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ORIGINAL ARTICLE

Stereoselective synthesis of diazaspiro[5.5]undecane derivatives *via* base promoted [5 + 1] double Michael addition of *N*,*N*-dimethylbarbituric acid to diaryliedene acetones

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N,*N*-Dimethylbarbituric acid
diaryliedene acetone

Abstract The nitrogen containing spiro-heterocycle is one of the privileged synthetic motif that constitutes various naturally occurring molecules and displays a broad range of pharmaceutical and biological activities. A new methodology was developed for the synthesis of 2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraones spiro-heterocyclic derivatives *via* cascade cyclization of [5 + 1] double Michael addition reaction of *N*,*N*-dimethylbarbituric acid with the derivatives of diarylidivinylketones in the presence of diethylamine at ambient temperature. The developed protocol is highly capable of furnishing diazaspiro[5.5]undecane derivatives **3a–m** in excellent yields (up to 98%), from easily accessible symmetric and non-symmetric divinylketones **2a–m**, containing aryl and heteroaryl substituents. The diazaspiro-heterocyclic structure was mainly elucidated by NMR and X-ray crystallographic techniques. The single-crystal X-ray studies revealed that, the

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cyclohexanone unit of spirocycles often prefers a chair conformation rather than twisted conformation. The intermolecular hydrogen bonding and C_{Ar}—H···π, π–π stacking interactions driving forces are mainly responsible for the crystal packing.

1. Introduction

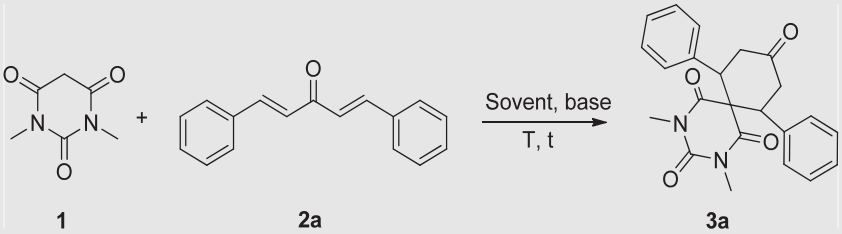
Spiro-heterocycles scaffold is one of the eye-catching building blocks in organic synthesis due to their interesting conformational features as well as structural importance in biological systems (Pradhan et al., 2006). These spirocycles moiety by and large found in various biologically active natural products and clinical pharmaceuticals (Kotha et al., 2009; Bartoli et al., 2011). Beside the biological importance, these spirocycles have been extensively used for the synthesis of novel ligands, catalysts and some special organic optoelectronics synthetic materials (Saragi et al., 2007; Xie and Zhou, 2008; Ding et al., 2009). In addition, recent literature review suggests that the diazaspiro[5.5]undecane-1,3,5,9-tetraones motif has a wide range of therapeutic and biological properties such as CNS depressant (Behera et al., 2006), anticonvulsant (Rajopadhye and Popp, 1988), potent sedative-hypnotic (Kesharwani et al., 2009), antibacterial (Goel et al., 2005) and fungicidal (Behera et al., 2009). Moreover, these types of compounds can also be used as a yellow organic pigment and as a disperse dye with strong fluorescence property as it contains barbituric acid moiety (Theford et al., 2003; Karci, 2008; Wang and Kim, 2009). Due to their unique structural features, it has become one of the prominent research areas to the chemist. In order to access those versatile motifs, there is a need of synthetic strategy for the development of highly efficient methodology. So far, various literature has been documented for the synthesis of spirocycles compounds such as benzofuran spirocyclic (Li et al., 2013, 2014), Spirooxindole (Bencivenni et al., 2009; Chen et al., 2009; Wei and Gong, 2010; Jiang et al., 2010; Chen et al., 2011), spiro cyclohexanone rhodanines (Wu et al., 2012a,b) and spirocyclic azlactones (Weber et al., 2013). Over the last few decades, organocatalysis double Michael reaction of diversified donors with dienones has also been reported for the synthesis of several spirocyclic compounds (Xu et al., 2013; Weber et al., 2013; Fusco and Lattanzi, 2011; Wang et al., 2011; Li et al., 2011; Wu et al., 2011, 2012a,b). Moreover, double Michael addition reaction of diaryldienone with some active methylene compounds has been reported by Aggarwal et al under refluxing condition (Aggarwal et al., 2014). Michael addition reaction is one of the remarkable tool for C—C bond constructing process (Michael, 1887; Jung, 1991; Barakat et al., 2013; Islam et al., 2014; Al-Majid et al., 2014). Especially, intermolecular double-Michael reactions are the most powerful tool for the synthesis of spirocyclic product from the non-cyclic starting materials. Very few literature has been reported for the synthesis of diazaspiro[5.5]undecane derivatives, in spite of their enormous biological importance. Moreover, all the previously reported synthetic methodologies have some limitations, such as long reaction times, use of catalyst, substrate scope and high temperature. Therefore, a simple, convenient, facile and efficient methodology is required for constructing nitrogen containing spiro-heterocycles. Herein, we report, very useful, robust and environmentally benign methodologies for the synthesis of spiro-heterocyclic derivatives of diazaspiro[5.5]undecane-1,3,5,9-tetraones *via* double Michael reaction of 1,5-diaryl-1,4-pentadien-3-one derivatives with active methylene compound *N*,*N*-dimethylbarbituric acid in dichloromethane at room temperature, by simply using diethyl amine as base.

