Microwave assisted facile synthesis of Elvirol, Curcuphenol and Sesquichamaenol using Montmorillonite K-10 clay in dry media

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Short, simple and convergent syntheses of the title compounds have been accomplished with good overall yields using a Montmorillonite K-10 clay catalyzed Friedel–Crafts alkylation reaction in 'dry media' as the key step.

Development and incorporation of new methodologies in the synthesis of natural products is an endeavour of every synthetic organic chemist. Clay catalysts[1] are increasingly being used as heterogeneous catalysts due to their chemo- and regioselectivity, good efficiency and mild reaction conditions. Clay catalysts have both Brønsted and Lewis acid sites, either one dominating depending on the conditions of preparation;[2] in addition to this they are cheap, can be recycled and are eco-friendly compared to homogeneous acid catalysts.

In a continuation of our work[3] on developing greener and cleaner technologies we report herein a simple method for the Friedel–Crafts alkylation of various phenols with secondary halides using Montmorillonite K-10 clay as the Lewis acid catalyst at 200 °C in the absence of solvent as the key step. Various other methods[4] are known which use solid supports (silica, alumina, K-10) doped with various Lewis acids ($AlCl_3$, $FeCl_3$) in the presence of a solvent. These methods have the inherent disadvantage of resulting in hazardous wastes that are problematic to dispose of and cannot be recycled.

Wright *et al.*[5] have isolated (+)-Curcuphenol (**2**), a new sesquiterpene phenol, from the sponge *Didicus flavis* Van Soest (family: Latrunculiidae). McEnroe and Fenical[6] have also reported the isolation of (−)-Curcuphenol from a metabolite of the gorgonian soft coral *Pseudopterogorgia rigida* and from the terresterial plant *Lasiamthaea podocephala*. There are few literature[6,7] records for the synthesis of compound **2**.

Takase and co-workers[8] isolated a new phenolic sesquiterpene Sesquichamaenol (**3**) from an essential oil of the Benihi tree (*Chamaecyparis formosensis*) and assigned its structure on the basis of spectral data and total synthesis.

Bohlmann and Grenz[9] isolated Elvirol (**1**), a sesquiterpenic phenol from the roots of *Elvira biflora* DC. The synthesis of **1** is reported in the literature.[10,11] We report herein the short and simple synthesis of **1**, **2** and **3** resulting in better overall yields using an eco-friendly methodology. The reaction sequence leading to the syntheses of **1**, **2** and **3** is depicted in Scheme 1.

Results and discussion

Microwave assisted reduction[12] of 6-methylhept-5-en-2-one using (**6**) Al_2O_3 doped with $NaBH_4$ gave 6-methylhept-5-en-2-ol (**7**) in quantitative yield. Bromination[13] using PBr_3–pyridine in anhydrous diethyl ether at 0 °C afforded 6-bromo-2-methylhept-2-ene (**8**) in 73% yield after purification by silica gel column chromatography. Treatment of **8** with *p*-cresol or *m*-cresol on K-10 clay at 200 °C for 5 h gave a crude product, which upon purification by column chromatography furnished the title compounds **1** and **2** in 62% and 60% yields respectively. The characteristic peaks recorded in the aromatic region of the ^{1}H NMR spectrum of **1** are at δ 6.6 (d, 1H, adjacent to –OH), 6.9 (d, 1H, adjacent to $–CH_3$) and 7.1 ppm (s, 1H, adjacent to side chain). For compound **2** the peaks in the aromatic region appear at δ 6.6 (s, 1H, between –OH and $–CH_3$), 6.8 (d, 1H, adjacent to $–CH_3$) and 7.05 ppm (d, 1H, adjacent to side chain).

