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Synthesis of 2,8-Diarylpyrano[3,2-*g*]chromene-4,6-diones

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4,6-Bis[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]resorcinol **3** was generated in a Stille coupling between 4,6-diiodoresorcinol and 2 mol 5-tributylstannyl-3-(3,4,5-trimethoxyphenyl)isoxazole **2**. 4-Iodoresorcinol was coupled with 3-phenyl-5-tributylstannylisoxazole to give 5-(2,4-dihydroxyphenyl)-3-phenylisoxazole **7**. Selective iodination of **7** with ICl gave 5-(2,4-dihydroxy-5-iodophenyl)-3-phenylisoxazole **8**, which underwent Stille coupling with **2** to give 4-(3-phenylisoxazol-5-yl)-6-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]resorcinol **9**. Reductive ring cleavage of **3** and **9** followed by acid-catalysed cyclisation gave 2,8-bis(3,4,5-trimethoxyphenyl)pyrano[3,2-*g*]chromene-4,6-dione **4** and 2-phenyl-8-(3,4,5-trimethoxyphenyl)pyrano[3,2-*g*]chromene-4,6-dione **10**, respectively, in fair overall yields.

Only a few syntheses of pyrano[3,2-*g*]chromene-4,6-diones have been reported.[1,2] The most simple procedure is based on an acylation of 4,6-diacetylresorcinol with 2 mol of an acid anhydride followed by cyclodehydration. Some of the compounds have been found to possess antiallergic properties.[1]

In previous papers we have described syntheses of flavonoids based on the use of isoxazolines and isoxazoles as key intermediates.[3,4] Recently[5,6] this methodology was combined with the Stille coupling,[7] providing a synthetic route to highly hydroxylated and methoxylated flavones. It was found that iodophenols containing hydrogen in one of the positions *ortho* to iodine coupled to 5-tributylstannylisoxazoles in high yields with $Pd(AsPh_3)_4$, generated *in situ* from $Pd_2(dba)_3$ [bispalladium tris(dibenzylideneacetone)] and $AsPh_3$,[8] as a catalyst. We have now extended this work to a simple synthesis of the structurally related 2,8-diarylpyrano[3,2-*g*]chromene-4,6-diones.

The synthesis of the symmetrical 2,8-bis(3,4,5-trimethoxyphenyl)pyrano[3,2-*g*]chromene-4,6-dione **4**, started with the coupling between 4,6-diiodoresorcinol and 2 mol 5-tributylstannyl-3-(3,4,5-trimethoxyphenyl)isoxazole **2** (Scheme 1). High-yielding synthesis of starting materials **1** and **2** have been described in previous reports.[6,9] To obtain the optimum yield it was necessary to use an excess of **2**. During the coupling reaction **3** precipitated from the solvent (dioxane), and could be obtained in 61% yield by filtration. Recrystallisation of **3** gave crystals that were practically insoluble in most solvents. It was reduced suspended in a mixture of dioxane, ethanol and water by hydrogenation over Raney nickel in the presence of boric acid. Owing to the low solubility of **3**, the reduction proceeded more slowly than would normally be observed for the reduction of isoxazoles. The crude product was subjected to cyclisation in acetic acid containing a catalytic amount of HCl at 100°C for 2 h. The product **4** precipitated from the reaction medium, and was obtained in 62% yield (38% overall). Partial reduction of **3** followed by cyclisation gave a small amount of **11**.

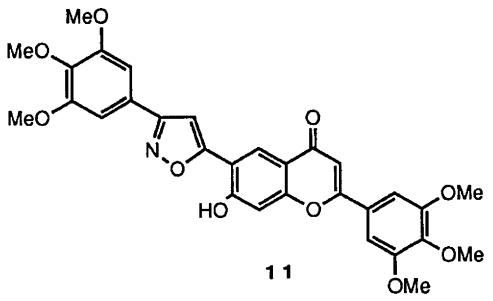

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Fig. 1.

Still more challenging was to prepare 2,8-diarylpyrano[3,2-*g*]chromene-4,6-diones with two different aromatic substituents. The two isoxazole moieties had to be joined to resorcinol in two separate steps. 3-Phenyl-5-tributylstannylisoxazole **6** underwent cross coupling with 4-iodoresorcinol to give **7** in 62% yield (Scheme 2). In analogy to the iodination of resorcinol,[9] **7** was selectively iodinated in the 5′-position by treatment with one equivalent of ICl in dry dioxane at room temperature.

