# Synthesis and Reactivity of Spiro[1,3,4-thiadiazoline-2,4′-thioflavans] and Analogues



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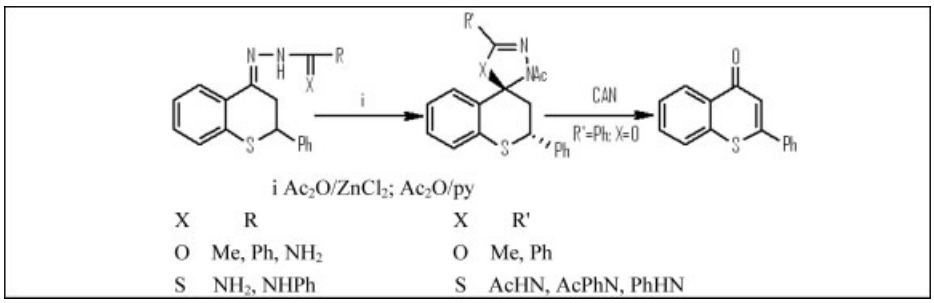


*Racemic* thioflavanone (thio)acylhydrazones undergo transformation into *racemic* 3-acetylspiro[1,3,4-oxa(thia)-diazoline-2,4′-thioflavans] with *trans* O(1) or S(1) and Ph(2′eq) under acetylating conditions. Conjugation between the ethylenic bond and $sp^2$ C(4) in thioflavones encumber both the formation of (thio)acylhydrazones and their subsequent spirocyclization. On the other hand, subsequent dehydrogenation of the thiopyran moiety of spiro compounds results in formation of $sp^2$ C(4) and simultaneous degradation of the spirodiazoline ring.

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## INTRODUCTION

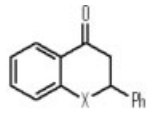
A great variety of natural benzopyrans, *e.g.*, chrom(an)ones, flav(an)ones, exhibit biological activity and have beneficial effects as free radical scavengers, antioxidants, CNS active agents, aldose reductase inhibitors [1], aromatase inhibitors [2], *etc*. Some synthetic (halogenated, nitro) derivatives have significant anxiolytic properties [3]. Carbonyl condensation products, *e.g.*, oximes [4], imines [5], acyl hydrazones, thiosemicarbazones [6] have been reported to display antimicrobial and estrogen receptor activities, respectively. Also flavone-related, naturally occurring 2-arylquinolines [7] and antimitotic 2-phenylquinolones [8] are known.

Recently, also the chemistry and the biological properties of the bioisosteric thioflavonoid compounds [9], including (spiro)heterocyclic derivatives [10], excite increasing interest. Thiochrom(an)ones and thioflav(an)ones as well as their 1-oxides and 1,1-dioxides have been reported to have antimicrobial [11], antiviral [12], and antitumor [8,9c,13] properties. The synthesis and herbicidal properties of benzothiopyran-4-one hydrazones [14a] and related cyclic *O*-*O*-acetals spiro[benzothiopyran-4,2′-dioxolanes] [14b] have been described, as well.

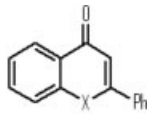
Formerly, we have observed that under physiological conditions the potentially biological active cyclic *N*,*O*- and *N*,*S*-acetals 3-acetyl-1,3,4-oxa(thia)diazolines undergo deacetylation and transform into (thio)acylhydrazones [15]. Therefore, in consideration of the aforementioned literature findings, as an extension of our examinations for the synthesis of 2-phenyltetrahydroquinoline (**5j**) [16] and flavanone-spiro-oxa(thia)diazolines (**5k**, **l**) [17a], respectively, we aimed at the synthesis of their bioisosteric spiro-thioflavonoid analogs [l7b].

## RESULTS AND DISCUSSION

As potential substrates for cyclization into oxa(thia)-diazolines **5a–i** under acetylating conditions, hydrazone derivatives **3** and **4** of thioflav(an)ones **1** and **2** were prepared from the corresponding carbonyl parent compounds **1** and **2**, respectively, by known methods (see Table 3 and Experimental section).



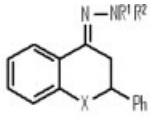
| | X |
|---|---|
| **1a** | S |
| **b** | SO |
| **c** | $SO_2$ |
| **d** | O |



| | X |
|---|---|
| **2a** | S |
| **b** | SO |
| **c** | $SO_2$ |
| **d** | O |

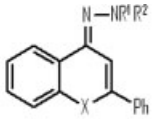
In comparison with aryl aralkyl ketones due to electronic (*e.g.*, conjugative) effects aryl vinyl ketones exhibit a diminished reactivity toward carbonyl condensation agents. This is markedly valid for the cyclic analogs (thio)flavones [18], capable of resonance between contributing (thio)benzopyrylium dipole structures. Moreover

also the oxidation state of sulfur in these unsaturated compounds (*e.g.*, **2a–c**) affects reactivity [19]. Nevertheless, analogously to the synthesis of flavone (acyl)hydrazones [18a,b] thioflavone hydrazone (**4a**) has been successfully produced [19b,c] by condensing hydrazine with thioflaven-4-thione [20] or its derivative 4-methylthioflavylium iodide [19b], instead of thioflavone (**2a**).

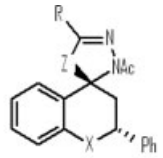


| | X | $R^1$ | $R^2$ |
|---|---|---|---|
| **3a** | S | H | H |
| **b** | S | H | Ac |
| **c** | S | Ac | Ac |
| **d** | S | H | CO-$NH_2$ |
| **e** | S | H | CS-$NH_2$ |
| **f** | S | H | CS-NHPh |
| **g** | $SO_2$ | H | CS-$NH_2$ |
| **h** | $SO_2$ | H | CO-$NH_2$ |
| **i** | $SO_2$ | H | CO-NHAc |
| **j** | S | H | CO-Ph |

As to the conjugation between the $sp^2$ C(4) and the C=C bond of the thioflaven ring, similarly to that previously found [17a] for the flavone analogs, this encumbered not only the formation of (thio)acylhydrazones but also their subsequent cyclization into spiro(thia)oxadiazolines. On the other hand, devoid of a chance for conjugation, dehydrogenation of the thiopyran ring of the spiroheterocycles **5** became difficult in comparison with that of the thioflavanone parent compound (**1a**) [21], nevertheless when eventually performed, it led to the cleavage of the diazoline rings with transformation of the spiro-C into the $sp^2$ hybrid state (C(4)=O,N). Therefore, the mutual action of the hybrid electron orbital states of C(4) and C(2), C(3) carbons was studied experimentally in detail with the (trans)formation of spirocompounds **5** and their precursors (acyl)hydrazones **3**, **4**, and related compounds as well.



