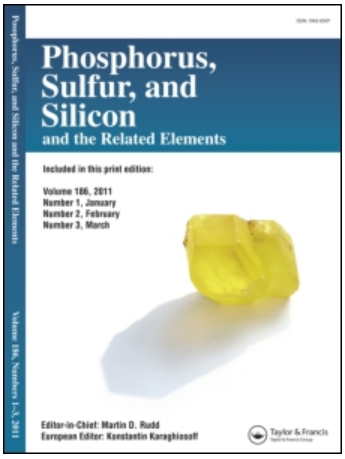

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SOME REACTIONS OF 3-AMINO-2-CARBOETHOXY-4,6-DIMETHYLTHIENO[2,3-b]-PYRIDINE. SYNTHESIS OF SOME NEW THIENOPYRIDOPYRIMIDINES

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To cite this Article Hassan, Kh. M. , El-Dean, A. M. Kamal , Youssef, M. S. K. , Atta, F. M. and Abbady, M. S.(1990) 'SOME REACTIONS OF 3-AMINO-2-CARBOETHOXY-4,6-DIMETHYLTHIENO[2,3-b]-PYRIDINE. SYNTHESIS OF SOME NEW THIENOPYRIDOPYRIMIDINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 47: 3, 283 — 289
To link to this Article: DOI: 10.1080/10426509008037980
URL: http://dx.doi.org/10.1080/10426509008037980

Phosphorus, Sulfur, and Silicon, 1990, Vol. 47, pp. 283–289
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SOME REACTIONS OF 3-AMINO-2-CARBOETHOXY-4,6-DIMETHYLTHIENO[2,3-*b*]-PYRIDINE. SYNTHESIS OF SOME NEW THIENOPYRIDOPYRIMIDINES

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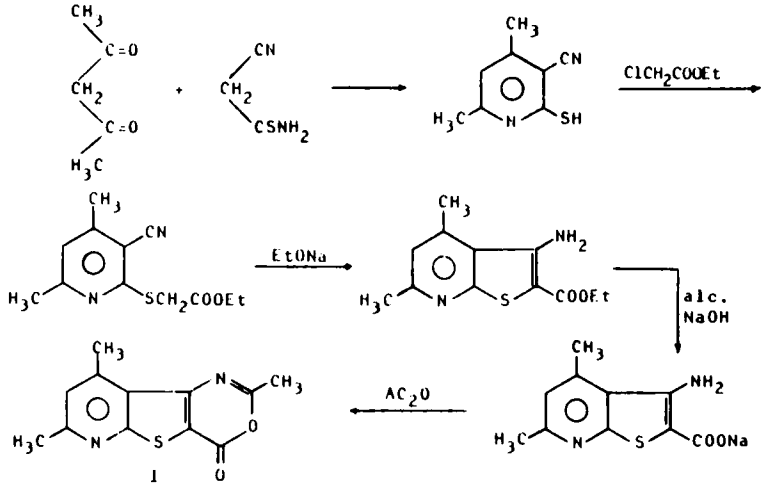
(Received May 24, 1989; in final form June 1, 1989)

Thienopyridine oxazinone (1) has been prepared and explored as a precursor by its reaction with some reagents namely, ammonium acetate, aliphatic amines, aromatic amines, hydrazine hydrate, thiosemicarbazide, and ethyl glycinate to give pyridothienopyrimidines (**II–VII**). The pyrimidinone compound (**II**) was converted to the 4-chloro derivative (**X**) by its reaction with excess $POCl_3$. Interaction of the 4-chlorocompound (**X**) with some reagents namely, hydrazine hydrate, methyl amine, aniline, sodium thiophenolate, ethyl glycinate, thiosemicarbazide and thiourea, yielded pyridothieno-pyrimidine derivatives (**XI–XVII**) substituted at 4-position, respectively.

Key words: Synthesis; oxazinone; thienopyridine; pyridothienopyrimidine.

