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Note

An efficient synthesis of lactarochromal from 6-amino-2,2-dimethylchroman-4-one

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Lactarochromal **1**, a metabolite of *Lactarius deliciosus*, has been synthesised starting from 6-amino-2,2-dimethylchroman-4-one **3,** which in turn, is prepared from paracetamol *via* the known intermediates. The amino compound **3** is then converted to the iodo compound **4,** followed by formylation of the latter using N-formylpiperidine to provide, efficiently, the natural product **1** in good yield.

Keywords: Lactarochromal, *Lactarius deliciosus*, 6-amino-2,2- dimethylchroman-4-one, 6-iodo-2,2-dimethylchroman-4-one, N- formylpiperidine

Lactarochromal **1**, a metabolite of the fungus *Lactarius deliciosus*, was isolated by Ayer and Trifonov[1], and characterized on the basis of spectroscopic data. Since structure **1** was based only on spectral data, a synthetic support[2] was provided to confirm the assigned structure by its facile synthesis utilising 2,2,6-trimethylchroman-4-one **2** as the key intermediate. However, the $K_2S_2O_8$-Cu (II) mediated oxidation[3] of the aromatic methyl group in **2** produced appreciable amount of the corresponding acid at the cost of desired product **1**. To circumvent this problem, it was preferred to introduce the formyl group directly on preformed chromanone skeleton at the last stage of synthesis. In accordance with this protocol, herein is reported an efficient and simple synthesis of **1** starting from 6-amino-2,2-dimethylchroman-4-one **3** **(Scheme I)**.

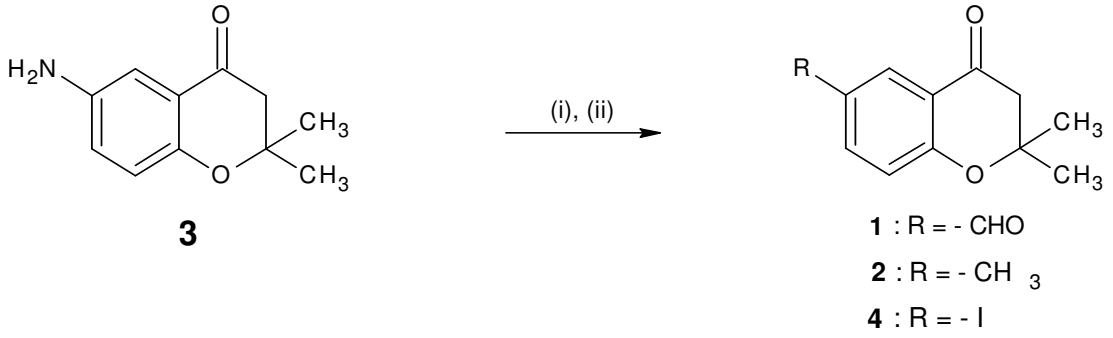
The starting material **3** for the synthesis of **1** was prepared, in the present case, starting from paracetamol *via* the known intermediates: 4′-acetoxyacetanilide[4], 2′-hydroxy-5-acetamidoacetophenone[5] and 6-acetamido-2,2-dimethylchroman-4-one[6]. The amino group of **3** was diazotized and the resulting diazonium salt was treated with aqueous KI to furnish the corresponding iodochroman-4-one **4**, hitherto unknown. The iodo compound **4** has been fully characterized by spectral data (see experimental section). Finally, the formyl group was introduced smoothly on the chromanone moiety by treating the lithium salt of **4** with N-formylpiperidine to furnish lactarochromal **1** as a crystalline solid in 93% yield. The melting point and spectral data (IR, ^{1}H and ^{13}C NMR and MS) of the synthetic **1** were in good agreement with the published[1,2] data.

Experimental Section

Melting points were determined by open capillaries and are uncorrected. Column chromatography was performed over silica gel (60-120 mesh size) and TLC on precoated plastic sheets. IR spectra were recorded on a Shimadzu FTIR-8001 (KBr pellet or neat). ^{1}H and ^{13}C NMR spectra were recorded on a Varian instrument and chemical shifts were recorded in ppm in $CDCl_3$ using $SiMe_4$ as internal standard. Mass spectra were obtained on Varian MAT 371 and Jeol D-300 mass spectrometer. All yields refer to isolated products unless stated otherwise.

