A Novel, One-Pot, Efficient Synthesis of 2-Aroyl-1,4-diaryl-7,9-dimethyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-triones

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Abstract: A novel and efficient synthesis of 2-aroyl-1,4-diaryl-7,9-dimethyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-triones is described. The reactive 1:1 zwitterionic intermediate, formed by the addition of triphenylphosphine to diaroylacetylenes, was trapped by a Knoevenagel condensation product prepared in situ by reaction of *N*,*N*-dimethylbarbituric acid and aromatic aldehydes, to afford the title compounds in excellent yields under mild reaction conditions.

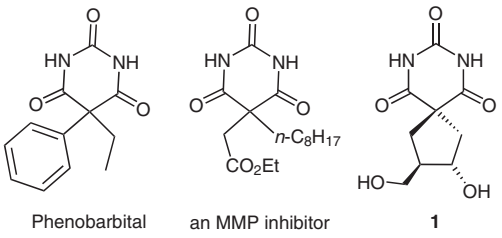
Key words: spiro compounds, cyclopentadienes, cyclizations, aldehydes, alkynes, heterocycles

Cyclopentadienes (Cps) are highly useful synthetic intermediates. Considerable attention has been focused on the synthesis of substituted Cps as useful construction units of fused-ring systems via inter- and intramolecular Diels–Alder reactions, as ligands in coordination chemistry and homogeneous catalysis for olefin polymerization.[1]

Several interesting methods have been reported for the direct preparation of substituted Cps, including: [3+2] annulation of allylidenetriphenylphosphoranes with 1,2-diacylethylenes,[2] reaction between isocyanides or triphenylphosphine, dimethyl acetylenedicarboxylate, and electrophilic styrenes,[3] Pt(II)- or Au(I)-catalyzed cyclization of 1,2,4-trienes,[4] acid-catalyzed cyclization of 1,4-pentadien-3-ols,[5] Pd-mediated cyclization of 1,5-hexadien-3-ols,[6] reaction of 1,1-dibromo-2-vinylcyclopropanes with methyl lithium,[7] cycloaddition of α,β-unsaturated Fischer carbene complexes to alkynes or alkenes,[8] electrophilic allylation of enolizable 1,3-dicarbonyl compounds and successive acid-catalyzed cyclizations,[9] insertion of aroyl cyanides or acid chlorides to zirconacyclopentenes,[10] reaction of zirconacyclopentadienes with a one-carbon-unit building block such as aldehydes, propynoates, acyl halides or 1,1-dihalides[11] and reaction of 1,4-dilithio-1,3-dienes with carboxylic acid derivatives, aldehydes or ketones.[12]

Barbituric acid has widely been used in the manufacture of plastics,[13] textiles,[14] polymers[15] and pharmaceuticals.[16,17] Pharmacologically active barbituric acids are either mono- or di-C-substituted derivatives. Several important drug molecules based on 5,5-disubstituted barbituric acid have been discovered.[18] Phenobarbital (Figure 1) is the most widely used anticonvulsant worldwide and the oldest still in use.[19] It also has sedative and hypnotic properties.[20] Some examples have matrix metalloproteinase (MMP) inhibitory activity (Figure 1).[21] In addition to the pharmaceutical value, 5,5-dialkylated barbituric acids are also useful building blocks for the assembly of supramolecular structures via non-covalent interactions.[22] In this respect, Fenniri et al. recently devised helical nanotubes.[23]

Spirobarbiturates are a class of compounds known for their interesting physiological activity.[24] Compound **1** (Figure 1) has been used as a conformationally locked unit in the construction of modified oligonucleotides.[25]



Phenobarbital an MMP inhibitor **1**

Figure 1 Examples of pharmaceutically or pharmacologically important barbiturates

Herein we report a novel synthesis of spirocyclopentadienyl-*N*,*N*-dimethylbarbituric acids using simple starting materials. Thus, a mixture of *N*,*N*′-dimethylbarbituric acid (**2**), aromatic aldehydes **3** and diaroylacetylenes **5**, in the presence of triphenylphosphine, underwent a smooth reaction at ambient temperature to afford 2-aroyl-1,4-diaryl-7,9-dimethyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-triones **6a–i** in 90–96% yield (Scheme 1, Table 1).

