New Routes for the Synthesis Novel Heterocyclic via Formation of C-N Bond and via Cleavage a Thiazine Ring of 1,4-Benzothiazine

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Abstract

The reactions of 2-aminothiophenol with acetylacetone in refluxing DMSO or ethanol was investigated. Treatment of **1** with enaminone **5** gave 1,4-benzothiazine derivative **6**. A reasonable mechanism represented the formation of pyridone derivative **11** by treatment of **2** with malononitrile. Reactions of **2** with cyanoacetohydrazide, thiosemicarbazide, hydrazine hydrate and phenyl hydrazine afforded the compounds **13**, **15** and, **17a-b** respectively. Condensation of **13** with 4-methoxy benzaldehyde gave **18**. The latter compound reacted with malononitrile gave pyridone derivative **19**. A reasonable mechanism interpreted the formation of pyrazolo[3,4-b]pyridine derivative **20** from the reaction of **13** with DMF-DMA via cleavage of a thiazine ring of 1,4-benzothiazine. The structures of all newly synthesized compounds elucidated by elemental analysis ¹H-NMR and ¹³C-NMR spectra, Ms and X-ray crystallographic investigations. The reported crystal structures of these novel 1,4-benzothiazine derivatives are expected to be a remarkable contribution to the crystallographic database of heterocyclic compounds.

Keywords: 2-Aminothiophenol; benzo[b][1,4]thiazine; pyrazole; pyridine; pyrazolopyridine; 2,2'-disulfanediyl dianiline

Introduction

Benzothiazines are considered to be suitable candidates for different pharmacological activities, such as anticancer [1] antiproliferative agents [2], antimicrobial [3], antifungal activity [4]. In some cases 1,4-benzothiazines are also known for their utility as dyes, photographic developers, ultraviolet absorbers light and antioxidants [5]. In continuation of our interest in the synthesis of functionally substituted heterocyclic compounds [6-8], we report here the behavior of 2-acetyl-3-methyl-4H-benzo[b][1,4]thiazine toward carbon and nitrogen nucleophiles in the synthesis of pyrazole, pyridine and pyrazolopyridine derivatives.

Materials and Methods

General Procedures: Melting points are reported uncorrected and determined on a Gallenkamp apparatus. The Infrared spectra recorded on a Jasco FT/IR-6300 FT-IR uses KBr disks. ¹H-NMR and ¹³C-NMR spectra were measured on a Bruker DPX 400 MHz and Bruker AVANCE II 600 MHz spectrometers, with DMSO-d₆ or CDCl₃ as solvent using TMS as an internal

standard. The chemical shifts expressed as a δ unit in parts per million (ppm) and TMS = 0.00 ppm. The following abbreviation is used: s = singlet, d = doublet, t = triplet; q = quartet; m = multiple; br = broad. Mass spectra measured on GC/MS DFS, THERMO instrument. Microanalyses performed on a CHNS-Vario. Micro Cube Analyzer; Single crystal X-ray crystallography was performed using Rigaku Rapid II and Bruker X8 Prospector diffractometers.

Procedures for the Synthesis of 1-(3-Methyl-4H-benzo[b][1,4]thiazine-2-yl)ethanone Derivatives:

1-(3-Methyl-4H-benzo[b][1,4]thiazine-2-yl)ethanone (2): A mixture of **1** (1.25g, 10.0mmol) and 2,4-pentanedione (1.01g, 10.0 mmol) in DMSO (20mL) was refluxed for 2h. The reaction mixture was allowed to cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from ethanol as the red crystal. Yield: 1.86g, (91%). Mp. 194-195 °C; (lit mp. 192°C [10]) ; FT- IR_νmax/cm⁻¹: 3277 (NH), 1603(CO) ; ¹H-NMR(DMSO-d₆) δ ppm: 2.20(s, 3H, CH₃), 2.24 (s, 3H, CH₃), 6.65-6.96(m, 4H, aromatic-H), 8.89(bs, 1H,

NH, D₂O exchangeable); ¹³C-NMR(DMSO-d₆): δ ppm: 20.9(CH₃), 29.8(CH₃), 79.7(C-2), 114.9, 120.0, 124.6, 125.9, 126.9, 138.8, 126.9(aromatic carbons & C-3), 190.2(CO); MS *m/z*(%): 205 [M⁺, 78%]. *Anal.* Calcd. for C₁₁H₁₁NO (205.28): C, 64.36, H, 5.40; N, 6.82%. Found: C 64.38; H, 5.34; N, 6.78%.

