Synthesis of Coumarins by Flash Vacuum Pyrolysis of 3-(2-Hydroxyaryl)propenoic Esters†,[1]

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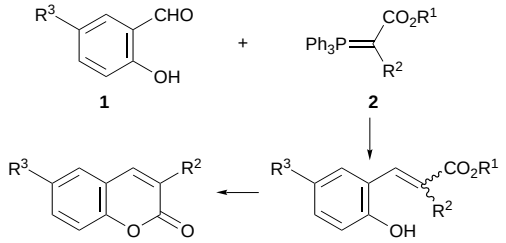
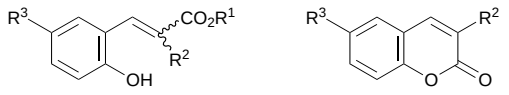
Flash vacuum pyrolysis of 3-(2-hydroxyaryl)propenoic esters gives coumarins (and other fused α-pyrones) in high yield.

The preparation of coumarins and other fused α-pyrones by tandem Wittig olefination–cyclisation processes from 3-(2-hydroxyaryl)propenoic esters has been a popular synthetic route to such ring systems since it was first exploited by Mali and Yadav in 1977 (Scheme 1).[2,3] Cyclisation may take place directly under the olefination conditions, particularly when substantial amounts of *Z* alkenes are obtained, but there are often problems with the cyclisation of *E* alkenes which are normally the major products from the Wittig reactions of stabilised ylides. These problems have been addressed either by heating the substrate neat,[2,4] or *in situ* in an inert solvent,[2,3] or in diethylaniline,[5] or alternatively by photochemical isomerisation,[6,7] but all of these methods suffer from disadvantages of variable yields and conditions, or inconvenient work-up, or both. We now show that the cyclisation takes place consistently in high yield when the isolated 3-(2-hydroxyaryl)propenoic esters are subjected to flash vacuum pyrolysis (FVP).



Scheme 1

The Wittig reactions of the appropriate aldehyde **1** with the phosphoranes **2** (R^1 = Me, R^2 = H and R^1 = Et, R^2 = Me) take place under very mild conditions (room temperature, dry dichloromethane, 2 h), to give the alkenes **3–8** in 75–88% yields after dry flash chromatography on silica to remove triphenylphosphine oxide. From the magnitude of the vicinal coupling constants in their ^{1}H NMR spectra, the product in most cases is predominantly the *E* isomer contaminated with only a trace of the *Z* isomer, and such materials have been found to be difficult to cyclise to the corresponding coumarin by traditional methods.



3 R^1 = Me, R^2 = H, R^3 = H
4 R^1 = Me, R^2 = H, R^3 = Cl
5 R^1 = Me, R^2 = H, R^3 = NO_2
6 R^1 = Et, R^2 = Me, R^3 = H
7 R^1 = Et, R^2 = Me, R^3 = Cl

9 R^2 = H, R^3 = H
10 R^2 = H, R^3 = Cl
11 R^2 = H, R^3 = NO_2
12 R^2 = Me, R^3 = H
13 R^2 = Me, R^3 = Cl

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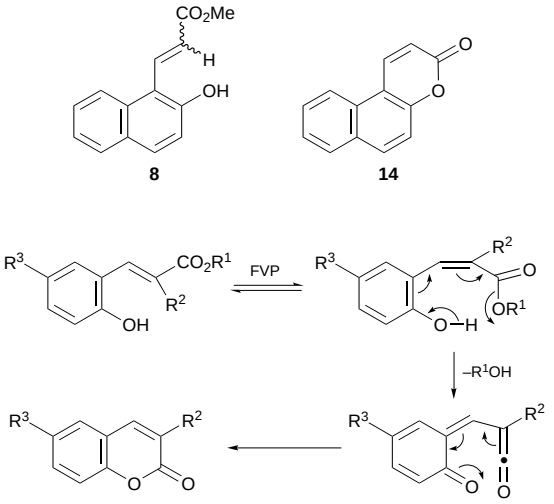
The alkenes **3–8** were therefore subjected to FVP at a furnace temperature of 750 °C. Under these conditions, *E* and *Z* alkenes are known[8] to equilibrate, and the latter are able to eliminate the appropriate alcohol in a concerted process. The resulting ketene intermediates then undergo electrocyclisation to the corresponding coumarin **9–13** or fused pyrone **14** which condenses at the exit point of the furnace (Scheme 2). From a practical stand-point, there are a number of advantages of this cyclisation method. First, the yields are consistently high (75–96%), and the conditions are sufficiently mild to be compatible with a range of substituents on both the alkene and the benzene ring. The work-up is simple, consisting only of scraping the product from the trap or dissolving it out in an appropriate solvent. No significant by-products are obtained. Finally, the ester precursors are conveniently volatile and suffer little or no decomposition in the inlet of the FVP apparatus, so the method is capable of being scaled up to multi-gram quantities.



