Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Pyridine-2(1H)-thione in Heterocyclic Synthesis: Synthesis of Some New Nicotinic Acid Ester, Thieno[2, 3-b]pyridine, Pyrido[3′, 2′: 4, 5]thieno [3, 2-d]pyrimidine, and Thiazolylpyrazolo[3, 4-b]pyridine Derivatives

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Published online: 15 Aug 2006.

To cite this article: Mohamed A. M. Gad-Elkareem , Azza M. Abdel-Fattah & Mohamed A. A. Elneairy (2006) Pyridine-2(1H)-thione in Heterocyclic Synthesis: Synthesis of Some New Nicotinic Acid Ester, Thieno[2, 3-b]pyridine, Pyrido[3′, 2′: 4, 5]thieno [3, 2-d]pyrimidine, and Thiazolylpyrazolo[3, 4-b]pyridine Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 181:4, 891-911, DOI: 10.1080/10426500500272152

To link to this article: http://dx.doi.org/10.1080/10426500500272152

Phosphorus, Sulfur, and Silicon, 181:891–911, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500272152

Pyridine-2(1*H*)-thione in Heterocyclic Synthesis: Synthesis of Some New Nicotinic Acid Ester, Thieno[2,3-*b*]pyridine, Pyrido[3′,2′:4,5]thieno [3,2-*d*]pyrimidine, and Thiazolylpyrazolo-[3,4-*b*]pyridine Derivatives

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*Nicotinic acid esters **3a–c** were prepared by the reaction of pyridine-2(1*H*)-thione derivative **1** with α-halo-reagents **2a–c**. Compounds **3a–c** underwent cyclization to the corresponding thieno[2,3-*b*]pyridines **4a–c** via boiling in ethanol/piperidine solution. Compounds **4a–c** condensed with dimethylformamide-dimethylacetal (DMF-DMA) to afford 3-{[(N,N-dimethylamino)methylene]amino}thieno[2,3-*b*]-pyridine derivatives **6a–c**. Moreover, compounds **4a–c** and **6a–c** reacted with different reagents and afforded the pyrido[3′, 2′ : 4, 5]thieno[3,2-*d*]pyrimidine derivatives **10a–d, 11a–c, 12a,b, 14a,b**, **17**, and **19**. In addition, pyrazolo[3,4-*b*]pyridine derivative **20** (formed via the reaction of **1** with hydrazine hydrate) reacted with ethylisothiocyanate yielded the thiourea derivative **21**. Compound **21** reacted with α-halocarbonyl compounds to give the 3-[(3*H*-thiazol-2-ylidene)amino]-1*H*-pyrazolo[3,4-b]pyridine derivatives **23a–c, 25**, and **27a,b**.*

Keywords Ethyl nicotinates; pyridinethiones; pyridothienopyrimidines; thiazolylpyrazolo[3, 4-*b*]pyridines; thieno[2, 3-*b*]pyridnes

INTRODUCTION

In the last few years, our research group has devoted much attention to the construction of new pyridine and annelated pyridine derivatives[1–8] of expected biological activities. On account of the reported biological activities of a pyridine ring that can be found in a

Received March 1, 2005; accepted June 10, 2005.
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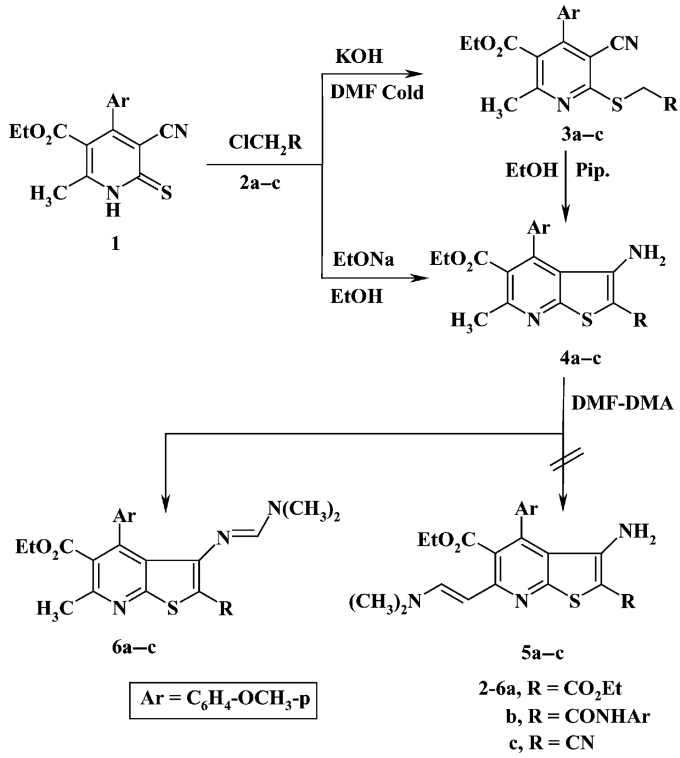
broad variety of drugs, such as milirinone, which is useful for treatment of the heart,[9] acetylcholine enhancement useful in the treatment of Alzheimer disease[10] and substituted pyridine derivatives were used as antitumer[11] and antiamnesic[12] agents. Recently, ethyl nicotinate derivatives were reported to be used as agrochemical fungicid[13] and anticancer[14] agents. Also, *S*-alkylpyridines posses neurotropic activity.[15] Moreover, thieno[2, 3-*b*]pyridines are of special importance due to the reported biological activities such as antibacterial,[3,8,16–20] antihypertensive,[21] and ganodotropin-releasing hormone antagonizing activity [22,23] and have neurotropic activity.[15] Some thieno[2, 3-*b*]-pyridine-2-carboxylate derivatives were reported to be used as anti-inflammatory.[24] (1)Benzothieno[2, 3-*b*]pyrimidines were used as phospho diestrase V inhibitors.[25] In addition, pyridothienopyrimidines have found applications as analgesics,[26] antipyretics,[27] antiflammatories,[28] antianaphylactic,[29,30] and antimicrobial[19,31] activities. Pyrazolo[3, 4-*b*]pyridines have been used in treating thrombocytopenia, erythropenia,[32] and pemcytopenia;[33] they also are useful for the treatment of depression and obsessive compulsive disorder.[34] They have been used as CRF antagonists,[35] platelet aggregation inhibitors,[36] and antimicrobial.[3,4,37] On the other hand, several substituted thiazolyl derivatives are reported to possess anti-inflammatory, antioxidant,[38–40] lipoxygenase inhibitors,[40] anticancer,[41] anti–HIV,[41] and antimicrobial[3,4,41–43] activities. The previously mentioned findings stimulated the interest for the synthesis of some new ethyl nicotinate, thieno[2, 3-*b*]pyridine, pyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine, and thiazolylpyrazolo[3, 4-*b*]pyridine derivatives of expected biological activities.

RESULTS AND DISCUSSION

It has been found that pyridine-2(1*H*)-thione **1**[44] reacted with ethyl chloroacetate (**2a**) in KOH/DMF solution under stirring at r.t. to afford the corresponding ethyl-5-cyano-6-[(2-ethoxy-2-oxoethyl)thio]nicotinate derivative **3a** via dehydrochloronation. The structure of **3a** was confirmed by elemental analysis and spectral data. The IR spectrum of **3a** showed the presence of absorption bands due to C≡N at 2224 and two C=O at 1750 and 1723 cm^{-1} function groups. In a similar manner, compound **1** reacted with each of 2-chloro-*N*-(4-methoxyphenyl)acetamide (**2b**) and chloroacetonitrile (**2c**) to afford the corresponding ethyl nicotinate derivatives **3b**,**c**. The ^1H NMR spectrum of compound **3b** exhibited the two singlet signals at $\delta = 4.03$ and $\delta = 8.79$ ppm assignable for SCH_2 and NH. The structure of compounds **3a–c** was further elucidated via its cyclization to the corresponding

thieno[2, 3-*b*]pyridine derivatives **4a–c** upon boiling in ethanol containing a few drops of piperidine as a catalyst. The IR spectra of compounds **4a–c** showed the presence of the absorption bands of the newly born NH_2 group (cf, Scheme 1 and Experimental Section).



