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International Journal of Pharmaceutical and Phytopharmacological Research

Int.J.Pharm.Phytopharmacol.Res. 2011, 1(1): 17-22

New Method for Synthesis of 3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid and 1- feruloyl-β-D-glucose

Kunal M. Gokhale*

**Lecturer in Pharmacy, Dr.L.H.Hiranandani College of Pharmacy, Ulhasnagar*

Received on: *15/08/2011* ***Accepted on:*** *20/08/2011*

ABSTRACT

Ferulic acid and its esters with polyhydroxy compounds have been tested for LDL-Cholesterol lowering, tumor suppressor activities and also have chemopreventive role in development of cancer. The conventional methods to obtain Ferulic acid [3-(4-hydroxy-3-methoxy phenyl) prop-2-enoic acid], a member of caffeic acid family, from natural resources are expensive whereas available synthetic methods suffer from limitations like long reaction time and low yield.

3-(4-hydroxy-3-methoxy phenyl) prop-2-enoic was synthesized using Cu(I)CN and tert-butylhypohalite with better yield. The reaction was carried out at ambient temperature and also involves simple work up. 1-Feruloyl-β-D-glucose, a substrate for serine carboxypeptidases was also synthesized with overall yield of 85%.

Key Words: Ferulic acid, 3-(4-hydroxy-3-methoxy phenyl) prop-2-enoic acid, tert-Butylhypohalite, Cu(I) CN, 1- Feruloyl-β-D-glucose.

INTRODUCTION

Ferulic acid is a member of Caffeic acid family. It is present as such in *Ferula foetida*. Otherwise it occurs usually as ester or amide derivative in natural products[1]. It is found in the seeds of brown rice, whole wheat and oat as well as in coffee, apple, orange and pineapple. Ferulic acid is useful anti-oxidant responsible for neutralizing reactive oxygen species (ROS) and found to have a Pro-apoptotic effect in cancer cells thereby leading to their destruction[2]. It also has antitumour activity against Breast cancer and Liver cancer[3]. It is found to be responsible for lowering of Benzopyrene, 4- nitroquinoline-1-oxide like carcinogens[4].Various derivatives of Ferulic acid are found to be important as far as the pharmacological activity is concerned. Trans-feruloyl-β-sitostanol was found to reduce Low Density Lipoprotein- Cholesterol (LDL-C) levels in humans up to 15%[5].O-tocopheryl-succinyl-O-ethyl ferulate was found to reduce replication rate of HIV-1 virus in infected cells in *in-vitro* by 80%.[(6)] Chemopreventive role of (E) form of Caffeic acid & related Polyphenolic compounds in development of Gastric and Colorectal cancer was also established[7].

The usual method for synthesizing ferulic acid by using vanillin and malonic acid is carried out for 3 weeks. Other method on similar basis uses vanillin and malonic acid condensation in presence of aromatic bases like aniline; time required for the conventional method was reduced greatly to15 hrs but with the compromisation in the yields of the final product[8]. Attempts to obtain better yield of ferulic acid by making the use of advances in microwave assisted organic synthesis were also not very encouraging. Ferulic acid can also be obtained from culturing pseudomonas in medium containing Clove oil[9].Wittig-Horner

Method[10] by making the use of Triphenylphosphonoacetate (TEPA) with acetylated hydroxyl aromatic aldehydes in liq/liq two phase systems is also applicable.

Aromatic nitriles are important pharmaceuticals and agrochemicals and are important intermediate in synthesis of Carboxylic acids, Benzyl amines and other important chemicals. There is a continued interest in the development of procedures for the effective generation of aromatic nitriles from the corresponding hydrocarbons, especially under mild conditions. There are several cyanation methods available for generation of carbonyl compounds from their corresponding aromatic halides. The substitution of aromatic halides by cyanides is amongst the other general route for preparation of aromatic nitriles. It includes the use of Zinc Cyanide, Potassium Cyanide and Sodium Cyanide etc. The nitriles are also found to be developed from carboxylic acids[11].The well known synthesis via Rossenmund-von-Braun reaction[12] with stoichiometric amounts of Copper (I) Cyanide [Cu(I)CN] unfortunately requires harsh conditions. Tert-butyl hypohalites are well known oxidizing agents[13-15].These agents are so versatile that they are found to be useful in debenzylation[16],deoximation[17] and also for synthesis of 1, 2-diols[18].1- feruloyl-β-D-glucose is commoner substrate for serine carboxypeptidase-like acyltransferases and serves as acyl donor in the biosynthesis of numerous secondary metabolites. In addition, it is involved in plant cell wall cross-linking and is also ideal substrate for studying the kinetics of lignifications involving hydroxycinnamates[19, 20].

