A STUDY OF THE MICHAEL REACTION OF 2'-HYDROXYCHALCONES AND A FACILE FORMATION OF 4H-PYRAN DERIVATIVES

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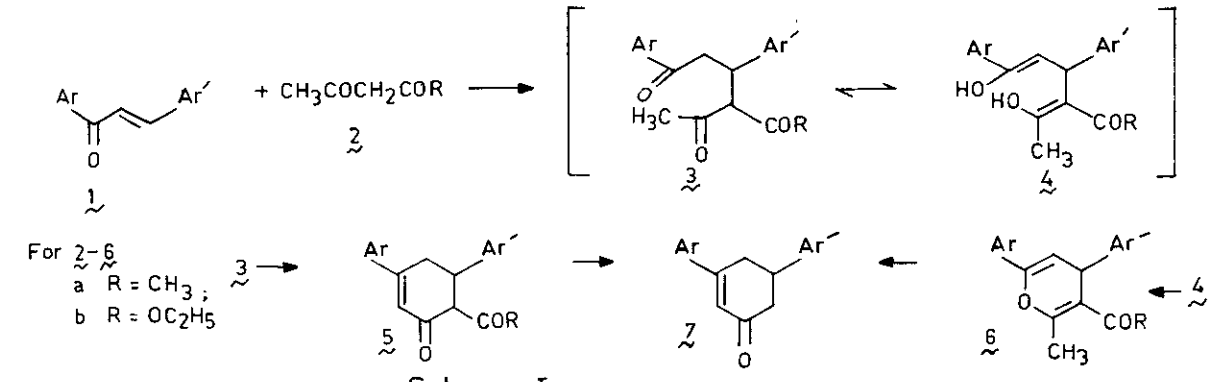
Abstract - 2'-Hydroxychalcones (8a) and (8b) when subjected to the Michael reaction with acetyl acetone in the presence of ethanolic piperidine gave the 4H-pyran derivatives (9a) and (9b) besides the cyclohexenone derivatives (10a & 11a) and (10b & 11b) respectively. However, 8c yielded under the same conditions only the 4H-pyran derivative (9c) together with some 5,7-dimethoxyflavanone (12c). Thus 4H-pyrans have, for the first time, been characterised during Michael condensation of chalcones having no electron withdrawing group in the α-position. Ethyl acetoacetate gives only cyclohexenone derivatives.

