FUSED HETEROCYCLES 9*
SYNTHESIS OF TRICYCLIC PYRAZOLINES BY THE REACTION OF E-3-ARYLIDENEFLAVANONES WITH PHENYLHYDRAZINE

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Dedicated to Prof. Dr. Vitomir Sunjić on the occasion of his 60th birthday

Abstract: Stereoselective synthesis of trans,trans-2,3,3a,4-tetrahydro-3-aryl-2,4-diphenyl[1]benzopyrano[4,3-c]pyrazoles 13-24 have been performed by the reaction of E-3-arylideneflavanones 1-12 with phenylhydrazine in hot pyridine. Structures of these new tricyclic pyrazolines have been elucidated by IR, 1H- and 13C-NMR spectroscopies.

Introduction

3-Arylideneflavanones (termed flavindogenides) are well known flavanone derivatives which can be synthesized by the reaction of flavanones and aromatic aldehydes. For this purpose, an acid-catalyzed condensation was used for a long time (1-6). However, this procedure afforded the target compounds contaminated with the starting flavanones in many cases. For this reason, we have developed a new method for the synthesis of E-3-arylideneflavanones by the piperidine-catalyzed reaction of flavanone with aromatic aldehydes (7,8). These E-isomers can then be photocatalytically isomerized into Z-3-arylideneflavanones (6,9). We have also unambiguously elucidated the stereochemistry of both E- and Z-3-arylideneflavanones by NMR spectroscopy (10). The easy availability of both E- and Z-3-arylideneflavanones made possible several chemical transformations.

An interesting chemical transformation of the 3-arylideneflavanones is their oxidation to form either 3-aroylflavones (11-13) or 3-α-hydroxybenzylflavones (11,14). Other oxidation reactions provide their epoxides (15-19). Another useful chemical conversion is their base-catalyzed exo-endo double bond migration to obtain the otherwise inaccessible 3-benzylflavones (20). However, the synthesis of nitrogen-containing heterocyclic compounds starting from 3-arylideneflavanones has hitherto received less attention (21).
Results and Discussion

Pyrazolines have been prepared from 3-arylideneflavanones both by their reaction with diazomethane (21-23) and with hydrazine derivatives (24,25). Since the reaction with hydrazines were restricted only to those 3-benzylideneflavanones which bear an unsubstituted phenylmethylenec unit, it seemed expedient to prolong this reaction to 3-arylideneflavanones possessing either a substituted phenylmethylenec or an arylmethylene group to investigate the influence of the substituent or the space demand of the aryl group.

Synthesis of tricyclic pyrazolines by the reaction of exocyclic α,β-unsaturated ketones with hydrazines has been studied by several research groups (24-26). This reaction provides tricyclic pyrazolines with two new centres of chirality which gives rise to the formation of diastereomeric mixtures of pyrazolines. Since the 3-arylideneflavanones have a centre of chirality, tricyclic pyrazolines obtained from them possess three centres of chirality which theoretically may result in the formation of four diastereomeric structures rendering the stereochemical outcome of the reaction even more complex. Acid-catalyzed reaction of exocyclic α,β-unsaturated ketones with hydrazines (28,29,31,34) afforded a mixture of cis- and trans-3-H,3a-H-diastereomers of tricyclic pyrazolines. For this reason, this procedure seems to be inconvenient for the synthesis of tricyclic pyrazolines starting from 3-arylideneflavanones. In our previous studies (24,36) it has been found that the reaction of some exocyclic α,β-enones with hydrazines in hot pyridine provided trans-3-H,3a-H-diastereomers of tricyclic pyrazolines as stereohomogeneous products. As a continuation, in our present paper we report on the stereoselective synthesis of tricyclic pyrazolines by the reaction of 3-arylideneflavanones 1-12 with phenylhydrazine. Since we wanted to neglect the influence of the stereoisomerism of the starting materials, in our present study we investigated this reaction only of E-3-arylideneflavanones where the carbonyl group and the aryl moiety are on the opposite sides of the C=C double bond.

