Synthesis of Novel Trispiroheterocycles through 1,3-Dipolar Cycloaddition of Azomethine Ylides and Nitrile Oxide

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The 1,3-dipolar cycloaddition of an azomethine ylide generated by a decarboxylative route from sarcosine and isatin to 1-benzyl-3,5-diarylmethylidene-piperidin-4-ones afforded novel di-spiro-indolo/pyrrolidino/piperidines in moderate yields. Further cycloaddition of these di-spiro compounds to nitrile oxide afforded tri-spiro-indolo/pyrrolidino/piperadino/isoxazolines in moderate yields with high regio- and stereoselectivity.

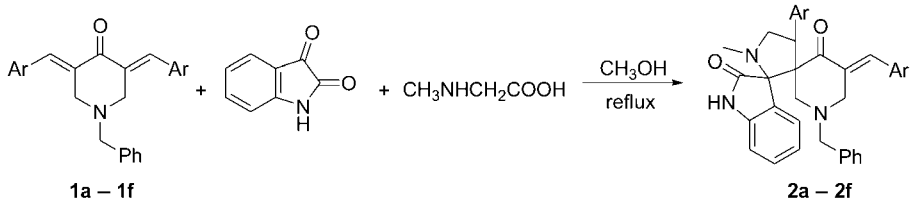
Keywords spiroheterocycle, 1,3-dipolar cycloaddition, azomethine ylide, nitrile oxide

Introduction

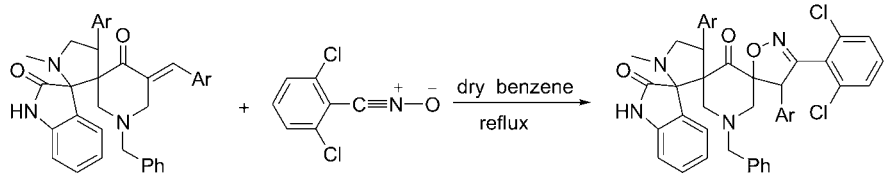
Pyrrolidine,[1-3] isoxazoline[4-6] and piperidine[7-9] substructures exhibit important biological activities. The 1,3-dipolar cycloaddition of nitrile oxides to azomethine ylide to alkenes affords pyrrolidines and isoxazolines. Spiroheterocycles with pyrrolidine or isoxazoline substructures are an important class of organic compounds based on their biological activities,[10-12] which are motifs in many pharmacologically relevant alkaloids.[13,14] One of the most widely used methods for the synthesis of these compounds is via the intermolecular 1,3-dipolar cycloaddition reaction to exocyclic double bonds.

Due to the importance of pyrrolidines, isoxazolines and piperidines, we investigate the synthesis of novel spiro-pyrrolidines via azomethine ylide cycloaddition to 1-benzyl-3,5-diarylmethylidene-piperidin-4-one and their subsequent cycloaddition to nitrile oxide to obtain novel tri-spiro heterocycles (Scheme 1). Recently, Perumal[15] reported a tandem azomethine ylide/nitrile oxide cycloaddition to 1-methyl-3,5-diarylmethylidene-piperidin-4-one, which only obtained cycloreversion mono-spiro-isoxazoline compounds. The present work is the first report on the synthesis of tri-spiro-indolo/pyrrolidino/piperadino/isoxazolines.

Scheme 1



1a – 1f **2a – 2f**



2a – 2f **3a – 3f**

Ar: **a**, C_6H_5; **b**, 4-ClC_6H_4; **c**, 2-ClC_6H_4; **d**, 2,4-$Cl_2C_6H_3$; **e**, 4-$CH_3OC_6H_4$; **f**, 4-$CH_3SC_6H_4$

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Experimental

Materials and instruments

2,6-Dichloro-benzonitrile oxide[16] and 1-benzyl-3,5-diarylmethylidene-piperidin-4-one (**1**)[17] were prepared according to the reported procedures. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C, TMS was used as an internal reference for ^{1}H and ^{13}C chemical shifts, and $CDCl_3$ used as solvent. Elemental analysis was conducted on an Elementar analyzer (varioEL II). MS data were measured on a Finnigan LCQ Advantage MAX mass spectrometer. IR spectra were recorded on a Perkin-Elmer spectrometer (Spectrum one). Melting points were measured by a Yanaco MP500 melting points apparatus and uncorrected.

