Synthesis and Stereochemistry of 3-Acetyl-5-aminospiro[1,3,4-thiadiazoline-2,4'-thioflavans]

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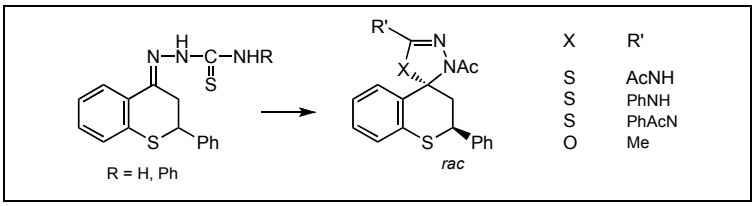

Under acetylating conditions *racemic* thioflavanone thiosemicarbazones cyclize into *racemic* 3-acetyl-spiro[1,3,4-thiadiazoline-2,4'-thioflavans] and a *racemic* 3-acetylspiro[1,3,4-oxadiazoline-2,4'-thioflavan] with *trans* O(1) or S(1) and Ph(2'$_{eq}$). Hindered rotation of the endocyclic N(3) acetyl group spirothiadiazolines caused the formation of isomers separable by HPLC. X-ray diffraction analyses, ^{1}H-, ^{13}C-, and ^{15}N NMR measurements as well as MOPAC QM calculations were performed to reveal the structures of these isomers.

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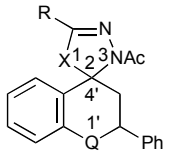
INTRODUCTION

Several natural and synthetic benzopyrans *e.g.* chrom(an)ones, flav(an)ones exhibit biological activity. Recently, also thioflavonoid compounds (*e.g.* as potential antimicrobial and antitumor agents) [1] including spiro heterocyclic derivatives [2] attract increased attention. As an extension of our previous examinations for the synthesis of 2-phenyltetrahydroquinoline- (**1e**) [3] and flavan spirothiadiazolines (**1d**) [4], respectively, as well as for the chemistry of 1,3,4-thiadiazoles [5] we aimed at the synthesis of the bioisosteric spirothioflavonoid analogs.

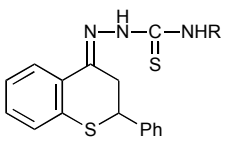
RESULTS AND DISCUSSION

As potential substrates for the synthesis of spirothioflavans **1a-c**, racemic thioflavanone thiosemicarbazones (**2a,b**) were prepared and cyclized into the corresponding 5-acetamido-3-acetylspiro-1,3,4-thiadiazolines under acylating conditions (Ac_2O/pyridine or $Ac_2O/ZnCl_2$). It is worth mentioning that upon treatment with Ac_2O/py at 145°C (bath) for 45 min phenylthiosemicarbazone **2b** transformed to thiadiazoline **1c** and oxadiazoline **1f** after purification by column chromatography in 60% and 6% isolated yield, respectively. The degradation of thiosemicarbazones under acylating conditions is well documented [4,6].

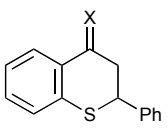
In consequence of heterocyclization, C(4) of the thiopyran ring became sp^3 hybridized and asymmetric, thus enabling the formation of racemic 2-diastereomers. Our previous investigations indicated that treatment of the chiral open-chain *O*-acetylated D-galactose thiosemi-



Compund	Q	X	R
1a	S	S	AcNH
1b	S	S	PhNH
1c	S	S	PhAcN
1d	O	S	AcNH
1e	NAc	S	AcNH
1f	S	O	Me

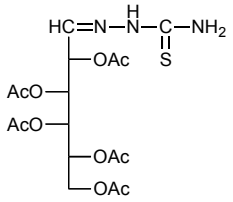


Compund	R
2a	H
2b	Ph



Compund	X
3a	O
3b	NNH_2
3c	NNHAc

carbazone (**4**) with the Ac_2O/py and $Ac_2O/ZnCl_2$ couples afforded the (+) and (–) diastereomers of thiadiazoline **5b** in unlike proportions [7]. However, treating the cyclic ketone derivatives racemic flavanone [4] and racemic or (1*R*)-camphor [6a] as well as dihydrocodeinone [8] thiosemicarbazones gave only one of the possible spirothiadiazoline diastereomers (*e.g.* that of **1d**).



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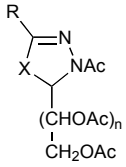
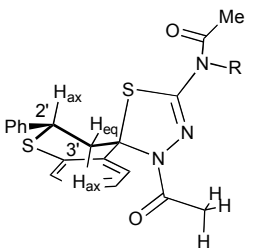


Compund	X	R	n	
5a	O	Ph	3	D-*arabino*
5b	S	AcNH	4	D-*galacto*

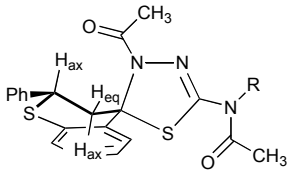
The stereochemistry of thioflavan derivatives **1-3** was investigated by NMR measurements. The high $J_{2',3'}$ coupling constants reveal that the Ph(2') group has an equatorial position which is common for flavan compounds. For the spiro compounds (**1**) the ^{13}C NMR spectra reveal the formation of a *N,O*- or *N,S*-acetalic sp^3 C(4',2). Moreover, in the ^1H NMR spectra the signals for H(5) are not downfield shifted unlike those of flavans bearing sp^2 C(4).

