Photochemical Reactions of 4-Flavanols in the Presence of Ketone Sensitizers

Morio Suzuki, Jiro Amano, Motonobu Morioka, Hideo Mizuno,
and Ryoka Matsushima*
Department of Industrial Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432

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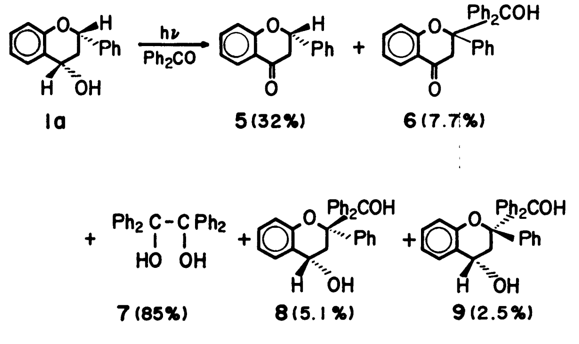
Irradiation of an oxygen-free benzene solution of *cis*-4-flavanol **1a** by a mercury lamp in the presence of benzophenone gave 4-flavanone (32%), benzopinacol (85%), *cis*- and *trans*-2-(diphenylhydroxymethyl)-4-flavanols (7.6%), and 2-(diphenylhydroxymethyl)-4-flavanone (7.7%), whereas photolysis of *cis*-4-acetoxyflavane under similar conditions gave *cis*-2-(diphenylhydroxymethyl)-4-acetoxyflavane(24%), 2,2′-bi-4-acetoxyflavane (6%), and benzopinacol. Photolysis of **1a** in acetone gave 4-flavanone (3.6%), *trans*-4-(1-hydroxy-1-methylethyl)-4-flavanols (9.9%). The *cis* isomers of the parent and substituted 4-flavanols showed higher reactivities than the corresponding *trans* isomers.

For epimeric cycloalkanols, significant structural effects on oxidation rates are known.[1,2] Significant rate ratios, *cis*/*trans*=3.3—12, have been reported for the oxidation of a series of *cis* and *trans* substituted 4-chromanols with chromic acid,[3] and the observed ratio has been attributed to the stereoelectronic effect[1] and the strain relaxation of the chromate esters of the substrates.

The present work was undertaken to determine the structural effects on the photoreactions of 4-flavanols with ketones. It has been assumed that the hydrogen atom at the 4-position on the dihydropyrane ring is quasi-axial for the *cis* isomer **1a** and quasi-equatorial for the *trans* isomer **1b**, while the hydrogen atom at the 2-position is axial for both isomers.[4,5] The rates of the photoreactions of these isomeric substrates with ketones are expected to depend on the respective structures. It was observed, however, that not only the rate, but also the course of the photoreaction, changed remarkably with changes in the structures of the 4-flavanols and ketones.

Results and Discussion

*Photoreactions of **1a** and **1b** with Benzophenone.* A deaerated benzene solution of *cis*-4-flavanol **1a** (0.02 M) containing benzophenone (0.02 M) gave 4-flavanone **5**, 2-(diphenylhydroxymethyl)-flavanone **6**, benzopinacol **7**, and *cis*- and *trans*-2-(diphenylhydroxymethyl)-4-flavanols **8** and **9**, upon irradiation with a 100 W high-pressure mercury lamp for 100 min (Scheme 1). The NMR signal of the proton at the 3-position of **6** showed a singlet at δ=3.49 ppm. This suggests rapid inversion of the carbon at the 2-position of the dihydropyrane ring of **6**. Photolysis of *trans*-4-flavanol **1b** under similar conditions gave **5** and **7** as the main products, but the rate or the yields were significantly lower than those for **1a** (Table 1).



Scheme 1. Photolysis of **1a** with benzophenone.

Table 1. Main products and their yields in the photoreactions of **1a** and **1b** with benzophenone

Substrate	Product, %		Recovery, %	
	5	**7**	Substrate	Benzophenone
1a	32	85	40[a]	trace
1b	15	60	53[a]	20

a) No epimerization product (*via* inversion at the 4-position) was detected.