3-Arylideneflavanones 1-12 were allowed to react with phenylhydrazine in hot pyridine to afford tricyclic pyrazolines 13-24 (Scheme 1). Structures of new compounds 13-24 have been elucidated by microanalysis, IR and 1H- and 13C-NMR spectroscopies (cf. Experimental). In the IR spectra a characteristic C=N band was found at around 1595-1598 cm⁻¹ referring to the formation of a pyrazoline ring. In the 1H-NMR spectra both the chemical shift values and the multiplicities of the aliphatic protons are in full harmony with the presence of a tricyclic pyrazoline ring system. This is
Scheme 1

\[
\begin{align*}
1 &- 12 & & 7 &- 19 \\
2 &- 14 & & 8 &- 20 \\
3 &- 15 & & 9 &- 21 \\
4 &- 16 & & 10 &- 22 \\
5 &- 17 & & 11 &- 23 \\
6 &- 18 & & 12 &- 24
\end{align*}
\]

The cis and trans isomers of these pyrazolines can be differentiated by NMR measurements. In their \(^1\)H-NMR spectra the 10.2-10.5 Hz \(J_{3,3a}\) coupling constant values refer to an antiperiplanar orientation of protons 3-H and 3a-H. The 11.2-11.5 Hz \(J_{3a,4}\) coupling constant values reveal a trans-arrangement of protons 3a-H and 4-H. Except for compounds 15 and 19, one series of signals were detected in all \(^1\)H- and \(^{13}\)C-NMR spectra and no minor reaction product could be isolated or even detected in the crude reaction mixture. On this basis it can be concluded that the stereochemical outcome of the reaction seems to be independent on the substituent in the meta- or para-position of the phenyl group of the phenylmethylene moiety and on its replacement by a heteroaromatic or a condensed aromatic group. Thus, trans-3-H,3a-H,trans-3a-H,4-H tricyclic pyrazolines are obtained in a completely stereoselective reaction. However, if a methoxy (3) or a chloro (7) substituent is in the ortho-position of this phenyl group, over the trans-3-H,3a-H,trans-3a-H,4-H-isomers (15 and 19) a minor component can also be detected by TLC and by \(^1\)H-NMR measurements in the crude reaction mixtures. We failed to isolate and characterize these minor products by column chromatography, but we suppose that these substances may probably be cis-3-H,3a-H,trans-3a-H,4-H-isomers. Formation of these latter isomers maybe a consequence of a steric hindrance originating from the presence of an ortho-substituent in the phenyl ring. In summary, we managed to work out a simple and convenient method for the stereoselective synthesis of trans,trans-2,3,3a,4-tetrahydro-3-aryl-2,4-diphenyl[1]benzopyrano[4,3-c]pyrazoles by the utilization of 3-arylideneflavanones as easily available starting materials.
Fused heterocycles, synthesis of tricyclic pyrazolines by the reaction of E-3-arylideneflavanones with phenylhydrazine

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, $\delta$ = 0.0 ppm) at room temperature. The IR spectra (KBr discs) were measured with a Perkin-Elmer 16 PC instrument. TLC was performed on Kieselgel 60 F254 (Merck) layers using hexane:acetone (7:3 v/v) as eluent. Stalling materials 1-12 were synthesized by the piperidine-catalyzed condensation of flavanone with aromatic aldehydes (7,8).

General procedure for the preparation of compounds 13-24

A mixture of 3-arylideneflavanone (1-12, 10.0 mmol), Phenylhydrazine (60.0 mmol) and pyridine (50.0 ml) was refluxed for 6 h, 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,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-methylphenyl)[1]benzopyrano[4,3-c]pyrazole (13):** This compound was obtained as white crystals in 79% yield, m.p. 130-131 °C; IR: vC=N 1597 cm$^{-1}$; $^1$H-NMR (δ): 2.24 (3H, s, CH$_3$), 3.68 (1H, t, J = 10.5 Hz, 3a-H), 4.68 (1H, d, J = 10.2 Hz, 3-H), 5.08 (1H, d, J = 11.4 Hz, 4-H), 6.56-7.94 (18 arom. H, m); $^{13}$C-NMR (δ): 59.6 (C-3a), 68.4 (C-3), 83.2 (C-4).

**Anal. Calcd. for C$_{29}$H$_{24}$N$_2$0: C, 83.62; H, 5.81; N, 6.72. Found: C, 83.54; H, 5.85; N, 6.76.**

**trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-isopropylphenyl)[1]benzopyrano[4,3-c]pyrazole (14):** This substance was prepared as white crystals in 76% yield, m.p. 149-150 °C; IR: vC=N 1598 cm$^{-1}$; $^1$H-NMR (δ): 1.20 (6H, d, J = 6.9 Hz, CH(CH$_3$)$_2$), 2.81 (1H, m, CH), 3.71 (1H, t, J = 10.6 Hz, 3a-H), 4.70 (1H, d, J = 10.3 Hz, 3-H), 5.09 (1H, d, J = 11.3 Hz, 4-H), 6.60-8.02 (18 arom. H, m); $^{13}$C-NMR (δ): 59.6 (C-3a), 68.5 (C-3), 83.2 (C-4).

