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**Research Article**

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# Synthesis and investigation of biological activities of a new α-methylene-γ-butyrolactone using cobaloxime-catalyzed radical cyclization

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**ABSTRACT**

*α-methylene-β,γ-diphenyl-γ-butyrolactone was synthesized by the bromoprop-2-yn-1-yloxylation of cis-stilbene. Cobaloxime catalyzed radical cyclization of the resulting1-bromo-1, 2-diphenylethylprop-2-yn-1-yl ether, gave 2,3-diphenyl-4-methylene tetrahydrofuran and oxidation of the latter with chromium trioxide in the presence of pyridine, afforded the target product in 62.5% yield. Synthesis of this α-methylene-β,γ-diphenyl-γ-butyrolactone led to efficient anti microbial activity. It was found that it is effective against Gram-positive bacteria, Gram-negative bacteria and yeast. Its extensive inhibition effect is particularly against yeast.*

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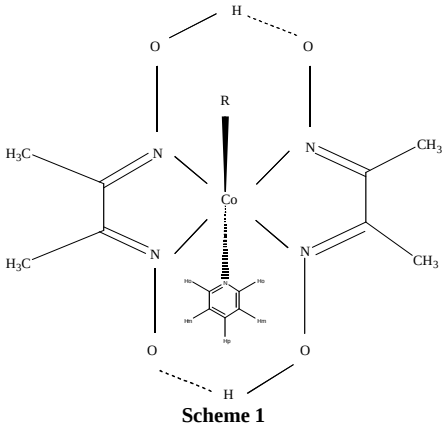
## INTRODUCTION

Vitamin $B_{12}$, also known as Cobalamin, is a complex organometallic compound in which a cobalt atom is situated within a corrin ring, a structure similar to the porphyrin from which haem is formed [1]. 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 (Scheme 1)[2]. Cobaloxime is an organic radical carrier [3, 4].




**Scheme 1**

This behavior made these complexes useful agents for preparation of the α-methylene-γ-butyrolactone structural unit. This structural unit characterizes a rapidly expanding group of sesquiterpenes, which are known to possess significant biological activity. Cytotoxic, anti-inflammatory, phytotoxic, allergenic and antimicrobial properties are shown not only by highly functionalized, complex sesquiterpene lactones but also simple representatives have been

studied for their biological effects [5]. Because of their broad range of biological activities and their interesting structural features, α-methylene-γ-butyrolactones present a scientific challenge which is reflected in an increasing number of investigations and synthesis of these heterocycles [6].

## EXPERIMENTAL SECTION

***Synthesis of Cobaloxime***

1. Cobaloxime was synthesized according to the reported method [10], and identified by spectroscopic data. IR spectra were recorded on a Shimadzu 470 spectrophotometer. $^1$HNMR spectra were measured on a Bruker DRX-500 Avance instrument in deuterochloroform containing tetramethylsilane (TMS) as an internal standard. MS analysis was performed using a 5973 HP mass-selective detector.

***Synthesis of cis 1-bromo-1, 2-diphenylethylprop-2-yn-1-yl ether***

2. To a cold magnetically stirred solution (– 40°C) of *N*-bromosuccinimide (0.7 g, 4 mmol) in propyn-2-ol (5 ml), a solution of *cis*-stilbene (0.54 g, 3 mmol) in dichloromethane (20 ml) was added gradually for 2 h. The reaction mixture was stirred for 2 h at 0 °C and then for 48 h at room temperature. Sodium hydroxide (1 N, 5 ml) was added to the solution, and the mixture was extracted with carbon tetrachloride (3×20 ml). The organic phase was washed with 10 N NaOH. The solvent was evaporated under reduced pressure to give a mixture of products. The mixture was purified by preparative TLC (light petroleum:diethyl ether, 14:1) to provide 1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether **2** (0.67 g, 2.14 mmol) in 80% yield. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ : 2.5 (t, J = 2.35Hz, 1H), 4.0 (dd, J = 15.9, 2.33Hz, 1H), 4.3 (dd, J = 15.9, 2.33Hz , 1H), 5.05 (dd, J = 8.3Hz , 2H), 7.1-7.3 (m, 10H) ppm. IR ($CCl_4$): 3300 (m), 3020 (w), 1076 (s), 760 (m), 700 (s), 680 (m) cm$^{1-}$.

