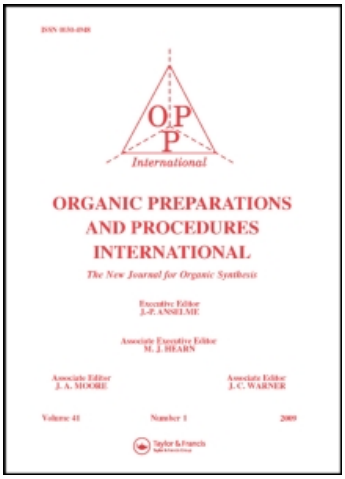

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Wakharkar, R. D. , Deshpande, V. H. , Landge, A. B. and Upadhye, B. K.(1988) 'SYNTHESIS OF MICROMINUTIN AND 4-METHYLMICROMINUTIN', Organic Preparations and Procedures International, 20: 5, 527 — 532
To link to this Article: DOI: 10.1080/00304948809356299
URL: http://dx.doi.org/10.1080/00304948809356299

ORGANIC PREPARATIONS AND PROCEDURES INT. 20(5), 527-532 (1988)

SYNTHESIS OF MICROMINUTIN AND 4-METHYLMICROMINUTIN†

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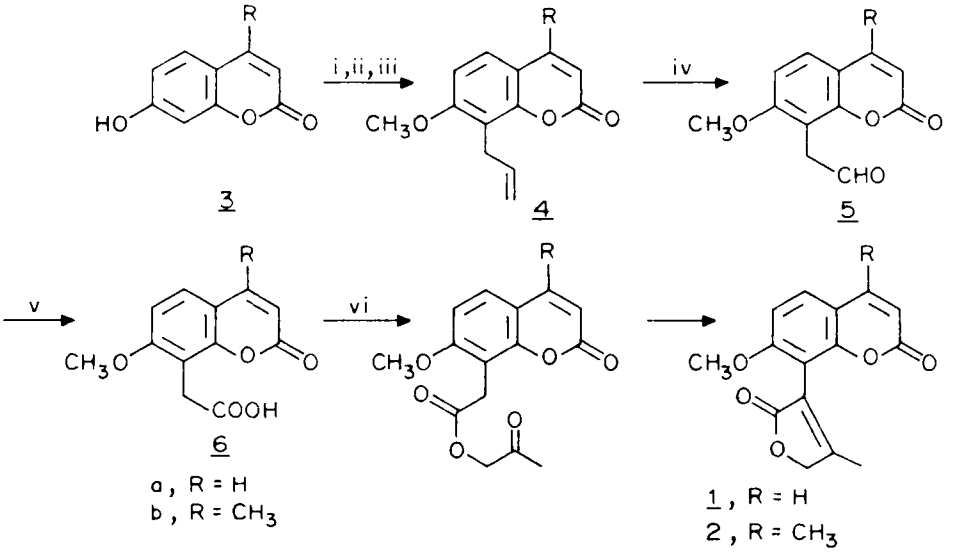
Microminutin (1) isolated from the leaves of Micromelum minutin, contains a γ-butenolide moiety at the C-8 of the coumarin nucleus and exhibits cytotoxic activity.[1] Its structural novelty prompted us to undertake its synthesis. Recently, we developed[2] a method for the preparation of 3-aryl-4-methyl-2(5H)-furanone which suggested simple and attractive strategy for the construction of 1 and its 4-methyl analogue 2.



i = $CH_2=CHCH_2Br$, K_2CO_3, acetone;[3] ii = N,N-dimethylaniline, Δ;[4]
iii = DMS, K_2CO_3, acetone; iv = OsO_4, $NaIO_4$;[5] v = Jones reagent;[6]
vi = CH_3COCH_2Cl, K_2CO_3, CH_3CN.

