Heteroatom Chemistry
Volume 18, Number 4, 2007

Reactions with 3,6-Diaminothieno[2,3-*b*]-pyridines: Synthesis and Characterization of Several New Fused Pyridine Heterocycles

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Received 15 December 2005; revised 12 March 2006

ABSTRACT: *6-Aminopyridine-2(1H)thiones* **1** *reacting with α-halo-compounds* **2a–c** *afforded the alkylthiopyridine derivatives* **3a–c** *which in turn cyclized to the corresponding thieno[2,3-b]pyridine derivatives* **4a–c**. *Several thieno[2,3-b]pyridine derivatives* **7, 16, 19**, *pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine derivatives* **6a,b, 11a–c, 21** *and pyrido[3′,2′:4,5]thieno[3,2-c]pyridazine derivatives* **13, 17** *were prepared starting from compounds* **4a–c**.
 Heteroatom Chem 18:405–413, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20313

INTRODUCTION

Synthesis and characterization of pyridines, thieno[2,3-*b*]pyridines, and pyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidines became the main target of this research group. Several publications demonstrated this research effort [1–9]. This is because these derivatives possess diverse biological activities and are widely used in pharmaceutical and medicinal preparations. Alkylthiopyridines possess neurotropic [10], cardiovascular [11], antimicrobial [7] activities and are used as an adenosine receptor ligand [12,13]. Moreover, thieno[2,3-*b*]pyridines possess a wide range of biological activities such as antimicrobial [7,14–16], anti-inflammatory [17], ganadotropin releasing hormone antagonizing [18], antiviral [19,20], and neurotropic activities [10]. Furthermore, pyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidines were reported to have antiallergic [21], antiprotozoals [22], antianaphylactic [23,24], and antimicrobial [14,15] activities. The above findings stimulated the interest for the synthesis of additional new numbers of these derivatives that are required in medicinal chemistry programs.

RESULTS AND DISCUSSION

It has been found that 6-amino-4-(4-methoxyphenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) [25] reacted with chloroacetonitrile (**2a**) in cold DMF in the presence of potassium hydroxide to give a reaction product resulting from equimolecular addition of the reagent to the reactant with the loss of one molecule of hydrogen chloride. The IR spectrum of this reaction product showed among its absorption bands those corresponding to the presence of one NH_2 (3380, 3327 cm^{-1}) and CN (2252, 2211 cm^{-1}) functions. Its ^1H NMR spectrum revealed only signals of $-OCH_3$(3.86 ppm), $-SCH_2CN$ (4.35 ppm), NH_2 (8.23 ppm), and

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aromatic protons. The reaction product could then be formulated as 2-amino-6-[(cyanomethyl)thio]-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile **3a**.

In a similar manner, **1** reacted with chloroacetone (**2b**) and chloroacetamide (**2c**) to give 2-amino-4-(4-methoxyphenyl)-6-[(2-oxopropyl)thio]-pyridine-3,5-dicarbonitrile (**3b**) and 2-{[6-amino-3,5-dicyano-4-(4-methoxyphenyl)pyridin-2-yl]thio}-acetamide (**3c**) respectively. The structure of **3b,c** was also established based on analytical and spectral data, which were in a good agreement with the assigned structure in each case (cf. Scheme 1 and the Experimental section).

The structure of each of **3a–c** was further established via their cyclization by boiling their solutions in ethanolic potassium hydroxide to give the corresponding 3,6-diaminothieno[2,3-*b*]pyridine derivatives **4a–c** respectively. The IR spectrum of each of **4a–c** showed the presence of additional bands of a new NH_2 group and the disappearance of the CN band in each case proving that the cyclization reaction involved addition to the nitrile function at position-3 at the pyridine ring of **3a–c** (cf. Scheme 1).

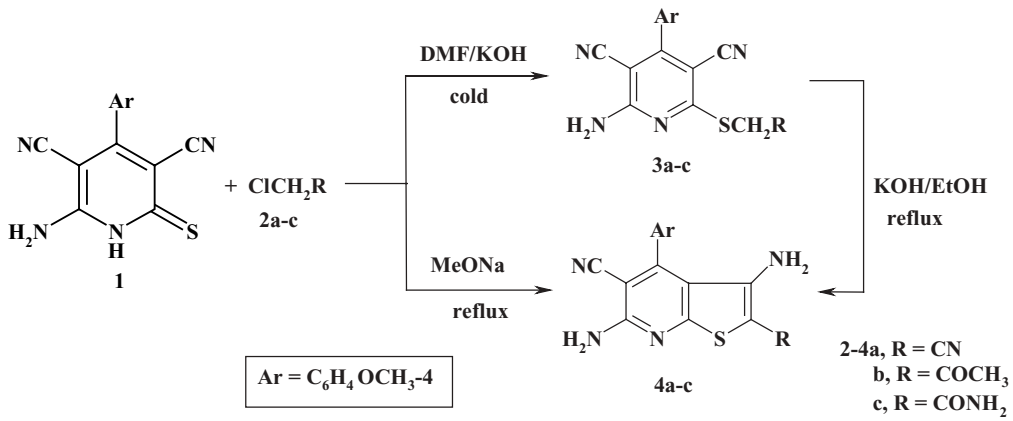
Moreover, an additional proof for the structure of **4a–c** came from their independent synthesis by performing the reactions of **1** with each of **2a–c** in boiling sodium methoxide solutions. Compounds **4a–c** prepared via this route were found completely identical in all aspects with **4a–c** previously synthesized as described before (cf. Scheme 1 and the Experimental section).

