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Ultrasound-Assisted Regio- and Stereoselective Synthesis of Bis-[1`,4`-diaryl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] Derivatives via 1,3-Dipolar Cycloaddition

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

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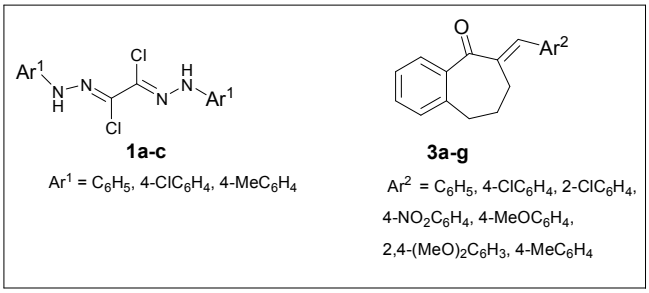
The 1,3-dipolar cycloaddition reaction of the bis-hydrazonoyl chlorides with 2-arylidene-1-benzosuberone derivatives afforded the corresponding bis-[1`,4`-diaryl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] derivatives. The reaction is carried out under ultrasonic irradiation as well as under conventional heating. The factors affecting the optimization of the cycloaddition reaction are examined in details. X-ray crystallographic analysis was used in the establishment of the regio- and stereochemistry of the cycloaddition products.

Introduction

Ultrasound, as an environmentally sustainable technique, has found several applications in synthetic organic chemistry, in materials science, in medicinal chemistry and in life sciences.[1-5] Compared with conventional heating, the key advantages of the ultrasound irradiation are: 1) increasing the yields, 2) decreasing the reaction time and 3) increasing the products' purity and selectivity.[6,7] 1,3-Dipolar cycloaddition is one of the most valuable synthetic routes for the synthesis of five-membered heterocycles.[8,9] Spiropyrazoline derivatives are involved in several pharmaceutical agents, such as antiviral and antibacterial activities,[10,11] anti-cancer agents,[12] as well as acetyl-CoA carboxylase inhibiting activities.[13] Benzosuberone moiety (6,7,8,9-tetrahydrobenzo- cyclohepten-5-one) was found in variety of biologically active compounds that proved to have anti-cancer,[14-16] anti-proliferative[17] and antiangiogenic agents[18,19] as well as human aminopeptidase[20,21] and acetylcholinesterase inhibiting activities.[22] In continuation of our research work on the [3+2] and [4+1] cycloadditions towards pyrazole synthesis and on the chemistry of bis-hydrazonoyl chlorides **1a-c**,[23-31] we report here their first example of ultrasound-assisted 1,3-dipolar cycloaddition with 2-arylidene-1-benzosuberones **3a-g** for the construction of the bis-[1-oxo-spiro-benzosuberane-2,5`-pyrazoline] derivatives **4a-m**. The regio- and stereoselectivity of the cycloaddition mode will be examined by measuring the X-ray crystallographic analysis of the products.



Results and discussion

Effect of parameters like choice of solvent, type of the used base, mode of activation (ultrasonic irradiation and conventional heating) will be extensively examined. Firstly, using triethylamine (TEA) as a base, the effect of solvents (ethanol, benzene, toluene and chloroform) on the 1,3-dipolar cycloaddition reactions of the bis-nitrilimine **2a**, [generated *in situ* from the bis-hydrazonoyl chloride **1a** with base], with 2-benzylidene-1-benzosuberone (**3a**), as a model reaction, was evaluated under ultrasound irradiation and conventional heating and the results are listed in Table 1. Thus, when the 1,3-dipolar cycloaddition of **2a** with **3a** using EtOH/Et_3N under ultrasonic irradiation at 70 °C (110 watt), the starting substrates were completely consumed after 3 hours to afford only one isolable product. The HRMS of the obtained pure product showed a peak at *m/z* 730.3302, this value corresponds to the molecular formula $C_{50}H_{42}N_4O_2$. This result declared that the cycloaddition reaction proceeded between **2a** and **3a** in 1:2 molar ratio. Since the bis-nitrilimine **2a** has two possible 1,3-dipole

attacking sites, there are three expected cycloadducts for which structures **4a, 5a** and **6a** can be assigned (Scheme 1). The ^{1}H NMR spectrum of the reaction product revealed sets of multiplets in the region δ 1.0-2.94 due to the aliphatic CH_2's protons and a singlet signal at δ 4.97 in addition to aromatic protons signals in the region δ 6.72- 7.51. The singlet at δ 4.97 is due to the pyrazoline-4H proton which is close to analogously reported pyrazoline-4H proton at δ ≈ 5 [23,32] and not consistent with the pyrazoline-5H proton which appears at δ value >5.6.[33] These data support the bis-[1`,4`-diphenyl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] structure (**4a**) and rules out the other regioisomeric structures **5a** or **6a** (Scheme 1). Further, the ^{13}C NMR spectrum showed five *sp*^{3} carbon-signals in the region δ 21.8-79.4 among them a peak at 79.35 due to spiropyrazoline-5-C atom which is close to analogous reported simple structures.[32] The regio- and stereoselective formation of structure **4a** was unequivocally evidenced by measuring its X-ray single crystal analysis (**Figure 1**).[34]

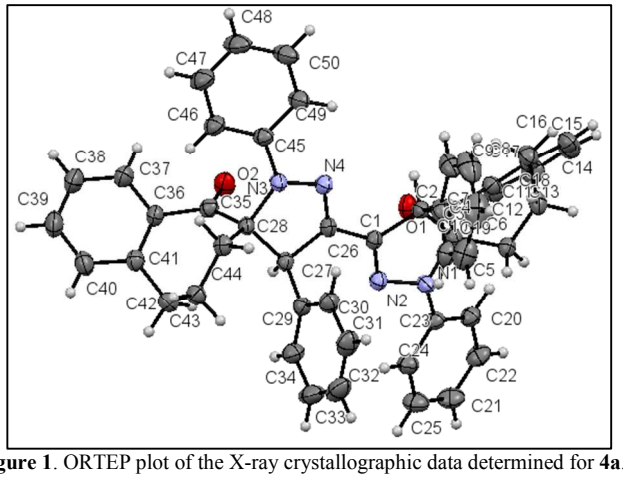


Figure 1. ORTEP plot of the X-ray crystallographic data determined for **4a**.

