Synthesis and stereochemical structures of novel spiro[benzocycloheptene-6(5*H*), 3'-[3*H*]pyrazol]-5-ones

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Reaction of a variety of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-ones **1a–f** with nitrilimines (generated *in situ* by triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **2**) in refluxing benzene, afforded the corresponding spiro[benzocycloheptene-6(5*H*),3'-[3*H*]pyrazol]-5-ones **3a–h** and not the isomeric forms spiro[benzocycloheptene-6(5*H*),4'-[4*H*]pyrazol]-5-ones **4** in a highly regioselective manner. The stereochemical configuration of the isolated products was established to be 3'*R*, 4'*S* based on single crystal X-ray diffraction of **3a**.

Keywords: 1,3-dipolar cycloaddition reactions, nitrilimines, 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-ones, spiro[benzocycloheptene-6(5*H*)-3'-[3*H*]pyrazol]-5-ones.

Stereoselective 1,3-dipolar cycloaddition reactions have received much attention in the last two decades.[1] In this respect, the cycloadditive route has been successfully exploited in both inter-[2] and intramolecular[3] versions, and the number of available examples increases constantly. Many papers deal with stereoselective cycloadditions as key steps in the construction of complex targets such as natural products or their analogues,[4] while simpler systems have been studied to acquire an accurate rationale of the observed stereoselectivities.[5] Nitrilimines represent an important class of highly reactive 1,3-dipoles used intensively for cycloaddition reactions with alkenes,[6] alkynes,[7] azomethines,[8] allenes[9] or heterocyclic residues.[10]

Here we investigate the reaction of nitrilimines with a variety of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-ones not only to isolate the corresponding spiropyrazoline containing compounds, but also to study the regioselectivity of the reaction. The stereochemical configuration of the isolated products will also be considered. The interest in the synthesis of this heterocyclic system is also due to the biological properties associated with pyrazoline derivatives such as antidepressants,[11] and their monoamine oxidase,[12] human acyl-CoA:cholesterol acyltransferase[13] and low density lipoprotein oxidation[14] inhibitory activities. In addition due to the fluorescence properties of 2-pyrazoline derivatives[15] they are widely used as whitening agents for textile fibres, plastics and paper.[16] More recently, these compounds have also been reported as hole transporting or emitting materials in organic electro-luminescence devices.[17]

Reaction of a variety of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-ones **1a–f** with nitrilimines (generated *in situ* by triethylamine (TEA) dehydrohalogenation of the corresponding hydrazonoyl chlorides **2a,b**) in refluxing dry benzene, afforded only one regioisomer. The structures of these were established to be 2', 4', 6, 7, 8, 9-hexahydro-2', 4', 5'-triarylspiro[benzocycloheptene-6(5*H*), 3'-[3*H*]pyrazol]-5-ones **3** rather than 2', 3', 6, 7, 8, 9-hexahydro-2', 3', 5'-triaryl spiro[benzocycloheptene-6(5*H*), 4'-[4*H*]pyrazol]-5-ones **4** based on spectroscopic (IR, ^{1}H, ^{13}C-NMR, MS) and elemental analyses data (see the Scheme).

The IR spectra of **3a–h** reveal the presence of a strong carbonyl stretching vibration band at ν = 1685–1673 cm^{-1}, excluding any cycloaddition reaction involving this function. ^{1}H NMR spectra of **3a–h** exhibit the appearance of a singlet signal at δ = 4.76–5.15 assignable for the pyrazole H-4'. The appearance of this signal at the mentioned chemical shift value excludes the presence of the other regioisomer **4** which is expected to exhibit its signal at a chemical shift value higher than δ ~ 5.6.[18]

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Conclusive support for the proposed structure was delivered by the ^{13}C NMR spectrum (APT) of **3a** "as a representative example". The pyrazole C-4' and spiro carbons resonated at δ = 60.89, 81.92, respectively in accordance with other similar structures.[19] In addition the carbonyl carbon was observed at δ = 206.38.

Single crystal X-ray diffraction analysis of **3a**[20] (Fig. 1) supports not only the proposed structure but also reveals that the isolated product is 3'*R*, 4'*S*. Intramolecular torsion angles N(2)–C(5)–C(13)–C(7) = –111.69(7), C(9)–C(5)–C(13)–C(7) = 63.17(6), C(14)–C(7)–C(13)–C(5) = –130.60(7), C(16)–C(7)–C(13)–C(5) = 48.74(6), N(2)–C(5)–C(13)–H(13) = 130.47(7), C(9)–C(5)–C(13)–H(13) = –54.67(6), C(14)–C(7)–C(13)–H(13) = –14.60(6), C(16)–C(7)–C(13)–H(13) = 164.74(8)° confirm this stereochemical configuration. Attempts were made to isolate or identify any other regio- or stereochemical isomers from the reaction mother liquors but were unsuccessful.

