

Isocoumarins: Part VIII[†] – Synthesis of methoxy- and benzo-3-methylisocoumarins[‡]

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Abstract. Synthesis of 6-methoxy-, 5,6-dimethoxy-, 5,6-benzo- and 7,8-benzo-3-methylisocoumarins by an acid-catalysed path has been described. The path uses aromatic aldehydes as the starting materials, while isochromans are the key intermediates.

Keywords. Isochromans; isocoumarins.

1. Introduction

Isocoumarins and their 3,4-dihydroderivatives having C₃ methyl group and –OCH₃ or –OH groups in the aromatic ring are widely distributed in nature (Nishikawa 1933; Barry 1964; Gupta 1977). In our earlier work (Bhide and Shah 1980; Bhide and Brahmhatt 1980) we have reported the synthesis of several such 3-methylisocoumarins in which we have used heteroatom-directed ortholithiation as the key step. We report here another general synthesis of 3-methylisocoumarins by an acid-catalysed path starting with readily available aromatic aldehydes.

2. Results and discussion

The starting materials for the synthesis are aromatic aldehydes (Ia–d; chart 1) which were converted to 2-nitro-1-aryl-1-propenes (IIa–d) in 60 to 80% yield by condensing them with nitroethane in a base. These nitro derivatives upon Fe/FeCl₃ – HCl reduction gave 1-aryl-2-propanones (IIIa–d) in 60 to 70% yield. The ketones upon reduction with NaBH₄ furnished β-oxy-α-aryl-propanes (IVa–d) in 70 to 80% yield. The chloromethylation of alcohols with CH₂O/HCl directly converted them into the corresponding isochromans (Va–d, chart-2) in about 50% yield. The isochromans (Va–d) were then oxidised with CrO₃/AcOH to give the corresponding 3-methyl-3,4-dihydroisocoumarins (VIa–d) in 30% yield, which were further converted to the corresponding 3-methylisocoumarins (VIIa–d) by the N-bromosuccinimide/triethylamine method in 40% yield.

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[‡]The paper is dedicated to Prof N S Narasimhan on his 60th birthday

