Heteroatom Chemistry
Volume 11, Number 2, 2000

Reactivity of 3-(Benzothiazol-2-yl)-3-Oxopropanenitrile: A Facile Synthesis of Novel Polysubstituted Thiophenes

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Received 4 June 1999; revised 24 September 1999

ABSTRACT: *The reaction of 3-(benzothiazol-2-yl)-3-oxopropanenitrile* **1** *with active methylene reagents* **2a–d** *and sulfur afforded polysubstituted thiophenes* **3a–c** . *The synthetic potential of the β-enaminonitrile moiety in* **3a** *was explored. The reaction of* **3a** *with active methylene reagents* **2a–e** *afforded thieno[2,3-b]pyridine derivatives* **6–8.** *Refluxing of* **3a** *with acetic anhydride alone, with acetic anhydride/pyridine mixture, or with carbon disulfide in pyridine afforded the acetamido* **9,** *thieno[2,3-d]pyrimidine* **10,** *and pyrimidinedithiol* **11** *derivatives, respectively. The pyrimidinedithiol* **11** *was alkylated smoothly with methyl iodide to give the bis(methylthio) derivative* **12.** *Also, compound* **3a** *reacted with trichloroacetonitrile to give the thieno[2,3-d]pyrimidine derivative* **14.** *Compound* **3a** *reacted with triethyl orthoformate or formamide to give the ethoxymethylideneamino* **15** *and thieno[2,3-d]pyridine* **16,** *respectively. Compound* **15** *reacted with hydrazine to afford thieno[2,3-d]pyridine* **17,** *which reacted with various reagents such as chloroacetyl chloride, ethyl cyanoacetate, diethyl oxalate, or chloroethylformate to give 1,2,4-triazolo[1,5:1,6]pyrimidino-[4,5-b]thiophene derivatives* **18a–c** *and* **19,** *respectively.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:94–101, 2000

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INTRODUCTION

In recent years, there has been increasing interest in syntheses of heterocyclic compounds that have biological and commercial importance. Benzothiazole compounds play an important role in modern organic synthesis, not only because they constitute a particularly useful class of heterocyclic compounds [1–5], but also because they are of great biological interest. They have been found to have antiviral [6], antibacterial [7], antimicrobial [8], and fungicidal activities [9]. They are also useful as antiallergic [10], anthelmintic [11], and anti-inflammatory [12] agents, and as histamine H_2-antagonists [13], appetite depressants [14], intermediates for dyes [15], plant protectants [16], and photographic sensitizers [17].

In continuation of our studies on the chemistry of 3-(benzothiazol-2-yl)-3-oxopropanenitrile [1,2,19] and as a part of our program directed toward developing new approaches to a variety of heterocycles incorporating the benzothiazole moiety [1–5] of potential biological activity, we report here the scope and applicability of 3-(benzothiazol-2yl)-3-oxopropanenitrile as a unique precursor for the synthesis of some previously unreported polyfunctionally substituted thiophenes and their fused derivatives in which a benzothiazole ring is incorporated.

RESULTS AND DISCUSSION

When 3-(benzothiazol-2-yl)-3-oxopropanenitrile **1** was allowed to react with active methylene reagents

2a–d and elemental sulfur in refluxing dioxane containing a catalytic amount of triethylamine, the thiophene derivatives **3a–c** were obtained (Scheme 1).

