Synthesis of ω-(2-oxocyclododecyl)alkanoic acids by alkylation of cyclododecanone with ω-haloalkanoic esters under conditions of phase-transfer catalysis

L. I. Zakharkin, G. N. Antonova, and L. S. Podvisotskaya*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
28 ul. Vavilova, 117813 Moscow, Russian Federation.
Fax: +7 (095) 135 5085

ω-(2-Oxocyclododecyl)alkanoic acids have been obtained by alkylation of cyclododecanone with alkyl 3-bromopropionate, 5-iodopentanoate, and 11-bromoundecanoate under conditions of phase-transfer catalysis.

Key words: cyclododecanone, phase-transfer catalysis, alkylation, alkyl ω-haloalkanoates.

Cyclododecanone (**1**), unlike lower cyclic ketones, is smoothly alkylated under conditions of phase-transfer catalysis by *n*-alkyl halides,[1] acetals of β-bromopropionic aldehyde, and 1-halo-3-alkoxypropanes.[2] The use of alkyl ω-haloalkanoates for alkylating compound **1** under conditions of phase-transfer catalysis to obtain ω-(2-oxocyclododecyl)alkanoic acids is not documented. These acids are of interest for syntheses of macrocyclic compounds and α,ω-difunctional long-chain aliphatic compounds. For example, 3-(2-oxocyclododecyl)propionic acid or its esters are the starting compounds for the synthesis of valuable aromatic substances such as decamethylene-δ-valerolactone,[3] pentadecanolide (exaltolide),[4] and cyclopentadecanone (exaltone)[5] as well as macrocyclic ketoimides and *N*-acetylketolactams.[6]

The main method of preparation of ω-(2-oxocyclododecyl)alkanoic acids consists in alkoxycarbonylation of compound **1** by dialkyl carbonates under the action of sodium hydride, interaction of the sodium or potassium derivative of 2-alkoxycarbonylcyclododecanone obtained with esters or nitriles of ω-haloalkanoic acids, followed by the elimination of the 2-alkoxycarbonyl group on heating with strong acids.[7]

We propose an alternative, simpler method of preparation of ω-(2-oxocyclododecyl)alkanoic acids, based on alkylation of compound **1** by alkyl ω-haloalkanoates under conditions of phase-transfer catalysis (PTC) in a solid alkali—liquid system in the presence of crown-ethers.

The reaction of ethyl 3-bromopropionate with compound **1** in toluene containing finely ground potassium hydroxide in the presence of dibenzo-18-crown-6-ether at 80—90 °C resulted in 3-(2-oxocyclododecyl)propionic acid (**2**) in 52 % yield (Scheme 1).

In our opinion, in this case the reaction proceeds through an intermediate formation of ethyl 3-(2-oxocyclododecyl)propionate and its saponification under the action of alkali to a potassium salt of this acid, which on addition of water following completion of the reaction passes into the aqueous layer. Acidification of the latter gives pure acid **2**.

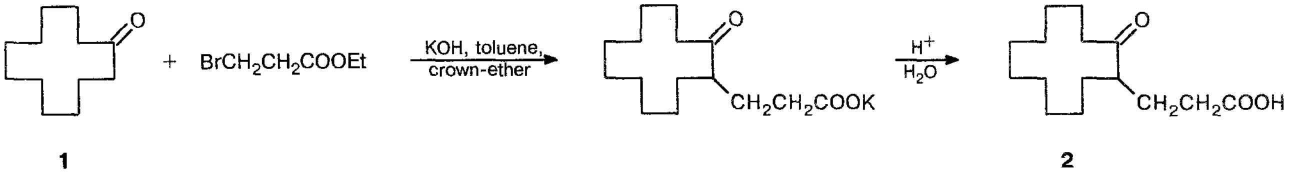
Analogously, *tert*-butyl 5-(2-oxocyclododecyl)pentanoate (**4**) was synthesized from compound **1** and *tert*-butyl 5-iodopentanoate (**3**) in 65 % yield (Scheme 2).

Saponification of ester **4** under conditions of alkylation of compound **1** by ester **3** does not take place. 5-(2-Oxocyclododecyl)pentanoic acid (**5**) was obtained by hydrolysis of ester **4** in acetic acid in the presence of hydrochloric acid in 92 % yield.

Alkylation of compound **1** by *tert*-butyl 11-bromodecanoate (**6**) under PTC conditions requires more drastic conditions and results in potassium 11-(2-oxocyclododecyl)undecanate (**7**), acidification of which gives 11-(2-oxocyclododecyl)undecanoic acid (**8**) (Scheme 3).

Alkylation of compound **1** by methyl iodoacetate under PTC conditions results in 2-oxocyclododecylacetic acid in only 10 % yield.

