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Effect of solvent on the regioselective synthesis of spiropyrazoles

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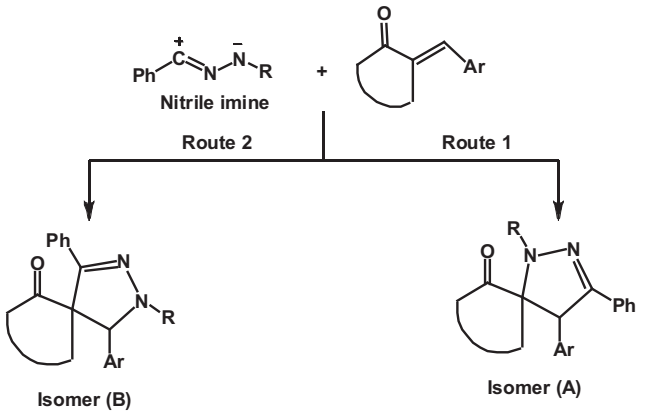
ABSTRACT

1,3-Dipolarcycloaddition reactions of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1**) with nitrilimines **3** were investigated in benzene and chloroform. The reaction products were 2′,4′,6,7,8,9-hexahydro-2′,4′,5′-triaryl spiro[benzocycloheptene-6(5*H*),3′(3*H*-pyrazol)-5-ones (**4**) or 2′,3′,6,7,8,9-hexahydro-2′,3′,5′-triaryl spiro[benzocycloheptene-6(5*H*),4′(4*H*-pyrazol)-5-ones (**5**). X-ray crystallographic analysis was carried out for compound **5b**. It was found that the regioselectivity of the produced compounds was altered based on changing solvent type.

1. Introduction

The varied bioactivities of spiroazoles have encouraged scientists to develop efficient methods to synthesize these compounds and their analogues. Spiroazoles have prodigious pharmacological activities, such as, anti-tumor,[1,2] antihyperglycemic,[3,4] antimycobacterial,[5] and antifungal[6] activities. Also, they have vasodilation activity[7] due to their pivotal role in the expansion of blood vessels by relaxation of smooth muscle cells within their walls, especially large, and smaller arterioles, and large veins. Moreover, spiroazoles of natural origin have been used as antipyretic, antihypertensive, and anticonvulsant medications[8] for the treatment of headache, vertigo, and epilepsy.

Numerous elegant methods have been published to demonstrate the construction of spiroazoles, such as, (a) 1,3-dipolarcycloaddition of nitrile imines to a thione group (C=S) to afford spiro[1,3,4]thiadiazoles;[9,10] (b) cycloaddition of mercaptoacetic acid onto an imine group (C=N) to afford spirothiazolidine[11] derivatives; (c) 1,3-dipolarcycloaddition of nitrile *N*-oxide to an exocyclic double bond (C=C) to give spiro isoxazoles;[12] (d) 1,3-dipolarcycloaddition of nitrilimines to exocyclic double bond (C=C) to give spiro pyrazoles.[7,13–16] The regioselectivity of latter cycloadditions proceed *via* two pathways: route 1: the electron rich nitrogen of the dipole adds to the α-carbon of the carbonyl to give regio-isomer (**A**); route 2: the electron rich nitrogen of the dipole adds to β-carbon to give another regio-isomer (**B**) (Scheme 1).



Scheme 1.

Previous reports[7,13–16] established the formation of regio-isomer (**A**) as the reaction product, based on spectroscopic data and X-ray crystallography. It is worth mentioning that all previous cycloaddition reactions were carried out in benzene or toluene as solvent. In the present work, we study the effect of two solvents (benzene and chloroform) on the regioselective cycloaddition of nitrilimines and an exocyclic double bond (C=C). The structure of the product was confirmed by X-ray crystallography.

2. Results and discussion

1,3-Dipolarcycloaddition reactions of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones[17–19] (1) with nitrilimines

