FUSED HETEROCYCLES 10*
SYNTHESIS OF TRICYCLIC FUSED PYRAZOLINES BY THE REACTION OF (*Z*)-3-ARYLIDENE-1-THIOFLAVANONES WITH HYDRAZINES

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Abstract: 2,3,3a,4-Tetrahydro-3-aryl-4-phenyl[1]benzothiopyrano[4,3-c]pyrazoles **6-15** have been synthesized by the reaction of (*Z*)-3-arylidene-1-thioflavanones **1-5** with hydrazines. Structures of all new compounds have been elucidated by microanalyses, IR, ^{1}H- and ^{13}C-NMR spectroscopies.

Introduction

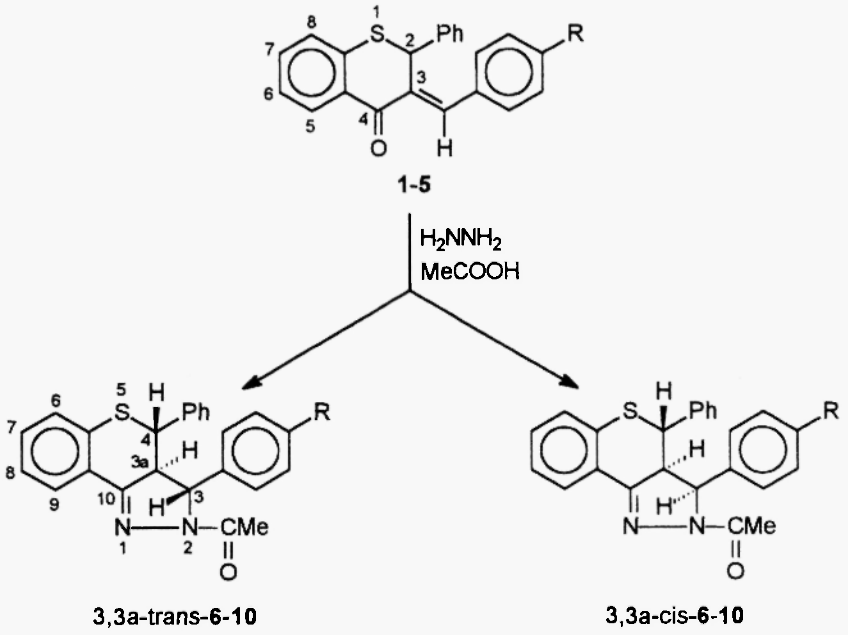
Pyrazolines are well known nitrogen-containing five-membered heterocyclic compounds. Because of their important bioactivities (1-6), an increasing attention has been paid to these substances. As a result, various procedures have been developed for their synthesis and numerous pyrazolines have been communicated in the literature (7-9). One of the most popular procedures for their preparation is based on the reaction of α,β-unsaturated ketones with hydrazines under various reaction conditions to obtain 2-pyrazolines (10-13). Synthesis of tricyclic fused pyrazolines by the reaction of exocyclic α,β-enones with hydrazines has also been investigated in several laboratories (14-29). As a continuation of our previous studies in this field (17,26,27), herein we report on the synthesis of tricyclic fused pyrazolines by the reaction of (*Z*)-3-arylidene-1-thioflavanones with hydrazines.

Results and Discussion

Formerly we have worked out a simple and convenient procedure for the synthesis of (*Z*)-3-arylidene-1-thioflavanones by the piperidine-catalyzed reaction of 1-thioflavanone with aromatic aldehydes (30). This easy access to these exocyclic α,β-unsaturated ketones made available for us to study their various chemical transformations, *viz.* their rearrangement into the previously unknown 3-benzyl-1-thioflavones (31), 1,3-dipolar cycloaddition with diazomethane (32-34), oxidative transformations (35-38) and their reaction with 2-aminothiophenol to afford tetracyclic 1,5-benzothiazepines (39).

