Synthesis of 4-Substituted Flavans from 4α-Halogenoflavans

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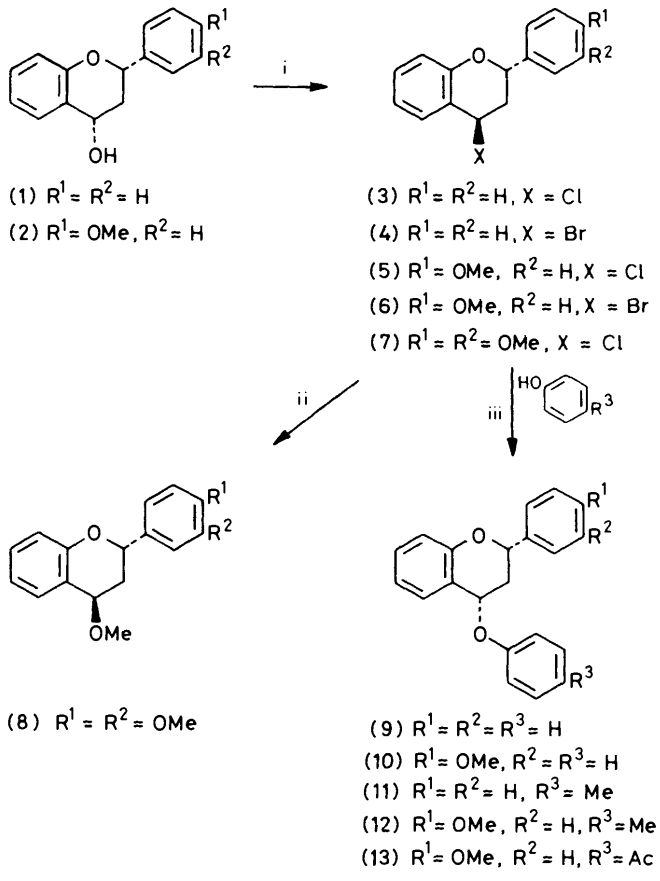
The reactions of flavan-4α- or -4β-ols unsubstituted in ring A with phosphorus or similar halides give 4α-halogenoflavans which react with a variety of nucleophiles (phenolate ions, thiophenolate ions, amines, and alcohols) yielding the corresponding 4-substituted flavans whose stereochemistries depend upon the ratio of S_N1 to S_N2 reactions occurring. Biflavonoids have been synthesised by the reaction of 4α-halogenoflavans with flavonols under conditions of phase transfer catalysis.

Despite their potential for the synthesis of polyflavonoids, 4-halogenoflavans have hitherto received little attention. In 1954 Shriner and Schaeffer [1] prepared a 4-bromoflavan of unassigned stereochemistry by the action of phosphorus tribromide on a flavan-4-ol and from it, by the action of piperidine, obtained a 4-piperidinoflavan, again of unknown stereochemistry. Later Kamat *et al.*[2] prepared two 4-bromoflavans by treating the corresponding flavan-4β-ol (1) or (2) with phosphorus tribromide in ether and claimed to have obtained flavan-4α-ols from them by treatment with concentrated alcoholic potassium hydroxide. These authors assumed that the bromoflavans they obtained were of β-configuration (2,4-*cis*). We have used their procedure to prepare from flavan-4β-ols a series of 4-halogenoflavans (3), (4), (5), (6), and (7) (Scheme 1) which, however, are shown to have an α-configuration (2,4-*trans*) by n.m.r.[3] ($\Sigma J_{2,3}$ 13—14 Hz and $\Sigma J_{3,4}$ 6.0—6.5 Hz), indicating that the reactions proceed with inversion of configuration at the 4-position. Other phosphorus halides, *e.g.* diphenylphosphoryl chloride or phosphoryl chloride, give the same 4α-halogenoflavans as does thionyl chloride in ether or in chloroform. Concentrated hydrochloric acid in dioxane at room temperature also converts 4′-methoxyflavan-4β-ol (2) into 4α-chloro-4′-methoxyflavan (5) and treatment of flavan-4α-ol with phosphorus trichloride or tribromide gives 4α-chloroflavan or 4α-bromoflavan with retention of configuration.

The 4α-halogenoflavans are crystalline solids which slowly decompose both by reaction with atmospheric moisture and by elimination of hydrogen halide to give unstable flav-3-enes. The lability of the halogen atom at C-4 is illustrated by the fact that 'recrystallisation' of 4α-chloro-3′,4′-dimethoxyflavan (7) from methanol gave 4α,3′,4′-trimethoxyflavan (8) quantitatively.

