abstract. The reaction of ethyl 2,2-dimethoxycyclopropane-1-carboxylates **1a-d** and methyl 2,2,6,6-tetramethoxybicyclo[2.2.0]hexane-1-carboxylates **5a** and **5b** with RuO_4 in CCl_4 at room temperature leads in both cases to the oxidative ring opening by regioselective scission of the electron-rich C1-C2 bond for **1a-d**, and both C1-C2 and C1-C6 bonds for **5a** and **5b**. Methyl ethyl oxobutanedioates **2a-d** were obtained in the first case while the 3-substituted ethyl methyl 2-oxopentanedioates **6a** and **6b** in the second one. In the same reaction conditions, cyclopropanes substituted with electron withdrawing groups, namely cyclopropyl methyl ketone (**3a**) and cyclopropane-1,1-dicarboxylic acid (**3b**) are unreactive; methyl 2,2-dimethoxycyclobutane-1-carboxylate **4** is unreactive as well.

As a continuation of our studies on the RuO_4 oxidation of organic substrates[2-6] we have now undertaken an investigation of the reactivity of small-size cycloalkane rings towards this oxidising agent. Our study started from the simple consideration that since the cyclopropane ring shows "double bond character" and does give a number of reactions characteristic of alkenes like additions of strong acids and halogens, catalytic hydrogenation and cycloadditions[7,8], it could also be prone to be oxidatively cleaved by ruthenium tetroxide, a reagent that readily reacts with the carbon-carbon double bond either by causing its cleavage[9-11] or, as we have recently observed, by adding oxygen to it producing α-ketols, 1,2-diols or epoxides[2-6].

Therefore, in searching for suitable cyclopropane derivatives which could be subjected to the RuO_4 oxidation, our attention was at first attracted by some electron-rich ethyl 2,2-dimethoxycyclopropane-1-carboxylates, namely compounds **1a-d**. These compounds seemed to be good candidate for our purposes because, as has recently been shown by one of us, they are reactive in a number of cycloaddition reactions[12]; on the other hand, by analogy with the analogous reaction of OsO_4, the first stage of the reaction scission of alkenes with RuO_4, that is the formation of the ruthenate ester, can be considered itself a cycloaddition reaction[11]. Indeed, when compounds **1a-d** were reacted with RuO_4 in carbon tetrachloride at room temperature the three-membered ring underwent oxidative scission at the C_1-C_2, electron-rich, σ bond.

In particular, oxidation of compound **1b** gave the methyl substituted methyl ethyl oxobutanedioate **2b** in 36% yield along with a 56% of a hydrolysis product, namely ethyl methyl methylbutanedioate[13]. The high percentage of the latter compound is ascribable to the very high sensitivity of compound **1b** to water and to the fact that the oxidant is generated in the biphasic system CCl_4-H_2O and then recovered in the organic layer. The reaction was performed as follows. $RuO_2 \cdot 2H_2O$ (350 mg, 2.1 mmol) and a six molar excess of $NaIO_4$ (2.69 g) were vigorously stirred in CCl_4-H_2O (18:18 mL) until all the black dioxide converted into the yellow RuO_4. The organic, RuO_4-containing, solution was separated, dried over $MgSO_4$ and filtered into a flask to which was immediately added, in one portion, freshly distilled **1b** (130 mg, 0.69 mmol) prepared as previously described[13]. The reaction was very rapid as evidenced by the instantaneous darkening of the solution, due to the precipitation of RuO_2, and by TLC and NMR analyses of the reaction mixture, performed just after the addition of the substrate to RuO_4, which revealed the complete disappearance of the starting product. The reaction was quenched by the addition of a few drops of isopropyl alcohol and the suspension was centrifuged. The supernatant was recovered and the black solid was washed three times with acetone. The combined organic phases were carefully taken to dryness giving 110 mg of a smelling volatile oil which was separated by HPLC on a Hibar LiChrosorb Si-60 (250 x 10 mm) column using hexane-EtOAc (87:13) to yield 34 mg (38%) of **2b**[14] and 63 mg (56%) of the hydrolysis product. ^{1}H-NMR analysis indicated that a 25% amount of the β-ketoester **2b** was present in the enol form[14].

