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 allergenic 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 iodoophenols containing hydrogen in one of the positions ortho to iodine coupled to 5-tributylstannylisoxazoles in high yields with Pd(AsPh)₃, generated in situ from Pd₃(dba)₃, [bis(triphenylphosphine)platinum] tris(dibenzylideneacetone)] and AsPh₃, 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-trimethoxyphenyln)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 re-

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Fig. 1.

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.

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.
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).
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/SS2000 database, 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 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–methylcyclohexane. M.p. 247–258°C. Mass: $m/z = 253$ (M$^+$). $^1$H NMR (CD$_2$OD–CDC$_3$, 1:1, 40°C): 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$_2$OD–CDC$_3$, 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-Dihydroxyphenyl)-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. Mass: $m/z = 379$ (M$^+$). $^1$H NMR (CD$_2$OD–CDC$_3$, 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$_2$OD–CDC$_3$, 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.

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 (CDC$_3$): 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. Mass: $m/z = 253$ (M$^+$). $^1$H NMR (CD$_2$OD–CDC$_3$, 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$_2$OD–CDC$_3$, 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. Mass: $m/z = 379$ (M$^+$). $^1$H NMR (CD$_2$OD–CDC$_3$, 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$_2$OD–CDC$_3$, 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, 0.066 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$_2$OD–CDC$_3$, 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 H₂ atmosphere over Raney nickel. After 3 h, 2 equivs. of H₂ 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 methyloclohexane (3 ml) was slowly added. The precipitate was filtered, washed (acetic acid–methyloclohexane 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⁺). 1H NMR (CDCl₃): 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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