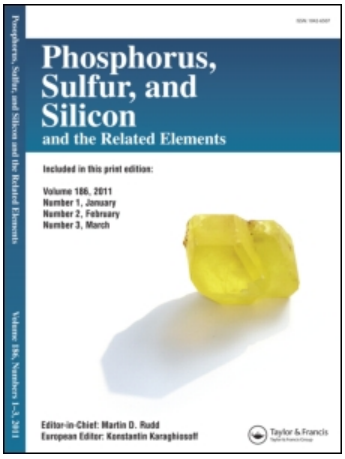

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Heterocyclization of Orthoaminoester and Orthoamino-nitrile-thieno[2, 3-*c*]pyridine: The Facile Synthesis of Fused Pyridothienopyrimidines

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Heterocyclization of Orthoaminoester and Orthoamino-nitrile-thieno[2,3-*c*]pyridine: The Facile Synthesis of Fused Pyridothienopyrimidines

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*A highly efficient and versatile synthetic approach to the synthesis of pyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidines (**4**, **14**, **15**, **21**) and their heterofused (e.g., triazolo-, triazino-, imidazo-, and tetrazolo-,) pyridothienopyrimidines (**5–9**, **16**, **17**, **22–24**) is described utilizing 2-amino-3-cyano-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-6-carboxylic acid ethyl ester (**2**) and diethyl 2-isothiocyanate-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (**10**) as starting materials.*

Keywords Cyclization; heterofused; hydrazine hydrate; orthoaminoester; orthoaminonitrile

Orthomino, *o*-isothiocyanate, -ester, and orthoaminocyano thiophene derivatives have been found to be important intermediates in the chemistry of pyrimidine. Therefore, they have attracted much attention during recent years.[1–9] The resulting pyrimidine derivatives have found a wide application in a variety of synthetic transformations. Various heterocycles have been built to produce the corresponding fused pyrimidines, which show marked biological activities,[10–13] and these interesting activities have driven our work during the last few years, for which we have been interested in the synthesis of fused pyrimidines.[14–19] The present article follows that line of research by reporting on a new series of reactions leading the formation of fused pyridothienopyrimidines starting from the bi-functional *o*-amino-ester and -nitrile compounds.

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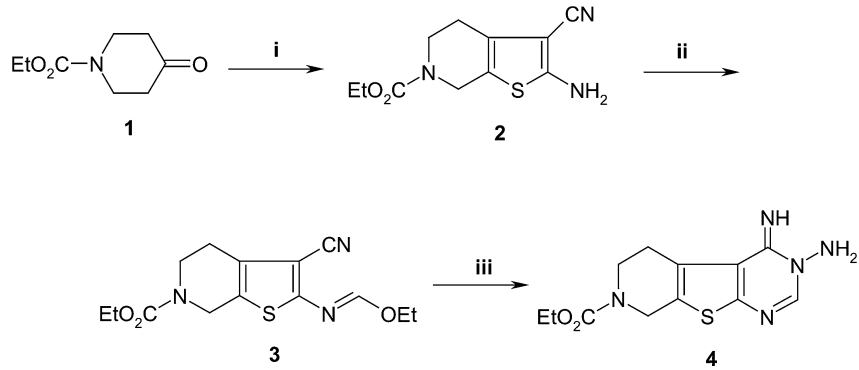
RESULTS AND DISCUSSION

In connection with our interest to study the chemistry of pyrimidines, we have devised the following route for the efficient synthesis of heterofused, 1,2,4-triazoles and 1,2,4-triazine by novel methods. The key compound 2-amino-3-cyano-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-6-carboxylic acid ethyl ester (**2**) was synthesized by the condensation of *N*-carbethoxy-4-piperidone (**1**), sulfer, and malononitrile following the Gewald synthesis.[20]

The synthesis of model compounds pyridothienopyrimidine **4** and heterofused triazino- and triazolo-derivatives **5–9** required the condensation of compound **2** with triethylorthoformate in the presence of a catalytic amount of acetic anhydride to give 2-ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-6-carboxylic acid ethyl ester (**3**). The treatment of compound **3** with hydrazine hydrate in ethanol at r.t. afforded the target 3-amino-4-imino-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**4**) in an 85% yield (Scheme 1).