***Synthesis of 2,3-diphenyl-4-methylenetetrahydrofuran***

3. To a magnetically stirred solution of 1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether **2** (0.63 g, 2 mmol) in ethanol (10 ml), 10 N sodium hydroxide (0.2 ml) and sodium borohydride (76 mg, 2 mmol) were added, and the mixture was warmed under an atmosphere of nitrogen up to 50°C. Chloro-bis (dimethylglyoximato)(pyridine) cobalt (III) [cobaloxime] (0.48 mg, 0.12 mmol) was added in 1.5 h at 50–60 °C. The reaction mixture was stirred at the same temperature for 3 h. Ethanol was removed under reduced pressure and a saturated solution of sodium chloride (10 ml) was added. The mixture was extracted with light petroleum: diethyl ether (4:1) (3×10 ml). The organic phase was washed with saturated sodium chloride and evaporated in a vacuum. The residue was purified by preparative TLC (a 7:1 mixture of light petroleum and diethyl ether as an eluent) to give 2, 3-diphenyl- 4 methylenetetrahydrofuran **3** as oil (0.24 g, 1 mmol) in 50% yield. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ : 3.7 (d, J = 2.53Hz, 1H), 4.73 (d, J = 2.31Hz , 1H), 4.75 (d, J = 2.31Hz, 1H), 4.9 (s, 1H), 4.93 (s, 1H), 5.15 (d, J = 2.53Hz , 1H), 7.1-7.4 (m, 10H) ppm. IR (Neat): 3000-3050 (m), 2880 (m), 1660 (m), 1050 (s), 750 (s), 700 (s) cm$^{-1}$.

***Synthesis of α-methylene-β,γ-diphenyl- γ -butyrolactone***

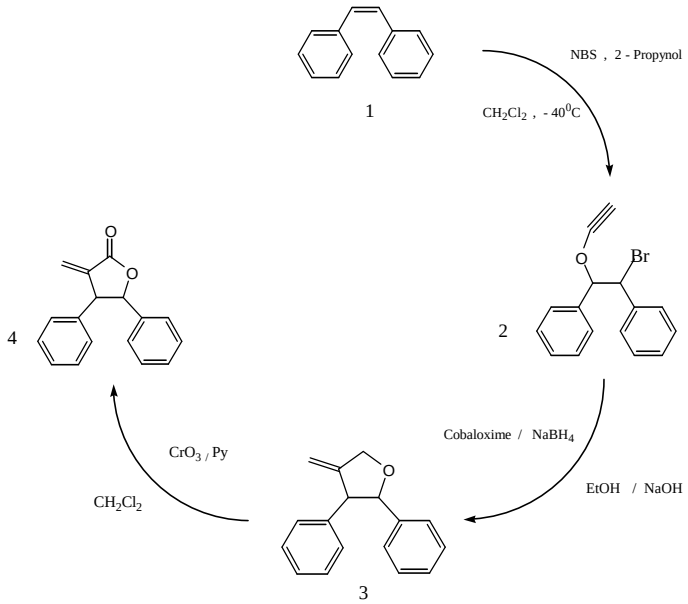
4. To a solution of pyridine (1 ml) in dichloromethane (10 ml), chromium trioxide (1 g, 10 mmol) was added, and the mixture was stirred for 20 min. Compound **3** (0.12 g, 0.5 mmol) was dissolved in dichloromethane (5 ml), added to the reaction mixture, refluxed for 3 h and the resulting mixture was filtered. The residue was washed with dichloromethane (3×10 ml), and the filtrate was washed with saturated sodium bicarbonate, 2N hydrochloric acid and passed through a short silica gel column to remove chromium compounds. The solvent was evaporated in a vacuum, and the residue was separated by TLC (a 7:1 mixture of light petroleum and diethyl ether) to obtain product **4** as an oil (0.08 g, 0.31 mmol) in 62.5% yield. $^1$HNMR (500 MHz, $CDCl_3$): $\delta$ : 4.0 (m, 1H), 5.40 (d, J = 7.69Hz, 1H), 5.47 (m, 1H), 6.47 (d, J = 3.17Hz, 1H), 7.2-7.5 (m, 10H) ppm. IR ($CCl_4$): 3000–3050 (w), 2850–2900 (m), 1760 (s), 1645 (m), 1600 (m), 1130 (s), 750 (s), 700 (s). MS, m/z (%): 250 (3.4), 144 (55.3), 116 (100), 77 (7.2), 51(5.0).

