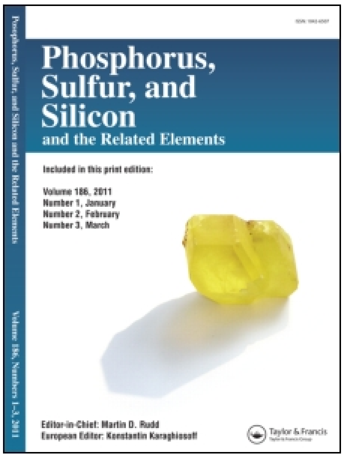

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Pokhodylo, Nazariy T. , Shyyka, Olga Ya. , Savka, Roman D. and Obushak, Mykola D.(2010) 'Novel Selected Tandem Transformations of the Amino and Carbonyl/Nitrile Groups in the Gewald Thiophenes', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 10, 2092 — 2100

To link to this Article: DOI: 10.1080/10426500903496739

URL: http://dx.doi.org/10.1080/10426500903496739

Phosphorus, Sulfur, and Silicon, 185:2092–2100, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903496739

NOVEL SELECTED TANDEM TRANSFORMATIONS OF THE AMINO AND CARBONYL/NITRILE GROUPS IN THE GEWALD THIOPHENES

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Novel transformations of the amino and carbonyl/nitrile groups in the Gewald thiophenes were studied for thienopyrimidine synthesis. It was found that 2-amino-thiophene-3-carboxamides and ethyl 2-(acetylamino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate did not yield tetrazole derivatives, neither in the reaction with triethyl orthoformate and sodium azide, nor in the reaction with phosphorus oxychloride and sodium azide, correspondingly. On the contrary, derivatives of thieno[2,3-d]pyrimidin-4(3H)-one and thieno[2,3-d][1,3]oxazin-4-one were isolated. New 2-azidothiophenes [2-azido-4,5,6,7-tetra hydro-1-benzothiophene-3-carbonitrile and 2-azido-4,5,6,7-tetrahydro-1-benzothiophen-3-yl(phenyl)methanone] were synthesized and used in anionic domino reactions with activated acetonitriles to yield thieno[3,2-e][1,2,3]triazolo[1,5-a]pyrimidines and/or 2-(5-amino-1H-1,2,3-triazol-1-yl)thiophenes. Finally, a new ring system of thieno[3,2-e]pyrazolo[1,5-a]pyrimidine was synthesized via a domino reaction of ethyl 2-[(2Z)-2-(1-chloro-2-ethoxy-2-oxoethylidene)hydrazino]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate with activated acetonitriles.

Keywords Domino reactions; thienopyrimidines, thieno[3,2-*e*]pyrazolo[1,5-*a*]pyrimidines; thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines

INTRODUCTION

The derivatives of condensed pyrimidines have been of great interest for many years due to the fact that many bicyclic compounds containing the pyrimidine ring play an important role in biological processes. Thienopyrimidines, as one of such ring systems, are a focus of research because of their biological activity.[1] Recently, thieno[2,3-*d*]pyrimidin-4-one derivatives have been discovered as moderately potent inhibitors of TGase 2 (tissue transglutaminase),[2] novel selective and potent α_{1D} antagonists,[3] cytotoxic agents selective for p21-deficient cells,[4] highly potent dual 5-HT_{1A} and 5-HT_{1B} antagonists as potential antidepressant drugs,[5] and necroptosis inhibitors, and they have shown equipotent analgesic and anti-inflammatory activities.[7] Some derivatives of thienopyrimidines have also found

Received 18 October 2009; accepted 18 November 2009.

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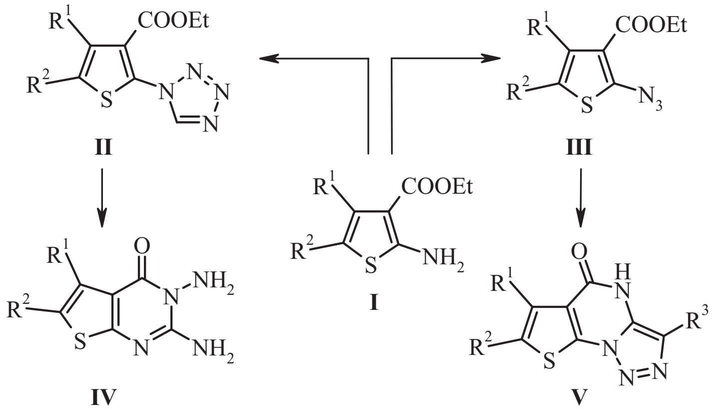
application in technical aims—as novel ionophores in plasticized poly(vinyl chloride) matrix membrane sensors for uranyl ions[8] and as fluorescent dyes for biomolecule detection.[9] This is probably due to the fact that many compounds can be readily prepared from a diverse array of the Gewald 2-aminothiophenes via tandem transformation of the amino and carbonyl/nitrile groups providing annulation of new ring systems containing nitrogen heterocycles.