1-(2-Methyl-2,3-dihydrobenzo[d]thiazol-2-yl)propane-2-one (3): A mixture of **2** (1.25g, 10 mmol) and 2,4-pentanedione (1.01g, 10.0 mmol) in ethanol (20mL) was refluxed for 2h. The reaction mixture was allowed to cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from methanol as yellow crystal. Yield: 1.8g, (88%). Mp. 88-90°C; FT-IR *v*max/cm⁻¹: 3333 (NH), 1706(CO); ¹H-NMR(DMSO-d₆) δ ppm: 1.63(s, 3H, CH₃), 2.12 (s, 3H, CH₃), 3.19(dd, *J*=16Hz, 2H, CH₂), 6.43(s, 1H, NH, D₂O exchangeable), 6.53-6.96(m, 4H, aromatic-H); ¹³C-NMR (DMSO-d₆): δ ppm: 29.5 (CH₃), 30.80 (COCH₃), 55.8 (C-2), 74.4(methylene carbon), 108.8, 118.3, 121.1, 124.9, 125.9, 126.3 (aromatic-carbons), 206.1(CO); MS *m/z*(%): 207 [M⁺, 12]. *Anal.* Calcd. for C₁₁H₁₃NOS (207.29): C, 63.74; H, 6.32; N, 6.76%. Found: C 63.50; H, 6.29; N, 6.75%.

(4H-Benzo[b][1,4]thiazin-2-yl)(thiophen-2-yl)methanone (6): A mixture of **2** (1.25g, 10.0mmol) and enaminone **5** (1.88g, 10.0 mmol) in ethanol (20mL) was refluxed for 3h. The reaction mixture was allowed to cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from ethanol as the red crystal. Yield: 2.09g, (81%). Mp. 230-232°C; FT-IR *v* max/cm⁻¹: 1620 (CO); ¹H-NMR(DMSO-d₆): δ ppm: 6.57-7.84(m, 8H, aromatic-H) 9.25(s, 1H, NH, D₂O exchangeable); ¹³C-NMR(DMSO-d₆): δ ppm: 102.9, 116.0, 119.5, 125.3, 126.8, 127.7, 127.4, 130.1, 131.4, 136.4, 141.6, 143.8(aromatic -H), 177.3(C=O); MS *m/z*(%): 259 [M⁺, 77%]. *Anal.* Calcd. for C₁₃H₉NOS₂ (259.35): C, 60.20, H, 3.50, N, 5.40%. Found: C 60.17, H, 3.56, N, 5.22%.

5-(2-Aminophenylthio)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile(11): A mixture of **2** (2.05g, 10.0mmol) and malononitrile (0.66g, 10.0mmol) in absolute ethanol (30mL), containing a few drops of triethylamine was heated under reflux for 3h. The solid product, so formed, was collected by filtration and crystallized from ethanol as golden brown crystal. Yield: 1.81g, (67 %). Mp. 271-272 °C; FT-IR *v* max/cm⁻¹: 3441-3441 (NH₂), 3278 (NH), 2219(CN), 1662(CO); ¹H-NMR(DMSO-d₆): δ ppm: 2.19(s, 3H, CH₃), 2.24 (s, 3H, CH₃), 6.47-6.93(m, 4H, aromatic-H), 8.87(bs, 2H, NH₂, D₂O exchangeable), 12.82(s, 1H, NH, D₂O exchangeable); ¹³C-NMR(DMSO-d₆): δ ppm: 21.1(CH₃), 29.2(CH₃), 115.9, 117.7, 120.1, 124.6, 125.9, 126.9, 127.1, 138.8, 145.7, 157.4, 159.9 (aromatic-carbons & CN), 163.6(CO); MS *m/z*(%): 271 [M⁺, 100%]. *Anal.* Calcd. for C₁₄H₁₃N₃OS (271.34): C, 61.97, H, 4.82, N, 15.49%. Found: C, 62.16; H, 5.01; N, 15.25%.

