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Fused thieno[2,3-*b*]pyridines: synthesis and characterization of new condensed pyridothienopyrimidines

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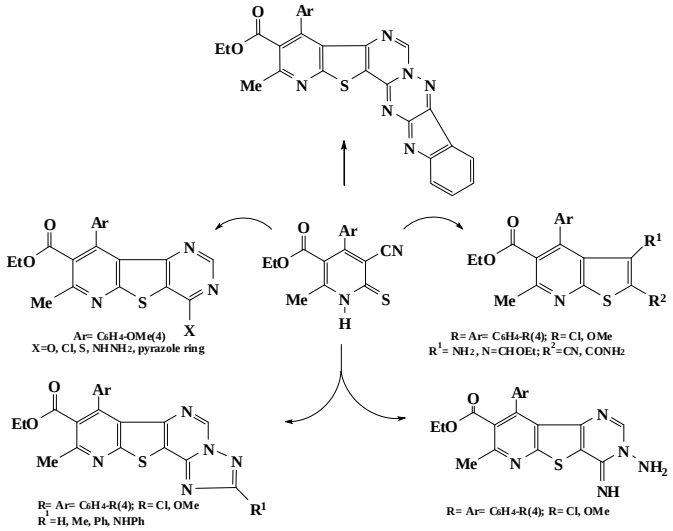
Abstract

Reaction of cyanopyridine-2(1*H*)-thiones **2a,b** with chloroacetonitrile gave the corresponding 3-aminothieno[2,3-*b*]pyridine-2-carbonitriles **4a,b**. Condensation of **4a,b** with triethyl orthoformate produced the methanimidate derivatives **6a,b** which upon treatment with hydrazine hydrate resulted in the formation of 3-amino-4-iminopyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines **7a,b**. Aminothieno[2,3-*b*]pyridine-2-carboxamide **5** was prepared and reacted with triethyl orthoformate to give pyrimidine-4(3*H*)-one derivative **14**. Chlorination of **14** with phosphorus oxychloride gave 4-chloropyrimidine **15**, which in turn was reacted with hydrazine hydrate to produce 4-hydrazinopyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **17**. Compounds **7a,b** and **17** were used as precursors for synthesizing other new pyridothienopyrimidines as well as triazolopyrido-thienopyrimidines, and pyridothienopyrimidotriazinoindoles. Structural formulas of all newly synthesized compounds were confirmed by elemental and spectral (IR, NMR, and mass) analyses.



Keywords: Thienopyridines, thienopyrimidines, pyridothienopyrimidines, triazolopyridothienopyrimidines, pyridothienopyrimidotriazinoindoles

Introduction

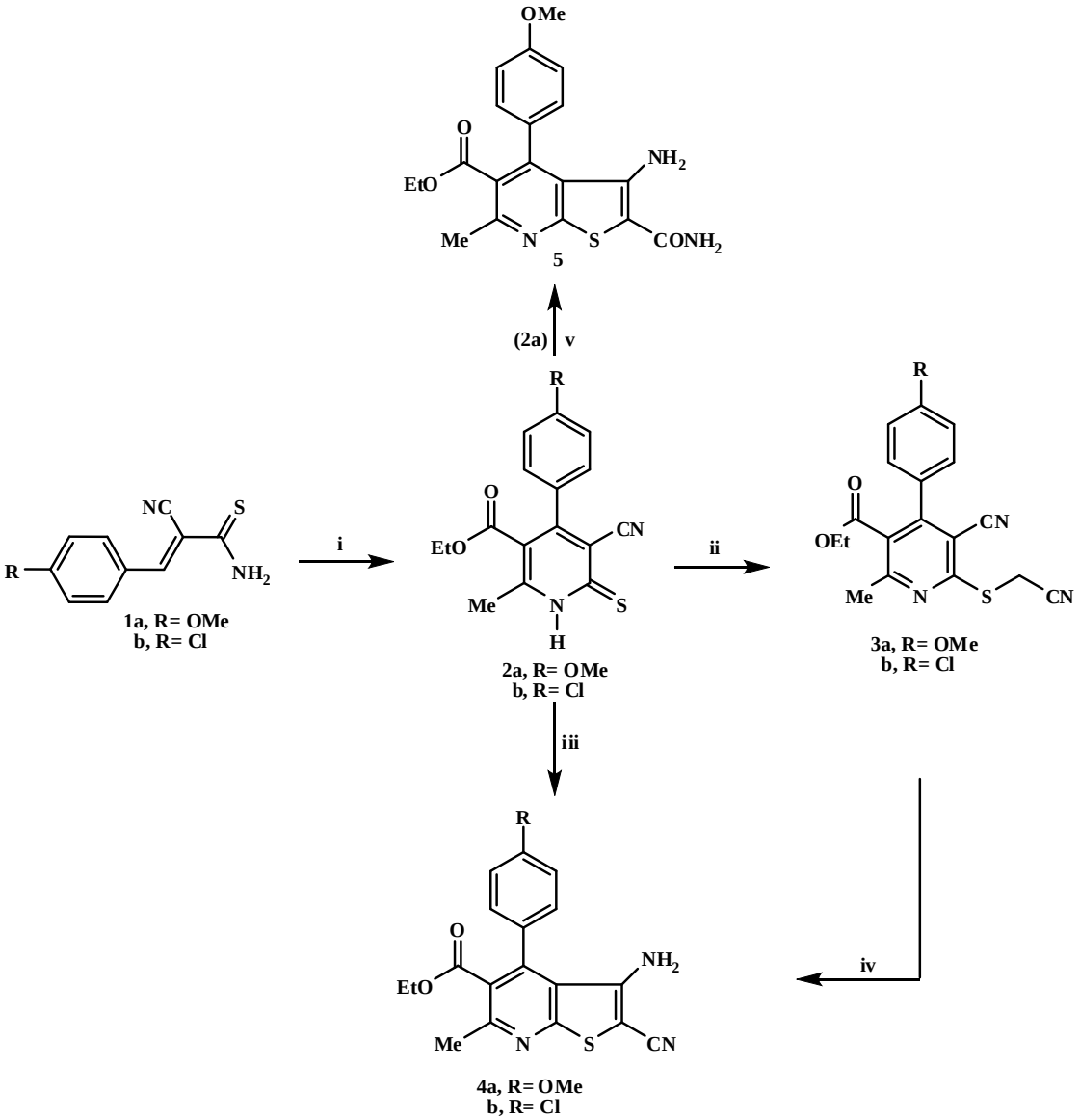
Many thieno[2,3-*b*]pyridines have been synthesized and investigated in relation to their biological and pharmacological importance.[1,2] Some of them proved to possess antiviral, [3,4] anti-diabetic,[5] antimicrobial,[6,7] anti-inflammatory,[8] antitumor,[9] antiparasitic[10] and neurotropic activities.[11] Also, thienopyrimidine derivatives have been the subject of several chemical and biological studies on account of their wide spectrum of biological activity.[12,13] Furthermore, some pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines are reported to exhibit antimicrobial,[6,7] antiallergic,[14] antiprotozoal[15] and anti-anaphylactic activities.[16,17] In view of the above observations and as a continuation of our previous work on pyridothienopyrimidines,[18-20] we describe herein the synthesis and characterization of the title compounds which are expected to be biologically active ones owing to the incorporation of different pharmacophores.

Results and Discussion

The broad synthetic utility reported for several 3-cyano-pyridine-2(1*H*)-thiones as starting materials of many heterocyclic systems, especially thieno[2,3-*b*]pyridines, prompted us to use 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2(1*H*)-thiones **2a,b** as starting compounds in this investigation. These compounds **2a,b** were prepared by the reaction of arylidenecyanothioacetamides **1a,b** with ethyl acetoacetate in the presence of piperidine as a basic catalyst, according to the reported methods. [21] Reaction of 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2(1*H*)-thiones **2a,b** with chloroacetonitrile, by refluxing in ethanol in the presence of sodium acetate, gave the corresponding 3-aminothieno[2,3-*b*]pyridine-2-carbonitriles **4a,b** rather than the expected 2-(cyanomethylthio) pyridines **3a,b**. The latter compounds **3a,b** were carefully obtained by reacting **2a,b** with chloroacetonitrile at room temperature. On heating compounds **3a,b** in ethanol containing sodium acetate, they underwent intramolecular Thorpe-Ziegler cyclization forming the corresponding thienopyridines **4a,b**. In contrast, 3-amino-4-(4-methoxyphenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridine-2-carboxamide **5** was prepared by reacting compounds **2a** with chloroacetamide in ethanol containing a slightly excess amount of sodium ethoxide according to our reported method [21] (Scheme 1).