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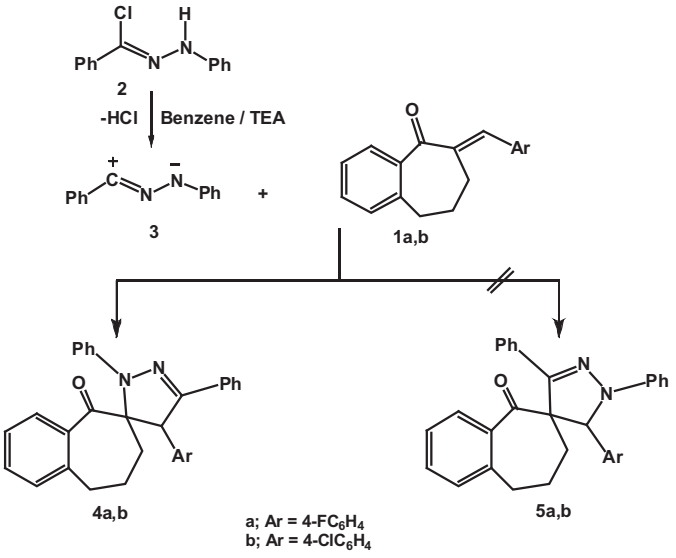
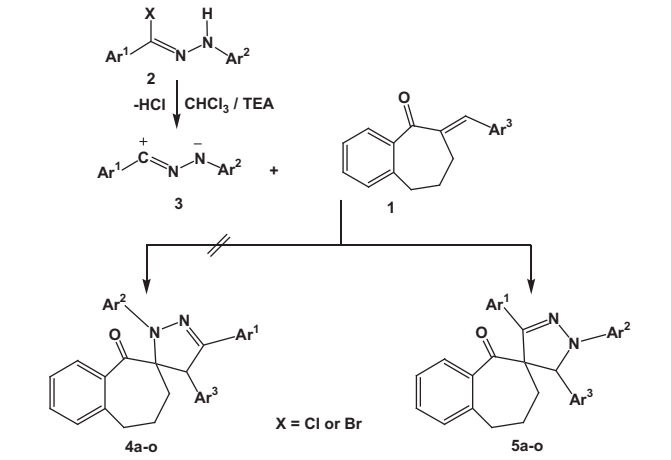
3 in dry benzene in the presence of a catalytic amount of triethylamine were reported by Girgis et al.[20] The reaction proceeded regioselectively to provide 2′,4′,6,7,8,9-hexahydro-2′,4′,5′-triaryl spiro[benzocycloheptene-6(5*H*),3′(3*H*-pyrazol)-5-ones (**4**) (regio-isomer A—Scheme 1) rather than 2′,3′,6,7,8,9-hexahydro-2′,3′,5′-triaryl spiro[benzocycloheptene-6(5*H*),4′(4*H*-pyrazol)-5-ones (**5**) (regio-isomer B—Scheme 1) based on spectroscopic data and X-ray crystallographic data (Scheme 2). The same regio-isomer **4a** was obtained when the reaction carried out in dry toluene.



Scheme 2.



No.	Ar^1	Ar^2	Ar^3	No.	Ar^1	Ar^2	Ar^3
a	C_6H_5	C_6H_5	4-FC_6H_4	i	Ph-CH=CH-	C_6H_5	3,4-$(CH_3O)_2C_6H_3$
b	C_6H_5	C_6H_5	4-ClC_6H_4	j	Ph-CH=CH-	C_6H_5	3,4,5-$(CH_3O)_3C_6H_2$
c	C_6H_5	C_6H_5	3,4-$Cl_2C_6H_3$	k	2-thienyl	4-$NO_2C_6H_4$	4-FC_6H_4
d	C_6H_5	C_6H_5	3,4-$(CH_3O)_2C_6H_3$	l	2-thienyl	4-$NO_2C_6H_4$	4-ClC_6H_4
e	C_6H_5	C_6H_5	3,4,5-$(CH_3O)_3C_6H_2$	m	2-thienyl	4-$NO_2C_6H_4$	3,4-$Cl_2C_6H_3$
f	Ph-CH=CH-	C_6H_5	4-FC_6H_4	n	2-thienyl	4-$NO_2C_6H_4$	3,4-$(CH_3O)_2C_6H_3$
g	Ph-CH=CH-	C_6H_5	4-ClC_6H_4	o	2-thienyl	4-$NO_2C_6H_4$	3,4,5-$(CH_3O)_3C_6H_2$
h	Ph-CH=CH-	C_6H_5	3,4-$Cl_2C_6H_3$				

Scheme 3.

These reactions were creative strategies toward the construction of spiropyrazoles. Consequently, we attempted these reactions using chloroform as polar solvent, instead of benzene, to investigate the effect of polarity on the regioselectivity of the reaction products. Thus, 1,3-Dipolarcycloaddition of **1** with Nitrilimines **3**, generated in *situ* from the corresponding hydrazonoyl halides **2**, in chloroform in the presence of triethylamine gave the respective regio-isomer **5** instead of **4** (Scheme 3). Both the arylmethylene and nitrilimine moieties were chosen as they have differing steric and electronic effects on reaction outcome.

The elucidation for the structure of regio-isomer **5** was based on spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS), elemental analyses, and X-ray crystallography. ^{1}H NMR spectroscopy revealed a singlet at δ=5.41–5.58 ppm assignable to the H-3′ pyrazole of regio-isomer **5**,[21,22] while the H-4′ pyrazole of regio-isomer **4** would appear at lower chemical shift.[13–15,20,23] Also, the ^{13}C NMR spectrum of compound **5** revealed a sp^3-spiro carbon signal (adjacent to sp^2-carbon atom) at δ=79.17–79.19 ppm, while the sp^3-spiro carbon signal (adjacent to sp^3-nitrogen atom) of compound **4** would appear at δ=81.03 ppm[15,16] The aforementioned spectral data provides firm support for the regioselective addition of the nitrilimine **3** to the arylidene olefinic moiety of compound **1** to give the spiro [benzocycloheptene-6(5*H*),4′(4*H*-pyrazol)]-5-ones (**5**) and rules out the other regio-isomer **4** (Scheme 3). Single crystal X-ray diffraction of **5b** was measured and illustrated in Fig. 1, and the selected bond lengths and bond angles are depicted in Table 1.

