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# Synthesis of α-methylene-β,γ-diphenyl-γ-butyrolactone using cobaloxime-catalysed radical cyclisation

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α-Methylene-β,γ-diphenyl-γ-butyrolactone was synthesised by the bromoprop-2-yn-1-yloxylation of stilbene **1**. Cobaloxime-catalysed radical cyclisation of the resulting 1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether **2** gave 2,3-diphenyl-4-methylene-tetrahydrofuran **3**; oxidation of the latter with chromium trioxide in the presence of pyridine afforded target product **4** in a total yield of 25%.

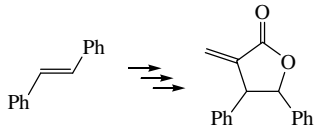
The α-methylene-γ-butyrolactone structural unit is present in a wide variety of sesquiterpenes and other natural products[1] and responsible for the biological activity of these compounds.[2] For example, sesquiterpene lactones with an α-methylene-γ-butyrolactone exhibit biological activities as allergenic, cytotoxic and antitumor agents, regulators of plant growth and antimitotic activity.[3,4]

The use of cobaloxime-catalysed radical cyclisation is a way for producing the α-methylene-γ-butyrolactone skeleton.[5] Cobaloxime is an organic radical carrier.[6,7] This behaviour made these complexes useful agents for preparation of the α-methylene-γ-butyrolactone structural unit.

We reported that indene can undergo catalytic cyclisation with cobaloxime to form α-methylene-γ-butyrolactone skeleton units.[8] In order to examine a new alkene upon the catalytic application of cobaloxime complexes in organic cyclisation reactions, we decided to prepare a new compound including the α-methylene-γ-butyrolactone unit.

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

Bromoprop-2-yn-1-yloxylation of *trans*-stilbene with *N*-bromosuccinimide and propyn-2-ol in carbon tetrachloride at –15 °C yielded 1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether **2** (80%) as a white powder.



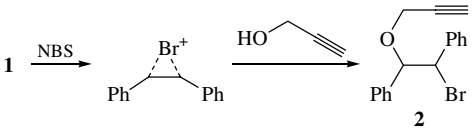

**1** **4**

**Scheme 1**

† Cobaloxime was synthesised according to the reported method[10] and identified by spectroscopic data. IR spectra were recorded on a Shimadzu 470 spectrophotometer. $^1$H NMR spectra were measured on a Bruker DRX-500 Avance instrument in deuterochloroform containing tetramethylsilane (TMS) as an internal standard. Capillary GC analysis was performed using GC 6890 HP (capillary column HPS MS, 30 m), and a 5973 HP mass-selective detector. Column chromatography was carried out using 60 $GF_{254}$ silica gel (Merk).

In the usual synthesis of these compounds, the temperature of –35 °C is used. But at this temperature, *trans*-stilbene crystallises and does not react. Therefore, the reaction was performed at –15 °C.

The desired reaction product (compound **2**) was separated by thin-layer chromatography (TLC) (light petroleum–diethyl ether, 14:1) and its structure was established by IR and $^1$H NMR spectroscopy (Scheme 2).‡




**Scheme 2**

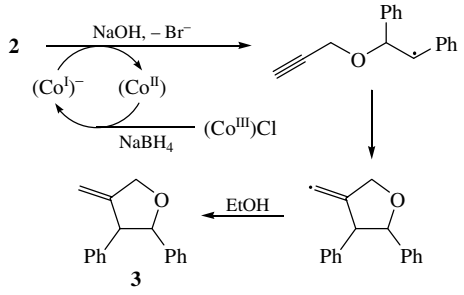
Cyclisation of 1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether **2** was carried out in the presence of cobaloxime in 10 N NaOH and sodium borohydride in ethanol to form 2,3-diphenyl-4-methylenetetrahydrofuran **3** in 50% yield, as an oil.§

