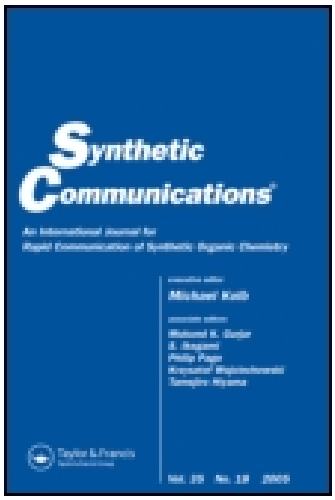

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Synthesis of 6-Substituted/Unsubstituted-7,9-diaryl-1,2,4,8-tetraazaspiro[4.5]-decan-3-thiones

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ABSTRACT

Some 2,6-diarylpiperidin-4-one thiosemicarbazones (**1a–8a**), obtained from the corresponding 2,6-diarylpiperidin-4-ones (**1–8**) on oxidative cyclization with H_2O_2 at 0°C provide 7,9-diaryl-1,2,4,8-tetraaza spiro[4.5]decan-3-thiones (**1b–8b**) in excellent yields. The structures of these compounds have been established on the basis of their elemental, analytical and spectral data.

2,6-Disubstituted piperidines forms a biologically important class of compounds due to their pharmacological activities and their presence in a variety of alkaloids.[1] The 1,2,4-triazole nucleus[2–5] has been incorpo-

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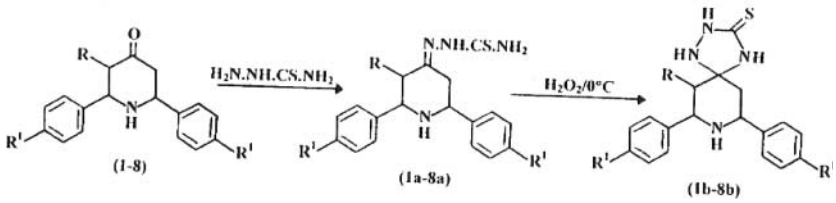

Scheme 1.

rated in a wide variety of therapeutically interesting drugs including H1/H2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, anti anxiety agents, sedatives, analgesic, anti convulsants etc. Therefore it was planned to synthesize a system which combines these two biolabile components together to give a compact structure like title compounds.

1,2,4-Triazolidine-3-thiones were normally obtained from ketone thiosemicarbazones by oxidative cyclization. Earlier MnO_2,[6,7] $FeCl_3{\cdot}6H_2O$,[6,8] *meta*-chloroperbenzoic acid (*m*-CPBA),[9] H_2O_2[10] had been used for synthesizing 1,2,4-triazolidine-3-thiones from steroidal and non-steroidal homocyclic ketone thiosemicarbazones. 2,6-Diarylpiperidin-4-one thiosemicarbazones[11] (**1a–8a**) upon oxidative cyclization using MnO_2 provides a mixture of 7,9-diaryl-1,2,4,8-tetraaza spiro[4.5]decan-3-thiones and 7,9-diaryl-1,2,4,8-tetraazaspiro[4.5]decan-3-ones in equal ratio. The use of $FeCl_3{\cdot}6H_2O$ in the place of MnO_2 also produced the same results but in 3:1 ratio. When *m*-CPBA[12] is used, predominantly title compounds along with a little of *N*-hydroxy piperidin-4-one derivatives and other nonseperable compounds resulted. When tried with H_2O_2 at 0°C as cyclizing agent remarkable results are obtained. Herein we report oxidative cyclization of thiosemicarbazones of piperidinyl heterocycles using H_2O_2 at 0°C for the first time to the best of our knowledge, which results solely the title compounds in excellent yields (Sch. 1).

EXPERIMENTAL

All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Perkin-Elmer 297 IR spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz on Bruker amx 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR spectra

were recorded at 125 MHz on Brucker amx 400 MHz spectrophotometer using $CDCl_3$. The mass spectra were recorded on a VG analytical 7070E instrument equipped with VG 11-250 data acquisition system.