In the recovered 4-flavanol resulting from the irradiation of **1a** and benzophenone, no epimerized product, **1b**, was detected, nor was any pinacol-type dimer, 4,4′-bi-4-flavanol, **12**. The lack of the formation of **12** is not necessarily due to the steric hinderance of the coupling of the 4-(4-hydroxyflavanyl) radical, **A**, since **12** can be formed as the main product in the photoreaction of **1a** with acetone, as is shown below (Scheme 4). The lack of formation of **12** (4) and **1b** (5, 6), may imply that radical **A** rapidly reacts with ground state benzophenone to give benzophenone ketyl radical **B** (3), before coupling and disproportionation or reaction with **B** (4—6). The benzophenone ketyl radical, which is stabilized by two phenyl groups, is assumed to be more stable than radical **A**, which is stabilized by only one phenyl group. Hence, radical **A** could transfer a hydrogen atom from its oxygen atom to a ground-state benzophenone molecule, thus producing a benzophenone ketyl radical and a molecule of flavanone (3), as is proposed for the photochemical reduction of aliphatic alcohols with benzophenone. On the other hand, the formation of a small amount of the cross coupling products, **8** and **9**, may imply the intermediacy of the 2-(4-hydroxyflavanyl) radical, **C** (2). This radical would combine with **B** giving an epimeric mixture, **8** and **9** (8).

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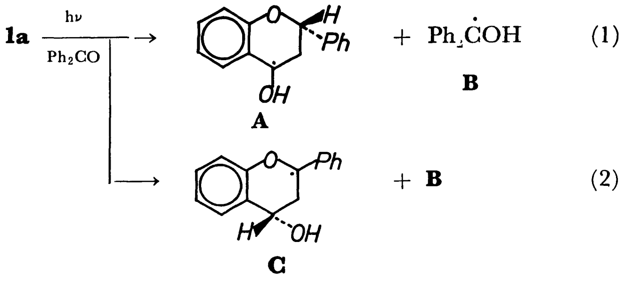
* To whom correspondence should be addressed.



$$\mathbf{A} + Ph_2CO \longrightarrow \mathbf{5} + \mathbf{B} \qquad (3)$$

$$\mathbf{A} + \mathbf{A} \;\text{—//}\!\!\rightarrow\; \mathbf{12} \qquad (4)$$

$$\mathbf{A} + \mathbf{A} \;\text{—//}\!\!\rightarrow\; \mathbf{5} + \mathbf{1a} \text{ or } \mathbf{1b} \qquad (5)$$

$$\mathbf{A} + \mathbf{B} \;\text{—//}\!\!\rightarrow\; Ph_2CO + \mathbf{1a} \text{ or } \mathbf{1b} \qquad (6)$$

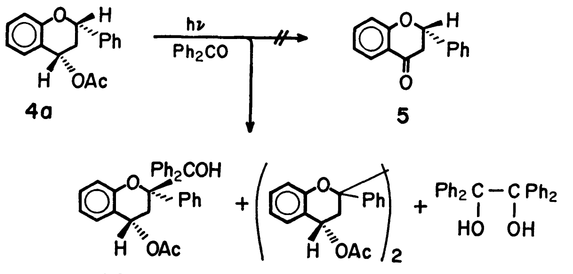
$$\mathbf{B} + \mathbf{B} \longrightarrow \mathbf{7} \qquad (7)$$

$$\mathbf{C} + \mathbf{B} \longrightarrow \mathbf{8} + \mathbf{9} \qquad (8)$$

Scheme 2. Photolysis of **1a** and benzophenone.

Product **6** may be formed by further photoreaction of **5**, **8**, or **9**. However, it seems likely that the main source of **6** is **5**, since the yields of **8** and **9** are low and photolysis of **5** and benzophenone actually gave **6** under similar conditions.