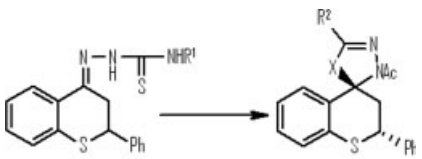
| | X | $R^1$ | $R^2$ |
|---|---|---|---|
| **4a** | S | H | H |
| **b** | S | H | Ac |
| **c** | S | Ac | Ac |
| **d** | S | H | CS-$NH_2$ |
| **e** | $SO_2$ | H | CS-$NH_2$ |
| **f** | $SO_2$ | H | Ac |
| **g** | S | H | CO-Ph |



| | X | Z | R |
|---|---|---|---|
| **5a** | S | O | Me |
| **b** | S | O | Ph |
| **c** | S | S | AcHN |
| **d** | S | S | PhHN |
| **e** | S | S | AcPhN |
| **f** | SO | O | Me |
| **g** | SO | O | Ph |
| **h** | $SO_2$ | O | Me |
| **i** | $SO_2$ | O | Ph |
| **j** | NAc | S | AcHN |
| **k** | O | O | Me |
| **l** | O | S | AcHN |

Spirocyclization of *racemic* thioflavanone (thio)acylhydrazones **3** into spiro(thia)oxadiazolines **5a–e** was accomplished (see Table 4) in good yields by using acetylating agents $Ac_2O$/py or $Ac_2O/ZnCl_2$ previously successfully applied [16,17,21] for (spiro)cyclization of various ketone (thio)acylhydrazones. As a result of the heterocyclization, C(4) of the thiopyran ring became $sp^3$ hybridized and asymmetric, thus theoretically enabling the formation of *racemic* 2,4-diastereomers. Newly spirothiadiazolines **5c**,**d**,**e** with trans S(1) and Ph($2'_{eq}$) structures were stated to form HPLC separable isomers in solution due to a hindered rotation of the endocyclic N(3)Ac group [17b] (Scheme 1). Recently, the stereostructure of 3-acetylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] (**5a**) and 3-acetylspiro[1,3,4-thiadiazoline-2,4′-thioflavans] (**5c**,**d**,**e**), prepared likewise under acetylating conditions, has been stated by $^1$H- and $^{13}$C NMR, as well as X-ray analytical methods and MOPAC QM calculations to have *trans* O(1) or S(1) and Ph($2'_{eq}$) [17b]. The ''anomalous'' $^1$H NMR spectra (remarkable downfield shift of signals H($3'_{ax}$), attributed to the anisotropy

**Scheme 1**



| | | | X | $R^2$ |
|---|---|---|---|---|
| **3e** | $R^1$=H | **5a** | O | Me |
| **f** | $R^1$=Ph | **c** | S | AcHN |
| | | **d** | S | PhHN |
| | | **e** | S | PhAcN |

**Table 1**

200 MHz $^1$H NMR($CDCl_3$) data of thioflavans **3a-c**.[a]

| Compound | δ (ppm) | | | *J* (Hz) | | | δ other |
|---|---|---|---|---|---|---|---|
| | $H(2_{ax})$ | $H(3_{ax})$ | $H(3_{eq})$ | $2_{ax},3_{ax}$ | $2_{ax},3_{eq}$ | $3_{ax},3_{eq}$ | |
| **3a** | 4.35 | 2.88 | 3.27 | 12.4 | 3.5 | 16.8 | 5.39 (2H,$NH_2$) |
| **3b** | 4.40 | 3.02 | 3.31 | 12.5 | 3.5 | 17.0 | 9.08 (NH), 2.38 (Ac) |
| **3c** | 4.47 | 2.92 | 3.08 | 11.5 | 3.5 | 15.5 | 2.34 (2Ac) |

[a] For data of **1a-c** see ref. [22a].

effect of the near *N*(3)Ac C=O group) are observed also in the present work (Tables 1 and 2) confirming the analogous stereostructure of spiro products **5a**,**b**,**f–i**. Treatment of semicarbazone **3d** with $Ac_2O/ZnCl_2$ at room temperature for **3d** afforded oxadiazoline **5a** (Scheme 2) but with $Ac_2O$/py at 100°C for 3 h **5a** and diacetylhydrazone **3c**. Similarly, on treatment with $Ac_2O$/py at 145°C (bath) for 45 min phenylthiosemicarbazone **3f** underwent transformation to give thiadiazoline **5e** (mp 192–194°C, from EtOAc) and oxadiazoline **5a** (mp 210.5–212°C, from $CHCl_3$/EtOAc), after purification by column chromatography, in 60 and 6% yields, respectively [17b]. The degradation of semicarbazones [23] and thiosemicarbazones [17a,23a,c] under acylating conditions is well documented. By treatment with $Ac_2O/ZnCl_2$ at room temperature, thioflavanone acetylhydrazone (**3b**) was transformed into spiro-oxadiazoline **5a** (see Scheme 2 and Table 4). Under similar conditions, however, semicarbazone 1,1-dioxide **3h** resisted cyclization and also degradation to the corresponding acetylhydrazone, instead acetylsemicarbazone **3i** was formed (Scheme 3), 200 MHz $^1$H NMR(DMSO-$d_6$, δ, ppm): 11.53 and 10.75, 2 brs, 2H, 2NH; 2.14, s, 3H, Ac. Attempted syntheses of **5h** and **5j** by treating **3h** and **3g**, respectively, with $Ac_2O$/pyridine at 100°C for 3 h resulted in the formation of multicomponent mixtures.

Thus, the tendency for spiro-cyclization seems to be diminished or even ceased by the presence of strong electron-withdrawing components at position 1. Therefore, the synthesis of spiro-oxadiazoline 1′-oxides and 1′,1′-dioxides was attempted by oxidation of the corresponding spirothioflavans. Hot $NaIO_4$/aq. 2-PrOH (substrate/oxidant ratio, 1:4) has been reported [24] to transform thioflavanone (**1a**) into thioflavone 1,1-dioxide (**2c**). Presumably due to the absence of a $sp^2$ hybridization at position 4, under similar conditions (mole ratio 1:8) spiro-oxadiazoline **5a** was transformed, without dehydrogenation, into a mixture of the corresponding 1′-oxide **5f** and 1′,1′-dioxide **5h**. The selective syntheses of sulfoxides **5a**→**5f** and **5b**→**5g** were accomplished by treatment with $NaIO_4$/aq. 2-PrOH or with dimethyldioxirane generated *in situ* by potassium peroxymonosulfate ($2\ KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in aq. $Me_2CO$. Potassium permanganate oxidation of spiro-oxadiazoline **5a**,**b** afforded the corresponding sulfones **5h**,**i** in very good yields (see Scheme 4 and Experimental section).

The effect of a C(2)=C(3) unsaturation and also that of the oxidation state of sulfur in the benzo heterocycle

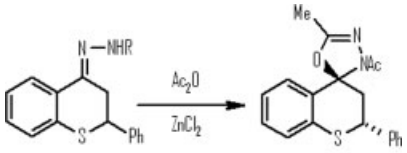
**Table 2**

200 MHz $^1$H NMR($CDCl_3$) data of 5-substituted 3-acetylspiro[1,3,4-oxadiazoline-2,4′-thioflavans] as well as 1′- and 1′,1′-oxides **5a,b,f–i**.

| Compound | δ (ppm)[a] | | | *J* (Hz) | | | δ $CH_3$ |
|---|---|---|---|---|---|---|---|
| | $H(2'_{ax})$ | $H(3'_{ax})$ | $H(3'_{eq})$ | $2'_{ax},3'_{ax}$ | $2'_{ax},3'_{eq}$ | $3'_{ax},3'_{eq}$ | |
| **5a** | 4.70 | 3.59 | 2.50 | 13.3 | 2.1 | 13.8 | [b] |
| **5b** | 4.83 | 3.65 | 2.62 | 13.5 | 2.0 | 14.0 | [c] |
| **5f** | 4.40 | 3.66 | 2.57 | 7.4 | 0.8 | 8.5 | [d] |
| **5g** | 4.55 | 3.74 | 2.70 | 13.5 | 1.5 | 15.5 | [e] |
| **5h** | 4.90 | 4.33 | 2.63 | 13.5 | 1.3 | 14.7 | [f] |
| **5i** | 5.03 | 4.40 | 2.75 | 13.6 | 1.7 | 14.7 | [g] |

[a] The $H(3'_{ax})$ signals of spiro compounds are downfield shifted in comparison with those of hydrazones **3** (cf. Table 1). This can be attributed to the carbonyl neighbouring anisotropy effect of Ac(3) [17b].
[b] 2.28, Ac(3); 2.07, Me(5).
[c] 2.40, Ac(3); 2.08, Me(5).
[e] 2.39, Ac(3).
[f] 2.31, Ac(3); 2.07, Me(5).
[g] 2.44, Ac(3).