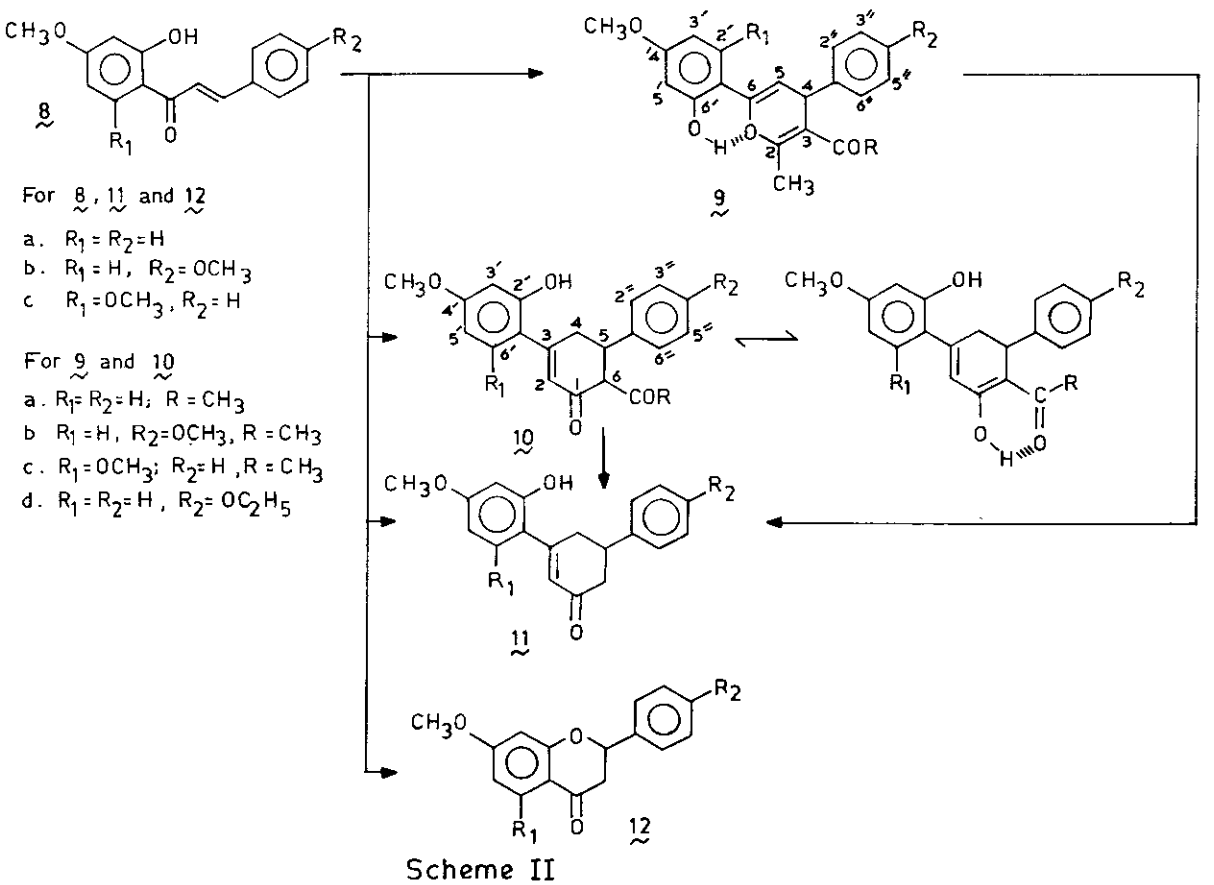
Chalcones (either completely unsubstituted or substituted only in the styryl part) are known to undergo the Michael reaction with many nucleophiles but the adduct is rarely isolable[1-4]. Among further changes which the adduct usually undergoes is the formation of 3,5-diphenylcyclohex-2-en-1-one derivatives (5 and 7)[3,5,6,7] as shown in scheme 1.

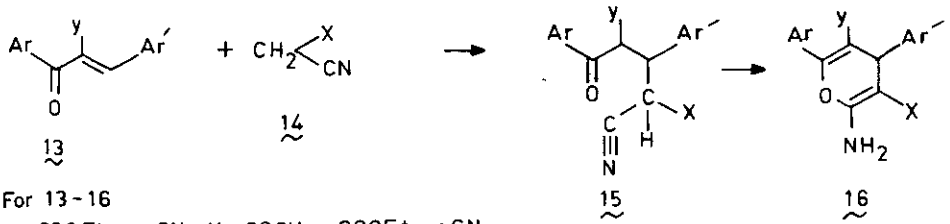
This further change with acetylacetone (2a) and ethyl acetoacetate (2b) seemed to us quite reasonable as thermodynamically controlled products. But the possibility of an alternative cyclisation of 3 as (4) to give 4H-pyrans (6) as kinetically controlled products was also visualised by us. The failure to get 6 earlier may be because chromatography was not used to purify the products and NMR spectra also were not used for identification purposes. We now report here the results of our detailed studies on the Michael condensation of several 2'-hydroxychalcones with acetylacetone and ethyl acetoacetate.

