AN EFFICIENT PROCEDURE FOR THE PREPARATION OF 4-THIOFLAVONES BY THE REACTION OF FLAVONES WITH LAWESSON'S REAGENT

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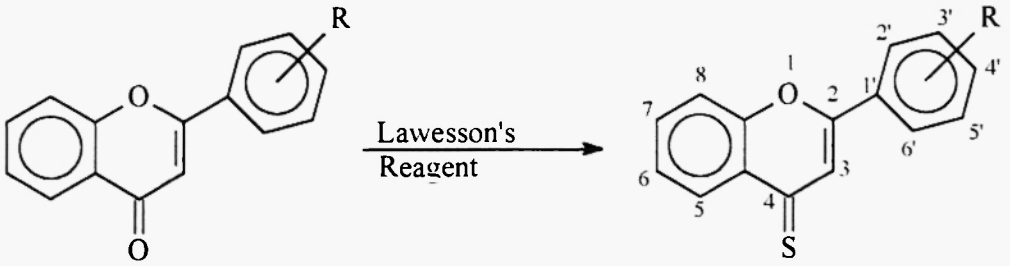
Dedicated to Prof. Dr. György Kalaus on the occasion of his 60th birthday

Abstract: A simple and convenient procedure has been worked out for the preparation of 4-thioflavones by the reaction of flavones with Lawesson's Reagent.

Flavones (2-phenyl-4*H*-1-benzopyran-4-ones) are well known natural products of the plant kingdom (1-3), some of which have been found to possess important bioactivities (4,5). To obtain even more potent derivatives, quite a large variety of their chemical transformations have been performed. However, their conversion into 4-thioflavones has hitherto received less attention, although such sulfur-containing flavones may be useful intermediates for further transformations and/or may offer new and advantageous bioactivities as well. The unsubstituted 4-thioflavone was prepared by several research groups (6-12). For this purpose, mainly phosphorus pentasulfide was used as a thiation agent. In one case (10) this source of sulfur-atom was replaced by silicon disulfide or boron sulfide, but these two reagents are, unfortunately, extremely sensitive to water. Again, according to our knowledge, the conversion of flavones into 4-thioflavones *via* 4,4-dichloro-flavenes has hitherto been published in one case (11). Since this conversion of substituted flavones has been described only in few cases (11,13-15), the data available do not make possible to evaluate the influence of the substituents on the thiation of the flavones. For this reason, our aim was to find an effective thiation agent which acts under simple and convenient reaction conditions and offers beneficial yields irrespective of the substitution pattern of the starting flavone. In our previous studies (16-18), the Lawesson's Reagent (19) proved to be the choice of thiation agent for the conversion of chromones and 1-thiochromones into their 4-thio analogues. We report herein on the utilization of this versatile thiation agent for the conversion of flavones into 4-thioflavones.

Scheme 1



1 - 12 **13 - 24**

1, 13: R = 4-Me
2, 14: R = 2-OMe
3, 15: R = 3-OMe
4, 16: R = 4-OMe
5, 17: R = 3,4-$(OMe)_2$
6, 18: R = 3,5-$(OMe)_2$
7, 19: R = 3,4,5-$(OMe)_3$
8, 20: R = 2-Cl
9, 21: R = 4-Cl
10, 22: R = 2,4-Cl_2
11, 23: R = 3,4-Cl_2
12, 24: R = 4-NO_2

Flavones **1-12** were allowed to react with Lawesson's Reagent in hot anhydrous toluene to afford 4-thioflavones **13-24** (Scheme 1). Structures of compounds prepared have been elucidated by microanalysis, IR and ^{1}H- and ^{13}C-NMR spectroscopies (*cf.* Experimental). In the IR spectra the disappearance of the C=O band and the appearance of a C=S band at around 1150-1180 cm^{-1} unequivocally prove the replacement of the oxygen by a sulfur atom. This finding was corroborated by the C=S signal observed in their ^{13}C-NMR spectra between 201.5 and 203.0 ppm. The whole ^{1}H- and ^{13}C-NMR spectra were in full harmony with the presence of a 4-thioflavone skeleton.

