Synthesis of 1-(2-Formyl-3,5-Dimethoxy-4-Methylphenyl) -4-Methylpentan-2-One

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(Received 20th May, 1984)

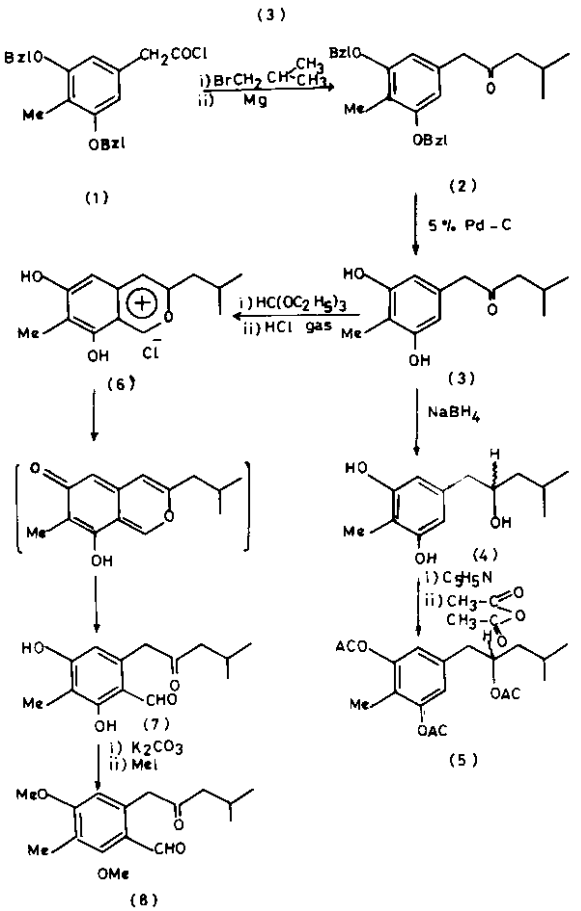
Summary: The title compound (8) which is an intermediate towards the isochroman system, possibly related to the fungal metabolites of rotiorin type has been synthesised. Reaction of 3,5-dibenzyloxy-4-methylphenylacetyl chloride (1) with isobutyl magnesium bromide furnished 1-(3,5-dibenzyloxy-4-methylphenyl)-4-methylpentan-2-one (2) which was debenzylated to 1-(3,5-dihydroxy-4-methylphenyl)-4-methylpentan-2-one (3). Formylation of the ketone (3) gave benzopyrillium salt (6) which was decomposed to 1-(2-formyl-3,5-dihydroxy-4-methylphenyl)-4-methylpentan-2-one (7) and on methylation gave 1-(2-formyl-3,5-dimethoxy-4-methylphenyl)-4-methylpentan-2-one (8). (±)-1-(3,5-Diacetoxy-4-methylphenyl)-4-methylpentan-2-ylacetate (5) was obtained from (±)-1-(3,5-dihydroxy-4-methylphenyl)-4-methylpentan-2-ol (4) which was synthesised from the ketone (3).

Introduction

3,5-Dibenzyloxy-4-methylphenylacetyl chloride (1) (and its derivatives) is an essential starting material for the synthesis of fungal metabolites of the sclerotionin group [1], was synthesised by a novel route [2,3,4] and on reaction [5] with isobutyl magnesium bromide in dry ether with anhydrous ferric chloride as a catalyst gave (2) by Grignard reaction. The structure of the ketone (2) was confirmed by the appearance of new peaks in ^{1}HNMR spectrum at 7.89 (3H, m, CH_2-$CH(CH_3)_2$ and at 9.26 (6H,d-$CH(CH_3)_2$ J = 6 c.p.s.). Debenzylation [6] of ketone (2) with palladised charcoal over hydrogen in absolute ethanol and ethyl acetate gave dihydroxy phenol (3) which on formylation [7] with triethyl orthoformate and dry hydrogen chloride gas furnished a highly unstable benzopyrillium salt (6). Decomposition of this salt (6) with base yielded keto-aldehyde (7), structure was confirmed by the appearance of new peaks of a carbonyl (ν^{film}_{max} 1630 (m) cm^{-1}) group in IR spectrum and at τ-0.29 (1H, s, ArCHO) in ^{1}HNMR spectrum. The keto-aldehyde (7) was methylated with methyl iodide and anhydrous potassium carbonate in dry acetone to give the title compound (8). Reduction of dihydroxy phenol (3) with sodium borohydride in ethanol at room temperature furnished alcohol (4) which on acetylation with pyridine-acetic anydride gave acetate (5).

