

Syntheses of Flavonoids via the Isoxazoline Route

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Syntheses of naturally occurring 7-hydroxyflavanone, liquiritigenin and the corresponding chalcones (isoliquiritigenin) are described.

In a previous article a methodology for the construction of the flavonoid skeleton was described.¹ The parent flavanone **1** was prepared by selective chlorination of salicylaldehyde oxime to salicylhydroxamoyl chloride, which was cycloadded to styrene. Reductive cleavage of the isoxazoline ring to the β -hydroxy ketone and acid-catalyzed cyclization gave **1** (Scheme 1). By using substituted styrenes, phenylacetylenes or salicylaldehyde oximes the reaction could find wider application. However, there are limitations because most substituted styrenes or phenylacetylenes are not commercially available or are difficult to prepare. This is the case for hydroxy-substituted derivatives which are of special interest because naturally occurring flavonoids contain several hydroxy or methoxy groups in the A and C rings. Another problem is that halogenation of benzaldehyde oxime containing several electron-donating groups leads primarily to nuclear chlorination. 2,4-Dihydroxybenzaldehyde oxime and 1 mol of *N*-chlorosuccinimide gave, e.g., practically 100% nuclear chlorination. Therefore conditions had to be found to circumvent these problems.

Introduction of protecting groups. 2,4-Dihydroxybenzaldehyde was chosen as an electron-rich aromatic substrate for our studies. Acetylation of the hydroxy groups was unsuitable but the *t*-butyldimethylsilyl group was found to be a useful protecting group. It sterically shielded the *ortho* positions and decreased the electron-donating effect of the oxygen atoms. The *t*-butyldimethylsilyl ethers survived the oximation, chlorination and also partially the cycloaddition and reduction steps. Only a minute amount of nuclear chlorination product was observed. The silyl groups were removed by heating the ethers with potassium fluoride in acetic acid (Scheme 2).

The trimethylsilyl derivatives were too unstable to be useful under our experimental conditions; the trimethylsilyl groups were lost in the oximation step. 2,4,6-Tri-*t*-butyldimethylsilyloxybenzaldehyde oxime was also prepared and tested. Chlorination with NCS gave the chloroxime but the

bulky silyl groups hindered effectively the cycloaddition to styrene. The *t*-butyldimethylsilyl phenol ethers were easily prepared by heating *t*-butyl(chloro)dimethylsilane, triethylamine and the phenol in dry acetonitrile.

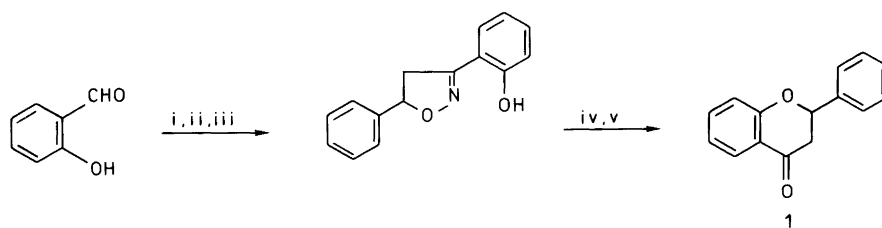
The isoxazoline **4a** was obtained in a yield of 61% from **3** and styrene. Catalytic hydrogenation of **4a** led partly to loss of one silyl group – tentatively the one in the *ortho*-position. The acid-catalyzed elimination of water was carried out on the crude mixture in the presence of fluoride ions, which gave directly the chalcone **9** in a satisfactory yield. Compound **9** was cyclized to the flavanone **10** by treatment with base followed by neutralization with dilute hydrochloric acid. The cycloaddition to give **4b** was accompanied by partial desilylation. The crude product was therefore directly desilylated with fluoride ions and hydrolyzed in basified methanol to give the corresponding trihydroxyisoxazoline. Catalytic hydrogenation to give **7** followed by acid-catalyzed elimination of water gave the chalcone isoliquiritigenin (**8**) which is in equilibrium with the cyclized 7,4'-dihydroxyflavanone liquiritigenin (**11**). The flavonoids **8–11** are naturally occurring compounds, which have been synthesized previously by other methods.^{2–4}

Experimental

General. ¹H and ¹³C NMR spectra were obtained with a Varian Gemini 200 spectrometer. Me₄Si was used as an internal standard. Units for chemical shifts are ppm. Mass spectra were obtained with a Micromass 7070 F. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. Preparative TLC was performed on silica gel 60 Pf₂₅₄₊₂₆₀ (art. No. 7748), layers (0.18 × 20 × 20 cm) on glass plates. Column chromatography: Kieselgel 60 (0.063–0.200 mm), Merck.