Single crystal X-ray crystallographic data of **3a**

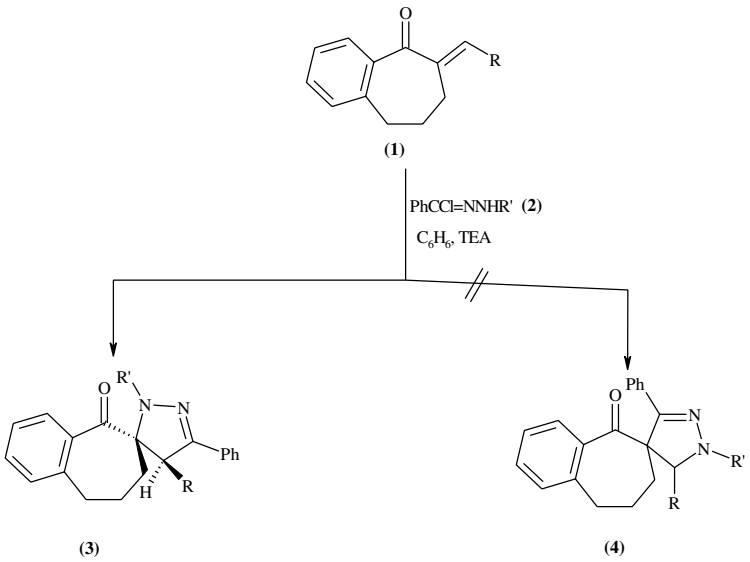
The crystallographic data were collected at T = 298°K on a Kappa CCD Enraf Nonius FR 590 diffractometer using a graphite monochromator with *Mo–*K_α radiation (λ = 0.71073 Å). The crystal structure was determined by SIR[21] and refined by maXus[22] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{31}H_{26}N_2O$, M_r = 442.562, triclinic, crystallises in space group *P*-1, Cell lengths a = 9.6718(5), b = 11.8500(6), c = 12.2942(5) Å, Cell angles α = 63.672(2), β = 68.677(3), γ = 84.776(3)°, V = 1172.27(10) Å^3, Z = 2, D_c = 1.254 g/cm^3, θ values 2.910–27.485°, absorption coefficient μ (*Mo-*K_α) = 0.08 mm^{-1}, F(000) = 468. The unique reflections measured 5327 of which 2501 reflections with threshold expression $I>3\sigma(I)$ were used in the structural analysis. Convergence for 307 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2)+0.03000\ F_o^2]$. The final agreement factors were R = 0.049 and wR = 0.047 with a goodness-of-fit of 1.107.

Experimental

Melting points are uncorrected and recorded on a digital Electrothermal 9100 melting point apparatus. IR spectra (KBr) were recorded on a Bruker Vector 22 spectrophotometer. ^{1}H NMR spectra were recorded on Varian GEMINI 200 MHz and Varian MERCURY 300 MHz spectrometers. ^{13}C NMR spectra (APT) were recorded on a Varian MERCURY (75 MHz). Mass spectra were recorded on a Finnigan SSQ7000 (EI, 70 eV). The starting compounds **1a–f** were prepared according to the previously reported procedures.[23]

Reaction of **1a–f** *with* **2a,b** *(general procedure)*

A mixture of equimolar amounts of **1a–f** and the appropriate **2a,b** (5 mmol) in dry benzene (25 ml) containing triethylamine (7.5 mmol) was boiled under reflux for the appropriate time. The reaction mixture was filtered off to remove the triethylamine



1a; R= Ph
1b; R= 4-ClC_6H_4
1c; R= 4-FC_6H_4
1d; R= 4-$CH_3C_6H_4$
1e; R= 4-$CH_3OC_6H_4$
1f; R= 2-thienyl

2a; R'= Ph
2b; R'= 4-$CH_3C_6H_4$

3a; R= R'= Ph
3b; R= Ph, R'= 4-$CH_3C_6H_4$
3c; R= 4-ClC_6H_4, R'= Ph
3d; R= 4-ClC_6H_4, R'= 4-$CH_3C_6H_4$
3e; R= 4-FC_6H_4, R'= Ph
3f; R= 4-$CH_3C_6H_4$, R'= Ph
3g; R= 4-$CH_3OC_6H_4$, R'= Ph
3h; R= 2-thienyl, R'= Ph

Scheme 1

salt and then evaporated till dryness under reduced pressure. The remaining residue was triturated with methanol (5 ml). Thus, the separated solid was collected and crystallised from a suitable solvent affording the corresponding **3a–h**.