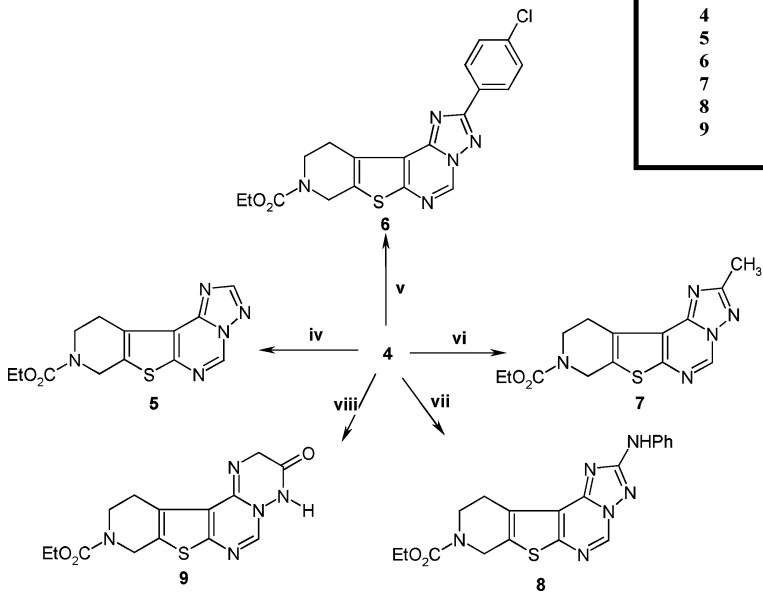


SCHEME 1

The structure of compound **4** was established by ^{1}H, ^{13}C-NMR, and IR spectra as well as elemental analysis. The elemental analysis was consistent with a molecular formula of $C_{12}H_{15}N_5O_2S$. The IR spectroscopy of **4** showed absorption bands at 3300–3200 and 1680 cm^{-1} related to the NH_2, NH, and carbonyl group, respectively. The ^{1}H-NMR showed two broad singlets at $\delta_H = 5.60$ and 7.93 ppm, assigned to the NH_2 and NH-imino protons, respectively. The ^{13}C-NMR supported the ^{1}H-NMR spectroscopy by the appearance of three signals at $\delta_C = 151.31$, 154.62, and 156.09 ppm, corresponding to C-2, C=NH, and C=O present in compound **4**.

Interestingly, on condensation of **4** with triethylorthoformate, the corresponding 9,10-dihydropyrido[4′3′,4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,2-*f*]pyrimidine-8(7H)-carboxylic acid ethyl ester (**5**) was obtained in an 84% yield. Similarly, the triazolo derivatives **6**, **7**, and **8** were prepared by the interaction of **4** with *p*-chloro-benzaldehyde, acetic anhydride, and phenyl isothiocyanate, respectively. On the other hand, the 1,2,4-triazino moiety was built in compound **9** by the treatment **4** with chloroacetyl chloride in DMF catalyzed by triethylamine (Scheme 2).

Compound	Yield %
3	80
4	85
5	84
6	90
7	88
8	72
9	75

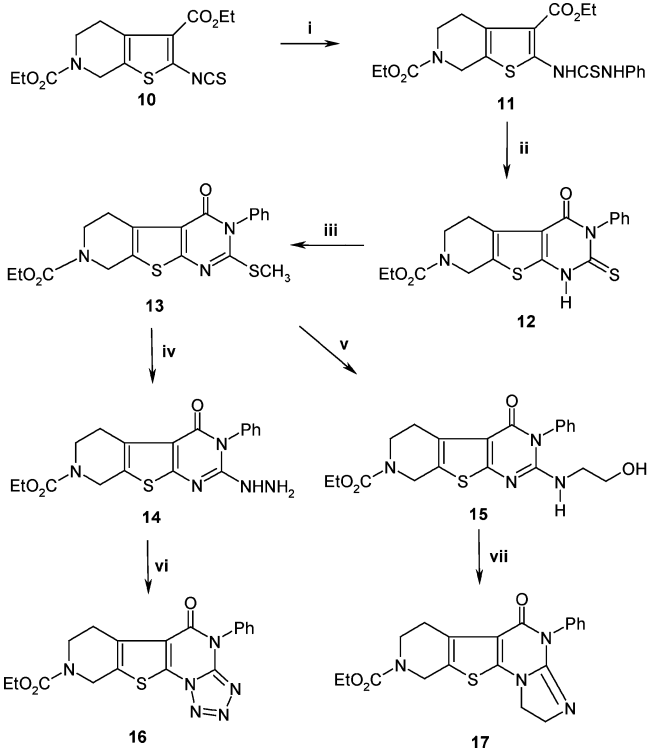


SCHEME 2 *Reagents and conditions:* i: $CH_2(CN)_2$, S, morpholine, EtOH. r.t.; ii: $CH(OEt)_3$, Ac_2O, reflux 8 h; iii: $N_2H_4{\cdot}H_2O$, EtOH, stirring 2 h; iv: $CH(OEt)_3$, Ac_2O, reflux 3 h; v: P-chlorobenzaldehyde, AcOH, reflux 3 h; vi: Ac_2O, reflux 3 h; vii: PhNCS, pyridine, reflux 4 h; viii: $ClCH_2COCl$, DMF, Et_3N, stirring 5 h.

The ^{1}H-NMR and IR were used to identify the 1,2,4-triazolo compounds **5–8**; neither IR or ^{1}H-NMR spectra supported the presence of the NH and NH_2 group protons that existed in **4**. Moreover, the ^{1}H NMR spectra revealed two singlet signals at $\delta_H = 9.42$ and 2.68 ppm, which were assigned to the triazolo proton in compound **5** and CH_3-protons in compound **7**, respectively. The ^{1}H-NMR spectra showed two

double-doublets and a multiplet at $\delta_H = 7.63$, 7.95, and 7.11–7.52 ppm, corresponding to aromatic protons related to compounds **6** and **8**, respectively.