Attempts to elucidate the effect of solvent's polarity on the stability of regio-isomeric structures of **4a** and **5a** were achieved. Thus, refluxing of product **4a** in chloroform, as polar solvent, did not interchange its regio-isomeric structure. Moreover, heating of product **5a** in non polar solvents, such as benzene, toluene, or xylene gave the same structure. These results implied that, these products are stable under these conditions.

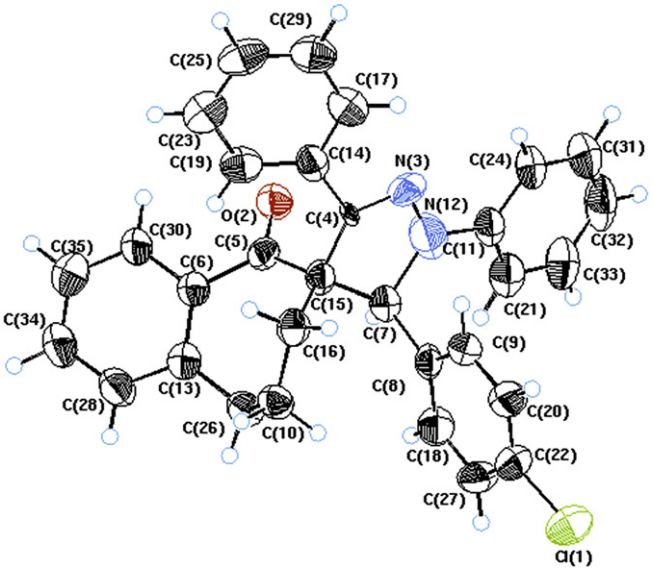


Fig. 1. X-ray crystal structure of compound **5b**.

In conclusion, we have found that there are two regioselective routes possible during the synthesis of spiropyrazoles depending on the type of solvent. This was confirmed by Single crystal X-ray diffraction. Further investigation for thermodynamic and kinetic products by molecular calculations will be performed in another study.

Table 1
Selected bond lengths and bond angles in the ORTEP of compound **5b** in the crystal. The crystallographic numbering does not reflect systematic numbering

Bond length, Å	Bond length, Å	Bond length, Å
C_4–C_{15}, 1.476 (3)	C_5–C_{15}, 1.549 (4)	O_2–C_5, 1.219 (3)
C_4–N_{12}, 2.168 (4)	C_7–C_{15}, 1.570 (3)	C_{11}–N_{12}, 1.482 (4)
C_7–C_{15}, 1.570 (3)	C_{15}–C_1, 1.539 (4)	C_{19}–C_{23}, 1.409 (4)
C_7–N_{12}, 1.533 (3)	C_{17}–C_{29}, 1.374 (4)	C_5–C_6, 1.505 (4)
Angle (ω)	**Angle (ω)**	**Angle (ω)**
C_4–N_3–N_{12}, 109.1 (2)	N_{12}–C_4–C_{14}, 146.5 (2)	N_3–C_4–C_{15}, 112.7 (2)
N_3–C_4–N_{12}, 34.39 (12)	C_{14}–C_4–C_{15}, 126.8 (2)	C_8–C_7–N_{12}, 109.7 (2)
N_3–N_{12}–C_7, 113.0 (2)	O_2–C_5–C_{15}, 118.7 (2)	C_4–C_{15}–C_7, 100.6 (2)
N_3–N_{12}–C_{11}, 123.7 (3)	O_2–C_5–C_6, 118.9 (3)	C_4–C_{15}–C_{16}, 109.6 (3)

3. Experimental

3.1. General

Melting points were measured on an Electrothermal IA 9000 series digital melting point apparatus. IR spectra were recorded in potassium bromide discs on Pye Unicam SP 3300 and Shimadzu FTIR 8101 PC infrared spectrophotometers. NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer operating at 300 or 400 MHz (^{1}H NMR) or 75 or 100 MHz (^{13}C NMR) and run in deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GC–MS-QP1000 EX mass spectrometer at 70 eV. Elemental analyzes were measured by using a German made Elementar vario LIII CHNS analyzer. 6-Arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones[17–19] and hydrazonoyl halides[24–26] were prepared as previously reported in the respective literature.

3.2. Crystallographic analysis

The crystals were mounted on a glass fiber. All measurements were performed on an ENRAF NONIUS FR 590. The data were collected at a temperature of 25 °C using the ω scanning technique to a maximum of a 20 of 22.986°. The structure was solved by direct method using SIR 92 and refined by full-matrix least squares. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically.

