A Simple Synthesis of 8-Hydroxy-6-methoxy-3-methylisocoumarin

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Summary: Direct condensation of 3,5-dimethoxyhomophthalic acid with acetic anhydride yielded the 6,8-dimethoxy-3-methylisocoumarin (1b). Selective demethylation of the 8-methoxy group in (1b) afforded the title isocoumarin (1a) in good yield . The 8-acetoxy derivative (1c) was also prepared. An efficient route for the synthesis of 3,5-dimethoxyhomophthalaldehydic acid (8b) and 3,5-dimethoxyhomophthalic acid (10) has also been described.

Introduction

The title isocoumarin, among other metabolites was isolated from the phytopathogenic fungus *Certacystis fimbriata* [1] (1969) and *Streptomyces mobaraensis* [2] (1971). The structure (1a) was assigned on the basis of spectroscopic and chemical degradation evidence. The presence of the 3-methyl group, suggested by biosynthetic considerations, was confirmed by alkaline hydrolysis of the isocoumarin to the keto-acid [2]. The substitution pattern in the aromatic ring was shown by methylation followed by oxidation to corresponding phthalic acid, which was later on dehydrated to the anhydride [3].

Results and Discussion

Although the precursor 6,8-dimethoxy-3-methylisocoumarin (1b) had been synthesized,

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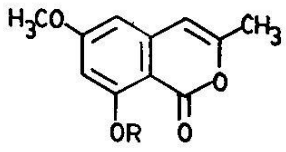
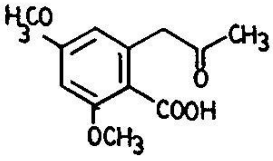
during various studies, however, it has never been demethylated selectively to the title isocoumarin (1a). One method for preparation of (1b) involved the oxidative cleavage [3,4] of 5,7-dimethoxy-2-hydroxy-2-methylindanone (5) preseumably *via* the ozonolysis of its trimethylsilyl ether. Alternatively, the indanone (4) was converted into enol trifluoroacetate which upon ozonolysis afforded directly the isocoumarin (1b).

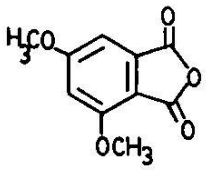


(1)



(2)

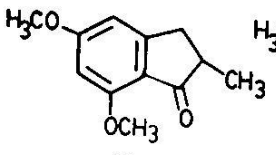
1a; R = H
1b; R = CH_3
1c; R = Ac



(3)

In another synthesis [5], 3,5-dimethoxyhomophthalic anhydride was treated with acetic anhydride and pyridine to furnish the 4-carboxy-6,8-dimethoxy-3-methylisocoumarin (6) which was decarboxylated to isocoumarin (1b).

In this article, we wish to report a simple two step synthesis of the title isocoumarin (1a) from 3,5-dimethoxyhomophthalic acid (10) which was obtained from 3,5-dimethoxyphenylacetic acid.



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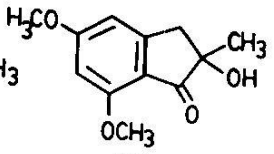
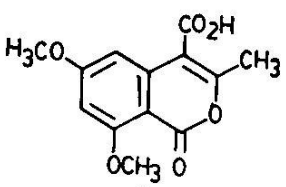


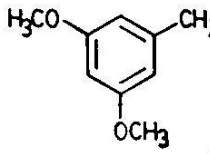
(5)



(6)

Thus, Vilsmeier Haack formylation of ethyl 3,5-dimethoxyphenylacetate (7) afforded the formyl ester [7] (8a) which on hydrolysis gave homophthalaldehydic acid (8b). Potassium permanganate oxidation of (8a) gave the carboxy ester (9) which on alkaline hydrolysis furnished the desired homophthalic acid [6] (10). It may be mentioned that repeated efforts to oxidize the homophthalaldehydic acid (8b) directly to (10) were unsuccessful.