**Scheme 2**

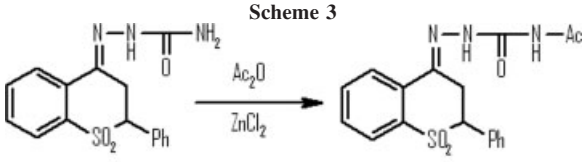



**3e** R=H **b** R=Ac **5a**

could be well demonstrated. Thus, though treatment with $Ac_2O$/py at 100°C has been reported [17a] to transform flavone thiosemicarbazone into the corresponding diacetylhydrazone, a similar treatment of thioflavone thiosemicarbazone (**4d**) afforded (see Experimental section) spirothiadiazoline **6** and diacetylhydrazone **4c** in 56 and 18% yields, respectively. However, on treatment with $Ac_2O$/py even under milder conditions (see Experimental section), thioflavone 1,1-dioxide thiosemicarbazone (**4e**) was degraded to acetylhydrazone **4f** in 69% yield and no 3-acetyl-5-acetylaminospiro[1,3,4-thiadiazoline-2,4′-thioflaven] 1′,1′-dioxide could be isolated (Scheme 5).

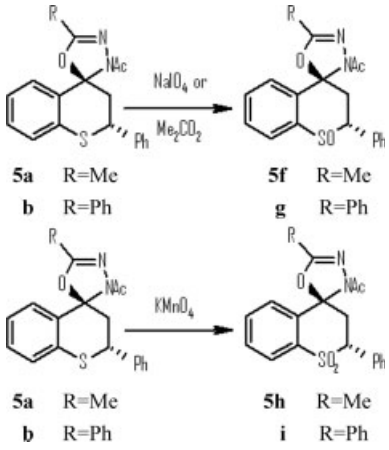
As an alternative rout for preparing spiro[oxa(thia)-diazoline-2,4′-thioflavens] the dehydrogenation of the corresponding thioflavan analogs **5** was investigated. The powerful one-electron acceptor oxidant CAN is known [24,25] to dehydrogenate thioflavanone (**1a**) to thioflavone (**2a**) readily at room temperature. However, for transforming spirothioflavans **5** into the corresponding thioflaven analogs, CAN turned out to be unsuitable as this agent transformed **5b** into thioflavone (**2a**) with simultaneous degradation of the spiro-oxadiazoline moiety (see Scheme 6 and Experimental section). This early experience prompted us to investigate the dehydrogenation of thiopyran [21,24,22] and that of the *N*,*S*-acetal 1,3,4-thiadiazoline [26] or *N*,*O*-acetal 1,3,4-oxadiazoline [27] systems separately, by using various types of oxidants and dehydrogenating agents of diverse mechanisms of action. Also the attempts for dehydrogenating the thiopyran ring of spirocompound **5** by iodobenzene 1,1-diacetate (IBDA, (diacetoxyiodo)-benzene) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced unsatisfactory results. After treating spiro-oxadiazoline **5a** with IBDA for preserving the diazoline moiety at room temperature in AcOH for 7 d or in MeOH for 14 d the substrate could be recovered in *ca*. 60% yield.

**Scheme 3**




**3h** **3i**

**Scheme 4**




**5a** R=Me **b** R=Ph **5f** R=Me **g** R=Ph

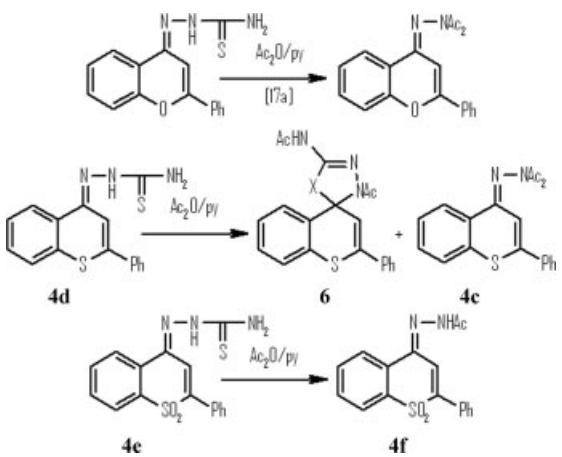
**5a** R=Me **b** R=Ph **5h** R=Me **i** R=Ph

Moreover, reaction of spiro-oxadiazoline **5b** with hot DDQ/dioxane/TsOH led to the formation of a mixture comprising substrate **5b** and degradation product thioflavone **2a**.

For dehydrogenation of the benzoheterocycle, in comparison with flavanones, as an additional reaction rout is known the transformation of thiochromanone 1-oxides (*e.g*. **1b**) into thiochromones (*e.g*. **2a**) in alkaline solution [28,19b] or under Pummerer-type reaction conditions [29,19b,25b]. Thus, treatments with $Ac_2O$/TsOH or $Ac_2O$/dimethylaminopyridine (DMAP) have been reported [22b] to transform **1b** into **2a**, but with the $Ac_2O/Et_3N$ couple *via* cleavage of the thiopyran ring, into disulfide **7** (Scheme 6).

On the basis of these findings, the dehydrogenation of spirocompounds **5** (X = S) to the corresponding spirothioflavens *via* transformation of the spirothioflavan 1-oxides (X = SO) under acetylating conditions in the presence of acid or base (nucleophilic) catalysts, hence under circumstances successfully applied just for the

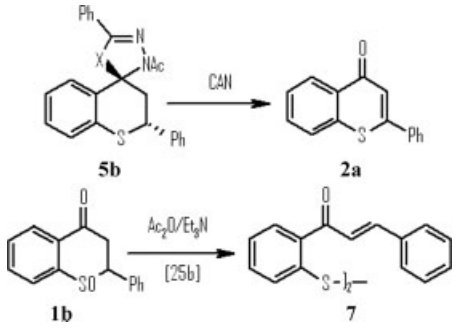
**Scheme 5**




**4d** **6** **4c**

**4e** **4f**

**Scheme 6**

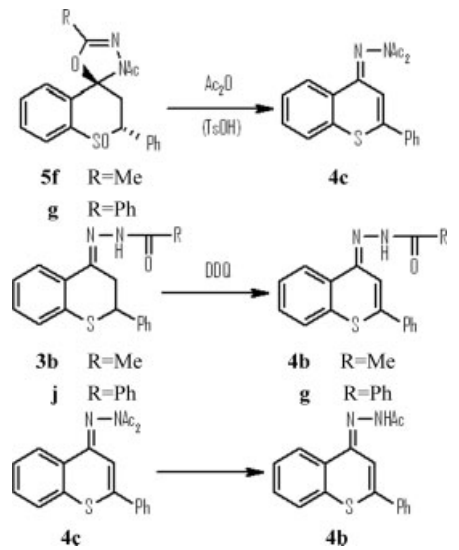


spirocyclization, seemed to be feasible. However, presumably due to the lack of a $sp^2$ C(4) moiety similar treatments of sulfoxide **5f** with $Ac_2O/Et_3N$ at room temperature for 48 h and that of **5g** with the $Ac_2O$/DMAP couple at room temperature for 72 h or with $Ac_2O$/py at 100°C for 22 h were found to be ineffective and the unchanged substrates could be recovered in 78, 90, and 67% yields, respectively. Treatment with $Ac_2O$/(TsOH) transformed spirothioflavan 1′-oxides, both **5f** and **5g**, into thioflavone diacetylhydrazone (**4c**) with cleavage of the oxadiazoline ring and a subsequent transacetylation, respectively (see Experimental section); thus, 2,3-dehydrogenation of the benzothiopyran ring was accompanied by a $sp^3 \rightarrow sp^2$ change at C(4) (Scheme 7).

