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OXIDATIVE RING CONTRACTION OF CYCLOALKANONES: A FACILE METHOD FOR SYNTHESIS OF MEDIUM RING CYCLOALKANECARBOXYLIC ACIDS

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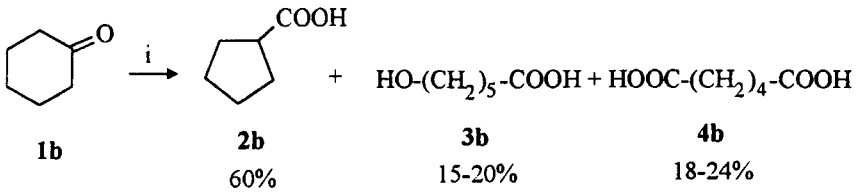
Abstract: Cycloalkanones (**1**) oxidized with 30% hydrogen peroxide in the presence of poly(bisanthracenyl) diselenide (**5b**) as catalyst, produce cycloalkanecarboxylic acids (**2**) having one carbon atom less in the ring that the substrate. Although preparative yield of acids **2** does not exceed 60% the reaction can be applied as a simple way for synthesis of cycloalkanecarboxylic acids with five to seven-membered ring.

The cycloalkanecarboxylic acids, particularly cyclopentane and cyclohexanecarboxylic acid, are important group of compounds used as intermediates in industrial organic chemistry and for synthesis of the natural products, their analogs and drugs.[1-3] Despite of several methods applied for their synthesis, the problem is still open.[4,5] One of the simplest procedures is based on the oxidation of easily available cycloalkanones (mainly cyclohexanone) with hydrogen peroxide in the presence of selenium (IV) oxide as catalyst[3,6,7]. This approach is attractive because most of the starting cycloalkanones (**1**) are several times cheaper than cycloalkanecar-

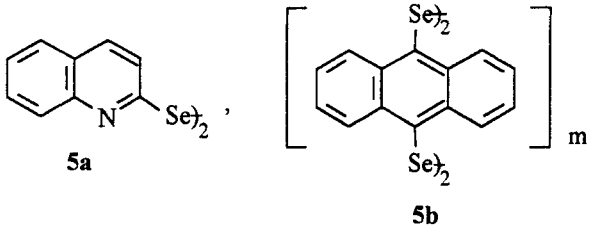
boxylic acids (**2**) and the oxidant is also cheap and environmentally friendly.[8] Unfortunately, formation of cycloalkanecarboxylic acids competes with the Baeyer-Villiger rearrangement of cycloalkanones and subsequent hydrolysis of lactones formed to hydroxy acids or their oxidation to dicarboxylic acids take place. In effect, this complex process leads to desired cycloalkanecarboxylic acids in the yields not exceeding 37% (for cyclopentanecarboxylic acid).

The main goal of the work presented here was to make the reaction more selective and efficient by using hydrogen peroxide in the presence of organoselenium catalyst instead of selenium (IV) oxide. This approach was based on the known fact that aryl diselenides are oxidized with hydrogen peroxide to arenepe-roxyseleninic acids, being highly active oxygen donors[9]. It corresponds to our earlier works on chemoselective oxidation of different classes of organic compounds, such as sulfides, aromatic aldehydes and ketones, and their azomethine derivatives.[10-12]

In this work we have found that oxidation of cyclohexanone (**1b**) with 30% hydrogen peroxide in tert-butanol in the presence of different selenium catalysts (listed in Experimental) leads to the mixture of products containing cyclopentanecarboxylic acid (**2b**), 5-hydroxypentanecarboxylic acid (**3b**) and adipic acid (**4b**) (Scheme). The highest preparative yield of desired **2b** (60%) was achieved when bis(2-quinolyl) diselenide (**5a**) or poly(bisanthracenyl) diselenide (**5b**) was used as catalyst, while acids **3b** and **4b** wery only the minor products. It also was found that although catalytical effectivness of **5a** and **5b** was similar, diselenide **5b** was more stable under the reaction conditions and no deposition of elemental selenium was observed when reaction was prolonged for several days.