Reaction of **1a**, **1c** and **1d** with RuO_4 was performed as for **1b**. However, when compound **1d** was oxidised, desiccation of the ruthenium tetroxide-containing organic phase was unnecessary and the reaction was very slow requiring 48h to go to completion possibly due to the higher steric hindrance to the attack of RuO_4 caused by the presence of two methyl groups at C-3. In this case, the oxidation product **2d**[14] was obtained in 60% yield. Compound **1c** linking an ethyl group at C-3 proved to be only slightly more resistant to the hydrolysis than **1b** and its oxidation gave a 49% of **2c**[14] accompanied by a 40% of the hydrolysis product ethyl methyl ethylbutanedioate[13]. Compound **1a** proved to be exceedingly sensitive to water and acceptable amounts of the oxidation product **2a**[14] could be obtained only after two successive desiccation steps of the oxidant organic phase over $CaSO_4$. ^{1}H-NMR analysis of the crude reaction material revealed it to be composed of an approximately 1:1 mixture of compound **2a** and ethyl methyl butanedioate[13], the hydrolysis product. However, when the reaction mixture was worked-up in the usual manner, only a poor yield in the recovered material was obtained. ^{1}H-NMR analysis of this mixture showed a very different ratio of the aforementioned products which indicated a consistent loss of **2a** possibly due to its volatility. Thus, in this case the yield cannot be given for the isolated **2a**. The structural identity of **2a** was proven by the existence of two singlet signals at δ 3.80 and 3.76 (relative areas in the approximate ratio of 3:2), attributable to the ester methoxy group and H_2-3 protons, in the proton spectrum of the crude reaction mixture. Furthermore, the absence in the same spectrum of the olefin enol proton signal, which was expected to resonate at about 6 ppm[15], indicated that compound **2a** was all present in the keto form. Further evidence for structure **2a** was gained by comparison of the above ^{1}H-NMR data with those exhibited by a synthetic sample of diethyl oxobutanedioate.



1

a; $R^1=R^2=H$
b; $R^1=H$; $R^2=Me$
c; $R^1=H$; $R^2=Et$
d; $R^1=R^2=Me$

2

a; $R^1=R^2=H$
b; $R^1=H$; $R^2=Me$
c; $R^1=H$; $R^2=Et$
d; $R^1=R^2=Me$

3

a; $R^1=R^2=COOH$
b; $R^1=H, R^2=COCH_3$

4

5

a; R=H
b; $R=CO_2Me$

6

a; R=H
b; $R=CO_2Me$

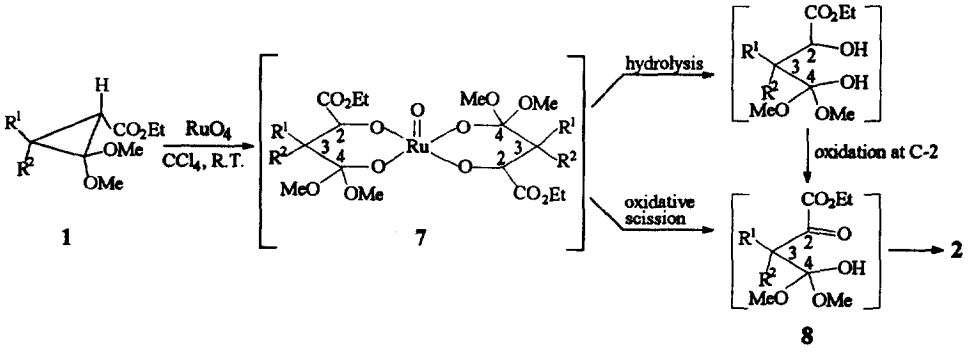
Having ascertained that the above electron-rich cyclopropanes **1a-d** are cleaved by RuO_4, we tested the chemical reactivity of two cyclopropanes substituted with electron withdrawing groups, namely cyclopropane-1,1-dicarboxylic acid (**3a**) and cyclopropyl methyl ketone (**3b**), in the conditions used for the scission of compounds **1a-d**. Interestingly, compounds **3a** and **3b** were recovered unreacted also on prolonged treatment (4 days) indicating that RuO_4 preferably attacks electron-rich cyclopropane σ bonds.