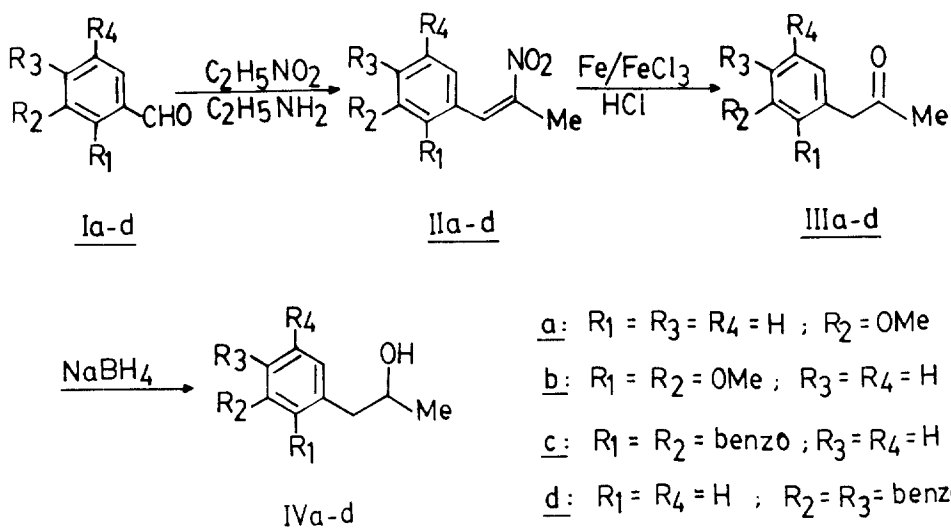


Chart 1

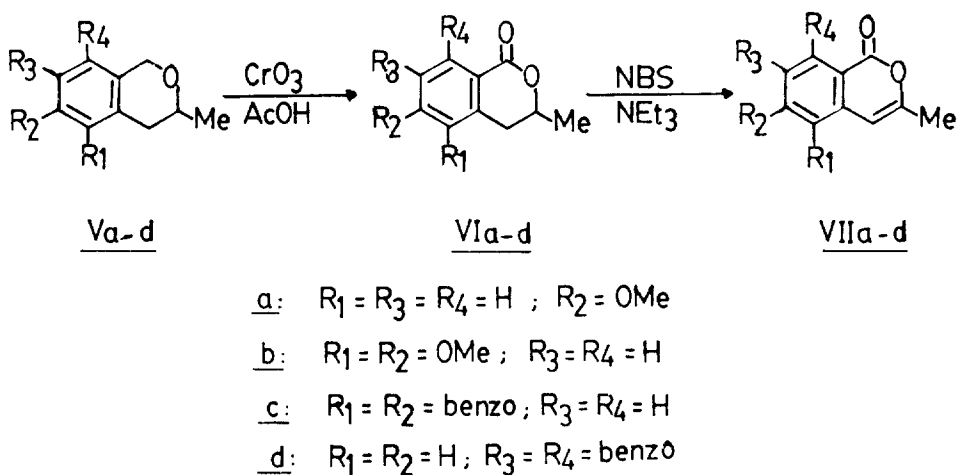


Chart 2

It must be mentioned here that (Vc) was not obtained when chloromethylation was done using $\text{CH}_2\text{O}/\text{HCl}$ in ether as solvent. This may be due to electrophilic substitution and cyclization at the less reactive 2 position of naphthalene. The isochroman (Vc) was indeed obtained by modifying the reaction conditions. The chloromethylation was then done using trioxane-HCl in the presence of anhydrous AlCl_3 as catalyst and CS_2 as solvent.

It is interesting to note that in the PMR spectra of VIb and VIc the signals of benzylic protons were observed as an 8-line pattern instead of a doublet. The nonequivalence of benzylic protons must be due to the methoxyl functional group and the ring residue at position 5. Such type of observation has been reported by us earlier (Bhide and Brahmabhatt 1980).

The structures of all the compounds have been supported by elemental analysis and spectral data.

3. Experimental

IR spectra of the compounds were recorded on a Perkin Elmer model 983, while UV spectra were taken in 95% ethanol either on a Beckman DK-2 or specord UV-Vis spectrophotometer. Rf values are in 20% ethylacetate–benzene. PMR spectra were recorded on a Varian A 60 instrument with TMS as the internal standard.

3.1 2-Nitro-1-aryl-1-propenes (IIa–d)

Substituted aldehydes (Ia–d) (0.11 mol), nitroethane (8 ml, 0.11 mol) and 20 drops of 75% ethylamine were mixed and kept in a refrigerator for 8 to 10 days as per standard procedure (Pepper and Saha 1964). The yellow solid products obtained were recrystallised from rectified spirit. IIa: Yield 12 g (61%), m.p. 44° (Found: C, 62.3; H, 5.5; N, 7.4%; C₁₀H₁₁O₃N requires C, 62.2; H, 5.7; N, 7.3%). IIb: Yield 18.9 g (82%), m.p. 80° (Found: C, 59.3; H, 5.6; N, 6.4%; C₁₁H₁₃O₄N requires C, 59.2; H, 5.8; N, 6.3%). IIc: Yield 11.4 g (57.3%), m.p. 64° (Found: C, 73.1; H, 5.3; N, 6.7%; C₁₃H₁₁O₂N requires C, 73.2; H, 5.2; N, 6.6%). IId: Yield 14.3 g (65.6%), m.p. 84° (Found: C, 73.3; H, 5.1; N, 6.7%; C₁₃H₁₁O₂N requires C, 73.2; H, 5.2; N, 6.6%).

