Regioselective synthesis and stereochemical structure of 1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-ones

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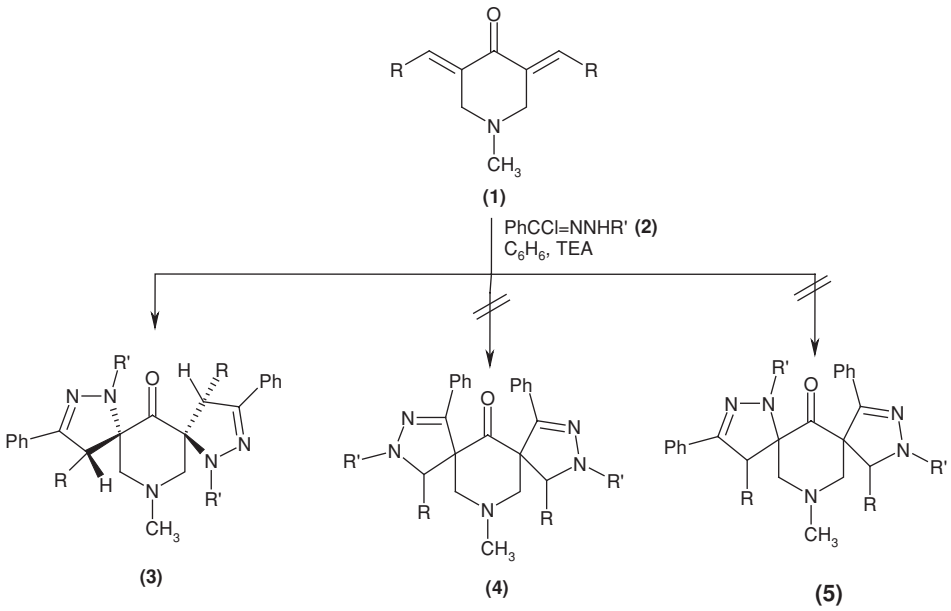
A facile regioselective synthetic approach towards 1,3,4,8,10,11-hexaaryl-13-methyl-1,2,8,9,13-pentaazadispiro [4.1.4.3]tetradeca-2,9-dien-6-ones **3a–g** was achieved through the reaction of 3,5-bis(arylmethylene)-1-methyl-4-piperidinones **1a–f** with nitrilimines (generated *in situ* by triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **2a,b**). The stereochemical configuration of the isolated products was established to be 4*S*, 5*R*, 7*R*, 11*S* based on a single crystal X-ray diffraction study of **3b**.

Keywords: 1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-ones, 3,5-bis(arylmethylene)-4-piperidinones, nitrilimines, 1,3-dipolar cycloaddition reactions

Spiro-compounds represent an important class of naturally occurring substances characterised by highly pronounced biological properties.[1,2] The most developed procedure for the synthesis of these compounds depends mainly on a cycloaddition reaction to exocyclic double bonds.[3-6] Nitrilimines are considered very reactive 1,3-dipoles and are used intensively for construction of numerous spiro-compounds due to their high regio- and stereoselective properties.[7-10]

In the present work, it was intended to investigate the reaction of a variety of 3,5-bis(arylmethylene)-1-methyl-4-piperidinones **1** with nitrilimines to study the regioselectivity of these reactions with neighbouring olefinic linkages and to establish the stereochemical structure of the isolated dispiro-compounds. The interest in the synthesis of these ring systems is due to the biological properties associated with pyazoline containing compounds as antidepressant,[11] monoamine oxidase[12,13] and low density lipoprotein oxidation[14] inhibitory activities.

Reaction of a variety of 3,5-bis(arylmethylene)-1-methyl-4-piperidinones **1a–f** with nitrilimines (generated *in situ* by triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **2a,b**) in refluxing dry benzene (see Caution in Experimental Section) afforded only one product as indicated by TLC (silica gel F_{254}). The structure was established as 1,3,4,8,10,11-hexaaryl-13-methyl-1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-ones **3a–g** based on spectroscopic (IR, ^{1}H, ^{13}C NMR) as well as elemental analysis data (Scheme 1).



