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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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-diaza-spiro[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 diaryl-divinylketones 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...
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 diazaspion[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 benzo furan spirocyclic (Li et al., 2013, 2014), Spiro oxindole (Benvenitti et al., 2009; Chen et al., 2009; Wei and Gong, 2010; Jiang et al., 2010; Chen et al., 2011), spiro cyclohexanone rhodanes (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 dienes 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 compound 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, intramolecular 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 diazaspion[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 diazaspion[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 diazaspion compounds, containing N,N-dimethylbarbiturate scaffold with the help of double Michael addition reaction of diaryldiene 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 chose 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 (CH2Cl2), chloroform (CHCl3), tetrahydrofuran (THF), acetonitrile and toluene. The outcomes were summarized in Table 1.

At the outset, the reaction was performed at room temperature in CH2Cl2 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-diazaspion[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 & 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (t)</th>
<th>Time (h)</th>
<th>Base</th>
<th>Base eqv.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>CH2Cl2</td>
<td>rt</td>
<td>24</td>
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<td>–</td>
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<td>2</td>
<td>CH2Cl2</td>
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<td>24</td>
<td>NHEt2</td>
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<td>–</td>
</tr>
<tr>
<td>3</td>
<td>CH2Cl2</td>
<td>rt</td>
<td>24</td>
<td>NHEt2</td>
<td>0.5</td>
<td>–</td>
</tr>
<tr>
<td>4c</td>
<td>CH2Cl2</td>
<td>rt</td>
<td>24</td>
<td>NHEt2</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
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<td>rt</td>
<td>16</td>
<td>NHEt2</td>
<td>2</td>
<td>80</td>
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<tr>
<td>6</td>
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<td>rt</td>
<td>2</td>
<td>NHEt2</td>
<td>2.5</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>CH2Cl2</td>
<td>40 °C</td>
<td>45 min</td>
<td>NHEt2</td>
<td>2.5</td>
<td>90</td>
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<td>rt</td>
<td>2</td>
<td>NHEt2</td>
<td>2.5</td>
<td>94</td>
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<tr>
<td>9</td>
<td>ACN</td>
<td>rt</td>
<td>24</td>
<td>NHEt2</td>
<td>2.5</td>
<td>60</td>
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<tr>
<td>10</td>
<td>THF</td>
<td>rt</td>
<td>24</td>
<td>NHEt2</td>
<td>2.5</td>
<td>70</td>
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<td>11b</td>
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<td>NHEt2</td>
<td>2.5</td>
<td>–</td>
</tr>
<tr>
<td>12b</td>
<td>Toluene</td>
<td>80 °C</td>
<td>24</td>
<td>NHEt2</td>
<td>2.5</td>
<td>–</td>
</tr>
<tr>
<td>13a</td>
<td>CH2Cl2</td>
<td>rt</td>
<td>24</td>
<td>NHEt2</td>
<td>2.5</td>
<td>65</td>
</tr>
<tr>
<td>14c</td>
<td>CH2Cl2</td>
<td>rt</td>
<td>24</td>
<td>Py</td>
<td>2.5</td>
<td>60</td>
</tr>
</tbody>
</table>

* Reaction conditions: N,N-dimethylbarbituric acid (2 mmol), dibenzylidene acetone (2 mmol), different solvents, different temperature.
* No reaction.
* Reaction was incomplete.
* 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 CH2Cl2 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 diarylidene 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 1H NMR as illustrated in Fig. 2. The 1H 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 C2 and C6 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 C3 and C5 positions. On the other hand a triplet was appeared at 3.72 with J = 14.68 Hz for the axial protons of C2 and C6 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,
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

