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CLAISEN REARRANGEMENTS—III[1]
CONVENIENT SYNTHESES OF THE COUMARINS, OSTHENOL, DEMETHYLSUBEROSIN AND COUMURRAYIN[2]

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Abstract—A simple 3-step method for the introduction of a 3,3-dimethylallyl unit *ortho* to a phenolic OH group is described. 7-Hydroxycoumarin, **1**, was converted to its 1,1-dimethylallyl ether, **5**, by reaction with 3-chloro-3-methylbutyne followed by partial hydrogenation. Pyrolysis of **5** gave mainly the C-8 Claisen rearrangement product, osthenol, **10**, and also the C-6 isomer, **14**. In a similar manner, coumurrayin, **13**, was prepared from 5-methoxy-7-hydroxycoumarin in 57% overall yield.

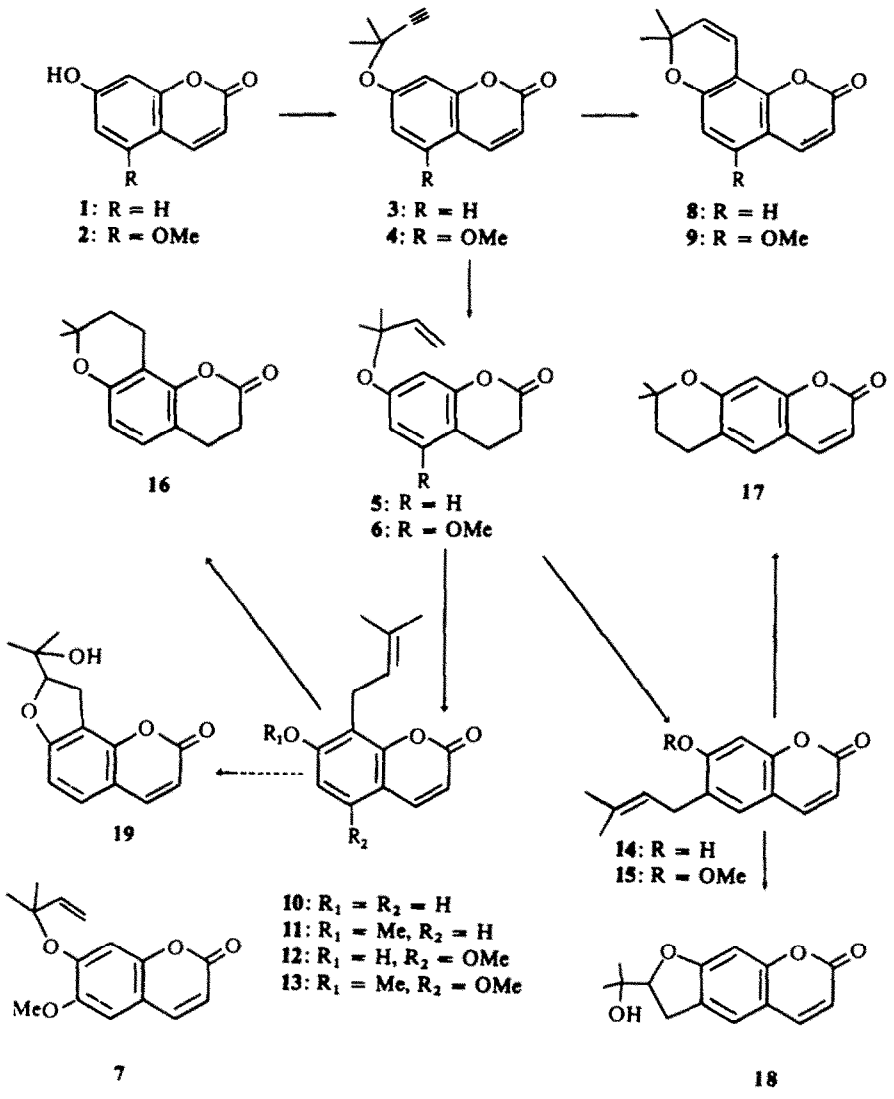
RECENTLY we investigated[1, 3, 4] the Claisen rearrangement of phenol 3,3-dimethylallyl ethers and found the reaction to be suitable for introducing the relatively uncommon 1,1-dimethylallyl unit into a coumarin nucleus. By this means, the natural coumarins, obliquetin,[5] rutacultin[6] and pinnarin[7] were synthesised.[3, 4]

It occurred to us that if the corresponding 1,1-dimethylallyl ethers could be prepared, their pyrolyses might result in the introduction of a 3,3-dimethylallyl unit *ortho* to the phenolic OH group. At the outset of this work, two general methods[8–13] were available for the synthesis of coumarins having this, widely encountered, structural feature. Both methods require C-dimethylallylation of a phenol, either before[8–11] or after[9, 12, 13] formation of the pyrone ring, but both are of very limited synthetic value.