The parent ketones (**1–8**) were prepared by adopting the literature method.[13]

General Method of Preparation of Ketone Thiosemicarbazones[11] (1a–8a): The mixture of ketone (0.01 mol) and thiosemicarbazide (0.01 mol) in glacial acetic acid was refluxed for 3 h and was concentrated to one third of its original volume. After cooling, the mixture was poured over crushed ice. The solid product thus obtained was filtered off and recrystallized twice from methanol to give thiosemicarbazone as crystalline solid.

Synthesis of 7,9-diphenyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (1b): To a solution of **1a** (0.005 mol) in chloroform (40 mL) was treated with excess hydrogen peroxide (30%, 20 mL) and stirred for 3 h at 0°C. After completion of reaction, the organic layer was separated and dried over anhydrous sodium sulphate. The solvents were removed under reduced pressure. The crude product thus obtained was purified over silica gel column (pet. ether–ethyl acetate 5:2) and recrystallized from methanol as needles.

IR (KBr) (cm^{-1}): 3341.5, 3317.1, 2362.1, 1608.8, 1492.4, 1453.8, 1350.0, 1293.8, 1202.9, 1069.9, 1028.0 etc. ^{1}H NMR (δ ppm): 4.22 (dd, $^3J = 11.86$ Hz; 2.89 Hz, 2H) H_7 and H_9, 2.04–2.28 (m, 4H) H_6 and H_{10}, 7.30–7.54 (m, 10H) aryl protons, 8.44 (s (broad), 2H) HN–CS–NH, 7.12 (s, 1H) NH at 1, 1.93 (s, 1H) NH at 8. ^{13}C NMR (δ ppm): 59.534 (C_7, C_9), 38.849 (C_6, C_{10}), 78.659 (C_5), 180.386 (C=S), 124.938, 126.717, 127.260, 147.829 (aryl carbons). Mass (*m*/*z*): 324 (M^+), (M.F: $C_{18}H_{20}N_4S$), 294, 264, 249, 209, 194, 179, 145, 133, 105 (100%), 91, 77, 65, 51. The compounds (**2b–8b**) were synthesized by adopting the same procedure as given for (**1b**). The analytical data of compounds (**1b–8b**) are given in Table 1.

6-Methyl-7,9-diphenyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (2b). IR (KBr) (cm^{-1}): 3424.2, 3345.7, 3320.1, 2360.7, 1590.1, 1492.3, 1453.7, 1376.6, 1351.0, 1268.1, 1075.7 etc. ^{1}H NMR (δ ppm): 4.27 (dd, $^3J = 12.01$ Hz; 2.67 Hz, 1H) H_9, 3.79 (d, $^3J = 10.85$ Hz, 1H) H_7, 2.10–2.34 (m, 3H) H_6 and H_{10}, 7.17–7.48 (m, 10H) aryl protons, 8.39 (br. s, 2H) NH–CS–NH, 6.89 (s, 1H) NH at 1, 1.89 (s, 1H) NH at 8, 0.82 (d, $J = 6.54$ Hz, 3H) CH_3 at 6. ^{13}C NMR (δ ppm): 65.742 (C_7), 59.358 (C_9), 39.961 (C_6), 38.077 (C_{10}), 79.238 (C_5), 180.963 (C=S), 12.050 (CH_3), 124.629, 126.125, 126.468, 127.281, 127.578, 139.987, 147.554 (aryl carbons). Mass (*m*/*z*): 338 (M^+), (M.F: $C_{19}H_{22}N_4S$), 308, 278, 263, 222, 208, 194, 189, 179, 147, 132, 118 (100%), 91, 77, 65, 55, 51.

Table 1. Analytical data of compounds (**1b–8b**).

Compound	R	R^1	Yield (%)	M.p (°C)	Elemental analysis C (%)	H (%)	N (%)
1b	H	H	87	92	66.68	6.17	17.27
2b	CH_3	H	79	84–85	67.45	6.50	16.57
3b	H	CH_3	83	101–102	68.19	6.81	15.90
4b	CH_3	CH_3	75	89	68.84	7.11	15.31
5b	H	Cl	84	123–125	55.09	5.00	14.29
6b	CH_3	Cl	75	105–106	56.17	4.93	13.78
7b	H	OCH_3	81	78	62.48	6.26	14.60
8b	CH_3	OCH_3	72	67	63.34	6.51	14.09