1a; R = Ph
1b; R = 4-ClC_6H_4
1c; R = 4-FC_6H_4
1d; R = 4-$H_3CC_6H_4$
1e; R = 4-$H_3COC_6H_4$
1f; R = 2-thienyl
2a; R' = Ph
2b; R' = 4-$H_3CC_6H_4$

3a; R = R' = Ph
3b; R = Ph, R' = 4-$H_3CC_6H_4$
3c; R = 4-ClC_6H_4, R' = Ph
3d; R = 4-FC_6H_4, R' = Ph
3e; R = 4-$H_3CC_6H_4$, R' = Ph
3f; R = 4-$H_3COC_6H_4$, R' = Ph
3g; R = 2-thienyl, R' = Ph

Scheme 1

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The IR spectra of **3a–g** reveal a strong absorption band at ν = 1715–1710 cm^{-1} assignable for to stretching vibration band of the carbonyl function, eliminating the possibility that any cycloaddition reaction took place at this moiety. The ^{1}H NMR spectra of **3a–g** exhibit only one 2H singlet signal at δ = 3.90–4.22 assignable to the chemically equivalent H-4 and H-11. The appearance of this signal in the mentioned chemical shift region ruled out the presence of any other regio-cycloadduct isomers such as **4** or **5** which are expected to exhibit their corresponding signals at chemical shift values further downfield than δ > 5.6.[15-18]

The ^{13}C NMR spectrum (APT) of **3b** "as a representative example" adds good support for the established structure, and reveals two sharp signals at δ = 61.24, 78.28 assignable to the chemically equivalent C-4, C-11 and spiro C-5/C-7, respectively in addition to the carbonyl carbon at δ = 205.78. These values are in accord with data from many other similar structures.[17,18]

Further confirmatory evidence for the established structure was obtained through single crystal X-ray diffraction analysis of **3b** which reveals the stereochemistry of the isolated product as 4*S*, 5*R*, 7*R*, 11*S*. It may also be noted that, the piperidinone ring system adopts a modified boat form configuration, such that the attacking nitrilimine molecules (dipole systems) approach the two olefinic linkages (reacting dipolarophiles) from two opposite faces eventually giving rise to **3** in a high regioselective manner (Figs 1 and 2).[19]

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

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 SHELXS-97[20] and refined by maXus[21] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{48}H_{43}N_5O$, M_r = 705.906, triclinic, crystallises in space group *P*-1, Cell lengths "a = 9.8571(8), b = 11.6022(8), c = 19.0810(10) Å", Cell angles "α = 100.675(4), β = 101.820(4), γ = 107.333(5)°", V = 1966.8(3) Å^3, Z = 2, D_c = 1.192 g/cm^3, θ values 2.910–27.485°, absorption coefficient μ (*Mo-*K_α) = 0.07 mm^{-1}, F(000) = 748. The unique reflections measured 7644 of which 3028 reflections with threshold expression $I>3.00\sigma(I)$ were used in the structural analysis. Convergence for 487 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 = 0.071 and wR = 0.057 with a goodness-of-fit of 1.769.

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 in $CDCl_3$. The ^{13}C NMR spectrum (APT) was recorded on a Varian MERCURY (75 MHz) spectrometer in $CDCl_3$. The starting compounds **1a–f**,[22] **2a,b**[23] were prepared according to the previously reported procedures.

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

A mixture of **1a–f** (2.5 mmol) and the corresponding **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 triethylamine hydrochloride and then evaporated to dryness under reduced pressure. The remaining residue was triturated with methanol (5 ml). The separated solid was collected and crystallised from *n*-butanol affording **3a–g**.

CAUTION: appropriate precautions have to be taken because of the toxicity of benzene.

1,3,4,8,10,11-Hexaphenyl-13-methyl-1,2,8,9,13-pentaazadispiro [4.1.4.3]tetradeca-2,9-dien-6-one (**3a**): Reaction time 48 h, yellow crystals, m.p. 286–288 °C, yield 77%. IR: ν 1712, 1596, 1493 cm^{-1}. ^{1}H NMR: δ 1.74 (s, 3H, NCH_3), 2.49 (d, 2H, J=12.8 Hz, H-12a/14a), 2.84 (d, 2H, J=13 Hz, H-12b/14b), 3.95 (s, 2H, H-4/11), 7.09–7.54 (m, 30H, arom. H). Anal. for $C_{46}H_{39}N_5O$ (677.81): calcd. C 81.5, H 5.8, N 10.3; found C 81.7, H 6.0, N 10.5%.