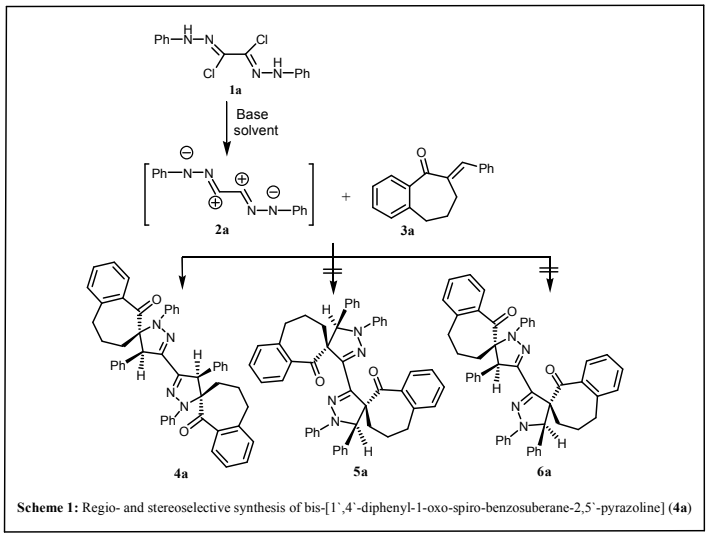
The yield of the product **4a** under ultrasound irradiation was found to be 87% after 3 hours, however, when the same cycloaddition reaction was repeated under conventional heating at reflux temperature using EtOH/Et_3N, the reaction completed after 36 hours but with sharp decrease in the isolated yield (35%) (Table 1, entry 1). When the same reaction between **2a** and **3a** was repeated using benzene instead of ethanol in the presence of Et_3N, the yield of the product **4a** was very poor either under conventional heating (11% after 36 h) or ultrasound irradiation (13% after 3 h) (Table 1, entry 2) and the substrate **3a** was incompletely reacted. Further, toluene was also not appropriate solvent where the yield of **4a** was 15% after 36 h of conventional heating and 19% after 3 h of ultrasound irradiation, with incomplete reaction of the substrate **3a**. No reaction at all took place either under conventional heating or ultrasound irradiation when chloroform was used as a solvent, where the starting substrate **3a** was completely recovered. Therefore, ethanol is the solvent of choice for conducting this 1,3-dipolar cycloaddition reaction under ultrasonic condition.

Next, using ethanol as reaction solvent, the effect of further organic and inorganic bases (DABCO, DBU and CsF) on the behaviour of this cycloaddition reaction was also evaluated. Thus, when EtOH/DABCO system was applied, compound **3a** was isolated in 56% yield (after 3 h of ultrasound irradiation) and in 29% yield (after 36 h of conventional heating) (Table 1, entry 5). The use of EtOH/DBU resulted in the formation of compound **4a** in 44% yield (after 3 h of ultrasound irradiation) and in 25% yield (after 36 h of conventional heating) (Table 1, entry 6). The inorganic base CsF was not appropriate the cycloaddition of **1a** with **3a** where only traces of **4a** was detected by TLC both under conventional heating and ultrasound irradiation and the starting substrate **3a** was almost completely recovered (Table 1, entry 7).

Table 1. Optimization of the reaction conditions for synthesis of **4a**

Entry	Solvent	Base	Yield% of **4a**[a]))) [3h][d]	Δ [36h][e]
1	ethanol	TEA	87	35[b]
2	benzene	TEA	13[b]	11[b]
3	toluene	TEA	19[b]	15[b]
4	chloroform	TEA	Trace[c]	Trace[c]
5	ethanol	DABCO	56	29[b]
6	ethanol	DBU	44[b]	25[b]
7	ethanol	CsF	Trace[c]	Trace[c]

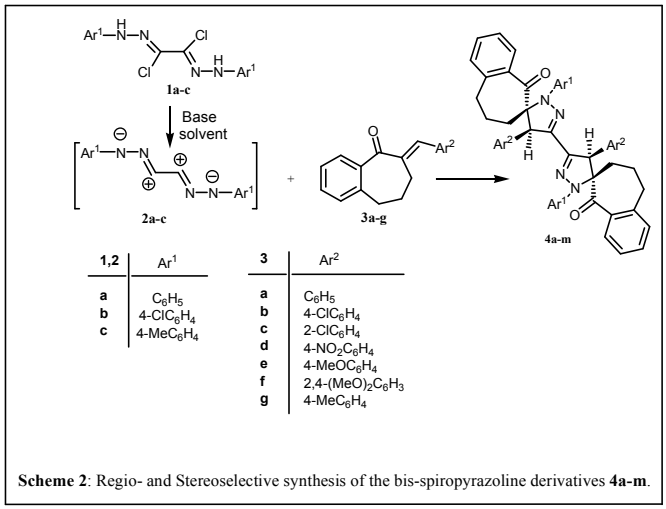
[a]*Reaction conditions*: bis-hydrazonoyl chloride **1a** (2 mmoles), 2-benzylidene-1-benzosuberone **3a** (4 mmoles), base (4 mmoles) and solvent (25 mL) under sonication (at 70 °C for 3h) or conventional heating (at reflux for 36 h).
[b]Benzosuberone derivative **3a** was detected.
[c]Benzosuberone derivative **3a** was completely recovered.
[d]))) = ultrasonic irradiation.
[e]Δ = conventional heating.



Scheme 1: Regio- and stereoselective synthesis of bis-[1`,4`-diphenyl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (**4a**)

Under the optimized reaction conditions above, we investigated the substrate scope of this reaction as shown in **Scheme 2**. The methodology was found to be applicable to a range of the substrates; 2-arylidene-1-benzosuberone derivatives **3a-g** and bis-hydrazonoyl chlorides **1a-c**. Thus, the regioselective 1,3-dipolar cycloaddition reaction of the bis-nitrilimine **2a** with the 2-arylidene-1-benzosuberone derivatives **3a-g** was conducted using EtOH/Et_3N under both ultrasonic irradiation and conventional heating and afforded the corresponding bis-[1`,4`-diaryl-1-oxo-spiro-benzo-suberane-2,5`-pyrazoline] derivatives **4a-g**, **Scheme 2**. The yields of the cycloadducts **4a-g** varied between 76 and 91% (after 3 h of sonication) and between 25 and 42% yields (after 36 h of

conventional heating) as shown in **Table 2**, entries 1-7. Similar to compound **4a**, the regio- and stereoselective formation of the bis-[1`,4`-diaryl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] structures **4b-g** were determined from their full spectral data (IR, HRMS, ^{1}H and ^{13}C NMR spectra) and by measuring the single crystal X-ray analyses of compounds **4b-d** as depicted in Figures 2-4.[34]



Scheme 2: Regio- and Stereoselective synthesis of the bis-spiropyrazoline derivatives **4a-m**.