3-(3,9a-Dimethyl-3a,9,9a-trihydropyrazolo[4,3-b]benzo[1,4]thiazin-1-yl)-3-oxopropanenitrile (13): A mixture of **2** (2.05g, 10.0mmol) and 2-cyanoacetohydrazide (0.99g, 10.0

mmol) in ethanol (20mL) and acetic acid (1mL) was refluxed for 2h. The reaction mixture was allowed to cool at room temperature. The solid product, so formed, was collected by filtration and crystallized from ethanol as the pale red crystal. Yield: 2.31g, (81%). Mp. 157-159 °C; FT-IR *v*max/cm⁻¹: 3307 (NH), 2261(CN), 1669(CO); ¹H-NMR(DMSO-d₆): δ ppm: 1.91(s, 6H, 2CH₃), 3.89(dd, 2H, *J*=19Hz, CH₂), 4.77(s, 1H, H-3a), 6.57(s, 1H, NH, D₂O exchangeable), 6.80-7.21(m, 4H, aromatic-H); ¹³C-NMR(DMSO-d₆): δ ppm: 13.9(CH₃), 25.5(CH₂), 39.1(CH₃), 61.7(C-3a), 83.2(C-9a), 115.7 (CN), 118.6, 120.7, 121.5, 128.2, 128.8, 144.4, 156.3, 159.95(CO); MS *m/z*(%): 286 [M⁺, 65%]. *Anal.* Calcd. for C₁₄H₁₄N₄SO (286.35): C, 58.72, H, 4.93, N, 19.57%. Found: C 58.66, H, 5.10, N, 19.42%.

3,9a-Dimethyl-3a,9,9a-trihydropyrazolo[4,3-b]benzo[1,4]thiazin-1-yl-carbothioamide(15): A mixture of **2** (2.05g, 10.0mmol) and thiosemicarbazide (0.91g, 10.0 mmol) in ethanol (20mL) was refluxed for 2h. The solid product, so formed, was collected by filtration and crystallized from ethanol as the red crystal. Yield: 1.97g, (71%). Mp. 164-166°C; FT-IR *v* max/cm⁻¹: 3419-3374(NH₂), 3261 (NH); ¹H-NMR(DMSO-d₆) δ ppm: 1.95(s, 3H, CH₃), 1.98(s, 3H, CH₃), 4.79(s, 1H, H-3a), 6.84-7.55(m, 4H, aromatic-H), 7.80 (s, 2H, NH₂, D₂O exchangeable), 8.63(s, 1H, NH, D₂O exchangeable); ¹³C-NMR(DMSO-d₆): δ ppm: 13.7(CH₃), 27.2(CH₃), 62.2(C-3a), 85.1(C-9a), 118.6, 120.9, 121.7, 127.9, 128.8, 144.3, 153.8(aromatic-carbons), 174.3(CS). MS *m/z*(%): 278 [M⁺, 98%]. *Anal.* Calcd. for C₁₂H₁₄N₄S₂ (278.40): C, 51.77, H, 5.07, N, 20.12%. Found: C 51.85, H, 5.23, N, 20.29%.

2-(3,5-Dimethyl-1H-pyrazol-4-ylthio)benzenamine(17a): A mixture of **2** (2.05g, 10.0mmol) and hydrazine hydrate (0.54g, 10.0 mmol) in ethanol (20mL) was refluxed for 3h. The solid product, so formed, was collected by filtration and crystallized from ethanol as the pale brown crystal. Yield: 1.55g, (71%). Mp. 147-151°C; FT-IR *v* max/cm⁻¹: 3449-3364(NH₂), 3185 (NH); ¹H-NMR(DMSO-d₆) δ ppm: 2.14(s, 6H, 2CH₃), 5.08 (s, 2H, NH₂, D₂O exchangeable), 6.44-6.89(m, 4H, aromatic-H), 12.03(bs, 1H, NH, D₂O exchangeable); ¹³C-NMR(DMSO-d₆) δ ppm: 10.9(2CH₃), 102.7, 114.7, 116.9, 119.6, 124.2, 126.8, 128.6, 139.3 146.0(aromatic-carbons); MS *m/z*(%): 219 [M⁺, 100%]. *Anal.* Calcd. for C₁₁H₁₃N₃S (219.30): C, 60.24, H, 5.97, N, 19.16%. Found: C 60.21, H, 5.83, N, 19.01%.

