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Useful Synthesis of 8-Allyl 5,7-Dimethoxycoumarins

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USEFUL SYNTHESIS OF 8-ALLYL 5,7-DIMETHOXYCOUMARINS.

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Abstract : A convenient two-step Synthesis of 8-allyl 5,7-Dimethoxycoumarins (**8a-e**) is described from 2-hydroxy 4,6-dimethoxybenzaldehyde (**5**).

5,7 - Dimethoxycoumarins having allyl group at C_8-position constitute an important class of naturally occurring coumarins[1]. Coumurrayin (**1**) contains 3, 3-dimethylallyl group at C_8-position while in pinnarin (**2**) it is 1,1-dimethylallyl[1]. Several other derivatives of 8-allylcoumarins, like **3** and **4** have also been reported from natural sources[1-4]. 8-Allyl 5,7-dioxygenatedcoumarins are valuable not only because they occur in nature but these are also useful intermediates for the synthesis of naturally occurring coumarins (like **3** and **4**), pyranocoumarins[5] and furocoumarins[6,7]. Mainly three approaches have been reported for the synthesis of 8-allyl 5,7-dioxygenated

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coumarins. Two approaches involve the formation of 7-allyloxy-5-methoxycoumarin[6,7], in the key step while in third 5-prenyloxy-7-methoxycoumarin[5] is involved.

All the reported methods[5-7] make use of preformed coumarins for the synthesis of 8-allyl 5,7-dioxygenated coumarins. We report herein a convenient two-step approach for the synthesis of 8-allyl 5,7-dimethoxy coumarins (**8a-e**) from 2-hydroxy 4,6 - dimethoxy benzaldehyde[8] (**5**). Reaction of **5** with allyl bromide, in DMF solution, in presence of K_2CO_3, at room temperature provided allyloxybenzaldehyde **6** in 92% yield. The aldehyde **6** on reaction with phosphoranes[9-11] (**7a-e**) at 200°C gave the desired coumarins (**8a-e**) in good yields. In the reaction of **6** with **7a-e** at 200°C three reactions, namely, Claisen rearrangement, Wittig reaction and cyclization of the hydroxycinnamate, occur one after another to provide coumarins (**8a-e**). The advantage of the present method is that it does not require preformed coumarin and provides 8-allyl and 3,8-disubstituted 5,7-dimethoxycoumarins in two steps from the readily available aldehyde **5**.

The 8-allylcoumarins **8a-c** could be easily converted to the corresponding epoxide by reacting them with m-chloroperbenzoic acid. Thus, coumarins **8a-c** on reaction with m-chloroperbenzoic acid in methylene chloride furnished the corresponding epoxides **9a-c** in 75, 57, 77 % yield.

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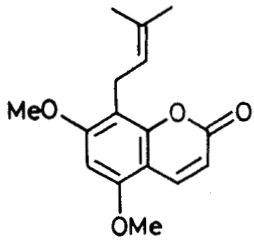

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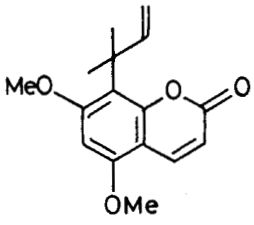

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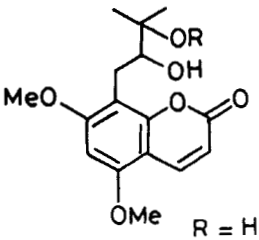

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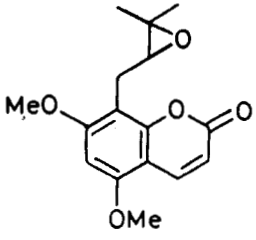