General procedure for the synthesis of 4'-aryl-5"-arylmethylidene-1"-benzyl-1'-methyl-2,3-dihydro-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-3"-piperidine-2,4"-dione (2a—2f)

A mixture of **1** (1 mmol), isatin (1 mmol) and sarcosine (1 mmol) was dissolved in methanol (40 mL) and heated to reflux for 24 h. After completion of the reaction as evidented by TLC, The solvent was evaporated in vacuum. The residue was purified by column chromatography employing petroleum ether/ethyl acetate mixture (4∶1, *V/V*) as eluent to obtain **2**.

1"-Benzyl-5"-benzylidene-1'-methyl-4'-phenyl-2,3-dihydro-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-3"-piperidine-2,3"-dione (2a) White solid, yield 80%; m.p. 207—208 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.88 (d, J=12.5 Hz, 1H), 2.16 (s, 3H), 2.78 (dd, J=3.0, 14.5 Hz, 1H), 3.16 (d, J=13.5 Hz,1H), 3.36—3.41 (m, 2H), 3.47 (dd, J=2.0, 12.5 Hz, 1H), 3.62 (d, J=13.0 Hz, 1H), 3.97 (dd, J=9.0, 10.5 Hz, 1H), 4.83 (dd, J=7.0, 11.0 Hz, 1H), 6.64 (d, J=7.5 Hz, 1H), 6.91—6.99 (m, 5H), 7.09—7.20 (m, 8H), 7.24—7.26 (m, 3H), 7.32 (t, J=7.5 Hz, 3H), 7.45 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.67, 46.35, 53.95, 57.00, 57.07, 62.18, 65.68, 76.12, 108.81, 122.16, 126.90, 127.01, 127.37, 127.84, 128.05, 128.21, 128.27, 128.62, 128.73, 128.85, 129.74, 129.94, 133.14, 135.04, 136.83, 137.80, 138.48, 141.94, 177.45, 199.07; IR (KBr) ν: 1699.6, 1682.0 cm^{-1}; ESI MS *m/z*: 540 [M+H]$^+$. Anal. calcd for $C_{36}H_{33}N_3O_2$: C 80.12, H 6.16, N 7.79; found C 80.00, H 6.26, N 7.58.

1"-Benzyl-5"-(4-chlorobenzylidene)-4'-(4-chlorophenyl)-1'-methyl-2,3-dihydro-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-3"-piperidine-2,3"-dione (2b) White solid, yield 82%; m.p. 211—212 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.85 (d, J=13.0 Hz, 1H), 2.13 (s, 3H), 2.73 (dd, J=2.5, 14.5 Hz, 1H), 3.15 (d, J=13.0 Hz, 1H), 3.33—3.38 (m, 2H), 3.44 (dd, J=2.0, 12.5 Hz, 1H), 3.63 (d, J=13.0 Hz, 1H), 3.89 (dd, J=9.0, 10.5 Hz, 1H), 4.78 (dd, J=7.5, 10.5 Hz, 1H) , 6.68 (d, J=7.5 Hz, 1H), 6.83 (d, J=8.5 Hz, 2H), 6.92—6.98 (m, 3H), 7.06—7.12 (m, 3H), 7.16 (d, J=8.5 Hz, 2H), 7.19—7.23 (m, 3H), 7.28 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.56 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.60, 45.61, 53.82, 57.03, 57.13, 62.23, 65.43, 76.07, 108.95, 122.12, 127.13, 127.18, 127.75, 128.15, 128.42, 128.53, 128.67, 128.97, 131.04, 131.08, 132.74, 133.32, 133.42, 134.70, 136.54, 136.62, 136.96, 141.99, 177.48, 199.72; IR (KBr) ν: 1712.9, 1693.6 cm^{-1}; ESI MS *m/z*: 608 [M+H]$^+$. Anal. calcd for $C_{36}H_{31}Cl_2N_3O_2$: C 71.05, H 5.13, N 6.90; found C 70.94, H 5.23, N 6.82.