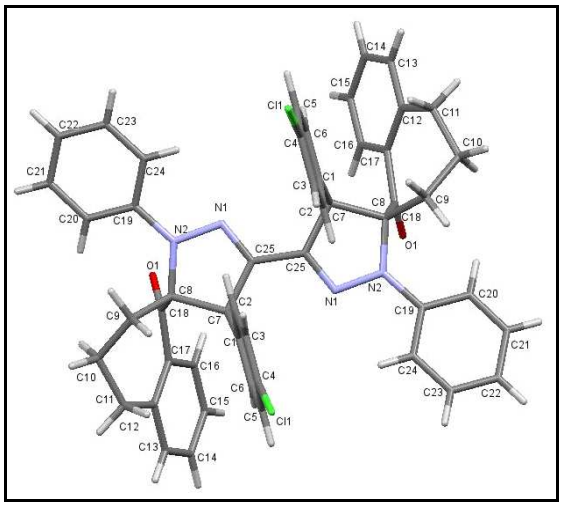


Figure 2. The X-ray crystallographic data determined for **4b**.

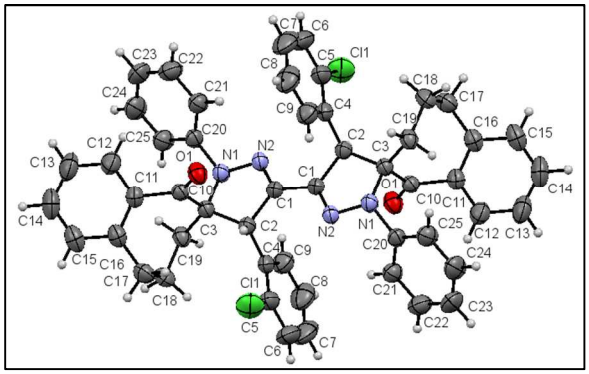


Figure 3. ORTEP plot of the X-ray crystallographic data determined for **4c**.

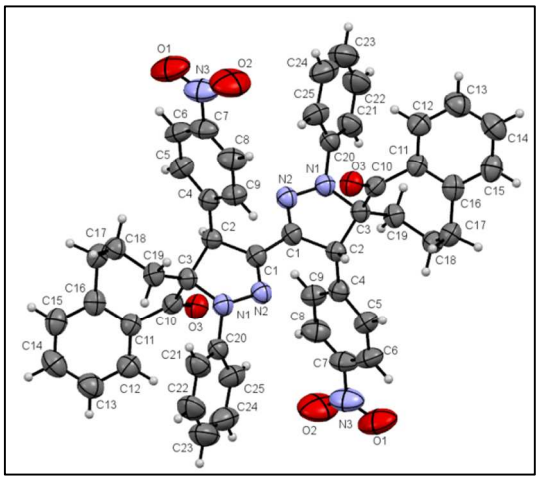


Figure 4. ORTEP plot of the X-ray crystallographic data determined for **4d**

To further expand and to generalize the highly regio- and stereoselective behavior of the cycloaddition reaction as examined between the bis-nitrilimine **2a** and dipolarophiles **3a-g**, the 1,3-dipolar cycloaddition reaction of the bis-nitrilimine **2b** with the dipolarophiles **3a,b,f** was similarly conducted and the data are outlined in Table 2, entries 8-10. Thus, ultrasonic irradiation of the bis-nitrilimine **2b** with the dipolarophiles **3a,b,f** in ethanol in the presence of Et_3N afforded the desired bis-[1-oxo-spiro-benzosuberane-2,5`-pyrazoline] derivatives **4h,i,j** in 83, 88 and 84% isolated yields, respectively. The same compounds **4h,i,j** were obtained from the reaction of **2b** with **3a,b,f** in 38, 45 and 41% yields, respectively, when refluxed under conventional heating for 36 h in ethanol in the presence of Et_3N. Structures **4h,i,j** were established from their spectral data (IR, HRMS, ^{1}H and ^{13}C NMR spectra) as shown in the experimental section.

Finally, the regio- and stereoselective 1,3-dipolar cycloaddition reaction of the bis-nitrilimine **2c** and dipolarophiles **3a,b,f**, was similarly performed. Thus, carrying out the reaction of **2c** with **3a,b,f** in ethanol solvent and Et_3N as base resulted in the formation of the bis-[1-oxo-spiro-benzosuberane-2,5`-pyrazoline] derivatives **4k,l,m** in 90, 87 and 72% yields, respectively (under ultrasonic irradiation) and in 37, 51 and 22% yields, respectively (under conventional heating) as shown in Table 2, entries 11-13. The single crystal X-ray analysis of compound **4l** showed in **Figure 5**,[34] provided a firm support the for the regio- and stereoselective manner of the cycloaddition process.

Table 2. 1,3-Dipolar cycloaddition reactions of **1a-c** with 3-arylidenebenzosuberones **3a-g**

Entry	Reactants	Products	Ar^1	Ar^2	Yield% **4a-m**[a]))) [3h][b]	Δ [36h][c]
1	**1a + 3a**	**4a**	C_6H_5	C_6H_5	87	35
2	**1a + 3b**	**4b**	C_6H_5	4-ClC_6H_4	91	42
3	**1a + 3c**	**4c**	C_6H_5	2-ClC_6H_4	85	33
4	**1a + 3d**	**4d**	C_6H_5	4-$NO_2C_6H_4$	86	32
5	**1a + 3e**	**4e**	C_6H_5	4-$MeOC_6H_4$	79	29
6	**1a + 3f**	**4f**	C_6H_5	2,4-$(MeO)_2C_6H_3$	76	25
7	**1a + 3g**	**4g**	C_6H_5	4-MeC_6H_4	80	36
8	**1b + 3a**	**4h**	4-ClC_6H_4	C_6H_5	83	38
9	**1b + 3b**	**4i**	4-ClC_6H_4	4-ClC_6H_4	88	45
10	**1b + 3f**	**4j**	4-ClC_6H_4	2,4-$(MeO)_2C_6H_3$	84	41
11	**1c + 3a**	**4k**	4-MeC_6H_4	C_6H_5	90	37
12	**1c + 3b**	**4l**	4-MeC_6H_4	4-ClC_6H_4	87	51
13	**1c + 3f**	**4m**	4-MeC_6H_4	2,4-$(MeO)_2C_6H_3$	72	22

[a]*Reaction conditions*: bis-hydrazonoyl chlorides **1a-c** (2 mmoles), 2-arylidene-1-benzosuberones **3a-g** (4 mmoles), Et_3N (4 mmoles) and EtOH (25 mL) under sonication (at 70 °C for 3h) or conventional heating (at reflux for 36 h).
[b]Benzosuberone derivatives **3a-g** were completely consumed.
[c]Benzosuberone derivatives **3a-g** were detected by TLC.