The synthesized 3,6-diamino-2,5-dicyanothieno[2,3-*b*]pyridine derivative **4a** seemed to be an excellent candidate for the synthesis of other desired heterocyclic derivatives through its participation in a number of chemical reactions with different reagents. Thus, the reaction of **4a** with formic acid afforded a reaction product, which showed the absorption bands of NH_2, NH, ring-CO and CN groups in its IR spectrum. Its ^{1}H NHR spectrum revealed only the signals of NH_2, NH and a new singlet signal at $\delta = 7.97$ ppm corresponding to the 2H-pyrimidine ring and OCH_3 group in addition to the aromatic protons. Consequently, this reaction product could be formulated as the 7-amino-9-(4-methoxyphenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carbonitrile **(6a)** most likely formed via the intermediacy of the carboxamidothieno[2,3-*b*]pyridine derivative **5a** that on cyclization by loss of the element of water yielded **6a** (cf. Scheme 2).

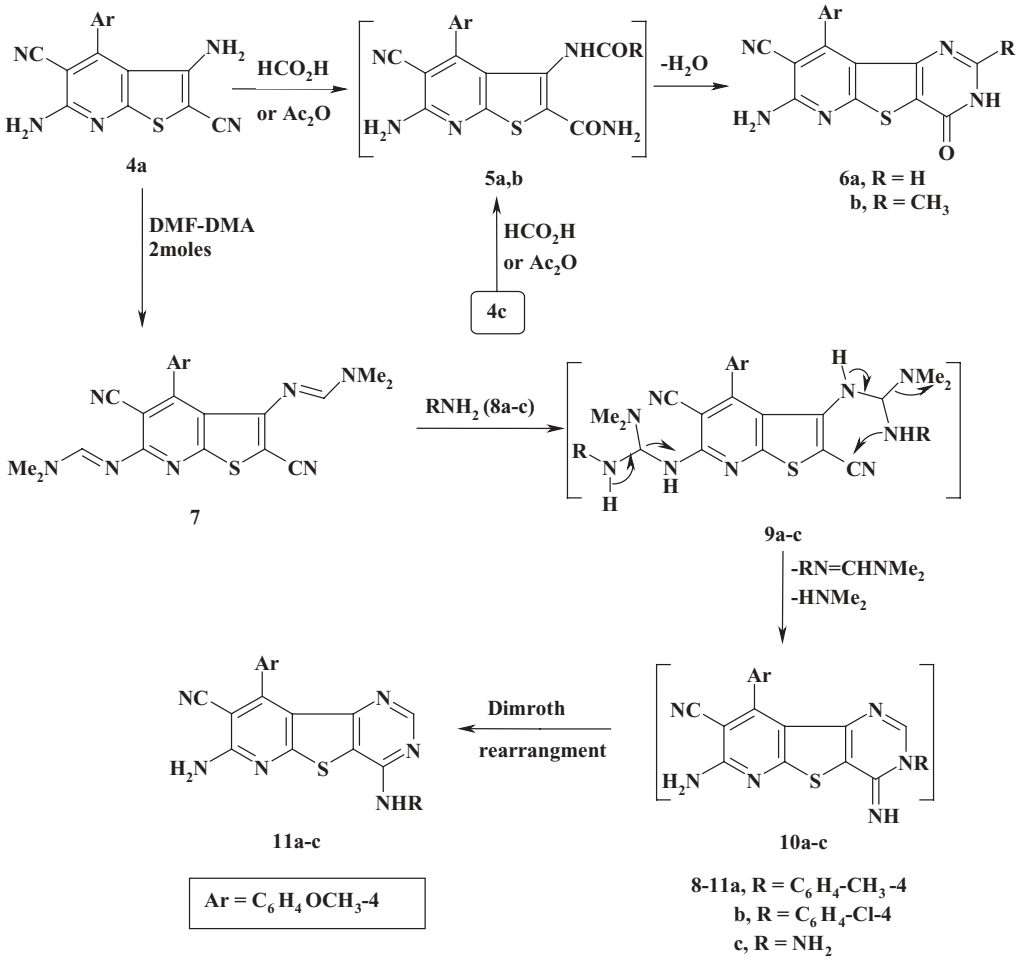
Under practically the same reaction conditions, **4a** reacted with acetic anhydride to give also 7-amino-9-(4-methoxyphenyl)-2-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carbonitrile (**6b**) that is also most likely formed via first acetylation of the amino group at postion-3 of the thiophene ring in **4a** followed by hydrolysis to give **5b** and cyclization to **6b** via loss of water (cf. Scheme 2).

A solid and conclusive evidence for the structure of **6a,b** came from their independent synthesis via the reaction of **4c** with each of formic acid and acetic anhydride respectively. Compounds **6a,b** prepared via this route were found to be identical in all aspects (mp, mixed mp, analytical and spectral data) with **6a,b** previously synthesized as described before (cf. Scheme 2 and the Experimental section).

Compound **4a** reacted also with two molecules of DMF–DMA to give the corresponding bis-3,6-{[(*N*,*N*-dimethylamino)methylene]amino}-2,5-dicyanothieno[2,3-*b*]pyridine derivative **7**. The structure of **7** was established based on elemental analysis and spectral data studies (cf. the Experimental section).



