Facile Synthesis of 2-Substituted Naphtho[2,1-*b*]pyran-3-ones using Microwaves†

J. Chem. Research (S), 1997, 178–179†

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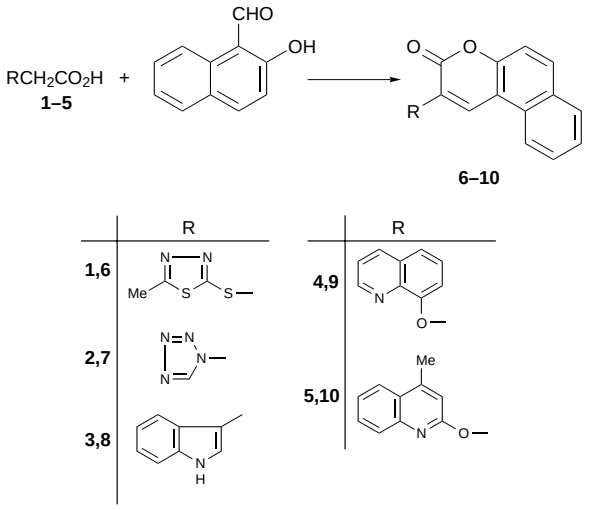
2-Substituted naptho[2,1-*b*]pyran-3-ones have been synthesised by a novel one-pot method which involves cyclocondensation of 2-hydroxy-1-naphthaldehyde with 5-methyl-1,3,4-thiadiazol-2-ylsulfanyl-, 1*H*-1,2,3,4-tetrazol-1-yl-, 1*H*-indol-3-yl-, quinolin-8-yloxy- and 4-methylquinolin-2-yloxy-acetic acids in the presence of DCC–DMSO using microwaves as well as conventional heating.

Nowadays there is considerable interest in the rapid synthesis of a variety of heterocyclic compounds under microwave irradiation in domestic microwave ovens.[1] In continuation of our work on microwave-assisted synthesis[2,3] we report herein a new facile method for the synthesis of 2-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)-, 2-(1*H*-1,2,3,4-tetrazol-1-yl)-, 2-(1*H*-indol-3-yl)-, 2-(quinolin-8-yloxy)- and 2-(4-methylquinolin-2-yloxy)-naphtho[2,1-*b*]pyran-3-ones in the presence of dicyclohexylcarbodimide (DCC) and dimethyl sulfoxide (DMSO) using conventional heating as well as microwave irradiation.

Thiadiazole,[4] tetrazole,[4] indole[5] and quinoline[6] derivatives are well known for their biological importance. Naptho[2,1-*b*]pyran-3-ones have shown antimicrobial,[7] antiinflammatory[8] and anticancer[9] activities. In view of the biological importance of the above-mentioned species and the importance of MORE (microwave-induced organic reaction enhancement) chemistry, we thought it worthwhile to develop a new method for rapid synthesis of the title compounds incorporating thiadiazole, tetrazole, indole and quinoline rings and to screen the products for biological activity.

5-Methyl-1,3,4-thiadiazol-2-ylsulfanyl-, quinolin-8-yloxy- and 4-methylquinolin-2-yloxy-acetic acids were prepared starting from 5-methyl-1,3,4-thiadiazole-2-thiol, 8-hydroxyquinoline and 2-hydroxy-4-methylquinoline respectively by treatment with ethyl bromoacetate[3] followed by hydrolysis of the ester using aqueous KOH to give the corresponding acid (**1, 4, 5**). 1*H*-1,2,3,4-Tetrazol-1-yl- and 1*H*-indol-3-yl-acetic acids (**2, 3**) are commercially available.

2-Hydroxy-1-naphthaldehyde was condensed with an appropriate substituted acetic acid (**1–5**) in the presence of DCC using DMSO as solvent to obtain the corresponding naphtho[2,1-*b*]pyran-3-ones (**6–10**). In the classical approach, cyclocondensation of an aldehyde with acids **1–5** requires 18–20 h, with heating at 100–120 °C. Some impurities also formed in the final hours of the reactions. In contrast, the same reaction required 6–8 min when carried out under microwave irradiation and no such impurities were observed. No appreciable differences in yields of reactions were observed. The title compounds were characterised on the basis of analytical and spectral data (Experimental section). The IR spectra showed absorption at 1710–1730 cm^{-1} due to the lactone of the coumarin ring. In the ^1H NMR spectra, a singlet at δ 8.3–8.5 was assigned to the 1-H proton of the naphtho[2,1-*b*]pyran-3-one ring. The reaction is depicted in Scheme 1.



Scheme 1

Experimental

Mps (uncorrected) were recorded on an Electrothermal apparatus. IR (KBr) were recorded on a Perkin-Elmer spectrometer (model 599) and ^1H NMR spectra were recorded on a Hitachi R-600 FT spectrometer using Me_4Si as internal standard. Mass spectra were recorded on a JEOL-JMS-DX 303 mass spectrometer. The purities of the compounds were checked on silica gel coated Al plates (Merck).

