Pergamon

Tetrahedron 57 (2001) 5335–5338

TETRAHEDRON

A short synthesis of 5-methoxy-2,2-dimethyl-2*H*-1-benzopyran-6-propanoic acid methyl ester

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Received 9 March 2001; accepted 25 April 2001

Abstract—5-Methoxy-2,2-dimethyl-2*H*-1-benzopyran-6-propanoic acid methyl ester was prepared in five steps and approximately 20% overall yield from 2,4-dihydroxybenzaldehyde. The two key reactions are the chromenylation between the unchelated hydroxyl group and C-3 of the resbenzaldehyde and the demethoxycarbonylation-alkylation of dimethyl malonate with a quaternary ammonium iodide.

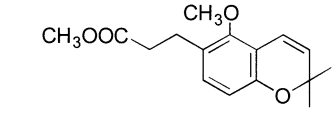
1. Introduction

The natural product 5-methoxy-2,2-dimethyl-2*H*-1-benzopyran-6-propanoic acid methyl ester (**1**) was isolated from the roots of the endemic Guyana tree *Hortia regia* (Rutaceae)[1] and the structure was assigned in an early application of the two-dimensional NMR techniques which provide direct ^{1}H-^{13}C and indirect two and three-bond ^{1}H-^{13}C connectivity data.[1]

The 2,2-dialkyl-2*H*-1-benzopyran moiety occurs widely in nature and is found in many biologically active compounds. Methods for preparation range from well-established more general sequences,[2] the earlier of which have been reviewed,[3] to more specific schemes targeted to particular substitution patterns on the aromatic or pyran ring.[4–6] The synthesis of **1** was undertaken to provide material for bioactivity studies, as closely related structures have been shown in vitro to interact non-covalently with sickle hemoglobin (HbS), preventing its polymerization and the resultant sickling of red blood cells.[7]

2. Results and discussion

This preparation hinges initially on the chromenylation of 2,4-dihydroxybenzaldehyde (**2**) with 3-methylbut-2-enal (**3**) to give 6-formyl-5-hydroxy-2,2-dimethyl-2*H*-1-benzopyran (**4**) (Scheme 1). The regiochemistry of this modest yielding reaction, developed by Crombie et al.,[5] can be explained by invoking the resonance structures **5**, **5a**, **6**, **6a** of the anion of **2**.[6] The stability of the chelate system is retained in **5** and **5a** and it is likely that the greatest electron density in the anion overall resides on the carbon which is negatively charged in



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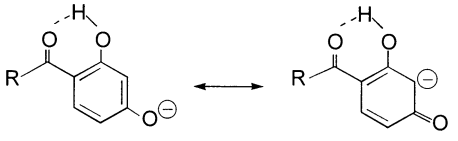
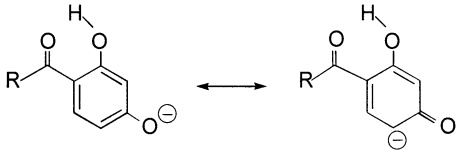
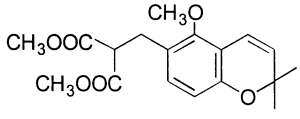


5 **5a**



6 **6a**



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Keywords: alkylation; benzopyran; chromene; dealkylation; decarboxylation.

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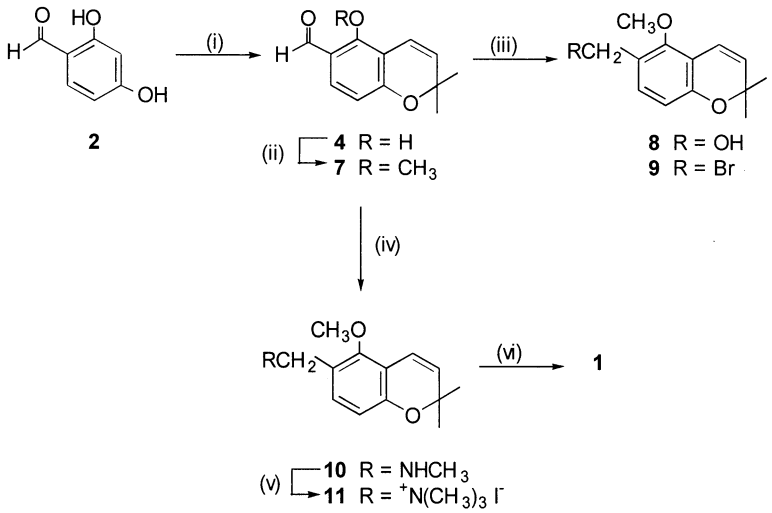