SCHEME 1



SCHEME 2

The reaction of **7** with aromatic amines and hydrazine hydrate constituted an easy and logical route for the synthesis of other heterocyclic derivatives. Thus, **7** reacted with p-toluidine (**8a**) in glacial acetic acid to give a reaction product of molecular formula $C_{24}H_{18}N_6OS$ which corresponded to the addition of the amine to **7** and the loss of one molecule of *N*,*N*-dimethyl-*N*′-p-tolylformamidine and one molecule of dimethylamine. The IR spectrum of the reaction product showed the absorption bands of one NH_2, NH (3474, 3356, 3201 cm^{-1}) and CN (2212 cm^{-1}) functions. Its ^1H NMR spectrum revealed the signals of CH_3 ($\delta = 2.30$ ppm), NH_2($\delta = 7.44$–7.60 ppm and Ar—H), NH ($\delta = 9.42$ ppm), 2H-pyrimidine at $\delta = 8.31$ ppm, OCH_3, and aromatic protons. Accordingly, and in addition to analytical data, this compound could be formulated as the 7-amino-4-[(4-methylphenyl)amino]pyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carbonitrile derivative **11a** via Dimroth rearrangement [26].

In the same manner, the reaction of **7** and p-chloroaniline (**8b**) resulted in the formation of the 7-amino-4-[(4-chlorophenyl)amino]pyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carbonitrile derivative **11b** while its reaction with hydrazine hydrate afforded the 7-amino-4-hydrazinopyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidine-8-carbonitrile derivative **11c** via Dimroth rearrangement [27]. The structure assigned for **11b,c** was established on the basis of elemental analysis and spectral data studies (cf. Scheme 2 and the Experimental section).

The formation of each of **11a–c** is assumed to proceed via first addition of the aromatic amine or the hydrazine **8a–c** to compound **7** to give the non-isolable intermediates **9a–c**. Each of **9a–c** then loses one molecule of the schiff's base and one molecule of dimethylamine to give the cyclized products **10a–c** which underwent Dimroth rearrangement to yield the final isolable **11a–c**. The above results find a great

support by the previous reports in the recent literature concerning the same rearrangement reaction [26,27] (cf. Scheme 2 and the Experimental section).

Compound **4b** took its role also in the synthesis of a number of new fused heterocyclic pyridine derivatives. Thus, **4b** reacted with nitrous acid to give the corresponding bis-2,6-diazonium salt intermediate **12** which could be in situ cyclized via dehydrochlorination involving the acetyl group and hydrolysis of the 6-diazonium salt to afford the corresponding 7-hydroxypyrido-[3′,2′:4,5]thieno[3,2-*c*]pyridazine derivative **13** (or its tautomer **14**). The IR spectrum of the reaction product showed the absorption bands of OH at 3404 cm^{-1}, CN at 2230 cm^{-1}, and C=O at 1718 cm^{-1}. Its ^1H NMR spectrum revealed only the signals of CH_2 of pyridazine at $\delta = 3.78$ ppm, OCH_3 at $\delta = 3.85$ ppm, and OH at $\delta = 5.9$ ppm (D_2O exchangeable) in addition to the aromatic protons, thus confirming the structure of **13** rather than **14** (cf. Scheme 3 and the Experimental section).

Furthermore, **4b** reacted with one molecule of DMF–DMA to afford a reaction product that could be formulated as the condensation product on the amino group of the thiophene ring (**15**) or the condensation product on the amino group of the pyridine ring (**16**). However, structure **16** was assigned for this reaction product based on chemical evidence because the spectral data were of no value in discriminating the two structures (Scheme 3).

Thus, **16** reacted with nitrous acid to give the corresponding diazonium salt that could be in situ cyclized via dehydrochlorination to afford the corresponding pyrido[3′,2′:4,5]thieno[3,2-*c*]pyridazine derivative **17** (or its tautomer **18**). The IR spectrum of the reaction product showed the absorption bands of CN at 2217 cm^{-1} and ring-CO at 1705 cm^{-1} functions. Its ^1H NMR spectrum revealed a new singlet signal at $\delta = 3.70$ ppm which corresponded to the methylene group at the pyridazine ring, thus confirming structure **17** rather than its tautomer **18** to represent the reaction product (cf. Scheme 3 and the Experimental section).

It is remarkable to report, here, that an unexpected reaction took place on reacting **16** with hydrazine hydrate, which gave back the starting **4b** and this could be considered as a further solid evidence for the structure of both **4b** and **16** (cf. Scheme 3).

Compound **16** reacted also with another molecule of DMF–DMA to give the corresponding condensation product **19**. Structure of **19** was established based on elemental analysis and IR spectral data that showed the absorption bands of CN and (CH_3CO—) functions only while the bands related to the presence of NH_2 were entirely absent. Its ^1H NMR revealed the signals of the newly formed —$N(CH_3)_2$ and —N=CH protons at $\delta = 2.64$ and 6.70 ppm and absence of any signals which may be attributed to the presence of NH_2 protons (cf. Scheme 3 and the Experimental section).

