Tetrahedron Vol 45, No. 21, pp. 6867 to 6874, 1989
Printed in Great Britain

0040-4020/89 $3.00+.00
Pergamon Press plc

MUSHROOM TYROSINASE[1] CATALYSED SYNTHESIS OF COUMESTANS, BENZOFURAN DERIVATIVES AND RELATED HETEROCYCLIC COMPOUNDS

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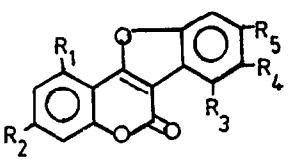
(*Received in UK* 9 *August* 1989)

Abstract: Full details of an improved synthesis of coumestan derivatives and their structural analogues, viz., wedelolactone, 11-hydroxy aureol, 11-hydroxy coumestrol along with benzofuran derivatives and related heterocyclic systems are reported by coupling of in situ generated o-quinones from catechols catalysed by mushroom tyrosinase with various reactants.

Coumestans, 6H-benzofuro[3,2-c] [1] benzopyran-6-one are the oxygenated class of aromatic natural products known to possess phytoalexine[2] and oestrogenic activities[3]. Many biologically active compounds such as wedelolactone, coumestrol, aureol, medicagol, psoralidin, pisatin and trifiliol contain the basic skeleton 1. Wedelolactone isolated[4] from Wedelia calandulaceae possess the heamostatic activity[4]. Similarly coumestrol from Trifolium repens and pisatin from pea pods of Pisum sativum are known for oestrogenic and antifungal activities respectively[4].



1

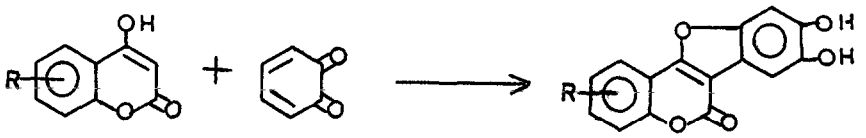
$R_1=R_2=R_3=H$; R_4 & R_5 = OH;	11,12-Dihydroxy coumestan
$R_1=R_4=R_5=OH$; $R_2=OMe$, $R_3=H$;	Wedelolactone
$R_1=R_3=R_4=H$; R_2 & $R_5=OH$;	Coumestrol
$R_1=R_2=R_5=OH$; R_3 & $R_4=H$;	Aureol
$R_1=R_3=H$; $R_2=OH$; R_4 & R_5=Methylene dioxy	Medicagol
$R_1=R_4=H$; R_2 & $R_3=OH$; $R_5=OMe$	Trifiliol
$R_1=R_3=R_4=H$; $R_5=OH$; R_2=Isopentenyl	Psoralidin

Several methods[5,6] are known for the synthesis of compounds of type 1. The simplest one is the reaction of o-quinone 3 with the compounds of type 2 (Scheme I).

In these procedures the o-quinone 3 have been generated from the oxidation of catechol either by potassium ferricyanide or potassium iodate and sodium acetate or anodic oxidation of catechol[6]. However, these reactions are not very convenient owing to the difficulty in isolation of the products in very pure state.

IICT-H Communication No.2417.

Quinones are synthetically very important intermediates[7]. Many biosyntheses are also known to pass through quinonoid intermediates[8]. Among the various recent methods for quinone generation[9] an enzymatic approach for the regioselective oxidation of phenols to quinones by polyphenol oxidase enzyme is also known, though in poor yields[10]. Currently more emphasis are made to promote organic reactions by biotransformation due to its advantage of mild conditions of temperature and pH.



2 3 4

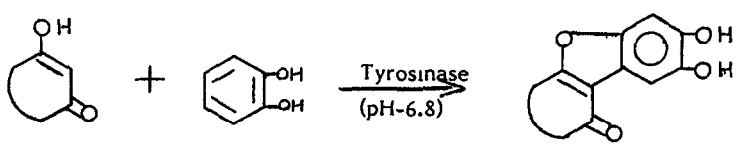
Scheme I

In our preliminary communication we had demonstrated[11] a probable biogenetic type synthesis of coumestans by coupling of *in situ* generated o-quinones by mushroom tyrosinase oxidation of catechol and 4-hydroxy coumarins in phosphate buffer (pH 6.8) in quantitative yields.