The present work aims at synthesizing Ferulic acid using Cu (I) CN and t-butylhypochlorite or t-butylhypoiodite with good yield, better purity and optimization of reaction time (Fig.1). It also involves synthesis of Feruloyl glucose (Fig.2)

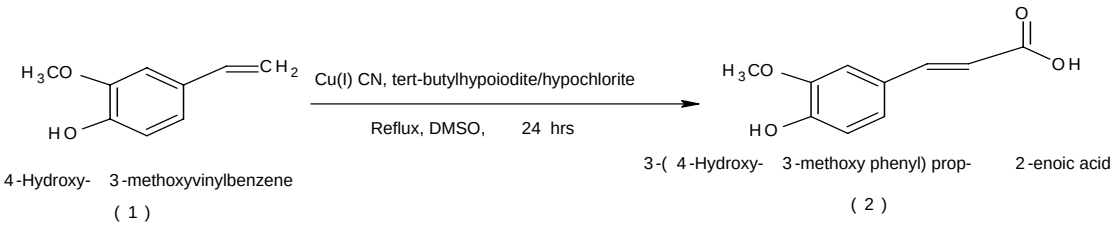

Fig.1: Synthesis of Ferulic acid

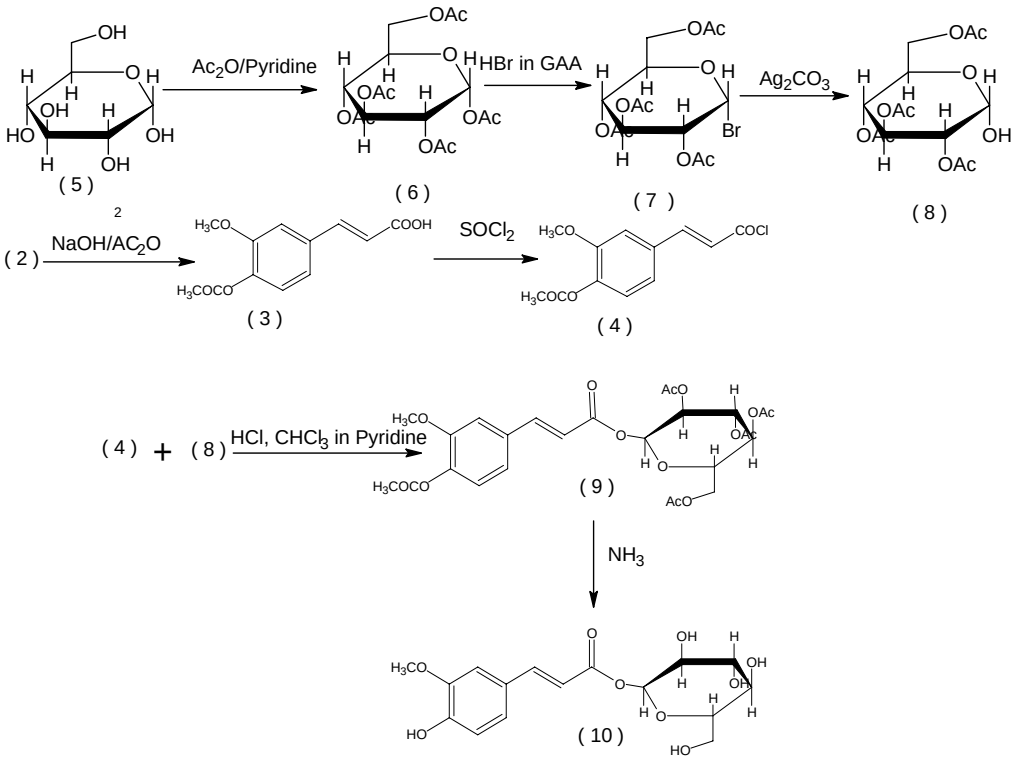

Fig.2: Synthesis of Feruloyl Glucose

MATERIALS AND METHODS

Chemistry

Purity of the starting materials used in the reaction was confirmed by melting point, boiling point, TLC. The purity and structure of compounds synthesized were confirmed by melting point, boiling point, TLC, Infrared (IR) Spectroscopy and Nuclear Magnetic Resonance (NMR) Spectroscopy. The melting point and boiling point of the compounds reported were uncorrected and were recorded by open capillary method on THERMONIK- Campbell Melting Point apparatus and they were in good agreement with the literature reported values.

All the reactions were monitored by the TLC technique, using pre-coated Silica gel plates (Silica gel 60 F_{254}, Merck). TLC was generated by "Ascending Development of the Mobile Phase" method. Development of the spectrum was recorded on the "Perkin Elmer FTIR spectrometer-Spectrum RX1". Solids were recorded as KBr pellets and liquids as thin film of $CHCl_3$.

The proton magnetic spectra's were recorded on "Jeol JNM MY60 FT-FTNMR System". Chemical shifts were reported in parts per million (δ ppm) downfield with respect to TMS (Trimethylsilane). Fractionally distilled solvents were used for Column Chromatography and were dried before use. All the solvents used in reactions were of commercial grade and used as such without purification. 4-hydroxy-3-methoxyvinylbenzene, Copper (I) Cyanaide [Cu (I) CN], tert-butyl hypochlorite and tert-butyl hypoiodide were obtained from Omkar Chemicals, Mumbai and used without further purification.

Experimental