The reactions were carried out by first dissolving *N*,*N*-dimethylbarbituric acid in hot water and then adding the aldehyde. After a few minutes, when nearly complete conversion into the corresponding 5-arylmethylidene-*N*,*N*-dimethylbarbituric acid **4**[26] was indicated by TLC, a solution of triphenylphosphine in dichloromethane was added to the mixture. A solution of dibenzoylacetylene in dichloromethane was then slowly added and the reaction mixture was stirred at ambient temperature. The reaction proceeded spontaneously and went to completion within one hour. The ^{1}H NMR spectra of the crude products

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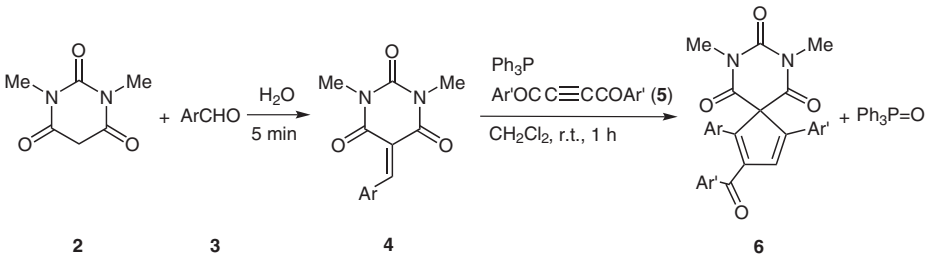
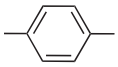
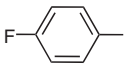
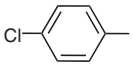
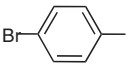
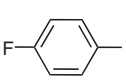
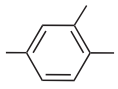


Scheme 1

clearly indicated the formation of the spirocyclopentadienyl-*N*,*N*-dimethylbarbituric acids **6** in excellent yields. No product other than **6** and triphenylphosphine oxide could be detected by NMR spectroscopy.

The structures of the isolated products **6a–i** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **6b** displayed the molecular ion [M$^+$] peak at $m/z = 476$, which was consistent with the structure of the isolated product. The ^{1}H NMR spectrum of **6b** exhibited three single sharp lines arising from the aryl methyl group (δ = 2.22 ppm), *N*-methyl substituents (δ = 3.26 ppm) and the vinylic proton of the five-membered ring (δ = 7.18 ppm), along with the characteristic signals with appropriate chemical shifts and coupling constants for the fourteen protons of the three aryl groups. The ^{1}H-decoupled ^{13}C NMR spectrum of **6b** showed four signals arising from the spiro-carbon atom (δ = 74.0 ppm), urea carbonyl (δ = 150.6 ppm), two equivalent amide carbonyls (δ = 164.5 ppm) and the ketone function (δ = 192.6 ppm) as well as eighteen other distinct resonances, which are in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section. Single-crystal X-ray analysis of **6b** conclusively confirmed the structure of the isolated products. An ORTEP diagram of **6b** is shown in Figure 2.[27]

Table 1 Synthesis of 7,9-Diazaspiro[4.5]deca-1,3-diene-6,8,10-triones **6a–i**

6	Ar	Ar′	Yield (%)[a]
a			96
b			92
c			90
d			95
e			95
f			95
g			91
h			92
i			94

[a] Isolated yield.