Promoted by the presence of the bifunctional *ortho*-amino and -ester groups, which is considered as a precursor for the preparation of the thioxopyrimidinone derivative **12** by the reaction of diethyl 2-isothiocyanate-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (**10**)[14] with aniline in dichloromethane to give the open-form **11**. The latter was subjected to ensuing cyclization in sodium ethoxide solution, yielding the target compound **12**. *S*-methylation of compound **12** with methyl iodide afforded the target product 3-phenyl-2-thiomethyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7-carboxylic acid ethyl ester (**13**) (Scheme 3).



Compound	Yield %
11	90
12	92
13	95
14	55
15	40
16	62
17	35

SCHEME 3 *Reagents and conditions*: i: $PhNH_2$; CH_2Cl_2, stirring 2 h; ii: EtONa, reflux 1 h; iii: CH_3I, 1N NaOH, stirring 2 h; iv: $N_2H_4 \cdot H_2O$, EtOH, reflux 15 h; v: $HOCH_2CH_2NH_2$, 15 h; vi: $NaNO_2$, HCl, AcOH, stirring; vii: $POCl_3$, reflux 14 h.

Treating the *S*-methylated pyridothienopyrimidine **13** with excess hydrazine hydrate afforded the 2-hydrazino compound **14**, which is considered a good starting material for the synthesis of the tetracyclic ring system **16** via a diazotization reaction. The same approach to obtaining 3-phenyl-2-[1-hydroxyethan]-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**15**) can be achieved by the treatment of compound **13** with ethanolamine. The open structure **15** underwent direct cylization to build the imidazo moiety **17** (Scheme 3).

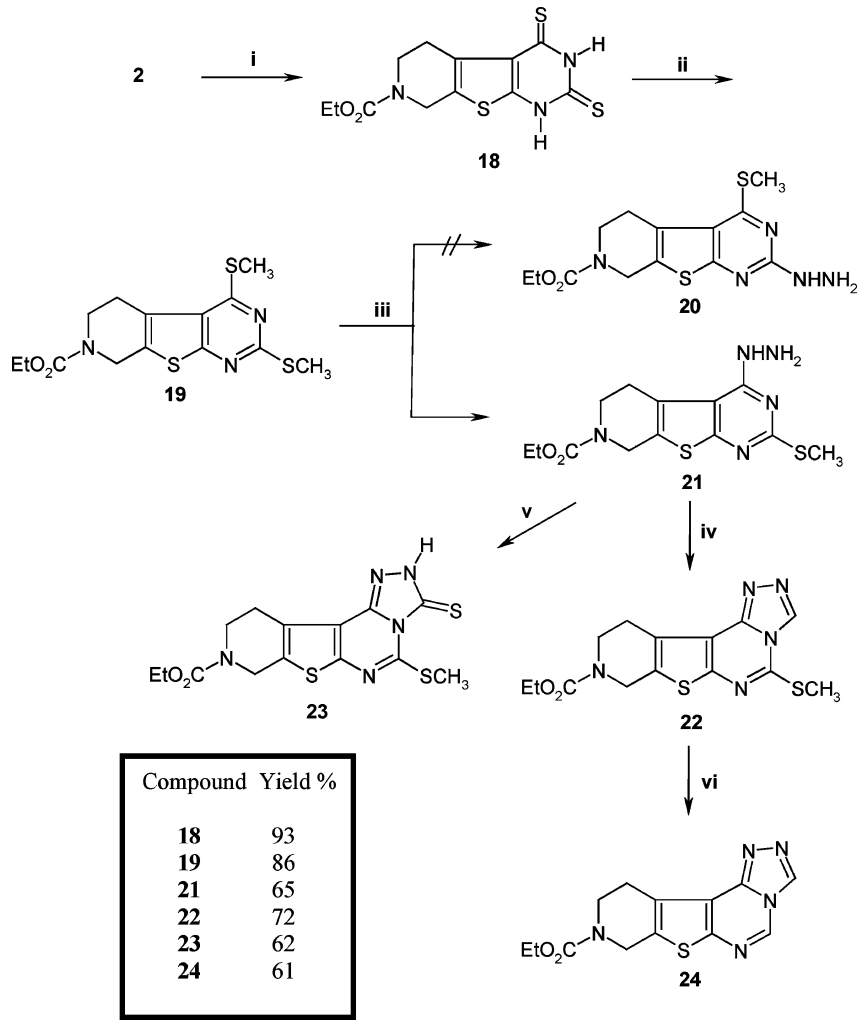
The structure of compound **13** was proved by the help of the ^{1}H-NMR, ^{13}C-NMR, and IR spectra as well as elemental analysis. Elemental analysis of **13** was in accordance to its molecular formula as $C_{19}H_{19}N_3O_3S_2$. The ^{1}H-NMR spectrum of **13** showed a triplet and quartet corresponding to ester protons. The methyl protons were found to resonate as a singlet at $\delta_H = 2.49$ ppm, whereas the aromatic protons appeared at δ_H = 7.27–7.55 ppm. The ^{13}C-NMR supported the ^{1}H-NMR spectrum by showing three signals at $\delta_C = 15.21$, 127.11, 128.11, 129.87, and 130.98 ppm corresponding to SCH_3 and (Ar-C) present in compound **13** (see the Experimental section). The IR spectrum of **13** showed the absorption of the CH-arom. and the carbonyl groups at 3000 and 1710–1680 cm^{-1}, respectively. Combining these spectral and analytical data, compound **13** was identified as 3-phenyl-2-thiomethyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester.