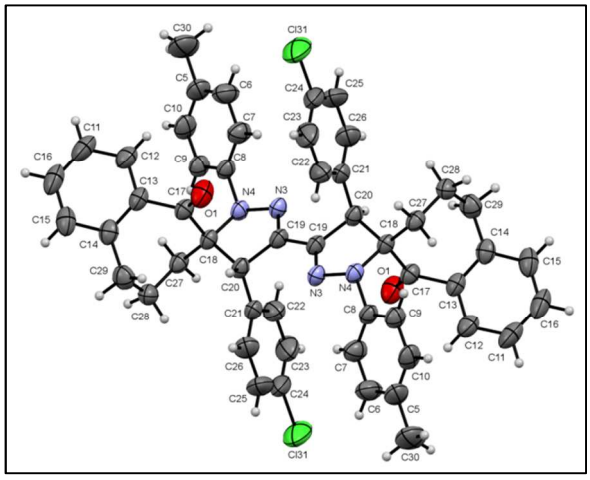


Figure 5. ORTEP plot of the X-ray crystallographic data determined for **4l**.

Experimental

General:

Melting points were recorded on a Griffin melting point apparatus and are reported uncorrected. IR spectra were recorded using KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^{1}H-NMR (400 MHz) or (600 MHz) and ^{13}C-NMR (100 MHz) or (150 MHz) spectra were recorded at 25 °C using $CDCl_3$ or DMSO-d_6 as solvent with TMS as internal standard on a Bruker DPX 400 or 600 super-conducting NMR spectrometer. Chemical shifts are reported in ppm. Low-resolution electron impact mass spectra [MS (EI)] and High-resolution electron impact mass spectra [HRMS (EI)] were performed on high resolution GC-MS (DFS) thermo spectrometers at 70.1 eV using magnetic sector mass analyzer. Follow up of the reactions and checking homogeneity of the prepared compounds was made by thin layer chromatography (TLC). The crystal structures were determined by a Rigaku R-AXIS RAPID diffractometer and Bruker X8 Prospector and the single crystal data collections were made by using Cu- Kα radiation. The data were collected at room temperature. The structure was solved by direct methods and was expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The structure was solved and refined using the Bruker SHELXTL Software Package (Structure solution program- SHELXS-97 and Refinement program-SHELXL-97).[35] Data were corrected for the absorption effects using the multi-scan method (SADABS). Sonication was performed in MKC6, Guyson ultrasonic bath (Model-MKC6, Operating frequency 38 kHz +/- 10% and an output power of 110 Watts) with digital timer (6 sec. to 100 min.) and heater allows solution heating to be set from 20 °C to 80 °C in 1 °C increments. The inside tank dimensions are 150 x 300 x 150 mm (length x width x depth) with a fluid capacity of 6 liters. 2-Arylidene-1-benzosuberone derivatives **3a-g** was prepared according to the literature procedures.[36]

***N,N′*-Diphenylethane(bis-hydrazonoyl dichloride) (1a).**
Yield: (76%); recrystallized from acetic acid as yellowish white crystals; mp. 190-191 °C (Lit. mp.[37] 188-190 °C); ^{1}H-NMR (DMSO-d_6): δ = 6.86-6.91 (m, 2H, Ar-H), 7.25-7.33 (m, 8H, Ar-H), 10.36 (s, 2H, NH); ^{13}C-NMR (DMSO-d_6): δ = 113.63, 117.74, 120.96, 129.12, 143.65.

***N,N′*-Di-(4-chlorophenyl)ethane(bis-hydrazonoyl dichloride) (1b).**
Yield: (77%); recrystallized from acetic acid as luster buff crystals; mp. 224–225 °C (Lit. mp.[38] 223-225 °C); ^{1}H-NMR (DMSO-d_6): δ =

7.31-7.32 (m, 8H, Ar-H), 10.34 (s, 2H, NH); ^{13}C-NMR (DMSO-d_6): δ = 115.16, 118.39, 124.51, 128.98, 142.58.

***N,N′*-Di-(4-tolyl)ethane(bis-hydrazonoyl dichloride) (1c).** Yield: (80%); recrystallized from acetic acid as luster pale yellow crystals, mp. 199–200 °C (Lit. mp.[38] 198-200 °C); ^{1}H-NMR (DMSO-d_6): δ = 2.24 (s, 6H, 2CH$_3$), 7.10 (d, *J* = 7.8 Hz, 4H, Ar-H), 7.22 (d, *J* = 7.8 Hz, 4H, Ar-H), 10.05 (s, 2H, NH); ^{13}C-NMR (DMSO-d_6): δ = 20.30, 113.60, 117.22, 129.52, 129.61, 141.42.

Synthesis of bis-[1`,4`-diaryl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] 4a-m.

General Method A

To a mixture of the appropriate bis-hydrazonoyl chloride **1a-c** (2 mmol) and the appropriate 2-arylidene-1-benzosuberone derivative **3a-g** (4 mmol each) in the appropriate dry solvent (ethanol, benzene, toluene or chloroform) (25 mL), triethylamine (0.6 mL, 4 mmol) was added portion-wise. The mixture was heated at refluxing temperature and the reaction was followed up by TLC and continued for 36 h, then left to cool to room temperature. The solvent was removed, in each case, under reduced pressure and the residue was triturated with methanol to give yellow or pale-brown colored products. The solid products that formed were filtered off, washed with ethanol, dried and recrystallized from dimethylformamide (DMF)/ethanol (3:1) to afford the corresponding bis-[1`,4`-diaryl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] derivatives **4a-m** as pure products.

General Method B

To a mixture of the appropriate bis-hydrazonoyl chloride **1a-c** (2 mmol) and the appropriate 2-arylidene-1-benzosuberone derivative **3a-g** (4 mmol each) in the appropriate dry solvent (ethanol, benzene, toluene or chloroform) (25 mL), triethylamine (0.6 mL, 4 mmol) was added portion-wise. The reaction mixture was sonicated in MKC6**,** Guyson ultrasonic bath (Model-MKC6, operating frequency 38 kHz +/- 10% and an output power of 110 Watts) for 3h at 70 °C. The reaction was controlled by TLC and continued until the starting substrates were completely consumed, then left to cool to room temperature. The solid products that formed were filtered off, washed with ethanol, dried and recrystallized from dimethylformamide (DMF)/ethanol (3:1) to afford the corresponding bis-[1`,4`-diaryl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] **3a-m** as pure products.