2', 4', 6, 7, 8, 9-Hexahydro-2', 4', 5'-triphenylspiro[benzocycloheptene-6(5H), 3'-[3H]pyrazol]-5-one (**3a**): Reaction time 60 h, pale yellow crystals from *n*-butanol, m.p. 175–177 °C, yield 72%. IR: ν 1677, 1595, 1489 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.43–2.87 (m, 6H, $3CH_2$), 4.83 (s, 1H, pyrazole H-4'), 6.94–7.60 (m, 19H, arom. H). ^{13}C NMR ($CDCl_3$) "APT": δ 23.22, 29.86, 34.08 (CH_2), 60.89 (pyrazole CH-4'), 81.92 (spiro-C), 120.56, 122.58, 126.53, 127.04, 128.28, 128.36, 128.42, 128.74, 129.04, 129.12, 129.26, 129.81, 131.80 (arom. CH), 132.17, 136.20, 138.77, 144.23, 150.29 (quaternary arom. C), 206.38 (C=O). MS: *m/z* (%) 442 [(M), 50], 324 (22), 323 (100), 310 (33), 309 (20). Anal. for $C_{31}H_{26}N_2O$ (442.54) : calcd. C 84.1, H 5.9, N 6.3; found C 84.25, H 6.0, N 6.4.

4', 5'-Diphenyl-2', 4', 6, 7, 8, 9-hexahydro-2'-(4-methylphenyl) spiro[benzocycloheptene-6(5H),3'-[3H]pyrazol]-5-one (**3b**): Reaction time 50 h, pale yellow crystals from *n*-butanol, m.p. 182–184 °C, yield 92%. IR: ν 1678, 1598, 1504 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.42–2.05 (m, 3H, benzocycloheptene H), 2.31 (s, 3H, CH_3), 2.37–2.84 (m, 3H, benzocycloheptene H), 4.84 (s, 1H, pyrazole H-4'),

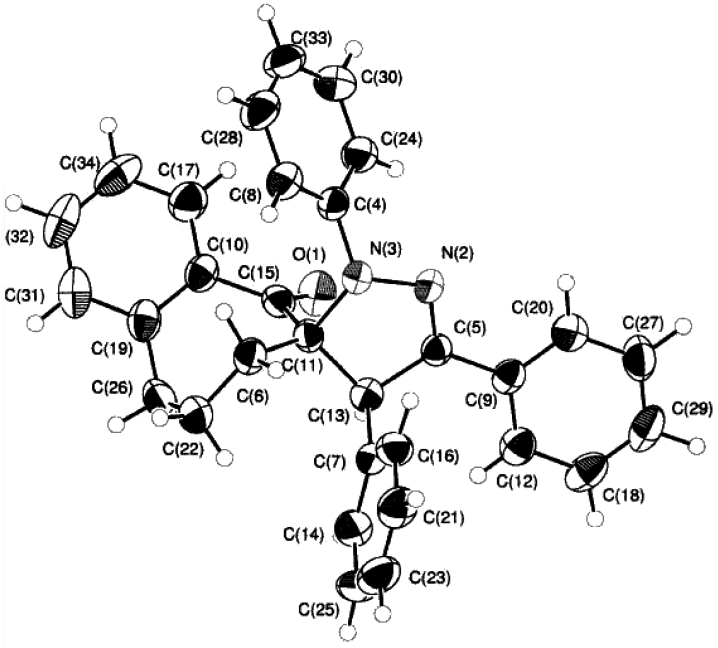


Fig. 1 Structure of **3a** from single crystal X-ray diffraction.

6.94–7.59 (m, 18H, arom. H). MS: *m/z* (%) 456 [(M), 70], 338 (27), 337 (100), 324 (33), 323 (17). Anal. for $C_{32}H_{28}N_2O$ (456.56) : calcd. C 84.2, H 6.2, N 6.1; found C 84.2, H 6.2 , N 6.1.

4'-(4-Chlorophenyl)-2', 5'-diphenyl-2', 4', 6, 7, 8, 9-hexahydrospiro [benzocycloheptene-6(5H), 3'-[3H]pyrazol]-5-one (**3c**): Reaction time 65 h, yellow crystals from *n*-butanol, m.p. 172–174 °C, yield 92%. IR: ν 1679, 1595, 1491 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.40–2.90 (m, 6H, $3CH_2$), 4.81 (s, 1H, pyrazole H-4'), 6.97–7.57 (m, 18H, arom. H). MS: *m/z* (%) 478 [(M+2), 29], 476 [(M), 100], 358 (17), 357 (60), 344 (8), 343 (7). Anal. for $C_{31}H_{25}ClN_2O$ (476.983) : calcd. C 78.1, H 5.3, N 5.9; found C 78.15, H 5.4, N 5.8.

