Cinnamylation of Phenolic Compounds with Cinnamyl Alcohol: One Step Synthesis of Flavans

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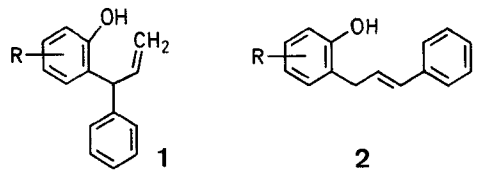
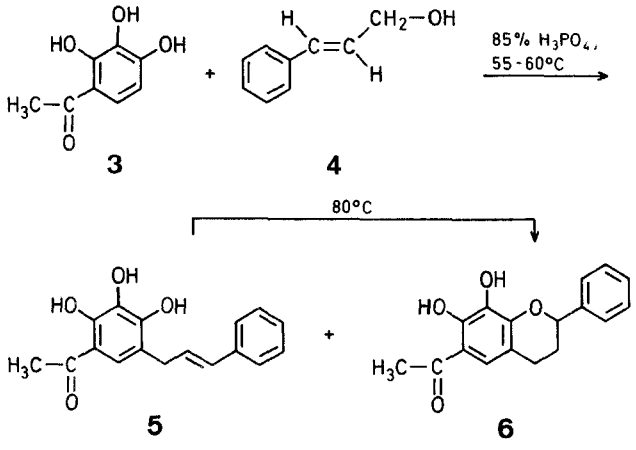
Cinnamylation of phenolic compounds with cinnamyl alcohol in the presence of different aqueous acid catalysts (e.g. acetic acid[1,2,3], formic acid[4], citric acid[5]) has been carried out to provide evidence on the proposed biogenetic pathway for neoflavanoids[1,4]. Under these conditions a mixture of two open chain products, 3,3-diarylpropenes **1** and 1,3-diarylpropenes **2**, is obtained and no cyclised products (e.g. flavans or 4-phenylchromans) are formed. Flavans have been synthesised[6,7,8] by other methods involving a number of steps. It is known that flavans lower cholestrol content in blood[9], but recently it has been reported[10] that flavans also possess antiviral activity. In view of this, it was considered of interest to develop a convenient method for their synthesis.

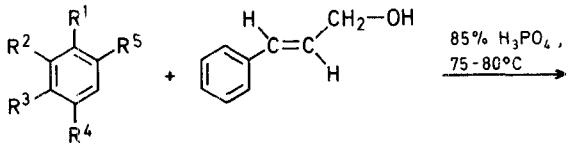


1 2

It has been observed that the aqueous acid-catalysed condensation of phenolic compounds with 2-methylbut-3-en-2-ol yields open chain products[11] but in the presence of orthophosphoric acid, only cyclised products are obtained[12]. The present work describes the cinnamylation of phenolic compounds **3** and **7a–c** with cinnamyl alcohol (**4**) in the presence of orthophosphoric acid to give flavans in one step.

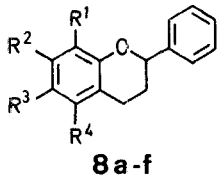


3 **4** **5** **6**



7a-c **4**

7,8	R¹	R²	R³	R⁴	R⁵
a	H	OH	CO–CH₃	H	OH
b	H	OH	H	OH	H
c	H	H	Cl	H	OH



8a-f

The condensation of 2,3,4-trihydroxyacetophenone (**3**) with cinnamyl alcohol (**4**) was carried out at 55–60 °C when a mixture of two products was obtained (overall yield 60%). They were separated by column chromatography and identified as 5-cinnamyl-2,3,4-trihydroxyacetophenone (**5**) and 6-acetyl-7,8-dihydroxy-2-phenyl-3,4-dihydro-2*H*-1-benzopyran (**6**) on the basis of their characteristic ferric reaction and ^{1}H-N.M.R. spectra. The structures of **6** and **5** were further confirmed by the formation of di- and tri-acetates, respectively. Compound **5** was converted to flavan **6** on heating with orthophosphoric acid at 80 °C. The formation of flavan **6** in 55% yield as the sole product was achieved by carrying out the reaction at 75–80 °C.