We are currently interested in the novel application of the amino group in the Gewald 2-aminothiophenes, which opens access for design of the thienopyrimidine framework.[10,11] In our previous articles, we described transformation of the animo group in alkyl 2-aminothiophene-3-carboxylates **I** into the tetrazole ring **II** and the azido moiety **III**, and their utilization in the synthesis of hardly available 2,3-diaminopyrimidines **IV** and a new ring system of thieno[3,2-*e*][1,2,3]triazolo[1,5-a]pyrimidines **V**, correspondingly (Scheme 1). Such reactions have received attention because of their application in the synthesis of new nitrogen-containing heterocyclic compounds in a readily synthetic protocol.

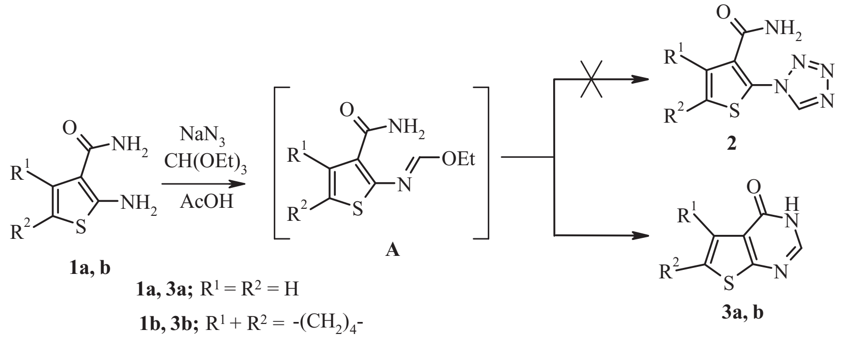


Scheme 1

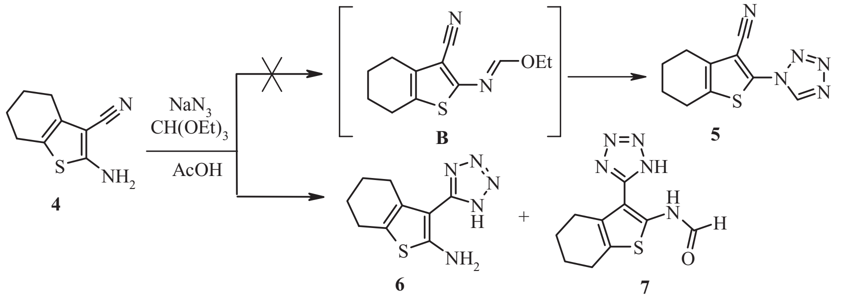
RESULTS AND DISCUSSION

Due to the importance of thienopyrimidines and our interest in the development of a synthetic path for their preparation, in this article we report the application of 3-(cyano, carbamoyl and phenylcarbonyl)-2-aminothiophenes in the above mentioned approaches and the chemoselectivity problems accompanying them.

First of all, we used cyano, carbamoyl derivatives in the reaction with triethyl orthoformate and sodium azide for tetrazole derivative synthesis. It was found that replacement of the carboxylic group by the carbamoyl one did not yield the tetrazole ring due to the concurrent formation of the pyrimidine ring (Scheme 2). The internal nucleophile (a nitrogen atom in the amide group) placed near the reaction center (an azomethine carbon atom in intermediate **A**) attacks it faster than azide ion. Variation of the temperature modes of this reaction does not lead to tetrazole compounds. Formation of the pyrimidine ring is easily estimated via ^{1}H NMR spectroscopic analyses. The characteristic 2-H proton signal was found at 7.83 ppm instead of the expected tetrazole one at approximately 10 ppm.