2-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-ylthio)benzenamine (17b): A mixture of **2**, 2.05, 10.0mmol) and phenyl hydrazine (1.08g, 10.0 mmol) in ethanol (20 mL) was refluxed 3 h. The solid product, so formed, was collected by filtration, washed with ethanol and crystallized from ethanol as pale brown crystal. Yield: 2.30g, (78%). Mp. 99-101°C; FT-IR *v* max/cm⁻¹: 3441-3324(NH₂); ¹H-NMR(DMSO-d₆) δ ppm: 2.19(s, 3H, CH₃), 2.36 (s, 3H, CH₃), 5.21(s, 2H, NH₂, D₂O exchangeable), 6.48-7.56(m, 9H, aromatic-H); ¹³C-NMR(DMSO-d₆) δ ppm: 11.4(CH₃), 11.9(2CH₃), 106.6, 114.8, 117.1, 118.6, 124.2, 127.2, 127.5, 129.1, 129.3, 139.3, 143.1, 146.4, 151.4 (aromatic-carbons). MS *m/z*(%): 295 [M⁺, 90%]. *Anal.* Calcd. for C₁₇H₁₇N₃S (295.40):

C, 69.12, H, 5.80, N, 14.22%. Found: C, 69.04, H, 5.73, N, 13.99%.

2-[(3,9a-Dimethyl-3a,9,9a-trihydro-1H-pyrazolo[4,3-b]benzo[1,4]thiazin-1-oxo)-3-(4-methoxyphenyl)]acrylonitrile (18): A mixture of **13** (2.86g, 10.0mmol) and p-methoxy benzaldehyde (1.36, 10.0 mmol) in ethanol (20mL) was refluxed for 3h. The solid product, so formed, was collected by filtration, washed with ethanol and crystallized from ethanol as the gray crystal. Yield: 2.90g, (72%). Mp. 120-122°C; FT- IR ν max/cm⁻¹: 3341 (NH); 2213(CN) 1662(CO); ¹H-NMR(DMSO-d₆) δ ppm : 1.94(s, 3H, CH₃), 1.96 (s, 3H, CH₃), 3.85 (s, 3H, OCH₃), 4.81(s, 1H, H-3a), 6.64(s, 1H, NH, D₂O exchangeable), 6.82-7.94(m, 9H, aromatic-H, & H-3); ¹³C-NMR(DMSO-d₆) δ ppm: 14.1(CH₃), 25.3(CH₃), 55.6(OCH₃), 61.1(C-3a), 83.5(C-9a), 102.9 (C-2), 114.5(CN), 116.3, 118.6, 121.6, 124.4, 128.2, 128.9, 129.6, 131.8, 144.3, 151.5, 155.9, 159.3(aromatic-carbons & C-3) 164.2(CO); MS m/z (%) : 404 [M⁺, 91 %]. Anal. Calcd. for C₂₂H₂₀N₄O₂S (404.48): C, 65.33, H, 4.98, N, 13.85%. Found: C, 65.11, H, 4.88, N, 13.72%.

6-(3,9a-Dimethyl-3a,9,9a-trihydropyrazolo[4,3-b]benzo[1,4]thiazin-1-yl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3, 5-dicarbonitril (19): A mixture of **18** (4.04gm, 10.0 mmol) and malononitrile (0.66gm, 10.0 mmol) in ethanol (20mL) and 2-3 drops of piperidine were refluxed for 2-3h. The solid product, so formed, was collected by filtration and crystallized from ethanol as brown crystal. Yield: 3.11g, (69%). Mp. 226-228°C; FT- IR ν max/cm⁻¹: 3336 (NH), 2218(CN), 1662(CO); ¹H-NMR(DMSO-d₆) δ ppm: 2.01(s, 3H, CH₃), 2.10(s, 3H, CH₃), 3.93(s, 3H, OCH₃), 4.19(s, 1H, H-3a), 6.67(s, NH, D₂O exchangeable), 6.82-8.54(m, 9H, aromatic-H, & NH, D₂O exchangeable). ¹³C-NMR(DMSO-d₆) δ ppm: 14.4(CH₃), 21.1(CH₃), 62.2(-3a), 83.7(C-9a), 97.7, & 99.0(C-3 & C-5), 116.1 & 119.0 (CN), 121.2, 122.0, 122.1, 124.6, 125.4, 126.9, 128.6, 129.3, 131.1, 133.8, 134.0, 144.8, 156.8, 160.4 (aromatic