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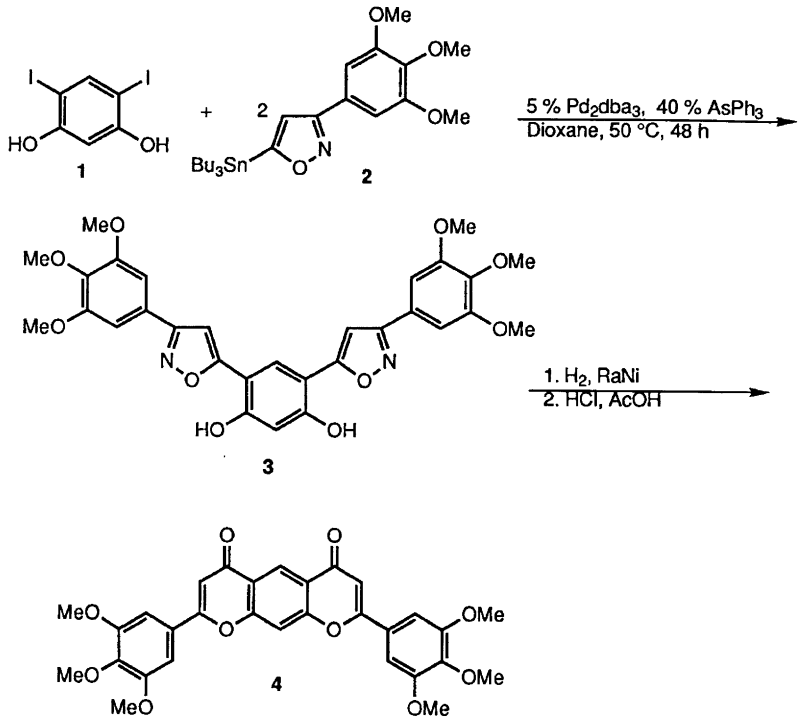
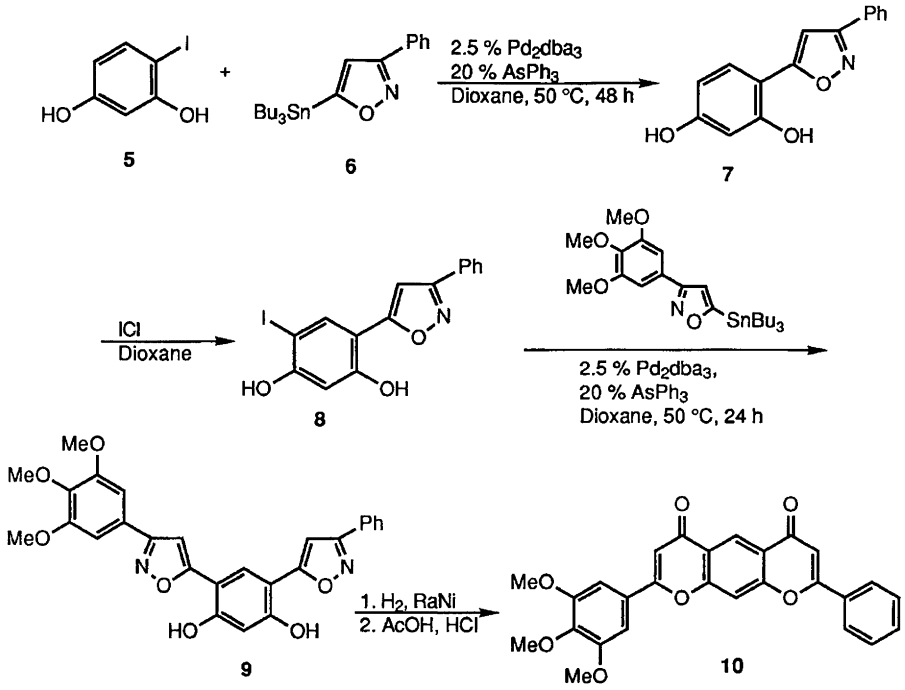


Scheme 1.

After chromatography **8** was isolated in 80% yield. The isoxazole **2** coupled to **8** quantitatively. During the cross-coupling reaction **9** partly precipitated from the reaction medium but attempts to filter **9** off were unsatisfactory. However, preparative TLC of the crude product yielded **9** in 97% yield. It was not possible to recrystallize **9**. It precipitated as a jelly-like substance from the solvent. Reductive ring cleavage and cyclisation of **9** gave **10** in 53% yield (25% overall).