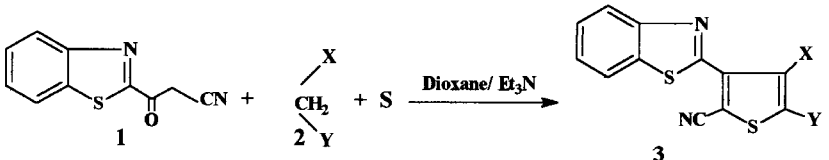
The structures of **3a–c** were established based on analytical and spectral data (see Table 1) together with a study of the reactivity of the resulting products toward various reagents. Thus, when compound **3a** was fused with malononitrile **2a**, a single product was obtained with molecular formula $C_{16}H_8N_6S_2$. Of three possible isomeric structures **4, 5**, and **6** (Scheme 2) that were considered for the reaction product, both structures **4** and **5** were readily excluded based on the ^{1}H NMR spectrum of the isolated product, which revealed the presence of two D_2O-exchangeable protons at δ = 7.03 and 8.35 ppm that could be attributed to two amino groups. Structures **4** and **5** would be expected to show a singlet signal at ~δ 4–5 ppm assigned for methylene protons. Therefore, structure **6** is assigned to the product isolated. The structure of **6** is supported by the independent synthesis of the same product by the reaction of **3a** with cyanoethanethioamide **2c** (as demonstrated by m.p., mixed m.p., and spectral data).

Similarly, compound **3a** reacted with ethyl cyanoacetate **2b** or ethyl acetoacetate **2e** to afford thieno[2,3-*b*]pyridinone derivatives **7a,b,** respectively (Scheme 2). The ^{1}H NMR spectra of **7a,b** revealed the presence of a broad D_2O-exchangeable signal at δ 9.01–9.39 ppm due to the pyridinone NH, one at δ 8.0–8.13 ppm due to amino groups, and one in **7b** at δ = 2.56 ppm due to the $COCH_3$ group, in addition to the aromatic protons. The IR spectrum of **7a** clearly indicated the presence of NH_2, NH, and CN groups at 3420–3195 and 2230–2220 cm^{-1}, respectively. However, in compound **7b** NH_2, NH, CN, and carbonyl groups were found to be present.

Also, the reaction of **3a** with benzoylacetonitrile **2d** afforded the thieno[2,3-*b*] pyridine derivative **8**. Compound **8** was formed by addition of the methylene group in **2d** to the cyano group of **3a** followed by cyclocondensation via elimination of a water molecule. Assignment of the structure of **8** was established based on its spectroscopic data. The ^{1}H NMR spectrum revealed the presence of a multiplet signal at δ 7.21–8.36 ppm due to aromatic protons in addition to an amino group. Both amino and cyano groups in compound **8** appeared in the IR spectrum at 3335–3189 and 2223–2195 cm^{-1}, respectively. The mass spectrum of **8** gave the correct molecular weight. The structure of **8** is supported by the independent synthesis of the same product from **3a** and benzylidenemalononitrile (m.p., mixed m.p., and spectral data).

The reaction of **3a** with acetic anhydride alone gave an acetamido derivative **9** while reaction of **3a** with acetic anhydride/pyridine mixture gave the thieno[2,3-*d*] pyrimidine derivative **10**. The ^{1}H NMR spectra of **9** revealed the presence of a broad peak at δ = 9.84 ppm due to NH and a singlet at δ = 2.46 due to the methyl group in addition to the aromatic protons. The thieno[2,3-*d*]pyrimidine **10** was confirmed based on the obtained analytical and spectral data. The ^{1}H NMR spectrum of **10** revealed the presence of a broad signal at δ = 11.4 ppm due to the presence of an NH group exchangeable with D_2O and a singlet signal at δ = 2.61 ppm due to the methyl group, in addition to the aromatic protons. The IR spectra clearly indicated the presence of the pyrimidine-NH group, the cyano group, and the carbonyl group at 3180, 2221, and 1665 cm^{-1}, respectively.

