# CINNAMOYLATION OF CHROMANS : FORMATION OF FLAVONOIDS AND NEOFLAVONOIDS

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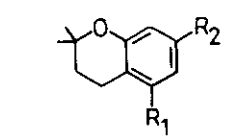
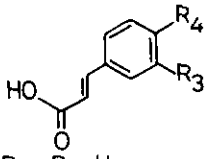
Abstract - Cinnamoylation of chroman 1 with acid 4 in presence of fused zinc chloride and phosphorus oxychloride gave chalcone 8 and with acids 5-7, the chalcones 9-11 and dihydrocoumarins 15-17 respectively. A similar reaction of chroman 2 with acids 4 and 5 afforded the chalcones 12 and 13 and dihydrocoumarins 18 and 19 while chroman 3 reacted with acid 4 to yield the chalcone 14 and flavanone 20.

In connection with our work on dihydropyrano- and pyranoisoflavones[1-3], we required dihydropyranochalcones as synthons. While the introduction of a cinnamoyl moiety into phenol features as one of the important biogenetic pathways leading to the formation of neoflavonoids[4] and forms the crux of a bioreductive process, the bio-oxidative process on the other hand envisions the coupling of a phenol with a biological cinnamyl equivalent such as cinnamyl pyrophosphate[5,6]. It is also postulated[7] that the same cinnamoyl coenzyme A that is responsible for a large and important branch of flavonoids by C-acylation is also responsible by an O-acylation sequence for 4-phenylcoumarins and their dihydro analogues, γ,γ-diphenylallyl compounds and dalbergenones. In view of this, clipping of pendent cinnamoyl fragment to a phenol is of significant interest for synthetic studies.

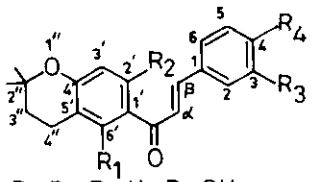
The most common method of introducing the cinnamoyl moiety which results in the formation of chalcones is the Claisen-Schmidt condensation of acetophenones with aryl aldehydes[8]. The reaction of cinnamoyl chloride with phloroglucinol in presence of aluminium chloride to yield the flavanone has been reported[9]. The method involving cinnamoylation, however, is much less exploited. In our present work, we demonstrate for the first time a laboratory analogy which lends credence to the common biogenetic pathway leading to both flavonoids and neoflavonoids. While doing so, the potentiality of $ZnCl_2$-$POCl_3$ reagent[10] to bring about acylations has been demonstrated.



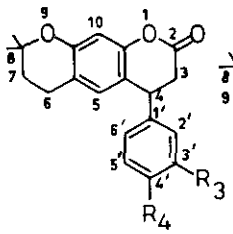
1 $R_1$=H, $R_2$=OH
2 $R_1$=OH, $R_2$=$OCH_3$
3 $R_1$=$R_2$=OH



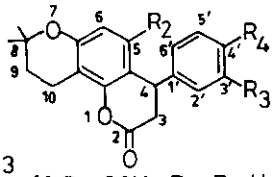
4 $R_3$=$R_4$=H
5 $R_3$=H, $R_4$=$OCH_3$
6 $R_3$, $R_4$= 
7 $R_3$=$R_4$=$OCH_3$



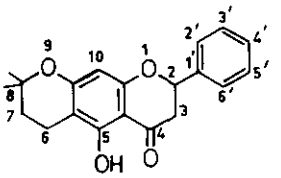
8 $R_1$=$R_3$=$R_4$=H, $R_2$=OH
9 $R_1$=$R_3$=H, $R_2$=OH, $R_4$=$OCH_3$
10 $R_1$=H, $R_2$=OH, $R_3$, $R_4$= 
11 $R_1$=H, $R_2$=OH, $R_3$=$R_4$=$OCH_3$
12 $R_1$=OH, $R_2$=$OCH_3$, $R_3$=$R_4$=H
13 $R_1$=OH, $R_2$=$R_4$=$OCH_3$, $R_3$=H
14 $R_1$=$R_2$=OH, $R_3$=$R_4$=H