Michael condensation of 2'-hydroxychalcones with acetylacetone

The Michael condensation of 2'-hydroxy-4'-methoxychalcone[8] (8a) with acetylacetone *in refluxing ethanolic piperidine gave a product* (M) which proved to be


Ar
Ar'
+ CH3COCH2COR
2
1
3
4
For 2-6
a R = CH3 ;
b R = OC2H5
5
7
6
Scheme I


CH3O
OH
R2
R1
8
9
For 8 , 11 and 12
a. R1 = R2 = H
b. R1 = H, R2 = OCH3
c R1 = OCH3 , R2 = H
For 9 and 10
a. R1 = R2 = H; R = CH3
b R1 = H, R2 = OCH3, R = CH3
c. R1 = OCH3; R2 = H , R = CH3
d. R1 = R2 = H , R2 = OC2H5
10
11
12
Scheme II


Ar
Ar'
y
+ CH2
X
CN
13
14
15
16
NH2
For 13-16
X = COOEt or CN, Y = COCH3, COOEt. or CN

a complex mixture on TLC. But when directly refluxed with aq. ethanolic KOH, only one product was isolated which was identified as 3-(2-hydroxy-4-methoxyphenyl)-5-phenylcyclohex-2-en-1-one (11a) as follows. Thus, IR spectrum indicated a conjugated carbonyl group at ν_{max} 1650 cm^{-1}; the NMR spectrum[9] showed two doublets of two protons each, one at 2.80 (J=10Hz) due to $-CH_2$ adjacent to the carbonyl group and the other at 3.00 (J=11Hz) due to an allylic group. Further, the benzylic methine group resonated as a multiplet centered at 3.40 and olefinic proton as a singlet at 6.48. Finally MS (see experimental) showing both the molecular ion peak and the base ion peak at m/z 294 could be explained.
In another experiment, the product (M) was separated by column chromatography yielding three different products. The first product was identified as 3-acetyl-2-methyl-4-phenyl-6-(2-hydroxy-4-methoxyphenyl)-4H-pyran (9a) on the basis of spectral data. Thus, IR indicated the presence of a conjugated carbonyl group at ν_{max} 1620 cm^{-1}, and NMR showed three singlets at 1.84, 2.24 and 3.75 due to one olefinic methyl-, one acetyl- and one methoxy- group, respectively, besides two doublets of one proton each for 4H of the pyran ring 4.20 (J=7Hz) and 3.11 (J=7Hz) and the signals of the intact benzene rings of the starting material. The second product was assigned the structure of 6-acetyl-3-(2-hydroxy-4-methoxyphenyl)-5-phenylcyclohex-2-en-1-one (10a) which is in dynamic equilibrium as shown in scheme 2. Thus, IR spectrum displayed one broad and intense band between 1550 and 1705 cm^{-1} due to chelation and conjugation and in the NMR spectrum, the signals for cyclohexenone ring protons are broad.

Thus, the Michael addition of acetylacetone to 2'-hydroxy-4'-methoxychalcone (8a) resulted in the formation of 4H-pyran derivative (9a) and two cyclohexenone derivatives (10a and 11a). Further, it was noted that both 4H-pyran derivative (9a) and 6-acetylcyclohexenone derivative (10a) when refluxed either pure or together with aqueous alcoholic potash yielded the same deacetylated cyclohexenone derivative (11a). It indicated that 4H-pyran ring is unstable in aqueous alkali and undergoes recyclisation to give the stable cyclohexenone ring. A parallel series of experiments with 2'-hydroxy-4,4'-dimethoxychalcone[10] (8b) gave exactly the same results as in the above case. However, 2'-hydroxy-4',6'-dimethoxychalcone[11] (8c) behaved differently. Here, a mixture of only 3-acetyl-2-methyl-4-phenyl-6-(2-hydroxy-4,6-dimethoxyphenyl)-4H-pyran (9c) and 5,7-dimethoxyflavanone[14] (12c) formed. It is interesting to note that no cyclohexe-

