Synthesis of Angular Pyrrolocoumarins

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Abstract: The new pyrrolocoumarin 3 was synthesized in two steps from 7-amino-4-methylcoumarin by selective o-chloroacetylation at position 8 and subsequent cyclization (the Sugasawa route to indoles). Regioselective inverse electron demand Diels–Alder reaction of 3 with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate or 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine then gave the angular pyridazinepyrrolocoumarins 4 and 5, respectively, in good yield.

Key words: antitumour agents, Diels–Alder reaction, electrophilic aromatic substitution, indoles, polycycles

Natural coumarins and their synthetic analogues constitute an important class of compounds with properties of pharmacological or industrial relevance. In particular, both linear and angular furcoumarins are important as photochemotherapeutic agents that are used to treat a variety of skin diseases, thanks to their ability to intercalate in double-stranded DNA and undergo photoaddition to thymine, thereby blocking cell growth and replication.

In the course of our continuing research on polycondensed coumarin derivatives including furcoumarins fused to pyridazines, we have recently synthesized a benzoganglicin which we found to have significant antitumoral activity. In view of this, and of the known tendency of nitrogenated polycyclic compounds to have greater antitumoral activity than their oxygenated analogues because of their greater capacity to bind to DNA and to replication-related enzymes, we wished to synthesize nitrogenated isosteres of benzoganglicins. As precursors, and as potential antitumour agents in their own right, we needed to prepare angular pyrrolocoumarins without any substituents on the pyrrole ring. Pyrrolocoumarins are nitrogenated isosteres of furcoumarins that in spite of the tendency noted above have been studied much less extensively than the latter. Known linear pyrrolocoumarins without pyrrole-ring substituents have absorption peaks in the near UV-A region (320–400 nm), and some linear and angular benzopyrrolocoumarins have also been obtained, using Fisher methodology.

In this communication we report the direct, selective first synthesis of a 4'-5',6'-unsulfated angular pyrrolocoumarin and its easy conversion to the desired angular pyridazinepyrrolocoumarins by inverse electron demand Diels–Alder reactions with tetrazines.

Pyrrolocoumarin 3 was synthesized in two steps and 54% overall yield from 7-aminocephalocoumarin using the general methodology introduced by Sugasawa for synthesis of indoles. Chloroacetylation of 1 with chloroacetonitrile, 2 M boron trichloride–dimethyl sulfide and aluminum trichloride in dichloromethane afforded compound 2 as the only product in 90% yield (whereas the Fisher method produces a mixture of C-6 and C-8 isomers). The use of gallium trichloride instead of aluminum trichloride, though previously reported to improve the chloroacetylation of indoles, gave similar yields. The occurrence of electrophilic substitution at C-8 but not at C-6 is presumably due to valence-bond stabilization brought about by the aromatic nature of the pyrone ring of the coumarin.

Compound 2 was converted directly into 3 in 60% yield by reduction with sodium borohydride in refluxing dioxane. When the reaction was performed at room temperature, the product was the intermediate α-chloromethylbenzyl alcohol 6 in nearly quantitative yield which was transformed into compound 3 by treatment with sodium hydride at room temperature under basic conditions; however, the yield of this latter step was only 25%, giving an overall yield of less than 25% from 2 (Scheme).

The enamine nature of pyrrolocoumarin 3 dominates its reactivity and facilitates its inverse electron demand Diels–Alder reactions with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate and 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine, which afforded the desired pyridazinepyrrolocoumarins 4 and 5 in 69 and 45% yield, respectively (Scheme). These cycloadditions were carried out with an additional equivalent of tetrazine in order to promote dehydration and prevent the rearrangement of the intermediate following the release of diatomic nitrogen. Under these conditions aromatization was favoured rather than the opening of the pyrrole ring, whereas reaction of furcoumarins with tetrazines opens their furan ring. The crystal structure of 4, determined by X-ray diffraction, confirms the expected structure (Figure). The pyrrolocoumarin skeleton is completely flat and form a dihedral angle of only 2.6(1)° with the pyridazine ring, N(1)H and O(6) form an intramolecular hydrogen bond. The cycloaddition of other heteroaromatic dienes to pyrrolocoumarin 3, and the derivatization of their pyridazine
rings, are now in progress with a view to biological evaluation of a series of these compounds.

Melting points were determined in a Reichert Kofler thermopan or in capillary tubes in a Büchi 510 apparatus, and are uncorrected. IR spectra were recorded in a Perkin-Elmer 1640FT spectrometer. 1H and 13C NMR spectra were recorded in a Bruker AMX spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ/c100 values, J in Hz). Mass spectra were obtained using a Hewlett Packard 5988A spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B microanalyser. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm). Single crystal X-ray crystallographic structure determination was performed at r.t. on a Siemens Smart CCD area-detector diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å). The structure was resolved by direct methods and refined by full-matrix least-squares on F2.

Hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included in ideal positions and refined with isotropic displacement parameters. Atomic scattering factors and anomalous dispersion corrections for all atoms were taken from International Tables for X-ray Crystallography.