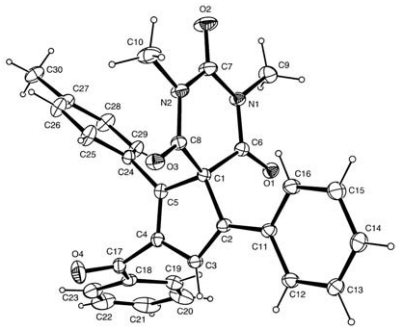
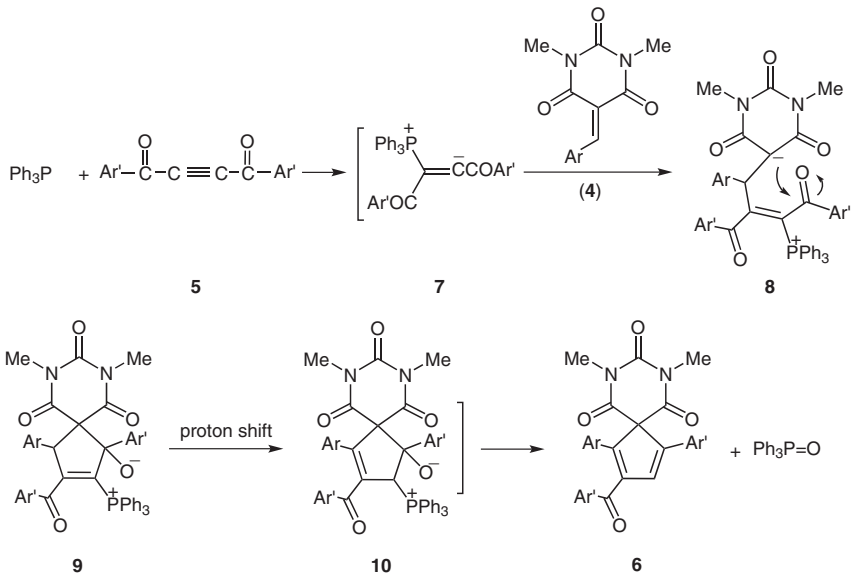


Figure 2 Molecular structure of **6b**

A mechanistic rationalization for this reaction is provided in Scheme 2. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[28–31] it is reasonable to assume that the zwitterionic intermediate **7**, formed from the initial addition of triphenylphosphine to the electron-deficient acetylenic compound **5**, is trapped by the electron-deficient 5-arylmethylidene-*N*,*N*-dimethylbarbituric acid **4** prepared in situ, leading to the 1:1:1 adduct **8**, which undergoes intramolecular cyclization to betaine **9**. This intermediate can undergo a proton shift to form a new betaine **10**, from which triphenylphosphine oxide is removed to afford the isolated spirocyclopentadienyl-*N*,*N*-dimethylbarbituric acids **6**.

In summary, we have succeeded in synthesizing 2-aroyl-1,4-diaryl-7,9-dimethyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-triones of potential synthetic and pharmacological interest via a novel, one-pot reaction between *N*,*N*-dimethylbarbituric acid, aromatic aldehydes and diaroylacetylenes, in the presence of triphenylphosphine. High yields of the products, relatively short reaction times and the use of simple starting materials are the main advantages of this method. The reaction is performed under neutral, mild conditions, and the starting materials and



Scheme 2

reagents can be mixed without any activation or modification. In view of extensive use of cyclopentadienes and barbituric acid derivatives in chemistry and medicinal chemistry, the spirocyclopentadienyl-*N*,*N*-dimethylbarbituric acids prepared in the present study may find useful applications in synthetic organic, bioorganic and medicinal chemistry.