none derivative formed in this mixture and the 4H-pyran derivative was in larger yields than with other chalcones (8a) and (8b). Obviously, 4H-pyran derivative (9c) is more stable than other pyrans (9a & 9b). However, treatment of (9c) with hot aqueous alkali afforded again thermodynamically stable cyclohexenone derivative (11c). This shows that 4H-pyran derivative can become a major product of the Michael condensation of chalcones with acetylacetone in favourable cases. A perusal of literature on the synthesis of 4H-pyran derivatives revealed that these have also been prepared earlier by the Michael reaction using such nucleophiles as malononitrile and ethyl cyanoacetate, but the aryl styryl ketone (13) must possess an electron withdrawing group like $COCH_3$, COOEt or CN in the α-position[13]. Thus, when (13) was condensed with (14) 2-amino-4H-pyran derivative (16) was obtained in good yield by Soto et al.[14-17], but the chalkone (13) having α-position free gave only the cyanoketone (15). In our case, 4H-pyrans are formed even when α-position is free and a milder nucleophilic reagent like acetylacetone is used.

Michael condensation of 2'-hydroxychalcones with ethyl acetoacetate

The chalcone (8a) when refluxed with ethanolic piperidine afforded only one product viz. 6-carbethoxy-3-(2-hydroxy-4-methoxyphenyl)-5-phenylcyclohex-2-en-1-one (10d) which on subsequent heating with aq. potash yielded the decarbethoxy derivative (11a), identical with the one described above. In the case of 2'-hydroxy-4',6'-dimethoxychalcone (8c), the product was a mixture from which only 5,7-dimethoxyflavanone (12c) could be obtained pure. The remaining mixture (P) after alkaline treatment gave the same cyclohexenone derivative (11c) as obtained with acetylacetone. Thus, with ethyl acetoacetate, the 4H-pyran derivatives are either too labile to be isolated or not formed in the reaction.

EXPERIMENTAL

Unless stated otherwise, mp's are uncorrected and in degree centigrade; light petroleum had boiling range 60-80°C; silica gel was used for column chromatography and TLC; solvent systems for TLC were: (A) benzene:EtOAc (4:1); (B) benzene: EtOAc (3:1); R_f values refer to TLC; uv data were recorded on a Perkin-Elmer Model 554 spectrophotometer in MeOH and figures within brackets refer to log ϵ values; IR spectra were measured on a Perkin-Elmer Infracord spectrophotometer using KBr disc; ^{1}H-NMR spectra were recorded on a Perkin Elmer R-32 (90MHz) spectrometer using $CDCl_3$ for 9a, 9b and 9c, DMSO-d_6 for 10a, 10b and 10d and

Table 1: Experimental data for new compounds

Compound*	mp °C	TLC R_f (Solvent)	Mol.formula C	H	O	Requires %C	H	Found %C	H	UV λ_{max} in nm (log ϵ)	IR ν_{max} (cm^{-1})
9a	145-6	0.4 (A)	21	20	4	74.98	5.99	74.67	6.40	208(4.43), 274(4.21)	3500,1620,1590
9b	107-8	0.39 (A)	22	22	5	72.11	6.05	72.40	6.00	212(4.69), 272(4.45)	3500,1620,1590
9c	135-6	0.39 (A)	22	22	5	72.11	6.05	72.40	6.40	206(4.63), 286(4.45)	3500,1680,1590
10a	189-9	0.55 (B)	21	20	4	74.98	5.99	75.20	6.30	202(4.49), 340(4.26)	3350,1705,1550
10b	171-2	0.53 (B)	22	22	5	72.11	6.05	71.80	5.80	202(4.82), 334(4.20)	3370,1705,1570
11a	195-6	0.5 (B)	19	18	3	77.53	6.16	77.80	6.30	202(4.41), 330(4.04)	3500,1650,1610
11b	192-3	0.5 (B)	20	20	4	74.05	6.22	73.60	5.80	202(4.53), 330(4.20)	3500,1650,1610
11c	174-5	0.52 (B)	20	20	4	74.05	6.22	74.50	6.50	204(4.71), 306(3.39)	3200,1620,1590

* All the compounds were crystallised from ethanol.

