STUDIES ON NOVEL REARANGEMENT OF BENZOXAZOLETHIOL

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Abstract: A new chemoselective approach to synthesize a series of benzoimidazole **2a-c, 3, 4a, b** and benzoxazol-2-thiol derivatives **5a-c, 6, 7a,b.** Benzoxazol-2-thiol derivatives under action of N-nucleophiles, by using this methodology, two series of heterocyclic systems were synthesized. 7-Chloro-2-methyl/or aryl-benzo-[4,5]imidazo[1,2,4] thiadiazole derivatives **8,9** and **10a-c** were prepared via cyclocondensation and condensation elimination reaction.
Key words: Benzoxazolthiol, chemoselective, benzoimidazol, N- nucleophiles

Introduction

A review of the literature revealed that compounds possessing benzoxazole moiety showed significant (in vitro) antibacterial activity especially against some enteric Gram-negative rods suchas *K*lebsiella pneumoniae, *P*seudomoanas aerugiunasa and the yeast *C*andida albicans[1-8]. Therefore, we directed our research to elaborate chemoselective procedures for the synthesis of a variety of hetero cyclic compounds of biological interest.

Result and Discussion

As a result of our research we found that depending on reaction conditions, 5-substituted-benzoxazl-2-thiol (**1**) reacted with different N- nucleophiles in two ways, namely, oxazole ring opening (Figure-1) and without one (Figure-3).

Indeed, in glacial acetic acid at refluxing temperature, reaction between benzoxazol-2-thiol derivative **1** and different primary amines, hydrazine hydrate and substituted - hydrazine hydrates took place with ring opening [9] (Figure-1).

The benzoimidazole derivatives were synthesized via stirring of **1** with primary amines, hydrazine hydrate and substituted phenyl hydrazine in presence of n-butanol at room temperature. ^{1}H-NMR of these compounds shows signals at d (ppm) 2.32, 2.31, 2.12, 2.19, 2.09, 2.12 (s,1H,exchangeable with D_2O, SH) for **2a-c, 3, 4a,b** (cf.,exp).

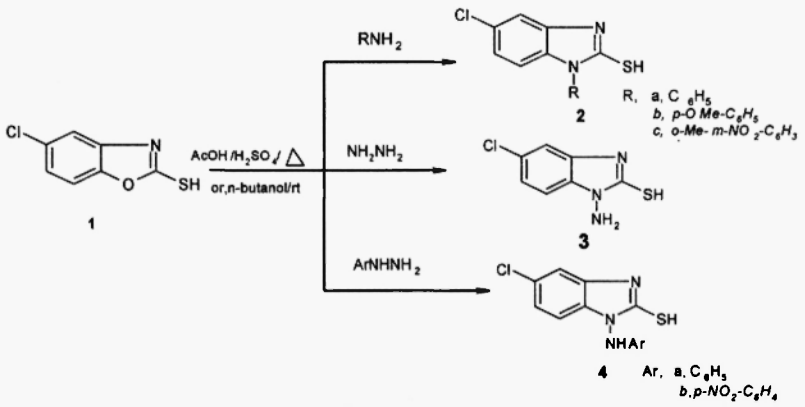

Figure-1

A mechanism that can be accounted for these products (**2a-c, 3, 4a,b**) may be analogous to acidic hydrolysis of benzoxazol-2-thiol derivative to the corresponding **II & III** (Figure-2). Therefore, when the reaction carried out in aqueous acidic media, the reaction mechanism might take place through :

i) Formation of 2-(R-imino)-benzoxazol-2-thiol derivatives. ii) Nucleophilic attack of water on C_2 of oxazol ring with simultaneous ring opening. iii) E_2 Isomerization and subsequent cyclization of III to form N-substitutedbenzoxazol-2-thiol derivatives [10] (Figure-2).

