Supporting Information
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Novel Isoxazolinyl Spiropyrrolidinediones: 1,3-Dipolar Cycloaddition of 1-benzyl-3,3-dimethyl-5-methyleneppyrrolidin-2,4-dione

Yaser Bathich, Sharifah Edayu binti Syed Monudeen Khan, Ahmad Sazali Hamzah

Institute of Science, Universiti Teknologi Mara, 40450 Shah Alam, Selangor, Malaysia

bathich@gmail.com, asazali@salam.uitm.edu.my

Supporting Information

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General Methods:

Chemical Shifts are given in ppm. The TMS signal is taken as the reference (δ = 0.00 ppm). Coupling constants (J) are given in Hertz (Hz). All 1H and 13C NMR spectra were obtained for substances dissolved in CDCl3. Proton chemical shifts are reported in ppm relative to CHCl3 (δ = 7.26 ppm). 13C chemical shifts are reported in ppm relative to CHCl3 (δ = 77.16 ppm). 1H- and 13C-NMR assignments were confirmed by DEPT and 2D COSY. Thin layer chromatography was performed on precoated aluminum sheets (silica gel 60 F254) purchased from E. Merck (layer thickness 0.2 mm). The TLC plate was treated by staining with a solution prepared from 2 g KMnO4, 20 g K2CO3, 5 mL of NaOH solution (5%) in 300 mL water and developed by heating with a heat gun. Melting points were measured with Bamstead Electrothermal 9100 apparatus. Elemental analysis was performed on Flash Elemental Analyzer 110 series. All solvents and reagents used were purified and dried according to standard methods. N-hydroxybenzimidoyl chloride was prepared according to literature1 starting from benzaldehyde.

2,2-dimethyl-acetoacetic acid methyl ester (4)

To a vigorously stirred solution of methyl acetoacetate (5.0 g, 43.05 mmol) in DMF, K2CO3 (3.5 eq., 150.7 mmol, 20.82 g) was added, after 1 hour stirring, Mel (3.5 eq., 150.7 mmol, 21.39 g) was added at room temperature under nitrogen gas. To this reaction mixture a catalytic amount of bmimBF4 (15% mol, 6.46 mmol, 1.46 g) was added, then the mixture was stirred overnight.

The reaction mixture was filtered and the solid was washed with ether, the filtrate was diluted with water (200 mL), and extracted with ether (3 x 100 mL), washed (brine) and dried (MgSO4), filtered and concentrated to give 5.02 g (81%) of yellowish oil.

The analytical data: 1H-NMR (CDCl3): δ = 1.31 [2s, 6H, C(CH3)2], 2.11 (s, 3H, 4-H), 3.67 (s, 3H, OCH3). 13C NMR (CDCl3): δ = 22.0 [2q, C(CH3)2], 25.8 (q, C-4), 52.6 (q, OCH3), 55.9 [s, C(CH3)2], 174.3 (C-1), 205.9 (C-3). This compound was prepared by different literature procedures2.

4-bromo-2,2-dimethyl-acetoacetic acid methyl ester (5)

47.77 g (2.5 eq., 213.89 mmol) of CuBr2 was poured in 100 mL of ethyl acetate, brought to reflux, and then 12.3 g (85.55 mmol) of 4 in 10 mL of ethyl acetate was added to the mixture, refluxed overnight. Next, the mixture was cooled to room temperature, and rest of CuBr2 was washed with ethyl acetate, then the filtrate was concentrated to give 18.42 g (97% crude) of yellowish oil, used for the next step without further purification.3

The analytical data: 1H-NMR (CDCl3): δ = 1.39 [2s, 6H, C(CH3)2], 3.65 (s, 3H, OCH3), 4.05 (s, 2H, 4-H). 13C NMR (CDCl3): δ = 22.7 [2q, C(CH3)2], 31.5 (t, C-4), 53.0 (q, OCH3), 55.2 [s, C(CH3)2], 173.6 (C-1), 199.5 (C-3).

1-benzyl-3,3-dimethylpyrrolidin-2,4-dione (6)

To 680 mg (3.05 mmol) of 5 in 30 mL THF, 653 mg(2 eq., 6.1 mmol) of benzyl amine was added at −10 °C, stirred for 1 h (temperature allowed to rise) then quenched with 30 mL HCl (2 N). The mixture was added to water (30 mL), partitioned against ether (3 x 30 mL), washed (brine), dried

with MgSO₄, filtered and concentrated to give 600 mg of yellowish oil, which was chromatographed (SiO₂, column 1 cm x 15 cm, Petroleum ether/ethyl acetate 9:1 gradually until 1:1) to yield 310 mg (47%) of yellowish oil.