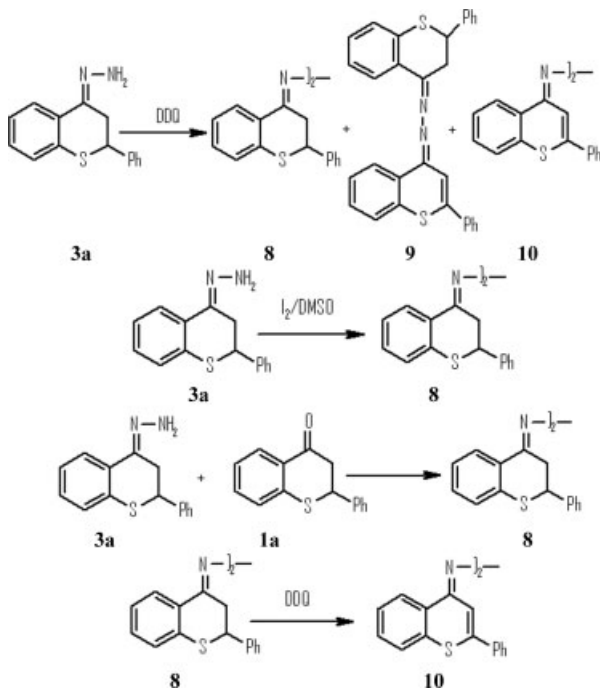
Owing to the unsatisfactory results with the dehydrogenation of spirocompounds **5**, also similar transformation of their nitrogen-containing precursors thioflavanone (acyl)hydrazones (**3**) with $sp^2$ C(4) was investigated. Treatment with DDQ dehydrogenated acylhydrazones **3b**,**j** to acetylhydrazone **4b** (prepared also by partial deacetylation of diacetylhydrazone **4c**, see Experimental section) and benzoylhydrazone **4g**, respectively, in very good yields, but it converted thiosemicarbazone **3e** in dioxane solution to give a multicomponent mixture. Reaction with DDQ transformed hydrazone **3a** into the corresponding azine **8** as well as its partially and fully dehydrogenated derivatives **9** and **10**, respectively. Azine **8** was obtained also by treating hydrazone **3a** with $I_2$/DMSO or by condensing hydrazone **3a** with thioflavanone (**1a**). DDQ dehydrogenation of azine **8** afforded azine **10** in 80% yield (see Scheme 8 and Experimental section). Attempts for dehydrogenating azine **8–10** by treatment with hot $NaIO_4$/aq. dioxane or hot IBDA/MeOH (or dioxane) were unsuccessful as in these cases very complex mixtures of products were formed. Hypervalent iodine oxidation of hydrazine [30] to the reductive, instable diimide and that of aromatic hydrazones to azines [31] have been reported already.

The synthesis of thioflavanone hydrazones [19b] (*e.g.*, by boiling thioflavanone **1a** with $N_2H_4 \cdot H_2O$/EtOH to give the corresponding hydrazone **3a**) is a clear-cut reaction. Because of a reversible flavanone (**1d**) $\rightleftharpoons$ 2′-hydroxychalcone (2-cinnamoyl-phenol, 2-hydroxyphenyl stiryl ketone) transformation, on treatment with hydrazine flavanone undergoes reaction, depending on the reaction conditions, to give the corresponding hydrazone and 3-(2-hydroxyphenyl)-5-phenyl-4,5-dihydropyrazole, respectively [32a,b,18e]. An analogous treatment of flavone (**2d**) with hydrazine or the thermal rearrangement of flavone hydrazone has been reported to afford the

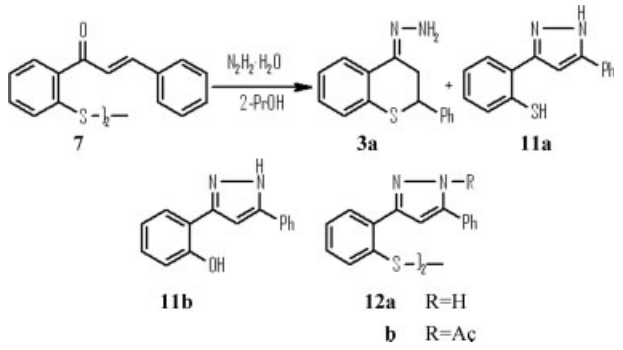
**Scheme 7**



**Scheme 8**



**Scheme 9**




corresponding pyrazole derivative **11b** [32b,18e]. As a result of the special electron shell structure the more pronounced nucleophilicity and the conjugative interaction of sulfur [19] within the heterocycle may appear in some characteristic properties of the molecule, thus extending our synthetic works with (thio)flavonoids [16,17a,21,24,22a] we (re)examined the reaction between thioflavone and hydrazine. Recently we have found [33] that the treatment of thioflavone (**2a**) with $N_2H_4 \cdot H_2O$ in hot 2-PrOH leads to the formation of 3-(2-mercaptophenyl)-5-phenylpyrazole (**11a**) which by a subsequent spontaneous oxidation in a $CHCl_3$ solution affords disulfide **12a**. (It is well known that the oxidation of alkyl- and arylthiols by molecular oxygen to disulfides may be catalyzed by aliphatic amines or alkali hydroxides [34].) As due to the possibility for a prototropic change, the structure of pyrazoles [35] with aromatic substituents cannot be unequivocally elucidated by IR and NMR spectrometry, this has been carried out [33] eventually by a MALDI-TOF mass spectrometric study of the acetyl derivative **12b**.

In connection with our previous findings [22b] that heterolysis of disulfide **7** leads to the formation of thioflavanone (**1a**) and 2-benzylidenebenzo[*b*]thiophen-3(2*H*)-one (thioaurone) we attempted the transformation of disulfide **7** with $N_2H_4 \cdot H_2O$/2-PrOH to obtain the 4,5-dihydro analogs of **11a** or **12a**. However, this reaction afforded thioflavanone hydrazone (**3a**) and pyrazole **11a** which was isolated as disulfide **12a** (see Scheme 9 and Experimental section).

## CONCLUSION

Thioflavanone (thio)acylhydrazones transform into 3-acetylspiro[1,3,4-(thia)oxadiazoline-2,4′-thioflavans] with trans S(l) or O(l) and Ph($2'_{eq}$) under acetylating conditions. The presence of 2,3-unsaturation or oxidation of sulfur of thioflav(an)one render more difficult both the synthesis of (thio)acylhydrazones and the subsequent spirocyclization. Additional 2′,3′-dehydrogenation of the spirocompounds with various dehydrogenating agents had no result or was accompanied by degradation of the spirodiazoline ring with a simultaneous $sp^3 \rightarrow sp^2$ change at C(4).

## EXPERIMENTAL

Melting points (uncorrected): Kofler block. Solutions were concentrated under reduced pressure in a rotary evaporator (<50°C, bath), TLC: Kieselgel 60 $F_{254}$ (Merck, Alurolle). IR (KBr disks): Perkin-Elmer 16 PC-FT spectrometer. 200 MHz $^1$H- and 50 MHz $^{13}$C NMR: Bruker WP 200 SY, 360 MHz $^1$H- and 90 MHz $^{13}$C NMR: Bruker AM 360 spectrometer; for recording the $^{13}$C spectra, *J*-echo techniques were used.

**General operations of processing the reaction mixtures** (see Tables 3 and 4). (**A**) The product was collected by filtration in the cold. (**B**) The cold mixture was poured into ice-water. (**C**) A solution of the product in $CHCl_3$ was treated with fuller's earth and charcoal and then concentrated. (**D**) For decomposing the excess of BzCl, drop-by-drop water (1.25 mL) was added with cooling and stirring and the mixture was kept at room temperature for 1 h. (**E**) The mixture was concentrated. (**F**) The residue was triturated with MeOH in the cold. (**G**) The residue was triturated with water in the cold.

**Dehydrogenation of thioflavanone (1a) by $PhI(OAc)_2$ to 2a.** A solution of **1a** (0.120 g, 0.5 mmol) and $PhI(OAc)_2$ (0.247 g, 0.75 mmol) in MeOH (5 mL) was kept at room temperature for 12 d and then concentrated (finally at *ca*. 1 Torr). A solution of the residue in MeOH (0.5 mL) deposited on seeding TLC homogeneous and with an authentic compound identical thioflavone (**2a**, 0.082 g, 68.6%; when reacted at boiling for 2 d, in a sixfold scale, a 86.2% yield has been observed [21]), mp 125.5°C.