Ketalization of 6-methylhept-5-en-2-one with ethylene glycol gave **9** on doping with Montmorillonite K-10 clay under microwave irradiation. 6-Methyl(ethylene-2,2-dioxy)hept-5-ene (**9**) which was subjected to hydroboration–iodination[14] using acetoxyborohydride and iodine in anhydrous THF to yield (ethylene-2,2-dioxy)-5-iodo-6-methylheptane (**10**). Friedel–Crafts alkylation of **10** with *p*-cresol on K-10 clay at 200 °C for 5 h gave the crude product which upon purification by column chromatography using *n*-hexane as eluent afforded the title compound **3** in 70% yield. The characteristic peaks recorded in the aromatic region of the ^{1}H NMR spectrum of compound **3** were at δ 6.6 (d, 1H, adjacent to –OH), 6.9 (d, 1H, adjacent to $–CH_3$) and 7.1 ppm (s, 1H, adjacent to side chain). The spectral data for the title compounds **1**, **2** and **3** corresponded with values reported in the literature.[8]

Experimental

General

^{1}H NMR spectra were recorded in CCl_4 on a 300 MHz Bruker spectrometer using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 337 spectrophotometer. Montmorillonite K-10 clay was purchased from Aldrich. Microwave assisted reactions were carried out in a BPL BMO 700T (640 W) microwave oven. Unless otherwise stated, all organic extracts were dried over anhydrous sodium sulfate. Silica gel (ASC, Bombay) impregnated with calcium sulfate was used for TLC.

6-Methylhept-5-en-2-ol (7)

Freshly prepared $NaBH_4$–Al_2O_3 (1.13 g, 3.0 mmol of $NaBH_4$) was thoroughly mixed with pure 6-methylhept-5-en-2-one (**6**, 0.38 g, 3.0 mmol) in a test tube which was placed inside the microwave oven and irradiated at 640 W for 1 min. Upon completion of the reaction (TLC monitoring), the product was extracted with methylene chloride (2 × 10 mL). Removal of solvent under reduced pressure provided pure 6-methylhept-5-en-2-ol (**7**) in 93% yield (0.36 g). IR (neat)/ν_{max}: 3440, 2980, 1640, 1305, 890 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.1 (d, 3H, J = 12 Hz, $–CH_3$), 1.3 (m, 2H, saturated methylene), 1.5, 1.6 (2s, 6H, =

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$C(CH_3)_2$), 2.0 (m, 2H, CH_2CH=), 3.8 (m, 1H, –C*H*OH), 4.1 (br s, 1H, –OH, D_2O exchangeable), 5.3 (t, 1H, J = 7 Hz, –C*H*=C<).

6-Bromo-2-methylhept-2-ene (8)

To an ice cooled and well stirred solution of 6-methylhept-5-en-2-ol (**7**, 0.384 g, 3 mmol) in anhydrous diethyl ether (50 mL) was added a few drops of pyridine followed by PBr_3 (0.28 g, 1 mmol) in diethyl ether (15 mL) dropwise over approximately 30 min. The mixture was stirred for approximately 2 h at 0 °C and for 1 h at room temperature. The reaction mixture was washed with 5% aq. $NaHCO_3$ (20 mL), extracted with diethyl ether (3 × 20 mL), washed with water and dried over Na_2SO_4. Evaporation of solvent followed by purification of the crude product by neutral alumina column chromatography using *n*-hexane–EtOAc (9 : 1) as eluent afforded pure (**8**) in 73% yield (0.418 g). IR (neat)/ν_{max}: 2980, 1310, 890, 570 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.05 (d, 3H, J = 12 Hz, –CH_3), 1.2 (m, 2H, saturated methylene), 1.5, 1.6 (2s, 6H, =C(CH_3)$_2$), 2.0 (m, 2H, –CH_2CH=), 3.6 (m, 1H, –C*H*Br), 5.3 (t, 1H, J = 7 Hz, –C*H*=C<).

Elvirol (1)