Scheme 2

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz respectively for solutions in [$^2H_6$]DMSO unless otherwise stated. Coupling constants (*J*) are quoted in Hz.

Methyl 3-Arylpropenoates.[2]—The appropriate aldehyde **1** (4 mmol) was dissolved in dry dichloromethane (50 ml), and methyl (triphenylphosphoranylidene)acetate **2** (R^2 = H) (1.337 g, 4 mmol) was added with continuous stirring. After 2 h the solvent was removed *in vacuo* and the crude material was subjected to dry flash chromatography on silica to remove the triphenylphosphine oxide. The material isolated was pure enough for further use.

The following compounds were made using this procedure: Salicylaldehyde gave *methyl 3-(2-hydroxyphenyl)propenoate* **3** (0.62 g, 88%), mp 136–137 °C (from ethanol); (Found: C, 67.4; H, 5.6. $C_{10}H_{10}O_3$ requires C, 67.35; H, 5.65%); δ_H 7.87 (1 H, d, ^3J 16.0), 7.58 (1 H, m), 7.23 (1 H, m), 6.91 (1 H, m), 6.86 (1 H, m), 6.60 (1 H, d, ^3J 16.0) and 3.70 (3 H, s); δ_C 167.09 (q), 140.40, 131.88 (q), 131.63, 128.72, 120.56 (q), 119.05, 116.71, 116.05 and 51.20; *m/z* 178 (M^+, 31), 146 (100), 118 (82), 103 (25), 91 (34), 65 (10) and 32 (14). 2-Hydroxy-5-chlorobenzaldehyde gave *methyl 3-(2-hydroxy-5-chlorophenyl)propenoate* **4** (0.68 g, 80%), mp 145–147 °C (from

ethanol); (Found: C, 56.1; H, 3.3. $C_{10}H_6ClO_3$ requires C, 56.4; H, 3.3%); δ_H 7.79 (1 H, d, ^3J 16.0), 7.67 (1 H, d, ^4J 2.5), 7.24 (1 H, dd, ^3J 8.7 and ^4J 2.5), 6.91 (1 H, d, ^3J 8.7), 6.67 (1 H, d, ^3J 16.0) and 3.48 (3 H, s); δ_C 116.82 (q), 155.44, 138.50 (q), 130.96, 127.78, 123.02 (q), 122.27 (q), 118.28, 117.69 and 51.29; *m/z* 214 (M^+, 11%), 212 (M^+, 29), 182 (37), 180 (100), 154 (33), 152 (94), 127 (11), 125 (36), 99 (12), 89 (44) and 63 (30). 2-Hydroxy-5-nitrobenzaldehyde gave *methyl* 3-(2-*hydroxy*-5-*nitrophenyl*)*propenoate* **5** (0.67 g, 75%), mp 198–200 °C (from ethyl acetate); (Found: C, 53.7; H, 4.0; N, 6.0. $C_{10}H_9NO_5$ requires C, 53.85; H, 4.1; N, 6.35%); δ_H 8.48 (1 H, d, ^4J 2.8), 8.17 (1 H, dd, ^3J 9.1 and ^4J 2.8), 7.80 (1 H, d, ^3J 16.3), 7.07 (1 H, d, ^3J 9.0), 6.80 (1 H, d, ^3J 16.3) and 3.70 (3 H, s); δ_C 166.59 (q), 162.35 (q), 139.78 (q), 137.91, 126.80, 124.94, 121.16 (q), 119.91, 116.49 and 51.45; *m/z* 223 (M^+, 26%), 191 (100), 117 (22), 89 (24) and 63 (13). 2-Hydroxy-1-naphthaldehyde gave methyl 3-(2-*hydroxy*-1-*naphthyl*)*propenoate* **8** (0.77 g, 85%), mp 145–148 °C (from ethyl acetate); (Found: C, 73.3; H, 5.3. $C_{14}H_{12}O_3$ requires C, 73.7; H, 5.35%); δ_H 8.29 (1 H, d, ^3J 16.0), 8.16–7.23 (6 H, m), 6.88 (1 H, d, ^3J 16.0) and 3.18 (3 H, s); δ_C (one quaternary missing), 160.21 (q), 153.47 (q), 140.58, 133.38, 130.04 (q), 128.95, 128.51, 126.26, 122.42, 116.96, 115.49, 113.02 (q) and 48.70; *m/z* 228 (M^+, 50%), 196 (94), 168 (100), 141 (31), 140 (17), 139 (37) and 115 (26).