3.2 1-Aryl-2-propanones (IIIa–d)

Compounds (IIa–d) (0.11 mol) were converted to (IIIa–d) according to the reported method (Heinzelman 1963). The substances were dissolved in hot water (700 ml) and ethanol (300 ml) and iron powder (40 g), ferric chloride (1.6 g) and concentrated HCl (10 N, 24 ml) were added very slowly with continuous stirring for 6 to 8 h, the solution being concentrated to half the original volume. The precipitated black iron oxide was filtered out and washed with hot water and benzene. The combined washings were extracted with benzene and dried (Na₂SO₄). Removal of benzene gave IIIa–d as brown liquids, which were purified by distillation. IIIa: Yield 12 g (65.6%), b.p. 120° (10 mm), Rf 0.6 (Found: C, 73.0; H, 7.4%; C₁₀H₁₂O₂ requires C, 73.2; H, 7.3%). IIIb: Yield 15 g (70.4%), b.p. 130° (10 mm), Rf 0.56 (Found: C, 68.2; H, 7.3%; C₁₁H₁₄O₃ requires C, 68.0; H, 7.2%). IIIc: Yield 13.1 g (64.8%), b.p. 128° (10 mm), Rf 0.61 (Found: C, 84.6; H, 6.7%; C₁₃H₁₂O requires C, 84.8; H, 6.5%). IIId: Yield 13.1 g (64.8%), b.p. 135° (10 mm), Rf 0.62 (Found: C, 84.7; H, 6.6%; C₁₃H₁₂O requires C, 84.8; H, 6.5%). Compounds IIIa–d exhibit characteristic carbonyl bands at about 1710 cm⁻¹.

3.3 β-Oxy-α-aryl-propanes (IVa–d)

NaBH₄ (0.26 mol) was added slowly with stirring to a solution of (IIIa–d) (0.06 mol) in methanol (100 ml). The mixture was stirred for 16 h, water was added and the solution then extracted with methylene chloride. The methylene chloride extract was washed with water and dried (Na₂SO₄). Removal of methylene chloride gave (IVa–d) as

yellow liquids, which were purified by distillation. **IVa**: Yield 7 g (69.3%), b.p. 125° (10 mm), Rf 0.55 (Found: C, 72.1; H, 8.3%; $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.4%). **IVb**: Yield 9.3 g (79.5%), b.p. 135° (10 mm), Rf 0.44 (Found: C, 67.4; H, 8.3%; $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%). **IVc**: Yield 7.7 g (69.4%), b.p. 136° (10 mm), Rf 0.58 (Found: C, 83.7; H, 7.6%; $C_{13}H_{14}O$ requires C, 83.9; H, 7.5%). **IVd**: Yield 7.7 g (69.4%), m.p. 68°, Rf 0.57 (Found: C, 83.8; H, 7.4%; $C_{13}H_{14}O$ requires C, 83.9; H, 7.5%).

Compounds **IVa-d** exhibit characteristic OH bands around 3400–3500 cm^{-1} and C–O stretching frequency at 1260 cm^{-1} .

3.4 3-Methylisochromans (**Va-d**)

3.4a Preparation of (Va, b and d): Alcohols (**IVa, b and d**) (0.03 mol) were taken in dry ether (180 ml). To this 37% formalin solution (2 ml) and concentrated HCl (10 N, 2 ml) were added with constant shaking. The reaction mixture was allowed to stand at room temperature for 2 h and then was warmed on a water bath at 40° for 15 min. On cooling it was diluted with water and extracted with ether. The ether extract after drying (Na_2SO_4) was evaporated to give **Va, b and d**. These were purified by column chromatography using silica gel and benzene as an eluent. **Va**: Yield 3.0 g (56.6%), b.p. 110° (10 mm), Rf 0.61 (Found: C, 74.0; H, 7.7%; $C_{11}H_{14}O_2$ requires C, 74.2; H, 7.9%). **Vb**: Yield 3.1 g (50%), b.p. 120° (10 mm), Rf 0.5 (Found: C, 69.3; H, 7.5%; $C_{12}H_{16}O_3$ requires C, 84.8; H, 7.1%). **Vd**: Yield 3.9 g (66%), b.p. 105° (10 mm), Rf 0.66 (Found: C, 84.6; H, 6.8%; $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%).