7,9-*bis*(*p*-Methylphenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (3b). IR (KBr) (cm^{-1}): 3331.3, 3298.2, 2347.3, 1603.9, 1500.7, 1468.1, 1341.0, 1300.8, 1210.4, 1028.9, 1001.0 etc. ^{1}H NMR (δ ppm): 4.24 (dd, $^3J = 11.87$ Hz; 2.90 Hz, 2H) H_7 and H_9, 2.03–2.26 (m, 4H) H_6 and H_{10}, 7.25, 7.37 (2d, 8H) aromatic, 8.46 (br. s, 2H) NHCSNH, 7.12 (s, 1H) NH at 1, 1.92 (s, 1H) NH at 8, 2.40 (s, 6H) aryl CH_3. ^{13}C NMR (δ ppm): 58.826 (C_7, C_9), 38.947 (C_6, C_{10}), 78.684 (C_5), 179.998 (C=S), 20.574 (aryl CH_3) 127.852, 128.468, 136.974, 146.438 (aryl carbons). Mass (m/z): 352 (M^+), (M.F: $C_{20}H_{24}N_4S$), 322, 292, 277, 236, 222, 207, 159, 147, 118 (100%), 105, 91, 78, 65, 50.

6-Methyl-7,9-*bis*(*p*-methylphenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (4b). IR (KBr) (cm^{-1}): 3436.7, 3328.5, 3294.0, 2349.2, 1584.2, 1501.4, 1474.2, 1420.9, 1384.7, 1320.4, 1270.2, 1201.5, 1134.3, 1027.4 etc. ^{1}H NMR (δ ppm): 4.25 (dd, $^3J = 12.00$ Hz; 2.68 Hz, 1H) H_9, 3.80 (d, $^3J = 10.84$ Hz, 1H) H_7, 2.09–2.34 (m, 3H) H_6 and H_{10}, 7.29–7.43 (m, 8H) aromatic, 8.38 (br. s, 2H) NH-CS-NH, 6.90 (s, 1H) NH at 1, 2.43 (s, 6H) aryl CH_3, 1.88 (s, 1H) NH at 8, 0.83 (d, $J = 6.54$, 3H) CH_3 at 6. ^{13}C NMR (δ ppm): 65.008 (C_7), 59.574 (C_9), 40.018 (C_6), 38.178 (C_{10}), 79.274 (C_5), 180.894 (C=S), 11.999 (CH_3 at 6), 20.987 (aryl CH_3), 128.310, 128.522, 129.779, 131.610, 135.679, 137.852, 138.644, 146.135 (aryl carbons). Mass (m/z): 366 (M^+), (M.F: $C_{21}H_{26}N_4S$), 336, 306, 291, 250, 236, 222, 203, 161, 146, 132 (100%), 119, 91, 77, 65, 55.

7,9-*bis*(*p*-Chlorophenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (5b). IR (KBr) (cm^{-1}): 3363.7, 3307.4, 2398.0, 1602.2, 1450.3, 1437.4, 1378.3, 1247.8, 1187.8, 1074.7, 1037.3 etc. ^{1}H NMR (δ ppm): 4.26 (dd,

$^3J = 11.87$ Hz; 2.89 Hz, 2H) H_7 and H_9, 2.05–2.29 (m, 4H) H_6 and H_{10}, 7.32, 7.38 (2d, 8H) aromatic, 8.46 (br. s, 2H) NH-CS-NH, 7.07 (s, 1H) NH at 1, 1.87 (s, 1H) NH at 8. ^{13}C NMR (δ ppm): 58.695 (C_7, C_9), 38.750 (C_6, C_{10}), 78.641 (C_5), 180.102 (C=S), 128.252, 128.405, 133.204, 146.742 (aryl carbons). Mass (m/z): 392 (M^+), (M.F: $C_{18}H_{18}N_4SCl_2$), 362, 332, 317, 276, 262, 247, 179, 167, 139 (100%), 111, 95, 75, 65, 50.

