UV-induced isomerisation and ring transformation of (*E*)-3-arylidene-1-thiochromanones and -1-thioflavanones

Gábor Tóth,*[a] Judit Halász,[a] Albert Lévai,[b] Csaba Nemes[b] and Tamás Patonay[b]

[a] *Technical Analytical Research Group of the Hungarian Academy of Sciences,*
Institute for General and Analytical Chemistry, Technical University, St. Gellért tér 4,
H-1111 Budapest, Hungary
[b] *Department of Organic Chemistry, Lajos Kossuth University, Egyetem tér 1,*
H-4010 Debrecen, Hungary

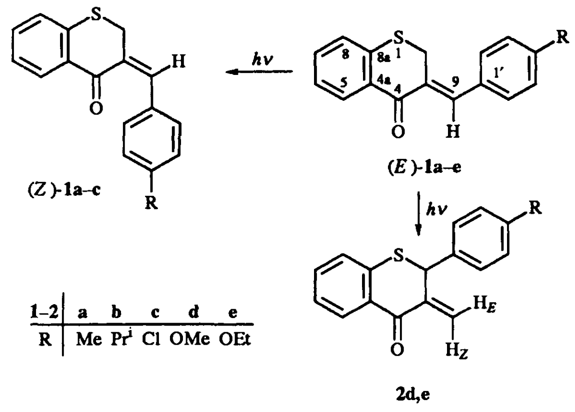
Depending on the substituent of the arylidene moiety, photoisomerisation of (*E*)-3-arylidene-1-thiochroman-4-ones 1 and 3 afforded either the expected (*Z*)-1 and (*Z*)-3 isomers or the products (2d,e and 4c,d) of an unprecedented phototransformation.

We have developed a simple and convenient method for synthesising (*E*)-3-arylidene-1-thiochroman-4-ones (*E*)-**1** and (*E*)-3-arylidene-2-phenyl-1-thiochroman-4-ones (*E*)-**3** [(*E*)-3-arylidene-1-thioflavan-4-ones] by the piperidine-catalysed reaction of 1-thiochroman-4-one or 1-thioflavan-4-one with aromatic aldehydes.[1–3] Since we planned a comparative investigation of the reactivities of the *E* and *Z* isomers of these compounds, it was necessary to develop an efficient method for the preparation of the *Z* isomers as well. Except for the (*Z*)-3-benzylidene-6-methyl-1-thioflavan-4-one[4] no substituted derivative of such *Z* compounds has hitherto been reported in the literature.

Previously we have reported that the UV-irradiation of (*E*)-3-benzylidene-chromanone and -flavanone and their 1-thio analogues resulted in the formation of their *Z* isomers.[5,6] Now we aim to prepare derivatives of these compounds substituted in the arylidene moiety. ^{1}H NMR data of the *E* and *Z* isomers show a characteristic downfield shift (*ca.* 0.3 ppm) of the $\delta_{2\text{-H}_2}$ chemical shift of the *E* isomers compared with those of the *Z* isomers as a result of the spatial proximity of the aryl group, while a paramagnetic shift was observed for the $\delta_{9\text{-H}}$ signal due to the anisotropy of the C-4=O moiety.[5,7] ^{13}C NMR investigations revealed a γ-steric interaction on the C-2 signal of the *E* isomers which resulted in a 5–8 ppm upfield shift in comparison with the *Z* isomers. In the *E* isomers there is conjugation between the C-4=O and C-9 aryl group, while in the *Z* isomers, because of steric reasons, the C-9 aryl moiety is nearly perpendicular to the plane of the carbonyl group, which is reflected in a $\Delta\delta$ *ca.* 1 ppm C-4 downfield shift in these isomers.[6] These observations make possible an unambiguous differentiation of the *Z* and *E* isomers.[6]

Results and discussion

(*E*)-3-Arylidene-1-thiochroman-4-ones [(*E*)-**1a–e**] in anhydrous benzene dried on sodium was irradiated with a mercury arc lamp (Scheme 1). The careful drying of the solvent with sodium is essential to eliminate the acid traces which may help the reconversion of the *Z* isomers formed into the starting *E* isomers. For the same reason, acid-free C_6D_6 and $CDCl_3$ were used for the 250 and 62.5 MHz NMR studies. Photoisomerisation of (*E*)-**1a–c** afforded (*Z*)-**1a–c** as sole isolable products in moderate yields (35–46%). A longer irradiation time resulted in an increase in decomposition instead of a higher yield. However, the same reaction of compounds (*E*)-**1d,e** gave 3-methylidene-1-thioflavan-4-ones (**2d,e**) and no *Z* isomers could be detected in the reaction mixtures.