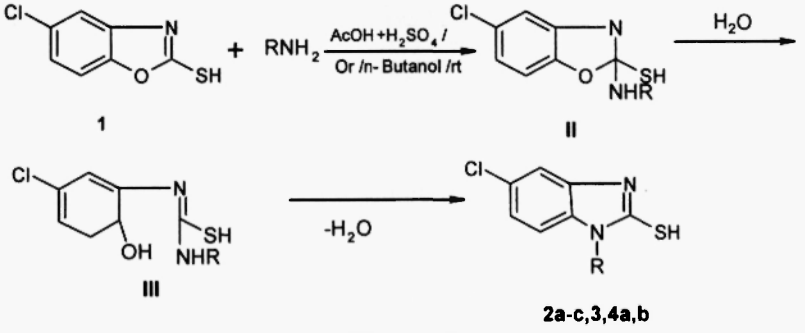

Figure-2

Starting from our assumption of two possible mechanisms of the rearrangements and varying reaction conditions from aqueous acidic media, acidic media (80%acetic acid and drops of sulfuric acid) and solvent with high boiling point such as n-butanol, we have benzoxazole derivatives **5a-c, 6** and **7a, b** (Figure-3).

5-Chlorobenzoxazole derivatives **5a-c, 6, 7a,b** were synthesized when **1** stirred under refluxing temperature for 10hrs with primary amines, hydrazine hydrate and substituted phenyl hydrazine in presence of n-butanol. The release of hydrogen sulfides were detected through the reaction.

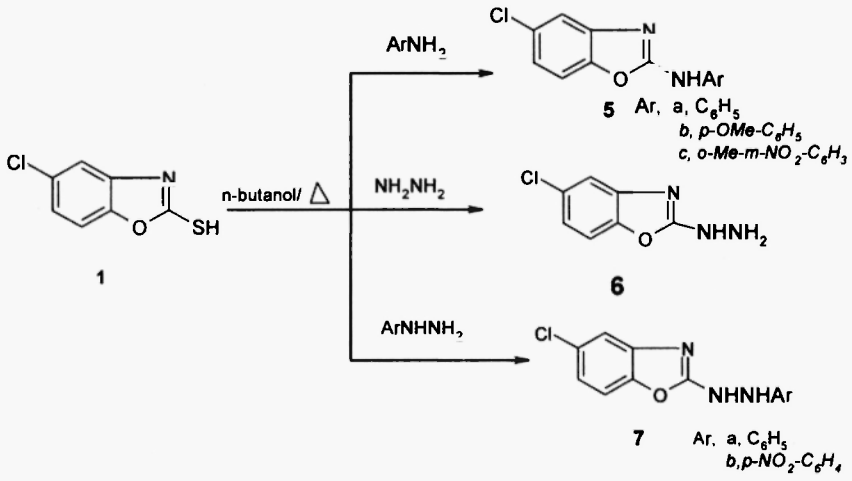

Figure-3

A possible mechanism of this feature might take place via : i) Nucleophilc attack of NH_2 on C_2 of benzoxazol ring . ii) Ring opening and E/Z isomerization of the intermediate (IV,V). iii) Subsequent liberation of hydrogen sulfide [11] (Figure -4).

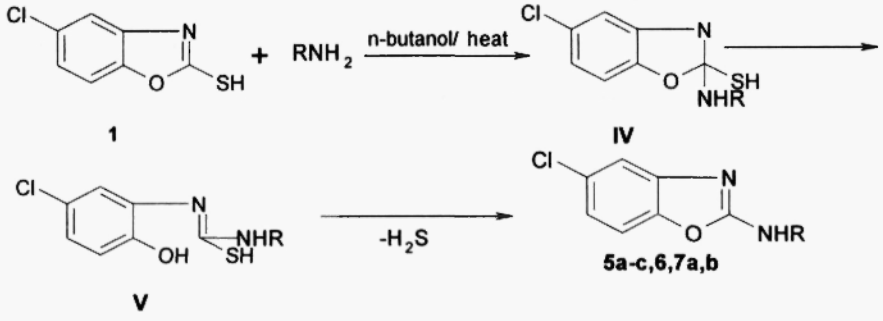

Figure -4

In continuation of our interest in the synthesis of fused heterocyclic compounds [12-15]. We reported here simple methods for synthesis of 7-chloro-2-methyl/or aryl- benzo-[4,5]imidazo[1,2,4]thiadiazole **8** and **10a-c** through cyclocondensation reactions upon treating with triethylorothoacetate, and aromatic aldehydes namely (benzaldehyde, anisaldehyde and N,N- dimethylaminobenzaldehyde) [12-15,17] (Figure-5).

Similarly[17], reaction of **3** with ethylchloroformate in presence of pyridine afforded **9** (Figure-5). The mass spectra showed expected molecular ion peak at 225.59 (53%). IR spectra exhibit absorption bands at cm $^{-1}$ 3120 (NH) and 1670 (cyclic amide) and the structure of **9** was confirmed from its ^{1}H-NMR (exp.).