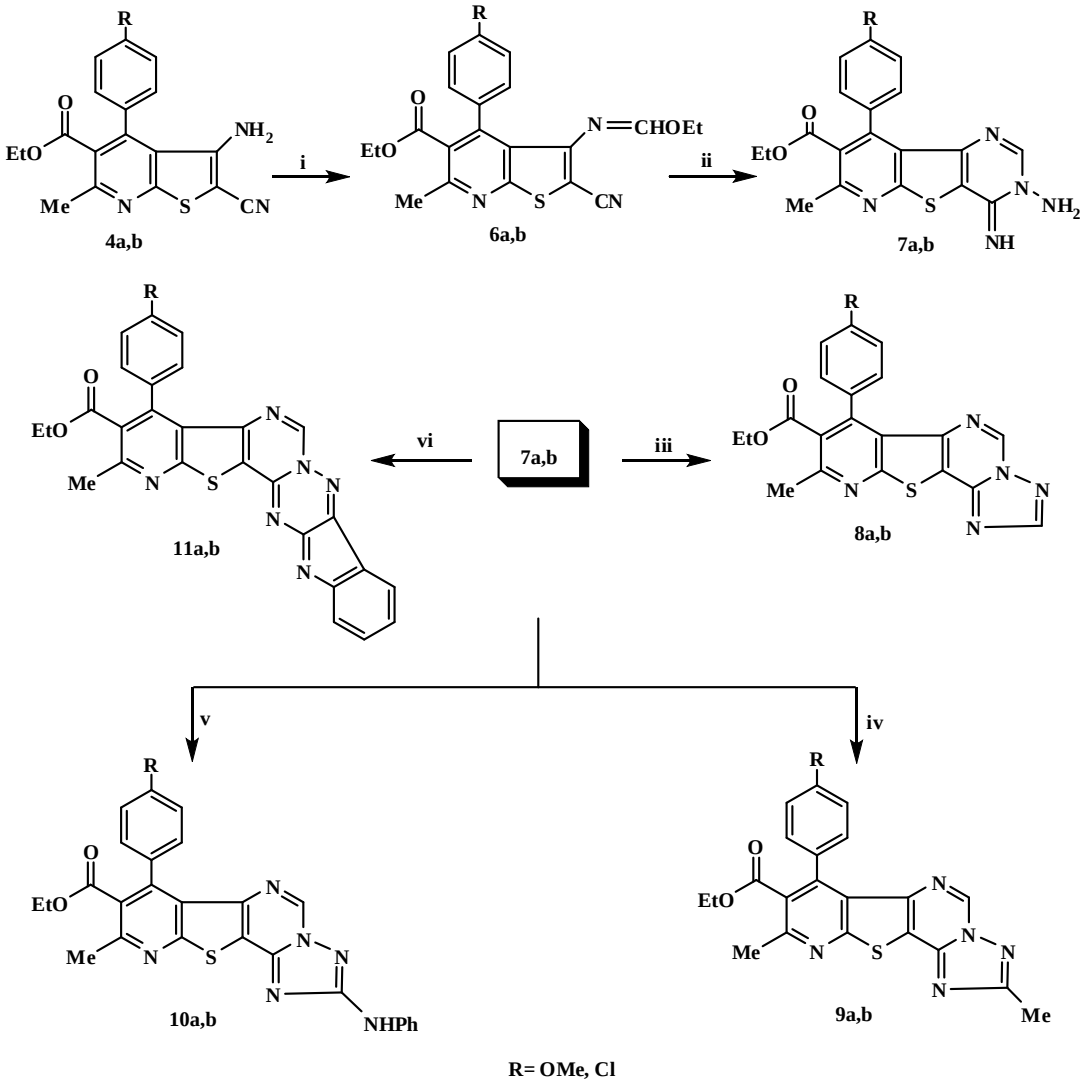
The condensation of *o*-aminocarbonitriles **4a,b** with triethyl orthoformate by refluxing in acetic anhydride produced the methanimidate derivatives **6a,b**. Treatment of compounds **6a,b** with hydrazine hydrate in dioxane at room temperature resulted in the formation of ethyl 3-amino-9-aryl-3,4-dihydro-4-imino-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylates **7a,b** in good yields. Compounds **7a,b,** having the aminoimine structure, were utilized as new precursors for synthesizing novel fused heterocyclic compounds containing pyrido-thienopyrimidine moiety. Thus, refluxing compounds **7a,b** with an excess amount of triethyl orthoformate, under neat condition furnished ethyl 7-aryl-9-methyl[1,2,4]triazolo[2'',3''-*c*]-pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylates **8a,b**. On the other hand, the 2-methyl analogs **9a,b** were prepared by reacting compounds **7a,b** with acetic anhydride at reflux temperature. Heating compounds **7a,b** with phenyl *iso*-thiocyanate in dry pyridine for a long time led to the formation of anilinotriazolopyridothienopyrimidines **10a,b**. When compounds **7a,b** were allowed to react with isatin, a cyclocondensation reaction occurred and the fused hexacyclic compounds **11a,b** were obtained in good yields (Scheme 2).

On treatment of compound **7a** with phenacyl bromide in boiling ethanol containing an equimolar amount of sodium acetate, the product was identified as 2*H*-pyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[1,6-*b*][1,2,4]triazine **12** rather than the related isomer **13** (Scheme 3).



Scheme 1. Reagents and conditions: (i) Ethyl acetoaceate, piperidine, EtOH, 6 h; (ii) Chloroacetonitrile, AcONa, EtOH, stir. 3 h; (iii) Chloroacetonitrile, AcONa, EtOH, 3 h; (iv) Sodium acetate, EtOH, 3 h; (v) Chloroacetamide, EtONa, EtOH, 3 h.

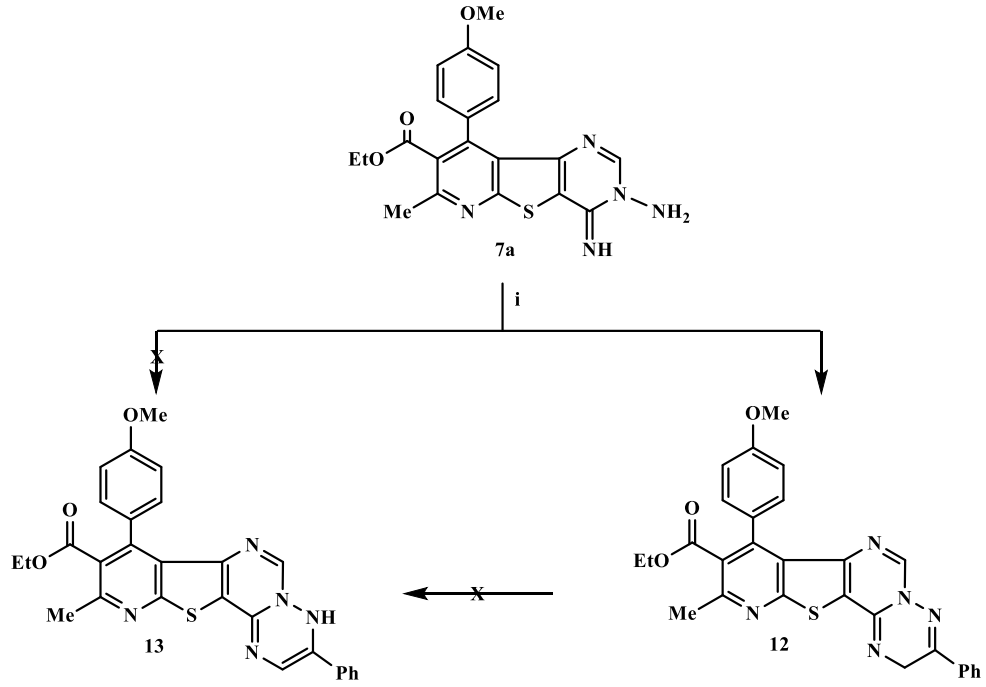
This assignment based on the spectral data of this product. Thus, its IR spectrum revealed the absence of any band attributed to ν NH and its ^{1}H NMR spectrum confirmed the presence of a characteristic signal corresponding to CH_2 group in the triazine ring. Refluxing *o*-aminocarboxamide **5** with triethyl orthoformate in acetic anhydride led to the formation of ethyl 9-(4-methoxyhenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate **14**.



Scheme 2. Reagents and conditions: (i) Triethyl orthoformate, Ac_2O, 2 h; (ii) Hydrazine hydrate, dioxane, stir. 4 h; (iii) Triethyl orthoformate, 3 h; (iv) Acetic anhydride, 2 h; (v) Phenyl *iso*-thiocyanate, steam bath 8 h; (vi) Isatin, EtOH, 3 h.