3.3. Crystal data

For compound **5b**: $C_{31}H_{25}ClN_2O$, M=477.007, Monoclinic, a=21.1086 (8), b=9.1011 (3), c=12.8520 (4) Á, v=2465.69 (15), α=90.00°, β=92.9753 (11)°, γ=90.00°, space group: $P2_1/c$, Z=4, D_x=1.285 Mg m^{-3} 1737 reflections measured, θ_{max}=27.49. Fig. 1 illustrates the structure as determined.[27]

3.4. Synthesis of 2′,4′,6,7,8,9-hexahydro-2′,4′,5′-triaryl spiro [benzocycloheptene-6(5*H*),3′(3*H*-pyrazol)-5-ones (4a,b)

To a mixture of equimolar amounts of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1**) and the appropriate hydrazonoyl chlorides **2a**,**b** (1 mmol) in dry benzene or dry toluene (25 mL) was added triethylamine (0.14 mL, 1 mmol). The reaction mixture was refluxed for 20 h. The solvent was evaporated and the residue was triturated with methanol. The solid that formed was filtered and crystallized from dioxane to give compounds **4a**,**b**.

*3.4.1. 2′,5′-Diphenyl-4′-(4-fluorophenyl)-2′,4′,6,7,8,9-hexahydrospiro [benzocycloheptene-6(5H),3′(3H-pyrazol)-5-one (**4a**).*[20] As yellow crystals (0.30 g, 66%), mp 154–156 °C [literature mp 153–155 °C];[20] [Found: C, 80.64; H, 5.65; N, 6.14 $C_{31}H_{25}FN_2O$ requires C, 80.85; H, 5.47; N, 6.08%]; ν_{max} (KBr) 1670 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.40–2.88 (m, 6H, 3CH_2), 4.80 (s, 1H, *pyrazole–H-4′*), 6.97–7.02 and 7.24–7.58 (m, 14H, *ArH*), 7.14 (d, *J*=8 *Hz*, 2H, *ArH*), 7.78 (d, *J*=8 Hz, 2H, *ArH*); δ_C (100 MHz, DMSO-d_6) 21.45, 28.27, 31.45 (3CH_2), 57.53 (pyrazole–*CH*), 81.13 (spiro–*C*), 115.89, 119.61, 123.01, 126.39, 126.88, 127.78, 128.51, 128.84, 131.31, 132.29, 132.91, 133.04, 138.51, 143.78, 151.34, 160.62, 162.89 (*Ar–C*), 206.23 (*C=O*); *m/z* 460 (M^+, 30), 341 (100), 328 (20), 230 (10), 104 (30), 77 (55%).

*3.4.2. 4′-(4-Chlorophenyl)-2′,5′-diphenyl-2′,4′,6,7,8,9-hexahydrospiro [benzocycloheptene-6(5H),3′(3H-pyrazol)-5-one (**4b**).*[20] As yellow crystals (0.38 g, 80%), mp 172–174 °C [literature mp 172–174 °C];[20] [Found: C, 78.14; H, 5.32; N, 5.74 $C_{31}H_{25}ClN_2O$ requires C, 78.06; H, 5.28; N, 5.87%]; ν_{max} (KBr) 1678 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.40–2.87 (m, 6H, 3CH_2), 4.81 (s, 1H, *pyrazole–H-4′*), 6.95–7.01 and 7.23–7.58 (m, 14H, *ArH*), 7.12 (d, *J*=8 Hz, 2H, *ArH*), 7.69 (d, *J*=8 Hz, 2H, *ArH*); *m/z* 478 (M^++2, 8), 477 (M^++1, 12), 476 (M^+, 22), 357 (100), 344 (13), 77 (78%).

3.5. Synthesis of 2′,3′,6,7,8,9-hexahydro-2′,3′,5′-triaryl spiro [benzocycloheptene-6(5*H*),4′(4*H*-pyrazol)-5-ones (5a–o)

To a mixture of equimolar amounts of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**1**) and the appropriate hydrazonoyl halides **2** (1 mmol) in chloroform (20 mL) was added triethylamine (0.14 mL, 1 mmol). The reaction mixture was refluxed until all of the starting materials had disappeared (7–10 h, monitored by TLC). The solvent was evaporated and the residue was triturated with methanol. The solid that formed was filtered and crystallized from appropriate solvent to give compounds **5a**–**o**.

*3.5.1. 2′,5′-Diphenyl-3′-(4-fluorophenyl)-2′,3′,6,7,8,9-hexahydrospiro [benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (**5a**).* As yellow crystals (0.39 g, 84%) (from ethanol), mp 164–166 °C; [Found: C, 80.64; H, 5.65; N, 6.14 $C_{31}H_{25}FN_2O$ requires C, 80.85; H, 5.47; N, 6.08%]; ν_{max} (KBr) 1660 (C=O) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.12–2.78 (m, 6H, 3CH_2), 5.50 (s, 1H, *pyrazole–H*), 6.97–7.02 and 7.24–7.48 (m, 14H, *ArH*), 7.16 (d, *J*=8 Hz, 2H, *ArH*), 7.72 (d, *J*=8 Hz, 2H, *ArH*); δ_C (100 MHz, DMSO-d_6) 21.47, 28.17, 31.42 (3CH_2), 57.53 (pyrazole–*CH*), 79.01 (spiro–*C*), 115.69, 119.61, 122.11, 126.19, 126.81, 127.88, 128.54, 128.88, 131.29, 132.25, 132.91, 132.94, 138.51, 143.77, 151.30, 160.42, 162.86 (*Ar–C*), 206.13 (*C=O*); *m/z* 462 (M^++2, 4), 460 (M^+, 30), 341 (100), 328 (20), 230 (10), 104 (30), 77 (55%).