Pyrimidines have occupied a unique place and have remarkably contibuted to biological and medical chemistry. Various analogues of thiopyrimidines processes effective antibacterial, antifungal, antiviral, insecticidal and miticidal activities.[1–3] Also, pyrimidine fused heterocycles have great importance in the field of medicinal chemistry. Thiazolopyrimidines for example have some analgesic activity and are devoid of cerebal nervous system activity.[4]

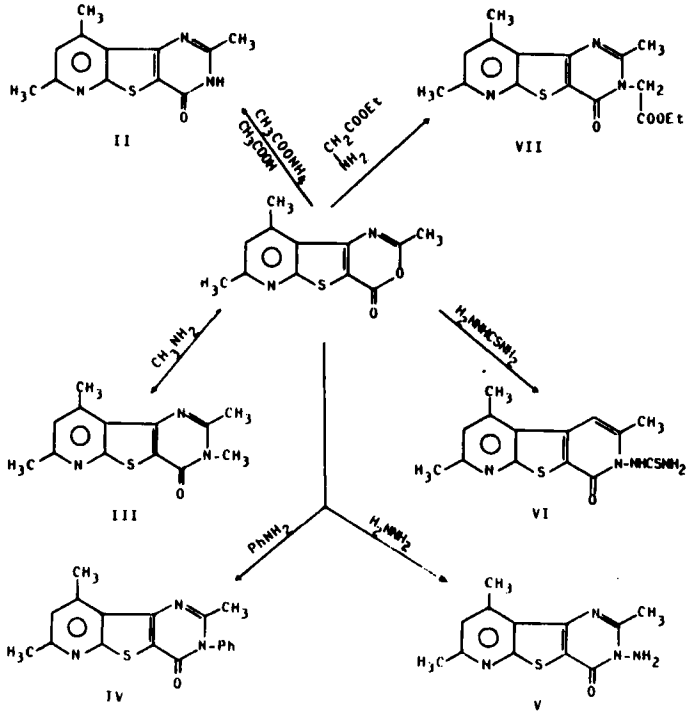
Within this respect, the present work is aimed to examine the chemistry of 3-amino-2-carboethoxy-4,6-dimethylthieno[2,3-*b*]pyridine to be used as a starting material[5–9] for the synthesis of some unreported thienopyridopyrimidines. This was achieved by the preparation of 2,7,9-trimethyl pyrido[3′,2′:4,5]thieno[3,2-*d*]oxazine-4-one[10](**I**) as follows:



The structure of compound (**I**) is in agreement with the reported data.

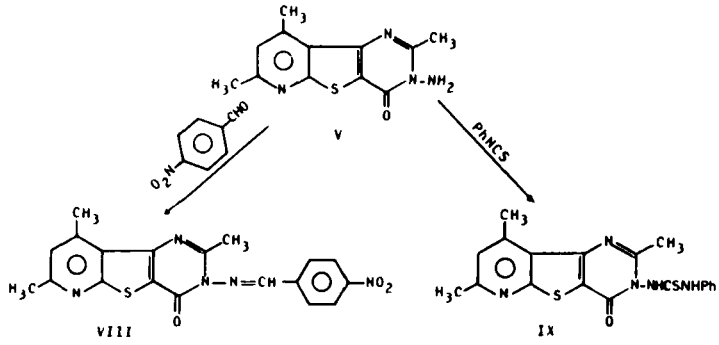
It was of interest to us to explore the oxazinone (1) to propagate its reaction with some reagents to build up the target pyrimidine ring.