***Thioflavone acetylhydrazone (4b).*** (**a**) A mixture of thioflavanone acetylhydrazone (**3b**, 0.371 g, 1.25 mmol), DDQ (0.307 g, 1.32 mmol, 98%), anhydrous dioxane (12 mL), and a catalytic amount of *p*-toluenesulphonic acid (TsOH) was boiled with stirring for 24 h, then cooled to give a solid (0.597 g, a mixture of **4b** and $DDQH_2$), which when stirred with aq. $NaHCO_3$ in excess, in the presence of some 2-PrOH as a humidifier, afforded undissolved title acetyl-hydrazone **4b** (0.250 g, 68%), mp 256–257°C.

(**b**) A mixture of diacetylhydrazone **4c** (0.168 g, 0.5 mmol), MeOH (10 mL) and pyridine (2 drops) was boiled with stirring for 6 h to give, on cooling, acetylhydrazone **4b** (0.131 g, 89%), mp 257.5°C. A similar partial deacetylation was observed during purification of **4c** by CC [Kieselge1 60, Merck; $CHCl_3$/EtOAc (95:5)], when **4b**, mp 258°C was isolated. IR(KBr, ν, $cm^{-1}$): 1666 (s, Amide-I). $^1$H NMR(200 MHz, DMSO-$d_6$, δ, ppm): 11.17 (s, 0.7 H, NH) and 10.79 (s, 0.3 H, NH) presumably due to an *E*/*Z* isomerism, 8.33–8.25 (m, 1 H, H(5)), 7.90–7.78 (m, 2 H, H—Ar), 7.61 (s, 1 H, H(3)), 7.58–7.43 (m, 6 H, H—Ar), 2,29 (s, 2.1 H, 0.7 Ac) and 2.07 (s, 0.9 H, 0.3 Ac). *Anal*. Calcd. for $C_{17}H_{14}N_2OS$ C, 69,4; H, 4.8; N, 9.5; S, 10.9. Found: C, 69.3; H, 4.8; N, 9.6; S, 11.0.

***Thioflavone thiosemicarbazone (4d).*** A mixture of thioflavone (**2a**, 10.008 g, 42 mmol), powdered thiosemicarbazide (6.000 g, 65.8 mmol), MeOH (100 mL), and conc. HCl (1 mL, 11.7 mmol) was boiled with stirring for 65 h and then cooled.

**Table 3**

Preparation and properties of thioflavanone hydrazones **3** (see also ref. [17b]).

| Product | Reaction components (mmol) | | Solvent (mL) | Reaction temp. (°C)[b] (time (h)) | Workup[c] | % Yield crude[d] (pure) | Mp (°C) (solvent) | Formula[a] (mol. mass) |
|---|---|---|---|---|---|---|---|---|
| **3b** | **3a** | $Ac_2O$[e] | py[f] | 15 | B | 100[g,h] | 243 | $C_{17}H_{16}N_2OS$ |
| | (10) | (40) | (10) | (3.5) | | | ($CHCL_3$/hexane) | (296.4) |
| **3c** | **3a** | $Ac_2O$(530) | | 23 | B | | 137 | $C_{19}H_{18}N_2O_2S$ |
| | (20) | $ZnCl_2$(37)[f] | | (20)[i] | C[j] | (6.7) | (PhH/hexane) | (338.4) |
| **3i** | **3h**[k] | $Ac_2O$(185) | | 23 | B | 99.5 | 241 | $C_{18}H_{17}N_3O_4S$ |
| | (5) | $ZnCl_2$(13)[f] | | (62) | | (69) | (EtOH) | (371.4) |
| **3j** | **3a** | BzCl | py[f] | <10 (0.2)[l] | D | 99[m] | 237–238 | $C_{22}H_{18}N_2OS$ |
| | (10) | (11) | (15) | 23 (7) | B | (85)[n] | ($CHCl_3$/2-PrOH) | (358.4) |

[a] The C, H, N, and S analyses date for the products are agreeing with the theoretical values within ± 0.3–0.4% limit.
[b] Bath if not bp.
[c] For general operations of processing the reaction mixtures see Experimental.
[d] Without workup of the mother liquors if not stated otherwise.
[e] To a solution of **3a** in pyridine was added $Ac_2O$ dropwise with cooling and stirring during 10 min.
[f] Anhydrous.
[g] TLC homogeneous.
[h] Mp 242°C.
[i] The mixture was stirred at least until the dissolution was complete.
[j] To give spiro compound isomer **5a** see also Table 4. The $CHCl_3$ mother liquor was concentrated and the residue stirred with PhH at room temperature to extract **3c**, IR (KBr, v, $cm^{-1}$); 1725 (s), 1689 (s), 1652 (m), 1610 (s).
[k] TLC ($CHCl_3$/MeOH(9:1)) homogeneous; mp 253–254°C, ref. [19b] 245–247°C (EtOH); the sample was a generous gift of J Bálint Ph.D and prepared [19b] by boiling a mixture of thioflavanone 1,1-dioxide (**1c**), semicarbazide hydrochloride (in 10% excess), and EtOH containing a catalytic amount of concd. HCl for ca. 4 h.
[l] Dropwise addition of BzCl to a solution of **3a** in anhydrous pyridine with ice cooling and stirring.
[m] TLC almost homogeneous, 234–236°C.
[n] IR (KBr, v, $cm^{-1}$): 1642 (s).

The solid was collected by filtration and washed several times with water and then with hexane to give crude product **4d** (10.877 g, 83%), mp 208–210°C (ref. [19b] 204–207°C (from EtOH)). The mother liquor was concentrated and the residue triturated with water to give a second crop (1.624 g, 12%) of **4d**. $C_{16}H_{13}N_3S_2$.

***Thioflavone thiosemicarbazone 1,1-dioxide(4e).*** A mixture of powdered sulfone **2c** (0.270 g, 1 mmol), powdered

**Table 4**

Preparation and properties of 3-acetylspiro[1,3,4-thiadiazoline-2,4′-thioflavans] **5a,b**.[a]

| Product | Reaction components (mmol) | | Reaction temp. (°C)[b] (time (h)) | Workup[c] | % Yield crude (pure)[d] | Mp(°C) (solvent) | Formula[e] (mol.mass) |
|---|---|---|---|---|---|---|---|
| **5a** | **3b** | $Ac_2O$(64) | 25 | B[h] | 99[i,j] | 210–211 | $C_{19}H_{18}N_2O_2S$ |
| | (2) | $ZnCl_2$(4.4)[f] | (20)[g] | C | (95) | ($CHCl_3$/EtOAc) | (338.4) |
| | **3a** | $Ac_2O$(53) | 23 | B[h] | 95 | 210–211 | |
| | (2) | $ZnCl_2$(3.7)[f] | (20)[g] | C | (85)[k] | ($CHCl_3$/EtOAc) | |
| | **3a** | $Ac_2O$(159) | 135 | B[h] | 99.5 | 210 | |
| | (10) | py(124)[l] | (2) | C | (60) | ($CHCl_3$/EtOAc) | |
| **5b** | **3j** | $Ac_2O$(106) | 100 | E,F | 99 | 206 | $C_{24}H_{20}N_2O_2S$ |
| | (4) | py(74)[l] | (4) | C | (88) | (EtOAc) | (400.5) |

[a] For preparation of analogous spiro 1,3,4-thiadiazolines (**5c,d,e**) see ref. [17b].
[b] Bath, if not bp.
[c] For general operations of processing the reaction mixtures see Experimental.
[d] Without workup of mother liquors if not stated otherwise.
[e] The C,H,N, and S analyses data for the products are agreeing with the theoretical values within ± 0.3-0.4% limit.
[f] To a solution of anhydrous $ZnCl_2$ in $Ac_2O$ was added the substrate.
[g] The reaction mixture was stirred at least until the dissolution was complete.
[h] To give a crude product.
[i] TLC homogeneous product.
[j] Mp 206-208 °C.
[k] From the mother liquor TLC homogeneous diacetythydrazone **3c**,(6.7%), mp 137°C (from PhH/hexane) could be isolated, cf. Table 3.
[l] Pyridine, anhydrous.

thiosemicarbazide (0.100 g, 1.1 mmol), MeOH (4.7 mL), and MeOH/HCl (0.3 mL *ca*. 0.35 mmol HCl; prepared by mixing 4.5 mL MeOH and 0.5 mL conc. HCl) was boiled with stirring for 9 h to give crude thiosemicarbazone **4e** (0.318 g, 92.5), mp 234–236°C, identical with an authentic [19b] compound (found mp 233–236°C, reported [19b] 192°C (from EtOH)). $C_{16}H_{13}N_3O_2S_2$. The crude product was pure enough for subsequent transformations.

