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Synthesis of new alpha-methylene-gamma-butyrolactoneskeleton using cobaloxime (pseudo vitamin B_{12}) as catalyst

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ABSTRACT

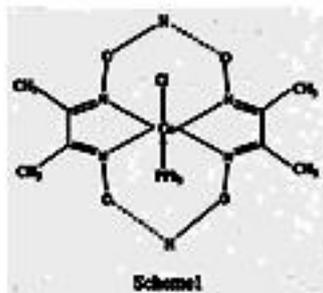
The alpha-methylene-gamma-butyrolactone skeleton belongs to a group of natural compounds, which are called sesquiterpenes. These compounds, have already known to possess biological activities for example anti-tumor, antimicrobial, allergenic, etc. Here a new route to the synthesis of this skeleton is reported using allybenzene and premadecobaloximecatalyst in three steps, such as bromoetherification of alkene, cyclization in the presence of cobaloxime and ultimate oxidation lead to preparation of target alpha-methylene-gamma-butyrolactone. Main products were isolated and characterized via IR, ^1H NMR and GC-Mass.

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INTRODUCTION

A large number of research activities concerning presence of alpha-methylene-gamma-butyrolactone have been reported [1,2,3]. These sesquiterpenes skeleton is reported as anti-HIV, anti-cancer, anti-allergenic, etc [4]. However, for synthesis of these type compounds several different methods were reported. One of these methods is to use electro-organic chemistry [5]. The advantage of this method in comparison to other reported methods is to product super-nucleophilic particles such as (Co^+) ion which has sufficient ability for alkylation [6]. Cobalt complex alkylation was used for synthesis of organic compounds as a one of powerful radical sources. Cobaloxime compounds of bis dimethyl cobalt(III) which were generally called pseudo vitamin B_{12} , was used to synthesize sequentially numbered key rings and providing targets alpha-methylene-gamma-butyrolactone (Scheme 1) [7,8]. Similar products were also reported from aldehydes [9].



This complex performs the cyclization process via ions (Co^+) , (Co^{2+}) and (Co^{3+}) [10,11]. Here, we are reporting a new route for synthesis of alpha-methylene-gamma-butyrolactone. For this purpose we utilized premade fresh cobaloxime as catalyst in an electron transfer cycle via three steps; initially, preparing of bromoether from allybenzene in the presence of NBS and propargyle alcohol. Next step preparation

of methylene oxalane from bromoetherin the presence of chloro-cobaloxime catalyst. Lastly, oxidation of the methylene oxalane to target alpha-methylene-gamma-butyrolactone utilizing Jones reagent.

Experimental Section:

In general, each step was isolated through [SiO₂:60-7730 mesh]. IR spectra were taken with KBr disk for solid and CCl₄ for a solution using Shimadzu 470 spectrometer. ¹H NMR spectra were recorded using instrument, DRX-500MHz Avance with internal standard TMS and CDCl₃. GC-Mass was recorded using instrument 689HP in acetone.

Preparation of bis(dimethyl glyoximate) triphenyl phosphine cobalt (III):

Dry EtOH 96% (40ml), DH (1.129g, 9.4mmol), CoCl₂·6H₂O (1.28g, 4.3mmol) were added to round-bottom flask the mixture was heated and stirred at 60 °C. To this mixture was added PPh₃ (2.36g, 9mmol). At this stage the color of solution gradually was turned from dark green to purple and finally to stable brownish. After the solution was cooled by remaining 30 min at room temperature. Filtered and the precipitate was washed with H₂O, Et₂O and dry EtOH (1.336g, 2.53mmol, 53.2%). IR (KBr): 518 (Co-N), 698 (bend aromatic), 1085 (N-O), 1285, 1438, 1550 (C=N), 2945 (C-H), 3400 (O-H) cm⁻¹. ¹H NMR (500MHz, CDCl₃): δ: 2.02 (s, 12H, CH₃), 7.3-7.5 (m, 15H, Ar-H) ppm.

