Indian Journal of Chemistry
Vol. 47B, October 2008, pp. 1597-1599

Note

Facile syntheses of 4-hydroxy-7-methyl-1-indanone, isolated from cyanobacterium *Nostoc commune*

Shrivallabh P Kamat*[a], Jose C Menezes[a], Bhushan M Siddhaye[a] & Shashikumar K Paknikar[b]

[a]Department of Chemistry, Goa University, Goa, 403 206, India

[b]Siddharth Chemicals, Kundai Industrial Estate, Kundai, Goa 403 115, India

E-mail: shrivkamat@yahoo.com

Received 9 January 2008; accepted (revised) 30 July 2008

Two different high yielding synthetic routes both starting with 6-methylcoumarin **2** have been described to prepare 4-hydroxy-7-methyl-1-indanone **1**, a constituent of cyanobacterium *Nostoc commune* having antibacterial activity. In the first route, methylative lactone ring opening of the coumarin **2** followed by catalytic hydrogenation of the cinnamyl double bond and subsequent PPA cyclization gives the methyl ether **5** of **1** which on demethylation gives **1** in excellent yield. Alternatively, catalytic hydrogenation of **2** followed by fusion with anhydrous $AlCl_3$ gives high yield of **1** in just two steps.

Keywords: 6-Methylcoumarin, 1-indanone, pterosins, cyanobacterium, *Nostoc commune*

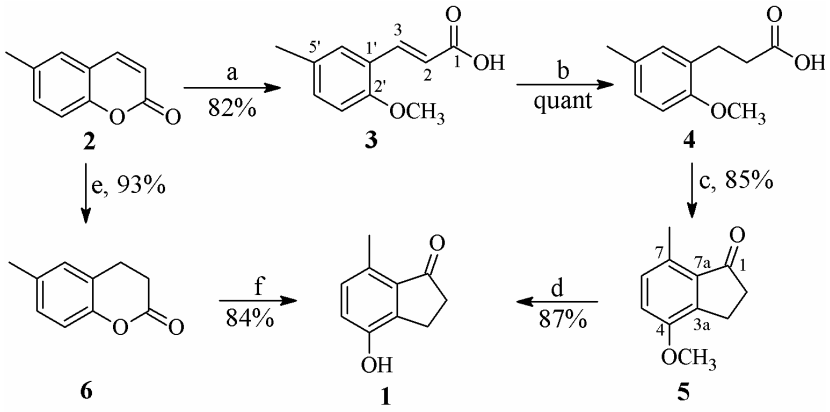
Naturally occurring 1-indanone derivatives form a rare class of natural products generally called pterosins[1]. Some of these pterosins possess antimicrobial activity and some are moderately toxic for HeLa cells[1]. Sticher and co-workers[2], during their search for naturally occurring bioactive compounds isolated indanone **1** as yellow oil (3 mg) from the cells of the cultured cyanobacterium *Nostoc commune* (EAWAG 122b) and was shown to exhibit antibacterial activity. The structure assigned to **1** as 4-hydroxy-7-methyl-1-indanone is well supported by an elaborate spectral data (IR, NMR, and MS). It may be noted that **1** was obtained[3] in low yield during the synthesis of bicyclodionenes, 30 years prior to its isolation as a natural product. Herein are reported two simple and efficient syntheses of **1** starting with easily obtained 6-methylcoumarin **2** (**Scheme I**).

6-Methyl coumarin **2** was prepared by Pechmann condensation of *p*-cresol with maleic acid using known procedure[4]. Reaction of **2** with dimethyl sulphate in the presence of aqueous sodium hydroxide[5] gave a white crystalline solid (m.p. 112°C). No reports were found on the expected product 2-methoxy-5-methylcinnamic acid **3** in the literature, although 2-hydroxy-5-methylcinnamic acid (m.p. 118°C) is reported[4]. Therefore, ^{1}H, ^{13}C NMR and MS data on **3** were recorded. The presence of two singlets at δ 2.28 (Ar-CH_3), 3.80 (Ar-OCH_3), two doublets at 5.96 and 7.21 (J=12.6 Hz) in its ^{1}H NMR spectrum and LCMS m/z 215.0713 $[M + Na]^+$ confirmed the structure **3**. Catalytic hydrogenation of **3** over 10% Pd-C in ethanol gave 3-(2′-methoxy-5′-methylphenyl)propanoic acid **4** in quantitative yield. In the ^{1}H NMR spectrum of **4**, the disappearance of the two doublets due to olefinic protons and appearance of two triplets at δ 2.66 and 2.92 (J=7.6 Hz) due to C_2 and C_3 methylenes supported the saturation of the cinnamyl double bond. Reaction of **4** with polyphosphoric acid[6] at 70°C afforded the methyl ether of the required 1-indanone whose ^{1}H, ^{13}C NMR and MS data clearly indicated it to be 4-methoxy-7-methyl-1-indanone **5**. Demethylation[7] of **5** using hydrobromic acid in acetic acid gave **1** in 87% yield.