**Degradation of thioflavone thiosemicarbazone 1,1-dioxide (4e) to acetylhydrazone 4f.** A mixture of thiosemicarbazone **4e** (1.030 g, 3 mmol), $Ac_2O$ (4.5 mL, 48 mmol) and anhydrous pyridine (3 mL, 37 mmol) was stirred at 51°C bath for 5 h and kept at room temperature for 16 h. The crystalline solid was collected by filtration, washed with $Ac_2O$ and hexane, dried over KOH and silica gel in vacuum desiccator to give TLC [$CHCl_3$/EtOAc (8:2), $CHCl_3/Et_2O$ (8:2), or $CHCl_3$/MeOH (95:5)] homogeneous crude product (0.678 g, 69.2%), mp 275–276°C (the hot melt resolidified and melted finally at 281–282°C) or when recrystallized from $CHCl_3$/EtOH, mp 275°C. The $Ac_2O$/py mother liquor was concentrated, the solid residue was triturated with anhydrous EtOH (1 mL) in the cold to give a second crop of **4f** (0.079 g, 8.1%), mp 278°C and then 284°C. IR(KBr, ν, $cm^{-1}$): 1678 (s), 1638 (m), 1562 (m). $^1$H NMR(200 MHz, DMSO-$d_6$, δ, ppm); 8.36–8.31 and 8.08–8.03 (both m and 1 H, 2 H-Ar), 7.97 (s, 1 H, H(3)) 7.90–7.86 and 7.84–7.72 (both m and 2 H, 4 H—Ar), 7.63–7.58 (m, 3 H, H—Ar), 2.34 (s, 3 H, Ac). *Anal*. Calcd. for $C_{17}H_{14}N_2O_3S$ C, 62.6; H, 4.3; N, 8.6; S 9.8. Found C, 63.0; H, 4.4; N, 8.4; S, 10.0.

***Thioflavone benzoylhydrazone (4g).*** A mixture of thioflavanone benzoylhydrazone (**3j**, 0.166 g, 0.462 mmol), DDQ (0.112 g, 0.485 mmol, 98%), anhydrous dioxane (4 mL), and a catalytic amount of TsOH was boiled with stirring tor 14 h, then cooled and concentrated. For the removal of $DDQH_2$, the residue was stirred with aq. $NaHCO_3$ in the presence of some drops of 2-PrOH as a humidifier to leave undissolved crude product **4g** (0.152 g, 92%). A solution of the crude product in $CHCl_3$ was treated with charcoal and concentrated. Crystallization of the residue from 2-PrOH (7 mL) afforded pure **4g** (0.121 g, 73%), mp 240°C. $^1$H NMR(360 MHz, DMSO-$d_6$,δ, ppm): 11.28 (bs, 1 H, NH), 8.47 (bs shaped m, 1 H, H(5)), 7.90–7.83 (m, 4 H, H(6,7,8) and H(3)), 7.61–7.51 (m, 10 H, 2 Ph). *Anal*. Calcd. for $C_{22}H_{16}N_2OS$ C, 74.1; H, 4.5; N, 7.9. Found C, 74.3; H, 4.6; N, 7.9.

**Attempted dehydrogenation of spirothioflavan 5a by $PhI(OAc)_2$.** A mixture of finely powdered **5a** (0.169 g, 0.5 mmol), $PhI(OAc)_2$ (0.247 g, 0.75 mmol) and MeOH (5 mL) was stirred at room temperature for 14 d. The solid was collected by filtration to give TLC homogeneous starting **5a** (0.104 g, 62%), mp 215–216°C.

For a transformation of thioflavanone (**1a**) to **2a**, under similar conditions, see Experimental section.

**CAN degradation of spiro-oxadiazoline 5b to thioflavone (2a).** According to the literature method [25] for the CAN dehydrogenation of thioflavanone (**1a**), to a solution of finely powdered spirocompound **5b** (0.401 g, 1 mmol) in MeCN (30 mL), placed in a separatory funnel, was added a solution of CAN (3.838 g, 7 mmol) in water (10 mL). The mixture was shaken carefully and when the effervescence ceased, diluted with water (50 mL) and extracted with $Et_2O$ (6 × 12 mL). The $Et_2O$ solution was washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Separation of the multicomponent residue by CC (Silica Woelm 100–200 μm, $CHCl_3/Et_2O$ (95:5)] afforded thioflavone (**2a**, 0.096 g, 40%), mp 124°C [ref. [25] 124.5–125.5°C (from anhydrous EtOH), ref. [36] 122–123°C (from MeOH)]. $^1$H NMR(200 MHz, $CDCl_3$, δ, ppm): 8.58–8.53 (m, 1 H, H(5)), 7.73–7.50 (m, 8 H, H—Ar), 7.25 [s, 1 H, H(3) (for $CHCl_3$ was δ 7.26); ref. [37] 7.27 (s, 1 H, H(3) ($CDCl_3$); Bruker 300 spectrometer), ref. [36] 7.35 ($CDCl_3$; Varian T-60 and/or EM-390 instruments)]. The product was identical in all respects [inclusive also TLC and IR(KBr)] with an authentic compound.

**Attempted dehydrogenation of spirothioflavan 5b by DDQ.** A mixture of **5b** (0.200 g, 0.5 mmol), DDQ (0.243 g, 0.525 mmol, 98%), anhydrous dioxane (6 mL), and anhydrous 4-toluenesulfonic acid (a catalytic amount) was stirred at room temperature for 5 h and at 93°C (bath) for 17 h, then concentrated. For the removal of TsOH and $DDQH_2$, the doughy residue was partitioned between aq. $NaHCO_3$ and $CHCl_3$. The organic layer washed with water and dried ($MgSO_4$) contained [TLC, $CHCl_3$/EtOAc (95:5)] *ca*. equal amounts of unchanged **5b** and thioflavone (**2a**) as the major components besides traces of four minor ones.

***3-Acetyl-5-methylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′-oxide (5f).*** (**a**) To a solution of $NaIO_4$ (0.428 g, 2 mmol) in water (10 mL) were added **5a** (0.169 g, 0.5 mmol) and 2-PrOH (10 mL). The mixture was boiled with stirring for 5 h, cooled and then concentrated. The residue was diluted with water up to *ca*. 30 mL to give **5f** (0.103 g, 85%), mp 209–212°C.