carbons), 164.8(CO); m/z (%) : 468 [M⁺, 47 %]. Anal. Calcd. for C₂₅H₂₀N₆O₂S (468.14): C, 64.09; H, 4.30; N, 17.94%. Found: C, 64.21, H, 4.35; N, 17.67%.

5-(2-Aminophenylthio)-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-3-ol (20): A mixture of **13** (2.86g, 10.0mmol) and DMFDMA (1.33g, 10.0mmol) in 1,4-dioxane (20mL) was refluxed for 6h. The solid product, so formed, was collected by filtration and crystallized from ethanol as yellow crystal. Yield: 2.08g, (73%). Mp. 274-276°C; FT- IR ν max/cm⁻¹: 3438-3348 (NH₂ & OH), 3235(NH); ¹H-NMR(DMSO-d₆) δ ppm: 2.55(s, 3H, CH₃), 2.66 (s, 3H, CH₃), 3.40 (br, 1H, OH, D₂O exchangeable), 5.15 (s, 2H, NH₂, D₂O exchangeable), 6.34-6.89(m, 4H, aromatic-H), 11.53(br, 1H, NH, D₂O exchangeable). ¹³C-NMR(DMSO-d₆) δ ppm: 16.7(CH₃), 25.3(CH₃), 104.6, 115.2, 117.8, 118.4, 119.2, 126.9, 127.3, 146.3, 149.9, 152.5, 156.3, 163.2(aromatic-carbons); m/z (%) : 286 [M⁺, 90 %]. Anal. Calcd. for C₁₄H₁₄N₄OS (286.35): C, 58.72, H, 4.93, N, 19.57%. Found: C 58.63, H, 5.20, N, 19.52%.

Result & Discussion

We have reports here the behavior of both 2-amino thiophenol and 1-(3-methyl-4H-benzo[b][1,4]thiazin-2-yl) ethanone toward carbon and nitrogen nucleophiles in the synthesis of pyridine, pyrazole, pyrazolopyridine derivatives. The importance and the utility of 1,4-benzothiazine (1,4-BT) derivatives have led to the development of a wide variety of methods for the preparation of 1,4-benzothiazines have been reported [9]. One of the methods employed for the preparation of 1,4-benzothiazines involves nucleophilic substitution of disulfide by β -keto esters and 1,3-diketones in presence base [9]. Recently Forsal *et al* [10] also have reported that condensation of 2-amino thiophenol with acetylacetone in boiling ethanol afforded 60% yield of 1,4-BT derivative **3** and trace of a yellow crystal of 2,2'-disulfanediyl dianiline **4** (Scheme 1).

Scheme 1: Reported structure for the products of reaction of 2-aminothiophenol with acetylacetone [10]

Table 1: Selected bond lengths (Å) & bond angles for compound 3

Bond	Bond length (Å)	Bond	Bond angle (°)
N1-C4	1.469(2)	C3-S1-C4	90.90(8)
S1-C4	1.8594(16)	C9-N1-C4	113.40(14)
C4-C5	1.524(2)	N1-C4-C10	111.26(14)
C5-H5B	0.97	C6-C5-C4	116.58(14)
C5-H5A	0.97	C6-C5-H5A	108.1
C4-C10	1.525(3)	O1-C6-C11	121.61(17)

When the reaction is carried according to this method and under the same reaction conditions reported in Literature [10], the 1-(3-methyl-4H-benzo[b][1,4]thiazin-2-yl)ethanone **2** is not isolated. In our hand, we isolate 1-(2-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)propan-2-one **3** from the reaction of **1** with acetyl acetone in refluxing ethanol in an excellent yield. The structure of the isolated product was confirmed by elemental analysis; spectral data and X-ray crystallography [11] (cf. Figure 1 and Table 1).