Analogously, compound **2** was proved to be a key intermediate for other subsequent conversions. Thus, when it was allowed to react with carbon disulfide in alcoholic KOH, the reaction produced compound **18**. This was triturated with methyl iodide to yield ethyl-2,4-bithiomethyl-5,8-dihydropyrido[4′,3′ :4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylate (**19**), which was confirmed easily by the ^{1}H-NMR spectrum that exhibited a singlet for the two CH_3-protons at $\delta_H = 2.61$ ppm (Scheme 4).

Surprisingly, on reacting **19** with excess hydrazine hydrate in the presence of pyridine as a solvent to synthesize the 2,4-dihydrazino compound, the process removed only one –SCH_3 by –$NHNH_2$ in ethyl-4-hydrazino-2-thiomethyl-5,8-dihydropyrido[4′,3′ :4,5]thieno[2,3-d]pyrimidine-7(6H)-carboxylate (**21**). The structure of **21** was synthetically proved by its cyclization using triethylorthoformate and carbon disulfide to give **22** and **23**. On reducing **22** by Raney Ni in ethanol, we isolated our known compound ethyl-7,10-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[2,1-*f*]pyrimidine-8(9*H*)-carboxylate (**24**).[13] The aforementioned synthetic proof indicated

the prevalence of SCH_3 group in position 2 without change in compound **21** (Scheme 4).

In conclusion and by the results in hand, we might serve in the synthesis new classes of fused pyridothienopyrimidines using efficient, facile, and elegant methods of preparation.



Compound	Yield %
18	93
19	86
21	65
22	72
23	62
24	61

SCHEME 4 *Reagents and conditions*: i: CS_2, alc. KOH, reflux 5 h; ii: CH_3I, 1N NaOH, stirring 1 h; iii: $N_2H_4 \cdot H_2O$, pyridine, reflux 4 h; iv: $CH(OEt)_3$, reflux 4 h; v, iv: CS_2, KOH, CH_3OH, reflux 3 h; vi: raney Ni, ethanol, reflux 2 h.

EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Carol Erba CHN-S Elemental Analyzer 1108. The ^{13}C and ^{1}H NMR spectra were obtained using sa Bruker AC 300 (^{1}H: 300.13 MHz, ^{13}C :75.5 MHz). The solvents were deuterated dimethyl sulfoxide and chloroform. The δ-values are given in ppm and the internal standard was tetra-methylsilane. The IR spectra were recorded on a Nicolet 250 FT-IR spectrophotometer as potassium bromide pellets.

2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-6-carboxylic Acid Ethyl Ester (3)

A mixture of **2** (2.51 g, 10 mmol) with a few drops of acetic anhydride in triethylorthoformate (20 mL) was refluxed for 8 h. The separated crystalline product was obtained on cooling at r.t. Yield: 2.4 g (80%), colorless plates (ethanol), m.p. 90–92°C, IR (KBr): υ = 2210 (CN), 1715 (ester C=O), 1618 (C=N) cm^{-1}, ^{1}H NMR (DMSO-d_6): $\delta = 1.21$ (t, 3H, $COOCH_2CH_3$), 1.35 (t, 3H, OCH_2CH_3), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-5), 4.11 (q, 2H, $COOCH_2CH_3$), 4.35 (q, 2H, OCH_2CH_3), 4.55 (s, 2H, H-7), 8.55 (s, 1H, CH), ^{13}C NMR (DMSO-d_6): $\delta = 14.38$ (CH_3), 14.38 (CH_3), 23.39 (C-4), 40.93 (C-5), 42.02 (C-7), 60.86 (CH_2), 60.97 (CH_2), 113.38 (CN), 123.99 (C-3), 129.60 (C-7a), 146.09 (C-3a), 154.55 (C=O), 159.07 (CH=N), 163.58 (C-2).