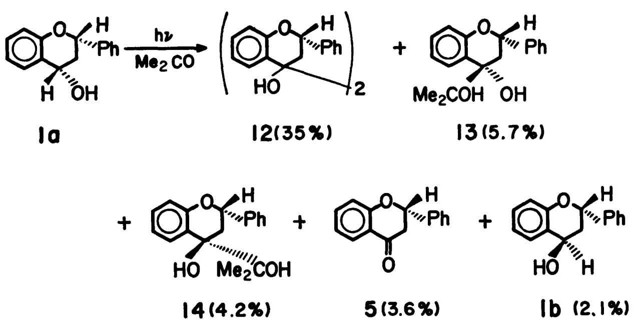
*Photoreaction of **4a** with Benzophenone.* Photolysis of *cis*-4-acetoxyflavane **4a** and benzophenone under conditions similar to those for **1a** gave no **5**, but 2,2′-bi-4-acetoxyflavanes **11** and a cross coupling product, *cis*-2-(diphenylhydroxymethyl)-4-acetoxyflavane **10**, besides benzopinacol **7**, as shown in Scheme 3. Because of the insolubility of **11**, its NMR spectrum was not obtained. The NMR signal due to the proton of the 4-position of **10** showed a quartet at $\delta=5.42$ (1H, $J=11$ Hz), which implies that the diphenylhydroxymethyl group at the 2-position and the hydrogen atom at the 4-position are of *cis* conformation.4)



Scheme 3. Photolysis of **4a** with benzophenone.

In contrast to the results of **1a** (Scheme 1), high yields of products derived from the *cis*-2-(4-acetoxyflavanyl) radical and the lack of products derived from the *cis*-4-(4-acetoxyflavanyl) radical may be noted. The inefficiency of the abstraction of the hydrogen atom at the 4-position of **4a** may be due to the electron-withdrawing effect of the acetyl group6) as well as steric hinderance.

Photolysis of a mixture of **4a** and the *trans* isomer **4b** in the presence of benzophenone gave the following ratio of the consumption rates, *cis*/*trans*=3.6.



Scheme 4. Photolysis of **1a** with acetone.

*Photoreaction of **1a** with Acetone.* Photolysis of **1a** in acetone gave 4,4′-bi-4-flavanols, **12** (mixture of isomers), *cis*- and *trans*-4-(1-hydroxy-1-methylethyl)-4-flavanols, **13** and **14**, 4-flavanone, **5**, and **1b**, besides the recovered **1a** (40%), as shown in Scheme 4. The photochemical behavior of **1a** and acetone (acetone acts as a photosensitizer as well as the solvent) differs markedly from that with benzophenone in the following respects: a) neither 4-flavanone, **5**, nor acetone pinacol, **15**, was obtained, while **5** and **7** were the main products in the **1a**–benzophenone system, b) dimeric products, **12** were obtained in a significant yield, while they none were detected in the photolysis of **1a** and benzophenone, c) cross-coupling products, **13** and **14**, derived from radical **A** were obtained instead of the cross-coupling products analogous to **8** and **9** in Scheme 1, d) the formation of **1b**, *i.e.*, epimerization at the 4-position, was observed.

Radical **A**, which is stabilized due to its benzylic structure, is assumed to be more stable than ketyl radical **D**. Hence the latter should transfer a hydrogen atom from an oxygen atom to **1a**, to produce acetone and radical **A** (13), before collisional coupling with another **D** resulting in **15** (14). For similar reasons, the reaction of **A** with acetone giving **D** and **5** (12) is assumed to be unfavorable (an endothermic process) and hence racical **A** should either couple to give **12** (10) or disproportionate resulting in **5** and **1a** or **1b** (11). In the case of the **1a**–benzophenone system, however, radical **A** should rapidly undergo process (3) because of the higher stability of **B**, before the coupling and disproportionation processes (4)—(6) can occur.