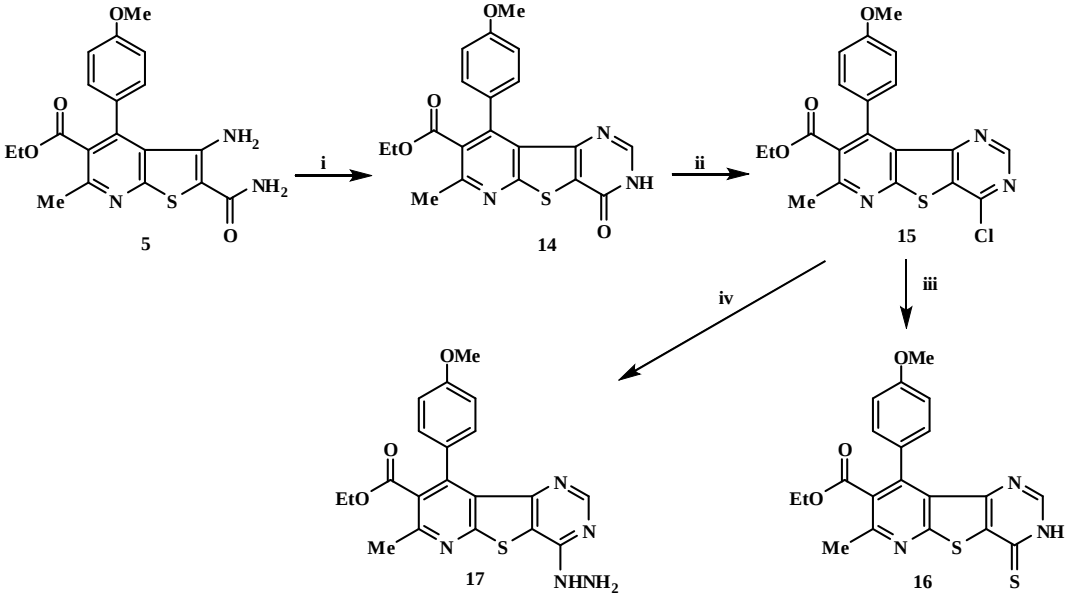
Chlorination of **14**, by heating with an excess amount of phosphorus oxychloride, produced ethyl 4-chloro-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**15**) in a good yield. The latter compound underwent a nucleophilic substitution reaction upon treatment with thiourea to give pyrimidine-2(1*H*)-thione **16**. Also, the reaction of **15** with hydrazine hydrate gave 4-hydrazinopyrimidine derivative **17** (Scheme 4).

The compound **17** was also served as a facile point to departure to other pyridothieno-pyrimidine derivatives. Thus, its condensation with 4-chlorobenzaldehyde gave 4-(4-chlorobenzylidene) hydrazinopyrimidine derivative **18**. Similarly, the hydrazone **19** was obtained by reacting compound **17** with acetophenone (Scheme 7). Heating compound **17** with acetylacetone at reflux temperature produced the dimethylpyrazole derivative **20**. Treatment of compound **17** with ethyl (ethoxymethylene)cyanoacetate led to the formation of ethyl 4-(3'-amino-4'-ethoxycarbonylpyrazol-2'-yl)-7-methyl-9-(4-methoxy-phenyl)pyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidine-8-carboxylate (**21**) (Scheme 5).

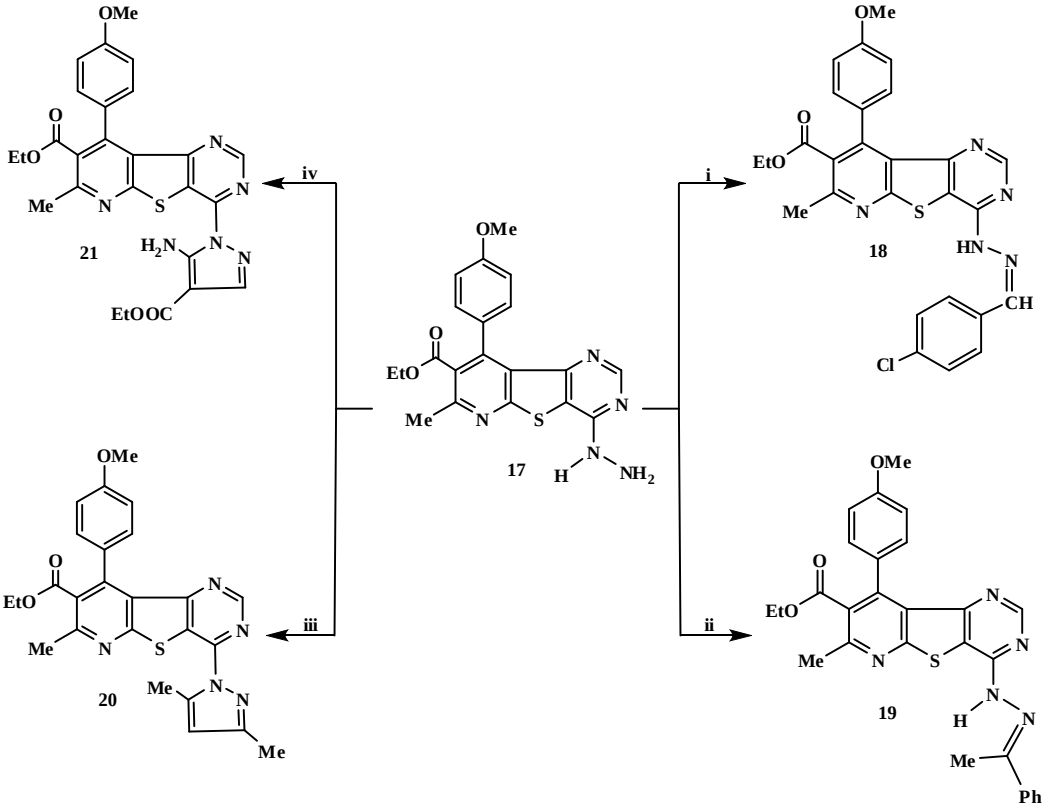


Scheme 3. Reagent and condition: (i) Phenacyl bromide, AcONa, EtOH, 3 h.

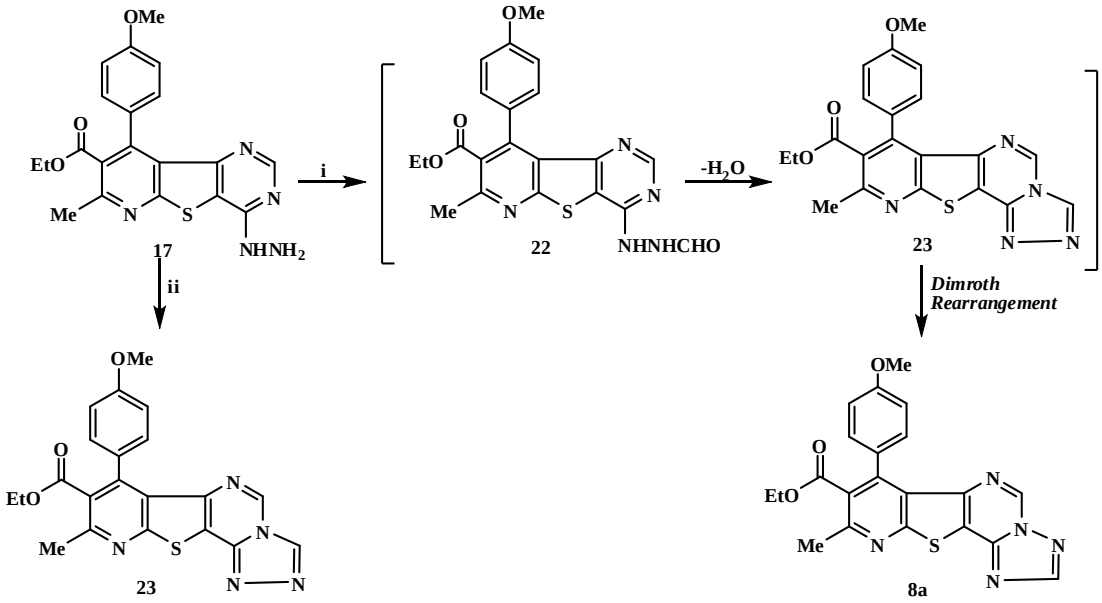
Heating hydrazino compound **17** in formic acid for a long time resulted in the formation of triazolo derivative **8a** rather than the expected isomer **23** (Scheme 6). From the thermodynamic point of view, [22] the compound **8**a seems to be more stable than the corresponding isomer **23**. The pathway of the latter reaction may be involving firstly the usual formation of compound **23** *via* the intermediacy of acid hydrazide **22**. Under the applied reaction conditions, [22] compound **23** underwent spontaneously *Dimroth in situ* to give the most stable isomer **8a**. The triazole intermediate **23** was successfully prepared by heating hydrazino compound **17** with triethyl orthoformate, under the neat condition, at reflux temperature (Scheme 6). Beside elemental and spectral analyses, the above structure **8a** was further confirmed by comparison with authentic sample (m. p., mixed mp and TLC) previously prepared in this paper.