Synthesis of 3-(4-hydroxy-3-methoxy phenyl) prop-2-enoic acid ***(2)***

4-hydroxy-3-methoxy vinylbenzene (**1**), (0.026 mole) was added to the mixture containing (1 mole) of t-butylhypochlorite and DMSO as a solvent (25 ml). The mixture was allowed to reflux for 4 hrs. Then Cu (I) CN (1mole) was added and reaction was kept overnight at reflux temperature. After 24 hours the reaction mixture was allowed to cool to room temperature and filtered at vacuum. The unreacted Cu(I) CN was washed twice with water. The filtrate was evaporated by using vacuum. The yellow liquid obtained was subjected to hydrolysis by using conc.H_2SO_4 and Water. The Ferulic acid **(2)** obtained at the end as yellow crystalline solid which was then recrystallized by using Ethanol. The yellow liquid obtained above appears as a bright yellow spot on TLC (Solvent System: Hexane: Ethyl acetate; 7:3). The product after hydrolysis appears as a dark brown spot on TLC (Solvent System: Hexane: Ethyl acetate; 1:1).The synthesis of ferulic acid by using t-butylhypoiodite (1 mole) was also carried out by keeping all other reagents same.

Melting Point: 172^0C (Uncorrected)**,** IR (KBr) cm^{-1}: 3437, 1690, 1659, 1617

^{1}HNMR ($CDCl_3$) δ 7.862(d,1H, OH), 7.817-6.991(m,3H, Aromatic), 6.7-6.9 (m, 2H, vinylic C-H) (d,2H, CH=CH), 3.942(s,3H, OCH_3)

Synthesis of 3-(4-acetyloxy-3-methoxyphenyl)-2-propenoic acid ***(3)***

Ferulic acid (**2**), (0.025 mole) was added to solution of NaOH (0.082 mole) in 25 ml Water, and the mixture was cooled to below 10^0 C. Acetic anhydride (0.032 mole) was then added to the cold solution. The solution was then stirred at 20^0 C for 10 min. and then at room temperature for 20 min. Then the pH of the solution was adjusted to 4-5 by adding 10% sulphuric acid. The resulting white precipitate was filtered and washed with water. Recrystalization from absolute ethanol gave colorless needles (3.85g, 77%).