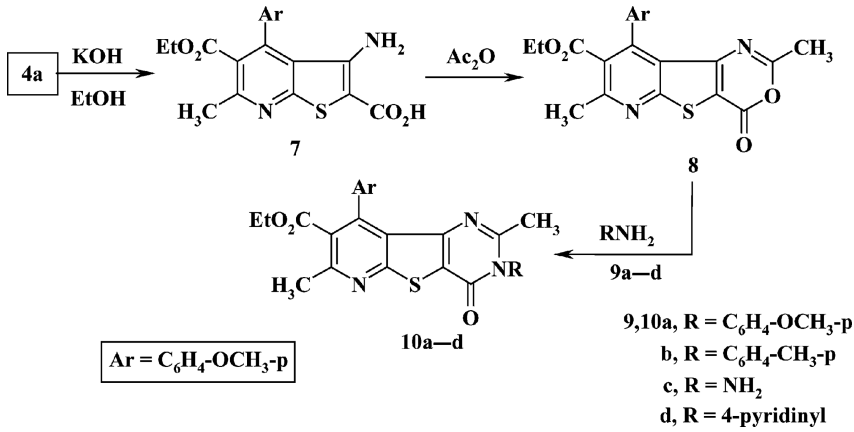
SCHEME 1

An unequivocal support for the structure **4a–c** was achieved via their synthesis by another route, by the reaction of **1** and each of **2a–c** in ethanolic sodium ethoxide solution to afford the same reaction products **4a–c** (cf, Scheme 1 and Experimental Section).

The condensation of **4a** with DMF-DMA in dry xylene under reflux yielded the corresponding 3-{[(*N*, *N*-dimethylamino)-methylene]amino}-6-methylthieno[2, 3-*b*]pyridine derivative **6a** rather than the possible alternative 3-amino-6-[2-(*N*, *N*-dimethylamino)-vinyl]thieno[2, 3-*b*]pyridine derivative **5a**. Compound **5a** was ruled out based on spectral data and chemical transformations; thus, the IR spectrum of **6a** showed the absence of the absorption band due to the NH_2 group while its ^{1}H NMR revealed the signals

at $\delta = 2.65$ ppm for CH_3 at $\delta = 2.80$ ppm for $N(CH_3)_2$ and absence of any signals due to NH_2 protons. Similarly, compounds **4b,c** condensed with DMF-DMA to give the corresponding 3-{[(*N*, *N*-dimethylamino)methylene]amino}-6-methylthieno[2, 3-*b*]pyridine derivatives **6b,c** rather than 3-amino-6-[2-(*N*, *N*-dimethylamino)-vinyl]thieno[2, 3-*b*]pyridine derivatives **5b,c** (cf, Scheme 1 and Experimental Section).

The hydrolysis of compound **4a** in 10% ethanolic potassium hydroxide solution afforded after acidification the corresponding thieno[2, 3-*b*]pyridine-2-carboxylic acid derivative **7** which, in tern, reacted with acetic anhydride and afforded the corresponding 2-methylpyrido[3′,2′:4,5]thieno[3, 2-*d*][1,3]oxazine-4-one derivative **8**. The IR spectrum of compound **8** showed the presence of the absorption band of the newly C=O of oxazinone ring at 1754 cm^{-1}, and the absence of the absorption band corresponded to NH_2 group while its ^1H NMR spectrum indicated the presence of singlet signal due to $C_{(2)}$-CH_3 at $\delta = 3.59$ ppm, and an absence of any signals may be attributed to NH_2 or OH protons (cf, Scheme 2 and Experimental Section).

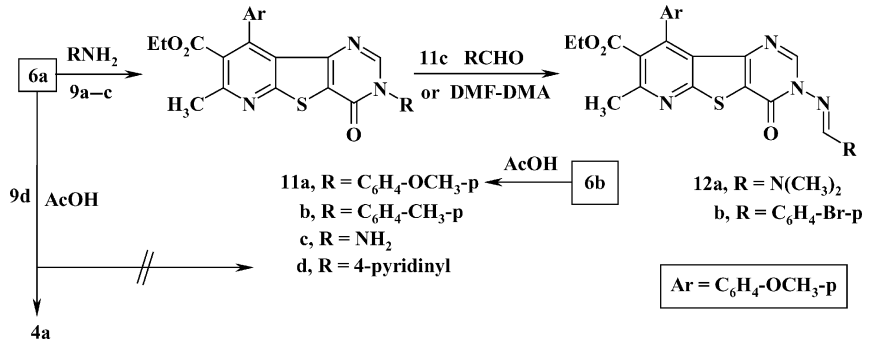


SCHEME 2

The reaction of the oxazinone derivative **8** with p-anisidine (**9a**) in acetic acid afforded the corresponding 2-methyl-3-(4-methoxyphenyl)pyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine derivative **10a**. The IR spectrum of **10a** showed the absence of the absorption band of C=O of the oxazinone ring while its ^1H NMR spectrum revealed the presence of the signals of the additional C_6H_4-OCH_3 protons. Analogously, compound **8** reacted with p-toluidine (**9b**), hydrazine hydrate (**9c**), and 4-aminopyridine (**9d**) to give the corresponding

pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivatives **10b–d** in a respective manner (cf, Scheme 2 and Experimental Section).

The reactivity of the formamidine derivative **6a** towards aromatic amines was investigated. Thus, **6a** reacted with p-anisidine (**9a**) in glacial acetic acid to afford the corresponding 3-(4-methoxyphenyl)pyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine derivative **11a** via the loss of one molecule of each of dimethylamine and ethanol. The ^{1}H NMR spectrum of **11a** did not reveal any signals attributed to $N(CH_3)_2$, and 2-ethoxycarbonyl protons and revealed the signals of the new C_6H_4-OCH_3 at $\delta = 3.88$ and 7.31–7.37 ppm. A strong evidence for the structure **11a** came from its synthesis via another route by heating compound **6b** in glacial acetic acid under reflux[5] to give the same reaction product **11a** (cf, Scheme 3 and Experimental Section).



SCHEME 3

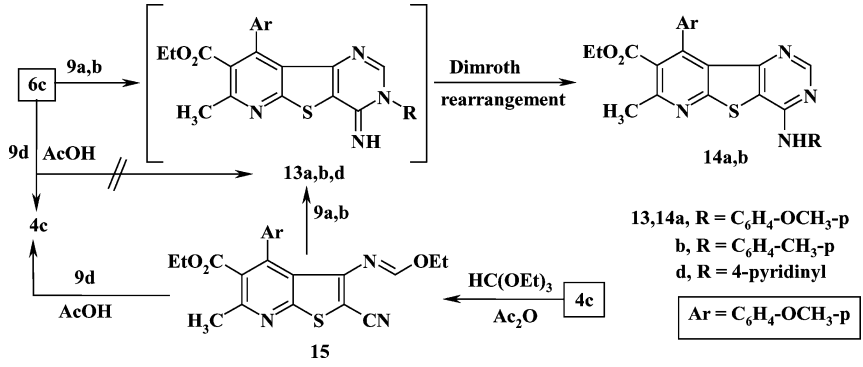
In the same manner, compound **6a** reacted with p-toluidine (**9b**) and hydrazine hydrate (**9c**) to yield the corresponding pyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine derivatives **11b,c**. In contrast behavior, the reaction of **6a** with 4-aminopyridine (**9d**) afforded 3-aminothieno[2, 3-*b*]pyridine derivative **4a** instead of the expected 3-pyridin-4-ylpyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine derivative **11d**. The formation of **4a** in this reaction product proceed via (*N*, *N*-dimethylamino)methylene group exchange.[45] The condensation of 3-aminopyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine derivative **11c** with each of DMF-DMA and p-bromobenzaldehyde afforded the corresponding condensation products **12a**,**b** respectively (cf, Scheme 3 and Experimental Section).