Experimental

All melting points are uncorrected. IR was recorded on a Perkin-Elmer IR spectrophotometer Model-157G (ν^{film}_{max} cm^{-1}) in KBr unless otherwise specified. ^{1}HNMR spectra were



measured on Perkin-Elmer R-12A (60 MHz) spectromter in $CDCl_3$ or $(CD_3)_2CO$ using tetramethylsilane as an internal standard (s, singlet; d, doublet; t, triplet; m,multiplet; br, broad).

1-(3,5-Dibenzyloxy-4-methyl)-3 methylpentan-2-one (2)

Oxalyl chlorride (1g) was added to the solution of 3,5-dibenzyloxy-4-methylphenylacetic acid (0.75 g) in dry benzene (20 ml). The solution turned yellow with vigorous effervescenes. After 24 hours, the solvent was evaporated in vacuo. This process was repeated till there was no more smell of oxalyl chloride. A Grignard reagent was prepared from isobutyl bromide (0.51 g) and magnesium (0.11 g) in dry ether (20 ml). The final solution was added dropwise to a stirred solution of the acid chloride and anhydrous ferric chloride (7 mg) in dry ether (10 ml) at 58°C. The red solution was stirred for ½ hour at room temperature, heated under reflux for 1 hour and poured into the aqueous sodium carbonate (5%, 30 ml). Ice was added to the reaction mixture and was stored at 0°C overnight. The emulsion was acidifed with dilute hydrochloric acid, the ethereal layer was separated and the aqueous layer was extracted with ether (3 x 30 ml). The combined ethereal extracts were washed with brine (5%, 20 ml), sodium carbonate (5%, 4 x 20), finally with brine (5%, 20 ml), and dried (Mg So_4). The solvent was evaporated in vacuo to give a red oil which was absorbed on silica (60 g). Elution with ether and light petroleum (1:20) gave 1-(3,5-dibenzyloxy-4-methylphenyl)-4-methylpentan-2-one (0.45 g, 53%) as needles from methanol, m.p. 56-57°C, ν^{film}_{max} 1700 (s), 1592 cm^{-1} $\tau(CDCl_3)$ 2.72 (10H, s, $2C_6H_5CH_2$-), 3.66 (2H, s, Ar-H), 5.04 (4H, s, $2C_6H_5CH_2$) 6.54 (2H, s, Ar-CH_2), 7.89 (3H, m, CH_2-$CH(CH_3)_2$) 9.26 (6H, d, -$CH(CH_3)_2$ J = 6 c.p.s.) (Found: C, 80.5; H, 7.5 $C_{27}H_{30}O_3$ requires C, 80.6; H, 7.5%).

1-(3,5-Dihydroxy-4-methylphenyl)-4-methylpentan-2-one (3)

A solution of 1-(3-,5-dibenzyloxy-4-methylphenyl)-4-methylpentan-2-one (1g) in absolute ethanol (140 ml) and ethyl acetate (56 ml) was hydro-

genated with Pd-/c (5%, 0.4 g). The reaction mixture was filtered and the solvent was evaporated in vacuo to give 1-(3,5-dihydroxy-4-methylphenyl)-4-methylpentan-2-one (10.5g 91%) which formed prisms from ethanol m.p. 113-115°C ν_{max}^{film} 3320 9m), 3160 (w), 1682 (s), 1625 (w), 1590 (s) cm^{-1} $(CD_3)_2CO$ 2.23 (2H, s, Ar-H), 6.53 (2H, s, 2 OH exchangeable), 3.11 (2H, s, $ArCH_2$-), 7.71 (2H, s, Ar-CH_2COCH_2-), 7.89 (3H, s, Ar-Me). (Found:C, 70.1; H, 8.2 $C_{13}H_{18}O_3$ requires C, 70.2, H, 8.2%).