Compounds **Va, b and d** exhibit a characteristic cyclic ether stretching frequency at 1230 cm^{-1} .

3.4b Preparation of (Vc): Through a mixture of alcohol (**IVc**) (0.03 mol), trioxane (5 g, 0.05 mol) and anhydrous $AlCl_3$ (0.5 g) in dry CS_2 (80 ml), dry HCl gas was passed for 3 to 4 h at room temperature. It was refluxed for 2 h, cooled and decomposed with HCl. Work up as above yielded **Vc** as a sticky mass. This was purified by column chromatography over silica gel using benzene as an eluent. Yield 1.1 g (18.6%), m.p. 70° (Found: C, 84.5; H, 6.9%; $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%). The compound exhibits a characteristic cyclic ether stretching frequency at 1230 cm^{-1} .

3.5 3-Methyl-3,4-dihydroisocoumarins (**VIa-d**)

Isochromans (**Va-d**) (0.008 mol) were treated with a solution of CrO_3 (1.8 g, 0.018 mol) in acetic acid (15 ml). The reaction mixture was kept at room temperature for 3 h and then warmed on a water bath at 60° for 15 min. The mixture was cooled, diluted with water and extracted with methylene chloride. The extract was washed with saturated sodium bicarbonate solution, water and then dried (Na_2SO_4). Removal of the solvent gave 3-methyl-3,4-dihydroisocoumarins (**VIa-d**). The compounds were purified by column chromatography on silica gel using benzene as the eluent. **VIa**: Yield 0.5 g (31.2%), m.p. 80° (Found: C, 68.6; H, 6.2%; $C_{11}H_{12}O_3$ requires C, 68.8; H, 6.3%). This compound was identical (using mixed melting points) to the sample prepared by the lithiation method (Bhide *et al* 1981). **VIb**: Yield 0.69 g (40.6%), m.p. 105–107° (Found: C, 64.5; H, 6.1%; $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.3%); IR (KBr): 1710 (δ lactone), 2960 cm^{-1} (CH_3 stretching); UV: 265, 328 nm ($\log \epsilon$ 4.34, 3.18); PMR ($CDCl_3$): 1.45 δ

$$\begin{array}{c} \text{---O} \\ | \\ \text{---CH}_2\text{---CH---CH}_3 \end{array}$$

(3H, *d*, $J = 7.0$ Hz, $-\text{CH}_2\text{---CH---CH}_3$), 2.9δ (2H, 8 lines, the AB part of an ABX system, $J_{AB} = 16$ Hz, $J_{BX} = 11$ Hz, $J_{AX} = 4$ Hz), 3.8 and 3.9δ (6H, two singlets, two $-\text{OCH}_3$

$$\begin{array}{c} \text{O} \\ | \\ \text{---CH}_2\text{---CH---CH}_3 \end{array}$$

groups), 4.5δ (1H, complex pattern of the X part of an ABX system, $-\text{CH}_2\text{---CH---CH}_3$), 6.85δ (1H, *d*, $J_0 = 9.0$ Hz, H_7), 7.8δ (1H, *d*, $J_0 = 9.0$ Hz, H_8). VIc: Yield 0.53 g (31.3%), m.p. 125° (Found: C, 79.3; H, 5.6%; $\text{C}_{14}\text{H}_{12}\text{O}_2$ requires C, 79.2; H, 5.7%); IR (KBr): 1710 cm^{-1} (δ lactone); UV: 245, 285 nm ($\log \epsilon$ 4.79, 4.17); PMR (CDCl_3): 1.65δ (3H, *d*,

$$\begin{array}{c} \text{---O} \\ | \\ \text{---CH}_2\text{---CH---CH}_3 \end{array}$$

