Short Communication:

Cerium(IV)oxidations, Part IX[1]:

Cyclization of Diethyl 4-Phenylbutane-1,1-dicarboxylate

Cer(IV)-Oxidationen, 9. Mitt.: Zyklisierung von 4-Phenyl-butylmalonsäure-diethylester

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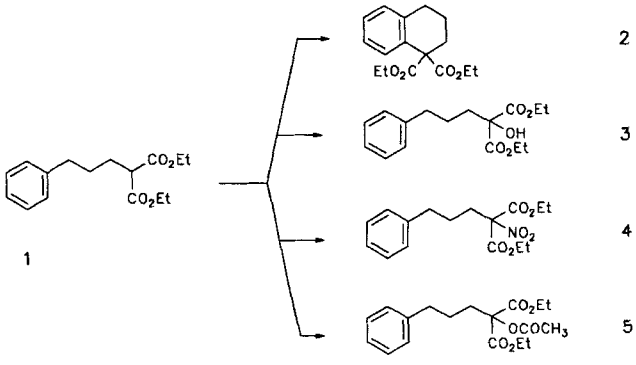
The oxidative cyclization of *N*-benzyl-β-aminoketones using cerium(IV)sulphate is a valuable method for the synthesis of various substituted 1,2,3,4-tetrahydroisoquinolines[2-4]. Investigations of the reaction mechanism showed the formation of an oxoalkyl radical in the first step followed by a radical aromatic substitution. In order to gain more insight into the mechanism of the oxidative cyclization we extended our investigations to nitrogen-free systems such as diethyl 4-phenylbutane-1,1-dicarboxylate (**1**).

Methyl acetoacetate and acetylacetone[6] give ESR signals characteristic of the corresponding oxoalkyl radicals R-$\dot{C}$(Cs=O)$_2$ (measured in a flow cell in sulfuric acid in the presence of cerium(IV)sulphate, g_0 = 2.0156 and 2.0052, respectively). Therefore, it is probable that the phenylbutane dicarboxylate **1** will also form an oxoalkyl radical which is able to attack the phenyl ring forming a tetrahydronaphthalene derivative. Due to the poor solubility of **1** in sulfuric acid the reaction was performed in glacial acetic acid using cerium ammonium nitrate (CAN).

First oxidations of diethyl 4-phenylbutane-1,1-dicarboxylate (**1**) were carried out in glacial acetic acid containing 0.3% water at 80°C and a molar ratio of substrate/CAN = 1:2. The reaction was terminated after 3 h by addition of water. Four derivatives could be isolated from the reaction by means of column chromatography, and the structures were elucidated by ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic data: The expected cyclization product **2**, a nitro derivative **4**, and an alcohol **3** as well as the corresponding acetate **5** (Scheme 1). In contrast to other CAN-oxidations of comparable compounds, *e.g.* esters of 5-aryl-3-oxopentanoic acids[7], no nitrate derivative was obtained.

The structure of the nitro product **4** has been assigned by means of EI-MS and IR-spectra: The loss of 46 mu observed in EI-MS results from a loss of NO_2 proved by high resolution measurement of this peak. No loss of NO was observed. These data exclude a R-O-N=O structure whose formation is also likely during the reaction. A further hint for the R-NO_2 structural element is the IR-absorption at 1570 cm^{-1}.



Scheme 1: Oxidation of diethyl 4-phenylbutane-1,1-dicarboxylate (**1**)