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

<table>
<thead>
<tr>
<th>#</th>
<th>Diaryliden 2b–m</th>
<th>R1 / R2</th>
<th>3b–m</th>
<th>Yield (%)b</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>p-CH3Ph</td>
<td>3b</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>p-ClPh</td>
<td>3e</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>2,6-Cl2Ph</td>
<td>3d</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>2,4-Cl2Ph</td>
<td>3e</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>p-BrPh</td>
<td>3f</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>m-NO2Ph</td>
<td>3g</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td>p-CH3OPh</td>
<td>3h</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td>2-Naphthyl</td>
<td>3i</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>2j</td>
<td>2-Thiophene</td>
<td>3j</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>2k</td>
<td>2-Furan</td>
<td>3k</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>2l</td>
<td>m-BrPh</td>
<td>3l</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>2m</td>
<td>Ph &amp; p-CH3Ph</td>
<td>3m</td>
<td>96</td>
</tr>
</tbody>
</table>

a Reaction conditions: N,N-dimethylbarbituric acid (1) (2 mmol), diaryliden 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 diaryliden acetones.
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.

<table>
<thead>
<tr>
<th></th>
<th>Compound 3a</th>
<th>Compound 3h</th>
<th>Compound 3i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C23H22N2O4</td>
<td>C25H25N2O6</td>
<td>C31H26N2O4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>390.42</td>
<td>449.47</td>
<td>609.90</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Wavelength (Mo Kα radiation, λ)</td>
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<td>0.71073 Å</td>
<td>0.71073 Å</td>
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<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/n</td>
<td>C2/c</td>
<td>P1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 11.5470 (6) Å</td>
<td>a = 37.494 (2) Å</td>
<td>a = 8.2784 (4) Å</td>
</tr>
<tr>
<td></td>
<td>b = 14.5322 (7) Å</td>
<td>b = 7.8447 (4) Å</td>
<td>b = 12.7854 (7) Å</td>
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<tr>
<td></td>
<td>c = 11.7043 (6) Å</td>
<td>c = 15.3990 (8) Å</td>
<td>c = 15.1885 (8) Å</td>
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<tr>
<td></td>
<td>β = 99.3103 (15)°</td>
<td>β = 95.955 (3)°</td>
<td>α = 108.445 (2)°</td>
</tr>
<tr>
<td>Volume</td>
<td>1938.15(17) Å</td>
<td>4504.9 (4) Å</td>
<td>1453.37 (13) Å</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.338 Mg m−3</td>
<td>1.325 Mg m−3</td>
<td>1.394 Mg m−3</td>
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<tr>
<td>Absorption coefficient</td>
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<td>0.10 mm−1</td>
<td>μ = 0.36 mm−1</td>
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<tr>
<td>F(000)</td>
<td>824</td>
<td>1896</td>
<td>632</td>
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<tr>
<td>Crystal size</td>
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<td>0.59 × 0.41 × 0.35 mm</td>
<td>0.35 × 0.23 × 0.321 mm</td>
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<td>Theta range for data collection</td>
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<td>θmax = 30.6°, θmin = 2.7°</td>
<td>θmax = 30.6°, θmin = 2.6°</td>
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<tr>
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<td>Completeness to theta = 30.57°</td>
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<td>Absorption correction</td>
<td>Multi-scan</td>
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</tr>
<tr>
<td>Goodness-of-fit on F2</td>
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<td>1.08</td>
<td>1.12</td>
</tr>
</tbody>
</table>

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.
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 yield, 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). All the major solvents were dried by using slandered drying techniques mentioned in the literature. Recrystallization of the compound from DCM/Et2O at room temperature after 2 days.

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). All the major solvents were dried by using slandered drying techniques mentioned in the literature. Recrystallization of the compound from DCM/Et2O at room temperature after 2 days.

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 CH2Cl2 was charged into a 50 mL round bottom flask under inert atmosphere. The Et2NH (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 the reaction, the crude 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 CHCl3/n-heptane.