The work was extended to study the reactivity of 2-cyano-3-{[(*N*, *N*-dimethylamino)methylene]amino}thieno[2, 3-*b*]pyridine derivative **6c** towards aromatic amines **9a**,**b**,**d**. Thus, **6c** reacted with p-anisidine (**9a**) in glacial acetic acid under reflux to yield the

corresponding 4-[(4-methoxyphenyl)amino]pyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine derivative **14a**. The IR spectrum of **14a** indicated the absence of CN group and presence of NH at 3209 cm^{-1}, while its ^1H NMR revealed NH at $\delta = 7.07$ ppm, which lost after a D_2O-exchange. The formation of **14a** from **6c** and p-anisidine (**9a**) is assumed to procced through the *Dimorth rearrangement*[45] of the initial cyclization product **13a** under the reaction condition to yield **14a**.

Similarly, **6c** reacted with p-toluidine (**9b**) under the same reaction condition to afford 4-[(4-methylphenyl)amino]pyrido[3′,2′:4,5]thieno-[3, 2-*d*]pyrimidine derivative **14b**.

A hard evidence for structure **14a**,**b** came from its synthesis through another route via the condensation of **4c** with triethylorthoformate and the subsequent condensation of the so formed 2-cyano-3-[(ethoxymethylene)amino]thieno[2, 3-*b*]pyridine derivative **15** with **9a**,**b** to afford a product identical in all respect (m.p., mixed m.p., and spectral data) with **14a**,**b** (cf. Scheme 4 and Experimental Section).

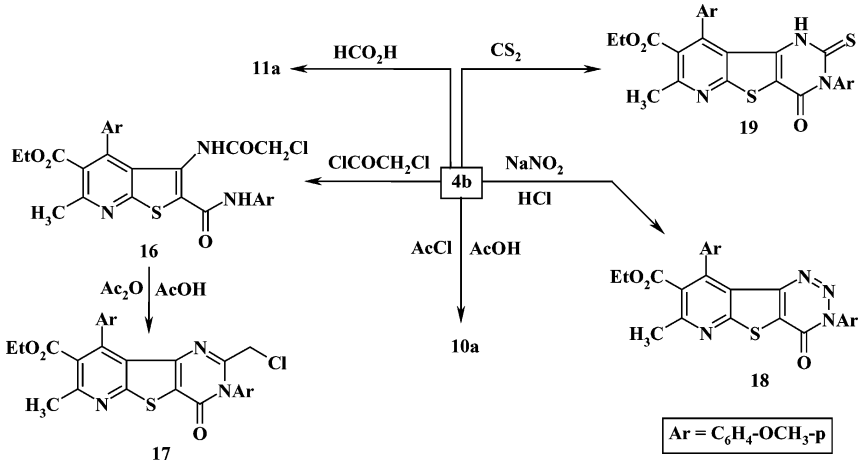


SCHEME 4

In contrast to its behavior towards aromatic amines **9a,b**, compound **6c** reacted with 4-aminopyridine (**9d)** afforded 3-amino-2-cyanothieno[2,3-*b*]pyridine derivative **4c** instead of the expected 4-(pyridin-4-ylamino)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivative **14d**. The formation of **4c** in this reaction is assumed to proceed via the (*N*, *N*-di-methylamino)methylene group exchange.[45] The same behavior was observed in the reaction of compound **15** with **9d** to give **4c** instead of **14d** (cf. Scheme 4 and Experimental Section).

Work was also extended to study the reactivity of the aminocarboxamide system in compound **4b**. Thus, the treatment of compound **4b** with chloroacetyl chloride in DMF solution afforded the corresponding 3-[(2-chloroacetyl)amino]thieno[2, 3-*b*]pyridine derivative **16**. The IR (cm^{-1}) spectrum of compound **16** showed the presence of two NH at

3377 and 3291 and two carbonyl at 1722 and 1647 function groups. The ^{1}H NMR spectrum of **16** revealed signals at $\delta = 3.50$ (s, 2H, $COCH_2Cl$), 8.47 (s, 1H, NH), and 8.70 (s, 1H, NH). The cyclization of compound **16** via heating its solution in a mixture of acetic anhydride and acetic acid yielded the corresponding 2-chloromethylpyrido[3′,2′:4,5]thieno-[3, 2-*d*]pyrimidine derivative **17**, while the acetylation of **4b** using acetyl chloride in glacial acetic acid afforded compound **10a**. The treatment of **4b** with formic acid[5] afforded the corresponding 3-(4-methoxyphenyl)pyrido[3′,2′:4,5]thieno[3, 2-*d*]pyrimidine derivative **11a** (cf, Scheme 5 and Experimental Section).



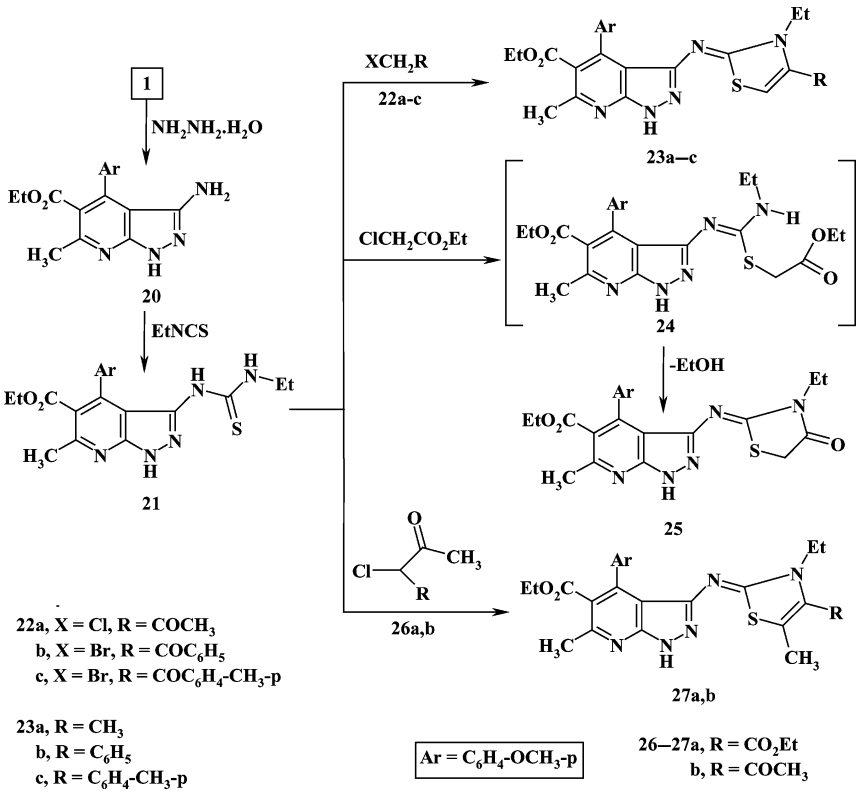
SCHEME 5

Diazotization and self coupling of the amino amide system in compound **4b** afforded the corresponding pyrido[3′,2′:4,5]thieno[3, 2-*d*]-[1,2,3]triazinone derivative **18**. The reaction of **4b** with carbon disulfide in pyridine afforded the pyridothienopyrimidine derivative **19**. The structure of compounds **18** and **19** was established based on the elemental analyses and spectral data (cf. Scheme 5 and Experimental Section).