On the other hand, changing the reaction condition as has been reported in the literature [10] the 2-acetyl 3-methyl- 1,4BT **2** was readily prepared in an excellent yield by the treatment of 2-aminothiophenol **1** with acetyl acetone in the refluxing DMSO for two hours (cf. Scheme 2). The structure of **2** confirmed by the X-ray crystallography [12](cf. Figure 2).

Figure1: Perspective view and atom labeling of X-rays structure of **3**.

Figure 2: Perspective view and atom labeling of X-rays structure of **2**

Scheme 2: Reactions of 2-aminothiophenol with acetyl acetone and enaminone

Figure 3: Perspective view and atom labeling of X-rays structure of 2,2'-disulfaneyldianiline (4).

Moreover, treatment of 2-aminothiophenol **1** with malononitrile in the refluxing acetic acid was unsuccessful. In fact, gave the only single product of light yellow crystal in excellent yield. The structure of the product was established by elemental analysis, spectral data and unambiguously confirm by X-ray crystallography as 2,2'-disulfaneyldianiline **4** [13] (Scheme 2, Figure 3).

The previous result prompted us to investigate the behavior of **1** towards enaminones as the procedures for the synthesis of fused heterocyclic systems. Therefore, treatment of compound **1** with enaminone **5** in the refluxing ethanol afforded the red crystal **6** in excellent yield and identified as 4H- benzo[*b*][1,4]thiazin-2-yl) (thiophen-2-yl) methanone (**6**). The structure of **6** was confirmed on the basis of elemental analysis and spectral data (*cf.* Material & Methods Section). The X-ray crystallography unambiguously confirmed the structure of **6** [14] (*cf.* Figure 4 and Table2), The latter compound failed to condense with malononitrile in refluxing ethanol containing piperidine as the catalyst.

Figure 4: Perspective view and atom labeling of the X-rays structure of **6**.

Condensation of compound **2** with malononitrile in ethanol in the presence of a catalytic amount of triethylamine under the reflux afforded pyridine derivative **11** in good yield (Scheme 3). The mass spectrum of **11** revealed a molecular ion peak [M⁺] with *m/z* 271, which is compatible with molecular formula C₁₄H₁₃N₃OS. The isolated product was identified on the basis of spectral data (*cf.* Material & Methods Section). The structure of **11** was further confirmed by X-ray crystallography [15] (*cf.* Figure 5). The selected bond lengths and bond angles for the aforementioned compound are listed in (Table 3). It is observed that two molecules of **11** are present in one asymmetric unit of these crystals; they are chemically same, but different in crystallographic point of view, due to nonequivalence in symmetry characteristics within the unit cell. The formation of **11** is assumed to occur *via* nucleophilic addition of the amino group to carbonyl carbon and subsequent loss of water molecule to give non-isolable intermediate **8**, which underwent in situ cyclization *via* the Michael addition of amino group on the activated double bond to give non-isolable intermediate **9**. The intermediate **10** converted to **11** *via* cleavage of a thiazine ring of 1, 4-benzothiazine (Scheme 3).

Scheme 3: Proposed pathway for formation of 1, 2-dihydropyridine-3-carbonitrile derivative **11**

Figure 5: Perspective view and atom labeling of X-rays structure of 11.

Table 2: Selected bond lengths (°A) & bond angles for compound 6

Bond	Bond length (°A)	Bond	Bond angle(°)
S1-C10	1.716(4)	S1-C10-C9	117.8(3)
C10-C11	1.397(5)	C10-C11-C12	111.6(3)
C9-C10	1.484(5)	O1-C9-C10	118.1(3)
C8-C9	1.428(5)	C7-C8-C9	125.9(4)
S3-C8	1.779(4)	C10-S1-C13	92.07(19)
O1-C9	1.243(5)	N1-C7-C8	125.8(4)

Table 3: Selected bond lengths (°A) & bond angles for compound 11

Bond	Bond length (°A)	Bond	Bond angle(°)
S1-C7	1.770(4)	C7-S1-C1	103.70(18)
N3-C13	1.347(5)	C13-N3-C12	125.9(3)
C7-C13	1.386(6)	O1-C12-N3	120.8(3)
C8-C7	1.415(5)	C10-C8-C7	119.1(3)
O1-C12	1.232(5)	C13-C7-S1	119.5(3)
C10-C12	1.438(5)	C1-C6-N1	120.8(5)