(**b**) To a suspension of powdered **5a** (3.384 g, 10 mmol) in $Me_2CO$ (300 mL) were added, both in small portions, powdered OXONE (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 3.60 g, 5.85 mmol) and water (35 mL) with stirring at 4–8°C (bath temperature) during 6 h. The mixture was stirred with cooling for 4 h and at room temperature for 14 h, and then filtered. The filtrate was concentrated and the residue crystallized from EtOAc to give crude **5f** (3.395 g, 96%), mp 200–202°C, contaminated (TLC) with a small amount of **5a**. Purification of the crude product by CC [silica gel 60; $CHCl_3$/EtOAc (9:1)] and subsequent crystallization from EtOAc afforded TLC homogeneous **5f** (2.381 g, 67%), mp 208–209°C. IR(KBr, ν, $cm^{-1}$): 1046 (s, S=O); $^{13}$C NMR(50 MHz, $CDCl_3$, δ, ppm): 166.19 (*C*=O), 153.89 (C(5)), 143.39, 134.50 and 132.88 (3 quat. aromatic C), 131.18, 130.92, 129.07, 128.99 (2 C), 128.48 (2 C), 127.22, and 126.29 (9 aromatic =CH), 97.65 (spiro C(2,4′)), 62.99 (C(2′)), 34.08 (C(3′)), 22.02 ($CH_3$—CO), 11.36 ($CH_3$(5)). *Anal*. Calcd. for $C_{19}H_{18}N_2O_3S$ C, 64.4; H, 5.1; N 7.9; S, 9.05. Found: C, 64.1; H, 5.1; N, 7.8; S, 9.1.

***3-Acetyl-5-phenylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′-oxide (5g).*** (**a**) To a solution of **5b** (3.604 g, 9 mmol) in hot 2-PrOH (290 mL) was added a solution of $NaIO_4$ (3.850 g, 18 mmol) in warm water (100 mL). The mixture was boiled for 2 h and then diluted with water up to *ca*. 600 mL to give crude **5g** (2.917 g, 78%) contaminated with a small amount of sulfone **5i**. Purification by CC [Silica Woelm 100–200 μm, $CHCl_3$/EtOAc (95:5)] afforded TLC homogeneous product **5g** (1.929 g, 51.5%) mp 216–218°C (from $CHCl_3$/EtOAc). IR(KBr, ν, $cm^{-1}$): 1044 (s, S=O). *Anal*. Calcd. for $C_{24}H_{20}N_2O_3S$ C, 69.2; H, 4.8; N 6.7; S 7.7. Found: C 69.4; H 4.9; N, 6.6; S, 7.6.

(**b**) To a suspension of powdered **5b** (4.005 g, 10 mmol) in $Me_2CO$ (300 mL) were added, both in small portions,

powdered OXONE (potassium peroxymonosulfate, 3.70 g, 6 mmol) and water (35 mL) with stirring at 4–8°C (bath temperature) during 4 h. The mixture was stirred on with cooling for 7 h and at room temperature for 12 h and then filtered; the solid was washed with water to leave undissolved crude **5g** (2.071 g, 50%). The aq. $Me_2CO$ mother liquor was concentrated, the residue triturated with water to give a second crop of **5g** (1.967 g 47%). A solution of the crude products in $CHCl_3$ was treated with charcoal and concentrated. The residue was crystallized from EtOAc to give pure title compound **5g** (3.666 g 88%), mp 208–210°C, TLC identical with the product described in (**a**).

***Transformation of spiro[oxadiazoline-2,4′-thioflavan] 1′-oxides 5f and 5g into thioflavone diacetylhydrazone (4c).*** (**a**) A mixture of 5-methyl spirocompound **5f** (3.544 g, 10 mmol), $Ac_2O$ (50 mL, 530 mmol) and TsOH (like a pea) was heated at 98°C (bath) with stirring for 16 h, then cooled and concentrated. The cold residue was triturated with ice/water for 1 h, and then extracted with $CHCl_3$. The $CHCl_3$ solution was washed with aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Recrystallization of the residue two times from EtOAc afforded pale yellow crystals of **4c** (1,534 g, 46%), mp 175°C. IR(KBr, ν, $cm^{-1}$): 1720(s), 1706(s), 1690(s), 1682(s), 1648(w), 1592(s). $^1$H NMR(360 MHz, $CDCl_3$, δ, ppm): 8.77–8.75 (m, 1 H, H(5)), 7,58–7.43 (m, 8 H, H—Ar), 6.80 (s, 1 H, H(3), 2.47 (s, 6 H, 2 Ac). $^{13}$C NMR(90 MHz, $CDCl_3$, δ, ppm): 170.28 (2 C, 2 *C*=O), 162.56, 148.81, 136.98, and 134.45 (quat. aromatic C), 130.62 (2 C), 129.15 (2 C), 127.82, 127.02 (3 C), and 126.34 (aromatic CH), 111.99 (C(3)), 25.90 (2 C, *C*$H_3$—C=O). *Anal*. Calcd. for $C_{19}H_{16}N_2O_2S$ C, 67.8; H, 4.8; N, 8.3; S, 9.5. Found: C, 67.8; H, 4.8; N, 8.4; S, 9.6.

(**b**) A mixture of 5-pheny1 spirocompound **5g** (0.833 g, 2 mmol), $Ac_2O$ (10 mL, 106 mmol) and TsOH (like a pepper) was heated at 100°C (bath) with stirring for 18 h, then cooled and concentrated. The cold residue was triturated with MeOH (2 mL) for 2.5 h and then water (*ca*. 7 mL) was added in portions to give a solid (0.707 g). A solution of the product in $CHCl_3$ was treated with charcoal and concentrated. The residue was crystallized from EtOAc to give **4c** (0.292 g, 43%), mp 174.5–175°C, identical (TLC, IR) with the product obtained from the 5-methyl spirocompound **5f** aforementioned in (**a**).

***3-Acetyl-5-methylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′,1′-dioxide (5h).*** To a suspension of powdered spirothioflavan **5a** (1.692 g, 5 mmol) in 96% AcOH (50 mL) were added, both in small portions, powdered $KMnO_4$ (1.613 g, 10.2 mmol) and water (10 mL) at room temperature with cooling and stirring during 45 min. The mixture was stirred further for 1.5 h and then under cooling 30% $H_2O_2$ (*ca*. 1.2 mL) was added drop-by-drop until discoloration. The mixture was diluted with water up to *ca*. 200 mL, kept at 4°C for 1.5 h to give crystalline crude 1′,1′-dioxide **5h** (1.449 g, 78%), mp 224–225°C. Recrystallization from PhMe afforded pure **5h** (1.313 g 71%), mp 227°C. IR(KBr, ν, $cm^{-1}$): 1314 (s), 1154 (s), 1138 (s) ($SO_2$). *Anal*. Calcd. for $C_{19}H_{18}N_2O_4S$ C, 61.6; H, 4.9; N, 7.6; S, 8.7. Found: C, 61.8; H, 4.9; N, 7.5; S, 8.6.

***3-Acetyl-5-phenylspiro[1,3,4-oxadiazoline-2,4′-thioflavan] 1′,1′-dioxide (5i).*** To a solution of spirothioflavan **5b** (0.401 g, 1 mmol) in 96% AcOH (16 mL) was added powdered $KMnO_4$ (0.395 g, 2.5 mmol) in small portions with stirring at room temperature during 20 min. The mixture was stirred further for 2 h, and then for dissolving the oxidant, water (12 mL) was added in portions during 1.5 h. After an additional stirring for 1 h the precipitated solid was collected by filtration, washed with water to give TLC homogeneous crude **5i** (0.389 g, 90%), mp 227–228°C. A solution of the crude product in $CHCl_3$ was treated with charcoal and concentrated. The residue was boiled in 2-PrOH (3 mL) to give analytically pure **5i** (0.378 g, 87%), mp 228°C. IR(KBr, ν, $cm^{-1}$): 1312 (s), 1156 (s) and 1136 (s) ($SO_2$). *Anal*. Calcd. for $C_{24}H_{20}N_2O_4S$ C, 66.6; H, 4.7; N, 6.5; S, 7.4. Found: C, 66.5; H, 4.7; N, 6.4; S, 7.4.