In contrast to the spiro[1,3,4-oxadiazoline-2,4'-thioflavan] **1f**, the ^1H NMR spectra of the TLC homogeneous and thoroughly purified 1,3,4-thiadiazoline analogs **1a-c** (with correct elemental analysis data but yet altering mp) revealed the unexpected presence of two related species in both $CDCl_3$ and $(CD_3)_2SO$ solutions. Two different samples of the TLC homogeneous spirothiadiazoline **1c** could be separated into their components by analytical HPLC. The pure major component of the product (melting at 195 – 196 °C, with smaller retention time) when subjected recurrently to HPLC under unaltered conditions, revealed itself again to be a mixture of the two original species, thus documenting conversion under mild conditions and in inert solvents. On the basis of our previous observations with 2-monosubstituted 3-acyl-1,3,4-thiadiazolines, this conversion does not appear to be a configurational change of the acetalic spiro C(4',2) (see stereoformulae **A** and **B**).

Previously, C(2) epimerization of the cyclic *N,O*-acetal 2-monosubstituted (–)-2-[D-*arabino*-(tetra-acetoxybutyl)]-3-acetyl-5-phenyl-1,3,4-oxadiazoline (**5a**) by treatment with $Ac_2O/ZnCl_2$ into the (+) diastereomer [9], moreover, a thermal rearrangement [10] of a 2,2-disubstituted oxadiazoline 3-benzoyl-2-(9-fluorenylidene)-5-methyl-1,3,4-oxadiazoline at 145 °C into the isomeric 3-acetyl-2-(9-fluorenylidene)-5-phenyl-1,3,4-oxadiazoline were observed. These transformations can take place *via* formation of an open-chain azomethine imine intermediate. 2,2-Disubstituted 3-acetyl-1,3,4-oxadiazolines have been reported [11] to form equilibrium mixtures with their open-chain azomethine imine forms especially in solvents of high dielectric constant. In contrast to the oxadiazoline derivative of D-arabinose (**5a**) above, presumably due to the greater nucleophilicity of S in comparison to that of O, (+)-5-acetamido-2-[D-*galacto*-(penta-acetoxy)pentyl]-3-acetyl-1,3,4-thiadiazoline diastereomer [(+) **5b**] resisted transformation into the C(2) epimeric (–) thiadiazoline diastereomer [7] upon treatment with $Ac_2O/ZnCl_2$ at 85–90 °C for 1 h or at 41 °C for 16 h.



A



B

According to the above findings duplication of ^1H NMR spectra and changes during HPLC runs cannot be interpreted by a configurational alteration of the spiro C or by a change of conformation of the thiochroman ring as for both species the spectra reveal *trans*-diaxial $J_{2',3'}$ coupling constants. On the basis of literature data, however, inversion of N(3) and/or hindered rotation of its acetyl group should also be taken into consideration. The stereochemistry of the nitrogen of cyclic *N,O*- and *N,S*-acetals [12] and that of the *N*-acyl groups in heterocyclic compounds [12a,13] or acid hydrazides [14] have been comprehensively studied. It has

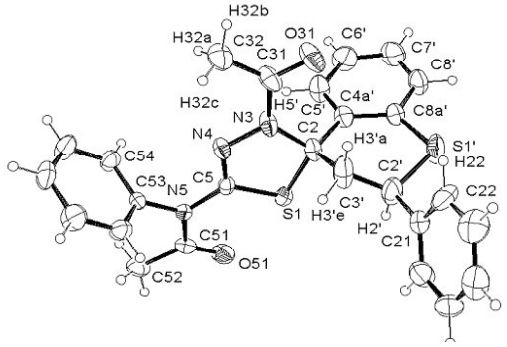


Figure 1. ORTEP view and partial numbering scheme of **1c**. The IUPAC numbering was retained for the tricyclic spiro ring system. Selected bond distances (Å): N(3)-N(4) 1.387(5); N(4)-C(5) 1.283(5); N(5)-C(5) 1.389(5); N(5)-C(51) 1.397(6); C(51)-O(51) 1.211(5); S(1)-C(2) 1.862(5); S(1)-C(5) 1.740(4); S(1')-C(2') 1.760(6); S(1')-C(8a') 1.743(5). Torsion angles (°) N(4)-N(3)-C(31)-C(32) -5.4 ; C(5)-N(5)-C(51)-C(52) -173.3; C(5)-N(5)-C(53)-C(54) 80.0; S(1')-C(2')-C(21)-C(22) 56.5; S(1')-C(2')-C(3')-C(2) 58.9.

been found that 1-acetyl vicinal diazol(in)es the N^2,O-*trans* form predominates [12a].

X-ray crystallography. View of **1c** and **1f** is shown at Figure 1 and Figure 2, respectively. For other details of structure determination see Experimental. The absolute configurations for both compounds are C(2)-(*R*) and C(2')-(*S*) and their enantiomer pair.