These results prompted us to investigate the behavior of 1-(3-methyl-4H-benzo[b][1,4]thiazin-2-yl)ethanone **2** towards nitrogen nucleophiles as potential approaches to fused heterocyclic systems in hopes of obtaining compounds of high pharmaceutical activities. Thus, treatment of compound **2** with 2-cyanoacetohydrazide in the refluxing ethanol afforded trihydropyrazolo [4,3-*b*]benzo[1,4]thiazine derivative **13** (Scheme 4). The structure of the final product confirmed by their correct elemental and spectral data. The X-ray crystallographic

afforded an unambiguous evidence of structure **13** [16] (*cf.* Figure 6 & Table 4). In a similar manner, another class of trihydropyrazolo [4,3-*b*]benzo[1,4]thiazine derivative **15** has prepared by reacting 1,4-benzothiazine derivative **2** with thiosemicarbazide in the refluxing ethanol. It is believed that **15** is produced *via* mechanistic route displayed in Scheme 4 involving intermediate **14**. The chemical structure of **15** was unambiguously confirmed by X-ray crystallographic as trihydropyrazolo [4,3-*b*] benzo[1,4]thiazine derivative **15** [17] (*cf.* Figure 7 & Table 5).

Scheme 4: Reactions of 2-acetyl -3-methyl-1,4-benzothiazine 2 with hydrazine derivatives

Table 4: Selected bond lengths (°A) & bond angles for compound 13

Bond	Bond length (°A)	Bond	Bond angle(°)
O1-C12	1.221(4)	C1-S1-C9	97.62(15)
N2-C7	1.499(4)	N3-N2-C12	120.0(3)
N2-N3	1.406(4)	N2-C7-C9	99.4(3)
N2-C12	1.355(4)	N3-C8-C11	121.5(4)
C7-C10	1.510(5)	O1-C12-C13	122.0(3)
C7-C9	1.555(5)	O1-C12-N2	121.0(3)

Figure 6: Perspective view and atom labeling of X-rays structure of 13.

Figure 7: Perspective view and atom labeling of X-rays structure of 15.

Table 5: Selected bond lengths (°A) & bond angles for compound 15

Bond	Bond length (°A)	Bond	Bond angle(°)
S2-C9	1.69(3)	C9-N2-N3	118.0(2)
N2-C9	1.35(3)	C9-N4-H4B	120.0
N2-C7	1.51(3)	C10-N3-N2	109.0(2)
N2-N3	1.39(3)	C8-C7-C12	111.0(2)
N4-C9	1.33(4)	N4-C9-S2	121.0(2)
C10-C12	1.49(4)	C11-C10-C12	124.0(3)

Moreover, the reaction of **2** with hydrazine hydrate (**16a**) and phenyl hydrazine (**16b**) in refluxing ethanol afforded in each case pyrazole derivatives **17a** & **17b** in good yield. (Scheme 4). The structure of compounds **17a-b** established *via* their analytical and spectral data presented in Material & Methods Section. The X-ray crystallographic pictures afforded an unambiguous evidence of structures **17a-b**, [18] and [19](*cf.* Figure 8 and 9). The selected bond lengths and bond angles for the aforementioned compounds are listed in (Table 6 & 7).

Figure 8: Perspective view and atom labeling of X-rays structure of 17a. **Figure 9:** Perspective view and atom labeling of X-rays structure of 17b.**Table 6:** Selected bond length (°A) & bond angle for compound 17a

Bond	Bond length (°A)	Bond	Bond angle(°)
S1-C1	1.776(4)	N2-N3-C9	110.4(4)
N1-C2	1.391(7)	C1-S1-C7	103.01(19)
N2-C8	1.344(6)	N3-N2-C8	107.7(3)
C9-C11	1.486(4)	S1-C1-C2	116.0(3)
C1-C6	1.379(6)	S1-C7-C9	126.5(3)
N2-N3	1.366(4)	N2-C8-C7	108.3(3)