1,8-Bis(4-methylphenyl)-13-methyl-3,4,10,11-tetraphenyl-1,2,8,9, 13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (**3b**): Reaction time 50 h, yellow crystals, m.p. 266–268 °C, yield 80%. IR: ν 1715, 1606, 1510 cm^{-1}. ^{1}H NMR: δ 1.70 (s, 3H, NCH_3), 2.42 (s, 6H, $ArCH_3$), 2.45 (d, 2H, J=13 Hz, H-12a/14a), 2.80 (d, 2H, J=13 Hz, H-12b/14b), 3.91 (s, 2H, H-4/11), 7.07–7.41 (m, 28H, arom. H). ^{13}C NMR: δ 21.24, 45.60 (CH_3), 58.62 (NCH_2), 61.24 (C-4/11), 78.28 (spiro C-5/7), 121.42, 126.71, 128.14, 128.46, 128.84, 129.13,

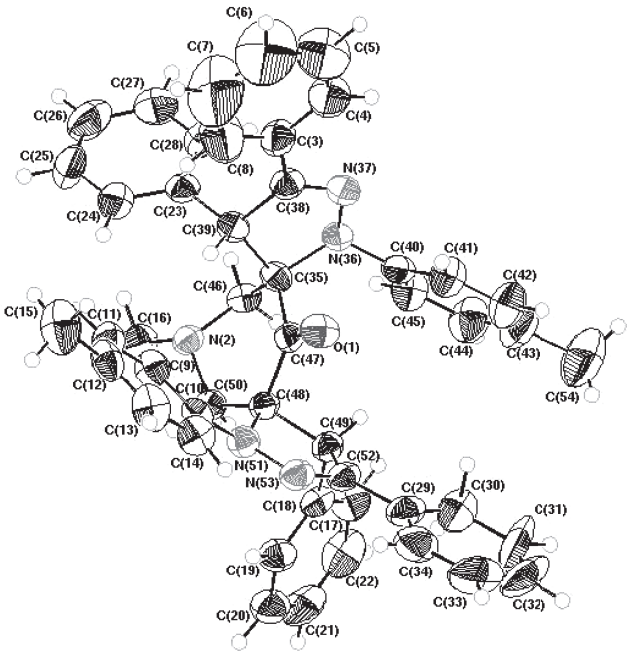

Fig. 1 Single crystal X-ray diffraction structure of **3b**.

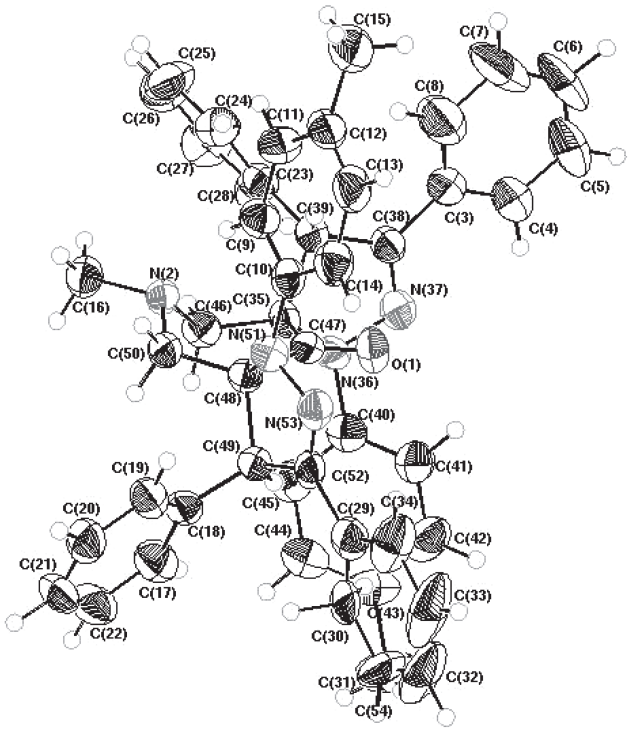

Fig. 2 Single crystal X-ray diffraction structure of **3b**.