3-Amino-4-imino-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5] thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (4)

To a stirred suspension of **3** (6.1 g, 20 mmol) in absolute ethanol (40 mL), hydrazine hydrate (1.5 g, 30 mmol) was added. The reaction mixture was stirred at r.t. for 2 h. The precipitate that formed was filtered off, washed with cold ethanol, and recrystalized from dioxane to produce white needles. Yield: 4.9 g (85%), m.p. 152–154°C, (Found: C, 49.02; H, 5.01; N, 23.63; S, 10.91. Calc. for $C_{12}H_{15}N_5O_2S$ (293.35): C, 49.13; H, 5.15; N, 23.87; S, 10.73), IR (KBr): υ = 3360–3280 (NH_2, NH), 1708 (ester C=O), 1615 (C=N) cm^{-1}, ^{1}H NMR (DMSO-d_6): $\delta = 1.21$ (t, $J = 7$ Hz, 3H, $COOCH_2CH_3$), 3.00 (t, $J = 5.6$ Hz, 2H, H-5), 3.65 (t, $J = 5.6$ Hz, 2H, H-6), 4.11 (q, $J = 7$ Hz, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 5.60 (b, 2H, NH_2), 7.93 (b, 1H, NH), 8.35 (s, 1H, CH), ^{13}C NMR (DMSO-d_6): $\delta = 14.42$ (CH_3), 26.09 (C-5), 40.87 (C-6), 42.79 (C-8), 60.92 (CH_2), 119.68 (C-4a), 127.95 (C-4b), 129.84 (C-8a), 148.22 (C-2), 151.31 (C-9a), 154.62 (C=NH), 156.09 (C=O).

9,10-Dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo [3,2-*f*]pyrimidine-8(7*H*)-carboxylic Acid Ethyl Ester (5)

Compound **4** (0.59 g, 2 mmol) in triethylorthoformate (5 mL) was heated under reflux for 3 h. The solid product that formed was collected and recrystalized from methanol to produce white needles. Yield: 0.5 g (84%), m.p. 160–161°C, IR (KBr): $\upsilon = 1700$ (ester C=O), 1610 (C=N) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.24$ (t, 3H, $COOCH_2CH_3$), 3.17 (t, 2H, H-10), 3.69 (t, 2H, H-9), 4.18 (q, 2H, $COOCH_2CH_3$), 4.68 (s, 2H, H-7), 9.12 (s, 1H, H-4), 9.42 (s, 1H, H-2).

2-(4-Chlorophenyl)-9,10-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,2-*f*]pyrimidine-8(7*H*)-carboxylic Acid Ethyl Ester (6)

A mixture of **4** (1.47 g, 5 mmol) and *p*-chlorobenzaldehyde (0.7 g, 5 mmol) in 15 mL of acetic acid was heated under reflux for 3 h. The resulting precipitate was collected and crystallized from dioxane to produce pale yellow needles. Yield: 1.8 g (90%), m.p. 175–176°C, IR (KBr): $\upsilon = 3090$ (arom. CH), 1705 (ester C=O), 1605 (C=N) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.29$ (t, 3H, $COOCH_2CH_3$), 3.15 (t, 2H, H-10), 3.85 (t, 2H, H-9), 4.18 (q, 2H, $COOCH_2CH_3$), 4.75 (s, 2H, H-7), 7.63 (d, 2 ArH), 7.95 (d, 2 ArH), 9.12 (s, 1H, H-4).

2-Methyl-9,10-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,2-*f*]pyrimidine-8(7*H*)-carboxylic Acid Ethyl Ester (7)

A solution of **4** (0.59 g, 2 mmol) in acetic anhydride (5 mL) was refluxed for 3 h. The reaction mixture was allowed to cool and poured in ice water. The precipitate that formed was filtered off, washed with cold water, and recrystalized from ethanol to produce white needles. Yield: 0.56 g (88%), m.p. 181–182°C, IR (KBr): $\upsilon = 2950$ (aliph. CH), 1705 (ester C=O), 1610 (C=N) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta =$ 1.30 (t, 3H, $COOCH_2CH_3$), 2.68 (s, 3H, CH_3), 3.27 (t, 2H, H-10), 3.87 (t, 2H, H-9), 4.20 (q, 2H, $COOCH_2CH_3$), 4.83 (s, 2H, H-7), 9.09 (s, 1H, H-4).

2-(Phenylamino)-9,10-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,2-*f*]pyrimidine-8(7*H*)-carboxylic Acid Ethyl Ester (8)

A mixture of **4** (0.59 g, 2 mmol) and phenyl isothiocyanate (0.27 g, 2 mmol) in pyridine (10 mL) was refluxed for 4 h. On cooling, the

formed solid product was collected by filtration. Yield: 0.57 g (72%), yellow crystals (ethanol), m.p. 200–202°C, IR: (KBr) $\upsilon = 3075$ (arom. CH), 1708 (ester C=O), 1620 (C=N) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.18$ (t, 3H, $COOCH_2CH_3$), 3.05 (t, 2H, H-10), 3.65 (t, 2H, H-9), 4.16 (q, 2H, $COOCH_2CH_3$), 4.64 (s, 2H, H-7), 7.11–7.52 (m, 5ArH), 9.18 (s, 1H, H-4), 10.45 (s, 1H, NH).

