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Short Communication

Convenient Method for the Synthesis of 1,2,4-Substituted Dithiazoles

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Abstract: A simple, novel and suitable method has been developed for the one step synthesis series of 3-substituted imino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenylformamidino]-amino-1,2,4-dithiazoles**(VIa-f)**was carried out by oxidative cyclisation of 2-(3-substituted-2,4-dithiobiureto-formamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazoles **(Va-f)** by making use of liquid bromine in chloroform medium as an oxidative cyclising agent.
Keywords: Dithiazoles, Synthesis, an oxidative cyclising agent.

INTRODUCTION

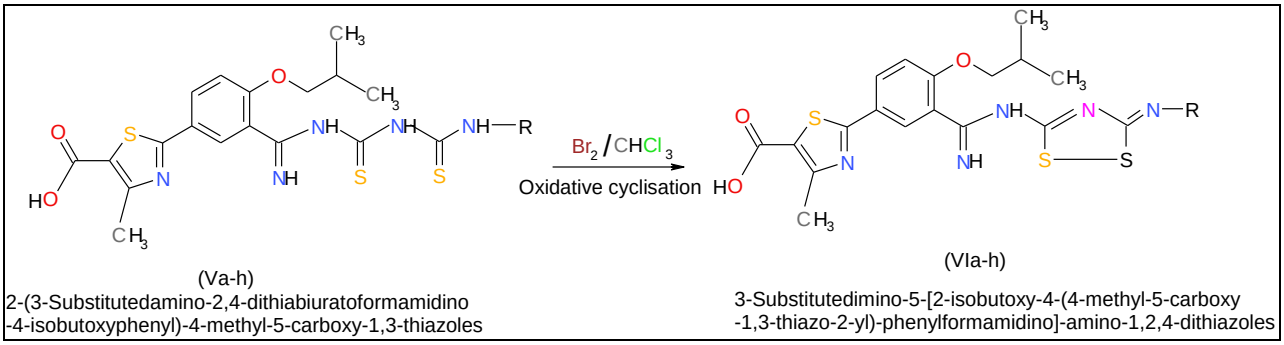
Heterocyclic compound is one of the most complex and intriguing part of organic transformation and its compounds constitute the largest and most varied family in organic chemistry [1-4]. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents [5]. Nowadays, dithiazole containing nucleus is widely used in medicinal and biological sciences [6]. Dithiazole nucleus useful in pharmaceutical, industrial, biological, agricultural and medicinal fields [7-13]. These types of drugs showed a various range of anti-tubercular [14], anti-fungal [15], anti-cancer [16], anti-oxidant [17], anti-inflammatory [18], anti-bacterial [19] and anti-diabetic [20] properties few of them active against different micro-organism like *E. coli, C. alibicans* and *S.Aureus*.

The literature survey proposed that heterocyclic compounds containing nitrogen and nitrogen and sulphur have gained immense important in human life. It was noticed that thiadizoles are effective against copper corrosion [21] and used as additive in lubricating oil [22]. Dabolkar and Ansari briefly investigated the oxidative cyclisation of cyanoamidinosubstitutedthiocarbamide and N-substitutedformamidinothiocarbamide [23].

As a part of research work presently being undertaken in the synthesis of various heteroacycles and heterocycles, it was thought interesting to investigate the oxidative cyclisation of 2-(3-substitutedamino-2,4-dithiobiuretoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazoles**(Va-f)** with liquid bromine in chloroform medium to obtained a novel series of 3-substitutedimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenylformamidino]-amino-1,2,4-dithiazoles**(VIa-f)** which are heither to unknown.

RESULT AND DISCUSSION

By considering all these things, we have developed new research scheme. During designing this scheme it was also planned to developed a new route for the synthesis of 3-substitutedimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenylforma - midino]amino-1,2,4-dithiazoles by theoxidative cyclisation of 2-(3-substitutedamino-2,4-dithiobiuretoforma-midino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazoles, hydro chloric acid and various thioureas. The main objective of this work is to synthesize a novel series of3-substitutedimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl) phenylformamidino]amino-1,2,4-dithiazoles and also to set up new reaction condition to reduce the time span of such type of reactions and at the same time it was also thought to increase the yield of product by maintaining the purity and green chemistry parameters. This work is useful to incoming researcher in organic chemistry for the synthesis of dithiazole. In the synthesized compound the dithiazole substituent may enhance the potency of the compounds. We synthesised 3-substitutedimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenyl formmidino]amino-1,2,4-dithiazoles Scheme1.



