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A Convenient Synthesis of Crotylbenzaldehydes and 2-Methylformyl-Chromans

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Condensation of hydroxybenzaldehydes viz., 2,3,4-trihydroxy-, 2,4-dihydroxy-, 2,4-dihydroxy-6-methyl-, and 2,4-dihydroxy-3-iodo-6-methylbenzaldehydes with buta-1,3-diene in the presence of orthophosphoric acid yields crotylbenzaldehydes in one step. The latter compounds on cyclisation afford the corresponding 2-methylformylchromans.

(Keywords: Buta-1,3-diene; Crotylbenzaldehydes; Regiospecific crotylation; Orthophosphoric acid)

Eine einfache Synthese von Crotylbenzaldehyden und 2-Methylformyl-chromanen

Die Kondensation von Hydroxybenzaldehyden (2,3,4-Trihydroxy-, 2,4-Dihydroxy-, 2,4-Dihydroxy-6-methyl-, und 2,4-Dihydroxy-3-jod-6-methylbenzaldehyd) mit Buta-1,3-dien in Gegenwart von Orthophosphorsäure ergibt in einer Stufe Crotylbenzaldehyde. Diese lassen sich durch Cyclisierung zu den entsprechenden 2-Methylformylchromanen umsetzen.

Introduction

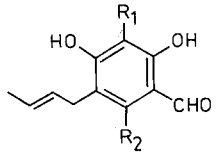
A number of 2-methylchromenes have been described[1] and some of them are reported to possess antijuvenile hormone activity[2]. In view of the facile dehydrogenation[3] of 2,2-dimethylchromans to the corresponding chromenes, the possibility of conversion of 2-methylchromans into 2-methylchromenes may not be ruled out. A few methods[4—9] for nuclear crotylation and 2-methylchroman formation are known but they are tedious and give poor yields. With this view, the condensation of hydroxybenzaldehydes with buta-1,3-diene in presence of orthophosphoric acid has been carried out which resulted in the formation of crotylbenzaldehydes. These were cyclised to the

corresponding 2-methylformylchromans in quantitative yield. No synthesis of formyl substituted 2-methylchromans has been reported so far.

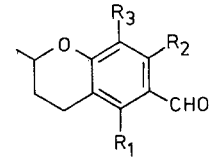
Results and Discussion

The condensation of 2,3,4-trihydroxybenzaldehyde with buta-1,3-diene in the presence of orthophosphoric acid gave only one product A (yield 70%). Elemental analysis of compound A showed the introduction of one butenyl unit. Its ^{1}H-NMR spectrum displayed in the aliphatic region signals at δ 5.48 (m, $-CH=CH-$), 3.20 (d, $J = 4$ Hz, $-CH_2-$) and 1.66 (d, $J = 5$ Hz, CH_3) (typical for a but-2-enyl group) along with the other expected signals. It was thus assigned the structure of 5-(but-2′-enyl)-2,3,4-trihydroxybenzaldehyde (**1**). When **1** was heated with orthophosphoric acid at 95—100°, 6-formyl-7,8-dihydroxy-2-methyl-3,4-dihydro-2*H*-1-benzopyran (**2**) was obtained.

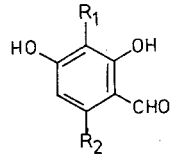
Its ^{1}H-NMR spectrum was in agreement with the structure, showing a singlet of one proton at δ 11.22 (chelated hydroxyl group), another singlet of one aromatic proton at 6.28, a multiplet at 4.06–4.28 (methyne proton), a distinctive triplet ($J = 7$ Hz) at 2.73 assigned to methylene group, a multiplet at 1.63–1.95 (methylene group) and a doublet of three protons at 1.40 ppm for the methyl group.



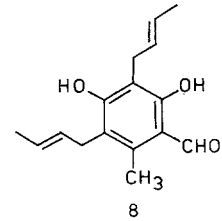
1, $R_1 = OH$; $R_2 = H$
5, $R_1 = R_2 = H$
11, $R_1 = H$; $R_2 = CH_3$
12, $R_1 = I$; $R_2 = CH_3$



2, $R_1 = H$; $R_2 = R_3 = OH$
6, $R_1 = OH$; $R_2 = R_3 = H$
7, $R_1 = R_3 = H$; $R_2 = OH$
13, $R_1 = OH$; $R_2 = CH_3$; $R_3 = H$
14, $R_1 = CH_3$; $R_2 = OH$; $R_3 = H$



3, $R_1 = CH(CH_3)CH=CH_2$; $R_2 = H$
4, $R_1 = CH_2CH=CH.CH_3$; $R_2 = H$
9, $R_1 = CH(CH_3)CH=CH_2$; $R_2 = CH_3$
10, $R_1 = CH_2CH=CH.CH_3$; $R_2 = CH_3$