15 $R_3$=H, $R_4$=$OCH_3$
16 $R_3$, $R_4$= 
17 $R_3$=$R_4$=$OCH_3$



18 $R_2$=$OCH_3$, $R_3$=$R_4$=H
19 $R_2$=$R_4$=$OCH_3$, $R_3$=H



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Chroman 1 on reaction with cinnamic acid 4 in presence of $ZnCl_2$-$POCl_3$ yielded chalcone 8 exclusively and in excellent yield. The IR spectrum of 8 showed absorption at 1630 $cm^{-1}$ (α,β-unsaturated carbonyl) and its NMR spectrum showed a doublet at δ 7.84 for the $C_\beta$ proton and a singlet at δ 12.84 for the $C_{2'}$-OH proton. The $C_\alpha$ proton, the $C_6$, proton and the aromatic protons appeared as a multiplet at δ 7.2-7.7. With acids 5-7, however, 1 gave in addition to the chalcones 9-11, the dihydrocoumarins 15-17 respectively. The IR spectrum of 15 showed absorption at 1765 $cm^{-1}$ ( δ -lactone carbonyl) and the NMR spectrum exhibited a doublet at δ 2.94 (J = 8 Hz) for two C-3 protons, a triplet at δ 4.18 (J = 8 Hz) for a C-4 proton and an AA'BB' pattern at δ 6.88 (J = 8 Hz) and 7.10 (J = 8 Hz) as two doublets for aromatic protons of the 4-phenyl function. The site of carbon-carbon bond formation in all these cases is the C-6 position of 1 which is clearly evident from the appearance of sharp singlets at δ 6.32, 6.38, 6.38 and 6.26 for the C-3' proton of chalcones 8-11 and at 6.56 and 6.52 for the dihydrocoumarins 15 and 16.

Chroman 2 was reacted with acids 4 and 5 to yield in both cases, the chalcones 12 and 13 and the dihydrocoumarins 18 and 19 respectively. Chroman 3 on similar reaction with acid 4 gave the chalcone 14 and the flavanone 20 respectively. The NMR spectrum of the flavanone showed a two-proton multiplet

Table 1. Physical Characteristics of Products

| Compd. No. | Yield (%) | Eluent (pet.ether-ethyl acetate) | Mp (°C) (solvent) | Lit. Mp (°C) | Molecular formula | Elemental analysis calc.(%) C | Elemental analysis (found) H |
|---|---|---|---|---|---|---|---|
| 8 | 83 | Benzene | 192-193 (benzene) | 183-184[11] | $C_{20}H_{20}O_3$ | 77.92 (78.06) | 6.49 (6.38) |
| 9 | 21 | 98:2 | 147-148 (pet.ether-EtOAc) | 146-147[11] | $C_{21}H_{22}O_4$ | 74.56 (74.99) | 6.51 (6.71) |
| 10 | 15 | 97:3 | 201-203 (methanol) | 202-203[11] | $C_{21}H_{20}O_5$ | 71.59 (71.97) | 5.68 (5.80) |
| 11 | 14 | 95:5 | 120-121 (methanol) | 120[11] | $C_{22}H_{24}O_5$ | 71.74 (71.46) | 6.52 (6.73) |
| 12 | 32 | 98:2 | 120-121 (pet.ether) | - | $C_{21}H_{22}O_4$ | 74.56 (74.89) | 6.51 (6.35) |
| 13 | 34 | 96:4 | 112-113 (pet.ether-EtOAc) | - | $C_{22}H_{24}O_5$ | 71.74 (72.05) | 6.52 (6.63) |
| 14 | 17 | 90:10 | 228-229 (pet.ether-EtOAc) | - | $C_{20}H_{20}O_4$ | 74.07 (74.32) | 6.17 (6.22) |
| 15 | 62 | 95:5 | 145-146 (pet.ether-EtOAc) | - | $C_{21}H_{22}O_4$ | 74.55 (74.22) | 6.51 (6.83) |
| 16 | 21 | 93:7 | 125-126 (pet.ether-EtOAc) | - | $C_{21}H_{20}O_5$ | 71.59 (71.22) | 5.68 (5.44) |
| 17 | 18 | 93:7 | 119-121 (pet.ether-EtOAc) | - | $C_{22}H_{24}O_5$ | 71.74 (71.32) | 6.52 (6.65) |
| 18 | 35 | 95:5 | 145-146 (pet.ether-EtOAc) | - | $C_{21}H_{22}O_4$ | 74.55 (74.67) | 6.51 (6.25) |
| 19 | 10 | 94:6 | 165-166 (pet.ether-EtOAc) | - | $C_{22}H_{24}O_5$ | 71.74 (72.16) | 6.52 (6.55) |
| 20 | 36 | 98:2 | 140-141 (pet.ether-EtOAc) | - | $C_{20}H_{20}O_4$ | 74.07 (74.44) | 6.17 (6.33) |