A comparison of IR and NMR spectra of the synthetic compound with those recorded on the natural product[2] established their identity beyond doubt. Though the natural compound was isolated (3 mg) as yellow oil, the melting point recorded on the synthetic sample showed excellent agreement with that obtained by Tobias[3].

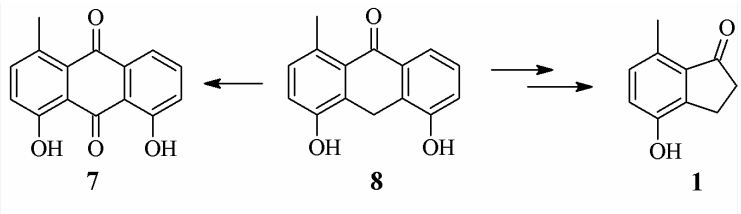
Meanwhile, a report on the conversion of 3,4-dihydrocoumarin into 4-hydroxyindan-1-one by fusion with aluminium chloride[8] prompted us to convert the same starting compound 6-methylcoumarin into the required 1-indanone **1** in just two steps. Catalytic hydrogenation[9] of **2** in ethyl acetate resulted in its clean conversion into 3,4-dihydro-6-methylcoumarin **6** in 93% yield. Fusion of **6** with anhydrous aluminium chloride[8] afforded 4-hydroxy-7-methyl-1-indanone **1** in 84% yield.

Thus, these short and high yielding syntheses make available relatively large amounts of **1** for bioactivity studies. The biogenetic origin of this structurally simple natural product **1** is of interest and deserves attention especially in view of its co-occurrence[2] with the anthraquinone **7** in cyanobacterium *Nostoc commune*. It is proposed that the anthrone **8**, the



a) aq. NaOH, $(CH_3)_2SO_4$ b) H_2, 10% Pd-C, ethanol c) PPA, 70°C
d) HBr, AcOH e) H_2, 10% Pd-C, ethyl acetate f) $AlCl_3$, 180-210°C, 30 min.

Scheme I



Scheme II

obvious biosynthetic intermediate of **7** (Ref. 10), also gets transformed into **1** by its oxidative modifications (**Scheme II**).

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Shimadzu 8101-A FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz respectively on a Bruker WT 300 FT-NMR spectrometer with TMS as internal standard and chemical shifts are recorded in the δ scale. All yields refer to isolated products unless stated otherwise.

3-(2′-Methoxy-5′-methylphenyl)prop-2-enoic acid, 3. A mixture of 6-methylcoumarin **2** (3.4 g, 21.25 mmole) and aq. NaOH (20 g, 500 mmole in 75 mL H_2O) was warmed on a steam bath with stirring until all the coumarin dissolved. Dimethyl sulphate (33.5 g, 266 mmole) was then added during a period of 1.5 hr while maintaining the temperature of the reaction mixture below 50°C. Stirring was continued at 50°C for 1 hr, cooled to 5°C and acidified with 2N HCl. The acid regenerated was dissolved in diethyl ether (20 mL) and extracted with sat. $NaHCO_3$ (2 × 10 mL). The bicarbonate extract was neutralized with 2N HCl to give colorless solid which was filtered, washed with water and dried to give **3** (1.69 g, 82% based on recovered coumarin **2**). Purification by recrystallization from aq. ethanol gave white crystals, m.p. 112°C; IR (KBr): 2972, 1690 (CO), 1620, 1249, 1032, 808 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, Ar-CH_3), 3.80 (s, 3H, OCH_3), 5.96 (d, *J*=12.6 Hz, 1H, H-2), 6.77 (d, *J*=8.4 Hz, 1H, H-3'), 7.12 (d, *J*=8.4 Hz, 1H, H-4'), 7.21 (d, *J*=12.6 Hz, 1H, H-3), 7.33 (s, 1H, H-6'); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4 (*C*H_3), 55.4 (O*C*H_3), 110.3 (C-3'), 118.9 (C-2), 123.4 (C-1'), 129.1 (C-5'), 131.1 (C-6'), 131.2 (C-4'), 141.3 (C-3), 155.1 (C-2'), 171.7 (C-1); LCMS: *m/z* 215.0713 $[M + Na]^+$; Calcd for $C_{11}H_{12}O_3Na^+$: 215.0684.

3-(2′-Methoxy-5′-methylphenyl)propanoic acid, 4. 3-(2′-methoxy-5′-methylphenyl)prop-2-enoic acid **3** (1.68 g, 8.75 mmole) was dissolved in dry ethanol (25 mL) and hydrogenated over 10% Pd-C (0.25 g) at RT until absorption of hydrogen ceased (5 hr). Filtration, followed by evaporation of the solvent gave **5** as colorless liquid (1.69 g) in quantitative yield. IR (KBr): 1713 (CO), 1504, 1254, 1036, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, Ar-CH_3), 2.66 (t, *J*=7.6 Hz, 2H, H-2), 2.92 (t, *J*=7.6 Hz, 2H, H-3), 3.80 (s, 3H, OCH_3), 6.75 (d, *J*=8.1 Hz, 1H, H-3'),

6.98 (d, *J*=2.4 Hz, 1H, H-6'), 7.0 (d, *J*=8.1, 2.4 Hz, 1H, H-4'); LCMS: *m/z* 217.0849 $[M + Na]^+$; Calcd for $C_{11}H_{14}O_3Na^+$: 217.0841.