2. Results and discussion

In order to find out a simple, cost-effective and sustainable synthetic strategy, we initiated our research for the synthesis of diazaspiro compounds, containing *N*,*N*-dimethylbarbiturate scaffold with the help of double Michael addition reaction of diaryliedene acetones derivatives and active methylene compound *N*,*N*-dimethylbarbituric acid in dichloromethane at ambient temperature. Previously, Aggarwal group carried out this reaction using ethylene glycol as solvent at 100 °C, but it has some shortcoming, since it requires high temperature and high boiling solvent. To overcome these drawbacks, we decided to perform the reaction at room temperature using dichloromethane, which has reduced the effort for workup and purification process. Initially, we choosed dibenzylidene acetone **2a** and *N*,*N*-dimethylbarbituric acid **1** as model substrate for the double Michael reaction using various solvent in basic medium. Aiming at screening the optimal parameters, the reaction was tested with the use of different mol% of diethylamine in several solvents such as dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), tetrahydrofuran (THF), acetonitrile and toluene. The outcomes were summarized in Table 1.

At the outset, the reaction was performed at room temperature in CH_2Cl_2 without using any base but the reaction remains unsuccessful. Then the reaction was performed in same solvent using different mol% of diethylamine and the results were shown in Table 1, entries 2–6. With the use of 10 and 50 mol% of diethylamine in DCM, no noticeable product formation was observed within 24 h (Table 1, entries 2 & 3), while with the use of 1 equiv. of diethylamine, 2,4-Dimethyl-7,11-diphenyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone **3a** (yield 33%) was obtained (Table 1, entries 2 & 3). In order to improve the yield of the reaction, diethylamine 2 equiv. and 2.5 equiv. were used successively for 16 h and 2 h at room temperature, which afforded good to excellent yield (80% and 98%) respectively (Table 1, entries 5[c] & 6). When the reaction was performed at slightly elevated temperature (40 °C), very good yield was obtained within 40–45 min reaction time (Table 1, entry 7). The reaction was further screened in different solvents such as chloroform, acetonitrile, tetrahydrofuran and toluene at room temperature. The results show that the reaction underwent in chloroform smoothly, producing excellent yield (94%) while in case of acetonitrile and tetrahydrofuran, only 70% and

Table 1 Optimization of the model reaction to form **3a** by using a double Michael addition reaction of *N*,*N*-dimethylbarbituric **1** acid with divinyl ketone **2a**.[a]



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Entry	Solvent	Temperature (t)	Time (h)	Base	Base eqv.	Yield[d] (%)
1[b]	CH_2Cl_2	rt	24	–	–	–
2	CH_2Cl_2	rt	24	$NHEt_2$	0.1	–
3	CH_2Cl_2	rt	24	$NHEt_2$	0.5	–
4[c]	CH_2Cl_2	rt	24	$NHEt_2$	1	33
5[c]	CH_2Cl_2	rt	16	$NHEt_2$	2	80
6	CH_2Cl_2	rt	2	$NHEt_2$	2.5	98
7	CH_2Cl_2	40 °C	45 min	$NHEt_2$	2.5	90
8	$CHCl_3$	rt	2	$NHEt_2$	2.5	94
9	ACN	rt	24	$NHEt_2$	2.5	60
10	THF	rt	24	$NHEt_2$	2.5	70
11[b]	Toluene	rt	24	$NHEt_2$	2.5	–
12[b]	Toluene	80 °C	24	$NHEt_2$	2.5	–
13[c]	CH_2Cl_2	rt	24	NEt_3	2.5	65
14[c]	CH_2Cl_2	rt	24	Py	2.5	60

[a] Reaction conditions: *N*,*N*-dimethylbarbituric acid (2 mmol), dibenzylidene acetone (2 mmol), different solvents, different temperature.
[b] No reaction.
[c] Reaction was incomplete.
[d] Isolated yield.

75% yields were observed (Table 1, entries 8–10). However, in toluene the reaction remains unsuccessful even at 80 °C (Table 1, entries 11 & 12). Finally, the reaction was tested again, using triethylamine and pyridine as base in DCM at room temperature, yielded moderate yield (65% and 60%) respectively (Table 1, entries 13 & 14). It is obvious that the solvent CH_2Cl_2 remains the best choice for this double Michael reaction, as it is yielding diazaspiro compound **3a** with excellent yield with the use of diethylamine at room temperature.

From the above discussion, we realized that, dichloromethane was the most practical choice for this double Michael reaction of diarylidene acetone **2a** with *N*,*N*-dimethylbarbituric acid **1**. In order to illustrate the generality of this of this reaction, the scope of substrates were extended up to various diarylidene acetone derivatives **2b–m** under the optimized reaction parameters. Twelve examples were carried out and the results were depicted in Table 2.

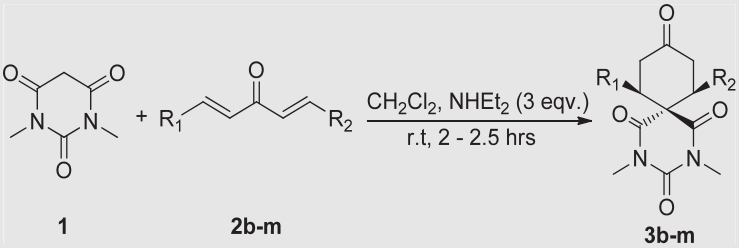
As it is evident from Table 2, that the substrates **2b–m** were reacted well under the optimized parameters and the corresponding diazaspiro products **3b–m** were obtained in excellent yield (89–98%) (Table 2, entries 1–12). Higher yields in case of all substrates signifying that the electron-withdrawing and electron-donating substituents at different positions on the aromatic ring do not have any remarkable influence on the reactivity of the reaction. However slightly lower yields were observed in case of substrates **2d** and **2e**, which could be attributed to the bulky environment of the substrate (Table 2, entries 3 & 4).