***Determination of the antimicrobial activity of the synthesized α-methylene-γ-butyrolactone***

The antimicrobial activity of this compound was carried out according to the agar disc diffusion method against Gram-positive, Gram-negative bacteria and yeast by agar diffusion test. Filter discs containing 150 (µl) of the active substance dissolved in dichloromethane was placed on the test plates. The plates were incubated at 37°C for 18 to 24 h, and the antimicrobial activity was determined by measuring zones of growth inhibition. Typical results of antibacterial properties of α-methylene-γ-butyrolactone are shown in Table 1 [12].

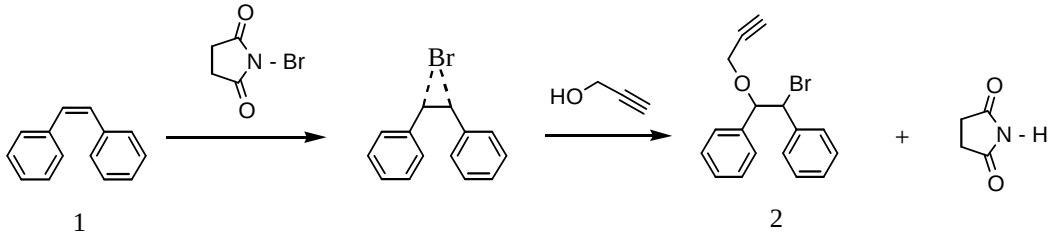
## RESULTS AND DISCUSSION

The importance of compounds with an α-methylene-γ-butyrolactone skeleton and the feasibility of using cobalt-mediated radical cyclization reactions prompted us to exploit the catalytic potential of cobaloxime [chloro-bis (dimethylglyoximato) (pyridine)] cobalt (III) in the synthesis of α-methylene-β,γ-diphenyl- γ-butyrolactone **4,** starting from *cis*-stilbene **1** (Scheme 2) [7].