Scheme 1. *Reagents*, yield: (i) $(CH_3)_2C{=}CHCHO$ (**3**)/Me_2CO/py, 44%; (ii) $CH_3I/K_2CO_3/Me_2CO$, 81%; (iii) $NaBH_4$/EtOH, 96%; (iv) CH_3NH_2/THF/EtOH, then $NaBH_4$, 94%; (v) $CH_3I/K_2CO_3/Me_2CO$, 89%; (vi) $CH_2(COOCH_3)_2/K_2CO_3$/DMF, 75%.

5a.[6,8] After some modification of the procedure reported for 2,4-dihydroxyacetophenone[5a] the optimized yield of **4** was 44%. This is comparable to that obtained from the microwave activated reaction between **2** and **3**;[9] none of the product of chromenylation at C-5 of **2**[9] was obtained and the unconverted starting material (**2**) was largely recovered. The phenolic group of **4** was then methylated under standard conditions to provide the methyl ether (**7**).

We had envisaged that alkylation of a malonate ester with the benzylic bromide (**9**) derived from **7** via the alcohol (**8**) followed by hydrolysis, decarboxylation and re-esterification, or possibly application of the Krapcho dealkoxycarbonylation procedure,[10] would furnish **1**. Accordingly, the aldehyde (**7**) was reduced to **8** in good yield, however all attempts to convert this alcohol to the bromide (**9**) were unsuccessful.

Resort was therefore made to preparation of the quaternary ammonium salt (**11**) for use as the electrophile in the malonate reaction. Reaction of the aldehyde (**7**) with methylamine and in situ reduction with sodium borohydride afforded the secondary amine (**10**) which was then treated with excess iodomethane to afford **11**. It was anticipated that alkylation of dimethyl malonate with **11** would furnish the methyl diester (**12**) which could then be subjected to dealkoxycarbonylation conditions (NaCl, wet DMSO)[10] to afford the target compound (**1**).

In an initial attempt to prepare the diester (**12**) the salt (**11**) was treated with five molar equivalents of dimethyl malonate and potassium carbonate in dry DMSO. The only isolated product was the target compound (**1**), in 11% yield**.** This result, although unexpected, was not entirely surprising as the reaction conditions were similar to those required for demethoxycarbonylation, i.e. a nucleophile (iodide) in a dipolar aprotic solvent. To enhance the yield of the alkylation reaction, which required heating for several hours at high temperature, DMSO was replaced with the more thermally stable DMF. The reaction of **11** with dimethyl malonate and potassium carbonate in DMF for 24 h produced the diester (**12**) and the monoester (**1**) in yields of 40 and 27% respectively. Increasing the reaction time to 39 h resulted in the complete demethoxycarbonylation of **12** and formation of the single product **1**, reproducibly in 70–75% yield. It is known that carbanions initially formed from dealkoxycarbonylations of geminal diesters can be trapped by various electrophiles to produce α-alkylated esters.[10e] Additionally, tetramethylammonium acetate has been used routinely to effect demethoxycarbonylation of substituted malonate diesters with no apparent formation of α-methylated products arising from alkylation by the tetramethylammonium cation.[10d] In the reaction of **11** with dimethyl malonate the initially formed diester (**12**) is cleaved by iodide in the reaction mixture. This use of a tetraalkylammonium salt as electrophile and nucleophile in the alkylation-dealkoxycarbonylation of malonate has evidently not been reported previously.

3. Conclusion

This synthesis of **1** is an application of the site-selective chromenylation of 2,4-dihydroxy aromatic carbonyl compounds and demonstrates the use of a quaternary ammonium iodide as the source of both the electrophile and the nucleophile in the alkylative demethoxycarbonylation of dimethyl malonate.

