Regioselective Synthesis of Linear and Angular Pyridazine Furocoumarins

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Dedicated to the memory of Prof. Yolanda Rodríguez-Esteva of the Chemistry Faculty of Habana University

Abstract: With a view to develop a general regioselective route to pyrazidine analogues of benzofurocoumarins, the angular compound 3 and the linear compound 9 were synthesized. In both cases the key step in the construction of the fused pyrazidine ring was a Diels–Alder reaction of the intermediate dihydrofuro-3-ones with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine. The furocoumarinone precursor 2 of compound 3 was synthesized in 60% yield by regioselective Friedel–Crafts rearrangement of 7-(chloroacetyloxy)coumarin (1). The benzofuranone 7, the precursor of compound 9, was obtained in a preparatively useful scale and 34% overall yield from ethyl 2,4-dimethoxycinnamate (4) in 3 steps by regioselective Friedel–Crafts chloroacetylation and further cyclization. The coumarin skeleton of compound 9 was completed in the final step by lactonization with BBBr3.

Key words: Diels–Alder reactions, electrophilic aromatic substitutions, polycycles, heterocycles, regioselectivity

Furocoumarins are of pharmacological interest due to their capacity to link covalently to DNA1 and other biological macromolecules2 upon irradiation with long-wavelength UV light (UVA, 320–400 nm). This photoreactivity is generally greatest for linear furocoumarins (psoralens), among which 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP) and 4,8,5’-trimethylpsoralen are currently in clinical use for PUVA (Psoralen + UVA) therapy of various skin diseases.3,4

Certain adverse side-effects of PUVA therapy have been attributed to the cross-linking of DNA molecules by psoralens through di-adduct formation.3 To avoid this, multifunctional PUVA agents are sought that retain the high photoreactivity and intercalation capacity of psoralens. An interesting class of such agents is constituted by the benzoangelicins and benzopsoralens,5 in which the reactive double bond of the furocoumarin furan ring is deactivated by fusing it to an aromatic ring. Evaluation of this class of compounds has shown that they are not only much less phototoxic than psoralens, but also have increased capacity to intercalate and photoreact with DNA.6,7

In this work we studied the regioselective synthesis of linear and angular pyrazidine analogues of benzofurocoumarins, reasoning that the inclusion of nitrogen atoms in the polycyclic skeleton may improve interaction with DNA.8

We had initially attempted the synthesis of pyrazidinefurocoumarins by inverse electron demand Diels–Alder reactions between furocoumarins and 1,2,4,5-tetrazines, but the reaction was accompanied by the release of diatomic nitrogen and the opening of the furan ring.9 Although the Diels–Alder reactions of 1,2,4,5-tetrazines with many electron-rich dienophiles have been extensively studied,10–13 very few reactions with carbonyl compounds as dienophiles had been reported.14 Since some reactions of dihydrofurocoumarinones are accompanied with the enol form,15 we decided to examine dihydrofuro[2,3-h]coumarin-9-one (2) as dienophile in the Diels–Alder reaction for the fusing of the pyrazidine ring. Gratifyingly, reaction of this substrate with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine did indeed bring about cycloaddition of the diene to the enolic double bond of the furan ring, with concomitant loss of N2 and water, giving the angular pyrazidineangelicin 3 in good yield (Scheme 1).

Scheme 1 Reagents and conditions: a) AlCl3, 120 °C; b) 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine, dioxane, reflux

The Fries rearrangement of 7-(chloroacetoxy)coumarins afford the angular dihydrofuro[2,3-h]coumarin-9-ones in good yield but the linear isomers are only obtained in traces.16 The regioselective electrophilic substitution at C-6 has been accompanied by disruption of the aromaticity of the pyrone ring.17 In this work we use the Friedel–Crafts chloroacetylation of ethyl 2,4-dimethoxycinnamate (4) and further lactonization for the regioselective synthesis of the desired linear isomer.