**Anal. Calcd. for C$_{31}$H$_{28}$N$_2$0: C, 83.75; H, 6.35; N, 6.30. Found C, 83.82; H, 6.31; N, 6.26.**

**trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(2-methoxyphenyl)[1]benzopyrano[4,3-c]pyrazole (15):** This compound was obtained as colourless plates in 46% yield, m.p. 189-190 °C; IR: vC=N 1597 cm$^{-1}$; $^1$H-NMR (δ): 3.30 (3H s, OCH$_3$), 3.92 (1H, t, J = 11.2 Hz, 3a-H), 5.08 (1H, d, J = 11.5 Hz, 4-H), 5.24 (1H d, J = 10.3 Hz, 3-H), 6.52-7.98 (18 arom. H, m); $^{13}$C-NMR (δ): 54.7 (C-3), 58.6 (C-3a), 82.9 (C-4).

**Anal. Calcd. for C$_{29}$H$_{24}$N$_2$0$_2$: C, 80.53; H, 5.59; N, 6.47. Found: C, 80.61; H, 5.55; N, 6.42.**

**trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(3-methoxyphenyl)[1]benzopyrano[4,3-c]pyrazole (16):** This compound was prepared as white crystals in 81% yield, m.p. 163-164 °C; IR: vC=N cm$^{-1}$; $^1$H-NMR (δ): 3.61 (3H s, OCH$_3$), 3.72 (1H, t, J = 10.3 Hz, 3a-H), 4.68 (1H, d, J = 10.2 Hz, 3-H), 5.10 (1H, d, J = 11.3 Hz, 4-H), 6.26-7.98 (18 arom. H, m); $^{13}$C-NMR (δ): 59.6 (C-3a), 68.7 (C-3), 82.9 (C-4).

**Anal. Calcd. for C$_{29}$H$_{24}$N$_2$0$_2$: C, 80.53; H, 5.59; N, 6.47. Found: C, 80.46; H, 5.62; N, 6.51.**

**trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-methoxyphenyl)[1]benzopyrano[4,3-c]pyrazole (17):** This substance was obtained as pale yellow crystals in 81% yield, m.p. 136-137 °C; IR: vC=N cm$^{-1}$; $^1$H-NMR (δ): 3.67 (1H t, J = 10.5 Hz, 3a-H), 3.71 (3H s, OCH$_3$), 4.65 (1H, d, J = 10.2 Hz, 3-H), 5.07 (1H, d, J = 11.3 Hz, 4-H), 6.59-7.94 (18 arom. H, m); $^{13}$C-NMR (δ): 59.6 (C-3a), 68.3 (C-3), 83.2 (C-4).

**Anal. Calcd. for C$_{29}$H$_{24}$N$_2$0$_2$: C, 80.53; H, 5.59; N, 6.47. Found: C, 80.60; H, 5.63; N, 6.51.**

**trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(4-fluorophenyl)[1]benzopyrano[4,3-c]pyrazole (18):** This compound was obtained as pale yellow crystals in 81% yield, m.p. 136-137 °C; IR: vC=N
trans,trans-2,3,3a,4-Tetrahydro-3-(2-chlorophenyl)-2,4-diphenyl[1]benzopyrano[4,3-c]pyrazole (19): This substance was obtained as pale yellow crystals in 41% yield on purification by column chromatography, m.p. 142-143 °C; IR: vC=N 1598 cm\(^{-1}\); \(^1\)H-NMR (δ): 3.68 (1H, t, J = 10.6 Hz, 3a-H), 4.70 (1H, d, J = 10.5 Hz, 3-H), 6.64-7.98 (18 arom. H, m); \(^1\)C-NMR (δ): 59.8 (C-3a), 68.2 (C-3), 83.1 (C-4).


trans,trans-2,3,3a,4-Tetrahydro-3-(3-chlorophenyl)-2,4-diphenyl[1]benzopyrano[4,3-c]pyrazole (20): This compound was obtained as white crystals in 79% yield, m.p. 149-150 °C; IR: vC=N 1597 cm\(^{-1}\); \(^1\)H-NMR (δ): 3.68 (1H, t, J = 10.9 Hz, 3a-H), 4.67 (1H, d, J = 10.5 Hz, 3-H), 5.29 (1H, d, J = 10.2 Hz, 4-H), 6.70-7.97 (18 arom. H, m); \(^1\)C-NMR (δ): 59.4 (C-3a), 64.2 (C-3), 82.7 (C-4).

