Asian Journal of Chemistry; Vol. 23, No. 10 (2011), 4268-4270

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis, Spectrochemical and Antimicrobial Activity of Heterocyclic α-Diketones, Dithiosemicarbazones and of 3,13-Diacylamino-7.9-diaryl-6-methyl-4,14-dithia-1,2,8,11,12-pentazadispiro[4,4,4]tetradeca-2,12-dienes

R. THILAKAM*, V. JAYAMANI, A.K. GAYATHIRI and R. KALPANA

Department of Chemistry, Sri Sarada College for Women (Autonomous), Salem-636 016, India

*Corresponding author: E-mail: ayyasamyvj@yahoo.co.in

(*Received*: 16 August 2010; *Accepted*: 3 June 2011) AJC-10024

New heterocyclic α-diketones, their corresponding dithiosemicarbazones and dispiro compounds are prepared from 2,6-diaryl-4-piperidones. The synthesized compounds are characterized by spectral and analytical data. They are also screened for their antibacterial and antifungal activity against *Staphylococcus aureus* and *Candida albicans*.

Key Words: Piperidindiones, Dithiosemicarbazones, Dispiro tetradecadienes, Heterocyclization, Antimicrobial activity.

INTRODUCTION

1,3,4-Thiadiazoles are associated with diverse biocidal activities[1] by virtue of the toxophoric N=C-S grouping. A large number of 4-thiazolidinones have been reported to be antifungal[2], antibacterial[3] and antileukemic[4] agents. The substituted 1,3,4-thiadiazoles are also reported to have applications in many fields such as dyes[5], lubricating composition, optically active liquid crystals, photographic materials and as herbicides, fungicide[5] and bactericides in agriculture. They are also used as diuretic[6], CNS depressants[7], hypoglycemic[8], antiinflammatory[9] and antimicrobial[10,11] agents.

One of the methods to prepare 1,3,4-thiadiazoles involve cyclization of thiosemicarbazones, which are also reported to have various applications. Thiosemicarbazones are well known as antifungal[12] and antibacterial[12] drugs. Thiosemicarbazones and their derivatives are also reported as antibacterial[13], antitubercular[14], antimalarial[15], anticancer and antiviral drugs[16].

2,6-Diaryl-4 piperidones are reported as synthons for preparing spiro heterocycles[17-19]. The introduction of an inbuilt spiro system in an heterocyclic ring may cause an increase in the biological potency of the system (since N=C-S linkage is responsible for the bilogical activity of many sulphur and nitrogen containing heterocyclics spiro piperidinyl-1,3,4-thiadiazolines may be expected to have bilogical activity. These observations led us to make an attempt to synthesise the title compounds and study their antimicrobial activity.

One of the main route available for the synthesis of 3,13-diacylamino-7.9-diaryl-6-methyl-4,14-dithia-1,2,8,11,12-pentaza dispiro[4,4,4]tetradeca-2,12-diene starts from thiosemicarbazones and its heterocyclization with a suitable cyclizing agent.

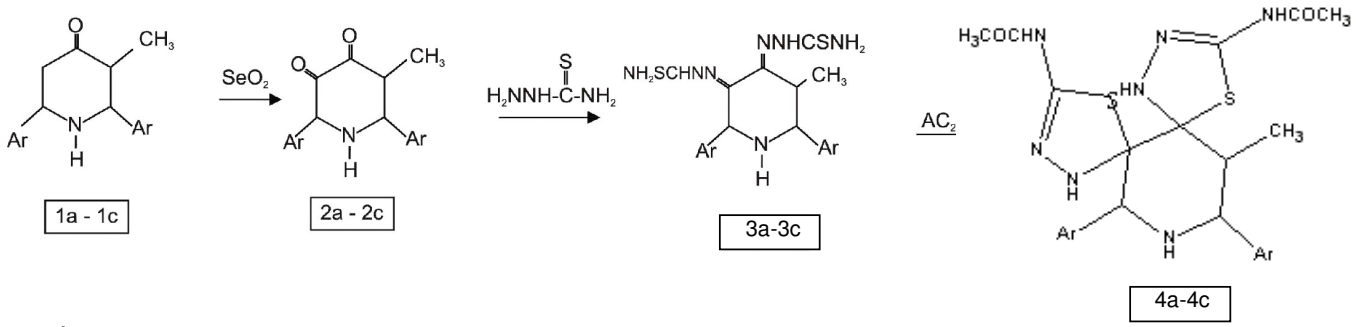
In the present work, dispiropiperidinyl thiadiazolines are synthesized from thiosemicarbazones of α-diketones. The synthon 2,6-diaryl piperidin-4-one (**1**) on oxidation with SeO_2 in presence of glacial CH_3COOH gives piperdin-4,5-dione (**2**) and this on condensation with thiosemiscarbazide in alcoholic medium yielded dithiosemicarbazone (**3**), which is heterocyclized with Ac_2O and conc. H_2SO_4 to form dithiapentazadispirotetradecadiene (**4**) as shown in **Scheme-I**.