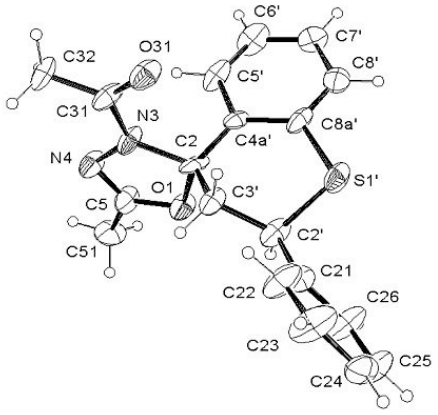


Figure 2. ORTEP view and partial numbering scheme of **1f**. The IUPAC numbering was retained for the tricyclic spiro ring system. Selected bond distances (Å): N(3)-N(4) 1.412(8); N(4)-C(5) 1.289(10); C(5)-C(51) 1.491(10); O(1)-C(2) 1.465(8); O(1)-O(5) 1.338(9); S(1')-C(2') 1.783(10); S(1')-C(8a') 1.791(9). Torsion angles (°) N(4)-N(3)-C(31)-C(32) -4.7; S(1')-C(2')-C(21)-C(22) 100.1; S(1')-C(2')-C(3')-C(2) 67.6.

Hydrogen atoms of C(32) and C(52) methyl groups were refined using the riding model. The results indicate, that at least in the solid state there are several hydrogen atoms in proximity of 2.54-3.00Å to N(4), O(31) and S(1) or O(1). Among them, the short intramolecular X-H distances in **1c** are N(4)-H(32c) 2.589; N(4)-H(32a) 2.720; O(31)-H(32b) 2.460; O(31)-H(32c) 2.990; S(1)-H(3'e) 2.805 Å while for **1f** N(4)-H(32a) 2.535; N(4)-H(32c) 2.885; O(31)-H(32b) 2.497; O(31)-H(3'a) 2.566; O(1)-H(3'e) 2.597; O(1)-H(2') 2.500 O(1)-H(51a) 2.619; O(1)-H(51c) 2.694 Å. NMR results (*vide infra*) suggest that the stereoisomer **A** persists in solution. However, though NMR overall conformations are similar to the solid-state structure, amide *E-Z* isomerism is clearly observed in some thiadiazoline derivatives.

^{1}H, ^{13}C and ^{15}N NMR studies. For the oxadiazoline compound **1f** full ^{1}H, ^{13}C and ^{15}N assignment and analysis were carried out (Table 1). The phenyl ring attached to the thioflavan ring is equatorial, since H(2') has a coupling of 13 Hz to H(3'$_{ax}$).

The ^{1}H NMR spectrum reveals that **1f** contains only one (conformational) isomer we call 'anomalous' since the chemical shift of the H(3'$_{ax}$) proton appears at higher chemical shift (3.63 ppm) than it's geminal partner H(3'$_{eq}$) (2.54 ppm). We attribute this *anomalous* behavior to the carbonyl neighbouring anisotropy effect of the *N*-acetyl

Table 1

^{1}H-, ^{13}C- and ^{15}N NMR data of **1f** with 'anomalous' ^{1}H NMR spectrum

1f, $CDCl_3$ 100% anomalous	Type	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Coupling constants (Hz)
2	C	99.26	-	
2'	CH	42.25	4.747 ax	$^3J_{2'3'ax}$=13.0 $^3J_{2'3'eq}$=1.5
3'	CH_2	39.17	2.542 eq 3.634 ax	$^2J_{3'eq3'ax}$ = -13.8
5	C	154.12	-	
4a'	C	130.02	-	
8a'	C	136.10	-	
21	C	139.48	-	
22	CH	128.28	7.488	
23	CH	129.30	7.398	
24	CH	128.73	7.358	
25	CH	129.30	7.398	
26	CH	128.28	7.488	
31	C	166.52	-	
32	CH_3	22.85	2.320	
51	CH_3	12.01	2.102	
5'	CH	127.15	7.324	
6'	CH	130.19	7.262	
7'	CH	125.54	7.153	
8'	CH	126.96	7.207	
		δ ^{15}N (ppm)		
3	N	64.68		$^3J_{3N,32H}$ = 2.0
4	N	125.56		$^3J_{4N,51H}$ = 3.2 $^4J_{4N,32H}$ = 2.2

group. Indeed, X-ray structure gives ~ 2.6 Å distance between the carbonyl oxygen and H(3'$_{ax}$) that explains it's anomalous ^{1}H chemical shift. While the equivalent aromatic H(22), H(26) protons give strong NOE-s to H(2') and H(3') protons of the thioflavan ring, a medium NOE is clearly detected between the Me(32) group and the aromatic H(5') proton of the thioflavan ring (X-ray distance 3.96 Å), *E*-isomer, O(31)-C(31)-N(3)-N(4). In a hypothetical *Z*-isomer generated by 120° rotation of the N(3)-C(31) bond of the X-ray structure the H(5')- Me(32) distance would be 5.5 Å, contradicting with NOE. This supports the hypothesis that rotation around the N(3)-C(31) bond is strongly hindered in chloroform solution, and only one rotational isomer is present.