The reaction of **3a** with carbon disulfide in pyridine proceeded by the addition of carbon disulfide



2	X	Y
a	CN	CN
b	CN	CO_2Et
c	CN	$CSNH_2$
d	CN	COC_6H_5
e	$COCH_3$	CO_2Et

3	X	Y
a	CN	NH_2
b	CO_2Et	NH_2
c	CN	C_6H_5

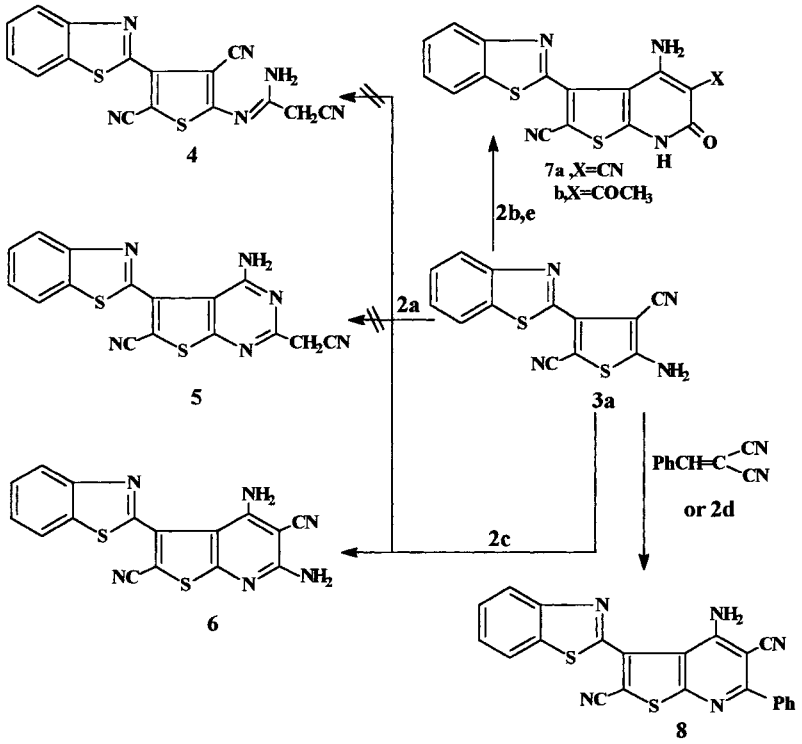
SCHEME 1

TABLE 1 ^{1}H NMR, IR, and Mass Spectroscopic Data

	^{1}H NMR (δ, TMS)	*IR (KBr, cm^{-1})*	*MS (m/z%)*
3a	7.21–7.93 (4H, m), 8.12 (2H, br).	3335, 3193 (NH_2), 2226, 2215 (CN), 1641 (C = N).	282 (M^+, 22), 266 (12), 240 (6) 214 (5), 134 (100), 91 (62).
3b	1.37 (3H, t), 4.41 (2H, q), 7.31–8.32 (6H, m)	3320, 3200 (NH_2), 2235 (CN); 1705 (C = O). 2227, 2218 (CN)	
3c	7.15–7.9 (9H, m).		343 (M^+, 79), 317 (54), 291 (30), 214 (32), 136 (62), 77 (100).
6	7.03(2H, s), 7.4–8.12 (4H, m), 8.35 (2H, br).	3328, 3197 (NH_2), 2235, 2218 (CN).	
7a	7.08–7.86 (4H, m), 8.13 (2H, br), 9.39 (1H, s).	3420, 3280, 3195 (NH_2, NH), 2230, 2220 (CN), 1665 (C = O)	
7b	2.56(3H, s), 7.35–8.0 (6H, m), 9.01 (1H, s).	3410, 3310, 3171 (NH_2, NH), 2225 (CN), 1708, 1660 (C = O), 1636 (C = N).	366 (12), 364 (M^+, 62), 348 (35), 320 (51), 279 (43), 232 (28), 136 (100), 98 (18).
8	7.21–8.36 (11H, m).	3335, 2189 (NH_2), 2223, 2195 (CN)	411 (4), 410 (8), 409 (M^+, 78), 381 (36), 365 (42), 309 (28), 257 (31), 135 (48), 77 (100).
9	2.46 (3H, s), 7.0–7.93 (4H, m), 9.84 (1H, s).	3200 (NH), 2218, 2225 (CN), 1692 (C = O).	
10	2.61 (3H, s), 7.56–7.91 (4H, m), 11.4 (1H, br, exchangeable with D_2O).	3180 (NH), 2221 (CN), 1665 (C = O)	326 (7), 325 (8), 324 (M^+, 46), 296 (61), 254 (39), 228 (51), 135 (81), 108 (100).
11	7.36–8.12 (4H, m), 14.05–14.1 (2H, br, exchangeable with D_2O).	3180, 3100 (NH), 2228 (CN), 1230 (C = S).	
12	2.63 (6H, s), 7.2–8.31 (4H, m)	2220 (CN), 1630 (C = N).	
14	7.35–8.32 (m, 6H, Ar-H and NH_2), 9.31 (1H, s)	3450, 3350, 3196 (OH and NH_2), 2226 (CN)	
15	1.3 (3H, t), 4.32 (2H, q), 7.1–8.12 (4H, m), 8.61 (1H, s)	3003–2940 (CH str.), 2934–2836 (Ali. CH), 2225, 2218 (CN)	
16	7.2–8.12 (5H, m), 8.32 (1H, s), 10.40 (2H, br).	3310, 3210 (NH_2), 2210 (CN)	
17		3380, 3305, 3155 (NH_2, NH), 2220, (CN)	326 (4), 325 (6), 324 (M^+, 16), 308 (32), 267 (100), 241 (18), 136 (76), 108 (31).
