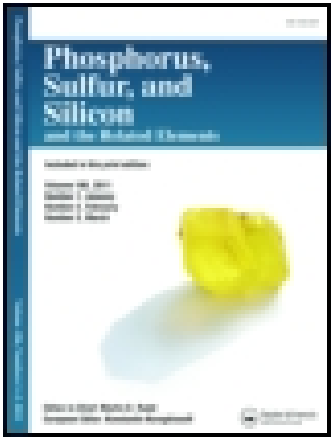

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

SYNTHESIS AND REACTIONS OF SOME NEW HETEROCYCLIC COMPOUNDS CONTAINING THIENO[2,3-c] PYRIDAZINE MOIETY

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Published online: 04 Oct 2006.

To cite this article: Sh. M. Radwan (2000) SYNTHESIS AND REACTIONS OF SOME NEW HETEROCYCLIC COMPOUNDS CONTAINING THIENO[2,3-c] PYRIDAZINE MOIETY, Phosphorus, Sulfur, and Silicon and the Related Elements, 163:1, 153-169, DOI: 10.1080/10426500008046617

To link to this article: http://dx.doi.org/10.1080/10426500008046617

Phosphorus, Sulfur and Silicon, 2000, Vol. 163, pp. 153-169
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SYNTHESIS AND REACTIONS OF SOME NEW HETEROCYCLIC COMPOUNDS CONTAINING THIENO[2,3-c] PYRIDAZINE MOIETY

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(Received December 12, 1999; In final form January 12, 2000)

Saponification of ethyl 3-amino-4,5-diphenylthieno[2,3-c]pyridazine-2-carboxyate (1) with alcoholic sodium hydroxide, followed by acidification, afforded the corresponding acid 2. Also, reaction of 1 with ethanolamine and formamide, respectively, gave compounds 5 and 6. Compound 2 reacts with orthophosphoric acid under different conditions to give some new thieno[2,3-c] pyridazine derivatives 3 and 4, which were subjected to reactions to produce compounds 7–18. Furtheremore, compounds 5 and 6 were used to synthesize some substituted pyrimido[4′,5′:4,5]-thieno[2,3-c]pyridazine derivatives 21–30.

Keywords: Thienopyridazine; pyridothienopyridazine; pyrimidothieno-pyridazine; triazolo-pyrimidothienopyridazine

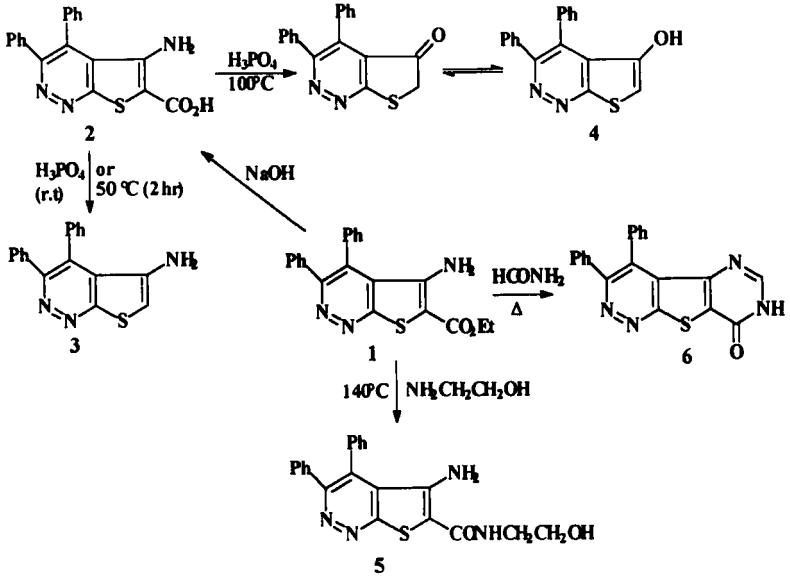
INTRODUCTION

Pyridazine and related heterocyclic have been found to be biologically important compounds with cardiotonic,[1] antitumor,[2] antidepressive,[3] and antimicrobial activities,[4] and therefore this work deals with the synthesis of some new heterocyclic systems containing the thieno[2,3-c] pyridazine moiety attached to or fused with other pharmacophores.

* Corresponding Author.