i = 30% H_2O_2, cat. (**5a** or **5b**), t-BuOH, 65°C, 3.5 h



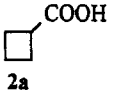
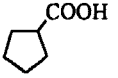
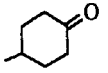
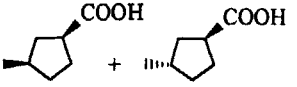
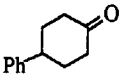
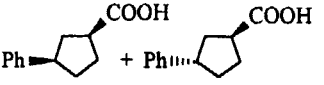
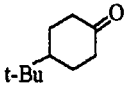
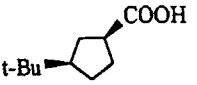
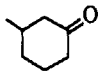
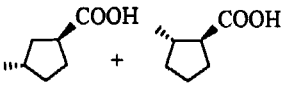
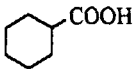
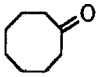
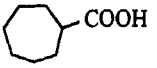
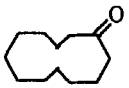
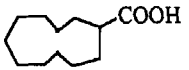
5a **5b**

Scheme

Poly(bisanthracenyl) diselenide (**5b**) was also applied for hydrogen peroxide oxidation of other cycloalkanones, such as cyclopentanone (**1a**), substituted cyclohexanones (**1c-1f**), cycloheptanone (**1g**), cyclooctanone (**1h**) and cyclododecanone (**1i**). In all cases cycloalkanecarboxylic acids (**2a-2i**) were produced and isolated in 10-60% yield (Table). Taking into consideration that cycloalkanones used as the substrates are cheap and easily available, the elaborated method for their conversion into cycloalkanecarboxylic acids seems to be useful, particularly for the acids having five-, six- and seven-membered ring.

When cyclohexanones having bulky substituent in 4-position such as **1e** was oxidized, 3-substituted cyclopentanecarboxylic acid (**2e**) with *cis* configuration was formed exclusively. 4-Methylcyclohexanone (**1c**) and 4-phenylcyclohexanone

Table. Hydrogen peroxide oxidation of cycloalkanones (1) to cycloalkanecarboxylic acids (2) catalysed by diselenide **5b**

Substrate	Reactions time	Cycloalkanecarboxylic acid	Yield, %
 **1a**	5h	 **2a**	15
 **1b**	5h	 **2b**	60
 **1c**	22h	 **cis-2c** 3 : 1 **trans-2c**	46
 **1d**	3 days	 **cis-2d** 10 : 1 **trans-2d**	47
 **1e**	36h	 **cis-2e**	40
 **1f**	15h	 **2fa** 2 : 1 **2fb**	40
 **1g**	3 days	 **2g**	50
 **1h**	3 days	 **2h**	36
 **1i**	20 days (4 days)[15]	 **2i**	10 (50)[5]

(**1d**) produced both isomeric **2c** and **2d,** nevertheless isomers *cis* were the major products. Under the similar reaction conditions, 3-methylcyclohexanone (**1f**) gave 3-methylcyclopentanecarboxylic acid (**2fa**) and 2-methylcyclopentanecarboxylic acid (**2fb**), both of them having *trans* configuration. These results correspond to the regio- and stereoselectivity of the thallium(III) oxidation of substituted cyclohexanones.[5] It suggests that the mechanism of the oxidative ring contraction of cycloalkanones with hydrogen peroxide in the presence of diselenides is similar to the mechanism of their thallium(III) oxidation.[2,5,13,14]

EXPERIMENTAL

Melting points were determined with a Digital Melting Point Apparatus Electrothermal IA 9100. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker DRX 300 spectrometer: ^{1}H-NMR 300 Mhz; ^{13}C 75 MHZ, coupling constants (J) in Hz. The reaction products presented in Table were analysed using Hewlett-Packard 5890 apparatus with capillary column HP-1 (25 m, 0.2 mm) 120/6/280 °C.

