Fused Heterocycles. 8 [1]. An Efficient Procedure for the Stereoselective Synthesis of *trans*-2,3,3a,4-Tetrahydro-3-aryl-2-phenyl[1]benzopyrano[4,3-*c*]pyrazoles and their [1]Benzothiopyrano Analogues

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Dedicated to Professor Dr. Gábor Bernáth on the occasion of his 65th birthday.

Stereoselective synthesis of *trans*-2,3,3a,4-tetrahydro-3-aryl-2-phenyl[1]benzopyrano[4,3-*c*]pyrazoles **13-18** and their [1]benzothiopyrano analogues **19-24** has been performed by the reaction of 3-arylidenechromanones **1-6** and 3-arylidene-1-thiochromanones **7-12** with phenylhydrazine in hot pyridine. The structure and stereochemistry of the compounds prepared have been elucidated by ir, ^1H and ^{13}C nmr measurements.

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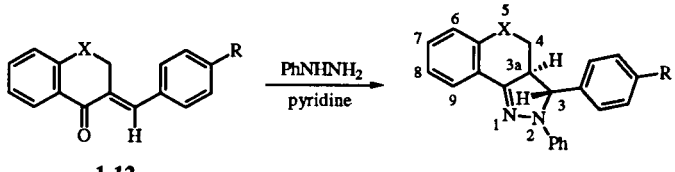
The dihydropyrazoles (pyrazolines) are well known nitrogen-containing heterocyclic compounds. Owing to some interesting and important bioactivities of this type of compounds, [2-7] increasing attention has been focused on this ring system. One of the most popular procedures used for the synthesis of pyrazolines is based on the reaction of α,β-enones with hydrazines. The reaction of chalcones and related α,β-unsaturated ketones with hydrazines was investigated under various reaction conditions and a large number of 2-pyrazolines were obtained in this way [8-12]. Synthesis of tricyclic pyrazolines by the reaction of so-called exocyclic α,β-unsaturated ketones has also been studied by several research groups [13-23]. This latter reaction provides tricyclic pyrazolines with two new centres of chirality which gives rise to the formation of diastereomeric mixtures of pyrazolines. Mixtures of *cis* and *trans* isomers were obtained in a case where exocyclic α,β-enones were allowed to react with hydrazine derivatives either in acetic acid [15,19] or in ethanolic solution in the presence of hydrochloric acid [16,22]. It has also turned out that both the *cis* and *trans* 3H,3a-H-diastereomers of these tricyclic pyrazolines can be rearranged into each other under acidic reaction conditions [23]. On all these bases, it appears that the acidic reaction conditions are not convenient for a completely diastereoselective synthesis of tricyclic pyrazolines by the reaction of exocyclic α,β-unsaturated ketones and hydrazines. 2-Arylidene-1-indanones, -1-tetralones and -1-benzosuberones were allowed to react with hydrazines in hot ethanolic or methanolic solutions [13,14,18,20], but nothing was mentioned on the stereochemistry of tricyclic pyrazolines obtained in this way. Therefore, it is unknown whether this latter reaction conditions offer any stereoselectivity or not. In our preliminary account [17] we reported that the reaction of some exocyclic α,β-unsaturated ketones with methylhydrazine or phenylhydrazine in hot pyridine provided *trans*-diastereomers of tricyclic pyrazolines. As a continuation, in our present paper we report on the stereoselective synthesis of tricyclic pyrazolines with fused benzopyrano and benzothiopyrano ring system. Since we wanted to neglect the influence of the stereoisomerism of the starting materials, in our present study we investigated this reaction only of those isomers of 3-arylidenechromanones and -1-thiochromanones where the carbonyl group and the aryl moiety are on the opposite sides of the C=C double bond.

Scheme 1



1-12 **13-24**

	X	R
1,13	O	Me
2,14	O	*i*-Pr
3,15	O	OMe
4,16	O	F
5,17	O	Cl
6,18	O	Br

	X	R
7,19	S	Me
8,20	S	*i*-Pr
9,21	S	OMe
10,22	S	F
11,23	S	Cl
12,24	S	Br

3-Arylidenechromanones **1-6** and 3-arylidene-1-thiochromanones **7-12** were allowed to react with phenylhydrazine in hot pyridine and *trans*-2,3,3a,4-tetrahydro-3-aryl-2-phenyl[1]benzopyrano[4,3-*c*]pyrazoles **13-18** and *trans*-2,3,3a,4-tetrahydro-3-aryl-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazoles **19-24** were obtained (Scheme 1) in high yields. Structures of new compounds **13-24** have been elucidated by microanalyses, ir, and ^1H and ^{13}C nmr spectroscopic measurements (*cf.* Experimental). In the ir spectra a characteristic C=N band between 1590 and 1600 cm^{-1} refers to the formation of a pyrazoline ring. In the ^1H