EXPERIMENTAL

Melting point of the compounds are determined in open capillaries with a Tempo apparatus and are uncorrected. IR spectra is recorded with a varian 300 instrument at 300 MHz. ^1H NMR spectra is recorded with an amx 400 instrument. Chemical shifts are reported downfield relative to tetramethyl silane and are expressed in ppm.

General procedure for preparation of 2,6-diaryl-3-methyl piperidin-4,5-diones (2a-c): Compound **1a-1c** were mixed with SeO_2 and glacial acetic acid (25 mL) and refluxed for 4 h in a water bath. Excess SeO_2 was removed by filtration and excess solvent was distilled off. Red orange filtrate was added to crushed ice and neutralized with ammonia. The solid separated was filtered, washed with water and repeated. Recrystallization from ethanol give compounds **2a-c**.

2,6-Di-(*p*-methoxy phenyl)-3-methyl piperidin-4,5-dione (2a): IR (KBr, ν_{max}, cm^{-1}):1744 and 1685 (C=O) ; 3252 (2° NH); 1429 (OCH_3); 3010 (aromatic C-H), 1604 (aromatic



Ar
a = *p*-OCH_3-C_6H_4
b = *p*-$N(CH_3)$-C_6H_4
c = C_6H_5

Scheme-I

C=C skeletal), 1179 (aromatic in-plane bending) and bands below 835 (aromatic out of plane bending), ^{1}H NMR (δ ppm): 0.9 (3H, CH_3 at C_3) ; 1.2 (1H, NH); 3.8-4 (3H, OCH_3); 6.8-7.8 (8H, Ar H); 2.2 to 2.8 (m, 3H, C_2, C_6 and C_3H), ^{13}C NMR (δ ppm) :198, 202, 136, 132, 130, 129, 128, 65, 59, 55, 52, 12.

2,6-Di(*p*-N,N-dimethylamino phenyl)-3-methyl piperidin-4,5-dione (2b): IR (KBr, ν_{max}, cm^{-1}): 1770 and 1674 (C=O); 3334 (2° NH); 1409 [-N $(CH_3)_2$], 3010, 1674-450, 820, 725 (aromatic), ^{1}H NMR (δ ppm): 0.9 (d, 3H, CH_3); 1.25 (S,1H, NH) ;3.74-3.89, (m, 2H, C_2 and C_6H), 2.35 (t, 1H, C_3H) 2.1 (S, 12H, N $(CH_3)_2$; 7.22-7.26, (m, 8H, Ar-H). ^{13}C NMR (δ ppm): 193, 198, 136, 132, 130, 129, 128, 65, 59, 52, 44, 12.

2,6-Diphenyl-3-methyl piperidin-4,5-dione (2c): IR (KBr ν_{max}, cm^{-1}): 1776 and 1750 (C =O); 3398 (2° NH); 3010 (C-H aryl). 2900 (C-H aliphatic); 1537 (C=C aryl). ^{1}H NMR (δ ppm): 0.7-0.9 (d, 3H, CH3); 1.2 (S, 1H, NH); 2.7(dd, 4H C_2, C_6 and C_5H); 6.8-7.7 (m,8H, aryl). ^{13}C NMR (δ ppm): 193, 198 (C=O at C-4, C-5).

