Synthetic applications of benzothiazole containing cyanoacetyl group

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1. Introduction

Thiazoles and benzothiazole derivatives represent a well known important group of heterocyclic compounds due to their biological and pharmaceutical activities. Thus many diverse biological activities such as bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, tuberculostatic, anti-inflammatory, and antithyroidal have been found to be associated with thiazole and benzothiazole derivatives. Benzothiazoles with a cyanoethyl group at position-2 have been the subject of extensive study in the recent past. Numerous reports have appeared in the literature, which highlight their chemistry and uses. However, heterocycles containing cyanoacetyl group are relatively unexplored, probably because their preparation involves displacement of the halide in halo-acetyl substituted heterocycles with e.g. cyanide ion \cite{1}, or from an allyl carboxylate using acetonitrile in the presence of a strong base like sodium amide which usually afforded low yields of impure products \cite{2}. Acetyl chloride itself is not particularly useful in this respect since it undergoes dimerization \cite{3}. Cyanocetylation of uracils or their derivatives \cite{4-6} and enamines \cite{7} has been reported to be successfully achieved by heating the respective substrate with a mixture of acetic anhydride and cyanoacetic acid as a cyano-acetylation mixture. The structure of the reactive species formed in this case has been assigned as a cyano-ketene. The use of this cyano-acetylation mixture (cyanoacetic acid and acetic anhydride) has somehow been forgotten and instead other less convenient reagents like the pyrrole derivative \cite{1} has been used \cite{8} (Scheme 1). The phenolic ester 2 of cyanoacetic acid is also suggested for cyano-acetylation since it generates cyano-ketene when heated \cite{9}. In the last two decades, we have been involved in a program aiming to develop new simple procedures or novel precursors for the synthesis of heterocyclic compounds of biological interest to be evaluated as biodegradable agrochemicals \cite{10-14}. In continuation with this program some heterocyclic compounds containing the benzothiazole nucleus were required for biological activity studies. 2-(Benzof[\textit{d}]thiazol-2-yl)-3-oxopentanedinitrile, 4, (obtained by cyano-acetylation of 3) seemed a versatile candidate to fulfill this objective (Scheme 2).

2. Experimental

All melting points are recorded on Gallenkamp electric melting point apparatus. The IR spectra \nu (cm\textsuperscript{-1}) (KBr) were recorded on a Perkin Elmer Infrared Spectrophotometer Model 157. The \textsuperscript{1}H NMR spectra were obtained on a Varian Spectrophotometer at 200 MHz, using TMS as an internal reference and DMSO-\textit{d}_6 as solvent. The \textsuperscript{13}C NMR spectra were recorded on JEOL-ECA500 (National Research Center, Egypt).
2.1. 2-(Benzo[d]thiazol-2-yl)-3-oxopentanedinitrile, 4

To a solution of cyanoacetic acid (0.85 g, 0.01 mol) and acetic anhydride (15 mL) that was heated on water bath for 5 min, 2-(benzo[d]thiazol-2-yl)acetone (3) (1.74 g, 0.01 mol) was added and the reaction mixture was refluxed for 20 min at 85-95 °C. Left to cool, and the formed solid was filtered off, dried and recrystallized from ethanol to afford 2.94 g (54%) of product. MS: (m/z, %): 241 (M+, 100), 203 (18.2), 143 (75.8), 111 (57.6), 63 (100.0). Anal. Calcd. for C12H7N3O3S: C, 54.94; H, 2.82; N, 16.04.

2.2. 2-(Benzo[d]thiazol-2-yl)-3-(4-chlorophenyl)-acrylonitrile, 5

To a solution of 4 (2.41 g, 0.01 mol) and p-chlorobenzaldehyde (1.41 g, 0.01 mol) in ethanol (20 mL), was added a few drops of piperidine and the reaction mixture was refluxed for 4 h, then left to cool (Scheme 3). The precipitate that formed was filtered off, washed with ethanol and purified by recrystallization from ethanol to afford 2.11 g (71%) of product; mp > 200 °C; yellow solid; IR (KBr) (υ, cm⁻¹): 3119 (NH), 2188 (C=O), 1689 (C=O). 1H NMR (DMSO-δ, 6): 3.42 (s, 3H, CH3), 6.22 (s, 2H, NH2), 7.32–8.70 (m, 5H, Ar-H). MS: (m/z, %): 241 (M+, 36.4), 203 (18.2), 143 (75.8), 111 (57.6), 63 (1000). Anal. Calcd. for C12H9ClN3O2: C, 60.20; H, 3.78; N, 15.31.