nmr spectra both the chemical shift values and the multiplicities of the signals unambiguously reveal the characteristics of a tricyclic pyrazoline ring system. This is corroborated by the chemical shift values of the aliphatic carbon atoms in the ^{13}C nmr spectra. On the basis of the ^{1}H and ^{13}C nmr data, it can also be concluded that one diastereomer was formed in each case since one series of signals could be detected in all nmr spectra. No minor reaction product could be isolated or even detected in the crude reaction mixtures by careful tlc monitoring or by ^{1}H nmr measurements. The *cis* and *trans* isomers of such tricyclic pyrazolines can easily be differentiated by nmr measurements. In the ^{1}H nmr spectra the 11.03-11.87 Hz $J_{3,3a}$ coupling constant values reveal the antiperiplanar orientation of protons 3-H and 3a-H. Chemical shift values of 4.68-4.71 ppm for 3-H and 3.58-3.62 ppm for 3a-H corroborate the *trans*-orientation of these two protons in comparison with the published ^{1}H nmr data for similar tricyclic pyrazolines [19,21,23].

In summary, it can be concluded that we have succeeded to introduce a simple and convenient procedure for the preparation of *trans*-2,3,3a,4-tetrahydro-3-aryl-2-phenyl[1]benzopyrano[4,3-*c*]pyrazoles and *trans*-2,3,3a,4-tetrahydro-3-aryl-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazoles in a completely diastereoselective reaction. The course and stereochemical outcome of the reaction seem to be independent on the substituent in the *para*-position of the arylidene moiety and on the type of the heteroatom of the six-membered heterocyclic ring of the starting material.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on Bruker WP 200 SY and Varian Gemini 200 spectrometers at 200/50 MHz in deuteriochloroform with tetramethylsilane as the internal reference. The ir spectra were measured in potassium bromide pellets on a Perkin-Elmer 16 PC instrument. Elemental analyses were performed in-house on a Carlo Erba EA 1106 analyzer. Thin-layer chromatography (tlc) was performed on Kieselgel 60 F_{254} (Merck) layer using hexane-acetone (7:3 v/v) as eluent. The starting materials (**1-12**) were synthesized according to known procedures [24,25].

Reaction of 3-Arylidenechromanones **1-6** and 3-Arylidene-1-thiochromanones **7-12** with phenylhydrazine. General Procedure.

A mixture of 3-arylidenechromanone (**1-6**) or 3-arylidene-1-thiochromanone (**7-12**) (10.0 mmoles), phenylhydrazine (50.0 mmoles) and pyridine (30.0 ml) was refluxed for 6 hours, then poured into water and acidified with dilute hydrochloric acid. The residue was filtered off, washed with water, and crystallized from acetic acid to afford compounds **13-24.**

trans-2,3,3a,4-Tetrahydro-3-(4-methylphenyl)-2-phenyl[1]benzopyrano[4,3-*c*]pyrazole (**13**).

This compound was obtained as white crytals in 71% yield, mp 152-153°; ir: ν 1598, 1576, 1513, 1498, 1470, 1466, 1366, 1229, 1204, 1120, 1046, 1031, 848, 755, 692 cm^{-1}; ^{1}H nmr: δ 2.38 (3H, s, CH_3), 3.60 (1H, ddd, J = 12.01, 5.86 Hz, 3a-H), 4.20 (1H, dd, J = 12.33, 10.13 Hz, 4-H_{ax}), 4.62 (1H, dd, J = 10.01, 5.82 Hz, 4-H_{eq}), 4.69 (1H, d, J = 11.72 Hz, 3-H), 6.80-7.90 (13 arom H, m). ^{13}C nmr: δ 20.9, 53.7, 68.9, 69.8, 115.0, 116.4, 117.3, 120.4, 121.7, 124.7, 126.1, 128.9, 130.2, 135.0, 137.8, 138.5, 145.5, 146.9, 155.9.

Anal. Calcd. for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.22. Found: C, 81.06; H, 5.90; N, 8.26.

trans-2,3,3a,4-Tetrahydro-3-(4-isopropylphenyl)-2-phenyl[1]benzopyrano[4,3-*c*]pyrazole (**14**).