4. Experimental

4.1. General

Melting points were determined on a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Perkin–Elmer 735B or a FT-IR SPECTRUM 1000 spectrometer as KBr pellets or films on NaCl discs. Mass spectral data (high resolution and low resolution electron impact, EI) were determined at an ionising voltage of 70 eV on a Micromass 70–250S spectrometer. NMR data were recorded on a Bruker AC200F or Varian UNITY-400 spectrometer with $CDCl_3$ as solvent and TMS as internal standard. Column chromatography was performed using BDH (40–63 μm)

or Whatman silica gel (60Å 230–400 mesh ASTM). Analytical TLC analyses were carried out using Whatman polyester or aluminum backed plates precoated with silica gel UV_{254} (0.20 mm). Chromatograms were visualized under ultraviolet light (254 and 366 nm) before spraying with phosphomolybdic acid/ceric sulfate spray. Solvents used were distilled from an all glass system.

Analytical grade Me_2CO was dried over molecular sieves (4 Å). CH_2Cl_2 (drum) was distilled and dried over $CaCl_2$; this was followed by a second distillation from anhydrous $CaSO_4$ and storage over molecular sieves (type 4Å). Super dry EtOH was prepared with Mg/I_2 using the standard procedure.[11] DMF was stirred with anhydrous $CaSO_4$ (powder) overnight at room temperature, distilled and stored over molecular sieves (type 4Å). DMSO was distilled from anhydrous $CaSO_4$ under vacuum and stored over molecular sieves. Toluene was dried over anhydrous $CaCl_2$.

4.1.1. 6-Formyl-5-hydroxy-2,2-dimethyl-2*H*-1-benzopyran (4). A solution of 2,4-dihydroxybenzaldehyde (**2**) (4.87 g, 5.6 mL, 58 mmol) in dry Me_2CO (6 mL) was added during a 5.5 h period to a stirred solution of 3-methylbut-2-enal **3** (4.00 g, 29 mmol) in pyridine (2.29 g, 2.34 mL, 29 mmol) at 120° and heating was continued for a further 18 h. The Me_2CO was evaporated and the pyridine was removed by azeotrope distillation with toluene to afford crude **4**. The crude mixture was purified by column chromatography with 1% EtOAc-hexane as eluent to afford pure **4** (2.59 g, 44%) as an oil which solidified, mp 69–70°, lit.[12] 70°. Calc. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.54; H, 5.93. δ_C (50 MHz) 194.5 (*C*=O), 160.5 (*C*OH), 158.6 (C=*C*O), 134.7 (CH=*C*HC(CH$_3$)$_2$), 128.5 (*C*H=CHC-O), 115.2 (C=*C*CHO), 115.0 (*C*H=CHC(CH$_3$)$_2$), 109.4 (*C*=CO), 108.8 (CH=*C*HC-O), 78.1 (O*C*(CH$_3$)$_2$), 28.4 (C(*C*H$_3$)$_2$); other spectral properties were in agreement with those reported.[9,12]