(Va-h)
2-(3-Substitutedamino-2,4-dithiabiuratoformamidino
-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazoles

(VIa-h)
3-Substitutedimino-5-[2-isobutoxy-4-(4-methyl-5-carboxy
-1,3-thiazo-2-yl)-phenylformamidino]-amino-1,2,4-dithiazoles

Where R= -phenyl, -t-butyl, -methyl, -ethyl, p-chlorophenyl, -o-tolyl.

Experimental

General remarks

All reagents were purchased from commercial suppliers and used without further purification. Dry methanol and diethyl ether were purchased from Aldrich and were used as such. All reactions were run in oven-dried round bottom flask or vial containing a teflon-coated stir bar and sealed with septum. Analytical thin layer chromatography was carried out on silica pre-coated glass plates (Silica gel 60 F254, 0.25 mm thickness) and visualized with UV light at 254 nm. ^{1}H NMR spectra were recorded on Bruker 400-MHz Ultrashield Advance II 400 model (400 and 100 MHz, respectively) at ambient temperature with $CDCl_3$ or DMSO-d6as solvents. Data for ^{1}H are recorded as follows: δ chemical shift (ppm), multiplicity (s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), DMSO-d6 (δ 2.50 ppm) or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. Liquid chromatography/mass spectrometry (LC/MS) data was obtained to verify molecular mass and analyze purity of products. The specifications of the LC/MS instrument are the following: Electrospray (+) ionization, mass range of 100-1000 Da, 20V cone voltage, Acquity BEH C-18 column (2.1 x 100mm, 1.7 µm), and gradient mobile phase consisting of 5 mm ammonium acetate in water and acetonitrile, and a flow rate of 0.5 ml/min.

General procedure for the Synthesis of 3-tert-butylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenylformamidino]-amino-1,2,4-dithiazoles

In a china dish pest of 3-tert-butylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenylformamidino]-amino-1,2,4-dithiazole **(Vb)** was prepared by adding minimum amount of chloroform to it liquid bromine in chloroform was added with constant stirring. Initially the colour of bromine disappear, the addition was continued till colour of bromine persisted to the reaction mixture. The reaction mixture was allowed to stand for 4 hours and then on basification with dilute ammonium hydroxide solution, afforded brown coloured products. Recrystalized from ethanol. Yield 86%, m.p. 172^{0}C.

3-Phenylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenylforma -midino]amino-1,2,4-dithiazoles (3a): (441 mg, 84%) yellow solid; melting point 210 ^{0}C;^{1}H NMR (400 MHz,DMSO-d_6): 11.4040 (1 H S), 7.1244 (1 H, S *J=14.8Hz*), 7.435 (1 H, S *J=14.8Hz*), 7.203(1H, S), 6.756 (5 H S), 4.1312 (2 H S), 4.1402 (1 H S), 2.5041 (2 H d *J=12Hz*), 1.6116 (1 H *J=12Hz* m), 1.283 (6 H d),1.411 (1 H S)^{13}C: 196.3, 190.2, 163.3 162.5, 155.3, 147.5, 144.3, 142.1, 141.2, 137.5, 132.4, 131.5, 128.0, 41.1, 34.2, 28.2, 24.8. IR: 3105.48 S, 2238.22 s, 1706.15 S, 1059.18 S, LCMS calcd for $C_{24}H_{23}N_5O_3S_3$. (M^+) 524, found 525.

3-Tert-butylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenyl formamidino]amino-1,2,4-dithiazoles (3b): (436.02 mg, 86%) brown solid; melting point 241^{0}C;^{1}H NMR (400 MHz,DMSO-d_6): 12.1240 (1 H S), 8.4144 (1 H, S *J=16.7Hz*), 7.554 (1 H, S *J=16.7Hz*), 7.142 (1H, S), 4.0112 (1 H S), 2.4541 (2 H d *J=12Hz*), 1.716 (1 H *J=12Hz* m), 1.0124 (6 H d),1.211 (3 H S)1.111 (9 H S)^{13}C: 201.3, 193.2, 165.3 163.5, 150.3, 144.5, 134.3, 138.1, 140.2, 141.5, 134.5, 130.5, 120.0, 40.1, 36.2, 29, 22.8. IR: 3346.1S, 3105.48 s, 2228.21S, 1624.3S, 1160.5 S, 617.8 s, LCMS calcd for $C_{22}H_{29}N_5O_3S_3$(M^+) 506, found 507.