1-(2-Formyl-2,5-dihydroxy-4-methylphenyl)-4-methylpentan-2-one (7)

A solution of 1-(3,5-dihydroxy-4-methyphenyl)-4-methylpentan-2-one (100 mg) in triethylorthoformate (0.5 ml) was treated with hydrogen chloride gas for 5 seconds. As the solution darkened, anhydrous ether (30 ml) was added and a yellow precipitate formed. The precipitate was filtered after cooling and was dissolved in absolute ethanol (4 ml) and excess of solid potassium acetate was added. Therein the colour of the solution changed from its initial yellow to a deep orange and subsequent dilution with water (25 ml) caused a gradual loss of colour, but no precipitate formed. Subsequent warming of the solution on a steam bath ½ hour produced a reddish tinge and prolonged cooling afforded a precipitate of crude 1-(2-formyl-3,5-dihydroxy-4-methylphenyl)-4-methylphenyl)-4-methylpentan-2-one (60 mg, 54%). Purification of a sample from aqueous methanol gave red brown prisms m.p. 128-130°C ν_{max}^{film} 3130 (w), 1714 (s), 1630 (m), 1600 (s) cm^{-1}. $(CDCl_3)$- 2.67 (1H, s, Ar-OH), 5.96 (2H, s, Ar-CH_2-). (Found:C, 66.7; H, 7.2 $C_{14}H_{18}O_4$ require C, 67.2; H, 7.2%).

1-(2-Formyl-3,5-dimethoxy-4-methylphenyl)-4-methylpentan-2-one (8)

A solution of 1-(2-formyl-3,5-dihydroxy-4-methylphenyl)-4-methylpentan-2-one (100 mg), anhydrous potassium carbonate (1 g) methyl iodide in excess in dry acetone (5 ml), were heated under reflux for 3 hours. The reaction mixture was filtered when hot and the filterate was evaporated in vacuo to leave a yellow oil which was adsorbed on silica (5 g). Elution with ether and light petroleum ether (1:50) gave 1-(2-formyl-3,5-dimethoxy-4-methylphenyl)-4-methylpentan-2-one (100 mg, 90%) as needles from ether and light petroleum m.p. 55-57°C ν_{max}^{film} 1720 (s), 1675 (s), cm^{-1}. τ $(CDCl_3)$-0.29 (1H, s, Ar-CHO), 3.45 (1H, s, Ar-H), 5.96 (2H, s, Ar-CH_2-), 6.12 (3H, s, OCH_3), 6.16 (3H, s, OMe). (Found: 69.3; H, 8.0 $C_{16}H_{22}O_4$ requires C, 69.0, H, 8.0%).

(+)-1-(3,5-Diacetoxyl-4-methylphenyl)-4-methylpentan-2-ylacetate (5)

Sodium borohydride (0.2 g) was added to a stirred solution of 1-(3,5-dihydroxy-4-methylphenyl)-4-methylpentan-2-one (100 mg) in absolute ethanol (10 ml) at room temperature for 1/2 hour, the temperature was then raised to 50°C for 2 hours and then water was added. The reaction mixture was acidifed with dilute sulphuric acid, extracted with methylene chloride (3 x 50 ml), dried (Mg So_4) and the solvent was evaporated in vacuo to give a yellow oil which was used in the next step of synthesis. A solution of this oil (100

mg) in pyridine (0.2 ml), and acetic anhydride (0.3 ml) was stirred at room temperature overnight, water was added and the product was extracted with ether (3 x 20 ml). The combined extracts were washed with brine, hydrochloric acid (2%, 10 ml), sodium bicarbonate (5%, 2 10 ml), finally with brine and dried ($Mg\ So_4$).

The solvent was evaporated in vacuo to give (+)-1-(3,5-diacetonyl-4-methylphenyl)-4-methylpentan-2-ylacetate (100 mg 64% as a yellow oil ν^{film}_{max} 1765 (s), 1740 (s), 1630 (w), 1580 (w) cm^{-1}. ($CDCl_3$) 3.18 (2H, s, Ar-H), 4.85 (1H, m, $Ar-CH_2-CH-$) 7.18 (2H, d, $Ar-CH_2-$, J = 7. c.p.s) 7.69 (6H, s, 2 $OCOCH_3$), 8.02 (6H, s, $OCOCH_2$ + $Ar-CH_3$). (Found: C, 64.7; H, 7.4 $C_{19}H_{26}O_6$ requires C, 65.1; H, 7.5%).

Acknowledgement

This work has been done under the supervision of Prof. W.B.Whalley to whom we are grateful.

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