The work was further extended to shed more light on the reactivity of 3-aminopyrazolo[3,4-*b*]pyridine derivative **20** (prepared by the reaction of **1** with hydrazine hydrate)[44] towards isothiocyanate. Thus, compound **20** reacted with ethyl isothiocyanate in pyridine solution to afford the thiourea derivative **21**. The structure of **21** was infered by elemental analysis, spectral data, and chemical transformations. The IR spectrum of **21** showed the absence of the absorption band due to the NH_2 group.

The ^{1}H NMR spectrum of **21** revealed 3NH protons at $\delta = 7.58, 9.96,$ and 12.53 ppm, which lost after the D_2O-exchange.

The reaction of the thiourea derivative **21** with α-halocarbonyl compounds was investigated. Thus, compound **21** reacted with chloroacetone (**22a**) in an ethanol solution contaning sodium acetate under reflux to give the corresponding 3-[(3-ethyl-4-methyl-3*H*-thiazol-2-ylidene)amino]-1*H*-pyrazolo[3, 4-*b*]pyridine derivative **23a** via the loss of one molecule of each of hydrogen chloride and water. The structure of compound **23a** was elucidated by elemental analysis and spectral data. ^{1}H NMR spectrum of **23a** revealed the signal of thiazole-$C_{(5)}$H at $\delta = 5.87$ and only one NH at $\delta = 10.94$ ppm (cf. Scheme 6 and Experimental Section).



SCHEME 6

Similarly, compound **21** reacted with ω-bromoacetophenone **22b** and p-methyl-ω-bromoacetophenone **22c** under the same reaction conditions to give the corresponding 3-[(thiazol-2-ylidene)amino]-1*H*-

pyrazolo[3, 4-*b*]pyridine derivatives **23b,c** respectively. The reaction of ethyl chloroacetate with **21** gave the corresponding 3-[(3-ethyl-4-oxothiazolidin-2-ylidene)amino1*H*-pyrazolo[3, 4-*b*]pyridine derivative **25** through the intermediate **24** via the loss of ethanol molecule.[3,4] The ^{1}H NMR spectrum of **25** indicated the presence of CH_2 protons of the thiazole moiety at $\delta = 3.96$ ppm. Also, compound **21** reacted with ethyl-2-chloro-3-oxobutanoate (**26a**) and 3-chloropentane-2,4-dione (**26b**) to afford the corresponding 3-[(3-ethyl-3*H*-thiazol-2-ylidene)amino]-1*H*-pyrazolo[3, 4-*b*]pyridine derivatives **27a,b**, respectively. The structures of **27a,b** were confirmed based on elemental analyses and spectral data (cf. Scheme 6 and the Experimental Section).

EXPRIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra in KBr discs were recorded on BRUKER Vector 22 FT-IR spectrophotometer. ^{1}H NMR spectra were determined in DMSO-D_6 and $CDCl_3$ at 300 MHz on Varian Mercury VX spectrometer using TMS as an internal standared. Chemical shifts are expressed as δ ppm units and coupling conestant J as Hz. Mass spectra were recorded on GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

Compounds 1 and 20 were prepared according to the literature procedures.[44] * In the ^{1}H NMR data means that these protons are D_2O-exchange.

The Reaction of 1 With α-Halocarbonyl Compounds 2a–c

General Procedure

A mixture of compound **1** (10 mmoles) and each of compounds **2a–c** (10 mmoles) in DMF (30 mL) containing KOH (12 mmoles) was stirred at r.t. for 2 h then poured onto ice-cold water and acidified with dil. HCl. The solid products obtained were filtered off, washed with water, and crystallized from ethanol to give compounds **3a–c**, respectively.

Ethyl-5-cyano-6-[(2-ethoxy-2-oxoethyl)thio]-4-(4-methoxyphenyl)-2-methylnicotinate (3a)

Yellow crystals (68%, ethanol), m.p. 118°C, IR υ (cm^{-1}): 2224 (CN), 1750 (CO aliph.ester), 1723 (CO arom. ester), 1606 (C=N). Anal. for $C_{21}H_{22}N_2O_5S$ (414), calcd.: C, 60.86; H, 5.31; N, 6.76; S, 7.72. Found, C, 60.94; H, 5.43; N, 6.68; S, 7.62%.

Ethyl-5-cyano-6-({2-[(4-methoxyphenyl)amino]-2-oxoethyl}-thio)-4-(4-methoxyphenyl)-2-methylnicotinate (3b)

Pale yellow crystals (64%, ethanol), m.p. 178°C, IR υ (cm^{-1}): 3323 (NH), 2221 (CN), 1724 (CO-ester), 1672 (CO-amide), 1610 (C=N). ^{1}H NMR ($CDCl_3$), δ 0.96–1.03 (t, J = 7.2 Hz, 3H, CH_2 $\underline{CH_3}$); 2.68 (s, 3H, CH_3); 3.78 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.03 (s, 2H, SCH_2CO); 4.06–4.13 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.834–6.878 (d, J = 8.8 Hz, 2H, Ar-H); 6.968–7.012 (d, J = 8.8 Hz, 2H, Ar-H); 7.325–7.408 (m, 4H, Ar-H)); 8.79 (s, 1H, NH). Anal. for $C_{26}H_{25}N_3O_5S$ (491) calcd: C, 63.54; H, 5.09; N, 8.55; S, 6.51. Found, C, 63.41; H, 5.19; N, 8.40; S, 6.63%.

Ethyl-5-cyano-6-[(cyanomethyl)thio]-4-(4-methoxyphenyl)-2-methylnicotinate (3c)

Yellow crystals (70%, ethanol), m.p. 138–140°C, IR υ (cm^{-1}): 2248 (CN), 2220 (CN), 1727 (CO) 1601 (C=N). Analysis for $C_{19}H_{17}N_3O_3S$ (367) calcd: C, 62.12; H, 4.63; N, 11.44; S, 8.72. Found, C, 62.00; H, 4.50; N, 11.68; S, 8.60%.

Synthesis of Compounds 4a–c

Route A: Cyclization of Compounds 3a–c

A solution of compounds **3a–c** (10 mmoles) in ethanol (30 mL) containing a catalytic amount of piperidine (0.5 mL) was heated under reflux for 3 h. The solid products obtained after cooling were filtered off and crystallized from ethanol to afford compounds **4a–c**.

Route B

A mixture of compound **1** (10 mmoles) and compounds **2a–c** (10 mmoles) in ethanolic sodium ethoxide (prepared from 0.02 atom sodium metal and 40 mL ethanol) was heated under reflux for 4 h and then cooled. The reaction mixtures were then poured onto ice-cold water and neutralized by diluted HCl. The solid products obtained were filtered off and crystallized from ethanol to give compounds **4a–c**.

Diethyl-3-amino-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]-pyridine-2,5-dicarboxylate (4a)

Yellow crystals (68%, ethanol), m.p. 164°C, IR υ (cm^{-1}): 3478, 3367 (NH_2), 1725 (CO-pyrid.ester), 1674 (CO-ester in thiophene with H-bond), 1606 (C=N). ^{1}H NMR ($CDCl_3$),: δ 0.99–1.03 (t, J = 7.2 Hz, 3H, CH_2 $\underline{CH_3}$); 1.34–1.38 (t, J = 7.0 Hz, 3H, CH_2 $\underline{CH_3}$); 2.69 (s, 3H, CH_3); 3.86 (s, 3H, OCH_3); 4.02–4.09 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 4.24–4.35 (q, J = 7.0 Hz, 2H, CH_2CH_3); 5.54 (s, 2H, NH_2*); 6.98–7.022 (d, 2H,

Ar-H, J = 8.4); 7.268–7.310 (d, 2H, Ar-H, J = 8.4). Anal. for $C_{21}H_{22}N_2O_5S$ (414) calcd: C, 60.86; H, 5.31; N, 6.76; S, 7.72. Found, C, 60.98; H, 5.20; N, 6.65; S, 7.90%.