Thus, interaction of I with ammonium acetate, methyl amine, aniline, hydrazine hydrate, thiosemicarbazide, and ethyl glycinate gave the corresponding tricyclic 3-substituted 2,7,9-trimethyl-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4[3H]one derivatives (**II–VII**) as follows:



The structures of compounds II–VII were established on the basis of elemental analysis as well as spectroscopic data. The IR spectra of (**II**) showed a broad band at 2400–3200 cm^{-1} (NH) and a band at 1680 cm^{-1} (C=O); compounds (**III**) and (**IV**) showed bands at 1660 cm^{-1}, 1670 cm^{-1} (C=O); compound (**V**) showed bands at 3280, 3200 cm^{-1} (NH_2) and at 1660 cm^{-1} (C=O), compound (**VI**) showed bands at 3400, 3240, 3140 cm^{-1} ($NHCSNH_2$), and at 1680 cm^{-1} (C=O); compound (**VII**) showed absorption bands at 1730 cm^{-1} (C=O, ester group) and at 1680 cm^{-1} (C=O) group of pyrimidine ring. The ^1H NMR of (**IV**), in $CDCl_3$ showed the following signals, δ2.30, 2.65, 2.90 (3s, 9H, $3CH_3$), δ7.00 (s, 1H, CH pyridine), and δ7.20–7.55 (m, 5H, CH phenyl). Compound (**V**) in CF_3COOH showed the following signals, at δ3.00 (s, 6H, $2CH_3$), δ3.30 (s, 3H, CH_3); δ7.70 (s, 1H, CH-pyridine); and δ9.89 (s, 2H, NH_2).

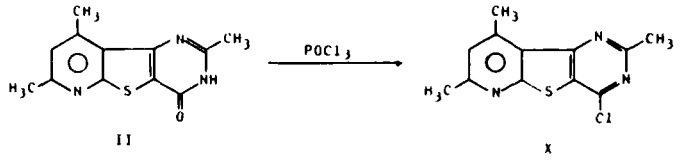
The reactivity of the 3-amino group in compound (**V**) was tested through its ease of reactions with *p*-nitrobenzaldehyde and/or phenyl isothiocyanate giving the corresponding derivatives (**VIII**) and (**IX**).



The structure of compound (**VIII**), (**IX**) was supported by the correct elemental analysis as well as the spectral data. The IR and ^{1}H NMR spectra of these compounds were in agreement with the proposed structures.

It must be pointed out that, the 2-methyl group does not react with p-nitrobenzaldehyde under the reaction conditions. This was indicated by the ^{1}H NMR spectrum which reveals the presence of the signals for the three methyl groups in the compound (**VIII**).

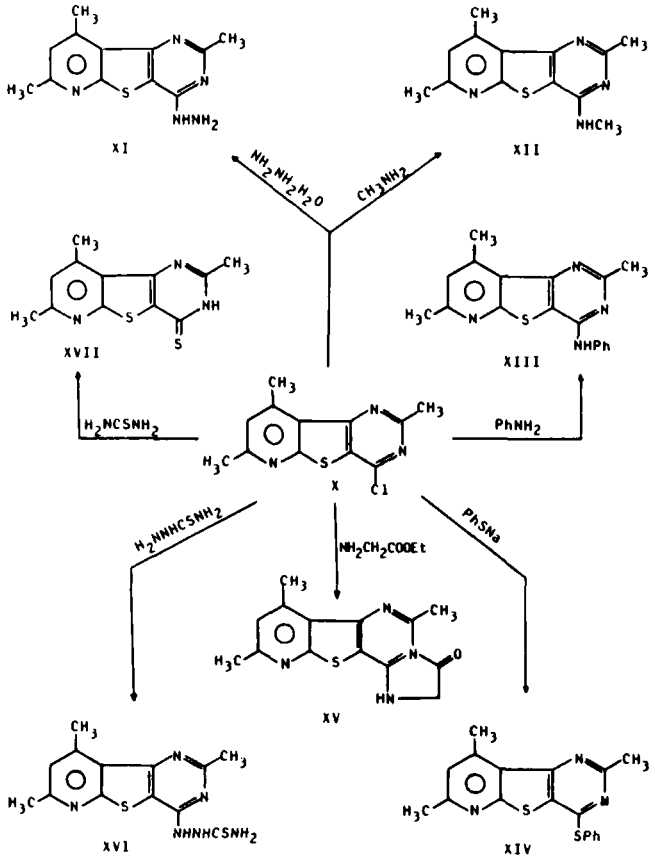
Chlorination of compound (**II**) was successfully attempted by its interaction with excess $POCl_3$ giving (**X**).