The analytical data: ¹H-NMR (CDCl₃): δ = 1.24 [2s, 6H, C(CH₃)₂], 3.66 (s, 2H, 5-H), 4.61 (s, 2H, 1'-H), 7.15-7.38 (m, 5 H, C₆H₅). ¹³C NMR (CDCl₃): δ = 20.8 [2q, C(CH₃)₂], 46.1 (t, C'-1), 47.4 (s, C-3), 53.9 (t, C-5), 128.3, 128.6, 129.2 (3 d, β, m, −C of C₆H₅), 135.5 (s, i-C of C₆H₅), 175.9 (C-2), 210.0 (C-4). IR: 2970 (w), 2931 (w), 2328 (w), 2302 (w), 1769 (s), 1677 (vs), 1535 (w), 1435 (s), 1359 (w), 1292 (s), 1240 (m), 1192 (m), 1106 (s) cm⁻¹.

1-benzyl-3,3-dimethyl-5-methylenepyrrolidin-2,4-dione (7)

To a solution of 6 (170 mg, 0.78 mmol) in 20 mL THF, 316 mg (3.13 mmol, 4 eq) of diisopropyl amine was added and refluxed for 30 min. Next, 126 mg (1.56 mmol, 2 eq) of formaldehyde in 10 mL THF was added to the mixture and refluxed for 4 hours, H₂O (10 mL) was added to the mixture and refluxed overnight. The reaction mixture was quenched with 5 mL HCl (2 M), then added to water (15 mL) and partition against ether (2 x 30 mL), washed with brine (20 mL), and dried with MgSO₄, filtrated and concentrated in vacuum to give 139 mg (78 %) of analytically and spectroscopically pure pyrrolidin-2,4-dione 7 in the form of a colorless solid (m. p. 117-118 °C).

The analytical data: ¹H-NMR (CDCl₃): δ = 1.30 [2s, 6H, C(CH₃)₂], 4.48 (sb, 1 H, 5'-Hₐ), 4.81 (s, 2 H, 1'-H), 5.16 (sb, 1 H, 5'-H₈), 7.19-7.34 (m, 5 H, C₆H₅). ¹³C NMR (CDCl₃): δ = 20.6 [2q, C(CH₃)₂], 43.8 (t, C'-1), 45.5 (s, C-3), 93.0 (t, C-5), 127.5, 128.1, 129.2 (3 d, β, α, m, −C of C₆H₅), 135.0 (s, i-C of C₆H₅), 140.4 (s, C-5), 176.1 (C-2), 200.1 (C-4). IR: 2971 (w), 2932 (w), 2869 (w), 1755 (w), 1716 (vs), 1623 (vs), 1495 (w), 1453 (s), 1436 (w), 1394 (m), 1358 (s), 1334 (vs), 1303 (w), 1207 (w), 1177 (vs), 1155 (m), 1105 (m), 1079 (m), 1054 (m), 941 (m), 869 (vs), 736 (vs), 696 (s) cm⁻¹.

Elemental Analysis: C₁₄H₁₉NO₂. Calculated C 73.34, H 6.59, N 6.11; Found C 73.40, H 6.85, N 6.13

Ethyl Chlorooximidoacetate (8)

According to lit.⁴ 34.85 g (251.5 mmol) of ethyl glycinate hydrochloride and 20.75 mL (247 mmol) of conc. HCl were added to 48 mL H₂O at −5 °C with stirring, and then 17.35 g (1 eq) of NaNO₂ (in 25 H₂O) was added. A second equivalent of hydrochloric acid (20.75 mL of conc. HCl, 247 mmol) and of sodium nitrite (17.35 g in 50 H₂O) was then added in the same manner. The reaction mixture was partitioned against ether (5 x 100 mL) and dried (MgSO₄), then concentrated in vacuo (8 mbar). Crystallization from hexane gave 14.39 g (38 %; lit.³: 54 %) of analytically and spectroscopically pure ethyl chlorooximidoacetate as colorless crystals (m. p. 75-76 °C; lit.³: 80°C).