A plausible mechanism has been proposed for the double Michael addition reaction of diaryliedene acetones and *N*,*N*-dimethylbarbituric acid for the formation of diazaspiro derivatives (Fig. 1). The active methylene group of the compound **1** was activated by abstracting one of the methylene protons by diethylamine, which in turn enhance the formation of enolate form (1A). Then this enolate attacks to one of the double bonds of the diarylidene acetone **2a–m** by intermolecular Michael addition reaction, leading to the formation of intermediate (**3**) which underwent rearrangement process and gave another intermediate (**4**). Again the second active methylene proton was activated by diethylamine intermediate (**5**) which involves second intramolecular Michael addition reaction to the another double bond in a best suitable fashion so the stable spiro products **3a–m** were formed with aryl groups in the equatorial position.

The formation of diazaspiro product **3a** was confirmed exclusively by ^{1}H NMR as illustrated in Fig. 2. The ^{1}H NMR spectrum of the diazaspiro compound **3a**, shows a doublet of doublet at 2.59 & 2.63 with coupling values J = 15.36 Hz and 4.40 Hz, for the equatorial protons of C_2 and C_6 positions, while another doublet of doublet appeared at 3.99 and 4.02 with J = 14.68 Hz and 4.40 Hz due to the axial protons of C_3 and C_5 positions. On the other hand a triplet was appeared at 3.72 with J = 14.68 Hz for the axial protons of C_2 and C_6 positions (see Fig. 2).

The compounds of **3a, 3h** and **3i** were obtained as crystals by slow diffusion of diethyl ether into the solution of pure compounds **3a, 3h** and **3i** in dichloromethane at room temperature and allowed to stand for 2 days. Data were collected on a Bruker APEX-II D8 Venture area diffractometer,

Table 2 Substrate screening, cascade [5 + 1] double Michael addition[a] reaction of diarylidene acetone derivatives (**2b-m**) with *N*,*N*-dimethyl barbituric acid (**1**).



#	Diarylidene **2b–m**	R_1/R_2	*3b–m*	Yield (%)[b]
1	**2b**	*p*-CH_3Ph	**3b**	96
2	**2c**	*p*-ClPh	**3c**	97
3	**2d**	2,6-Cl_2Ph	**3d**	89
4	**2e**	2,4-Cl_2Ph	**3e**	91
5	**2f**	*p*-BrPh	**3f**	93
6	**2g**	*m*-NO_2Ph	**3g**	95
7	**2h**	*p*-CH_3OPh	**3h**	97
8	**2i**	2-Naphthayl	**3i**	96
9	**2j**	2-Thiophene	**3j**	98
10	**2k**	2-Furan	**3k**	98
11	**2l**	*m*-BrPh	**3l**	95
12	**2m**	Ph & *p*-CH_3Ph	**3m**	96

[a] Reaction conditions: *N*,*N*-dimethylbarbituric acid (**1**) (2 mmol), diarylidene acetone derivatives (**2b–m**) (2 mmol).
[b] isolated yield.

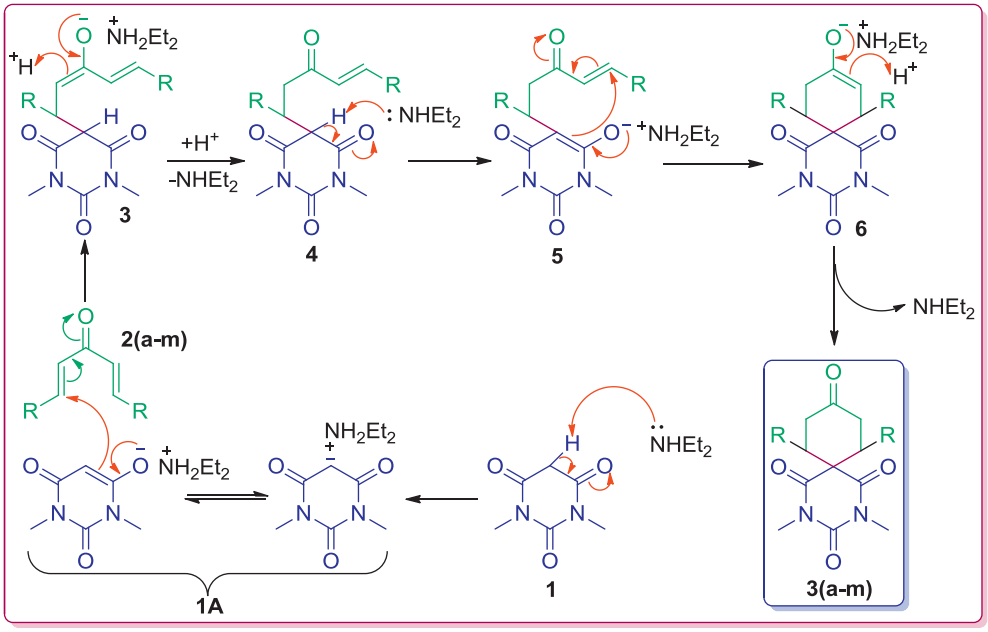


Figure 1 A possible mechanistic pathway for [5 + 1] double Michael addition of *N*,*N*-dimethylbarbituric acid to diaryliedene acetones.

equipped with graphite monochromatic Mo Kα radiation at 293 (2) K. Cell refinement and data reduction were carried out by Bruker SAINT. SHELXS-97 was used to solve structure (Sheldrick, 2008; Spek, 2009). The final refinement was carried out by full-matrix least-squares techniques with anisotropic thermal data for non-hydrogen atoms on *F2*. All the hydrogen atoms were placed in calculated positions (Table 3). The crystal structures for compounds **3a, 3h & 3i** are shown in Fig. 3.

