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Synthesis of Some Novel Coumarinolignans: Newer Catalyst for Phenolic Oxidative Coupling

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Abstract: A newer catalyst was investigated as a catalyst for oxidative coupling of coumarin with propenyl phenols and alkene substrates. This resulted in dimerization of the two through C-O-C linkage yielding some novel coumarinolignanoids. These were characterized by elemental analysis, FT-IR, ^{1}H NMR spectral studies. The rate of reaction was enhanced significantly there by decreasing the overall time of reaction and good product yield was also obtained.

Key words: Coumarinolignans, oxidative coupling, catalyst, spectral study

Introduction

Lignans and neolignans are formed in nature by oxidative dimerization of various C_6-C_3 phenols (Haworth, 1942; Rao, 1978; Gottileb, 1972). Lignans are widely spread in nature (Cole and Weidkopf, 1978) and have broad range of biological activities (Mcrea and Towers, 1984) viz., antitumour (Lopez-Perez *et al*., 2004; Chang *et al.,* 2003.) antifungal etc., (Kamikado *et al.,* 1975; Russell *et al.,* 1976). The biosynthesis and *in vitro* synthesis of lignin and lignans follow oxidative coupling pathway. Oxidation of phenols generates phenoxy radicals, which couple with little selectivity. Formation of C-C and C-O bonds takes place mainly at ortho and para positions of phenolic hydroxyl. Non phenolic oxidative coupling, cycloaddition to quinone monoketals and conjugate addition by acyl anion equivalents have emerged as new synthetic approach for the formation of lignans and neolignans. Yet these methods could not surpass the classical methods of phenolic oxidative coupling, Diel's Alder reaction and Stobbe condensation.

A number of oxidants have been used for β-5-coupling propenyl phenols. Diphenyl selenoxide was used as mild and selective oxidant for intramolecular coupling between a phenol and a catechol that was supposed to proceed via catechol selenurane intermediates (Marino and Schwartz, 1979) . Lee and Cordell, studied biomemitic synthesis of a series of coumarinolignans utilizing both chemical and enzymatic approaches (Lee and Cordell, 1988). The oxidizing agents used in this work included Ag_2O, DDQ, $FeCl_3$ and the enzymes were HRP (Horseradish Peroxide), Tyrosinase, HRP-H_2O_2 and maple extracts. Each of the compounds in the series were subjected to testing in P-388 lymphocyte leukemia test system *in vitro* gave the positive result. Some of natural coumarinolignans like cleomiscosin A, aquillochin, daphneticin and propacin were synthesized by making use of diphenyl selenoxide (Tanaka *et al.,* 1988).

The oxidative phenol coupling of substituted catechol with isoeugenol or coniferyl alcohol in the presence of silver oxide was one-step biomemtic synthesis that resulted in high yield of natural flavanolignans silybin and isosilybin (Merlini and Zanarotti, 1980). Free radical coupling

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mechanism where the first step is intramolecular *O*-β coupling of two phenoxy radicals was suggested (Taylor and Battersby, 1967). Intramolecular cyclization of intermediate product by glacial acetic acid in the presence of sulphuric acid leads to an easy preparation of some natural coumarinolignans of Jatropha glandulifera (Parthasarthy and Pardha, 1984).

Synthesis of furofuranoid lignans through Mukaiyama cyclisation that impressed the cis ring fusion and stereochemistry at fourth chiral center was found to be controlled by transition state conformation (Stevens *et al.,* 1992). Lin and Cordell, (1984). in a previous attempt had synthesized the coumarinolignans through chemical and enzymic oxidation. Silver oxide was used as a chemical oxidant whereas HRP was enzymic oxidant . Oxidative cross coupling of p-hydroxycinnamic alcohols with dimeric arylglycerol β-aryl ether lignin model compound was studied with silver oxide, HRP and wet chloroform oxidation (Syrjanen and Brunow, 1998).

In the present study, we have prepared some coumarinolignanoids by phenolic oxidative coupling of esculetin with coniferyl alcohol (Compd-1), ferulic acid ester (Compd-2), vinyl acetate (Compd-3) and acrylic acid (Compd-4). The products obtained were expected to be regioisomers. The spectroscopic analyses of the recrystallized samples were carried out.