2.3. 5-Amino-6-(benzo[d]thiazol-2-yl)-7-(1,4-diphenyl-1H-pyrazol-3-yl)-1-methylpyrrole[2,3-d]pyrimidine-2(1H,3H)-dione, 8

To a mixture of 4 (2.41 g, 0.01 mol) and 1,4-diphenyl-1H-pyrazole (12) (1.50 g, 0.01 mol) in DMF (15 mL) a catalytic amount of TEA was added (Scheme 4). The reaction mixture was refluxed for 6 h, allowed to cool and poured into ice cold water. The precipitated solid obtained was filtered off, dried and recrystallized from ethanol to furnish 3.24 g (70.5%) of 8; mp 198-200 °C; yellow solid; IR (KBr) (υ, cm⁻¹): 3450 (NH2), 1689 (CO), 1610 (C=N). 1H NMR (DMSO-δ): 6.22 (s, 2H, NH2), 7.51–8.18 (m, 4H, Ar-H), 9.3 (s, 1H, CH), 10.1 (s, 1H, NH). MS: (m/z, %): 340 (M+, 438), 336 (100), 298 (78.4), 259 (52.9), 258 (43.4), 257 (44.4), 174 (14.4), 125 (20.0), 84 (100.0). Anal. Calcd. for C21H13N3OS: C, 64.75; H, 3.06; N, 9.44. Found: C, 64.84; H, 3.17; N, 9.51.

2.4. 5-Amino-6-(benzo[d]thiazol-2-yl)-7-(1,4-diphenyl-1H-pyrazol-3-yl)-1-methylpyrrole[2,3-d]pyrimidine-2(1H,3H)-dione, 11

To a mixture of 4 (2.41 g, 0.01 mol), 6-aminomethylpyrimidine-2,4(1H,3H)-dione (9) (1.41 g, 0.01 mol) and 1,4-diphenyl-1H-pyrazole-3-carbaldehyde (10) (2.48 g, 0.01 mol) in DMF (15 mL), a catalytic amount of TEA was added (Scheme 5). The reaction mixture was refluxed for 6 h, allowed to cool and poured into ice cold water. The precipitated solid obtained was filtered off, dried and recrystallized from ethanol to furnish 3.24 g (54%) of 11; mp 165 °C; pale yellow powder; IR (KBr) (υ, cm⁻¹): 3400, 3365 (NH2), 3220 (NH), 1695 (amidic CO). 1H NMR (DMSO-δ): 6.5 (s, 3H, CH3), 6.27 (s, 2H, NH2), 7.51–8.18 (m, 4H, Ar-H), 9.3 (s, 1H, CH), 10.1 (s, 1H, NH). MS: (m/z, %): 543 (M+, 10). Anal. Calcd. for C21H13N3OS: C, 66.28; H, 3.89; N, 18.04. Found: C, 66.26; H, 3.83; N, 18.01.
2.6. 2-(Benz[d]thiazol-2-yl)-4-(4-methylbenzylidene)-3-oxopentanedinitrile, 15

A mixture of 4 (2.41 g, 0.01 mol), p-tolualdehyde (1.20 g, 0.01 mol) and freshly fused sodium acetate (1.23 g, 0.015 mol) in glacial acetic acid (15 mL) was refluxed for 4 h over a water bath (Scheme 7). The precipitated solid was filtered and recrystallized from ethanol to give 2.08 g (76%) of 19; mp 246 °C; brown powder; IR (KBr) (υ, cm⁻¹): 3325, 3309 (NH₂), 1642 (CO). 1H NMR (DMSO-δ6): δ: 4.25 (s, 1H, CH₂), 7.3-8.12 (m, 4H, Ar-H). 13C NMR (DMSO-δ6): δ: 33.25, 33.09 (NH₂), 2199 (CN). 1H NMR (DMF-δ6): δ: 7.71 (d, 1H, CH), 7.4-8.19 (m, 8H, Ar-H), 8.6 (s, 2H, NH₂), 8.77 (s, 1H, CH₂). MS: (m/z, %): 195 (M⁺, 100), 193 (M⁺, 97), 151 (39.2%), 118.08, 115.99, 114.66, 75.52, 40.40, 40.12, 39.84, 39.56, 39.28, 39.01, 38.73. MS: (m/z, %): 258 (M++2, 11.8), 201 (17.2), 63 (43.5). Anal. Calcd. for C₂₀H₁₃N₃OS: C, 69.95; H, 3.31; N, 10.63. Found: C, 69.94; H, 3.37; N, 10.71.