4-Oxo-2,3,4,8,10,11-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,2-*f*]pyrimidine-9-carboxylic Acid Ethyl Ester (9)

To a mixture of **4** (0.293 g, 1 mmol) and chloroacetyl chloride (0.17 g, 1.5 mmol) in DMF (5 mL), triethylamine (0.101 g, 1 mmol) was added. The reaction mixture was stirred at r.t. for 5 h and then poured into ice water. The precipitate that formed was filtered off, washed with water, and recrystalized from ethanol to produce pale yellow needles, 0.25 g (75%), m.p. 139–140°C, IR (KBr): $\upsilon = 3280$ (NH), 1710 (ester C=O), 1665 (C=O), 1615 (C=N) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.18$ (t, 3H, $COOCH_2CH_3$), 3.14 (t, 2H, H-11), 3.65 (t, 2H, H-10), 4.14 (q, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, C-2), 4.67 (s, 2H, H-8), 9.15 (s, 1H, H-5), 10.83 (s, 1H, NH).

Diethyl-2-(3-phenyl-thioureido)-4,7-dihydro-5*H*-thieno[2,3-*c*]-pyridine-3,6-dicarboxylate (11)

Isothiocyanate compound **10** (3.4 g, 10 mmol) was dissolved in dichloromethane (30 mL) and then an equivalent amount of aniline was added. The mixture was stirred at r.t. for 2 h. The solid product that precipitated was filtered off and recrystalized from methanol to produce white crystals, 3.9 g (90%), m.p. 179–181°C, IR (KBr): $\upsilon = 3270$ (NH), 3080 (arom. CH), 1705 (ester C=O), 1680 (ester C=O) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.26$ (t, 6H, $2COOCH_2CH_3$), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-5), 4.11 (q, 4H, $2COOCH_2CH_3$), 4.55 (s, 2H, H-7), 7.26–7.56 (m, 5H, ArH), 9.55 (s, 1H, NH), 11.02 (s, 1H, NH).

Ethyl-4-oxo-3-phenyl-2-thioxo-1,2,3,4,5,,8-hexahydropyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylate (12)

A mixture of **11** (4.3 g, 10 mmol) and a solution of sodium ethoxide (0.3 g sodium in 30 mL absolute ethanol) was refluxed for 1 h. After removing the solvent, the residue was diluted with water and acidified with HCl. The product was collected by filtration, washed with water, dried and recrystallized from DMF/n hexane to produce white crystals. Yield: 3.6 g (92%), m.p. 273–275°C, IR (KBr): $\upsilon = 3250$ (NH), 3040 (arom. CH), 1708

(ester C=O) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.95 (t, 2H, H-5), 3.72 (t, 2H, H-6), 4.14 (q, 2H, $COOCH_2CH_3$), 4.63 (s, 2H, H-8), 7.22–7.54 (m, ArH), 10.50 (s, H, NH).

Ethyl-4-oxo-3-phenyl-2-thiomethyl-3,4,5,8-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylate (13)

To a suspension of **12** (1.16 g, 3 mmol) in 1*N* sodium hydroxide (12 mL), methyl iodide (0.72 g, 5 mmol) was added. The reaction mixture was stirred at r.t. for 2 h. The solid was precipitated, collected, washed with water, and dried. Yield: 1.14 g (95%), colorless crystals (methanol), m.p. 160–161°C, (Found: C, 56.64; H, 4.59; N, 10.31; S, 15.94. Calc. for $C_{19}H_{19}N_3O_3S_2$ (401.51): C, 56.84; H, 4.77; N, 10.47; S, 15.81), IR (KBr): $\upsilon = 3060$ (arom. CH), 1710 (ester C=O), 1680 (C=O) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.30$ (t, 3H, $COOCH_2CH_3$), 2.49 (s, 3H, SCH_3), 3.05 (t, 2H, H-5), 3.75 (t, 2H, H-6), 4.21 (q, 2H, $COOCH_2CH_3$), 4.68 (s, 2H, H-8), 7.27–7.55 (m, 5ArH), ^{13}C NMR (DMSO-d_6): $\delta = 14.23$ (CH_3), 15.21 (SCH_3), 24.87 (C-5), 40.21 (C-6), 41.20 (C-8), 60.79 (CH_2), 110.94 (C-4a), 114.63 (C-4b), 121.45 (C-8a), 127.11, 128.11, 129.87, 130.98 (Ar-C), 131.69 (C-9a), 155.22 (C-2), 157.12 (C=O), 164.86 (C=O).

Synthesis of 14 and 15

To a stirred suspension of **13** (10 mmol) in absolute ethanol (10 mL), hydrazine hydrate 80% or amino ethanol (5 mL) was added. The reaction mixture was heated under reflux for 15 h. Excess solvent was removed and the residue was poured into water. The precipitates that formed were filtered off, washed with cold ethanol, and recrystalized from methanol.