4.2.1. 2,4-Dimethyl-7,7,11-diphenyl-2,4-diazaspiro[5.5]jundecane-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; 1H NMR (400 MHz, CDCl3) δ: 2.59 & 2.63 (dd, 2H, J = 15.36 Hz, 4.40 Hz, CH2a), 2.85 (s, 3H, −NCH3), 3.01 (s, 3H, −NCH3), 3.72 (t, 2H, J = 14.68 Hz, CH2b), 3.99 & 4.03 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH3), 7.06–7.08 (m, 4H, Ar=H), 7.21–7.26 (m, 6H, Ar=H); 13C NMR (100 MHz, CDCl3) δ: 27.98, 28.39, 42.99, 50.55, 60.95, 125.76, 128.69, 128.94, 137.17, 149.70, 169.04, 170.71, 208.29; IR (KBr, cm−1) νmax = 2959, 2925, 1716, 1675, 1484, 1422, 1381, 1125, 755, 706; [Anal. Calcd. for C25H22N2O4: 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+H]+, found 390.21, C25H22N2O4 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/Et2O at room temperature after 2 days.

4.2.2. 2,4-Dimethyl-7,11-di-p-tolyld-2,4- diazaspiro[5.5]jundecane-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; 1H NMR (400 MHz, CDCl3) δ: 2.25 (s, 3H, CH3), 2.55 & 2.58 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH2b), 2.87 (s, 3H, −NCH3), 3.01 (s, 3H, −NCH3), 3.68 (t, 2H, J = 14.68 Hz, CH2b), 3.94 & 3.98 (dd, 2H, J = 13.92 Hz, 4.40 Hz, CH3), 6.93 (d, 4H, J = 8.04 Hz, Ar=H), 7.01 (d, 4H, J = 8.04 Hz, Ar=H); 13C NMR (100 MHz, CDCl3) 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) νmax = 3019, 2970, 1740, 1678, 1441, 1370, 1221, 902, 672, 520; [Anal. Calcd. for C25H22N2O4: 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+H]+, found 418.3, C25H22N2O4 requires 418.19.

4.2.3. 7,11-Bis(4-chlorophenyl)-2,4-dimethyl-2,4- diazaspiro[5.5]jundecane-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 (889.2 mg, 1.92 mmol, 97%); m.p. 211–213 (224–226) °C; 1H NMR (400 MHz, CDCl3) δ: 2.55 & 2.58 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH2b), 2.89 (s, 3H, −NCH3), 3.04 (s, 3H, −NCH3), 3.64 (t, 2H, J = 14.68 Hz, CH2b), 3.95 & 3.98 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH3), 6.99 (d, 4H, J = 8.80 Hz, Ar=H), 7.22 (d, 4H, J = 8.80 Hz, Ar=H); 13C NMR (100 MHz, CDCl3) δ: 28.49, 28.68, 42.94,
Diarylidene acetone 2f (780 mg, 2 mmol) reacted with compound 1 (312.1 mg, 2 mmol) according to GPl yielded white solid spiro-product 3f (941 mg, 1.92 mmol, 96%); m.p. 205–207 °C; 1H NMR (400 MHz, CDCl3) δ: 2.55 & 2.58 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH3(2a)); 2.90 (3H, −NCH3); 3.02 (s, 3H, −NCH3); 3.59 (t, 2H, J = 14.68 Hz, CH2(3a)); 3.94 & 3.97 (dd, 2H, J = 14.40 Hz, 4.40 Hz, CH); 6.92 (4H, J = 8.80 Hz, Ar–H); 13C NMR (100 MHz, CDCl3) 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, 149.63, 169.91, 205.60; IR (KBr, cm−1) v max = 2920, 1718, 1673, 1444, 1375, 1008, 1045, 828, 747, 465; [Anal. Calcd. for C23H20Br2N2O4: 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+] 545.98.

4.2.7. 2,4-Dimethyl-7,11-bis(3-nitrophenoxy)-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraene (3g)