2,4-Di(t-butyldimethylsilyloxy)benzaldehyde (2). 2,4-Dihydroxybenzaldehyde (1.02 g, 7.38 mmol) and *t*-butyl(chloro)dimethylsilane (2.62 g, 17.4 mmol) were heated to reflux in dry acetonitrile (15 ml). Triethylamine (1.87 g, 18.4 mmol) was added dropwise over 20 min to minimize precipitation, and the mixture was refluxed for 2 h, cooled

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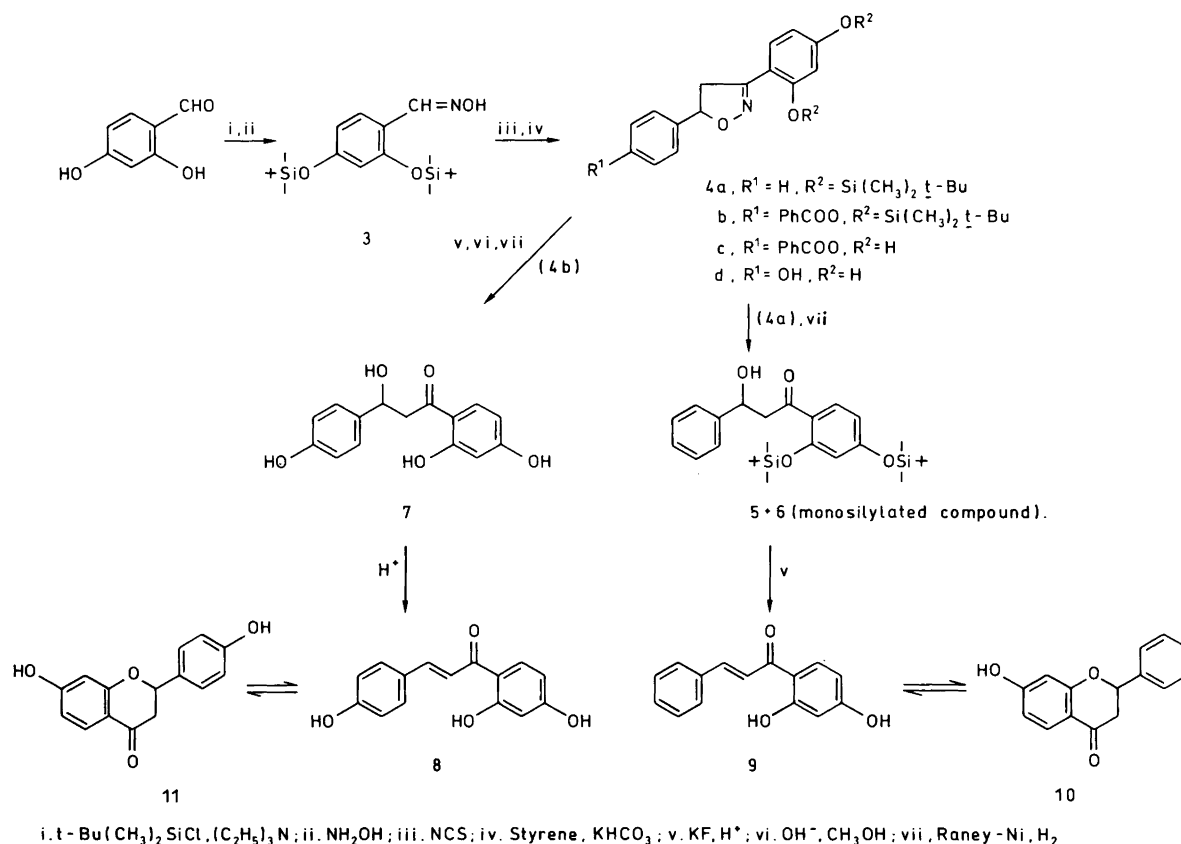
i, NH_2OH ; ii NCS, iii Styrene, KHCO_3 ; iv Raney -Ni, H_2 ; v H^+ .

Scheme 1.

to room temperature and part of the acetonitrile was evaporated *in vacuo*. Chloroform (25 ml) was added, and the solution was washed twice with water, dried over MgSO_4 , filtered and evaporated *in vacuo* to give **2** as a light yellow oil in practically quantitative yield. $^1\text{H NMR}$ (CDCl_3): δ 0.22 (6 H, s), 0.26 (6 H, s), 0.96 (9 H, s), 1.00 (9 H, s), 6.28 (1 H, d, J 2 Hz), 6.50 (1 H, dd, J 2 and 9 Hz), 7.71 (1 H, d, J 9 Hz), 10.3 (1 H, s). MS: m/z 366.5 (M^+), 351.3 ($M^+ - \text{CH}_3$), 309.3 [$M^+ - \text{C}(\text{CH}_3)_3$].