To test our hypothesis in the umbelliferone (**1**) series, the 1,1-dimethylallyl ether (**5**) was required. It was expected that this could be prepared by partial hydrogenation* of the corresponding 1,1-dimethylpropargyl ether (**3**). The latter ether was obtained in 77% yield when **1** was heated with 3-chloro-3-methylbut-1-yne[16] and K_2CO_3 in acetone, the reaction being catalysed by small amounts of KI and water. The m.p. 136–140°, of **3** is fairly broad and the NMR spectrum, recorded after allowing **3** to melt on a Kofler block, was found to contain additional signals as a pair of doublets (J = 10 Hz) at τ 4·32 and 3·30. Hlubucek *et al.*[17] have shown that **3**, on heating in diethylaniline, rearranges smoothly to the chromene, **8**. It would appear that rearrangement also occurs to a small extent at the m.p.

Hydrogenation of **3** over Pd-$BaSO_4$ poisoned with thiourea gave variable results. However, when quinoline-sulphur was employed as poison,[18] partial hydrogenation consistently afforded the 1,1-dimethylallyl ether, **5**, in high yield. Pyrolysis of **5** at 130° for 1 hr gave two isomeric phenols, having similar mobilities (chromatoplate),

* This route to 1,1-dimethylallyl ethers was suggested to us by Professor R. A. Raphael for the synthesis[14] of **7**, a coumarin erroneously thought to be of natural origin.[15]



which could however be separated by careful TLC. Each phenol contained resonances in its NMR spectrum characteristic of a C-3, 3-dimethylallyl grouping,[15] an unsubstituted coumarin pyrone ring and a phenolic OH. The major product (74%) possesses two *ortho* aromatic protons (τ 3·12 and 2·78, J = 9 Hz) and the minor (14%), two *para* aromatic protons (τ 2·93 and 2·81). From this evidence the former compound was deduced to be osthenol[19] (**10**), the result of Claisen rearrangement to C-8, and the latter, 7-demethylsuberosin[20] (**14**). The structure of osthenol was confirmed by the synthesis of its methyl ether, osthol[8] (**11**) and the cyclic ether, dihydroseselin[9] (**16**). Correspondingly **14** was converted to suberosin[9] (**15**) and dihydroxanthyletin[9] (**17**).

Application of the above synthetic sequenced to 7-hydroxy-5-methoxycoumarin (**2**) afforded, via **4**, **6** and **12**, coumurrayin[21] (**13**) in 57% yield, far superior to either of

the C-alkylation methods used previously.[10–12] In the 5-methoxycoumarin series, pyrolysis of the 1,1-dimethylallyl ether, **6**, at 160° resulted exclusively in rearrangement to C-8. A surprising observation was made during attempts to purify **6** by preparative TLC when rearrangement was found to occur on the chromatoplate, again generating only **12**. A similar synthetic route to the ether (**5**) was reported[22] after the completion of our work. It was found however that when the pyrolysis of **5** was carried out in diethylaniline, only osthenol was isolated.

The current interest in routes to *ortho* isoprenylphenols has resulted[23–24] in the development of several new synthetic methods. The advantage of our 3-step sequence lies in the relatively mild conditions required for insertion of the isoprenyl group and in the favourable overall yield. Moreover, this simple route to *ortho* isoprenylphenols can in principle be extended to provide syntheses of more complex natural coumarins. For example, in an analogous manner to the conversion[20] of **14** to (±) marmesin (**18**), osthenol (**10**) should on oxidation give (±) columbianetin (**19**).[25, 26] This reaction and the scope of further oxidative manipulation are currently being investigated.

EXPERIMENTAL

M.ps were determined with a Kofler hot stage apparatus. IR spectra of $CHCl_3$ solns were recorded on a Perkin–Elmer 257 spectrophotometer. NMR spectra of solns in $CDCl_3$ with TMS as internal standard were recorded by Mrs. S. Hamilton and Mr. J. Gall with a Varian T-60 spectrometer. Coupling constants quoted are observed values. Mass spectra were recorded by Mr. A. Ritchie with an AEI-GEC MS12 mass spectrometer. Microanalyses were performed by Mr. J. M. L. Cameron and his staff. Kieselgel G (Merck) was used for preparative TLC. Light petroleum refers to the fraction of b.p. 60–80°.

