SYNTHESIS OF SOME NEW 1-(3-OXO-1,4-BENZOXAZIN-6-YL) ETHANONE (4-ARYL-1,3-THIAZOL-2-YL) HYDRAZONES

G. Jagath Reddy* and K. Srinivasa Rao
R & D Laboratories, Dr. Jagath Reddy's Heterocyclics
81, S.V.Co-op Industrial Estate, Balanagar, Hyderabad 500 037, India
E-mail: jagathreddy@usa.net
and
Md. Khalilullah and D. Latha
Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad 500 072, India

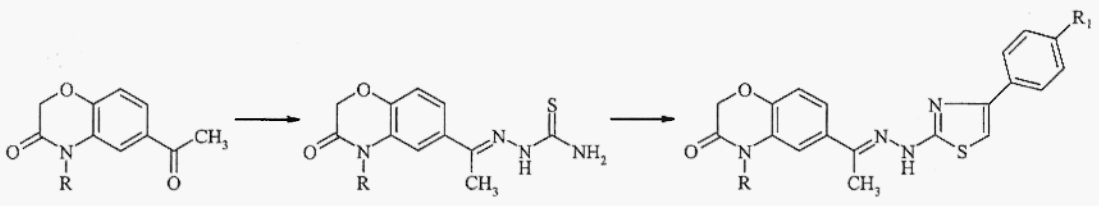
Abstract : A series of some new 1-(3-oxo-1,4-benzoxazin-6-yl)ethanone (4-aryl-1,3-thiazol-2-yl)hydrazones (5 & 6) have been synthesized.

Introduction

Heterocycles containing the thiazole ring are associated with a wide range of biological properties such as antiprotozoal, anticonvulsant and antidepressant activities[1]. Thiazole ring is found in a number of biologically active natural products such as patallozoles[2], cyclothiazomycins[3], mycothiazoles[4] and dolabetltins[5]. These are mostly isolated from marine sources. Various heterocyclic substituted thiazoles have been reported to possess anticancer properties[6]. In addition, recently several 3-oxo-1,4-benzoxazine scaffold linker heterocycles have been reported as antipsychotic[7], antidepressant, antianxiety[8] and compounds with dual action as anticoagulant and antiaggregatory agetns[9]. In continuation of our work on new benzoxazines[10-12], we report herein the synthesis of 1-(3-oxo-1,4-benzoxazin-6-yl)ethanone (4-aryl-1,3-thiazol-2-yl)hydrazones.

Results and Discussions

6-Acetyl-3-oxo-1,4-benzoxazines (**1** & **2**) were obtained by Friedel-crafts acylation of 3-oxo-1,4-benzoxazine with acetyl chloride in the presence of aluminium chloride. Reaction of **1** & **2** with thiosemicarbazide in the presence of acetic acid yielded the corresponding thiosemicarbazones **3** & **4** in good yields. Condensation of **3** & **4** with various 2-bromo-1-arylethanones in anhydrous ethanol under reflux gave the substituted ethanone hydrazone derivatives as crystalline solids.



1 R = H
2 R = CH_3

3 R = H
4 R = CH_3

5 R = H
6 R = CH_3

The structures of the title compounds **5 & 6** were established by IR, ^{1}H-NMR and mass spectra. The infrared spectra of these compounds showed absorption bands around 1680 cm^{-1} for lactam carbonyl. In the ^{1}H-NMR spectra, the title compounds exhibited a singlet around δ 4.59 for $-OCH_2$ of benzoxazine ring, two broad singlets around δ 3.15 and 10.80 for thiazole NH and benzoxazine ring NH protons respectively. The imino methyl protons appeared as a singlet around δ 2.25 apart from other aromatic and thiazole protons.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin Elmer system 2000 FT IR spectrometer in KBr pellets. ^{1}H-NMR spectra were recorded on a Varian 200 MHz instrument with TMS as internal standard and in $CDCl_3$ + DMSO-d_6 mixture. Chemical shifts were expressed in δ ppm. Mass spectra were recorded on Hewelett Packard, Mass spectrometer operating at 70 eV.

