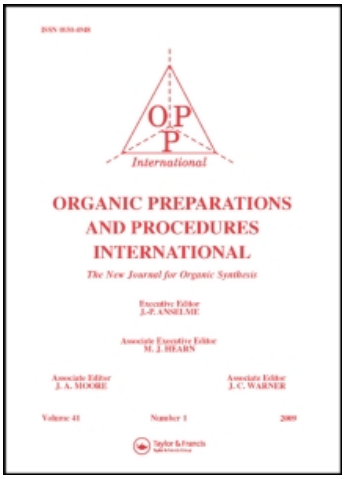

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SYNTHESIS OF SPIRO-1-PYRAZOLINES BY THE REACTION OF Z-3-ARYLIDENE-1-THIOFLAVANONES WITH DIAZOMETHANE

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SYNTHESIS OF SPIRO-1-PYRAZOLINES BY THE REACTION OF Z-3-ARYLIDENE-1-THIOFLAVANONES WITH DIAZOMETHANE

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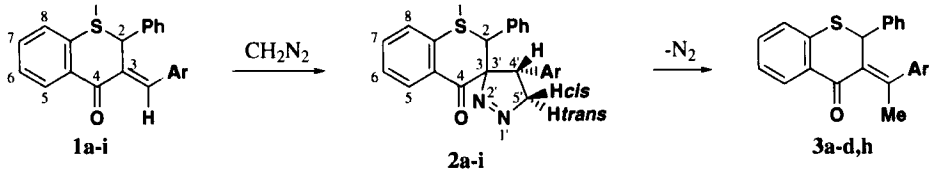
Dedicated to Prof. Dr. Waldemar Adam on the occasion of his 65th birthday.

Pyrazolines constitute a group of important nitrogen-containing five-membered heterocyclic compounds utilized in drug research.[1] Among their most important biological activities are antiimplantation,[2] antiarrhytmic[3] and other effects. Various procedures have been developed for their syntheses and numerous pyrazolines and related compounds have been described in the literature.[4] A frequently used reaction is the cycloaddition of diazoalkanes to carbon-carbon double bonds.[5] The investigation of the 1,3-dipolar cycloaddition of diazomethane to α,β-unsaturated ketones[6] has led to the conclusion that the thermodynamically more stable 2-pyrazoline is isolated as the exclusive product after spontaneous isomerization of the initially formed 1-pyrazoline isomer in each case. However, similar 1,3-dipolar cycloaddition of exocyclic α,β-unsaturated ketones and diazomethane has provided stable spiro-1-pyrazolines.[7-14]

The 1,3-dipolar cycloaddition of diazomethane to *E*- and *Z*-isomers of exocyclic α,β-unsaturated ketones, *viz.* 2-arylidene derivatives of 1-indanone, 1-tetralone, and 1-benzosuberone, 3-arylidenechromanones, 1-thiochromanones, flavanones, aurones, and 1-thioaurones[8-10,13,14] was found to be completely regioselective and stereospecific; spiro-1-pyrazolines in which the methylene moiety of the diazomethane is connected to the β-carbon atom of the α,β-enone and the stereochemistry of the starting α,β-unsaturated ketone has been retained. Although the reaction of the 3-arylideneflavanones with diazomethane has been thoroughly investigated,[8,10,14] the similar reaction with their 1-thio analogues has hitherto received much less attention.[10,14] For this reason, it appeared expedient to perform a detailed investigation with a series of 3-arylidene-1-thioflavanones to complete our previous studies in this field. Herein we report the synthesis of spiro-1-pyrazolines by the reaction of these α,β-enones with diazomethane and on the thermal denitrogenation of pyrazolines obtained.

Z-3-Arylidene-1-thioflavanones **1a-i** synthesized by the piperidine-catalyzed reaction of 1-thioflavanone and aromatic aldehydes[15] were allowed to react with diazomethane in a mixture of anhydrous ether and methylene chloride to obtain *trans*-spiro-1-pyrazolines **2a-i** in good yields. The structure and stereochemistry of **2a-i** were elucidated by ^{1}H and ^{13}C NMR spectroscopic measurements.