$$\mathbf{1a} \xrightarrow[Me_2CO]{h\nu} \mathbf{A} + \underset{\mathbf{D}}{Me_2\dot{C}OH} \rightarrow \mathbf{13} + \mathbf{14} \qquad (9)$$

$$\mathbf{A} \xrightarrow{\mathbf{A}} \mathbf{12} \qquad (10)$$

$$\mathbf{A} \xrightarrow{\mathbf{A}} \mathbf{5} + \mathbf{1a} \text{ or } \mathbf{1b} \qquad (11)$$

$$\mathbf{A} \xrightarrow{Me_2CO}\!\!\!\!\!\!\!\!\!/\!/\;\; \mathbf{5} + \mathbf{D} \qquad (12)$$

$$\mathbf{D} \xrightarrow{\mathbf{1a}} \mathbf{A} + Me_2CO \qquad (13)$$

$$\mathbf{D} \xrightarrow{\mathbf{D}}\!\!\!\!\!\!/\!/\;\; \underset{HO\quad OH}{Me_2C\text{-}CMe_2}\ \mathbf{15} \qquad (14)$$

Scheme 5. Photolysis of **1a** with acetone.

Table 2. Relative reactivities of the *cis* and *trans* isomers of the substituted 4-flavanols with benzophenone

Substrate	Form	Rel. reactivity^a)
4-Chromanol		1.00
1a	*cis*	1.8
1b	*trans*	0.17
2a	*cis*	2.2
2b	*trans*	0.91
3a	*cis*	1.3
3b	*trans*	0.18

a) The relative reactivity is based on that of 4-chromanol.

In Scheme 5 process (9) represents the cross-coupling reaction within the solvent cage.

No suitable explanation is available as yet, as to why no cross-coupling products analogous to **8** and **9**, shown in Scheme 1, were formed in the photolysis of the **1a**–acetone system.

Relative Photoreactivities of cis- *and* trans-*4-Flavanols with Benzophenone.* Table 2 shows the relative consumption rates, as compared with the consumption rate of 4-chromanol, for the photolysis of **1a**, **1b**, *cis*-7-methoxy-4-flavanol **2a**, *trans*-7-methoxy-4-flavanol **2b**, *cis*-7-chloro-4-flavanol **3a**, and *trans*-7-chloro-4-flavanol **3b**.

It may be noted that a) the reactivities of the *cis* isomers (**1a**, **2a**, **3a**) are higher than the corresponding *trans* isomers (**1b**, **2b**, **3b**), and b) that the order of the reactivities is **2a**>**1a**>**3a**, **2b**>**1b**≒**3b**. Yamaguchi *et al.*3) have explained the relative reactivities of the *cis*- and *trans*-substituted chroman-4-ols with chromic acid in terms of the stereoelectronic effect1) and the strain relaxation of the chromate esters of the substrates. Also, in the present photoreaction system, the stereoelectronic effect may be assumed to be one of the factors controlling the relative reactivities of the isomers. In addition to these effects, abstraction of the hydrogen atoms from these substrates by triplet benzophenone is assumed to be significantly sterically hindered for effective encounter collisions. A reactivity ratio *cis*/*trans* of 3.6 was found for the photoreaction of isomeric 4-acetoxyflavanes **4a** and **4b**. The products resulting from the photolysis of **4a** or **4b** and benzophenone (Scheme 3) imply that the intermediate radical is not the radical at the 4-position but is that at the 2-position. The latter is not conjugated with the 5,6-fused benzene ring and is free from the stereoelectronic effect. Thus, the reactivity ratio of 3.6 for isomeric 4-acetoxyflavanols is assumed to be due to the steric hinderance for encounter collisions. The abstraction of hydrogen atoms would be sterically less favorable for the *trans* isomers than for the *cis* isomers, since for the *trans* isomers the phenyl group at the 2-position would interfer with the attack of the triplet benzophenone.

The order of the reactivities indicates that electron releasing substituents stabilize the intermediate radical, such as **A**, and accelerate the reaction rate.

Experimental

The light souce was a 100-W high pressure mercury lamp (Riko Kagaku) immersed in a 200-ml reaction vessel. Each solution was bubbled using a purified nitrogen stream before and during photolysis. The temperature was maintained at 20—25 °C. The melting points are uncorrected. NMR and IR spectra were obtained by using Hitachi IRA-1 and R-24 spectrometers, respectively.