General procedure for preparation of 2,6-diaryl-3-methyl piperidin-4,5-dithiosemicarbazones (3a-c): 2,6-Diaryl piperidin-4,5-di-thiosemicarbazones. To a boiling solution of 2,6-diaryl piperidin-4,5-dione (**2a**) (0.012 m) in ethanol (0.03 m) and a few drops of conc. HCl an ethanolic solution of thiosemicardazide (0.03 m) was added dropwise with stirring. The reaction mixture was refluxed for 3 h on a water bath. After cooling the solid product was filtered off and recrystallized from ethanol to get **3a**. Compounds **3b** and **3c** are prepared similarly.

2,6-Di(*p*-methoxyphenyl)-3-methyl piperidin-4,5-dithiosemicarbazone (3a): IR (KBr ν_{max}, cm^{-1}): 1490 (C=N); 1396 (C=S); 3428 (1° NH_2); 3246 (2° NH); 1602-1458 (C=C aryl); 1414 (N-C-N). ^{1}H NMR (δ ppm): 0.9 (3H, CH_3 at C_3); 1.2 (1H, NH); 3.8-4 (1H, OCH_3); 8.4 (1H, C=N $NHCSNH_2$); 9.8 (2H, - C=N $NHCSNH_2$); 6.8-7.7 (8H, Ar-H).

2,6-Di(*p*-N,N-dimethyl aminophenyl)-3-methyl piperidin -4,5-dithiosemicarbazone (3b): IR (KBr ν_{max}, cm^{-1}): 1660 (C=N); 1352 (C=S); 3450 (1° NH_2); 3324 (2° NH); 1591-1513 (C=C aryl); 1450 (N-C-N). ^{1}H NMR (δ ppm): 1.27 [(4H, NH and CH_3); 2.93 (12H, N $CH_3)_2$]; 8.22 (1H, C=NNH $CSNH_2$); 9.7-9.9 (2H, C=NNH $CSNH_2$); 6.7 -7.36 (8H, ArH).

2,6-Diphenyl 3-methyl piperidin-4,5-dithiosemicarba -zone (3c): IR (KBr ν_{max}, cm^{-1}): 3410 (NH_2); 3250 (NH); 3147 (C-H aryl); 2924 (C-H ali); 1688 (C=N); 1604 (C=C aryl); 1375 (C=S). ^{1}H NMR(δ ppm): 0.8 (3H, CH_3 at C_3); 1.2 (1H, NH); 6.9-7.7 (8H, ArH); 8.32 (1H, C=NNH $CSNH_2$); 10.5 (2H, C=NNH $CSNH_2$).

General procedure for preparation of 3,13-diacyl-amino-7.9-diaryl-6-methyl-4,14-dithia-1,2,8,11,12-pentaza dispiro[4,4,4]tetradeca-2,12-diene (4a-c): Compound **3a** (0.0041 m) was treated with freshly distilled acetic anhydride (5 mL) and conc. H_2SO_4 (1 mL) and the mixture was refluxed for 6-7 h on a water bath. Then it was poured on crushed ice, the solid mass separated was filtered, washed and dried. It was purified over neutral alumina column (ethanol-ethyl acetate 4:1) and recrystallized from ethanol to get **4a** as dark brown solid. Compound **4b** (as black solid) compound **4c** (as coffee brown solid) were prepared similarly.

3,13-Diacylamino-7.9-di(*p*-methoxyphenyl)-6-methyl 4,14,dithia-1,2,8,11,12- pentaza dispiro[4,4,4]tetradeca-2,12 - diene (4a): IR (KBr, ν_{max}, cm^{-1}): 3150 (N-H); 2973 [(C-H) aryl]; 2838 (C-H ali); 1720 (C=O); 1604 (C=N); 1542 (C=C aryl); 1256 (C-N); 1053 (N-N); 645 (C-S-C). ^{1}H NMR (δ ppm): 0.9 (3H, CH_3 C-3); 1.2 (1H, NH); 3.7-3.9 (12H, $0CH_3$ and $NHCOCH_3$); 6.8-7.7 (8H, ArH).

3,13-Diacylamino-7.9-di(*p*-N,N dimethylamino phenyl) -6-methyl 4,14, dithia-1,2,8,11,12-pentaza dispiro[4,4,4] tetradeca 2,12 -diene (4b): IR (KBr, ν_{max}, cm^{-1}): 3149 (N-H); 2998 (C-H aryl); 2850 (C-H ali); 1600 (C=O); 1589 (C=N); 1552 (C=C aryl); 1056 (N-N); 756 (C-S-C); 2770 (N $CH_3)_2$. ^{1}H NMR (δ ppm): 0.9 (3H, CH_3 C-3); 1.32 (1H, NH); 3.10-3.19 (12H, $NCH_3)_2$, $NHCOCH_3$); 6.8-8 (8H, ArH).