Ethyl-2-hydrazino-4-oxo-3-phenyl-3,4,5,,8-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylate (14)

Yield: 2.1 g (55%), m.p. 112–113°C, IR (KBr): $\upsilon = 3370$–3280 (NH_2, NH), 3070 (arom. CH), 1710 (ester C=O), 1680 (C=O) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.28$ (t, 3H, $COOCH_2CH_3$), 2.65 (b, 2H, NH_2), 3.07 (t, 2H, H-5), 3.52 (t, 2H, H-6), 4.17 (q, 2H, $COOCH_2CH_3$), 4.64 (s, 2H, H-8), 5.26 (b, H, NH), 7.25–7.54 (m, 5H, ArH).

Ethyl-2-(hydroxyethylamino)-4-oxo-3-phenyl-3,4,5,,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylate (15)

Yield: 1.6 g (40%), m.p. 88–90°C, IR (KBr): $\upsilon = 3430$–3300 (OH), 3230 (NH), 3080 (arom. CH), 2920 (aliph. CH), 1709 (ester C=O) cm^{-1},^1H

NMR (DMSO-d_6): $\delta = 1.29$ (t, 3H, $COOCH_2CH_3$), 2.51 (b, H, OH), 2.97 (t, 2H, H-5), 3.47 (t, 2H, H-6), 3.54–3.71 (m, 4H, $2CH_2$), 4.16 (q, 2H, $COOCH_2CH_3$), 4.58 (s, 2H, H-8), 4.63 (s, H, NH), 7.26–7.58 (m, 5H, ArH).

Ethyl-5-oxo-4-phenyl-4,5,,6,9-tetrahydropyrido[4′,3′:4,5] thieno[2,3-*d*]tetrazolo[5,1-*b*]pyrimidine-8(7*H*)- carboxylate (16)

To a solution of **14** (0.39 g, 1 mmol) in conc. HCl (5 mL) and glacial acetic acid (5 ml) at 0°C, a cold solution of (10%) sodium nitrite (7 mL, 10 mmol) was added with stirring for 10 min. The formed precipitate was filtered, washed with water, and recrystalized from ethanol to produce buff crystals. Yield: 0.25 g (62%), m.p. 205–207°C, IR (KBr): $\upsilon = 3065$ (arom. CH), 1712 (ester C=O), 1675 (C=O) cm^{-1},^{1}H NMR (DMSO-d_6): $\delta = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.89 (t, 2H, H-6), 3.53 (t, 2H, H-7), 4.13 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-9), 7.25–7.51 (m, 5H, ArH).

Ethyl-5-oxo-4-phenyl-1,2,4,5,,6,9-hexahydropyrido[4′,3′:4,5] thieno[2,3-*d*]imidazo[2,1-*b*]pyrimidine-8(7*H*)- carboxylate (17)

A mixture of compound **15** (0.42 g, 1 mmol) and phosphoryl chloride (10 mL) was refluxed for 14 h. Excess solvent was removed and the residue was poured into water. After extraction with chloroform, the organic layer was washed with sodium bicarbonate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum. Yield: 0.14 g (35%), yellow crystals (methanol/n-hexane), m.p. 132–133°C, IR (KBr): $\upsilon = 3085$ (arom. CH), 1707 (ester C=O) cm^{-1}, ^{1}H NMR (DMSO-d_6): $\delta = 1.24$ (t, 3H, $COOCH_2CH_3$), 2.86 (t, 2H, H-6), 3.65 (t, 2H, H-7), 3.85–4.05 (m, 4H, $2CH_2$), 4.17 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-9), 7.28–7.59 (m, 5H, ArH).

Ethyl-2,4-dithioxo-1,2,3,4,5,8-hexahydropyrido[4′,3′:4,5]thieno [2,3-*d*]pyrimidine-7(6*H*)-carboxylate (18)

To suspension of **2** (2.5 g, 10 mmol) in 10 % alcoholic potassium hydroxide (15 mL), 5 mL of carbon disulfide was added. The mixture was refluxed for 5 h. Excess solvent was removed. The residue diluted with water and acidified with HCl. The product was filtered off, washed with water, dried and recrystallized from DMF/water to produce yellow crystals, 3 g (93%), m.p. 251–252°C, IR (KBr): $\upsilon = 3270$ (NH), 1710 (ester

C=O), 1612 (C=N) cm^{-1},^{1}H NMR (DMSO-d_6): $\delta = 1.21$ (t, $J = 7$ Hz, 3H, $COOCH_2CH_3$), 3.07 (t, $J = 5.6$ Hz, 2H, H-5), 3.62 (t, $J = 5.6$ Hz, 2H, H-6), 4.06 (q, $J = 7$ Hz, 2H, $COOCH_2CH_3$), 4.53 (s, 2H, H-8), 13.25 (bs, 2H, 2NH), ^{13}C NMR (DMSO): $\delta = 14.37$ (CH_3), 27.22 (C-5), 40.92 (C-6), 42.58 (C-8), 60.93 (CH_2), 115.33 (C-4a), 126.19 (C-4b), 130.73 (C-8a), 148.70 (C-9a), 154.70 (C=O) 169.21 (C=S), 181.27 (C=S)

