ABSTRACT

Isodecaprenol (V, 50 carbon chain) was anticipated to occur via a zinc chloride catalyzed coupling reaction obtained Coenzyme Q

INTRODUCTION

frequently referred to as the “miracle nutrient”, [2] CoQ

in biomedical science; the combination of a polar head group

in the human body accounts for its another name: ubiquinone. It

mitochondrial electron transfer chain because it is present in every

role in maintaining human health and vigor.

It is naturally synthesized in the body. The quinone ring of CoQ10 is

synthesized from the aminoacids, tyrosine and phenylalanine and

the polyrenyl side chain is synthesized from acetyl-CoA. A few of its

many intrinsic worth are involvement in mitochondrial processes

such as respiration, cellular production of ATP, maintenance of heart

muscle strength, quenching of free radicals in the battle against

aging, and enhancement of the immune system [3]. CoQ9 was found

in rodents like mice and rats, while CoQ9, CoQ7 and CoQ6 were found

in yeast and bacteria [4,5]. Literature review suggested that the

CoQ9 exerts its antioxidant property by its reduced form (Figure 1)

found from the studies on rat liver.

Like CoQ10, CoQ9 is not simply a compound responsible for energy
transduction in mitochondrial membrane in rat heart; it also serves

as a functional element in the cells and possesses ability for redox
cycling. The CoQ9 differs from CoQ10 with respect to the number of

isoprenoid units in the tail: CoQ10 has ten units in contrast to the

presence of nine units in CoQ9. The majority of the CoQ10 is found in

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A NEW METHOD OF SYNTHESIS OF COENZYME Q10 FROM ISOLATED SOLANESOL FROM TOBACCO WASTE

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RESULTS: Coenzyme Q10 has been semi-synthesized by a novel process from the solanesol isolated from tobacco waste (biological waste) using readily available and inexpensive precursors like PCl3, ethyl acetoacetate, Grignard reagent and benzohydroquinone derivative via the formation of important precursor Isodecaprenol and optimizing the each reaction. The overall yield of Coenzyme Q10 was 17.24% under the optimized conditions.

Conclusion: This process achieved CoQ10 starting from an abundantly available solanesol from tobacco waste. Further improvement in the coupling reaction between Isodecaprenol (V) and Benzohydroquinone (VII) in the presence of Lewis acid may lead to a better and viable synthetic process. Hence this process may be economical and potential to be used for large-scale production.

Keywords: Coenzyme Q10, Isodecaprenol, Solanesol, Coupling reaction.
mammalian hearts including human myocardium [6] and is not an essential nutrient, because it can be synthesized in the body. And also found high amounts of CoQ₀ in several food products including meat, fish, peanuts and broccoli [7].

It is also used in the treatment of periodontal disease, diabetes, Parkinson’s, Alzheimer’s, Huntington’s disease and to help counteract the aging process. It is also effective in relieving certain brain disorders by temporarily restoring mitochondrial activity in cells. There are two major factors that lead to deficiency of CoQ₁₀ in humans: reduced biosynthesis, and increased utilization by the body. It is not toxic (there are no reported side effects). It is generally employed as a supplement, rather than a replacement for standard medical treatment. Dietary intake of CoQ₁₀ is about 2-5 mg/day, which is inadequate for the body under pathophysiological conditions [8]. Although much of society is lack of awareness of the importance of ubiquinone, but chemists have devoted considerable effort in attempting to devise economically viable routes to this nutraceutical [9] as well as its lower homologues [10] since the first effort in attempting to devise economically viable routes to this synthetic process for Coenzyme Q₁₀ [9].

The authors describe herein a new, short and highly efficient semi-synthetic method.