Table. Compounds **5**,**6**, and **8b–f** prepared

Product No.	R¹	R²	R³	R⁴	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
5	–	–	–	–	25[c]	181–183°	$C_{17}H_{16}O_4$ (284.3)	2.42 (s, 3H); 3.41 (d, 2H, J = 6 Hz); 6.35 (m, 1H); 7.12–7.3 (m, 7H); 8.1 (br. s, 2H, exchangeable with D_2O); 13.2 (s, 1H, exchangeable with D_2O)[d]
6 (= **8a**)	OH	OH	CO–CH₃	H	55 35[c]	168–170°	$C_{17}H_{16}O_4$ (284.3)	2.28 (m, 2H); 2.59 (s, 3H); 2.9 (m, 2H); 5.2 (dd, 1H, J = 11 Hz, 4 Hz); 5.46 (s, 1H, exchangeable with D_2O); 7.06 (s, 1H); 7.39 (s, 5H); 12.58 (s, 1H, exchangeable with D_2O)
8b[e]	H	H	CO–CH₃	OH	30	144–146°	$C_{17}H_{16}O_3$ (268.3)	2.18 (m, 2H); 2.52 (s, 3H); 2.78 (m, 2H); 5.1 (dd, 1H, J = 11 Hz, 4 Hz); 6.41 (d, 1H, J = 8 Hz); 7.2–7.45 (m, 6H); 13.24 (s, 1H, exchangeable with D_2O)
8c[e]	H	OH	CO–CH₃	H	40	183–185°	$C_{17}H_{16}O_3$ (268.3)	2.18 (m, 2H); 2.51 (s, 3H); 2.78 (m, 2H); 4.95 (dd, 1H, J = 11 Hz, 4 Hz); 6.47 (s, 1H); 7.35 (m, 6H); 13.4 (s, 1H, exchangeable with D_2O)
8d[f]	H	H	H	OH	20	120–122°	$C_{15}H_{14}O_2$ (226.3)	2.08 (m, 2H); 2.68 (m, 2H); 4.95 (dd, 1H, J = 11 Hz, 4 Hz); 6.41–7.38 (m, 8H)
8e[f]	H	OH	H	H	50	oil	$C_{15}H_{14}O_2$ (226.3)	1.97 (m, 2H); 2.7 (m, 2H); 4.98 (dd, 1H, J = 11 Hz, 4 Hz); 6.7 (d, 1H, J = 8 Hz); 6.98–7.24 (m, 7H)
8f	H	H	Cl	H	55	77–78°	$C_{15}H_{13}ClO$ (244.7)	2.15 (m, 2H); 2.87 (m, 2H); 4.97 (dd, 1H, J = 11 Hz, 4 Hz); 6.68–7.35 (m, 8H)

[a] Yield based on the starting phenolic compound, reaction carried out at 75–80 °C.
[b] Satisfactory microanalyses obtained: C ± 0.22, H ± 0.2.
[c] See experimental.
[d] In acetone-d_6.
[e] Mixture of **8b** and **8c** separated by column chromatography on silica gel, eluting with petroleum ether for **8b** and benzene/petroleum ether (1:1) for **8c**.
[f] Mixture of **8d** and **8e** separated by column chromatography on silica gel, eluting with petroleum ether.

2,4-Dihydroxyacetophenone **(7a)**, on similar reaction with cinnamyl alcohol **(4)** at 75–80 °C, gave a mixture of two products which were separated by column chromatography and identified as 6-acetyl-5-hydroxy-2-phenyl-3,4-dihydro-2*H*-1-benzopyran **(8b)** and 6-acetyl-7-hydroxy-2-phenyl-3,4-dihydro-2*H*-1-benzopyran **(8c)**. The reaction of cinnamyl alcohol **(4)** with resorcinol **(7b)** under identical conditions gave a mixture of two products, 5-hydroxy-2-phenyl-3,4-dihydro-2*H*-1-benzopyran **(8d)** and 7-hydroxy-2-phenyl-3,4-dihydro-2*H*-1-benzopyran **(8e)**. 4-Chlorophenol **(7c)** on similar condensation afforded 6-chloro-2-phenyl-3,4-dihydro-2*H*-1-benzopyran **(8f)**. The structures of all these products were assigned on the basis of their microanalyses, colour reactions, and ^{1}H-N.M.R. data (Table).

Condensation of 2,3,4-Trihydroxyacetophenone (3) with Cinnamyl Alcohol (4); Typical Procedure:

A solution of cinnamyl alcohol (**4**; 1.2 g, 8.9 mmol) in benzene (5 ml) is added to a well stirred suspension of 2,3,4-trihydroxyacetophenone (**3**; 1 g, 5.95 mmol), orthophosphoric acid (85%; 2 ml), and benzene (5 ml) during a period of 6 h maintaining the temperature at 55–60 °C. Stirring is continued for another 12 h. The organic layer is separated, the acid layer is neutralised with 5% sodium hydrogen carbonate solution (80 ml) and extracted with ether (3 × 20 ml). The combined benzene layer and ether extract is evaporated and the residue is found to be a mixture of two products (T.L.C., 1:9 acetone/benzene; R_f = 0.25 and 0.1). They are separated by column chromatography on silica gel, eluting with benzene/petroleum ether (1:1) and benzene/petroleum ether (3:1) to give **6** and **5**, respectively.

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