3-Methylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenyl formamidino]amino-1,2,4-dithiazoles (3c): (418.05 mg, 90%) brown solid; melting point 196^{0}C;^{1}H NMR (400 MHz,DMSO-d_6): 11.6210 (1 H S), 7.6544 (1 H, S *J=15.8Hz*), 7.6540 (1 H, S *J=15.8Hz*), 7.4210(1H, S), 4.0122 (1 H S), 2.3521 (2 H d *J=10Hz*), 1.8796 (1 H *J=10Hz* m), 1.3680 (6 H d),1.9877 (3 H S), 1.6810 (3 H S)^{13}C: 198.5, 188, 166 160.5, 154.8, 149, 146, 143, 140.6, 135.7, 130.4, 129.3, 126.2, 46.2, 39.2, 30.2, 25.8.IR: 3354.62S, 2254.22 s, 1845.15 S, 1089.18 S, LCMS calcd for $C_{19}H_{23}N_5O_3S_3$. (M^+) 464, found 465.

3-Ethylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenyl formamidino]amino-1,2,4-dithiazoles (3d): (421.25 mg, 88%) brown solid; melting point 210 ^{0}C;^{1}H NMR (400 MHz,DMSO-d_6): 10.9842 (1 H S), 8.0444 (1 H, S *J=13.9Hz*), 7.9854 (1 H, S *J=13.9Hz*), 7.4570 (1H, S), 3.6841 (1 H S), 3.1402 (1 H S), 2.6351 (2 H d *J=14.8Hz*), 1.6954 (1 H *J=14.8Hz* m), 1.3651 (6 H d),2.0124 (2 H q), 1.7410 (3 H S), 1.411 (3 H t)^{13}C: 198.3, 192.2, 165.5 162.6, 157.3, 148.5, 145.3, 142.1, 138.2, 134.5, 128.4, 125.9, 126.0, 40.9, 36.7, 28.2, 24.8. IR: 3105.48 S, 2238.22 s, 1706.15 S, 1059.18 S, LCMS calcd for $C_{20}H_{25}N_5O_3S_3$. (M^+) 478, found 479.

3-p-Chlorophenylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenyl formamidino]amino-1,2,4-dithiazoles (3e): (476.55 mg, 85%) brown solid; melting point 210 ^{0}C;^{1}H NMR (400 MHz,DMSO-d_6): 11.7548 (1 H S), 8.6541 (1 H, S *J=17.7Hz*), 7.457 (1 H, S *J=17.7Hz*), 7.6541(1H, S), 6.6574 (2 H S), 6.4251 (2 H S), 3.5460 (2 H S), 3.5412 (1 H S), 2.6847 (2 H d *J=15Hz*), 1.1816 (1 H *J=15Hz* m), 1.2411 (6 H d),1.6540 (1 H S)^{13}C: 201.3, 193.8, 166.3 163.5, 157.3, 149.9, 148.3, 144.1, 143.8, 139.8, 130.4, 129.1, 128.7, 40.4, 35.2, 28.2, 26.8. IR: 3198.48 S, 2278.22 s, 1726.15 S, 1045.18 S, LCMS calcd for $C_{24}H_{24}N_5O_3S_3Cl$. (M^+) 560, found 561.

3-p-Tolylimino-5-[2-isobutoxy-5-(4-methyl-5-carboxy-1,3-thiazo-2-yl)-phenyl formamidino]amino-1,2,4-dithiazoles (3f): (443.62 mg, 82%) brown solid; melting point 210 ^{0}C;^{1}H NMR (400 MHz,DMSO-d_6): 12.541 (1 H S), 8.5412 (1 H, S *J=18.2Hz*), 8.2314 (1 H, S *J=18.2Hz*), 7.3543(1H, S), 6.806 (2 H S), 6.2541 (2 H S) 4.5412 (2 H S), 4.2546 (1 H S), 2.9842 (2 H d *J=11Hz*), 1.9816 (1 H *J=11Hz* m), 1.0223 (6 H d),1.8445 (1 H S)^{13}C: 200, 195.7, 168.6 167.9, 160.3, 154.5, 149.3, 147.1, 145.9, 139.5, 136.4, 130.5, 126, 40.4, 39.4, 26.3, 22.3. IR: 3251.48 S, 2254.22 s, 1845.15 S, 1154.18 S, LCMS calcd for $C_{25}H_{27}N_5O_3S_3$. (M^+) 540, found 541.

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