At this stage we decided to test whether also electron-rich cyclobutane rings could be cleaved with RuO_4. An easily accessible substrate of this kind was compound **4**, the hydrolysis product of **5b**, a bicyclo system recently

synthesised by one of us[16], whose substitution pattern at the C-1 and C-2 carbons is the same as that exhibited by compounds **1a-d**. However, this compound when subjected to the RuO_4 oxidation in the above conditions proved to be unreactive. On the other hand, the two bicyclo[2.2.0]hexane derivatives **5a** and **5b**, once again carrying the same substituents at the C-1/C-2 or C-1/C-6 couple of carbons as that of compounds **1a-d** and **4**, were cleaved at both the C_1-C_2 and C_1-C_6 σ bonds affording the 3-substituted ethyl methyl 2-oxopentanedioates **6a** and **6b** in 81% and 82% yields, respectively.

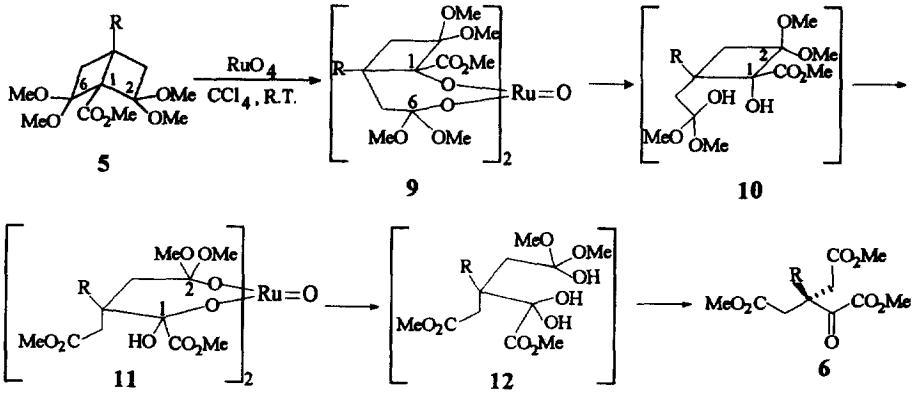
From a mechanistic point of view, it seems reasonable to suppose that the RuO_4 oxidation of compounds **1a-d**, **5a** and **5b** could involve the formation of a ruthenate ester of the type involved in the reaction of α-pinene[6] or 7-dehydrocholesteryl acetate[4] with this oxidant. For analogy with the RuO_4 oxidation of carbon-carbon double bounds, it can be hypothesised that the ruthenate ester intermediate for the oxidation of the cyclopropanes **1a-d** could have the dimeric structure **7** formed by the cycloaddition of RuO_4 to the electron-rich C_1-C_2 bond of two cyclopropane units (Scheme 1). The oxidative scission of esters **7**, or their hydrolytic scission followed by oxidation at C-2, would lead, as happens for the analogous reaction of RuO_4 with alkenes, which are converted into α-ketols[2,3] to the β-hydroxyketones **8**, that successively convert into alkyl substituted methyl ethyl oxobutanedioates **2**.

Scheme 1



The extension of the above mechanistic hypothesis to the oxidation of compounds **5a** and **5b** could explain the oxidative scission of the bicyclo[2.2.0]hexane system as depicted in the Scheme 2. Possibly, in this case the strain of the bicyclo system play an important role in the scission reaction of the first attacked cyclobutane ring. Thus, the attack of RuO_4 at either of the two C_1-C_2 or C_1-C_6 bonds, for example at the C_1-C_6 one, would generate the ruthenate ester **9** whose opening would afford the dihydroxycompound **10**, analogous to the 1,2-diol obtained in the oxidation of an alkene[2,3]. Because of the presence of a newly generated OH group at C-1, the C_1-C_2 bond of this intermediate is likely enough electron-rich to underwent the attack of a second RuO_4 molecule with formation once again of a ruthenate ester (**11**) the opening of which would give the *gem*-diol **12** that successively evolve to the α-ketoester **6**.