Scheme 2.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Because of low solubilities it was not possible to obtain ^{13}C NMR spectra of compounds **3**, **9** and **10**. Mass spectra of compounds **7** and **8** were recorded on a V.G. Micro-Mass 7070F spectrometer operating at 70 eV. Low-resolution mass spectra of **4** and **10** were obtained with a Varian MAT 311 A/ SS200 datasystem, operating at 70 eV.

4,6-Bis[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]resorcinol **3.** 4,6-Diiodoresorcinol[9] **1** (0.33 g, 0.90 mmol), $Pd_2(dba)_3$ (41 mg, 0.045 mmol) and $AsPh_3$ (0.11 g, 0.36 mmol) in dry dioxane (7 ml) were stirred for 15 min at 20°C under nitrogen. 5-Tributylstannyl-3-(3,4,5-trimethoxyphenyl)isoxazole[6] **2** (1.41 g, 2.70 mmol) in dioxane (2 ml) was added to the solution through a septum via syringe and the temperature was raised to 50°C. The product **3** precipitated continuously as it was formed. After 48 h the flask was cooled to room temperature. The precipitate was filtered off and washed with chloroform to give **3** (0.32 g, 0.55 mmol, 61%). An analytical sample was prepared by recrystallisation from acetone. M.p. 328–330°C. ^{1}H NMR (CD_3OD–$CDCl_3$ 1:1): δ 3.86 (6 H, s), 3.94 (12 H, s), 6.68 (1 H, s), 7.09 (2 H, s), 7.12 (4 H, s), 8.43 (1 H, s).

2,8-Bis(3,4,5-trimethoxyphenyl)pyrano[3,2-g]chromene-4,6-dione **4**. Compound **3** (0.10 g, 0.17 mmol) suspended in dioxane–ethanol–water (2:2:1, 25 ml) containing boric acid (21 mg, 0.35 mmol) was reduced in an H_2 atmosphere over Raney nickel. After 3 h two equivalents of H_2 had been absorbed. The suspension was filtered through a layer of Celite and the solvent was evaporated off. The residue was stirred for 1.5 h at 100°C in glacial acetic acid (3 ml) containing 1 drop of concentrated HCl. The mixture was cooled to room temperature and the precipitate was filtered, washed with acetic acid and dried to give **4** (59 mg, 0.108 mmol, 62%). An analytical sample was prepared by recrystallisation from acetone–chloroform to give white crystals. M.p. 344–345°C. MS: $m/z = 546$ (M^+). ^{1}H NMR ($CDCl_3$): δ 3.95 (6 H, s), 3.99 (12 H, s), 6.77 (2 H, s), 7.12 (4 H, s), 7.70 (1 H, s), 9.08 (1 H, s). ^{13}C NMR 56.9, 61.6, 104.3, 106.9, 107.7, 122.1, 126.5, 126.7, 142.1, 154.1, 158.9, 164.2, 177.6.

7-Hydroxy-3′,4′,5′-trimethoxy-6-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]flavone **11**. Compound **3** was reduced and cyclized as described in the above procedure with the exception that the reduction was stopped after 1 h. After the cyclisation reaction the solvent was evaporated off and the residue was separated by preparative TLC (silica gel, 5% MeOH in $CHCl_3$) to give **4** ($R_f = 0.7$–0.8) and **11** ($R_f = 0.3$–0.4) in poor yields. ^{1}H NMR ($CDCl_3$) **11**: δ 3.72 (3 H, s), 3.75 (3 H, s), 3.78 (6 H, s), 3.79 (6 H, s), 6.50 (1 H, s), 6.92 (1 H, s), 6.93 (2 H, s), 6.96 (2 H, s), 7.09 (1 H, s), 8.54 (1 H, s).

5-(2,4-Dihydroxyphenyl)-3-phenylisoxazole **7**. 4-Iodoresorcinol (0.71 g, 3.0 mmol), $Pd_2(dba)_3$ (68 mg, 0.075 mmol) and $AsPh_3$ (0.18 g, 0.6 mmol) were stirred in dry dioxane (15 ml) for 15 min under nitrogen. 3-Phenyl-5-tributylstannylisoxazole **6** (1.69 g, 3.9 mmol) in dioxane (2 ml) was added to the solution through a septum via syringe and the temperature was raised to 50°C. After 48 h the reaction mixture was cooled to room temperature and filtered through a 20 mm layer of silica gel. The solvent was evaporated off and the residue was stirred in refluxing chloroform (5 ml) for 30 min. The suspension was kept at −5°C for 3 h. The precipitate was filtered off and washed with chloroform to give the product **7** (0.47 g, 1.86 mmol, 62%). An analytical sample was prepared by recrystallisation from acetone–methylcyclohexane. M.p. 274–276°C. MS: $m/z = 253$ (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 6.40–6.47 (2 H, m), 7.16 (1 H, s), 7.41–7.49 (3 H, m), 7.70 (1 H, d, $J = 9.5$ Hz), 7.79–7.86 (2 H, m). ^{13}C NMR (CD_3OD–$CDCl_3$ 1:3): δ 100.6, 104.3, 108.5, 109.1, 128.3, 129.8, 130.4, 131.0, 131.4, 158.1, 161.8, 164.7, 169.5.