18a	5.13 (2H, s), 7.4–8.2 (4H, m), 9.98 (1H, s).	2950 (CH str.), 2223 (CN), 1610 (C = N).	372 (3), 371 (M^+, 28), 345 (33), 211 (72), 135 (76), 76 (100).
18b	4.56(2H, s), 9.36–8.18 (4H, m), 9.82 (1H, s).	2945 (CH, str.), 2228, 2213 (CN), 1613 (C = N).	
18c	1.47 (3H, t), 4.65 (2H, q), 7.21–8.12 (4H, m), 9.52 (1H, s).	2935 (CH, str.), 1703 (C = O), 2221 (CN), 1615 (C = N)	
19	1.45 (3H, t), 4.71 (2H, q), 7.12–8.32 (4H, m), 8.9 (1H, s).	2965 (CH, str.), 2218 (CN), 1710, 1672 (C = O).	

to the amino group, followed by cyclization through nucleophilic attack of the sulfur atom on the cyano group, which subsequently underwent rearrangement to give the pyrimidinedithiole derivative **11** [18,19]. Compound **11** reacted smoothly with methyl iodide in ethanolic solution containing sodium ethoxide to give the *bis*(methylthio) derivative **12** (Scheme 3). The structure of the pyrimidinedithiol **11** was deduced on the basis of analytical and spectral data. Thus, the IR spectrum revealed the presence of two NH groups at 3180 and 3160 cm^{-1}, and one cyano stretching band at 2228 cm^{-1} and another one at 1230 cm^{-1} due to the C = S group, and the ^{1}H NMR spectrum revealed the presence of a D_2O-exchangeable signal at δ 14.05–14.12 ppm due to 2SH protons, in addition to a multiplet signal due to aromatic protons. The structure of *bis*(methylthio) derivative **12** was based on the ^{1}H NMR spectrum, which revealed the presence of a singlet signal at δ = 2.63 ppm due to $2SCH_3$ groups.

Compound **3a** reacted with boiling trichloroacetonitrile to yield the thieno[2,3-*d*] pyrimidine derivative **14** (Scheme 3), presumably via the acyclic intermediate **13**. The trichloromethyl moiety in the intermediate **13** was apparently substituted by a hydroxyl group in the final product **14** during the work up. Ready substitution of a CCl_3 moiety by nucleophiles has been previously reported [20]. The ^{1}H



SCHEME 2

NMR spectrum of it was in agreement with the proposed structure **14** (Table 1).