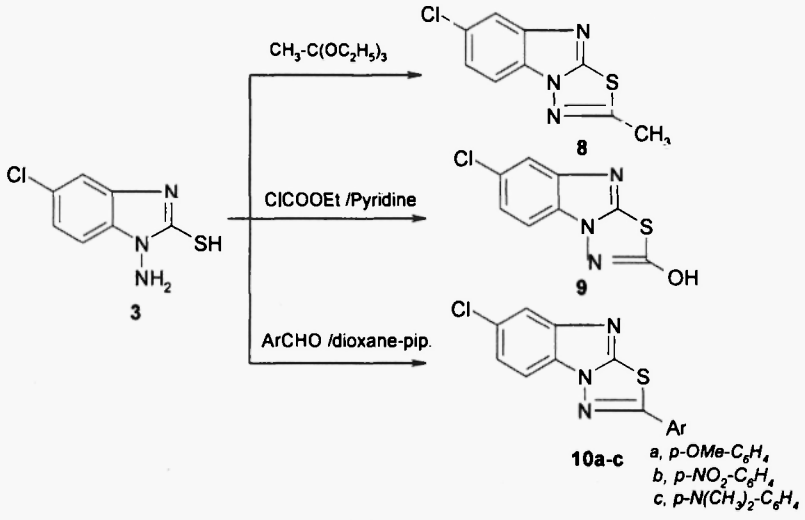

Figure-5

Experimental

Melting points are uncorrected, the purity and the reaction controlled time were detected by TLC, Microanalyses were performed by micro analytical Unit, NRC. All compounds gave satisfactory values for C,H,Cl, N and S within range of ±0.04. IR spectra (KBr) were recorded on Perkin Elmer 580 spectrophotometer. ^{1}H-NMR were carried on JNM,FT-NMR-EX270, run ^{1}H-NMR 270MHz, in DMSO-d $_{6}$ using TMS as internal standard and chemical shifts are expressed in d ppm. Mass spectra were recorded on Varian Mat 112 spectrometer.

5-Chloro-benzoxazol-2-thiol 1[17].

5-Chloro-1-aryl-1H-benzoimidazole-2-thiol 2a-c

1-Amino-5-chloro-1H-benzoimidazole-2-thiol 3

1-Arylamino-5-chloro-1H-benzoimidazole-2-thiol4a,b

Method1

An equimolar amounts (0.37g, 2mmol) of **1** and appropriate aromatic amine (aniline, *p*-anisidine and *m*-nitro-*o*-toluedine), hydrazin hydrate. phenylhydrazine or *p*-nitrophenyl

hydrazine was heated in 30ml acetic acid and one drop of sulfuric acid for 9hrs.The reaction mixture was cooled, poured into crushed ice and the solid so formed was collected by filtration and crystallized from appropriate solvent .

Method 2

An equimolar amounts (0.37g,2mmol) of **1** and appropriate aromatic amine (aniline, *p*-anisidine and *m*-nitro-*o*-toluedine), hydrazine hydrate, phenyl hydrazine or *p*-nitrophenyl hydrazine was stirred in 30ml n-butanol at room temperature for 10hrs. The reaction mixture was left in the refrigerator over night and the solid so formed was collected by filtration and was crystallized from appropriate solvent.

2a; lit. [18].

2b; Crystallization: EtOH; yield%; 62%; m.p.205-7°C; M. $FC_{14}H_{11}ClN_2OS$; M. Wt. 290.77; ^{1}H-NMR.dppm ; 6.92-7.62 (m,7H,Ar-H), 3.72 (s,3H,OCH_3), 2.31(s,1H, exchangeable with D $_2$O, SH); ^{13}c-NMR; 55.6(OCH_3), 115.1, 115.1, 115.6, 116.1, 123.0, 123.0, 124.4 (C-aromatic), 129.4 (C_5), 130.1(N-Ar), 134.5 (c_5), 141.7 (c_2), 142.3 (C_5), 159.2 (C-OCH_3); and MS (z/e%) 291, 292 (32,45),185 (100%).

2c; Crystallization: EtOH; yield% 33; m.p.248-250 °C; M. F. .C $_{14}H_{10}ClN_3O_2S$; M. Wt.. 319.77; ^{1}H-NMR.dppm ; 7.34-8.25 (m,6H,Ar-H), 1.12 (s, 3H, CH_3), 2.12 (s,1H, exchangeable with D_2O, SH and 332,333 (56,59), 199 (100%).