The structures of **3a, 3h** and **3i** were confirmed by X-ray crystal structure analysis (Bruker AXS GmbH). CCDC-1007513; CCDC-1004326 and CCDC-1004327 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the

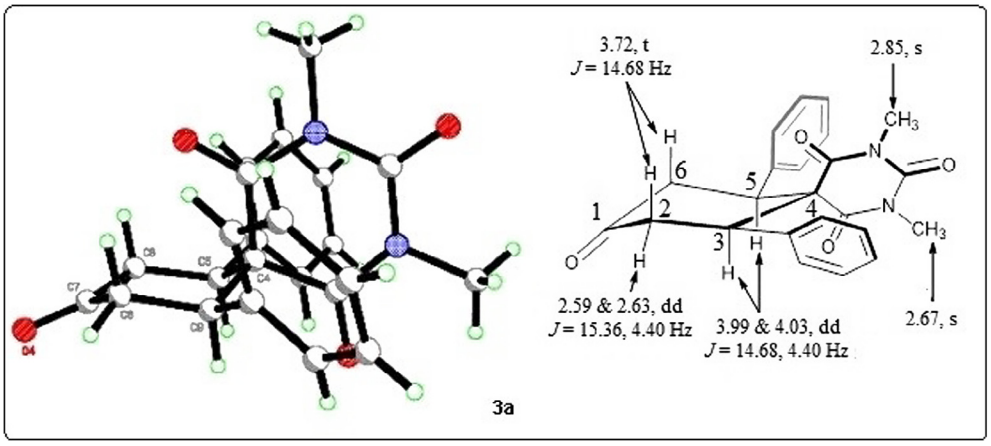


Figure 2 Schematic representation of the chair conformation of the spirocycles *Cis*-**3a.**

Table 3 The crystal and experimental data of compounds **3a, 3h** and **3i.**

	Compound **3a**	Compound **3h**	Compound **3i**
Empirical formula	$C_{23}H_{22}N_2O_4$	$C_{25}H_{25}N_2O_6$	$C_{31}H_{26}N_2O_4{\cdot}CHCl_3$
Formula weight	390.42	449.47	609.90
Temperature (K)	100	100	100
Wavelength (Mo $K\alpha$ radiation, λ)	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	$C2/c$	P1
Unit cell dimensions	a = 11.5470 (6) Å b = 14.5322 (7) Å c = 11.7043 (6) Å β = 99.3103 (15)°	a = 37.494 (2) Å b = 7.8447 (4) Å c = 15.3990 (8) Å β = 95.955 (3)°	a = 8.2784 (4) Å b = 12.7854 (7) Å c = 15.1885 (8) Å α = 108.445 (2)° β = 105.303 (2)° γ = 93.295 (2)°
Volume	1938.15(17) Å^3	4504.9 (4) Å^3	1453.37 (13) Å^3
Z	4	8	2
Density (calculated)	1.338 Mg m^{-3}	1.325 Mg m^{-3}	1.394 Mg m^{-3}
Absorption coefficient	0.09 mm^{-1}	0.10 mm^{-1}	μ = 0.36 mm^{-1}
F(000)	824	1896	632
Crystal size	0.41 × 0.29 × 0.20 mm	0.59 × 0.41 × 0.35 mm	0.35 × 0.23 × 0.321 mm
Theta range for data collection	θ_{max} = 30.6°, θ_{min} = 2.3°	θ_{max} = 30.6°, θ_{min} = 2.7°	θ_{max} = 30.6°, θ_{min} = 2.6°
Index ranges	h = −16/16 k = −20/20 l = −16/16	h = −53/53 k = −11/11 l = −22/22	h = −11/11 k = −18/18 l = −21/21
Reflections collected/unique	107,047/5461	98,664/4506	36,460/6087
Completeness to theta = 30.57°	0.999	0.998	0.999
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Goodness-of-fit on F^2	1.06	1.08	1.12

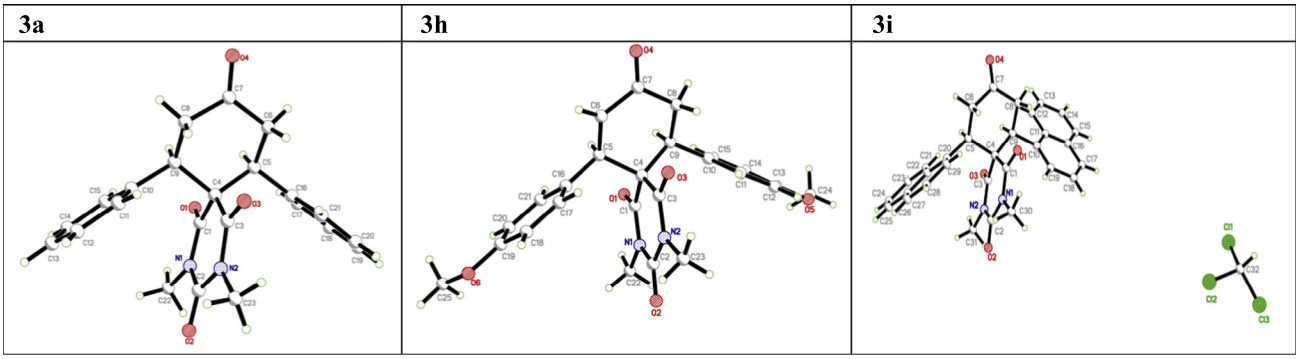


Figure 3 The ORTEP diagram of the final X-ray model of compound **3a, 3h and 3i** with displacement ellipsoids drawn at 30% probability level. H-Atoms were placed and not included in refinement.

