SYNTHESIS OF 2-(1,3-DIARYPYRAZOL-5-YLAMINO)-4(3-OXO-2H-1,4-BENZOXA/THIAZIN-6-YL)-THIAZOLES

K. N. Jayaveera and S. Sailaja

Oil Technological Research Institute, Jawaharlal Nehru Technological University, Anantapur – 515001 and

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; Fax # 91-40-23773487.

Abstract

A number of 2-(1,3-Diarylpyrazol-5-ylamino)-4-(3-oxo-2H-1,4-benzoxa/thiazin-6-yl)-thiazoles (**5a-k** & **6a-d**) have been prepared.

Introduction

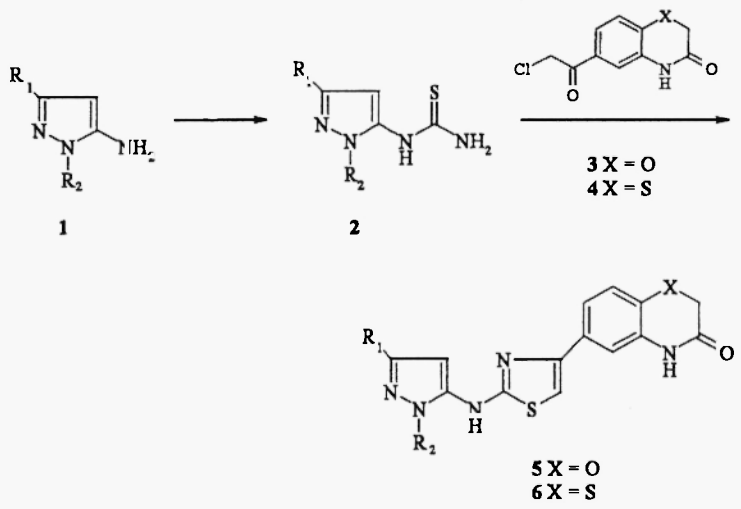
The emergence of pyrazole based drugs like Celecoxib[1] and Sildenafil citrate[2] has created great interest in the synthesis of a variety of this class of compounds. Thiazole ring forms a part of a number of synthetic[3] and natural products[4] of medicinal interest. Several substituted aminopyrazoles and aminothiazoles are known to exhibit antimicrobial activities[5]. Furthermore, several substituted benzoxazines and benzothiazines have been reported as antihypertensive[6], antiulcer[7] and herbicidal agents[8]. In view of this and in continuation of our work on new 1,4-benzoxazines[9], we report herein the synthesis of 2-pyrazolylamino-4-benzoxa/thiazinyl thiazoles as possible antibacterial and antifungal agents.

Results and Discussion

The various aminopyrazoles (**1**) required in the present work were prepared by reaction of benzoylacetonitriles with phenylhydrazines in a modified reaction condition using montomorillonite K10 under acid free conditions[10]. The aminopyrazoles **1** were converted into the corresponding thioureas **2** by reaction of **1** with benzoylisothiocyanate followed by hydrolysis according to the reported methods[11]. 6-Chloroacetyl benzoxa/thiazinones **3** & **4** were prepared by chloroacetylation of benzoxa/thiazinones under Friedel-crafts reaction conditions. Reaction of **3** & **4** with **2** in refluxing ethanol gave the desired pyrazolylaminobenzoxa/thiazinyl thiazoles **5** & **6** in good yields (Scheme -1). The structures of various **5** & **6** thus prepared were established based on their ^{1}H NMR and analytical data (Table -1). In the ^{1}H NMR spectra compounds 5 & 6 exhibited typical singlets for OCH_2 (δ 4.56), SCH_2 (δ 3.77), pyrazole (6.81), thiazole (6.84) and lactam NH (10.2-10.5) protons apart from aromatic protons.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra recorded in KBr pellets. ^{1}H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard, chemicals shifts expressed in δ ppm and Mass spectra on Hewlett Packard Mass spectrometer operating at 70 eV.