1a-i 2a-i 3a-d,h

a) 2-Me-C_6H_4 b) 3-Me-C_6H_4 c) 4-Me-C_6H_4 d) 4-iPr-C_6H_4
e) 4-(Me_2N)-C_6H_4 f) 4-MeO-C_6H_4 g) 4-F-C_6H_4 h) 2-Cl-C_6H_4 i) 2-thienyl

The spiro-1-pyrazoline structure of compounds **2a-i** was unequivocally established by the multiplicity and coupling constant values observed in their ^1H NMR spectra (*cf.* Experimental Section). This conclusion has been confirmed further by the chemical shift data of the aliphatic carbon atoms in their ^{13}C NMR spectra. All these NMR spectroscopic properties also corroborate that the methylene part of the diazomethane is connected to the β-carbon atom of the starting α,β-enone, *viz.* this 1,3-dipolar cycloaddition is completely regioselective, providing only one regioisomer spiro-1-pyrazoline in each case. The aliphatic protons of the other possible regioisomer spiro-1-pyrazoline would appear as two singlets. NOE cross peaks observed on the *ortho*-protons of phenyl groups connected to the C-2 and C-4' carbon atoms on the irradiation of the H-2 proton speak for a *trans*-arrangement of the carbonyl group and the aryl group at the C-4' atom. Thus, the 1,3-dipolar cycloaddition of diazomethane to Z-3-arylidene-1-thioflavanones is a stereospecific one-step process affording *trans*-spiro-1-pyrazolines as sole isolable products, similarly to the 3-arylideneflavanones.[8,10] It is also worth mentioning that the substitution pattern of starting materials **1a-i** has little influence on the outcome of this cycloaddition. It should be emphasized that even the *ortho*-substituent of the phenyl group in the arylidene moiety does not affect the formation of a stereohomogeneous *trans*-spiro-1-pyrazoline.

Further corroboration of the structures of selected representatives of the spiro-1-pyrazolines (**2a-d,h**) was achieved by thermolysis above their melting points to afford products **3a-d,h**. The denitrogenated substances were fully characterized by their ^1H and ^{13}C NMR spectroscopic properties. These spectroscopic data unequivocally showed that th 3-(methylphenyl)-methylene-1-thioflavanones were obtained, again similarly to the denitrogenation of the *trans*-spiro-1-pyrazolines[16] synthesized by the reaction of 3-arylideneflavanones and diazomethane. The β-methyl α,β-enones may originate only from those regioisomer spiro-1-pyrazolines where the methylene group is attached to the β-carbon atom of the starting material. NOE detected on the *ortho*-protons of the C-2 phenyl group on the irradiation of the methyl group indicates a *trans*-orientation of the carbonyl and the aryl groups in compounds **3a-d,h**. Thus, the stereochemistry of the starting α,β-enones is retained even in the denitrogenated products.

EXPERIMENTAL SECTION

Mps (uncorrected) were determined on a Kofler hot-stage apparatus. ^1H and ^{13}C NMR spectra were recorded by a Varian Gemini 200 spectrometer at 200/50 MHz in $CDCl_3$ at ambient temperature in the presence of TMS as an internal reference (δ). Elemental analyses were performed on a Carlo Erba 1106 analyzer. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) layer using hexane-acetone (7:3 v/v) as eluent. The starting materials **1a-i** were synthesized according to a known procedure.[15]

Reaction of *Z*-3-Arylidene-1-thioflavanones with Diazomethane. General Procedure for the Synthesis of Spiro-1-pyrazolines 2a-i.- A mixture of the appropriate *Z*-3-arylidene-1-thioflavanone (**1a-i**, 5.0 mmoles) dissolved in anhydrous methylene chloride (50 mL) and diazomethane prepared from N-nitroso-N-methylurea (25.0 mmoles) in anhydrous ethereal solution (60 mL) was left to stand in a refrigerator for 48 h, then the solvent was evaporated *in vacuo*, and the residue was crystallized from methanol to afford spiro-1-pyrazolines **2a-i.**

General Procedure for the Thermal Denitrogenation of Spiro-1-pyrazolines.- Spiro-1-pyrazoline (**2a-d, h,** 2.0 mmoles) was heated at 160° for 30 min and the resudue was crystallized from methanol to obtain denitrogenated products **3a-d, h.**