2,4-Di(t-butyltrimethylsilyloxy)benzaldehyde oxime (3). To a solution of **2** (3.66 g, 10.0 mmol) in methanol–water (9:1, 60 ml) was added a solution of hydroxylamine hydro-

chloride (1.00 g, 14.4 mol) and triethylamine (1.46 g, 14.4 mmol) in methanol–water (9:1, 20 ml). The mixture was stirred at room temperature for 20 h. Most of the methanol was evaporated *in vacuo* and the oxime was extracted with dichloromethane. Drying of the organic phase over MgSO_4 and evaporation of the solvent *in vacuo* gave crude **3**, which was purified by column chromatography (SiO_2 , CH_2Cl_2) to give **3** as a white semicrystalline compound. The yield was 85%. $^1\text{H NMR}$ (CDCl_3): δ 0.18 (6 H, s), 0.21 (6 H, s), 0.96 (9 H, s), 0.99 (9 H, s), 6.28 (1 H, d, J 2.7 Hz), 6.45 (1 H, dd, J 2.7 and 8.7 Hz), 7.58 (1 H, d, J 8.7 Hz), 8.35 (1 H, s), 9.4 (1 H, br s). MS: m/z 381.7 (M^+), 324.6 [$M^+ - \text{C}(\text{CH}_3)_3$].



Scheme 2.

3-[2,4-Di(*t*-butyldimethylsilyloxy)phenyl]-5-phenylisoxazoline (**4a**). Compound **3** (1.90 g, 4.98 mmol) was chlorinated with *N*-chlorosuccinimide (NCS) (0.77 g, 5.77 mmol) in dry chloroform (10 ml) at 50°C for 45 min. The solution was cooled to room temperature and styrene (0.78 g, 7.49 mmol), potassium hydrogencarbonate (1.5 g) and one drop of water were added. The mixture was stirred at room temperature overnight. Filtration, washing with water, drying over MgSO₄ and evaporation of the solvent *in vacuo* gave crude **4a** as a yellow oil. It was purified by preparative TLC (SiO₂, diethyl ether–light petroleum 1:9) and gave a yield of 1.48 g (61%). ¹H NMR (CDCl₃): δ 0.15–0.25 (12 H, m), 0.92 (9 H, s), 0.96 (9 H, s), 3.39 (1 H, dd, *J* 8 and 17 Hz), 3.78 (1 H, dd, *J* 10 and 17 Hz), 5.64 (1 H, dd, *J* 8 and 10 Hz), 6.33 (1 H, d, *J* 2 Hz), 6.47 (1 H, dd, *J* 2 and 8 Hz), 7.25–7.40 (5 H, m), 7.51 (1 H, d, *J* 8 Hz). MS: *m/z* 482.8 (*M*⁺), 425.5 [*M*⁺–C(CH₃)₃].

Isloxazoline **4b**. The oxime **3** (2.38 g, 6.25 mmol) was chlorinated with NCS (0.84 g, 6.25 mmol) in ethyl acetate (10 ml) at 65°C for 0.5 h. The color changed to green and then brown. After cooling, 4-benzoyloxystyrene⁵ (1.12 g, 5 mmol), potassium hydrogencarbonate (1.5 g) and 2 drops of water were added and the mixture was stirred for 24 h at 25°C. The mixture was worked up as described for **4a** to give 3.5 g of crude **4b**, which contained unchanged 4-benzoyloxystyrene. According to the ¹H NMR spectrum the product was partly desilylated. It was reacted further without purification.

4-Benzoyloxystyrene was prepared according to Ref. 5.