1"-Benzyl-5"-(2-chlorobenzylidene)-4'-(2-chlorophenyl)-1'-methyl-2,3-dihydro-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-3"-piperidine-2,3"-dione (2c) White solid, yield 81%; m.p. 246—248 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.95 (d, J=12.5 Hz, 1H), 2.12 (s, 3H), 2.77 (dd, J=2.5, 14.5 Hz, 1H), 3.07 (d, J=13.5 Hz, 1H), 3.18 (dd, J=2.0, 13.0 Hz, 1H), 3.24 (d, J=14.5 Hz, 1H), 3.44—3.50 (m, 2H), 3.98 (dd, J=9.5, 10.5 Hz, 1H), 5.15 (dd, J=7.5, 10.5 Hz, 1H), 6.71 (d, J=7.5 Hz, 2H), 6.86—6.87 (m, 2H), 6.96—7.01 (m, 2H), 7.10—7.22 (m, 7H), 7.29 (d, J=7.5 Hz, 1H), 7.33—7.37 (m, 2H), 7.40 (s, 1H), 7.65 (bs, 1H), 8.01 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.78, 42.68, 54.38, 57.39, 57.76, 62.62, 63.24, 108.88, 122.94, 126.13, 126.52, 126.71, 126.94, 127.99, 128.11, 128.45, 128.66, 129.26, 129.59, 129.64, 129.68, 130.94, 133.52, 133.83, 134.90, 135.02, 135.99, 136.79, 137.16, 141.90, 176.85, 197.59; IR (KBr) ν: 1703.3, 1689.8 cm^{-1}; ESI MS *m/z*: 608 [M+H]$^+$. Anal. calcd for $C_{36}H_{31}Cl_2N_3O_2$: C 71.05, H 5.13, N 6.90; found C 70.84, H 5.16, N 6.97.

1"-Benzyl-5"-(2,4-dichlorobenzylidene)-4'-(2,4-dichlorophenyl)-1'-methyl-2,3-dihydro-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-3"-piperidine-2,3"-dione (2d) White solid, yield 80%; m.p. 221—222 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.90 (d, J=12.5 Hz, 1H), 2.11 (s, 3H), 2.72 (dd, J=2.5, 15 Hz, 1H), 3.06 (d, J=13.5 Hz, 1H), 3.16 (dd, J=2.5, 13.0 Hz, 1H), 3.21 (d, J=14.5 Hz, 1H), 3.46—3.51 (m, 2H), 3.89 (t, J=9.0 Hz, 1H), 5.09 (t, J=9.0 Hz, 1H), 6.62 (d, J=8.5 Hz, 1H), 6.72 (d, J=7.5 Hz, 1H), 6.86—6.88 (m, 2H), 6.94—6.99 (m, 2H), 7.10 (d, J=7.5 Hz, 1H), 7.15—7.19 (m, 4H), 7.32—7.38 (m, 4H), 7.56 (bs, 1H), 7.97 (d, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.71, 42.13, 54.18, 57.45, 57.85, 62.70, 63.15, 77.25, 109.14, 122.89, 126.31, 126.59, 127.03, 127.10, 127.99, 128.10, 128.40, 128.84, 129.04, 129.62, 130.32, 131.86, 133.10, 133.94, 134.10, 134.90, 135.51, 135.65, 136.54, 136.93, 142.07, 177.25, 197.25; IR (KBr) ν: 1707.1, 1678.2 cm^{-1}; ESI MS *m/z*: 677 [M+H]$^+$. Anal. calcd for $C_{36}H_{29}Cl_4N_3O_2$: C 63.83, H 4.31, N 6.20; found C 63.94, H 4.27, N 6.24.

1"-Benzyl-5"-(4-methoxybenzylidene)-4'-(4-methoxyphenyl)-1'-methyl-2,3-dihydro-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-3"-piperidine-2,3"-dione (2e) White solid, yield 85%; m.p. 215—216 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.92 (d, J=13.0 Hz, 1H), 2.13 (s, 3H), 2.80 (dd, J=2.5, 14.5 Hz, 1H), 3.14 (d, J=13.0 Hz, 1H), 3.35—3.38 (m, 2H), 3.42 (dd, J=2.0, 13.0 Hz, 1H), 3.64 (d, J=13.5 Hz, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 3.90 (dd, J=9.0, 11 Hz, 1H), 4.78 (dd, J=7.5, 11.0 Hz, 1H), 6.67 (d, J=7.5 Hz, 1H), 6.72 (d, J=9.0 Hz, 2H),