Triphenylphosphine, *N*,*N*-dimethylbarbituric acid and aldehydes were obtained from Merck (Germany) and Fluka (Switzerland), and were used without further purification. Diaroylacetylenes **5** were prepared according to literature procedures.[32] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured as solutions in $CDCl_3$ with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

Compounds 6; General Procedure

N,*N*-Dimethylbarbituric acid (**2**; 0.312 mg, 2 mmol) was dissolved in hot H_2O (60 °C, 5 mL) and the appropriate aldehyde (2 mmol) was rapidly added and stirred at ambient temperature for 5 min. The Knoevenagel condensation product, 5-arylmethylidene-*N*,*N*-dimethylbarbituric acid, was precipitated under the reaction conditions. A solution of triphenylphosphine (0.524 g, 2 mmol) in CH_2Cl_2 (1 mL) was added to the reaction mixture and a solution of the appropriate diaroylacetylene (2 mmol) in CH_2Cl_2 (1 mL) was added over 5 min. The reaction mixture was stirred at 25 °C for 1 h. The aqueous layer was separated from the heterogeneous reaction mixture by suction, the organic solvent was evaporated and the solid residue was purified by column chromatography (*n*-hexane–EtOAc, 3:1). The solvent was removed and the residue was recrystallized (*n*-hexane-EtOAc, 1:1). The yields refer to the products obtained by column chromatography before recrystallization.

2-Benzoyl-7,9-dimethyl-1,4-diphenyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6a)

Yield: 0.89 g (96%); yellow crystals; mp 189–190 °C.

IR (KBr): 1745 and 1686 (C=O), 1589, 1495, 1445, 1375, 1339, 1283, 1247, 1175, 1121, 1043, 885, 858, 752, 725, 694 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.22 (s, 6 H, 2 × CH_3), 6.96 (dd, *J* = 7.6, 1.2 Hz, 2 H, 2 × CH), 7.11–7.17 (m, 3 H, 3 × CH), 7.18 (s, 1 H, CH), 7.21 (dd, *J* = 7.0, 1.4 Hz, 2 H, 2 × CH), 7.25–7.33 (m, 5 H, 5 × CH), 7.40 (t, *J* = 7.4 Hz, 1 H, CH), 7.83 (d, *J* = 7.3 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.9 (NCH_3), 73.9 (C), 125.6, 128.0, 128.3, 128.4, 128.7, 129.1, 129.2 and 129.4 (8 × CH), 131.4 and 132.0 (2 × C), 133.2 and 133.4 (2 × CH), 136.3, 145.1, 147.8 and 149.1 (4 × C), 150.4 (C=O, urea), 164.3 (C=O, amide), 192.3 (C=O, ketone).

MS: *m*/*z* (%) = 462 (100) [M$^+$], 348 (19), 302 (8), 271 (18), 243 (12), 215 (27), 174 (12), 105 (59), 77 (21).

Anal. Calcd for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.06. Found: C, 75.2; H, 4.9; N, 5.9.

2-Benzoyl-7,9-dimethyl-1-(4-methylphenyl)-4-phenyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6b)

Yield: 0.88 g (92%); pale-yellow crystals; mp 185 °C.

IR (KBr): 1747 and 1686 (C=O), 1591, 1501, 1445, 1375, 1339, 1281, 1246, 1177, 1119, 1045, 885, 858, 752, 719, 690 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, CH_3), 3.26 (s, 6 H, 2 × CH_3), 6.87 (d, *J* = 8.0 Hz, 2 H, 2 × CH), 6.97 (d, *J* = 8.0 Hz, 2 H, 2 × CH), 7.18 (s, 1 H, CH), 7.22 (dd, *J* = 7.0, 1.5 Hz, 2 H, 2 × CH), 7.28–7.36 (m, 5 H, 5 × CH), 7.44 (tt, *J* = 7.3, 1.3 Hz, 1 H, CH), 7.87 (dd, *J* = 8.0, 1.3 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_3), 29.1 (NCH_3), 74.0 (C), 125.8, 128.0 and 128.4 (3 × CH), 128.6 (C), 128.8, 129.2, 129.3 and 129.6 (4 × CH), 132.2 (C), 133.3 and 133.6 (2 × CH), 136.5, 139.3, 145.0, 147.8 and 149.5 (5 × C), 150.6 (C=O, urea), 164.5 (C=O, amide), 192.6 (C=O, ketone).