Bis-[1`,4`-diphenyl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4a). As yellow crystals, mp. 270–271 °C; IR (KBr): ν/cm^{-1} 1690 (CO); ^{1}H-NMR (DMSO-d_6): δ = 1.00-1.05 (m, 2H, *H* of CH$_2$), 1.36-1.41 (m, 2H, *H* of CH$_2$), 1.65-1.69 (m, 2H, *H* of CH$_2$), 2.29-2.35 (m, 2H, *H* of CH$_2$), 2.73-2.77 (m, 2H, *H* of CH$_2$), 2.91-2.94 (m, 2H, *H* of CH$_2$), 4.97 (s, 2H, pyrazole-*CH*), 6.72 (d, *J* = 7.8 Hz, 4H, Ar-H), 6.88 (t, *J* = 7.8 Hz, 4H, Ar-H), 7.14 (t, *J* = 7.2 Hz, 4H, Ar-H), 7.27 (t, *J* = 7.8 Hz, 4H, Ar-H), 7.31-7.38 (m, ,10H, Ar-H) and 7.51 ppm (t, *J* = 7.8 Hz, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ = 21.84, 27.97, 32.07 (*CH*$_2$), 58.91 (pyrazole-*CH*), 79.35 (spiro-*C*), 118.20, 121.52, 126.93, 127.76, 128.17, 128.48, 128.70, 129.22, 129.27, 132.46, 136.35, 137.68, 139.24, 142.46, 144.16 and 205.19 ppm (Ar-C and CO); MS (EI): m/z (%) 732 (M$^+$+2, 13.45), 731 (M$^+$+1, 46.83), 730 (M$^+$, 77.05); HRMS (EI): *m/z* calcd. for $C_{50}H_{42}N_4O_2$ (M$^+$) 730.3302, found: 730.3302. **Crystal Data**, $C_{50}H_{42}N_4O_2$, M = 730.92, monoclinic, a = 11.0471(4) Å, b = 18.9631(7) Å, c = 22.9273(8) Å, V = 4728.9(3) Å^3, α = γ = 90°, β = 100.077(2)°, space group: P 1 21/c 1, Z = 4, D_{calc} = 1.232 g cm^{-3} , No. of reflection measured 53472, θ $_{max}$ = 66.71°, R1 = 0.0581.[34]

Bis-[1`-phenyl-4`-(4-chlorophenyl)-1-oxo-spiro-benzosuberane-2,5`- pyrazoline] (4b). As yellow crystals, mp. 277–278 °C; IR (KBr): ν/cm^{-1} 1686 (CO); ^{1}H-NMR (DMSO-d_6): δ = 0.93-1.01 (m, 2H, *H* of CH$_2$), 1.38-1.46 (m, 2H, *H* of CH$_2$), 1.69-1.74 (m, 2H, *H* of CH$_2$), 2.31-2.37 (m, 2H, *H* of CH$_2$), 2.72-2.76 (m, 2H, *H* of CH$_2$), 2.94-3.00 (m, 2H, *H* of CH$_2$), 5.09 (s, 2H, pyrazole-*CH*), 6.75 (d, *J* = 8.0 Hz, 4H, Ar-H), 6.89-6.95 (m, 4H, Ar-H), 7.14-7.22 (m, 8H, Ar-H), 7.27 (d, *J* = 7.6 Hz, 2H, Ar-H), 6.35 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.42 (d, *J* = 8.0 Hz, 4H, Ar-H) and 7.52 ppm (t, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ = 22.13, 27.86, 31.88 (*CH*$_2$), 57.95 (pyrazole-*CH*), 79.21 (spiro-*C*), 118.39, 121.90, 126.97, 128.36, 128.58, 129.29, 130.81, 132.43, 132.68, 135.68, 137.75, 139.14, 142.46, 142.92, 144.06 and 205.10 ppm (Ar-C and CO); MS (EI): m/z (%) 800 (M$^+$+2, 44.95), 799 (M$^+$+1, 29.46), 798 (M$^+$, 55.89); HRMS (EI): m/z Calcd. for $C_{50}H_{40}Cl_2N_4O_2$ (M$^+$) 798.2523, found 798.2523. **Crystal Data,** $C_{50}H_{40}Cl_2N_4O_2$, M = 799.76, orthorhombic, a = 22.2297(8) Å, b = 11.6884(5) Å, c = 15.5606(6) Å, V = 4043.1(3) Å^3, α = β = γ = 90°, space group: P c c a, Z = 4, D_{calc} = 1.314 g cm^{-3} , No. of reflection measured 12902, θ $_{max}$ = 66.62°, R1 = 0.0498.[34]

Bis-[1`-phenyl-4`-(2-chlorophenyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4c). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1} 1687 (CO); ^{1}H-NMR (DMSO-d_6): δ = 1.21-1.27 (m, 2H, *H* of CH$_2$), 1.50-1.56 (m, 2H, *H* of CH$_2$), 1.93-1.97 (m, 2H, *H* of CH$_2$), 2.34-2.39 (m, 2H, *H* of CH$_2$), 2.76-2.86 (m, 4H, 2*H* of CH$_2$), 5.29 (s, 2H, pyrazole-*CH*), 6.52 (d, *J* = 7.6 Hz, 2H, Ar-H), 6.79 (d, *J* = 8.0 Hz, 4H, Ar-H), 6.98 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.08-7.23 (m, 10H, Ar-H) and 7.30-7.54 ppm (m, 8H, Ar-H),; ^{13}C-NMR (DMSO-d_6): δ = 22.17, 29.70, 32.82 (*CH*$_2$), 54.49 (pyrazole-*CH*), 81.43 (spiro-*C*), 120.93, 123.40, 127.10, 127.66, 128.17, 128.79, 129.24, 129.73, 129.97, 130.80, 132.07, 133.97, 134.39, 138.24, 138.92, 143.81, 146.38 and 206.09 ppm (Ar-C and CO); MS (EI): m/z (%) 800 (M$^+$+2, 46.78), 799 (M$^+$+1, 32.08), 798 (M$^+$, 62.71); HRMS (EI): m/z Calcd. for $C_{50}H_{40}Cl_2N_4O_2$ (M$^+$) 798.2523, found 798.2523. **Crystal Data,** $C_{50}H_{40}Cl_2N_4O_2$, M = 799.76, triclinic, a = 11.4329(4) Å, b = 13.7041(5) Å, c = 15.7697(5) Å, V = 2244.11(13) Å^3, α = 66.387(2)°, β = 82.782(2)° , γ = 89.224(2)°, space group: P-1 (#2), Z = 2, D_{calc} = 1.292 g cm^{-3} , No. of reflection measured 22943, 2 θ $_{max}$ = 66.66°, R1 = 0.0453.[34]