1–2	a	b	c	d	e
R	Me	Pr^i	Cl	OMe	OEt

Scheme 1

Table 1 ^{1}H Chemical shifts of (*Z*)-**1** and **2** (C_6D_6)

	(*Z*)-**1a**[a]	(*Z*)-**1b**	(*Z*)-**1c**	**2d**	**2e**
2-H	3.91	3.37	3.35	4.89	4.81
5-H	8.28	8.49	8.38	8.46	8.30
6-H	7.25	6.90	6.91	6.87	6.78
7-H	7.40	6.96	6.99	6.93	6.85
8-H	7.31	7.11	7.10	7.09	6.98
9-H_E	6.93	6.57	6.34	5.09	5.00
9-H_Z	—	—	—	6.48	6.35
2′,6′-H	7.48	7.68	7.32	7.29	7.18
3′,5′-H	7.17	7.11	7.13	6.73	6.65
Others	Me	Pr^i		OMe	OEt
	2.39	2.75		3.32	3.50
		1.18			1.07

[a] Measured in acid free $CDCl_3$.

On the basis of ^{1}H and ^{13}C NMR measurements it can be concluded that instead of the S–C-2H$_2$–C-3=C-9–Ar moiety of the 3-arylidene-1-thiochromanones an S–C-2H–C-3=C-9H$_2$ structural element has been introduced (Tables 1 and 2). In the ^{1}H NMR spectrum the 2-H signal is broad and non-resolved at 4.89 and 4.81 ppm, respectively, while the 9-H_Z 6.48/6.35 and 9-H_E 5.09/5.00 signals of the terminal methylidene group are triplets with a 1.5 Hz coupling constant [^2J(9-H_E, 9-H_Z) ≈ ^4J(2-H, 9-H) ≈ 1.5 Hz]. The assignment was corroborated by the 9-H_z (33.6%), 2-H (2.2%) and 2′,6′-H (1.5%) NOE values measured on the irradiation of the 9-H_E. A *ca.* 1.4 ppm difference in the chemical shifts of the terminal methylidene protons is a consequence of the anisotropic effect of the C-4=O

Table 2 ^{13}C Chemical shifts of **1** and **2** (C_6D_6)

	(*Z*)-**1a**[a]	(*Z*)-**1b**	(*Z*)-**1c**	**2d**	**2e**
C-2	36.8	37.1	36.8	50.2	50.3
C-3	130.8	131.6	133.0	145.5	145.6
C-4	186.6	186.4	186.0	185.1	185.0
C-4a	131.9	133.2	133.9	132.3	132.3
C-5	129.7	130.2	130.2	130.3	130.3
C-6	124.9	125.3	125.4	125.9	125.9
C-7	132.7	132.9	133.2	133.3	133.3
C-8	127.2	127.5	127.6	127.9	127.9
C-8a	141.3	141.9	141.9	140.7	140.8
C-9	137.4	137.6	135.9	123.6	123.6
C-1′	132.0	133.1	132.7	129.4	129.2
C-2′,6′	129.4	130.6	131.5	129.8	129.8
C-3′,5′	128.6	126.4	128.4	114.3	114.8
C-4′	138.6	149.8	134.6	159.8	159.2
Others	Me	Pr^i		OMe	OEt
	21.1	34.2		54.7	63.2
		23.8			14.8

[a] Measured in acid free $CDCl_3$.

Table 3 Results of semi-selective 1D INEPT [*J*(C,H) = 7 Hz] measurements

	Proton	Carbon
(*Z*)-**1a**	2-H$_2$	C-3; C-4; C-8a; C-9
	9-H	C-2; C-3; C-4; C-1′; C-2′,6′
(*Z*)-**1b**	2-H$_2$	C-3; C-4; C-8a
	9-H	C-4; C-2′,6′
	9-H[a]	C-2; C-3; C-4; C-1′
(*Z*)-**1c**	2-H$_2$	C-3; C-4; C-8a; C-9
	9-H	C-2; C-3; C-4; C-2′,6′
	9-H[a]	C-2; C-3; C-4; C-1′; C-2′,6′
2d	2-H	C-3; C-4; C-8a; C-9; C-1′; C-2′,6′
	5-H	C-4; C-7; C-8a
	8-H	C-4a; C-6