2.7. 2-Amino-3-(benz[d]thiazol-2-yl)-4H-chromeno[2,3-b]pyridin-4-one, 16

A mixture of 4 (2.41 g, 0.01 mol), salicylaldehyde (1.22 g, 0.01 mol) in ethanol (15 mL) containing a catalytic amount of piperidine was refluxed for 4 h. left to cool at room temperature and poured into ice cold water. The precipitated solid was filtered off, dried and recrystallized from ethanol to afford 1.87 g (73%) of 16; mp 300 °C; red crystal; mp 246 °C; red crystal; IR (KBr) (υ, cm⁻¹): 3300-3400 (NH₂), 1642 (CO). 1H NMR (DMSO-δ6): δ: 2.49 (s, 3H, CH₃), 5.70 (s, 1H, methine proton), 6.30 (s, 1H, vinyllic proton), 7.19-8.10 (m, 8H, Ar-H). MS: (m/z, %): 345 (M⁺, 100.0), 159 (39.2), 118.08, 115.99, 114.66, 75.52, 40.40, 40.12, 39.84, 39.56, 39.28, 39.01, 38.73. MS: (m/z, %): 258 (M++2, 11.8), 201 (17.2), 63 (43.5). Anal. Calcd. for C₁₂H₈N₄OS: C, 56.24; H, 3.15; N, 21.86. Found: C, 56.19; H, 3.25; N, 21.83.

2.8. 2-Amino-3-(benz[d]thiazol-2-yl)-benzo[5,6]-4H-chromeno[2,3-b]pyridin-4-one, 17

A mixture of 4 (2.41 g, 0.01 mol) and 2-hydroxy-1-naphthaldehyde (1.72 g, 0.01 mol) in ethanol (30 mL) was refluxed for 1 h (Scheme 9). The solid product obtained was filtered off, dried and recrystallized from ethanol to furnish 3.08 g (78%) of 17; mp 260 °C; deep yellow powder; IR (KBr) (υ, cm⁻¹): 3300-3400 (NH₂). 1H NMR (DMF-δ6): δ: 6.93 (d, 1H, CH), 7.71 (d, 1H, CH), 7.4-8.19 (m, 8H, Ar-H), 8.6 (s, 2H, NH₂), 8.77 (s, 1H, CH₂). MS: (m/z, %): 395 (M⁺, 92), 311 (30.6), 222 (18.7), 174 (100.0), 69 (69.4). Anal. Calcd. for C₂₂H₁₈N₂O₃S: C, 69.86; H, 3.31; N, 10.63. Found: C, 69.94; H, 3.37; N, 10.71.
To a mixture of 4 (2.41 g, 0.01 mol) and benzalacetophenone (2.08 g, 0.01 mol) in ethanol (20 mL), a catalytic amount of piperidine was added (Scheme 11). The reaction mixture was refluxed for 12 h, the formed solid was left to cool at room temperature, filtered off, dried and recrystallized from ethanol to afford 2.53 g (68%) of 21; mp 295 –C yellow powder; IR (KBr) (υ cm–1): 3441 (OH), 3134 (NH), 2211 (CN), 1631 (CO). 1H NMR (DMSO-d6): δ 7.41-8.09 (m, 11H, Ar-H), 8.2 (s, 1H, NH), 9.79 (s, 1H, OH). Anal. Calc. for C21H13N3O6S: C, 67.91; H, 3.53; N, 11.31. Found: C, 67.97; H, 3.56; N, 11.39.

