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Reactions of Cobaloxime with Substituted Styrenes

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Alkenes (**2a-c**) reacted with N-bromosuccinimide and 2-propynol in dichloromethane at -30ºC and formed an oily mixture of regioisomeric (**3a-c, 4a-c**). Isomers (**3a-c**) which were the main products formed oxolanes (**5a-c**) in the presence of cobaloxime. The oxidation of (**5a-c**) with excess CrO_3.py in dichloromethane produce α-methylene-γ-butyrolactone (**7a-c**).

Key Words: Cobaloxime, α-Methylene-γ-butyrolactone, Cyclization reaction.

INTRODUCTION

The reactions of cobalt atom in vitamin B_{12} could be reproduced by a simpler complexes and compounds of bis(dimethylglyoximato)cobalt (III) that were commonly called cobaloximes[1]. This discovery was follwed by numerous publications confirming that cobaloximes were correctly regarded as model compounds[2] for B_{12}.

Cobaloxime compounds can be applied as catalysts to organic cyclization reactions to develop a new approach and to the synthesis of compound possessing α-methylene-γ-butyrolactone fragment[3].

Sesquiterpene lactones containing α-methylene-γ-butyrolactone fragment have shown posses considerable biological activity (allergic, cytotoxic, antitumour and also growth-controlling and anti-mitotic[4,5] therefore, these substances attract much attention of chemists and in the last decade many publications have appeared on such syntheses[6,7].

In order to extend the application range of cobaloxime complexes in catalyzing the organic cyclization reactions, we aimed to synthesize new compounds with α-methylene-γ-butyrolactone fragment. For this purpose, cobaloxime (Fig. 1) that is a kind of important model complex of coenzyme B_{12} is synthesized and acts as a homogeneous catalyst in organic cyclization reactions in order to prepare a new compound with a α-methylene-γ-butyrolactone unit.

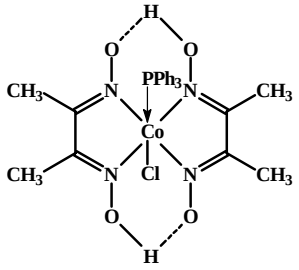


Fig. 1. Cobaloxime

EXPERIMENTAL

IR spectra were recorded on spectrophotometer Shimadzu 470. ^{1}H NMR spectra were recorded on spectrometer Bruker DRX-500 Avance in $CDCl_3$, internal reference TMS. 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 reported method[8].

2-[(2-Propynyl)oxy]ethyl bromides (3a-c): To the solution of N-bromosuccinimide (4.3 g, 250 mmol) in 20 mL of 2-propynol cooled to -30ºC was added within 2 h, a solution of starting olefin (20 mmol) in 10 mL of dichloromethane. The reaction mixture was stirred at -20ºC for 2 h and then overnight at room temperature. To the solution obtained 25 mL of 1N solution of sodium hydroxide was added. 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. The mixture was separated by column chromatography (petroleum ether : ether, 6:8). We isolated bromide **3a** in amount 2.73 g, (54% yield). IR spectrum (KBr, ν_{max}) cm^{-1}: 3300 s, 3020 w, 2900 s, 2100 m, 1600 m, 1440 m, 1375 s, 1180 w, 1095 s, 1060 w, 820 s, 640 s. ^{1}H NMR spectrum ($CDCl_3$) δ, ppm: 2.3 s (3H), 2.4 t (1H, J=2.2 Hz), 3.55 dd (HH), 4.0 dd (HH, J=15.7, 2.2 Hz), 4.7 dd (1H, J=7.9, 4.6 Hz), 7.2 q (4H).