We therefore attempted simultaneous formation of the furanone and pyranone ring by demethylation and lacton-
ization of compound 5a, which was prepared as a 7:1 mixture with its monodemethylated derivative 5b by a Friedel–Crafts reaction between ethyl 2,4-dimethoxycinnamate (4) and excess chloroacetyl chloride at 0 °C in the presence of AlCl₃ (Scheme 2, reaction a; combined yield 40%). Unfortunately, when compound 5a was treated with BBr₃ under the conditions reported for the preparation of hydroxycoumarins by demethylation and concomitant lactonization, the starting material decomposed.

Eventually we found that treatment of 5a with 1 equivalent of BBr₃ at −30 °C simultaneous deprotected the oxygen ortho to the haloacetyl group and replaced the chloride of 5a with bromine, affording 6 in 93% yield. This allowed the furanone ring to be constructed by stirring 6 with K₂CO₃ in acetone at room temperature, which gave 7 in 92% (a similar yield was obtained from the minor product of reaction a, 5b). However, attempts to complete the desired furocoumarinone by BBr₃ treatment of 7 were unsuccessful.

In view of the above results, we decided to subject the furanone ring to the Diels–Alder reaction before completion of the coumarin moiety. This approach proved successful. Treatment of 7 with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine afforded compound 8 in 71% yield. The previously elusive lactonization could be accomplished by reacting 8 with BBr₃ to furnish the desired compound 9 in 68% yield.

In conclusion, dihydrofuro[2,3-h]coumarin-9-one (2), regioselectively obtained by Fries rearrangement of 7-(chloroacetoxy)coumarin (1), afforded the angular pyridazinofurocoumarin 3 in good yield by Diels–Alder reaction with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine. Compound 7, synthesized from ethyl 2,4-dimethoxycinnamate (4) in 34% overall yield, was transformed into the linear pyridazinofurocoumarin 9 in two steps and 48% overall yield. The synthesis of an extensive series of pyridazinofurocoumarins with different substituents is in progress with a view to evaluate them as DNA-intercalating drugs and photochemotherapeutic agents.

Melting points were determined in capillary tubes in a Büchi 510 apparatus, and are uncorrected. IR spectra were recorded in a Perkin-Elmer 1640 FT spectrometer. ¹H and ¹³C NMR spectra (the multiplicity of carbons were determined by DEPT experiments) were recorded in a Bruker AMX spectrometer at 300 MHz and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts are given as δ values, J in Hz). Mass spectra were obtained using a Hewlett Packard 5988A spectrometer. Elemental analyses were performed by a Perkin-Elmer 240B microanalyzer and were within ±0.4% of calculated values in all cases. 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).

8.11-Bis(trifluoromethyl)pyridazine[4,5-j]angelicin (3)

2,3-Dichloro-5,6-dicyanobenzoquinone (228 mg, 1 mmol) was added to a solution of 1,2-dihydro-3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (220 mg, 1 mmol) in dioxane (5 mL) and the mixture was stirred for 15 min at r.t. The precipitate was filtered and the solid dihydrofuro[2,3-h]coumarin-9-one (2) in 34% overall yield, was transformed into the linear pyridazinofurocoumarin 9 in two steps and 48% overall yield. The synthesis of an extensive series of pyridazinofurocoumarins with different substituents is in progress with a view to evaluate them as DNA-intercalating drugs and photochemotherapeutic agents.

Ethyl 5-Chloroacetyl-2,4-dimethoxycinnamate (5a) and Ethyl 5-Chloroacetyl-4-hydroxy-2-methoxycinnamate (5b)

Ethyl 2,4-dimethoxycinnamate (4; 0.944 g, 4 mmol) was added to a cold solution of AlCl₃ (1.2 g, 8.8 mmol) in chloroacetyl chloride (10 mL) and stirred for 3 h at 0 °C under Ar. The reaction was quenched by adding H₂O cautiously and the product was extracted with CH₂Cl₂. The organic phase was washed withaq. sat. solution of NaHCO₃ and dried (Na₂SO₄). Filtration and solvent evaporation afforded a residue which was chromatographed on silica gel using CH₂Cl₂ as eluent, giving 5a as a white solid; yield: 440 mg (35%). Further elution with CH₂Cl₂-MeOH, 98:2 afforded 5b; yield 60 mg (5%).