The analytical data: ¹H NMR (CDCl₃): δ = 1.39 (t, J = 7.1 Hz, 3 H, CH₂CH₃), 4.41 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 7.29 (s, 1 H, NOH). ¹³C NMR (CDCl₃): δ = 13.9 (q, CH₂CH₃), 63.9 (t, CH₂CH₃), 132.8 (s, C=N), 158.8 (s, C=O). IR: 3320 (s), 2970 (m), 1745 (s), 1720 (m), 1720 (m), 1615 (m), 1465 (m), 1440 (m), 1410 (m), 1375 (m), 1360 (m), 1290 (s), 1060 (s), 1040 (m), 980 (m), 840 (m), 800 (w), 780 (m), 735 (m) cm⁻¹.

2,3-O-Cyclohexylidene-(S)-glyceraldoxime (9)

To a mixture of H₂O/ethyl acetate (3:1, 500 mL) 1,2:5,6-di-O-cyclohexylidene-D-mannitol 10 (30.0 g, 87.6 mmol) was added and the pH adjusted to 8-9 by addition of NaOH solution (ca. 3 mL, 1.0 N). Next, sodium periodate (18.73 g, 87.60 mmol) was added portion wise, then the mixture was stirred at room temp. for 2.5 h. The organic phase was extracted with ethyl acetate (5 x 75mL) and the combined organic solutions were dried (MgSO₄) to give, after evaporating the solvent (50 mbar), 29.2 g ("98\%") of a colorless oil.

The oil was dissolved in 400 mL MeOH and 90.0 g (378 mmol) of K₂CO₃ and 23.1 g (333 mmol) of NH₂OH.HCl (dissolved in 400 mL H₂O) were added at 0 °C. The mixture was stirred overnight. The total volume was then reduced to one third by evaporation (15 mbar, 50 °C) followed by extraction with CH₂Cl₂ (5 x 60 mL). The combined organic solutes were dried (MgSO₄) and concentrated in vacuo (5 mbar), then the residual oil was filtered through silica gel (column 2 cm x 5 cm, petroleum ether/ethyl acetate 6:4) to yield 31.2 g of the oxime 10 as a colorless oil (97\%, E:Z = 60:40). The analytical and spectroscopic data were in accordance with the literature 5.

The analytical data: IR: ν = 3350 (sb), 2920 (vs), 2845 (s), 1650 (w), 1440 (s), 1355 (s), 1320 (m), 1270 (s), 1240 (m), 1220 (m), 1150 (s), 1130 (m), 1085 (s), 1120 (s), 951 (s), 835 (s), 815 (m), 760 (w), 680 (w), 640 (w) cm⁻¹. ¹H NMR (CDCl₃, E:Z = 60:40) : δ = 1.42 - 1.63 (m, C(CH₂)₅), 3.87, 3.80 (A for ABX, 3-Ha), 4.17, 4.35 (B for ABX, 3-Hb), 4.65, 5.08 (dX for ABX, 2-H), 7.39, 6.96 (d, J = 7.5 Hz, 1-H), 9.1, 9.35 (sb, 1 H, NOH). ¹³C NMR (CDCl₃, E:Z = 60:40) : (E) Isomer : δ = 23.8, 23.9, 25.0, 35.0, 36.2 (5 t, C(CH₂)₅), 67.0 (t, C-3), 72.9 (d, C-2), 111.0 (s, i-C), 149.8 (d, C-1). (Z) Isomer:  = 34.8, 35.7 (5 t, C(CH₂)₅), 67.5 (t, C-3), 70.3 (d, C-2), 110.4 (s, i-C), 153.0 (d, C-1); the other signals were overlapped by those of the major diastereomer.

2,3-O-Cyclohexylidene-D-glyceroxyhydroximoyl chloride (10)

According to literature 6, 10.4 g (77.94 mmol) of NCS was added portion wise to a solution of 26.24 g (141.7 mmol) 2,3-O-cyclohexylidene-D-glyceraldoxime 9 in 200 mL of abs. DMF. HCl gas (from HCl vapor on bottle with conc. HCl 37%) was then introduced by means of a syringe into the solution several times until the reaction started (the color changed to green). After 5 min, a second portion of NCS (10.4 g, 77.94 mmol) was added and the reaction was kept with stirring for 3 h at room temp. To this mixture 500 mL of ice water was added, then it was extracted with ether (5 x 75 mL). The extracts were washed with water (2 x 100 mL) and dried (MgSO₄). Finally, the solvent was evaporated (10 mbar) to afford 30.87 g of the oximoyl chloride 10 (99\%) as green oil. The analytical data complied with the literature values 7.