MS: *m*/*z* (%) = 476 (86) [M$^+$], 461 (23), 430 (7), 361 (12), 277 (20), 257 (16), 236 (21), 181 (14), 149 (14), 119 (14), 105 (100), 77 (57).

Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.62; H, 5.08; N, 5.88. Found: C, 75.6; H, 5.1; N, 5.8.

2-Benzoyl-7,9-dimethyl-1-(3-methylphenyl)-4-phenyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6c)
Yield: 0.86 g (90%); pale-yellow crystals; mp 117–118 °C.

IR (KBr): 1749, 1686 and 1645 (C=O), 1597, 1580, 1437, 1373, 1348, 1277, 1247, 1179, 1124, 1040, 899, 866, 750, 727, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 3.25 (s, 6 H, 2 × CH_3), 6.77 (d, *J* = 9.0 Hz, 1 H, CH), 6.78 (s, 1 H, CH), 7.00 (d, *J* = 7.6 Hz, 1 H, CH), 7.05 (t, *J* = 7.4 Hz, 1 H, CH), 7.22 (s, 1 H, CH), 7.23 (dd, *J* = 7.5, 1.5 Hz, 2 H, 2 × CH), 7.28–7.36 (m, 5 H, 5 × CH), 7.43 (tt, *J* = 7.3, 1.2 Hz, 1 H, CH), 7.83 (dd, *J* = 7.8, 1.3 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 29.0 (NCH_3), 74.1 (C), 125.1, 125.7, 128.4, 128.5, 128.8, 129.0, 129.2, 129.5 and 130.0 (9 × CH), 131.4 and 132.2 (2 × C), 133.2 and 133.5 (2 × CH), 136.6, 138.2, 145.0, 147.7 and 149.6 (5 × C), 150.6 (C=O, urea), 164.5 (C=O, amide), 192.5 (C=O, ketone).

MS: *m*/*z* (%) = 476 (100) [M^+], 461 (50), 361 (16), 347 (16), 285 (17), 228 (19), 173 (20), 105 (94), 77 (34).

Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.62; H, 5.08; N, 5.88. Found: C, 75.4; H, 5.2; N, 5.7.

2-Benzoyl-1-(4-fluorophenyl)-7,9-dimethyl-4-phenyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6d)
Yield: 0.91 g (95%); pale-yellow crystals; mp 213 °C.

IR (KBr): 1749, 1686 and 1666 (C=O), 1595, 1552, 1500, 1445, 1375, 1339, 1285, 1255, 1223, 1175, 1164, 1123, 1043, 887, 858, 752, 714 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.26 (s, 6 H, 2 × CH_3), 6.86 (dd, $^3J_{F-H}$ = 8.6 Hz, $^3J_{H-H}$ = 8.7 Hz, 2 H, 2 × CH), 6.98 (dd, $^3J_{H-H}$ = 8.7 Hz, $^4J_{F-H}$ = 4.9 Hz, 2 H, 2 × CH), 7.17 (s, 1 H, CH), 7.21 (dd, *J* = 7.4, 1.5 Hz, 2 H, 2 × CH), 7.30–7.37 (m, 5 H, 5 × CH), 7.47 (tt, *J* = 7.4, 1.0 Hz, 1 H, CH), 7.84 (dd, *J* = 7.3, 1.3 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1 (NCH_3), 74.1 (C), 115.8 (d, $^2J_{F-C}$ = 21.8 Hz, CH), 125.8 (CH), 127.7 (d, $^4J_{F-C}$ = 3.4 Hz, C), 128.5, 129.0, 129.2 and 129.5 (4 × CH), 130.2 (d, $^3J_{F-C}$ = 8.4 Hz, CH), 132.1 (C), 133.4 and 133.5 (2 × CH), 136.3, 145.8, 148.0 and 148.2 (4 × C), 150.4 (C=O, urea), 163.0 (d, $^1J_{F-C}$ = 250.6 Hz, CF), 164.3 (C=O, amide), 192.3 (C=O, ketone).