The 8-allyl-7-methoxy coumarins (4a and 4b) were prepared by a known sequence of reactions[3,4] from umbeliferone (3a) and 4-methylumbeliferone (3b). Subsequent oxidations of 4a and 4b with osmium tetroxide and sodium periodate[5] followed by Jones' reagent[6] provided the required ostholic acid (6a) and 4-methylostholic acid (6b) as shown in the scheme. Treatment of 6a and 6b with equivalent amounts of chloroacetone in the presence of excess of potassium carbonate in dry acetonitrile at reflux temperature resulted directly in the formation of 1 and 2 in 20 and 45% yield, respectively. TLC showed that the esterification was complete within 1 hr. Separate treatment of 7a and 7b, which were isolated and characterised separately with potassium carbonate in dry acetonitrile afforded similar yields of 1 and 2. Attempts to improve the yields of the aldol condensation of 7a using sodium hydride,[7] crown ether,[7] triethylamine,[8] pyridine[9] and basic alumina[10] in most of the cases gave unreacted 7a. Microminutin and 4-methylmicrominutin were identified by spectroscopic analysis. The IR, ^{13}C, ^{1}H NMR and mass spectra of 1 were identical with those of natural microminutin.

EXPERIMENTAL SECTION

IR spectra were recorded on a Perkin-Elmer spectrometer. PMR and ^{13}C spectra were obtained with FT 80 and FT 90 spectrometers using Me_4Si as an internal standard. Mass spectral analyses were conducted using Finnigan MAT automated GC/MS 1020 electron impact, 70 ev. All melting points were uncorrected.

Preparation of 5a and 5b.- To a solution of 0.002 mole of 4a or 4b in 50ml ethyl acetate and 50 ml water, osmium tetroxide (0.06 g, 0.0002 mole) was added at room temperature with stirring. After 15 min., sodium periodate (3.0 g, 0.01 mole) was added portionwise over 1.5 hr. Stirring was continued further for 4 hrs at room temperature. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 ml). The combined organic layer was washed with water, dried over anhydrous sodium

sulfate and concentrated to dryness under reduced pressure to give 0.305g and 0.296 g (70 and 64% yield) of 5a and 5b respectively.

5a, mp. 156-157° (ethanol-pet ether), lit.[4] 156-159°.

5b, mp. 136-137° (ethanol-pet ether).

IR (Nujol): 1770, 1600 cm^{-1}. NMR ($CDCl_3$): δ 2.4 (d, J = 1.5Hz, 3H, C_4-CH_3), 3.88 (s, 3H, -OCH_3), 3.98 (d, J = 1.5Hz, 2H, C_8 - CH_2), 6.1 (d, J = 1.5Hz, 1H, C_3-H), 6.8 (d, J = 9Hz, 1H, C_6-H), 7.5 (d, J = 9Hz, 1H, C_5-H), 9.65 (t, J = 1.5Hz, 1H, -CHO). MS: M^+ 232.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.26

Found : C, 67.09; H, 5.31

Preparation of Ostholic Acid and 4-Methylostholic Acid (6a and 6b).- To a solution of 0.001 mole of 5a or 5b in acetone was added Jones' reagent (0.5 ml) at 0°. The reaction mixture was stirred at 0° for 30 min. The solvent was removed under reduced pressure and the solid residue was treated with water and collected. The colourless solid was dissolved in saturated sodium bicarbonate solution. The pure acid obtained by acidification of the sodium bicarbonate extract was collected, washed with water and dried. Crystallisation of the products from methanol afforded 0.117 g and 0.133 g (50 and 54% yield) of 6a and 6b respectively.

6a, mp. 252-253°; lit.[11] 255-257°.

6b, mp. 247-248°.

IR (Nujol): 1710, 1600 cm^{-1}. ^1H NMR ($CDCl_3$ + acetone d_6): δ 2.3 (d, J = 1.5Hz, 3H, C_4-CH_3), 3.7 (s, 2H, C_8-CH_2), 3.85 (s, 3H, -OCH_3), 5.95 (d, J = 1.5Hz, 1H, C_3-H), 6.85 (d, J = 9Hz, 1H, C_6-H), 7.5 (d, J =9Hz, 1H, C_5-H). MS: M^+ 248.

Anal Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.84

Found : C, 62.88; H, 5.12

Preparation of Microminutin (1) and 4-Methylmicrominutin (2).- The mixture

of 0.001 mole of acids 6a or 6b, anhydrous potassium carbonate (2.5 g, 0.02 mole) in 50 ml dry acetonitrile and chloroacetone (0.1 ml, 0.0011 mole) was heated to reflux for 8-9 hrs. The reaction was monitored by TLC (silica gel, 8:2 pet. ether-acetone). After completion of the reaction, it was cooled to room temperature and filtered. The solid residue was washed with acetonitrile and the combined filtrate was concentrated to dryness under reduced pressure. The residue was purified by passing through a column of silica gel (pet. ether-acetone) to obtain 0.055 g and 0.140 g (20% and 45% yield) of 1 and 2 respectively.