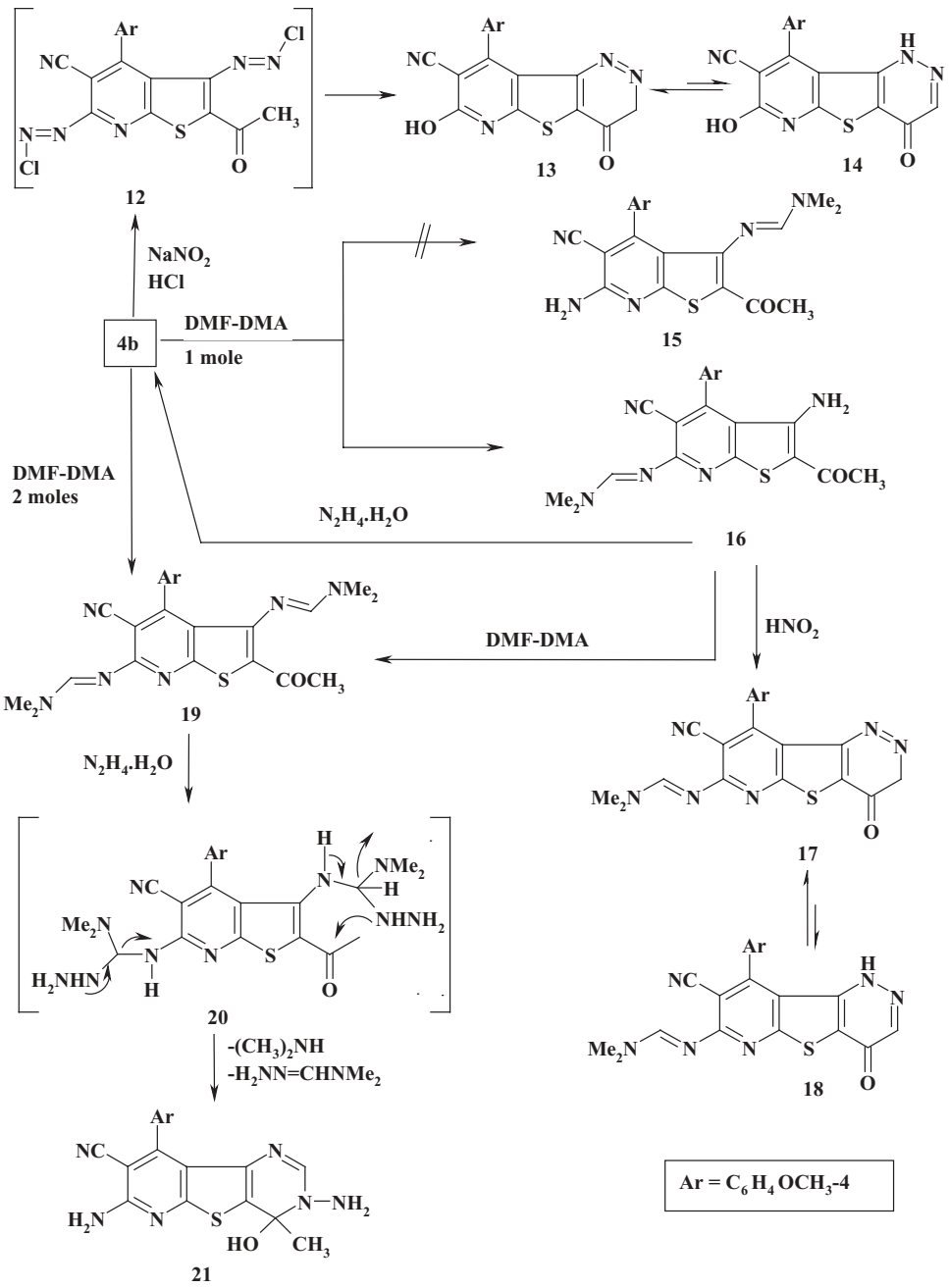
Compound **19** could also be synthesized via the reaction of **4b** with two molecules of DMF–DMA. Compound **19** prepared via this route was found to be identical in all aspects (mp, mixed mp, analytical and spectral data) with **19** previously synthesized as described before (cf. the Experimental section).

On the other hand, the reaction of **19** with hydrazine hydrate gave a reaction product of molecular formula $C_{18}H_{16}N_6O_2S$ that corresponded to addition of two molecules of the hydrazine to **19** with the loss of one molecule of each of dimethylamine and *N*,*N*-dimethylhydrazonoformamide [26]. The IR spectrum of this reaction product showed the absorption bands related to the presence of two NH_2, OH and CN functions. Its ^1H NMR revealed signals of CH_3 at $\delta = 1.98$ ppm, two NH_2 at $\delta = 5.26$, 6.07 ppm (D_2O exchangeable), OH at $\delta = 7.03$ ppm (D_2O exchangeable) and 2H-pyrimidine at $\delta = 7.01$ ppm, in addition to the OCH_3 and aromatic protons. Moreover, the molecular ion peak of the reaction product was not observed [28] in its mass spectrum due to the highly unstable M^+. The base beak was found at $m/z = 352$ (100%) corresponding to M^+ (380)–N_2 (28) (cf. Scheme 3, Fig. 1 and the Experimental section).

Based on the above data the reaction product was formulated as 3,7-diamino-4-hydroxy-9-(4-methoxyphenyl)-4-methyl-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carbonitrile (**21**). The formation of **21** was assumed to proceed via addition of two molecules of hydrazine to **19** to give the intermediate adduct **20** which underwent in situ cyclization to **21** with loss of one molecule of dimethylamine and *N*,*N*-dimethylhydrazonoformamide [26]. The structure of compound **21** find a great support by the previous report in the recent literature concerning the similar ring system [29].