3b and **3c** were also isolated in amount 3.47, 4.44 g, respectively (yields: 58 and 71 %), by chromatography (pure dichloromethane). IR spectrum (CCl_4), cm^{-1}: **3b** : 3500 m, 3280 s, 3080 s, 2980 s, 2820 m, 2100 w, 1590 s, 1500 s, 1450 m, 1375 m, 1250 s, 1135 s, 1060 s, 1020 s, 800 s, 640 m. ^{1}H NMR spectrum ($CDCl_3$) : **3b**: 1.7 d (3H, J=6.7 Hz), 2.4 t (1H, J=11.2 Hz), 3.92 s (3H), 3.95 dd (1H, J=15.7, 2.2 Hz), 4.22 dd (1H, J=15.7, 2.2 Hz), 4.26 m (1H), 4.6 d (1H, J=5.91 Hz), 5.7 s (1H), 6.92 m (3H). IR spectrum: (neat), cm^{-1}: **3c** : 3275 s, 3050 w, 2925 s, 2820 m, 2100 w, 1590 s, 1510 s, 1460 s, 1365 m, 1250 s, 1130 s, 1060 s, 1020 s, 805 m, 650 m. ^{1}H NMR spectrum: ($CDCl_3$), δ, ppm, **3c** : 1.7 d (3H, J=6.7 Hz), 2.4 t (1H, J=2.1 Hz), 3.8 s (3H), 3.75 s (3H), 3.9 dd (1H, J=15.7, 2.1 Hz), 4.19 dd (1H, J=15.8, 2.1 Hz), 4.25 m (1H), 4.58 d (1H, J=6 Hz), 6.8 m (3H).

3-Methylene oxolanes (5a-c): To a stirred solution of bromides (**3a-c**) (6 mmol) in 50 mL of ethanol was added 0.6 mL of 10 N solution of sodium hydroxide and 228 mg (6 mmol) of sodium borohydride. The mixture was heated to 50ºC in an argon atmosphere then [chlorobis(dimethylglyoximato)(triphenylphosphine)]cobalt(III)[Cobaloxime] (0.4 mol) was added within 1.5 h at 50-60ºC. The reaction mixture was stirred at this temperature for another 0.5 h and after that ethanol was evaporated in a vacuum. 50 mL of saturated solution of NaCl was added in this residue and the reaction products were extracted with petroleum ether. The combined extracts were washed with saturated aqueous solution of NaCl, dried with anhydrous sodium sulfate and evaporated in a vacuum. The residue was subjected to column chromatography (petroleum ether: ether, 15:2). 0.6 g of oily compound **5a** was isolated, yield 58 %. IR spectrum: ($CHCl_3$) cm^{-1} : 3500 m, 3050 m, 2900 w, 2850 w, 1640 w, 1510 w, 1450 w, 1410 m, 1370 w, 1090 m, 1020 w, 695 m.

RESULTS AND DISCUSSION

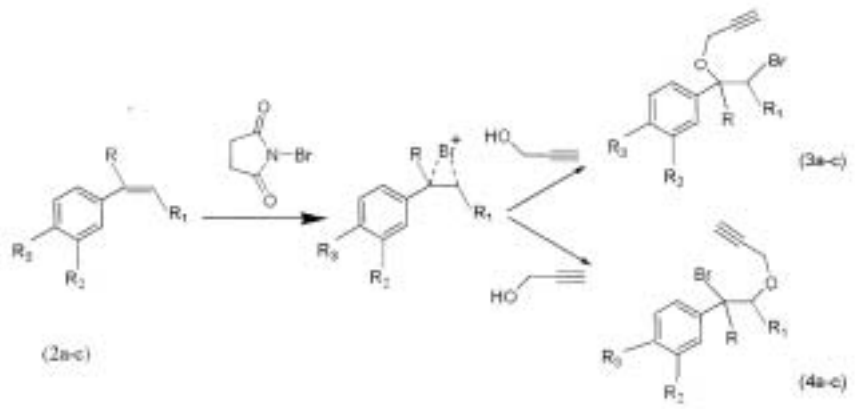
Reactions of alkenes (**2a-c**) with N-bromosuccinimide and 2-propynol in dichloromethane at -30ºC afforded an oily mixture of regioisomeric (**3a-c, 4a-c**) (Table-1). Isomers (**3a-c**) are the main reaction products (**Scheme-1**) due to higher reactivity of the benzyl position in the intermediate bromonium cations. Compounds (**3a-c**) were separated by column chromatography on silica gel. The strucutre of compounds were determined by spectral methods (IR, ^{1}H NMR).