1, mp. 145-150°; lit.[1] 154-155°.

IR ($CHCl_3$): 1740, 1675, 1560 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.01 (s, 3H, C_4'-CH_3), 3.88 (s, 3H, -OCH_3), 4.9 (s, 2H, C_5'-CH_2), 6.23 (d, J = 9Hz, 1H, C_3-H), 6.92 (d, J = 9Hz, 1H, C_6-H), 7.5 (d, J = 9Hz, 1H C_5-H), 7.67 (d, J = 9Hz, 1H, C_4-H). ^{13}C NMR: (22.63 MHz, $CDCl_3$): δ 172.4, 162.9, 161.1, 160.6, 152.9, 143.7, 129.9, 120.3, 113.6, 113.4, 108.3, 107.5, 73.3, 56.4, 13.8. MS: M^+ 272.

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.41

Found : C, 66.02; H, 4.38

2, mp. 218-219° (aq. ethanol).

IR (Nujol): 1740, 1680, 1600, 1590 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.00 (s, 3H, C_4'-CH_3), 2.35 (d, J = 1.5Hz, 3H, C_4-CH_3), 3.83 (s, 3H, -OCH_3), 4.85 (s, 2H, C_5'-CH_2), 6.06 (d, J = 1.5Hz, 1H, C_3-H), 6.9 (d, J = 9Hz, 1H, C_6-H), 7.59 (d, J = 9Hz, 1H, C_5-H). ^{13}C NMR: (22.63 MHz, $CDCl_3$): δ 172.4, 162.8, 160.7, 160.6, 152.7, 152.6, 120.3, 114.2, 112.3, 107.8, 107.2, 73.1, 56.4, 18.5 and 13.5. MS: M^+ 286.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.89

Found : C, 66.95; H, 5.03

Preparation of Esters 7a and 7b. Method A.- Ostholic acid 6a or 6b 0.001 mole dissolved in dry acetonitrile (50 ml) was refluxed for 30 min. with anhydrous potassium carbonate (2.5 g, 0.02 mole) and chloroacetone

(0.1 ml, 0.011 mole). The reaction mixture was cooled to room temperature and was worked up as in the previous experiment to yield 0.280 g and 0.300.g (98% and 99%) of the esters 7a and 7b respectively.

7a, mp. 127-128° (ethanol).

IR (Nujol): 1750, 1710, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H, $-COCH_3$), 3.92 (s, 3H, $-OCH_3$), 4.0 (s, 2H, C_8-CH_2), 4.52 (s, 2H, $O-CH_2CO$), 6.23 (d, J = 9Hz, 1H, C_3-H), 6.88 (d, J = 9Hz, 1H, C_6-H), 7.42 (d, J = 9Hz, 1H, C_5-H), 7.6 (d, J = 9Hz, 1H, C_4-H). MS: M^+ 290.

Anal. Calcd. for $C_{15}H_{14}O_6$: C, 62.07; H, 4.83

Found : C, 61.77; H, 4.99

7b, mp. 177-178° (ethanol).

IR (Nujol): 1750, 1730, 1710, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, $-COCH_3$), 2.4 (d, J = 5Hz, 3H, C_4-CH_3), 3.84 (s, 3H, $-OCH_3$), 3.96 (s, 2H, C_8-CH_2), 4.56 (s, 2H,$-O-CH_2CO$), 6.06 (d, J = 1.5Hz, 1H, C_3-H), 6.84 (d, J = 9Hz, 1H, C_6-H), 7.44 (d, J = 9Hz, 1H, C_5-H). MS: M^+ 304.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.26

Found : C, 62.94; H, 5.18

Method B.- 7a was prepared by using triethylamine instead of potassium carbonate in the above method (Method A), wherein 95% yield of the ester 7a was obtained.

Acknowledgement.- One of the authors (B.K.U.) is thankful to the CSIR, New Delhi for financial support.

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(Received December 31, 1987; in revised form June 17, 1988)