1-(3-Oxo-1,4-benzoxazin-6-yl)ethanone thiosemicarbazone (3)

A mixture of 1-(3-oxo-1,4-benzoxazin-6-yl)ethanone (**1**) (0.1 mol), thiosemicarbazide (0.01 mol), ethanol (20 ml) and acetic acid (5 ml) was refluxed for 8-10 hrs. It was cooled, filtered and recrystallized from ethanol to give pure **3** as a white crystalline solid, yield (74%), m.p 174°C; IR (KBr): νmax 1680 cm^{-1} (CONH). ^{1}H-NMR spectrum could not be taken because of solubility problem.

Compound **4** was similarly prepared. Yield (72%), m.p 176°C.

1-(3-Oxo-1,4-benzoxazin-6-yl)ethanone (4-phenyl-1,3-thiazol-2-yl) hydrazone (5a)

A mixture of **3** (0.001 mol) and 0.001 mol 2-bromo-1-phenylethanone (0.001 mol) was refluxed in anhydrous ethanol (20 ml) for 4-6 hrs. At the end of the reaction as monitored by TLC, the solvent was evaporated *in vacuo*, the residue treated with sodium bicarbonate solution to neutral pH, the separated solid was filtered and recrystallized from methanol to give pure **5a** as crystalline solid. m.p. 274°C, yield 72%: IR (KBr): νmax 3511, 3436, 1680, 1619 cm^{-1}. Physical and spectra data of **5a** are listed in Table-1.

Compounds **5a-e** & **6a-e** reported in **Table-1** were similarly prepared.

Table-1 : Physical data of compounds 5 & 6

Compd	R_1	Yield %	m.p °C	Mol. formula	^{1}H NMR ($CDCl_3$ + drop DMSO-d_6), δ ppm	MS m/z [M_+]
5a	H	72	274	$C_{19}H_{16}N_4O_2S$	2.24(s, 3H), 3.15(bs, 1H), 4.58(s, OH_2), 7.01-7.86(m, 9H, ArH + thiazole H), 10.81(bs, 1H)	364[M^+]
5b	OCH_3	74	261	$C_{20}H_{18}N_4O_3S$	2.24(s, 3H), 3.14(bs, 1H), 3.94(s, 3H), 4.59(s, OCH_2), 6.98-7.81(m, 8H), 10.81(bs, 1H)	394[M^+]
5c	Cl	76	275	$C_{19}H_{15}ClN_4O_2S$	2.25(s, 3H), 3.15(bs, 1H), 4.59(s, OCH_2), 6.96(d, 1H), 7.27(dd, 1H), 7.34(m, 2H), 7.44(d, 2H), 7.86(d, 2H), 10.80(bs, 1H)	399 [M^++1]
5d	Br	78	284	$C_{19}H_{15}BrN_4O_2S$	2.24(s, 3H), 3.14(bs, 1H), 4.58(s, OCH_2), 6.96-7.86(m, 8H, ArH + thiazole H), 10.81(bs, 1H)	445[M^++2]
5e	SCH_3	71	229	$C_{20}H_{18}N_4O_2S$	2.24(s, 3H). 2.53(s, 3H), 3.14(bs, 1H), 4.58(s, OCH_2), 6.98-7.87(m, 8H, ArH + thiazole H), 10.8(bs, 1H)	
6a	H	69	266	$C_{20}H_{18}N_4O_2S$	2.34(s, 3H), 2.54(bs, 1H), 3.45(s, 3H), 4.58(s, OCH_2), 6.95-7.87(m, 9H),	378[M^+]
6b	OCH_3	73	264	$C_{21}H_{20}N_4O_3S$	2.36(s, 3H), 2.54(bs, 1H), 3.45(s, 3H), 3.94(s, 3H), 4.59(s, OCH_2), 6.95-7.86(m, 8H)	408[M^+]
6c	Cl	74	267	$C_{20}H_{17}ClN_4O_2S$	2.35(s, 3H), 2.54(bs, 1H), 3.45(s, 3H), 4.59(s, OCH_2), 6.95(d, 1H), 7.26(dd, 1H), 7.34(m, 2H), 7.43(d, 2H), 7.84(d, 2H)	
6d	Br	75	269	$C_{20}H_{17}BrN_4O_2S$	2.34(s, 3H), 2.54(bs, 1H), 3.43(s, 3H), 4.59(s, OCH_2), 6.95-7.86(m, 8H)	459[M^++2]
6e	SCH_3	70	175	$C_{20}H_{20}N_4O_2S_2$	2.35(s, 3H), 2.53(s, 3H). 2.55(bs, 1H), 3.43(s, 3H), 4.59(s, OCH_2), 6.96-7.87(m, 8H)	