Table 2. Spectral Data of Products

| Compd. No. | IR(nujol) data ($cm^{-1}$) | $^1H$-NMR ($CDCl_3/TMS_{int}$) $\delta$ |
|---|---|---|
| 8 | 1630, 1565, 1480, 1450, 1350, 1280, 1240, 1150, 1115 | 1.38(s,$C_{2''}$-6H, gem-dimethyl), 1.84(t, J = 7 Hz, $C_{3''}$-2H), 2.78(t, J = 7 Hz, $C_{4''}$-2H), 6.32(s,$C_{3'}$-H), 7.20-7.70 (m,$C_\alpha$-H, $C_{6'}$-H and aromatic Hs-7H), 7.84(d,J = 16 Hz, $C_\beta$-H), 12.84(s,$C_{2'}$-OH). |
| 9 | 1630, 1575, 1480, 1440, 1360, 1285, 1240, 1150, 1110 | 1.38(s,$C_{2''}$-6H,gem-dimethyl), 1.84(t,J = 7 Hz, $C_{3''}$-2H), 2.78(t,J = 7 Hz , $C_{4''}$-2H), 3.88(s, $C_4$-$OCH_3$), 6.38(s,$C_{3'}$-H), 6.95(d, J = 10 Hz, $C_3$-H and $C_5$-H), 7.52-7.68 (m, $C_\alpha$-H, $C_{6'}$-H, $C_2$-H and $C_6$-H), 7.86(d,J = 16 Hz, $C_\beta$-H), 13.12 (s,$C_{2'}$-OH). |
| 10 | 1625, 1550, 1500, 1450, 1375, 1300, 1250, 1150, 1110 | 1.4(s,$C_{2''}$-6H, gem-dimethyl), 1.86(t, J = 7 Hz, $C_{3''}$-2H), 2.8(t, J = 7Hz,$C_{4''}$-2H), 6.06(s,$C_3$-O$\underline{CH_2}$O-$C_4$-2H), 6.38(s,$C_{3'}$-H), 6.8-7.7(m,$C_\alpha$-H,$C_{6'}$-H and aromatic-5H), 7.8(d, J = 16 Hz, $C_\beta$-H), 13.02 (s,$C_{2'}$-OH). |
| 11 | 1630, 1575, 1550, 1500, 1450, 1375, 1350, 1300, 1265, 1140 | 1.42(s,$C_{2''}$-6H,gem-dimethyl), 1.86(t, J = 7 Hz, $C_{3''}$-2H), 2.82 (t, J = 7 Hz, $C_{4''}$-2H), 4.0(s,$C_3$- and $C_4$-methoxyls-6H), 6.26(s,$C_{3'}$-H), 6.94(d, J = 9 Hz, $C_5$-H), 7.18(dd, J = 3 and 9 Hz, $C_2$-H), 7.34 (d, J = 3 Hz, $C_6$-H), 7.44(d, J = 16 Hz, $C_\alpha$-H), 7.64(s,$C_{6'}$-H), 7.88(d,J = 16 Hz, $C_\beta$-H), 13.06(s, $C_{2'}$-OH). |
| 12 | 1620, 1570, 1450, 1420, 1340, 1280, 1210, 1150, 1120 | 1.4(s,$C_{2''}$-6H, gem-dimethyl), 1.84(t, J = 7 Hz, $C_{3''}$-2H), 2.68(t, J = 7 Hz, $C_{4''}$-2H), 3.4(s,$C_{2'}$-methoxyl-3H), 5.4(s, $C_{3'}$-H), 7.2-8.1(m,$C_\alpha$-H,$C_\beta$-H and aromatic-5H), 14.72(s,$C_{6'}$-OH). |
| 13 | 1630, 1610, 1580, 1470, 1410, 1380, 1325, 1280, 1260, 1210, 1150, 1110 | 1.4(s,$C_{2''}$-6H, gem-dimethyl), 1.82(t,J = 7 Hz, $C_{3''}$-2H), 2.66(t,J = 8 Hz, $C_{4''}$-2H), 3.9(2s, $C_4$- and $C_{2'}$-methoxyls-6H), 5.92(s,$C_{3'}$-H), 6.96(d,J = 8 Hz, $C_3$-H and $C_5$-H), 7.58(d, J = 8 Hz, $C_2$-H and $C_6$-H), 7.76(d,J = 16 Hz, $C_\alpha$-H), 7.92(d, J = 16 Hz, $C_\beta$-H), 14.84(s, $C_{6'}$-OH). |
| 14 | 3300-3200(br), 1625, 1580, 1500, 1450, 1400, 1330, 1225, 1150, 1100 | 1.06(s,$C_{2''}$-6H,gem-dimethyl),1.78(t,J = 7 Hz, $C_{3''}$-2H),2.44(t,J = 7 Hz,$C_{4''}$-2H),5.88(s,$C_{3'}$-H), 6.9-7.6(m,aromatic-5H),7.96(d,J=16, Hz,$C_\alpha$-H), 8.2(d,J = 16 Hz, $C_\beta$-H). |