Melting Point: 196^0C (198^0C-200^0C), IR (KBr) cm^{-1}: 1690, 1659, 1617

^{1}HNMR ($CDCl_3$) δ 7.887(d,1H, OH), 7.618-7.126(m,3H,Aromatic), 6.7-6.9 (m, 2H,vinylic C-H), 3.881(s,3H,OCH3), 2.325(s,3H,OCH3)

Synthesis of 3-(4-acetyloxy-3-methoxyphenyl)-2-propenoyl chloride ***(4)***

Thionyl chloride (7 mmol) was added dropwise over 10 minutes to the suspension of 3-(4-acetyloxy-3-methoxyphenyl)-2-propenoic acid (0.01 mole) (**3**) in dry dichloromethane (15 ml) containing catalytic amount of DMF at 0^0 C, under the atmosphere of nitrogen. The mixture was allowed to warm to room temperature (25^0 C-30^0 C) and stirred for further 20 min. The resulting colorless solution was then evaporated in vacuum to obtain acid chloride as Pale yellow solid. It was used as such without purification, due to instability.

Note: IR, NMR, M.P. was not recorded due to higher instability.

Synthesis of α-D-glucopyranosepentaacetate ***(6)***
Anhydrous D-glucose (**5**) (0.025mole) was added to solution containing acetic anhydride (0.25mol) and dry Pyridine (25 ml) at 0^0 C. The solution was stirred at 0^0 C until glucose was dissolved. Further solution was stirred at room temperature for 18 hrs. and then poured on crushed ice with vigorous stirring. α-D-glucopyranosepentaacetate precipitated after few minutes. Purification was affected by 3 recrystallizations from Ethanol (Yield: 77%).
Melting Point: 113^0C (110^0C-112^0C), IR (KBr) cm^{-1}: 1742, 1653, 1560
^{1}HNMR ($CDCl_3$) δ7.285(s,5H, H), 4.190(2H, CH_2), 2.191-2.032(s,12H, acetyl CH_3)

Synthesis of 1-bromo-2, 3, 4, 6-glucopyranosetetraacetate ***(7)***
α-D-glucopyranosepentaacetate (**6**) (0.01 mole) was added to 50 ml of HBr in Glacial Acetic acid (33%); the mixture was stirred at room temperature, until clear solution obtained (5min) and filtered into 100 ml of Chloroform. Organic layer was washed with water (2 x 50ml), dried over sodium sulphate and evaporated in vacuum. The brominated tetraacetylglucose was obtained as pale yellow syrup (Yield: 95%). Spectral characteristics match with available data.

Synthesis of 2, 3, 4, 6-glucopyranosetetraacetate ***(8)***
A solution of 1-bromo-2, 3, 4, 6-glucopyranosetetraacetate **(7)** (0.01 mole) in 3ml of dry acetone in 50 ml flask was cooled to 0^0 C in an ice bath. To the cold solution 2-3 drops of water and 2g (7 mmole) of Ag_2CO_3 was added in portions within time period of 15 minutes. The mixture was stirred well during addition and 30 minutes longer. The mixture was then warmed to 50^0 C and filtered. The mass of silver salt was washed with 65 ml of dry acetone. Filtrate was warmed with 65 ml of more acetone, filtered and washed again with acetone. The combined filtrates were concentrated under reduced pressure until most of the solution crystallizes. The mixture was warmed to dissolve the crystals, this solution was then poured into beaker and an equal volume of absolute ether was added. The resulting solution was cooled in freezing mixture with gentle stirring. The glucosetetraacetate crystallizes quickly after 10 minutes, filtered, air dried (Yield: 92%).
Melting Point: 130^0C (132^0C-134^0C), IR (KBr) cm^{-1}: 3479, 1747
^{1}HNMR ($CDCl_3$) δ 7.285(s,1H, OH), 4.190(2H, CH_2), 2.191-2.032(s,15H, acetyl CH_3)