MS: *m*/*z* (%) = 480 (29) [M^+], 430 (9), 366 (12), 302 (14), 279 (19), 167 (43), 149 (100), 105 (38), 83 (42), 69 (64), 57 (79).

Anal. Calcd for $C_{29}H_{21}FN_2O_4$: C, 72.49; H, 4.41; N, 5.83. Found: C, 72.3; H, 4.5; N, 5.6.

2-Benzoyl-1-(4-chlorophenyl)-7,9-dimethyl-4-phenyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6e)
Yield: 0.94 g (95%); pale-yellow crystals; mp 215–216 °C.

IR (KBr): 1749, 1685 and 1668 (C=O), 1595, 1580, 1549, 1495, 1445, 1375, 1337, 1285, 1248, 1175, 1119, 1088, 1043, 887, 856, 750, 708 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.27 (s, 6 H, 2 × CH_3), 6.95 (d, *J* = 8.5 Hz, 2 H, 2 × CH), 7.15 (s, 1 H, CH), 7.16 (d, *J* = 8.5 Hz, 2 H, 2 × CH), 7.21 (dd, *J* = 7.4, 1.5 Hz, 2 H, 2 × CH), 7.30–7.37 (m, 5 H, 5 × CH), 7.48 (t, *J* = 7.4 Hz, 1 H, CH), 7.86 (dd, *J* = 7.2, 1.1 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2 (NCH_3), 74.0 (C), 128.6, 128.9, 129.0, 129.2, 129.4, 129.5 and 129.6 (7 × CH), 130.2 and 132.0 (2 × C), 133.5 and 133.6 (2 × CH), 135.5, 136.3, 146.1, 147.5 and 147.6 (5 × C), 150.4 (C=O, urea), 164.3 (C=O, amide), 192.2 (C=O, ketone).

MS: *m*/*z* (%) = 498 (32) [M^+, ^{37}Cl], 496 (81) [M^+, ^{35}Cl], 382 (27), 305 (19), 270 (18), 249 (16), 213 (31), 174 (36), 105 (100), 77 (44).

Anal. Calcd for $C_{29}H_{21}ClN_2O_4$: C, 70.09; H, 4.26; N, 5.64. Found: C, 69.9; H, 4.5; N, 5.5.

2-Benzoyl-1-(4-bromophenyl)-7,9-dimethyl-4-phenyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6f)
Yield: 1.03 g (95%); pale-yellow crystals; mp 207–208 °C.

IR (KBr): 1749 and 1686 (C=O), 1595, 1505, 1449, 1373, 1337, 1283, 1240, 1175, 1115, 1069, 1047, 885, 856, 750, 720 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.27 (s, 6 H, 2 × CH_3), 6.80 (d, *J* = 8.5 Hz, 2 H, 2 × CH), 7.13 (s, 1 H, CH), 7.20 (dd, *J* = 7.6, 1.6 Hz, 2 H, 2 × CH), 7.30 (d, *J* = 8.5 Hz, 2 H, 2 × CH), 7.31–7.37 (m, 5 H, 5 × CH), 7.49 (t, *J* = 7.4 Hz, 1 H, CH), 7.86 (dd, *J* = 7.5, 1.3 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2 (NCH_3), 73.9 (C), 123.7 (C), 125.9, 128.6, 129.1, 129.2, 129.6 and 129.7 (6 × CH), 130.6 (C), 131.9 (CH), 132.0 (C), 133.5 and 133.6 (2 × CH), 136.2, 146.1, 147.6 and 148.5 (4 × C), 150.4 (C=O, urea), 164.2 (C=O, amide), 192.2 (C=O, ketone).