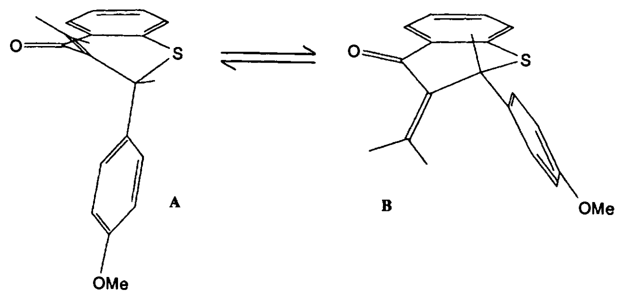
[a] *J*(C,H) = 3 Hz.

group on the neighbouring proton. The presence of the S–C-2H–C-3=C-9H$_2$ structural unit has been proven by ^{13}C DEPT measurements. The C-9 signal showed a *ca.* 14 ppm diamagnetic shift and the C-2 signal a *ca.* 13 ppm paramagnetic shift in the rearranged products **2** compared with the (*Z*)-3-arylidene-1-thiochroman-4-ones **1**, which is in accordance with the presence of the aryl substituent on C-2 instead of C-9. A further proof of this fact is the semi-selective 1D INEPT[8] measurement starting from 2-H, optimised for the *J*(C,H) = 7 Hz long-range coupling, which reveals the carbon atoms at two or three bond distances (C-1′, C-2′,6′, C-3, C-4, C-8a and C-9) (Table 3). Semi-selective 1D INEPT measurements starting from 5-H and 8-H allowed the unambiguous assignment of the ^{13}C signals of the condensed aromatic ring. The significant paramagnetic shift of C-3 signals (*ca.* 14 ppm) in the case of the ring-transformed products **2** is in accordance with the fact that a phenyl group in the β-position of the C-3=C-9 double bond results in a diamagnetic shift, while a phenyl group at the β-position of the C-3–C-2 single bond results in a paramagnetic shift.

Conformational effects

In the course of the conformational analysis of the (*E*)- and (*Z*)-3-arylideneflavanones and their thio analogues we have found that the condensed six-membered ring may adopt two, energetically slightly different envelope conformers (**A** and **B**) where the C-2 phenyl group is axial in **A** and equatorial in **B**.[6] In flavanone and 1-thioflavanone the equatorial arrangement of the C-2 phenyl group is more favourable than the axial one. In the *E* and *Z* isomers, as a result of the presence of the C-3 *exo* double bond the axial position is more favourable owing to the 1,3-allylic strain,[9] and the ratio of the envelope **A** is enhanced in the conformational equilibrium. In the *E* isomer as a result of a steric interaction between the C-2 phenyl group and the *peri*-positioned β-substituent of the *exo* double bond, the **A** $\rightleftharpoons$ **B** conformational equilibrium is shifted in the direction of **A** (*ca.* 90%). It has also been concluded that the ^3J(C-8a, 2-H) coupling constants make possible a nearly quantitative description of the **A** $\rightleftharpoons$ **B** conformational equilibrium. Investigation of model compounds show that the expected coupling constant values are *J*(C-8a, 2-H$_{eq}$) *ca.* 8 Hz and *J*(C-8a, 2-H$_{ax}$) *ca.* 1 Hz. In compound **2d** *J*(C-8a, 2-H) is 3.6 Hz which reveals an **A** : **B** conformer ratio of *ca.* 37 : 63.

In the case of compound **2d** AM1 (Mopac-6, version 1990)[10] calculations have also been performed and the results are in accordance with the NMR data (the energies of the two conformers are very similar with ΔE *ca.* 1.3 kcal mol^{-1}† in favour of the **B** conformer). Conformation of the C-2 aryl group can be evaluated from the ^3J(C-2′,6′,2-H) coupling constants. If the C-2–H bond and the connecting C-2–aromatic ring are coplanar, the coupling constant should be 5–6 Hz which gradually decreases with the ratio of this conformer.[5,6,11] Conformational analysis is made difficult by the fact that an **A** $\rightleftharpoons$ **B** conformational equilibrium should be considered in the case of compound **2d**. In conformer **B** the *exo* double bond is in spatial proximity to the aromatic ring which adopts a perpendicular position to this and, therefore, the C-2′–C-1′–C-2–2-H moiety is almost coplanar. In the case of compound **2d** the AM1 calculations gave the dominant conformer of the aryl group for both conformers (see Scheme 2). The C-2′–C-1′–C-2–2-H dihedral angle is 11° for conformer **B** and −56° for conformer **A**. ^3J(C-2′,6′,2-H) = 4.2 Hz coupling constant, an average value determined by semi-selective 2D INEPT[12] measurement is in accord with the results of the semi-empirical calculations, since 5–6 and 2–3 Hz coupling constants belong to dihedral angles 11 and 56°, respectively, and the observed value belongs to a fast equilibrium.