The ready reaction of the 4α-chloroflavan with methanol encouraged us to investigate the possibility of synthesising 4-aryloxyflavans by the action of salts of phenols. 4α-Chloro-4′-methoxyflavan (5) did not react at room temperature with potassium phenolate but at 100 °C reaction occurred yielding a mixture of 4α- and the hitherto unknown 4β-phenoxy-4′-methoxyflavan (10) together with 4′-methoxy-4β-(2-hydroxyphenyl)flavan (14). At 50 °C 4β-aryloxyflavans free of the 4α-compounds were produced in low yield (20—30%, see Table 1) along with 4-aryl compounds and flav-3-enes and their decomposition products. In order to increase the yields in this synthesis by reducing the proportion of the 4-halogenoflavan decomposing to a flav-3-ene and to remove the need for tedious separations of the 4β-aryloxyflavans from the accompanying 4-arylflavans, we investigated the value of the technique of phase transfer catalysis which McKillop *et al.*[4] successfully developed for the synthesis of aromatic ethers. We found that the best yields (40—50%, see Table 1) of 4β-aryloxyflavans (9), (12), (13), and (15) free from 4-arylflavans, were obtained with a stoicheiometric amount of the phase transfer catalyst at room temperature and that the isolation of the products was simple.



(1) $R^1 = R^2 = H$
(2) $R^1 = OMe$, $R^2 = H$
(3) $R^1 = R^2 = H$, X = Cl
(4) $R^1 = R^2 = H$, X = Br
(5) $R^1 = OMe$, $R^2 = H$, X = Cl
(6) $R^1 = OMe$, $R^2 = H$, X = Br
(7) $R^1 = R^2 = OMe$, X = Cl
(8) $R^1 = R^2 = OMe$
(9) $R^1 = R^2 = R^3 = H$
(10) $R^1 = OMe$, $R^2 = R^3 = H$
(11) $R^1 = R^2 = H$, $R^3 = Me$
(12) $R^1 = OMe$, $R^2 = H$, $R^3 = Me$
(13) $R^1 = OMe$, $R^2 = H$, $R^3 = Ac$

All compounds are racemic. Relative stereochemistry is indicated

Scheme 1. *Reagents:* i, PX_3–ether; ii, MeOH; iii, phase transfer catalyst

Structural distinction between 4-aryloxyflavans [5] and 4-arylflavans [6] is most easily made from mass spectral evidence (Table 2). The base peak of either 4α- or 4β-aryloxyflavans results from the loss of the 4-substituent from the molecular ion, the percentage of which is quite small, whereas the base peak of 4-arylflavans results from a retro-Diels–Alder fission [3,7] and the percentage of molecular ion is appreciable (see Scheme 2). The difference arises because the 4-aryloxyflavans contain a much better leaving group (aryloxy) than do the 4-arylflavans, in which the leaving group would be aryl. However, for highly methoxylated flavans this structural

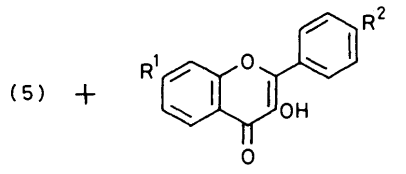
Table 1. 4β-Aryloxyflavans from 4α-halogenoflavans

4β-Aryloxyflavan	Method [a]	M.p. (°C)	Yield (%)	Found (%)		Requires (%)		$\Sigma J_{2,3}$ (Hz)	$\Sigma J_{3,4}$ (Hz)
				C	H	C	H		
(9)	D	158—159	23	83.4	6.1	83.4	6.1	13.2	17.0
	PT	158—159	47	83.5	6.1				
(10)	D	137—138	30	79.2	6.1	79.5	6.1	13.8	16.8
(11)	D	99—100	25	83.6	6.4	83.5	6.35	13.6	16.6
(12)	D	118.5—119.5	24	79.6	6.4	79.7	6.4	13.7	16.8
	PT	119—120	42	79.8	6.4				
(13)	PT	146—147	52	77.0	5.9	77.0	5.9	13.5	16.1

Table 3. 4-Aminoflavans from 4α-halogenoflavans

4-Aminoflavan	M.p. (°C)	Yield (%)	Found (%) C	H	N	Requires (%) C	H	N	$\Sigma J_{2,3}$ (Hz)	$\Sigma J_{3,4}$ (Hz)
(19)	92.0—92.5	24	83.6	6.7	4.4	83.8	6.7	4.4	13.1	16.5
(22)	146.5—148	6	83.5	6.3	4.7				13.4	6.0
(20)	162—163	16	83.4	6.4	4.8	83.7	6.4	4.7	13.1	16.3
(23)	154—156	8	65.2	6.4	4.15	65.5	6.4	4.0	13.7 [a]	6.0 [a]
(21)	99—100	30	65.3	6.4	4.2				13.2 [a]	*b*

[a] N.m.r. of free amines. [b] Not ascertainable.