Materials and Methods

Melting points were determined in an open capillary and are uncorrected. All the reagents used were of AR grades. The solvents were purified by standard method and dried before use. FT-IR spectra were recorded on KBr using Perkin-Elmer Spectrum 2000 FTIR spectrometer. ^{1}H NMR was recorded with d_6-DMSO with Brucker spectrospin advance 300 spectrometer. Elemental analysis was carried out on Perkin Elmer 2400 series II CHN S/O Analyser.

Esculetin, ferulic acid ester and coniferyl alcohal was prepared according to the procedure given with some modifications (Jeager *et al.,* 1993). The schematic representation of preparation of esculetin, ferulic acid ester and coniferyl alcohal is shown below:

Preparation of Esculetin

Preparation of Benzoquinone

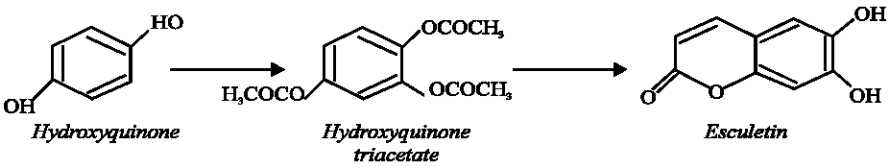
A mixture of hydroxyquinone (10 g), potassium bromate 97 g, water (100 mL) and sulphuric acid (5 mL, 1 N) was warmed to 60°C in round bottom flask on water bath till a clear solution was obtained. The reaction started immediately and black intermediate separated. The temperature was raised to 75°C after which the reaction was stopped. Oxidation was completed in 15-20 min indicated by the formation of yellow soild. The reaction mixture was filtered. Yield 9 g. M.Pt. 116°C (Lit 116-118°C).

Preparation of Hydroxyquinone Triacetate

Analar sulphuric acid (1.6 mL) was added slowly to acetic anhydride (50 mL) in 100 mL conical flask. The temperature was allowed to rise and to this solution was added benzoquinone (16 g) slowly with constant shaking over a period of 10 min. The temperature was kept between 40-50°C, shaking was done for additional 5 min and the reaction mixture was poured into ice cold water. The white solid separated was filtered dried and recrystallised from ethanol as colourless liquid. M.Pt. 96°C (Lit; 97-98°C)

Preparation of Esculetin

A mixture of hydroxyquinone triacetate (24 g), malic acid (918 g) and analar sulphuric acid (36 mL) was heated on a water bath for half an hour under dry condition. The reaction mixture



Preparation of esculetin

was cooled and poured over crushed ice. The brown solid obtained was filtered, washed thoroughly with ice-cold water and dried. It was re crystallized from ethanol as yellow needles, Yield 9 g. M.Pt. 269°C (Lit 270-271°C)