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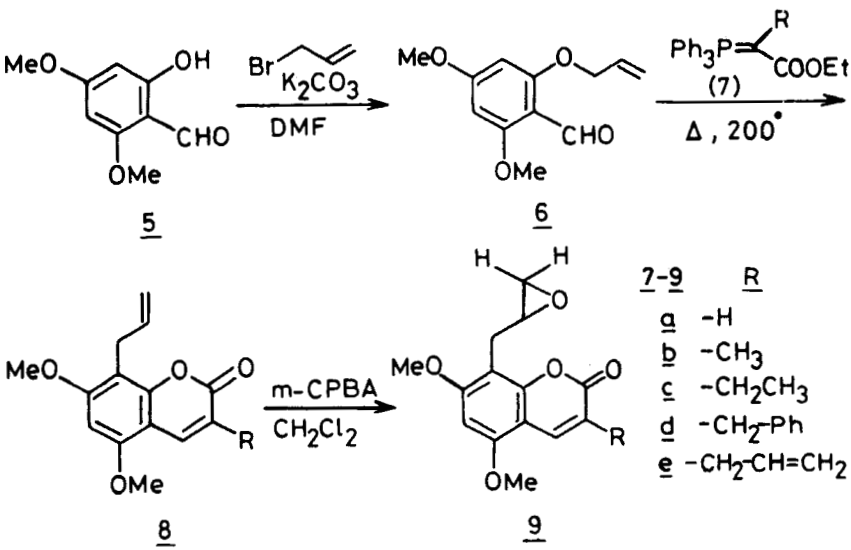

5 6 7-9 R a -H b -CH_3 c -CH_2CH_3 d -CH_2-Ph e -CH_2-CH=CH_2 8 9

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EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer 337 IR spectrophotometer and ^{1}H-NMR, in $CDCl_3$ solutions on Jeol FX 90 Q instrument. Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard and coupling constants in hertz.

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2-Allyloxy 4,6-dimethoxybenzaldehyde (6) :

A mixture of 2-hydroxy 4,6-dimethoxybenzaldehyde[8] (0.2g, 1 mmol), potassium carbonate (0.28g, 2 mmol) and allylbromide (0.2 ml, 2.3 mmol) in N,N-dimethylformamide (2 ml) was stirred at room temperature for 3h. The reaction mixture was poured in ice cold water (50 ml) and extracted with methylenedichloride (2x10ml). The organic layer was washed successively with 2N NaOH and water. It was dried over Na_2SO_4 and evaporated to give **6** as a light yellow oil (0.220 g, 92%), IR : 1675cm^{-1}; ^{1}H-NMR : 3.88 and 3.91 (2xs, 6H, 2xOMe), 4.63 (d, J=6Hz, 2H, Ar-CH_2), 5.25-5.68 (m, 2H, CH=CH_2), 5.88-6.40 (m, 3H, $\underline{CH}$=CH_2 and 2xArH), 10.48 (s, 1H, CHO), (Found : C, 64.53; H, 6.09 $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35).

General Procedure for 8-allyl 5,7-dimethoxycoumarins (8a-e) :

A mixture of 2-allyloxy 4,6-dimethoxybenzaldehyde (**6**, 0.45 mmol) and phosphorane (**7a-e**, 0.71 mmol) was

heated at 200°C for 6-11h as shown against the individual compounds (monitored by TLC). The residue obtained was chromatographed over silica gel using n-hexane-ethyl acetate (9:1, for **8a,b** and 99:1 in case of **8c-e**) to give 8-allylcoumarins (**8a-e**). All these coumarins (**8a-e**) were recrystallised from n-hexane-methylenedichloride.

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8a : Heated for 6h, m.p 132°, yield 72% ; IR : 1720 cm^{-1}; ^{1}H-NMR : 3.54 (d,J=6Hz,2H,Ar-CH_2), 3.97 (s, 6H, 2xOMe),4.97-5.25 (m,2H,CH=CH_2),5.77-6.13 (m,1H,CH=CH_2), 6.22 (d,J=9Hz,1H,C_3-H),6.42 (s,1H,C_6-H),8.08 (d,J=9Hz, 1H,C_4-H), (Found C, 68.32; H, 5.37 $C_{14}H_{14}O_4$ requires C,68.28; H, 5.73).

8b : Heated for 8h, m.p.105°, yield 62%,IR : 1720 cm^{-1}; ^{1}H-NMR : 2.05 (s,3H, C_3-CH_3), 3.57 (d,J=6 Hz,2H, Ar-CH_2), 3.97 and 4.00 (2xs,6H,2xOMe), 4.91-5.37 (m,2H,CH=CH_2),5.94-6.28 (m,1H,CH=CH_2),6.42 (s,1H,C_6-H), 7.94 (s,1H,C_4-H), (Found C,69.39 ; H, 6.01 $C_{15}H_{16}O_4$ requires C, 69.21; H, 6.20).