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The analytical data: \( ^1H \) NMR (CDCl\(_3\)): \( \delta = 1.40-1.79 \) [m, C(CH\(_2\)_3)], 4.14 (dd, \( J_{2,3a} = 5.8 \), \( J_{3a,3b} = 8.7 \) Hz, 1 H, 3-H\(_a\)), 4.20 (dd, \( J_{2,3b} = 6.7 \), \( J_{3a,3b} = 8.7 \) Hz, 1 H, 3-H\(_b\)), 4.83 (dd, \( J_{2,3a} = 5.8 \), \( J_{2,3b} = 6.7 \) Hz, 1 H, 2-H), 9.75 (sb, 1 H, NOH). \( ^{13}C \) NMR (CDCl\(_3\)): \( \delta = 23.81, 23.83, 25.0, 35.0, 35.5 \) (5 t, C(CH\(_2\)_3)), 66.6 (t, C-3), 75.9 (d, C-2), 112.1 (s, \( i-C \)), 139.4 (d, C-1).

(5S)-6-Benzyl-8,8-dimethyl-1-oxa-3-phenyl-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (11)

To 1.0 g (4.36 mmol) of 7 in 100 mL ether, 680 mg (4.36 mmol) of \( N \)-hydroxybenzimidoyl chloride was added with stirring at 0 \(^\circ\)C. To this reaction mixture 9.6 mL (0.5 M, 4.80 mmol, 1.1 eq) of triethylamine solution in ether was added drop wise with a rate of 8-10 drops per min, and then kept stirring overnight. The mixture was quenched with HCl (30 mL, 1.0 M), partitioned against ether (3 × 50 mL), and the combined organic phases were washed with sat. NaHCO\(_3\) (50 mL), water (2 × 50 mL), then dried (MgSO\(_4\)), filtered and concentrated to give 1.41 g of crude yellowish oil. Crystallization from ether produced 1.15 g (76 %) of 11 as light yellowish crystals (m.p. 92–93 \(^\circ\)C).

The analytical data: \( ^1H \) NMR (CDCl\(_3\)): \( \delta = 1.37, 1.48 \) [2 s, 6 H, C(CH\(_3\)_2)], 2.92 (d, \( J = 17.9 \) Hz, 1 H, 4-H\(_a\)), 3.58 (d, \( J = 17.9 \) Hz, 1 H, 4-H\(_b\)), 4.02 (d, \( J = 15.7 \) Hz, 1 H, 1-H\(_a\)), 5.23 (d, \( J = 15.7 \) Hz, 1 H, 1-H\(_b\)), 7.06-7.52 (m, 10 H, CH\(_2\)C\(_6\)H\(_5\), C(H\(_2\)\(_3\))). \( ^{13}C \) NMR (CDCl\(_3\)): \( \delta = 20.2, 21.9 \) [2q, C(CH\(_3\)_2)], 38.8 (t, C-4), 43.2 (t, C-1'), 45.0 (s, C-8), 98.0 (s, C-5), 127.1, 128.2, 139.0, 129.1, 129.8 (6 d, \( \alpha-C \), \( \beta-C \) of CH\(_2\)C\(_6\)H\(_5\), C\(_6\)H\(_5\)), 131.1 (s, \( i-C \) of C\(_6\)H\(_5\)), 137.0 (s, \( i-C \) of CH\(_2\)C\(_6\)H\(_5\)), 156.0 (s, C-3), 175.8 (s, C-7), 207.0 (s, C-9). IR: 1773 (s), 1710 (vs), 1600 (m), 1495 (w), 1332 (m), 1293 (vs), 1359 (s), 1333 (s), 1295 (w), 1220 (w), 1182 (s), 1129 (vs), 1078 (s), 1046 (m), 894 (vs), 820 (vs) cm\(^{-1}\).

(5R)-Ethyl 6-benzyl-8,8-dimethyl-7,9-dioxo-1-oxa-2,6-diazaspiro[4.4]non-2-ene-3-carboxylate (12)

