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A REGIOSELECTIVE SYNTHESIS OF 3-ISOPRENYL-4-HYDROXYCOUMARINS [1]

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ABSTRACT: the dianion of ethyl 3-(2-hydroxyphenyl)-3-oxopropanoate can be regioselectively alkylated with isoprenyl bromides to give, after hydrolytic work-up, the corresponding 3-substituted-4-hydroxycoumarins.

The direct alkylation of 4-hydroxycoumarin by carbon electrophiles is hampered by regioselectivity and polyalkylation problems, and is of limited synthetic value under both classical[2] and phase-transfer conditions.[3] To circumvent these difficulties, we developed an indirect alkylation procedure[4] that takes advantage of the regioselective condensation of 4-hydroxycoumarin and aldehydes.[5] The resulting 3,3'-alkylidenebis-4-hydroxycoumarins are then reductively cleaved with $NaBH_3CN$ in refluxing methanol.[4] However, this procedure could not be applied to α,β-unsaturated aldehydes, and thus

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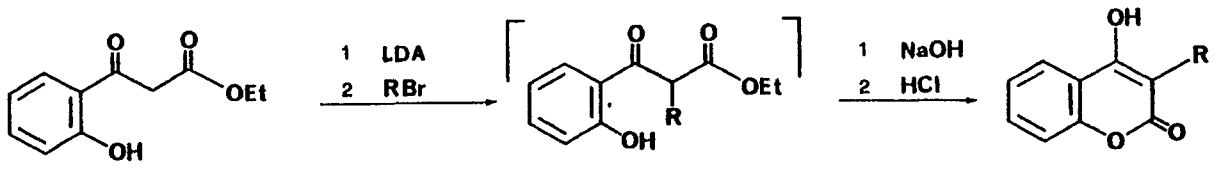
allyl groups could not be introduced. 3-Allyl-4-hydroxycoumarins have been prepared by Claisen rearrangement of 4- allyloxycoumarins, [6] but this procedure is unsuitable for γ,γ-disubstituted allyl groups like those of isoprenoid residues, since their corresponding α,α-disubstituted allyl-coumarinyl ethers are not readily available.

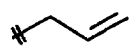
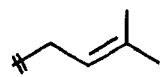
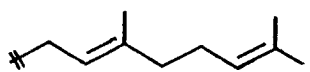
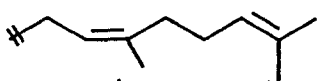
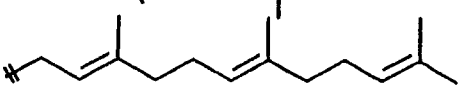
Our interest in prenylated coumarins was prompted by the discovery that a series of 3-prenyl-4-hydroxycoumarins are the causative agents of ferulosys, a haemorrhagic syndrome of livestock.[7] Since the isolation of the natural toxins is tedious and time-consuming,[7] a general method for the regioselective synthesis of 3-isoprenyl-4-hydroxycoumarins was investigated.

4-Hydroxycoumarin is a strong acid (pKa *ca* 4.1),[8] and relatively harsh conditions are required for the alkylation of its anion (dipolar aprotic solvents, prolonged reaction times and heating).[2] We reasoned that the much less acidic β-ketoester **1** might represent a synthetic equivalent of 4-hydroxycoumarin; **1** is easily available from *o* -hydroxyacetophenone[9] and can be transformed quantitatively into 4-hydroxycoumarin by treatment with aqueous bases at room temperature.

The alkylation of the dianion of **1** was tested with prenyl bromide as electrophile, and with a 0.5:1 molar ratio of halide to dianion. In no case alkylation at the phenolic hydroxyl was observed, whereas the regioselectivity of enolate alkylation and polyalkylation were dependent on the reaction conditions (solvent,base and temperature). NaH and K-tOBut in DMSO, DMF or THF gave mixtures of products, whereas with LDA in THF at -78 °C exclusively C-monoallylation took place. After hydrolysis of the alkylated β-ketoester (NaOH in ethanol-water), 3-prenyl-4-hydroxycoumarin (**3**) could be directly obtained in 85% yield.