To find out the reason for the formation of the different products, the reaction was carried out in presence of various amounts of water and at different temp.. The distribution of products was analysed by the means of gas chromatography. In almost non-aqueous systems (less than 0.015% water, determined by *Karl-Fischer* titrations) the formation of mainly the nitro- and alcohol-derivatives was observed, only a small amount of the cyclic product **2** could be detected. The yield of **2** increased significantly upon increasing the water content. It should be stressed that even in the presence of 0.05% water, the amount of cyclization product surpassed the others. Beyond 3% water the relative amounts of the products remained constant (Fig. 1). Increasing temp. (between 20°C and 80°C, 0.3% of water) also influenced the distribution of products. Over a small temp. range close to 60°C the ratio of nitro- **4** and cyclization-derivative **2** changed completely: whereas the nitro-derivative was predominant at lower temp., the tetrahydronaphthalene derivative **2** was formed beyond this limiting value in 70% yield. The amount of the alcohol **3** was more or less constant throughout the whole temp. range (Fig. 2). Further variation of the reaction temp. with different contents of water led to lower temp. for the inversion of the cyclo/nitro ratio (Table 1). In the case of high temp. and non-aqueous solvent, no cyclic derivative **2** could be obtained and only the alcohol,

nitro- and acetate-derivatives **3-5** were isolated. In conclusion, both parameters, the amount of water and the temp., control the reaction. The content of water was the main influence: high content of water led to the cyclic product **2**, whereas low content of water (less than 0.05%) led to an excess of nitro-**4**, alcohol-**3**, and acetate-**5** derivatives almost regardless to reaction temp.

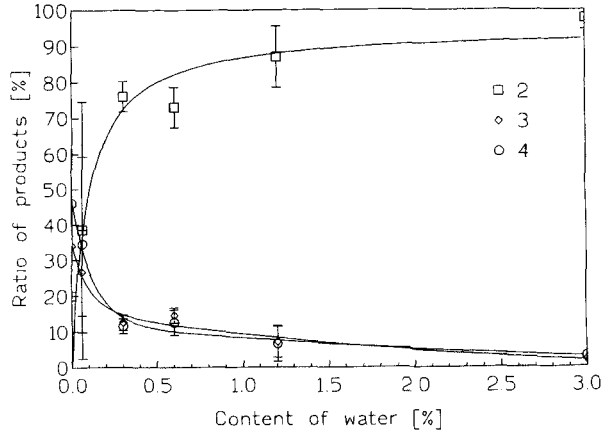


Fig. 1: Water concentrations *versus* product distribution based on at least three experiments. Error bars represent standard deviations.

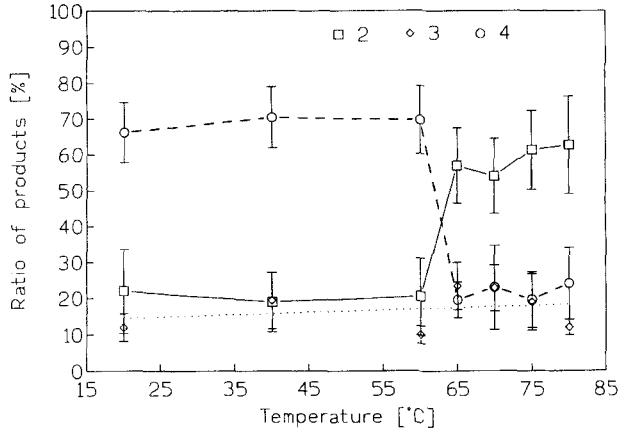


Fig. 2: Relationship between reaction temp. and product distribution average of at least four experiments; 0.3% water, 180 min. Error bars represent standard deviation.

Table 1: Ratio of products dependent on temp. and content of water

Temperature	Content of water	Ratio of products (%)*				
(°C)	(%)	1	2	3	4	5
40	0.3	0	9	13	78	0
40	3	20	75	2.5	2.5	0
90	0.3	0	64	20	16	0
90	0.017	0	0	19	60	21