A mixture of 6-bromo-2-methylhept-2-ene (**8**, 0.382 g, 2.0 mmol), *p*-cresol (0.432 g, 4.0 mmol) and K-10 clay was heated for 5 h at 200 °C. The reaction mixture was allowed to cool and was extracted with diethyl ether. Evaporation of the solvent gave a crude product which was purified by silica gel column chromatography using *n*-hexane–EtOAc (9 : 1) as eluent. The pure title compound (**1**) was afforded in 62% yield (0.270 g) with its isomer (**4**) in 25% yield (0.108 g) and a disubstituted product in 10% yield. IR (neat)/ν_{max}: 3250, 1590, 1480, 1245, 890, 810 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.2 (d, 3H, J = 12 Hz, –CHCH_3), 1.5 (s, 3H, $H_3CC(CH_2)CH_3$), 1.6 (m, 2H, saturated methylene), 1.66 (s, 3H, $H_3CC(CH_2)CH_3$), 1.8 (m, 2H, –CH_2CH=), 2.3 (s, 3H, ArCH_3), 2.8 (m, 1H, benzylic proton), 5.2 (t, 1H, J = 7 Hz, –C*H*=C<), 5.4 (br s, 1H, –OH, D_2O exchangeable), 6.6 (d, 1H, J = 8 Hz, Ar*H*, adjacent to –OH), 6.9 (d, 1H, J = 8 Hz, Ar*H*, adjacent to –CH_3), 7.1 (s, 1H, Ar*H*, adjacent to side chain).

Curcuphenol (2)

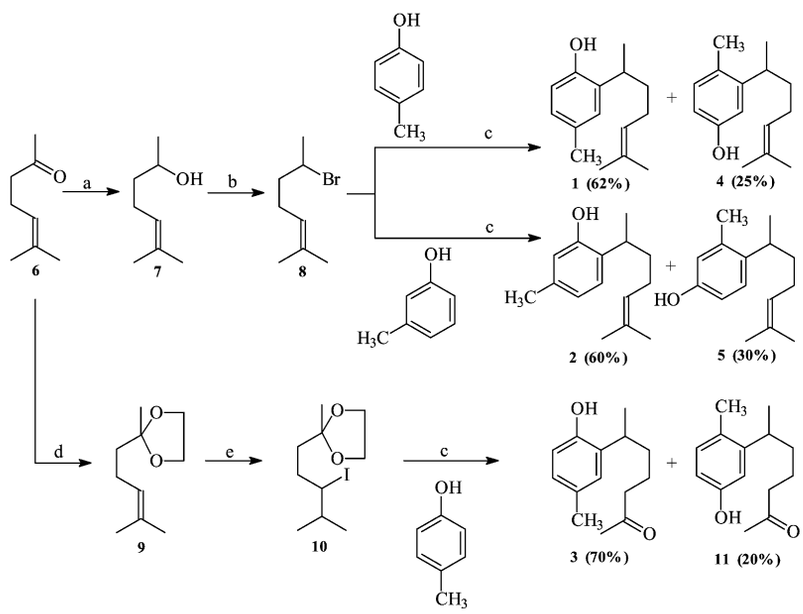
A mixture of 6-bromo-2-methylhept-2-ene (**8**, 0.382 g, 2.0 mmol) and *m*-cresol (0.432 g, 4.0 mmol) was heated on K-10 clay for 5 h at 200 °C. The reaction mixture was worked up as described above to furnish pure (**2**) in 60% yield (0.29 g) with its isomer (**5**) in 30% yield (0.14 g), as well as an undesired product (7%). IR (neat)/ν_{max}: 3250, 1590, 1480, 1245, 890, 810 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.2 (d, 3H, J = 7 Hz, –CHCH_3), 1.5 (s, 3H, $H_3CC(CH_2)CH_3$), 1.6 (m, 2H, saturated methylene), 1.8 (s, 3H, $H_3CC(CH_2)CH_3$), 1.9 (m, 2H, –CH_2CH=), 2.3 (s, 3H, ArCH_3), 2.95 (m, 1H, benzylic proton), 4.6 (br s, 1H, –OH, D_2O exchangeable), 5.2 (t, 1H, J = 7 Hz, –C*H*=C<), 6.5 (s, 1H, J = 8 Hz, Ar*H*, adjacent to –OH), 6.8 (d, 1H, J = 8 Hz, Ar*H*, adjacent to –CH_3), 7.05 (d, 1H, Ar*H*, adjacent to side chain).

