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Synthesis and Isomerization of Thienotriazolopyrimidine and Thienotetrazolopyrimidine Derivatives with Potential Anti-inflammatory Activity

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ABSTRACT: *Several derivatives containing the thieno[2,3-d]pyrimidine system were prepared starting from 2-amino-4,5-dihydronaphtho[2,1-b]thiophene-1-carbonitrile (***1***). In particular, the synthesis and structure characterization of 8,9-dihydronaphtho-[1′,2′:4,5]thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine derivatives* **13–16** *and their isomerization to 8,9-dihydronaphtho[1′,2′:4,5]thieno[3,2-e][1,2,4]-triazolo[1,5-c]pyrimidine derivatives* **17–20** *under different suitable reaction conditions were reported and verified with X-ray analysis. Moreover, compounds* **13, 14** *and* **22** *were tested as potential anti-inflammatory agents and derivative* **14** *showed potent activity in carrageenan test.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:226–234, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20114

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INTRODUCTION

The synthesis of thieno[1,2,4]triazolopyrimidines has attracted attention of many investigators [1–11] and since the first synthesis of thieno[3,2-*e*][1,2,4]-triazolo[4,3-*c*]pyrimidines by Robba et al. [12], many derivatives have been described and proved to have pronounced biological activities [2,7,13,14]. Previous observations revealed that the above pyrimidine derivatives can isomerize under different suitable reaction conditions to the thermodynamically more stable thieno[3,2-*e*][1,2,4]triazolo-[1,5-*c*]pyrimidines [3–7]. This isomerization was reported earlier by Miller and Rose [15,16] when they treated [1,2,4]triazolo[4,3-*c*]pyrimidine derivatives with acid, base, or thermally. Nevertheless, this pattern of isomerization appears to have been overlooked by a number of workers [17–19].

This work is aimed at the synthesis and pharmacological study of thienotriazolo[4,3-*c*]pyrimidines **13–16** and thienotriazolo[1,5-*c*]pyrimidines **17–20** and conversion of the [4,3-*c*] derivatives to the thermodynamically more stable [1,5-*c*] isomers under different suitable reaction conditions. Moreover, the formation of azidothieno[2,3-*d*]pyrimidine **21**

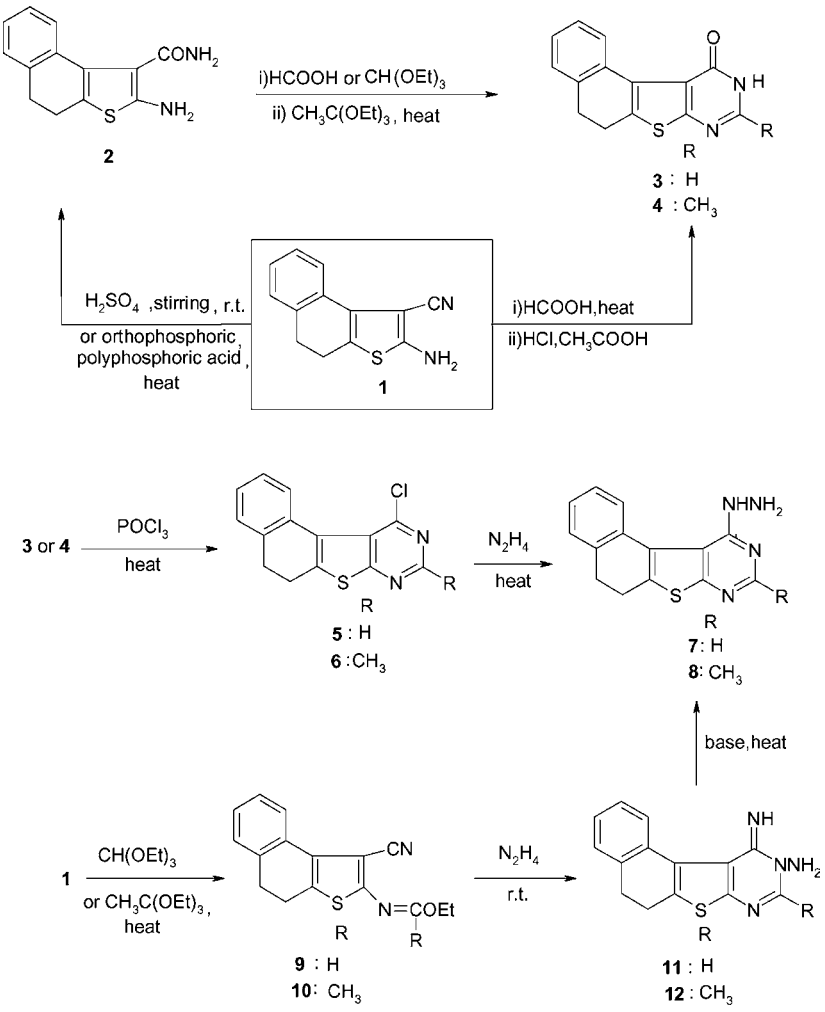
and thieno[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine **22** was discussed.

