Short Communication

A Convenient Synthesis of Flavones. Synthesis of Apigenin

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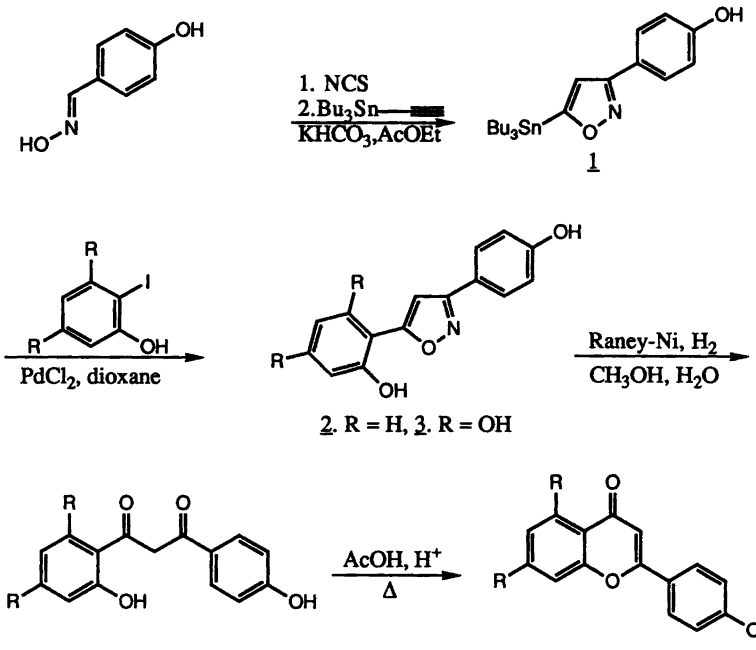
In previous articles we have described novel syntheses of flavones[1,2] and the structurally related 4-quinolones[3] via the isoxazole route. These studies have been extended and in the present paper we present a preliminary account of a flavone synthesis of some general significance.

Most naturally occurring flavones contain several hydroxy groups in the A- and B-rings. Our previous synthetic procedure required hydroxy-substituted styrenes or phenylacetylenes, which unfortunately are unstable or difficult to prepare and not commercially available. The chlorination of an arylaldoxime also limits to a certain extent the number of hydroxy groups in the benzene ring because of competing nuclear chlorination. This can, however, be circumvented by silylation.[1b]

The present procedure started with a 1,3-dipolar cycloaddition of an aromatic nitrile oxide to tributylstannylacetylene[4] to give 3-aryl-5-tributylstannylisoxazole,[5] **1** (Scheme 1). The nitrile oxide was generated by chlorination of the corresponding benzaldoxime with *N*-chlorosuccinimide and subsequent treatment with potassium hydrogencarbonate.

One hydroxy group (as in salicylaldehyde oxime or *p*-hydroxybenzaldehyde oxime), a methylenedioxy group,[6] or two methoxy groups (veratraldehyde oxime) do not allow nuclear chlorination. *O*-Silylated 2,4-dihydroxybenzaldehyde oxime gave selectively the hydroximoyl chloride, whereas the unprotected oxime gave practically 100 % nuclear chlorination.[1b] Tributylstannyl-substituted isoxazoles undergo Pd-catalyzed Heck-type coupling with iodobenzenes.[5] We applied this reaction directly to 2-iodophenol and obtained **2** in 50 % yield. Reductive ring cleavage over Raney-Ni[1] and subsequent heating of the 1,3-diketone **4** in acetic acid with a catalytic amount of hydrochloric acid gave 4′-hydroxyflavone **6**. This flavone does not seem to be a naturally occurring compound.

Still more challenging was to prepare the highly hydroxy-



Scheme 1.

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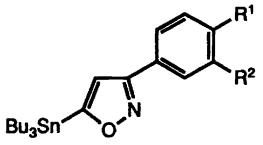
lated flavone apigenin **7**, which required monoiodinated phloroglucinol as reactant. This compound is unstable and has recently become available.[7] From iodophloroglucinol we prepared **3** in a yield of ca. 35 %. We have reason to believe that this step can be improved. Catalytic reduction and cyclisation gave apigenin **7**, identical with an authentic sample. Interestingly, the iodophenols and **1** could be used in the reaction without protection of the hydroxy groups.