6.85 (d, J=9.0 Hz, 2H), 6.91 (t, J=7.5 Hz, 1H), 6.94 (d, J=7.5 Hz, 2H), 6.99—7.01 (m, 2H), 7.07—7.12 (m, 2H), 7.16—7.22 (m, 4H), 7.38 (d, J=8.5 Hz, 2H), 7.68 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.65, 45.77, 54.41, 55.24, 55.26, 57.17, 57.39, 62.53, 65.18, 76.38, 108.78, 113.60, 113.78, 122.06, 126.97, 127.42, 127.77, 128.07, 128.69, 130.59, 130.73, 130.90, 132.12, 137.11, 137.73, 142.01, 158.47, 160.00, 177.63, 199.00; IR (KBr) v: 1709.0, 1693.6 cm^{-1}; ESI MS m/z: 600 [M+H]$^+$. Anal. calcd for $C_{38}H_{37}N_3O_4$: C 76.10, H 6.22, N 7.01; found C 76.17, H 6.10, N 7.08.

1"-Benzyl-5"-[4-(methylthio)benzylidene]-4'-[4-(methythio)phenyl]-1'-methyl-2,3-dihydro-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-3"-piperidine-2,3"-dione (2f) White solid, yield 85%; m.p. 198—200 ℃ ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.90 (d, J=12.5 Hz, 1H), 2.14 (s, 3H), 2.43 (s, 3H), 2.48 (s, 3H), 2.79 (dd, J=2.5, 14.5 Hz, 1H), 3.15 (d, J=13.0 Hz, 1H), 3.34—3.39 (m, 2H), 3.43 (dd, J=2.0, 13.0 Hz, 1H), 3.64 (d, J=13.0 Hz, 1H), 3.91 (dd, J=11.0, 10.5 Hz, 1H), 4.77 (dd, J=7.5, 11.0 Hz, 1H), 6.65 (d, J=7.5 Hz, 1H), 6.88 (d, J=8.0 Hz, 2H), 6.92 (t, J=7.5 Hz, 1H), 6.98—7.00 (m, 2H), 7.04 (d, J=8.5 Hz, 2H), 7.08—7.10 (m, 2H), 7.15 (s, 1H), 7.18—7.22 (m, 5H), 7.38 (d, J=8.5 Hz, 2H), 7.43 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.01, 15.98, 34.62, 45.96, 54.22, 57.10, 57.13, 62.42, 65.31, 76.30, 108.96, 122.08, 125.37, 126.54, 127.07, 127.26, 127.74, 128.13, 128.69, 128.86, 130.24, 130.62, 131.44, 132.20, 135.46, 136.72, 136.89, 137.45, 140.33, 142.12, 177.81, 198.86; IR (KBr) v: 1702.8, 1689.8 cm^{-1}; ESI MS m/z: 632 [M+H]$^+$. Anal. calcd for $C_{38}H_{37}N_3O_2S_2$: C 72.23, H 5.90, N 6.65; found C 72.10, H 5.99, N 6.60.

General procedure for the synthesis of 4,4"-diaryl-1'-benzyl-3-(2,6-dichlorophenyl)-1"-methyl-4,5,2''',3'''-tetrahydro-1'''*H*-isoxazole-5-spiro-3'-piperidine-2"-spiro-3"-indole-4',2"-diones (3a—3f)

A mixture of **2** (1 mmol) and 2,6-dichloro-benzonitrile oxide (1.5 mmol) was dissolved in dry benzene (30 mL) and heated to reflux for 24 h. After completion of the reaction as evident from TLC, the solvent was evaporated in vacuum. The residue was purified by column chromatography employing petroleum ether/ethyl acetate mixture (5∶1, *V*/*V*) as eluent to obtain **3**.