4.1.2. 6-Formyl-5-methoxy-2,2-dimethyl-2*H*-1-benzopyran (7). A mixture of the chromene (**4**) (2.04 g, 10 mmol), K_2CO_3 (4.12 g, 29.8 mmol) and MeI (2.13 g, 0.94 mL, 15 mmol) in analytical grade Me_2CO (40 mL) was refluxed for 4 h and stirred at room temperature overnight. The mixture was concentrated, treated with H_2O (15 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined CH_2Cl_2 solution was washed with H_2O (15 mL), dried (Na_2SO_4) and the solvent removed in vacuo to afford a yellow oil, which was chromatographed with 3% Me_2CO-hexane to afford **7** (1.77 g, 81%) as a pale yellow oil. ν_{max} (film)/ cm^{-1} 1670, 1635; δ_H (200 MHz) 10.15 (1H, s, C*H*O), 7.65 (1H, d, *J* 9.6, C*H*=CHC-O), 6.65 (1H, d, *J* 9.6, *C*H=CHC(C*H*$_3$)$_2$), 6.60 (1H, d, *J* 9.6, CH=C*H*C-O), 5.70 (1H, d, *J* 9.6, CH=C*H*C(CH$_3$)$_2$), 3.90 (3H, s, OC*H*$_3$), 1.45 (6H, s, C(C*H*$_3$)$_2$); δ_C (50 MHz) 188.4 (*C*=O), 160.1 (*C*OCH$_3$), 159.9 (C=*C*O), 130.5 (CH=*C*HC(CH$_3$)$_2$), 129.8 (*C*H=CHC-O), 122.5 (C=*C*CHO), 115.9 (*C*H=CHC(CH$_3$)$_2$), 114.4 (*C*=CO), 113.4 (CH=*C*HC-O), 77.7 (O*C*(CH$_3$)$_2$), 64.4 (O*C*H$_3$), 28.2 (C(*C*H$_3$)$_2$); EIMS *m/z* 218 [M]$^+$ (28), 203 (100), 160 (35) 57 (13); HREIMS *m/z* 218.0939 (calcd for $C_{13}H_{14}O_3$, 218.0943).

4.1.3. 6-Hydroxymethyl-5-methoxy-2,2-dimethyl-2*H*-1-benzopyran (8). A solution of the aldehyde (**7**) (217 mg, 0.96 mmol) in 95% EtOH (5 mL) was cooled in an ice bath and $NaBH_4$ (108 mg, 2.85 mmol) was added portionwise over 10 min. The mixture was stirred at room temperature for 3 h, poured into H_2O (5 mL) and extracted with CH_2Cl_2 (2×5 mL). The CH_2Cl_2 solution was dried (Na_2SO_4), filtered and concentrated in vacuo to afford **8** (210 mg, 96%) as a colourless oil. ν_{max} (film)/cm^{-1} 3500–3100, 1630; δ_H (200 MHz) 7.05 (1H, d, *J* 10.0, C*H*=CHC-O), 6.55 (2H, d, *J* 10.0, C*H*=CHC(CH$_3$)$_2$ and CH=C*H*-O), 5.65 (1H, d, *J* 10.0, CH=C*H*C(CH$_3$)$_2$), 4.60 (2H, s, OC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 2.30 (1H, br s, O*H*), 1.45 (6H, s, C(C*H*$_3$)$_2$); δ_C (50 MHz) 154.4 (C=*C*OCH$_3$), 153.8 (C=*C*O), 130.6 (CH=*C*HC(CH$_3$)$_2$), 129.3 (*C*H=CHC-O), 125.8 (C=*C*CH$_2$OH), 116.8 (*C*H=CHC(CH$_3$)$_2$), 114.8 (*C*=CO), 112.4 (CH=*C*HC-O), 75.8 (O*C*(CH$_3$)$_2$), 62.6 (O*C*H$_2$), 60.8 (O*C*H$_3$), 27.6 (C(*C*H$_3$)$_2$); EIMS *m/z* 220 [M]$^+$ (29), 205 (100), 190 (20), 175 (13), 161 (15); HREIMS *m/z* 220.1099 (calcd for $C_{13}H_{16}O_3$, 220.1097).