Bis-[1`-phenyl-4`-(4-nitrophenyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4d). As yellow crystals, mp. 257–258 °C; IR (KBr): ν/cm^{-1} 1683 (CO); ^{1}H-NMR (DMSO-d_6): δ = 1.05-1.10 (m, 2H, *H* of CH$_2$), 1.41-1.45 (m, 2H, *H* of CH$_2$), 1.94-1.98 (m, 2H, *H* of CH$_2$), 2.27-2.32 (m, 2H, *H* of CH$_2$), 2.66-2.70 (m, 2H, *H* of CH$_2$), 2.84-2.89 (m, 2H, *H* of CH$_2$), 5.07 (s, 2H, pyrazole-*CH*), 6.57 (d, *J* = 7.2 Hz, 2H, Ar-H), 6.71 (d, *J* = 7.8 Hz, 4H, Ar-H), 6.99 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.12 (t, *J* = 7.8 Hz, 4H, Ar-H), 7.18 (d, *J* = 7.8 Hz, 4H, Ar-H), 7.38-7.42 (m, 6H, Ar-H) and 7.52 ppm (d, *J* = 8.4 Hz, 4 H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ = 21.36, 28.56, 31.14 (*CH*$_2$), 58.03 (pyrazole-*CH*), 79.71 (spiro-*C*), 120.49, 122.94, 126.60, 127.12, 128.29, 128.33, 128.60, 131.20, 131.89, 132.15, 136.34, 138.02, 138.61, 143.44, 146.28 and 206.00 ppm (Ar-C and CO); MS (EI): m/z (%) 822 (M$^+$+2, 9.89), 821 (M$^+$+1, 27.65), 820 (M$^+$, 45.12); HRMS (EI): m/z Calcd. for $C_{50}H_{40}N_6O_6$ (M$^+$) 820.3004, found 820.3004. **Crystal Data**, $C_{50}H_{40}N_6O_6$, M = 820.91, monoclinic, a = 13.204(5) Å, b = 9.770(4) Å, c = 16.496(6) Å, V =2026(2) Å^3, α = γ = 90°, β = 107.826(8) °, space group: P2$_1$/c (#14), Z = 4, D_{calc} = 1.346 g cm$^{-3,}$ No. of reflection measured 15286, θ $_{max}$ = 50.10°, R1 = 0.0664.[34]

Bis-[1`-phenyl-4`-(4-anisyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4e). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1}

1687 (CO); ^{1}H-NMR (DMSO-d_6): δ = 1.07-1.12 (m, 2H, *H* of CH_2), 1.39-1.45 (m, 2H, *H* of CH_2), 1.65-1.70 (m, 2H, *H* of CH_2), 2.29-2.35 (m, 2H, *H* of CH_2), 2.74-2.78 (m, 2H, *H* of CH_2), 2.90-2.95 (m, 2H, *H* of CH_2), 3.79 (s, 6H, 2OCH_3), 4.91(s, 2H, pyrazole-*CH*), 6.74 (d, *J* = 7.8 Hz, 4H, Ar-H), 6.86-6.90 (m, 10H, Ar-H), 7.14 (t, *J* = 7.8 Hz, 4H, Ar-H), 7.22 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.27 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.35 (t, *J* = 7.8 Hz, 2H, Ar-H) and 7.52 ppm (t, *J* = 7.8 Hz, 2H, Ar-H); ^{13}C-NMR ($CDCl_3$ at 50 °C): δ = 23.46, 29.08, 34.26 (CH_2), 55.26 (OCH_3) 59.12 (pyrazole-*CH*), 81.26 (spiro-*C*), 118.30, 121.16, 121.62, 126.60, 127.13, 128.34, 128.73, 129.09, 130.75, 131.90, 137.42, 139.39, 142.70, 144.07, 159.04 and 204.16 ppm (Ar-C and CO); MS (EI): m/z (%) 792 (M^++2, 20.97), 791 (M^++1, 60.25), 790 (M^+, 100); HRMS (EI): m/z Calcd. for $C_{52}H_{46}N_4O_4$ (M^+) 790.3513, found 790.3514.

Bis-[1`-phenyl-4`-(2,4-dimethoxyphenyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4f). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1} 1685 (CO); ^{1}H-NMR (DMSO-d_6): δ = 1.29-1.34 (m, 2H, *H* of CH_2), 1.48-1.53 (m, 2H, *H* of CH_2), 1.62-1.65 (m, 2H, *H* of CH_2), 2.30-2.35 (m, 2H, *H* of CH_2), 2.78-2.86 (m, 2H, 4*H* of CH_2), 3.69 (s, 6H, 2OCH_3), 3.81 (s, 6H, 2OCH_3), 5.20 (s, 2H, pyrazole-*CH*), 6.18 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.45 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.65-6.74 (m, 6H, Ar-H), 6.86 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.08-7.15 (m, 4H, Ar-H), 7.22 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.28 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.37 (t, *J* = 7.6 Hz, 2H, Ar-H) and 7.51 ppm (t, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ = 22.91, 29.34, 33.48 (CH_2), 50.88 (pyrazole-*CH*), 55.85, 56.06 (OCH_3), 81.25 (spiro-*C*), 98.91, 105.83, 117.17, 118.82, 121.64, , 126.98, 128.64, 129.35, 129.49, 130.88, 132.10, 138.53, 139.81, 143.53, 144.98, 158.37, 160.82 and 205.43 ppm (Ar-C and CO); MS (EI): m/z (%) 852 (M^++2, 14.15), 851 (M^++1, 41.79), 850 (M^+, 65.08); HRMS (EI): m/z Calcd. for $C_{54}H_{50}N_4O_6$ (M^+) 850.3725, found 850.3725.