By analogy to the report of Tada *et al.*,[9] it is believed that the reaction takes the steps presented in Scheme 3, in which cobaloxime(I) is prepared *in situ via* the reduction of chlorocobaloxime(III) by sodium borohydride and cobaloxime(I) thus formed is oxidised 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 cyclisation reaction, a small amount of cobaloxime was used and no organocobalt intermediate was isolated. 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 $CrO_3$·Py in dichloromethane, which provided desired compound **4** as a white powder in 62.5% yield. This product was characterised by IR and $^1$H NMR spectroscopy and mass spectrometry.¶

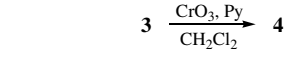
Only one stereoisomer of compound **4** was detected and characterised. The coupling constant ($J$ 7.65 Hz) of this compound in $^1$H NMR spectra indicated a *trans* configuration for the two hydrogen atoms adjacent to phenyl groups.




(Co$^{III}$)Cl = Chloro-bis(dimethylglyoximato)-(triphenylphosphine) cobalt(III)

**Scheme 3**

We conclude that the method described does not require vigorous reaction conditions and would be useful for the synthesis of cyclopentane annulated α-methylene-γ-butyrolactones.

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‡ *Synthesis of 1-bromo-1,2-diphenylethylprop-2-yn-1-yl ether* **2**. To a cold magnetically stirred solution (–15 °C) of *N*-bromosuccinimide (0.7 g, 4 mmol) in propyn-2-ol (5 ml), a solution of *trans*-stilbene (0.54 g, 3 mmol) in carbon tetrachloride (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 the product and by-products. The mixture was separated by 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 ($CDCl_3$) $\delta$: 2.4 (t, 1H, $J$ 2.18 Hz), 3.8 (dd, 1H, $J$ 16 and 2.24 Hz), 4.1 (dd, 1H, $J$ 16 and 2.24 Hz), 5.1 (dd, 2H, $J$ 15.1 and 7.4 Hz), 7.3 (m, 10H). IR ($CCl_4$, $\nu$/cm$^{-1}$): 3250 (br. s), 3020 (w), 1076 (s), 750 (br. s), 700 (s), 645 (br. s).

§ *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)(triphenylphosphine)cobalt(III) [cobaloxime] (0.48 mg, 0.12 mmol) was added for 1.5 h at 50–60 °C. The reaction mixture was stirred at the same temperature for 3 h. Ethanol was evaporated 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 an oil (0.24 g, 1 mmol) in 50% yield. $^1$H NMR ($CDCl_3$) $\delta$: 3.7 (dd, 1H, $J$ 2.53 Hz), 4.75 (dd, 1H, $J$ 13.3 and 2.2 Hz), 4.78 (d, 1H, $J$ 2.5 Hz), 4.9 (d, 2H, $J$ 9.6 Hz), 5.1 (dd, 1H, $J$ 2.53 Hz), 7.3 (m, 10H). IR (Neat, $\nu$/cm$^{-1}$): 3000–3050 (br. s), 2580 (br. s), 1660 (br. s), 1050 (s), 750 (s), 700 (s).

¶ *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 filtered. The residue was washed with dichloromethane (3×10 ml), and the filtrate was washed with saturated sodium bicarbonate, 2 N 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 a white powder (0.08 g, 0.31 mmol) in 62.5% yield, mp 37 °C. $^1$H NMR ($CDCl_3$) $\delta$: 4.00 (d, 1H, $J$ 7.65 Hz), 5.40 (d, 1H, $J$ 7.69 Hz), 5.47 (d, 1H, $J$ 2.79 Hz), 6.5 (d, 1H, $J$ 2.76 Hz), 7.3 (m, 10H). IR ($CCl_4$, $\nu$/cm$^{-1}$): 3000–3050 (w), 2850–2900 (br. s), 1760 (s), 1645 (br. s), 1600 (br. s), 1130 (s), 750 (s), 700 (s). MS, m/z (%): 250 (3.4), 144 (55.3), 116 (100), 77 (7.2).