Scheme 11

2.12. 2-(5-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-7-yl)-2-(benzo[d]thiazol-2-yl)acetonitrile, 23

To a mixture of 4 (2.41 g, 0.01 mol) and 6-amino-1,3-dimethylpyrimidin-2,4-(1H,3H)-dione (13) (1.55 g, 0.01 mol) in glacial acetic acid (20 mL), freshly fused sodium acetate (1.23 g, 0.015 mol) was added (Scheme 12). The reaction mixture was refluxed for 12 h, left to cool at room temperature, poured into ice cold water. The precipitated solid after neutralization was filtered off, dried and recrystallized from ethanol to afford 3.1 g (82%) of 23; mp 260 –C; yellow powder; IR (KBr) (υ cm–1): 3418, 3581 (NH2), 2216 (CN). 1H NMR (DMSO-d6): δ 3.25 (s, 3H, CH3), 3.37 (s, 3H, CH3), 4.89 (s, 1H, CH), 5.9 (s, 1H, C=H, pyridine), 6.22 (br., 2H, NH). 7.30-8.10 (m, 4H, Ar-H). MS: (m/z, %): 348 (M+2CH3, 15.8), 202 (2.6), 115 (21.1), 97 (47.4), 56 (100.0). Anal. Calc. for C21H13N4O6S: C, 57.15; H, 3.73; N, 22.21. Found: C, 57.21; H, 3.81; N, 22.28.

Scheme 12

2.13. 5-Amino-4-(benzo[d]thiazol-2-yl)-3-hydroxythiophen-2-carbonitrile, 24

A mixture of 4 (2.41 g, 0.01 mol), orthoboric sulfur (0.32 g, 0.01 mol), and TEA (3 mL) were kept on a water bath at 50–60 oC for 5 h, left to cool then poured into ice cold water and acidified by conc. HCl (Scheme 13). The formed solid was filtered off, dried and recrystallized from ethanol to afford 2.19 g (80%) of 24; mp 208 –C; orange powder; IR (KBr) (υ cm–1): 3454 (OH), 3396, 3345 (NH). 1H NMR (DMSO-d6): δ 6.12 (s, br., 1H, OH), 6.67 (s, br., 2H, NH). 7.21-8.32 (m, 4H, Ar-H). 13C NMR (DMSO-d6): δ 159.24, 158.14, 157.62, 156.75, 156.27, 154.89, 152.50, 149.31, 148.12, 147.37, 147.19, 146.91, 146.43, 146.25, 145.89, 145.52, 145.16, 144.79, 144.42, 143.95, 143.21, 142.83, 142.35, 141.88, 141.41, 141.04, 139.87, 139.50, 139.13, 138.76, 138.40, 138.03, 137.66, 137.29, 136.92, 136.55, 136.18, 135.81, 135.44, 135.07, 134.70, 134.33, 133.96, 133.59, 133.22, 132.85, 132.46, 132.09, 131.72, 131.35, 130.98, 130.61, 130.24, 129.87, 129.50, 129.13, 128.75, 128.38, 128.01, 127.64, 127.27, 126.90, 126.53, 126.16, 125.79, 125.42, 125.05, 124.68, 124.31, 123.94, 123.56, 123.19, 122.83, 117.90, 115.93, 115.40, 114.20, 84.65, 75.48, 45.75, 39.84, 30.73, 29.4, MS: (m/z, %): 274 (M-, 1), 258 (50.4), 201 (100.0), 173 (56.5), 146 (47.8), 122 (30.4), 93 (95.7), 69 (87.0). Anal. Calc. for C21H13N3O3S: C, 52.76; H, 2.58; N, 15.37. Found: C, 52.76; H, 2.51; N, 15.45.