8. $R^1 = R^2 = OCH_3$
9. $R^1 = OH$, $R^2 = OCH_3$

The stannnyl compounds **8** and **9** were synthesized similarly. MS and ^1H NMR spectra of the compounds corresponded to the expected structures. In forthcoming publications the synthesis of a number of flavones will be described.

Experimental

3-(4-Hydroxyphenyl)-5-tributylstannylisoxazole **1**. To 4-hydroxybenzaldehyde oxime (2.06 g) in 10 ml of ethyl acetate were added consecutively potassium hydrogen carbonate (3.0 g), one drop of water, tributylstannylacetylene (3.15 g) and *N*-chlorosuccinimide (2.0 g). The mixture was stirred at room temperature for 20 h. The suspension was filtered through a layer of Celite and evaporated. Chromatography on a silica gel column (10 % MeOH in $CHCl_3$) yielded 3.21 g (71 %) of **1**. ^1H NMR ($CDCl_3$): δ 0.7–1.7 (27 H, m), 6.60 (1 H, s), 6.88 (2 H, d, J = 8.5 Hz), 7.68 (2 H, d, J = 8.5 Hz).

3-(4-Hydroxyphenyl)-5-(2,4,6-trihydroxyphenyl)isoxazole **3**. **1** (450 mg) and $PdCl_2$ (50 mg) in anhydrous dioxane (10 ml) were heated to 105 °C under nitrogen. Iodophloroglucinol (400 mg) in anhydrous dioxane (5 ml) was added in portions of 1 ml over 1 h. The suspension was heated under reflux for 3 h, filtered and evaporated and the residue chromatographed on a silica gel column (diethyl ether) to give **3** (100 mg, 35 %). ^1H NMR (CD_3OD–$CDCl_3$ 1:2): δ 5.92 (2 H, s), 6.85 (2 H, d, J = 8.5 Hz), 6.92 (1 H, s), 7.64 (2 H, d, J = 8.5 Hz).

4',5,7-Trihydroxyflavone (apigenin) **7**. **3** (100 mg) was catalytically reduced with Raney-Ni in aqueous methanol in the presence of H_3BO_3. After 1 h, a quantitative amount of hydrogen had been absorbed. The reaction mixture was filtered through a layer of Celite, and the solvent evaporated *in vacuo*. The 1,3-diketone was refluxed in AcOH (1.5 ml) and 1 drop of conc. HCl for 1 h. The mixture was cooled, filtered and the precipitate was recrystallized from ethanol to give apigenin (40 %), identical with an authentic sample. ^1H NMR (CD_3OD): δ 6.18 (1 H, d, J = 2 Hz), 6.43 (1 H, d, J = 2 Hz), 6.56 (1 H, s), 6.90 (2 H, d, J = 8.5 Hz), 7.82 (2 H, d, J = 8.5 Hz).

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References

1. (a) Thomsen, I. and Torssell, K. B. G. *Acta Chem. Scand., Ser. B 42* (1988) 303; (b) Almtorp, G., Bachmann, T. L. and Torssell, K. B. G. *Acta Chem. Scand. 45* (1991) 212.
2. For a general discussion of the use of isoxazoles in synthesis see: Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis, Novel Strategies in Synthesis.* VCH Verlagsgesellschaft, Weinheim 1988.
3. Thomsen, I. and Torssell, K. B. G. *Acta Chem. Scand., Ser. B 42* (1988) 309.
4. Bottaro, J. C., Hanson, R. N. and Seitz, D. E. *J. Org. Chem. 46* (1981) 5221.
5. (a) Kondo, Y., Uchiyama, D., Sakamoto, T. and Yamanaka, H. *Tetrahedron Lett. 30* (1989) 4249; (b) Sakamoto, T., Kondo, Y., Uchiyama, D. and Yamanaka, H. *Tetrahedron 47* (1991) 5111.
6. Larsen, K. E. and Torssell, K. B. G. *Tetrahedron 40* (1984) 2985.
7. Thomsen, I. and Torssell, K. B. G. *Acta Chem. Scand. 45* (1991) 539.

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