References

1. a) J. M. Singh, *J. Med. Chem*, **13**, 1019, (1970).

   b) C. J. Sharpe, R. S. Shadbolt, A. Ashferd, J. W. Ross, *J. Med. Chem*, **14**, 977, (1972).

   c) I. F. Miller, R. E. Bamboly, *J. Med. Chem*, **15**, 415, (1972).

2. T. M. Zabriskie, C. L. Mayne, C. M. Ireland, *J. Am. Chem. Soc*, **110**, 7919, (1988).

3. M. Aoki, T. Ohtsuka, Y. Itezono, K. Yokase, K. Furihate, H. Seto, *Tetrahedron letters*, **32**, 821, (1991).

4. P. Gows, Y. Kakou, E. Quina, *J. Am. Chem. Soc*, **110**, 4365, (1988).

5. H. Sona, T. Kondo, M. Kirya, H. Ishikawa, M. Gika, K. Yameda, *J. Org. Chem*, **60**, 4774, (1995).

6. D. Blerer, A. Machure, W. Fu, F. Achibe, G. H. Ladouceur, M. J. Burke, H. B. Bichary, J. Dumas, R. Sibley, W. J. Scott, J. Johnson, D. Asgani, PCT. Int WO 0327, 085, (2003); *Chem. Abstr*, **138**, 287663v, (2003).

7. T. R. Belliotti, D. J. Wustrow, W. A. Brink, K. T. Zoski, Y. H. Shih, S. Z. Whetzei, I. M. Georgic, A. E. Corbin, H. C. Akunne, T. G. Hettner, T. A. Pugsley, D. Wise, *J. Med. Chem*, **42**, 5181, (1999).

8. P. J. Atkinson, S. M. Bromidge, M. S. Duxon, L. M. Gaster, M. S. Hadley, B. Hammaond, C. N. Johnson, D. N. Middlemiss, S. E. North, G. W. Price, H. K. Rami, G. J. Riley, C. M. Scott, T. E. Shaw, K. R. Starr, G. Stemp, K. M. Thewlis, D. R. Thomas, M. Thompson, A. K. K. Vong, J. N. Watson, *Bioorg. Med. Chem. Letters*, **15**, 717, (2005).

9. P. S. Anderluh, M. Anderluh, J. Has, J. Mrav Ljak, M. S. Dolenc, M. Stegnar, D. Kikelj, *J. Med. Chem*, **48**, 3110, (2005).

10. P. S. N. Reddy, Pragati Reddy, G. Jagath Reddy, K. Srinivasa Rao, *Heterocyclic Commun*, **11**, 35, (2005).

11. K. N. Jayaveera, S. Sailaja, G. Jagath Reddy, K. Srinivasa Rao, *Heterocyclic Commun*, **11**, 105, (2005).

12. G. Jagath Reddy, S. Sailaja, K. Srinivasa Rao, *Indian. J. Chem*, **44B**, 204, (2004).

Received on January 6, 2006