3,13-Diacylamino-7.9-diphenyl-6-methyl 4,14, dithia-1,2,8,11,12-pentaza dispiro[4,4,4]tetradeca 2,12- diene (4c). IR (KBr, ν_{max}, cm^{-1}): 3400-3200 (N-H); 2976 (C-H ali); 1716 (C=N); 1601 (C=C aryl); 1056 (N-N); 754 (N-C-S). ^{1}H NMR (δ ppm): 0.8 (3H, CH_3 C-3); 1.2 (1H, NH); 7-7.3 (8H, ArH); 3.32-3.9 (3H, NH $COCH_3$).

RESULTS AND DISCUSSION

The present communication deals with the preparation of 3-methyl-2,6-diaryl piperidin-4-one (**1**) following literature procedure[20]. Selective oxidation of the synthon 2,6-diary-l -4-piperidone (**1**) leads to α-diketone (**2**), which is converted to 4,5-dithiosemicarbazone (**3**) with thiosemicarbazides, which in turn is heterocyclilzed to form dispiro piperidinyl

TABLE-1

Compound	Ar	m.p. (°C)	Yield (%)	Elemental analysis (%): Found (calcd.)		
				C	H	N
2a	*p*-$C_6H_4OCH_3$	89	76.48	71.00 (70.80)	6.01 (6.19)	4.26 (4.13)
2b	*p*-$C_6H_4N(CH_3)2$	79	76.68	77.33 (77.42)	5.95 (6.09)	4.93 (5.02)
2c	C_6H_5	106	85.00	72.14 (72.33)	7.23 (7.40)	11.36 (11.51)
3a	*p*-C_6H_4-OCH_3	101	52.45	53.96 (54.43)	4.91 (5.57)	19.76 (20.21)
3b	*p*-C_6H_4-$N(CH_3)_2$	97	66.83	56.03 (56.36)	6.12 (6.46)	23.78 (24.60)
3c	C_6H_5	126	75.00	56.12 (56.47)	4.92 (5.42)	22.87 (23.05)
4a	*p*-C_6H_4 OCH_3	140	66.91	54.51 (54.83)	5.32 (5.45)	17.01 (17.22)
4b	*p*-$C_6H_4N(CH_3)_2$	114	67.66	56.21 (56.47)	6.12 (6.12)	20.08 (21.18)
4c	C_6H_5	102	59.10	55.62 (56.85)	4.86 (5.30)	18.51 (19.25)

thiadiazoline (**4**). The oxidation of 2,6-diaryl-4 piperidone is carried out with the selective oxidant SeO_2 in glacial acetic acid medium gives a good yield of piperidine 4,5-dione (**2a**). Two vibrational frequencies are observed in the region 1744 and 1685 cm^{-1} revealing the presence of two C=O groups. The ^1H NMR spectrum of **2a** shows a signal at 3.8-4.0 δ for OCH_3, 1.2-3 δ for NH, C_2-H,C_3-H and C_6-H of piperidin nucleus. ^{13}C NMR signals are observed at 198 and 202 corresponding to two C=O groups at C-4 and C-5 of the piperidone.

Nucleophilic addition of **2a** with thiosemicarbazide in presence of ethanol leads to the formation of 2,6-diaryl-piperidin-4,5-dithiosemicorbazone (**3a**). The IR spectrum recorded the presence of >C=N stretch at 1685cm^{-1}, > C=S stretch at 1396 cm^{-1}, NH stretch at 3428 and 3241 cm^{-1} for 1° NH_2 and 2° NH stretch of thiosemicarbazones respectively. The proton NMR signals appeared at 3.8-4 δ for -OCH_3, 7.8-8.2 δ for NH of >C=N.NHCS NH_2 and 9.8 δ for NH_2 of >C=N.NHCS NH_2.