RESULTS AND DISCUSSION

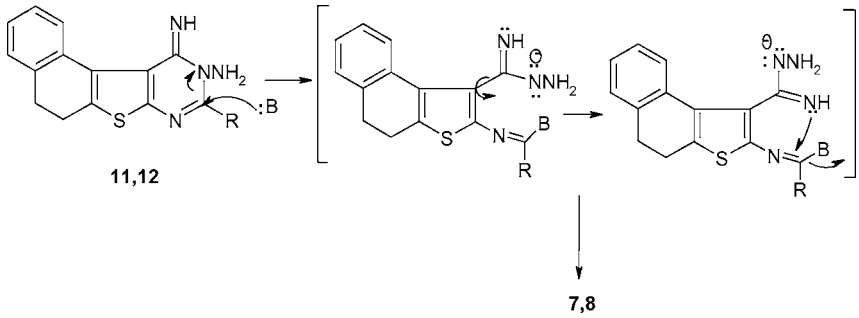
2-Amino-4,5-dihydronaphtho[2,1-*b*]thiophene-1-carbonitrile (**1**) was the starting compound that was treated with concentrated sulfuric acid at room temperature or heating with a mixture of orthophosphoric acid: polyphosphoric acid (1:1), gave the corresponding carboxamide derivative **2** (Scheme 1). Its IR spectrum revealed the absence of a band characteristic for the cyano group and showed absorption frequencies at 3390–3250 $cm^{-1}(\nu_{2NH_2})$ and 1625 cm^{-1} (ν_{CO}); moreover, the ^1H NMR spectrum showed signal at δ 4.60–4.70 ppm (br s, 2H, CO*N*H_2, exchangeable with D_2O).

On heating compound **2** with formic acid or triethyl orthoformate or treatment of compound **1** with formic acid at reflux temperature, compound **3** was obtained in good yield. On the other hand, heating of compound **2** with triethyl orthoacetate or heating compound **1**, as reported recently [2], with a mixture of acetic acid : hydrochloric acid (1:1) gave compound **4**; the structure of compounds **3** and **4** was confirmed by spectral data (see Experimental section, [2]). Compounds **3** and **4** were converted into their corresponding 11-chloro derivatives **5** and **6** [2], respectively, when heated with phosphorus oxychloride at reflux temperature. The mass spectra of compounds **5** and **6** [2] gave fragments showing the isotopic pattern due to the presence of chlorine atom (see Experimental section, [20]).

When compounds **5** and **6** were treated with hydrazine hydrate in ethanol at reflux temperature, they afforded the corresponding hydrazino derivatives **7** and **8** [2], respectively. The ^1H NMR spectrum of compound **7** showed signal at δ 4.40–4.80 ppm (br s, 2H, NH_2, exchangeable with D_2O), and signal at δ 7.10 ppm (s, 1H, NH, exchangeable with D_2O).



