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Synthesis of a New α-Methylene-γ-butyrolactone Skeleton with the Use of Cobaloxime as Catalyst

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Abstract—A mixture of regioisomeric 2-bromo-1-indanyl and 1-bromo-2-indanyl 2-propynyl ethers was obtained in 10.5 : 1 ratio and separated by chromatography. Radical cyclization of the prevailing isomer in the presence of [chlorobis(dimethylglyoximato)(pyridine)]cobalt(III) (cobaloxime) afforded 3-methylene-tetrahydrofuran fragment; the oxidation of the latter with excess chromium(VI) oxide complex with pyridine in dichloromethane furnished a new α-methylene-γ-butyrolactone in 59% yield.

The outstanding stability of vitamin B_{12} and its derivatives was attributed to the presence of a porphyrin-like cycle. A great number of sigma-bonded cobalt complexes with analogous tetradentate organic ligands was synthesized [1].

In 1964 Schrauzer [2] discovered that the reactions of cobalt atom in vitamin B_{12} could be reproduced by a lot simpler complexes, compounds of bis(dimethylglyoximato)cobalt(III) that were commonly called cobaloximes. This discovery was followed by numerous publications confirming that cobaloximes were correctly regarded as model compounds for B_{12} [3]. As alternative models were also developed other chelates that well reproduced the reactions of vitamin B_{12} both in qualitative and quantitative respect. Since they are easy to prepare, and the necessary reagents are present in any chemical laboratory, these reagents get popular in organic synthesis [4].

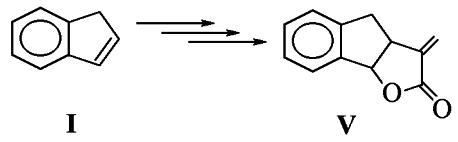
One recent study of cobaloximes concerned their application as catalysts to organic cyclization reactions, namely, to development of a new approach to the synthesis of compounds possessing α-methylene-γ-butyrolactone fragment [5].

Sesquiterpene lactones containing α-methylene-γ-butyrolactone fragment bonded to various moieties belong to a fast growing group of natural compounds. It was shown that some of them possess considerable biological activity (allergic, cytotoxic, antitumor, and also growth-controlling and antimitotic) [6]. Because of biological activity of these compounds and isolation from the natural sources of only small amounts thereof efficient preparation procedures for these substances attract much attention of chemists, and in the last decade many publications has appeared on such syntheses [7].

In this study that we undertook in order to extend the application range of cobaloxime complexes in catalysis of organic cyclization reactions we aimed to synthesize a new compound with a α-methylene-γ-butyrolactone fragment.

The availability of the initial compounds and readily occurring radical cyclization catalyzed by cobalt compounds prompted us to utilize the catalytic potential of cobaloxime, [chlorobis(dimethylglyoximato)(pyridine)]cobalt(III)*, for the synthesis of a representative of a new class of such compounds, α-methylene-γ-butyrolactone (**V**) fused to cyclopentane ring of indene (**I**) (Scheme 1).

Scheme 1.



I **V**

Reaction of indene with N-bromosuccinimide and 2-propynol in dichloromethane at –35°C afforded oily mixture of regioisomeric bromoindanyl 2-propynyl ethers **II, III** in overall yield 95.6% and isomer ratio 10.5 : 1.Isomer **II** is the main reaction product (Scheme 2) due to higher reactivity of the benzyl position in the intermediate bromonium cation. The isomers were separated by colum chromatography on

* [chlorobis(dimethylglyoximato)(pyridine)]cobalt(III) = $(Co^{III})Cl$.

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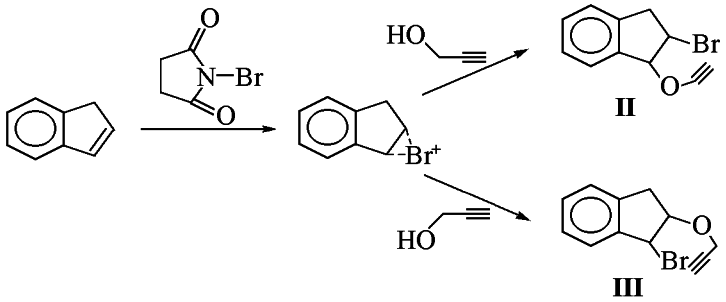
Scheme 2.