Ethyl-3-amino-2-{[(4-methoxyphenyl)amino]carbonyl}-4-(4-methoxyphenyl)-6-methythieno[2,3-b]pyridine-5-carboxylate (4b)

Yellow crystals (63%, ethanol), m.p. 176–177°C, IR υ (cm^{-1}): 3477, 3320, 3220 (NH_2 and NH), 1725 (CO-ester), 1630 (CO-amide with H-bond). Anal. for $C_{26}H_{25}N_3O_5S$ (491) a clcd: C, 63.54; H, 5.09; N, 8.55; S, 6.51. Found, C, 63.66; H, 5.18; N, 8.43; S, 6.63%.

Ethyl-3-amino-2-cyano-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-5-carboxylate (4c)

Yellow crystals (68%, ethanol), m.p. 198–200°C, IR υ (cm^{-1}): 3475, 3343 (NH_2), 2198 (CN), 1728 (CO), 1628 (C=N).^{1}H NMR ($CDCl_3$): δ 0.97–1.04 (t, J = 7.4 Hz, 3H, CH_2 $\underline{CH_3}$); 2.67 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 4.00–4.11 (q, J = 7.4 Hz, 2H, $\underline{CH_2}CH_3$); 4.37 (s, 2H, NH_2*); 6.993–7.035 (d, J = 8.4 Hz, 2H, Ar-H); 7.259–7.301 (d, J = 8.4 Hz, 2H, Ar-H). Anal. for $C_{19}H_{17}N_3O_3S$ (367) calcd: C, 62.12; H, 4.63; N, 11.44; S, 8.72. Found, C, 62.25; H, 4.78; N, 11.31; S, 8.87%.

The Reaction of 4a–c with DMF-DMA

A mixture of compounds **4a–c** (10 mmoles) and DMF-DMA (13 mmoles) in dry xylene (30 mL) was heated under reflux for 6 h. The reaction mixture was cooled and triturated with petroleum ether (40-60). The solid product obtained was filtered off and crystallized from ethanol to give compounds **6a–c**, respectively.

Diethyl-3-{[(N,N-dimethylamino)methylene] amino}-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-2,5-dicarboxylate (6a)

Yellow crystals (48%), m.p. 130°C, IR υ (cm^{-1}): 1724 (CO), 1703 (CO), 1632 (C=N). ^{1}H NMR ($CDCl_3$): δ 0.95–1.00 (t, J = 7.2 Hz, 6H, two CH_2 $\underline{CH_3}$); 2.65 (s, 3H, CH_3), 2.80 (s, 6H, $N(CH_3)_2$), 3.81 (s, 3H, OCH_3), 3.98–4.05 (q, J = 7.2 Hz, 4H, two $\underline{CH_2}CH_3$), 6.82–7.10 (m, 4H, Ar-H), 7.13 (s, 1H, N=CH). Anal. for $C_{24}H_{27}N_3O_5S$ (469), calcd.: C, 61.40; H, 5.75; N, 8.95; S, 6.82. Found, C, 61.56; H, 5.61; N, 8.80; S, 6.55%.

Ethyl-3-{[(N,N-dimethylamino)methylene]amino}-2-{[(4-methoxyphenyl)amino]carbonyl}-4-(4-methoxyphenyl)-6-methylthieno[2,3-b] pyridine-5-carboxylate (6b)

Yellow crystals (53%,), m.p. 228–229°C, IR υ (cm^{-1}): 3221 (NH), 1718 (CO-ester), 1657 (CO-amide), 1626 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.92–0.97 (t, J = 7.2 Hz, 3H, CH_2 $\underline{CH_3}$); 2.57 (s, 3H, CH_3); 2.7 (s, 6H, $N(CH_3)_2$); 3.72 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 4.02–4.05 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.889–6.919 (d, J = 9 Hz, 2H, Ar-H); 6.973 (s, 1H, N=CH); 7.002–7.031 (d, J = 8.7 Hz, 2H, Ar-H); 7.146–7.175 (d, J = 8.7 Hz, 2H, Ar-H); 7.457–7.487 (d, J = 9 Hz, 2H, Ar-H); 10.91 (s, 1H, NH). Anal. for $C_{29}H_{30}N_4O_5S$ (546) calcd.: C, 63.73; H, 5.49; N, 10.25; S, 5.86. Found, C, 63.58; H, 5.32; N, 10.11; S, 5.98%.

Ethyl-2-cyano-3-{[(N,N-dimethylamino)methylene]amino}-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-5-carboxylate (6c)

Yellow crystals (53%), m.p. 136–138°C, IR υ (cm^{-1}): 2198 (CN), 1723 (CO), 1627 (C=N). Anal. for $C_{22}H_{22}N_4O_3S$ (422) calcd.: C, 62.56; H, 5.21; N, 13.27; S, 7.58. Found, C, 62.68; H, 5.10; N, 13.40; S, 7.43%.

3-Amino-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-2-carboxylic acid (7)

A solution of compound **4a** (10 mmoles) in ethanol (30 mL) containing 10% KOH was heated under reflux for 3 h. The reaction mixture was cooled, poured onto ice-cold water, and neutralized with dilute HCl. The solid product obtained was filtered off and crystallized from ethanol to give compound **7** as yellow crysals (61%), m.p. 176°C, IR υ (cm^{-1}): 3441–3338 (NH_2 and OH), 1728 (CO-ester), 1662 (CO-acid with H-bond), 1606 (C=N). ^{1}H NMR (DMSO-d_6): δ 1.04–1.11 (t, J = 7.2 Hz, 3H, $\underline{CH_2}$ CH_3); 2.60 (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 3.96–4.05 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 5.65 (hump, 2H, NH_2*); 7.094–7.138 (d, J = 8.8 Hz, 2H, Ar-H); 7.319–7.363(d, J = 8.8 Hz, 2H, Ar-H); 12.75 (hump, 1H, OH*). Anal. for $C_{19}H_{18}N_2O_5S$ (386) calcd.: C, 59.06; H, 4.66; N, 7.25; S, 8.29. Found, C, 59.16; H, 4.54; N, 7.36; S, 8.18%.

Ethyl-9-(4-methoxyphenyl)-2,7-dimethyl-4-oxo-4H-pyrido[3′,2′:4,5] thieno[3,2-d][1,3]oxazine-8-carboxylate (8)

A solution of compound **7** (10 mmoles) in acetic anhydride (30 mL) was heated under reflux for 4 h and then cooled. The solid product obtained was filtered off and crystallized from ethanol to afford compound **8** as yellow crystals (48%), m.p. 317–318°C, IR υ (cm^{-1}): 1754 (CO oxazinone), 1721 (CO-ester), 1610 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.96–0.99 (s, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.61 (s, 3H, CH_3-$C_{(7)}$); 3.59

(s, 3H, CH_3-$C_{(2)}$); 3.96–4.01 (q, J = 7.2 Hz, 2H, $CH_2\underline{CH_3}$); 6.986–7.014 (d, J = 8.4 Hz, 2H, Ar-H); 7.293–7.321 (d, J = 8.4 Hz, 2H, Ar-H). Anal. for $C_{21}H_{18}N_2O_5S$ (410) calcd.: C,61.46; H, 4.39; N, 6.82; S, 7.80. Found, C, 61.32; H, 4.28; N, 6.93; S, 7.69%.