Materials. *cis*-4-Flavanol **1a**,7) *cis*-7-methoxy-4-flavanol **2a**, and *cis*-7-chloro-4-flavanol **3a** were prepared from 4-flavanone,8) 7-methoxy-4-flavanone,9) and 7-chloro-4-flavanone,10) respectively, by reduction with sodium borohydride. *trans*-4-Flavanol **1b**,11) *trans*-7-methoxy-4-flavanol **2b**, and *trans*-7-chloro-4-flavanol **3b** were prepared from **1a**, **2a**, and **3a**, respectively, by treatment with phosphorus tribromide in ether followed by hydrolysis in a *t*-butyl alcohol-water solution of potassium hydroxide. *cis*-4-Acetoxyflavane **4a** and *trans*-4-acetoxyflavane **4b**, were prepared from **1a** and **1b**, respectively, by acetylation in acetic anhydride-pyridine.

Table 3. Yields and physical constants of a series of 4-flavanols

Substrate	Yield, %	Mp (solvent)^a)	NMR ($CDCl_3$) δ, ppm	IR, cm^{-1}
1a	87	147—148 (M)	1.9—2.1 (M, 2H), 4.5 (d, 1H), 5.0 (q, 1H) 5.2 (q, 1H), 6.7—7.6 (m, 9H)	3410, 1580 1210
1b	61	117—118 (B)	2.0—2.2 (m, 2H), 2.4 (s, 1H), 4.7 (t, 1H) 5.2 (q, 1H), 6.7—7.5 (m, 9H)	3410, 1580 1210
2a	72	102—103 (M)	1.7—2.6 (m, 2H), 2.2 (s, 1H), 3.7 (s, 3H) 4.9 (q, 1H), 5.1 (q, 1H), 6.4—7.6 (m, 8H)	3230, 1605
2b	65	110—111 (B)	1.7—2.3 (m, 2H), 2.3 (s, 2H), 3.7 (s, 3H) 4.7 (t, 1H), 5.2 (q, 1H), 6.4—7.5 (m, 8H)	3220, 1600 1570
3a	69	103—104 (EW)	1.7—2.5 (m, 2H), 2.3 (s, 1H), 4.9 (q, 1H) 5.1 (q, 1H), 6.8—7.4 (m, 8H)	3330, 1590 1560, 1104
3b	45	49—51 (BH)	2.0—2.2 (m, 2H), 2.2 (s, 1H), 4.7 (t, 1H) 5.2 (q, 1H), 7.3—6.9 (m, 8H)	3400, 1600
4a		85—86 (E)	1.6—2.8 (m, 2H), 2.0 (s, 3H), 5.1 (q, 1H) 6.1 (q, 1H), 6.7—7.5 (m, 9H)	1700
4b		97—98 (E)	2.0 (s, 3H), 2.0—2.3 (m, 2H), 5.2 (q, 1H) 6.0 (t, 1H), 6.7—7.6 (m, 9H)	1700

a) Solvents for crystallization; M: methanol, E: ethanol, B: benzene, EW: ethanol-water, BH: benzene-hexane.

4-Chromanol was prepared by reduction of chromanone[12] with sodium borohydride. The yields and the phydical constants of these substrates are summarized in Table 3.