In continuation of our programme on synthetic perspectives of enzyme polyphenol oxidase and to widen the scope of the above reaction (Scheme I) we wish to report the full details of this finding for the general synthesis of biologically active natural products possessing the basic skeleton 1 and related heterocycles.

Results and Discussion

A variety of substrates possessing the general structure of 5 react efficiently with o-quinone (3) generated by mushroom tyrosinase catalysed oxidation of catechol (6) to give coupling products of the type 7 as shown in Scheme II.



5 6 7

Scheme II

The enzyme polyphenol oxidase catalyses hydroxylation of phenols with oxygen to catechol and subsequent dehydrogenation to o-quinones[12,13]. Regioselective oxidation of aromatic compounds is often desirable but is a difficult problem in organic synthesis[14]. The attempts to use polyphenol oxidase as a practical catalyst have been unsuccessful because the instability of o-quinones(3)in water[15] causes rapid polymerisation to polyaromatic pigments[16] also inactivating the enzyme[12,17].

Klibanov et al.[10] have overcome this problem by carrying the oxidation of phenol in $CHCl_3$ using freshly precipitated enzyme from phosphate buffer (pH 7). However, we did not get any product from the reaction of 2 and catechol in the presence of mushroom tyrosinase in chloroform. The reasonable explanation could be suggested as the coupling reaction of compounds of type 2 and o-quinone(3)involves a polar mechanism and therefore would require very polar medium.

We found that the reaction underwent smoothly in phosphate buffer (pH 6.8) giving rise quantitative yields of corresponding products. The optimum pH for the oxidation of catechol to 3 by mushroom tyrosinase was found to be 6.8 and temperature 30°C. The reaction of compounds (8a-8r) listed in Table 1, with in situ generated 3 by mushroom tyrosinase catalysed catechol oxidation gave almost quantitative yields of products (9a-9r). TLC and HPLC analysis confirmed the formation of only one product. The substrates(8o-8r) where their solubility was poor in phosphate buffer acetonitrile as cosolvent was found to be helpful. In general, the yields of the coupling products have been uniformly good and do not seem to depend on the substitution pattern of the substrates.(Table 1) .

Although the oxidation of phenol to 3 by the tyrosinase enzyme and the synthesis of 1 by chemically [5] or anodically generated[6] 3 and 2 is not new. This approach is convenient preparative route to 1. under mild conditions and more close to the biogenetic type of syntehsis of 1.

Experimental

Melting points were determined in open capillaries with mettler FP-51 melting point apparatus and are uncorrected. IR spectrum (νmax in cm^{-1} were recorded in KBr pellets on Perkin-Elmer model 283 B spectrophotometer. ^1H NMR spectra were obtained on Brucker 300 MHz or Varian FT-80 A MHz instruments in DMSO-d_6 using TMS as internal standard. Mass spectra were run on VG micromass 7070 H. Mushroom tyrosinase (50,000 units) was purchased from sigma chemical Co (USA). Compounds (8k-8o) were obtained commercially from Aldrich Chem Co. Remaining substrates were synthesized as described below:

Synthesis of substituted 4-hydroxy coumarins (8a-8g)

The compounds 8a-8g were synthesized by following the literature procedure[17]. A representative procedure of 8a is given as follows:

To a mixture of 0-hydroxy acetophenone 1.3 g; (0.01 mole) and pulverised sodium 2.3 g (0.1 mole) was added diethylcarbonate (40 ml) at 0°C gradually. The reaction mixture was

heated to reflux for 4 hr. on a water bath. After the reaction was over, unreacted sodium was destroyed by adding sufficient quantity of methanol. Then contents were poured in to cold water and water solution was extracted with ether (150 ml; 3 x 50 ml each time) to remove unreacted material. The aqueous layer was neutralised with dilute HCl while cooling a cream colored solid separated out after complete neutralisation. Solid separated was filtered and washed with water, dried and recrystallised from methanol as colourless rods (1.30 g, 82%) m.p.213°C (lit. 213°-214°C). M/z: 162 (M^+); IR (KBr) 3100, 1710, 1640, cm^{-1} ^{1}H-NMR; 6.70-7.10 (4H,M); 5.90 (1H,S).

Compounds 8b-8g were made according to the above method utilising appropriately substituted o-hydroxy acetophenones.