Synthesis of 1-(Acetyl feruloyl)-2, 3, 4, 6-glucopyranosetetraacetate[21] ***(9)***
Acetylferuloylchloride (**4**) (0.03mole) and tetraacetylglucose (**8**) (0.01 mole) were added to 10ml of $CHCl_3$ and 1.5ml of Pyridine with stirring, the heat was evolved during addition. After stirring for 2 days at room temperature, 10ml of $CHCl_3$ was added to the reaction mixture with continuous agitation. The extraction was carried out with 2N Amonium sulphate (10ml) solution, then with saturated Sodium bicarbonate (10ml) and finally with water (2 x 10ml).Organic layer was dried over sodium sulphate and boiled with activated charcoal, evaporated to dryness and shaken with 3-4 fold quantity (30-40ml) of dry Ether. The compound precipitated as yellowish white needles (Yield: 73%).
Melting Point: 169^0C (165^0C-167^0C), IR (KBr) cm^{-1}: 1751 1627
^{1}HNMR($CDCl_3$):7.924(s,5H,H),7.659-7.162 (m,3H,Aromatic), 6.5-6.7 (m,2H,Vinylic CH), 4.190(s, 2H, CH_2), 3.917 (s, 3H, OCH_3),2.362-2.0369(s,15H, Acetyl CH_3)

Synthesis of 1- feruloyl-β-D-glucose ***(10)***
1-(Acetyl feruloyl)-2, 3, 4, 6-glucopyranosetetraacetate (**9**) (0.01 mole) was added under N_2 atmosphere to the flask containing 25ml of Liq.NH_3 saturated with Ethanol at room temperature. Slow stream of Liq.NH_3 was introduced to the flask for 2-3 hrs. Finally solution was allowed to stand for 30 minutes and evaporated in vacuum. The yellow syrup remaining behind was extracted with 40ml of water, from this on standing at 0^0 C crystals of feruloyl glucose along with small qty. of ferulic acid crystallizes out.(This was monitored by TLC, Solvent system used was Methanol: Glacial acetic acid: Chloroform; 4:1:2.2) Product mixture was filtered, dried and recrystallised from Ethanol. Finally feruloyl glucose was obtained as colorless prisms; it was then filtered and dried at vacuum pump (Yield: 85%).
Melting Point: 124^0C (120^0C-124^0C), IR (KBr) cm^{-1}: 3430, 1751, 1627
NMR:7.867(s, 1H, OH),7.602-7.065(m, 3H, aromatic),6.76.991(m, 2H,vinylic CH),
4.190(s,2H,CH_2), 3.942(s,3H,OCH_3), 2.342(s, 3H, OCH_3)
$[\alpha]_D^{20}$: -11.65

RESULT AND DISCUSSION

The reaction of 4-hydroxy-3-methoxy vinylbenzene and Cu(I) CN, tert-butylhypoiodite offers the final product of Ferulic acid with yield of 60% whereas with tert-butylhypochlorite the yield was poor; this may be attributed to better leaving capacity of tert-butylhypoiodite than tert-butylhypochlorite. This new method successfully offers the Ferulic acid with the use of Cu(I) CN and tert-butylhypoiodite in better yield and optimization of reaction time. Feruloyl glucose which is an important biotechnological compound was also synthesized with overall yield of 85%.

CONCLUSION

The present work offers novel method for synthesis of ferulic acid using Cu (I) CN and t-butylhypoiodite with reaction time lesser than two days and also gives Feruloyl glucose with better yield. Due to successful synthesis of Feruloyl glucose author is thinking to prepare several such polyhydroxy, polyphenolic esters of ferulic acid and also to evaluate their biologic potential as scavenger of free radicals responsible to cause various pathological conditions including cancer. And it is also necessary to evaluate their potential to inhibit production of carcinogenic metabolite.

ACKNOWLEDGEMENT

Author is thankful to H(S)NC Board, Mumbai and Dr. (Mrs.) S. S. Bhalerao, Principal, Dr. L H Hiranandani College of Pharmacy, Ulhasnagar for providing facilities to carry out work.. Author also thanks Dr V. N. Telvekar, Reader, Dept. of Pharmaceutical Sciences and Technology, ICT, Matunga, Mumbai for their guidance and support throughout the work and also thankful to Dept. of Pharmaceutical sciences and technology, ICT, Matunga, Mumbai ICT for recording the IR, ^{1}HNMR spectra.

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***Corresponding Author**: Mr.Kunal M.Gokhale*
Lecturer in Pharmacy,
Dr.L.H.Hiranandani College of Pharmacy,
Smt.CHM Campus, Opposite Railway Station,
Ulhasnagar, Dist.Thane, Pin-421003,
Maharashtra (India)
Telephone No. (0251)2561463
Fax No. (0251)2733693
Mobile No.9819313292
Email ID: kunal2206598@gmail.com