1'-Benzyl-3-(2,6-dichlorophenyl)-1"-methyl-4,4"-diphenyl-4,5,2"',3"'-tetrahydro-1"'*H*-isoxazole-5-spiro-3'-piperidine-5'-spiro-3"-pyrrolidine-2"-spiro-3"'-1-indole-2"',4'-dione (3a) White solid, yield 83%; m.p. 225—226 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.56 (d, J=14.0 Hz, 1H), 2.13 (s, 3H), 2.31 (d, J=14.0 Hz, 1H), 2.71 (d, J=13.0 Hz, 1H), 3.07 (d, J=13.0 Hz, 1H), 3.19 (d, J=13.0 Hz, 1H), 3.42—3.49 (m, 2H), 4.01 (t, J=10.0 Hz, 1H), 4.46 (dd, J=8.0, 10.0 Hz, 1H), 5.87 (s, 1H), 6.62 (d, J=6.0 Hz, 1H), 6.65—6.78 (m, 2H), 6.83—6.86 (m, 2H), 6.98—7.10 (m, 9H), 7.12—7.18 (m, 5H), 7.24—7.36 (m, 1H), 7.51 (d, J=6.0 Hz, 2H), 7.70 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.87, 49.33, 52.90, 54.84, 57.52, 58.73, 62.51, 66.23, 76.84, 88.95, 109.93, 122.77, 127.13, 127.43, 127.48, 127.53, 127.98, 128.21, 128.66, 129.03, 129.30, 129.36, 129.94, 130.36, 131.24, 132.12, 136.19, 137.57, 137.95, 143.26, 156.31, 177.67, 202.99; IR (KBr) v: 1714.8, 1699.0 cm^{-1}; ESI MS m/z: 727 [M+H]$^+$. Anal. calcd for $C_{43}H_{36}Cl_2N_4O_3$: C 70.97, H 4.99, N 7.70; found C 70.91, H 5.12, N 7.58.

1'-Benzyl-4,4"-bis-(4-chlorophenyl)-3-(2,6-dichlorophenyl)-1"-methyl-4,5,2"',3"'-tetrahydro-1"'*H*-isoxazole-5-spiro-3'-piperidine-5'-spiro-3"-pyrrolidine-2"-spiro-3"'-indole-2",4'-dione (3b) White solid, yield 80%; m.p. 242—244 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.58 (d, J=14.0 Hz, 1H), 2.13 (s, 3H), 2.29 (d, J=14.0 Hz, 1H), 2.67 (d, J=13.0 Hz, 1H), 3.04 (d, J=13.0 Hz, 1H), 3.22 (d, J=13.5 Hz 1H), 3.43—3.47 (m, 2H), 3.93 (t, J=10.0 Hz, 1H), 4.39 (dd, J=8.0, 10.0 Hz, 1H), 5.84 (s, 1H), 6.64—6.66 (m, 1H), 6.76—6.79 (m, 3H), 6.98—7.00 (m, 2H), 7.02—7.05 (m, 1H), 7.11—7.19 (m, 6H), 7.26—7.31 (m, 5H), 7.44 (d, J=8.5 Hz, 2H), 7.68—7.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.41, 48.74, 52.94, 54.89, 57.52, 58.11, 62.47, 66.07, 76.83, 88.75, 109.57, 122.28, 126.58, 126.95, 127.44, 127.90, 128.35, 128.39, 128.61, 129.01, 130.15, 130.74, 131.07, 131.22, 132.91, 134.16, 135.67, 136.00, 136.86, 142.66, 155.49, 176.88, 202.28; IR (KBr) v: 1716.3, 1696.7 cm^{-1}; ESI MS m/z: 795 [M+H]$^+$. Anal. calcd for $C_{43}H_{34}Cl_4N_4O_3$: C 64.84, H 4.30, N 7.03; found C 64.99, H 4.38, N 6.89.