General Procedure for Synthesis of Naphtho[2,1-b]*pyran-3-ones* (**6–10**).—2-Hydroxy-1-naphthaldehyde (5 mmol, 0.86 g), the appropriate substituted acetic acid (6.25 mmol) and DCC (7.8 mmol, 1.6 g) were mixed in DMSO (16 ml) in a 100 ml conical flask covered with a funnel. The reaction mixture was irradiated in a microwave oven at low power setting. TLC was run after every 2 min to check the progress of the reaction. Once reaction was complete (in 8–10 min), the reaction mixture was treated with 15% aqueous acetic acid (100 ml) and stirred for 2 h before extraction with diethyl ether (2 × 50 ml). Dicyclohexylurea which separated at the interface of the two layers was removed by filtration. The organic layer was washed with 5% $NaHCO_3$ (50 ml) and 5% sodium metabisulfite (50 ml) solution to remove unreacted acid and 2-hydroxy-1-naphthaldehyde respectively. Finally, the ether layer was washed with water, dried over Na_2SO_4 (anhydrous) and evaporated to afford a residue which was triturated with benzene–ethyl acetate to afford the corresponding naptho[2,1-*b*]pyran-3-ones.

2-(5-*Methyl*-1,3,4-*thiadiazol*-2-*ylsulfanyl*)*naphtho*[2,1-b]*pyran*-3-*one* (**6**), yield 67%, had mp 213–214 °C; ν_{max}/cm^{-1} 1710 (lactone of coumarin); δ_H ($CDCl_3$ + [$^2H_6$]DMSO) 2.72 (3 H, s, CH_3 ring), 7.15–8.19 (6 H, m, arom.), 8.41 (1H, s, 1-H); *m/z* 326 (M^+) (Found: C, 58.75; H, 3.10; N, 8.55. $C_{16}H_{10}N_2O_2S_2$ requires C, 58.89; H, 3.06; N, 8.58%).

2-(1H-1,2,3,4-*Tetrazol*-1-*yl*)*naptho*[2,1-b]*pyran*-3-*one* (**7**), yield 61%, had mp 234–235 °C; ν_{max}/cm^{-1} 1720 (lactone of coumarin); δ_H ($CDCl_3$ + [$^2H_6$]DMSO) 7.12–8.31 (6 H, m, arom.), 8.53 (1 H, s, 1-H), 9.51 (1 H, s, 5′-H of tetrazole ring); *m/z* 264 (M^+) (Found: C, 63.80; H, 3.08; N, 21.24. $C_{14}H_8N_2O_2$ requires C, 63.63; H, 3.03; N, 21.21%).

2-(1H-*Indol*-3-*yl*)*naphtho*[2,1-b]*pyran*-3-*one* (**8**), yield 58%, had mp 208 °C; ν_{max}/cm^{-1} 1715 (lactone of coumarin); δ_H ($CDCl_3$ + [$^2H_6$]DMSO) 7.18–8.19 (11 H, m, arom.), 8.35 (1 H, br s, NH), 8.50 (1 H, s, 1-H); *m/z* 311 (M^+) (Found: C, 80.82; H, 4.19; N, 4.54. $C_{21}H_{13}NO_2$ requires C, 81.02; H, 4.18; N, 4.50%).

2-(*Quinolin*-8-*yloxy*)*naphtho*[2,1-b]*pyran*-3-*one* (**9**), yield 64%, had mp 179–180 °C; ν_{max}/cm^{-1} 1710 (lactone of coumarin); δ_H ($CDCl_3$ + [$^2H_6$]DMSO) 7.13–8.21 (12 H, m, arom.), 8.32 (1 H, s,

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

1-H); *m*/*z* 339 (M^+) (Found: C, 77.74; H, 3.80; N, 4.11. $C_{22}H_{13}NO_3$ requires C, 77.87; H, 3.83; N, 4.12%).

2-(4-*Methylquinolin*-2-*yloxy*)*naphtho*[2,1-b]*pyran*-3-*one* (**10**), yield 60%, had mp 202–203 °C; ν_{max}/cm^{-1} 1720 (lactone of coumarin); δ_H ($CDCl_3$ + [$^2H_6$]DMSO) 2.40 (3 H, s, CH_3 ring), 7.18–8.06 (11 H, m, arom.), 8.5 (1 H, s, 1-H); *m*/*z* 353 (M^+) (Found: C, 78.02; H, 4.26; N, 3.99. $C_{23}H_{15}NO_3$ requires C, 78.18; H, 4.24; N, 3.96%).

We are grateful to the University Grant Commission for financial support.

Received, 22nd January 1997; Accepted, 17th February 1997
Paper E/7/00516D

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