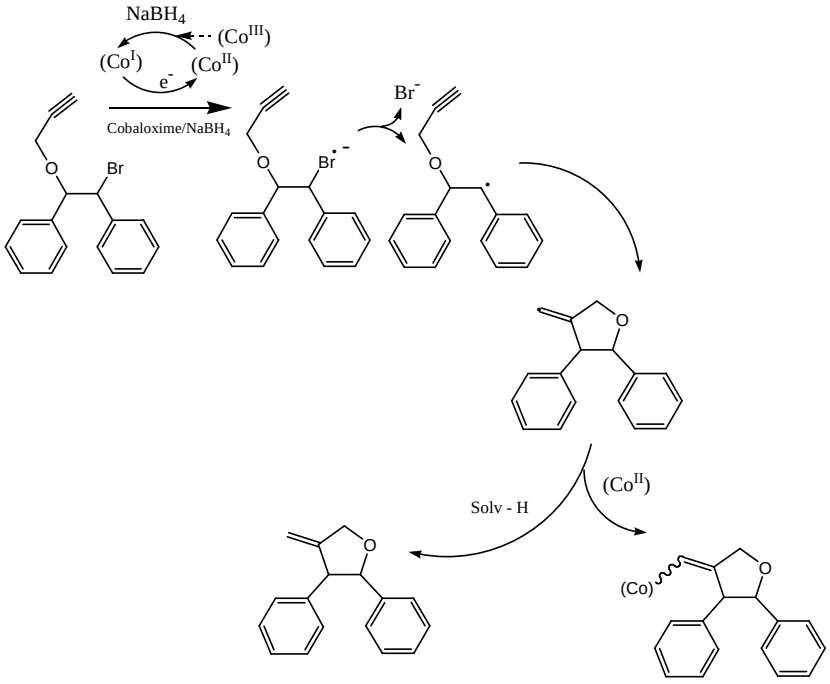

**Scheme 2**

Bromoprop-2-yn-1-yloxylation of *cis*-stilbene with *N*-bromosuccinimide and propyn-2-ol in dichloromethane at –40°C yielded 1-bromo-1, 2-diphenylethylprop-2-yn-1-yl ether **2** (80%) as oil. The desired reaction product (compound **2**) was separated by preparative TLC (light petroleum:diethyl ether, 14:1) and its structure was characterized by IR and $^1$HNMR spectroscopy (Scheme 3). Cyclization of 1-bromo-1, 2-diphenylethylprop-2-yn-1-yl ether **2** was carried out in the presence of cobaloxime, 10N NaOH and sodium borohydride in ethanol to form 2,3-diphenyl-4-methylenetetrahydrofuran **3** in 50% yield, as an oil.




**Scheme 3**

By analogy to the report of Tada *et al* [8] it is believed that the reaction takes the steps presented in Scheme 4, in which cobaloxime (I) is prepared *in situ* via the reduction of chlorocobaloxime (III) by sodium borohydride, and cobaloxime (I) thus formed is oxidized by brominated product **2** to cobaloxime (II). Since sodium borohydride easily reduces cobaloxime (II) to cobaloxime (I), the cobaloxime can recycle in the reaction system. In the cyclization reaction, a small amount of cobaloxime (12 mmol) was used and no organocobalt intermediate was isolated (Scheme 4).



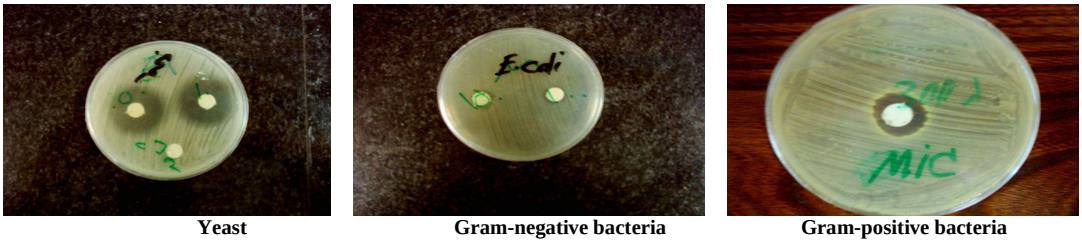

**Scheme 4**

Final step in the synthesis of α-methylene-β,γ-diphenyl-γ-butyrolactone was carried out by oxidation of 2,3-diphenyl-4-methylenetetrahydrofuran **3** with an excess of $CrO_3 \cdot Py$ in dichloromethane, which provided the desired compound **4** as an oil in 62.5% yield. The product was characterized by IR and $^1$HNMR spectroscopy and Mass spectrometry. Only one stereoisomer of compound **4** was detected and characterized. We conclude that the described method does not require vigorous reaction conditions and would be useful for the synthesis of cyclopentane annulated α-methylene-γ-butyrolactones. The products of reactions were investigated by IR and $^1$HNMR and Mass spectroscopy. In comparison with our previous work [9], we noticed that the chemical shifts and coupling constants of *cis*-1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether are different from those of *trans*-1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether [9]. Synthesized lactone has shown biological activity for Gram$^+$, Gram$^-$ bacteria and yeast (Table 1), (Scheme 5) [10].

**Table 1. Typical results of antimicrobial properties of α-methylene-β,γ-diphenyl-γ-butyrolactone, diameter of inhibition zones in mm**

| | |
|---|---|
| Gram positive bacteria (Staphylococcus sp) | 17.0 |
| Gram negative bacteria (E-coli) | 7.0 |
| Yeast | 31.0 |

**Antimicrobial properties of compound 4**




**Yeast** **Gram-negative bacteria** **Gram-positive bacteria**

**Acknowledgment**
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