Reaction of 8, 6a, and 6c With Aromatic Amines 9a,b,d

A solution of each of **8**, **6a**, and **6c** (10 mmoles) in glacial acetic acid (40 mL) was treated with **9a**,**b**,**d** (12 mmoles). The reaction mixture was heated under reflux for 3 h and then cooled. The solid product obtained was filtered off and crystallized from the proper solvent to give compounds **10a**,**b**,**d**, **11a**,**b**, **4a**, **14a**,**b**, and **4c**, respectively.

Ethyl-3,9-bis(4-methoxyphenyl)-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (10a)

Yellow crystals from toluene/pet. ether (65%), m.p. 156–158°C, IR υ (cm^{-1}): 1721 (CO-ester), 1679 (CO—$C_{(4)}$), 1607 (C=N), ^{1}H NMR ($CDCl_3$): δ 1.00–1.07 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.2 (s, 3H, CH_3-$C_{(2)}$); 2.73 (s, 3H, CH_3-$C_{(7)}$); 3.85 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 4.06–4.16 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.93–7.13 (m, 6H, Ar-H); 7.332–7.376 (d, J = 8.8 Hz, 2H, Ar-H). Anal. for $C_{28}H_{25}N_3O_5S$ (515) calcd.: C, 65.24; H, 4.85; N, 8.15; S, 6.21. Found, C, 65.36; H, 4.71; N, 8.00; S, 6.36%.

Ethyl-9-(4-methoxyphenyl)-2,7-dimethyl-3-(4-methylphenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (10b)

Yellow crystals from toluene/pet. ether (58%), m.p. 188–190°C, IR υ (cm^{-1}): 1717 (CO-ester), 1660 (CO—$C_{(4)}$), 1605 (C=N), Anal. for $_{28}H_{25}N_3O_4S$ (499), calcd.: C, 67.33; H, 5.01; N, 8.41; S, 6.41. Found, C, 67.53; H, 5.20; N, 8.23; S, 6.25%.

Ethyl-9-(4-methoxyphenyl)-2,7-dimethyl-4-oxo-3-(4-pyridinyl)-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (10d)

Pale yellow crystals from toluene/pet. ether (55%) m.p. 260–262°C, IR υ (cm^{-1}): 1731 (CO-ester), 1657 (CO—$C_{(4)}$), 1610 (C=N). Anal. for $C_{26}H_{22}N_4O_4S$ (486), calcd.: C, 64.19; H, 4.52; N, 11.52; S, 6.58. Found, C, 64.31; H, 4.36; N, 11.38; S, 6.72%.

Ethyl-3,9-bis(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido [3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (11a)

Pale yellow crystals from dioxane (52%), m.p. 207–208°C. IR υ (cm^{-1}): 1726 (CO-ester), 1682 ($C_{(4)}$=O), 1609 (C=N). ^{1}H NMR ($CDCl_3$) δ 1.04–

1.08 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.76 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 4.06–4.17 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.96–7.03 (m, 4H, Ar-H); 7.31–4.37 (m, 4H, Ar-H); 7.96 (s, 1H, $C_{(2)}$-H). Anal. for $C_{27}H_{23}N_3O_5S$ (501), calcd.: C, 64.67; H, 4.59; N, 8.38; S, 6.38. Found, C, 64.78; H, 4.71; N, 8.24; S, 6.22%.

Ethyl-9-(4-methoxyphenyl)-7-methyl-3-(4-methylphenyl)-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (11b)

Yellow crystals from ethanol (59%), m.p. 252–54°C. IR υ (cm^{-1}): 1724 (CO-ester), 1681 ($C_{(4)}$=O), 1607 (C=N). Anal. for $C_{27}H_{23}N_3O_4S$ (485), calcd.: C, 66.80; H, 4.74; N, 8.66; S, 6.60. Found, C, 66.68; H, 4.61; N, 8.82; S, 6.76%.

Ethyl-9-(4-methoxyphenyl)-4-[(4-methoxyphenyl)amino]-7-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (14a)

Pale yellow crystals from ethanol (66%), m.p. 250–52°C, IR υ (cm^{-1}): 3209 (NH); 1719 (CO), 1602 (C=N). ^{1}H NMR ($CDCl_3$): δ 0.99–1.06 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$); 2.72 (s, 3H, CH_3); 3.86 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.07-4.11 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$); 6.92–7.00 (m, 4H, Ar-H), 7.07 (s, 1H, NH*); 7.331–7.374 (d, J = 8.4 Hz, 2H, Ar-H) 7.391–7.435 (d, J = 8.8 Hz, 2H, Ar-H); 8.46 (s, 1H, $C_{(2)}$-H). MS, M^+, 500 (100%). Anal. for $C_{27}H_{24}N_4O_4S$ (500), calcd.: C, 64.80; H, 4.80; N, 11.20; S, 6.40. Found, C, 64.68; H, 4.61; N, 11.35; S, 6.66%.

Ethyl-9-(4-methoxyphenyl)-4-[(4-methylphenyl)amino]-7-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (14b)

Yellow crystals from ethanol (68%), m.p. 268–70°C, IR υ (cm^{-1}): 3230 (NH); 1718 (CO), 1605 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.00–1.07 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.38 (s, 3H, CH_3); 2.73 (s, 3H, CH_3); 3.89 (s, 3H, OCH_3); 4.08–4.11 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.92 (s, 1H, NH*); 6.921–7.012 (d, J = 8.2 Hz, 2H, Ar-H); 7.194–7.236 (d, J = 8.4 Hz, 2H, Ar-H); 7.340–7.381 (d, J = 8.2 Hz, 2H, Ar-H); 7.401–7.443 (d, J = 8.4 Hz, 2H, Ar-H); 8.50 (s, 1H, $C_{(2)}$-H). Anal. for $C_{27}H_{24}N_4O_3S$ (484), calcd.: C, 66.94; H, 4.96; N, 11.57; S, 6.61. Found, C, 66.80; H, 4.75; N, 11.46; S, 6.78%.

Reaction of 8 and 6a With Hydrazine Hydrate

A solution of each of **8** and **6a** (10 mmoles) in hydrazine hydrate (40 mL) was heated under reflux for 3 h. The solid products obtained after

cooling were filtered off and crystallized from dioxane to give **10c** and **11c**, respectively.

Ethyl-3-amino-9-(4-methoxyphenyl)-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (10c)

Yellow crystals (58%), m.p. 316–317°C, IR υ (cm^{-1}): 3365, 3267 (NH_2), 1716 (CO-ester), 1664 ($C_{(4)}$=O), 1611 (C=N). Anal. for $C_{21}H_{20}N_4O_4S$ (424), calcd.: C, 59.43; H, 4.71; N, 13.20; S, 7.54. Found, C, 59.30; H, 4.85; N, 13.38; S, 7.41%.

Ethyl-3-amino-9-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (11c)

Yellow crystals (62%), m.p. 218°C, IR υ (cm^{-1}): 3298, 3204 (NH_2), 1718 (CO-ester), 1669 ($C_{(4)}$=O), 1607 C=N). ^{1}H NMR (DMSO-d_6): δ 0.92–0.96 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.61 (s, 3H, CH_3), 3.41 (br, 2H, NH_2*); 3.80 (s, 3H, OCH_3); 4.02–4.04 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.961–6.989 (d, J = 8.4 Hz, 2H, Ar-H); 7.242–7.270 (d, J = 8.4 Hz, 2H, Ar-H); 8.25 (s, 1H, $C_{(2)}$-H). MS, M^+, 410 (100%), M+1, 411 (26.7%). Anal. for $C_{20}H_{18}N_4O_4S$ (410), calcd.: C, 58.53; H, 4.39; N, 13.65; S, 7.80. Found, C, 58.70; H, 4.50; N, 13.48; S, 7.96%.