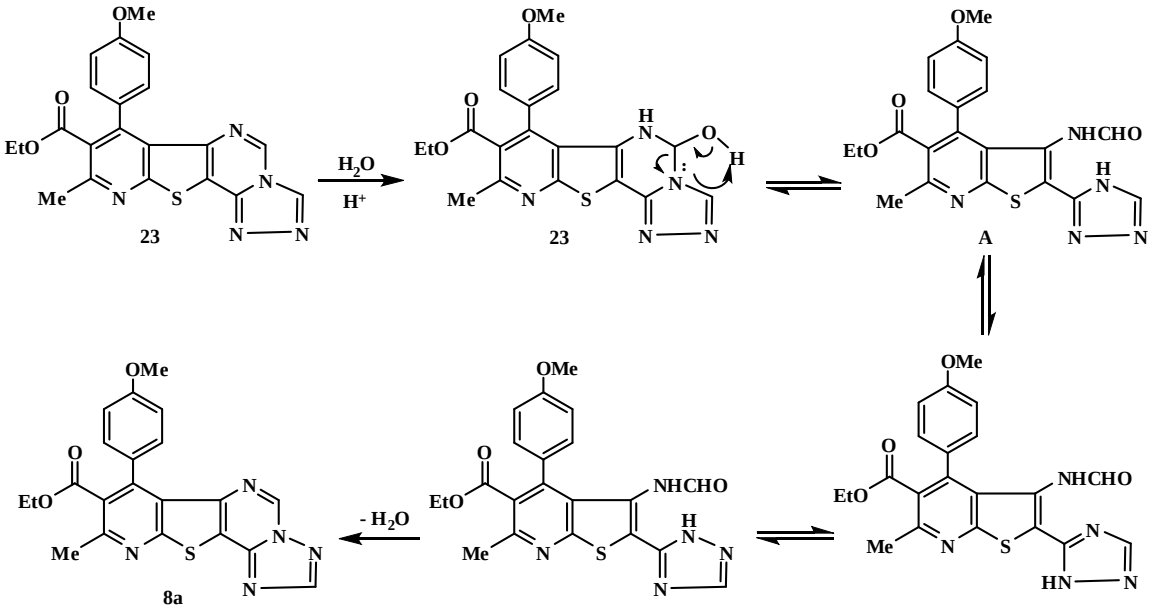
Scheme 4. Reagents and conditions: (i) Triethyl orthoformate, Ac_2O, 4 h; (ii) Phosphorus oxychloride, dioxane, steam bath 3 h; (iii) Thiourea, EtOH, 6 h; (iv) Hydrazine hydrate, EtOH, 2 h.



Scheme 5. Reagents and conditions: (i) 4-Chlorobenzaldehyde, AcOH, EtOH, 4 h; (ii) Acetophenone, AcOH, EtOH, 4 h; (iii) Acetyl acetone, 4 h; (iv) Ethyl (ethoxymethylene) cyanoacetate, EtOH, 4 h.



Scheme 6. Reagents and conditions: (i) Formic acid, 3 h; (ii) Triethyl orthoformate, 4 h.



Scheme 7. The mechanism of the Dimroth rearrangement for triazole derivative **23**.

The mechanism of the Dimroth rearrangement [23] under investigation is given in scheme 7. This rearrangement is promoted here by aqueous acid (Formic acid 85%). It involves initially covalent hydration of **23**. The hydroxy group enters position 5, then the pyrimidine ring opens and forms the carbonyl intermediate A; the CO group then attacks the most nucleophilic *N*-2 of the triazole ring and cyclizes to give the rearranged triazolopyrimidine **8a**.

Experimental Section

General. Starting materials were obtained from commercial suppliers and used without further purification. All melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}). The NMR spectra were taken on a Varian EM-390, 90 MHz spectrometer or on a JEOL LA 400 MHz FT-NMR spectrometer using TMS as an internal standard. Chemical shifts are given in δ ppm and coupling constant (*J*) is given in Hz. Electron impact (EI) MS spectra were carried out on a JEOL JMS-600 spectrometer. Elemental analyses (C, H, N and S) were performed on an Elemental Analyses system GmbH vario EL V2.3 1998 CHNS Mode (Assiut University). The reactions were monitored by TLC.

4-Aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2(1*H*)-thiones (2a,b). These compounds were prepared according to the reported method.[21]

4-Aryl-3-cyano-2-cyanomethylthio-5-ethoxycarbonyl-6-methylpyridines (3a,b). To a suspension of compound **2a,b** (10 mmol) and sodium acetate trihydrate (1.36 g, 10 mmol) in ethanol (40. mL), chloroacetonitrile (0.64 mL, 10 mmol) was added. The resulting mixture was stirred at room temperature for 3 h. The white precipitate that formed was collected and recrystallized from ethanol to give **4a,b**.

3-Cyano-2-cyanomethylthio-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylpyridine (3a). Prepared as white needles in 92% yield; mp 121-122 °C. IR (KBr) cm^{-1}: 2250 (C≡N, non conjugated), 2220 (C≡N, conjugated), 1731 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30-7.32 (dd, *J* 2.3 Hz, 2H, Ar-H), 6.97-7.00 (dd, *J* 2.3 Hz, 2H, Ar-H), 4.05-4.11 (q, *J* 7.0 Hz, 2H, OCH_2), 4.07 (s, 2H, SCH_2), 3.85 (s, 3H, OCH_3), 2.67 (s, 3H, CH_3), 0.98-1.02 (t, *J* 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 166.6, 161.0, 159.2, 158.8, 152.6, 129.7, 126.7, 126.2, 115.8, 114.3, 114.1, 105.1, 61.9, 55.4, 23.4, 15.9, 13.7; MS: *m/z* 367 (M^+, 100%), 352 (M^+-CH_3, 12%), 337 (M^+-2CH_3, 25%), 322 (M^+- OC_2H_5, 14%). Anal. Calcd. for $C_{19}H_{17}N_3O_3S$ (367.1)): C, 62.11; H, 4.66; N, 11.44; S, 8.73%. Found: C, 62.43; H, 4.49; N, 11.90; S, 8.92%.

(4-Chlorophenyl)-3-cyano-2-cyanomethylthio-5-ethoxycarbonyl-6-methylpyridine (**3b**). Prepared as white needles in 90% yield; mp 97-99 °C. IR (KBr) cm^{-1}: 2248 (C≡N, none conjugated), 2217 (C≡N, conjugated), 1735 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.46-7.49 (dd, *J* 2.3 Hz, 2H, Ar-H), 7.29-7.32 (dd, *J* 2.3 Hz, 2H, Ar-H), 4.05-4.10 (m, 4H, SCH_2 and OCH_2), 2.70 (s, 3H, CH_3), 0.98-1.01 (t, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 159.7, 159.1, 151.6, 136.5, 132.5, 129.5, 129.1, 126.4, 115.7, 113.6, 104.9, 62.1, 23.5, 16.0, 13.6. MS: *m/z* 371 (M^+, 100%), 373 (M^++2, 42%), 343 (24%), 336 (10%), 326 (M^+- OC_2H_5, 15%). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2S$ (371.1): C, 58.14; H, 3.79; N, 11.30; S, 8.62%. Found: C, 58.46; H, 3.72; N, 11.65; S, 8.27%.

3-Amino-4-aryl-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridine-2-carbonitriles (4a,b).

Method (**A**) To a mixture of compound **2a,b** (10 mmol) and sodium acetate trihydrate (1.50 g, 11 mmol) in ethanol (40 mL), chloroacetonitrile (0.64 mL, 10 mmol) was added. The resulting mixture was heated under reflux for 3 h. The precipitate that formed on cooling was collected and recrystallized from ethanol to afford **4a,b**.

3-Amino-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (**4a**). Prepared as yellow needles in 90% yield; mp 184-185 °C. IR (KBr) cm^{-1}: 3476, 3342 (NH_2); 2976 (C-H, aliphatic); 2199 (C≡N); 1729 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27-7.30 (dd, *J* 2.4 Hz, 2H, Ar-H), 7.00-7.03 (dd, *J* 2.4 Hz, 2H, Ar-H), 4.32 (s, 2H, NH_2), 4.01-4.06 (q, *J* 7.0 Hz, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 2.67 (s, 3H, CH_3), 0.99-

1.03 (t, *J* 7.2 Hz, 3H, CH_3 of ester); ^{13}C NMR and Dept 135 (100 MHz, $CDCl_3$) δ ppm: 167.5, 161.3, 160.6, 156.3, 149.3, 143.8, 130.0 (CH), 127.6, 125.4, 118.5, 114.7, 114.1 (CH), 61.6 (OCH_2), 55.4 (OCH_3), 23.1 (CH_3 at C-6), 13.8 (CH_3 of ester group). MS: *m/z* 367 (M^+, 100%), 339 (M^+-CO, 10%), 322 (M^+-OEt, 15%), 321 (M^+- EtOH, 15%). Anal. Calcd. for $C_{19}H_{17}N_3O_3S$ (367.1): C, 62.11; H, 4.66; N, 11.44; S, 8.73%. Found: C, 62.00; H, 4.70; N, 11.83; S, 9.02%.