Reaction of **3a** with triethyl orthoformate afforded the ethoxymethylideneamino derivative **15**. The ^{1}H NMR spectra of **15** revealed the presence of a singlet peak at δ = 8.61 ppm due to the N=CH group. Ammonolysis of **15** in methanol afforded the thieno[2,3-*d*] pyrimidine derivative **16** (Scheme 4). The structure of **16** was supported by spectral data and by synthesis of the same product by the reaction of **3a** with formamide (m.p., mixed m.p., and spectral data). The ^{1}H NMR spectra of **16** revealed a singlet signal at δ = 8.32 ppm due to the pyrimidine H-2 and another one at δ = 10.4 ppm due to the amino group, in addition to aromatic protons.

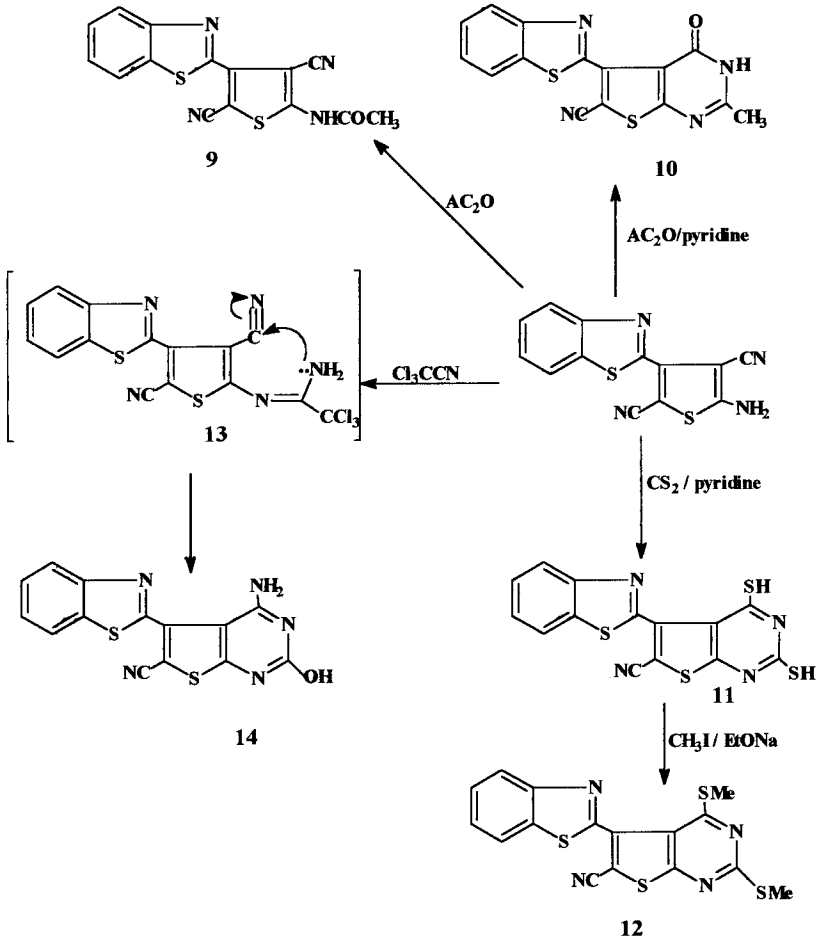
Reaction of **15** with hydrazine hydrate afforded the corresponding thieno[2,3-*d*]pyrimidine derivative **17**. The reaction of **15** with phenylhydrazine under various conditions gave an addition product, from which elimination of ethyl formate phenylhydrazone gave the enaminonitrile **3a** (m.p., mixed m.p., and spectral data). Reaction of **17** with chloroacetyl chloride, ethyl cyanoacetate, or diethyl oxalate afforded 1,2,4-triazolo[1\',5\':1,6]pyrimidino[4,5-*b*]thiophene **18a–c,** respectively. In the ^{1}H NMR spectra of **18a–c**, the signal due to the pyrimidine H-5 ring is clearly apparent between δ 9.52–9.98 ppm, and other signals at δ = 5.13 and 4.56 ppm due to CH_2Cl in **18a** and CH_2CN in **18b**, respectively, are observed. Condensation of **17** with ethyl chloroformate afforded the 1,2,4-triazolo[1\',5\':1,6]pyrimidino[4,5-*b*]thiophene-3-ethoxycarbonyl derivative **19**. The structure of **19** was established based on analytical and spectral data (see Table 1 and 2).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were determined with a Pye Unicam SP 3-300 spectrophotometer (KBr); ^{1}H NMR spectra were determined with a Varian Gemini NMR spectrometer (200 MHz) with tetramethylsilane (TMS) as internal standard (δ in ppm); MS were determined with a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV; Elemental analyses were performed at the Microanalytical Center at Cairo University. 3-(Benzothiazol-2-yl)-3-oxopropanenitrile (**1**) was prepared according to a published procedure [1]. All compounds gave satisfactory elemental analyses (C, H, N, S, Cl).