Scheme 2 Preferred conformations of compound **2d** obtained by AM1

Mechanism for ring transformation

The unprecedented ring transformation of compounds (*E*)-**1d**,**e** may probably take place as shown in Scheme 3. Homolytic splitting of the S–C-2 bond maybe promoted by the stabilisation of the radical centre on the arylidene group with alkoxy substituent.

(*E*)-3-Arylidene-1-thioflavan-4-ones **3** have also been included in our study. Since beside the *E*→*Z* isomerisation a ring transformation may take place as well, formation of four products, *viz.* (*E*)-**3**, (*Z*)-**3**, (*E*)-**4** and (*Z*)-**4** (Scheme 4) should be considered. Irradiation of the (*E*)-**3a**,**b** resulted in the formation of (*Z*)-**3a**,**b** which is reflected in the characteristic changes of the 2-H; 9-H and C-2 chemical shift values (Table 4). In the case of (*E*)-**3c** a mixture was obtained and in the ^{1}H spectrum two major components (55 and 28%) and two minor components

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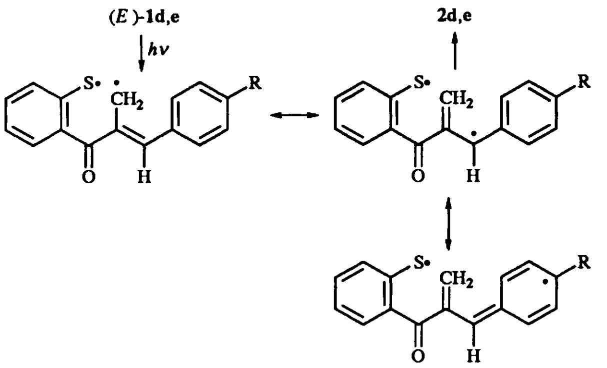
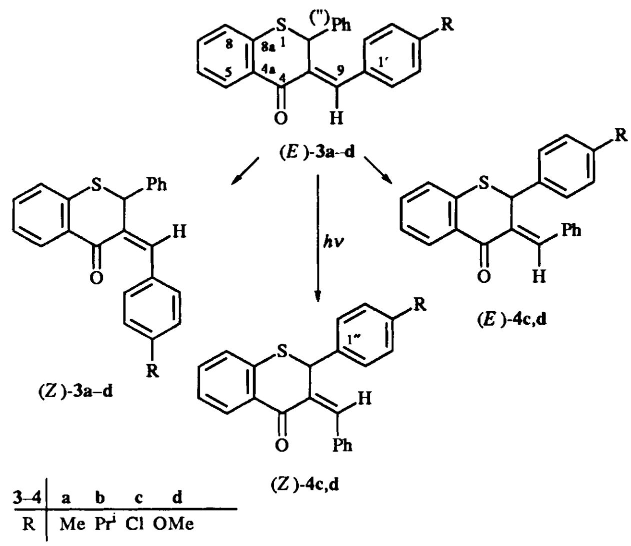
† 1 cal = 4.184 J.



Scheme 3



Scheme 4

Table 4 Characteristic ^1H and ^{13}C chemical shifts of 3 and 4 (C_6D_6)[a]

	$\delta_{2\text{-H}}$	$\delta_{9\text{-H}}$	$\delta_{C\text{-}2}$	$\delta_{C\text{-}4}$	$\delta_{C\text{-}9}$	$\delta_{C\text{-}1''}$
(*Z*)-**3b**	4.98	6.73	53.9	187.2	137.7	
(*E*)-**3b**	5.77	8.32	46.4	185.6	138.7	
(*Z*)-**3c**	4.93	6.48	53.2	186.9	136.1	
(*Z*)-**4c**	4.76	6.62				
(*E*)-**3c**	5.53	8.04	46.0	185.4	137.0	
(*E*)-**4c**	5.55	8.20				
(*Z*)-**3d**	4.99	6.72	54.0	187.2	137.1	138.1
(*Z*)-**4d**	5.01	6.70	53.2	187.4	137.9	129.1
(*E*)-**3d**	5.79	8.30	46.4	185.5	138.8	140.7
(*E*)-**4d**	5.71	8.24				

[a] The chemical shifts of compounds **3**–**4c**,**d** were obtained from the spectra of the isomeric mixtures.

(7 and 10%) have been detected, but in the ^{13}C NMR spectra assignment of only the two major components could be made. On the basis of the 2-H, 9-H and C-2 signals, the component which is present in 55% is (*Z*)-**3c** and that present in 28% is the starting compound (*E*)-**3c**.