3-Amino-4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (**4b**). Prepared as yellow needles in 93% yield; mp 175-176 °C. IR (KBr) cm^{-1}: 3484, 3343, 3228 (NH_2), 2977 (C-H aliphatic), 2200 (C≡N), 1727 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.49-7.52 (dd, *J* 2.4 Hz, 2H, Ar-H), 7.31-7.34 ((dd, *J* 2.4 Hz, 2H, Ar-H), 4.23 (s, 2H, NH_2), 4.03-4.09 (q, *J* 7.4 Hz, 2H, OCH_2), 2.69 (s, 3H, CH_3), 1.00-1.03 (t, *J* 7.2 Hz, 3H, CH_3); ^{13}C NMR and DEPT 135 (100 MHz, $CDCl_3$) δ ppm: 167.1, 161.4, 156.5, 148.7, 142.5, 136.1, 132.0, 130.1 (CH), 129.0 (CH), 127.1, 118.0, 114.5, 61.8 (OCH_2), 23.2 (CH_3 at C-6), 13.7 (CH_3 of ester group); MS: *m/z* 371 (M^+, 100%), 373 (M^++2, 39%), 343 (M^+- CO, 21%) and 326 (M^+- OEt, 12%). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2S$ (371.1): C, 58.14; H, 3.79; N, 11.30; S, 8.62%. Found: C, 58.23; H, 3.70; N, 11.48; S, 8.72%.

Method (B). A suspension of compound **3a,b** (10 mmol) and sodium acetate trihydrate (0.14 g, 1 mmol) in ethanol (30 mL) was heated at reflux for 3 h. The crystalline product that formed on cooling was collected and recrystallized from ethanol in the form of yellow needles of **4a,b**. These products are identical with those reported in method A in all aspects (yield: 83-88%).

3-Amino-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-2-carboxamide (5). This compound was prepared according to the reported method.[21]

Ethyl *N*-{4-aryl-2-cyano-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridin-3-yl}-methanimidates (6a,b). A mixture of compound **4a,b** (10 mmol), triethyl orthoformate (5 mL) in acetic anhydride (15 mL) was heated under reflux for 2 h and then allowed to cool. The solid that formed was collected and recrystallized from ethanol to afford **6a,b**.

Ethyl *N*-{2-cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridin-3-yl}-methanimidate (6a). Prepared as white needles in 90% yield; mp 154-155 °C. IR (KBr) cm^{-1}: 2974, 2836 (C-H aliphatic), 2212 (C≡N), 1731 (C=O), 1632 (C=N); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.54 (s, 1H, N=CH), 7.10-7.12 (d, *J* 8.4 Hz, 2H, Ar-H), 6.89-6.92 (d, *J* 8.8 Hz, 2H, Ar-H), 4.03-4.08 (q, *J* 7.2 Hz, 2H, OCH_2 of ester group), 3.84 (s, 3H, OCH_3), 3.60-3.65 (q, *J* 6.8 Hz, 2H, OCH_2 of ethoxygroup), 2.69 (s, 3H, CH_3 at C-6), 1.12-1.16 (t, *J* 7.2 Hz, 3H, CH_3 of ethoxygroup), 0.98-1.01 (t, *J* 7.0 Hz, 3H, CH_3 of ester group); ^{13}C NMR and DEPT 135 (100 MHz, $CDCl_3$): δ 167.7, 160.7, 159.9, 156.5 (N=CH), 156.3, 151.2, 145.0, 130.5 (CH), 128.5, 126.8, 122.5, 114.1, 114.0, 112.9 (CH), 91.9, 62.9 (OCH_2), 61.6 (OCH_2), 55.3 (OCH_3), 23.1 (CH_3 at C-6), 13.7 (CH_3 of ester group), 13.6 (CH_3 of ethoxy group); MS: *m/z* 423 (M^+, 100%), 378 (M^+- OEt, 13%), 367 (46%) and 132 (13%). Anal. Calcd. for $C_{22}H_{21}N_3O_4S$ (423.1): C, 62.40; H, 5.00; N, 9.92; S, 7.57%. Found: C, 62.17; H, 4.79; N, 9.57; S, 7.82%.

Ethyl *N*-{4-(4'-chlorophenyl)-2-cyano-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridin-3-yl}-methanimidate (6b). Obtained as white needles in 92% yield; mp 146-147 °C. IR (KBr) cm^{-1}: 2981 (C-H aliphatic), 2213 (C≡N), 1727 (C=O), 1634 (C=N); ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.59 (s, 1H, N=CH), 7.37-7.39 (dd, *J* 2.0 Hz, 2H, Ar-H), 7.14-7.16 (dd, *J*=2.0 Hz, 2H, Ar-H), 4.03-4.09(q, *J* 8.0 Hz, 2H, OCH_2 of ester), 3.56-3.62 (q, *J* 7.0 Hz, 2H, OCH_2 of ethoxy group), 2.70 (s,3H, CH_3), 1.17 -1.20 (t, *J* 7.0 Hz, 3H, CH_3 of ethoxygroup), 0.98-1.02 (t, *J* 7.2 Hz, 3H, CH_3 of ester group); ^{13}C NMR and DEPT 135 (100 MHz, $CDCl_3$) δ ppm: 167.2, 160.7, 156.8, 156.5 (N=CH), 150.8, 143.8, 134.7, 133.2, 130.6 (CH), 128.0, 127.7 (CH), 122.1, 113.8, 92.1, 63.2 (OCH_2), 61.7 (OCH_2), 23.2 (CH_3 at C-6), 13.7 (CH_3 of ester group), 13.7 (CH_3 of ethoxy group); MS: *m/z* 427 (M^+, 100%), 429 (M^++2, 41%), 382 (M^+-OEt, 14%), 371 (60%), 343 (21%). Anal. Calcd. for $C_{21}H_{18}ClN_3O_3S$ (427.1): C, 58.95; H, 4.24; N, 9.82; S, 7.49%. Found: C, 58.82; H, 4.31; N, 9.67; S, 7.72%.

Ethyl 3-amino-9-aryl-3,4-dihydro-4-imino-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylates (7a,b). To a suspension of compound **6a,b** (5 mmol) in dioxane (20 mL), hydrazine hydrate 99% (2 mL) was added. The reaction mixture was stirred at room temperature for 4 h. The solid that formed was collected and recrystallized from ethanol to give **7a,b**.

Ethyl 3-amino-3,4-dihydro-4-imino-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**7a**). Obtained as white needles in 78% yield; mp 204-206 °C. IR (KBr) cm^{-1}: 3306, 3157 (NH, NH_2), 2979 (C-H aliphatic), 1707 (C=O), 1609 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.89 (s, 1H, CH pyrimidine), 7.27-7.29 (d, *J* 8.8 Hz, 2H, Ar-H), 6.93-6.95 (d, *J* 8.8 Hz, 2H, Ar-H), 4.77 (s, 2H, NH_2), 4.05-4.08 (q, *J* 7.0 Hz, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 2.71 (s, 3H, CH_3), 1.00 -1.04 (t, *J* 7.0 Hz, 3H, CH_3 of ester); ^{13}C NMR and DEPT 135 (100 MHz, $CDCl_3$) δ ppm: 168.3, 161.9, 159.8, 155.4, 154.4, 148.2 (CH pyrimidine), 145.9, 145.9, 130.7 (CH), 128.6, 126.9, 124.0, 121.4, 112.9 (CH), 61.5 (OCH_2), 55.2 (OCH_3), 23.1 (CH_3 at C-6), 13.8 (CH_3 of ester group); MS: *m/z* 409 (M^+, 100%), 393 (M^+- NH_2, 19%); 367 (17%) and 365 (10%). Anal. Calcd. for $C_{20}H_{19}N_5O_3S$ (409.1): C, 58.67; H, 4.68; N, 17.10; S, 7.83%. Found: C, 58.44; H, 4.70; N, 17.36; S, 7.61%.