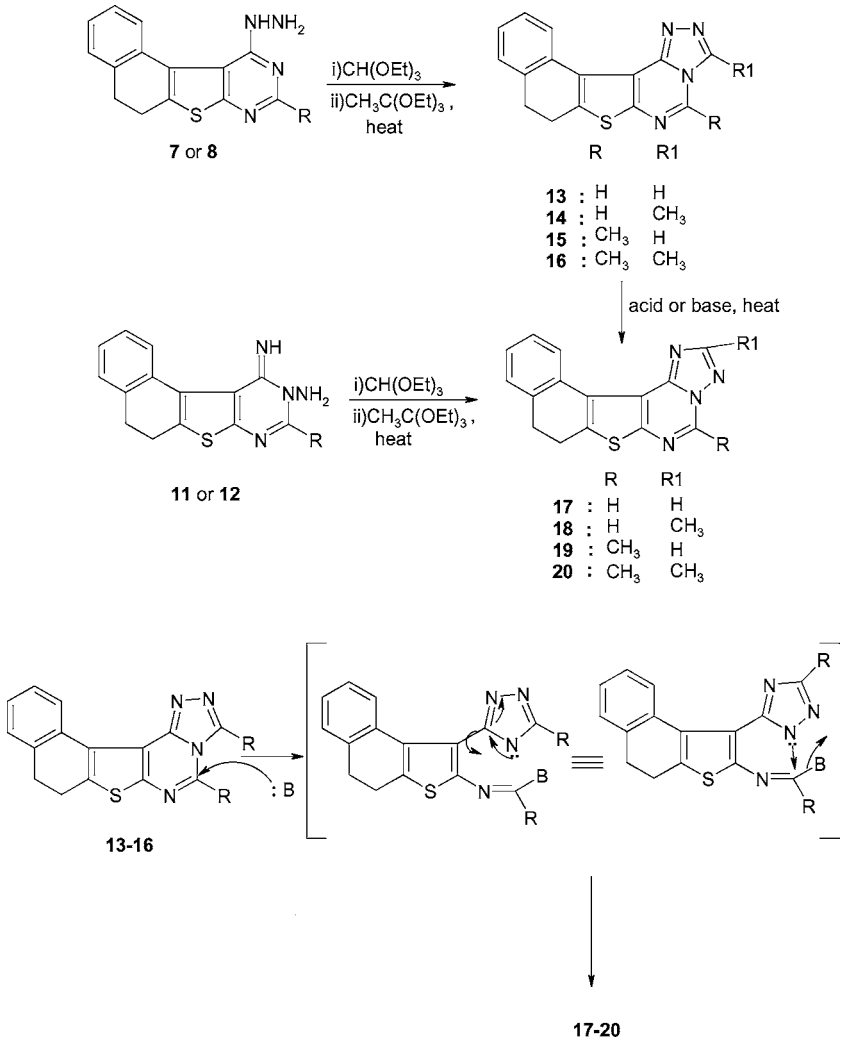
SCHEME 1



SCHEME 2

When the imino derivatives **11** [20] and **12** [2] were heated in a basic medium, they underwent a Dimroth type rearrangement to give compounds **7** and **8** through a sequence of ring opening and ring closure reactions (Schemes 1, 2).

Heating of compound **7** or **11** with triethyl orthoformate or triethyl orthoacetate at reflux temperature gave compounds **13** and **14** or **17** and **18**, respectively (Scheme 3). Likewise, heating compound **8** or **12** with triethyl orthoformate or triethyl



SCHEME 3

orthoacetate at reflux temperature gave compounds **15** and **16** or **19** and **20**, respectively. It was noticed that the two isomeric series of triazolopyrimidine derivatives **13–16** and **17–20** showed no appreciable difference in the fragmentation pattern under electron impact (see Experimental section, [2,20]); however, the ^{1}H NMR spectra of triazolo[4,3-*c*]pyrimidine derivatives **13–16** revealed that the substituents R and R_1 showed signals more downfield than those in their isomeric triazolo[1,5-*c*]pyrimidine derivatives **17–20** (Table 1). This confirmed that the products obtained from the reaction with hydrazino derivatives **7** and **8** differ than those obtained from the reaction with imino derivatives **11** and **12**. Not only the spectral data revealed this observation but also the physical data, where the melting points (mp) and rates of flow (R_f values) of derivatives **13–14** were higher than those of derivatives **17–20** (see Experimental section, [2,20]).

When triazolo[4,3-*c*]pyrimidine derivatives **13–16** were heated in either acid or basic medium they were isomerized to the thermodynamically more stable triazolo[1,5-*c*]pyrimidine derivatives **17–20**, respectively, through a series of ring opening and ring closure reactions (Scheme 3). This isomerization was also verified with a single X-ray analysis for compounds **13** and **17** (obtained from isomerization of **13**) (Fig. 1, Table 2; and Fig. 2, Table 3). These results were in agreement with those reported in some earlier reports [3–7].

Heterocyclic azides especially azidomethines can exist in equilibrium with their tetrazolo tautomers, and this equilibrium is affected by many factors: *p*H, temperature, the nature of the substituents around the (C=N), and the solvent used [21–23]. This equilibrium can be shifted in either direction by controlling these factors, and the IR spectroscopy is helpful in revealing which form is predominant, since the azido structure can show a characteristic band in the region ν 2100–2200 cm^{-1}. Thus, when chloro derivatives **5** and **6** were treated at 70°C with

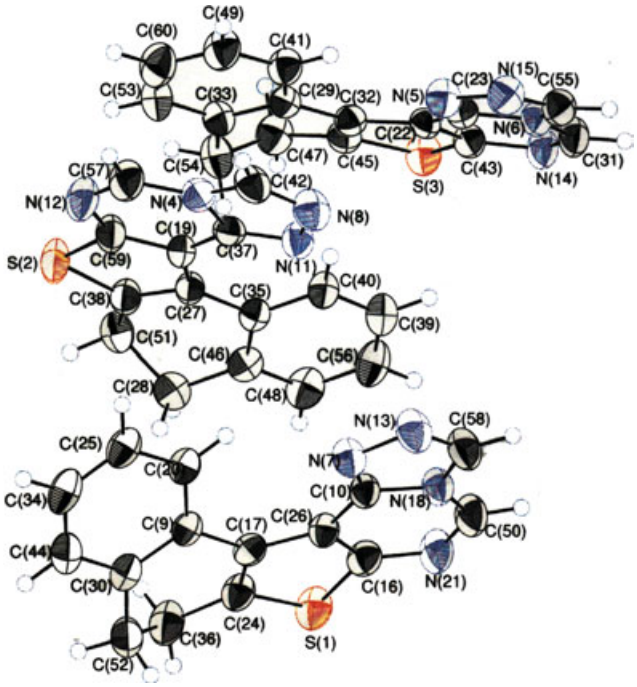


FIGURE 1 Single crystal X-ray structure of compound **13**, because $Z = 12$ and space group $= P21/c$, so there are three molecules appear in the asymmetric unit cell.

sodium azide in glacial acetic acid, they afforded compounds **21** and **22**, respectively (Scheme 4). Analytical and spectral data are in agreement with the proposed structures (See Experimental section). In particular, the IR spectrum of compound **21** showed absorption frequency at ν 2110 cm^{-1} indicative for the azido group, while IR spectrum of compound **22** did not; this datum indicates that compound **21** has the azido structure, without excluding the tetrazolo structure in tautomeric equilibrium while compound **22** has only the tetrazolo structure.