* Average of at least three experiments. Error ± 10%

These results gave rise to the questions whether water is involved in the formation of some of the products as described by *Martin* for similar reactions[8] and how each product was formed during the reaction. The cyclic derivative is likely to be a product of the above mentioned radical mechanism. Therefore, its formation cannot be influenced by the polarity of the reaction solvent, and in particular by water[9]. The ratio of products gained with high amounts of water demonstrates that water suppresses the formation of the nitro- and alcohol-derivative. This is an indication for a non-radical mechanism. From this the question arose whether a cerium(IV) or cerium(III)salt is necessary for the formation the derivatives **3-5**. Therefore, analogous reactions of cerium(III) ammonium nitrate (synthesized according to[10]) with **1** were carried out. They gave the nitro- and alcohol-derivative **3** and **4** and no cyclic product. Again this reaction is influenced by water: Increasing amounts of water (about 5%) suppress the reaction completely and no conversion of the 4-phenylbutane-1,1-dicarboxylate **1** was observed. Additional experiments have shown that the nitro- and alcohol-derivatives were not formed from **1** in the presence of a mixture of glacial acetic acid/nitric acid without any cerium salts.

From these results the conclusion can be drawn that the cyclization product is formed by a radical pathway (compare with the results of the oxidation of **1** with manganese(III) acetate[11,12]) whereas the nitro- and alcohol-derivatives are produced by a cerium(III) catalysed reaction. Thus, an oxidative mechanism is unlikely in these case. The acetate is possibly a subsequent product of the alcohol. These preliminary results have to be proved by further variations of β-dicarbonyl derivatives. They will give more informations about the mechanism of the formations of the by-products.

Experimental Part

NMR spectra: Varian XL 300 spectrometer at 299.956 MHz; Bruker AM 400 spectrometer at 400 MHz. - IR spectra: Perkin-Elmer Model 298 spectrometer. - Mass spectra: Kratos MS 50 spectrometer. - GC analyses: Packard 428 gas chromatograph equipped with a 2 m x 0.2 mm glass column (*SE-30, silicon gum-rubber, 3.8% at Chromosorb W-AW DMCS 80 - 100 mesh*). - *Karl-Fischer* titrations: Metrohm KF-Titrator E 551. - CAN (99%, Merck) was used without further purification. - Acetic acid (Riedel deHaen) was dried by adding 15 g P_2O_5 (Fluka) to 150 g acetic acid. After 12 h the acid was distilled at 118°C. - Column chromatography: silica gel 60, 70 - 230 mesh (Merck).

Diethyl 4-phenylbutane-1,1-dicarboxylate (**1**) was synthesized using a standard procedure[13].

Oxidation procedure

CAN (0.36 g, 0.66 mMol) was dissolved in glacial acetic acid (20 mL). The temp. was raised to 80°C. The mixture was flushed with dry N_2 during the reaction to obtain an O_2-free medium. After 1 h the required temp. was adjusted and **1** (0.33 mMol) was added. After stirring for 3 h 20 mL water were added. The mixture was extracted three times with 20 mL CH_2Cl_2. The org. layers were washed with $NaHCO_3$ solution (50 mL) and water (3

x 50 mL). After drying the org. layer over $MgSO_4$ the solvent was removed and a crude, light yellow oil was obtained. Products were isolated cc by (CH_2Cl_2/hexane = 70:30).

Measurement of product distribution

To observe the reaction process at 15, 30, 60, 120, and 180 min samples of 1 mL were taken and added to water (10 mL). After work-up (see above) the org. solvent was removed and the crude product was dissolved in diethyl ether (1 mL). The product distribution was measured by gc. External standard calibration enables identification and quantification of the products.

Diethyl-4-phenylbutane-1-dicarboxylate (**1**)[14]

Oil. - $C_{16}H_{22}O_4$ (278.2). - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.25 (t; 6H, J = 7 Hz, 2x CH_2-C<u>H</u>$_3$), 1.66 (m; 2H, CH_2), 1.95 (m; 2H, CH_2), 2.65 (t; J = 7 Hz, 2H, CH_2), 3.35 (t, J = 7 Hz, 1H, CH), 4.2 (q, 4H, J = 7 Hz, 2x C<u>H</u>$_2$-CH_3), 7.15-7.29 (m, 5H aromat.). - IR (film): 2920, 1750, 1600, 1200, 1450, 850, 750, 700 cm^{-1}. - MS (70 eV, m/z): 278 ($M^{+\bullet}$, 25%), 232 (26), 173 (66), 158 (83), 104 (100).