Ethyl 3-amino-9-(4-chlorophenyl)-3,4-dihydro-4-imino-7-methylpyrido[3',2':4,5]thieno [3,2-*d*]pyrimidine-8-carboxylate (**7b**). Obtained as white needles in 85% yield; mp 208-209 °C. IR (KBr) cm^{-1}: 3309, 3161 (NH, NH_2), 2986 (CH aliphatic), 1708 (C=O), 1613 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.87 (s, 1H, CH pyrimidine), 7.38-7.40 (dd, *J* 2.4 Hz, 2H, Ar-H), 7.27-7.29 (dd, *J* 2.4 Hz, 2H, Ar-H), 4.78 (s, 2H, NH_2), 4.05-4.10 (q, *J* 7.0 Hz, 2H, OCH_2), 2.72 (s, 3H, CH_3), 1.00 -1.03 (t, *J* 7.2 Hz, 3H, CH_3 ester); ^{13}C NMR and DEPT 135 (100 MHz, $CDCl_3$) δ ppm: 167.8, 161.9, 155.7, 154.3, 148.3 (CH pyrimidine), 145.6, 144.6, 134.6, 133.1, 130.7 (CH), 128.0, 127.7 (CH), 123.7, 121.6, 61.7 (OCH_2), 23.2 (CH_3 at C-6), 13.7 (CH_3 ester); MS: *m/z* 413 (M^+, 100%), 415 (M^++2, 41%), 397 (M^+- NH_2, 13%), 371 (16%). Anal. Calcd. for $C_{19}H_{16}ClN_5O_2S$ (413.1): C, 55.14; H, 3.90; N, 16.92; S, 7.75%. Found: C, 55.09; H, 4.11; N, 16.78; S, 8.00%.

General procedures for the synthesis of ethyl 7-aryl-9-methyl[1,2,4]triazolo[2'',3''-*c*] pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylates (8a,b)

Method (A). Compound **7a,b** (2 mmol) in triethyl orthoformate (10 mL) was heated at reflux for 3 h. The precipitate that formed while hot was collected and recrystallized from ethanol to afford **8a,b**.

Ethyl 7-(4-methoxyphenyl)-9-methyl[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylate (8a). Obtained as white fine needles in 76% yield; mp 205-206 °C. IR (KBr) cm^{-1}: 1726 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.11 (s, 1H, CH pyrimidine), 8.46 (s, 1H, CH triazole), 7.34-7.36 (d, 2H, Ar-H), 6.99-7.02 (dd, 2H, Ar-H), 4.10-4.14 (q, 2H, OCH_2), 3.91 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3), 1.03-1.05 (t, 3H, CH_3 ester); MS: *m/z* 419 (M^+, 100%), 387 (20%); 347 (11%). Anal. Calcd. for $C_{21}H_{17}N_5O_3S$ (419.1): C, 60.13; H, 4.09; N, 16.70; S, 7.64%. Found: C, 60.08; H, 4.11; N, 16.56; S, 7.39%.

Ethyl 7-(4-chlorophenyl)-9-methyl[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylate (8b). Obtained as white fine needles in 80% yield; mp 244-245 °C. IR (KBr) cm^{-1}: 2979 (C-H, aliphatic), 1727 (C=O), 1623 cm^{-1} (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.98 (s, 1H, CH pyrimidine), 8.47 (s, 1H, CH triazole), 7.45-7.47 (d, 2H, Ar-H), 7.34-7.36 (d, 2H, Ar-H), 4.08-4.14 (q, 2H, OCH_2), 2.78 (s, 3H, CH_3), 1.03-1.06 (t, 3H, CH_3 ester); MS: *m/z* 423 (M^+, 100%), 425 (M^++2, 40%). Anal. Calcd. for $C_{20}H_{14}ClN_5O_2S$ (423.1): C, 56.67; H, 3.33; N, 16.52; S, 7.56%. Found: C, 56.80; H, 3.31; N, 16.77; S, 7.34%.

Method (B). Compound **17** (1.64 g; 4 mmol) in formic acid 85% (20 mL) was heated at reflux for 6 h. The precipitate that formed on cooling was collected by filtration and recrystallized from ethanol in the form of white needles of compound **8a** (yield: 67%). This product is identical to that reported above in all aspects.

Ethyl 7-aryl-2,9-dimethyl[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylates (9a,b). Compound **7a,b** (2 mmol) in acetic anhydride (10 mL) was heated under reflux for 2 h. The crystalline precipitate that formed while hot was collected by filtration and recrystallized from ethanol to give **9a,b**.

Ethyl 2,9-dimethyl-7-(4-methoxyphenyl)[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-8-carboxylate (9a). Obtained as white crystals in 88% yield; mp 220-221°C. IR (KBr) cm^{-1}: 2964 (C-H aliphatic), 1736 (C=O), 1612 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H, CH pyrimidine), 7.34-7.36 (dd, *J* 1.8 Hz, 2H, Ar-H), 6.99-7.01 (dd, *J* 1.8 Hz, 2H, Ar-H), 4.08-4.14 (q, *J* 7.0 Hz, 2H, OCH_2), 3.91 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3), 2.67 (s, 3H, CH_3 triazole), 1.03-1.06 (t, *J* 7.0 Hz, 3H, CH_3 of ester); ^{13}C NMR and DEPT 135 (100 MHz, $CDCl_3$) δ ppm: 168.1, 165.9, 162.1, 160.0, 156.0, 148.8, 145.5, 144.5, 136.6 (CH pyrimidine), 130.5 (CH), 128.9, 126.9, 122.9, 119.2, 113.2 (CH), 61.6 (OCH_2), 55.3 (OCH_3), 23.2 (CH_3 pyridine), 14.5 (CH_3 triazole), 13.8 (CH_3 ester); MS: *m/z* 433 (M^+, 100%), 404 (M^+- Et, 25%); 388 (M^+- EtO, 30%) and 360 (M^+- CO_2Et, 35%). Anal. Calcd. for $C_{22}H_{19}N_5O_3S$ (433.1): C, 60.96; H, 4.42; N, 16.16; S, 7.40%. Found: C, 61.13; H, 4.41; N, 16.00; S, 7.18%.

Ethyl 7-(4-chlorophenyl)-2,9-dimethyl[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylate (9b). Obtained as white crystals in 85% yield; mp 245-247 °C. IR (KBr) cm^{-1}: 2979 (C-H aliphatic), 1727 (C=O), 1623 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.980 (s, 1H, CH pyrimidine), 7.455-7.471 (dd, *J* 2.0 Hz, 2H, Ar-H), 7.340-7.361 (dd, *J* 2.0 Hz, 2H, Ar-H), 4.087-4.141(q, *J* 7.2 Hz, 2H, OCH_2), 2.787 (s, 3H, CH_3), 2.682 (s, 3H, CH_3 attached to triazole ring), 1.030 -1.065 (t, *J* 7.0 Hz, 3H, CH_3 of ester); ^{13}C NMR and DEPT 135 (100 MHz, $CDCl_3$) δ ppm: 167.69, 166.02, 162.20, 156.30, 148.75, 144.28, 144.16, 136.76 (CH pyrimidine), 134.89, 133.20, 130.58 (CH), 128.45, 128.07(CH), 122.56, 119.52, 61.84 (OCH_2), 23.29 (CH_3 attached to pyridine ring), 14.57(CH_3 attached to triazole ring), 13.73 (CH_3 of ester group); MS: *m/z* 437 (M^+, 100%), 439 (M^++2, 41), 408 (M^+-Et, 25%), 392 (M^+-OC_2H_5, 41), 365 (M^+- CO_2Et, 22%) and 356 (13%). Anal. Calcd. for $C_{21}H_{16}ClN_5O_2S$ (437.1): C, 57.60; H, 3.68; N, 15.99; S, 7.32%. Found: C, 57.23; H, 3.70; N, 15.70; S, 7.54%.

Ethyl 2-anilino-7-aryl-9-methyl[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylates (10a,b). To a solution of compound **7a,b** (5 mmol) in pyridine (10 mL), phenyl isothiocyanate (0.65 mL, 5 mmol) was added. The reaction mixture was heated on a steam bath for 8 h and then allowed to stand at room temperature overnight. The precipitate that formed was collected and recrystallized from DMF-H_2O mixture to afford **10a,b**.

Ethyl 2-anilino-7-(4-methoxyphenyl)-9-methyl[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylate (10a). Prepared as pale yellow crystals in 73% yield; Yield: 73%; mp 285-286 °C. IR (KBr) cm^{-1}: 3500 (NH), 2976 (C-H aliphatic), 1720 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.92-7.83 (m, 11H, CH pyrimidine, NH and Ar-H), 4.02 (q, 2H, OCH_2), 3.77 (s, 3H, OCH_3), 2.68 (s, 3H, CH_3), 0.97 (t, 3H, CH_3 of ester); MS: *m/z* 510 (M^+, 3%), 393 (M^+-PhNCN, 100%), 365 (42%), 349 (13%), 321 (18%). Anal. Calcd. for $C_{27}H_{22}N_6O_3S$ (510.1): C, 63.52; H, 4.34; N, 16.46; S, 6.28%. Found: C, 63.34; H, 4.11; N, 16.43; S, 6.30%.