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2,4-Dihydroxybenzaldehyde on similar condensation with buta-1,3-diene gave a mixture of three products (B, C and D), which were separated on silica gel. Elemental analysis showed the introduction of one butadiene (C-4) unit in B, C and D. Compound B was assigned the structure of 3-(prop-1′-methyl-2′-enyl)-2,4-dihydroxybenzaldehyde (**3**) on the basis of its ^{1}H-NMR spectrum which showed besides other signals a multiplet of one proton at δ 4.10–4.34, two double doublets at 5.32 and 5.39 integrating for two protons in all and another multiplet at 6.10–6.31 of one proton, thus confirming the presence of a 1-methyl-prop-2-enyl group. The structure of C and D were established as 3-(but-2′-enyl)-2,4-dihydroxybenzaldehyde (**4**) and 5-(but-2′-enyl)-2,4-dihydroxybenzaldehyde (**5**) on the basis of their ^{1}H-NMR spectra data. Compounds **4** and **5** when heated separately with orthophosphoric acid at 95–100° furnished 6-formyl-5-hydroxy-2-methyl-3,4-dihydro-2*H*-1-benzopyran (**6**) and 3,4-dihydro-6-formyl-7-hydroxy-2-methyl-2*H*-1-benzopyran (**7**), respectively.

Similarly, 2,4-dihydroxy-6-methylbenzaldehyde on condensation with buta-1,3-diene gave four compounds (E, F, G and H) which were again separated by column chromatography. Elemental analysis of the faster moving compound E showed the introduction of two butenyl units. It was identified as 3,5-di-(but-2′-enyl)-2,4-dihydroxy-6-methylbenzaldehyde (**8**) on the basis of its ^{1}H-NMR spectrum. F was assigned the tentative structure of 3-(prop-1′-methyl-2′-enyl)-2,4-dihydroxy-6-methylbenzaldehyde (**9**) or its 5-alkenylated isomer. The ^{1}H-NMR spectrum of compound G showed, besides other usual signals, a singlet of one aromatic proton at δ 6.16 whereas that of H showed a singlet at 6.18 ppm. Therefore a clear distinction between the structures of G and H could not be made on the basis of ^{1}H-NMR spectral data and hence either one of the compounds could be assigned the structure of 3-(but-2′-enyl)-2,4-dihydroxy-6-methylbenzaldehyde (**10**) or 5-(but-2′-enyl)-2,4-dihydroxy-6-methylbenzaldehyde (**11**). However, confirmation of the structures was provided by comparision of an authentic sample of **11**, prepared as follows: 2,4-Dihydroxy-3-iodo-6-methylbenzaldehyde when reacted with but-1,3-diene, underwent regiospecific crotylation at 5-position resulting in the formation of 5-(but-2′-enyl)-2,4-dihydroxy-3-iodo-6-methylbenzaldehyde (**12**) in 70% yield. **12** on heating with zinc and hydrochloric acid afforded **11**. Hence compounds G and H could be assigned the structure of **10** and **11**, respectively. These compounds (**10**, **11**) on heating with orthophosphoric acid at 95–100° furnished 2,7-dimethyl-6-formyl-5-hydroxy-3,4-dihydro-2*H*-1-benzopyran (**13**) and 2,5-dimethyl-6-formyl-7-hydroxy-3,4-dihydro-2*H*-1-benzopyran (**14**), respectively.

Crotylbenzaldehydes and 2-methylformylchromans may be used as

important precursors for the synthesis of furocoumarins, furochalcones and pyranocoumarins, all well known naturally occurring and biologically active compounds.

Acknowledgement

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Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer, with Si*Me*$_4$ as internal standard. Silica gel (60–120 mesh) was used for all chromatographic separations.

Reaction of 2,3,4-Trihydroxybenzaldehyde with Buta-1,3-diene: General Procedure

Buta-1,3-diene was bubbled into a mixture of 2,3,4-trihydroxybenzaldehyde (2 g, 13.0 mmol), orthophosphoric acid (85%, 2 ml) and xylene (10 ml) with constant stirring at 35–40 °C for 1–2 h. Stirring was continued for 15 h more and then the mixture neutralised with sodium hydrogen carbonate solution (5%, 100 ml). It was extracted woth ether, the organic phase washed with water, dried (Na_2SO_4) and the solvent distilled off. The residue was placed on a column of silica gel and eluted with benzene–petroleum ether (9 : 1) to give **1**; yield: 1.9 g (70%); m. p. 133–134 °C.