To 1.0 g (4.36 mmol) of 7 in 100 mL ether, 800 mg (5.28 mmol, 1.2 eq) of Ethyl Chlorooximidoacetate was added with stirring at 0 \(^\circ\)C. To this reaction mixture 10.56 mL (0.5 M, 5.28 mmol, 1.2 eq) of triethylamine solution in ether was added drop wise with a rate of 8-10 drops per min, and then kept stirring overnight. The mixture was quenched with HCl (50 mL, 1.0 M), partitioned against ether (3 × 50 mL), and the combined organic phases were washed with sat. NaHCO\(_3\) (50 mL), water (2 × 50 mL), and then dried (MgSO\(_4\)), filtered and concentrated to give 1.60 g of crude yellowish oil, which was chromatographed (SiO\(_2\), column 2 cm × 15 cm, Petroleum ether/ethyl acetate 9:1 gradually until 7:3) to yield after crystallization from ether 910 mg (61%) of 12 as colorless crystals (m.p. 99–100 \(^\circ\)C). It was possible to get X-ray structure of 12. 8

The analytical data: \( ^1H \) NMR (CDCl\(_3\)): \( \delta = 1.32, 1.43 \) [2 s, 6 H, C(CH\(_3\)_2)], 1.34 (t, \( J = 7.1 \) Hz, 3 H, CH\(_2\)C\(_2\)H\(_5\)), 2.78 (d, \( J = 19 \) Hz, 1 H, 4-H\(_a\)), 3.40 (d, \( J = 19 \) Hz, 1 H, 4-H\(_b\)), 4.01 (d, \( J = 15.6 \) Hz, 1 H, 1-H\(_a\)), 4.31 (q, \( J = 7.1 \) Hz, 2 H, \( t-C\(_2\)H\(_2\)CH\(_3\)\)), 5.13 (d, \( J = 15.6 \) Hz, 1 H, 1-H\(_b\)), 7.11-7.38 (m, 5 H, C\(_6\)H\(_5\)). \( ^{13}C \) NMR (CDCl\(_3\)): \( \delta = 14.3 \) (q, C\(_2\)H\(_5\)), 20.2, 21.9 [2q, C(CH\(_3\)_2)], 36.9 (t, C-4), 43.2 (t, C-1'), 44.8 (s, C-8), 62.7 (t, C\(_2\)H\(_2\)CH\(_3\)), 99.7 (s, C-5), 128.1, 128.5, 129.2 (3 d, \( \alpha-C \), \( \beta-C \) of C\(_6\)H\(_5\)), 136.2 (s, \( i-C \) of C\(_6\)H\(_5\)), 150.8 (s, C-3), 159.3 (COCH\(_2\)CH\(_3\)), 175.6 (s, C-7), 205.6 (s, C-9). m/e: 344.2 (calculated 344.14). IR: 2985 (w), 2971 (w), 2938 (w), 1781 (m), 1718 (vs), 1601 (m), 1464 (w), 1443 (m), 1415 (w), 1391 (s), 1376 (w), 1340 (s), 1284(w), 1263 (s), 1180 (s), 1111 (s), 1104 (m), 1004 (m), 905 (m), 814 (s), 740 (vs), 725 (s), 696 (vs) cm\(^{-1}\).

(5S) and (5R)-6-Benzyl-3-((1S)-1,4-dioxaspiro[4.5]decan-2-yl)-8,8-dimethyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (13a and 13b)

To 650 mg (2.84 mmol) of 7 in 100 mL ether, 750 mg (3.41 mmol, 1.2 eq) of 2,3-O-cyclohexylidene-D-glycerohydroximoyl chloride 10 was added with stirring at 0 °C. To this reaction mixture 7.5 mL (0.5 M, 3.75 mmol, 1.1 eq) of triethylamine solution in ether was added drop wise with a rate of 8-10 drops per min, and then kept stirring overnight. The mixture was quenched with HCl (50 mL, 1.0 M), partitioned against ether (3 x 50 mL), and then dried (MgSO4), filtered and concentrated to give 1.81 g of crude yellowish oil, which was chromatographed (SiO2, column 2 cm x 15 cm, Petroleum ether/ethyl acetate 9:1) to yield 502 mg (43%) of (5S)-6-Benzyl-3-((1S)-1,4-dioxaspiro[4.5]decan-2-yl)-8,8-dimethyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene-7,9-dione 13a as colourless crystal (m.p. 130-131 °C), and 378 mg (32%) of (5R)-6-Benzyl-3-((1S)-1,4-dioxaspiro[4.5]decan-2-yl)-8,8-dimethyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene-7,9-dione 13b as colourless oil in 75% overall yield, corresponding to a d.r. of 57:43. It was possible to get X-ray structure of 13a.9

The analytical data:

A) Major diastereomer:
(5S)-6-Benzyl-3-((1S)-1,4-dioxaspiro[4.5]decan-2-yl)-8,8-dimethyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (13a)