4.1.4. 6-(*N*-methyl)-Aminomethyl-5-methoxy-2,2-dimethyl-2*H*-1-benzopyran (10). The aldehyde (**7**) (1.24 g, 5.7 mmol) was dissolved in absolute EtOH and CH_3NH_2 (4.3 mL of 2M solution in THF, 8.5 mmol) was added under nitrogen. The mixture was refluxed for 3.5 h, cooled in an ice bath and $NaBH_4$ (0.66 g, 17.3 mmol) was added portionwise over 5 min. The mixture was stirred for 50 min and concentrated to remove the EtOH. H_2O (15 mL) was added to the residue and the aqueous solution extracted with $CHCl_3$ (3×10 mL). The organic extract was washed with H_2O (10 mL), dried (anhydrous Na_2SO_4), filtered and concentrated in vacuo to afford **10** (1.24 g, 94%) as a yellow oil. ν_{max} (film)/ cm^{-1} 3500-3200, 1638, 1610; δ_H (400 MHz) 7.03 (1H, d, *J* 8.5, C*H*=CHC-O), 6.56 (1H, d, *J* 9.9, C*H*=CHC(CH$_3$)$_2$), 6.55 (1H, d, *J* 8.5, CH=C*H*C-O), 5.63 (1H, d, *J* 9.9, CH=C*H*C(CH$_3$)$_2$), 3.77 (3H, s, OC*H*$_3$), 3.68 (2H, s, C*H*$_2$N), 2.42 (3H, s, NC*H*$_3$), 1.42 (6H, s, C(C*H*$_3$)$_2$); δ_C (50 MHz) 154.5 (C=*C*OCH$_3$), 152.5 (C=*C*O), 130.0 (CH=*C*HC(CH$_3$)$_2$), 129.5 (*C*H=CHC-O), 124.5 (C=*C*CH$_2$N), 117.0 (*C*H=CHC(CH$_3$)$_2$), 114.5 (*C*=CO), 112.0 (CH=*C*HC-O), 75.0 (O*C*(CH$_3$)$_2$), 62.0 (O*C*H$_3$), 50.0 (*C*H$_2$N), 35.0 (N*C*H$_3$), 27.5 (C(*C*H$_3$)$_2$); EIMS *m/z* 233 [M$^+$] (41), 218 (100), 203 (41), 187 (37), 173 (24), 159 (14); HREIMS *m/z* 233.1413 (calcd for $C_{14}H_{19}NO_2$ 233.1416).

4.1.5. 5-Methoxy-2,2-dimethyl-2*H*-1-benzopyran-6-methylenetrimethylammonium iodide (11). The amine (**10**) (1.68 g, 7.2 mmol) was dissolved in analytical grade Me_2CO (30 mL) and K_2CO_3 (3.82 g, 27.6 mmol) and MeI (6.16 g, 2.7 mmol, 43.4 mmol) were added. The mixture was refluxed for 7 h, stirred at room temperature overnight (15 h) and concentrated in vacuo. The residue was treated with H_2O (20 mL) and extracted with $CHCl_3$ (3×10 mL). The organic solution was washed with H_2O (10 mL), dried (Na_2SO_4), filtered and the solvent removed to afford a pale yellow oil. EtOAc was added and after concentration an off-white solid (2.51 g, 89%) was obtained. This was triturated with EtOAc to afford **11** (2.23 g, 79%) as a white solid, mp 183–185°. Calc for $C_{16}H_{24}NO_2I$: C, 49.37; H, 6.21; N, 3.60. Found: C, 49.43; H, 6.22; N, 3.52. ν_{max} (KBr)/cm^{-1} 1630, 1598, 1484, 1376, 1282; δ_H (200 MHz) 7.50 (1H, d, *J* 8.5, C*H*=CHC-O), 6.60 (1H, d, *J* 8.5, CH=C*H*C-O), 6.50 (1H,

d, *J* 10.0, C*H*=CHC(CH$_3$)$_2$), 5.70 (1H, d, *J* 10.0, CH=C*H*C(CH$_3$)$_2$), 4.80 (2H, s, C*H*$_2$N), 3.85 (3H, s, OC*H*$_3$), 3.40 (9H, s, N(C*H*$_3$)$_3$), 1.40 (6H, s, C(C*H*$_3$)$_2$); δ_C (50 MHz) 156.6 (C=*C*OCH$_3$), 156.6 (C=*C*O), 134.4 (CH=*C*HC(CH$_3$)$_2$), 130.1 (*C*H=CHC-O), 116.3 (*C*H=CHC(CH$_3$)$_2$), 114.8 (C=*C*CH$_2$N), 113.1 (CH=*C*HC-O), 112.1 (*C*=CO), 76.4 (O*C*(CH$_3$)$_2$), 64.1 (*C*H$_2$N), 63.6 (OCH$_3$), 52.9 (N(*C*H$_3$)$_3$), 27.8 (C(*C*H$_3$)$_2$); LREIMS *m/z* 247 [cation-CH$_3$]$^+$ (2), 203 (100), 188 (20), 173 (37), 158 (10), 58 (21).