TABLE 1

Compd. No.	δC_5-H	δC_5-CH_3	δC_3-H	δC_2-H	δC_3-CH_3	δC_2-CH_3
13	9.40	–	9.50	–	–	–
14	9.25	–	–	–	2.80	–
15	–	2.90	9.60	–	–	–
16	–	2.90	–	–	3.00	–
17	8.50	–	–	9.30	–	–
18	9.18	–	–	–	–	2.65
19	–	2.80	–	8.40	–	–
20	–	2.60	–	–	–	2.80

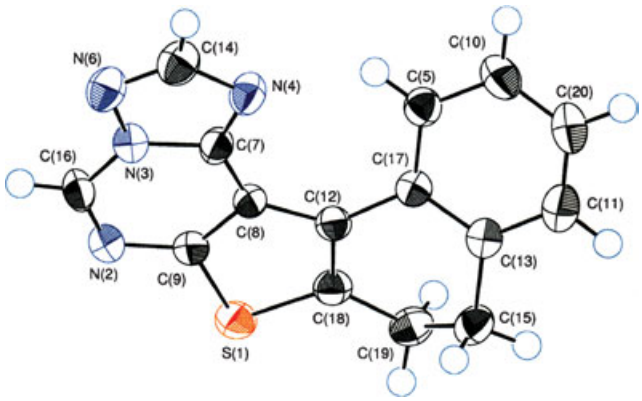


FIGURE 2 Single crystal X-ray structure of compound **17**.

TABLE 2 Crystal Data, Bond Lengths, and Bond and Torsion Angles of **13**

Crystal Data	
Crystal system	Monoclinic
Space group	*P 21*/c
a (Å)	18.3549 (3)
b (Å)	10.7746 (2)
c (Å)	21.9151 (8)
α (°)	90.00
β (°)	12.E1 (18)
γ (°)	90.00
V (Å^3)	3754.0 (2)
Z	12
D_x (cm^{-1})	1.87
R	0.096
wR	0.088
Bond length (Å)	
C10–N18	1.390 (2)
N7–N13	1.405 (2)
N13–C58	1.292 (2)
N18–C58	1.365 (2)
Bond and torsion angles (°)	
N7–C10–C26	134.35 (12)
C10–N18–C50	124.15 (12)
C50–N18–C58	130.92 (13)
C10–N7–N13	106.54 (11)
N7–C10–N18	107.84 (12)
C50–N18–C58–N13	178.80 (4)
C26–C10–N18–C58	−178.60 (3)
C26–C10–N7–N13	178.80 (4)

TABLE 3 Crystal Data, Bond Lengths, and Bond and Torsion Angles of **17**

Crystal Data	
Crystal system	Triclinic
Space group	*P* − 1
a (Å)	8.1829 (6)
b (Å)	8.2483 (6)
c (Å)	10.4999 (10)
α (°)	105.206 (3)
β (°)	107.287 (3)
γ (°)	102.409 (7)
V (Å^3)	619.13 (9)
Z	2
D_x (cm^{-1})	0.52
R	0.140
wR	0.110
Bond length (Å)	
N3–C7	1.388 (3)
N3–N6	1.372 (3)
N4–C14	1.358 (4)
N6–C14	1.314 (3)
Bond and torsion angles (°)	
N3–N6–C14	100.80 (2)
N3–C7–N4	108.70 (2)
N4–C7–C8	135.50 (3)
N6–N3–C16	125.30 (2)
C7–N4–C14	102.60 (2)
C16–N3–N6–C14	177.90 (5)
N6–N3–C16–N2	−175.30 (6)
C14–N4–C7–C8	−178.10 (6)

The absence of azido group and the formation of tetrazolo structure in compound **22** may be due to the effect of an electron donating group (CH_3), which stabilizes the tetrazolo structure.

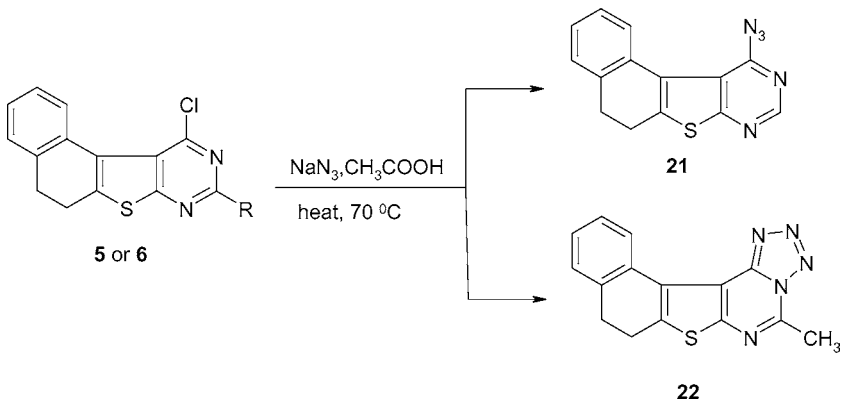
PHARMACOLOGY

Animals

Animal Albino male rates (100–120 g) were used in the pharmacological test. They were kept under constant conditions and allowed free access to water and standard diet. Biological experiments were performed in accordance with the local animal values.