5-(2,4-Dihydroxy-5-iodophenyl)-3-phenylisoxazole **8**. To compound **7** (0.18 g, 0.71 mmol) dissolved in dry dioxane (4 ml) at 20°C with vigorous stirring was added ICl (0.12 g, 0.71 mmol) in dry dioxane (3.5 ml) via syringe over a period of 15 min. After 5 h ethyl acetate (20 ml) was added and the solution was extracted twice with 10% aqueous $KHCO_3$ (20 ml), then twice with 10% aqueous $NaHSO_3$ (10 ml) and finally with water. The organic layer was dried over $MgSO_4$. The crude product was purified by flash chromatography (silica gel, diethyl ether) to give **8** (0.215 g, 0.57 mmol, 80%). An analytical sample was prepared by recrystallisation from ethyl acetate–methylcyclohexane. M.p. 225–227°C. MS: $m/z = 379$ (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 6.50 (1 H, s), 7.04 (1 H, s), 7.38–7.45 (3 H, m), 7.77–7.83 (2 H, m), 8.14 (1 H, s). ^{13}C NMR (CD_3OD–$CDCl_3$ 1:3): δ 74.1, 101.3, 104.0, 111.2, 128.4, 130.5, 130.9, 131.6, 138.7, 158.1, 160.3, 164.7, 168.0.

4-[3-Phenylisoxazol-5-yl]-6-[3-(3,4,5-trimethoxyphenyl)-isoxazol-5-yl]resorcinol **9**. Compound **8** (0.10 g, 0.264 mmol), $Pd_2(dba)_3$ (6 mg, 0.0066 mmol) and $AsPh_3$ (16 mg, 0.053 mmol) in dry dioxane (3 ml) were stirred for 15 min at 20°C under nitrogen. 5-Tributylstannyl-3-(3,4,5-trimethoxyphenyl)isoxazole (**2**) (0.18 g, 0.34 mmol) in dioxane (2 ml) was added to the solution through a septum via syringe and the temperature was raised to 50°C. After 24 h the solvent was evaporated off and the residue was purified by preparative TLC (silica gel, 7.5% ethanol in $CHCl_3$, $R_f = 0.05$–0.2) to give **9** (0.125 g, 0.257 mmol, 97%). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 3.85 (3 H, s), 3.95 (6 H, s), 6.59 (1 H, s), 7.03 (1 H, s), 7.08 (2 H, s), 7.10 (1 H, s), 7.38–7.46 (3 H, m), 7.78–7.86 (2 H, m), 8.42 (1 H, s).

2-Phenyl-8-(3,4,5-trimethoxyphenyl)pyrano[3,2-g]chromene-4,6-dione **10**. Compound **9** (0.125 g, 0.26 mmol) suspended in dioxane–ethanol–water (2:2:1 35 ml) containing boric acid (32 mg, 0.51 mmol) was reduced in an H_2 atmosphere over Raney nickel. After 3 h, 2 equivs. of H_2 had been absorbed. The suspension was filtered through a layer of Celite, and the solvent was evaporated off. The residue was stirred for 1.5 h at 100°C in glacial acetic acid (3 ml) containing 1 drop of concentrated HCl. The mixture was cooled to room temperature and methylcyclohexane (3 ml) was slowly added. The precipitate was filtered, washed (acetic acid–methylcyclohexane 1:1) and dried to give **10** (63 mg, 0.138 mmol, 53%). Recrystallisation from ethanol–dichloromethane gave white crystals. M.p. 343–344°C. MS: $m/z = 456$ (M^+). ^{1}H NMR ($CDCl_3$): δ 3.96 (3 H, s), 3.99 (6 H, s), 6.79 (1 H, s), 6.85 (1 H, s), 7.15 (2 H, s), 7.55–7.59 (3 H, m), 7.76 (1 H, s), 7.92–7.97 (2 H, m), 9.14 (1 H, s).

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