Scheme 13

2.14. 5-(Benzo[d]thiazol-2-yl)-3-(benzo[d]thiazol-2-yl)cyanoethyl-6- imino-4-oxo-4,5,6,7-tetrahydrothieno[2,3-b]pyridine-2-carbonitrile, 25

A mixture of 4 (2.41 g, 0.01 mol), orthoboric sulfur (0.32 g, 0.01 mol), morpholine (few drops) and DMF (3 mL) were kept on a water bath at 50–60 °C for 5 h, left to cool, poured into ice cold water and acidified by conc. HCl (Scheme 13). The formed solid was filtered off, dried and recrystallized from ethanol to afford 3.58 g (72%) of 25; mp 183 –C; brown powder; IR (KBr) (υ cm–1): 3220 (NH), 2195, 2220 (CN). 1H NMR (DMSO-d6): δ 3.6 (s, 1H, CH), 4.4 (s, 1H, CH), 7.2-8.1 (m, 8H, Ar-H), 9.8 (s, 1H, NH, cyclic), 13.7 (bs, 1H, NH). MS: (m/z, %): 470 (M+2CN), 273 (13.6), 241 (31.3), 201 (100.0), 146 (30.2), 108 (22.3), 69 (38.9). Anal. Calc. for C21H13N3O3S: C, 58.05; H, 2.44; N, 16.92. Found: C, 58.14; H, 2.49; N, 16.97.

3. Results and Discussion

In continuation of our program and following our previous interest [15-20] in the synthesis of new heterocyclic compounds of anticipated biological activity, it has been found that cyanacetylation of 2-(benzo[d]thiazol-2-yl)acetonitrile, 3, will lead to an excellent building block for the synthesis of target compounds. Thus, when 3 was treated with cyanacetic acid, it afforded the corresponding 2-(benzo[d]thiazol-2-yl)-3-oxopentanecarbonitrile, 4, as tested by thin-layer chromatography (TLC) (Scheme 2).

Reactions of this type have not been previously reported, however they were found to give products in excellent yields under very mild conditions. Moreover, the resulting benzothiazole derivative 4 has latent functional substituents, which render it to be a versatile starting substrate for further chemical transformations that open new routes for the
preparation of substituted benzothiazole derivatives with possible biological activity.

Its structural assignment was proved by spectroscopic analyses. The IR spectrum of the latter product revealed absorption bands at 2188, 2199 cm\(^{-1}\) due to two CN groups, a very weak band near 1780 cm\(^{-1}\) that was attributed to the carbonyl group. Its \(^1H\) NMR spectrum revealed singlet signals at \(\delta\) 4.52 and 5.10 ppm due to CHs and CH proton, respectively, beside an aromatic multiplet in the region of \(\delta\) 6.67-7.5 ppm. Moreover, the mass spectrum showed m/z at 241(M\(^+\)), 201[M−CH,CN] (100%), 173 [M−COCH,CN] (20.8%).

Now, we have extended our synthetic program to the synthesis of otherwise inaccessible heterocyclic ring system utilizing compound 4 as the key starting material. A mixture of 4 and p-chlorobenzaldehyde reacted in refluxing ethanol in the presence of catalytic amounts of piperidine to yield a product which may be formulated as 5 or 6 (Scheme 3). Structure 6 was ruled out on the basis of \(^1H\) NMR spectrum of the reaction product, which revealed a multiplet at \(\delta\) 7.32-8.12 ppm due to the aromatic and the vinylc proton being embedded in it. In addition, the IR spectrum showed absorption bands at 2188 cm\(^{-1}\) due to the CN group, indicating the presence of one cyano group and the absence of any bands in the region of CO group absorption. Mass spectroscopic measurements showed m/z 297 (M\(^+\)) which indicates structure 5.

The structure of 5 was further confirmed by an alternative synthesis. The treatment of 3 with p-chlorobenzaldehyde in refluxing ethanol in the presence of piperidine (catalytic amounts) yielded a product completely identical in all respects (m.p., mixed m.p., IR and \(^1H\) NMR) with 5.

Pyrimidine is the parent hetero ring of a very important group of compounds that are extensively studied due to their occurrence in living systems. Compounds containing a pyrimidine ring has been reported to exhibit antibacterial and antifungal as well as anti-HIV activity [21,22]. On the other hand, substitution of a pyridine ring to benzene ring often is compatible with retention of biological activity and occasionally the moiety is an essential part of the pharmacophore. Such substitution of an NH for CHs is an example of the common medicinal strategy known as bioisosterism. Therefore, 5-amino-6-[benzo[d]thiazol-2-yl]-7-(4-chlorophenyl)-2-thioxo-2,3-dihydropyrido[2,3-b]pyrimidin-4(1H)-one 8 was synthesized by refluxing equimolar amounts of compound 4, 6-aminothiouracil 7 and p-chlorobenzaldehyde in ethanol in the presence of a catalytic amount of piperidine. The reaction proceeded according to Scheme 4.