The structure of (**X**) was supported by the correct elemental and spectral analysis; the IR spectrum of (**X**) showed the absence of the absorption bands due to the (NH) and (C=O) groups.

The scope and the synthetic utility of the prepared 4-chloro derivative (**X**) can be seen from its reaction with some reagents namely, hydrazine hydrate, methyl amine, aniline, thiophenol, ethyl glycinate, thiosemicarbazide, and/or thiourea, giving the corresponding pyrimidine derivatives (**XI–XVII**).

The structure of compounds (**XI–XVII**) was confirmed on the basis of elemental analysis and spectral data. The IR spectra of these compounds showed the absorption bands at 3340, and 3300–2800 cm^{-1} due to ($NHNH_2$) (compound **XI**); at 3600–2900 cm^{-1} due to NH group (compound (**XII**) and (**XIII**)); 1670 cm^{-1} due to (CO) group in compound (**XV**); 3340, 3280, and 3170 cm^{-1} due to $NHNHCSNH_2$ group in compound (**XVI**); and at 3140 cm^{-1} due to NH in compound (**XVII**). The ^{1}H NMR spectrum of (**XI**) in DMSO-d_6 showed signals at δ2.45, 2.60, 2.90 (3s, 9H, $3CH_3$); δ4.75 (s, 2H, NH_2); δ7.05 (s, 1H, CH pyridine) and δ8.75 (s, 1H, NH). Compound (**XV**) in DMSO-d_6 showed signals at δ2.50, 2.55, 2.85 (3s, 9H, $3CH_3$); δ7.9 (s, 1H, CH pyridine), δ7.20 (s, 2H, CH_2 imidazole ring). Compound (**XVII**) in CF_3COOH showed signals at δ2.9, 3.00, 3.35 (3s, 9H, $3CH_3$); δ7.7 (s, 1H, CH pyridine).



It must be pointed out that, the tetracyclic compound (**XV**) is the sole product obtained from the reaction of (**X**) with ethyl glycinate. Further support for the structure of (**XVII**) is coming from its methylation with methyl iodide in ethanol in presence of sodium acetate giving the methylthio derivative (**XVIII**).

Also, compound (**XVIII**) gave a correct elemental analysis and its IR spectrum showed the absence of the band characteristic for (NH) group.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye-Unicam SP 3-100 and Perkin-Elmer 599 B spectrophotometers. ^{1}H NMR spectra were recorded with a Varian EM-390 90 MHz spectrometer in the suitable deuterated solvent using TMS as internal standard. Analtyical data were obtained using Perkin-Elmer 240 C microanalyser.

2,7,9-Trimethylpyrido[3',2':4,5]thieno[3,2-d]oxazin-4-one (**I**) 3-Amino-2-carboethoxy-4,6-dimethylthiono[2,3-b]pyridine (0.1 mole) was refluxed for one hour with ethanolic sodium hydroxide (200 ml, 4%). The precipitate sodium salt was filtered, washed with alcohol and dried. The sodium salt (20 gm) was refluxed for 3 hrs with acetic anhydride (100 ml). On cooling, the precipitate was filtered off and recrystallized from xylene as white crystals in 91% yield, m.p. 208–10°C.

Anal. Calcd. For $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02% Found: C, 58.50; H, 3.80; N, 11.10; S, 12.95%.

2,7,9-Trimethyl pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H) one (**II**) A mixture of compound (**I**) (10 gm) and ammonium acetate (10 gm) in acetic acid (50 ml) was refluxed for 2 hrs. The solid product was filtered off and recrystallized from acetic acid as white needles in 50% yield, m.p.>350°C.

Anal. Calcd. For $C_{12}H_{11}N_3OS$: C, 58.76; H, 4.52; N, 17.13; S, 13.05% Found: C, 58.40; H, 4.80; N, 16.90; S, 13.40%.