Diarylidene acetone 2g (648 mg, 2 mmol) reacted with compound 1 (312.1 mg, 2 mmol) according to GPl yielded white solid spiro-product 3g (912 mg, 1.9 mmol, 95%); m.p. 232–234 °C; 1H NMR (400 MHz, CDCl3) δ: 2.66 & 2.69 (dd, 2H, J = 15.40 Hz, 4.40 Hz, CH3(26)); 2.87 (s, 3H, −NCH3); 3.06 (s, 3H, −NCH3); 3.75 (t, 2H, J = 14.68 Hz, CH3(17)); 4.14 & 4.18 (dd, 2H, J = 13.92 Hz, 4.40 Hz, CH), 7.42–7.51 (m, 4H, Ar–H); 7.91 (s, 2H, Ar–H), 8.13 (d, 2H, J = 8.04 Hz, Ar–H); 13C NMR (100 MHz, CDCl3) δ: 28.36, 28.71, 42.63, 49.98, 60.09, 122.40, 124.01, 130.28, 133.95, 138.95, 146.84, 168.26, 169.84, 205.46; IR (KBr, cm−1) v max = 2953, 2715, 1673, 1527, 1420, 1381, 901, 808, 731, 681, 451; [Anal. Calcd. for C23H20Br2N2O4: C, 50.57; H, 4.20; N, 11.66; Found: C, 50.56; H, 4.32; N, 11.43]; LC/MS (ESI, m/z): [M+] 480.13, C23H19BrN3O4 requires 480.13.

4.2.8. 7,11-Bis(4-methoxyphenoxy)-2,4-dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraene (3h)

Diarylidene acetone 2h (588 mg, 2 mmol) reacted with compound 1 (312.1 mg, 2 mmol) according to GPl yielded white solid spiro-product 3h (873 mg, 1.94 mmol, 97%); m.p. 131–133 °C; 1H NMR (400 MHz, CDCl3) δ: 2.53 & 2.56 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH3(26)); 2.88 (s, 3H, −NCH3); 3.01 (s, 3H, −NCH3); 3.68 (t, 2H, J = 14.68 Hz, CH3(17)); 3.72 (s, 3H, OCH3); 3.91 & 3.94 (dd, 2H, J = 13.92 Hz, 4.40 Hz, CH), 6.73 (d, 4H, J = 8.80 Hz, Ar–H); 6.96 (d, 4H, J = 8.80 Hz, Ar–H); 13C NMR (100 MHz, CDCl3) δ: 28.01, 28.45, 43.29, 49.73, 55.26, 61.39, 114.17, 128.64, 129.21, 149.98, 159.51, 162.25, 171.79, 208.54; IR (KBr, cm−1) v max = 2957, 2838, 1713, 1670, 1690, 1510, 1449, 1420, 1248, 1031, 831, 729, 530, 452; [Anal. Calcd. for C23H18Br2N2O4: 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+] 450.18, C23H19BrN3O4 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 colourless crystal suitable for X-ray analysis was obtained from recrystallization of the compound from DCM/Et2O at room temperature after 2 days.

4.2.9. 2,4-Dimethyl-7,11-dil(naphthalen-1-yl)-2,4-diaza-spiro[5.5]undecane-1,3,5,9-tetraene (3i)

Diarylidene acetone 2i (668 mg, 2 mmol) reacted with compound 1 (312.1 mg, 2 mmol) according to GPl yielded white solid spiro-product 3i (941 mg, 1.92 mmol, 96%); m.p. 218–220 °C; 1H NMR (400 MHz, CDCl3) δ: 1.98 (s, 3H, −NCH3); 2.75 & 2.79 (dd, 2H, J = 15.40 Hz, 4.40 Hz, CH3(17)); 3.22 (s, 3H, −NCH3); 3.89 (t, 2H, J = 15.04 Hz, CH3(17)); 5.11 & 5.14 (dd, 2H, J = 13.92 Hz, 4.40 Hz, CH), 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 = 8.04 Hz, Ar–H).
4.2.10. 2,4-Dimethyl-7,11-di(thiophen-2-yl)-2,4-
diazaspiro[5.5]junedacene-1,3,5,9-tetraene (3j)
Diarylidene aceton 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; 1H NMR (400 MHz, CDCl 3): δ: 2.80 & 2.83 (dd, 2H, J = 15.4 Hz, 4.40 Hz, CH 2e2a), 3.11 (3H, −NCH 3), 3.14 (3H, −NCH 3), 3.66 (t, 2H, J = 14.64 Hz, CH 2a1), 4.34 &
4.37 (dd, 2H, J = 13.92 Hz, 4.40 Hz, CH 2a1), 6.84 (2H, J = 3.72 Hz, Ar−H), 6.93–6.95 (m, 2H, Ar−H), 7.23 (2H, J = 5.12 Hz, Ar−H); 13C 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 37 H 27 N 2 O 4 S 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 546.11, C 23 H 25 Br 2 N 2 O 4 requires 545.98.