*3.5.2. 3′-(4-Chlorophenyl)-2′,5′-diphenyl-2′,3′,6,7,8,9-hexahydrospiro [benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (**5b**).* As yellow crystals (0.38 g, 80%) (from dioxane), mp 158–160 °C; [Found: C, 78.14; H, 5.32; N, 5.74 $C_{31}H_{25}ClN_2O$ requires C, 78.06; H, 5.28; N, 5.87%]; ν_{max} (KBr) 1670 (C=O) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.09–2.77 (m, 6H, 3CH_2), 5.49 (s, 1H, *pyrazole–H*), 6.95–7.01 and 7.23–7.48 (m, 14H, *ArH*), 7.12 (d, *J*=8 Hz, 2H, *ArH*), 7.68 (d, *J*=8 Hz, 2H, *ArH*); δ_C (100 MHz, DMSO-d_6) 21.45, 28.13, 31.31 (3CH_2), 57.51 (pyrazole–*CH*), 79.17 (spiro–*C*), 119.72, 122.22, 126.15, 126.80, 127.78, 128.45, 128.50, 128.53, 128.77, 128.85, 131.17, 132.25, 132.58, 135.74, 138.47, 143.71, 151.47 (*Ar–C*), 206.03 (*C=O*); *m/z* 478 (M^++2, 4), 477 (M^++1, 8), 476 (M^+, 14), 357 (100), 218 (13), 144 (26), 111 (5), 77 (78%).

*3.5.3. 3′-(3,4-Dichlorophenyl)-2′,5′-diphenyl-2′,3′,6,7,8,9-hexahydrospiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (**5c**).* As yellow solid (0.43 g, 84%) (from ethanol), mp 174–176 °C; [Found: C, 72.64; H, 4.62; N, 5.34 $C_{31}H_{24}Cl_2N_2O$ requires C, 72.80; H, 4.73; N, 5.48%];

ν_{max} (KBr) 1674 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.12–3.07 (m, 6H, 3CH_2), 5.56 (s, 1H, *pyrazole–H*), 6.86–7.71 (m, 17H, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.38, 28.11, 31.03 (3CH_2), 56.81 (pyrazole–*CH*), 79.18 (spiro–*C*), 120.21, 121.34, 122.67, 123.11, 124.56, 126.18, 126.83, 127.54, 128.60, 128.74, 128.80, 130.72, 130.92, 131.07, 132.27, 137.94, 138.23, 138.55, 143.67 (*Ar–C*), 206.06 (*C=O*); *m/z* 514 (M^++4, 7), 512 (M^++2, 15), 510 (M^+, 22), 391 (100), 255 (13), 144 (29), 104 (26), 77 (98%).

3.5.4. 3′-(3,4-Dimethoxyphenyl)-2′,5′-diphenyl-2′,3′,6,7,8,9-hexahydrospiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5d***). As yellow solid (0.39 g, 77%) (from ethanol/dioxane), mp 98–100 °C; [Found: C, 78.64; H, 6.14; N, 5.46 $C_{33}H_{30}N_2O_3$ requires C, 78.86; H, 6.02; N, 5.57%]; ν_{max} (KBr) 1681 (C=O) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.28–3.10 (m, 6H, 3CH_2), 3.71 (s, 6H, 2(OCH_3)), 5.44 (s, 1H, *pyrazole–H*), 6.89–7.67 (m, 17H, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.28, 28.18, 31.15 (3CH_2), 51.34, 52.08 (OCH_3), 56.85 (pyrazole–*CH*), 79.14 (spiro–*C*), 120.25, 121.11, 122.61, 123.17, 124.59, 126.44, 126.93, 127.51, 128.64, 128.74, 128.88, 130.82, 130.98, 131.17, 132.57, 137.94, 138.83, 139.35, 143.69 (*Ar–C*), 206.16 (*C=O*); *m/z* 503 (M^++1, 24), 502 (M^+, 67), 388 (100), 251 (15), 77 (50%).