MATERIALS AND METHODS

Chemistry

All reagents and solvents were used as purchased without further purification. Melting points were determined on a standard Boetius apparatus and are uncorrected. The purification. Melting points were determined on a standard Boetius apparatus and are uncorrected. The protective filters. The major chemicals ethyl acetoacetate, tetrahydrofuran (8 ml) over a period of 30 minutes and the reaction mixture was stirred at room temperature for 2 to 3 hr. The mixture was further stirred at room temperature for 2 to 3 hr. The mixture was further stirred at room temperature for 2 to 3 hr. The mixture was further stirred at room temperature for 2 to 3 hr. The mixture was further stirred at room temperature for 2 to 3 hr.

Experimental

Synthesis of solanesol chloride (II) from solanesol (I)

Phosphorus trichloride (1 ml, 0.01 mol) was added to a cooled dimethyl formamide (2 ml) at 10 °C slowly and the mixture was allowed to stand at room temperature for 90 minutes. To the mixture obtained, a solution of solanesol, 1 (5.0 g, 0.007 mol) in toluene (10 ml) slowly at 10 °C. After addition, the reaction mixture was stirred for 90 min, poured into cold water (50 ml) and extracted with ethyl acetate (2 x 20 ml). Ethyl acetate extract was dried over sodium sulphate and concentrated under vacuum to give solanesol chloride, II (3.40 g).

1-Chloro-3,7,11,15,19,23,27,31,35-nonanethyloxycarboxy-2,6,10,14,18,22,26,30,34-nonaene (II): White solid, yield 78.0 %, mp 40-42 °C. IR (KBr, cm⁻¹): 2928 (CH), 2926 (CH), 1632 (C=C), 1446 (CH₂), 1372 (CH₂), 846 (C-H). 1H NMR (CDCl₃, δ ppm): 2.13-2.16 (4H, 2CH₂), 1.75 (3H, 2CH₃), 1.15 (5H, 5CH₂), 0.78-0.89 (5H, CH₃). 13C NMR (CDCl₃, δ ppm): 146.0, 135.8, 135.7, 124.6, 45.6, 38.2, 29.7, 27.0, 25.5 and 21.4. LC-MS [APCI-ESI-MS (80 eV)] (m/z %): 763 (M + Na), 614 (M + H, 512 (M + 138), 471 (M - 179), 409 (M - 241). Anal. Calcld for C₄₅H₇₃Cl: C, 83.14; H, 11.24; Cl, 5.46. Found: C, 83.38; H, 11.21; Cl, 5.45.

Synthesis of solanesol (II) from solanesol chloride (II)

To a stirred mixture of solanesol chloride, II (3.40 g, 0.005 mol), toluene (15 ml), tetra-n-butylammonium bromide (TBAB) as phase transfer catalyst (PTC) (1.70 g, 0.005 mol) and potassium carbonate (0.7 g, 0.005 mol), was added ethyl acetate (0.65 g, 0.005 mol) and then the reaction mixture was stirred under reflux for 4 to 5 hr at room temperature. The reaction mass was cooled, washed with water (5 ml), dried over sodium sulphate and concentrated under vacuum to yield solanesol, III (3.0 g) as an oil.

3-(3,7,11,15,19,23,27,31,35)-nonanethyloxycarboxy-2,6,10,14,18,22,26,30,34-nonaene-ethyl acetate (III): White solid, yield 80.0 %, mp 34-36 °C. IR (KBr, cm⁻¹): 2957 (CH₂), 2923 (CH₃), 1743 (C=O), 1698 (C=C), 1447 (CH₂), 1372 (CH₂), 1236 [(C=O)-0]. 1H NMR (CDCl₃, δ ppm): 0.78-0.89 (5H, 5CH₂), 1.23-1.27 (3H, 2CH₃), 1.42 (3H, CH₃), 1.67 (3H, CH₃), 1.70 (3H, CH₃), 2.04 (2H, 2CH₂), 2.75 (3H, 2CH₃). 0.49-0.54 (9H, 9 CH₃). 4.09-4.14 (4H, 4H, 4CH₂). LC-MS [APCI-ESI-MS (80 eV)] (m/z %): 766 (M + Na), 587 (M - 156). 171 (M - 572), 92 (M - 651). Anal. Calcld for C₃₅H₅₂O: C, 83.27; H, 11.04; O, 6.46. Found: C, 83.82; H, 11.04; O, 6.45.