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra in KBr discs were recorded on a Bruker Vector 22 FT-IR spectrophotometer. ^1H NMR spectra were determined in DMSO-d_6 and $CDCl_3$ at 300 MHz on a Varian Mercury VX spectrometer using TMS as an internal standard. Chemical shifts are expressed as δ ppm and J as Hz units. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical



SCHEME 3

Center of Cairo University. Compounds **1** [25] were prepared according to the literature procedures.

In all the ^{1}H NMR spectra * = Lost after D_2O exchange.

Reactions with Halogen-containing Compounds in Cold KOH/DMF Solution:General Procedure

A solution of **1** (0.01 mole) in DMF (20 ml) containing 0.01 mole of KOH was treated with **2a–c** (0.01 mole). The reaction mixtures were stirred at room temperature for 2 h, poured onto ice-cold water, and neutralized with dilute HCl (10%). The precipitates that formed were collected by filtration and crystallized from ethanol to yield **3a–c** respectively.

*6-Amino-2-[(cyanomethyl)thio]-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (***3a***).* White crystals from ethanol (69%), mp 232–234°C; IR (cm^{-1})

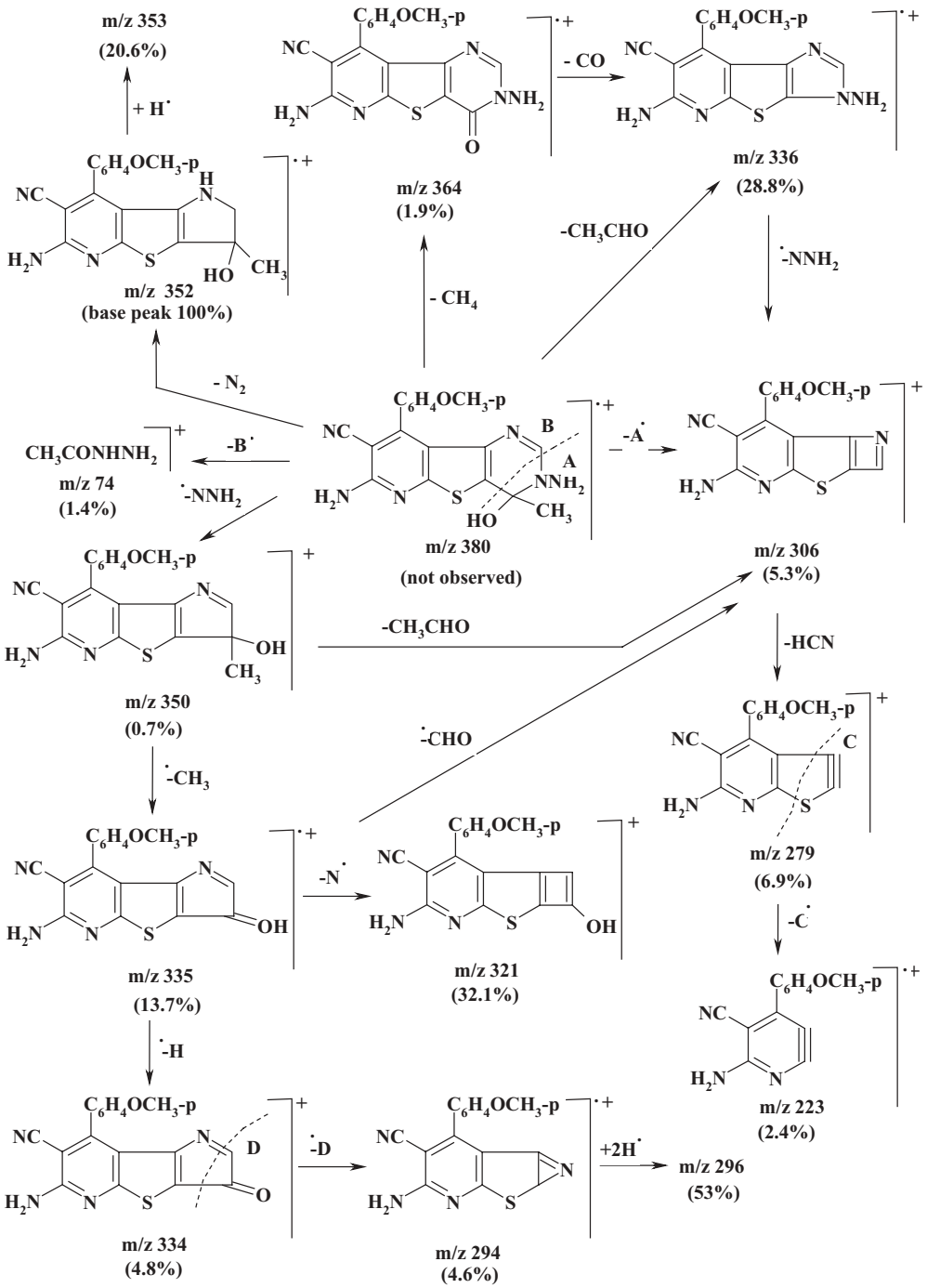


FIGURE 1 Fragmentation pattern of compound (21).