Diethyl tetralin-1,1-dicarboxylate (**2**)[15]

m.p. 57°C. - $C_{16}H_{20}O_4$ (276.2). - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.27 (t; 6H, J = 7 Hz, 2x CH_2-C<u>H</u>$_3$), 1.85 (m; 2H, CH_2), 2.43 (m; 2H, CH_2), 2.83 (t; J = 7 Hz, 2H, CH_2), 4.23 (q; 4H, J = 7 Hz, 2x C<u>H</u>$_2$-CH_3), 7.1-7.4 (m; 4H aromat.). - IR (KBr): 2920, 1730, 1440, 1240, 750 cm^{-1}. - MS (70 eV, m/z): 276 ($M^{+\bullet}$, 29%), 202 (66), 129 (100).

Diethyl 1-hydroxy-4-phenylbutane-1,1-dicarboxylate (**3**)[15]

Oil. - $C_{16}H_{22}O_5$ (294.2). - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.27 (t; 6H, J = 7 Hz, 2x CH_2-C<u>H</u>$_3$), 1.66 (m; 2H, CH_2), 2.65 (t; J = 7 Hz, 2H, CH_2), 3.75 (s; 1H, OH), 4.24 (q; J = 7 Hz, 4H, C<u>H</u>$_2$-CH_3), 7.15-7.31 (m; 5H aromat.). - IR (film): 3500, 2980, 1740, 1450, 1220, 1040, 860, 750, 700 cm^{-1}. - MS (70 eV, m/z): 294 ($M^{+\bullet}$, 30%), 248 (32), 202 (56), 178 (45), 147 (63), 129 (65), 104 (100).

Diethyl 1-nitro-4-phenylbutane-1,1-dicarboxylate (**4**)

Oil. - $C_{16}H_{21}NO_6$ (323.3). - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.3 (t; 6H, J = 7 Hz, 2x CH_2-C<u>H</u>$_3$), 1.9 (m; 2H, CH_2), 2.42 (m; 2H, CH_2), 2.96 (t; J = 7 Hz, 2H, CH), 4.33 (q; 4H, J = 7 Hz, 2x C<u>H</u>$_2$-CH_3), 7.15-7.33 (m; 5H aromat.). - IR (KBr): 2980, 1760, 1660, 1570, 1450, 1260, 860, 750, 700 cm^{-1}. - MS (CI-methan, HR, m/z): 324.1471 ≡ $C_{16}H_{22}NO_6$ [(M+1)$^+$, 62%], 278.1534 ≡ $C_{16}H_{22}O_4$ [(M-NO_2) 100], 173 (11).

Diethyl 1-acetoxy-4-phenylbutane-1,1-dicarboxylate (**5**)[15]

Oil. - $C_{18}H_{24}O_6$ (336.4). - MS (70 eV, m/z): 336 ($M^{+\bullet}$; 5%), 294 (12), 184 (19), 129 (27), 104 (100), 43 (90). This compound could not be isolated from the oxidation reaction, but a GC-MS was obtained from the reaction mixture. For complete identification **5** was synthesized by reaction of **3** with 4-diethylaminopyridine/acetic anhydride in dry CH_2Cl_2 [16]. Mass spectra of the synthesized and the found compound were identical. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.25 (t; J = 7 Hz, 6H, 2x CH_2-C<u>H</u>$_3$), 1.68 (m; 2H, CH_2), 2.15 (s; 1H, CH_3-CO), 2.22 (m; 2H, CH_2), 2.63 (t; J = 7 Hz, 2H, CH_2), 4.22 (q, J = 7 Hz, 4H, 2x C<u>H</u>$_2$-CH_3), 7.15-7.34 (m, 5H aromat.). - IR (film): 2920, 1750, 1450, 1370, 1260, 1100, 1020, 800, 750, 700 cm^{-1}.

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