Bis-[1`-phenyl-4`-(4-tolyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4g). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1} 1686 (CO); ^{1}H-NMR (CDCl3 at 50 °C): δ = 1.31-1.35 (m, 2H, *H* of CH_2), 1.48-1.52 (m, 2H, *H* of CH_2), 1.78-1.81 (m, 2H, *H* of CH_2), 2.31(s , 6H, 2CH_3), 2.34-2.39 (m, 2H, *H* of CH_2), 2.77-2.84 (m, 4H, 2*H* of CH_2), 4.78 (s, 2H, pyrazole-*CH*), 6.60 (d, *J* = 7.2 Hz, 4H, Ar-H), 6.94 (d, *J* = 7.8 Hz, 4H, Ar-H), 7.14 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.25-7.40 (m, 12H, Ar-H), 7.43 (t, *J* = 7.8 Hz, 2H, Ar-H) and 7.53 ppm (t, *J* = 7.8 Hz, 2H, Ar-H); ^{13}C-NMR (CDCl3 at 50 °C): δ = 20.58 (CH_3), 22.01, 29.15, 32.48 (CH_2), 59.53 (pyrazole-*CH*), 81.27 (spiro-*C*), 118.90, 122.21, 126.53, 127.08, 127.45, 128.07, 128.84, 129.02, 129.73, 130.43, 131.76, 136.62, 137.70, 139.17, 143.71 and 204.78 ppm (Ar-C and CO); MS (EI): m/z (%)760 (M^++2, 16.95), 759 (M^++1, 40.33), 758 (M^+, 67.18); HRMS (EI): m/z Calcd. for $C_{52}H_{46}N_4O_2$ (M^+) 758.3615, found 758.3614.

Bis-[1`-(4-chlorophenyl)-4`-phenyl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4h). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1} 1687 (CO); ^{1}H-NMR ($CDCl_3$): δ = 1.32-1.36 (m, 2H, *H* of CH_2), 1.50-1.55 (m, 2H, *H* of CH_2), 1.77-1.82 (m, 2H, *H* of CH_2), 2.32-2.39 (m, 2H, *H* of CH_2), 2.80-2.82 (m, 4H, 2*H* of CH_2), 4.75 (s, 2H, pyrazole-*CH*), 6.63 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.07 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.17 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.31-7.38 (m, 8H, Ar-H), 7.43 (t, *J* = 7.6 Hz, 4H, Ar-H) and 757-7.61 ppm (m, 4 H, Ar-H); ^{13}C-NMR (CDCl3): δ = 23.34, 29.08, 34.23 (CH_2), 59.81 (pyrazole-*CH*), 81.52 (spiro-*C*), 119.35, 126.29, 127.21, 127.64, 127.77, 128.26, 129.26, 129.51, 130.71, 132.16, 136.23, 137.06, 139.41, 141.14, 144.00 and 204.00 ppm (Ar-C and CO); MS (EI): m/z (%) 800 (M^++2, 41.25), 799 (M^++1, 31.08), 798 (M^+, 49.98); HRMS (EI): m/z Calcd. for $C_{50}H_{40}Cl_2N_4O_2$ (M^+) 798.2523, found 798.2523.

Bis-[1`,4`-di-(4-chlorophenyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4i). As yellow crystals, mp. 291–292 °C; IR (KBr): ν/cm^{-1} 1682 (CO); ^{1}H-NMR (DMSO-d_6): δ = 1.06-1.08 (m, 2H, *H* of CH_2), 1.43-1.45 (m, 2H, *H* of CH_2), 1.96-1.98 (m, 2H, *H* of CH_2), 2.26-2.30 (m, 2H, *H* of CH_2), 2.69-2.71 (m, 2H, *H* of CH_2), 2.84-2.89 (m, 2H, *H* of CH_2), 5.03 (s, 2H, pyrazole-*CH*), 6.72 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.15 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.19-7.25 (m, 4H, Ar-H), 7.31-7.41 (m, 6H, Ar-H), 7.44 (t, *J* = 7.8 Hz, 2H, Ar-H) and 7.50 ppm (d, *J* = 8.4 Hz, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ = 21.46, 28.55, 31.37 (CH_2), 58.06 (pyrazole-CH), 80.08 (spiro-C), 119.52, 121.38, 126.53, 126.77, 127.53, 128.18, 128.39, 128..87, 132.21, 132.27, 135.99, 138.17, 138.36, 142.35, 146.24 and 205.25 ppm (Ar-C and CO); MS (EI): m/z (%) 868 (M^++2, 52.28), 867 (M^++1, 22.05), 866 (M^+, 37.48); HRMS (EI): m/z Calcd. for $C_{50}H_{38}Cl_4N_4O_2$ (M^+) 866.1743, found 866.1743.

Bis-[1`-(4-chlorophenyl)-4`-(2,4-dimethoxyphenyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4j). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1} 1685 (CO); ^{1}H-NMR ($CDCl_3$): δ = 1.55-1.58 (m, 2H, *H* of CH_2), 1.76-1.80 (m, 2H, *H* of CH_2), 2.34-1.41 (m, 2H, *H* of CH_2), 2.76-2.81 (m, 2H, *H* of CH_2), 2.87-2.91 (m, 2H, *H* of CH_2), 3.09-3.13 (m, 2H, *H* of CH_2), 3.63 (s, 6H, 2OCH_3), 3.86 (s, 6H, 2OCH_3), 5.31 (s, 2H, pyrazole-*CH*), 6.27 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.34 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.47 (s, 2 H, Ar-H), 6.68 (d, *J* = 7.6 Hz, 4H, Ar-H), 7.05 (d, *J* = 8.0 Hz, 4H, Ar-H), 7.14 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.33 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.44 (t, *J* = 7.6 Hz, 2H, Ar-H) and 7.52 ppm (d, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C-NMR (CDCl3): δ = 23.60, 29.66, 34.34 (CH_2), 50.91 (pyrazole-*CH*), 55.56, 55.58 (OCH_3), 81.47 (spiro-*C*), 97.85, 104.67, 117.61, 119.14, 127.15, 127.82, 128.33, 129.02, 129.37, 130.84, 131.44, 131.86, 138.01, 140.03, 144.97, 158.16, 160.54 and 204.74 ppm (Ar-C and CO); MS (EI): m/z (%) 920 (M^++2, 55.82), 919 (M^++1, 41.98), 918 (M^+, 66.13), 887 (40.07), 799 (100), 459 (M^+/2, 9.25); HRMS (EI): m/z Calcd. for $C_{54}H_{48}Cl_2N_4O_6$ (M^+) 918.2945, found 918.2946.

