SYNTHESIS OF 2-(1,3-DIARYLPYRAZOL-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 Celecoxib¹ and Sildenafil citrate² has created great interest in the synthesis of a variety of this class of compounds. Thiazole ring forms a part of a number of synthetic³ and natural products⁴ of medicinal interest. Several substituted aminopyrazoles and aminothiazoles are known to exhibit antimicrobial activities⁵. Furthermore, several substituted benzoxazines and benzothiazines have been reported as antihypertensive⁶, antiulcer⁷ and herbicidal agents⁸. In view of this and in continuation of our work on new 1,4-benzoxazines⁹, 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 montmorillonite K10 under acid free conditions¹⁰. The aminopyrazoles **1** were converted into the corresponding thioureas **2** by reaction of **1** with benzoylisothiocyanate followed by hydrolysis according to the reported methods¹¹. 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 ¹H NMR and analytical data (Table -1). In the ¹H NMR spectra compounds **5** & **6** exhibited typical singlets for OCH₂ (δ 4.56), SCH₂ (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. ¹H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard, chemical shifts expressed in δ ppm and Mass spectra on Hewlett Packard Mass spectrometer operating at 70 eV.

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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 ($R_1 = 4\text{-CH}_3\text{C}_6\text{H}_4$, $R_2 = \text{C}_6\text{H}_5$) 223° , 82%; **2b** ($R_1 = 4\text{-ClC}_6\text{H}_4$, $R_2 = \text{C}_6\text{H}_5$) 209° , 84%; **2c** ($R_1 = 4\text{-BrC}_6\text{H}_4$, $R_2 = \text{C}_6\text{H}_5$) 222° , 83%; **2d** ($R_1 = 4\text{-FC}_6\text{H}_4$, $R_2 = \text{C}_6\text{H}_5$) 211° , 86%; **2e** ($R_1 = 4\text{-CH}_3\text{C}_6\text{H}_4$, $R_2 = 4\text{-ClC}_6\text{H}_4$) 229° , 81%; **2f** ($R_1 = R_2 = 4\text{-ClC}_6\text{H}_4$) 189° , 79%; **2g** ($R_1 = 4\text{-BrC}_6\text{H}_4$, $R_2 = 4\text{-ClC}_6\text{H}_4$) 171° , 78%; **2h** ($R_1 = 4\text{-CH}_3\text{C}_6\text{H}_4$, $R_2 = 2,4\text{-diF}$) 222° , 79%; **2i** ($R_1 = 4\text{-ClC}_6\text{H}_4$, $R_2 = 2,4\text{-diF}$) 208° , 84%; **2j** ($R_1 = 4\text{-FC}_6\text{H}_4$, $R_2 = 2,4\text{-diF}$) 219° , 87%; **2k** ($R_1 = 4\text{-BrC}_6\text{H}_4$, $R_2 = 2,4\text{-diF}$) 218° , 79%.

General procedure for the preparation of 2-pyrazolylamino-4-benzoxa/thiazin-6-yl 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 NaHCO₃ 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 ($R_1 = 4\text{-CH}_3\text{C}_6\text{H}_4$, $R_2 = \text{C}_6\text{H}_5$)

Pyrazolyl thiourea **2** ($R_1 = 4\text{-CH}_3\text{C}_6\text{H}_4$, $R_2 = \text{C}_6\text{H}_5$) was converted into **6a** according to the general procedure described above to give **6a** as white crystalline solid 72%, m.p 233°. $^1\text{H NMR}$ ($\text{CDCl}_3 + \text{DMSO-}d_6$, 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 $\text{C}_{27}\text{H}_{21}\text{N}_5\text{OS}_2$ 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 ₃ C ₆ H ₄	C ₆ H ₅	201	65	C ₂₇ H ₂₁ N ₅ O ₂ S	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 ₆ H ₄	C ₆ H ₅	248	67	C ₂₆ H ₁₈ ClN ₅ O ₂ S	4.57(s, 2H), 6.73(s, 1H), 7.12-7.83(m, 13H), 9.72(bs, 1H), 10.18(s, 1H)
5c	4-BrC ₆ H ₄	C ₆ H ₅	251	64	C ₂₆ H ₁₈ BrN ₅ O ₂ S	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 ₆ H ₄	C ₆ H ₅	239	68	C ₂₆ H ₁₈ FN ₅ O ₂ S	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 ₃ C ₆ H ₄	4-ClC ₆ H ₄	252	71	C ₂₇ H ₂₁ N ₅ O ₂ S	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 ₆ H ₄	4-ClC ₆ H ₄	253	76	C ₂₆ H ₁₇ Cl ₂ N ₅ O ₂ S	4.54(s, 2H), 7.04-7.82(m, 13H), 9.75(bs, 1H), 10.50(s, 1H)
5g	4-BrC ₆ H ₄	4-ClC ₆ H ₄	219	74	C ₂₆ H ₁₇ BrClN ₅ O ₂ S	4.56(s, 2H), 7.06-7.81(m, 13H), 9.76(bs, 1H), 10.51(s, 1H)
5h	4-CH ₃ C ₆ H ₄	2,4-diFC ₆ H ₃	242	73	C ₂₇ H ₂₁ N ₅ O ₂ S	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 ₆ H ₄	2,4-diFC ₆ H ₃	261	67	C ₂₆ H ₁₆ ClF ₂ N ₅ O ₂ S	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 ₆ H ₄	2,4-diFC ₆ H ₃	253	73	C ₂₆ H ₁₆ F ₂ N ₅ O ₂ S	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 ₆ H ₄	2,4-diFC ₆ H ₃	260	69	C ₂₆ H ₁₆ BrF ₂ N ₅ O ₂ S	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 ₃ C ₆ H ₄	C ₆ H ₅	233	72	C ₂₇ H ₂₁ N ₅ O ₂ S	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 ₆ H ₄	C ₆ H ₅	243	67	C ₂₆ H ₁₈ ClN ₅ O ₂ S	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 ₆ H ₄	C ₆ H ₅	239	69	C ₂₆ H ₁₈ BrN ₅ O ₂ S	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 ₆ H ₄	C ₆ H ₅	261	68	C ₂₆ H ₁₈ FN ₅ O ₂ S	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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