ν 3380, 3327 (NH_2), 2252, 2211 (two CN), 1607 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H, OCH_3), 4.35 (s, 2H, SCH_2), 7.10 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.53 (d, $J = 8.0$ Hz, 2H, Ar–H), 8.23 (hump, 2H, NH_2*). Anal. for $C_{16}H_{11}N_5OS$ (321) Calcd: C, 59.80; H, 3.45; N, 21.79; S, 9.98. Found: C, 59.50; H, 3.70; N, 22.00; S, 10.20%.

6-Amino-2-[(acetylmethyl)thio]-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile **(3b)**. White crystals from ethanol (70%), mp 210–212°C; IR (cm^{-1}) ν 3431, 3334 (NH_2), 2211 (CN), 1726 (C=O), 1610 (N=C); ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3H, $COCH_3$), 3.86 (s, 3H, OCH_3), 4.21 (s, 2H, SCH_2), 7.11 (d, $J = 8.0$ Hz, 2H, Ar–H), 7.50 (d, $J = 8.0$

Hz, 2H, Ar—H), 7.97 (hump, 2H, NH_2*). Anal. for $C_{17}H_{14}N_4O_2S$ (338) Calcd: C, 60.34; H, 4.17; N, 16.56; S, 9.48. Found: C, 60.60; H, 3.90; N, 16.20; S, 9.70%.

6-Amino-2-[(carboxamidomethyl)thio]-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (**3c**). Yellow crystals from ethanol (63%), mp 225–228°C; IR (cm^{-1}) ν 3470, 3401, 3363, 3169 (two NH_2), 2213 (CN), 1687 (C=O), 1617 (N=C). Anal. for $C_{16}H_{13}N_5O_2S$ (339) Calcd: C, 56.63; H, 3.86; N, 20.64; S, 9.45. Found: C, 56.40; H, 4.10; N, 20.90; S, 9.10%.

Synthesis of **4a–c**

Method A (*Cyclization of* **3a–c**). A solution of **3a–c** (0.01 mole) in ethanol (30 ml), containing 0.02 mole of potassium hydroxide, was heated under reflux for 3 h. The reaction mixture was then cooled, poured onto ice-cold water, neutralized with dilute HCl (10%) and the precipitated solid products were filtered off, washed with water and then crystallized from dioxan to yield **4a–c**.

Method B (Reaction of **1** *with* **2a–c**). A solution of **1** (0.01 mole) in methanolic sodium methoxide (prepared from 0.02 atom of sodium metal in 30 ml of methanol), was treated with **2a–c** (0.01 mole) and then heated under reflux for 3 h. The reaction mixture was then cooled, poured onto ice-cold water, and neutralized with dilute HCl (10%). The solid products so formed were filtered off and crystallized from dioxan to yield **4a–c**.

3,6-Diamino-4(4-methoxyphenyl)thieno[2,3-b]-pyridine-2,5-dicarbonitrile (**4a**). Yellow crystals from dioxan (75%), mp 300–302°C; IR (cm^{-1}) ν 3454, 3380 3339, 3220 (two NH_2), 2215, 2188 (two CN), 1624 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H, OCH_3), 5.36 (s, 2H, NH_2*), 7.17 (d, $J = 8.0$ Hz 2H, Ar—H), 7.45–7.57 (m, 4H, NH_2^* & Ar—H). Anal. for $C_{16}H_{11}N_5OS$ (321) Calcd: C, 59.80; H, 3.45; N, 21.79; S, 9.98. Found: C, 60.00; H, 3.10; N, 22.10; S, 9.70%.

2-Acetyl-3,6-diamino-4(4-methoxyphenyl)thieno-[2,3-b]pyridine-5-carbonitrile (**4b**). Orange crystals from dioxan (72%), mp 268–269°C; IR (cm^{-1}) ν 3464, 3360 3319, 3213 (two NH_2), 2217 (CN), 1630 (C=O), 1610 (N=C); ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H, $COCH_3$), 3.42 (s, 1H, NH_2^*), 3.87 (s, 3H, OCH_3), 7.16 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.44 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.57 (s, 2H, NH_2^*); MS: (*m*/*z*) 338 (100%), 337 (71.3%), 336 (4.3%), 325 (6.1%), 323 (51.4%), 296 (7.4%), 295 (21.2%). Anal. for $C_{17}H_{14}N_4O_2S$ (338) Calcd: C, 60.34; H, 4.17; N, 16.56; S, 9.48. Found: C, 60.10; H, 4.50; N, 16.30; S, 9.70%.

3,6-Diamino-5-cyano-4-(4-methoxyphenyl)thieno-[2,3-b]pyridine-2-carboxamide (**4c**). Orange crystals from dioxan (68%), mp 280–283°C; IR (cm^{-1}) ν 3470, 3401, 3363, 3323, 3169 (three NH_2), 2217 (CN), 1655 (C=O), 1602 (N=C). Anal. for $C_{16}H_{13}N_5O_2S$ (339) Calcd: C, 56.63; H, 3.86; N, 20.64; S, 9.45. Found: C, 56.40; H, 4.20; N, 21.00; S, 9.20%.

Reactions of **4a** *or* **4c** *with Formic Acid and Acetic Anhydride: General Procedure*

A solution of **4a** or **4c** (0.01 mole) in formic acid or in acetic anhydride (20 ml) was heated under reflux for 5 h. The solid products obtained after cooling were filtered off and then crystallized from the proper solvent to yield **6a,b** respectively.