Scheme 2

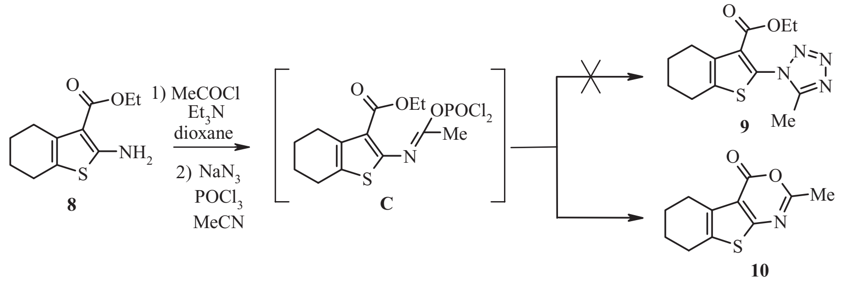


Scheme 3

Furthermore, in case of the compound **4** under the same conditions, 1,3-dipolar cycloaddition of the cyano group with azide ion occurred more rapidly than the formation of intermediate **B** (Scheme 3). As a result, 5-substituted tetrazoles **6** and **7** were extracted from the reaction mixture. Obviously, formation of the electron-deficient tetrazole ring decreases reactivity of the amino group, which is proven by low yields of the compound **7**. It is noteworthy that alkyl 2-aminothiophene-3-carboxylates gave tetrazole derivatives (type **5**) in approximately 80% yields.[10]

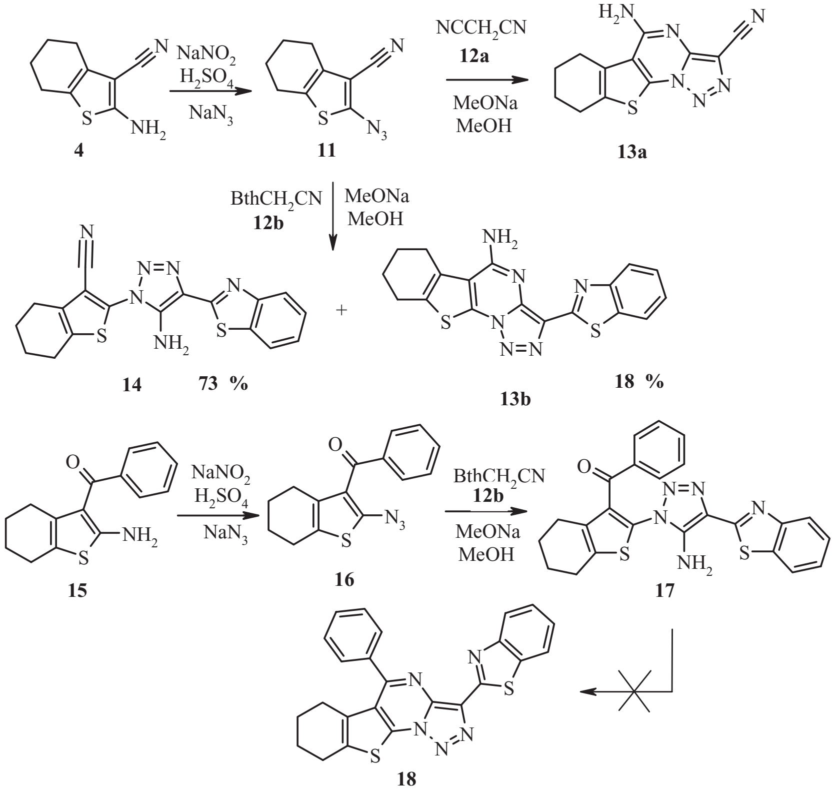
Unexpectedly the reaction occurred when ethyl 2-(acetylamino)thiophene-3-carboxylates were used for the synthesis of 1,5-disubstitutied tetrazole derivatives by the one-pot reaction with phosphorus oxychloride and sodium azide (Scheme 4).[12] It is likely that a concurrent reaction involving the carboxylate moiety proceeded in the same manner, as in case of the compound **3**. Closure of intermolecular reaction centers in intermediate **C** provided oxazinone derivative formation. In addition, the reaction was accompanied by isolation of tarry products, which complicate separation of the product **10**.