Compound (8h)

To a solution of 2.2g (0.02 m) of resorcinol and 1.7 g (0.02 m) of cyanoacetic acid in 6.8 ml of dry ether were mixed with 1.0 g of freshly fused finely powdered zinc chloride and immediately a very rapid stream of dry HCl was passed through. The zinc chloride began to go into the solution slowly and solution turned to dark colour and ultimately became bluish white. After two hours pasty mass began to separate out which on standing overnight completely solidified. Supernatant layer was decanted and requisite amount of water was added to the residue. This results in the complete solidification of oily portion to give 1.0 g yield (48%) of 7-hydroxyketamide m.p. 340°C.

The ketamide was hydrolysed by heating on water bath with 3.4 ml of 50% sulphuric acid. First clear solution was obtained. After 2 hrs crystalline compound separated which was recrystallised from hot water to give 0.7 g yield (66%) of fine crystalline 4,7-dihydroxy coumarin (8h) m.p.262°C (Lit.260°C)[19] M/z 178 (M^+); IR (KBr): 3300, 1700 and 1640 cm^{-1} ^{1}H-NMR (DMSO-d_6) 6.5-7.16 (3H,M) 5.90 (1H,S).

Compound (8i)

Dry HCl was passed for 4 hours into a solution of 3.0 g (0.023 m) of phloroglucinol and 3.0 g (0.035 m) of cyanoacetic acid in 15 ml of dry ether. The solution became faintly reddish in colour and after 2 hrs a crystalline compound separated which was recrystallised from 50% ethanol to give fine needles of 2.0g of 5,7-dihydroxyketamide. m.p.298°C (dec) (Lit.300°C).

The ketamide obtained was heated for one hour under reflux with 20ml of 36% HCl. The clear solution on cooling gave lumps of crystals, which were filtered and dried and dissolved in ethyl acetate. The ethyl acetate was concentrated to give residue which was recrystallised from hot water to give 1.2 g yield (54%) of fine crystalline 4,5,7-trihydroxy coumarin (8i) m.p. 245°C (Lit. 246°C)[19] m/z 194 (M^+); IR; 3300, 1700, 1640 cm^{-1} ^{1}H-NMR (DMSO-d_6) 7.12 (1H, s), 6.76 (1H, s), 5.96 (1H, s).

Compound (8j)

A mixture of (8i) 0.9 g; (0.05 mole) and 15.0 g of sodium carbonate (0.15 mole) in 50 ml

of water was added dropwise 15 ml of dimethyl sulphate. The mixture was stirred for one hour and heated on water bath at 80°C for additional one hour. The reaction mixture was cooled and acidified with 10% HCl and kept overnight. The solid separated was filtered to give 0.6 g yield (66%) of crystalline 4,5 dihydroxy-7-methoxy coumarin (8j) m.p. (188°C) (Lit. 190°C).[5] m/z 208 (M^+) IR: (KBr) 3300, 1700, and 1640, cm^{-1}; ^1H NMR (DMSO-d_6): 7.16 (1H, s), 6.82 (1H, s), 5.96 (1H, s), and 3.76 (3H, s).

Compound (8p)

Malon anillic acid 1.8 g (0.01 mole) was dissolved into a clear solution of polyphosphoric acid (prepared by dissolving 10 g of P_2O_5 in 6 ml of phosphoric acid). The reaction mixture was heated at 140°C for 3 hrs. After cooling, hydrochloric acid (30 ml, 1N) was added to the mixture and whole content was neutralised with NaOH solution. The crude product precipitated was filtered and recrystallised from acetic acid to give 1.4 g yield (78%) m.p. 360°C (Lit.360°C)[22] m/z 161 (M^+), IR (KBr) 2900(b), 1660, 1600 cm^{-1} ^1H-NMR (DMSO-d_6 7.24 - 8.16 (4H, M); 5.84 (1H, s); 3.60 (1H, s).