7-O-(1,1-*Dimethylpropargyl)umbelliferone* **3**. K_2CO_3 (0·85 g) and KI (0·15 g) were added to a soln of umbelliferone (0·80 g) in aqueous acetone (2% v/v; 100 ml) and the mixture stirred at room temp for 1 hr. 3-Methyl-3-chlorobut-1-yne[16] (1 g) was then added and the mixture refluxed gently for 6 hr. On cooling, more K_2CO_3 (0·85 g) and 3-methyl-3-chlorobut-1-yne (1 g) were added and refluxing continued for a further 24 hr. Work up, by evaporation and extraction into EtOAc, gave, on evaporation of solvent, a yellow solid. Crystallisation from EtOAc-light petroleum afforded 7-O-(1,1-*dimethylpropargyl)umbelliferone* as pale yellow needles, m.p. 136–140° (0·71 g; 63%) (Found: C, 73·7; H, 5·45. $C_{14}H_{12}O_3$ requires: C, 73·65; H, 5·3%); ν_{max} 3300, 1730 and 1616 cm^{-1}; mass spectral peaks at *m/e* 228 (M^+), 213, 162 and 134 (relative abundance 10, 18, 100 and 81%); NMR signals at τ 8·27 (6H, s), 7·32 (1H, s), 3·74 (1H, d, J = 9·5 Hz), 2·98 (1H, dd, J = 8·5 and 2 Hz), 2·70 (1H, bs), 2·65 (1H, d, J = 8·5 Hz) and 2·36 (1H, d, J = 9·5 Hz). The mother liquors of crystallisation, after separation by TLC (2 × $CHCl_3$) and crystallisation from EtOAc-light petroleum gave more **3** (0·16 g; 14%).

Catalytic hydrogenation. 5% Pd-$BaSO_4$ (Englehard Industries) (30 mg) was added to a soln of **3** (100 mg) and the quinoline-sulphur poison[18] (0·3 ml) in EtOAc (40 ml). After hydrogenation at room temp for 1 hr, the uptake of hydrogen was ~1 mole. After freeing from catalyst and solvent, separation of the residue on TLC [2 × ether-light petroleum (2:3)] gave (i) 7-O-(1,1-*dimethylallyl)umbelliferone* (**5**) as colourless needles m.p. 75–78° (from ether-light petroleum) (96 mg; 96%) (Found: C, 73·3; H, 6·35. $C_{14}H_{14}O_3$ requires: C, 73·0; H, 6·15%); mass spectral peaks at *m/e* 230 (M^+), 163, 162, 134, 69 and 41 (relative abundance 4, 12, 100, 60, 54 and 51%); NMR signals at τ 8·45 (6H, s), 4·77 (1H, d, J = 18 Hz), 4·77 (1H, d, J = 10 Hz), 3·85 (1H, dd, J = 18 and 10 Hz), 3·77 (1H, d, J = 9·5 Hz), 3·15 (1H, dd, J = 10 and 2 Hz), 3·07 (1H, bs), 2·72 (1H, d, J = 10 Hz) and 2·40 (1H, d, J = 9·5 Hz); and (ii) **1** (~1 mg).

Pyrolysis. The ether **5** (69 mg) was heated in a sublimation block at 130° for 1½ hr. The resultant oil was separated by TLC [3 × ether-light petroleum (3:7) followed by 2 × $CHCl_3$-light petroleum (4:1)] into (i) osthenol (**10**), which crystallised from EtOAc-light petroleum as colourless needles, m.p. 129–131° (lit.[19] 124–125°) (51 mg; 74%) (Found: C, 73·1; H, 6·15. Calc. for $C_{14}H_{14}O_3$: C, 73·0; H, 6·15%); mass spectral peaks at *m/e* 230 (M^+), 215, 187, 175 and 146 (relative abundance 68, 25, 27, 100 and 24%); NMR signals at τ 8·27 (3H, bs), 8·14 (3H, bs), 6·40 (2H, bd, J = 7 Hz), 4·72 (1H, bt, J = 7 Hz), 3·75 (1H, d, J = 9·5 Hz), 3·12 (1H, d, J = 9 Hz), 2·78 (1H, d, J = 9 Hz), 2·67 (1H, bs, disappears on addition of D_2O) and 2·35 (1H,

d, $J = 9{\cdot}5$ Hz); (ii) 7-demethylsuberosin **14** which crystallised from C_6H_6 as pale yellow plates, m.p. 133–134° (lit.[20] 133·5–134°) (10 mg, 14%); mass spectral peaks at *m/e* 230 (M^+), 215, 176, 175 and 147 (relative abundance 42, 16, 11, 100 and 41%); NMR signals at τ 8·27 (3H, bs), 8·22 (3H, bs), 6·63 (2H, bd, $J = 7$ Hz), 4·67 (1H, bt, $J = 7$ Hz), 3·78 (1H, d, $J = 9{\cdot}5$ Hz), 2·93 (1H, s), 2·81 (1H, s), 2·33 (1H, d, $J = 9{\cdot}5$ Hz) and 1·96 (1H, bs, disappears on addition of D_2O); identical, mixed m.p., TLC, IR and NMR with an authentic sample; and (iii) **1** (2 mg, 5%).