Afterwards we decided to explore the feasibility of the synthesis of 2-azidothiophenes and their application in the thieno[3,2-*e*][1,2,3]triazolo[1,5-a]pyrimidine system preparation by anionic domino reactions. New azides **11** and **16** were obtained by the diazotization of amines **4** and **15** with sodium nitrite in sulfuric acid, followed by treatment with sodium azide. In case of the compound **1b,** its diazotization led to intermolecular cyclization of diazonium salt, yielding thieno[2,3-*d*]-1,2,3-triazine, as described by Santer and Deinhammer.[13] Attempts to transform it into an azide did not give a positive result. Moreover, yields



Scheme 4

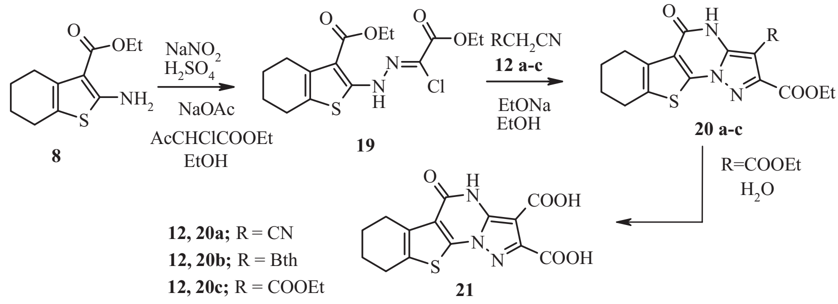
of azides **11** and **16** were poorer than those of ethyl 2-azido-3-thiophenecarboxylates described in Pokhodylo et al.[11] Azides **11** and **16** were allowed to react with propanedinitrile **12a** and 1,3-benzothiazol-2-ylacetonitrile **12b**, which were selected due to the fact that they exhibited high reactivity in such reactions.[11] Under these conditions, the cycloaddition reaction proceeded smoothly to completion at room temperature, and triazoles were isolated in good yields and high purity after simple filtration. However, domino reaction occurred satisfactorily in case of the compound **13a**. On the contrary, 1,3-benzothiazol-2-ylacetonitrile **12b** reacted with azide **11** to form thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **13b** as a



Scheme 5

minor product at 18% yield and noncyclic aminotriazole **14** at 73% yield, respectively. Furthermore, aminotriazole **17**, instead of the expected thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **18**, was isolated in the reaction of azide **16**. Our attempts to cyclize the compound **17** into pyrimidine were unsuccessful. This is possibly due to weak reactivity and a sterically shielded carbonyl group. Moreover, low solvation of compounds **13** and **17** complicated their further transformations (Scheme 5).

As a continuation of our interest in the synthesis of novel polycyclic thienopyrimidine systems, one-pot synthesis of the title thieno[3,2-*e*]pyrazolo[1,5-*a*]pyrimidine compounds via reaction of hydrazonoyl halides **19** with activated acetonitriles was studied. Such an approach has been used previously for construction of pyrazolo[1,5-*a*]quinazoline by Evdokimoff.[14] By the coupling of ethyl 2-chloro-3-oxobutanoate with the diazotized arylamine **8** in NaOAc-buffered solution of EtOH, hydrazonoyl chloride **19** was synthesized (Scheme 6). Treatment of hydrazonoyl chloride **19** with ethyl cyanoacetate, propanedinitrile, or 1,3-benzothiazol-2-ylacetonitrile in ethanolic sodium ethoxide solution at room temperature afforded products **20a–c**, respectively. Compound **20c** without isolation underwent hydrolysis to form dicarboxylic acid **21** in moderate yields. The structures of the isolated products were established by analytical and spectroscopic data.



Scheme 6

In conclusion, having established some chemical modifications of the Gewald 2-aminothiophenes, we determined the scope of their synthetic application in various thienopyrimidines preparation.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H). The ^{1}H chemical shifts were reported in parts per million relative to tetramethylsilane or deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Compounds **1b**, **4**, **8**, and **15** were prepared according to the method of Gewald et al.[15]

Reaction Conditions for Preparation of Compounds 3a,b and Mixtures 6 and 7

A suspension of 5 mmol of the required thiophene **1a,b** or **4**, triethyl orthoformate (3.79 mL, 0.023 mol), and sodium azide (0.39 g, 0.006 mol) in glacial acetic acid (4 mL) was stirred and heated under reflux for 2 h. The reaction mixture was cooled to room temperature, and 0.7 mL of conc. HCl was added. The solid was filtered off, the filtrate was evaporated, and the residue was recrystallized from ethanol.