3; Crystallization: EtOH; yield% 70%; m.p.192-4°C; M. F. .$C_7H_6ClN_3S$; M. Wt.. 199.67; IR, cm^{-1}: 3480- 3365, ^{1}H-NMR.dppm; 6.82-7.42 (m,3H,Ar-H), 4.05 (s,2H, exchangeable with D_2O, NH_2), 2.19 (s,1H,. exchangeable with D_2O, SH) and MS, (z/e%) 199, 200 (35,39), 185 (100%).

4a; Crystallization: MeOH; yield% 45%; m.p.228-30°C; M. F. .$C_{13}H_{10}ClN_3S$; M. Wt.. 275.76;

IR, cm^{-1}. 3180(NH), ^{1}H-NMR. dppm ; 8.62 (s,b, exchangeable with D $_2$O, NH), 7.42-8.01 (m,8H, Ar-H), 2.09 (s,1H exchangeable with D_2O, SH) and MS, (z/e%) 276, 277, 278 (55,57,59), 134 (100%).

4b; Crystallization: benzene; yield% 45%; m.p.210-2 °C; M. F. .C $_{13}H_9ClN_4SO_2$; M. Wt.. 320.76;

IR, cm^{-1}; 3160(NH), ^{1}H-NMR.dppm; 8.12 (s,b,1H, exchangeable with D_2O, NH), 7.12-8.02 (m, 7H.Ar-H), 2.12 (s.!H, exchangeable with D_2O, SH) and MS. (z/e%) 321,322 (43,46), 134 (100 %).

2-(Arylamino)-5-choro-benzoxazle 5a-c

2-(hydrazino)-5-choro-benzoxazle 6

2-(Arylhydrazino)-5-choro-benzoxazle 7a,b

General Procedure

An equimolecular amounts (0.37g, 2mmol) of **1** and appropriate aromatic amine (aniline, *p*-anisidine and *m*-nitro-*o*-toludine), hydrazine hydrate phenyl hydrazine or *p*-nitrophenyl hydrazine was stirred under refluxing temperature in 30ml n-butanol for 10hrs.The reaction mixture was cooled was left in the refrigerator over night and the solid so formed was collected by filtration and was crystallized from appropriate solvent .

5a; Crystallization: EtOH; yield% 62; m.p.231-3°C; M. F. .$C_{13}H_9ClN_2O$; M. Wt.. 244.76; IR, cm^{-1}; 3165 (NH),), ^{1}H-NMR.dppm 7.41-8.30 (m,8H,Ar-H),7.82 (s,b,1H, exchangeable with D_2O, NH) and MS. (z/e%) 244,245 (45,49), 189(100%).

5b; Crystallization: EtOH; yield% 62%; m.p.23°C;M. F. .$C_{13}H_9ClN_2O$; M. Wt.. 244.68; IR, cm^{-1}; 3167 (NH), 7.32-8.10 (m,7H,Ar-H), 6.02 (s,b,1H, exchangeable with D_2O, NH), 1.64(s,3H,CH_3) and MS. (z/e%) 275,276(44,46), 195(10%).

5c; Crystallization: benzene; yield% 32%; m.p.26°C;M. F. $C_{14}H_{10}ClN_3O_3$; M. Wt.. 303.70; IR, cm^{-1}; 3210(NH) , ^{1}H-NMR.dppm 7.30-8.08 (m,6H,Ar-H),6.12 12 (s,b,1H, exchangeable with D_2O, NH), 1.12 (s, 3H, CH_3) and MS. (z/e%) 320, 321 (52,54), 189 (100%).

6; Crystallization: EtOH; yield% 75; m.p.235-7°C; M. F. .$C_7H_6ClN_3O$; M. Wt.. 183.56; IR, cm^{-1}; 3467-3350 and 3190 (NH_2 , NH); ^{1}H-NMR.dppm 8.52 (s,b,1H, exchangeable with D_2O, NH), 8.01(s,2H, exchangeable with D_2O, NH_2), 6.82-7.43 (m, 3H,Ar-H) and MS. (z/e%) 183 (56), 185 (100%).