Previously we have synthesized tricyclic fused pyrazolines by the reaction of (*E*)-3-arylideneflavanones and phenylhydrazine (27). This reaction proved to be completely diastereoselective providing *trans,trans*-isomers as solely isolable products. This finding prompted us to perform similar reactions of the related (*Z*)-3-arylidene-1-thioflavanones.

Scheme 1



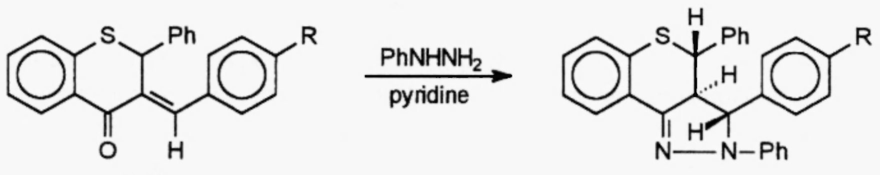
1, **6**: R = H
2, **7**: R = Me
3, **8**: R = iPr
4, **9**: R = OMe
5, **10**: R = F

(*Z*)-3-Arylidene-1-thioflavanones **1-5** were allowed to react with hydrazine hydrate in hot acetic acid and a mixture of *3,3a-trans*- and *3,3a-cis*-diastereomers of tricyclic pyrazolines **6-10** was obtained in each case (Scheme 1). Our finding is in harmony with the results of Sangwan observed in the case of the same reaction of various exocyclic α,β-unsaturated ketones (6,20). Owing to their very similar chromatographic properties, we failed to separate these two diastereomeric pyrazolines even by careful column chromatography or preparative layer chromatography. Nevertheless, the different chemical shift values of the 3-H, 3a-H, 4-H and N-acetyl protons and the coupling constants in their ^{1}H-NMR spectra made possible the differentitation of the *trans*- and *cis*-diastereomers and to determine their ratio without separation. As described by Sangwan (6,20), *cis*- and *trans*-diastereomers of such N-acetylated tricyclic fused pyrazolines can only be differentiated by a combined utilization of the chemical shift and coupling constant values since the coupling constant values of the two diastereomers may be almost the same in some cases. This seems to be true for our compounds **6-10** as well. These assignment have been corroborated by their ^{13}C-NMR spectra (*cf.* Experimental).

Compounds **1-5** were reacted also with phenylhydrazines in hot acetic acid but intractable, multicomponent mixtures were obtained. For this reason, similar to the related

3-arylideneflavanones (27), (*Z*)-3-arylidene-1-thioflavanones **1-5** were allowed to react with phenylhydrazine in hot pyridine to afford tricyclic fused pyrazolines **11-15** (Scheme 2). Structures of new compounds **11-15** have been elucidated by microanalyses, IR and ^{1}H- and ^{13}C-NMR spectra (*cf.* Experimental).

Scheme 2



1-5 **11-15**

1, **11**: R = H
2, **12**: R = Me
3, **13**: R = iPr
4, **14**: R = OMe
5, **15**: R = F

A characteristic C=N band was found in their IR spectra. In their ^{1}H-NMR spectra the chemical shifts, multiplicities and the coupling constant values are in agreement with the presence of a tricyclic fused pyrazoline ring system which is corroborated by the chemical shifts of the aliphatic carbon atoms in their ^{13}C-NMR spectra. In their ^{1}H-NMR spectra the 11.8-12.1 Hz $J_{3,3a}$ coupling constant values prove the *trans*-orientation of protons 3-H and 3a-H, while the 9.0-9.2 Hz $J_{3a,4}$ coupling constants reveal an *antiperiplanar*-arrangement of protons 3a-H and 4-H. Since one series of signals were detected both in the ^{1}H- and ^{13}C-NMR spectra, this procedure provides the *trans,trans*-diastereomers of tricyclic fused pyrazolines **11-15** as sole isolable products.