Preparation of Ferulic Acid Ester

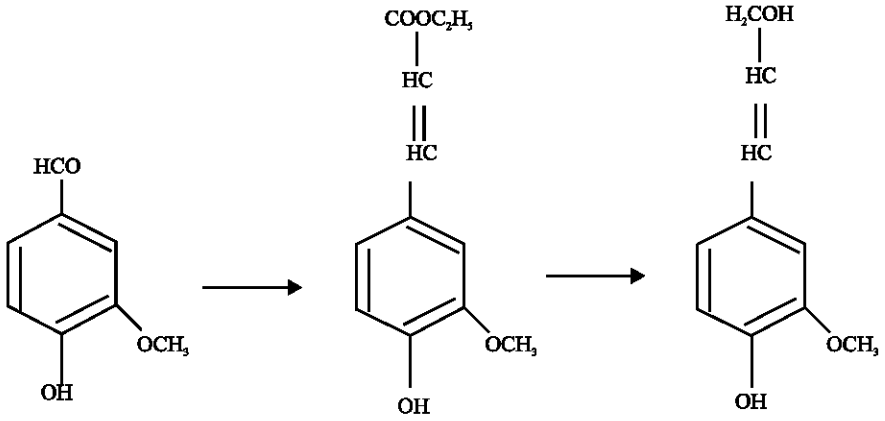
Prepared molecular sodium from 0.04 mole of clean sodium dried xylene contained in a three-necked flask fitted with mechanical stirrer and reflux condenser. When cold xylene was poured off as completely as possible. 0.016 mole of ethyl acetate containing 0.5 mL of absolute alcohol in a flask was cooled rapidly to 0°C and 0.032 moles of verteraldehyde was added slowly (during 90 min) from dropping funnel while the mixture was stirred. The temperature was kept between 0-5°C and was not allowed to rise above 10°C. The stirring was continued when practically all the sodium had reacted. 0.58 mL of glacial acetic acid was added followed by an equal amount of water. The layer of ester was separated and the aqueous layer was extracted with 25 mL of ethyl acetate. The combined organic layer was washed with 150 mL of 1:1 hydrochloric acid and dried with magnesium sulphate. Ethyl acetate was distilled off on water bath and residue distilled Sunder diminished pressure. Yield 75°C. M.Pt. 77°C (Lit 77-78°C)

Preparation of Coniferyl Alcohol

Dry bowl was set up to serve later as cooling bath in a fume cupboard. A three-necked flask with stirrer, dropping funnel and a double surface condenser attached with guard tube containing calcium chloride to open ends. The mechanical stirrer should be powerful one. It must be emphasized that all operations, including weighing with solid lithium aluminium hydride must be conducted in fume cupboard during weighing etc., the front of fume chamber is pulled down so that there is narrow opening to allow hands to enter.

The dropping funnel was removed from the flask neck and replaced by a funnel with a very short wide stem to introduce 0.090 g of lithium aluminium hydride into the flask and 5 mL of sodium dried ether to transfer last traces. The dropping funnel and guard tube were replaced and the stirrer was set in motion and solution of 0.5 g of ferulic acid ester in 15 mL of diethyl ether in dropping funnel. After stirring for 10 min the ferulic acid ester solution was added so that ether refluxed gently; the reaction mixture became viscous and four 25 mL portion of ether added during reduction to facilitate stirring. The stirring was continued for 10 min.

Excess of lithium aluminium hydride was decomposed by drop wise addition 10 mL ethyl acetate. The reaction product was filtered from sludge through sintered glass funnel. The ethereal solution was dried with magnesium sulphate and the ether was distilled off on rotary evaporator. The sludge remaining in filter funnel was dissolved in 20% sulphuric acid; the resulting solution was extracted with ether. The ether was removed by means of rotary evaporator. The residue was crystallized on cooling. Yield 70%. M.Pt. 79°C (Lit = 78-82°C)



Vertaraldehyde Ferulic acid ester Coniferyl alcohol

Preparation of ferulic acid ester and coniferyl alcohol

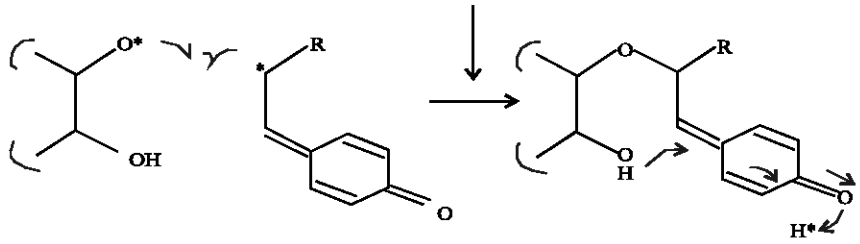
Preparation of Coumarinolignans

The synthesis of lignans were done according to a reported procedure (Merlini and Zanarotti, 1980). Accordingly, coniferyl alcohol (0.6 g; 3 mmol), ferulic acid ester (0.66 g; 3 mmol) , vinyl acetate (0.258 g; 3 mmol) and acrylic acid (0.216 g; 3 mmol) were dissolved in dry benzene-methanol (18:5 V/V; 150 mL) separately each for synthesizing [Compd-1, Compd-2, Compd-3 and Compd-4 respectively. To these added esculetin 0.534 g (3 mmol) and TiO_2 (3 mmol) and suspension was stirred at room temperature. After 30 min of stirring added 3-4 mL hydrogen peroxide and stirring was continued until Thin Layer Chromatography (TLC) showed no starting material. The mixture was filtered and solvent evaporated. Product was recrystallized with methanol/water/ethyl acetate.