The analysis of ^{15}N spectra gives further interesting points to structure elucidation. We did not observe measurable couplings between the H(3') protons and N(3) nitrogen atom in ^{1}H-^{15}N multiple-bond correlation experiments: consequently the appropriate dihedral angles must be close to 90°. This is close to the X-ray results obtained for the given C(2) configuration (52 or –67.3° for H(3')-C(3')-C(2)-N(3) dihedral angles). On the other hand, the Me(32) protons exhibit a surprising four bond coupling to N(4) nitrogen, supporting partial sp^2 bond character of N(3) subject to hyperconjugation and planar

Table 2

^{1}H-, ^{13}C- and ^{15}N NMR data of the isomers of **1a**.

^{1}H	δ (ppm)		*J* (Hz)		^{13}C	δ (ppm)	
$CDCl_3$	*major* 100% *anomalous*	*minor* 21.6% *normal*	*major*	*minor*		*major*	*minor*
3'a	3.702	3.030	$^{2}J_{3'a\text{-}3'e}$ = -13.0	$^{2}J_{3'a\text{-}3'e}$ = -14.6	2	81.63	79.70
3'e	2.759	3.452	$^{3}J_{3'e\text{-}2'}$ = 1. 7	$^{3}J_{3'e\text{-}2'}$ = 3.2	3'	42.83	50.72
2'	4.692	4.794	$^{3}J_{3'a\text{-}2'}$ = 12.7	$^{3}J_{3'a\text{-}2'}$ = 11.7	2'	43.38	44.28
Me(32)	1.814	1.838	-	-	Me(32)	22.89	22.93
DMSO	*major* 100% *normal*	*minor* 61% *anomalous*	*major*	*minor*		*major*	*minor*
3'a	3.030	3.679	$^{2}J_{3'a\text{-}3'e}$ = -14. 6	$^{2}J_{3'a\text{-}3'e}$ = -14.7	2	79.06	81.25
3'e	3.533	2.697	$^{3}J_{3'e\text{-}2'}$ = 5.3	$^{3}J_{3'e\text{-}2'}$ = 3.2	3'	50.98	42.52
2'	4.758	4.758	$^{3}J_{3'a\text{-}2'}$ = 13.5	$^{3}J_{3'a\text{-}2'}$ = 11.7	2'	44.99	41.94
Me(32)	2.069	2.057	-	-	Me(32)	23.33	23.29
^{15}N(3) 360K	90.12	84.99					
^{15}N(4) 360K	66.46	68.88					

arrangement of atoms involved in long-range spin-spin coupling pathway.

In contrast to **1f**, according to the appropriate NMR spectra, all thiadiazoline compounds gave mixtures of rotational isomers in solution. These compounds were measured in $CDCl_3$ and DMSO solutions, in some cases at different temperatures. Only their characteristic NMR data are presented in Tables 2 and 3.

It can be seen that in $CDCl_3$ solution, always the anomalous conformers dominate while this relation is reversed in DMSO. In $CDCl_3$, N(3) of **1a** of the minor (normal) isomer couples to H(3') protons, while this is not true for the anomalous major isomer. In DMSO, N(3) of **1a** of the major (normal) isomer couples to H(3') protons, while couplings to the anomalous isomer are weak. Four bond nitrogen – proton couplings persist in both isomers. From the detailed NMR analysis of **1a** and **1c** we found that the most sensitive parameters to the observed N-acetyl conformational isomerism are the C(3') and N(3) chemical shifts (in the anomalous conformers they have *ca*. 10 or 5 ppm lower values). For the C(3') this is similar to a γ-gauche effect, since the proposed conformers can be transformed to each other by 60 or 120° rotations.

In case of **1c** in DMSO solution, increasing the temperature from 300K to 360K decreased the ratio of the major/minor isomer from 2.69 to 2.58. In DMSO, N(3) of **1c** of the major (normal) isomer couples to both H(3') protons, while in the anomalous isomer these couplings are weak, like in **1a** or **1f**. However, in **1c**, N(3) and N(4) in both isomers exhibits 3.5- 4 Hz couplings to the C(32) methyl protons. Summing up these data show that normal isomers dominate in DMSO, but independent of the