TABLE-1

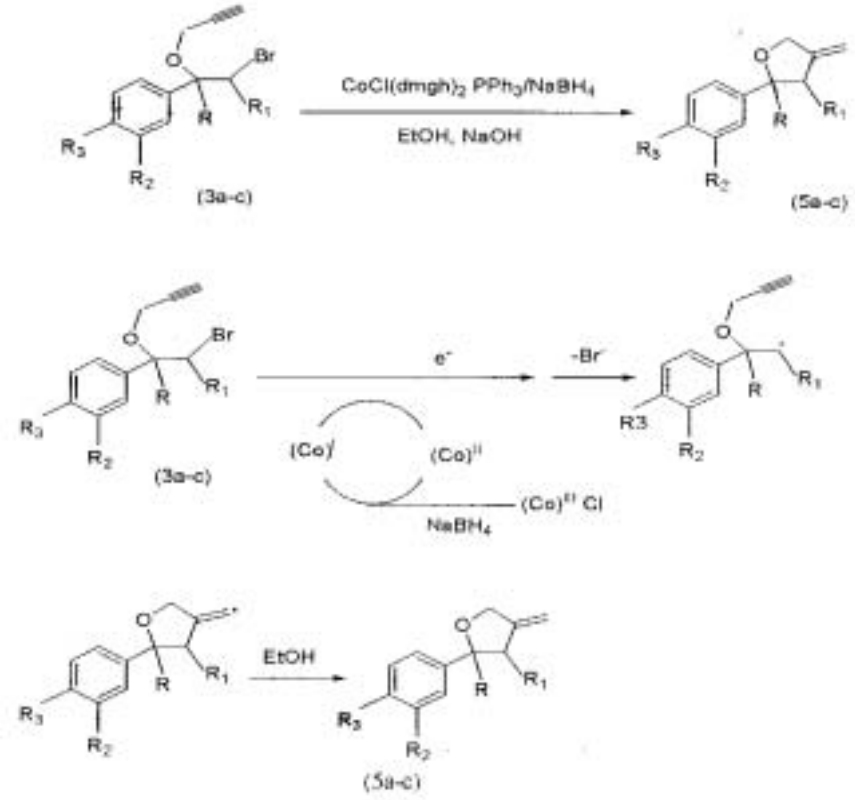
Entry	R	R_1	R_2	R_3	Yield of products (%)		
					3a-c	**5a-c**	**7a-c**
2a	H	H	H	CH_3	54	58	68
2b	H	CH_3	OCH_3	OH	58	35	60
2c	H	CH_3	OCH_3	OCH_3	71	43	63

The cyclization of (**3a-c**) was carried out in ethanol in the presence of cobaloxime with 10 N NaOH and sodium borohydride.

The desired products (**5a-c**) were obtained as an oily substance, the spectral characteristics (IR, ^{1}H NMR) of the reaction product were consistent with the assumed structures. The reaction proceeds[9] along the stages represented in **Scheme-2**. Cobaloxime (Co^I) arises *in situ* by reduction of chloro cobaloxime (Co^{III})[10] by sodium borohydride; thus, formed cobaloxime (Co^I) is oxidized by (bromide) into cobaloxime (Co^{II}) since sodium borohydride readily reduces cobaloxime (Co^{II}) into (Co^I), the latter is recovered in the reaction system.



Scheme-1

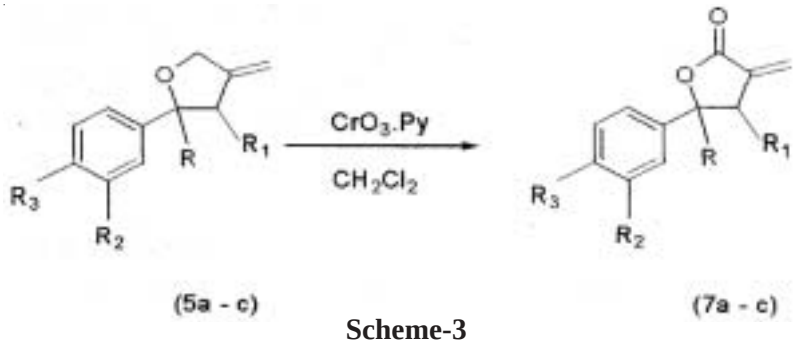


Scheme-2

In cyclization, a small amount of cobaloxime was used and no intermediate organocobalt compounds were isolated (**6a-c**).

The last stage of the synthesis of α-methylene-γ-butyrolactone was performed by oxidation of (**5a-c**) with excess CrO_3-py in dichloromethanol[11]. The target compound was obtained as an oily substance (**Scheme-3**). It

was characterized by IR and ^{1}H NMR. Since the reaction described doesn't require stringent conditions, it may present a convenient synthetic rout to compounds containing cyclopentane ring fused with α-methylene-γ-butyrolactone[12].