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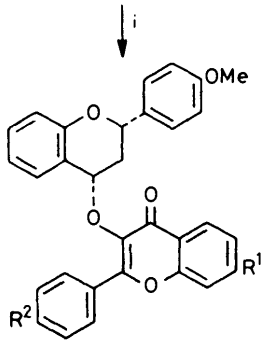


(25) $R^1 = R^2 = H$

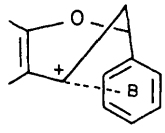
(26) $R^1 = OMe$, $R^2 = H$

(27) $R^1 = H$, $R^2 = OMe$

Scheme 3. *Reagents:* i, phase transfer catalyst

like phenols, they would react with 4α-halogenoflavans in a phase transfer system to give 2,4-*cis*-biflavonoids. Interaction of equimolecular quantities of a 4α-chloroflavan, a flavonol, *N*-benzyltri-n-butylammonium bromide, and sodium hydroxide in a mixture of water and dichloromethane did indeed give biflavonoids (25), (26), and (27) of the expected structure and 2,4-*cis*- (4β-) stereochemistry [$\Sigma J_{2,3}$ 13.3—13.7 Hz and $\Sigma J_{3,4}$ 16.7—17.3 Hz for the compounds (25), (26), and (27)] (Scheme 3).

The observed stereochemical courses of the substitution reactions of 4α-halogenoflavans suggest competition between S_N2 and S_N1 mechanisms, the former proceeding with inversion to give 4β-products and the latter giving, predominantly or wholly, 4α- (2,3-*trans*-) products. The S_N1 reactions occur through intermediates with 4-carbonium ion character and the marked preference of nucleophiles for attacking the α-face of such an anion is probably due to shielding of the β-face by the 2-aryl group since models show that the heterocyclic ring can adopt a conformation (28) in which the π-electrons of the aryl group could interact with a positive charge at C-4.[8] It would be expected that in the kinetically controlled reactions of 4α-halogenoflavans with nucleophiles, the ratio of S_N2 to S_N1, and hence the ratio of 4β- to 4α-products, would increase with the nucleophilicity and concentration of the nucleophile and with decreasing temperature and decreasing



(28)

polarity of the reaction medium, and decrease with the presence in the flavan of substituents able to stabilise a 4-carbonium ion (28).

The results described above are generally in agreement with these expectations. Thus, for example, the reactions of 4α-halogenoflavans at 100 °C with powerful nucleophiles (thiophenolate ion, benzylamine) gave solely 4β-products, whereas weaker nucleophiles (aniline, phenolate ions) at 100 °C gave mixed 4α- and 4β-products, and boiling methanol gave only the 4α-methoxy isomer. Phenolate ions at 50 °C or room temperature (with phase transfer catalysis) gave solely 4β-products.

As expected,[9] the reaction of flavan-4α-ol and flavan-4β-ol with phosphorus halides, thionyl chloride, or hydrogen chloride, all of which are Lewis acids, gave 4α-halides, presumably through the 4-carbonium ion (28).

Experimental

Measurements of n.m.r. spectra were made in $CDCl_3$ unless otherwise stated. Mass spectra were recorded on a Varian MAT CH7 instrument using direct insertion. Merck silica HF_{254} was used for t.l.c. and PF_{254} for p.l.c. Light petroleum refers to that fraction with b.p. 40—60 °C, and ether to diethyl ether.

3′,4′-*Dimethoxyflavan*-4β-*ol*.—3′,4′-Dimethoxyflavan-4-one (4.7 g) was reduced with sodium borohydride (2.6 g) in methanol (600 ml) at room temperature. Addition of 0.7% aqueous acetic acid (1.6 l) gave 3′,4′-*dimethoxyflavan*-4β-*ol* which separated from ethanol as needles (3.4 g), m.p. 159—160 °C (Found: C, 71.3; H, 6.25. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%).