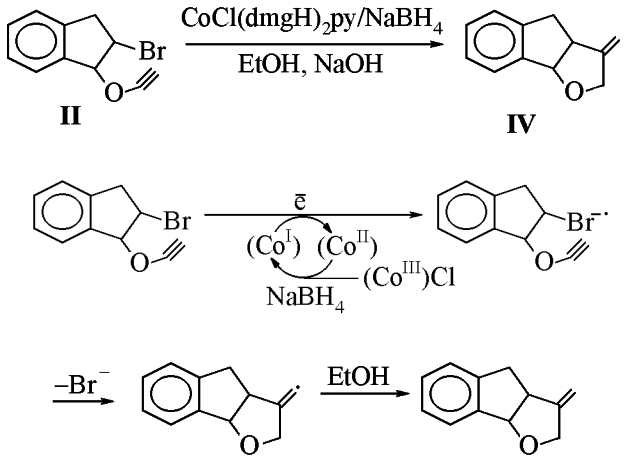


silica gel (eluent petroleum ether–ethyl ether, 6 : 1). The structure of compounds was determined by spectral methods (IR, ^{1}H NMR, mass spectra).

The cyclization of bromoindanyl ether was carried out in ethanol in the presence of cobaloxime, 10 N NaOH, and sodium borohydride. The desired 3-methylenetetrahydrofuran **IV** was obtained in 56.7% yield as an oily substance. The spectral characteristics (IR, ^{1}H NMR, and mass spectra) of the reaction product were consistent with the assumed structure. Similarly to [8] we believe that the reaction proceeds along the stages represented in Scheme 3: cobaloxime (Co^I) arises *in situ* by reduction of chlorocobaloxime (Co^{III}) by sodium borohydride; thus formed cobaloxime (Co^I) is oxidized by bromide **II** into cobaloxime (Co^{II}). Since sodium borohydride readily reduces cobaloxime (Co^{II}) into (Co^I), the latter is recovered in the reaction system.

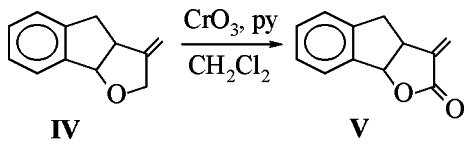
In cyclization was used a small amount of cobaloxime, and no intermediate organocobalt compounds were isolated. The last stage of the synthesis of α-methylene-γ-butyrolactone **V** was performed by

Scheme 3.



oxidation of indanotetrahydrofuran **IV** with excess CrO_3–Py in dichloromethane. The target compound was obtained in 59% yield as oily substance (Scheme 4). It was characterized by IR, ^{1}H NMR, and mass spectra. Since the reaction described does not require stringent conditions it may present a convenient synthetic route to compounds containing cyclopentane ring fused with α-methylene-γ-butyrolactone.

Scheme 4.



EXPERIMENTAL

IR spectra were recorded on spectrophotometer Shimadzu 470. ^{1}H spectra were registered on spectrometer Bruker 80-FT (80 MHz) in deuterochloroform, internal reference TMS. GLC analyses were performed on chromatograph Buck Scientific 910 equipped with a capillary column MXT-5, 15 m long. Mass spectra were measured on Shimadzu Mass-QP1100EX instrument. The column chromatography was performed on silica gel Merck 60GF254 (art. nos. 7730, 7733). The solvents were dried by standard procedures.

Cobaloxime was synthesized by method in [9] and was identified by spectral data. Indene was distilled prior to use.

2-Bromoindanyl 2-propynyl ethers II, III. To a solution of *N*-bromosuccinimide (4.3 g, 24 mmol) in 20 ml of 2-propynol cooled to –35°C was added within 2 h a solution of freshly distilled indene (2.3 g, 20 mmol) in 10 ml of dichloromethane. The reaction mixture was stirred at –25°C for 2 h more and then overnight at room temperature. To the solution