MS: *m*/*z* (%) = 542 (59) [M^+, ^{81}Br], 540 (58) [M^+, ^{79}Br], 426 (18), 349 (12), 289 (17), 270 (25), 213 (63), 174 (75), 159 (24), 105 (100), 77 (50).

Anal. Calcd for $C_{29}H_{21}BrN_2O_4$: C, 64.34; H, 3.91; N, 5.17. Found: C, 64.3; H, 3.9; N, 5.1.

2-Benzoyl-1-(2-furyl)-7,9-dimethyl-4-phenyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6g)
Yield: 0.82 g (91%); yellow crystals; mp 175–177 °C.

IR (KBr): 1744, 1684 and 1675 (C=O), 1593, 1487, 1443, 1416, 1371, 1333, 1281, 1244, 1165, 1124, 1042, 908, 876, 814, 752, 716, 685 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.38 (s, 6 H, 2 × CH_3), 6.34 (dd, *J* = 3.5, 1.6 Hz, 1 H, CH), 6.75 (d, *J* = 3.5 Hz, 1 H, CH), 6.99 (s, 1 H, CH), 7.20 (d, *J* = 7.3 Hz, 2 H, 2 × CH), 7.28 (d, *J* = 1.6 Hz, 1 H, CH), 7.29–7.34 (m, 3 H, 3 × CH), 7.48 (dd, *J* = 7.5, 7.7 Hz, 2 H, 2 × CH), 7.58 (t, *J* = 7.3 Hz, 1 H, CH), 8.02 (d, *J* = 7.3 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2 (NCH_3), 70.9 (C), 113.1, 113.8, 125.8, 128.8, 128.9, 129.2 and 129.6 (6 × CH), 132.2 (C), 133.6 and 134.4 (2 × CH), 136.7, 139.0 and 140.7 (3 × C), 143.6 (CH), 147.1 and 147.3 (2 × C), 151.3 (C=O, urea), 164.7 (C=O, amide), 192.1 (C=O, ketone).

MS: *m*/*z* (%) = 452 (100) [M^+], 338 (45), 309 (11), 281 (17), 261 (13), 252 (18), 205 (20), 176 (20), 155 (16), 126 (11), 105 (96), 77 (40).

Anal. Calcd for $C_{27}H_{20}N_2O_5$: C, 71.67; H, 4.46; N, 6.19. Found: C, 71.6; H, 4.6; N, 6.1.

2-Benzoyl-7,9-dimethyl-4-phenyl-1-(2-thienyl)-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6h)
Yield: 0.86 g (92%); pale-yellow crystals; mp 172–173 °C.

IR (KBr): 1745, 1687 and 1672 (C=O), 1595, 1497, 1444, 1375, 1338, 1284, 1247, 1178, 1117, 1045, 900, 875, 812, 752, 720, 690 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.33 (s, 6 H, 2 × CH_3), 6.80 (dd, *J* = 3.8, 5.0 Hz, 1 H, CH), 6.84 (dd, *J* = 3.7, 1.0 Hz, 1 H, CH), 7.05 (s, 1 H, CH), 7.19 (d, *J* = 7.3 Hz, 2 H, 2 × CH), 7.27 (dd, *J* = 5.0, 3.9 Hz, 1 H, CH), 7.29–7.33 (m, 3 H, 3 × CH), 7.37 (dd, *J* = 7.8, 7.6 Hz, 2 H, 2 × CH), 7.49 (t, *J* = 7.4 Hz, 1 H, CH), 7.93 (dd, *J* = 7.2, 1.2 Hz, 2 H, 2 × CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2 (NCH_3), 73.2 (C), 125.8, 127.8, 127.9, 128.6, 129.0, 129.1, 129.2 and 129.6 (8 × CH), 132.1 and 132.7 (2 × C), 133.6 and 134.0 (2 × CH), 136.1, 141.8, 144.9

and 148.5 (4 × C), 150.8 (C=O, urea), 164.4 (C=O, amide), 192.7 (C=O, ketone).