Ethyl-2,4-dithiomethyl-5,8-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylate (19)

To a suspension of **18** (0.98 g, 3 mmol) in 1*N* sodium hydroxide (12 mL), methyl iodide (1.44 g, 10 mmol) was added. The reaction mixture was stirred at r.t. for 1 h. The solid was precipitated, filtered off, washed with water, and dried. Yield: 0.92 g (86%), orange crystals (methanol). m.p. 134–135°C, IR (KBr): $\upsilon = 1710$ (ester C=O), 1615 (C=N) cm^{-1}, ^{1}H NMR (DMSO-d_6): $\delta = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.61 (s, 6H, $2CH_3$), 2.96 (t, 2H, H-5), 3.68 (t, 2H, H-6), 4.06 (q, 2H, $COOCH_2CH_3$), 4.64 (s, 2H, H-8).

Ethyl-4-hydrazino-2-thiomethyl-5,8-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylate (21)

To a stirred suspension of **19** (3.5 g, 10 mmol) in pyridine (30 mL), hydrazine hydrate 80% (2 mL) was added. The reaction mixture was heated under reflux for 4 h. The precipitate that formed after cooling was filtered off, washed with cold ethanol, and recrystalized from methanol to produce gray needles. Yield: 2.2 g (65%), m.p. 176–177°C, (Found: C, 44.38; H, 5.17; N, 30.19; S, 9.89. Calc. for $C_{12}H_{17}N_7O_2S$ (323.38): C, 44.57; H, 5.30; N, 30.32; S, 9.68), IR (KBr): $\upsilon = 3380$–3270 (NH_2, NH), 1702 (ester C=O), 1630 (C=N) cm^{-1},^{1}H NMR (DMSO-d_6): δ=1.21 (t, 3H, $COOCH_2CH_3$), 2.56 (s, 3H, SCH_3), 2.61 (b, 2H, NH_2), 2.85 (b, 1H, NH), 3.08 (t, 2H, H-5), 3.78 (t, 2H, H-6), 4.21 (q, 2H, $COOCH_2CH_3$), 4.85 (s, 2H, H-8).

Ethyl-4-thiomethyl-7,10-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[2,1-*f*]pyrimidine-8(9*H*)-carboxylate (22)

A mixture of compound **21** (0.65 g, 2 mmol) and triethylorthoformate (10 mL) was refluxed for 4 h. After cooling at r.t., the formed product was filtered off, dried, and recrystallized from ethanol to produce colorless crystals. Yield: 0.50 g (72%). m.p. 192–194°C, IR (KBr): $\upsilon = 1706$ (ester C=O), 1613 (C=N) cm^{-1}, ^{1}H NMR (DMSO-d_6): $\delta = 1.30$ (t, 3H,

$COOCH_2CH_3$), 2.81 (s, 3H, SCH_3), 3.29 (t, 2H, H-10), 3.85 (t, 2H, H-9), 4.22 (q, 2H, $COOCH_2CH_3$), 4.77 (s, 2H, H-7), 8.79 (s, H, CH).

Ethyl-3-thioxo-4-thiomethyl-2,3,7,10-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[2,1-f]pyrimidine-8(9*H*)-carboxylate (23)

To a mixture of **21** (0.65 g, 2 mmol) and KOH (0.112 g, 2 mmol) in methanol (10 mL), carbon disulfide (1 mL) was added. The mixture was refluxed for 3 h. After removing the solvent on vacuum, the residue was diluted with water and acidified with HCl. The solid product was filtered off, washed with water, dried, and recrystalized from DMF/water to produce yellow crystals. Yield: 0.47 g (62%), m.p. 285–287°C, IR (KBr): $\upsilon = 3220$ (NH), 1705 (ester C=O), 1610 (C=N) cm^{-1}, ^1H NMR (DMSO-d_6): $\delta = 1.28$ (t, 3H, $COOCH_2CH_3$), 2.71 (s, 3H, SCH_3), 3.24 (t, 2H, H-10), 3.82 (t, 2H, H-9), 4.20 (q, 2H, $COOCH_2CH_3$), 4.73 (s, 2H, H-7), 9.86 (b, 1H, NH).

Ethyl–7,10-dihydropyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[2,1-*f*]pyrimidine-8(9*H*)-carboxylate (24)

To a solution of compound **22** (0.7 g, 2 mmol) in ethanol (10 mL), Raney nickel catalyst (0.2 g) was added. The mixture was gently refluxed under a hydrogen atmosphere for 2 h. The catalyst was removed by filtration. The solvent was removed under vacuum to give white needles in a 61% yield. (M.p. 212–214°C Lit.[13])

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