Cycloalkanones (Aldrich, Fluka) of purity above 97 % were used without additional purification. The diselenides tested as catalysts, such as: 2-pyridyl, 6-methyl-2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl (**5a**), 2-pyrimidynyl, 5-pyrimidinyl, 2- and 4-nitrophenyl, 2,4-dinitrophenyl, 2-(N-benzoylamino)phenyl, 2-(N-benzenesulfonylamino)phenyl, 2,2-(N-methylamino)phenyl and pentafluorophenyl were synthesized according to the ref.[16-20]

Other diselenides: 2,6-dichlorophenyl, 3,5-dichloro-2-pyridyl, 3-nitro-2-pyridyl, 2-nitro-4-(trifluoromethyl)phenyl, 4-chloro-2-nitrophenyl, trifluoromethylphenyl,

2-aminophenyl, 2-formylaminophenyl, 3,5-di(trifluoromethyl)phenyl, 2-amino-4-trifluoromethylphenyl, pentachlorophenyl, pentabromophenyl, poly[bis(1,2-phenylene)], poly[bis(1,4-phenylene)] and 3,3-difluoro(1,2-diselenaindan) were delivered by Prof. Dr. Ludwik Syper from our laboratory. Diphenyl diselenide was purchased from Aldrich and poly(bisanthracenyl) diselenide (**5b**) was synthesized in the way reported below.

Preparation of lithium diselenide [21]

To a freshly purified THF[22] (50 ml) poured into dry round-bottom long-neck flask of 100 ml capacity, lithium[23] (0.15-0.20 g) and 4,4'-di(tert-butyl)biphenyl (0.1 g) were added. The flask was stopped with stopcock connected to the vacuum (water jet pump) until THF started to boil. Then vacuum was turn out and the flask was immersed into an ultrasonic bath until the permanent deep green color appeared (ca 15 min). Selenium powder (8g, 100 mmol) was added to the flask and it was degassed *in vacuo*, stoppered and sonificated at 40 - 50 ^{0}C until all lithium was consumed (ca 4 h). After the reaction finished, HMPT (40 ml) was added and thus obtained solution of lithium diselenide was directly used in the next step of synthesis.

Poly(bisanthracenyl) diselenide (5b)

The solution of lithium diselenide was added to a stirred suspension of 9,10-dibromoanthracene (16.8 g , 50 mmol) in HMPT (20 ml). THF was distilled off and the reaction was continued at 100 ^{0}C for 22 h and then at 130 ^{0}C for 6 h. After cooling, methanol (200 ml) was added to the reaction mixture an it was stirred at room temperature for 3 h. The product **5b** was filtered off and washed subsequen-

tly with methanol, water and dried in vessicator. Anhydrous **5b** was suspended in chloroform (100 ml), refluxed for 1h, filtered off, washed with chloroform and dried in air. Red powder. Yield 16.02 g (96%), mp. 339-340 ^{0}C (decomp.), ν_{max} (KBr) cm^{-1} 3065 (CH aromatic), 1620, 1519 (C-C aromatic), 749 (CH aromatic, out of plane) 605, 558 (CSe). Sparingly soluble in the solvents used for NMR spectroscopy. Found: C, 50.01; H, 2.72. $(C_{14}H_8Se_2)_n$, $(334.14)_n$ requires C, 50.32; H, 2.41.

Synthesis of cycloalkanecarboxylic acids (2). General procedure:

To the stirred solution of corresponding cycloalkanone (**1**) (50 mmol) in tert-butanol (10-20 ml for **1a-1e** or 75 ml for **1g-1i**) heated to 65 ^{0}C with catalyst **5b** (0.10 g, 0.30 mmol), 30% aqueous hydrogen peroxide (10 ml, 100 mmol for **1a-1f**, or 20 ml, 20 mmol for **1g-1i**) was added dropwise for 45 min and the mixture was refluxed for period given in Table. While **1i** was oxidized 90% hydrogen peroxide (3 ml), was added after each four days period. The reaction was monitored by using of TLC or GC. After the reaction finished , a pinch of Pt/C was added and the solvent was distilled off by using short vacuum-jacketed column. The residue was treated with 10% aqueous potassium carbonate (50 ml) under vigorous stirring until the evolution of carbon dioxide ceased and washed with chloroform (3x5 ml). The phases were separated and the aqueous phase was adjusted to pH 1 with 1% aqueous hydrochloric acid (ca 400 ml). Then cycloalkanecarboxylic acid (**2a-2c, 2e-2g**) was distilled off with the steam. The distillate was extracted with chloroform (50 ml and 4x25 ml), the extract was dried with sodium sulfate and the solvent was evaporated in vacuo from the water bath of temperature not exceeding