The analytical data: 1H NMR (CDCl3): δ = 1.21-1.62 [m, 16 H, C(CH3)2, C(CH3)5], 2.81 – 2.95 (m, 1 H, 4-Ha), 3.23-3.37 (m, 1 H, 4-Hb), 3.88-3.99 (m, 1 H, 2-Ha), 4.01-4.20 (m, 2 H, 2'-Hb, 1''-Ha), 4.76-4.87 (m, 1 H, 1'-H), 4.97-5.11 (m, 1 H, 1''-Hb), 7.19-7.40 (m, 5 H, C6H5). 13C NMR (CDCl3): δ = 20.0, 22.0 [q, C(CH3)2], 23.9, 24.1, 25.2, 34.9, 35.9 [t, C(CH3)3], 36.9 (t, C-4), 44.8 (t, C-1’), 44.8 (s, C-8), 66.7 (t, C-2’), 70.5 (d, C-1’), 97.8 (s, C-5), 111.6 [s, C(CH2)5], 127.8, 128.1, 129.1 (3 d, o-), m- m-C of C6H5), 136.9 (s, o-C of C6H5), 158.0 (s, C-3), 175.9 (s, C-7), 206.8 (s, C-9). m/e: 412.2 (calculated 412.2). IR: 2938 (m), 2885 (w), 2869 (w), 1775 (m), 1706 (vs), 1621 (w), 1495 (w), 1433 (m), 1394 (s), 1340 (s), 1240 (w), 1165 (s), 1100 (vs), 1088 (vs), 1038 (s), 921 (m), 888 (m), 869 (s), 824 (s), 754 (s), 698 (vs), 632 (cm-1).

B) Minor diastereomer:
(5R)-6-Benzyl-3-((1S)-1,4-dioxaspiro[4.5]decan-2-yl)-8,8-dimethyl-1-oxa-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (13b)

1H NMR (CDCl3): δ = 1.11-1.60 [m, 16 H, C(CH3)2, C(CH3)5], 2.69 – 2.83 (m, 1 H, 4-Ha), 3.28-3.38 (m, 1 H, 4-Hb), 3.51-3.60 (m, 1 H, 2-Ha), 3.97-4.12 (m, 2 H, 2'-Hb, 1''-Ha), 4.68-4.79 (m, 1 H, 1’-H), 4.89-5.03 (m, 1 H, 1''-Hb), 7.11-7.31 (m, 5 H, C6H5). 13C NMR (CDCl3): δ = 20.2, 21.9 [q, C(CH3)2], 23.9, 24.1, 25.1, 34.9, 35.0 [5 t, C(CH3)3], 37.8 (t, C-4), 43.1 (t, C-1’), 44.8 (s, C-8), 66.8 (t, C-2’), 70.5 (d, C-1’), 97.6 (s, C-5), 111.4 [s, C(CH2)5], 127.6, 128.2, 129.2 (3 d, o-), m- m-C of C6H5), 136.8 (s, m-C of C6H5), 157.7 (s, C-3), 176.0 (s, C-7), 206.9 (s, C-9).

6-Benzyl-8,8-dimethyl-1-oxa-3-tolual-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (14)

To 1.0 g (4.36 mmol) of 7 in 100 ml ether, 0.74 g (4.36 mmol) of N-hydroxytolualmidoylchloride was added with stirring at 0°C. To this reaction mixture 0.49 g (0.25 M, 4.79 mmol, 1.1 eq) triethylamine solution in ether was added drop wise with a rate of 8-10 drops per min, and then keep stirring overnight. The mixture was quenched with HCl (30 ml, 2.0 M), partitioned against ether (3×50 ml), and the combined organic phases were washed with sat. NaHCO₃ (50 ml), water (2×50 ml), then dried over (MgSO₄), filtered and concentrated to give 1.50 g of crude yellowish oil. Crystallization from ether produced 1.18 g (75 %) of 14 as white powder (m.p. 123-124 °C).