The homophthalic acid (10) was refluxed with acetic anhydride [8] during 10-12 hours, to produce isocoumarin (1b) in 65% yield, which on selective demethylation of the 8-methoxy group using boron trichloride in dichloromethane at -78° gave the title isocoumarin (1a) in 90% yield. Treatment of (1a) with acetic anhydride in dry pyridine afforded the acetate (1c). In the IR spectrum of (1a) the carbonyl absorption was lowered from 1720 cm^{-1} in (1b) to 1685 cm^{-1} due to strong chelation with 8-hydroxylic proton and the ^{1}H-NMR showed the characteristic singlet at δ 6.28 for H-4. The IR ^{1}H-NMR and mass spectra of all compounds closely agreed to the reported ones.



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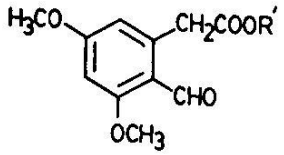
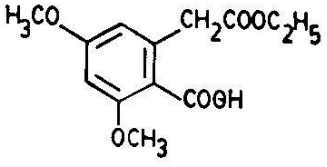
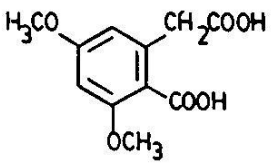


(8)

8a; R = C_2H_5
8b; R = H



(9)



(10)

Experimental

Melting points determined using MEL-TEMP MP-D apparatus are uncorrected. IR spectra recorded on a Hitachi Model-270 spectrophotometer as KBr discs or as neat liquids. ^{1}H-NMR (300 MHz) were recorded on a Bruker AM-300 and the EIMS on a MAT 112 S machine.

Ethyl 2-formyl-3,5-dimethylphenylacetate (8a)

Phosphorous oxychloride (2g, 0.013 mol) was added dropwsie to a stirred solution of ethyl 3,5-dimethoxyphenylacetate (7) (2.5 g, 0.011 mol) in freshly distilled N,N-dimethyl formamide at 55°C. The solution was then heated at 100°C, for 10 minutes and stirred overnight. After 24h at room temperature. The mixture was poured into aqueous sodium acetate (10%, 100 ml) with stirring, the resultant precipitate was filtered and crystallized from ethanol to yield ethyl-2-formyl-3,5-dimethoxy-phenylacetate (8a) (1.75 g, 0.00694 mol, 62%) as neeldes, m.p. 98°C (lit. [8] 108-110°C). IR (KBr): 2896, 1722, 1668, 1593, 889 cm^{-1}. m/z : 252 (M^+).

Ethyl 2-carboxy-3,5-dimethoxyphenylacetate (9)

Potassium permanganate (2.85 g, 0.018 mol) in neutral acetone (200 ml) was added dropwise for 1 h to a stirred solution of ethyl 2-formyl-3,5-dimethoxyphenlacetate (8a) (3g, 0.012 mol) in neutral aqueous acetone (250:250 ml) at 60-70°C. The reaction mixture was refluxed for 8h then the heating was stopped and the reaction mixture stirred overnight. The manganese dioxide was removed by filteration and the acetone was rotary evaporated. Aqueous $NaHCO_3$ (5%, 80 ml) was added and the mixture extracted with ethyl acetate, the extract being discarded. The aqueous layer was acidified, extracted with ethyl acetate, (3 x 100 ml) dried (Na_2SO_4 anhydrous) and the solvent rotary evaporated to leave ethyl 2-carboxy-3,5-dimethoxyphenylacetate (9) (2.0 g, 0.0078 mol, 65%) as white crystals; m.p. 112-113°C; IR (KBr): 3000-2500, 1722, 1685, 1572 cm^{-1}; m/z; 268 (M^+).