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3. Conclusion

In conclusion, we developed a simple, highly efficient, cost economical process for the synthesis of diazaspiro compounds through cascade [5 + 1] double Michael addition reaction using diethylamine as a powerful base at room temperature. The products were isolated in its pure form with excellent yields (up to 98%). Further exploration of the substrate scope for this reaction would be investigated in our laboratory and very shortly, we will report the biological evaluations of the obtained spiro compounds, which are in progress. This methodology provides substantial improvements in the reaction time, yields as well as make ease in the workup process. We also examined the crystal structure and packing of diazaspiro compound. Further studies on expanding the application of this method and the biological evaluation of these spiro-heterocycles derivatives are in progress.

4. Experimental

4.1. General remarks

All the glassware were oven-dried before use and the reactions were conducted under an inert atmosphere. The progress of the reaction was monitored by TLC (Merck Silica Gel 60 F–254 thin layer plates). The chemicals were purchased from Aldrich, and Fluka, etc., and were used without further purification, unless otherwise stated. Petroleum ether (PE), hexane and ethyl acetate were distilled prior to use especially for column chromatography. All the major solvents were dried by using slandered drying techniques mentioned in the literature. Melting points were measured on a Gallen-kamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Jeol-400 NMR spectrometer. ^{1}H NMR (400 MHz), and ^{13}C NMR (100 MHz) were run in deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of *ppm* and *J* -coupling constants are given in *Hz*. Mass spectrometric analysis was conducted by using ESI mode on AGILENT Technologies 6410–triple quad LC/MS instrument. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer, CHN mode.

4.2. General procedure of double Michael addition reaction for the synthesis of spiro-compounds *3a–m* (*GP1*)

A solution of *N*,*N*-dimethylbarbituric acid (**1**) (2 mmol) and diarylidene acetone derivatives (**2b–m**) (2 mmol) in 10 mL of dry CH_2Cl_2 was charged into a 50 mL round bottom flask under inert atmosphere. The Et_2NH (2.5 mmol) was then added to the reaction mixture and stirred at room temperature for up to 1.5–2 h, until TLC showed complete consumption of both the reactants. After the completion of reaction, the crud product directly subjected to column chromatography using 100–200 mesh silica gel and ethyl acetate/*n*-hexane (2:8, v/v) as an eluent to afford the pure products **3a–m**. The solid products were further crystallized from a mixture of $CHCl_3$/*n*-heptane.

4.2.1. 2,4-Dimethyl-7,11-diphenyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (*3a*) (Aggarwal et al., 2014)

Diarylidene acetone **2a** (468.2 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3a** (765 mg, 1.96 mmol, 98%); m.p. 125–127 (150–152) °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.59 & 2.63 (dd, 2H, J = 15.36 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.85 (s, 3H, —NC**H**$_3$), 3.01 (s, 3H, —NC**H**$_3$), 3.72 (t, 2H, J = 14.68 Hz, C**H**$_{2(a)}$), 3.99 & 4.03 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**), 7.06–7.08 (m, 4H, Ar—**H**), 7.21–7.26 (m, 6H, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.98, 28.39, 42.99, 50.55, 60.95, 127.56, 128.69, 128.94, 137.17, 149.70, 169.04, 170.71, 208.29; IR (KBr, cm^{-1}) ν_{max} = 2959, 2925, 1716, 1675, 1484, 1422, 1381, 1125, 755, 706; [Anal. Calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17; Found: C, 70.69; H, 5.65; N, 7.01]; LC/MS (ESI, m/z): [M$^+$], found 390.21, $C_{23}H_{22}N_2O_4$ requires 390.16.

The structure of **3a** was unambiguously deduced by single-crystal X-ray diffraction structure analysis (Bruker AXS GmbH). CCDC-1007513 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A colorless crystal suitable for X-ray analysis was obtained from recrystallization of the compound from DCM/Et_2O at room temperature after 2 days.

4.2.2. 2,4-Dimethyl-7,11-di-p-tolyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (*3b*) (Aggarwal et al., 2014)

Diarylidene acetone **2b** (524.3 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3b** (803 mg, 1.92 mmol, 96%); m.p. 122–124 (159–160) °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, C**H**$_3$), 2.55 & 2.58 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.87 (s, 3H, —NC**H**$_3$), 3.01 (s, 3H, —NC**H**$_3$), 3.68 (t, 2H, J = 14.68 Hz, C**H**$_{2(a)}$), 3.94 & 3.98 (dd, 2H, J = 13.92 Hz, 4.40 Hz, C**H**), 6.93 (d, 4H, J = 8.04 Hz, Ar—**H**), 7.01 (d, 4H, J = 8.04 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.13 27.94, 28.41, 43.15, 50.19, 61.08, 127.39, 129.58, 134.19, 138.39, 149.65, 169.29, 170.88, 208.63; IR (KBr, cm^{-1}) ν_{max} = 3019, 2970, 1740, 1678, 1441, 1370, 1221, 902, 672, 520; [Anal. Calcd. for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69; Found: C, 71.58; H, 6.37; N, 6.81]; LC/MS (ESI, m/z): [M$^+$], found 418.3, $C_{25}H_{26}N_2O_4$ requires 418.19.