General Procedure of the Reaction of 3-(Benzothiazol-2-yl)-3-oxoropanenitrile with Active Methyene Reagents **2a–d** *and Sulfur*

A solution of **1** (0.41 g, 2 mmol) in dioxane (25 mL) was treated with the appropriate active methylene



SCHEME 3

reagent (2 mmol) and sulfur (64 mg, 2 mmol) in the presence of a catalytic amount of triethylamine (0.5 mL). The reaction mixture was heated under reflux for 3 to 7 hours (TLC monitoring). The solvent was removed under reduced pressure, and the residue was triturated with ice/water and neutralized with concentrated HCl. The solid product, so formed, was collected by filtration and recrystallized from a suitable solvent (see Table 2).

General Procedure of the Reaction of 2-Amino-4-(benzothiazol-2-yl)thiophene -3,5-dicarbonitrile with **2a–e**

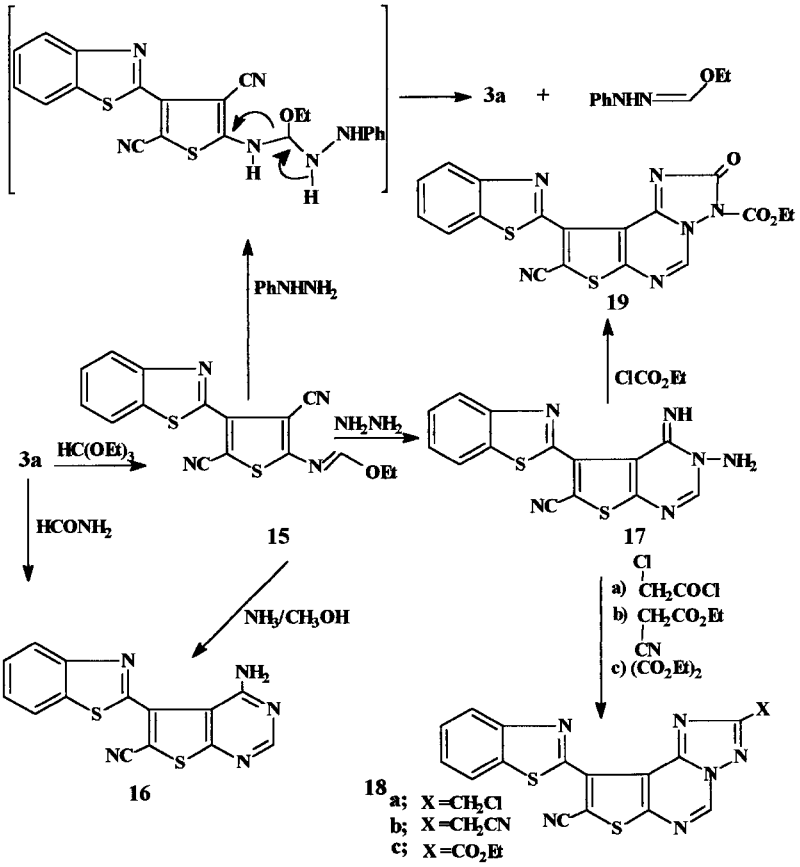
To a mixture of compound **3a** (0.56 g, 2 mmol) and the appropriate active methylene reagents **2a–e** (2 mmol), a few drops of triethylamine catalyst were added. The reaction mixture was fused on an oil bath at 160°C for 2 hours, and during this time the reaction mixture gradually solidified. After cooling, the resulting product in each case was triturated with methanol, and the product was filtered off and recrystallized from a suitable solvent to afford **6, 7a,b**, and **8**.