7-Amino-9-(4-methoxyphenyl)-4-oxo-3,4-dihydro-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile (**6a**). Pale yellow crystals from DMF (58%), mp >350°C; IR (cm^{-1}) ν 3457, 3351 (NH_2), 3223 (NH), 2218 (CN), 1658 (C=O), 1624 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H, OCH_3), 7.03 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.34–7.46 (m, 4H, NH_2^* & Ar—H), 7.97 (s, 1H, 2H-pyrimidine), 12.49 (hump, 1H, NH*). Anal. for $C_{17}H_{11}N_5O_2S$ (349) Calcd: C, 55.06; H, 3.19; N, 26.57; S, 5.07. Found: C, 55.30; H, 2.90; N, 26.30; S, 5.40%.

7-Amino-9-(4-methoxyphenyl)-2-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile (**6b**). Pale yellow crystals from AcOH (52%), mp 266–267°C; IR (cm^{-1}) ν 3479, 3372 (NH_2), 3218 (NH), 2219 (CN), 1657 (C=O), 1610 (N=C). Anal. for $C_{18}H_{13}N_5O_2S$ (363) Calcd: C, 55.72; H, 3.43; N, 25.99; S, 4.96. Found: C, 56.00; H, 3.20; N, 26.30; S, 5.20%.

Reactions with DMF-DMA in Dry Xylene: General Procedure

To a solution of the appropriate **4a, 4b,** or **16** (0.01 mole) in dry xylene (30 ml), DMF–DMA (0.012 mole) or (0.024 mole) was added and the reaction mixture was then heated under reflux for 3–5 h. The solid so obtained after cooling was collected by filtration and crystallized from the proper solvent to yield **7, 16**, or **19** respectively.

3,6-Bis{[(N,N-dimethylamino)methylene]amino}-4-(4-methoxyphenyl)thieno[2,3-b]pyridine-2,5-dicarbonitrile (**7**). Pale yellow crystals from ethanol (60%), mp 200–202°C; IR (cm^{-1}) ν 2223, 2196 (two CN), 1625 (N=C); ^{1}H NMR (DMSO-d_6) δ 3.04 (s, 6H, $N(CH_3)_2$), 3.15 (s, 6H, $N(CH_3)_2$), 3.85 (s, 3H, OCH_3),

7.03 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.27 (d, $J = 8.0$ Hz, 2H, Ar—H), 8.82 (s, 2H, two N=CH). Anal. for $C_{22}H_{21}N_7OS$ (431) Calcd: C, 61.23; H, 4.91; N, 22.72; S, 7.43. Found: C, 61.50; H, 5.20; N, 22.50; S, 7.10%.

*2-Acetyl-3-amino-6-{[(N,N-dimethylamino)methylene]amino}-4-(4-methoxyphenyl)thieno[2,3-b]pyridine-5-carbonitrile (***16***).* Orange crystals from dioxan (57%), mp 306–307°C; IR (cm^{-1}) ν 3481, 3330 (NH_2), 2218 (CN), 1622 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 2H, NH_2*), 2.36 (s, 3H, $COCH_3$), 3.22 (s, 6H, $N(CH_3)_2$), 3.89 (s, 3H, OCH_3), 7.06 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.36 (d, $J = 8.0$ Hz, 2H, Ar—H), 8.72 (s, 1H, N=CH). Anal. for $C_{20}H_{19}N_5O_2S$ (393) Calcd: C, 61.05; H, 4.87; N, 17.80; S, 8.15. Found: C, 61.30; H, 5.20; N, 17.50; S, 7.90%.

*2-Acetyl-3,6-bis{[(N,N-dimethylamino)methylene]amino}-4-(4-methoxyphenyl)thieno[2,3-b]pyridine-5-carbonitrile (***19***).* Orange crystals from dioxan (54%), mp 220–221°C; IR (cm^{-1}) ν 2221 (CN), 1653 (C=O), 1618 (N=C); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, $COCH_3$), 2.64 (s, 6H, $N(CH_3)_2$), 3.21 (s, 6H, $N(CH_3)_2$), 3.89 (s, 3H, OCH_3), 6.70 (s, 1H, N=CH), 6.94 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.22 (d, $J = 8.0$ Hz, 2H, Ar—H), 8.74 (s, 1H, N=CH). Anal. for $C_{23}H_{24}N_6O_2S$ (448) Calcd: C, 61.59; H, 5.39; N, 18.74; S, 7.15. Found: C, 61.40; H, 5.60; N, 19.00; S, 6.90%.

Reactions of **7** *with Aromatic Amine* **8a,b**

A solution of **7** (0.01 mole) in glacial acetic acid (20 ml) was treated with **8a,b** (0.02 mole). The reaction mixture was heated under reflux for 4 h. The solid product so formed after cooling was collected by filtration and crystallized from acetic acid to yield **11a,b**.

*7-Amino-9-(4-methoxyphenyl)-4-[(4-methylphenyl)amino]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile (***11a***).* Yellow crystals from AcOH (63%), mp 330–332°C; IR (cm^{-1}) ν 3474, 3356 (NH_2), 3201 (NH), 2212 (CN), 1616 (N=C); ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 7.05 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.15 (d, $J = 8.0$ Hz, 2H, Ar—H), 7.44–7.60 (m, 6H, NH_2^* & Ar—H), 8.31 (s, 1H, 2H-pyrimidine), 9.42 (s, 1H, NH*). Anal. for $C_{24}H_{18}N_6OS$ (438) Calcd: C, 65.74; H, 4.14; N, 19.17; S, 7.31. Found: C, 66.00; H, 4.40; N, 19.40; S, 7.10%.