***5-Acetamido-3-acetylspiro[1,3,4-thiadiazoline-2,4′-thioflaven] (6).*** A mixture of thíosemicarbazone **4d** (1.869 g, 6 mmol), $Ac_2O$ (15 mL, 159 mmol) and pyridine (3 mL, 37 mmol) was kept at 100°C for 3 h and then at 4°C for 18 h to give yellow crystals of crude diacetylhydrazone **4c** (0.367 g, 18%), mp 170–171°C, TLC [$CHCl_3$/MeOH (9:1)] identical with an authentic compound. The mother liquor was concentrated and the residue triturated with anhydrous EtOH under cooling, and for increasing the separation of crystals, gradually hexane (16 mL) was added then kept at room temperature for *ca*. 16 h to give a crystalline second crop of product (1.090 g). The mother liquor of the second crop was concentrated and the residue triturated with water to give a solid (0.874 g). The second and third crops of crude products contained the same compound as the major component [TLC, $CHCl_3$/MeOH (9:1)]. Purification of the third crop by CC [silica gel 60; $CHCl_3$/$Et_2O$ (8:2)] and when combined with the second crop, subsequent crystallization from $Et_2O$ with addition of hexane afforded pure **6** (1.328 g, 56%), mp 248–249°C. IR(KBr, ν, $cm^{-1}$): 1674 (s), 1646 (s), 1614 (s). $^1$H NMR(200 MHz,$CDCl_3$, δ, ppm): 9.20 (s, 1 H, N*H*Ac), 7.59–7.54 (m, 2 H, H—Ar), 7.39–7.22 (m, 7 H, H—Ar), 6.50 (s, 1 H, H(3′)), 2.43 (s, 3 H, Ac), 1.91(s, 3 H, Ac). $^{13}$C NMR(50 MHz, $CDCl_3$, δ, ppm): 169.74 and 169.47 (2 C=O), 145.02 (C(5)), 136.74, 133.42, 132.96, and 129.70 (3 quat. aromatic C, and C(2′)), 129.27, 128.72 (2 C), 128.01, 127.48, 126.75 (2 C), 126.33, and 125.16 (9 aromatic =CH), 120.08 (C(3′)), 79.92 (spiro C(2,4′)), 23.69 and 22.30 (2 *C*$H_3$—C=O). *Anal*. Calcd. for $C_{20}H_{17}N_3O_2S_2$ C, 60.7; H, 4.3; N, 10.6; S, 16.2. Found C, 60.8; H, 4.4; N, 10.6; S, 16.3.

***Thioflavanone azine (8).*** (**a**) To a solution of hydrazone **3a** (0.509 g, 2 mmol) in DMSO (3 mL) at *ca*. 60°C was added 0.1*M* $I_2$/DMSO (3 mL, 0.3 mmol). The mixture was kept at 100°C for 45 min and then gradually water (*ca*. 25 mL) was added to give crude **8** (0.471 g, 99%, mp 267°C) containing some unchanged **3a**. Heating the crude product in MeOH (5 mL) left undissolved pure **8** (0.358 g, 75%), mp 270–271°C (ref. [19b] 270°C (PhH), prepared by condensing thioflavanone **1a** with hydrazine hydrate).

(**b**) A mixture of thioflavanone (**1a**, 1.502 g, 6.25 mmol), hydrazone **3a** (1.272 g, 5 mmol), 2-PrOH (25 mL), and a catalytic amount of TsOH was boiled with stirring for 10 h to give crude (1.697 g, 71%; mp 269–270°C) or recrystallized **8** (1.495 g, 63%), mp 270°C (from Diglyme or PhH), TLC identical with the product described in (**a**). $C_{30}H_{24}N_2S_2$.

**Dehydrogenation of thioflavanone azine (8) to azine 10.** A mixture of azine **8** (0.119 g, 0.25 mmol), DDQ (0.122 g, 0.525 mmol, 98%), anhydrous dioxane (10 mL), and a catalytic amount of TsOH was boiled with stirring for 18 h then concentrated. The residue was washed with $CHCl_3$ and the

solid stirred with aq. $NaHCO_3$ in the presence of some drops of 2-PrOH as a humidifier to give **10** (0.095 g, 80%), purplish crystals of a metallic lustre, mp 283–286°C (ref. [19b] 280–285°C (from EtOH), prepared by treatment of 4-methylthiothioflavylium iodide or thioflaven-4-thione with $N_2H_4 \cdot H_2O$). $C_{30}H_{20}N_2S_2$.

**Reaction of thioflavanone hydrazone (3a) with DDQ, formation of azines 8 and 9.** A mixture of hydrazone **3a** (1.017 g 4 mmol), DDQ (0.973 g, 4.2 mmol, 98%) and anhydrous dioxane (20 mL) was stirred at room temperature for some minutes, whilst the deep green color of the solution, produced by a transiently formed charge-transfer complex, became brownish-red and under significant effervescence the mixture thickened. Hereupon, the mixture was boiled for 4 h with stirring, and then concentrated. For removing $DDQH_2$ the residue was stirred with aq. $NaHCO_3$ at room temperature to leave undissolved a brownish solid (0.967 g, mp 213–220°C) consisting of two major components (TLC, $CHCl_3$). Purification by CC (silica gel 60, $CHCl_3$) afforded azine **8** (0.387 g, 41%, mp 270°C (from PhMe) and orange-red crystals of **9** (0.104 g, 11%), mp 255–256°C (from $CHCl_3$/EtOAc). $^1$H NMR(200 MHz, $CDCl_3$, δ, ppm): 8.59–8.56 (m, 1 H, H(5)), 8.48–8.45 (m, 1 H H(5)), 7.81 (s, 1 H, =CH(3)), 7.71–7.66 (m, 2 H, H—Ar), 7.50–7.16 (m, 14 H, H—Ar), 4.48 (dd, 1 H, $J_{2,3e} = 3$ Hz, $J_{2,3a} = 13$ Hz, H(2)), 4.19 (q, 1 H, $J_{2,3e} = 3$ Hz, $J_{3e3a} = 17.5$ Hz, $H_e$(3)), 3.13 (q, 1 H, $J_{2,3a} = 13$ Hz, $J_{3e,3a} = 17.5$ Hz, $H_a$(3)). *Anal*. Calcd. for $C_{30}H_{22}N_2S_2$ C, 75.9; H, 4.7; N, 5.9. Found: C, 75.8; H, 4,6; N, 5,9.

**Transformation of 2-cinnamoylphenyl disulfide (7) into thioflavanone hydrazone (3a) and pyrazole 11a.** A mixture of 98% $N_2H_4 \cdot H_2O$ (9 mL, ∼180 mmol), 2-PrOH (25 mL) and **7** [22b] (4.307 g, 9 mmol, 18 mmol of chalcone moiety) was stirred at room temperature for 5 h and then the clear solution formed was kept at 100°C for 16 h. The solution was cooled and deep freezed at *ca*. −20°C for 2.5 d to give crude (2.093 g, 91.4%, yield calculated for 9 mmol, mp 116–117°C) or recrystallized **3a**, mp 120–121°C (from MeOH), identical [mp, TLC: $CHCl_3$/EtOAc (95:5), IR] with an authentic compound prepared from **1a** (see ref. [17b]). The mother liquor of the crude product was concentrated, the residue dissolved in $Me_2CO$ (3 mL) and for transforming **11a** into the more easily isolable disulfide **12a**, kept at 4°C for 4 d. The deposited crystals were collected by filtration and washed with $Me_2CO$/hexane (1:1) to give crude (0.190 g, 4.2%, mp 226–227°C) or recrystallized **12a**, mp 230°C (from 2-methoxyethyl ether with addition of water). The product is identical [mp, TLC: $CHCl_3$/MeOH (9:1), IR] with that obtained by treating thioflavone with hydrazine hydrate [33]. *Anal*. Calcd. for $C_{30}H_{22}N_4S_2$ C, 71.7; H, 4.4; N, 11.1. Found: C, 71.8; H, 4.5; N, 11.1.

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