Reaction of 3a with Benzylidenemalononitrile

To a suspension of sodium metal (0.2 g, 0.01 mol) in dioxane (50 mL), compound **3a** (2.82 g, 0.01 mol) was added. The reaction mixture was heated at reflux for 10 minutes, then benzylidenemalononitrile (1.54 g, 0.01 mol) was added. The solution was heated for 4 hours. The reaction mixture was poured into ice/cold water and acidified with concentrated HCl to pH 7. The solid product was collected by filtration and crystallized from dioxane to give **8** (m.p. and mixed m.p.).

2-Acetamido-4-(benzothiazol-2-yl)thiophene-3,5-dicarbonitrile (**9**)

A mixture of **3a** (1.13 g, 4 mmol) and acetic anhydride (30 mL) was refluxed for 5 hours, then cooled and poured onto crushed ice. The solid product thus



SCHEME 4

TABLE 2 Physical Data

	Yield (%)	*m.p (°C)*	*Color*	*Solvent*	*Mol. Formula (M. wt.)*
3a	83	255	Brown	DMF/ethanol	282.355
3b	59	175	Yellow	DMF/methanol	329.409
3c	61	296–297	Brown	DMF/ethanol	343.437
6	76	292–293	Brown	DMF	348.420
7a	71	263–264	Light brown	Dioxane	349.404
7b	68	274–275	Brown	Dioxane	366.431
8	61	296–298	Deep brown	DMF	409.502
9	68	263–264	Pale yellow	Acetic acid	324.393
10	52	>300	Brown	Acetic acid	324.393
11	68	286–287	Pale yellow	DMF/ethanol	358.498
12	83	219–220	Yellow	Dioxane	386.552
14	56	>300	Light brown	DMF/ethanol	325.382
15	61	202–203	Pale yellow	Ethanol	338.672
16	85	>300	Brown	DMF	309.672
17	81	282–283	Brown	Dioxane	324.398
18a	71	296–298	Light red	DMF	382.869
18b	62	>300	Brown	DMF	373.431
18c	56	261–262	Yellow	DMF	406.458
19	62	>300	brown	DMF/ethanol	422.458

formed was filtered off, washed several times with water, and recrystallized from acetic acid.

5-(Benzothiazol-2-yl)-6-cyano-2-methyl thieno[2,3-d]pyrimidine-4-(3H)-one (**10**)

A solution of **3a** (1.3 g, 4 mmol) was refluxed in acetic anhydride/pyridine mixture (30 mL, 2:1 v/v) was heated on a water bath for 15 hours. It was then cooled and poured into an ice/water mixture. The solid product thus formed was filtered off, washed several times with cold water, and recrystallized from acetic acid.

5-(Benzothiazol-2-yl)-6-cyano thieno[2,3-d]pyrimidine-2,4-dithiol (**11**)

A solution of **3a** (1.13 g, 4 mmol) in a mixture of dry pyridine (25 mL) and carbon disulphide (10 mL) was refluxed on a water bath for 8 hours and allowed to stand at room temperature for two days. The solution was then triturated with aqueous ethanol (50

mL). The precipitated solid was filtered off and recrystallized from DMF.