Results and Discussion

In the present study, titanium dioxide was analyzed as catalyst in the presence of hydrogen peroxide. The hydrogen peroxide has only been used in the presence of hoersradish peroxidase for the synthesis of coumarinolignans. The investigation is aimed to study the utility of hydrogen peroxide in the presence of transition metal oxide i.e. titanium oxide for the phenolic oxidative coupling. Titanium oxide acts as the most suitable semiconductor for catalytic and photo catalytic process, as it is chemically inert, non-photo corrosive and non-toxic in nature. TiO_2 absorbs light energy or photons that lead to charge separation or photo excitation with energies equal to or greater than band gap energy. An electron is therefore transferred to conduction band leaving a positive hole in the valence band and these holes have high affinity for electron (Davis *et al*., 1994). It has also been reported that with an increase in chemically adsorbed -OH on the surface, the polar properties and hydrophilicity of the surface is enhanced (Yu *et al*., 2002). Since hydrogen peroxide is able to disintegrate at room temperature in the presence of catalysts belonging to transition elements, hence there is probability of OH* radical .

These hydroxyl radicals in turn would abstracts proton from the two reactants giving rise to phenoxyl radicals and thus *O*-β coupling mechanism.



O-β coupling mechanism

Initially the coupling reactions were carried out in the presence of titanium dioxide to observe the course of reaction. The attempts were feebly successful. The reactions were carried out for up to 36 h in some cases and changing temperature up to 60°C however did not produce any good yields of products. The reaction was able to proceed when the catalytic amount of hydrogen peroxide was added. This was able to initiate the reaction soon and 8-12 h was the overall reaction of time. The yields of the product were quite high as compared to previous attempts of synthesis of lignans.

The FT-IR spectra of the synthesized compounds (Compd 1-4) in KBr were made and spectra were recorded in the range of γ_{max} 4000 - 400 cm^{-1}. The C-O-C group peaks observed in esculetin with coniferyl alcohol, ferulic acid ester, vinyl acetate and acrylic acid are observed in the range of γ_{max} 1270-1230 cm^{-1} and shifts in the range of γ_{max} 1282-1224 cm^{-1} confirming the coupling of the synthesized compounds.

Compd-1

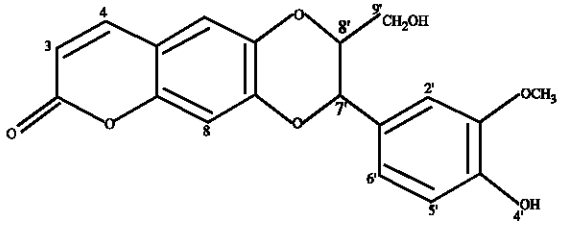
Brownish-Yellow solid; Yield (52%); FTIR (KBr), 3650, 3610.5, 3421.1, 1691, 1564.2, 1443,1282.7, 1228.5 cm^{-1}; δ_H (300 MHz; d_6-DMSO) 6.37 (1H, d, H-3,), 7.66 (1H , d, H-4), 7.23 (H-5, s, Ar), 7.1 (H-8, s, Ar,), 7.51 (H-2', s, Ar), 3.785 (H-3', s, OCH_3), 11.31 (H-4', d, OH), 7.3 (H-5', t, Ar), 7.32 (H-6', d, Ar), 5.5 (H-7', d, -CH), 4.491 (H-8', q, -CH), 3.9 (H-9', t, $-CH_2OH$), ; Calc. for $C_{19}H_{16}O_7$: C , 64.04; H, 4.49; O, 31.46 Found : C, 67.09; H, 4.42; O, 31.41.