The *benzoate* separated from benzene–light petroleum as needles, m.p. 93—94 °C (Found: C, 73.9; H, 5.7. $C_{23}H_{22}O_5$ requires C, 73.86; H, 5.65%); n.m.r. (benzene) $\Sigma J_{2,3}$ 12.9 Hz, $\Sigma J_{3,4}$ 16.2 Hz.

4α-*Chloroflavan* (3).—Flavan-4β-ol (200 mg) and phosphorus trichloride (0.1 ml) were stirred in dry ether (10 ml) for 2 h at 20 °C. Water (200 ml) was added and the mixture was extracted with ether (4 × 50 ml) and the extracts washed with aqueous sodium hydrogen carbonate (3 × 50 ml) and dried. Evaporation and recrystallisation of the residue from dry ether or from light petroleum gave 4α-*chloroflavan* (110 mg) as needles, m.p. 56—57 °C (analysis in Table 4).

Table 4. Preparation of 4α-halogenoflavans

4α-Halogenoflavan	Yield (%)	M.p. (°C)	Found (%)			Requires (%)			$\Sigma J_{2,3}$ (Hz)	$\Sigma J_{3,4}$ (Hz)
			C	H	Ha	C	H	Ha		
(3)	60 [a] 50 [b]	56—57	73.9	5.3	14.2	73.6	5.4	14.5	13.6	6.0
(4)	75 [a] 82 [b]	85—86 [c]								
(5)	77 [b]	94—95	69.8	5.7	13.2	69.9	5.5	13.0	13.6	6.4
(6)	34 [b]	102—103	60.5	4.7	25.0	60.2	4.7	25.0		
(7)	75 [b]	70—71	67.0	5.45	11.4	67.0	5.6	11.65	13.2	6.0

[a] From 4α-ol. [b] From 4β-ol. [c] Shriner and Schaeffer [1] record m.p. 85—87 °C.

Table 5. 4-Arylflavans (by-products of the direct method) from 4α-halogenoflavans

4-Arylflavan	M.p. (°C)	Found (%)		Requires (%)		$\Sigma J_{2,3}$ (Hz)	$\Sigma J_{3,4}$ (Hz)
		C	H	C	H		
4α-(2-Methoxyphenyl) [a]	193—195	83.4	6.4	83.5	6.3	14.0	8.0
4′-Methoxy-4β-(2-hydroxyphenyl) [b]	151—153	75.8	6.5	75.8	6.6	13.6	17.8
4β-(2-Methoxy-5-methylphenyl) [a]	100—101.5	83.4	6.7	83.6	6.7	13.2	18.0
4′-Methoxy-4β-(2-hydroxy-5-methylphenyl) [b]	171—173	76.0	6.7	76.2	6.9	13.6	18.0

[a] Isolated after methylation of the original product. [b] Containing 1 mol of methanol of crystallisation per mol of flavan.

Other 4α-halogenoflavans prepared by this method are collected in Table 4. They should be stored at 0 °C to diminish decomposition and are best prepared immediately before use.

Treatment of flavan-4β-ol with diphenylphosphoryl chloride in pyridine at 0 °C gave 4α-chloroflavan (64%), m.p. and mixed m.p. 56—57 °C.

4α-*Chloro*-4′-*methoxyflavan* (5).—(*a*) 4′-Methoxyflavan-4β-ol (500 mg) and thionyl chloride (0.25 mg) were stirred in dry ether (20 ml) for 4 h and worked up as described above to

from methanol gave 4′-*methoxy*-4β-(2-*hydroxy*-5-*methylphenyl*)*flavan* (79 mg) as plates (containing methanol), m.p. 171—173 °C (decomp.). (See Table 5 for analysis and n.m.r.)

(*b*) *Phase transfer method.* Dichloromethane (50 ml), water (50 ml), *p*-cresol (0.45 g), sodium hydroxide (0.18 g), 4α-chloro-4′-methoxyflavan (1.0 g) and benzyltri-n-butylammonium bromide (1.29 g) were agitated at 20 °C for 8 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 20 ml). The organic extracts were evaporated and the residue was taken up in ether

Details for the Synthesis of 4-*Aminoflavans* (*Table* 3). N-*Flavan*-4-*ylglycine Ethyl Ester Hydrochlorides*.—4α-Chloroflavan (245 mg) and glycine ethyl ester (1.03 g) were boiled in dioxane (15 ml) for 8 h. Ether (100 ml) was added and the mixture was washed with water (3 × 50 ml) and brine (2 × 50 ml). The residue obtained by removal of the solvent was applied to preparative layer plates in dichloromethane and eluted with ether–light petroleum (2 : 1 v/v). The fastest running band was identified as flav-3-ene. The faster of the next two bands gave an oil ($\Sigma J_{3,4}$ 6.0 Hz) which on treatment with hydrogen chloride in ether gave N-*flavan*-4α-*ylglycine ethyl ester hydrochloride* which separated from light petroleum as prisms (31 mg), m.p. 154—156 °C (see Table 3 for analysis).