In summary, our present results demonstrate that the Lawesson's Reagent (19) can be beneficially utilized for the conversion of flavones into 4-thioflavones. All 4-thioflavones (**13-24**) were obtained in high yields indicating that this conversion is not influenced by the substitution pattern of the 2-phenyl ring.

Experimental

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200/50 MHz in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm) at room temperature. The IR spectra (KBr discs) were measured with a Perkin-Elmer 16 PC instrument. TLC was performed on Kieselgel 60 F_{254} (Merck) layers using hexane:acetone (7:3 v/v) as eluent. Starting materials **1-12** were synthesized from the appropriate 2'-hydroxychalcones by known method (20,21).

General procedure for the preparation of compounds **13-24**

A mixture of flavone (**1-12**, 5.0 mmol), Lawesson's Reagent (3.0 mmol) and anhydrous toluene (30 ml) was refluxed for 3h. The solvent was evaporated under reduced pressure and the residue was crystallized from methanol to afford 4-thioflavones **13-24** (Scheme 1).

4'-Methyl-4-thioflavone (13): This compound was obtained as purple crystals in 83% yield, m.p. 144-145 °C [Lit. (14) m.p. 145-146 °C]; IR (ν cm^{-1}): 1171 (C=S); 1604 (C=C); ^{1}H-NMR (δ): 2.44 (s, 3H, Me), 7.26-8.62 (m, 8 arom. H + 2-H); ^{13}C-NMR (δ): 129.8 (C-3), 157.7 (C-2), 202.6 (C-4).

Anal. Calcd. for $C_{16}H_{12}OS$: C, 76.17; H, 4.79. Found: C, 76.08; H, 4.82.

2'-Methoxy-4-thioflavone (14): This substance was prepared as red plates in 75% yield, m.p. 122-123 °C; IR (ν cm^{-1}): 1177 (C=S), 1602 (C=C); ^{1}H-NMR (δ): 3.98 (s, 3H, Me), 7.02-8.62 (m, 8 arom. H + 2-H); ^{13}C-NMR (δ): 129.9 (C-3), 158.4 (C-2), 202.8 (C-4).

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.63; H, 4.51. Found: C, 71.54; H, 4.55.

3'-Methoxy-4-thioflavone (15): This compound was isolated as red crystals in 73% yield, m.p. 107-108 °C; IR (ν cm^{-1}): 1172 (C=S), 1608 (C=C); ^{1}H-NMR (δ): 4.91 (s, 3H, Me), 7.09-8.60 (m, 8 arom. H + 2-H); ^{13}C-NMR (δ): 130.0 (C-3), 154.1 (C-2), 202.5 (C-4).

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.63; H, 4.51. Found: C, 71.70; H, 4.48.

4'-Methoxy-4-thioflavone (16): This compound was obtained as purple plates in 86% yield, m.p. 143-144 °C [Lit. (13) m.p. 137 °C]; IR (ν cm^{-1}): 1180 (C=S), 1599 (C=C); ^{1}H-NMR (δ): 3.92 (s, 3H, Me), 7.02-8.64 (m, 8 aram. H + 2-H); ^{13}C-NMR (δ): 129.9 (C-3), 153.7 (C-2), 202.1 (C-4).

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.63; H, 4.51. Found: C, 71.58; H, 456.

3',4'-Dimethoxy4-thioflavone (17): This substnace was prepared as red crystals in 87% yield, m.p. 227-228 °C [Lit. (9) m.p. 229 °C]; IR (ν cm^{-1}): 1177 (C=S), 1595 (C=C); ^{1}H-NMR (δ): 3.98 (s, 3H, Me), 4.01 (s, 3H, Me), 6.97-8.61 (m, 7 arom. H + 2-H); ^{13}C-NMR (δ): 129.7 (C-3), 154.5 (C-2), 201.5 (C-4).

Anal. Calcd. for $C_{17}H_{14}O_3S$: C, 68.45; H, 4.73. Found: C, 68.51; H, 4.69.