6-Methyl-7,9-*bis*(*p*-chlorophenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (6b). IR (KBr) (cm^{-1}): 3418.8, 3375.3, 3299.4, 2394.6, 1587.7, 1488.4, 1474.1, 1361.7, 1348.4, 1241.0, 1091.3 etc. ^{1}H NMR (δ ppm): 4.27 (dd, $^3J = 12.00$ Hz; 2.67 Hz, 1H) H_9, 3.81 (d, $^3J = 10.85$ Hz, 1H) H_7, 2.09–2.37 (m, 3H) H_6 and H_{10}, 7.34–7.47 (m, 8H) aromatic, 8.44 (br. s, 2H) NH-CS-NH, 6.85(s, 1H) NH at 1, 1.90 (s, 1H) NH at 8, 0.82 (d, $J = 6.57$ Hz, 3H) CH_3 at 6. ^{13}C NMR (δ ppm): 64.847 (C_7), 59.362 (C_9), 39.833 (C_6), 38.002 (C_{10}), 79.301 (C_5), 180.907 (C=S), 12.040 (CH_3 at 6), 127.288, 128.726, 128.990, 131.364, 131.989, 133.922, 138.920, 146.443 (aryl carbons). Mass (m/z): 406 (M^+), (M.F: $C_{19}H_{20}N_4SCl_2$), 376, 346, 331, 290, 276, 262, 247, 223, 181, 166, 155, 138 (100%), 111, 94, 75, 65, 55, 50.

7,9-*bis*(*p*-Chlorophenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (7b): IR (KBr) (cm^{-1}): 3369.3, 3305.2, 2347.3, 1603.9, 1500.7, 1468.1, 1341.0, 1300.8, 1210.4, 1028.9, 1001.0 etc. ^{1}H NMR (δ ppm): 4.24 (dd, $^3J = 11.84$ Hz; 2.86 Hz, 2H) H_7 and H_9, 2.02–2.26 (m, 4H) H_6 and H_{10}, 6.89, 7.35 (2d, 8H) aromatic, 8.43 (br. s, 2H) NH-CS-NH, 7.17 (s, 1H) NH at 1, 1.91 (s, 1H) NH at 8, 3.90 (s, 6H) OCH_3. ^{13}C NMR (δ ppm): 58.847 (C_7, C_9), 38.974 (C_6, C_{10}), 78.630 (C_5), 180.159 (C=S), 54.618 (OCH_3), 115.544, 127.837, 141.903, 158.541 (aryl carbons). Mass (m/z): 384 (M^+), (M.F: $C_{20}H_{24}N_4SO_2$), 354, 324, 309, 268, 254, 239, 175, 163, 134 (100%), 117, 107, 75, 65, 50.

6-Methyl-7,9-*bis*(*p*-methoxyphenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione (8b). IR (KBr) (cm^{-1}): 3429.5, 3351.0, 3313.7, 3294.0, 2349.2, 1584.2, 1501.4, 1474.2, 1420.9, 1384.7, 1320.4, 1270.2, 1201.5, 1134.3, 1027.4 etc. ^{1}H NMR (δ ppm): 4.26 (dd, $^3J = 12.02$ Hz; 2.63 Hz, 1H) H_9, 3.80 (d, $^3J = 10.89$ Hz, 1H) H_7, 2.08–2.35 (m, 3H) H_6 and H_{10}, 6.85–6.87, 7.36–7.38 (m, 8H) aromatic, 8.44 (br. s, 2H) NH-CS-NH, 6.97 (s, 1H) NH at 1, 1.89 (s, 1H) NH at 8, 0.81 (d, $J = 6.58$ Hz, 3H) CH_3 at 6, 3.91 (s, 6H) OCH_3. ^{13}C NMR (δ ppm): 65.006 (C_7), 59.503 (C_9), 40.015 (C_6), 38.265 (C_{10}), 79.285 (C_5), 180.948 (C=S), 12.124 (CH_3 at 6), 54.895 (OCH_3), 114.383, 115.890, 128.005, 130.955, 134.746, 141.682, 157.266, 159.234 (aryl carbons). Mass (m/z): 398 (M^+), (M.F: $C_{21}H_{26}N_4SO_2$), 368, 338, 323, 282, 268, 254, 239, 219, 177, 162, 148 (100%), 135, 117, 107, 75, 65, 55, 50.

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