Cyclisation of 5-(But-2'-enyl)-2,3,4-trihydroxybenzaldehyde (**1**): *Formation of 6-Formyl-7,8-dihydroxy-2-methyl-3,4-dihydro-2H-1-benzopyran* (**2**): *General Procedure*

A mixture of **1** (0.2 g, 0.9 mmol) and orthophosphoric acid (1.5 ml) was heated on a boiling water bath (95–100 °C) for 1–2 h. The reaction mixture was poured into ice cold water (50 ml) and the separated solid extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and the solvent evaporated to give **2** which crystallised from benzene–petroleum ether as colourless needles; yield: 0.17 g (85%); m. p. 124–125 °C.

Unambiguous Synthesis of 5-(But-2'-enyl)-2,4-dihydroxy-5-methylbenzaldehyde (**11**)

A solution of **12** (0.5 g, 1.5 mmol) in ethanol (15.0 ml) was refluxed with zinc dust (0.5 g) and conc. hydrochloric acid (1.5 ml) for 1 h. The reaction mixture was filtered, the solvent evaporated and the residue treated with crushed ice to give **11**. It was crystallised from benzene–petroleum ether as colourless shining needles; yield: 0.25 g (80.9%); m. p. 130–131 °C.

Data for compounds **1**–**14**: Yield [%]; m. p. [°C]; molecular formula (all compounds gave satisfactory C–H-values); NMR ($CDCl_3/CD_3COCD_3$), δ [ppm].

1: 70%; 133–134°; $C_{11}H_{12}O_4$; NMR: 1.66 (d, $J = 5$ Hz, 3 H, $-CH_3$), 3.20 (d, $J = 4$ Hz, 2 H, $-CH_2-$), 5.48 (m, 2 H, $-CH=CH-$), 6.80 (s, 1 H, H-6), 9.53 (s, 1 H, $-CHO$), 12.73 (s, 1 H, 2-OH, D_2O exchangeable).

2: 85%; 124–125°; $C_{11}H_{12}O_4$; NMR: 1.40 (d, $J = 7$ Hz, 3 H, $-CH_3$), 1.63–1.95 (m, 2 H, 3-CH_2–), 2.73 (t, $J = 7$ Hz, 2 H, 4-CH_2–), 4.06–4.28 [m, 1 H, –C**H**(CH_3)–], 6.28 (s, 1 H, H-5), 9.47 (s, 1 H, –CHO), 11.22 (s, 1 H, 7-OH, D_2O exchangeable).

3: 5%; 119–120°; $C_{11}H_{12}O_3$; NMR: 1.41 (d, $J = 7$ Hz, 3 H, $-CH_3$), 4.10–4.34 (m, 1 H, –C**H**–CH_3), 5.32 and 5.39 (each dd, $J_{vic} = 17$ Hz, 10 Hz, $J_{gem} = 2$ Hz, 2 H, $=CH_2$), 6.10–6.31 (m, 1 H, –CH=), 6.40 (d, $J = 9$ Hz, 1 H, H-5), 6.71 (s, 1 H, 4-OH, D_2O exchangeable), 7.23 (d, $J = 9$ Hz, 1 H, H-6); 9.56 (s, 1 H, –CHO); 12.04 (s, 1 H, 2-OH, D_2O exchangeable).

4: 40%; 110–111°; $C_{11}H_{12}O_3$; NMR: 1.56 (d, $J = 5$ Hz, 3 H, $-CH_3$), 3.29 (d, $J = 4$ Hz, 2 H, $-CH_2$–), 5.50 (m, 2 H, –CH=CH–), 6.40 (d, $J = 9$ Hz, 1 H, H-5), 6.59 (s, 1 H, 4-OH, D_2O exchangeable), 7.21 (d, $J = 9$ Hz, 1 H, H-6), 9.58 (s, 1 H, –CHO), 11.66 (s, 1 H, 2-OH, D_2O exchangeable).

5: 40%; 130–131°; $C_{11}H_{12}O_3$; NMR: 1.65 (d, $J = 5$ Hz, 3 H, $-CH_3$), 3.23 (d, $J = 4$ Hz, 2 H, $-CH_2$–), 5.53 (m, 2 H, –CH=CH–), 6.36 (s, 1 H, H-3), 7.29 (s, 1 H, H-6), 9.68 (s, 1 H, –CHO), 11.76 (s, 1 H, 2-OH, D_2O exchangeable).

6: 80%; oil; $C_{11}H_{12}O_3$; NMR: 1.26 (d, $J = 7$ Hz, 3 H, $-CH_3$), 1.69–1.88 (m, 2 H, 3-CH_2–), 2.57 (t, $J = 7$ Hz, 2 H, 4-CH_2–), 3.89–4.13 [m, 1 H, –C**H**(CH_3)–], 6.28 (d, $J = 9$ Hz, 1 H, H-8), 7.10 (d, $J = 9$ Hz, 1 H, H-7), 9.52 (s, 1 H, –CHO), 11.75 (s, 1 H, 5-OH, D_2O exchangeable).