1

	R	Yield %
2		11
3		85
4		81
5		53
6		48

This procedure could be succesfully extended to the synthesis of 3- geranyl-(**4**), 3- neryl-(**5**) and 3-farnesyl-4-hydroxycoumarin(**6**). The latter (ferulenol) is the major haemorrhagic toxin involved in ferulosys.[10] Under these reaction conditions and with a 0.5:1 molar ratio of halide to dianion, allyl bromide gave a low yield, whereas saturated alkyl halides, including methyl iodide, were completely unreactive.

Although applicable only to very reactive allyllic substrates, our protocol complements other syntheses of C-3 substituted-4-hydroxycoumarins, allowing an easy entry into an increasing class of biologically active natural products1.[11]

EXPERIMENTAL

General: all reactions were carried out in flame-dried flask, equipped with septa for the addition of reagents by syringe techniques. n-Pentane was dried over $CaCl_2$, THF by distillation from Na-benzophenone, and diisopropylamine by distillation from CaH_2. Allyl- and dimethylallyl bromides were purchased from Fluka. All the other bromides were prepared from the corresponding allylic alcohols, that are all commercially available (Aldrich).

Preparation of isoprenyl bromides (reaction with nerol as representative).

To a cooled (0° C) and stirred solution of nerol (10 ml, 8.77 g, 56.8 mmol) in 150 ml pentane, a cooled (0°C) solution of PBr_3 (2.67 mmol, 7.68 g, 28.4 ml, 0.5 mol. equiv.) in pentane (10 ml) was added dropwise. After 40 min., the reaction was poured into water, and extracted with pentane. The organic

phase was washed with 5% $NaHCO_3$, water and brine. After drying ($MgSO_4$) and removal of the solvent, an oil was obtained (11.12 g, yield: 90 %) that was directly used for the alkylation reaction. Isoprenyl bromides were stored on Cu powder or silver threads at 4 °C.

Synthesis of 3-isoprenyl-4-hydroxycoumarins (synthesis of 3-geranyl-4-hydroxycoumarin as representative).

To a cooled (-20 °C) solution of diisopropylamine (1.50 ml, 1.07 g, 10.7 mmol) in THF (25 ml), BuLi (1.6 M in hexanes, 6.0 ml, 9.6 mmol) was added dropwise; after stirring at -20°C for 5 min., the solution was cooled to -78°C, and a solution of ethyl 3-(2-hydroxyphenyl)-3-oxopropanoate (1.00 g, 4.8 mmol) in 10 ml THF was added dropwise. The solution was stirred 1h at -78°C, 2 h at -10°C, and then recooled again at -78°C. A solution of 521 mg geranyl bromide (2.4 mmol, 0.5 mol. equiv.) in 5 ml THF was added dropwise. After 20 min. the cooling bath was removed, and the yellowish solution was stirred at room temperature overnight. The reaction was quenched with sat. NH_4Cl and extracted with $CHCl_3$ (the α-alkylated β-ketoester can be obtained from this phase by column chromatography (hexane-EtOAc 95:5, yield 80%)). After removal of the solvent, the residue was solved in 10 ml EtOH and 10 ml of 10% aqueous NaOH were added. After stirring 15 min. at room temp., the reaction mixture was cooled (0°C), and dil. HCl was added dropwise untill a pH value of *ca* 3 . The mixture was extracted with $CHCl_3$, and the organic phase washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (20 g silica gel, hexane-EtOAc 8:2 as eluant) to give 579 mg **4** (yield: 81 %) as a white powder.