This compound was prepared as white crystals in 78% yield, mp 160-161°; ir: ν 1597, 1578, 1512, 1497, 1471, 1457, 1387, 1367, 1294, 1230, 1200, 1121, 1052, 1028, 999, 849, 754, 692 cm^{-1}; ^{1}H nmr: δ 1.27 (6H, m, $CH(CH_3)_2$), 2.93 (1H, m, $CH(CH_3)_2$), 3.62 (1H, ddd, J = 12.04, 5.84 Hz, 3a-H), 4.19 (1H, dd, J = 12.31, 10.16 Hz, 4-H_{ax}), 4.63 (1H, dd, 10.06, 5.83 Hz, 4-H_{eq}), 4.69 (1H, d, J = 11.80 Hz, 3-H), 6.74-7.88 (13 arom H, m); ^{13}C nmr: δ 23.7, 33.6, 53.6, 69.0, 69.8, 115.0, 116.4, 117.3, 117.5, 120.3, 121.5, 121.7, 122.7, 124.7, 126.1, 126.3, 127.5, 128.9, 129.5, 131.0, 138.7, 145.5, 148.8, 155.9.

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.56; N, 7.60. Found: C, 81.42; H, 6.59; N, 7.64.

trans-2,3,3a,4-Tetrahydro-3-(4-methoxyphenyl)-2-phenyl[1]benzopyrano[4,3-*c*]pyrazole (**15**).

This compound was obtained as white crystals in 80% yield, mp 170-171°; ir: ν 1596, 1573, 1514, 1498, 1456, 1388, 1365, 1327, 1298, 1244, 1183, 1026, 997, 846, 754 cm^{-1}; ^{1}H nmr: δ 3.60 (1H, ddd, J = 12.07, 5.86 Hz, 3a-H), 3.81 (3H, s, OCH_3), 4.20 (1H, dd, J = 12.35, 10.13 Hz, 4-H_{ax}), 4.61 (1H, dd, J = 10.05, 5.86 Hz, 4-H_{eq}), 4.68 (1H, d, J = 11.81 Hz, 3-H), 6.80-7.90 (13 arom H, m); ^{13}C nmr: δ 53.6, 55.1, 68.9, 69.6, 114.8, 115.1, 116.4, 117.3, 120.4, 121.7, 124.7, 127.3, 128.8, 131.0, 133.4, 145.5, 146.9, 155.9, 159.6.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.65; N, 7.85. Found: C, 77.42; H, 5.68; N, 7.81.

trans-2,3,3a,4-Tetrahydro-3-(4-fluorophenyl)-2-phenyl[1]benzopyrano[4,3-*c*]pyrazole (**16**).

This compound was obtained as white crystals in 78% yield, mp 144-145°; ir: ν 1598, 1576, 1510, 1498, 1469, 1388, 1323, 1297, 1229, 1050, 1001, 840, 818, 693, 610 cm^{-1}; ^{1}H nmr: δ 3.59 (1H, ddd, J = 12.10, 5.84 Hz, 3a-H), 4.20 (1H, dd, J = 12.38, 10.14 Hz, 4-H_{ax}), 4.63 (1H, dd, J = 10.11, 5.83 Hz, 4-H_{eq}), 4.71 (1H, d, J = 11.87 Hz, 3-H), 6.83-7.91 (13 arom H, m); ^{13}C nmr: δ 53.7, 68.8, 69.3, 115.1, 116.2, 116.6, 117.3, 120.6, 121.8, 124.7, 127.7, 127.9, 128.9, 137.2, 137.3, 145.5, 146.7, 155.9.

Anal. Calcd. for $C_{22}H_{17}FN_2O$: C, 76.72; H, 4.98; N, 8.13. Found: C, 76.66; H, 4.95; N, 8.17.

trans-2,3,3a,4-Tetrahydro-3-(4-chlorophenyl)-2-phenyl[1]benzopyrano[4,3-*c*]pyrazole (**17**).

This compound was prepared as pale yellow crystals in 75% yield, mp 158-159°; ir: ν 1598, 1576, 1497, 1456, 1387, 1368, 1303, 1228, 1199, 1121, 1088, 1032, 1001, 849, 830, 694 cm^{-1}; ^{1}H nmr: δ 3.59 (1H, ddd, J = 12.05, 5.82 Hz, 3a-H), 4.21 (1H,

dd, J = 12.33, 10.13 Hz, 4-H_{ax}), 4.62 (1H, dd, J = 10.09, 5.86 Hz, 4-H_{eq}), 4.70 (1H, d, J = 11.77 Hz, 3-H), 6.88-7.90 (13 arom H, m); ^{13}C nmr: δ 53.6, 68.8, 69.3, 115.0, 116.1, 117.3, 120.7, 121.9, 127.6, 128.9, 129.2, 129.7, 131.2, 133.9, 140.0, 145.5, 146.6, 155.8.