Thieno[2,3-*d*]pyrimidin-4(3*H*)-one 3a. Yield: 0.46 g (61%); white solid; mp 245–247°C. (lit.[16] 246–247°C).

5,6,7,8-Tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one 3b. Yield: 0.75 g (73%); white crystals; mp 256–257°C (lit.[1] 255–257°C). ^{1}H NMR (DMSO-d_6): δ 1.73–1.93 (m, 4H, CH_2), 2.75 (t, $J = 5.6$ Hz, 2H, CH_2), 2.90 (t, $J = 5.8$ Hz, 2H, CH_2), 7.83 (s, 1H, CH), 12.16 (br.s, 1H, NH). (In ref.[17] ^{1}H NMR (300 MHz, $CDCl_3$): 1.86 (4H, d, J = 6 Hz, CH_2 at 6 and 7), 2.86 (2H, s, CH_2 at 5), 3.02 (2H, s, CH_2 at 8), 7.24 (1H, s, CH at 2), 8.07 (1H, br d, J = 6.0 Hz, NH at 3).

3-(2*H*-Tetrazol-5-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-amine 6. Yield: 0.54 g (49%); white crystals; mp 171–172°C (dec.). ^{1}H NMR (DMSO-d_6): δ 1.82 (br.s, 4H), 2.93 (br.s, 4H), 5.65 (br.s, 2H). MS (CI): m/z (%) = 222 (100%) [M+H$^+$]. Anal. requires for $C_9H_{11}N_5S$ (221.29) calcd./found: C, 48.85/49.04; H, 5.01/5.14; N, 31.65/31.44.

***N*-[3-(2*H*-Tetrazol-5-yl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]formamide 7.** Yield: 0.25 g (20%); white crystals; mp 194–195°C (dec.). ^{1}H NMR (DMSO-d_6): δ 1.89 (br.s, 4H), 2.66 (br.s, 2H), 2.80 (br.s, 2H), 8.45 (s, 1H), 12.37 (s, 1H). MS (CI): m/z (%) = 250 (100%) [M+H$^+$]. Anal. requires for $C_{10}H_{11}N_5OS$ (249.30) calcd./found: C, 48.18/48.45; H, 4.45/4.28; N, 28.09/27.91.

Synthesis of 2-Methyl-5,6,7,8-tetrahydro-4*H*-[1]benzothieno[2,3-*d*][1,3]-oxazin-4-one 10

Ethyl 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate **8** (2.25 g, 0.01 mol) was dissolved in dioxane, and Et_3N (0.7 mL, 0.01 mol) was added. The mixture was cooled to 0°C, and acetyl chloride (0.71 mL, 0.01 mol) was added while keeping the temperature below 5°C. The solution was left at room temperature for 1 h, and H_2O (5 mL) was then added. The obtained solid was filtered, washed with H_2O, crystallized (EtOH), and dried in vacuo.

The mixture of obtained the acetamide (0.01 mol) with NaN_3 (1.3 g, 0.02 mol) and $POCl_3$ (7.7 g, 0.05 mol) in MeCN (50 mL) was stirred under reflux for 10 h. The solvent and excess $POCl_3$ were removed under reduced pressure. The residue was cooled, neutralized with sat. $NaHCO_3$ solution, and evaporated to dryness. Compounds **10** were extracted and crystallized from EtOH. Yield: 0.40 g (18%); white crystals; mp 133–134°C. (lit.[18] 132.0–132.5°C).

General Procedure for the Synthesis of 2-Azidothiophenes 11 and16

The appropriate 2-aminothiophene **4** or **15** (0.02 mol) was dissolved in concentrated sulfuric acid (5 mL), and ice (15 g) was added. When the mixture was cooled to 0°C, the saturated sodium nitrite (1.73 g, 0.025 mol) aqueous solution was added while keeping the temperature below 5°C. After 10 min, any resinous sediment that has formed should be filtered. To the filtrate solution of the diazonium salt, sodium azide (1.3 g, 0.02 mol) in water (5 mL) was added dropwise. The solution was left for 15 min at room temperature, and azide was extracted by diethyl ether (3 × 10 mL). Ether was evaporated in vacuo. Azides were used without subsequent cleaning: **11**, yield 2.16 g, 53%; yellow solid, mp:

83–84°C (dec.); MS (m/z): 205 [M+H$^+$]; **16**, yield 2.32 g, 41%; dark red oil; MS (m/z): 284 [M+H$^+$].