Preparation 3-bromo-2-prop-2-enyloxy-propyl-benzene 3:

NBS (4.3g, 24mmol) was dissolved in propargyl alcohol (20ml). The solution was stirred at -35 °C. Allylbenzene (3.5ml) in CH₂Cl₂ (20ml) was added for 1h. The reaction was maintained at 16 °C for 1h and allowed to come to room temperature for 24h. After this time to this solution was added NaOH (1N, 25ml). The mixture was extracted with CH₂Cl₂ (3×20ml). Organic phase was washed with NaOH (1N, 10ml), separated and dried over anhydride MgSO₄. The solvent was removed. Oily phase was monitored through TLC and isolated through [SiO₂:60-7730 mesh, CH₂Cl₂:petroleum ether (4:17)] compound **3** (0.95g, 3.74mmol, 14.8%) as center cut was recovered. IR (CCl₄): 665 (C-Br), 1075 (C-O stretch), 2900 (C-H aliphatic), 3010 (Ar-H), 3300 (C≡H) cm⁻¹. ¹H NMR (500MHz, CDCl₃): δ: 2.5 (t, 1H, J=2.4Hz), 2.5 (t, 1H, J=2.4Hz, C≡H), 2.6 (d, J=5.4Hz, 2H), 3.3 (dd, J=4.3, 10.8 Hz, 1H, HC-Br), 3.4 (dd, J=5, 10.8 Hz, 1H, HC-Br), 3.9 (m, 1H, HC-O-C), 4.2 (d, J=2.4Hz, 2H, CH₂-O), 7.2 (m, 5H) ppm.

Preparation 2-benzyle-4-methylene-tetrahydrofuran 7:

To a stirred solution of **3** (0.85g, 3.34mmol) in EtOH (20ml) was added NaOH (10N, 0.5ml) and NaBH₄ (127mg, 3.34mmol) at 50 °C under argon atmosphere. Then, to this mixture cobaloxime catalyst (0.5mg, 0.85mmol) for 1.5h was added and stirred for additional 3h. After that EtOH solution was evaporated and the remaining oily residue was washed with saturated NaCl and extracted with petroleum ether: Et₂O (1:4), (3×15ml). The organic phase was dried over anhydride MgSO₄ and evaporated. The residue was chromatographed [SiO₂:60-7730 mesh, petroleum ether:Et₂O (1:8)] to isolate center cut oily compound **7** (0.61g, 3.5 mmol, 34%).

IR (CCl₄): 1090 (C-O, ether), 1450 (C=C, Ar-H), 1640 (C=C), 3000 (C-H, aliph) cm⁻¹. ¹H NMR (500MHz, CDCl₃): δ: 2.9 (d, J=6.3Hz, 2H), 3.39 (dd, J=4.38, 15.9 Hz, 1H), 3.9 (m, J=4.9 Hz, 1H, O-C-H), 3.4 (dd, J=5, 15.9 Hz, 1H), 6.4 (d, J=15.9 Hz, 1H, =C-H), 6.2 (dt, J=4.38, 15.9 Hz, 1H, =C-H), 7.2 (m, 5H, Ar-H) ppm.

Preparation of 5-benzyle-3-methylene-dihydrofuran-2-one 9:

Mixture solution of CH₂Cl₂ (24ml), pyridine (2ml) and CrO₃ (1.5g, 15mmol) was stirred for 20min. To this solution was added compound **7** (0.32g, 1.38 mmol), CH₂Cl₂ (10ml) and was refluxed at 60 °C for a further 3h and then filtered. The filtered was washed with CH₂Cl₂ and saturated NaHCO₃. The mixture was extracted with CH₂Cl₂ (3×20ml), and was washed with HCl (2N) for a second time. The mixture was purified through (SiO₂:60-7733 mesh) column chromatography. The column was washed with CHCl₃ and evaporated to dryness. The organic phase was chromatographed [SiO₂:60-7730 mesh, n-hexane:Et₂O (1:8)] to isolate center cut butyrolactone **9** (0.289, 1.106 mmol, 65%); IR (CCl₄): 695, 1090 (C-O, ether), 1450 (C=C, Ar-H), (1640, C=C) cm⁻¹. ¹H NMR (500MHz, CDCl₃): δ: 3.3 (d, J=4.5Hz, 2H), 3.8 (m, 2H, =C-H), 4.2 (m, 1H), 6.4 (m, 1H), 6.8 (d, J=14Hz, 2H), 7.2 (m, 5H, Ar-H) ppm. MS, m/z (%), 6890HP, acetone: 188 [C₁₂H₁₂O]⁺ (17%), 160 [C₁₁H₁₂O]⁺ (48%), 144 [C₁₁H₁₂O]⁺ (63%), 91 [C₇H₇]⁺ (97%).