1'-Benzyl-4,4"-bis-(2-chlorophenyl)-3-(2,6-dichlorophenyl)-1"-methyl-4,5,2"',3"'-tetrahydro-1"'*H*-isoxazole-5-spiro-3'-piperidine-5'-spiro-3"-pyrrolidine-2"-spiro-3"'-indole-2"',4'-dione (3c) White solid, yield 78%; m.p. 238—240 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.50 (d, J=14.0 Hz, 1H), 2.13 (s, 3H), 2.45 (d, J=14.0 Hz, 1H), 2.87 (d, J=13.0 Hz, 1H), 3.10 (d, J=13.0 Hz, 1H), 3.27 (d, J=13.0 Hz, 1H), 3.46—3.50 (m, 2H), 3.92 (t, J=9.5 Hz, 1H), 5.01 (dd, J=8.5, 9.5 Hz, 1H), 6.66 (d, J=7.5 Hz, 1H), 6.71 (s, 1H), 6.80—6.81 (m, 2H), 6.89—6.92 (m, 1H), 6.95—6.99 (m, 2H), 7.06—7.20 (m, 8H), 7.23—7.26 (m, 2H), 7.39 (dd, J=7.5, 1 Hz, 1H), 7.44 (d, J=8.5 Hz, 2H), 7.69 (bs, 1H), 8.08 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.55, 44.94, 53.08, 53.81, 54.52, 58.43, 63.01, 64.38, 77.87, 89.65, 109.32, 123.38, 125.84, 126.31, 126.80, 126.89, 126.96, 127.17, 127.85, 127.99, 128.05, 128.43, 128.56, 128.64, 128.74, 129.35, 129.46, 129.64, 129.67, 130.92, 131.10, 131.56, 134.48, 135.71, 135.93, 136.45, 137.42, 142.26, 155.51, 177.25, 201.05; IR (KBr) v: 1698.6, 1692.9 cm^{-1}; ESI MS m/z: 795 [M+H]$^+$. Anal. calcd for $C_{43}H_{34}Cl_4N_4O_3$: C 64.84, H 4.30, N 7.03; found C 64.93, H 4.25, N 7.15.

1'-Benzyl-4,4"-bis-(2,4-dichloro)phenyl-3-(2,6-dichlorophenyl)-1"-methyl-4,5,2"',3"'-tetrahydro-1"'*H*-isoxazole-5-spiro-3'-piperidine-5'-spiro-3"-pyrrolidine-2"-spiro-3"'-indole-2"',4'-dione (3d) White solid, yield 70%; m.p. 250—251 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.51 (d, J=14.0 Hz, 1H), 2.12 (s, 3H), 2.40 (d, J=14.0 Hz, 1H), 2.83 (d, J=12.5 Hz, 1H), 3.07 (d, J=12.5 Hz, 1H), 3.28 (d, J=13.0 Hz, 1H), 3.47—3.51 (m,

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2H), 3.85 (t, J=9.5 Hz, 1H), 4.92 (t, J=9.5 Hz, 1H), 6.64 (s, 1H), 6.68—6.71 (m, 1H), 6.81—6.82 (m, 2H), 6.91—6.97 (m, 2H), 7.06—7.18 (m, 8H), 7.26—7.30 (m, 3H), 7.39—7.40 (m, 1H), 7.55 (bs, 1H), 8.01 (d, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.51, 44.53, 52.97, 53.35, 54.57, 58.41, 62.96, 67.08, 77.78, 89.46, 109.40, 123.32, 126.38, 126.46, 126.71, 127.03, 127.11, 127.98, 128.02, 128.56, 128.87, 129.32, 129.56, 131.17, 132.01, 132.13, 133.17, 134.35, 134.72, 135.86, 137.01, 137.20, 142.19, 155.24, 176.90, 200.81; IR (KBr) v: 1703.2, 1696.4 cm^{-1}; ESI MS m/z: 863 $[M+H]^+$. Anal. calcd for $C_{43}H_{32}Cl_6N_4O_3$: C 59.67, H 3.73, N 6.47; found C 59.57, H 3.90, N 6.61.