Scheme-3

^{1}H NMR spectrum: ($CDCl_3$), δ, ppm: 2.3 s (3H), 3.45 dd (2H), 3.91 dd (2H), 4.5 dd (1H, J=4.3, 8 Hz), 5.2 d (1H), 5.9 m (1H), 7.2 q (4H).

The compounds **5b** and **5c** were isolated in amount (0.46, 0.60 g), yields 35 and 43%, respectively by chromatography (petroleum ether: ether, 2:1). IR spectrum ($CHCl_3$) cm^{-1}: **5b**: 3400 s, 3050 m, 2900 s, 2850 m, 1640 m, 1580 w, 1465 w, 1430 m, 1375 m, 1260 m, 1115 m, 1080 m, 735 s, 698 s. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, **5b** : 1.7 d (3H, J=6.75 Hz), 3.1 m (1H), 3.9 s (3H), 4.1 d (1H, J=15.7 Hz), 4.2 d (1H, J=15.7 Hz), 4.7 d (1H, J=5.95 Hz), 5.7 s (1H), 5.91 dd (1H, J=4.27, 1.6 Hz), 5.98 dd (1H, J=4.27, 1.6 Hz), 7 m (3H). IR spectrum ($CHCl_3$) cm^{-1}: **5c**: 3050 m, 2900 s, 2850 m, 1640 m, 1575 m, 1460 s, 1430 m, 1370 m, 1260 s, 1118 s, 1020 s, 740 s, 698 s. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, **5c** : 1.7 d (3H, J=6.7 Hz), 3.0 m (1H), 3.9 d (6H), 4.0 d (1H, J=15.7 Hz), 4.1 d (1H, J=15.7 Hz), 4.7 d (1H, J=5.9 Hz), 5.8 dd (1H, J=4.2, 1.6 Hz), 5.9 dd (1H, J=4.2, 1.6 Hz), 7.0 m (3H).

α-Methylene-γ-butyrolactone (7a-c): To 12 mL of pyridine in 120 mL of dichloromethane was added chromium (VI) oxide (12 g, 120 mmol) and the mixture was stirred for 20 min. Compounds (**5a-c**) (6 mmol) were dissolved in 5 mL of dichloromethane and added into the reaction mixture. The mixture was boiled for 1 h and filtered. The precipitate was washed with dichloromethane, the filtrate was washed with a saturated solution of sodium hydrogen carbonate, 2N HCl 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). α-Methylene-γ-butyrolactone **7a** was obtained as an oily substance 0.73 g, yield 68%. IR spectrum ($CHCl_3$), cm^{-1} : 3020 m, 2900 w, 2850 w, 1745 s, 1645 w, 1420 m, 1360 m, 1095 m, 1030 m. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.3 s (3H),

3.48 dd (2H), 4.7 dd (1H, J=7.9, 4.6 Hz), 5.2 d (1H), 5.9 m (1H), 7.2 q (4H).

The compounds **7b** and **7c** were obtained in amounts (0.84, 0.93 g), yields 60 and 63% by chromatography (petroleum ether: ether, 1:1). IR spectrum ($CHCl_3$), cm^{-1} :**7b** : 3400 s, 3050 m, 2900 s, 2850 m, 1750 s, 1640 m, 1580 w, 1465 m, 1430 m, 1375 m, 1260 s, 1115 s, 1020 s, 735 s, 690 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: **7b** : 1.7 d (3H, J=6.7 Hz), 3.1 m (1H), 3.9 s (3H), 4.8 d (1H, J=5.9 Hz), 5.7 s (1H), 5.9 dd (1H, J=4.3, 2.2 Hz), 6.0 dd (1H, J=4.5, 2.2 Hz), 7.1 m (3H). IR spectrum ($CHCl_3$), cm^{-1} :**7c** : 3050 m, 2900 s, 2850 m, 1740 s, 1640 w, 1575 w, 1465 m, 1425 m, 1375 m, 1260 s, 1115 s, 740 s, 695 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: **7c** : 1.7 d (3H, J=6.7 Hz), 3.2 m (1H), 3.9 d (6H), 4.8 d (1H, J=5.9 Hz), 5.9 dd (1H, J=4.5, 1.6 Hz), 5.97 dd (1H, J=4.5, 1.6 Hz), 7.1 m (3H).

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