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SELECTIVE FAVORSKII REARRANGEMENT IN MACROCYCLIC RINGS

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Summary. A mixture of 2,2-dibromo-12-chlorocyclododecanone (IIa) and 2,12-dibromo-2-chlorocyclododecanone (IIb) by Favorskii rearrangement gave selectively methyl 2-chloro-1-cycloundecene-1-carboxylate (IIIa).

We have accomplished a synthesis of civetone from phloionic acid of cork through eight steps[1,2]. The only step of low yield was a step of benzilic acid rearrangement. For this reason we thought of substituting benzylic by a selective Favorskii rearrangement. Recently we have proved a selectivity of 90% in Favorskii rearrangement of α-bromo-α'-chloroketones[3] and we are now reporting a selectivity of 99% in α,α,α'-dibromochloroketones.

Preparation of 2,2 -dibromo-12-chlorocyclododecanone (IIa) and 2,12-dibromo-2-chlorocyclododecanone (IIb). 2-Hydroxycyclododecanone[4] (Ia)(0.980 g; 4,95 mmol) in CH_2Cl_2 was treated with mesyl chloride (0.44 ml; 5.5 mmol) and trimethylamine (1 ml; 7.43 mmol) with stirring in a flask cooled with ice. Stirring was continued for 45 min.at room temperature and the mixture was poured into ice-water.Reaction product, extracted with dichloromethane, is 2-methanesulfonatecyclododecanone (1.345 g; 98,5%) (Ib). This methanesulfonatecyclododecanone (Ib) (1.309 g; 4.74 mmol) was heated at 85-90°C with LiCl (1.2 g; 28.3 mmol) in dimethylformamide (45 ml). Reaction product, purified through column chromatography of silica gel with hexane-ether (9:1) is 2-chlorocyclododecanone[5] (Ic) (0.930 g; 90,6%). 2-Chlorocyclododecanone (Ic) (1.000 g; 4.62 mmol) dissolved in acetic acid (6 ml) (with catalytic amount of HBr) was treated dropwise and stirring with another solution of bromine (0.524 ml; 10.15 mmol) in acetic acid. Temperature of the mixture was raised to 60°C, and the reaction continued with stirring over a period of five hours. The whole mixture was poured into ice-water; reaction product extracted with hexane and crystallised from methanol (1,490 g; 86,1%) is a mixture of

2,2-dibromo-12-chlorocyclododecanone (IIa) and 2,12-dibromo-2-chlorocyclododecanone (IIb).

Favorskii rearrangement of the last dibromochloroketones. Mixture of 2,2-dibromo-12-chlorocyclododecanone (IIa) and 2,12-dibromo-2-chlorocyclododecanone (IIb) (1.000 g; 2,67 mmol) in benzene (3 ml) was treated at room temperature with sodium methoxide (0.430 g; 7.96 mmol) in methanol (20 ml), by quick stirring for an hour. The whole mixture was poured over ice-water; reaction product extracted with ether (0.634 g; 97%) was an oil, identified with methyl 2-chloro-1-cycloundecene-1-carboxylate (IIIa) by spectroscopic evidence and specially by mass spectrum which contains a chlorine, but not a bromine. Both cis- and trans stereoisomers of IIIa were also separated by column and gas chromatography.

This result requires first two selective steps of bromide elimination in the mentioned Favorskii rearrangement. If any of the two steps were inverted by one step of chloride elimination, we would expect to get some methyl 2-bromo-1-cycloundecene-1-carboxylate (IIIb). This was tested by submiting rough products of rearrangement to gas chromatography in a Perkin-Elmer 3920B. The following four products were separated on a column OV-1, 3% at 170°C, with helium flow rate 30 ml/min, with injector and detector at 200°C: A, t_R 261 s with a relative area of 1.17% (impurity of unknown compound); B, t_R 433 s, identified as methyl 2-chloro-trans-1-cycloundecene-1-carboxylate (IIIa-trans), with a relative area of 17.9%; C, t_R 519 s, identified as methyl 2-chloro-cis-1-cycloundecene-1-carboxylate, (IIIa-cis), with an area 79.8%; D t_R 700 s, identified with a synthetic sample of methyl 2-bromo-cis-1-cycloundecene-1-carboxylate (IIIb).

Preparation of methyl 2-bromo-1-cycloundecene-1-carboxylate (IIIb). It was prepared by the following steps. Cyclododecanone (2,000 g. 10,99 mmol) in acetic acid (14 ml) was treated slowly and dropwise with another solution of bromine (1.8 ml; 34.87 mmol) in acetic acid (3 ml) with stirring over a period of four hours; the temperature was raised to 90°C for an additional hour. Reaction product, extracted with ether, was 2,2,12-tribromocyclododecanone (IIc) (4.037 g; 88%) crystallised from methanol[6]. This 2,2,12-tribromocyclododecanone (0.990 g; 2.36 mmol) in benzene (3 ml) was submited to the Favorskii rearrangement at room temperature with another solution of sodium methoxide (0.382 g;

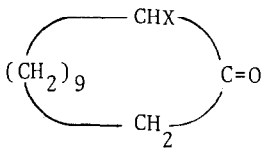
7,08 mmol) in methanol (18 ml). Reaction product, extracted with ether (0.657 g. 96%) was 2-bromo-1-cycloundecene-1-carboxylate (IIIb). Gas chromatography under previously mentioned conditions separated both trans- and cis-stereoisomers of (IIIb) with t_R 598 s and 700 s respectively.