*Photolyses of **1a** and **1b** with Benzophenone.* A 200-ml benzene solution containing 0.025 M **1a** and 0.07 M benzophenone was irradiated for 100 min. Isolation by column chromatography on silica gel gave **7** (0.62 g), **5** (0.29 g), **6** (0.19 g), **8** (0.05 g), **9** (0.10 g), in addition to the recovered **1a** (0.13 g). The photolysis of **1b** and the analysis of the products were carried out under conditions similar to those for **1a**, but only the main products **5** and **7** were isolated. The acetylation of **8** and **9** in pyridine-acetic anhydride gave *cis*-2-(diphenylhydroxymethyl)-4-acetoxyflavane **8′** and *trans*-2-(diphenylhydroxymethyl)-4-acetoxyflavane **9**. Products **5** and **7** were identified by comparing their mp and IR and NMR spectra with authentic samples. **6**: colorless needles from ethanol; mp 182—183 °C; IR (KBr): 3440, 1680 cm^{-1}; NMR ($CDCl_3$): δ 2.95 (s,1H), 3.49 (s, 2H), 6.7—7.9 (m, 19H). Found: C, 82.32; H, 5.49%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%. **8**: colorless needles from ethanol; mp 222—223 °C; IR: 3570, 3335, 1590 cm^{-1}. **8′**: colorless prisms from ethanol; mp 207—212 °C; IR: 3445, 1700 cm^{-1}; NMR ($CDCl_3$): δ 1.98 (s, 3H), 2.30 (q, 1H), 2.90 (s, 1H), 3.31 (q, 1H), 5.42 (q, 1H), 6.8—7.9 (m, 19H). $J_{3a-4}=11$ Hz, $J_{3a-3e}=13.4$ Hz, $J_{3e-4}=6.5$ Hz. **9′**: colorless prisms from ethanol; mp 212—213 °C; IR: 3445, 1700 cm^{-1}; NMR ($CDCl_3$) : δ 1.50 (s,3H), 2.67 (q, 1H), 2.98 (s, 1H), 3.20 (q, 1H), 5.71 (q, 1H), 6.8—7.8 (m, 14H). $J_{3a-3e}=16.0$ Hz, $J_{3a-4}=2.0$ Hz. Found: C, 79.34; H, 5.81%. Calcd for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82%.

*Photolysis of **4a** and Benzophenone.* A 200-ml benzene solution containing **4a** (0.025 M) and benzophenone (0.06 M) was irradiated for 10 h. Isolation of the products by column chromatography on silica gel gave **7** in an undetermined significant amount, **11** (0.08 g), and **10** (0.36 g), in addition to the recovered **4a** and benzophenone. **11**: colorless crystal from benzene-ethyl acetate; mp 275—280 °C; IR: 1720, 1220 cm.$^{-1}$ Found: C, 74.35; H, 5.68%. Calcd for $C_{34}H_{30}O_6$: C, 76.39; H, 5.66%. The NMR spectra of **11** was not obtained because of the low solubility in any suitable solvent.

*Photolysis of **1a** and Acetone.* A 150-ml acetone solution of **1a** (0.067 M) was irradiated for 60 h. Isolation by CC on silica gel, after acetylation with pyridine-acetic anhydride, gave **4a** (0.76 g), **4b** (0.05 g), **5** (0.08 g), bi-4-(acetoxyflavane) **12′** (0.79 g), and *cis*- and *trans*-4-(1-hydroxy-2-methylethyl)-4-flavanols **13** (0.16 g) and **14** (0.12 g). The TLC of **12** on silica gel with benzene gave four spots which were identified as isomeric mixtures by comparing their NMR spectra with those of authentic samples.[13] **13**: white crystals from CCl_4; mp 130—132 °C; IR: 3520, 3450 cm^{-1}; NMR ($CDCl_3$): δ 1.26 (s, 3H), 1.34 (s, 1H), 2.0—3.0 (m, 4H), 5.63 (q, 1H), 6.7—7.7 (m, 9H). **14**: colorless crystals from petroleum benzine; mp 125—130 °C; IR: 3400, 2900, 1600 cm^{-1}; NMR: δ 1.00 (s, 3H), 1.30 (s, 3H), 2.0—2.2 (m, 2H), 2.70 (s, 2H), 5.05 (q, 1H), 6.8—7.0 (m, 9H).

Relative Photoreactivities. A 100-ml benzene solution of each substrate (0.005 M) in the presence of 4-chromanol (0.005 M) and benzophenone (0.03 M) was irradiated for 20 min. After separation by PLC on silica gel with benzene, the NMR signal intensities for 4-chromanone at $\delta=4.39$ and 4-flavanones at $\delta=5.34$ ppm were measured. In the case of **4a** and **4b**, for which the photoreaction rates are slow compared to those of 4-chromanol, a 50-ml benzene solution containing **4a** (0.01 M), **4b** (0.01 M), and benzophenone (0.016 M) was irradiated for 3 h.

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