3.5.5. 2′,5′-Diphenyl-2′,3′,6,7,8,9-hexahydro-3′-(3,4,5-trimethoxyphenyl)spiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5e***). As orange solid (0.40 g, 75%) (from ethanol) mp 70–72 °C; [Found: C, 76.54; H, 6.16; N, 5.16 $C_{34}H_{32}N_2O_4$ requires C, 76.67; H, 6.06; N, 5.26%]; ν_{max} (KBr) 1678 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.25–2.47 (m, 6H, 3CH_2), 3.63 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.54 (s, 1H, *pyrazole–H*), 7.24–7.79 (m, 16H, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.41, 28.71, 31.23 (3CH_2), 51.36, 52.18 (OCH_3), 56.61 (pyrazole–*CH*), 79.19 (spiro–*C*), 120.21, 122.57, 123.14, 124.58, 126.21, 126.84, 128.62, 128.74, 128.91, 130.72, 130.92, 131.17, 132.25, 137.64, 138.13, 138.66, 143.65 (*Ar–C*), 206.16 (*C=O*); *m/z* 532 (M^+, 28), 338 (44), 149 (76), 91 (100%).

3.5.6. 3′-(4-Fluorophenyl)-2′,3′,6,7,8,9-hexahydro-2′-phenyl-5′-styrylspiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5f***). As yellow solid (0.39 g, 80%) (from ethanol/dioxane), mp 120–122 °C; [Found: C, 81.64; H, 5.62; N, 6.01 $C_{33}H_{27}FN_2O$ requires C, 81.46; H, 5.59; N, 5.76%]; ν_{max} (KBr) 1663 (C=O), 1593 (C=C) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.03–3.01 (m, 6H, 3CH_2), 5.52 (s, 1H, *pyrazole–H*), 6.98 (d, 1H, *J*=15.4 Hz, *CH*=), 7.00 (d, 1H, *J*=15.4 Hz, *CH*=), 7.05–7.40 (m, 18H, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.52, 27.99, 31.60 (3CH_2), 56.82 (pyrazole–*CH*), 79.22 (spiro–*C*), 112.83, 115.64, 119.18, 120.59, 122.06, 125.31, 126.34, 126.80, 128.11, 128.33, 128.93, 129.06, 133.06, 133.24, 136.15, 138.18, 143.23, 152.51, 159.96 (*Ar–C*), 206.30 (*C=O*); *m/z* 488 (M^++2, 5), 487 (M^++1, 22), 486 (M^+, 71), 367 (100), 77 (65%).

3.5.7. 3′-(4-Chlorophenyl)-2′,3′,6,7,8,9-hexahydro-2′-phenyl-5′-styrylspiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5g***). As yellow solid (0.35 g, 70%) (from ethanol), mp 134–136 °C; [Found: C, 78.84; H, 5.32; N, 5.64 $C_{33}H_{27}ClN_2O$ requires C, 78.79; H, 5.41; N, 5.57%]; ν_{max} (KBr) 1678 (C=O), 1593 (C=C) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.12–3.21 (m, 6H, 3CH_2), 5.54 (s, 1H, *pyrazole–H*), 6.94 (d, 1H, *J*=15.5 Hz, *CH*=), 7.15 (d, 1H, *J*=15.5 Hz, *CH*=), 7.19–7.48 (m, 18H, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.50, 24.67, 27.92 (3CH_2), 56.69 (pyrazole–*CH*), 79.15 (spiro–*C*), 119.23, 119.50, 119.81, 120.58, 122.20, 126.39, 126.64, 126.83, 128.08, 128.51, 128.72, 132.32, 132.81, 133.16, 136.12, 138.16, 143.18, 149.51, 152.48 (*Ar–C*), 205.48 (*C=O*); *m/z* 504 (M^++2, 47), 502 (M^+, 82), 383 (95), 253 (17), 130 (45), 77 (100%).

3.5.8. 3′-(3,4-Dichlorophenyl)-2′,3′,6,7,8,9-hexahydro-2′-phenyl-5′-styrylspiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5h***). As yellow solid (0.41 g, 76%) (from ethanol), mp 110–112 °C; [Found: C, 73.64; H, 4.62; N, 5.11 $C_{33}H_{26}Cl_2N_2O$ requires C, 73.74; H, 4.88; N, 5.21%]; ν_{max} (KBr) 1678 (C=O), 1593 (C=C) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.13–2.74 (m, 6H, 3CH_2), 5.58 (s, 1H, *pyrazole–H*), 6.98 (d, 1H, *J*=15.5 Hz, *CH*=), 7.05 (d, 1H, *J*=15.5 Hz, *CH*=), 7.15–7.48 (m, 17H, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.52, 24.65, 27.94 (3CH_2), 56.63 (pyrazole–*CH*), 79.18 (spiro–*C*), 119.23, 119.54, 119.88, 120.54, 122.19, 126.39, 126.61, 126.89, 128.15, 128.58, 128.91, 132.33, 132.85, 133.18, 136.15, 138.16, 139.11, 139.43, 143.15, 149.53, 151.98 (*Ar–C*), 205.88 (*C=O*); *m/z* 540 (M^++4, 7), 538 (M^++2, 24), 536 (M^+, 45), 417 (58), 77 (100%).