4.2.3. 7,11-Bis(4-chlorophenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (*3c*) (Ramachary et al., 2006)

Diarylidene acetone **2c** (604.1 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3c** (889 mg, 1.92 mmol, 97%); m.p. 211–213 (224–226) °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 & 2.58 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.89 (s, 3H, —NC**H**$_3$), 3.04 (s, 3H, —NC**H**$_3$), 3.64 (t, 2H, J = 14.68 Hz, C**H**$_{2(a)}$), 3.95 & 3.98 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**), 6.99 (d, 4H, J = 8.80 Hz, Ar—**H**), 7.22 (d, 4H, J = 8.80 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.49, 28.68, 42.94,

49.87, 60.58, 128.86, 129.01, 135.25, 135.52, 149.41, 168.75, 170.44, 207.20; IR (KBr, cm^{-1}) ν_{max} = 3015, 2970, 1740, 1678, 1437, 1369, 1218, 904, 672, 521; [Anal. Calcd. for $C_{23}H_{20}Cl_2N_2O_4$: C, 60.14; H, 4.39; N, 6.10; Found: C, 59.97; H, 4.46; N, 6.19]; LC/MS (ESI, *m/z*): [M^+], found 458.1, $C_{23}H_{20}Cl_2N_2O_4$ requires 458.08.

*4.2.4. 7,11-Bis(2,6-dichlorophenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3d**)*

Diarylidene acetone **2d** (734 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3d** (936 mg, 1.78 mmol, 89%); m.p. 149–151 (3e_sh104) °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.58 & 2.62 (dd, 2H, *J* = 16.12 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.93 (s, 3H, —NC**H**$_3$), 3.26 (s, 3H, —NC**H**$_3$), 3.42 (t, 2H, *J* = 15.40 Hz, C**H**$_{2(a)}$), 4.67 & 4.71 (dd, 2H, *J* = 13.92 Hz, 4.40 Hz, C**H**), 7.04 (d, 2H, *J* = 8.80 Hz, Ar—**H**), 7.15 & 7017 (dd, 2H, *J* = 8.76 Hz, 2.20 Hz, Ar—**H**), 7.38 (d, 2H, *J* = 2.20 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.51, 29.10, 43.55, 45.20, 57.36, 128.28, 130.55, 133.99, 134.98, 149.55, 167.90, 169.91, 205.63; IR (KBr, cm^{-1}) ν_{max} = 3015, 2970, 2030, 1977, 1722, 1776, 1585, 1470, 1446, 1376, 1223, 1106, 1050, 528, 751, 521, 469; [Anal. Calcd. for $C_{23}H_{18}Cl_4N_2O_4$: C, 52.30; H, 3.43; N, 5.30; Found: C, 52.41; H, 3.45; N, 5.37]; LC/MS (ESI, *m/z*): [M^+], found 526.10.1, $C_{23}H_{18}Cl_4N_2O_4$ requires 526.00.

*4.2.5. 7,11-Bis(2,4-dichlorophenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3e**)*

Diarylidene acetone **2e** (734 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3e** (957 mg, 1.82 mmol, 91%); m.p. 185–187 (3d_sh105) °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 & 2.61 (dd, 2H, *J* = 16.12 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.96 (s, 3H, —NC**H**$_3$), 3.26 (s, 3H, —NC**H**$_3$), 3.42 (t, 2H, *J* = 15.40 Hz, C**H**$_{2(a)}$), 4.67 & 4.71 (dd, 2H, *J* = 15.40 Hz, 4.40 Hz, C**H**), 7.11–7.17 (m, 2H, Ar—**H**), 7.21 (s, 2H, Ar—**H**), 7.11–7.38 (m, 2H, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.70, 29.14, 43.57, 45.24, 57.36, 127.75, 129.86, 130.50, 131.91, 133.02, 134.00, 149.55, 169.43, 169.91, 205.60; IR (KBr, cm^{-1}) ν_{max} = 2920, 1718, 1673, 1444, 1375, 1108, 1045, 828, 747, 465; [Anal. Calcd. for $C_{23}H_{18}Cl_4N_2O_4$: C, 52.30; H, 3.43; N, 5.30; Found: C, 52.41; H, 3.45; N, 5.37]; LC/MS (ESI, *m/z*): [M^+], found 526.10.1, $C_{23}H_{18}Cl_4N_2O_4$ requires 526.00.

*4.2.6. 7,11-Bis(4-bromophenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3f**) (Aggarwal et al., 2014)*

Diarylidene acetone **2f** (780 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3f** (1.0 g, 1.86 mmol, 93%); m.p. 205–207 (153–154) °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 & 2.58 (dd, 2H, *J* = 14.68 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.90 (s, 3H, —NC**H**$_3$), 3.02 (s, 3H, —NC**H**$_3$), 3.59 (t, 2H, *J* = 14.68 Hz, C**H**$_{2(a)}$), 3.94 & 3.97 (dd, 2H, *J* = 14.68 Hz, 4.40 Hz, C**H**), 6.92 (d, 4H, *J* = 8.80 Hz, Ar—**H**), 7.37(d, 4H, *J* = 8.80 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.16, 28.59, 42.82, 49.95, 60.40, 122.90, 129.25, 129.86, 132.22, 132.42, 149.90, 169.53, 170.48, 207.15; IR (KBr, cm^{-1}) ν_{max} = 3020, 1712, 1675, 1640, 1415, 1376, 1284, 1177, 1067, 979, 806, 547, 443; [Anal. Calcd. for $C_{23}H_{20}Br_2N_2O_4$: C, 50.39; H, 3.68; N, 5.11; Found: C, 50.51; H, 3.73; N, 5.17]; LC/MS (ESI, *m/z*): [M^+], found 546.11, $C_{23}H_{20}Br_2N_2O_4$ requires 545.98.