4.2.11. 7,11-Di(furan-2-yl)-2,4-dimethyl-2,4-
diazaspiro[5.5]junedacene-1,3,5,9-tetraene (3k)
Diarylidene aceton 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; 1H NMR (400 MHz, CDCl 3): δ: 2.67 & 2.71 (dd, 2H, J = 15.40 Hz, 4.40 Hz, CH 2e2a), 3.08 (3H, −NCH 3), 3.10 (3H, −NCH 3), 3.49 (t, 2H, J = 14.68 Hz, CH 2a1), 4.08 &
4.11 (dd, 2H, J = 13.96 Hz, 4.40 Hz, CH 2a1), 6.05 (2H, J = 3.64 Hz, Ar−H), 6.25–6.26 (m, 2H, Ar−H), 7.23 (2H, J = 1.40 Hz, Ar−H); 13C 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,
1599, 1721, 1670, 1446, 1420, 1377, 1011, 922, 738, 465;
[Anal. Calcd. for C 37 H 27 N 2 O 4 S 2 : 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 402.11, C 23 H 25 N 2 O 4 S 2 requires 402.07.

4.2.12. 7,11-Bis(3-bromophenyl)-2,4-dimethyl-2,4-
diazaspiro[5.5]junedacene-1,3,5,9-tetraene (3l)
Diarylidene aceton 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; 1H NMR (400 MHz, CDCl 3): δ: 2.57 & 2.61 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH 2a1), 2.91 (3H, −NCH 3), 3.06 (3H, −NCH 3), 3.64 (t, 2H, J = 14.68 Hz, CH 2a1), 3.92 &
3.96 (dd, 2H, J = 14.68 Hz, 4.40 Hz, CH 2a1), 6.98 (2H, J = 8.08 Hz, Ar−H), 7.11 (2H, J = 8.08 Hz, Ar−H), 7.22, (2H, Ar−H); 13C 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, 139.44, 144.99, 168.66, 170.29, 206.89; IR (KBr, cm −1 ) ν max = 2959, 2921, 1710,
1673, 1423, 1349, 1285, 1256, 1070, 787, 749, 695, 443;
Found: C, 50.51; H, 3.73; N, 5.17]; LC/MS (ESI, m/z): [M + ] + found 546.11, C 23 H 25 Br 2 N 2 O 4 requires 545.98.

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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.

References
nitroolefins catalyzed by a hydrogen bond donor catalyst Feist’s acid and preliminary study of antimicrobial activity. Sci. World J.
http://dx.doi.org/10.1155/2014/649197.
β-unsaturated ketones with simple Cu(II)oxazolineimidazoline
Stereoselective synthesis of diazaspiro[5.5]undecane derivatives


rocyclisation of the spiro compounds containing cyclohexanone and thiobarbituric acid with different bidentate nucleophilic reagents. 36, 3729–3742.

canetetraeno derivatives containing biological active heterocycles. Phosphorus Sulfur Silicon Relat. Elem. 184, 753–765.


isothiocyanato oxindoles to ketones: stereocontrolled synthesis of spirooxindoles bearing highly congested contiguous tetrastub-


Raju, J., Popp, F.D., 1988. Potential anticonvulsants. 11. Synthesis and anticonvulsant activity of spiro[1,3-dioxolane-2,3-
indolin]-2-ones and structural analogs. J. Med. Chem. 31, 1001–
1005.


isothiocyanato oxindoles to ketones: stereocontrolled synthesis of spirooxindoles bearing highly congested contiguous tetrastub-


3731.


om, pp. 1–68.