Carrageenan Foot Paws Oedema

The procedure of Winter et al. [24] was adopted. Albino male rates (100–120 g) were dosed orally with the tested compounds dissolved in 5% DMSO in a dose of 40 mg kg body mass 1 h before carrageenan



SCHEME 4

challenge. Foot paw oedema were induced by injecting 0.1 mL of carrageenan solution subcutaneously into the planter portion in the right-hind paw of each rat under light anesthesia. Initial foot paw was measured immediately following carrageenan challenge. The swelling in each test group of animals ($n = 5$), 3 h after carrageenan administration, was used to calculate the per cent oedema remained after administration of the reference and tested compounds compared with the control group.

RESULTS

A pharmacological study to evaluate the anti-inflammatory effects of the synthesized compounds **13, 14**, and **22** was performed and the results are summarized in Table 5. The anti-inflammatory activity was calculated as the per cent inhibition after administration of the reference and tested compounds compared to the control group. Compounds **13** and **22** showed lower inhibitory activity less than diclofenac (Voltaren) with a percentage inhibition of 43.72% and 56.32%, respectively, while compound **14** reduced the oedema more effectively than diclofenac with percentage inhibition of 86.43%, indicating 1.2 times higher than the anti-inflammatory activity of diclofenac.

The order of increase in anti-inflammatory effect was established as follows: **14** > **22** > **13**.

TABLE 4 Pharmacological and Some Toxicological Properties of Substituted Triazolo[4,3-*c*]pyrimidines **13, 14**, and Tetrazolo[1,5-*c*] Pyrimidine Derivative **22**

Compd. No.	*R*	*R_1*	*Solubility* [a]	*LD_{50}* [b] *p.o. (mg/kg)*	*Anti-inflammatory* [c]
13	H	H	DMSO	>500	+
14	H	CH_3	DMSO	>500	+++
22	–	CH_3	DMSO	>500	++

[a]Other solvent as Tween 80 (10%) and propylene glycol (40%) were tried. All compounds were completely soluble in DMSO. 5% DMSO solution in dist. H_2O was used to prepare doses for oral administration.
[b]Concentration higher than the above mentioned could not be prepared due to precipitation of compound in the solvent used, 5% DMSO.
[c]50 mg, 100 mg, and 150 mg/kg were tried for all compounds. 100 mg/kg dose was used to test and compare the anti-inflammatory activity between tested compounds, control, and reference compound used (diclofenac).
+ = Less active; ++ = slightly active; +++ = highly active.

TABLE 5 Anti-inflammatory Activity of Substituted Triazolo-[4,3-*c*]pyrimidines **13, 14**, and Tetrazolo[1,5-*c*]pyrimidine Derivative **22**

Groups	*Anti-inflammatory Activity*
Control	71.0 ± 2.40
Diclofenac (reference compound)	69.80 ± 7.90*
13	43.72 ± 6.90
14	86.43 ± 4.50
22	56.32 ± 9.80*

EXPERIMENTAL

All melting points are uncorrected and measured using electro-thermal IA 9100 apparatus. IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer, National Research Centre. ^{1}H NMR spectra were determined on a Jeol-Ex-300 NMR spectrometer, and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal reference (Cairo University, Faculty of Science). Mass spectra were recorded on EI + Q1 MSLMR UPLR, National Research Centre. Microanalyses were operated using Mario Elmentar apparatus, organic microanalysis unit, National Research Centre. The single crystal for the X-ray diffraction analysis of compounds **13** and **17** was obtained by slow evaporation of the corresponding ethanol solution. The X-ray determination was performed by the Central Services Laboratory, National Research Centre. Column chromatography was performed on (Merck) Silica gel 60 (particle size 0.06–0.20).

Compounds **1,4,6,8,9–12,18–20** prepared here are identical in all respects (mp, physical, and spectral data) with that prepared previously: compounds **1** {literature mp 140–142°C [2,20]}, **4** {literature mp 278–280°C [2]}, **6** {literature mp 150–152°C [2]}, **8** {literature mp 182–184°C [2]}, **9** {literature mp 120–122°C [20]}, **10** {literature mp 82–84°C [2]}, **11** {literature mp 180–182°C [20]}., **12** {literature mp 205–207°C [2]}, **18** {literature mp 160–162°C [20]}, **19** {literature mp 175–177°C [2]}, **20** {literature mp 170–172°C [2]}.

*2-Amino-4,5-dihydronaphtho[2,1-b]thiophene-1-carboxamide (**2**)*

(i) Compound **1** (0.226 g, 1 mmol) was added portion wise to 20 mL conc. sulfuric acid with stirring at room temperature for 7 h. The reaction mixture was poured into ice water, neutralized, filtered, dried, and recrystallized from dimethylformamide to give compound **2** (0.18 g, 74%).