8c : Heated for 8h, m.p. 106°, yield 69%, IR : 1715 cm^{-1}; ^{1}H-NMR : 1.25 (t,J=7Hz, 3H CH_2-CH_3), 2.61 (q,J=7Hz,2H,CH_2-CH_3), 3.62 (d,J=6Hz,2H,Ar-CH_2), 4.02 and 4.05 (2xs,6H,2xOMe), 4.97-5.48 (m,2H,CH=CH_2), 5.88-6.40 (m,1H,CH=CH_2), 6.54 (s,1H,C_6-H), 8.02 (s,1H,C_4-H),

(Found C, 69.90; H 6.59 $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61).

8d : Heated for 10h, m.p. 156-157°, yield 50%, IR : 1720 cm^{-1}; ^{1}H-NMR : 3.57 (d,J=6Hz,2H Ar-CH_2) 3.91, 3.94 and 3.97(3xs,8H,2xOMe,CH_2-Ph), 4.91-5.25 (m,2H,CH=CH_2), 5.82-6.34 (m,1H,CH=CH_2), 6.42 (s,1H,C_6-H), 7.48 (s,5H, Ph), 7.85 (s,1H,C_4-H), (Found C, 75.30; H,5.60 $C_{21}H_{20}O_4$ requires C,74.98 ; H,5.99).

8e : Heated for 11h, m.p 118°, yield 62%, IR : 1715 cm^{-1}; ^{1}H-NMR; 3.37 (d,J=6Hz,2H,C_3-CH_2), 3.62 (d,J=6Hz, 2H,C_8-CH_2) 4.02 (s,6H,2xOMe),4.94-5.54 (m,4H,2xCH=CH_2), 5.85-6.42 (m,2H,2xCH=CH_2), 6.54 (s,1H,C_6-H), 8.02 (s, 1H,C_4-H), (Found C,71.22; H, 6.31 $C_{17}H_{18}O_4$ requires C 71.31; H, 6.34).

General Procedure for 5,7-dimethoxy 8-epoxyallyl-coumarins (9a-c) :

To a solution of 8-allyl 5,7-dimethoxycoumarin (**8a-e**, 0.2 mmol) in methylenedichloride (5ml), m-chloroperbenzoic acid (0.59 mmol) was added and it was stirred at room temperature for 5-7h (monitored by TLC). The reaction mixture was filtered, washed successively with aqueous sodium sulphite, aqueous sodium bicarbonate and water. It was dried (Na_2SO_4) and evaporated to give a solid. On recrystallisation

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from n-hexane-ethyl acetate afforded epoxycoumarins (**9a-c**).

9a : m.p. 162-163°, yield 75% , IR : 1720 cm^{-1}; ^{1}H-NMR : 2.60-3.48 (m,5H,CH_2-CH-CH_2),4.02 (s,6H,2xOMe), 6.37 (d, J=9Hz,1H,C_3-H); 6.54 (s,1H,C_6-H); 8.25 (d,J=9Hz 1H, C_4-H), (Found C; 64.41; H, 5.14 $C_{14}H_{14}O_5$ requires C, 64.11; H, 5.38).

9b : m.p. 157-158°, yield 57%, IR : 1720 cm^{-1}; ^{1}H-NMR; 2.2 (s,3H,C_3-CH_3), 2.51-3.37 (m,5H,CH_2-CH-CH_2), 4.02 (s,6H,2xOMe), 6.54 (s,1H,C_6-H), 8.05 (s,1H,C_4-H), (Found C ; 65.11; H, 5.68 $C_{15}H_{16}O_5$ requires C; 65.21; H, 5.84).

9c : m.p. 143°, yield 77% , IR : 1715 cm^{-1}; ^{1}H-NMR : 1.25(t,3H,CH_2-CH_3),2.34-3.57 (m,7H,CH_2-CH-CH_2,CH_2-CH_3), 4.02 (s,6H,2xOMe),6.6 (s,1H,C_6-H),8.05 (s,1H,C_4-H), (Found C; 66.37; H, 6.09 $C_{16}H_{18}O_5$ requires C; 66.19; H, 6.25).

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