Table 1. Physical Data and Elemental Analyses of **2a-i** and **3a-d,h**

Cmpd	mp (°C)	Yield (%)	Formula	Analysis (Found) C	H	N
2a	140-141	73	$C_{24}H_{20}N_2OS$	74.98 (74.95)	5.24 (5.27)	7.28 (7.24)
2b	138-139	76	$C_{24}H_{20}N_2OS$	74.98 (75.04)	5.24 (5.21)	7.28 (7.31)
2c	134-135	82	$C_{24}H_{20}N_2OS$	74.98 (74.88)	5.24 (5.27)	7.28 (7.32)
2d	132-133	81	$C_{26}H_{24}N_2OS$	75.71 (75.76)	5.86 (5.83)	6.79 (6.82)
2e	142-143	74	$C_{25}H_{23}N_3OS$	72.62 (72.67)	5.61 (5.59)	10.16 (10.19)
2f	137-138	82	$C_{24}H_{20}N_2O_2S$	71.99 (72.08)	5.03 (5.07)	6.99 (6.95)
2g	138-139	78	$C_{23}H_{17}FN_2OS$	71.12 (71.26)	4.41 (4.45)	7.21 (7.18)
2h	143-144	77	$C_{23}H_{17}ClN_2OS$	68.24 (68.18)	4.23 (4.26)	6.92 (6.89)
2i	130-131	83	$C_{21}H_{16}N_2OS_2$	67.02 (67.07)	4.28 (4.25)	7.44 (7.47)
3a	128-129	51	$C_{24}H_{20}OS$	80.87 (80.83)	5.65 (5.67)	----
3b	138-139	69	$C_{24}H_{20}OS$	80.87 (80.81)	5.65 (5.62)	----
3c	165-166	74	$C_{24}H_{20}OS$	80.87 (80.91)	5.65 (5.68)	----
3d	152-153	69	$C_{26}H_{24}OS$	81.22 (81.18)	6.29 (6.31)	----
3h	136-137	54	$C_{23}H_{17}ClOS$	73.30 (73.34)	4.55 (4.53)	----

Table 2. ^{1}H and ^{13}C NMR Spectroscopic Data (δ, of Compounds **2** and **3**)

2a ^{1}H NMR: 2.09 (s, 3H, Me), 5.02 (d, 1H, J = 7.9 Hz, H-4'), 5.19 (s, 1H, H-2), 5.59 (dd, 1H, J = 18.3, 7.9 Hz, H-5'$_{cis}$), 5.91 (d, 1H, J = 18.3 Hz, H-5'$_{trans}$), 7.11-8.78 (m, 13 arom. H); ^{13}C NMR: 18.8 (2-Me), 36.7 (C-4'), 48.5 (C-2), 90.6 (C-5'), 103.8 (C-3'),186.7 (C-4)

2b ^{1}H NMR: 2.10 (s, 3H, Me), 4.03 (d, 1H, J = 7.6 Hz, H-4'), 4.38 (s, 1H, H-2), 4.97 (dd, 1H, 18.2, 7.7 Hz, H-5'$_{cis}$), 5.30 (d, 1H, J = 18.2 Hz, H-5'$_{trans}$), 6.60-8.14 (m, 13 arom. H); ^{13}C NMR: 23.8 (3-Me), 43.4 (C-4'), 48.6 (C-2), 89.7 (C-5'), 103.3 (C-3'), 187.4 (C-4)

2c ^{1}H NMR: 2.12 (s, 3H, Me), 4.02 (d, 1H, J = 7.3 Hz, H-4'), 4.41 (s, 1H, H-2), 4.96 (dd, 1H, J = 18.2, 7.8 Hz, H-5'$_{cis}$), 5.26 (d, 1H, J = 18.2 Hz, H-5'$_{trans}$), 6.68-8.16 (m, 13 arom. H); ^{13}C NMR: 20.7 (4-Me), 42.9 (C-4'), 89.8 (C-5'), 103.3 (C-3'), 187.7 (C-4)

2d ^{1}H NMR: 1.18 (s, 3H, Me), 1.23 (s, 3H, Me), 2.84 (m, C<u>H</u>Me$_2$), 4.07 (d, 1H, J = 7.4 Hz, H-4'), 4.41 (s, 1H, H-2), 5.01 (dd, J = 18.2, 7.4 Hz, H-5'$_{cis}$), 5.30 (d, J = 18.2 Hz, H-5'$_{trans}$), 6.38-8.15 (m, 13 arom. H); ^{13}C NMR: 23.8 (Me), 24.0 (Me), 33.6 (<u>C</u>HMe$_2$), 43.0 (C-4'), 48.6 (C-2), 89.8 (C-5'), 103.4 (C-3'), 187.4 (C-4)

2e ^{1}H NMR: 2.88 (s, 6H, N<u>Me</u>$_2$), 4.02 (d, 1H, J = 7.4 Hz, H-4'), 4.43 (s, 1H, H-2), 4.94 (dd, 1H, J = 18.1, 7.6 Hz, H-5'$_{cis}$), 5.25 (d, 1H, J = 18.1, H-5'$_{trans}$), 6.31-8.17 (m, 13 arom. H); ^{13}C NMR: 29.6 (N<u>Me</u>$_2$), 42.8 (C-4'), 48.5 (C-2), 89.7 (C-5'), 103.1 (C-3'), 187.5 (C-4)