The analytical data: ¹H NMR (CDCl₃): δ = 1.36, 1.46 [2s, 6H, C(CH₃)₂], 2.39 (s, 3H, C₆H₄CH₂), 2.90 (d, J = 17.7 Hz, 1H, 4-H₄), 3.57 (d, J = 17.7 Hz, 1H, 4-H₄), 4.02 (d, J = 15.5 Hz, 1H, 1'-H₄), 5.21 (d, J = 15.5 Hz, 1H, 1'-H₄), 7.13-7.33 (m, 9H, CH₂C₆H₅, C₆H₄CH₃). ¹³C NMR (CDCl₃): δ = 20.0, 21.5 [2q, C(CH₃)₂], 21.7 (q-C-1'), 38.8 (t, C-4), 42.9 (t, C-1'), 44.8 (s, C-8), 97.6 (s, C-5), 125.0, 126.9, 127.9, 128.0, 128.9, 129.5 (6d, α-), -m-, -p-C of CH₂C₆H₅, C₆H₄CH₃), 136.8 (s, i-C of CH₂C₆H₅), 141.4 (s, i-C of C₆H₄CH₃), 155.7 (s, C-3), 175.5 (s, C-7), 207.1 (s, C-9).

m/e: 362.2 (calculated 362.42). Elemental Analysis: C₂₃H₂₄N₂O₃, Calculated C 73.38, H 6.43, N 7.44; Found C 73.43, H 6.66, N 7.43

6-Benzyl-8,8-dimethyl-1-oxa-3-anisal-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (15)

To 1.0 g (4.36 mmol) of 7 in 100 ml ether, 0.81 g (4.36 mmol) of N-hydroxyanisalmidoylchloride was added with stirring at 0 °C. To this reaction mixture 0.49 g (0.25 M, 4.80 mmol, 1.1 eq) triethylamine solution in ether was added drop wise with a rate of 8-10 drops per min, and then keep stirring overnight. The mixture was quenched with HCl (30 ml, 2.0 M), partitioned against ether (3×50 ml), and the combined organic phases were washed with sat. NaHCO₃ (50 ml), water (2×50 ml), then dried over (MgSO₄), filtered and concentrated to give 1.45 g of crude yellowish oil. Crystallization from ether produced 1.38 g (84 %) of 15 as white powder (m.p. 135-136 °C).

The analytical data: ¹H NMR (CDCl₃): δ = 1.36, 1.46 [2s, 6H, C(CH₃)₂], 2.91 (d, J = 18 Hz, 1H, 4-H₄), 3.56 (d, J = 18 Hz, 1H, 4-H₄), 3.85 (s, 3H, OCH₃), 4.01 (d, J = 15 Hz, 1H, 1'-H₄), 5.23 (d, J = 15 Hz, 1H, 1'-H₄), 6.86-7.38 (m, 9H, CH₂C₆H₅, C₆H₄OCH₃). ¹³C NMR (CDCl₃): δ = 20.0, 21.7 [2q, C(CH₃)₂], 39.0 (t, C-4), 42.9 (t, C-1'), 44.8 (s, C-8), 55.4 (q, OCH₃), 97.5 (s, C-5), 114.2, 120.3, 127.9, 128.1, 128.4, 128.9 (6d, α-), -m-, -p-C of CH₂C₆H₅, C₆H₄OCH₃), 136.8 (s, i-C of CH₂C₆H₅), 155.2 (s, C-3), 161.6 (s, i-C of C₆H₄OCH₃), 175.5 (s, C-7), 207.1 (s, C-9).

m/e: 378.2 (calculated 378.42). Elemental Analysis: C₂₂H₂₂N₂O₃, Calculated C 72.91, H 6.12, N 7.73; Found C 73.16, H 6.27, N 7.75

6-Benzyl-8,8-dimethyl-1-oxa-3-isopropylphenyl-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (16)

To 1.0 g (4.36 mmol) of 7 in 100 ml ether, 0.87 g (4.36 mmol) of N-hydroxyanisalmidoylchloride was added with stirring at 0°C. To this reaction mixture 0.49 g (0.25 M, 4.79 mmol, 1.1 eq) triethylamine solution in ether was added drop wise with a rate of 8-10 drops per min, and then keep stirring overnight.
The mixture was quenched with HCl (30 mL, 2.0 M), partitioned against ether (3×50 mL), and the combined organic phases were washed with sat. NaHCO₃ (50 mL), water (2×50 mL), then dried over (MgSO₄), filtered and concentrated to give 1.50 g of crude yellowish oil. Crystallization from ether produced 1.10 g (65%) of 16 as yellowish crystal (m.p. 96-97 °C).