Pyrolyses of the ether **5** were carried out satisfactorily on scales up to 300 mg. Generally higher temps ($\sim 160°$) were employed, with results similar to those obtained above, and the bulk of the osthenol removed by fractional crystallisation prior to TLC separation.

Derivatives of osthenol

1. *Osthol* **11**. A mixture of **10** (48 mg), K_2CO_3 (50 mg) and MeI (0·1 ml) in acetone (5 ml) was refluxed for 4 hr. Work up gave **11** which crystallised from light petroleum as colourless needles, m.p. 82–84° (lit.[8] 83–84°) (44 mg, 86%); mass spectral peaks at *m/e* 244 (M^+), 229, 213, 201, 189 and 131 (relative abundance 100, 85, 42, 65, 53 and 44%); NMR signals at τ 8·32 (3H, bs), 8·15 (3H, bs), 6·47 (2H, bd, $J = 7$ Hz), 6·07 (3H, s), 4·73 (1H, bt, $J = 7$ Hz), 3·79 (1H, d, $J = 9{\cdot}5$ Hz), 3·18 (1H, d, $J = 9$ Hz), 2·72 (1H, d, $J = 9$ Hz) and 2·41 (1H, d, $J = 9{\cdot}5$ Hz).

2. *Dihydroseselin* **16**. A soln of **10** (25 mg) in MeOH (1 ml) and conc HCl (5 drops) was refluxed for 2 hr and then diluted with iced water (25 ml). The EtOAc extract of the soln was washed with K_2CO_3 aq, brine to neutrality, dried and evaporated. Crystallisation of the residue from ether-light petroleum gave **16** as pale yellow needles (21 mg, 82%), m.p. 101–103° (lit.[9] 103–104°); mass spectral peaks at *m/e* 230 (M^+), 215, 201, 187, 176, 175, 174 and 146 (relative abundance 68, 24, 13, 21, 12, 100, 21 and 21%); NMR signals at τ 8·62 (6H, bs), 8·14 (2H, t, $J = 7$ Hz), 7·08 (2H, t, $J = 7$ Hz), 3·82 (1H, d, $J = 9{\cdot}5$ Hz), 3·30 (1H, d, $J = 8{\cdot}5$ Hz), 2·80 (1H, d, $J = 8{\cdot}5$ Hz) and 2·41 (1H, d, $J = 9{\cdot}5$ Hz).

Derivatives of 7-demethylsuberosin

1. *Suberosin* **15**. Using the same procedure as for the conversion of **10** to **11**, **14** (24 mg) was converted to **15** giving an oil which was distilled at 100°/0·05 mm. On standing, the distillate solidified to give **15** as colourless plates (23 mg, 90%), m.p. 85–87° (lit.[9] 86–87°); mass spectral peaks at *m/e* 245, 244 (M^+), 230 and 229 (relative abundance 12, 76, 18 and 100%); NMR signals at τ 8·28 (3H, bs), 8·23 (3H, bs), 6·70 (2H, bd, $J = 7$ Hz), 6·09 (3H, s), 4·72 (1H, bt, $J = 7$ Hz), 3·80 (1H, d, $J = 9{\cdot}5$ Hz), 3·25 (1H, s), 2·85 (1H, s) and 2·42 (1H, d, $J = 9{\cdot}5$ Hz).

2. *Dihydroxanthyletin* **17**. Using the same procedure as for the conversion of **10** to **16**, **14** (20 mg) was converted to **17**, which crystallised from EtOH as colourless plates (18 mg, 88%), m.p. 123·5–125° (lit.[9] 124–125°); mass spectral peaks at *m/e* 231, 230 (M^+), 215, 176, 175 and 147 (relative abundance 27, 65, 40, 46, 100 and 56%); NMR signals at τ 8·63 (6H, bs), 8·16 (2H, t, $J = 7$ Hz), 7·17 (2H, t, $J = 7$ Hz), 3·85 (1H, d, $J = 9{\cdot}5$ Hz), 3·31 (1H, s), 2·87 (1H, s) and 2·45 (1H, d, $J = 9{\cdot}5$ Hz).