| Compd. No. | IR(nujol) data ($cm^{-1}$) | $^1H$-NMR ($CDCl_3$/TMS$_{int}$) $\delta$ |
|---|---|---|
| 15 | 1765, 1625, 1580, 1500, 1470, 1380, 1335, 1250, 1125 | 1.36(s,$C_8$-6H, gem-dimethyl), 1.78(t, J = 7 Hz, $C_7$-2H), 2.66(t, J = 7 Hz, $C_6$-2H), 2.94 (d, J = 8 Hz, $C_3$-2H), 3.84(s, $C_{4'}$-methoxyl-3H), 4.18(t, J = 8 Hz, $C_4$-H), 6.56(s, $C_{10}$-H), 6.6(s, $C_5$-H), 6.88 (d, J = 8 Hz, $C_{3'}$-H and $C_{5'}$-H), 7.1 (d, J = 8 Hz, $C_{2'}$-H and $C_{6'}$-H). |
| 16 | 1750, 1625, 1560, 1470, 1400, 1330, 1300, 1250, 1200, 1150 | 1.34(s,$C_8$-6H, gem-dimethyl), 1.74(t, J = 7 Hz, $C_7$-2H), 2.68 (t, J = 7 Hz, $C_6$-2H), 2.94(d, J = 8 Hz, $C_3$-2H), 4.22(t, J = 8 Hz, $C_4$-H), 6.02(s, $C_{3'}$-O$\underline{CH_2}$O-$C_{4'}$-2H), 6.52(s, $C_{10}$-H), 6.58(s,$C_5$-H), 6.8-7.3(m, aromatic-3H) |
| 17 | 1760, 1630, 1560, 1490, 1420, 1330, 1310, 1260, 1240, 1200, 1180 | -- |
| 18 | 1770, 1630, 1600, 1470, 1380, 1210, 1140, 1120 | 1.4(s,$C_8$-6H, gem-dimethyl), 1.84(t, J = 7 Hz, $C_9$-2H), 2.78(t, J = 7 Hz, $C_{10}$-2H), 3.04(d, J = 5 Hz, $C_3$-2H), 3.76 (s, $C_5$-methoxyl-3H), 4.6 (t, J = 5 Hz, $C_4$-H), 6.24(s,$C_6$-H), 7.1-7.4(m, aromatic-5H) |
| 19 | 1765, 1630, 1610, 1470, 1390, 1250, 1220, 1210, 1160, 1115 | -- |
| 20 | 1650, 1610, 1485, 1450, 1375, 1280, 1160, 1120 | 1.38(s,$C_8$-6H, gem-dimethyl), 1.78(t, J = 7 Hz, $C_7$-2H), 2.64(t, J = 7 Hz, $C_6$-2H), 3.06(m,$C_3$-2H), 5.48(dd, J = 4 and 12 Hz, $C_2$-H), 6.02(s, $C_{10}$-H), 7.2-7.6(m, aromatic-5H) and 11.78 (s, $C_5$-OH). |

at $\delta$3.06 (J = 4 Hz) for C-3 protons, a one-proton doublet of a doublet at $\delta$ 5.48 for C-2 proton and a singlet at $\delta$ 11.78 for deshielded phenolic hydroxyl proton. The chalcone 14 on cyclisation can result in both linear flavanone 20 and its angular isomer. However, we could obtain only one product which crystallised from petroleum ether-ethyl acetate as colourless fluffy needles, mp 140-141°C, while the angular isomer has been reported to be an oil[12]. Hence of the two possible structures, the product is assigned structure 20. All the chalcones prepared by cinnamoylation were identical with authentic samples obtained by the Claisen-Schmidt condensation of the appropriate acetyl chromans with the respective aryl aldehydes (mp., mixed mp., tlc, IR and NMR spectra). The physical and spectral properties of the compounds synthesised are given in Tables I and II.

## EXPERIMENTAL

In a typical experiment, to a mixture of the chroman(0.006 mole) and cinnamic acid (0.006 mole), freshly fused zinc chloride (4 g) and phosphorous oxychloride (15 ml) were added and the mixture was allowed to stand overnight (24 h) at room temperature after which it was poured into crushed ice with stirring. The resulting solid was filtered, air-dried and extracted with hot benzene-ethyl acetate. Removal of the solvent gave a residue which on TLC showed only one spot in the case of the product from 1 and 4 and two spots each in all other cases. Product 8 was purified and the mixture of products in the remaining cases was separated by column chromatography over silica gel and elution with appropriate solvents. Removal of solvent and crystallisation of the solid residue gave the pure products.

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