1'-Benzyl-4,4"-bis-(4-methoxyphenyl)-3-(2,6-dichlorophenyl)-1"-methyl-4,5,2"',3"'-tetrahydro-1"'*H*-isoxazole-5-spiro-3'-piperidine-5'-spiro-3"-pyrrolidine-2"-spiro-3"'-indole-2"',4'-dione (3e) White solid, yield 73%; m.p. 220—221 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.60 (d, J=14.0 Hz, 1H), 2.12 (s, 3H), 2.29 (d, J=14.0 Hz, 1H), 2.69 (d, J=13.0 Hz, 1H), 3.04 (d, J=13.0 Hz, 1H), 3.20 (d, J=13.5 Hz, 1H), 3.40—3.46 (m, 2H), 3.65 (s, 3H), 3.81 (s, 3H), 3.94 (t, J=9.5 Hz, 1H), 4.40 (dd, J=8.0, 10.5 Hz, 1H), 5.81 (s, 1H), 6.52 (d, J=8.5 Hz, 2H), 6.65 (d, J=7.5 Hz, 1H), 6.75 (d, J=8.5 Hz, 2H), 6.79—6.80 (m, 2H), 6.87 (d, J=8.5 Hz, 2H), 7.03—7.06 (m, 1H), 7.10—7.17 (m, 6H), 7.25—7.27 (m, 2H), 7.43 (d, J=8.5 Hz, 2H), 7.58 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.51, 48.74, 53.11, 55.07, 55.25, 57.75, 58.16, 62.59, 66.30, 76.92, 88.84, 109.43, 113.44, 113.63, 122.31, 123.67, 126.72, 127.11, 127.21, 127.52, 127.82, 128.70, 128.85, 128.95, 129.61, 130.68, 130.81, 130.93, 135.81, 137.34, 142.69, 156.04, 158.61, 159.21, 176.99, 202.90; IR (KBr) v: 1711.3, 1698.9 cm^{-1}; ESI MS m/z: 787 $[M+H]^+$. Anal. calcd for $C_{45}H_{40}Cl_2N_4O_5$: C 68.61, H 5.12, N 7.11; found C 68.39, H 5.34, N 6.95.

1'-Benzyl-4,4"-bis-[4-(methylthio)phenyl]-3-(2,6-dichlorophenyl)-1"-methyl-4,5,2"',3"'-tetrahydro-1"'*H*-isoxazole-5-spiro-3'-piperidine-5'-spiro-3"-pyrrolidine-2"-spiro-3"'-indole-2"',4'-dione (3f) White solid, yield 70%; m.p. 234—235 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.63 (d, J=14.0 Hz, 1H), 2.13 (s, 3H), 2.30 (d, J=14.0 Hz, 1H), 2.35 (s, 3H), 2.49 (s, 3H), 2.70 (d, J=13.0 Hz, 1H), 3.05 (d, J=13.0 Hz, 1H), 3.22 (d, J=13.5 Hz, 1H), 3.42—3.44 (m, 2H), 3.95 (t, J=10.0 Hz, 1H), 4.39 (dd, J=8.0, 10.0 Hz, 1H), 5.81 (s, 1H), 6.63 (d, J=7.5 Hz, 1H), 6.75 (d, J=8.0 Hz, 2H), 6.79—6.81 (m, 2H), 6.86 (d, J=8.0 Hz, 2H), 7.04—7.06 (m, 2H), 7.13—7.17 (m, 5H), 7.22 (d, J=8.5 Hz, 2H), 7.26—7.28 (m, 3H), 7.43 (d, J=8.0 Hz, 2H), 7.47 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.32, 15.94, 34.50, 49.00, 52.98, 55.04, 57.52, 58.34, 62.50, 66.25, 88.87, 109.46, 122.31, 125.72, 126.54, 126.84, 126.91, 127.10, 127.55, 127.86, 128.23, 128.69, 128.93, 129.01, 130.39, 130.94, 134.44, 135.79, 136.91, 137.18, 142.64, 155.78, 176.73, 202.61; IR (KBr) v: 1707.4, 1697.2 cm^{-1}; ESI MS m/z: 819 $[M+H]^+$. Anal. calcd for $C_{45}H_{40}Cl_2N_4O_3S_2$: C 65.92, H 4.92, N 6.83; found C 65.71, H 4.79, N 6.90.

Results and discussion

The 1,3-dipolar cycloaddition of the azomethine ylide generated *in situ* from isatin and sarcosine to 1-benzyl-3,5-diarylmethylidene-piperidin-4-one **1a**—**1f** afforded novel di-spiropyrrolidines **2a**—**2f** in moderate to good yields (80%—85%) (Scheme 1). This cycloaddition reaction proceeds with high stereo- and regioselectivity to afford only one isomer, which was evidenced from TLC and ^{1}H NMR of the crude reaction mixture. The ^{1}H NMR spectrum of **2b** demonstrates the presence of three CH_2 doublets at δ 1.85, 3.15, 3.63; two doublets of doublets of methylene proton at δ 2.73, 3.44, 3.89 and 4.78 and two singlets at δ 2.13 and 7.56 assignable to the NCH_3 and NH respectively. The ^{13}C NMR spectrum of **2b** demonstrates the presence of two spiro carbon atoms at δ 65.43 and 76.07, two carbonyl carbon atoms at δ 177.48 and 199.72. Further, the structure of the product was confirmed by X-ray diffraction analysis of **2a**[18] (Figure 1).