Ethyl 2-anilino-7-(4-chlorophenyl)-9-methyl[1,2,4]triazolo[2'',3''-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimidine-8-carboxylate (10b). Prepared as pale yellow crystals in 78% yield; mp 300-302 °C. IR (KBr) cm^{-1}: 3500 (NH), 1725 (C=O), 1644 (C=N). ^{1}H NMR (90 MHz, CF_3CO_2D) δ ppm: 8.10 (s, 1H, CH pyrimidine), 7.10-7.70 (m, 9H, Ar-H), 4.00-4.40 (q, 2H, OCH_2), 2.80 (s, 3H, CH_3), 1.00-1.30 (t, 3H, CH_3 of ester); MS: *m/z* 514 (M^+, 10%), 397 (M^+-PhNCN, 100%), 369 (58%), 353 (20%), 325 (27%). Anal. Calcd. for $C_{26}H_{19}ClN_6O_2S$ (514.1): C, 60.64; H, 3.72; N, 16.32; S, 6.23%. Found: C, 60.59; H, 3.83; N, 16.16; S, 6.11%.

Condensation of compounds 8a,b with isatin; formation of fused hexacyclic compounds 11a,b. A mixture of compound **7a,b** (2 mmol) and isatin (0.30 g, 2 mmol) in ethanol (20 mL) was heated under reflux for 3 h. The precipitate that formed while hot collected and recrystallized from dioxane to give **11a,b**.

3-Ethoxycarbonyl-4-(4-methoxyphenyl)-2-methylpyrido[3''',2''':4'',5'']thieno[3'',2'':4',5']-pyrimido[1',6':2,3][1,2,4]triazino[5,6-*b*]indole (11a). Prepared as red crystals in 82% yield; mp 334-335 °C. IR (KBr) cm^{-1}: 2947 (CH aliphatic), 1727 (C=O), 1634 (C=N); MS: *m/z* 520 (M^+, 100%), 519 (M^+-H, 29%), 491(M^+-Et, 26%). Anal. Calcd. for $C_{28}H_{20}N_6O_3S$ (520.1): C, 64.60; H, 3.87; N, 16.14; S, 6.16%. Found: C, 64.51; H, 3.91; N, 16.00; S, 6.18%.

4-(4-Chlorophenyl)-3-ethoxycarbonyl-2-methylpyrido[3''',2''':4'',5'']thieno[3'',2'':4',5']-pyrimido[1',6':2,3][1,2,4]triazino[5,6-*b*]indole (11b). Prepared as red crystals in 81% yield; mp 342-343 °C. IR (KBr) cm^{-1}: 1727 (C=O), 1631 (C=N). ^{1}H NMR (90 MHz, CF_3CO_2D) δ ppm: 9.70 (s, 1H, CH pyrimidine), 7.40-8.70 (m, 8H, Ar-H), 4.20-4.60 (q, 2H, OCH_2), 3.20 (s, 3H, CH_3), 1.00-1.30 (t, 3H, CH_3 of ester); MS: *m/z* 524 (M^+, 100%), 526 (M^++2, 40%), 495 (M^+-Et, 28%), 451 (M^+-CO_2Et, 14%). Anal. Calcd. for $C_{27}H_{17}ClN_6O_2S$ (524.1): C, 61.77; H, 3.26; N, 16.01; S, 6.11%. Found: C, 61.40; H, 3.23; N, 15.89; S, 6.07%.

Ethyl 8-(4-methoxyphenyl)-10-methyl-3-phenyl-2*H*-pyrido[3'',2'':4',5']thieno[3',2':4,5]-pyrimido[1,6-*b*][1,2,4]triazine-9-carboxylate (12). To a mixture of compound **7a** (0.82 g, 2 mmol) and phenacyl bromide (0.40 g; 2 mmol) in ethanol (20 mL), anhydrous sodium acetate (0.33 g; 4 mmol) was added. The reaction mixture was heated under reflux for 3 h. The precipitate that formed while hot was filtered, washed with water and recrystallized from ethanol to afford **12**. Obtained as pale yellow needles in 81% yield; mp 237-238 °C. IR (KBr) cm^{-1}: 2836 (C-H, aliphatic), 1716 (C=O), 1671 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.80 (s, 1H, CH pyrimidine), 6.88-7.73 (m, 9H, Ar-H), 4.76 (s, 2H, CH_2 triazine), 4.01-4.02 (q, 2H, OCH_2), 3.81 (s, 3H, OCH_3), 2.64 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); MS: *m/z* 509 (M^+, 100%), 405 (M^+-PhCN, 23%), 377 (17%). Anal. Calcd. for $C_{28}H_{23}N_5O_3S$ (509.1): C, 66.00; H, 4.55; N, 13.74; S, 6.29%. Found: C, 65.87; H, 4.41; N, 13.80; S, 6.40%.

Ethyl 9-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (14). A mixture of compound **5** (1.92 g, 5 mmol) and triethyl orthoformate (5 mL) in acetic anhydride (15 mL) was heated under reflux for 4 h. The precipitate that formed while hot was collected by filtration, washed with ethanol and crystallized from DMF to give **15**. Obtained as white needles in 80% yield; mp 298-299 °C. IR (KBr) cm^{-1}: 3220 (NH), 1731 (C=O, ester), 1659 (C=O, pyrimidinone); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.75 (s, 1H, NH), 8.03 (s, 1H, CH pyrimidinone), 7.26-7.28 (s, *J* 8.0 Hz, 2H, Ar-H), 6.98-7.00 (d, *J* 8.0 Hz, 2H, Ar-H), 4.06-4.08 (q, 2H, OCH_2), 3.83 (s, 3H, OCH_3), 2.64 (s, 3H, CH_3 at C-7), 0.95-0.97 (t, 3H, CH_3 ester); MS: *m/z* 395 (M^+, 100%), 366 (M^+- Et, 28%), 350 (M^+-OC_2H_5, 36%), 322 (M^+- CO_2Et, 22%). Anal. Calcd. for $C_{20}H_{17}N_3O_4S$ (395.1): C, 60.75; H, 4.33; N, 10.63; S, 8.11%. Found: C, 60.66; H, 4.41; N, 10.86; S, 7.85%.

Ethyl 4-chloro-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (15). A suspension of compound **14** (1.97 g, 5 mmol) in an excess amount of phosphorus oxychloride (25 mL) was heated under reflux on a steam bath for 3 h. The reaction mixture was cooled and then poured with vigorous stirring into ice-cooled water (150 mL). The solid that separated was filtered and crystallized from ethanol to afford **15**. Obtained as white pale yellow crystals in 79% yield; mp 166-167°C. IR (KBr) cm^{-1}: 2936 (C-H aliphatic), 1732 (C=O), 1608 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.81 (s, 1H, CH pyrimidine), 7.31-7.34 (dd, *J* 2.4 Hz, 2H, Ar-H), 6.99-7.01 (dd, *J* 2.4 Hz, 2H, Ar-H), 4.08-4.14 (q, *J* 7.0 Hz, 2H, OCH_2), 3.90 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3), 1.02-1.06 (t, *J* 7.2 Hz, 3H, CH_3 ester). Anal. Calcd. for $C_{20}H_{16}ClN_3O_3S$ (413.1): C, 58.04; H, 3.90; N, 10.15; S, 7.75; Cl, 8.57%. Found: C, 57.87; H, 4.11; N, 10.14; S, 8.13; Cl, 8.40%.

Ethyl 9-(4-chlorophenyl)-8-ethoxycarbonyl-7-methyl-4-thioxo-3,4-dihydro-pyrido[3',2':4, 5]thieno[3,2-*d*]pyrimidine-8-carboxylate (16). A mixture of 4-chloro compound **15** (2.07 g; 5 mmol) and thiourea (0.76 g; 10 mmol) in ethanol (30 mL) was heated under reflux for 6 h and then allowed to cool. The precipitated solid was collected, dissolved in sodium hydroxide solution 8% (20 mL) and filtered. The clear filtrate was acidified with acetic acid whereby a yellow product precipitated. It was collected by filtration and crystallized from

acetic acid to afford **16**. Obtained as yellow crystals in 80% yield; mp 276-277 °C. IR (KBr) cm^{-1}: 3150 (NH aliphatic), 1730 (C=O, ester); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.38 (s, 1H, CH pyrimidine), 7.34-7.36 (dd, *J* 2.2 Hz, 2H, Ar-H), 6.97-6.99 (dd, *J* 2.0 Hz, 2H, Ar-H), 6.65 (s, 1H, NH), 4.06-4.11 (q, *J* 7.2 Hz, 2H, OCH_2), 3.89 (s,3H, OCH_3), 2.74 (s, 3H, CH_3), 1.01-1.05 (t, *J* 7.2 Hz, 3H, CH_3 ester). Anal. Calcd. for $C_{20}H_{17}N_3O_3S_2$ (411.1): C, 58.38; H, 4.16; N, 10.21; S, 15.58%. Found: C, 58.17; H, 4.30; N, 10.08; S, 15.29%.