*7-Amino-4-[(4-chlorophenyl)amino]-9-(4-methoxyphenyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile (***11b***).* Yellow crystals from AcOH (65%), mp 336–338°C; IR (cm^{-1}) ν 3480, 3372 (NH_2), 3208 (NH), 2215 (CN), 1608 (N=C). Anal. for $C_{23}H_{15}N_6OSCl$ (458) Calcd: C, 56.49; H, 3.37; N, 25.34; S, 5.81; Cl, 3.21. Found: C, 56.20; H, 3.60; N, 25.10; S, 5.60; Cl, 3.50%.

Reactions with Hydrazine Hydrate: General Procedure

A solution of the appropriate **7** or **19** (0.01 mole) in hydrazine hydrate (20 ml) was heated under reflux for 6 h and then cooled. The solid so obtained was collected by filtration and crystallized from the proper solvent to yield **11c** and **21** respectively.

*7-Amino-4-hydrazino-9-(4-methoxyphenyl)pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile (***11c***).* Orange crystals from ethanol (52%), mp 135–137°C; IR (cm^{-1}) ν 3461, 3372, 3331, 3201 (two NH_2, NH), 2212 (CN), 1607 (N=C).^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H, OCH_3), 4.39 (s, 2H, NH_2*), 6.28 (s, 2H, NH_2*) 6.90 (d, $J = 8.2$ Hz, 2H, Ar—H), 7.25 (d, $J = 8.2$ Hz, 2H, Ar—H), 7.59 (s, 1H, NH*), 8.65 (s, 1H, 2H-pyrimidine). Anal. for $C_{17}H_{13}N_7OS$ (363) Calcd: C, 58.66; H, 3.72; N, 25.82; S, 5.91. Found: C, 58.30; H, 4.00; N, 26.10; S, 5.70%.

*3,7-Diamino-4-hydroxy-9-(4-methoxyphenyl)-4-methyl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile (***21***).* Orange crystals from dioxan (55%), mp 270–273°C; IR (cm^{-1}) ν 3500, 3431, 3358, 3300 (br, OH, two NH_2), 2209 (CN), 1607 (N=C); ^{1}H NMR (DMSO-d_6) δ 1.99 (s, 1H, CH_3), 3.87 (s, 3H, OCH_3), 5.26 (s, 2H, NH_2*), 6.07 (s, 2H, NH_2*), 7.01 (s, 1H, 2H-pyrimidine) 7.03–7.46 (m, 5H, OH* & Ar—H); MS: (*m/z*) 353 (20.6%), 352 (100%), 350 (0.7%), 336 (28.8%), 335 (13.7%), 334 (4.8%), 321 (32.1%), 306 (5.3%), 296 (53%), 294 (4.6%), 279 (6.9%), 223 (2.4%), 74 (1.4%). Anal. for $C_{18}H_{16}N_6O_2S$ (380) Calcd: C, 56.83; H, 4.24; N, 22.09; S, 8.43. Found: C, 57.10; H, 4.60; N, 22.30; S, 8.20%.

Reactions with Nitrous Acid

A cold solution of the appropriate **4b** or **16** (0.01 mole) in concentrated HCl (5 ml) and glacial acetic acid (5 ml) was treated with a cold saturated solution of sodium nitrite (0.02 mole) and then stirred in the ice chest for 30 min. The solid products obtained were filtered off, washed with water and then crystallized from ethanol to yield **13** and **17** respectively.

*7-Hydroxy-9-(4-methoxyphenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-c]pyridazine-8-carbonitrile (***13***).* Orange crystals from ethanol (45%), mp 145–148°C; IR (cm^{-1}) ν 3403 (br, OH), 2230 (CN), 1718 (C=O), 1607 (N=C). ^{1}H NMR (DMSO-d_6) δ 3.78

(s, 2H, CH_2), 3.85(s, 3H, OCH_3), 5.90 (s, 1H, OH*), 7.09–7.71 (m, 4H, Ar—H). Anal. for $C_{17}H_{10}N_4O_3S$ (350) Calcd: C, 58.28; H, 2.88; N, 15.99; S, 9.15. Found: C, 58.00; H, 3.20; N, 15.70; S, 9.40%.

*7-{[(N,N-Dimethylamino)methylene]amino}-9-(4-methoxyphenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]-thieno[3,2-c]pyridazine-8-carbonitrile (***17***).* Orange crystals from ethanol (43%), mp 135–137°C; IR (cm^{-1}) ν 2217 (CN), 1705 (C=O), 1607 (N=C). ^1H NMR (DMSO-d_6) δ 3.31 (s, 6H, $N(CH_3)_2$), 3.70 (s, 2H, CH_2), 3.87(s, 3H, OCH_3), 7.05–7.41 (m, 5H, Ar—H & N=CH). Anal. for $C_{20}H_{16}N_6O_2S$ (404) Calcd: C, 59.39; H, 3.99; N, 20.78; S, 7.93. Found: C, 59.70; H, 3.70; N, 21.00; S, 7.60%.

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