Compound (8q)

A mixture of 15 g (0.1 mole) N-methylanthranilic acid in 50 ml of acetic acid was refluxed for four hours. The reaction mixture was poured on to crushed ice. After basification with aqueous sodium hydroxide, the resulting solultion was acidified to litmus and cooled. The solid precipitate was filtered and washed with acetone to get pure compound of (8q) 6.0 g yield (35%) m.p. 252°C (Lit.250°C)[21] m/z 175 (M^+); IR (KBr); 2900(b) 1660 and 1600 cm^{-1}; ^1H-NMR (DMSO-d_6) 7.10-8.12 (4H, M) 5.90 (1H, s) 3.50 (3H, s).

Compound (8r)

A mixture of N-phenyl anthranilic acid 5.0 g; (0.023 mole) and acetic anhydride (20 ml) was heated in an oil bath, maintaining the temperature at 115°C for 4 hrs. The reaction mixture was poured on to 100 g of crushed ice in small portions while stirring and subsequently contents were allowed to stand overnight in refrigerator. The mixture was made alkaline by adding aqueous sodium hydroxide solution and filtered. Much of the material remained as resin. Acidification of the filtrate by the addition of dil. HCl to pH 5 caused precipitation which was collected by filtration and was washed several times with cold water. The crude product was then crystallised from ethanol to give 0.3g of (8q) yield (6%) m.p. 295°C (Lit. 297°C)[20] m/z 237 (M^+); IR (KBr); 2900(b), 1660 and 1600 cm^{-1}; ^1H-NMR (DMSO-d_6) 6.56-8.10 (9H, M) 5.94 (1H, s).

General Reaction Procedure

A representative procedure is illustrated for compound 9a as follows:

To a magnetically stirred solution of a mixture of 4-hydroxy coumarin (8a) 0.4 g; (0.0025 moles) and catechol 0.55 g (0.005 mole) in phosphate buffer (200 ml, pH = 6.8), tyrosinase (0.005 g; 50,000 units) enzyme was added and change in colour of the contents from violet

to brown was noticed. After additional stirring for one hour at room temperature 0.5 g of ascorbic acid was added to reduce the quinones produced to phenols. The reaction mixture was extracted with ether and combined ether extracts were dried over anhydrous sodium sulphate. Ether was removed and residue was recrystallised from ethanol-acetone mixture to give 0.57 g of **9a**, yield (96%), m.p. 310°C (Lit. 310°)[6], m/z 268 (M^+); IR(KBr): 3350, 1720, 1640, 1470, 1350, 1270 and 1240 cm^{-1}; ^1H NMR(DMSO-d_6): 7.10-7.20(1H, d); 6.70-6.74(1H, t); 6.61-6.70(1H, d); 6.30-6.58(1H, t); 6.40(1H, s); 6.30(1H, s).

Compounds (**9b-9h**) were exactly made according to general procedure described above starting from (**8b-8h**) and recrystallised from acetone. Compounds (**9o-9r**) were also prepared in the same fashion except that 5 per cent of acetonitrile was used as a cosolvent with buffer pH 6.8 to ensure the solubility of starting materials (**8o-8r**). Compound (**9o**) was recrystallised from methanol, whereas compounds (**9p-9r**) were from acetic acid-water mixture. Spectral details, yields and melting points of the products are given in Table 1.

Acknowledgement:

One of us (CMK) is thankful to CSIR, New Delhi, for the award of research fellowship.

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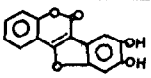
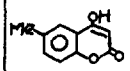
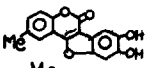
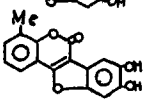
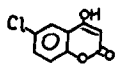
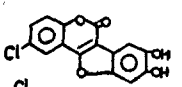
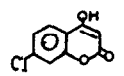
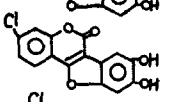
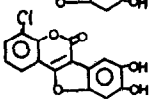
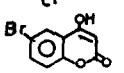
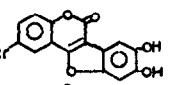
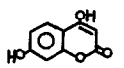
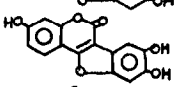
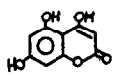
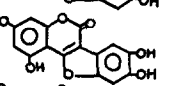
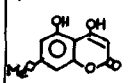
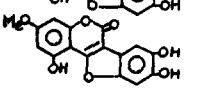
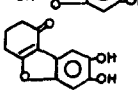
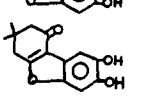
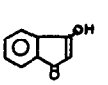
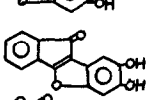
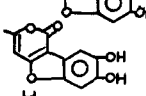
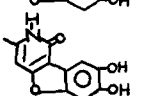
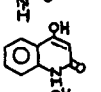
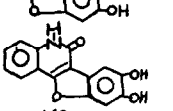
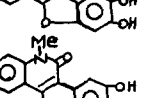
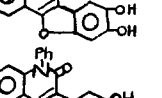
TABLE-I MUSHROOM TYROSINASE CATALYSED SYNTHESIS OF COUMESTANS & RELATED COMPOUNDS