Table 3

^{1}H-, ^{13}C- and ^{15}N NMR data of the isomers of **1c**

^{1}H	δ (ppm)		*J* (Hz)		^{13}C	δ (ppm)	
$CDCl_3$	*major* 100% *anomalous*	*minor 27%* *normal*	*Major*	*minor*		*major*	*minor*
3'a	3.776	3.122	$^{2}J_{3'a\text{-}3'e}$ = -13.2	$^{2}J_{3'a\text{-}3'e}$ = -14.4	2	83.22	81.26
3'e	2.785	3.576	$^{3}J_{3'e\text{-}2'}$ = 2.3	$^{3}J_{3'e\text{-}2'}$ = 3.9	3'	42.25	51.41
2'	4.781	4.770	$^{3}J_{3'a\text{-}2'}$ = 12.8	$^{3}J_{3'a\text{-}2'}$ = 11.9	2'	43.73	45.10
Me(32)	1.941	1.952	-	-	Me(32)	23.96	23.99
^{15}N(3) 295K	86.41	91.14					
^{15}N(4) 295K	79.91	79.91					
DMSO	*major* 100% *normal*	*minor* 38% *anomalous*	*major*	*minor*		*major*	*minor*
3'a	3.048	3.605	$^{2}J_{3'a\text{-}3'e}$ = -14. 6	$^{2}J_{3'a\text{-}3'e}$ = -13.0	2	80.68	82.74
3'e	3.497	2.767	$^{3}J_{3'e\text{-}2'}$ = 3.9	$^{3}J_{3'e\text{-}2'}$ = 2.4	3'	50.57	41.97
2'	4.731	4.784	$^{3}J_{3'a\text{-}2'}$ = 11.3	$^{3}J_{3'a\text{-}2'}$ = 12.8	2'	44.83	43.42
Me(32)	2.069	2.057	-	-	Me(32)	23.89	23.89
^{15}N(3) 360K	91.42	86.42					
^{15}N(4) 360K	77.54	80.85					

solvent, normal isomers always show N(3)-H(3') couplings while anomalous ones don't. As we can exclude the possibility of spiro isomers on the basis of X-ray diffraction studies the explanation of the conformational isomers stems from restricted rotation of the N(3)-Ac group. This was further verified by molecular modelling calculations.

Molecular modelling studies. We performed MOPAC QM calculations *in vacuo* in order to understand the hindered rotation of the N(3) acetyl group (MOPAC package of Hyperchem 7.1 application using the AM1 Hamiltonian).

The N(3) – C(31) distance was determined to be 1.37 Å from the X-ray elucidated structure. Minimization of the structure increased this distance to 1.42 Å. However, it reveals that there is a possible amide-type resonance between the ring and the N(3) acetyl carbonyl carbon

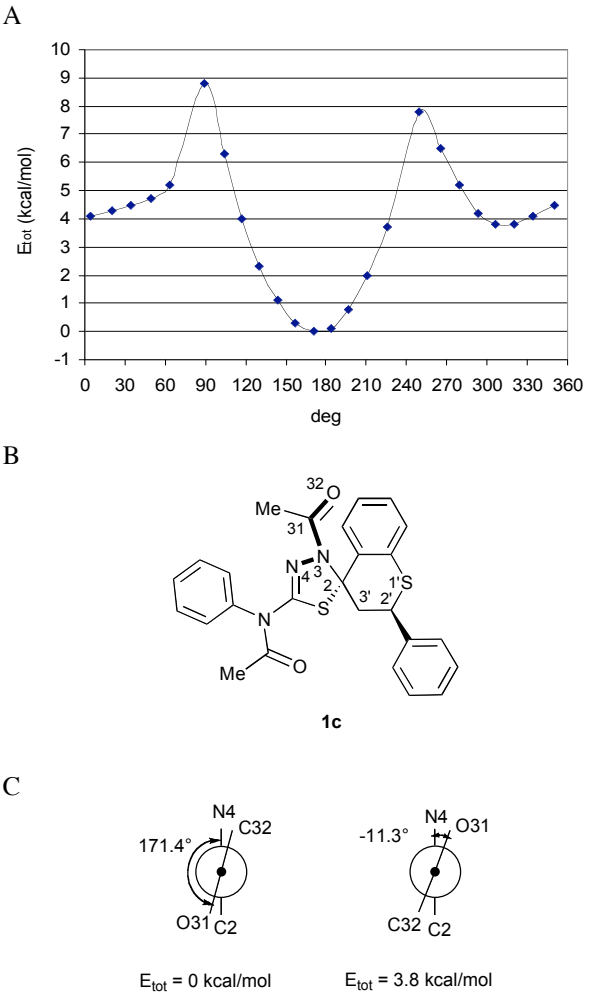


Figure 3 A and B: The rotational energy diagram of the dihedral angle O(31)-C(31)-C(3)-C(4) (drawn in bold) of **1c**. At the 180° position the spiro carbon atom C(2) and the methyl carbon of the acetyl group are in *anti* position that accords to the anomalous conformer. C: The dihedral angles O(31)-C(31)-C(3)-C(4) of the two rotamers at the energy minimized states without any contrains.

atoms, as expected. This was further characterized by mapping the conformational space of the acetyl group by varying the C(2)–N(3)–C(31)–C(32) dihedral angle (performing full AM1 minimalization at each point). The energy graph shown in Figure 3 displays that there are two distinct energy barriers during the rotation around the N(3)–C(31) bond, the higher one is 8.8 kcal/mol which gives further evidences to the presence of rotational isomers detected by the NMR experiments in solution. The "*in vacuo*" calculations carried out suggest the dominance of the anomalous conformer in accordance with the NMR data obtained in $CDCl_3$. This may be due to the fact, that an intramolecular H-bonding pattern is more preferred in $CDCl_3$ solution. However, DMSO as a good proton acceptor may compete with the intramolecular H-bonding, and may prefer the "normal" conformer. This means, that while the energy barrier remains high between the *E-Z* isomers, the energy minima are influenced and shifted by solvent effects.