(ii) Compound **1** (0.226 g, 1 mmol) was added to a mixture of 20 mL orthophosphoric acid: polyphosphoric acid (1: 1) with stirring for 1 h at room temperature, then the reaction mixture was heated at 90°C for 10 h, cooled, poured into water, filtered, dried, and recrystallized from dimethylformamide to give compound **2** (0.20 g, 82%), mp 206–208°C. Calcd for

$C_{13}H_{12}N_2OS$ (244.32): C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 63.80; H, 4.80; N, 11.30; S, 13.30. IR (KBr): ν_{2NH_2} 3390–3250 cm^{-1}, ν_{CO} 1625 cm^{-1}. ^1H NMR (DMSO-d_6, ppm): δ 2.80–2.95 (m, 4H, $2CH_2$), 4.60–4.70 (br s, 2H, CONH_2, D_2O exchangeable), 6.60 (s, 2H, NH_2, D_2O exchangeable), 7.10–7.30 (m, 3H, Ar-H), 8.10 (d, J = 9.80 Hz, 1H, Ar-H). MS, *m/z* (%): 244 (M^+, 81.80), 227 (100), 199 (15.97).

*5,6,10-Trihydronaphtho[1′,2′:4,5]thieno[2,3-d]pyrimidin-11-one (**3**)*

(i) Compound **1** (0.226 g, 1 mmol) or compound **2** (0.244 g, 1 mmol) was heated at reflux temperature in 20 mL formic acid for 20 h (compound **1**) or 5 h (compound **2**). The reaction mixture was cooled, poured into water, filtered, dried, and recrystallized from dioxane/methanol (1:1) to give compound **3** (0.22 g, 87% from compound **1**) or (0.24 g, 95% from compound **2**).

(ii) Compound **2** (0.244 g, 1 mmol) was heated at reflux temperature in 20 mL triethyl orthoformate for 6 h. The reaction mixture was evaporated under reduced pressure, and the residue was recrystallized from dioxane/methanol (1:1) to give compound **3** (0.20 g, 79%), mp 268–270°C. Calcd for $C_{14}H_{10}N_2OS$ (254.31): C, 66.12; H, 3.96; N, 11.02; S, 12.61. Found: C, 66.20; H, 3.80; N, 10.83; S, 12.40. IR (KBr): ν_{NH} 3100 cm^{-1}, ν_{CO} 1625 cm^{-1}. ^1H NMR (DMSO-d_6, ppm): δ 2.80–3.10 (m, 4H, $2CH_2$), 7.20–7.50 (m, 3H, Ar-H), 8.10 (s, 1H, C_9-H), 8.40 (d, J = 10.45 Hz, 1H, Ar-H), 12.15 (s, 1H, NH, D_2O exchangeable). MS, *m/z*(%): 254 (M^+, 100), 226 (5.67).

*9-Methyl-5,6,10-trihydronaphtho[1′,2′:4,5]thieno[2,3-d]pyrimidin-11-one (**4**)*

Compound **2** (0.226 g, 1 mmol) was heated at reflux temperature in 20 mL triethyl orthoacetate for 5 h, filtered while hot, washed with water, then methanol, dried, and recrystallized from dimethylformamide to give compound **4** (0.20 g, 75%), mp and literature mp 278–280°C. Calcd for $C_{15}H_{12}N_2OS$ (268.34): C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 66.90; H, 4.80; N, 10.30; S, 12.30. IR (KBr): ν_{NH} 3250 cm^{-1}, ν_{CO} 1665 cm^{-1}. ^1H NMR (DMSO-d_6, ppm): δ 2.60 (s, 3H, C_9-CH_3), 2.90–3.00 (m, 4H, $2CH_2$), 7.20–7.50 (m, 3H, Ar-H), 8.50 (d, J = 10.80 Hz, 1H, Ar-H), 12.50 (s, 1H, NH, D_2O exchangeable). MS, *m/z* (%): 268 (M^+, 100), 251 (3.27), 225 (8.75).

*11-Chloro-5,6-dihydronaphtho[1′,2′:4,5]thieno[2,3-d]pyrimidine (**5**).*

Compound **3** (0.254 g, 1 mmol) was heated at reflux temperature in 20 mL phosphorus oxychloride for 5 h, cooled, then the reaction mixture was poured into ice water, stirred, filtered, dried, and purified on silica gel using petroleum ether (40–60°C) : ethyl acetate (4 : 1) to give compound **5** (0.20 g, 74%), mp 144–146°C. Calcd for $C_{14}H_9ClN_2S$ (272.76): C, 61.65; H, 3.33; N, 10.27; S, 11.76. Found: C, 61.90; H, 3.10; N, 10.03; S, 12.10 ^1H NMR ($CDCl_3$, ppm): δ 2.90–3.00 (m, 4H, $2CH_2$), 7.20–7.40 (m, 3H, Ar-H), 7.75 (d, J = 11.20 Hz, 1H, Ar-H), 8.80 (s, 1H, C_9-H). MS, *m/z* (%): 274 (M^+, ^{37}Cl, 39.98), 272 (M^+, ^{35}Cl, 100), 237 (11.68), 235 (19.13), 210 (9.36), 208 (13.71).