MS: *m*/*z* (%) = 468 (100) [M$^+$], 354 (39), 325 (9), 261 (10), 174 (15), 155 (10), 105 (96), 77 (36).

Anal. Calcd for $C_{27}H_{20}N_2O_4S$: C, 69.22; H, 4.30; N, 5.98. Found: C, 69.2; H, 4.3; N, 5.9.

2-(2,5-Dimethylbenzoyl)-4-(2,5-dimethylphenyl)-1-(4-fluorophenyl)-7,9-dimethyl-7,9-diazaspiro[4.5]deca-1,3-diene-6,8,10-trione (6i)

Yield: 1.01 g (94%); pale-yellow crystals; mp 147–148 °C.

IR (KBr): 1747, 1686 and 1654 (C=O), 1566, 1501, 1439, 1371, 1283, 1252, 1217, 1161, 1113, 1049, 839, 825, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.20, 2.24, 2.27 and 2.47 (4 × s, 12 H, 4 × CH_3), 3.16 (s, 6 H, 2 × CH_3), 6.72 (br s, 1 H, CH), 6.78 (dd, $^3J_{F-H}$ = 8.6 Hz, $^3J_{H-H}$ = 8.7 Hz, 2 H, 2 × CH), 6.84 (s, 1 H, CH), 6.95 (d, *J* = 7.7 Hz, 1 H, CH), 6.99 (dd, *J* = 7.7, 1.1 Hz, 1 H, CH), 7.03 (dd, $^3J_{H-H}$ = 8.7 Hz, $^4J_{F-H}$ = 5.3 Hz, 2 H, 2 × CH), 7.06 (d, *J* = 1.1 Hz, 1 H, CH), 7.13 (d, *J* = 7.8 Hz, 1 H, CH), 7.39 (br s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 20.1, 20.6 and 20.8 (4 × CH_3), 28.9 (NCH_3), 77.9 (C), 115.2 (d, $^2J_{F-C}$ = 21.8 Hz, CH), 128.6 (CH), 129.2 (d, $^4J_{F-C}$ = 3.4 Hz, C), 129.9 (CH), 130.3 (d, $^3J_{F-C}$ = 8.6 Hz, CH), 130.7, 131.1 and 131.3 (3 × CH), 131.6 (C), 132.1 (CH), 134.2, 134.8, 135.0 and 135.1 (4 × C), 136.1 (CH), 136.8, 146.0, 146.8 and 149.3 (4 × C), 150.3 (C=O, urea), 162.7 (d, $^1J_{F-C}$ = 249.5 Hz, CF), 164.5 (C=O, amide), 194.6 (C=O, ketone).

MS: *m*/*z* (%) = 536 (57) [M$^+$], 427 (28), 393 (6), 380 (19), 273 (20), 261 (9), 246 (13), 133 (100), 105 (37), 79 (13).

Anal. Calcd for $C_{33}H_{29}FN_2O_4$: C, 73.87; H, 5.45; N, 5.22. Found: C, 73.7; H, 5.6; N, 5.1.

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(27) X-ray crystallographic data for compound **6b**: Empirical formula: $C_{30}H_{24}N_2O_4$; Crystal system = orthorhombic; Space group $P2_12_12_1$; Unit cell dimensions: *a* = 9.4114 (13) Å, *b* = 14.890 (2) Å, *c* = 18.003 (3) Å; *V* = 2522.79 (6) Å^3; *T* = 295 (2) K; *Z* = 4; D_{calcd} = 1.255 g·cm^{-3}; μ (Mo-Kα) = 0.084 mm^{-1}; 13788 reflections measured, 2689 unique reflections (R_{int} = 0.057), 1671 observed reflections, final *R*1 = 0.050, *wR*2 = 0.119 for I > 2σ(I). CCDC 656637 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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