CONCLUSION

Thioflavanone thiosemicarbazones cyclize into spiro-thiadiazoline-thiofavans and oxadiazoline thioflavans under acylating condition. The stereochemistry of the products were verified by NMR and X-ray data as well as QM calculations. *N*-Acetyl hindered rotation explains signal doubling in the NMR spectra. Additional investigations concerning the stereochemistry of this and similar reactions are in progress.

EXPERIMENTAL

Melting points (uncorrected): Kofler block. Solutions were concentrated under reduced pressure in a rotary evaporator (< 50 °C). TLC: Kieselgel 60 F_{254} (Merck, Alurolle). HPLC: HPLC-Merck Hitachi instrument with diode array detector L 7455 (at 257 nm). IR (KBr disks): Perkin-Elmer 16 PC-FT spectrophotomeer. The 200 MHz ^{1}H- and 50 MHz ^{13}C NMR spectra were obtained on a Bruker WP 200 SY spectrometer and are reported in parts per million (ppm) relative to TMS (δ), with coupling constants (*J*) in Hertz (Hz). For recording the 50 MHz ^{13}C NMR spectra, *J*-echo techniques were used. Standard 2D-NOESY experiments were carried out with a Bruker DRX500 instrument at 500 MHz using 800 ms mixing time. For the detection of one bond and long range carbon-proton connectivities standard HSQC and HMBC techniques were applied.

The heteronuclear long range *J*-couplings between protons and carbons and/or nitrogens were measured with a CPMG variant of the HSQMBC method [15]. In these experiments the long-range coupling evolution time was 50-70 ms. X-ray quality crystals of **1c** or **1f** were mounted onto a glass fiber using epoxy resin. Data were collected at 293(1)K on an Enraf Nonius MACH3 diffractometer using monochromated MoKα radiation (λ=0.71073Å), ω-2θ motion. Absorption correction was made using psi scans. The structure was solved using direct methods with the SIR-92 software [16] and refined on F^2 by full-matrix

least square methods with the use of the program SHELX-97 [17]. All non hydrogen atoms were refined anisotropically. Hydrogen atoms were included into geometric position using a riding model. Publication material was prepared with the WINGX-97 suite [18].

***racemic*-*N*-(3-Acetyl-2'-phenyl-2',3'-dihydro-3*H*-spiro-[1,3,4-thiadiazole-2,4'-thiochromen]-5-yl)acetamide (1a).** A mixture of thiosemicarbazone **2a** (1.254 g, 4 mmol), Ac_2O (10 mL), and anh. pyridine (2 mL) was heated at 100 °C (bath) for 3 h, and then concentrated. The cold residue was triturated with MeOH (2.5 mL) to give TLC ($CHCl_3$/Et_2O, 8:2) homogeneous crude **1a** (0.643 g, 40.5%, mp. 153-156 °C). The mother liquor was concentrated and the residue triturated with Et_2O (5 mL) and then hexane (20 mL) was added to give a second crop of **1a** (0.905 g, 56.9%, mp 152-154 °C). The crude products were combined and recrystallized from benzene or toluene, and dried at 100 °C/0.5 Torr to give pure **1a** (1.042 g, 65.5%), mp 205-206 °C. IR (KBr, ν, cm^{-1}): 3244 (NH), 2962 (CH_3), 1674 (CO), 1644 (C=N) and 1618 (aromatic); NMR see table 1.; *Anal*. Calcd. for $C_{20}H_{19}N_3O_2S_2$ C, 60.4; H, 4.8; N, 10.6; S, 16.0. Found: C, 59.8; H, 5.0; N, 10.3; S, 16.1.

***racemic*-3-Acetyl-*N*,2'-diphenyl-2',3'-dihydro-3*H*-spiro-[1,3,4-thiadiazole-2,4'-thiochromen]-5-yl)-amine (1b) and *racemic*-*N*-(3-acetyl-2'-phenyl-2',3'-dihydro-3*H*-spiro[1,3,4-thiadiazole-2,4'-thiochromen]-5-yl)-*N*-phenylacetamide (1c).**

(a) To a solution of anh. $ZnCl_2$ (3.00 g, 22 mmol) in Ac_2O (30 mL, 318 mmol) **2b** (2.727 g, 7 mmol) was added. The mixture was kept at room temperature with stirring until the dissolution was complete (3 days) and then poured into ice/water. The solid was collected by filtration, washed several times with water and dried (3.35 g). After repeated separation by column chromatography (silica gel 60, $CHCl_3$/EtOAc 98:2) TLC homogeneous ($CHCl_3$, threefold run) **1c** eluted first (1.33 g, 40%), mp 178-181 °C (from EtOAc/hexane). IR (KBr, ν, cm^{-1}): 1688 (CO), 1666 (CO), 1600 and 1591 (aromatic); NMR see Table 1.; *Anal*. Calcd. for $C_{26}H_{23}N_3O_2S_2$ C, 65.9; H, 4.9; N, 8.9. Found C, 66.0; H, 4.9; N, 8.8%. Secondly eluted **1b** (0.21 g, 7%), mp. 181 °C (from EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$) (δ, ppm) Major/minor δ ppm 4.73/4.61(dd, $J_{2'a3'a}$ = 11.2/13.6, $J_{2'a3'e}$ = 4.2/2.4 Hz, ($H2'_a$), 3.06/3.76(dd, $J_{3'a3'e}$ = 14.4/14.4 Hz, ($H3'_a$) 3.8/2.79(dd, ($H3'_e$), 6.32(br s, NH), 2.38/2.37 (2s, Ac), 7.0-7.6 (aromatics, overlap). *Anal*. Calcd. for $C_{24}H_{21}N_3OS_2$ C, 66.8; H, 4.9; N, 9.7. Found C, 66.5; H, 4.9; N, 9.8.