129.48, 130.09, 130.66 (arom. CH), 131.86, 132.95, 135.73, 142.78, 151.18 (arom. quaternary C), 205.78 (C=O). Anal. for $C_{48}H_{43}N_5O$ (705.86): calcd. C 81.7, H 6.1, N 9.9; found C 81.8, H 6.2, N 9.7%.

4,11-Bis(4-Chlorophenyl)-13-methyl-1,3,8,10-tetraphenyl-1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (**3c**): Reaction time 60 h, pale yellow crystals, m.p. 310–312 °C, yield 75%. IR: ν 1710, 1594, 1491 cm^{-1}. ^1H NMR: δ 1.83 (s, 3H, NCH_3), 2.50 (d, 2H, *J*=12.6 Hz, H-12a/14a), 2.87 (d, 2H, *J*=12.6 Hz, H-12b/14b), 3.92 (s, 2H, H-4/11), 7.00–7.48 (m, 28H, arom. H). Anal. for $C_{46}H_{37}Cl_2N_5O$ (746.71): calcd. C 74.0, H 5.0, N 9.4; found C 73.8, H 4.9, N 9.3%.

4,11-Bis(4-fluorophenyl)-13-methyl-1,3,8,10-tetraphenyl-1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (**3d**): Reaction time 55 h, yellow crystals, m.p. 309–311 °C, yield 67%. IR: ν 1712, 1598, 1503 cm^{-1}. ^1H NMR: δ 1.81 (s, 3H, NCH_3), 2.49 (d, 2H, *J*=12.6 Hz, H-12a/14a), 2.86 (d, 2H, *J*=12.6 Hz, H-12b/14b), 3.94 (s, 2H, H-4/11), 6.93–7.50 (m, 28H, arom. H). Anal. for $C_{46}H_{37}F_2N_5O$ (713.80): calcd. C 77.4, H 5.2, N 9.8; found C 77.2, H 5.1, N 9.95%.

4,11-Bis(4-methylphenyl)-13-methyl-1,3,8,10-tetraphenyl-1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (**3e**): Reaction time 50 h, yellow crystals, m.p. 302–304 °C, yield 85%. IR: ν 1712, 1595, 1494 cm^{-1}. ^1H NMR: δ 1.78 (s, 3H, NCH_3), 2.30 (s, 6H, $ArCH_3$), 2.53 (d, 2H, *J*=12.3 Hz, H-12a/14a), 2.84 (d, 2H, *J*=12.6 Hz, H-12b/14b), 3.93 (s, 2H, H-4/11), 6.90–7.51 (m, 28H, arom. H). Anal. for $C_{48}H_{43}N_5O$ (705.86): calcd. C 81.7, H 6.1, N 9.9; found C 81.4, H 5.95, N 9.8%.

4,11-Bis(4-methoxyphenyl)-13-methyl-1,3,8,10-tetraphenyl-1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (**3f**): Reaction time 50 h, yellow crystals, m.p. 265–267 °C, yield 65%. IR: ν 1711, 1601, 1507 cm^{-1}. ^1H NMR: δ 1.81 (s, 3H, NCH_3), 2.53 (d, 2H, *J*=12.6 Hz, H-12a/14a), 2.83 (d, 2H, *J*=12.6 Hz, H-12b/14b), 3.77 (s, 6H, $2OCH_3$), 3.90 (s, 2H, H-4/11), 6.74–7.48 (m, 28H, arom. H). Anal. for $C_{48}H_{43}N_5O_3$ (737.86): calcd. C 78.1, H 5.9, N 9.5; found C 78.2, H 5.95, N 9.7%.

4,11-Bis(2-thienyl)-13-methyl-1,3,8,10-tetraphenyl-1,2,8,9,13-pentaazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one (**3g**): Reaction time 65 h, yellow crystals, m.p. 274–276 °C, yield 64%. IR: ν 1710, 1596, 1493 cm^{-1}. ^1H NMR: δ 1.98 (s, 3H, NCH_3), 2.72 (d, 2H, *J*=12.9 Hz, H-12a/14a), 3.01 (d, 2H, *J*=12.9 Hz, H-12b/14b), 4.22 (s, 2H, H-4/11), 6.84–7.49 (m, 26H, arom. H). Anal. for $C_{42}H_{35}N_5OS_2$ (689.86): calcd. C 73.1, H 5.1, N 10.15; found C 73.3, H 5.2, N 10.1%.

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