3',5'-Dimethoxy-4-thioflavone (18): This compound was prepared as red crystals in 81% yield, m.p. 177-178 °C; IR (ν cm^{-1}): 1176 (C=S), 1608 (C=C); ^{1}H-NMR (δ): 3.88 (s, 6H, 2Me), 6.64-8.60 (m, 7 arom. H + 2-H); ^{13}C-NMR (δ): 130.1 (C-3), 154.2 (C-2), 202.6 (C-4).

3',4',5'-Trimethoxy-4-thioflavone (19): This compound was isolated as violet plates in 82% yield, m.p. 177-178 °C [Lit. (15) m.p. 166-167 °C]; IR (ν cm^{-1}): 1160 (C=S), 1604 (C=C), ^{1}H-NMR (δ): 3.97 (s, 3H, Me), 4.02 (s, 6H, 2Me), 7.23-8.64 (m, 6 arom. H + 2-H); ^{13}C-NMR (δ): 130.2 (C-3), 153.8 (C-2), 202.5 (C-4).

Anal. Calcd. for $C_{18}H_{16}O_4S$: C, 65.85; H, 4.91. Found: C, 65.78; H, 4.94.

2'-Chloro-4-thioflavone (20): This material was obtained as purple crystals in 84% yield, m.p.132-133 °C; IR (ν cm^{-1}): 1162 (C=S), 1612 (C=C); ^{1}H-NMR (δ): 7.29 (s, 1H, 2-H), 7.43-8.67 (m, 8 arom. H); ^{13}C-NMR (δ): 130.2 (C-3), 153.7 (C-2), 203.0 (C-4).

Anal. Calcd. for $C_{15}H_9ClOS$: C, 66.07; H, 3.32. Found: C, 66.12; H, 3.29.

4'-Chloro-4-thioflavone (21): This compound was isolated as red crystals in 75% yield, 196-197 °C [Lit. (14) mp. 196-198 °C]; IR (ν cm^{-1}): 1173 (C=S), 1619 (C=C); ^{1}H-NMR (δ): 7.29 (s, 1H, 2-H), 7.52-8.61 (M. 8 arom. H); ^{13}C-NMR (δ): 130.1 (C-3), 150.9 (C-2), 202.9 (C-4).

Anal. Calcd. for $C_{15}H_9ClOS$: C, 66.07; H, 3.32. Found: C, 66.11; H, 3.29.

2',4'-Dichloro-4-thioflavone (22): This compound was prepared as green crystals in 85% yield, m.p. 158-159 °C; IR (ν cm^{-1}): 1165 (C=S), 1610 (C=C); ^{1}H-NMR (δ): 7.29 (s, 1H, 2-H), 7.41-8.62 (m, 7 arom. H); ^{13}C-NMR (δ): 129.8 (C-3), 152.4 (C-2), 202.8 (C-4).

Anal. Calcd. for $C_{15}H_8Cl_2OS$: C, 58.66; H, 2.62. Found: C, 58.62; H, 2.64.

3',4'-Dichloro-4-thioflavone (23): This compoud was isolated as green crystals in 82% yield, m.p. 194-195 °C; IR (ν cm^{-1}): 1150 (C=S), 1605 (C=C); ^{1}H-NMR (δ): 7.28 (s, 1H, 2-H), 7.41-8.58 (m, 7 arom. H); ^{13}C-NMR (δ): 130.2 (C-3), 151.7 (C-2), 203.0 (C-4).

Anal. Calcd. for $C_{15}H_8Cl_2OS$: C, 58.66; H, 262. Found: C, 58.71; H, 2.59.

4'-Nitro-4-thioflavone (24): This substance was prepared as purple crystals in 78% yield, m.p. 249-250 °C; IR (ν cm^{-1}): 1171 (C=S), 1613 (C=C); ^{1}H-NMR (δ): 7.28 (s, 1H, 2-H), 7.43-8.59 (m, 8 arom. H); ^{13}C-NMR (δ): 130.5 (C-3), 151.6 (C-2), 203.0 (C-4).

Anal. Cald. for $C_{15}H_9NO_3S$: C, 63.61; H, 3.20. Found: C, 63.57; H, 3.22.

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