We have proved in this case a selectivity of 99% of bromide elimination of the Favorskii rearrangement. There is not any paper establishing this selectivity. However this finding is very interesting, because it is the basis of a general method to convert an asymmetric acyloin into an olefinic ester with good yield, when the tribromoketone (or dibromoketone) would give two compounds. Treatment with $NaOCH_3$, hydrolysis and decarboxylation of this olefinic ester would afford only one ketone[7]. We think that it is of special value in the synthesis of asymmetric macrocyclic ketones by acyloin condensation, where it may substitute the use of benzilic acid rearrangement (of low yield in this case) to shorten a ring by one carbon atom.

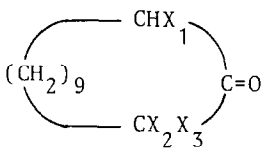
PHYSICAL DATA

Ia: m.p. 77-78°C; IR bands at 3380-3440 (OH) and 1710 cm-1 (CO); NMR ($DCCl_3$) (ppm) signals δ 4.4 (t, J=5Hz, 1H, CHOH), 3.6 (m, 1H, OH), 2.25 (m, 2H, CH_2CO), 1.9-1.25 (m, 18 H, 9 CH_2). Ib: m.p. 109-110°C .IR bands at 1730 (CO), 1340 and 1175 cm-1 (OSO_2CH_3); NMR signals ($DCCl_3$) (ppm) δ 5.10 (t, J=5.3 Hz, 1H, $CHSO_2$), 3.10 (s,3H,SO_2CH_3), 2.58 (dis. t, 2H, CH_2CO), 2.0-1.2 (m, 18H, $9CH_2$). Ic: m.p. 58-59°C. IR band at 1720 cm-1; NMR signals ($DCCl_3$) (ppm) δ 4.35 (dd, J=6 and 9.3 Hz, 1H,CHCl), 2.70 (m, 2H,CH_2CO), 1.9 (m, 4H, next $2CH_2$), 1.3 (m, 14H, $7CH_2$). IIa+IIb: m.p. 93-94.5°C; IR band 1730 cm-1 (CO); NMR signals ($DCCl_3$) (ppm) δ 5.2 (m, 1H, CHCl or CHBr), 2.7 (m, CH_2CX_2), 2.2 (m, 2H, $CHXCH_2$), 1.4 (m, 14H, $7CH_2$). IIIa(cis)[8] IR bands at 1732 (CO_2Me) and 1642 cm^{-1} (C=C); NMR signals ($DCCl_3$) (ppm) δ 3.71 (s, 3H, CO_2CH_3), 2.3-2.7 (m, 4H, $2CH_2C=$), 1.1-1.9 (m, 14H, $7CH_2$); mass spectrum: peaks at m/e (rel.int.) 246 (10.5%, isotopic M^+ with Cl), 244 (31.8% M^+), 149 (100%, M-HCl-CO_2CH_3), 213 (34.9%, M-OCH_3), 215 (11.3%, isotopic M-OCH_3). IIIa(trans): IR bands at 1720 (CO_2Me) and 1610 cm^{-1} (C=C); NMR signals ($DCCl_3$) (ppm) δ 3.73 (s, 3H, CO_2CH_3), 2.2-3.1 (m, 4H,$2CH_2C=$), 1.1-2.0(m, 14H, $7CH_2$); mass spectrum: peaks at m/e 246 (isotopic M^+ with Cl), 244 (M^+). IIc: m.p. 104-106°C; IR band 1730 (CO). NMR signals at 5.05 (dd, J=6 and 7.5 Hz, 1H, CHBr), 2.7 (dist. t, J=7.3 Hz,2H CH_2-CBr_2), 2.25 (m, 2H, CH_2CBr), 1.8-1.1 (m, 14H, $7CH_2$),IIIb(cis):

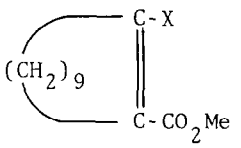
IR bands at 1730 (CO_2Me), 1672 cm^{-1} (C=C); NMR signals ($DCCl_3$) (ppm) 3.78 (s,3H, $^{CO}{}_2CH_3$); 2.3-2.7 (m, 4H, $2CH_2C=$), 1.9-1.1 (m, 14H, $7CH_2$).



Ia: X=OH
Ib: $X=OSO_2CH_3$
Ic: X=Cl



IIa: X_1=Cl, X_2=X_3=Br
IIb: X_1=X_2=Br, X_3=Cl
IIc: X_1=X_2=X_3=Br



IIIa: X=Cl
IIIb: X=Br

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