Ethyl-3-{[(N,N-dimethylamino)methylene]amino}-9-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-caroxylate (12a)

This compound was synthesized from compound **11c** (10 m moles) and DMF-DMA (10 m moles) in a manner similar to that described for the preparation of compound **6**. It was crystallized from dioxane to give yellow crystals, (58%), m.p. 179–180°C, IR υ (cm^{-1}): 1724 (CO-ester), 1670 ($C_{(4)}$=O), 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ 0.99–1.05 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$); 2.73 (s, 3H, CH_3), 3.03 (s, 6H, $N(CH_3)_2$); 3.88 (s, 3H, OCH_3); 4.04-4.14 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$); 6.939–6.980 (d, J = 8.2 Hz, 2H, Ar-H); 7.26 (s, 1H, N=CH); 7.308–7.35 (d, J = 8.2 Hz, 2H, Ar-H); 8.0 (s, 1H, $C_{(2)}$-H). Anal. for $C_{23}H_{23}N_5O_4S$ (465), calcd.: C, 59.35; H, 4.94; N, 15.05; S, 6.88. Found, C, 59.50; H, 4.81; N, 15.21; S, 6.72%.

Ethyl-3-{[(4-bromophenyl)methylene]amino}-9-(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-8-carboxylate (12b)

A suspension of **11c** (10 mmoles) and 4-bromobenzaldehyde (10 mmoles) in ethanol (50 mL) was heated under reflux for 3 h in the presence of piperidine (0.5 mL) as a catalyst. The solid product obtained

during reflux was collected after cooling by filtration and crystallized from dioxane to give compound **12b** as yellow crystals (62%), m.p. 263–264°C, IR υ (cm^{-1}): 1716 (CO-ester), 1681 ($C_{(4)}$=O), 1608 (C=N). Anal. for $C_{27}H_{21}N_4O_4SBr$ (577), calcd.: C, 56.15; H, 3.64; N, 9.70; S, 5.54; Br, 13.86. Found, C, 56.26; H, 3.51; N, 9.87; S, 5.40; Br, 13.71%.

Ethyl-2-cyano-3-[(ethoxymethylene)amino]-4-(4-methoxyphenyl)-6-methylthieno[2,3-b]pyridine-5-carnoxylate (15)

A solution of **4c** (10 mmoles) in acetic anhydride (30 mL) was treated with triethylorthoformate (25 mmoles). The reaction mixture was heated under reflux for 3 h and then cooled. The solid product obtained was filtered off and crystallized from ethanol to give **15** as yellow crystals (72%), m.p. 160–62°C, IR υ (cm^{-1}): 2212 (CN); 1730 (CO), 1630 (C=N). Anal. for $C_{22}H_{21}N_3O_4S$ (423), calcd.: C, 62.41; H, 4.96; N, 9.93; S, 7.56. Found, C, 62.30; H, 4.83; N, 9.78; S, 7.68%.

Ethyl-3-[(2-chloroacetyl)amino]-4-(4-methoxyphenyl)-2-{[(4-methoxyphenyl)amino]carbonyl}-6-methylthieno[2,3-b]-pyridine-5-carboxylate (16)

A mixture of compound **4b** (10 m moles) and chlorocetylchloride (12 m moles) in dimethylformamide (30 mL) was stirred at r.t. for 3 h. The reaction mixture was then poured onto ice-cold water. The solid product thus formed was filtered off and crystallized from ethanol to yield compound **16** as yellow crystals (61%), m.p. 215–216°C. IR υ (cm^{-1}): 3377, 3291 (2NH), 1722 (CO-ester), 1647 (CO-amides), 1611 (C=N). ^{1}H NMR ($CDCl_3$): δ 0.97–1.05 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.68 (s, 3H, CH_3); 3.50 (s, 2H, $COCH_2Cl$); 3.78 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 4.00–4.11 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.77–7.03 (m, 4H, Ar-H), 7.28–7.42 (m, 4H, Ar-H), 8.47 (s, 1H, NH), 8.70 (s, 1H, NH). Anal. for $C_{28}H_{26}N_3O_6SCl$ (567.5), calcd.: C, 59.20; H 4.58; N 7.40; S, 5.63; Cl, 6.25. Found, C, 59.31; H, 4.70; N, 7.25; S, 5.50; Cl, 6.10%.

Ethyl-2-chloromethyl-3,9-bis(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-8-carboxylate (17)

A solution of **16** (10 mmoles) in glacial acetic acid (30 mL) containing 5 mL of acetic anhydride was heated under reflux for 4 h and then cooled. The solid product obtained was filtered off and crystallized from ethanol to give **17** as yellow crystals (70%), m.p. 194–96°C. IR υ (cm^{-1}): 1713 (CO-ester), 1677 ($C_{(4)}$=O), 1606 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.00–1.07 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.75 (s, 3H, CH_3-$C_{(7)}$); 3.86 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.97 (s, 2H, $C_{(2)}$-CH_2Cl); 4.06–4.17 (q, J = 7.2 Hz, 2H,

$\underline{CH_2}CH_3$); 6.941–6.985 (d, J = 8.8 Hz, 2H, Ar-H); 7.002–7.046 (d, J = 8.8 Hz, 2H, Ar-H); 7.186–7.230 (d, J = 8.8 Hz, 2H, Ar-H); 7.329–7.373 (d, J = 8.8 Hz, 2H, Ar-H). Anal. for $C_{28}H_{24}N_3O_5SCl$ (549.5), calcd.: C, 61.14; H, 4.36; N, 7.64; S, 5.82; Cl, 6.46. Found, C, 61.00; H, 4.23; N, 7.76; S, 5.70; Cl, 6.59%.

Ethyl-3,9-bis(4-methoxyphenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-8-carboxylate (18)

A solution of **4b** (10 m moles) in acetic acid (30 mL) containing conc. HCl (1.0 mL) was treated with a cold saturated solution of sodium nitrite (15 m moles). The reaction mixture was stirred in ice bath for 1 h. The solid product thus formed was filtered off, washed with water, and crystallized from ethanol to afford **18** as yellow crystals (58%), m.p. 194°C. IR υ (cm^{-1}): 1724 (CO-ester), 1961 ($C_{(4)}$=O), 1608 (C=N). Anal. for $C_{26}H_{22}N_4O_5S$ (502), calcd.: C, 62.15; H, 4.38; N, 11.15; S, 6.37. Found C, 62.30; H, 4.24; N, 11.31; S, 6.20%.

Ethyl-3,9-bis(4-methoxyphenyl)-7-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxylate (19)

A mixture of compound **4b** (10 mmoles) and carbon disulfide (5 mL) in pyridine (30 mL) was heated under reflux for 8 h and then cooled. The reaction mixture was poured onto ice-cold water and acidified with diluted HCl. The solid product obtained was filtered off and crystallized from ethanol to give compound **19** as yellow crystals (48%), m.p. 198°C. IR υ (cm^{-1}): 3224 (NH), 1724 (CO-ester), 1673 ($C_{(4)}$=O), 1611 (C=N). Anal. for $C_{27}H_{23}N_3O_5S_2$ (533), calc.: C, 60.78; H, 4.31; N, 7.88; S, 12.00. Found, C, 60.92; H, 4.48; N, 7.73; S, 12.11%.