Synthesis of solanesol acetone (IV) from solanesol ester (III)

A mixture of solanesol ester, III (3.0 g, 0.004 mol) in methanol (15 ml), 10% methanolic potassium hydroxide solution (10 ml) were used as purchased without further purification. Melting points were determined on a standard Boetius apparatus and are uncorrected. The IR spectra were recorded in Perkin-Elmer BFXI FT-IR spectrophotometer using KBr disc method. 1H and 13C NMR spectra were recorded in the indicated solvent on a Bruker AMX 400 and 100 MHz respectively with tetramethylsilane (TMS) as internal standard (chemical shifts in δ ppm). The splitting patterns of 1H-NMR were as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The LC-MS [APCI-ESI-MS (80 eV)] spectra were recorded on Agilent HPILC 1100 series. The elemental analyses of the synthesized compounds were recorded on Carlo Erba 1100 system and were within ± 0.4% of the theoretical values. TLC was performed on Silica Gel F 254 plates (Merck) with visualization by UV (254 nm) chamber with protective filters. The major chemicals ethyl acetoacetate, tetrahydrofuran (8 ml) over a period of 30 minutes and the reaction mixture was stirred at room temperature for 2 to 3 hr. The reaction mass was cooled to 10°C and to this was added a solution of ammonium chloride (1.5 g) in water (10 ml). The pH of the reaction mass was adjusted to 7 with acetic acid, extracted with ethyl acetate (2 x 50 ml), dried over sodium sulphate and concentrated under vacuum to afford isodecaprenol, IV (1.2 g) as waxy solid.

3-Hydroxy-3-methyl-4-(3,7,11,15,19,23,27,31)-nonanethyloxycarboxy-2,6,10,14,18,22,26,30,34-nonaene-butanol-1-ene (IV): White solid, yield 72.50 %, mp 34-36 °C. IR (KBr, cm⁻¹): 3418 (OH), 2926 (CH₂), 2857 (CH₂), 1652 (C=C), 1444 (C=C), 1372 (CH₂). 1H NMR (CDCl₃, δ ppm): 1.24-1.27 (3H, 2CH₃), 1.55 (3H, CH₃), 1.59 (3H, CH₃), 1.67 (3H, CH₃), 1.95-1.99 (9H, 9 CH₃). 0.78-0.89 (5H, CH₃). 1.24-1.27 (3H, 2CH₃), 1.75 (3H, CH₃). 1.67 (3H, CH₃). 2.04 (2H, 2CH₂). 2.06-2.08 (2H, d, J = 7.6 Hz, CH₂). 2.13 (3H, CH₃). 2.63 (2H, CH₂). 2.09-4.14 (9H, 9H, 9 CH₃). 5.09-5.13 (2H, 2CH₂). LC-MS [APCI-ESI-MS (80 eV)] (m/z %): 772 (M + Na), 668 (M - 31), 533 (M - 166), 325 (M - 374), 262 (M - 437), 171 (M - 528).
Synthesis of Coenzyme Q_{10} (VI) from Isodecaprenol (V)

To a mixture of 2,3-dimethoxy-5-methyl-1,4-benzohydroquinone, VII (0.182 g, 0.001 mol) and isodecaprenol, V (1.2 g, 0.001 mol) in ethyl acetate (25 ml) was added anhydrous zinc chloride (0.2 g, 0.001 mol) and catalytic amount of acetic acid and stirring continued until clear solution obtained. Then solvent was removed, residue was heated to 35 °C for 2-3 hr. A temperature of 30 °C and reaction duration of 2 hr was ideal to give crude isodecaprenol of the formula V. This crude product was crystallized from acetone or acetonitrile to give isodecaprenol of high purity (HPLC-90%).