The analytical data: ¹H NMR (CDCl₃): δ = 1.26 [dd, J₁⁻₂''= 1.9, J₃a₂''= 6.0 Hz, 3H, C₆H₃CH(CH₃)₂], 1.28 [dd, J₁⁻₂''= 2.1, J₃a₂''= 6.0 Hz, 3H, C₆H₃CH(CH₃)₂], 1.36, 1.46 [2s, 6H, C(CH₃)₂], 2.90 [m, 1H, C₆H₃CH(CH₃)₂], 2.93 (d, J=18.0 Hz, 1H, 4-H₃), 3.57 (d, J=18.0 Hz, 1H, 4-H₃), 4.02 (d, J=15.0 Hz, 1H, 1'⁻H₄), 5.20 (d, J=15.0 Hz, 1H, 1'⁻H₄), 7.16-7.38 [m, 9H, CH₂C₆H₅, C₆H₃CH(CH₃)₂].

¹³C NMR (CDCl₃): δ = 20.0, 21.7 [2q, C(CH₃)₂], 23.7,23.8 [2q, C₆H₃CH(CH₃)₂], 34.1 [d, C₆H₃CH(CH₃)₂], 38.7 (t,C-4), 42.9 (t, C-1'), 44.8 (s, C-8), 97.5 (s, C-5), 125.4, 126.9, 127.0, 127.9, 128.0, 128.8, [6d, a-, m-, p-C of CH₂C₆H₅, C₆H₃CH(CH₃)₂], 136.8 (s, i-C of CH₂C₆H₅), 152.2 [s, i-C of C₆H₃CH(CH₃)₂], 155.7 (s, C-3), 175.6 (s,C-7), 207.0 (s,C-9).

m/e: 390.3 (calculated 390.47). Elemental Analysis: C₂₇H₂₆N₂O₃, Calculated C 73.82, H 6.71, N 7.17; Found C 73.87, H 6.95, N 7.20

6-Benzyl-8,8-dimethyl-1-oxa-3-ethylphenyl-2,6-diazaspiro[4.4]non-2-ene-7,9-dione (17)

To 1.0 g (4.36 mmol) of 7 in 100 ml ether, 0.80 g (4.36 mmol) of N-hydroxyethylphenylimidoylchloride was added with stirring at 0°C. To this reaction mixture 0.49 g (0.25 M, 4.79 mmol, 1.1 eq) triethylamine solution in ether was added drop wise with a rate of 8-10 drops per min, and then keep stirring overnight. The mixture was quenched with HCl (30 mL, 2.0 M), partitioned against ether (3×50 mL), and the combined organic phases were washed with sat. NaHCO₃ (50 mL), water (2×50 mL), then dried over (MgSO₄), filtered and concentrated to give 1.60 g of crude yellowish oil. Crystallization from ether produced 1.33 g (81%) of 17 as yellowish crystal (m.p. 111-112 °C).

The analytical data: ¹H NMR (CDCl₃): δ = 1.26 (t, J = 7.3 Hz, 3H, C₆H₃CH₂CH₂CH₃), 1.36, 1.46 [2s, 6H, C(CH₃)₂], 2.67 (q, J = 7.3 Hz, 2H, C₆H₃CH₂CH₃), 2.93 (d, J = 18 Hz, 1H, 4-H₃), 3.57 (d, J = 18 Hz, 1H, 4-H₃), 4.02 (d, J = 16 Hz, 1H, 1'⁻H₄), 5.20 (d, J = 16 Hz, 1H, 1'⁻H₄), 7.15-7.36 (m, 9H, CH₂C₆H₅, C₆H₃CH₂CH₃). ¹³C NMR (CDCl₃): δ = 15.3 (q, C-2'), 20.0, 21.7 [2q, C(CH₃)₂], 28.8 (t, C-1'), 38.8 (t,C-4), 42.9 (t, C-1'), 44.8 (s, C-8), 97.6 (s, C-5), 125.2, 126.9, 127.9, 128.0, 128.3, 128.9 (6d, o-, m-, p-C of CH₂C₆H₅, C₆H₃CH₂CH₃), 136.8 (s, i-C of CH₂C₆H₅), 147.6 (s, i-C of C₆H₃CH₂CH₃), 155.7 (s, C-3), 175.6 (s,C-7), 207.0 (s,C-9).
$^1$H-NMR (CDCl$_3$)

$^{13}$C-NMR (CDCl$_3$)
$^1$H-NMR (CDCl$_3$)

$^{13}$C-NMR (CDCl$_3$)
$^1$H-NMR (CDCl$_3$)

$^{13}$C-NMR (CDCl$_3$)
$^{1}$$H$-NMR (CDCl$_3$)

$^{13}C$-NMR (CDCl$_3$)