Reaction of compound (I) with amines (hydrazine hydrate, methylamine or aniline) A mixture of compound (**I**) and methylamine solution (40%, 30 ml), or aniline (0.4 ml in acetic acid 20 ml) or hydrazine hydrate (1 ml in ethanol 50 ml), the mixture was refluxed for two hrs. The solid product was collected and recrystallized from ethanol to give compounds (**III–V**). The physical constants of compounds (**III–V**) are represented in Table I.

3-Thiouredo-2,7,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d]pyrimidin4(3H)one (**VI**) A mixture of compound (**I**) (0.5 gm) and thiosemicarbazide (0.4 gm) was refluxed in acetic acid (20 ml) for two hrs. On cooling and dilution with water, the solid product formed was collected and crystallized from ethanol as white powder in 62% yield, m.p. 238–40°C.

Anal. Calcd. For $C_{13}H_{13}N_5OS_2$: C, 48.89; H, 4.10; N, 21.93; S, 20.08%, Found: C, 48.50; H, 4.30; N, 22.10; S, 19.95%.

3-Carboethoxymethyl-2,7,9-trimethyl pyrido[5',2':4,5]thieno[3,2-d]-pyrimidin-4(3H)one (**VII**) Ethyl glycinate hydrochloride (0.6 gm) and sodium acetate (0.5 gm) were refluxed in acetic acid (20 ml), the formed sodium chloride was filtered off, and then compound (**I**) (0.5 gm) was added. The mixture was refluxed for 3 hrs. The cooled reaction mixture was diluted with water, the solid product was filtered off and recrystallized from ethanol as white crystals in 30% yield, m.p. 208–10°C.

Anal. Calcd. For $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.67%. Found: C, 58.20; H, 4.90; N, 12.48; S, 9.75%.

3-(P-Nitrobenzylideneamino)-2,7,9-trimethyl pyrido[3',2':4,5]thieno-[3,2-d]pyrimidin-4(3H)one (**VIII**) A mixture of compound (**V**) (0.26 gm) and *p*-nitrobenzaldehyde (0.15 gm) was refluxed in pyridine (20 ml) for 3 hrs. The solid product was collected and recrystallized from acetic acid as yellow powder in 51% yield, m.p. 270–2°C.

Anal. Calcd. For. $C_{19}H_{15}N_5O_3S$: C, 58.01; H, 3.84; N, 17.80; S, 8.15%. Found: C, 57.80; H, 4.01; N, 18.10; S, 8.10%.

3-(3-Phenylthioureado)-2,7,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-4(3H)one (**IX**) A mixture of compound (**V**) (0.26 gm) and phenyl isothiocyanate (0.14 gm) in dry pyridine (20 ml) was refluxed for 3 hrs. The solid product was collected and recrystallized from pyridine in 76% yield, m.p. > 350°C.

Anal. Calcd. For. $C_{19}H_{17}N_5OS_2$: C, 57.70; H, 4.33; N, 17.71; S, 16.21%. Found: C, 58.05; H, 4.47; N, 18.01; S, 15.90%.

4-Chloro-2,7,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d]pyrimidine (**X**) Compound (**II**) (6 gm) was refluxed with excess phosphoryl chloride (30 ml) for 2 hrs. The cooled reaction mixture was poured into ice/water mixture with stirring. The solid product was filtered off and recrystallized from ethanol as white needles in 65% yield, m.p. 168–70°C.

Anal. Calcd. For. $C_{12}H_{10}ClN_3S$: C, 54.65; H, 3.82; Cl, 13.44; N, 15.93; S, 12.16%. Found C, 54.20; H, 3.44; Cl, 13.10; N, 16.25; S, 11.95%.

Reaction of compounds (**X**) *with amines (hydrazine, methyl amine and anilinel* Compound (**X**) and methyl amine hydrazine hydrate, methyl amine solution or aniline was refluxed for 1–6 hrs., the solid product was collected and recrystallized from ethanol to give compounds (**XI–XIII**). Physical constants of (**XI–XIII**) are represented in Table I.