RESULTS AND DISCUSSION

Our aim was to obtain an organic compound with new alpha-methylene-gamma-butyrolactone skeleton using cobaloxime complex. Cobaloxime belongs to a group of bis[(dimethylglyoximatecobalt(III))(bis-DH)], which was reduced to a super-nucleophile (Co^+). Here cobaloxime was prepared through mixing CoCl_2 , $6\text{H}_2\text{O}$, DH ligand and PPH_3 in EtOH. Bis[DH] was formed under vigorous stream of air [12] with 53.2% yield. IR spectrum reveals the C=N, at 1550, Co-N at 518, N-O at 1085, and O-H stretching at 3400cm^{-1} . ^1H NMR spectrum of bis[DHCo(III)] reveals δ 2.02(s, 12H), δ 7.3-7.5(m, 15H) ppm. In other efforts we used allylbenzene **1** for the production of alpha-methylene-gamma-butyrolactone **9** via compounds **2**, **3** and **7** in three steps. For preparation of bromoether **3** a mixture of allylbenzene **1**, propargyl alcohol and NBS was stirred at -35°C for 3h according to the reported literature with minor modification (in order to increase the reaction yield the mixture was stirred for 24h at room temperature) [13, 14]. Isomers **3** and **4** were recovered via bromonium ion **2** (Scheme 2). The main product **3** was prepared through more stable secondary carbocation. In IR spectrum of **3** acetylenic band at 3300, C-O at 1075 and C-Br at 665cm^{-1} was observed and in ^1H NMR δ 2.5(t, 1H), δ 2.6(d, 2H), δ 4.2(d, 2H) and aromatic protons at δ 7.2 (m, 5H) ppm were appeared.

Scheme 2:

Intramolecular preparation of THF derivative **7** was achieved from bromoether **3** in the presence of cobaloxime and NaBH_4 via intermediate radical **6** (Scheme 3). Since super-nucleophile (Co^+) is susceptible to air oxidation therefore was performed under argon atmosphere. To avoid C=C bond dimerization of prepared THF derivative **7** the temperature of reaction was maintained at 60°C . IR spectra of **7** were characterized C-H aromatic bending at 695 C=C alkene at 1450 and C-O at 1090cm^{-1} .

^1H NMR reveals C=C protons at δ 6.4(d, 1H), at δ 6.2(m, 1H) protons of THF ring at δ 2.9(d, 1H), δ 3.3(dd, 1H), (dt, 2H) and aromatic protons at δ 7.2 (m, 5H) ppm.

Scheme 3:

Lastly for preparation of target alpha-methylene-gamma-butyrolactone **9**, THF derivative **7** was refluxed at 60°C for 3h with CrO_3 .py and oxidized to alpha-methylene-gamma-butyrolactone **9** (Scheme 4) [14]. The IR spectrum of **9** reveals C=O of lactone as strong bond at 1770cm^{-1} , aromatic protons at 1440, 1500, 1600cm^{-1} and C=C aliphatic at 1645cm^{-1} . In ^1H NMR the terminal geminal protons of C=C appeared at δ 6.8 (d, 1H), δ 6.4 (m, 1H), benzylic protons at δ 3.3 (d, 2H) and aromatic protons δ 7.25(m, 5H) ppm were appeared. The GC-Mass C_7H_7^+ (67%), $\text{C}_{11}\text{H}_{22}\text{O}^+$ (48%) were characterized.

Scheme 4

Conclusion:

In this short note, we report a simple new procedure for preparation of alpha-methylene-gamma-butyrolactone⁹ in the presence of allylbenzene and premade cobaloxime catalyst in three steps, such as bromoetherification of alkene, cyclization in the presence of cobaloxime and ultimate oxidation for preparation of this target gamma butyrolactone.

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