6-Methylethylene-2,2-dioxyhept-5-ene (9)

Activated Montmorillonite K-10 clay (0.12 g) was doped with a mixture of 6-methylhept-5-en-2-one (**6**, 1.08 g, 8.6 mmol) and ethylene-1,2-diol (0.79 g, 12.89 mmol) and exposed to MWI (640 W) for 15 min. The reaction mixture was cooled and extracted with diethyl ether (2 × 20 mL), washed with brine (2 × 5 mL), dried and evaporated under reduced pressure to give a crude product. This was purified by silica gel column chromatography using hexane–ethyl acetate (9 : 1) as eluent to afford the product (**9**, 1.18 g) in 81% yield. IR (neat)/ν_{max}: 2980, 1620, 1450, 1040, 880, 660 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.2 (s, 3H, –CHCH_3), 1.4 (t, 2H, CH_2CH–), 1.65, 1.7 (2s, 6H, =C(CH_3)$_2$), 1.9 (m, 2H, –CH_2CH=), 3.95 (s, 4H, ethylenedioxy protons), 5.3 (t, 1H, J = 7 Hz, –C*H*=C<).

Ethylene-2,2-dioxy-5-iodo-6-methylheptane (10)

To a dry 100 mL reaction vessel equipped with magnetic stirring bar, septum inlet and reflux condenser was added sodium borohydride (0.76 g, 20 mmol) under a blanket of nitrogen, followed by addition of anhydrous THF (40 mL). The flask was immersed in an ice bath and mercuric acetate (3.18 g, 10 mmol) was added slowly under an N_2 atmosphere. The reaction mixture was stirred for 1 h at 0 °C. Then the reaction mixture was brought to room temperature and a solution of compound (**9**, 3.40 g, 20 mmol) in anhydrous THF (5 mL) was added dropwise. The contents were allowed to stir for 16 h at room temperature allowing complete hydroboration. To the above solution was added iodine (6.35 g, 25 mmol) at room temperature, followed by dropwise addition of a 3 M solution of NaOH (10 mL) in methanol (30 mL). After stirring for 10 min at room temperature, the reaction mixture was decanted



Scheme 1 *Reagents and conditions*: (a) $NaBH_4$, Al_2O_3, microwave irradiation (MWI); (b) pyridine, anhyd. Et_2O, PBr_3, 0 °C; (c) K-10 clay, 200 °C, 5 h; (d) $HOCH_2CH_2OH$, MWI; (e) $CH_3COO^-BH_3^+$, I_2.

and poured into ice cold water (50 mL) containing sodium thiosulfate (1 g) to remove excess iodine. The aqueous layer was extracted with diethyl ether (3 × 20 mL), dried and the solvent evaporated to yield a crude product which was purified by column chromatography over silica gel using *n*-hexane as eluent to furnish the pure product **10** in 88.6% yield (5.28 g). IR (neat)/ν_{max}: 2930, 1380, 1040, 880, 660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (d, 6H, J = 7 Hz, –CH(CH_3)$_2$), 1.2 (s, 3H, –CHCH_3), 1.3–1.5 (m, 5H, saturated methylenes and methine), 2.9–3.2 (m, 1H, –C*H*I), 3.95 (s, 4H, ethylenedioxy protons).

Sesquichamaenol (3)

A mixture of *p*-cresol (0.431 g, 1.9 mmol) and ethylene-2,2-dioxy-5-iodo-6-methylheptane (**10**, 0.598 g, 2.0 mmol) were heated on K-10 clay (1 g) at 200 °C for 5 h and worked up as usual. The crude product was purified by column chromatography on silica gel using *n*-hexane–EtOAc (9 : 1) to give pure title compound (**3**) in 70% yield (0.33 g) together with the other isomer (**11**) in 20% yield (0.09 g). IR (neat)/ν_{max}: 3430, 1695, 1613, 1513, 1265, 1205, 890, 810 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (d, 6H, J = 6.5 Hz, –CH(CH_3)$_2$), 1.5 (m, 3H, saturated methylenes and methine), 2.03 (s, 3H, –CH_3CO–), 2.3 (t, 2H, J = 7 Hz, –CH_2CO–), 2.6 (m, 1H, benzylic), 3.24 (s, 3H, ArCH_3), 5.3 (br s, 1H, –OH, D_2O exchangeable), 6.6 (d, 1H, J = 8 Hz, Ar*H*, adjacent to –OH), 6.9 (d, 1H, J = 8 Hz, Ar*H*, adjacent to –CH_3), 7.1 (s, 1H, J = 8 Hz, Ar*H*, adjacent to side chain).

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