RESULTS and DISCUSSION

Conversion of solanesol (I) to solanesol acetone (II)

Chlorination of solanesol was tried with phosphorous trichloride/thionyl chloride in solvents like benzene/toluene/dimethyl formamide. Reaction of solanesol with thionyl chloride in the mole ratio of 1:0.7 was proceeding at a temperature of 50-55 °C but the quality of the product, obtained, was poor. The preparation of solanesol chloride was then tried with phosphorous trichloride in the mole ratio of 1:0.5 gave good yield of solanesol chloride. Duration of 1.5 hr, a temperature of 25-30 °C and dimethylformamide, as a solvent, were the more preferred conditions.

Conversion of solanesol acetone (II) to solanesol ester (III)

Reaction of solanesol acetone of formula II with ethyl acetoacetate to form solanesol ester of the formula III was carried out in the presence of bases like NaOEt, K_{2}CO_{3} or NaOEt using TBAB, TEBAC or CTAB as PTC. Solvents for the reaction used were toluene, acetone, acetonitrile or dimethyl formamide at a temperature of 70-110 °C. Reaction in the presence of base like sodium ethoxide was progressing well, but the yield of the product was not good. Then the reaction was tried using alkali metal carbonate and TBAB as PTC. The reaction was preferably conducted in toluene, acetone, acetonitrile etc. using alkali metal carbonate and TBAB as PTC. The temperature of 90-100 °C and duration of 4-5 hr was ideal for the reaction.

Conversion of solanesol ester (III) to solanesol acetone (IV)

Hydrolysis of the solanesol ester was achieved in an alcohol like ethanol or methanol by using sodium hydroxide or potassium hydroxide. A temperature of 50-80 °C and duration of 2-4 hr was preferred. The reaction was more preferably carried out in 10-20% methanolic potassium hydroxide for 2 hr at a temperature 55-60 °C to give the solanesol acetone of formula IV.

Conversion of solanesol acetone (IV) to isodecaprenol (V)

Solanesol acetone in tetrahydrofuran was treated with vinyl magnesium bromide under nitrogen atmosphere at a temperature 5-
1:1. Temperature of the reaction was 35-40 °C. Quality of the product thus obtained, was good but not to satisfactory level. Then, condensation reaction was conducted in the presence of zinc chloride as Lewis acid. Coupling reaction was conducted using equimolar mixture of hydroquinone derivative of formula VII, isodecaprenol (V) and 0.5-1.5 moles of zinc chloride in the presence of catalytic amounts of aliphatic acids like acetic acids, propanoic acids, pivalic acid, monochloro acetic acid, trichloro acetic acid and trifluorooctylic acid at a temperature of 30-55 °C. At a temperature of 30-40 °C the rate of reaction was very slow. However, the best yield of coenzyme Q₁₀ formula VI was obtained, when the coupling reaction of equimolar mixture of hydroquinone VII, isodecaprenol V and zinc chloride was conducted in the presence of acetic acid or trichloroacetic acid at a temperature of 40-45 °C. Duration of reaction was 30-45 minutes.

CONCLUSION

Coenzyme Q₁₀ is a potentially useful compound having wide number of health applications especially those related to cardiovascular diseases. Though the CoQ₁₀ from biotechnology process can meet the current demand, no commercially viable synthetic process is available. In the present study, we have developed a simple and effective method for the synthesis of Coenzyme Q₁₀ by a novel process from the solanesol isolated from tobacco waste (biological waste) using readily available and inexpensive precursors like PCl₃, ethyl acetoacetate, Grignard reagent and hydroquinone derivative via the formation of important precursor Isodecaprenol. The key parameters of each reaction were also optimized and the overall yield of Coenzyme Q₁₀ VI was 17.24% under the optimized conditions. Hence this process was found to be economical, and has the potential to be used for large-scale process also.

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THE AUTHORS HAVE NO CONFLICT OF INTEREST

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