Table 2: NMR data of 4-H-pyran derivatives

No.	C_4-H	C_5-H	$C_{3'}$-H	$C_{5'}$-H	$C_{6'}$-H	$C_{3''}$,$_{5''}$-H	$C_{2''}$,$_{6''}$-H	C_2-CH_3	-$COCH_3$	-OCH_3	-C_6H_5	Chelated -OH
9a ~	3.11 (d, J=7Hz)	4.20 (d, J=7Hz)	6.30 (d, J=2.5Hz)	6.34 (dd, J=2.5 & 10Hz)	7.50 (d, J=10Hz)	-	-	1.84(s)	2.24(s)	3.75(s)	7.15(s)	12.58(s)
9b ~	3.07 (d, J=7Hz)	4.25 (d, J=7Hz)	6.30 (d, J=2.5Hz)	6.35 (dd, J=2.5 & 10Hz)	7.55 (d, J=10Hz)	6.73 (d, J=10Hz)	7.10 (d, J=10Hz)	1.84(s)	2.23(s)	3.70 &3.76 (6H,2s)	-	12.50(s)
9c ~	3.19 (d, J=7Hz)	4.16 (d, J=7Hz)	5.78 (d, J=2.5Hz)	5.90 (d, J=2.5Hz)	-	-	-	1.84(s)	2.24(s)	3.74 & 3.78 (6H,2s)	7.10(s)	13.84(s)

Table 3: NMR data of cyclohex-2-en-1-one derivatives

No.	C_2-H	C_4-H	C_5-H	C_6-H	$C_{3'}$-H	$C_{5'}$-H	$C_{6'}$-H	$C_{3''}$,$_{5''}$-H	$C_{2''}$,$_{6''}$-H	-$COCH_3$	-OCH_3	-C_6H_5
10a ~	6.32(s)	2.94 (d, J=10Hz)	3.27(m)	4.06 (d, J=12Hz)	6.42(m)	6.42(m)	7.17 (d, J=10Hz)	-	-	1.90 & 2.0 (3H,2s)	3.6 & 3.68 (3H,2s)	7.12(s)
10b ~	6.31(s)	2.91 (d, J=10Hz)	3.32(m)	4.01 (d, J=12Hz)	6.40(m)	6.40(m)	7.15 (d, J=10Hz)	6.76 (d, J=10Hz)	7.19 (d, J=10Hz)	1.88 & 1.97 (3H,2s)	3.64 & 3.68 (6H,2s)	-
11a ~	6.48(s)	3.0 (d, J=11Hz)	3.2-3.6(m)	2.80 (d, J= 10 Hz)	6.36 (d, J=2.5Hz)	6.76 (d, J=2.5Hz)	6.95 (d, J=9.0Hz)	-	-	-	3.75(s)	7.2(s)
11b ~	6.52(s)	3.0 (d, J=11Hz)	3.2-3.6(m)	2.85 (d, J=10Hz)	6.36 (d, J=2.5Hz)	6.86 (d, J=10Hz)	7.15 (d, J=10Hz)	6.86 (d, J=10Hz)	7.25 (d, J=10Hz)	-	3.80 & 3.82 (6H,2s)	-
11c ~	6.02(s)	2.91 (d, J=11Hz)	3.40-3.48(m)	2.88 (d, J=10Hz)	6.02(s)	6.26(s)	-	-	-	-	3.68 & 3.72 (6H,2s)	7.19(s)

$CDCl_3$ + TFA for 11a, 11b and 11c; Me_4Si (δ = 0) and coupling constants are given in Hz. All data on new compounds are given in Tables 1-3.

Condensation of 2'-hydroxy-4'-methoxychalcone (8a) with acetylacetone

To a solution of (8a)[8] (2.54 g; 10 mM) in EtOH (20 ml) was added acetylacetone (3.0 g; 30 mM) and piperidine (0.1 ml). The reaction mixture was refluxed for 3 h and then evaporated to dryness. TLC indicated the resulting oil (M) as a mixture of four compounds which was worked up in two ways. In the first method, the oil (M) was dissolved in EtOH (25 ml) and then refluxed with KOH (1.68 g/10 ml, 30 mM) for 3 h. It was diluted and acidified with dil HCl. The light brown product was found to be 3-(2-hydroxy-4-methoxyphenyl)-5-phenylcyclohex-2-en-1-one (11a); ms: m/z (%) 294 (100.0), 276(13.5), 266(9.5), 251(9.6), 203(40.0), 190(18.0), 163(15.3), 162(94.8), 161(9.6), 147(40.9), 137(25.9), 131(18.9), 103(13.8), 91(23.4), 77(17.0) and 51(9.4).