Bis-[1`-(4-tolyl)-4`-phenyl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4k). As yellow crystals, mp. 274–275 °C; IR (KBr): ν/cm^{-1} 1687 (CO); ^{1}H-NMR (DMSO-d_6): δ = 0.97-1.01 (m, 2H, *H* of CH_2), 1.32-1.35 (m, 2H, *H* of CH_2), 1.59-1.62 (m, 2H, *H* of CH_2), 2.17 (s , 6H, 2CH_3), 2.24-2.28 (m, 2H, *H* of CH_2), 2.68-2.72 (m, 2H, *H* of CH_2), 2.86-2.92 (m, 2H, *H* of CH_2), 4.93 (s, 2H, pyrazole-*CH*), 6.59 (d, *J* = 8.4 Hz, 4H, Ar-H), 6.84-6.88 (m, 4H, Ar-H), 6.92 (d, *J* = 8.4 Hz, 4H, Ar-H), 7.17 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.23 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.29-7.33 (m, 8H, Ar-H) and 7.40 ppm (t, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C-NMR (DMSO-d_6): δ = 20.18 (CH_3), 21.65, 28.06, 31.88 (CH_2), 58.76 (pyrazole-*CH*), 79.32 (spiro-*C*), 118.86, 120.80, 126.82, 128.08, 128.41, 128.85, 129.11, 129.17, 130.82, 132.23, 136.47, 137.94, 138.91, 140.26, 144.00 and 205.64 ppm (Ar-C and CO); MS (EI): m/z (%)760 (M^++2, 8.55), 759 (M^++1, 30.29), 758 (M^+, 56.11), 639 (100), 379 (M^+/2, 6.77) ; HRMS (EI): m/z Calcd. for $C_{52}H_{46}N_4O_2$ (M^+) 758.3615, found 758.3614.

Bis-[1`-(4-tolyl)-4`-(4-chlorophenyl)-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] (4l). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1} 1686 (CO); ^{1}H-NMR (CDCl3): δ = 1.30-1.35 (m, 2H, *H* of CH_2), 1.53-1.57 (m, 2H, *H* of CH_2), 1.74-1.79 (m, 2H, *H* of CH_2), 2.21-2.24 (m, 2H, H of CH_2), 2.26 (s , 6H, 2CH_3), 2.36-2.43 (m, 2H, *H* of CH_2), 2.78-2.80 (m, 4H, *H* of CH_2), 4.74 (s, 2H, pyrazole-*CH*), 6.65-6.81 (m, 8H, Ar-H), 6.97 (d, *J* = 8.0 Hz, 4H, Ar-H), 7.14 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.24 (d, *J* = 8.0 Hz, 4H, Ar-H), 7.32 (t, *J* = 7.6 Hz, 2H, Ar-H) and 7.41-7.47 ppm (m, 4H, Ar-H); ^{13}C-NMR (CDCl3): δ = 20.82 (CH_3), 23.40, 29.32, 34.20 (CH_2), 58.83 (pyrazole-*CH*), 81.50 (spiro-*C*), 119.40, 122.55, 127.35, 128.58,

129.21, 130.37, 131.24, 131.78, 132.10, 133.68, 135.47, 137.87, 139.05, 140.42, 143.71 and 204.69 ppm (Ar-C and CO); MS (EI): m/z (%) 828 (M^++2, 50.78), 827 (M^++1, 36.08), 826 (M^+, 60.25), 707 (100), 413 (M^+/2, 5.23) ; HRMS (EI): m/z Calcd. for $C_{52}H_{44}Cl_2N_4O_2$ (M^+) 826.2836, found 826.2835. **Crystal Data**, $C_{52}H_{44}Cl_2N_4O_2$, M = 827.86, monoclinic, a = 13.155(2)Å, b = 14.042(2) Å, c = 13.208(2) Å, V =2124.1(6) $Å^3$, α = γ = 90°, β = 119.470(9) °, space group: $P2_1/c$ (#14), Z = 4, D_{calc} = 1.294 g cm^{-3} , No. of reflection measured 4836, θ_{max} = 54.9°, R1 = 0.0467.[34]

Bis-[1`-(4-tolyl)-4`-(2,4-dimethoxyphenyl)-1-oxo-spirobenzosuberane-2,5`-pyrazol- ine] (4m). As yellow crystals, mp. >300 °C; IR (KBr): ν/cm^{-1} 1686 (CO); ^{1}H-NMR (CDCl3): δ = 1.38-1.42 (m, 2H, *H* of CH_2), 1.51-1.54 (m, 2H, *H* of CH_2), 1.74-1.76 (m, 2H, *H* of CH_2), 2.23 (s , 6H, $2CH_3$), 2.32-2.36 (m, 2H, H of CH_2), 2.75-2.78 (m, 2H, *H* of CH_2), 2.89-2.91 (m, 2H, *H* of CH_2), 3.65 (s, 6H, $2OCH_3$), 3.85 (s, 6H, $2OCH_3$), 5.37 (s, 2H, pyrazole-*CH*), 6.31 (t, *J* = 8.4 Hz, 2H, Ar-H), 6.48 (s, 2H, Ar-H), 6.68 (d, *J* = 7.8 Hz, 4H, Ar-H), 6.91 (d, *J* = 7.8 Hz, 4H, Ar-H), 7.12 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.32 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.38-7.41 (m, 4H, Ar-H) and 7.49 ppm (d, *J* = 8.4 Hz, 2H, Ar-H); ^{13}C-NMR (CDCl3): δ = 20.55 (CH_3), 23.30, 29.47, 33.99 (CH_2), 50.42 (pyrazole-*CH*), 55.31, 55.53 (2 OCH_3) 80.99 (spiro-*C*), 97.78, 104.43, 118.37, 123.28, 126.29, 126.76, 128.57, 129.31, 129.76, 130.33, 131.27, 131.38, 138.37, 139.58, 144.37, 158.05, 160.10 and 205.30 ppm (Ar-C and CO); MS (EI): m/z (%) 880 (M^++2, 11.29), 879 (M^++1, 34.05), 878 (M^+, 53.97), 759 (100), 439 (M^+/2, 7.31), 405 (57.11) ; HRMS (EI): m/z Calcd. for $C_{56}H_{54}N_4O_6$ (M^+) 878.4038, found 878.4038.

Conclusions

A direct and efficient one-pot 1,3-dipolar cycloaddition reaction of bis-hydrazonoyl chlorides **1a-c** with 2-arylidene-1-benzosuberone derivatives **3a-g** to give a series of novel class of the bis-[1`,4`-diaryl-1-oxo-spiro-benzosuberane-2,5`-pyrazoline] derivatives **4a-m** has been developed. Ultrasonic irradiation proved to be a superior and an efficient tool for promotion of such 1,3-dipolar cycloaddition reactions using ethanol as solvent and Et_3N as a base. The cycloaddition was elucidated as regio- and stereoselective process as examined by measuring the X-ray crystallographic data of five examples of the obtained cycloadducts.

Acknowledgements

The financial support for this research work was provided by the University of Kuwait through a research grant (SC03/14). The facilities of ANALAB and SAF supported by research grants GS01/01, GS01/05, GS01/03, and GS03/08 are gratefully acknowledged.

Notes and references

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