The following compounds were made using ethyl 2-(triphenylphosphoranylidene)propionate (**2**, R^2 = Me) in dichloromethane under reflux conditions for 1 h. The same molar amounts of reagents (4 mmol) and similar work-up were used as described in the general method given above. Salicylaldehyde gave *ethyl* 2-*methyl*-3-(2-*hydroxyphenyl*)*propenoate* **6** (0.67 g, 82%), mp 58–61 °C (from hexane); (Found: C, 69.4; H, 6.8. $C_{12}H_{14}O_3$ requires C, 69.8; H, 6.8%); δ_H 7.74 (1 H, s), 7.30–6.79 (4 H, m), 4.18 (2 H, q), 1.98 (3 H, s) and 1.26 (3 H, t); δ_C 167.68 (q), 134.36, 129.87, 129.76, 126.62 (q), 122.15 (q), 118.59, 115.76 (q), 115.32, 60.20, 14.07 and 13.92; *m/z* 206 (M^+, 15%), 160 (100), 132 (40), 131 (31) and 77 (10). 2-Hydroxy-5-chlorobenzaldehyde gave *ethyl* 2-*methyl*-3-(2-*hydroxy*-5-*chlorophenyl*)*propenoate* **7** (0.85 g, 88%), mp 93–95 °C (from *n*-hexane); (Found: C, 59.8; H, 5.4. $C_{12}H_{13}ClO_3$ requires C, 59.9; H, 5.4%); δ_H 7.63 (1 H, d, ^4J 2.5), 7.26 (1 H, s), 7.21 (1 H, dd, ^3J 8.5 and ^4J 2.5), 6.90 (1 H, d, ^3J 8.5), 4.18 (1 H, q), 1.96 (3 H, s) and 1.25 (3 H, t); δ_C 167.37 (q), 154.66 (q), 138.18 (q), 132.88, 129.40, 128.87, 128.12 (q), 123.85 (q), 116.94, 60.41, 14.07 and 13.87; *m/z* 242 (M^+, 5%), 240 (M^+, 12), 196 (22), 195 (30), 194 (100), 167 (17), 166 (38), 165 (31), 131 (19), 103 (22) and 77 (20).