General Procedure for the Synthesis of 1,2,3-Triazoles 13a,b, 14, and 17

To a solution of sodium methoxide (540 mg, 10.0 mmol) in dry methanol (20 mL), the substituted acetonitrile **12** (10.0 mmol) was added. To this solution, 2-azidothiophene **11** or **16** (10.0 mmol) in dry methanol (2 mL) was added dropwise, and the solid started to precipitate. The mixture was stirred for 24 h. The resulting suspension was filtered, and the solid product was washed with water and methanol to give the corresponding compounds **13a,b**, **14**, and **17**.

5-Imino-4,5,6,7,8,9-hexahydro[1]benzothieno[3,2-*e*][1,2,3]triazolo[1,5-*a*] pyrimidine-3-carbonitrile 13a. Yield: 1.94 g (72%); white crystals; mp >300°C. ^{1}H NMR (DMSO-d_6): δ 1.75–2.01 (m, 4H), 2.86–3.09 (m, 4H), 6.55 (br.s, 1H). MS (CI): m/z (%) = 271 (100%) [M+H$^+$]. Anal. requires for $C_{12}H_{10}N_6S$ (270.32) calcd./found: C, 53.32/53.13; H, 3.73/3.61; N, 31.09/31.28.

3-(1,3-Benzothiazol-2-yl)-6,7,8,9-tetrahydro[1]benzothieno[3,2-*e*][1,2,3] triazolo[1,5-*a*]pyrimidin-5(4*H*)-imine 13b. Yield: 0.68 g (18%); white crystals; mp >300°C. ^{1}H NMR (DMSO-d_6): δ 1.89–1.94 (m, 4H), 2.79–2.84 (m, 2H), 2.95–3.01 (m, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H). MS (CI): m/z (%) = 379 (100%) [M+H$^+$]. Anal. requires for $C_{18}H_{14}N_6S_2$ (378.48) calcd./found: C, 57.12/57.27; H, 3.73/3.61; N, 22.20/22.28.

2-[5-Amino-4-(1,3-benzothiazol-2-yl)-1*H*-1,2,3-triazol-1-yl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile 14. Yield: 2.76 g (73%); white crystals; mp >300°C. ^{1}H NMR (DMSO-d_6): δ 1.81–1.89 (m, 4H), 2.70 (br.s, 2H), 3.06 (br.s, 2H), 6.88–6.96 (br.s, 1H, NH_2), 7.26 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.92 (d, J = 8.6 Hz, 2H) MS (CI): m/z (%) = 379 (100%) [M+H$^+$]. Anal. requires for $C_{18}H_{14}N_6S_2$ (378.48) calcd./found: C, 57.12/57.04; H, 3.73/3.56; N, 22.20/22.16.

{2-[5-Amino-4-(1,3-benzothiazol-2-yl)-1*H*-1,2,3-triazol-1-yl]-4,5,6,7-tetrahydro-1-benzothien-3-yl}(phenyl)methanone 17. Yield: 3.89 g (85%); white crystals; mp >300°C. ^{1}H NMR (DMSO-d_6): δ 1.57–1.73 (m, 2H), 1.81–2.01 (m, 2H), 2.08–2.27 (m, 2H), 2.77–3.04 (m, 2H), 7.51–7.65 (m, 7H, NH_2 + Ph), 7.68 (t, J = 7.6 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H). MS (CI): m/z (%) = 458 (100%) [M+H$^+$]. Anal. requires for $C_{24}H_{19}N_5OS_2$ (457.58) calcd./found: C, 63.00/62.85; H, 4.19/4.09; N, 15.31/15.48.