*4.2.7. 2,4-Dimethyl-7,11-bis(3-nitrophenyl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3g**)*

Diarylidene acetone **2g** (648 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3g** (912 mg, 1.9 mmol, 95%); m.p. 232–234 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.66 & 2.69 (dd, 2H, *J* = 15.40 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.87 (s, 3H, —NC**H**$_3$), 3.06 (s, 3H, —NC**H**$_3$), 3.75 (t, 2H, *J* = 14.68 Hz, C**H**$_{2(a)}$), 4.14 & 4.18 (dd, 2H, *J* = 13.92 Hz, 4.40 Hz, C**H**), 7.42–7.51 (m, 4H, Ar—**H**), 7.91(s, 2H, Ar—**H**), 8.13 (d, 2H, *J* = 8.04 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.36, 28.71, 42.63, 49.98, 60.09, 122.40, 124.01, 130.28, 133.95, 138.95, 148.64, 168.26, 169.84, 205.46; IR (KBr, cm^{-1}) ν_{max} = 2953, 1715, 1673, 1527, 1420, 1381, 901, 808, 731, 681, 451; [Anal. Calcd. for $C_{23}H_{20}N_4O_8$: C, 57.50; H, 4.20; N, 11.66: Found: C, 57.56; H, 4.32; N, 11.43]; LC/MS (ESI, *m/z*): [M^+], found 480.03, $C_{23}H_{20}N_4O_8$ requires 480.13.

*4.2.8. 7,11-Bis(4-methoxyphenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3h**)*

Diarylidene acetone **2h** (588 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3h** (873 mg, 1.94 mmol, 97%); m.p. 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 & 2.56 (dd, 2H, *J* = 14.68 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.88 (s, 3H, —NC**H**$_3$), 3.01 (s, 3H, —NC**H**$_3$), 3.68 (t, 2H, *J* = 14.68 Hz, C**H**$_{2(a)}$), 3.72 (s, 3H, OC**H**$_3$), 3.91 & 3.94 (dd, 2H, *J* = 13.92 Hz, 4.40 Hz, C**H**), 6.73 (d, 4H, *J* = 8.80 Hz, Ar—**H**), 6.96 (d, 4H, *J* = 8.80 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.01, 28.45, 43.29, 49.73, 55.26, 61.39, 114.17, 128.64, 129.21, 149.98, 159.51, 169.25, 171.79, 208.54; IR (KBr, cm^{-1}) ν_{max} = 2957, 2838, 1713, 1670, 1609, 1510, 1449, 1420, 1248, 1031, 831, 729, 530, 452; [Anal. Calcd. for $C_{25}H_{26}N_2O_6$: C, 66.65; H, 5.82; N, 6.22; Found: C, 66.81; H, 5.71; N, 6.34]; LC/MS (ESI, *m/z*): [M^+], found 450.15, $C_{25}H_{26}N_2O_6$ requires 450.18.

The structure of **3a** was unambiguously deduced by single-crystal X-ray diffraction structure analysis (Bruker AXS GmbH). CCDC-1004326 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A colorless crystal suitable for X-ray analysis was obtained from recrystallization of the compound from DCM/Et_2O at room temperature after 2 days.

*4.2.9. 2,4-Dimethyl-7,11-di(naphthalen-1-yl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3i**)*

Diarylidene acetone **2i** (668 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3i** (941 mg, 1.92 mmol, 96%); m.p. 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.98 (s, 3H, —NC**H**$_3$), 2.75 & 2.79 (dd, 2H, *J* = 15.4 Hz, 4.40 Hz, C**H**$_{2(e)}$), 3.22 (s, 3H, —NC**H**$_3$), 3.89 (t, 2H, *J* = 15.04 Hz, C**H**$_{2(a)}$), 5.11 & 5.14 (dd, 2H, *J* = 13.92 Hz, 4.40 Hz, C**H**), 7.33–7.39 (m, 4H, Ar—**H**), 7.47 (t, 2H, *J* = 8.04 Hz, Ar—**H**), 7.57 (t, 2H, *J* = 8.04 Hz, Ar—**H**), 7.73 & 7.74 (dd, 2H,

J = 7.56 Hz, 2.40 Hz, Ar—**H**), 7.80 (d, 2H, J = 8.08 Hz, Ar—**H**), 8.22 (d, 2H, J = 8.80 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.03, 28.32, 44.37, 44.86, 59.34, 123.16, 124.20, 124.95, 126.19, 126.74, 128.94, 129.23, 130.91, 134.05, 134.22, 149.61, 169.47, 170.38, 208.33; IR (KBr, cm^{-1}) ν_{max} = 3049, 2919, 1711, 1666, 1421, 1374, 1266, 1241, 1018, 773, 467; [Anal. Calcd. for $C_{31}H_{26}N_2O_4$: C, 75.90; H, 5.34; N, 5.71; Found: C, 76.13; H, 5.41; N, 5.83]; LC/MS (ESI, m/z): [M^+], found 490.23, $C_{31}H_{26}N_2O_4$ requires 490.19.

The structure of **3i** was unambiguously deduced by single-crystal X-ray diffraction structure analysis (Bruker AXS GmbH). CCDC-1004327 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A colorless crystal suitable for X-ray analysis was obtained from recrystallization of the compound from DCM/Et_2O at room temperature after 2 days.