(b) A mixture of **2b** (7.78 g, 20 mmol), anh. pyridine (35 mL), and Ac_2O (35 mL) was kept at room temperature with stirring until the dissolution was complete (3 days) and then poured into ice/water. A solution of the dry crude product (9.62 g) in $CHCl_3$ was treated with fuller's earth and charcoal and then concentrated. The residue was crystallized several times from EtOAc to give pure and TLC homogenous ($CHCl_3$, threefold run, or $CHCl_3$/EtOAc 95:5) **1c** (7.10 g, 75%), mp 195-196 °C, identical (TLC) with **1c** prepared by Ac_2O/$ZnCl_2$ in (a). *Anal*. Found: C, 66.1; H, 4.9; N, 8.9.

(c) A mixture of **2b** (4.674 g, 12 mmol), Ac_2O (22 mL) and anh. pyridine (18 mL) was kept at 145 °C (bath, with stirring until dissolution was complete) for 45 min, and then concentrated. The cold residue was triturated with anh. EtOH (5 mL) to decompose any Ac_2O residues and in small portions hexane (25 mL) was added to give a crystalline product comprising two major components (TLC, $CHCl_3$/EtOAc 95:5). Repeated separation by column chromatography (silica gel 60, 0.040-0.063 mm, Merck; $CHCl_3$/EtOAc 98:2) afforded TLC ($CHCl_3$/EtOAc 95:5) homogeneous **1c** (3.36 g, 59%), mp 185-190 °C (from EtOAc) and TLC homogeneous 3-acetyl-5-methyl-2'-phenyl-2',3'-dihydro-3*H*-spiro[1,3,4-oxadiazole-2,4'-thiochromene] (**1f**, 0.251 g, 6.2%), mp 210.5-212 °C (from $CHCl_3$/EtOAc) originated, *via* spirocyclization, from the transiently formed transacetylation product thioflavanone acetylhydrazone (**3c**). *Anal*. Calcd. for $C_{19}H_{18}N_2O_2S$ C, 67.2; H, 5.3; N, 8.2. Found C, 67.4; H, 4.9; N, 8.3.

X-ray crystallographic data for 1c. Formula $C_{26}H_{23}N_3O_2S_2$, M = 473.59, monoclinic, space group $P2_1/n$, a = 12.3227(10) Å, b = 14.8950(10) Å, c = 13.3891(10), β = 101.16(1)°, V = 2411.1(3) $Å^3$, Z = 4, ρ_{calc}= 1.305, 4913 measured reflections of which 2515 were unique with I > 2σ(I), decay: 4%, R1 = 0.0734 and *w*R2 = 0.1491 for 4913 reflections and 300 parameters, GOF = 1.03. Residual electron density: 0.483/-0.363 e/$Å^3$.

HPLC investigation of the isomerization of spirothiadiazoline 1c (see Acknowledgement). A 10 μL solution of the TLC [$CHCl_3$ with 3-4-fold runs or $CHCl_3$/EtOAc (95:5)] homogeneous **1c** (mp 195 °C from EtOAc) in MeCN (2.5 mg/mL) was injected onto a Millipore RCM 8x10 cm column. Elution with 65:35 solvent mixture of MeCN and 4% aq. AcOH afforded a homogeneous eluate of retention time 10.20 min and a second one, a mixture with a minor component of retention time 10.95 min. Repeated HPLC analysis of the homogeneous first eluate yielded, again a homogeneous and a two-component eluate as above which indicated the transformation of the species with retention time of 10.20 min under the given conditions. Therefore, an eluate comprising the components (retention times 10.20 and 10.95 min, respectively) in a ratio of 1:0.04 was kept at room temperature and its aliquots, after standing for 7, 12, and 18 days were subjected to HPLC analysis to reveal altered ratios of 1:0.105, 1:0.18 and 1:0.25, respectively. This indicated a 1% average transformation into the thermodynamically more stable species.

In equilibrium the species of 10.95 min retention time is the major component as under similar conditions, HPLC analysis of another sample of **1c** (obtained from Et_2O solution with addition of hexane at room temperature), comprising the species of 10.95 min retention time as the major component did not display further change in this polar protic solvent system.

X-ray crystallographic data for 1f. Formula $C_{19}H_{18}N_2O_2S$, M = 338.41, triclinic, space group P-1, a = 7.8577(10) Å, b = 8.1805(10) Å, c = 13.077(6), α = 90.89(1)°, β = 90.21(2)°, γ = 96.13(1)°, V = 835.7(4) $Å^3$, Z = 2, ρ_{calc}= 1.345, 3093 measured reflections of which 1028 were unique with I > 2σ(I), decay: none, R1 = 0.0811 and *w*R2 = 0.2209 for 3093 reflections and 219 parameters, GOF = 0.925. Residual electron density: 0.308/-0.325 e/$Å^3$. Although two cell angle data are close to 90° in the structure of **1f**, no additional symmetry elements could be found.