obtained was added 25 ml of 1 N solution of sodium hydrogen carbonate, the reaction products were extracted into dichloromethane (3 × 20 ml). The extract was washed with 10 ml of 1 N NaOH, dried with anhydrous sodium sulfate, the solvent was evaporated on rotary evaporator. We obtained a mixture of compounds **II, III** in 10.5 : 1 ratio in amount 4.8 g (19.12 mmol), yield 96%. The mixture was separated by column chromatography. We isolated indanyl ether **II** in amount 4.2 g (16. 73 mmol). IR spectrum (CCl_4), cm^{-1}: 3300 s, 3020 m, 2100 w, 1600 w, 1060 s, 640 m. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.65 t, (1H, *J* 1.9, 5 Hz), 3.3 d.d (1H, *J* 17.7, 5 Hz), 3.8 d.d (1H, *J* 17.7, 6.6 Hz), 4.4 d (2H, *J* 1.9 Hz), 4.6 m (1H), 5.4 d (1H, *J* 3.5 Hz), 7.4 m (4H). Mass spectrum, *m/z* (I_{rel}, %): 252 (15), 250 (15), 213 (97), 211 (97), 197 (75), 195 (75), 171 (97.5), 115 (100), 77 (98), 39 (98.5). Also was isolated indanyl ether **III** (0.4 g, 1.59 mmol); IR spectrum (CCl_4), cm^{-1}: 3300 s, 3020 m, 2100 w, 1600 w, 1060 s, 640 m. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.7 t (1H, *J* 1.9 Hz), 3.6 m (2H), 4.6 m (3H), 5.2 d (1H, *J* 5.9 Hz), 7.5 m (4H). Mass spectrum, *m/z* (I_{rel}, %): 252 (2), 250 (2), 213 (29), 211 (29), 197 (12), 195 (12), 171 (32), 115 (100), 77 (37), 39 (98).

3-Methylene-3,3a,4,8b-tetrahydro-2*H*-indeno-[1,2-b]furan (IV). To a stirred solution of indanyl ether **II** (2.5 g, 10 mmol) in 50 ml of ethanol was added 1 ml of 10 N solution of sodium hydroxide and 380 mg (10 mmol) of sodium borohydride. The mixture was heated to 50°C in the nitrogen atmosphere, and thereto was added [chlorobis(dimethylglyoximato)(pyridine)]cobalt(III) (cobaloxime) (240 mg, 0.6 mmol) within 1.5 h while maintaining the temperature within the range 50–60°C. The reaction mixture was stirred at this temperature for another 3 h, and after that ethanol was evaporated in a vacuum.To the residue was added 50 ml of saturated water solution of NaCl, and the reaction products were extracted with a mixture petroleum ether–ethyl ether (4 : 1). The combined extracts were washed with a saturated water solution of NaCl, dried with anhydrous sodium sulfate, and evaporated in a vacuum. The residue was subjected to column chromatography. We isolated 1.13 g (6.5 mmol) of oily compound **IV**, yield 57%. IR spectrum (CCl_4), cm^{-1}: 3000–3050 w, 2850– 2900 s, 1650 w, 1600 w, 1060 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.6–3.7 m (3H), 4.1 m (1H), 4.4 m (1H), 4.9 m (2H), 5.6 d (1H, *J* 7.7 Hz), 7.2 m (4H). Mass spectrum, *m/z* (I_{rel},%): 172 (1), 132 (11), 115 (24).

3-Methylene-3,3a,4,8b-tetrahydro-2*H*-indeno-[1,2-b]furan-2-one (V). To 12 ml of pyridine dissolved in 120 ml of dichloromethane was added chromium(VI) oxide (12 g, 120 mmol), and the mixture was stirred for 20 min. Compound **IV** (1.03 g, 6 mmol) was dissolved in 5 ml of dichloromethane and added into the reaction mixture. Then the mixture was boiled for 3 h and filtered. The precipitate was washed with dichloromethane, the filtrate was washed with a saturated water solution of sodium hydrogen carbonate, 2 N hydrochloric acid, and the solution was passed through a short column charged with silica gel to remove the chromium compounds. The solvent was evaporated in a vacuum, and the residue was separated by column chromatography (eluent CCl_4–ethyl ether, 5 : 1). We obtained the target α-methylene-γ-butyrolactone **V** as oily substance (0.65 g, 3.5 mmol), yield 59%. IR spectrum (CCl_4), cm^{-1}: 3000–3050 w, 2850–2900 s, 1750 s, 1640 m, 1120 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.3 m (2H), 3.8 m (1H), 5.8 d (1H, *J* 2.6 Hz), 6.4 d (1H, *J* 2.6 Hz), 6 d (1H, 5.9 Hz), 7.4 m (4H). Mass spectrum, *m/z* (I_{rel},%): 186 (55), 158 (8), 142 (77).

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