7: 85%; 120–121°; $C_{11}H_{12}O_3$; NMR: 1.41 (d, $J = 7$ Hz, 3 H, $-CH_3$), 1.72–2.02 (m, 2 H, 3-CH_2–), 2.75 (t, $J = 7$ Hz, 2 H, 4-CH_2–), 4.12–4.32 [m, 1 H, –C**H**(CH_3)–]; 6.37 (s, 1 H, H-8), 7.31 (s, 1 H, H-5), 9.66 (s, 1 H, –CHO), 11.15 (s, 1 H, 7-OH, D_2O exchangeable).

8: 3%; 160–161°; $C_{16}H_{20}O_3$; NMR: 1.60 (d, $J = 5$ Hz, 3 H, $-CH_3$), 1.65 (d, $J = 5$ Hz, 3 H, $-CH_3$), 2.40 (s, 1 H, 6-CH_3), 3.21 (d, $J = 4$ Hz, 2 H, $-CH_2$–), 3.31 (d, $J = 4$ Hz, 2 H, $-CH_2$–), 5.37 (m, 2 H, –CH=CH–), 5.51 (m, 2 H, –CH=CH–), 6.10 (s, 1 H, 4-OH, D_2O exchangeable), 10.21 (s, 1 H, –CHO), 12.93 (s, 1 H, 2-OH, D_2O exchangeable).

9: 4%; 141–142°; $C_{12}H_{14}O_3$; NMR: 1.49 (d, $J = 7$ Hz, 3 H, –CH(C**H**$_3$)–], 2.56 (s, 1 H, 6-CH_3), 4.12–4.34 [m, 1 H, –C**H**(CH_3)–], 5.40 and 5.47 (each dd, 2 H, $J_{vic} = 17$ Hz, 10 Hz, $J_{gem} = 2$ Hz), 6.18–6.40 (m, 2 H, –CH= and H-5), 6.57 (s, 1 H, 4-OH, D_2O exchangeable), 10.32 (s, 1 H, –CHO), 13.16 (s, 1 H, 2-OH, D_2O exchangeable).

10: 38%; 148–149°; $C_{12}H_{14}O_3$; NMR: 1.51 (d, $J = 5$ Hz, 3 H, $=CH-CH_3$), 2.41 (s, 3 H, 6-CH_3), 3.20 (d, $J = 4$ Hz, 2 H, $-CH_2$–), 5.40 (m, 2 H, –CH=CH–), 6.16 (s, 1 H, H-5), 10.08 (s, 1 H, –CHO), 12.72 (s, 1 H, 2-OH, D_2O exchangeable).

11: 39%; 130–131°; $C_{12}H_{14}O_3$; NMR: 1.58 (d, $J = 5$ Hz, 3 H, $=CH-CH_3$), 2.42 (s, 3 H, 6-CH_3), 3.24 (d, $J = 4$ Hz, 2 H, $-CH_2$–), 5.35 (m, 2 H, –CH=CH–), 6.18 (s, 1 H, H-3), 10.32 (s, 1 H, –CHO), 12.74 (s, 1 H, 2-OH, D_2O exchangeable).

12: 70%; 161–162°; $C_{12}H_{13}IO_3$; NMR: 1.61 (d, $J = 5$ Hz, 3 H, $=CH-CH_3$), 2.41 (s, 3 H, 6-CH_3), 3.22 (d, $J = 4$ Hz, 2 H, $-CH_2$–), 5.37 (m, 2 H, –CH=CH–), 10.15 (s, 1 H, –CHO), 12.60 (s, 1 H, 2-OH, D_2O exchangeable).

13: 79%; oil; $C_{12}H_{14}O_3$; NMR: 1.36 [d, $J = 7$ Hz, 3 H, –CH(C**H**$_3$)], 1.60–1.81 (m, 2 H, 3-CH_2–), 2.43 (s, 3 H, 7-CH_3), 2.67 (t, $J = 7$ Hz, 2 H, 4-CH_2–), 4.03–4.23 [m, 1 H, –C**H**(CH_3)–], 6.20 (s, 1 H, H-8), 10.23 (s, 1 H, –CHO), 12.85 (s, 1 H, 5-OH), D_2O exchangeable).

14: 81%; 125–126°; $C_{12}H_{14}O_3$; NMR: 1.38 (d, $J = 7$ Hz, 3 H, $-CH(CH_3)$], 1.60–1.80 (m, 2 H, 3-CH_2-), 3.46 (s, 3 H, 5-CH_3), 2.69 (t, $J = 7$ Hz, 2 H, 4-CH_2-), 4.05–4.25 [m, 1 H, $-CH(CH_3)-$], 6.15 (s, 1 H, H-8), 10.12 (s, 1 H, $-CHO$), 12.86 (s, 1 H, 7-OH, D_2O exchangeable).

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