1-[2,4-Di(*t*-butyldimethylsilyloxy)phenyl]-3-hydroxy-3-phenylpropan-1-one (**5**) and the monosilylated compound (**6**). Compound **4a** (0.45 g, 0.93 mmol) was reduced catalytically with H₂ over Raney-Ni in ethanol (96%) containing boric acid (0.16 g). The solution was filtered through Celite to remove the catalyst, and most of the solvent was evaporated *in vacuo*. Dichloromethane and water were added, and the organic phase was separated and dried over MgSO₄, filtered and evaporated *in vacuo*. The product consisted of a mixture of mono- and di-silylated derivatives. For spectral identification a portion of the mixture of **5** and **6** was separated by preparative TLC (SiO₂, diethyl ether–light petroleum 1:4). **5**: ¹H NMR (CDCl₃): δ 0.06 (6 H, s), 0.23 (6 H, s), 0.89 (9 H, s), 0.96 (9 H, s), 3.2–3.45 (2 H, m), 5.32 (1 H, dd, *J* 4.5 and 7.5 Hz), 6.25–6.40 (2 H, m), 7.2–7.5 (5 H, m), 7.54 (1 H, d, *J* 8 Hz). **6**: ¹H NMR (CDCl₃): δ 0.23 (6 H, s), 0.96 (9 H, s), 3.27 (1 H, dd, *J* 4.5 and 17.3 Hz), 3.32 (1 H, dd, *J* 7.8 and 17.3 Hz), 5.32 (1 H, dd, *J* 4.5 and 7.8 Hz), 6.33 (1 H, dd, *J* 2.5 and 8.7 Hz), 6.38 (1 H, d, *J* 2.5 Hz), 7.25–7.5 (5 H, m), 7.54 (1 H, d, *J* 8.7 Hz), 12.4 (1 H, br s). MS: *m/z* 372.1 (*M*⁺).

2',4'-Dihydroxychalcone (**9**). The crude mixture of **5** and **6** (0.39 g) from above was heated at reflux in acetic acid (2

ml) with potassium fluoride (0.12 g) and conc. hydrochloric acid (0.2 ml) for 0.5 h. Most of the solvent was evaporated *in vacuo*, and water and chloroform were added. The solution was neutralized with sodium hydrogencarbonate. The phases were separated and the water phase was washed twice with chloroform. The combined organic phases were dried with MgSO₄, filtered and evaporated *in vacuo*. The residue was purified by preparative TLC (SiO₂, ethyl acetate–chloroform 1:4) to give **9**, 0.16 g, (72% from **4a** to **9**), m.p. 140–149°C (from CH₂Cl₂–CCl₄ 1:1), lit.^{3d} 147–149°C. ¹H NMR (CDCl₃): δ 6.26 (1 H, d, *J* 2.5 Hz), 6.30 (1 H, dd, *J* 2.5 and 10.5 Hz), 7.55 (1 H, d, *J* 15.2 Hz), 7.92 (1 H, d, *J* 15.2 Hz), 7.2–7.6 (5 H, m), 7.83 (1 H, d, *J* 10.5 Hz). MS: *m/z* 240 (*M*⁺).

7-Hydroxyflavanone (**10**). The chalcone **9** (0.13 g, 0.54 mmol) was treated with aqueous sodium hydroxide (2 ml, 0.5 M) under nitrogen for 1 h. The solution was acidified to pH ca. 4 with acetic acid and the precipitate, which consisted of a mixture of the chalcone **9** and the flavanone **10** (ca. 40%), was filtered off. Addition of a small amount of chloroform dissolved the chalcone. The remaining flavanone **10** was recrystallized from methanol. M.p. 195–197°C, lit.^{3d} 185–186°C. ¹H NMR (CD₃OD): δ 2.70 (1 H, dd, *J* 3.5 and 16 Hz), 2.93 (1 H, dd, *J* 13 and 16 Hz), 5.35 (1 H, dd, *J* 3.5 and 13 Hz), 6.34 (1 H, d, *J* 2 Hz), 6.45 (1 H, dd, *J* 2 and 8 Hz), 7.25–7.45 (5 H, m), 7.71 (1 H, d, *J* 8 Hz). MS: *m/z* 240 (*M*⁺).

5-(4-Benzoyloxyphenyl)-3-(2,4-dihydroxyphenyl)isoxazoline (**4c**). Crude **4b** (3.5 g) was heated in refluxing acetic acid (20 ml) with sodium acetate (1.9 g) and potassium fluoride (2.9 g) under N₂ for 2 h. Most of the acetic acid was evaporated *in vacuo* and the residue was neutralized with aqueous sodium hydrogencarbonate and extracted with ethyl acetate (15 ml). The organic phase was dried over MgSO₄, filtered and evaporated *in vacuo*. The residue was extracted with tetrachloromethane (2×5 ml) to remove the styrene giving crude **4c** as a dark brown oil (1.7 g). It was purified by preparative TLC (SiO₂, dichloromethane–ethanol 13:1) to give 1.2 g of light brown crystals (**4c**) m.p. 185°C, 64% (as calculated from the styrene). ¹H NMR (CDCl₃): δ 3.29 (1 H, dd, *J* 16.8 and 8.4 Hz), 3.75 (1 H, dd, *J* 16.8 and 10.7 Hz), 5.56 (1 H, dd, *J* 10.7 and 8.4 Hz), 6.29 (1 H, dd, *J* 8.5 and 2.3 Hz), 6.35 (1 H, d, *J* 2.3 Hz), 6.93 (1 H, d, *J* 8.5 Hz), 7.11 (2 H, d, *J* 8.7 Hz), 7.2–7.6 (5 H, m), 8.06 (2 H, dd, *J* 8.4 and 1.3 Hz).