Ethyl-3-{[(ethylamino)carbonothioyl]amino}-4-(4-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (21)

A mixture of **20** (10 mmoles) and ethylisothiocyanate (15 mmoles) in pyridine (30 mL) was heated under reflux for 6 h and then cooled. The reaction mixture was poured onto ice-cold water and acidified with diluted HCl. The solid product was filtered off, washed with water, and crystallized from ethanol to afford compound **21** as yellow crystals (69%), m.p. 216–18°C. IR υ (cm^{-1}): 3404, 3252, 3206 (3NH); 1726 (CO), 1605 (C=N). ^{1}H NMR ($CDCl_3$): δ 0.91–1.04 (t, J = 7.0 Hz, 3H, CH_2 $\underline{CH_3}$); 1.22–1.34 (t, J = 7.4 Hz, 3H, $CH_2\underline{CH_3}$); 2.78 (s, 3H, CH_3); 3.64–3.74 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$); 3.90 (s, 3H, OCH_3); 3.99–4.15 (q, J = 7.4 Hz, 2H, $\underline{CH_2}CH_3$); 7.105–7.148 (d, J = 8.6 Hz, 2H, Ar-H); 7.345–7.388 (d, J = 8.6 Hz, 2H,

Ar-H); 7.58 (s, 1H, NH*); 9.96 (s, 1H, NH*); 12.53 (hump, 1H, NH*). Anal. for $C_{20}H_{23}N_5O_3S$ (413), calc.: C, 58.11; H, 5.57; N, 16.95; S, 7.75. Found, C, 58.28. H, 5.41; N, 16.80; S, 7.87%.

The Reaction of 21 With α-Halocarbonyl Compounds

General Procedure

A mixture of **21** (10 mmoles) and each of **22a–c**, ethyl chloroacetate, and **26a,b** (10 mmoles) in ethanol (30 mL) containing 1.0 g of sodium acetate was heated under reflux for 4 h and then cooled. The reaction mixture was poured onto cold water. The solid product thus formed was filtered off, washed with water, and crystallized from the proper solvent to give **23a–c**, **25**, and **27a,b**, respectively.

Ethyl-3-[(3-ethyl-4-methyl-3H-thiazol-2-ylidene)amino]-4-(4-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (23a)

Yellow crystals from ethanol (66%), m.p. 256–58°C. IR υ (cm^{-1}): 3188 (NH); 1713 (CO), 1604 (C=N). ^1H NMR ($CDCl_3$): δ 0.91–0.97 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$); 1.04–1.32 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.18 (s, 3H, CH_3-$C_{(4)}$-thiazol.); 2.75 (s, 3H, CH_3-$C_{(6)}$); 3.92–3.96 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$); 3.86 (s, 3H, OCH_3); 4.07–4.09 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 5.87 (s, 1H, $C_{(5)}$-H-thiazol.); 6.924–6.966 (d, J = 8.2 Hz, 2H, Ar-H); 7.413–7.455 (d, J = 8.2 Hz, 2H, Ar-H); 10.94 (hump, 1H, NH*). Anal. for $C_{23}H_{25}N_5O_3S$ (451), calc: C, 61.19; H, 5.54; N, 15.52; S, 7.09. Found, C, 61.32; H, 5.68; N, 15.40; S, 7.25%.

Ethyl-3-[(3-ethyl-4-phenyl-3H-thiazol-2-ylidene)amino]-4-(4-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (23b)

Yellow crystals from ethanol (63%), m.p. 232–423°C. IR υ (cm^{-1}): 3192 (NH); 1720 (CO), 1607 (C=N). Anal. for $C_{28}H_{27}N_5O_3S$ (513), calc.: C, 65.49; H, 5.26; N, 13.64; S, 6.23. Found, C, 65.32; H, 5.39; N, 13.40; S, 6.45%.

Ethyl-3-{[3-ethyl-4-(4-methylphenyl)-3H-thiazol-2-ylidene] amino}-4-(4-methoxphenyl)-6-methyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylate (23c)

Yellow crystals from ethanol (60%), m.p. 266–268°C. IR υ (cm^{-1}): 3193 (NH); 1718 (CO), 1608 (C=N). ^1H NMR ($CDCl_3$): δ 0.76–0.82 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$); 0.97–1.04 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 2.4 (s, 3H, CH_3,p-tolyl); 2.76 (s, 3H, CH_3-$C_{(6)}$); 3.56–3.61 (q, J = 7.0 Hz, 2H,

$\underline{CH_2}CH_3$); 3.81 (s, 3H, OCH_3); 4.06–4.10 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 6.07 (s, 1H, $C_{(5)}$-H-thiazol.); 6.897–6.939 (d, J = 8.4 Hz, 2H, Ar-H); 7.17–7.27 (m, 4H, Ar-H); 7.427–7.470(d, J = 8.6 Hz, 2H, Ar-H); 11.05 (s, 1H, NH*). Anal. for $C_{29}H_{29}N_5O_3S$ (527), calc.: C, 66.03; H, 5.50; N, 13.28; S, 6.07. Found, C, 66.22; H, 5.68; N, 13.40; S, 6.25%.

Ethyl-3-[(3-ethyl-4-oxothiazolidin-2-ylidene)amino]-4-(4-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (25)

Yellow crystals from ethanol (68%), m.p. 246–248°C. IR υ (cm^{-1}): 3206 (NH); 1720 (CO), 1605 (C=N). ^{1}H NMR (DMSO-d_6): δ 0.69–0.73 (t, J = 6.8 Hz, 3H, $CH_2\underline{CH_3}$); 0.89–0.97 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$); 2.58 (s, 3H, CH_3); 3.37–3.357 (q, J = 6.8 Hz, 2H, $\underline{CH_2}CH_3$); 3.80 (s, 3H, OCH_3); 3.96 (s, 2H, CH_2); 3.98–4.05 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$); 6.97–7.01 (d, J = 8.0 Hz, 2H, Ar-H); 7.27–7.31 (d, J = 8.0 Hz, 2H, Ar-H); 13.49 (s, 1H. NH*). Anal. for $C_{22}H_{23}N_5O_4S$ (453), calc.: C, 58.27; H, 5.07; N, 15.45; S, 7.06. Found, C, 58.12; H, 5.20; N, 15.30; S, 7.20%.

Ethyl-3-[(4-ethoxycarbonyl-3-ethyl-5-methyl-3H-thiazol-2-ylidene) amino]-4-(4-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (27a)

Yellow crystals from ethanol (65%), m.p. 280–282°C. IR υ (cm^{-1}): 3197 (NH); 1729 (CO), 1697 (CO), 1607 (C=N). ^{1}H NMR ($CDCl_3$): δ 0.88–0.96 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$); 0.99–1.03 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); 1.28–1.35 (t, J = 7.4 Hz, 3H, $CH_2\underline{CH_3}$); 2.57 (s, 3H, CH_3-$C_{(5)}$thiazole); 2.76 (s, 3H, CH_3-$C_{(6)}$); 3.69–3.73 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$); 3.86 (s, 3H, OCH_3); 4.05–4.09 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$); 4.24–4.28 (q, J = 7.4 Hz, 2H, $\underline{CH_2}CH_3$); 6.923–6.961 (d, J = 7.6 Hz, 2H, Ar-H); 7.396–7.434 (d, J = 7.6 Hz, 2H, Ar-H); 11.13 (hump, 1H. NH). Anal. for $C_{26}H_{29}N_5O_5S$ (523), calc.: C, 59.65; H, 5.54; N, 13.38; S, 6.12. Found, C, 59.48; H, 5.49; N, 13.51; S, 6.23%.

Ethyl-3-[(4-acetyl-3-ethyl-5-methyl-3H-thiazol-2-ylidene)amino]-4-(4-methoxyphenyl)-6-methyl-1H-pyrazolo-[3,4-b]pyridine-5-carboxylate (27b)

Yellowish brown crystals from ethanol (64%), m.p. 248–50°C. IR υ (cm^{-1}): 3191 (NH); 1713 (CO-ester), 1655 (CO-acetyl), 1605 (C=N). Anal. for $C_{25}H_{27}N_5O_4S$ (493), calc.: C, 60.85; H, 5.47; N, 14.19; S, 6.49. Found, C, 60.98; H, 5.34; N, 14.31; S, 6.33%.

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