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 recorded with a Perkin-Elmer 16 PC instrument. Elemental analyses were measured in-house with a Carlo Erba 1106 EA instrument. TLC was performed on Kieselgel 60 F$_{254}$ (Merck) layer using hexane:acetone (7:3 v/v) as eluent. Starting materials **1-5** were synthesized as described previously by us (30).

General procedure for the synthesis of compounds **6-10**

A mixture of (*Z*)-3-arylidene-1-thioflavanone (**1-5**, 5 mmoles), hydrazine hydrate (50.0 mmoles) and acetic acid (30 ml) was refluxed for 3 hours, then poured onto crushed ice. The precipitate was filtered off, washed free of acid and crystallized from methanol to obtain tricyclic fused pyrazolines **6-10**.

2,3,3a,4-Tetrahydro-2-acetyl-3,4-diphenyl[1]benzothiopyrano[4,3-c]pyrazole (6): This compound was isolated as a *3,3a-trans:3,3a-cis* (6:4) diastereomeric mixture in 81% yield, m.p. 185-187 °C; IR: νC=O 1670 and νC=N 1596 cm^{-1}; ^{1}H-NMR (δ): 2.25 and 2.42 (3H, s, NAc), 4.01 (1H, m, 3a-H), 4.37 (1H, d, J = 5.9 Hz, 3-H$_{cis}$), 4.52 (1H, t, J = 12.0 Hz, 3-H$_{trans}$), 5.56 (1H, d, J = 10.6 Hz, 4-H), 6.62-8.26 (m, 14 arom. H); ^{13}C-NMR (δ): 21.1 and 21.7 (COCH$_3$), 45.1 and 45.6 (C-3a), 58.3 and 59.8 (C-3), 63.7 and 64.4 (C-4), 168.2 and 169.2 (C=O).

Anal. Calcd. for $C_{24}H_{20}N_2OS$: C, 74.98; H, 5.24; N, 7.28. Found: C, 74.94; H, 5.26; N, 7.25.

2,3,3a,4-Tetrahydro-2-acetyl-3-(4-methylphenyl)-4-phenyl[1]benzothiopyrano[4,3-c]pyrazole (7): This substance was obtained as a *3,3a-trans:3,3a-cis* (7:3) diastereomeric mixture in 90% yield, m.p. 193-195 °C; IR: νC=O 1670 and νC=N 1596 cm^{-1}; ^{1}H-NMR (δ): 2.28 (3H, s, CH$_3$), 2.36 and 2.42 (3H, s, NAc), 4.03 (1H, m, 3a-H), 4.32 (1H, d, J = 5.9 Hz, 3-H$_{cis}$), 4.48 (1H, t, J = 11.6 Hz, 3-H$_{trans}$), 5.51 (1H, d, J = 10.6 Hz, 4-H), 6.52-8.24 (m, 13 arom. H); ^{13}C-NMR (δ): 21.5 and 21.7 (COCH$_3$), 45.0 and 45.4 (C-3a), 58.3 and 59.7 (C-3), 64.2 and 64.7 (C-4), 168.3 and 169.5 (C=O).

Anal. Calcd. for $C_{25}H_{22}N_2OS$: C, 75.36; H, 5.57; N, 7.03. Found C, 75.39; H, 5.54; N, 7.06.