3,5-Dimethoxyhomophthalic acid (10)

Sodium hydroxide (5%, 85 ml) was added to a solution of ethyl 2-carboxy-3,5-dimethoxyphenyl-acetate (9) (2g, 0.0078 mol) in methanol (26 ml). The reaction mixture was refluxed for 1h and the methanol evaporated *in vacuo*. Acidification of aqueous layer directly afforded the 3,5-dimethoxy-homophthalic acid (10) (1.85 g, 0.0077 mol, 98.8%) as white solid, recrystallized from ethyl acetate-petroleum ether; m.p. 171-172°C; (lit. [6] 172-173°C); IR (KBr): 3000-2500, 1700, 1605, 1580 cm^{-1}; m/z: 240 (M^+).

3,5-Dimethoxyhomophthalaldehydic acid (8b)

Aqueous sodium hydroxide (5%, 65 ml) was added to a stirred solution of ethyl 2-formyl-3,5-dimethoxyphenylacetate (7) (1.5 g, 0.006 mol) in methanol (20 ml). The reaction mixture was refluxed for 45 min., the methanol evaporated and the aqueous phase acidified with dil. hydrochloric acid. Extraction with ethyl acetate followed by drying (anhyd. Na_2SO_4) and evaporation of solvent yielded 3,5-dimethoxyhomophthalaldehydic acid (8b) (1.2 g, 0.0053.mol, 89.3%). m.p. 173-174°C (lit. [8] 176°C). m/z: 224 (M^+).

6,8-Dimethoxy-3-methylisocoumarin (1b)

A mixture of homophthalic acid (10) (0.72 g, 0.003 mol) and acetic anhydride (0.92 g, 0.009 mol) was refluxed with stirring for 24 hours. After cooling, 5% sodium carbonate was added and the mixture extracted with ethyl acetate (3 x 30 ml). The organic phase was separated, dried and the solvent evaporated. The residue was purified by preparative thin layer chromatography (PTLC) on silica gel (60 HF), followed by recrystallization to afford 6,8-dimethoxy-3-methylisocoumarin (1b) (0.43 g, 0.00195 mol, 65%) m.p. 148-150°C (lit. [3,4] 157-160°C). IR (KBr): 1725, 1630, 1600 cm^{-1}. m/z : 220 (M^+)

8-Hydroxy-6-methoxy-3-methylisocoumarin (1a)

1.0 Molar solution of borontrichloride in dichloromethane (0.95 ml, 0.006 mol) was added dropwise to a stirred solution of 6,8-dimethoxy-3-methylisocoumarin (1b) (0.33 g, 0.0015 mol) at -78°C for 4 h. After stirring overnight, the mixture was poured into ice-water filtered and extracted with dichloromethane (3 x 20 ml). The combined extracts were washed, dried and concentrated. Purification on TLC (silica gel) with ethyl acetate afforded the 8-hydroxy-6-methoxy-3-methylisocoumarin (1a) (0.29 g, 0.0014 mol, 95%) as colourless

needles; m.p. 118-120°C (lit. 129°C); IR (KBr): 1685, 1600, 1595 cm^{-1}; δ ($CDCl_3$): 2.20 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.16 (1H, s, C_4- H), 6.28 (1H, d, C_5-H, J = 3Hz), 6.37 (1H, s, C_7-H), 11.23 (1H, s, OH, exchangeable); m/z : 206 (M^+).

8-Acetoxy-6-methoxy-3-methylisocoumarin (1c)

A solution of 8-hydroxy-6-methoxy-3-methylisocoumarin (1a) (0.25 g, 0.0012 mol) in dry pyridine (4 ml) and acetic anhydride (0.24 g, 0.0024 mol) was stirred overnight. Water was added and the reaction mixture was extracted with ether (3 x 50 ml), the extracts were washed and dried. Purification of residue by PTLC followed by recrystallization from ethyl acetate, afforded the 8-acetoxy-6- methoxy-3- methylisocoumarin (1c) (0.26 g, 0.001 mol, 90%); m.p. 89-90°C.

Acknowledgement

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