6-Iodo-2,2-dimethylchroman-4-one, 4

The amine **3** (0.4 g, 2.094 mmol) was dissolved in a mixture of H_2SO_4 (5 mL) and water (12 mL) with warming. The resultant clear solution was cooled to 0°C and treated with a solution of $NaNO_2$ (0.148 g, 2.144 mmol) in water (2.5 mL) dropwise with stirring. The mixture was stirred for an additional 1.0 hr at 0°C, and then a solution of KI (0.5 g, 3.017 mmol) in water (3 mL) was added dropwise. The reaction mixture was stirred overnight at RT. Extraction of the organic part with diethyl ether followed by evaporation of the solvent gave a red gum, which was chromatographed over silica gel and eluted with a gradient solvent system consisting of chloroform and methanol to give **4** (0.518 g, 82%) as yellow oil; IR (neat): 2990, 1690, 1465, 1410, 1375, 1280, 1220, 1140, 825 and 755 cm^{-1}; EIMS: *m/z* (%) 302 (100) [M$^+$], 286.9 (96), 246.9 (56), 245.9 (54), 217.9 (20), 176.1 (16) and 161 (18); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.15 (d, *J* = 2.5 Hz, 1 H, H-5), 7.7 (dd, *J* = 8.5 Hz, 2.5 Hz, 1 H, H-7), 6.72 (d, *J* = 8.5 Hz, 1 H, H-8), 2.72 (s, 2 H, CH_2) and 1.45 (s, 6 H, $2CH_3$); ^{13}C/APT-NMR ($CDCl_3$, 50.4 MHz): δ 191.1 (1C, C_{quat}), 159.5 (1C, C_{quat}), 144.5 (1C, CH), 135.1 (1C, CH), 121.9 (1C,



Reagents: (i) H_2SO_4, $NaNO_2$, H_2O, KI, 0 °C; (ii) *n*-BuLi, N - formylpiperidine, 0 °C, under N_2.

Scheme I

C_{quat}), 120.8 (1C, CH), 82.8 (1C, C_{quat}), 79.6 (1C, C_{quat}), 48.4 (1C, CH_2) and 26.5 (2C, $2CH_3$).

Lactarochromal, 1

To a stirred and cooled solution of **4** (0.2 g, 0.663 mmol) in dry diethylether (25 mL), *n*-butyl lithium (0.7 mL, 1.13 mmol, 1.6 M in hexane) was added dropwise, under nitrogen atmosphere. After 1 hr of stirring, N-formylpiperidine (0.1 g) was added. The reaction mixture was stirred for an additional 2 hr followed by acidification with ice-cold solution of 2N HCl and extracted with ether (3 × 50 mL). The combined ether layer was washed with a solution of 10% aqueous $NaHCO_3$, dried (anhyd. Na_2SO_4) and concentrated. The crude residue was purified further by column chromatography over silica gel using petroleum ether : diethylether (9:1) to give **1** (0.125 g, 93%) as a crystalline solid, m.p. 91°C (Lit., 89-91°C[1]); IR (neat): 2990, 1700, 1687, 1610, 1565, 1475, 1440, 1390, 1270, 1220, 1185, 1170, 1125 and 830 cm^{-1}; EIMS: *m/z* (%) 204.1 (66) [M^+], 189 (100), 149 (50), 148 (48), 147 (14) and 119 (16); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.89 (s, 1 H, CHO), 8.32 (d, *J* = 2.0 Hz, 1 H, H-5), 8.00 (dd, *J* = 8.8, 2.0 Hz, 1 H, H-7), 7.03 (d, *J* = 8.8 Hz, 1 H, H-8), 2.76 (s, 2 H, CH_2) and 1.48 (s, 6 H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 125.5 MHz): δ 191.1 (1C, C=O), 190.1 (1C, CH), 164.3 (1C, C_{quat}), 134.8 (1C, CH), 131.1 (1C, CH), 129.8 (1C, C_{quat}), 119.8 (1C, C_{quat}), 119.6 (1C, CH), 80.6 (1C, C_{quat}), 48.4 (1C, CH_2) and 26.5 (2C, $2CH_3$).

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