Heterocyclization of compound **3a** with concentrated sulphuric acid and acetic anhydride provided a fair yield of dithiapentaza dispirotetradecadiene **4a**. The IR spectrum gives frequencies at 3150 cm^{-1} due to-NH stretch 1720 cm^{-1} for >C=O stretch, 1604 cm^{-1} due to for >C=N stretch 1265 cm^{-1} for >C-N- 1053 cm^{-1} for N-N and 645 cm^{-1} for C-S-C. The proton NMR signals are obtained at 1.2 δ for NH 3.7-3.9 δ -OCH_3 and -$NHCOCH_3$. The characterization data of compounds **2-4** are given in Table-1.

The synthesized compounds are screened for their fungicidal activity against the fungi *Candida albicans* and bactericidal activity against *Staphylococcus aureus* in the concentration of 10 mg/mL in 1,4-dioxan using ciprofloxain as standard. Compounds **3a, 3b** and **3c** showed better activity against both the fungus and bacteria whereas compounds **4a, 4b** and **4c** showed milder activity in the concentration range observed.

ACKNOWLEDGEMENTS

The authors are thankful to the Management, Principal and Head of the Department of Chemistry, Sri Sarada College for Women (Autonomous) Salem for providing Laboratory facilities and constant encouragement and support. One of the authors (RT) is grateful to UGC, Hyderabad for providing the necessary financial assistance. Thanks are also due to SAIF, IIT Chennai and IISC Bangalore for recording the spectra.

REFERENCES

1. P.A. Kumar, V.L. Nag and C.S. Panda, *Indian J. Chem.*, **38B**, 998 (1999).
2. G.A. El Saraf, *Indian J. Chem.*, **31B**, 167 (1992).
3. C.S. Andotia, S. Dham, B. Mahajan and T.C. Langer, *J. Indian Chem. Soc.*, **69**, 169 (1992).
4. M. Rajopadhya and F.D. Popp, *J. Heterocycl. Chem.*, **24**, 1637 (1987).
5. T.-B. Wei, H. Liu, J.H. Hu, M.-L. Li, W.-X. Xiu, L.Z. Yang and Y.-M. Zhang, *Indian J. Chem.*, **45B**, 2754 (2006).
6. S.K. Jain and P. Mishra, *Indian J. Chem.*, **43B**, 184 (2004).
7. V. Jatava, P. Mishra, S. Kashawa and J.P. Stables, *Eur. J. Med. Chem.*, **43**, 1945 (2008).
8. J.M. Oke and M.O. Olowookorun, *Jpn. J. Pharmacol.*, **49**, 135 (1989).
9. K. Pande, K.K. Tangri, T.N. Bhalla, S. Ahmed and J.P. Barthwal, *Indian J. Pharm. Sci.*, **226** (1983).
10. A.M.M.E. Omar and O.M.A. Wafa, *J. Hetecocycl. Chem.*, **23**, 1339 (1986).
11. S. Rollas, S. Karakus, B.B. Durgan, M. Kiraz and H. Erdeniz, *Farmaco*, **51**, 811 (1996).
12. A.K. Bhatti, R.P. Bhamaria, M.R. Patel, R.A. Bellare and V. Delwala, *Indian J. Chem.*, **10A**, 694 (1972).
13. N.C. Desai, H.K. Shukla, B.R. Parekh and K.A. Thaker, *J. Indian Chem. Soc.*, **61**, 455 (1984).
14. D. Vanugopal, D. Panya and K.B. Nair, *J. Indian Chem. Soc.*, **66**, 344 (1989).
15. D.L. Klayman, J.P. Scovill, J. Brue and J.E. Bartosevich, *J. Med. Chem.*, **27**, 84 (1984).
16. A.K Parekh and K.K. Desai, *Indian J. Chem.*, **45B**, 1072 (2006).
17. V. Padmavathi, T.V. Ramana Reddy and K.A. Reddy, *Indian J. Chem.*, **46B**, 818 (2007).
18. V. Padmavathi, B.J.M. Reddy, D.R.C.V. Subbaiah and A. Padmaja, *Indian J. Chem.*, **45B**, 808 (2006).
19. S. Balasubramaian, C. Ramalingan and S. Kabilan, *Indian J. Chem.*, **41B**, 2402 (2002).
20. C.R. Noller and V. Baliah, *J. Am. Chem. Soc.*, **70**, 3853 (1948).