4.1.6. Dimethyl 6-methylene-5-methoxy-2,2-dimethyl-2*H*-1benzopyranyl malonate (12). A mixture of the quaternary ammonium salt (**11**) (104 mg, 0.27 mmol), CH$_2$(CO$_2$CH$_3$)$_2$ (88 mg, 0.08 mL, 0.66 mmol) and K$_2$CO$_3$ (127 mg, 0.92 mmol) in dry DMF (4 mL) was heated under N$_2$ for 24 h. Saturated brine (3 mL) was added and the mixture was extracted with CHCl$_3$ (4×3 mL). The CHCl$_3$ solution was washed with H$_2$O (3 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to afford a reddish-brown liquid. The crude liquid was chromatographed with 3% Me$_2$CO-hexane as eluent to afford two compounds as colourless oils, **12**, 36 mg, 40% and **1**, 20 mg, 27%. Compound **12** ν_{max} (film)/ cm^{-1} 1739; δ_H (200 MHz) 6.90 (1H, d, *J* 8.4, C*H*=CHC-O), 6.55 (1H, d, *J* 9.9, C*H*=CHC(CH$_3$)$_2$), 6.50 (1H, d, *J* 8.4, CH=C*H*C-O), 5.60 (1H, d, *J* 9.9, CH=C*H*C(CH$_3$)$_2$), 3.75 (3H, s, OC*H*$_3$), 3.70 (1H, t, C*H*CH$_2$), 3.70 (6H, s, C(CO$_2$C*H*$_3$)$_2$), 3.10 (2H, d, *J* 7.7, C*H*$_2$CH), 1.40 (6H, s, C(C*H*$_3$)$_2$); δ_C (50 MHz) 169.6 (*C*=O), 154.7 (*C*OCH$_3$), 153.2 (O*C*=C), 130.4 (CH=*C*HC(CH$_3$)$_2$), 130.2 (*C*H=CHC-O), 122.3 (*C*CH$_2$CH), 117.3 (*C*H=CHC(CH$_3$)$_2$), 114.9(OC=*C*), 112.3 (CH=*C*HC-O), 75.7 (O*C*(CH$_3$)$_2$), 62.0 (CH$_2$*C*H), 52.5(CH(CO$_2$*C*H$_3$)$_2$), 52.3 (O*C*H$_3$), 29.4 (*C*H$_2$CH), 27.7 (C(*C*H$_3$)$_2$); LREIMS *m/z* 334 [M]$^+$ (20), 319 (100), 245 (7), 213 (8), 203 (20), 185 (13), 173 (19); HREIMS *m/z* 334.1399 (calcd for C$_{18}$H$_{22}$O$_6$, 334.1416).

4.1.7. 5-Methoxy-2,2-dimethyl-2*H*-1-benzopyran-6-propanoic acid methyl ester (1). A mixture of the quaternary ammonium salt **(11)** (901 mg, 2.32 mmol), CH$_2$(CO$_2$CH$_3$)$_2$ (765 mg, 0.67 mL, 5.79 mmol) and K$_2$CO$_3$ (1.28 g, 9.28 mmol) in dry DMF (12 mL) was heated under N$_2$ at 156° for 39 h. Brine (20 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (3×15 mL). The combined organic solution was washed with H$_2$O (15 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to afford a reddish-brown liquid. The crude liquid was chromatographed with 2% Me$_2$CO-hexane as eluent to afford **1** (475 mg, 75%) as a colorless oil. Calc. for C$_{16}$H$_{20}$O$_4$: C, 69.55; H, 7.29. Found: C, 69.16; H, 7.32. HREIMS *m/z* 276.1355 (calcd for C$_{16}$H$_{20}$O$_4$ 276.1395). All spectral properties were in agreement with those reported for the natural product.

Acknowledgements

Thanks are due to the University of the West Indies Board for Postgraduate Studies for financial support and to Professor S. McLean of the University of Toronto for helpful comments and assistance with obtaining mass spectra.

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