SCHEME-1

General procedure for the preparation 1-(1,3-diaryl-pyrazol-5-yl)thiourea 2

To a mixture of ammonium thiocyanate (0.012 mole) in acetone (25 ml), benzoylchloride (0.01 mole) was added drop wise and the mixture was refluxed for 15 minutes. A solution of **1** (0.01 mole) in acetone (25 ml) was added drop wise to the above reaction mixture, so that a gentle reflux was maintained. The separated solid was filtered and refluxed with 10% aq. NaOH (25 ml). It was filtered and the filtrate was acidified with Conc HCl. The solid obtained was recrystallized from methanol to give pure **2**. The melting points and yields of different pyrazolyl thioureas prepared given below.

2a (R_1 = 4-$CH_3C_6H_4$, R_2 = C_6H_5) 223°, 82%; **2b** (R_1 = 4-ClC_6H_4, R_2 = C_6H_5) 209°, 84%; **2c** (R_1 = 4-BrC_6H_4, R_2 = C_6H_5) 222°, 83%; **2d** (R_1 = 4-FC_6H_4, R_2 = C_6H_5) 211°, 86%; **2e** (R_1 = 4-$CH_3C_6H_4$, R_2 = 4-ClC_6H_4) 229°, 81%; **2f** (R_1 = R_2 = 4-ClC_6H_4) 189°, 79%; **2g** (R_1 = 4-BrC_6H_4, R_2 = 4-ClC_6H_4) 171°, 78%; **2h** (R_1 = 4-$CH_3C_6H_4$, R_2 = 2,4-diF) 222°, 79%; **2i** (R_1 = 4-ClC_6H_4, R_2 = 2,4-diF) 208°, 84%; **2j** (R_1 = 4-FC_6H_4, R_2 = 2,4-diF) 219°, 87%; **2k** (R_1 = 4-BrC_6H_4, R_2 = 2,4-diF) 218°, 79%.

General procedure for the preparation of 2-pyrazolylamino-4-benzoxa/thiazin-6yl thiazoles 5 & 6.

A mixture of **2** (0.01 mole) and 6-chloroacetyl benzoxa/thiazinone (**3** or **4**, 0.01 mole) in ethanol (50 ml) was refluxed for 4-5 hrs. At the end of the reaction as monitored by TLC, the solvent was evaporated, the residue was neutralized with $NaHCO_3$ solution and the resulting solid was filtered and recrystallized from methanol to give pure (**5** & **6**).

2-(1-Phenyl-3-tolyl-pyrazol-5-yl)amino-4-(3-oxo-2H-1,4-benzothiazin-6-yl)-thiazole 6a (R_1 = 4-$CH_3C_6H_4$, R_2 = C_6H_5)

Pyrazolyl thiourea **2** (R_1 = 4-$CH_3C_6H_4$, R_2 = C_6H_5) was converted into **6a** according to the general procedure described above to give **6a** as white crystalline solid 72%, m.p 233°. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz): δ 2.38(s, 3H), 3.37(s, 2H), 6.81(s, 1H), 6.94(s, 1H), 7.19-7.82(m, 12H), 9.51(bs, 1H), 10.17(bs, 1H). Found: C, 69.63; H, 4.67; N, 15.26 $C_{27}H_{21}N_5OS_2$ requires C, 69.97, H, 4.53; N, 15.11%.

Table-1: Characterization data of compounds **5** & **6**.