Anal. Calcd. for C\(_{28}\)H\(_{20}\)ClN\(_2\): C, 76.97; H, 4.84; N, 6.41. Found: C, 76.93; H, 4.88; N, 6.37.

trans,trans-2,3,3a,4-Tetrahydro-3-(4-chlorophenyl)-2,4-diphenyl[1]benzopyrano[4,3-c]pyrazole (21): This compound was prepared as colourless plates in 78% yield, m.p. 155-156 °C; IR: vC=N 1596 cm\(^{-1}\); \(^1\)H-NMR (δ): 3.64 (1H, t, J = 11.0 Hz, 3a-H), 4.67 (1H, d, J = 10.3 Hz, 3-H), 5.08 (1H, d, J = 11.3 Hz, 4-H), 6.59-7.94 (18 arom. H, m); \(^1\)C-NMR (δ): 59.8 (C-3a), 68.1 (C-3), 83.0 (C-4).

Anal. Calcd. for C\(_{28}\)H\(_{20}\)ClN\(_2\): C, 76.97; H, 4.84; N, 6.41. Found: C, 76.92; H, 4.80; N, 6.46.

trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(2-thienyl)[1]benzopyrano[4,3-c]pyrazole (22): This compound was isolated as pale yellow crystals in 82% yield, m.p. 177-178 °C; IR: vC=N 1595 cm\(^{-1}\); \(^1\)H-NMR (δ): 3.81 (1H, t, J = 11.1 Hz, 3a-H), 5.00 (1H, d, J = 10.6 Hz, 3-H), 5.10 (1H, d, J = 11.4 Hz, 4-H), 6.08-7.98 (17 arom. H, m); \(^1\)C-NMR (δ): 59.7 (C-3a), 65.3 (C-3), 82.9 (C-4).

Anal. Calcd. for C\(_{26}\)H\(_{20}\)N\(_2\)OS: C, 76.45; H, 4.94; N, 6.85. Found: C, 76.51; H, 4.89; N, 6.81.

trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(3-pyridyl)[1]benzopyrano[4,3-c]pyrazole (23): This compound was isolated as white crystals in 76% yield, m.p. 139-140 °C; IR: vC=N 1597 cm\(^{-1}\); \(^1\)H-NMR (δ): 3.68 (1H, t, J = 10.9 Hz, 3a-H), 4.74 (1H, d, J = 10.7 Hz, 3-H), 5.10 (1H, d, J = 11.3 Hz, 4-H), 6.84-8.38 (18 arom. H, m); \(^1\)C-NMR (δ): 59.9 (C-3a), 66.5 (C-3), 82.8 (C-4).

Anal. Calcd. for C\(_{27}\)H\(_{21}\)N\(_3\)O: C, 80.37; H, 5.25; N, 6.94. Found: C, 80.42; H, 5.22; N, 6.90.

trans,trans-2,3,3a,4-Tetrahydro-2,4-diphenyl-3-(2-naphthyl)[1]benzopyrano[4,3-c]pyrazole (24): This compound was obtained as white crystals in 78% yield, m.p. 201-202 °C; IR: vC=N 1596 cm\(^{-1}\); \(^1\)H-NMR (δ): 3.71 (1H, t, J = 10.5 Hz, 3a-H), 4.87 (1H, d, J = 10.3 Hz, 3-H), 5.12 (1H, d, J = 11.2 Hz, 4-H), 6.75-7.98 (21 arom. H, m); \(^1\)C-NMR (δ): 59.4 (C-3a), 68.8 (C-3), 83.2 (C-4).

Anal. Calcd. for C\(_{32}\)H\(_{24}\)N\(_2\): C, 84.93; H, 5.34; N, 6.19. Found: C, 84.87; H, 5.37; N, 6.23.

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*For Part 8, see Ref. (36).
Fused heterocycles 9, synthesis of tricyclic pyrazolines by the reaction of E-3-arylideneflavanones with phenylhydrazine


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