Scheme 2  Reagents and conditions: a) CICH₂COCl, AlCl₃, 0 °C; b) 1 M BBr₃, CH₂Cl₂, –30 °C; c) K₂CO₃, acetone, r.t.; d) 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine, dioxane, reflux; e) 1 M BBr₃, CH₂Cl₂, reflux

Eventually we found that treatment of 5a with 1 equivalent of BBr₃ at −30 °C simultaneously deprotected the oxygen ortho to the haloacetyl group and replaced the chloride of 5a with bromine, affording 6 in 93% yield. This allowed the furanone ring to be constructed by stirring 6 with K₂CO₃ in acetone at room temperature, which gave 7 in 92% (a similar yield was obtained from the minor product of reaction a, 5b). However, attempts to complete the desired furocoumarinone by BBr₃ treatment of 7 were unsuccessful.

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IR (KBr): 2988, 2946, 1718, 1699, 1616, 1478, 1264, 1245, 1198, 1174, 1152 cm\(^{-1}\).

1H NMR (CDCl\(_3\), \(\delta\) = 7.89 (d, 1 H, J = 16.1 Hz, =CH–Ar), 7.82 (s, 1 H, H-4), 6.58 (s, 1 H, H-7), 6.45 (d, 1 H, J = 16.1 Hz, =CHCO2Et), 4.65 (s, 2 H, CH2CO2), 4.25 (q, 2 H, J = 7.1 Hz, CH2CH3), 3.96 (s, 3 H, CH3O), 1.32 (t, 3 H, J = 7.1 Hz, CH2CH3).

13C NMR (CDCl\(_3\)): \(\delta\) = 197.4 (C), 177.2 (C), 167.6 (C), 166.7 (C), 138.9 (CH), 124.5 (CH), 120.4 (C), 119.2 (CH), 114.6 (C), 95.6 (CH), 76.1 (C), 60.9 (CH3), 56.7 (CH), 14.7 (CH3).

MS: \(m/z\) (%) = 262 (M\(^+\)), 217 (100), 203.

(E)-8-[2-(Ethoxycarbonyl)ethenyl]-7-methoxy-1,4-bis(trifluoromethyl)benzofuro[2,3-p]pyridazine (8) This compound was prepared from 7 (131 mg, 0.5 mmol) in an analogous manner to 3. When the reaction was complete the solvent and excess tetrazene were removed under vacuum and the crude reaction mixture was purified by FC using CH\(_2\)Cl\(_2\) as eluent, giving 8 as a white solid; yield: 154 mg (71%); mp 168–170 °C.

IR (KBr): 3085, 2987, 1702, 1630, 1421, 1398, 1237, 1183, 1156, 1130, 1035, 966 cm\(^{-1}\).

1H NMR (CDCl\(_3\), \(\delta\) = 8.33 (s, 1 H, H-9), 8.05 (d, 1 H, J = 16.1 Hz, =CH–Ar), 7.36 (s, 1 H, H-6), 6.64 (d, 1 H, J = 16.1 Hz, =CHCO2Et), 4.31 (q, 2 H, J = 7.0 Hz, CH2CH3), 4.10 (s, 3 H, CH3O), 1.38 (t, 3 H, J = 7.0 Hz, CH2CH3).

13C NMR (CDCl\(_3\)): \(\delta\) = 161.7 (C), 163.2 (C), 160.0 (C), 152.6 (C), 138.6 (C), 124.8 (C), 124.5 (C), 123.6 (C), 121.6 (CH), 109.7 (C), 95.8 (CH3), 61.2 (CH3), 57.0 (CH3), 14.7 (CH3).

MS: \(m/z\) (%) = 435 ([M + 1]\(^+\), 10), 434 (M\(^+\)), 403, 389 (100), 375, 346.

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References

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