In the second experiment, the oil (M) was chromatographed on silica gel. On successive elution with (i) light petroleum (ii) light petroleum:benzene (1:1) and (iii) light petroleum:benzene (1:2), three fractions A, B and C were obtained.

Fraction A - crystallized from EtOH to yield the starting chalcone (8a) as yellow needles (550 mg), mp 108°C (lit.[8] mp 105°C).

Fraction B - yielded 3-acetyl-2-methyl-4-phenyl-6-(2-hydroxy-4-methoxyphenyl)-4H-pyran (9a) as a white solid (500 mg) showing brown ferric reaction.

To a solution of 9a (336 mg, 1 mM) in EtOH (5 ml) was added aq KOH (168 mg/1 ml, 3 mM). The mixture was refluxed for 3 h. It was cooled, diluted and then acidified with dil HCl. The solid separated was washed thoroughly with water and crystallised from EtOH to give (11a) (130 mg), mp and mmp 195-196°C; it showed a superimposable IR spectrum with the one obtained above.

Fraction C was an oily liquid and found to be a mixture by TLC. It was again separated by column chromatography. On successive elution with (i) light petroleum-benzene (1:2) and (ii) benzene only, two fractions C_1 and C_2 were obtained.

Fraction C_1 yielded 6-acetyl-3-(2-hydroxy-4-methoxyphenyl)-5-phenyl-cyclohex-2-en-1-one (10a) as a bright yellow solid (600 mg).

A solution of (10a) (336 mg, 1 mM) in EtOH (5 ml) was refluxed with aq KOH (168 mg/1 ml, 3 mM) for 3 h. After the usual work-up, as in the previous case, the

solid obtained was identified as 11a (135 mg), mp and mmp 195-196°C; and IR spectrum was superimposable with the one obtained above.

Fraction C_2 gave (11a) (400 mg).

Condensation of 2'-hydroxy-4,4'-dimethoxychalcone (8b) with acetylacetone

A solution of 8b (2.84 g, 10 mM) in EtOH (20 ml) was refluxed with acetylacetone (3.0 g, 30 mM) and piperidine (0.1 ml) for 3 h. The product (P) was worked up in two ways as in the case of (8a). In the first experiment, its EtOH solution (25 ml) was refluxed with aq KOH (1.68 g/10 ml, 30 mM) for 3 h. The light brown product was identified as 3-(2-hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)-cyclohex-2-en-1-one (11b); ms: m/z(%): 324(91.8), 203(41.8), 190(48.9), 161(30.2), 147(35.6), 137(33.3), 135(20.0), 134(78.5), 121(37.5), 119(21.9), 91(23.6), 44(17.6) and 43(55.5).

In another experiment, the product (P) was chromatographed.

Fraction A - crystallised from EtOH to yield (8b) as yellow needles (600 mg), mp 115-116°C (lit.[10] mp 113-114°C).

Fraction B - yielded 3-acetyl-2-methyl-4-(4-methoxyphenyl)-6-(2-hydroxy-4-methoxyphenyl)-4H-pyran (9b) as a white solid (520 mg), brown ferric reaction.

A solution of (9b) (366 mg, 1 mM) in EtOH (5 ml) and aq KOH (168 mg, 1 ml, 3 mM) was refluxed for 3 h and the product found to be 11b (140 mg).

Fraction C found to be a mixture by TLC, was rechromatographed.

Fraction C_1 yielded 6-acetyl-3-(2-hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)-cyclohex-2-en-1-one (10b) as a light yellow solid (700 mg).