2,3,3a,4-Tetrahydro-2-acetyl-3-(4-isopropylphenyl)-4-phenyl[1]benzothiopyrano[4,3-c]pyrazole (8): This compound was prepared as a *3,3a-trans:3,3a-cis* (7:3) diastereomeric mixture in 86% yield, m.p. 197-200 °C; IR: νC=O 1670 and νC=N 1594 cm^{-1}; ^{1}H-NMR (δ): 1.20 and 1.26 (6H, d, J = 6.8 Hz, CH(CH$_3$)$_2$), 2.27 and 2.43 (3H, s, NAc), 2.83 (1H, s, CH(CH$_3$)$_2$), 4.08 (1H, m, 3a-H), 4.38 (1H, d, J = 6.0 Hz, 3-H$_{cis}$), 4.54 (1H, t, J = 11.6 Hz, 3-H$_{trans}$), 5.54 (1H, d, J = 10.6 Hz, 4-H), 6.60-8.27 (m, 13 arom. H); ^{13}C-NMR (δ): 21.6 and 21.7 (COCH$_3$), 45.1 and 45.6 (C-3a), 58.2 and 59.6 (C-3), 64.2 and 64.6 (C-4), 168.3 and 168.6 (C=O).

Anal. Calcd. for $C_{27}H_{26}N_2OS$: C, 76.03; H, 6.14; N, 6.56. Found: C, 76.07; H, 6.12; N, 6.52.

2,3,3a,4-Tetrahydro-2-acetyl-3-(4-methoxyphenyl)-4-phenyl[1]benzothiopyrano[4,3-c]pyrazole (9): This substance was isolated as a *3,3a-trans:3,3a-cis* (6:4) diastereomeric mixture in 87% yield, m.p. 118-120 °C; IR: νC=O 1668 and νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 2.23 and 2.40 (3H, s, NAc), 3.72 and 3.80 (3H, s, OMe), 4.06, (1H, m, 3a-H), 4.35 (1H, d, J = 5.8 Hz, 3-H$_{cis}$), 4.51 (1H, t, J = 11.9 Hz, 3-H$_{trans}$), 5.50 (1H, d, J = 10.6 Hz, 4-H), 6.59-8.23 (m, 13 arom. H); ^{13}C-NMR (δ): 21.5 and 21.8 (COCH$_3$), 45.1 and 45.6 (C-3a), 55.0 and 55.2 (C-3), 63.2 and 63.9 (C-4), 168.4 and 169.6 (C=O).

Anal. Calcd. for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.48; H, 5.37; N, 6.72.

2,3,3a,4-Tetrahydro-2-acetyl-3-(4-fluorophenyl)-4-phenyl[1]benzothiopyrano[4,3-c]pyrazole (10): This compound was prepared as a *3,3a-trans:3,3a-cis* (6:4) diastereomeric mixture in 84% yield, m.p. 200-202 °C; IR: νC=O 1670 and νC=N 1602 cm^{-1}; ^{1}H-NMR (δ): 2.23 and 2.40 (3H, s, NAc), 4.02 (1H, m, 3a-H), 4.36 (1H, d, J = 5.8 Hz, 3-H$_{cis}$), 4.50 (1H, t, J = 11.5 Hz, 3-H$_{trans}$), 5.54 (1H, d, J = 10.6, 4-H), 6.52-8.26 (m, 13 arom. H); ^{13}C-NMR (δ): 21.5 and 21.8 (COCH$_3$), 45.2 and 45.6 (C-3a), 58.3 and 59.9 (C-3), 63.0 and 63.8 (C-4), 168.4 and 169.7 (C=O).

Anal. Calcd. for $C_{24}H_{19}FN_2OS$: C, 71.63; H, 4.76; N, 6.96. Found: C, 71.66; H, 4.74; N, 6.93.

General procedure for the preparation of compounds **11-15**

A mixture of (*Z*)-3-arylidene-1-thioflavanone (**1-5**, 10.0 mmoles), phenylhydrazine (30.0 mmoles), anhydrous pyridine (50 ml) was refluxed for 6 hours, then poured into water.

The precipitate was isolated by filtration, washed with water and crystallized from methanol .to afford substances **11-15**.