Compd.	R_1	R_2	M.p °C	Yield %	Mol. Formula	^{1}H NMR (δ ppm) 200 MHz ($CDCl_3$ + DMSO-d_6)
5a	4-$CH_3C_6H_4$	C_6H_5	201	65	$C_{27}H_{21}N_5O_2S$	2.37(s, 3H), 4.56(s, 2H), 6.71(s, 1H), 7.05-7.81(m, 13H), 9.73(bs, 1H), 10.46(s, 1H)
5b	4-ClC_6H_4	C_6H_5	248	67	$C_{26}H_{18}ClN_5O_2S$	4.57(s, 2H), 6.73(s, 1H), 7.12-7.83(m, 13H), 9.72(bs, 1H), 10.48(s, 1H)
5c	4-BrC_6H_4	C_6H_5	251	64	$C_{26}H_{18}BrN_5O_2S$	4.56(s, 2H), 6.72(s, 1H), 7.21-7.83(m, 13H), 9.73(bs, 1H) 10.49(s, 1H)
5d	4-FC_6H_4	C_6H_5	239	68	$C_{26}H_{18}FN_5O_2S$	4.58(s, 2H), 6.74(s, 1H), 7.18-7.82(m, 13H), 9.72(bs, 1H), 10.50(s, 1H)
5e	4-$CH_3C_6H_4$	4-ClC_6H_4	252	71	$C_{27}H_{21}N_5O_2S$	2.36(s, 3H), 4.57(s, 2H), 7.17-7.84(m, 13H), 9.74(bs, 1H), 10.49(s, 1H)
5f	4-ClC_6H_4	4-ClC_6H_4	253	76	$C_{26}H_{17}Cl_2N_5O_2S$	4.54(s, 2H), 7.04-7.82(m, 13H), 9.75(bs, 1H), 10.50(s, 1H)
5g	4-BrC_6H_4	4-ClC_6H_4	219	74	$C_{26}H_{17}BrClN_5O_2S$	4.56(s, 2H), 7.06-7.81(m, 13H), 9.76(bs, 1H), 10.51(s, 1H)
5h	4-$CH_3C_6H_4$	2,4-diFC_6H_3	242	73	$C_{21}H_{19}N_5O_2S$	2.39(s, 3H), 4.57(s, 2H), 7.12-8.27(m, 12H), 9.73(bs, 1H), 10.49(s, 1H)
5i	4-ClC_6H_4	2,4-diFC_6H_3	261	67	$C_{26}H_{16}ClF_2N_5O_2S$	4.57(s, 2H), 6.72(s, 1H), 7.02(m, 4H), 7.41(m, 4H), 7.62(m, 1H), 7.84(d, 2H), 9.72(bs, 1H), 10.50(s, 1H)
5j	4-FC_6H_4	2,4-diFC_6H_3	253	73	$C_{26}H_{16}F_3N_5O_2S$	4.56(s, 2H), 6.74(s, 1H), 7.13-8.24(m, 11H), 9.74(bs, 1H), 10.51(s, 1H)
5k	4-BrC_6H_4	2,4-diFC_6H_3	260	69	$C_{26}H_{16}BrF_2N_5O_2S$	4.57(s, 2H), 6.73(s, 1H), 7.12-8.26(m, 11H), 9.73(bs, 1H), 10.52(s, 1H)
6a	4-$CH_3C_6H_4$	C_6H_5	233	72	$C_{21}H_{21}N_5OS_2$	2.38(s, 3H), 3.37(s, 2H), 6.81(s, 1H), 6.94(s, 1H), 7.19-7.82(m, 12H), 9.51(bs, 1H), 10.17(bs, 1H)
6b	4-ClC_6H_4	C_6H_5	243	67	$C_{26}H_{18}ClN_5OS_2$	3.38(s, 2H), 6.82(s, 1H), 6.93(s, 1H), 7.21-7.83(m, 12H), 9.49(bs, 1H), 10.14(bs, 1H)
6c	4-BrC_6H_4	C_6H_5	239	69	$C_{26}H_{18}BrN_5OS_2$	3.37(s, 2H), 6.83(s, 1H), 6.94(s, 1H), 7.19-7.82(m, 12H), 9.48(bs, 1H), 10.16(bs, 1H)
6d	4-FC_6H_4	C_6H_5	261	68	$C_{26}H_{18}FN_5OS_2$	3.36(s, 2H), 6.81(s, 1H), 6.93(s, 1H), 7.23-8.34(m, 12H), 9.52(bs, 1H), 10.15(bs, 1H)

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