4'-(4-Chlorophenyl)-2', 4', 6, 7, 8, 9-hexahydro-2'-(4-methylphenyl)-5'-phenylspiro[benzocycloheptene-6(5H), 3'-[3H]pyrazol]-5-one (**3d**): Reaction time 65 h, pale yellow crystals from ethanol, m.p. 158–160 °C, yield 90%. IR: ν 1683, 1593, 1510 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35–1.95 (m, 3H, benzocycloheptene H), 2.25 (s, 3H, CH_3), 2.35–2.80 (m, 3H, benzocycloheptene H), 4.76 (s, 1H, pyrazole H-4'), 6.90–7.50 (m, 17H, arom. H). MS: *m/z* (%) 492 [(M+2), 82], 491 [(M+1), 92], 490 [(M), 76], 373 (100), 372 (93), 371 (82), 358 (99), 357 (98). Anal. for $C_{32}H_{27}ClN_2O$ (491.013): calcd. C 78.3, H 5.5, N 5.7; found C 78.2, H 5.5, N, 5.7.

2', 5'-Diphenyl-4'-(4-fluorophenyl)-2', 4', 6, 7, 8, 9-hexahydrospiro [benzocycloheptene-6(5H), 3'-[3H]pyrazol]-5-one (**3e**): Reaction time 55 h, yellow crystals from *n*-butanol, m.p. 153–155 °C, yield 70%. IR: ν 1676, 1598, 1508 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.40–2.85 (m, 6H, $3CH_2$), 4.82 (s, 1H, pyrazole H-4'), 6.96–7.57 (m, 18H, arom. H). MS: *m/z* (%) 460 [(M), 46], 342 (25), 341 (100), 328 (28), 327 (18). Anal. for $C_{31}H_{25}FN_2O$ (460.53): calcd. C 80.8, H 5.5, N 6.1; found C 80.7, H 5.4, N, 6.15.

2', 5'-Diphenyl--2', 4', 6, 7, 8, 9-hexahydro-4'-(4-methylphenyl)spiro [benzocycloheptene-6(5H), 3'-[3H]pyrazol]-5-one (**3f**): Reaction time 65 h, yellow crystals from *n*-butanol, m.p. 138–140 °C, yield 92%. IR: ν 1679, 1594, 1490 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.44–2.10 (m, 3H, benzocycloheptene H), 2.30 (s, 3H, CH_3), 2.38–2.86 (m, 3H, benzocycloheptene H), 4.79 (s, 1H, pyrazole H-4'), 6.94–7.60 (m, 18H, arom. H). MS: *m/z* (%) 456 [(M), 55], 338 (31), 337 (100), 324 (34), 323 (30). Anal for $C_{32}H_{28}N_2O$ (456.56): calcd. C 84.2, H 6.2, N 6.1; found C 84.2, H 6.2, N 6.2.

2', 5'-Diphenyl-2', 4', 6, 7, 8, 9-hexahydro-4'-(4-methoxyphenyl)spiro [benzocycloheptene-6(5H), 3'-[3H]pyrazol]-5-one (**3g**): Reaction time 70 h, colourless crystals from cyclohexane, m.p. 102–104 °C, yield 88%. IR: ν 1685, 1595, 1493 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.49–2.89 (m, 6H, $3CH_2$), 3.77 (s, 3H, OCH_3), 4.78 (s, 1H, pyrazole H-4'), 6.81–7.60 (m, 18H, arom. H). MS: *m/z* (%) 472 [(M), 100], 354 (17), 353 (64), 340 (11), 339 (12). Anal. for $C_{32}H_{28}N_2O_2$ (472.56) : calcd. C 81.3, H 6.0, N 5.9; found C 81.4, H 6.0, N 5.9.

2', 5'-Diphenyl-2', 4', 6, 7, 8, 9-hexahydro-4'-(2-thienyl)spiro [benzocycloheptene-6(5H), 3'-[3H]pyrazol]-5-one (**3h**): Reaction time 70 h, yellow crystals from benzene-light petroleum (60–80 °C) mixture as 1:20 v/v, m.p. 140–142 °C, yield 80%. IR: ν 1673, 1594, 1486 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.63–2.98 (m, 6H, $3CH_2$), 5.15 (s, 1H, pyrazole H-4'), 6.92–7.64 (m, 17H, arom. H). MS: *m/z* (%) 450 [(M+2), 9], 448 [(M), 100], 330 (10), 329 (42), 316 (13), 315 (9). Anal. for $C_{29}H_{24}N_2OS$ (448.564) : calcd. C 77.65, H 5.4, N 6.25; found C 77.6, H 5.3, N 6.2.

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