3.5.9. 3′-(3,4-Dimethoxyphenyl)-2′,3′,6,7,8,9-hexahydro-2′-phenyl-5′-styrylspiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5i***). As yellow solid (0.38 g, 72%) (from ethanol), mp 108–110 °C; [Found: C, 79.64; H, 6.14; N, 5.48 $C_{35}H_{32}N_2O_3$ requires C, 79.52; H, 6.10; N, 5.30%]; ν_{max} (KBr) 1659 (C=O), 1593 (C=C) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.19–2.45 (m, 6H, 3CH_2), 3.39 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.53 (s, 1H, *pyrazole–H*), 6.84 (d, 1H, *J*=15.6 Hz, *CH*=), 7.05 (d, 1H, *J*=15.6 Hz, *CH*=), 7.09–7.67 (m, 17H, *ArH*); δ_C (100 MHz, DMSO-d_6) 23.50, 26.62, 31.14 (3CH_2), 51.88, 52.28 (OCH_3), 57.23 (pyrazole–*CH*), 79.19 (spiro–*C*), 119.66, 119.84, 120.54, 120.98, 122.87, 126.39, 126.71, 126.89, 128.35, 128.88, 129.11, 132.36, 132.83, 133.27, 136.45, 138.36, 139.42, 139.88, 142.15, 147.53, 152.98 (*Ar–C*), 206.08 (*C=O*); *m/z* 528 (M^+, 96), 409 (100), 264 (26), 77 (70%).

3.5.10. 2′,3′,6,7,8,9-Hexahydro-2′-phenyl-5′-styryl-3′-(3,4,5-trimethoxyphenyl)spiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5j***). As dark yellow solid (0.40 g, 72%) (from ethanol), mp 94–96 °C; [Found: C, 77.64; H, 6.02; N, 5.11 $C_{36}H_{34}N_2O_4$ requires C, 77.40; H, 6.13; N, 5.01%]; ν_{max} (KBr) 1678 (C=O), 1593 (C=C) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.23–2.44 (m, 6H, 3CH_2), 3.61 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.55 (s, 1H, *pyrazole–H*), 6.96 (d, 1H, *J*=15.6 Hz, *CH*=), 7.00 (d, 1H, *J*=15.6 Hz, *CH*=), 7.04–7.49 (m, 16H, *ArH*); δ_C (75 MHz, DMSO-d_6) 25.50, 28.62, 32.17 (3CH_2), 51.94, 52.97 (OCH_3), 57.54 (pyrazole–*CH*), 79.16 (spiro–*C*), 119.51, 120.54, 121.87, 126.19, 126.74, 126.84, 128.18, 128.68, 129.11, 132.38, 132.86, 133.17, 136.65, 138.96, 139.47, 139.85, 142.19, 147.53, 152.78 (*Ar–C*), 206.05 (*C=O*); *m/z* 558 (M^+, 65), 439 (100), 77 (84%).

3.5.11. 3′-(4-Fluorophenyl)-2′,3′,6,7,8,9-hexahydro-2′-(4-nitrophenyl)-5′-thienyl spiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5k***). As orange solid (0.37, 73%) (from ethanol), mp 158–160 °C; [Found: C, 68.22; H, 4.45; N, 8.11; S, 6.14 $C_{29}H_{22}FN_3O_3S$ requires C, 68.09; H, 4.33; N, 8.21; S, 6.27%]; ν_{max} (KBr) 1659 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.10–2.28 (m, 6H, 3CH_2), 5.42 (s, 1H, *pyrazole–H*), 6.98–8.12 (m, 11H, *ArH*), 7.47 (d, 2H, *J*=6 Hz, *ArH*), 8.23 (d, 2H, *J*=6 Hz, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.99, 27.95, 32.42 (3CH_2), 56.01 (pyrazole–*CH*), 79.87 (spiro–*C*), 115.29, 115.83, 119.23, 120.62, 124.53, 126.88, 127.15, 127.61, 128.47, 129.03, 133.13, 133.63, 136.74, 138.10, 142.81, 145.10, 148.22 (*Ar–C*), 202.73 (*C=O*); *m/z* 511 (M^+, 24), 490 (74), 392 (44), 231 (70), 185 (60), 76 (100%).

3.5.12. 3′-(4-Chlorophenyl)-2′,3′,6,7,8,9-hexahydro-2′-(4-nitrophenyl)-5′-thienylspiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (***5l***). As red solid (0.43 g, 82%) (from ethanol/dioxane), mp 124–126 °C; [Found: C, 65.84; H, 4.27; N, 8.03; S, 6.13 $C_{29}H_{22}ClN_3O_3S$ requires C, 65.97; H, 4.20; N, 7.96; S, 6.07%]; ν_{max} (KBr) 1664 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.14–2.86 (m, 6H, 3CH_2), 5.51 (s, 1H, *pyrazole–H*), 7.03–8.21 (m, 15H, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.95, 28.03, 32.41 (3CH_2), 56.11 (pyrazole–*CH*), 79.77 (spiro–*C*), 115.22, 115.88, 120.22, 120.85, 125.80, 126.78, 127.45, 127.90, 128.43, 128.77, 129.05, 133.45, 136.58, 138.14, 142.47, 145.11, 148.32 (*Ar–C*), 203.03

(*C*=*O*); *m*/*z* 529 (M^++2, 10), 527 (M^+, 25), 388 (30), 375 (75), 328 (50), 282 (20), 104 (30), 76 (80%).