Preparation of Coumarins by Flash Vacuum Pyrolysis.—The appropriate propenoate was distilled at 10^{-2}–10^{-3} Torr into an empty silica pyrolysis tube (35 × 2.5 cm) which was maintained at 750 °C by an electrical furnace. The products were collected at the exit point of the furnace in a U-tube cooled with liquid nitrogen, and could be removed by scraping with a spatula or by dissolving them in a solvent. Pyrolysis conditions are given as follows: precursor, quantity of precursor, inlet temperature, furnace temperature, mean pressure, time of the pyrolysis, and product. Methyl 3-(2-hydroxyphenyl)propenoate [(0.063 g, 0.353 mmol), 100 °C, 750 °C, 5×10^{-3} Torr, 5 min] gave coumarin **9** (0.051 g, 87%), mp 68–69 °C (from *n*-hexane) (lit.,[9] 68 °C); δ_H 8.01 (1 H, d, ^3J 9.5), 7.60 (2 H, m), 7.34 (2 H, m) and 6.47 (1 H, d, ^3J 9.5); δ_C 159.90 (q), 153.39 (q), 144.16, 131.88, 128.35, 124.42, 118.63 (q), 116.18 and 116.10; *m/z* 146 (M^+, 91%), 118 (100), 90 (29), 89 (17) and 63 (21). Methyl 3-(2-hydroxy-5-chlorophenyl)propenoate [(0.060 g, 0.28 mmol), 100 °C, 750 °C, 5×10^{-3} Torr, 5 min] gave 6-chlorocoumarin **10** (0.048 g, 94%), mp 160–162 °C (from ethanol) (lit.,[10] 161–162 °C); δ_H 8.00 (1 H, d, ^3J 9.6), 7.84 (1 H, d, ^4J 2.5), 7.63 (1 H, dd, ^3J 8.9 and ^4J 2.5), 7.42 (1 H, d, ^3J 8.9) and 6.57 (1 H, d, ^3J 9.6); δ_C 159.39 (q), 152.07 (q), 142.98, 131.42, 128.14 (q), 127.47, 120.03 (q), 118.19 and 117.36; *m/z* 182 (M^+, 34%), 180 (M^+, 100), 154 (20), 152 (48), 89 (46) and 63 (35). Methyl 3-(2-hydroxy-5-nitrophenyl)propenoate [(0.065 g, 0.29 mmol), 140 °C, 750 °C, 5×10^{-3} Torr, 5 min] gave 6-nitrocoumarin **11** (0.042 g, 75%), mp 183–184 °C (from toluene) (lit.,[11] 181–182 °C); δ_H 8.67 (1 H, d, ^4J 2.7), 8.35 (1 H, dd, ^3J 9.0 and ^4J 2.7), 8.19 (1 H, d, ^3J 9.7), 7.56 (1 H, d, ^3J 9.0) and 6.65 (1 H, d, ^3J 9.7); δ_C 158.84 (q), 157.14 (q), 143.41 (q), 143.22 (q), 126.44, 124.27, 119.00 (q), 118.00 and 117.75; *m/z* 191 (M^+, 100%), 117 (18), 89 (23) and 63 (20). Ethyl 2-methyl-3-(2-hydroxyphenyl)propenoate [(0.065 g, 0.31 mmol), 100 °C, 750 °C, 5×10^{-3} Torr, 5 min] gave 3-methylcoumarin **12** (0.041 g, 82%), mp 90–92 °C (from ethanol) (lit.,[12] 69–70 °C); δ_H 7.86 (1 H, s), 7.63–7.27 (4 H, m) and 2.09 (3 H, s); δ_C 159.00 (q), 152.56 (q), 139.47, 130.59, 127.41, 124.82 (q), 124.33, 119.24 (q), 115.82 and 16.60; *m/z* 160 (M^+, 79%), 132 (68), 131 (100), 103 (15) and 77 (29). Ethyl 2-methyl-3-(2-hydroxy-5-chlorophenyl)propenoate [(0.064 g, 0.27 mmol), 100 °C, 750 °C, 5×10^{-3} Torr, 5 min] gave 3-methyl-6-chlorocoumarin **13** (0.049 g, 96%), mp 158–160 °C (from ethanol) (lit.,[12] 158–159 °C); δ_H 7.79 (1 H, s), 7.70 (1 H, d, ^4J 2.4), 7.54 (1 H, dd, ^3J 8.8 and ^4J 2.4), 7.38 (1 H, d, ^3J 8.8) and 2.08 (3 H, s); δ_C 160.68 (q), 151.15 (q), 138.17, 130.13, 128.04 (q), 126.46, 126.20 (q), 120.62 (q), 117.79 and 16.70; *m/z* 196 (M^+, 31%), 194 (M^+, 100), 168 (21), 167 (25), 166 (41), 165 (77), 131 (20), 103 (20), 77 (17) and 51 (32). Methyl 3-(2-hydroxy-1-naphthyl)propenoate [(0.070 g, 0.30 mmol), 140 °C, 750 °C, 5×10^{-3} Torr, 5 min] gave 5,6-benzocoumarin **14** (0.045 g, 75%), mp 118–120 °C (from ethanol) (lit.,[13] 117–118 °C); δ_H 8.26 (1 H, d, ^3J 9.8), 8.05 (1 H, d, ^3J 8.3), 7.85–7.45 (4 H, m), 7.28 (1 H, d, ^3J 8.3) and 6.64 (1 H, d, ^3J 9.8); δ_C (one quaternary missing) 160.76 (q), 153.49 (q), 138.85, 132.86, 129.96 (q), 128.75, 128.47, 125.87, 121.11, 116.66, 115.23 and 112.67 (q); *m/z* 196 (M^+, 100%), 168 (70), 139 (75), 115 (23) and 63 (21).

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