ENTRY	COUMARINS (8a-8r)	COUMESTANS (9a-9r)	yield %	m.p. °C	Lit. (m.p.)	Reaction time	m/z	^{1}H-NMR (DMSO-d_6) (δ- ppm)
1			96	308 (dec)	310 (Lit-6)	1 hr	268	7.1-7.2 (1H,d); 670-6.74 (1H,t); 6.61-6.70 (1H,d); 6.36-6.58 (1H,t) 6.40 (1H,s); 6.30 (1H,s);
2			96	298-300	>300 (Lit-23)	1 hr	282	6.90 (1H,s); 6.59 (2H,s); 6.40 (1H,s); 6.30 (1H,s); 1.6 (3H,s).
3			94	≃300	>300 (Lit-23)	1 hr	282	6.9 (1H,d); 6.84 (1H,d); 6.80 (1H,d); 6.40 (1H,d); 6.38 (1H,s); 1.56 (3H,s)
4			92	300-302	>300 (Lit. 23)	1 hr	302	7.00-7.10 (1H,d); 6.80 (1H,s); 6.60 (1H,d); 6.40 (1H,s); 6.30 (1H,s).
5			94	301-303	>300 (Lit-23)	1 hr	302	6.94 (1H,d); 6.82 (1H,d); 6.44 (1H,d); 6.40 (1H,s); 6.31 (1H,s);
6			92	298	>300 (Lit-23)	1 hr	302	6.95 (1H,d); 6.86 (1H,d); 6.82 (1H,d); 6.40 (1H,s); 6.30 (1H,s);
7			96	≃300	>300 (Lit-23)	1 hr	346	6.96 (1H, d): 6.8 (1H,d); 6.45 (1H,d); 6.40 (1H,s); 6.30 (1H,s);
8			95	≃ 333	>330 (Lit-6)	1hr	284	7.12-6.80(3H,m); 6.48 (1H.s); 6.30 (1H,s);
9			95	332-334	>330 (Lit-6)	1 hr	300	7.10 (1H,s); 6.80 (1H,s); 6.42 (1H,s) 6.34 (1H,s);
10			95	329-331	327 330 (Lit 4)	1 hr	314	7.10 (1H,d); 6.82 (1H,s); 6.42 (1H,s); 6.30 (1H,s); 3.76 (3H,s);
11			95	260	--	1 hr	218	7.20 (1H,s); 7.00 (1H,s); 3.00 (2H,s); 2.50 (2H,t); 2.12-2.20 (2H,m);
12			95	276-278	280 (Lit-6)	1 hr	246	7.16 (1H,s); 6.96 (1H,s); 3.06 (2H,s); 2.50 (2H,s); 1.10 (6H,s);
13			85	143	145 (Lit-6)	2 hrs	252	7.50-7.78 (4H,m); 7.20 (1H,s); 6.98 (1H,s);
14			90	342	345 (Lit-6)	2 hrs	232	7.18 (1H,s); 6.98 (1H,s); 6.36 (1H,s) 2.40 (3H.s);
15			90	≃ 334	>330 (Lit-6)	3 hrs	231	7.22 (1H,s); 7.12 (1H,s); 6.68 (1H,s); 2.60 (3H,s);
16			95	332	>330 (Lit-6)	5 hrs	267	7.30-8.28 (4H,m); 7.12 (1H,s); 7.08 (1H,s);
17			90	>330	--	5 hrs	281	7.32-8.20 (4H,m); 7.20 (1H,s); 7.12 (1H,s); 3.50 (3H.s)
18			90	>340	--	5 hrs	343	7.21-8.22 (9H,m); 7.18 (1H,s); 7.10 (1H,s);