$J = 6.0$ Hz, $-\text{CH}_2\text{---CH---CH}_3$), 3.34δ (2H, 8 lines, the AB part of an ABX system, $J_{AB} = 16$ Hz, $J_{AX} = 4$ Hz, $J_{BX} = 11$ Hz), 4.78δ (1H, complex pattern of the X part of

$$\begin{array}{c} \text{---O} \\ | \\ \text{---CH---CH---CH}_3 \end{array}$$

an ABX system, $-\text{CH---CH---CH}_3$), 7.9δ (6H, multiplet, aromatic protons). VIId: Yield 0.53 g (31.3%), m.p. 134° (Found: C, 79.0; H, 5.5%; $\text{C}_{14}\text{H}_{12}\text{O}_2$ requires C, 79.2; H, 5.7%); IR (KBr): 1710 cm^{-1} (δ lactone); UV: 238, 291, 305 nm ($\log \epsilon$ 4.57, 3.78, 3.93);

$$\begin{array}{c} \text{O} \\ | \\ \text{---CH}_2\text{---CH---CH}_3 \end{array}$$

PMR (CDCl_3): 1.56δ (3H, *d*, $J = 7.2$ Hz, $-\text{CH}_2\text{---CH---CH}_3$), 3.05δ (2H, *d*, $J = 11$ Hz,

$$\begin{array}{c} \text{---O} \\ | \\ \text{---CH}_2\text{---CH---CH}_3 \end{array}$$

benzylic protons), 4.68δ (1H, complex, $-\text{CH}_2\text{---CH---CH}_3$), 7.7δ (5H, multiplet, aromatic protons), 9.28δ (1H, *d*, $J_0 = 3.0$ Hz, H_{10}).

3.6 3-Methylisocoumarins (VIIa-d)

3-Methyl-3, 4-dihydroisocoumarins (VIIa-d) (0.0026 mol) were brominated with N-bromosuccinimide and dehydrobrominated with NEt_3 according to our earlier procedure (Narasimhan and Bhide 1971) to give (VIIa-d).

3.6a 6-Methoxy-3-methylisocoumarin (VIIa): Yield 0.150 g (30.6%), m.p. 86° (Found: C, 69.3; H, 5.2%; $\text{C}_{11}\text{H}_{10}\text{O}_3$ requires C, 69.5; H, 5.3%); IR (KBr): 1720 cm^{-1} (δ lactone); UV: 245 nm ($\log \epsilon$ 4.69).

3.6b 5,6-Dimethoxy-3-methylisocoumarin (VIIb): Yield 0.23 g (41%), m.p. $140\text{--}141^\circ$ (Found: C, 65.7; H, 5.1%; $\text{C}_{12}\text{H}_{12}\text{O}_4$ requires C, 65.5; H, 5.5%); IR (KBr): 1720 cm^{-1} (δ lactone); UV: 238, 248, 275, 322 nm ($\log \epsilon$ 4.98, 5.03, 4.23, 3.81).

3.6c 5,6-Benzo-3-methylisocoumarin (VIIc): Yield 0.15 g (28.3%), m.p. 164° (Found: C, 80.2; H, 4.6%; $\text{C}_{14}\text{H}_{10}\text{O}_2$ requires C, 80.0; H, 4.8%); IR (KBr): 1730 cm^{-1} (δ lactone); UV: 250, 300 nm ($\log \epsilon$ 4.84, 4.27).

3.6d 7,8-Benzo-3-methylisocoumarin (VIIId): Yield 0.32 g (64%), m.p. 150° (Found: C, 80.3; H, 4.5%; $\text{C}_{14}\text{H}_{10}\text{O}_2$ requires C, 80.0; H, 4.8%); IR (KBr): 1720 cm^{-1} (δ lactone); UV: 252, 262, 278 nm ($\log \epsilon$ 4.77, 4.41, 4.21).

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