Anal. Calcd. for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found: C, 73.16; H, 4.78; N, 7.73.

trans-2,3,3a,4-Tetrahydro-3-(4-bromophenyl)-2-phenyl[1]benzopyrano[4,3-*c*]pyrazole (**18**).

This compound was prepared as pale yellow crystals in 74% yield, mp 175-176°; ir: ν 1597, 1576, 1497, 1487, 1466, 1400, 1386, 1366, 1323, 1300, 1228, 1120, 1070, 1008, 848, 751, 691, 623 cm^{-1}; ^{1}H nmr: δ 3.58 (1H, ddd, J = 12.08, 5.84 Hz, 3a-H), 4.20 (1H, dd, J = 12.35, 10.15 Hz, 4-H_{ax}), 4.62 (1H, dd, J = 10.16, 5.84 Hz, 4-H_{eq}), 4.68 (1H, d, J = 11.79 Hz, 3-H), 6.78-7.90 (13 arom H, m); ^{13}C nmr: δ 53.6, 68.8, 69.4, 115.0, 116.1, 117.4, 120.7, 121.9, 127.9, 128.9, 129.3, 129.6, 131.2, 132.7, 140.6, 145.6, 146.6, 155.9.

Anal. Calcd. for $C_{22}H_{17}BrN_2O$: C, 65.19; H, 4.23; N, 6.91. Found: C, 65.25; H, 4.27; N, 6.93.

trans-2,3,3a,4-Tetrahydro-3-(4-methylphenyl)-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazole (**19**).

This compound was prepared as white crystals in 86% yield, mp 164-165°; ir: ν 1599, 1573, 1498, 1448, 1379, 1309, 1112, 1061, 819, 753, 690 cm^{-1}; ^{1}H nmr: δ 3.09 (1H, dd, J = 11.87, 4.68 Hz, 4-H_{eq}), 3.39 (1H, t, J = 11.92 Hz, 4-H_{ax}), 3.68 (1H, ddd, J = 12.47, 4.72 Hz, 3a-H), 4.74 (1H, d, J = 11.35 Hz, 3-H), 6.83-8.15 (13 arom H, m); ^{13}C nmr: δ 20.9, 29.7, 55.6, 73.1, 114.6, 120.3, 125.2, 125.9, 126.0, 126.6, 126.8, 128.9, 129.1, 130.1, 134.0, 137.7, 138.5, 146.3, 146.5.

Anal. Calcd. for $C_{23}H_{20}N_2S$: C, 77.51; H, 5.65; N, 7.86. Found: C, 77.43; H, 5.67; N, 7.83.

trans-2,3,3a,4-Tetrahydro-3-(4-isopropylphenyl)-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazole (**20**).

This compound was obtained as white crystals in 78% yield, mp 126-127°; ir: ν 1596, 1578, 1498, 1442, 1380, 1301, 1120, 1033, 995, 831, 750, 639 cm^{-1}; ^{1}H nmr: δ 1.28 (6H, m, CH(CH_3)$_2$), 2.94 (1H, m, CH(CH$_3$)$_2$), 3.10 (1H, dd, J = 11.95, 4.60 Hz, 4-H_{eq}), 3.38 (1H, t, J = 12.05 Hz, 4-H_{ax}), 3.68 (1H, ddd, J = 12.01, 4.72 Hz, 3a-H), 4.75 (1H, d, J = 11.07 Hz, 3-H), 6.86-8.14 (13 arom H, m); ^{13}C nmr: δ 23.7, 23.8, 29.9, 55.5, 73.2, 114.7, 120.3, 125.2, 126.0, 126.1, 126.6, 126.9, 127.6, 128.9, 129.2, 134.1, 138.9, 146.5, 146.6, 148.9.

Anal. Calcd. for $C_{25}H_{24}N_2S$: C, 78.10; H, 6.29; N, 7.28. Found: C, 78.15; H, 6.26; N, 7.25.

trans-2,3,3a,4-Tetrahydro-3-(4-methoxyphenyl)-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazole (**21**).