Scheme 2



To the best of our knowledge this is the first report on the oxidative scission of cyclopropane compounds with RuO_4.

Acknowledgements. This research was supported by grants of MURST and CNR (M. L. Graziano). Throughout the NMR work the facilities of the "Centro di Metodologie Chimico-Fisiche dell'Università degli Studi di Napoli" were used.

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14. **2a**: ^{1}H-NMR ($CDCl_3$, 270 MHz) (data from the crude reaction mixture) δ 3.79 (s, OCH_3), 3.76 (s, H_2-3). **2b**: FTIR (film) ν_{max} 1757, 1732, 1661 (enol form), 1635 (enol form) and 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 12.00 (enol OH); 4.36 (q, J=7.0 Hz, methylene protons of the ethoxyl group), 4.13 (q, J=7.4 Hz ,H-3), 3.86 (s, enol OCH_3), 3.75 (s, OCH_3), 2.01 (s, vinyl methyl of the enol form), 1.44 (d, J=7.3 Hz, 3-CH_3), 1.38 (t, J=7.0 Hz, methyl protons of the ethoxy group); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ 189.56, 170.20, 160.44, 62.76, 52.55, 48.38, 13.91,11.81. **2c** FTIR (film) ν_{max} 1760, 1733, 1663 (enol form) and 1247 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 12.36 (enol OH), 4.33 (q, J=7.6 Hz, methylene protons of the ethoxy group), 3.94 (t, J=6.9 Hz, H-3), 3.84 (s, enol OCH_3), 3.70 (s, OCH_3), 2.41 (q, J=7.7 Hz, methylene protons of the 3-Et of the enol form), 1.95 (quintet, J=6.8 Hz, methylene protons of the 3-Et), 1.36 (t, J=6.9 Hz, methyl protons of the ethoxy group for both the keto and the enol form), 1.05 (t, J=7.7 Hz, methyl protons of the 3-Et of the enol form), 0.97 (t, J=7.6 Hz, methyl protons of the 3-Et); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ 189.04, 169.46, 160.41, 62.82, 55.36, 52.47, 20.74, 13.92, 11.69. **2d**: FTIR (film) ν_{max} 1759,1733, and 1261 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 4.30 (2H, q, J=7.3 Hz, methylene protons of the ethoxy group), 3.69 (3H, s, OCH_3), 1.43 (6H, s, 3-Me's), 1.34 (3H, t, J=7.3 Hz, methyl protons of the ethoxy group); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ 191.64, 163.04, 160.04, 62.56, 52.56, 52.44, 21.81, 21.81, 13.90; **6a**: FTIR (film) ν_{max} 1736 cm^{-1}(broad); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 3.96 (1H, m, H-3), 3.88 (3H, s, OCH_3), 3.63 (6H, 2xOCH_3), 2.78 (2H, A part of an AB system further coupled centred at d 2.69, J= 16.7 and 8.4 Hz, H_a-4 and H_a-1'), 2.60 (2H, B part of an AB system further coupled centred at d 2.69, J= 16.7 and 6.0 Hz, H_b-4 and H_b-1'); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ 193.92, 171.41, 160.65, 53.01, 52.03 39.05, 35.45. **6b**: FTIR (film) ν_{max} 1735 cm^{-1} (broad); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 3.85, 3.74 (3H each, OCH_3's), 3.65 (6H, 2xOCH_3), 3.19 (2H, AB system, J_{AB}= 15.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.9 MHz) δ 186.91, 170.76, 169.41, 160.16, 56.43, 53.26, 53.19, 52.21, 38.47.
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