The formation of B can be attributed to the first formation of compound 5 as intermediate which undergo Michael reaction with 6-aminothiouracil 7 to yield the nonionisable intermediate A which undergo intra-molecular nucleophilic addition to the CN group to give the intermediate B which is aromatized under the reaction condition to afford the final isolable product 8 (Scheme 4). The structure of compound 8 was proved by its analytical and spectral analyses. The mass spectrum showed a molecular ion peak at m/z 438 (M\(^+\)). The IR spectrum showed absorption bands at 3402, 3389 cm\(^{-1}\) (NH), 3141 cm\(^{-1}\) (NH), 1698 cm\(^{-1}\) (C=O) and 1221 cm\(^{-1}\) (C=S). \(^1H\) NMR (DMSO-d\(_6\)) showed three D2O exchangeable protons at \(\delta\) 13.51, 13.59 ppm due to NH protons and at \(\delta\) 6.22 ppm due to NH: beside the aromatic protons. An alternative method for the synthesis of compound 8 was achieved by heating benzothiazole derivative 5 with 6-aminothiouracil 7 in DMF and in the presence of piperidine (catalytic amount) to give a product identical in all respects (m.p., mixed m.p., IR, and \(^1H\) NMR) with 8.

Similarly, it was found that refluxing a mixture of compound 4, 1-methyl-6-aminothiouracil 9 and 3-formylpyrazole 10 in DMF in the presence of TEA afforded the corresponding pyrido[3,4-b]pyridazine derivative 11 (Scheme 5).

The formation of 11 apparently proceeded according to the previously proposed mechanism and its structure was proved by analytical and spectral analyses. The IR spectrum of 11 revealed absorption bands at 3400, 3365 cm\(^{-1}\) (NH), 3220 and 1695 cm\(^{-1}\) (NH and amido CO group, respectively). The mass spectrum showed the molecular ion peak at m/z 543 (M\(^+\); 10%).

In a similar way, heating 4 with an equimolar amounts of piperonal 12 and 1,3-dimethyl-6-aminoaracil 13 in DMF in the presence of a catalytic amount of TEA gave the corresponding pyrido[4,3-b]pyridazine derivative 14 (Scheme 6).

On the other hand, it was found that refluxing 2-[benzo[d]thiazol-2-yl]-3-oxopentanedinitrile with p-tolualdehyde in glacial acetic acid in the presence of freshly fused sodium acetate afforded 2-[benzo[d]thiazol-2-yl]-4-(4-methylbenzylidene) 3-oxopentanedinitrile 15 (Scheme 7).

The \(^1H\) NMR spectrum of 15 showed singlet signals at \(\delta\) 2.49, 8.570, 8.630 ppm and multiplet signal at 8 7.19-8.10 ppm due to CHs, methine proton, vinylic proton and eight aromatic protons, respectively. Also mass spectrum showed molecular ion peak at m/z 343 (M\(^+\)). Unexpectedly, salicylaldehyde and 2-hydroxy-1-naphthaldehyde reacted with 4 in refluxing ethanol containing catalytic amounts of piperidine in a different way to that with p-chlorobenzaldehyde. Therefore, it was found that refluxing of 4 with salicylaldehyde and/or 2-hydroxy-1-naphthaldehyde in ethanol in the presence of piperidine afforded the corresponding chromenopyridine and benzochromenopyrimidine derivatives 16 and 17, respectively (Scheme 8 and 9).