2f ^{1}H NMR: 3.70 (s, 3H, Me), 4.02 (d, 1H, J = 7.3 Hz, H-4'), 4.38 (s, 1H, H-2), 4.98 (dd, 1H, J = 18.3, 7.6 Hz, H-5'$_{cis}$), 5.24 (d, 1H, J = 18.3 Hz, H-5'$_{trans}$), 6.34-8.11 (m, 13 arom. H); ^{13}C NMR: 42.7 (C-4'), 48.5 (C-2), 55.1 (MeO), 89.8 (C-5'), 103.2 (C-3'), 187.8 (C-4)

2g ^{1}H NMR: 4.07 (d, 1H, J = 7.3 Hz, H-4'), 4.34 (s, 1H, H-2), 4.96 (dd, 1H, J = 18.2, 7.6 Hz, H-5'$_{cis}$), 5.23 (d, J = 18.2 Hz, H-5'$_{trans}$), 6.34-8.12 (m, 13 arom H.); ^{13}C NMR: 42.7(C-4'), 48.5 (C-2), 89.7 (C-5'), 103.3 (C-3'), 187.6 (C-4)

2h ^{1}H NMR: 4.47 (s, 1H, H-2), 4.70 (d, 1H, J = 7.2 Hz, H-4'),4.98 (dd, 1H, J = 18.2, 7.9 Hz, H-5'$_{cis}$), 5.22 (d, 1H, J = 18.2 Hz, H-5'$_{trans}$), 6.54-8.16 (m, 13 arom. H); ^{13}C NMR: 38.9 (C-4'), 48.4 (C-2), 89.6 (C-5'), 104.0 (C-3'), 186.7 (C-4)

2i ^{1}H NMR: 4.41 (d, 1H, J = 7.3 Hz, H-4'), 4.64 (s, 1H, H-2), 4.98 (dd, 1H, J = 17.9, 7.6 Hz, H-5'$_{cis}$), 5.34 (d, J = 17.9 Hz, H-5'$_{trans}$), 6.18-8.12 (m, 12 arom. H); ^{13}C NMR:36.6 (C-4'), 48.4 (C-2), 89.9 (C-5'), 102.7 (C-3'), 187.3 (C-4)

3a ^{1}H NMR: 2.38 (s, 3H, 2-Me), 2,49 (s, 3H, C<u>Me</u>), 5.10 (s, 1H, H-2), 7.22-8.17 (m, 13 arom. H); ^{13}C NMR: 21.1 (C<u>Me</u>), 23.7 (2-Me), 47.5 (C-2), 133.2 (C-3), 148.5 (<u>C</u>Me), 188.0 (C-4)

3b ^{1}H NMR: 2.38 (s, 3H, 3-Me), 2.45 (s, 3H, C<u>Me</u>), 5.10 (s, 1H, H-2), 7.12-8.16 (m, 13 arom. H); ^{13}C NMR: 21.2 (C<u>Me</u>), 23.8 (3-Me), 47.6 (C-2), 133.2 (C-3), 148.8 (<u>C</u>Me), 187.9 (C-4)

3c ^{1}H NMR: 2.39 (s, 3H, 4-Me), 2.48 (s, 3H, C<u>Me</u>), 5.16 (s, 1H, H-2), 7.21-8.15 (m, 13 arom. H); ^{13}C NMR: 21.0 (C<u>Me</u>), 23.7 (4-Me), 47.5 (C-2), 133.3 (C-3), 149.0 (<u>C</u>Me), 188.4 (C-4)

3d ^{1}H NMR: 1.23 (s, 3H, Me), 1.28 (s, 3H, Me), 2.43 (s, 3H, C<u>Me</u>), 2.89 (m, 1H, C<u>H</u>Me$_2$), 5.13 (s, 1H, H-2), 7.18-8.13 (m, 13 arom. H); ^{13}C NMR: 21.2 (C<u>Me</u>), 23.7 (CH<u>Me</u>$_2$), 33.7 (<u>C</u>HMe$_2$), 47.5 (C-2), 133.3 (C-3), 149.0 (<u>C</u>Me), 188.5 (C-4)

3h ^{1}H NMR: 2.23 (s, 3H, C<u>Me</u>), 4.94 (s, 1H, H-2), 7.02-8.14 (m, 13 arom. H); ^{13}C NMR: 21.7 (C<u>Me</u>), 47.7 (C-2), 133.5 (C-3), 146.7 (<u>C</u>Me), 187.9 (C-4)

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