Preparation of Ethyl 2-[2-(1-Chloro-2-ethoxy-2-oxoethylidene) hydrazino]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate 19

To the solution of ethyl 2-chloro-3-oxobutanoate (3.29 g, 0.02 mol) in EtOH 100 mL sodium, acetate trihydrate (25 g) was added. The mixture was cooled to 0°C and treated with a cold solution of diazonium salt prepared by diazotizing an amine **8** (0.02 mol) dissolved in concentrated sulfuric acid (5 mL) and ice (15 g) with a saturated sodium nitrite (1.73 g, 0.025 mol) aqueous solution while keeping the temperature below 5°C. The addition of the diazonium salt was carried out with rapid stirring over a period of 20 min. The reaction mixture was kept basic by the addition, when necessary, of more NaOAc. When the addition was complete, the mixture was left for 1 h. Water was added, and the resulting red solid was removed by filtration and washed with H_2O. The crude product was crystallized from hexane. Yield: 5.02 g (71%); red crystals; mp 91–93°C. ^{1}H NMR (DMSO-d_6): δ 1.36 (t, J = 7.1 Hz, 6H), 1.71–1.84 (m, 4H), 2.60 (m, 2H), 2.71 (m, 2H), 4.30 (q, J = 7.1 Hz, 4H), 11.21 (s, 1H). MS (CI): m/z (%) = 360 (100%) [M+H$^+$]. Anal. requires for $C_{15}H_{19}ClN_2O_4S$ (358.85) calcd./found: C, 50.21/49.03; H, 5.34/5.21; N, 7.81/7.99.

General Procedure for the Thieno[3,2-*e*]pyrazolo[1,5-*a*]pyrimidines 20a,b,c

To a solution of sodium ethoxide (680 mg, 10.0 mmol) in dry ethanol (20 mL), the substituted acetonitrile **12** (10.0 mmol) was added. To this solution, hydrazonoyl chloride **19** (3.58 g, 10.0 mmol) in dry methanol (2 mL) was added dropwise, and a solid started to precipitate. The resulting suspension was filtered, and the solid product was washed with water and methanol.

Ethyl 3-cyano-5-oxo-4,5,6,7,8,9-hexahydro[1]benzothieno[3,2-*e*]pyrazolo[1,5-*a*]pyrimidine-2-carboxylate 20a. Yield: 1.85 g (54%); white crystals; mp >300°C. ^{1}H NMR (DMSO-d_6): δ 1.40 (t, J = 7.2 Hz, 3H), 1.81–1.89 (m, 4H), 2.69–2.76 (m, 2H), 2.92–2.98 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H). MS (CI): m/z (%) = 343 (100%) [M+H$^+$]. Anal. requires for $C_{16}H_{14}N_4O_3S$ (342.38) calcd./found: C, 56.13/56.32; H, 4.12/4.01; N, 16.17/16.36.

Ethyl 3-(1,3-benzothiazol-2-yl)-5-oxo-4,5,6,7,8,9-hexahydro[1]benzothieno[3,2-*e*]pyrazolo[1,5-*a*]pyrimidine-2-carboxylate 20b. Yield: 3.10 g (69%); white crystals; mp >300°C. ^{1}H NMR (DMSO-d_6): δ 1.45 (t, J = 7.2 Hz, 3H), 1.79–1.87 (m, 4H), 2.72–2.78 (m, 2H), 2.90–2.96 (m, 2H), 4.46 (q, J = 7.2 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.93 (d, J = 7.4 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H). MS (CI): m/z (%) = 452 (100%) [M+H$^+$]. Anal. requires for $C_{22}H_{18}N_4O_3S_2$ (450.54) calcd./found: C, 58.65/58.59; H, 4.03/4.19; N, 12.44/12.29.

5-Oxo-4,5,6,7,8,9-hexahydro[1]benzothieno[3,2-*e*]pyrazolo[1,5-*a*]pyrimidine-2,3-dicarboxylic Acid 21

The mixture (prepared as mention above for compounds **20**) was kept in an ice water bath for 3 h and then slowly heated under reflux for 1 h. The solid precipitated. Hot water was added to dissolve the precipitate (50 mL), and if necessary, a solution of sodium hydroxide should be added to pH 11–12 and heated under reflux for 1 h. The hot solution was poured to a concentrated HCl (10 mL) and left to crystallize. The obtained solid was filtered, washed with water twice, and crystallized from ethanol. Yield: 1.36 g (41%); white crystals; mp 274°C (dec.). ^{1}H NMR (DMSO-d_6): δ 1.84 (m, 4H), 2.77 (m, 1H), 2.93 (m, 1H). MS (CI): m/z (%) = 334 (100%) [M+H$^+$]. Anal. requires for $C_{14}H_{11}N_3O_5S$ (333.32) calcd./found: C, 50.45/50.68; H, 3.33/3.16; N, 12.61/12.41.

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