*4.2.10. 2,4-Dimethyl-7,11-di(thiophen-2-yl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3j**)*

Diarylidene acetone **2j** (520 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3j** (788 mg, 1.96 mmol, 98%); m.p. 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.80 & 2.83 (dd, 2H, J = 15.4 Hz, 4.40 Hz, C**H**$_{2(e)}$), 3.11 (s, 3H, —NC**H**$_3$), 3.14 (s, 3H, —NC**H**$_3$), 3.66 (t, 2H, J = 14.64 Hz, C**H**$_{2(a)}$), 4.34 & 4.37 (dd, 2H, J = 13.92 Hz, 4.40 Hz, C**H**), 6.84 (d, 2H, J = 3.72 Hz, Ar—**H**), 6.93–6.95 (m, 2H, Ar—**H**), 7.23 (d, 2H, J = 5.12 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.19, 28.61, 44.16, 45.44, 61.50, 125.48, 125.87, 126.96, 139.84, 149.83, 168.60, 170.90, 205.77; IR (KBr, cm^{-1}) ν_{max} = 2959, 2921, 1715, 1668, 1420, 1373, 1260, 1036, 799, 702, 501, 444; [Anal. Calcd. for $C_{19}H_{18}N_2O_4S_2$: C, 56.70; H, 4.51; N, 6.96; Found: C, 56.76; H, 4.43; N, 7.03]; LC/MS (ESI, m/z): [M^+], found 402.11, $C_{19}H_{18}N_2O_4S_2$ requires 402.07.

*4.2.11. 7,11-Di(furan-2-yl)-2,4-dimethyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3k**)*

Diarylidene acetone **2k** (456 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3k** (725 mg, 1.96 mmol, 98%); m.p. 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.67 & 2.71 (dd, 2H, J = 15.40 Hz, 4.40 Hz, C**H**$_{2(e)}$), 3.08 (s, 3H, —NC**H**$_3$), 3.10 (s, 3H, —NC**H**$_3$), 3.49 (t, 2H, J = 14.68 Hz, C**H**$_{2(a)}$), 4.08 & 4.11 (dd, 2H, J = 13.96 Hz, 4.40 Hz, C**H**), 6.05 (d, 2H, J = 3.64 Hz, Ar—**H**), 6.25–6.26 (m, 2H, Ar—**H**), 7.23 (d, 2H, J = 1.40 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.18, 28.80, 40.90, 43.32, 57.09, 107.39, 110.56, 142.56, 151.20, 151.32, 168.01, 170.75, 206.10; IR (KBr, cm^{-1}) ν_{max} = 3115, 1959, 1721, 1670, 1446, 1420, 1377, 1011, 922, 738, 465; [Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56; Found: C, 61.49; H, 5.11; N, 7.43]; LC/MS (ESI, m/z): [M^+], found 370.18, $C_{19}H_{18}N_2O_6$ requires 370.12.

*4.2.12. 7,11-Bis(3-bromophenyl)-2,4-dimethyl-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3l**)*

Diarylidene acetone **2l** (780 mg, 2 mmol) reacted with compound **1** (312.1 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3l** (1037 mg, 1.90 mmol, 95%); m.p. 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 & 2.61 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**$_{2(e)}$), 2.91 (s, 3H, —NC**H**$_3$), 3.06 (s, 3H, —NC**H**$_3$), 3.64 (t, 2H, J = 14.68 Hz, C**H**$_{2(a)}$), 3.92 & 3.96 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**), 6.98 (d, 2H, J = 8.08 Hz, Ar—**H**), 7.11 (t, 2H, J = 8.08 Hz, Ar—**H**), 7.22, (s, 2H, Ar—**H**), 7.37 (d, 2H, J = 7.36 Hz, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.09, 28.57, 42.67, 50.01, 60.52, 123.11, 126.25, 130.53, 130.69, 131.97, 139.22, 149.44, 168.66, 170.29, 206.89; IR (KBr, cm^{-1}) ν_{max} = 2959, 2921, 1710, 1667, 1423, 1349, 1285, 1256, 1070, 787, 749, 695, 443; [Anal. Calcd. for $C_{23}H_{20}Br_2N_2O_4$: C, 50.39; H, 3.68; N, 5.11; Found: C, 50.51; H, 3.73; N, 5.17]; LC/MS (ESI, m/z): [M^+], found 546.11, $C_{23}H_{20}Br_2N_2O_4$ requires 545.98.

*4.2.13. 2,4-Dimethyl-7-phenyl-11-(p-tolyl)-2,4-diazaspiro[5.5]undecane-1,3,5,9-tetraone (**3m**)*

Diarylidene acetone **2m** (496 mg, 2 mmol) reacted with compound **1** (312 mg, 2 mmol) according to **GP1** yielded white solid spiro-product **3m** (776 mg, 1.92 mmol, 96%); m.p. 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, C**H**$_3$), 2.55 & 2.59 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**$_{2(e)}$), 3.87 (s, 3H, —NC**H**$_3$), 3.01 (s, 3H, —NC**H**$_3$), 3.72 (t, 2H, J = 14.68 Hz, C**H**$_{2(a)}$), 3.94 & 3.98 (dd, 2H, J = 14.68 Hz, 4.40 Hz, C**H**), 6.92 (d, 4H, J = 8.08 Hz, Ar—**H**), 7.01 (d, 4H, J = 8.08 Hz, Ar—**H**), 7.21–7.25 (m, 1H, Ar—**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.12, 27.97, 28.40, 44.17, 43.15, 50.19, 61.8, 127.39, 128.92, 129.57, 134.18, 138.39, 149.98, 168.18, 170.89, 208.66; IR (KBr, cm^{-1}) ν_{max} = 29.57, 2924, 1717, 1672, 1446, 1419, 1377, 1285, 814, 730, 560, 509; [Anal. Calcd. for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93; Found: C, 71.36; H, 6.07; N, 7.01]; LC/MS (ESI, m/z): [M^+], found 404.11, $C_{24}H_{24}N_2O_4$ requires 404.17.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2015.03.007.

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