The structures of 2-amino-3-[benzo[d]thiazol-2-yl]-4H-chromeno[2,3-b]pyridin-4-one 16, and 2-amino-3-[benzo[d]thiazol-2-yl]-benzo[4,5]imidazo[2,3-b]pyridin-4-one 17 were established from their IR, \(^1H\) NMR and mass spectra. The mass spectrum of 16 showed molecular ion peak at m/z 345 (M\(^+\)) (100%), while 17 showed the molecular ion peak at 395 m/z (M\(^+\); 92%). The IR spectra of both 16 and 17 showed the absence of any peak in the region of 2180-2250 cm\(^{-1}\) and this confirms that both two CN groups were involved in the reaction, also the absence of two peaks in the region of 3300-3400 cm\(^{-1}\) due to the NHs group. 1H NMR spectrum of 16 showed a multiplet signal in the region of \(\delta\) 6.93-8.16 ppm due to eight aromatic protons, in addition to two singlet signals at \(\delta\) 8.60 and 8.77 ppm due to NHs protons and C=C in the pyran ring, respectively. On the other hand, \(^1H\) NMR of compound 17 could not be evaluated due to its insolubility in all possible solvents. These above results were found in complete agreement with a previously reported work [22,23]. Moreover, treatment of 4 with hydroxyamine hydrochloride afforded 2-[5-aminoisoxazol-3-yl]-2-[benzo[d]thiazol-2-yl]-acetonitrile 18 in high yield (Scheme 10).

Structure 18 was suggested for this product based on analytical and spectral data. Thus the mass spectrum of this product showed the molecular ion peak at m/z 256 (M\(^+\)), 201, 174 (100%). The IR spectrum revealed absorption bands at 3252, 3309 cm\(^{-1}\) (NH), 2199 cm\(^{-1}\) (CN). The \(^1H\) NMR (DMSO) spectrum revealed signals at \(\delta\) 8.72, 7.31-8.19 ppm due to NHs, the aromatic and the cyclic methine protons, respectively, and at \(\delta\) 4.25 ppm due to the CH proton. Treatment of 4 with hydrazine hydrate in refluxing ethanol afforded 3,7-diamino-4-[benzo[d]thiazol-2-yl]-4H-1,2-diazepin-5(6H)-one, 19 (Scheme 10).

The IR spectrum of 19 showed the absence of peaks in the region of 2180-2250 cm\(^{-1}\) due to the CN group, which indicates that both the CN groups were involved in this reaction. The mass spectrum of 19 gave the molecular ion peak at m/z 273 (M\(^+\)). Several isomeric structures of 19 were possible but the actual isomeric form was confirmed from its \(^1H\) NMR which showed doublet of doublet signal at \(\delta\) 2.42.5 ppm due to CHs protons, at \(\delta\) 3.76 ppm due to the CH proton beside the
multispectral signals at $\delta$ 7.26-8.12 ppm due to four aromatic protons and at $\delta$ 8.51 ppm (s, 4H, 2NH$_2$).

Compound 4 was also used as a precursor for the synthesis of the pyridine ring. Thus, treatment of 4 with benzoacetophenone 20 in refluxing ethanol containing catalytic amounts of TEA afforded compound 21a or its tautomer 21b (Scheme 11). The structure of the obtained product was confirmed by its IR, $^{1}$H NMR and mass spectrum. The mass spectrum showed the molecular ion peak at m/z 371 (M$^+$). The IR spectrum of this product did not show any signals around 5.46-6 ppm due to a CH proton and instead reveals a singlet (1H) at $\delta$ 9.79 ppm attributable to the OH proton and this confirms that the most stable tautomeric form is the enolic form since it showed multiplet bands for the OH, NH$_2$ and CO protons. The mass spectrum showed also the presence of multiplet signals at $\delta$ 5.9 ppm due to C$_3$-H in pyridine ring, singlet signal at $\delta$ 4.89 ppm due to NH$_2$, singlet at $\delta$ 6.22 ppm due to NH$_2$, singlet at $\delta$ 3.34 ppm due to OH and NH$_2$ protons respectively, in addition to multiplet signal at $\delta$ 7.21-8.32 ppm due to four aromatic protons. The mass spectrum showed the molecular ion peak at m/z 271 (M$^+$-2).

The IR spectrum of 25 showed stretching frequencies at 3220 cm$^{-1}$ due to NH group and at 2195, 2220 cm$^{-1}$ for two cyano functions. The mass spectrum showed the molecular ion peak at m/z 470 (M$^+$-1). Structure 25 was also established by its $^{1}$H NMR (cf. experimental).

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