Scheme 1



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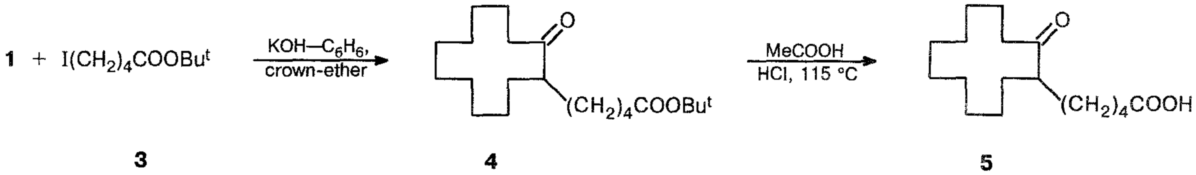
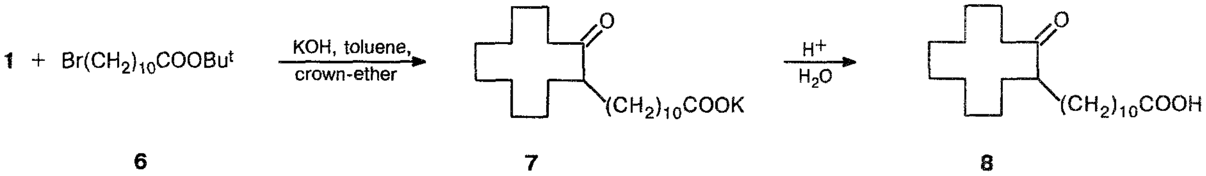
Scheme 2



Scheme 3



Experimental

3-(2-Oxocyclododecyl)propanoic acid (2). Ethyl 3-bromopropionate (20 g, 0.11 mol) was added with intense stirring to a mixture of compound **1** (30 g, 0.16 mol), finely ground potassium hydroxide (17 g, 0.3 mol), and dibenzo-18-crown-6-ether (0.5 g) in toluene (80 mL), and the mixture was heated at 80—90 °C for 6 h. Precipitation of a white sediment was observed in the course of the reaction, and the mixture finally become viscous. On cooling, water (200 mL) was added to the reaction mixture, and the sediment dissolved. The aqueous layer was separated, acidified with hydrochloric acid, and extracted with ether. The ethereal extract was dried with $MgSO_4$, ether was evaporated, and the residue was recrystallized from heptane. Acid **2** (14.5 g, 52 %) was obtained, m.p. 101—102 °C (*cf.* Ref. 8: m.p. 102—103 °C). Found (%): C, 70.59; H, 10.13. $C_{15}H_{24}O_3$. Calculated (%): C, 70.86; H, 10.24. Cyclododecanone (16.8 g) was recovered from the toluene layer.

***tert*-Butyl 5-(2-oxocyclododecyl)pentanoate (4).** *tert*-Butyl 5-iodopentanoate (8 g, 0.028 mol; b.p. 113—115 °C (3 Torr), $n_D{}^{20}$ 1.4850) was added with intense stirring to a mixture of compound **1** (10 g, 0.055 mol), benzene (50 mL), finely ground KOH (7 g, 0.125 mol), and crown-ether (0.3 g). The reaction mixture was heated at 70—80 °C for 4 h. After cooling, water (100 mL) was added, the benzene layer was separated and dried with $MgSO_4$. After removal of benzene, the residue was fractionated *in vacuo* to give 6.2 g (65 %) of ester **4**, b.p. 212—214 °C (1.5 Torr), m.p. 42—43 °C (from pentane). Found (%): C, 74.46; H, 11.11. $C_{21}H_{38}O_3$. Calculated (%): C, 74.56; H, 11.24. Cyclododecanone (4.1 g) was recovered.

5-(2-Oxocyclododecyl)pentanoic acid (5). A solution of compound **4** (6.6 g) in AcOH (45 mL) and conc. HCl (3 mL) was refluxed for 4 h. The reaction mixture was then cooled, poured into 150 mL of water, and extracted with benzene. The benzene layer was dried with $MgSO_4$. After removal of benzene, the residue was recrystallized from heptane to give 5.1 g (92 %) of acid **5**, m.p. 78—79 °C. Found (%): C, 72.25; H, 10.64. $C_{17}H_{30}O_3$. Calculation (%): C, 72.34; H, 10.64.

***tert*-Butyl 11-bromoundecanoate (6).** A solution of *tert*-butyl alcohol (2.5 g, 0.033 mol) in dimethylaniline (5 mL) was added dropwise with stirring to a mixture of 11-bromoundecanoyl chloride (8.7 g, 0.03 mol) and dimethylaniline (2 mL) at 0 °C, and the reaction mixture was left overnight at 20 °C. Then ether (20 mL) and water (20 mL) were added, the ethereal solution was washed with water and dilute HCl, and then with a solution of sodium carbonate and water, and it was dried with $CaCl_2$. After removal of ether, 8.3 g of ester **6** were obtained, m.p. 25 °C (from pentane). Found (%): C, 55.90; H, 9.04; Br, 25.05. $C_{15}H_{29}BrO_2$. Calculated (%): C, 56.07; H, 9.03; Br, 24.92.

11-(2-Oxocyclododecyl)undecanoic acid (8). KOH (5.6 g, 0.1 mol), and then a solution of compound **6** (7.8 g, 0.024 mol) in toluene (30 mL) were added with stirring to a mixture of compound **1** (6.7 g, 0.037 mol), crown-ether (0.2 g), and toluene (20 mL). The reaction mixture was heated with intense stirring at 90 °C for 8 h. Then it was cooled, 100 mL of water were added, and two layers, toluene and aqueous, formed. The aqueous layer was extracted with ether and acidified with dilute HCl, and solid acid **8** precipitated. The acid was extracted with ether, and the extract was dried with $CaCl_2$. After removal of ether, the residue was recrystallized from heptane to give 6.3 g (71 %) of acid **8**, m.p. 78—79 °C. Found (%): C, 75.29; H, 11.32. $C_{23}H_{42}O_3$. Calculated (%): C, 75.41; H, 11.47.

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