5-(Benzothiazol-2-yl)-2,4-bis(methylthio)thieno-[2,3-d]pyrimidine-6-carbonitrile (**12**)

A mixture of **11** (0.36 g, 1 mmol) and methyl iodide (2 mL) was dissolved in an ethanolic solution of sodium ethoxide prepared from sodium metal (0.023 g, 0.001 g-atom) and ethanol (20 mL). The reaction mixture was heated under reflux for 2 hours, concentrated, cooled, diluted with water, and left overnight. The precipitate obtained was filtered off, washed with water, and recrystallized from dioxane.

4-Amino-5-(benzothiazol-2-yl)-2-hydroxy thieno[2,3-d]pyrimidine-6-carbonitrile (**14**)

A mixture of **3a** (0.56 g, 2 mmol) and trichloroacetonitrile (2 mmol) was dissolved in (20 mL) of dimethylformamide, the reaction being catalyzed by (0.5 mL) of triethylamine. The reaction mixture was heated under reflux for 5 hours, after which it was left to cool overnight. On dilution with cold water and acidification with cold HCl (if necessary), the precipitate obtained was filtered off, washed with aqueous ethanol, and recrystallized from DMF.

4-(Benzothiazol-2-yl)-2-ethoxymethyleneamino thiophene-3,5-dicarbonitrile (**15**)

A mixture of **3a** (5.64 g, 20 mmol) and triethyl orthoformate (3 mL, 20 mmol) was refluxed for 2 hours. On cooling, a pale brown precipitate was filtered off and recrystallized from ethanol.

4-Amino-5-(benzothiazol-2-yl)thieno[2,3-d]pyrimidine-6-carbonitrile (**16**)

Method A: Compound **15** (1.35 g, 4 mmol) was treated with methanolic ammonia (50 mL) at room temperature for 72 hours. The separated solid was collected and recrystallized from DMF.

Method B: A mixture of **3a** (1.13 g, 4 mmol) and formamide (10 mL) was refluxed for 2 hours. After cooling, the precipitated brown crystalline product was filtered off, washed several times with cold ethanol, and recrystallized from DMF to give **16** (m.p. and mixed m.p.).

3-Amino-5-(Benzothiazol-2-yl)-4-imino-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonitrile (**17**)

A mixture of **15** (1.35 g, 4 mmol) and hydrazine hydrate (0.4 mL, 8 mmol) was heated in an open tube at 200°C for 15 minutes. On trituration with ether and on concentration, compound **17** was obtained, filtered off, and recrystallized from dioxane.

Reaction of **15** *with Phenylhydrazine*

Compound **15** (1.35 g, 4 mmol) was reacted with phenylhydrazine (0.5 mL, 4 mmol) according to the procedure described for **17** to give **3a**. A m.p. and mixed m.p. determination with an authentic sample gave no depression.

9-(Benzothiazol-2-yl)-2-substituted-[1,2,4]-triazolo[1',5':1,6]pyrimidino[4,5-b]thiophene-8-carbonitrile (**18a–c**)

To a mixture of compound **17** (1.3 g, 4 mmol) and chloroacetyl chloride, ethyl cyanoacetate or diethyl oxalate (4 mmol) containing a few drops of dry pyridine were added. The reaction mixture was fused on an oil bath at 150°C for 1 hour, and during this time the reaction mixture gradually solidified. After cooling, the resulting product in each case was triturated with a suitable solvent, and the product was filtered off and recrystallized from suitable solvent to afford **18a–c**, respectively.

Ethyl 9-(benzothiazol-2-yl)-8-cyano-2-oxo-[1,2,4]-triazolo[1',5':1,6]pyrimidino [4,5-b]thiophene-3-carboxylate (**19**)

The ester **19** was prepared by the reaction of **17** (1.28 g, 4 mmol) with ethyl chloroformate (0.5 g, 4 mmol) according to the procedure used for the synthesis of **18a–c**.

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