4-Phenylthio 2,7,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d]-pyrimidine (**XIV**) A mixture of compound (**X**) (0.5 gm) and sodium salt of thiophenol (0.5 gm) in ethanol was refluxed for 3 hrs. The solid

TABLE I

Physical constants of compounds (**III–V**) and compounds (**XI–XIII**).

Compd. Co.	M.P. °C.	Yield %	Molecular formula	Analytical data calcd./Found C	H	N	S
III	206	90	$C_{13}H_{13}N_3OS$	60.21	5.05	16.20	12.36
				59.90	5.30	15.90	12.40
IV	208–10	79	$C_{18}H_{15}N_3OS$	67.27	4.70	13.07	9.98
				67.00	4.40	12.80	10.15
V	203–5	95	$C_{12}H_{12}N_4OS$	55.37	4.65	21.52	12.32
				55.10	4.40	21.70	11.95
XI	278–80	86	$C_{12}H_{13}N_5S$	55.58	5.05	27.01	12.36
				55.70	4.70	27.13	12.50
XII	205–7	61	$C_{13}H_{14}N_4S$	60.44	5.46	21.49	12.41
				60.15	5.45	21.86	12.00
XIII	216–18	82	$C_{18}H_{16}N_4S$	67.48	5.03	17.49	10.00
				67.74	4.98	17.14	10.30

precipitate formed in dilution with water, was collected and recrystallized from ethanol as white crystals in 78% yield, m.p. 136–38°C.

Anal. Calcd. For. $C_{18}H_{15}N_3S_2$: C, 64.07; H, 4.48; N, 12.45; S, 19.00%. Found: C, 63.88; H, 4.18; N, 12.12; S, 18.84%.

2,7,9-Trimethyl imidazolo[1,2-c]pyrido[3',2':4,5]pyrimidin-3(2H)-one (**XV**) A mixture of compound (**X**) (0.5 gm) and ethyl glycinate hydrochloride (0.6 gm) in pyridine (20 ml) was refluxed for 2 hrs. The solid product formed on cooling and dilution with water was collected and recrystallized from ethanol as white crystals in 37% yield, m.p. 283–5°C.

Anal. Calcd. For. $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70; S, 11.28%. Found: C, 60.21; H, 4.50; N, 20.11; S, 10.90%.

4-Thiosemicarbazido-2,7,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d]-pyrimidine (**XVI**): A mixture of compound (**X**) (0.5 gm) and thiosemicarbazide (0.4 gm) was refluxed in ethanol for one hour. The solid product was filtered off and recrystallized from ethanol as white powder in 66% yield, m.p. 300–2°C.

Anal. Calcd. For. $C_{13}H_{14}N_6S_2$: C, 49.04; H, 4.43; N, 26.39; S, 20.14%. Found: C, 48.84; H, 4.11; N, 26.17; S, 19.93%.

2.7.9-Trimethyl pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-4(3H)-thione (**XVII**) A mixture of compound (**X**) (1 gm) and thiourea (0.6 gm) in ethanol was refluxed for one hour. The solid precipitate formed was filtered off and dissolved in boiling 10% NaOH. On acidification with acetic acid the solid product formed was collected and recrystallized from ethanol as yellow needles in 81% yield, m.p. 323–5°C.

Anal. Calcd. For. $C_{12}H_{11}N_3S_2$: C, 55.15; H, 4.24; N, 16.08; S, 24.53%. Found: C, 54.80; H, 4.54; N, 16.38; S, 24.50%.

4-Methylthio-2,7,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d]-pyrimidine (**XVIII**). To a hot solution of compound (**XVII**) (0.5 gm) in ethanol (30 ml) containing (0.55 gm) sod. acetate methyl iodide (0.85 gm) was added. The mixture was stirred for 15 min. The solid product was collected and recrystallized from ethanol as white powder in 95% yield, m.p. 173–5°C.

Anal. Calcd. For. $C_{13}H_{13}N_3S_2$: C, 56.70; H, 4.76; N, 15.26; S, 23.28%. Found: C, 56.66; H, 4.42; N, 14.97; S, 23.50%.

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