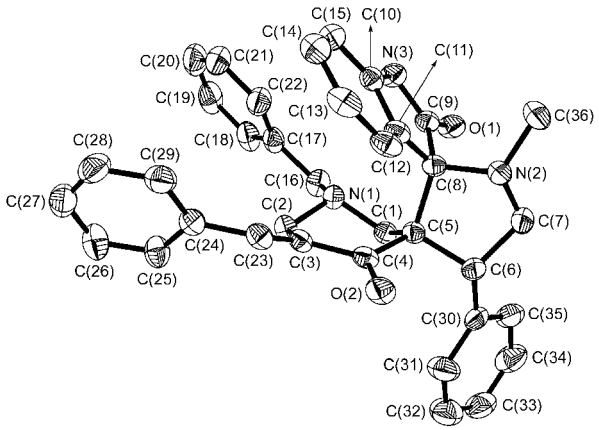

Figure 1 Molecular skeleton structure of compound **2a**.

The spiro-pyrrolidines **2** were subsequently reacted with nitrile oxide (Scheme 1) and tri-spiroheterocycles **3** were obtained in 70%—83% yields. The stereo- and regioselectivity of this cycloaddition reaction was evidenced from TLC and ^{1}H NMR of the crude reaction mixture. In the molecular structure of **2a**, the oxindole ring is located above the double bond plane of arylmethylidene, the 2,6-dichloro-benzonitrile oxide (PNO) can only attack the double bond plane of arylmethylidene from the other side which is less sterically hindered. This induced the stereoselectivity of the reaction (Figure 2). The structure of **3a**—**3f** was elucidated using NMR spectroscopic data and the part HMBC diagram of **3b** is shown in Figure 3. The complete stereochemistry of **3a** was obtained from corresponding single crystal X-ray diffraction research of **3a**[19] (Figure 4).

Conclusion

A facile and novel synthesis of tri-spiroheterocycles was accomplished by the 1,3-dipolar cycloaddition of

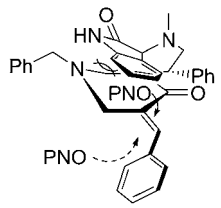

Figure 2 Stereoselectivity mechanism of **3**.

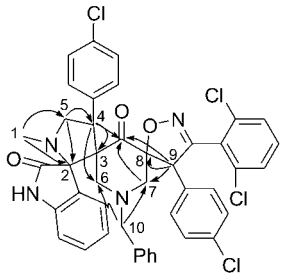

Figure 3 Part HMBC diagram of **3b**.

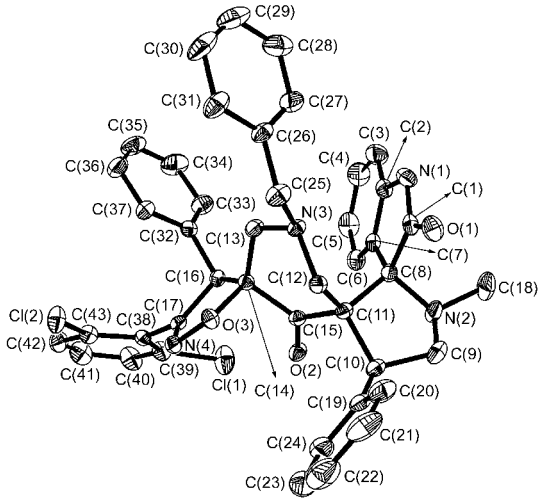

Figure 4 Molecular skeleton structure of compound **3a**.[19]

nitrile oxide with di-spiropyrrolidines, which were obtained by 1,3-dipolar cycloaddition of azomethine ylide to 1-benzyl-3,5-diarylmethylidene-piperidin-4-ones in moderate to good yields. The stereo- and regioselectivities of these reactions were demonstrated by single crystal X-ray diffraction.

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