*3.5.13. 3′-(3,4-Dichlorophenyl)-2′,3′,6,7,8,9-hexahydro-2′-(4-nitrophenyl)-5′-thienylspiro [benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (**5m**).* As orange solid (0.39 g, 70%) (from ethanol), mp 122–124 °C; [Found: C, 61.72; H, 3.65; N, 7.31; S, 5.84 $C_{29}H_{21}Cl_2N_3O_3S$ requires C, 61.93; H, 3.76; N, 7.47; S, 5.70%]; ν_{max} (KBr) 1674 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.18–2.38 (m, 6H, 3CH_2), 5.58 (s, 1H, *pyrazole–H*), 6.98–8.11 (m, 10H, *ArH*), 7.49 (d, 2H, *J*=6 Hz, *ArH*), 8.33 (d, 2H, *J*=6 Hz, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.88, 28.11, 31.93 (3CH_2), 56.61 (pyrazole–*CH*), 79.88 (spiro–*C*), 115.34, 115.93, 120.21, 120.64, 124.67, 126.11, 127.36, 127.68, 128.53, 129.14, 133.18, 133.72, 136.92, 138.07, 138.68, 139.11, 142.77, 145.32, 148.34 (*Ar–C*), 203.06 (*C*=*O*); *m*/*z* 565 (M^++4, 7), 563 (M^++2, 24), 561 (M^+, 42), 490 (25), 226 (46), 178 (42), 77 (100%).

*3.5.14. 3′-(3,4-Dimethoxyphenyl)-2′,3′,6,7,8,9-hexahydro-2′-(4-nitrophenyl)-5′-thienyl spiro [benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (**5n**).* As orange solid (0.45 g, 81%) (from ethanol), mp 120–122 °C; [Found: C, 67.52; H, 4.98; N, 7.41; S, 5.59 $C_{31}H_{27}N_3O_5S$ requires C, 67.25; H, 4.92; N, 7.59; S, 5.79%]; ν_{max} (KBr) 1654 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.19–2.47 (m, 6H, 3CH_2), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.50 (s, 1H, *pyrazole–H*), 7.03–8.12 (m, 10H, *ArH*), 7.48 (d, 2H, *J*=6 Hz, *ArH*), 8.25 (d, 2H, *J*=6 Hz, *ArH*); δ_C (75 MHz, DMSO-d_6) 21.88, 28.18, 31.95 (3CH_2), 51.84, 52.58 (OCH_3), 56.19 (pyrazole–*CH*), 79.74 (spiro–*C*), 115.31, 116.04, 120.05, 120.41, 124.61, 126.77, 127.19, 127.64, 128.93, 129.51, 133.18, 133.67, 136.57, 138.14, 138.83, 139.35, 143.09, 145.11, 148.17 (*Ar–C*), 203.06 (*C*=*O*); *m*/*z* 553 (M^+, 12), 490 (23), 76 (100%).

*3.5.15. 2′,3′,6,7,8,9-Hexahydro-2′-(4-nitrophenyl)-5′-thienyl-3′-(3,4,5-trimethoxyphenyl)-spiro[benzocycloheptene-6(5H),4′(4H-pyrazol)-5-one (**5o**).* As red crystals (0.47 g, 80%) (from ethanol/dioxane), mp 140–142 °C; [Found: C, 65.62; H, 4.95; N, 7.11; S, 5.54 $C_{32}H_{29}N_3O_6S$ requires C, 65.85; H, 5.01; N, 7.20; S, 5.49%.]; ν_{max} (KBr) 1678 (C=O) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.17–2.38 (m, 6H, 3CH_2), 3.67 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.54 (s, 1H, *pyrazole–H*), 6.93–8.12 (m, 9H, *ArH*), 7.48 (d, 2H, *J*=6 Hz, *ArH*), 8.25 (d, 2H, *J*=6 Hz, *ArH*); δ_C (100 MHz, DMSO-d_6) 21.91, 28.11, 32.23 (3CH_2), 51.66, 52.88 (OCH_3), 56.51 (pyrazole–*CH*), 79.79 (spiro–*C*), 115.32, 115.93, 120.21, 120.57, 123.94, 125.88, 127.21, 128.12, 129.14, 133.17, 136.25, 138.64, 138.88, 139.26, 143.65, 145.02, 148.12 (*Ar–C*), 205.16 (*C*=*O*); *m*/*z* 583 (M^+, 2), 490 (64), 231 (65), 185 (60), 76 (100%).

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27. All crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 827297. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.