*11-Hydrazino-5,6-dihydronaphtho[1′,2′:4,5]-thieno[2,3-d]pyrimidine (**7**)*

Compound **5** (0.272 g, 1 mmol) was dissolved in 20 mL absolute ethanol, then 2 mL of hydrazine hydrate (99%) was added and the reaction mixture was heated at reflux temperature for 3 h, evaporated under reduced pressure and the residue was recrystallized from dioxane to give compound **7** (0.25 g, 93%), mp 238–240°C. Calcd for $C_{14}H_{12}N_4S$ (268): C, 62.66; H, 4.51; N, 20.88; S, 11.95. Found: C, 62.90; H, 4.20; N, 20.43; S, 12.10. ^1H NMR (DMSO-d_6, ppm): δ 2.90–3.00 (m, 4H, $2CH_2$), 4.40–4.80 (br, 2H, NH_2, D_2O exchangeable), 7.10 (s, 1H, NH, D_2O exchangeable), 7.20–7.40 (m, 3H, Ar-H), 7.60 (d, J = 11.50 Hz, 1H, Ar-H), 8.40 (s, 1H, C_9-H). MS, *m/z* (%): 268 (M^+, 100), 250 (54.54), 237 (12.12), 224 (9.40).

Isomerization of **11** *and* **12** *to* **7** *and* **8**

Compounds **11** (0.268 g, 1 mmol) and **12** (0.282 g, 1 mmol) were dissolved in 20 mL absolute ethanol, then 1 mL hydrazine hydrate was added, and the reaction mixture was heated at reflux temperature for 2 h, evaporated under reduced pressure to give compounds **7** (0.24 g, 90%) and **8** (0.25 g, 89%). Products obtained from these isomerizations are identical in all respects (mp, *tlc*, physical, and spectral data) with compounds **7** (prepared here) and **8** obtained before [2].

*8,9-Dihydronaphtho[1′,2′:4,5]thieno[3,2-e]-[1,2,4]triazolo[4,3-c]pyrimidine (**13**)*

Compound **7** (0.268 g, 1 mmol) was heated at reflux temperature in 20 mL triethyl orthoformate for 10 h. The reaction mixture was cooled, filtered, dried, and recrystallized from dioxane to give compound **21** (0.20 g, 72%), mp 247–249°C. Calcd for $C_{15}H_{10}N_4S$ (278.34): C, 64.73; H, 3.62; N, 20.13; S, 11.52. Found: C, 64.90; H, 3.50; N, 20.03; S, 11.30. ^1H NMR (DMSO-d_6, ppm): δ 2.90–3.00 (m, 4H, $2CH_2$), 7.20–7.40 (m, 3H, Ar-H), 9.30 (d, J = 11.80 Hz, 1H, Ar-H), 9.40 (s,

1H, C_5-H), 9.50 (s, 1H, C_3-H). MS, *m/z* (%): 278 (M^+, 100), 250 (14.90), 233 (2.47), 223 (6.55).

*3-Methyl-8,9-dihydronaphtho[1′,2′:4,5]thieno-[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (***14***)*

Compound **7** (0.268 g, 1 mmol) was heated at reflux temperature in 20 mL triethyl orthoacetate for 10 h, then the reaction mixture was cooled, filtered, dried, and recrystallized from dioxane to give compound **14** (0.25 g, 86%), mp 270–272°C. Calcd for $C_{16}H_{12}N_4S$ (292.36): C, 65.73; H, 4.14; N, 19.16; S, 10.97. Found: C, 65.90; H, 3.80; N, 19.05; S, 11.30.^{1}H NMR (DMSO-d_6, ppm): δ 2.80 (s, 3H, C_3-CH_3), 2.90–3.00 (m, 4H, $2CH_2$), 7.20–7.40 (m, 3H, Ar-H), 9.25 (s, 1H, C_5-H), 9.30 (d, J = 12.15 Hz, 1H, Ar-H)). MS, *m/z*(%): 292 (M^+, 100), 264 (2.72), 251(11.88), 233 (2.73), 223 (6.61).

*5-Methyl-8,9-dihydronaphtho[1′,2′:4,5]thieno-[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (***15***)*

Compound **8** (0.282 g, 1 mmol) was heated at reflux temperature in 20 mL triethyl orthoformate for 10 h. The reaction mixture was cooled, filtered, dried, and recrystallized from dioxane to give compound **15** (0.25 g, 86%), mp 266–268°C. Calcd for $C_{16}H_{12}N_4S$ (292.36): C, 65.73; H, 4.14; N, 19.16; S, 10.97. Found: C, 65.92; H, 3.90; N, 19.20; S, 11.20.^{1}H NMR (DMSO-d_6, ppm): δ 2.90 (s, 3H, C_5-CH_3), 3.00–3.10 (m, 4H, $2CH_2$), 7.20–7.40 (m, 3H, Ar-H), 9.30 (d, J = 12.10 Hz, 1H, Ar-H), 9.60 (s, 1H, C_3-H). MS, *m/z* (%): 292 (M^+, 100), 265 (8.96), 250 (10.91), 237 (2.45), 223 (5.62).