7-O-(1,1-*Dimethylpropargyl*)-5-*methoxycoumarin* **4**. A soln of **2** (300 mg), 3-methyl-3-chlorobut-1-yne (600 mg), K_2CO_3 (600 mg) and KI (60 mg) in aqueous acetone (2% v/v, 60 ml) was refluxed for 24 hr. More 1,1-dimethylpropargyl chloride (600 mg) was then added and refluxing continued for another 24 hr. Work-up, as for **3**, gave a solid, which was separated by TLC (2 × $CHCl_3$) into (i) the acetylenic *ether* **4**, which crystallised from ether-light petroleum as pale yellow needles (292 mg, 74%), m.p. 140–144° (Found: C, 69·85; H, 5·55. $C_{15}H_{14}O_4$ requires: C, 69·75; H, 5·45%); NMR signals at τ 8·27 (6H, s), 7·33 (1H, s), 6·12 (3H, s), 3·85 (1H, d, $J = 9{\cdot}5$ Hz), 3·53 (1H, d, $J = 2$ Hz), 3·06 (1H, d, $J = 2$ Hz) and 2·05 (1H, d, $J = 9{\cdot}5$ Hz); and (ii) 5-*methoxyseselin* (**9**), which was sublimed at 140°/0·005 mm as pale yellow needles (39 mg, 10%), m.p. 156–158° (Found: C, 69·85; H, 5·5. $C_{15}H_{14}O_4$ requires: C, 69·75; H, 5·45%); NMR signals at τ 8·54 (6H, s), 6·12 (3H, s), 4·43 (1H, d, $J = 10$ Hz), 3·88 (1H, d, $J = 9{\cdot}5$ Hz), 3·77 (1H, s), 3·20 (1H, d, $J = 10$ Hz) and 2·07 (1H, d, $J = 9{\cdot}5$ Hz).

Hydrogenation of **4** *and subsequent pyrolysis*. **4** (50 mg) in EtOAc (20 ml) was hydrogenated over poisoned 5% Pd-$BaSO_4$ (16 mg) for 1 hr. Freeing from catalyst and solvent gave **6** as an oil (49 mg); NMR signals at τ 8·51 (6H, s), 6·17 (3H, s), 4·79 (1H, bd, $J = 10$ Hz), 4·78 (1H, bd, $J = 18$ Hz), 3·90 (1H, d, $J = 9{\cdot}5$ Hz), 3·86 (1H, dd, $J = 18$ and 10 Hz), 3·67 (1H, d, $J = 2{\cdot}5$ Hz), 3·43 (1H, d, $J = 2{\cdot}5$ Hz) and 2·10 (1H, d, $J = 9{\cdot}5$ Hz). This oil was heated in a sublimation block at 160° for 1 hr. The resulting solid was crystallised from EtOAc-light petroleum giving **12** as pale yellow needles (44 mg, 88%), m.p. 197–199° (lit.[12] 196–197°) (Found: C, 68·9; H, 6·15. Calc. for $C_{15}H_{16}O_4$: C, 69·2; H, 6·2%); NMR signals (deuteropyridine) at τ 8·33 (3H, bs), 8·04 (3H, bs), 6·31 (3H, s), 6·21 (2H, bd, $J = 6{\cdot}5$ Hz), 4·35 (1H, bt, $J = 6{\cdot}5$ Hz), 3·80 (1H, d, $J = 9{\cdot}5$ Hz), 3·42 (1H, s) and 2·01 (1H, d, $J = 9{\cdot}5$ Hz).

Coumurrayin **13**. **12** (32 mg) was converted to its methyl ether using K_2CO_3 (50 mg), MeI (0·5 ml) and acetone (10 ml). After refluxing for 5 hr, work-up yielded **13**, which crystallised from CCl_4 as pale yellow plates (30 mg, 89%), m.p. 155–157° (lit.[21] 157°) (Found: C, 70·1; H, 6·55. Calc. for $C_{16}H_{18}O_4$: C, 70·05; H, 6·6%); mass spectral peaks at *m/e* 274 (M^+), 259, 231, 219 and 206 (relative abundance 66, 100, 25, 20 and 21%); NMR signals at τ 8·34 (3H, bs), 8·18 (3H, bs), 6·58 (2H, bd, J = 6·5 Hz), 6·08 (3H, s), 4·82 (1H, bt, J = 6·5 Hz), 3·80 (1H, d, J = 9·5 Hz), 3·69 (1H, s) and 2·08 (1H, d, J = 9·5 Hz).

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