7-Amino-8-chloroacetyl-4-methylcoumarin (2)

A 2 M solution of BCl3–Me2S in CH2Cl2 (1 mL) was added under Ar at 0 °C to a solution of 7-amino-4-methylcoumarin (1; 175 mg, 1 mmol) in the same solvent (25 mL). ClCH2CN (0.127 mL, 2 mmol) and AlCl3 (267 mg, 2 mmol) were added, and the mixture was stirred for 30 min at 0 °C and then refluxed for 24 h. 1 M HCl (20 mL) was added, and refluxing was continued until complete dissolution of the precipitate (ca. 1 h). The phases were separated and the organic phase was washed with brine (2×10 mL), dried (Na2SO4) and concentrated under vacuum. The residue was purified by FC using CH2Cl2–EtOAc (9:1) as eluent; yield: 227 mg (90%); mp 236–237 °C.

IR (KBr): 3423, 3313, 1705 cm–1.

1H NMR (DMSO-d6): δ = 7.80 (s, 2 H, NH2), 7.60 (d, 1 H, H-5, J = 9.0 Hz), 6.80 (d, 1 H, H-6, J = 9.0 Hz), 6.10 (s, 1 H, H-3), 5.10 (s, 2 H, CH2), 2.30 (s, 3 H, CH3).


MS: m/z (%) = 252 ([M + 1]+, 100), 218 (33), 176 (12).

Anal. Calcd for C12H10ClNO3 (251.7): C, 57.27; H, 4.00; N, 5.57. Found: C, 57.01; H, 4.32; N, 5.27.

7-Amino-8-(2-chloro-1-hydroxyethyl)-4-methylcoumarin (6)

A mixture of compound 2 (252 mg, 1 mmol), NaBH4 (46 mg, 1.2 mmol) and dioxane–MeOH–H2O (7:2:1, 10 mL) was stirred for 15 min at r.t. A 5% aq solution of NH4Cl (3 mL) was added, and the precipitate was filtered, washed with EtOH and dried over P2O5 under vacuum; yield: 251 mg (99%); mp 236–237 °C.

IR (KBr): 3440, 3351, 3081, 1772 cm–1.

1H NMR (DMSO-d6): δ = 7.80 (s, 2 H, NH2), 7.60 (d, 1 H, H-5, J = 9.0 Hz), 6.80 (d, 1 H, H-6, J = 9.0 Hz), 6.10 (s, 1 H, H-3), 5.10 (s, 2 H, CH2), 2.30 (s, 3 H, CH3).


MS: m/z (%) = 252 ([M + 1]+, 100), 218 (33), 176 (12).

Anal. Calcd for C12H12ClNO4 (251.7): C, 57.27; H, 4.00; N, 5.57. Found: C, 57.01; H, 4.32; N, 5.27.
13C NMR (DMSO-d6): δ = 161.9, 159.3, 149.2, 147.9, 125.7, 119.3, 114.6, 113.1, 107.9, 67.0, 46.7, 18.1.

MS: m/z (%) = 254 ([M + 1]+, 10), 228 (14), 200 (100).

Anal. Calcd for C14H23ClNO4 (253.7): C, 56.82; H, 4.77; N, 5.52. Found: C, 57.09; H, 4.80; N, 5.34.

4-Methylpyrrolo[2,3-b]coumarin (3)

Method A: A mixture of compound 2 (252 mg, 1 mmol), NaBH4 (46 mg, 1.2 mmol) and dioxane–H2O (9:1, 5 mL) was refluxed for 35 h. The solvent was evaporated under vacuum and the precipitate was partitioned between H2O and EtOAc. The organic phase was dried (Na2SO4) and concentrated under vacuum, and the resulting residue was purified by flash chromatography using CH2Cl2–EtOAc (9:1) as eluent; yield: 120 mg (60%).

Method B: NaH (60% in mineral oil, 40.8 mg, 1 mmol) was added to a solution of 1,2-dihydro-3,6-bis(trifluoromethyl)-1H-pyrazine (252 mg, 1 mmol) and dioxane–H2O (9:1, 5 mL) was refluxed for 35 h. The mixture was allowed to cool, the precipitate was filtered, and the filtrate was washed with Et2O; yield: 43.7 mg (45%); mp > 350 °C.

IR (KBr): 3260, 1690, 1622, 1600, 1391, 1368, 1354, 897, 748 cm–1.

1H NMR (DMSO-d6): δ = 11.70 (s, 1 H, NH), 7.40 (m, 3 H, H-5, H-6, H-7), 6.20 (s, 1 H, H-3), 2.50 (s, 3 H, CH3).


MS: m/z (%) = 388 ([M + 1]+, 100), 389 (29), 387 (13), 370 (12), 368 (18).

Anal. Calcd for C14H23ClNO4 (378.24): C, 49.63; H, 1.82; N, 10.85. Found: C, 49.97; H, 1.80; N, 10.59.

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References


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(24) Atomic positions, a full list of bond lengths and angles and other crystallographic data have been deposited as Supplementary Publication No. CCDC 175053. Copies can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).