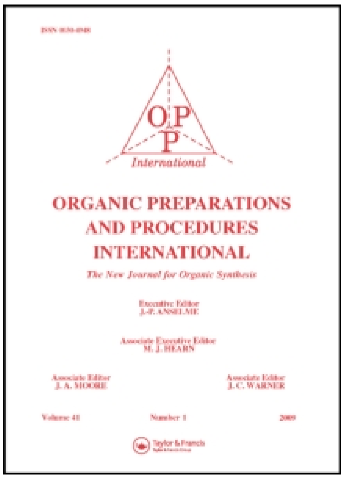

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CONVENIENT SYNTHESIS OF NIESHOUTIN (*CYCLOOBLZQUETIN*), A FUROCOUMARIN ISOLATED FROM THE HEARTWOOD OF *Ptaeroxylon obliquum*

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CONVENIENT SYNTHESIS OF NIESHOUTIN (*CYCLOOBLIQUETIN*), A FUROCOUMARIN ISOLATED FROM THE HEARTWOOD OF *Ptaeroxylon obliquum*

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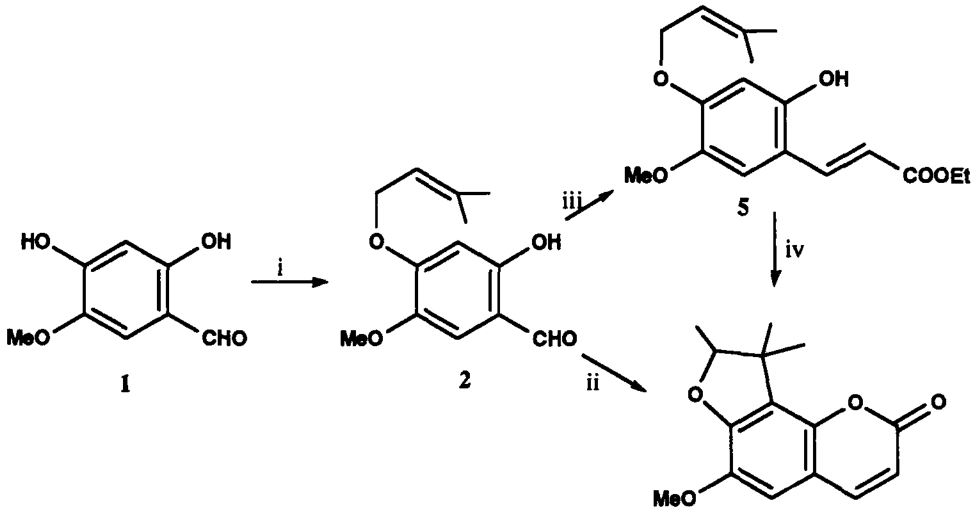
Several angular dihydrofurocoumarins have been isolated[1] from the heartwood of *Ptaeroxylon obliquum* (sneezewood) and most contain substituents in the dihydrofuran moiety. Moreover, a few including nieshoutin (cyclooobliquetin, **4**) contain three methyl groups in the dihydrofuran portion.[2] The assigned structure[3] **4** has been confirmed by synthesis. All the methods reported[2-4] for the synthesis of **4** make use of naturally occurring coumarins such as aesculetin and obliquetin. We report herein a convenient synthesis of nieshoutin (cyclooobliquetin **4**) which does not require preformed coumarin as a starting material. In our approach, 2,4-dihydroxy-5-methoxybenzaldehyde (**1**), obtained from 2,4,5-trimethoxybenzaldehyde,[5] was selectively allylated using prenyl bromide in refluxing acetone containing anhydrous potassium carbonate, to provide the corresponding prenyloxyphenol (**2**). Heating a mixture of **2** and phosphorane **3** at 150° for 6 hrs gave nieshoutin (cyclooobliquetin **4**) in 40% yield. Reaction of stable organophosphoranes with carbonyl compounds yields major amount of *E*-olefinic compounds.[6] It was anticipated that the conversion of



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i) $BrCH_2CH=CMe_2$, K_2CO_3, acetone, Δ, 3hrs
ii) $Ph_3P=CHCOOEt$ (3), 150°, 6 hrs iii) 3, THF, rt, 3 hrs iv) Δ, 150°, 6 hrs

2 into **4** using phosphorane **3** could proceed through the ethyl cinnamate (**5**), which on Claisen rearrangement followed by cyclization would provide **4**. Thus, in the conversion of **2** into **4** three reactions *viz.* Wittig reaction, Claisen rearrangement and cyclization, were achieved. In order to check the intermediacy of **5**, aldehyde **2** was reacted with phosphorane **3** at room temperature in tetrahydrofuran solution. As expected, ethyl cinnamate **5** was obtained in 70% yield. When **5** was heated at 150° for 6 hrs, nieshoutin (cycloobliquetin **4**) was obtained in 50% yield. The present two-step synthesis of **4** from **1** appears to be more convenient than earlier methods.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer-337 IR spectrophotometer and ^{1}H NMR spectra in $CDCl_3$ on a Perkin-Elmer R-32 (90 MHz) instrument. Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard and coupling constants in Hz.