E,E-3-farnesyl-4-hydroxycoumarin (ferulenol)[10] and 3-allyl-4-hydroxycoumarin[6] are known compounds. The other coumarins are new, and were characterized as follows:

3-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one (3-prenyl-4-hydroxycoumarin (3)) . White powder, m.p. 133-135°C; UV (EtOH), nm: 320, 307, 280, 251; IR (KBr) ν cm^{-1}: 3200, 1650, 1630, 1500, 1390, 1160, 1060, 960; ^1H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, J=7.9 Hz, 1H), 7.48 (t, J=7.7 Hz, 1H), *ca* 7.27 (2H, overlapped signals), 5.45 (t, J=7.3 Hz, 1H), 3.42 (d, J=7.3 Hz, 2H), 1.84 (s, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$)[12]: δ 160.93 (s,C-2), 102.99 (s, C-3), 163.46 (s, C-4), 122.65 (d, C-5), 123.82 (d, C-6), 131.64 (d, C-7), 117.00 (d, C-8), 152.44 (s, C-9), 116.42 (s, C-10), 24.01 (t, C-1'), 120.03 (d, C-2'), 139.21 (s, C-3'), 25.83 (q, C-4'), 18.13 (q, C-5'). EIMS (70 eV), m/z: 230 $(C_{14}H_{14}O_3)^+$ $(M)^+$ (46), 175 (48), 121 (100), 109 (50), 69 (100).

E-3-(3,7-dimethyl-2,6-octadienyl)-2H-1-benzopyran-2-one (3-geranyl-4-hydroxycoumarin (4)) . White powder, m.p. 71°C, UV (EtOH), nm: 320, 308, 280, 253; IR (KBr) ν cm^{-1}: 3200, 16665, 1630, 1490, 1450, 1385, 1250, 1170, 1150, 745; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, J=7.9 Hz, 1H), 7.50 (t, J=7.8, 1H), *ca* 7.28 (2H, overlapped signals), 5.45 (t, J=7.3, 1H), 5.06 (t, J=7.1, 1H), 3.44 (d, J=7.3 Hz, 2H), 1.83 (s, 3H), 1.71 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 160.91 (s, C-2), 103.29 (s, C-4), 163.89 (s, C-4), 122.62 (d, C-5), 123.28 (d, C-6), 131.36 (d, C-7), 116.15 (d, C-8), 152.10 (s, C-9), 115.93 (s, C-10), 23.50 (t, C-1'), 119.94 (d, C-2'), 141.24 (s, C-3'), 39.45 (t, C-4'), 25.86 (t, C-5'), 123.66 (d, C-6'), 132.29 (s, C-7'), 25.52 (q, C-8'), 17.51 (q, C-9'), 16.11

(C-10'). EIMS (70 eV), m/z: 298 $(C_{19}H_{22}O_3)^+$ $(M)^+$(45), 229 (50), 175 (60), 121 (100), 69 (93).

Z-3-(3,7-dimethyl-2,6-octadienyl)-2H-1-benzopyran-2-one(3-neryl-4-hydroxy -coumarin (5)) . White powder, m.p. 93 °C, UV (EtOH), nm: 320, 308, 278, 252; IR (KBr) cm^{-1}: 3250, 1660, 1630, 1490, 1450, 1390, 1225, 1170, 1150, 750; ^1H NMR (200 MHz, $CDCl_3$): δ 7.77 (d, J=7.9 Hz, 1H), 7.49 (t, J=7.6 Hz, 1H), *ca* 7.27 (2H, overlapped signals), 5.41 (t, J=7.3 Hz, 1H), 5.11 (t, J=7.2 Hz, 1H), 3.42 (d, J=7.3 Hz, 2H), 1.81 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 160.85 (s, C-1), 103.03 (s, C-2), 163.40 (s, C-4), 122.58 (d, C-5), 123.04 (d, C-6), 131.54 (d, C-7), 116.30 (d, C-8), 152.32 (s, C-9), 115.78 (s, C-10), 23.53 (t, C-1'), 120.68 (d, C-2'), 142.26 (s, C-3'), 31.95 (t, C-4'), 25.64 (t, C-5'), 123.73 (d, C-6'), 133.13 (s, C-7'), 25.92 (q, C-8'), 23.35 (q, C-9'), 17.62 (q, C-10'); EIMS (70 eV), m/z: 298 $(C_{19}H_{22}O_3)^+$$(M)^+$(52), 229 (62), 175 (95), 121 (100), 69 (88).

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