Ethyl 4-hydrazino-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (17). A mixture of compound **15** (2.07 g; 5 mmol) and hydrazine hydrate 99% (1.0 mL, 20 mmol) in ethanol (20 mL) was heated at reflux for 2 h. The precipitate was collected and recrystallized from dioxane to give **17**. Prepared as white crystals in 88% yield. mp 239-240 °C. IR (KBr) cm^{-1}: 3380, 3251 ($NHNH_2$), 2972 (C-H aliphatic), 1723 (C=O), 1659 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.04 (s, 1H, NH), 7.38 (s, 1H, CH pyrimidine), 6.93 -7.29 (m, 6H, NH_2 and Ar-H), 4.03-4.06 (q, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 2.71 (s, 3H, CH_3), 0.98 -1.00 (t, 3H, CH_3 ester). Anal. Calcd. for $C_{20}H_{19}N_5O_3S$ (409.1): C, 58.67; H, 4.68; N, 17.10; S, 7.83%. Found: C, 58.56; H, 4.43; N, 17.41; S, 7.62%.

Condensation of hydrazino compound 17 with 4-chlorobenzaldehyde or acetophenone; Formation of hydrazones 18 and 19 respectively. To a mixture of compound **17** (2.05 g; 5 mmol) and 4-chlorobenzaldehyde or acetophenone (5 mmol) in ethanol (20 mL), few drops of acetic acid were added. The reaction mixture was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from DMF-H_2O mixture to give **18** and **19** respectively.

Ethyl 4-(4-chlorobenzylidenehydrazino)-9-(4-methoxyphenyl)-7-methyl-pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (18). Prepared as yellow crystals in 90% yield; mp 250-252 °C. IR (KBr) cm^{-1}: 3200 (NH), 2981 (C-H, aliphatic), 1722 (C=O), 1598 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.54 (br. s, 1H, NH), 8.45 (s, 1H, CH pyrimidine), 7.80 (s, 1H, N=CH), 7.74-7.76 (d, *J* 8.0 Hz, 2H, Ar-H), 7.43-7.45 (d, *J* 8.4 Hz, 2H, Ar-H), 7.36-7.38 (d, *J* 8.8 Hz, 2H, Ar-H), 6.98-7.00 (d, *J* 8.8 Hz, 2H, Ar-H), 4.08-4.13 (q, *J* 7.2 Hz, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3), 1.03-1.06 (t, *J* 7.0 Hz, 3H, CH_3 of ester); MS: *m/z* 531 (M^+, 71%), 533 (M^+-ClC_6H_4CH=N, 100%), 533 (M^++2, 27%), 365 (43%), 321 (30%). Anal. Calcd. for $C_{27}H_{22}ClN_5O_3S$ (531.1): C, 60.96; H, 4.17; N, 13.16; S, 6.03%. Found: C, 60.78; H, 4.20; N, 13.00; S, 6.19%.

Acetophenone 8-ethoxycarbonyl-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-ylhydrazone (19). Prepared as yellow crystals in 88% yield; mp 225-226 °C. IR (KBr) cm^{-1}: 3186 (NH), 2974, 2926 (C-H, aliphatic), 1725 (C=O), 1610 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.648 (s, 1H, NH), 8.469 (s, 1H, CH pyrimidine), 7.95 (d, 2H, Ar-H), 7.25-7.51 (m, 5H, Ar-H), 6.98-700 (d, 2H, Ar-H), 4.07-4.12 (q, *J* 7.4 Hz, 2H, OCH_2), 3.90 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3), 2.36 (s, 3H, CH_3 hydrazone), 1.02-1.06 (t, *J* 7.4 Hz, 3H, CH_3 ester); MS: *m/z* 511 (M^+, 14%) 77 ($C_6H_5^+$, 100%). Anal. Calcd. for $C_{28}H_{25}N_5O_3S$ (511.1): C, 65.74; H, 4.93; N, 13.69; S, 6.27%. Found: C, 65.52; H, 4.70; N, 13.83; S, 6.02%.

Ethyl 4-(3,5-dimethyl-1-pyrazolyl)-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (20). A mixture of **17** (2.05 g; 5 mmol) and acetylacetone (15 mL) was gently heated at reflux for 4 h. The reaction mixture was triturated with ethanol (15 mL) and then left to cool. The precipitated product was collected and recrystallized from ethanol to give **20**. Obtained as white crystals in 77% yield; mp 146-147 °C. IR (KBr) cm^{-1}: 2977, 2838 (C-H, aliphatic), 1726 (C=O), 1610 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.73 (s, 1H, CH pyrimidine), 7.36-7.38 (d, *J* 8.8 Hz, 2H, Ar-H), 6.99-7.01 (d, *J* 8.4 Hz, 2H, Ar-H), 6.09 (s, 1H, CH pyrazole), 4.076-4.129 (q, *J* 7.0 Hz, 2H, OCH_2), 3.91 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3), 2.77 (s, 3H, CH_3 pyrazole), 2.38 (s, 3H, CH_3 pyrazole), 1.02-1.06 (t, *J* 7.2 Hz, 3H, CH_3 ester); MS: *m/z* 473 (M^+, 100%), 444 (M^+-Et, 25%), 428 (M^+-OEt, 11%), 400 (M^+-CO_2Et, 10%). Anal. Calcd. for $C_{25}H_{23}N_5O_3S$ (473.1): C, 63.41; H, 4.90; N, 14.79; S, 6.77%. Found: C, 63.09; H, 4.88; N, 14.70; S, 8.10%.

Ethyl 4-(5-amino-4-ethoxycarbonyl-1-pyrazolyl)-9-(4-methoxyphenyl)-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (21). A mixture of **17** (2.05 g; 5 mmol) and Ethyl (ethoxymethylene) cyanoacetate (0.85g; 5 mmol) in ethanol was heated at reflux for 4 h and then left to cool. The precipitated product was collected and recrystallized from ethanol to give **21**. Obtained as white crystals in 80% yield; mp 193-194 °C. IR (KBr) cm^{-1}: 3416, 3300 (NH_2), 2981, 2934, 2839 (C-H, aliphatic), 1720 (C=O, ester), 1689 (C=O, ester group attached to pyrazole ring), 1626 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.73 (s, 1H, CH pyrimidine), 7.99 (s, 1H, CH pyrazole), 7.65 (br. s, 2H, NH_2), 7.35-7.37 (dd, 1.8 Hz, 2H, Ar-H), 6.99-7.01 (dd, 1.6 Hz, 2H, Ar-H), 4.29-4.35 (q, *J* 7.0 Hz, 2H, OCH_2), 4.07-4.13 (q, *J* 7.0 Hz, 2H, OCH_2), 3.91 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3), 1.36-1.39 (t, *J* 7.0 Hz, 3H, CH_3 ester), 1.02-1.06 (t, *J* 7.0 Hz, 3H, CH_3 ester); MS: *m/z* 532 (M^+, 100%), 485 (21%), 457 (15%). Anal. Calcd. for $C_{26}H_{24}N_6O_5S$ (532.1): C, 58.64; H, 4.54; N, 15.78; S, 6.02%. Found: C, 58.43; H, 4.70; N, 15.83; S, 6.00%.

Ethyl 7-(4-methoxyphenyl-9-methyl[1,2,4]triazolo[4",3"-*c*]pyrido[3',2':4,5]thieno[2,3-*c*]pyrimidine-8-carboxylate (23). Compound **17** (2.05 g; 5 mmol) in triethyl orthoformate (15 mL) was heated at reflux for 4 h. The precipitate that formed while hot was collected and recrystallized from ethanol to afford **23**. Obtained as white crystals in 76% yield; mp 228-229 °C. IR (KBr) cm^{-1}: 3103 (C-H, aromatic), 1723 (C=O, ester), 1609 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.94 (s, 1H, CH pyrimidine), 8.76 (s, 1H, CH triazole), 7.31-7.34 (dd, *J* 2.4 Hz, 2H, Ar-H), 6.98-7.00 (dd, *J* 2.2 Hz, 2H, Ar-H), 4.09-4.14 (q, *J* 7.2 Hz, 2H, OCH_2), 3.90 (s, 3H, OCH_3), 2.77 (s, 3H, CH_3), 1.03-1.06 (t, *J* 7.2 Hz, 3H, CH_3 ester). Anal. Calcd. for $C_{21}H_{17}N_5O_3S$ (419.1): C, 60.13; H, 4.09; N, 16.70; S, 7.64%. Found: C, 60.24; H, 4.32; N, 16.58; S, 7.60%.

Conclusions

Ethyl 3-amino-9-aryl-3,4-dihydro-4-imino-7-methylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylates **7a,b** and ethyl 4-chloro-9-(4-methoxy-phenyl)-7-methyl-pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**17**) were synthesized and used as keys intermediate for synthesizing the promising pyridothienopyrimidines as well as triazolopyridothienopyrimidines and pyridothienopyrimidotriazinoindoles.

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