*3,5-Dimethyl-8,9-dihydronaphtho[1′,2′:4,5]-thieno[3,2-e][1,2,4]triazolo[4, 3-c]-pyrimidine (***16***)*

Compound **8** (0.282 g, 1 mmol) was heated at reflux temperature in 20 mL triethyl orthoacetate for 10 h, then the reaction mixture was cooled, filtered, dried, and recrystallized from dioxane to give compound **16** (0.24 g, 78%), mp 278–280°C. Calcd for $C_{17}H_{14}N_4S$ (306.39): C, 66.64; H, 4.61; N, 18.29; S, 10.47. Found: C, 66.80; H, 4.40; N, 18.10; S, 10.20.^{1}H NMR (DMSO-d_6, ppm): δ 2.90 (s, 3H, C_5-CH_3), 3.00 (s, 3H, C_3-CH_3), 3.10–3.20 (m, 4H, $2CH_2$), 7.20–7.40 (m, 3H, Ar-H), 9.20 (d, J = 12.50 Hz, 1H, Ar-H). MS, *m/z* (%): 306 (M^+, 100), 291 (1.73), 264 (29.15), 237 (3.87), 223 (8.55).

*8,9-Dihydronaphtho[1′,2′:4,5]thieno[3,2-e]-[1,2,4]triazolo[1,5-c]pyrimidine (***17***)*

Compound **11** (0.268 g, 1 mmol) was heated at reflux temperature in 20 mL triethyl orthoformate for 6 h, then the reaction mixture was cooled, filtered, dried, and recrystallized from ethanol to give compound **17** (0.22 g, 79%), mp 188–190°C. Calcd for $C_{15}H_{10}N_4S$ (278.34): C, 64.73; H, 3.62; N, 20.13; S, 11.52. Found: C, 64.50; H, 3.40; N, 20.30; S, 11.34. ^{1}H NMR ($CDCl_3$, ppm): δ 3.00–3.20 (m, 4H, $2CH_2$), 7.20–7.50 (m, 3H, Ar-H), 8.70 (d, J = 11.34 Hz, 1H, Ar-H), 8.50 (s, 1H, C_5-H), 9.30 (s, 1H, C_2-H). MS, *m/z* (%): 278 (M^+, 100), 250 (13.23), 233 (3.87), 223 (5.48).

Isomerization of **13–16** *to* **17–20**

Compounds **13** (0.278 g, 1 mmol), **14** (0.292), **15** (0.292 g, 1 mmol), and **16** (0.306 g, 1 mmol) were heated at reflux temperature in 20 mL absolute ethanol containing few drops of base (piperidine or sodium ethoxide) or in 20 mL formic acid for 6 h (compound **13**), 8 h (compound **14**), 10 h (compound **15**), and 15 h (compound **16**), then the reaction mixtures were evaporated under reduced pressure and the residues were recrystallized from dioxane to give compound **17** (0.25 g, 90%), **18** (0.27 g, 93%), **19** (0.26 g, 89%), and **20** (0.28 g, 92%). Products obtained from these isomerizations are identical in all respects (mp, *tlc*, physical, and spectral data) with compounds **17** (prepared here), **18** [20], **19** [2], and **20** [2], respectively.

*11-Azido-5,6-dihydronaphtho[1′,2′:4,5]thieno-[2,3-d]pyrimidine (***21***)*

Compound **5** (0.272 g, 1 mmol) was added to 20 mL glacial acetic acid containing sodium azide (0.13 g, 2 mmol) with stirring at 70°C for 2 h. Then the reaction mixture was cooled, filtered, washed with little amount of water then cold ethanol, dried, and recrystallized from ethanol to give compound **21** (0.21 g, 75%), mp 213–214°C. Calcd for $C_{14}H_9N_5S$ (279.33): C, 60.20; H, 3.25; N, 25.07; S, 11.48. Found: C, 59.94; H, 3.50; N, 24.93; S, 11.32. IR (KBr): ν_{N3}2210 cm^{-1}. ^{1}H NMR ($CDCl_3$, ppm): δ 3.00–3.20 (m, 4H, $2CH_2$), 7.20–7.60 (m, 3H, Ar-H), 9.20 (d, J = 12.15 Hz, 1H, Ar-H), 9.50 (s, 1H, C_9-H). MS, *m/z* (%): 279 (M^+, 26.97), 224 (17.40).

*5-Methyl-8,9-dihydronaphtho[1′,2′:4,5]thieno-[3,2-e]tetrazolo[1,5-c]pyrimidine (***22***)*

Compound **6** (0.286 g, 1 mmol) was added to 20 mL glacial acetic acid containing sodium azide (0.13 g, 2 mmol) with stirring at 70°C for 2 h. The reaction mixture was cooled, filtered, washed with little amount of water then cold ethanol, dried, and recrystallized from ethanol to give compound **22** (0.20 g, 68%), mp 241–242°C. Calcd for $C_{15}H_{11}N_5S$ (293.35): C, 61.42;

H, 3.78; N, 23.87; S, 10.93. Found: C, 61.20; H, 3.60; N, 24.03; S, 11.04. ^{1}H NMR ($CDCl_3$, ppm): δ 3.00–3.10 (m, 4H, $2CH_2$), 3.20 (s, 3H, C_5-CH_3), 7.20–7.50 (m, 3H, Ar-H), 9.15 (d, $J = 12.15$ Hz, 1H, Ar-H). MS, m/z (%): 293 (M^+, 47.65), 264 (100), 250 (3.42), 223 (13.79).

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