Irradiation of (*E*)-**3d** resulted in the formation of four products as well. The two *Z* isomers [(*Z*)-**3d** and (*Z*)-**4d**] have been differentiated by the C-1″ chemical shift since it is known that a *p*-OMe group results in a *ca.* 8 ppm diamagnetic shift. Semi-selective 1D INEPT measurements starting from the 2-H of the *Z* compound and optimised for *J*(C,H) = 7 Hz long-range coupling revealed the C-3, C-4, C-8a, C-9, C-1″ and C-2″,6″ signals. In (*Z*)-**3d** $\delta_{C\text{-}1''}$ is 138.1 ppm and 129.1 ppm in (*Z*)-**4d** which prove that in the latter isomer a *p*-OMe–phenyl group is connected to the C-2 atom, *viz.* a ring transformation took place due to the irradiation, similar to 3-arylidene-1-thiochroman-4-ones. Prolongation of the irradiation time resulted in a pronounced decomposition of **3** and **4** and after 12 h irradiation they could not be detected in the reaction mixture by NMR spectroscopy. Irradiation for 3 h resulted in *ca.* 50% decomposition and the formation of a four component mixture (*Z*)-**3d**:(*Z*)-**4d**:(*E*)-**3d**:(*E*)-**4d** = 1:2:1:1. We failed to isolate the rearranged products (*Z*)-**3d** and **4c**,**d** from the reaction mixture.

Table 5 Physical constants of the isolated products

Compound	Formula[a]	Yield (%)	Mp/°C
(*Z*)-**1a**	$C_{17}H_{14}OS$	35	53–55
(*Z*)-**1b**	$C_{19}H_{18}OS$	41	Yellow oil
(*Z*)-**1c**	$C_{16}H_{14}ClOS$	46	Yellow oil
2d	$C_{17}H_{14}O_2S$	42	94–95
2e	$C_{18}H_{16}O_2S$	36	77–78
(*Z*)-**3a**	$C_{23}H_{18}OS$	55	Yellow oil
(*Z*)-**3b**	$C_{25}H_{22}OS$	39	Yellow oil
(*Z*)-**3c**	$C_{22}H_{15}ClOS$	42	Yellow oil

[a] Elemental analyses (C,H) were in good agreement with the calculated values.

In summary, we have observed an unprecedented phototransformation of alkoxy substituted 3-arylidene-1-thiochroman-4-ones leading to 3-methylene-1-thioflavan-4-ones. This reaction may serve as a synthetic procedure for the preparation of 3-methyldiene-1-thioflavan-4-ones. A similar phototransformation with the analogous 3-arylidene-1-chroman-4-ones and 3-arylidene-1-flavan-4-ones was not observed.[7,13–15] The only example of such compounds is the 3-methylidene-1-thioflavan-4-one itself obtained by the reaction of 1-thioflavan-4-one with bis(dimethylamino)methane.[16]

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC-250 spectrometer at room temperature in $CDCl_3$ or in C_6D_6. Chemical shifts are given on the δ scale and referenced to internal TMS. In the 1D measurements 32 K data points were used for the FID. A delay time of 5 s was applied for homonuclear NOE experiments. The 1D semi-selective INEPT measurements were optimised for *J*(C,H) = 7 Hz coupling and 25 Hz selectivity. In the 2D semi-selective INEPT measurement the data matrices were 8 K × 64 data points and the spectral width in the F1 (proton) dimension was 10 Hz.

General procedure for the photoisomerisation of (*E*)-1a–e and (*E*)-3a–d

Compounds (*E*)-**1a**–**e** and (*E*)-**3a**–**d** (10 mmol) were dissolved in anhydrous benzene (300 cm^3) and irradiated with a 400 W mercury arc lamp at ambient temperature for 3 h. The solvent was evaporated under reduced pressure (*ca.* 20 Torr) and the residue was purified on a silica gel (Merck) column using dichloromethane:hexane (3:2 v/v) as eluent to afford substances (*Z*)-**1a**–**c**, **2d**,**e**, (*Z*)-**3a**–**c** (Schemes 1 and 4, Table 5).

Acknowledgements

The authors are grateful to the Hungarian National Research Foundation (Grant No. OTKA T 014864) and to the European Communities (COST Project D2/0005/94) for financial support. J. H. thanks the J. Varga Foundation (Budapest, Hungary) for a fellowship and Cs. N. the UNIVERSITAS Foundation of the Hungarian Commercial Bank (Debrecen, Hungary) for a grant.

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Paper 5/06316G
Received 25*th September* 1995
Accepted 1*st November* 1995