7a; Crystallization: CH_3CN; yield% 46; m.p.265°C; M. F. $C_{13}H_{10}ClN_3O$; M. Wt.. 259.69; IR, cm^{-1} 3210,3120 (2NH)), ^{1}H-NMR.dppm; 7.43-8.12 (m,8H,Ar-H), 7.30, 6.24 (s,b,each1H, exchangeable with D_2O, NH) and MS. (z/e%) 259, 260 (25,27), 189 (100%).

7b; Crystallization: n-butanol; yield% 55; m.p.240°C;M. F. .$C_{13}H_9ClN_4O_3$; M. Wt.. 304.69;

IR, cm^{-1} 3110,3120 (2NH)), ^{1}H-NMR.dppm; 8.72,7.51 (s,b.each1H, exchangeable with D_2O,NH), 7,31-7.81 (m,7H,Ar-H) and MS. (z/e%) 305, 306 (43,49), 189 (100%).

7-Chloro-2-methyl-benzo[4,5]imidazo[2,1b][1,2,4]thiadiazole 8

A solution of**3** (0.99g, 5mmol) in10ml of triethyl orthoacetate was heated under reflux for 10 hrs. The excess triethyl orthoacetate was evaporated under vacuum to obtain wax material. It was solidified from methanol and the obtained solid was crystallized from n-butanol .

8; Crystallization: n-butanol; yield% 45; m.p.256-8 °C; M. F. $C_9H_6ClN_3S$; M. Wt. 223.69; C ^{1}H-NMR.dppm; 7.45-8.21 (m,3H,Ar-H), 2.16 (s,3H,CH_3) and MS. (z/e%) 224 ,225 (54,56), 219 (100%).

7-Chloro-2-oxo-benzo[4,5]imidazo[2,1 b][1,2,4]thiadiazole 9

To a solution of **3** (0.99g, 5mmol) in 10 ml pyridine, ethyl chloroformate (0.56g, 5 mmol) was added in drop wise. The reaction mixture was heated under reflux for 12hrs. The reaction mixture was cooled and was poured into crushed ice, the solid formed was collected by filtration and was crystallized from benzene.

9; Crystallization: benzene; yield% 58; m.p.244-6°C; M. F. .$C_8H_4ClN_3O$; M. Wt.. 225.66;

IR cm^{-1} 3120 (NH) and 1670 (cyclic amide), ^{1}H-NMR.dppm; 7.52-7.98 (m,3H,Ar-H), 5.02 (s,b, exchangeable with D_2O, OH) and MS. (z/e%)225.59 (53%), 55 (100).

7-Chloro-2-aryl-benzo[4,5]imidazo[2,1b][1,2,4]thiadiazole 10a-c

An equimolecular amounts of **3** (0.99g,5mmol) and appropriate aromatic aldehyde (p-anisaldehyde, *p*-nitrobenzaldehyde and N,N-dimethlaminobenzaldehyde in 25ml of dioxane in presence of catalytic amounts of pipridine was heated for 9hrs. The reaction mixture was cooled, the solid so formed was collected by filtration and was crystallized form appropriate solvent .

10a; Crystallization: n-butanol; yield% 42;m.p.236-8°C;M.F.$C_{15}H_{10}ClN_3SO$; M.Wt. 315.79; ^{1}H-NMR.dppm; 7.34-8.10 (m,7H,Ar-H),1.93 (s, 3H,OCH_3); ^{13}C-NMR; 55.9 (OCH_3), 115.4, 116.7, 124.3, 127.8, 127.8, 129.5, 129.5, 132.1 (C-aromatic), 125.2 (C_6),129.1(C_7), 142.1(C_5), 142.5 (C_2), 140. 2, 172.0 (N-C-S) and MS. (z/e%) 315,316 (24, 25), 134 (100%) .

10b; Crystallization: EtOH; yield% 48; m.p.251-2°C; M. F. .$C_{14}H_7ClN_4SO_2$; M. Wt.. 330.76; ^{1}H-NMR. dppm; 8.85-7.34 (m,7H,Ar-H) and MS. (z/e%) 331,332 (32,36), 123 (100%).

10c; Crystallization: EtOH; yield% 65; m.p.216-8°C; M. F. .$C_{16}H_{13}ClN_4S$; M. Wt.. 328.83;. ^{1}H-NMR.dppm; 7.01-7.89 (m,7H,Ar-H),3.91 (s,6H,$N(CH_3)_2$), and MS. (z/e%) 328, 329 (37,39%), 134 (100%).

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