The slowest of the three bands similarly gave an oil (92 mg) which yielded N-*flavan*-4β-*ylglycine ethyl ester hydrochloride* as needles, m.p. 99—100 °C (see Table 3 for analysis).

3-(cis-4′-*Methoxyflavan*-4β-*yloxy*)-*flavone* (*-flav*-2-*en*-4-*one*) (25).—4α-Chloro-4′-methoxyflavan (393 mg), flavonol (3-hydroxyflavone) (370 mg), benzyltri-n-butylammonium bromide (450 mg), aqueous 2M-sodium hydroxide (1 ml), water (9.0 ml), and dichloromethane (10 ml) were stirred together vigorously for 12 h at room temperature. The layers were separated, the aqueous phase was twice washed with dichloromethane and the combined organic phase was washed repeatedly with aqueous sodium hydroxide until the washings were colourless, and then with dilute hydrochloric acid, and finally with saturated sodium hydrogen carbonate solution. Removal of the solvent from the dried solution and crystallisation of the residue from ethyl acetate gave the *biflavonoid* (25) as needles (450 mg), m.p. 168—170 °C (Found: C, 78.1; H, 5.1. $C_{31}H_{24}O_5$ requires C, 78.1; H, 5.1%); τ 1.58—3.33 (17 H, aromatics), 4.00 (1 H, q, 4-H), 5.05 (1 H, q, 2-H), 6.27 (3 H, s, OMe), 7.71—8.37 (2 H, complex, 3-H), $J_{2,3}$ 10.7 and 2.9, $J_{3,4}$ 10.2 and 6.9 Hz.

4′-*Methoxy*-3-(cis-4′-*methoxyflavan*-4β-*yloxy*)*flavone* (27). This compound was prepared as above from 4-chloro-4′-methoxyflavan (225 mg), 4′-methoxyflavonol (225 mg), benzyltri-n-butylammonium bromide (330 mg), dichloromethane (10 ml), water (9.5 ml), and aqueous sodium hydroxide (0.45 ml). The crude product (463 mg) was shown by t.l.c. to contain a slower running impurity which could not be removed by recrystallisation from ethyl acetate. A portion (170 mg) was purified by p.l.c. [3 small plates; 2 elutions with ether–light petroleum, 1 : 1; this caused streaking, but the major component (101 mg) could be recovered pure]. The *biflavonoid* (27) separated from ether as prisms, m.p. 151.5—152.5 °C (Found: C, 75.7; H, 5.2. $C_{32}H_{26}O_6$ requires C, 75.9; H, 5.2%); τ 1.63—3.30 (16 H, aromatics), 3.98 (1 H, q, 4-H), 5.04 (1 H, q, 2-H), 6.20 and 6.27 (2 × 3 H, 2 s, 2 × OMe), and 7.69—8.44 (2 H, complex, 3-H); $J_{3,4}$ 10.0 and 6.8, $J_{2,3}$ 10.5 and 3.1 Hz.

7-*Methoxy*-3-(cis-4′-*methoxyflavan*-4β-*yloxy*)*flavone* (26). This compound was prepared as above from 7-methoxyflavonol (225 mg). The crude product (452 mg) was recrystallised from ethanol to give the *biflavonoid* (26) as needles (192 mg), m.p. 188—190 °C (Found: C, 75.6; H, 5.3. $C_{32}H_{26}O_6$ requires C, 75.9; H, 5.2%), τ 1.79—3.35 (16 H, aromatics), 4.07 (1 H, q, 4-H), 5.10 (1 H, q, 2-H), 6.16 and 6.20 (2 × 3 H, 2 s, 2 × OMe), and 7.75—8.42 (2 H, complex, 3-H); $J_{3,4}$ 10.4 and 6.9, $J_{2,3}$ 10.6 and 2.7 Hz.

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