2,4-Dihydroxy-5-methoxybenzaldehyde (1).- To a suspension of 3 g of anhydrous aluminium chloride in methylene chloride (20 ml) was stirred at room temperature for 2 hrs, was added a solution of 2,4,5-trimethoxybenzaldehyde (1 g) in methylene chloride (15 ml). The reaction mixture was stirred at room temperature for 3 hrs and poured over crushed ice containing hydrochloric acid. It was extracted with methylene chloride (2 x 15 ml). The combined methylene chloride extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a solid which was purified by passing through a column of silica gel using benzene as eluent and recrystallised from benzene-hexane to give **1** as white crystals (0.70 g, 80%), mp. 152 , lit.[5] 152°.

2-Hydroxy-5-methoxy-4-prenyloxybenzaldehyde (2).- To a solution of 2,4-dihydroxy-5-methoxybenzaldehyde (0.50 g, 0.0029 mol) and of prenyl bromide (0.5 g, 0.003 mol) in acetone (25 ml) was added anhydrous potassium carbonate (0.45 g, 0.003 mol) and the mixture stirred at reflux, under nitrogen atmosphere for 3 hrs. The mixture was filtered and the solvent was removed under reduced pressure to give a semi-solid product. Chromatography over silica gel using benzene as an eluent gave a solid which on recrystallization from benzene-hexane furnished **2** as white crystals (0.380 g, 54%), mp 70-71°. IR (nujol): 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.69 and 1.72 (3H each, s, $-C(CH_3)_2$), 3.65 (3H, s, $-OCH_3$), 4.40 (2H, d, J = 6 Hz, $-\underline{CH_2}-CH=$), 5.20 -5-50 (1H, m, -CH=), 6.14 (lH, s, Ar-H), 6.62 (lH, s, Ar-H), 9.37 (lH, s, -CHO), 11.87 (1H, s, exchangeable with D_2O, -OH).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.36; H, 6.83

Nieshoutin (cycloobliquetin 4).- A mixture of prenyl ether **2** (0.14 g, 0.6 mmol) and phosphorane **3** (0.23 g, 0.65 mmol) was heated at 150° for 6 hrs. The crude product was purified by HPLC using ethyl acetate-hexane (1:4) as an eluent to give a yellow solid which on recrystallization from methylene chloride-hexane furnished **4** as pale yellow needles (0.062 g, 40%), mp. 125-126°, lit.[2,3] mp. 124° and 125-127°. IR (nujol) : 1725 cm^{-1} . ^{1}H NMR ($CDCl_3$): δ 1.29 (3H, s, $-CH_3$), 1.40 (3H, d, J = 6 Hz, $-CHCH_3$), 1.56 (3H, s, $-CH_3$), 3.79 (3H, s, $-OCH_3$), 4.42 (lH, m, $-C\underline{H}CH_3$), 5.95 (1H, d, J = 10

Hz, 6H), 6.55 (1H, s, 8H), 7.35 (lH, d, J = 10 Hz, 7H).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.38; H, 6.08

(E)-Ethyl 2-Hydroxy-5-methoxy-4-prenyloxycinnamate (5).- A solution of prenyl ether **2** (0.1 g, 0.00042 mol) and phosphorane **3** (0.17 g, 0.00048 mol) in anhydrous tetrahydrofuran (20 ml) was stirred at room temperature for 3 hrs. Evaporation of the solvent gave a semi-solid product which was chromatographed over silica gel using ethyl acetate-hexane (1:4) as an eluent to furnish **5** (0.09 g, 70%), mp. 67° (from chloroform-hexane). IR (nujol): 3520, 3425 and 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, J = 6 Hz, $-OCH_2C\underline{H}_3$), 1.70 and 1.75 (3H each, s, 2 x CH_3), 3.82 (3H, s, $-OCH_3$), 4.30 (2H, q, J = 6 Hz, $-OC\underline{H}_2CH_3$), 4.54 (2H, d, J = 6Hz $-O-C\underline{H}_2CH=$), 5.48 (1H, m, -CH=), 6.38 (1H, d, J = 16 Hz, $=C\underline{H}CO_2CH_2CH_3$), 6.45 (lH, s, ArH), 6.92 (1H, s, ArH), 8.04 (lH, d, J = 16 Hz, $-C\underline{H}=CHCO_2-$).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.32; H, 7.20

Conversion of Ester 5 into Nieshoutin (cycloobliquetin 4).- The ester **5** (0.07 g) was heated at 150° for 6 hrs. The residue obtained was purified by HPLC using ethyl acetate-hexane (1: 4) as an eluent to give **4** (0.03 g, 50%), m.p. 125°, identical (mp., CO-TLC, superimposable IR) with an authentic sample prepared above.

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