Table 7: Selected bond lengths (°A) & bond angles for compound 17b

Bond	Bond length (°A)	Bond	Bond angle(°)
C1-C7	1.7440(19)	N2-N3-C12	117.99(15)
N3-C9	1.356(2)	C12-C17-C16	119.5(3)
N3-C12	1.428(3)	C2-C1-S1	116.00(14)
N3-N2	1.371(2)	C7-C9-C10	128.51
C7-C9	1.372(3)	C17-C12-N3	121.3(2)
C7-C8	1.412(3)	N2-C8-C11	121.77(19)

Moreover, condensation of **13** with p-methoxy benzaldehyde in ethanol afforded **18**. Treatment of compound **18** with malononitrile in the refluxing ethanol afforded **19** in excellent yield (*cf.* Scheme 5). The structures of the compounds **18** and **19** confirmed by their elemental analysis and spectral data.

Furthermore, attempts to synthesize of compound **25** by treatment of compound **13** with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) in the refluxing 1,4-dioxane failed. In fact the product obtained was only pyrazolo-[3,4-*b*]pyridine-3-ol derivative **20** in good yield. The structure of **20** established *via* its analytical and spectral data. The X-ray crystallographic picture afforded an unambiguous evidence of structure **20**(*cf.* Figure 10 and Table 8). The crystal networks contain dioxane molecule as the space-filling solvent [20] (reaction solution). The

mechanism of formation of pyrazolo-[3,4-b]pyridine derivative **20** is assumed to occur *via* the sequence depicted in Scheme 6 through the non- isolable intermediate **22-24**. The plausible mechanism for the formation of the aforementioned compound may be assigned to the dissociation of compound **13** in DMF-DMA to compound **2** and 2-cyanoaceto hydrazide. Condensation of the methylene group in 2-cyanoaceto hydrazide with the carbonyl group in compound **2** gave the intermediate **22** which followed by the hydrolysis of the CN group gave the non-isolable intermediate

Scheme 5: Reactions of **13** with p-methoxy benzaldehyde, and DMF-DMA

Scheme 6: Proposed pathway for formation of 2H-pyrazolo-[3,4-b]pyridine-3-(7H)one derivative **20**

Figure 10: Perspective view and atom labeling of X-rays structure of 20.

Table 8: Selected bond lengths (°Å) & bond angles for compound 20

Bond	Bond length (°Å)	Bond	Bond angle(°)
S1-C1	1.772(6)	C1-S1-C9	106.2(3)
O1-C4	1.322(5)	N1-N2-C5	110.3(4)
N1-C4	1.330(7)	C2-C1-C6	121.2(5)
N1-N2	1.376(5)	N2-N1-C4	106.2(4)
N3-C6	1.355(7)	C5-N3-C6	113.8(4)
C2-C3	1.410(7)	N2-C5-N3	124.5(4)

Conclusion

The outcomes of the present study indicate that the behavior of 2-aminothiophenol with acetylacetone gave different product when the reaction carried in ethanol or DMSO, and also, we have corrected the wrong literature structure formed from the reaction mentioned earlier in ethanol. We have reported the synthesis of some unreported heterocyclic compound in which 1,4- benzothiazine fused to pyrazole. Also, we reported some heterocyclic compounds such as pyridine, and pyrazolo[3,4-b] pyridine derivatives *via* cleavage of a thiazine ring of [1,4] benzothiazine. The structure of the synthesis compounds elucidated by elemental analysis ¹H-NMR and ¹³C-NMR spectra, Ms, and X-ray crystallographic investigations.

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Author Contributions

F.A. Principal Investigator, designed the research work, collected the analysis of the spectroscopic data and wrote the manuscript. A. A., is the research associate performed work in the laboratory. All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare, they have no conflict of interests regarding the publication of this paper

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 14. The CCDC file 9935030 contains the supplementary crystallographic data for compounds 6 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via
 15. The CCDC file 9935032 contains the supplementary crystallographic data for compounds 11 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via
 16. The CCDC file 9935034 contains the supplementary crystallographic data for compounds 13 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via
 17. The CCDC file 9935035 contains the supplementary crystallographic data for compounds 15 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via
 18. The CCDC file 9935037 contains the supplementary crystallographic data for compounds 17a in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via
 19. The CCDC file 9935039 contains the supplementary crystallographic data for compounds 17b in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via
 20. The CCDC file 9935040 contains the supplementary crystallographic data for compounds 20 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via