This compound was prepared as white crystals in 71% yield, mp 193-194 °; ir: ν 1598, 1574, 1512, 1442, 1378, 1309, 1212, 1181, 1115, 1061, 1028, 895, 825, 753, 691 cm^{-1}; ^{1}H nmr: δ 3.07 (1H, dd, J = 11.85, 4.67 Hz, 4-H_{eq}), 3.36 (1H, t, J = 11.92 Hz, 4-H_{ax}), 3.65 (1H, ddd, J = 12.49, 4.64 Hz, 3a-H), 4.71 (1H, d, J = 11.33 Hz, 3-H), 6.81-8.10 (13 arom H, m); ^{13}C nmr: δ 29.8, 55.2, 55.6, 72.3, 114.7, 114.8, 120.3, 125.2, 125.9, 126.6, 126.8, 127.3, 128.9, 129.2, 133.4, 134.1, 146.4, 146.6, 159.6.

Anal. Calcd. for $C_{23}H_{20}N_2OS$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.12; H, 5.38; N, 7.49.

trans-2,3,3a,4-Tetrahydro-3-(4-fluorophenyl)-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazole (**22**).

This compound was prepared as pale yellow crystals in 77% yield, mp 158-159°; ir: ν 1597, 1506, 1490, 1445, 1377, 1298, 1223, 1090, 1057, 833, 753, 693, 565 cm^{-1}; ^{1}H nmr: δ 3.07 (1H, dd, J = 11.86, 4.60 Hz, 4-H_{eq}), 3.39 (1H, t, J = 11.97 Hz, 4-H_{ax}), 3.65 (1H, ddd, J = 11.81, 4.68 Hz, 3a-H), 4.76 (1H, d, J = 11.03 Hz, 3-H), 6.88-8.12 (13 arom H, m); ^{13}C nmr: δ 29.8, 55.6, 72.6, 114.7, 120.6, 125.3, 126.0, 126.4, 126.9, 127.7, 127.8, 128.9, 129.3, 134.0, 137.2, 137.3, 146.2, 146.6.

Anal. Calcd. for $C_{22}H_{17}FN_2S$: C, 73.32; H, 4.75; N, 7.77. Found: C, 73.41; H, 4.78; N, 7.74.

trans-2,3,3a,4-Tetrahydro-3-(4-chlorophenyl)-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazole (**23**).

This compound was obtained as pale yellow crystals in 75% yield, mp 173-174°; ir: ν 1598, 1575, 1490, 1439, 1377, 1310, 1253, 1154, 1031, 925, 754, 519 cm^{-1}; ^{1}H nmr: δ 3.06 (1H, dd, J = 11.84, 4.62 Hz, 4-H_{eq}), 3.40 (1H, t, J = 11.93 Hz, 4-H_{ax}), 3.63 (1H, ddd, J = 11.80, 4.66 Hz, 3a-H), 4.76 (1H, d, J = 11.06 Hz, 3-H), 6.85-8.12 (13 arom H, m); ^{13}C nmr: δ 29.8, 55.5, 72.7, 114.6, 120.6, 122.0, 125.2, 126.1, 126.4, 126.9, 127.8, 128.9, 129.4, 132.6, 134.0, 140.6, 146.0, 146.6.

Anal. Calcd. for $C_{22}H_{17}ClN_2S$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.31; H, 4.52; N, 7.48.

trans-2,3,3a,4-Tetrahydro-3-(4-bromophenyl)-2-phenyl[1]benzothiopyrano[4,3-*c*]pyrazole (**24**).

This compound was prepared as pale yellow crystals in 77% yield, mp 167-168°; ir: ν 1599, 1575, 1489, 1441, 1376, 1296, 1171, 1053, 1010, 827, 752, 695, 517 cm^{-1}; ^{1}H nmr: δ 3.08 (1H, dd, J = 11.82, 4.56 Hz, 4-H_{eq}), 3.39 (1H, t, J = 11.88 Hz, 4-H_{ax}), 3.63 (1H, ddd, J = 11.82, 4.64 Hz, 3a-H), 4.75 (1H, d, 11.20 Hz, 3-H), 6.89-8.13 (13 arom H, m); ^{13}C nmr: δ 29.7, 55.5, 72.6, 114.7, 120.7, 122.0, 125.3, 126.0, 126.3, 126.8, 127.8, 129.0, 129.3, 132.7, 134.0, 140.5, 146.0, 146.7.

Anal. Calcd. for $C_{22}H_{17}BrN_2S$: C, 62.72; H, 4.07; N, 6.65. Found: C, 62.61; H, 4.09; N, 6.63.

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