Compd-2

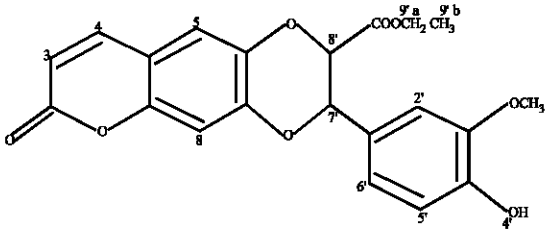
Buff solid; Yield (60%); FTIR (KBr) 3610.2, 3332.1, 1745.3, 1691.9, 1565, 1536.1, 1281, 1228.5 cm^{-1}; δ_H (300 MHz; d_6-DMSO) 6.39 (1H, d, H-3), 7.62 (1H , d, H-4), 7.27 (H-5, s, Ar), 7.3 (H-8, s, Ar,), 7.52 (H-2', s, Ar), 3.71 (H-3', s, OCH_3), 11.31 (H-4', d, OH), 7.3 (H-5', t, Ar), 7.33 (H-6', d, Ar), 5.8 (H-7', d, -CH), 3.81 (H-8', d, -CH), 3.85 (H-9a', q, $-CH_3CH_2COO$), 3.85 (H-9b', t, $-CH_3CH_2COO$) ; Calc. for $C_{21}H_{18}O_8$: C , 63.31; H, 4.52; O, 32.16 Found : C, 63.39; H, 4.50; O, 32.11.

Compd-3

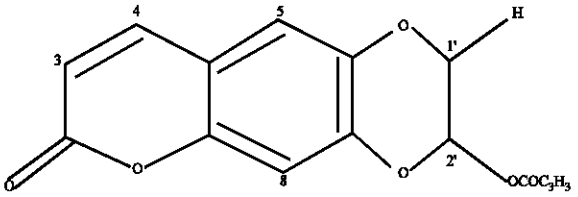
Orange-Brown solid; Yield (61%); FTIR (KBr) 3333.6, 1742.6, 1684, 1542, 1277.4, cm^{-1}; δ_H (300 MHz; d_6-DMSO) 6.33 (1H, d, H-3), 7.61 (1H, d, H-4), 7.3 (H-5, s, Ar), 7.16 (H-8, s, Ar,) , 7.5 (H-1', d, $-CH_2$), 2.36 (H-2', t, *-CH*), 2.05 (H-3', s, $OCOCH_3$); Calc. for $C_{13}H_{10}O_6$: C , 59.54; H, 4.52; O, 32.16. Found : C, 59.51; H, 4.56; O, 32.19.



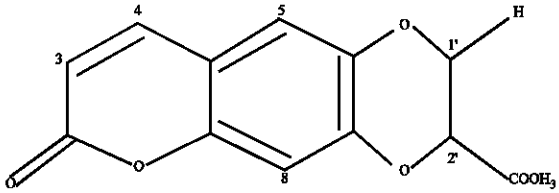
Compd-1



Compd-2



Compd-3



Compd-4

Compd-4

Orange-Yellow solid; Yield (62%); FTIR (KBr) 3333.2, 1760, 1699, 1686, 1599, 1522, 1291, cm^{-1}; δ_H (300 MHz; d_6-DMSO) 6.37 (1H, d, H-3), 7.66 (1H, d, H-4), 7.20 (H-5, s, Ar), 7.2 (H-8, s, Ar,) , 3.5 (H-1', d, $-CH_2$), 3.36 (H-2', t, *-CH*), 11.6 (H-3', d, -COO*H*) Calc. for $C_{12}H_8O_6$: C, 58.06; H, 3.22; O, 38.71 Found : C, 58.02; H, 3.21; O, 38.75.

Conclusions

In summary titanium dioxide in the presence of hydrogen peroxide is a viable method for carrying out synthesis of lignans through phenolic oxidative coupling. The coarse of reaction was significantly reduced when compared to previous attempts. Titanium oxide itself did not produce any good results. It suggests that the use of oxides of transition metals could further be explored to obtain a better yield of lignans.

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