A solution of (10b) (366 mg, 1 mM) in EtOH (5 ml) and aq KOH (168 mg/1 ml, 3 mM) was refluxed for 3 h when the product was found to be (150 mg).

Fraction C_2 gave 11b (325 mg).

Condensation of 2'-hydroxy-4',6'-dimethoxychalcone (8c) with acetylacetone

A mixture of 2'-hydroxy-4',6'-dimethoxychalcone[11] (8c) (2.84 g, 10 mM) in EtOH acetylacetone (3.0 g, 30 mM) and piperidine (0.1 ml) was refluxed for 3 h. The product was separated by column chromatography.

Fraction A - crystallised from EtOH to yield (8c) as yellow needles (625 mg), mp 92-93°C (lit.[11] mp 91-92°C).

Fraction B - yielded 3-acetyl-2-methyl-4-phenyl-6-(2-hydroxy-4,6-dimethoxyphenyl)-4H-pyran (9c) as a white solid (800 mg). A solution of (9c) (366 mg,

1 mM) in EtOH (5 ml) and aq KOH (168 mg/1 ml, 3 mM) was refluxed for 3 h. The light-brown product was identified as 3-(2-hydroxy-4,6-dimethoxyphenyl)-5-phenylclohex-2-en-1-one (11c) (140 mg).

Fraction C - crystallised from EtOH to yield 5,7-dimethoxyflavanone (12c) (500 mg), mp 138-139°C (lit.[12] mp 140°C).

Condensation of 2'-hydroxy-4'-methoxychalcone (8a) with ethyl acetoacetate

A solution of (8a) (2.54 g, 10 mM) in EtOH (20 ml) was refluxed with ethyl acetoacetate (2.6 g, 20 mM) and piperidine (0.1 ml) for 3 h. The mixture was cooled and diluted with H_2O. The separated solid crystallised from EtOH to give 6-carbethoxy-3-(2-hydroxy-4-methoxyphenyl)-5-phenylcyclohex-2-en-1-one (10d) (1.6 g), mp 171-172°C; R_f 0.39, solvent system (B); ^{1}H-NMR (DMSO-d_6): 0.94(3H, t, $-OCH_2\underline{CH_3}$), 2.87(2H, d, J=10Hz, C_4-H), 3.4-3.6(1H, m, C_5-H), 3.68(3H, s, $-OCH_3$), 3.86(2H, q, $-OC\underline{H_2}CH_3$), 3.96(1H, d, J=12Hz, C_6-H), 6.36(1H, s, C_2-H), 6.46(2H, m, $C_{3',5'}$-H), 7.25(1H, d, J=10Hz, $C_{6'}$-H) and 7.28(5H, s, $-C_6H_5$).

A solution of (10d) (366 mg, 1 mM) in EtOH (5 ml) was refluxed with aq KOH (168 mg/1 ml, 3 mM) for 3 h when (11a) (140 mg) was obtained.

Condensation of 2'-hydroxy-4',6'-dimethoxychalcone (8c) with ethyl acetoacetate

To a solution of (8c) (2.84 g, 10 mM) in EtOH (20 ml) was added ethyl acetoacetate (2.6 g, 20 mM) and piperidine (0.1 ml). The reaction mixture was refluxed for 3 h, cooled and then evaporated to dryness. TLC indicated the resulting oil as a mixture of compounds. It was chromatographed with (i) light petroleum, (ii) light petroleum - benzene, (iii) benzene only to give three fractions A, B & C.

Fraction A - crystallised from EtOH to yield (8c) as yellow crystals (600 mg), mp 92-93°C (lit.[11] mp 91-92°C).

Fraction B - crystallised from EtOH to give 5,7-dimethoxyflavanone (12c) (400 mg), mp 138-139°C (lit.[12] mp 140°C).

Fraction C - was an oily mixture which could not be separated further. It was directly hydrolysed by KOH (1.68 g/10 ml, 30 mM) when 11c was obtained.

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