30 ^{0}C. The residue was pure acid **2a-c, 2e-2g**. Acids **2d, 2h** and **2i** were isolated from the aqueous solution with pH 1 by extraction with chloroform (50 ml and 2x25 ml) and purified on silica gel using hexane-ethyl acetate-acetic acid 10:5:1 (**2h**) or 20:1:1 (**2d, 2i**) as an eluent.

The known acids **2a, 2b, 2e, 2fa, 2fb, 2g** and **2h** were isolated as pure individuals.[5,8,24] Acid **2c** was a mixture of both *cis*- and *trans*-isomers analysed by means of ^{1}H and ^{13}C NMR.[5] Generally, the estimation of the molar ratios of the pairs of regio- and stereoisomers was based on the integration of the signals in ^{1}H-NMR and/or appropriate C_{ring} signals in ^{13}C NMR spectra. For identification acid **2i** was converted into crystalline amide, mp 177 ^{0}C (ref.[25] 177-178 ^{0}C). Acid **2d** was a mixture of stereoisomers mentioned earlier in ref.[26] (no spectral data were reported).

3-Phenylcyclopentanecarboxylic acid (2d). Mixture of isomers *cis* and *trans* 10:1 . Colourless oil, ν_{max} (film) cm^{-1} 3500-2500 (COOH), 1702 (CO); ^{1}H NMR ($CDCl_3$)[27] 11.37(s, 1H, COOH), 7.10-7.30 (m, 5H, Ph), 2.90-3.30 (m, 2H, H-1, H-3), 2.35-2.45 (m, 1H, H-2), 1.90-2.25 (m, 4H, H-2, H-4, H-5, H-5), 1.60-1.90 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$) isomer *trans*[27] : 43.51 C-1, 37.86 C-2, 45.41 C-3, 35.01 C-4, 30.32 C-5, 183.75 C=0, 145.15 C-1(Ph), 127.45 and 128.93 C-2, C-6 or C-3, C-5(Ph), 126.56 C-4(Ph); isomer *cis*[27]: 44.00 C-1, 38.59 C-2, 46.65 C-3, 34.33 C-4, 29.66 C-5, 183.52 C=O, 144.69 C-1(Ph), 127 and 128.86 C-2, C-6 or C-3, C-5(Ph), 126.67 C-4(Ph); GC/MS 191 (7, M+1), 190 (58, M), 145 (27), 144 (59), 143(11), 129 (19), 128 (16), 119 (10), 118 (100), 117 (67), 116 (15), 115 (45), 104 (30), 103 (17), 91 (44), 78 (23), 77 (17), 73

(21), 65 (11), 51 (12) ; Found: C, 75.96; H, 7.36, ($C_{12}H_{14}0_2$), (190.24) requires C, 75.76; H, 7.42.

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15. The reaction was carried out in the presence of substantial amount (6% molar) of the catalyst **5b**.

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22. THF was distilled from $LiAlH_4$. To the distillate several pieces of sodium (or potassium) and benzophenone was added, the mixture was sonicated until it became permanent deep blue and THF was distilled using a Vigreux column. The contact with ambient atmosphere should be avoided.

23. From lithium (immersed in benzene), a piece (0.15-0.20 g) was taken, dried with filter paper and hammered to a thin foil on a greased with paraffin oil anvil. The foil was folded several times, and hammered again. The operation was repeated several times and finally the wound foil was cut with scisors in such a way that the pieces of lithium fell directly into the flask.

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27. Determined in the mixture of stereoisomers by ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC.

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