***racemic*-Thioflavanone thiosemicarbazone (2a).** A mixture of thioflavanone (**3a**, 12.02 g, 50 mmol), thiosemicarbazide (5.02 g, 55 mmol), MeOH (50 mL), and concd. HCl (1 drop) was boiled with stirring for 2 h. The product was collected by filtration in the cold, washed with MeOH, water, and hexane to give **2a** (14.77 g, 94.3%), mp 196-198 °C (ref. [19]. mp 206-208 °C, recrystallized from EtOH).

***racemic*-Thioflavanone 4-phenyl-3-thiosemicarbazone (2b).**

(a) A mixture of thioflavanone (**3a**), 1.202 g, 5 mmol), 4-phenyl-3-thiosemicarbazide (0.8362 g, 5 mmol, EtOAc (10 ml) and anh. 4-toluenesulfonic acid (a small particle) was boiled

with stirring for 7 h. The product was collected by filtration in the cold, washed with EtOAc/hexane (1:2) and hexane to give crude **2b** (1.533 g, 78.7%), mp 218-220 °C.

(b) A mixture of thioflavanone hydrazone (**3b**, 6.359 g, 25 mmol), phenyl isothiocyanate (3.549 g, 26.3 mmol), and EtOAc (20 mL) was boiled, till possible with stirring, for 2.5 h, then hexane (10 mL) was added. The product was collected by filtration in the cold, washed with EtOAc/hexane (1:2) and hexane to give crude **2b** (9.232 g, 94.8%, mp 223-224 °C), after recrystallization from AcOH, mp 223-224 °C. *Anal.* Calcd. for $C_{22}H_{19}N_3S_2$ C, 67.8; H, 4.9; N, 10.8; S, 16.5. Found: C, 67.7; H, 4.9; N, 10.7; S, 16.4.

***rac*-Thioflavanone hydrazone (3b).** A mixture of MeOH (6 mL), $N_2H_4 \cdot H_2O$ (1 mL, ~20 mmol, 98%) and thioflavanone (**3a**, 2.403 g, 10 mmol) was stirred at 60 °C (bath) for 4 h and then cooled to give hydrazone **3b** (2.508 g, 98.6%), mp 122 °C, identical (mp, TLC) with an authentic [19] compund. 200MHz ^{1}H NMR ($CDCl_3$) (δ, ppm): 2.88 (A*B*X, 1H, H(3_a), $J_{2,3a}$ = 12.4 Hz, $J_{3a,3e}$ = 16.8 Hz), 3.27 (*A*BX, 1H, H(3_e), $J_{2,3e}$ = 3.5 Hz), 4.35 (dd, 1H, H(2), $J_{2,3e}$ = 3.5 Hz, $J_{2,3a}$ = 12.4 Hz), 5.39 (s, 2H, NH_2), 7.14-7.45 (2m, 8H, aromatic), 7.97-8.05 (m, 1H, H(5).

Attempted C(2) epimerization of (5*R*)-1,2,3,4,5-penta-*O*-acetyl-5-C-[3-acetyl-5-(acetyl-amino)-2,3-dihydro-1,3,4-thiadiazol-2-yl]-D-arabinitol (5b). To a solution of anh. $ZnCl_2$ (0.15 g, 1.1 mmol) in Ac_2O (2 mL, 21.2 mmol) (+) **5b** [7] (0.1095 g, 0.2 mmol) was added. The solution was stirred at 41 °C for 16 h. The deep brown reaction mixture was deep-freezed and triturated with ice-water (~15 mL) to give colorless and TLC homogeneous ($CHCl_3$/Me_2CO 9:1, 6-fold run) crude product (0.069 g, 63%). For a 0.077 *M* solution: ^{1}H NMR ($CDCl_3$) (δ, ppm): 2.03-2.23 (singlets, 21 H, 2 N*Ac* and 5 O*Ac*), 3.83-4.27 (m, 2H), 5.02-5.07 (d, 1H) and 5.32-5.43 (m, 3H, CH and CH_2 signals of the pentaacetoxy-pentyl side chain), 5.84 (d, 1H, *J* = 10.0 Hz, S-C*H*R-N, ref.[7] : 5.83) and 8.88 (br s, 1H, NH); no traces of a 6.02 (d, 1H, *J* = 2 Hz) signal could be detected, characteristic of the S-C*H*R-N hydrogen of the (–) diastereomer. The product when crystallized from EtOAc had mp 216 °C , $[\alpha]_D^{23}$ +367 (c 1 in $CHCl_3$), ref. [7] mp 217 °C, $[\alpha]_D^{23}$ +367. After a similar treatment of (+) **5b** [7] at 85-90 °C (bath) for 1 h, the TLC homogenous crude product isolated in 99% yield proved to be unchanged starting material, mp 216 °C (from EtOAc).

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