3-(2,4-Dihydroxyphenyl)-5-(4-hydroxyphenyl)isoxazoline (**4d**). The isoxazoline **4c** (1.06 g, 2.8 mmol) was hydrolyzed in methanol (15 ml) with sodium hydroxide (0.33 g, 8.4 mmol) under nitrogen with stirring for 24 h. The solution was neutralized with conc. hydrochloric acid (9.0 mmol). The solvent was evaporated *in vacuo*, and the residue was purified twice by preparative TLC (SiO₂, dichloromethane–ethanol 13:1 and light petroleum–ethyl acetate 4:1) to give **4d** (0.57 g, 75%) as a light brown

viscous oil which slowly crystallized, m.p. 160–170°C. ¹H NMR (acetone-*d*₆, CDCl₃): δ 3.32 (1 H, dd, *J* 16.5 and 8.5 Hz), 3.74 (1 H, dd, *J* 16.5 and 10.3 Hz), 5.50 (1 H, dd, *J* 10.3 and 8.5 Hz), 6.38 (2 H, m), 6.78 (2 H, d, *J* 8.4 Hz), 7.04 (1 H, d, *J* 8.5 Hz), 7.17 (2 H, d, *J* 8.4 Hz). ¹³C NMR (acetone-*d*₆, CDCl₃): δ 159.5, 158.51, 157.91, 156.76, 130.29, 129.19, 128.93, 114.75, 106.90, 105.79, 102.26, 80.25, 41.82.

1-(2,4-Dihydroxyphenyl)-3-hydroxy-3-(4-hydroxyphenyl)propan-1-one (7). The isoxazoline **4d** (0.309 g, 1.14 mmol) in methanol–water (9:1, 10 ml) and boric acid (0.14 g) was reduced over Raney-Ni. The theoretical amount of hydrogen was absorbed. Usual work-up gave 0.315 g of a yellow semi-solid product, which, according to the ¹H NMR spectrum, consisted primarily of **7**. ¹H NMR (acetone-*d*₆, CDCl₃): δ 3.11 (1 H, dd, *J* 16.5 and 4 Hz), 3.29 (1 H, dd, *J* 16.5 and 9 Hz), 5.17 (1 H, dd, *J* 9 and 4 Hz), 6.3 (2 H, m), 6.73 (2 H, d, *J* 8 Hz), 7.20 (2 H, d, *J* 8 Hz), 7.59 (1 H, d, *J* 8 Hz). It was used without further purification for the preparation of **8** and **11**.

Isoliquiritigenin (8) and *liquiritigenin (11)*. Compound **7** (0.113 g, crude) was heated at reflux in aqueous sodium hydroxide (5 ml, 2.5%) for 1 h under N₂. The solution was acidified with conc. hydrochloric acid and extracted with ethyl acetate (2×15 ml). The organic phase was dried over MgSO₄, evaporated and the residue chromatographed on silica (chloroform–ethyl acetate 1:1). Products **8** and **11** were formed in the ratio 3:2. They had the same *R*_f values and were collected together. The total yield was 0.078 g, 65% (as calculated from the isoxazoline **4d**). ¹H NMR (acetone-*d*₆): **8**: δ 6.35 (1 H, d, *J* 2.6 Hz), 6.45 (1 H, dd, *J* 2.6 and 8.6 Hz), 6.92 (2 H, d, *J* 8.7 Hz), 7.73 (2 H, d, *J*

8.7 Hz), 7.76 (1 H, d, *J* 15.1 Hz), 7.82 (1 H, d, *J* 15.1 Hz), 8.10 (1 H, d, *J* 8.6 Hz). **11**: δ 2.65 (1 H, dd, *J* 2.8 and 16.8 Hz), 3.02 (1 H, dd, *J* 12.6 and 16.8 Hz), 5.43 (1 H, dd, *J* 2.8 and 12.6 Hz), 6.40 (1 H, d, *J* 2.3 Hz), 6.54 (1 H, dd, *J* 2.3 and 8.5 Hz), 6.88 (2 H, d, *J* 8.6 Hz), 7.39 (2 H, d, *J* 8.6 Hz), 7.71 (1 H, d, *J* 8.5 Hz). M.p. **8**: 185°C, lit.^{4c} 182–183°C, + 1 H₂O; **11**: 202°C, lit.^{4c} 202–204°C, + 1 H₂O.

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