***trans,trans*-2,3,3a,4-Tetrahydro-2,3,4-triphenyl[1]benzothiopyrano[4,3-c]pyrazole (11)**: This compound was isolated as white plates in 83% yield, m.p. 102-103 °C; IR: νC=N 1596 cm^{-1}; ^{1}H-NMR (δ): 3.98 (1H, dd, J = 9.1, 12.1 Hz, 3a-H), 4.57 (1H, d, J = 12.1 Hz, 3-H), 4.78 (1H, d, J = 9.1 Hz, 4-H), 6.66-8.14 (m, 19 arom. H); ^{13}C-NMR (δ): 50.3 (C-3a), 61.1 (C-3), 70.8 (C-4).

Anal. Calcd. for $C_{28}H_{22}N_2S$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.43; H, 5.28; N, 6.64.

***trans,trans*,2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-methylphenyl)[1]benzothiopyrano[4,3-c]pyrazole (12)**: This substance was obtained as white needles in 73% yield, m.p. 143-144 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 2.22 (3H, s, Me), 3.92 (1H, dd, J = 9.0, 11.9 Hz, 3a-H), 4.51 (1H, d, J = 12.0 Hz, 3-H), 4.73 (1H, d, J = 9.0 Hz, 4-H), 6.50-8.13 (m, 18 arom. H); ^{13}C-NMR (δ): 50.3 (C-3a), 60.9 (C-3), 70.4 (C-4).

Anal. Calcd. for $C_{29}H_{24}N_2S$: C, 80.53; H, 5.59; N, 6.47. Found. C, 80.48; H, 5.61; N, 6.43.

***trans,trans*-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-isopropylphenyl)[1]benzothiopyrano-[4,3-c]pyrazole (13)**: This compound was prepared as white plates in 78% yield, m.p. 81-82 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 1.20 (6H, d, J = 6.9 Hz, CH(CH$_3$)$_2$), 2.83 (1H, m, CH(CH$_3$)$_2$), 3.97 (1H, dd, J = 9.1, 11.9 Hz, 3a-H), 4.54 (1H, d, J = 11.9 Hz, 3-H), 4.74 (1H, d, J = 9.2 Hz, 4-H), 6.60-8.16 (m, 18 arom. H); ^{13}C-NMR (δ): 50.2 (C-3a), 60.9 (C-3), 70.5 (C-4).

Anal. Calcd. for $C_{31}H_{28}N_2S$: C, 80.84; H, 6.13; N, 6.08. Found: C, 80.79; H, 6.15; N, 6.04.

***trans,trans*-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-methoxyphenyl)[1]benzothiopyrano-[4,3-c]pyrazole (14)**: This compound was obtained as white needles in 82% yield, m.p. 139-140 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 3.70 (3H, s, OMe), 3.91 (1H, dd, J = 9.2, 12.0 Hz, 3a-H), 4.51 (1H, d, J = 12.0 Hz, 3-H), 4.69 (1H, d, J = 9.2 Hz, 4-H), 6.57-8.10 (m, 18 arom. H); ^{13}C-NMR (δ): 50.2 (C-3a), 61.0 (C-3), 70.3 (C-4).

Anal. Calcd. for $C_{29}H_{24}N_2OS$: C, 77.66; H, 5.39; N, 6.24. Found: C, 77.62, H, 5.41; N, 6.28.

***trans,trans*-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-fluorophenyl)[1]benzothiopyrano[4,3-c]pyrazole (15)**: This substance was isolated as pale yellow plates in 81% yield, m.p. 138-139 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 3.92 (1H, dd, J = 9.5, 11.8 Hz, 3a-H), 4.54 (1H, d, J = 11.8 Hz, 3-H), 4.74 (1H, d, J = 9.7 Hz, 4-H), 6.57-8.16 (m, 18 arom. H); ^{13}C-NMR (δ): 50.1 (C-3a), 61.2 (C-3), 70.3 (C-4).

Anal. Calcd. for $C_{28}H_{21}FN_2S$. C, 77.05; H, 4.85; N, 6.41. Found: C, 77.09; H, 4.83; N, 6.45.

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*For Part 9, see Ref. (27).

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