4-Methoxy-7-methyl-1-indanone, 5. A mixture of P_2O_5 (6.0 g) and orthophosphoric acid (6.0 mL) was stirred under anhydrous conditions in an oil bath at 90-95°C for about 1 hr. The resulting PPA was cooled to 70°C and to this was added dropwise while stirring 3-(2′-methoxy-5′-methylphenyl)propanoic acid **4** (1.62 g, 8.35 mmole). After stirring at 70°C for 4 hr, the reaction mixture was cooled and poured over crushed ice to give a cream coloured solid, which was filtered, washed with sat. $NaHCO_3$, water and dried. Purification by recrystallization from petroleum ether gave colorless crystals (1.25 g, 85%), m.p. 84°C; IR (KBr): 2963, 1703 (CO), 1500, 1258, 1047, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 3H, Ar-CH_3), 2.65 (m, 2H, H-3), 2.98 (m, 2H, H-2), 3.87 (s, 3H, OCH_3), 6.89 (d, *J*=8.1 Hz, 1H, H-6), 7.04 (d, *J*=8.1 Hz, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5 (*C*H_3), 22.0 (C-3), 36.7 (C-2), 55.5 (O*C*H_3), 114.3 (C-3a), 129.6 (C-5), 129.8 (C-7), 135.4 (C-6), 144.4 (C-7a), 154.8 (C-4), 207.9 (C-1); LCMS: *m/z* 177.0921 $[M + H]^+$; Calcd for $C_{11}H_{13}O_2^+$: 177.0915.

4-Hydroxy-7-methyl-1-indanone, 1. A mixture of 4-methoxy-7-methyl-1-indanone **6** (1.0g, 5.68 mmole) in glacial acetic acid (10 mL) and 48% HBr (50 mL) was refluxed for 1 hr. The reaction mixture was cooled to RT, diluted with water and extracted with diethyl ether. The combined organic extracts were washed with water, dried (anhyd. Na_2SO_4) and concentrated to give 0.8 g (87%) of solid which was purified by recrystallization from methanol to give pure **1** m.p. 194°C (Lit. ref. 3, 194-5°C); IR (KBr): 3186 (Ar-OH), 1680 (CO), 1506, 1288, 820 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.47 (s, 3H, Ar-CH_3), 2.62 (m, 2H, H-3), 2.98 (m, 2H, H-2), 6.96 (d, *J*=8.1 Hz, 1H, H-6), 7.02 (d, *J*=8.1 Hz, 1H, H-5), 9.69 (s, 1H, OH).

3,4-Dihydro-6-methylcoumarin, 6 (Ref 9). 6-Methylcoumarin (0.55 g, 3.44 mmole) was dissolved in ethyl acetate (15 mL) and hydrogenated over 10% Pd-C (0.06 g) at RT for 3 hr. Filtration followed by removal of the solvent gave **6** as colorless liquid which solidified on standing. Purification by recrystallization from petroleum ether gave colorless crystals of **6** (0.52 g, 93%), m.p. 80°C (Lit. ref. 9, 80-81°C). IR (KBr): 1744 (CO) cm^{-1}.

4-Hydroxy-7-methyl-1-indanone, 1. A mixture of 3,4-dihydro-6-methylcoumarin **6** (0.35 g, 2.16 mmole) and anhydrous $AlCl_3$ (1.6 g) was heated at 180-210°C for 30 min. The reaction was quenched with crushed ice, to which some conc. HCl was added, to yield a solid, which was filtered, washed with water and purified by recrystallization from methanol to give **1** (0.295 g, 84%) m.p. 194°C (Lit. ref. 3, 194-5°C).

Acknowledgements

The authors thank L D'Souza, NIO, Goa for recording NMR and MS data.

References

1 Syrchina A I & Semenov A A, *Chemistry of Natural Compounds*, 18, **1983**, 1.
2 Jaki B, Heilmann J & Sticher O, *J Nat Prod*, 63, **2000**, 1283.
3 Tobias M A, *J Org Chem*, 35, **1970**, 267.
4 Thompson T J & Edee R H, *J Am Chem Soc*, 47, **1925**, 2556.
5 Divakar K J & Rao A S, *Indian J Chem*, 14B, **1976**, 704.
6 Fieser L F & Fieser M, *Reagents in Organic Synthesis*, Vol 1, (John Wiley and Sons, New York), **1967**, 894.
7 Doxsee K M, Feigel M, Stewart K D, Canary J W, Knobler C B & Cram D J, *J Am Chem Soc*, 109, **1987**, 3098.
8 Loudon J D & Razdan R K, *J Chem Soc*, **1954**, 4299.
9 Yates P & Macas T S, *Can J Chem*, 66, **1988**, 1.
10 Dewick P M, *Medicinal Natural Products, a Biosynthetic Approach*, 2nd edn, (John Wiley and Sons, England), **2002**, 65.