RESULTS AND DISCUSSION

The starting compound, ethyl 3-amino-4,5-diphenylthieno[2,3-c]pyridazine-2-carboxylate (1),[5] upon saponification by heating in an ethanolic sodium hydroxide followed by acidification, yielded 3-amino-4,5-diphenylthieno[2,3-c]pyridazine-2-carboxylic acid (2). Heating of compound 1 with ethanolamine and formamide, respectively, gave 3-amino-4,5-diphenyl-2-[N-(2-hydroxyethyl)]-carbamoylthieno[2,3-c]pyridazine (5) and 3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c] pyridazin-8(7H)one (6) (Scheme 1). The latter compound was recently prepared by reaction of 3-amino-4,5-diphenylthieno[2,3-c]pyridazine-2-carboxamide with formic acid[6].

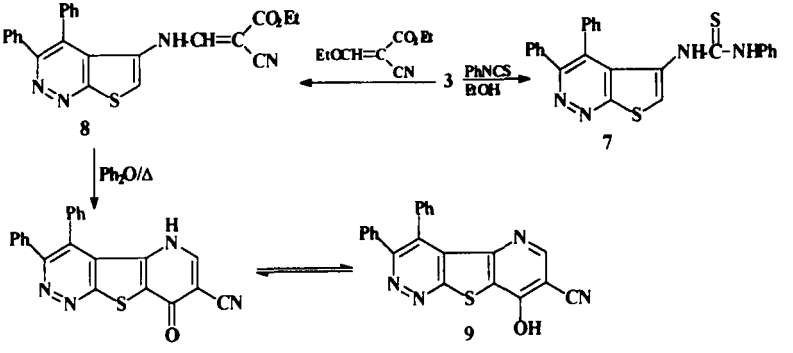


SCHEME 1

Upon treatment of acid 2 with orthophosphoric acid at room temperature for ~12 hours or at 50 °C for 2 hours, decarboxylation occurs to afford 3-amino-4,5-diphenylthieno[2,3-c] pyridazine (3). However, reaction with orthophosphoric acid at 100 °C, yielded 3-hydroxy-4,5-diphenylth-

ieno[2,3-c]pyridazine (4) which was identical with that obtained in our published work.[7]

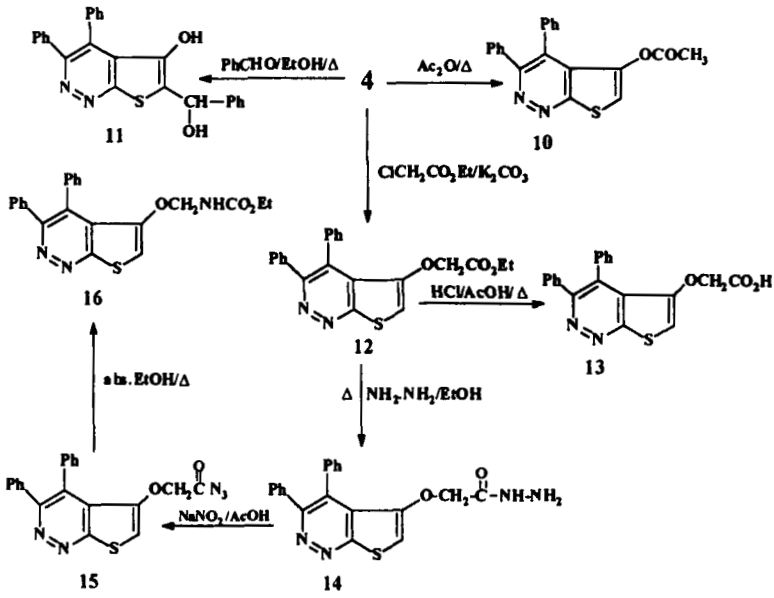
The reactivity of the amino group of compound 3 was tested by its reaction with phenyl isothiocyanate in the presence of triethylamine where (4,5-diphenylthieno[2,3-c]pyridazin-3-yl)phenylthiourea (7) was obtained (Scheme 2) An addition, the reaction of 3 with ethoxymethylene ethyl cyanoacetate in refluxing ethanol produced ethyl-(4,5-diphenylthieno[2,3-c]pyridazin-3-yl) aminomethylene cyanoacetate (8), which upon boiling in diphenyl ether,[8] cyclized into 3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-c]pyridazin-8(5H)one-7-carbonitrile (9) (Scheme 2).



SCHEME 2

In our previous work,[7] we proved that compound 4 exists predominantly in the enol form. Accordingly, compound 4 reacts with acetic anhydride and benzaldehyde in ethanol in the presence of piperidine, respectively, to yield 3-acetoxy-4,5-diphenylthieno[2,3-c]pyridazine (10) and the addition product, (3-hydroxy-4,5-diphenylpyridazin-2-yl)phenylcarbinol (11).

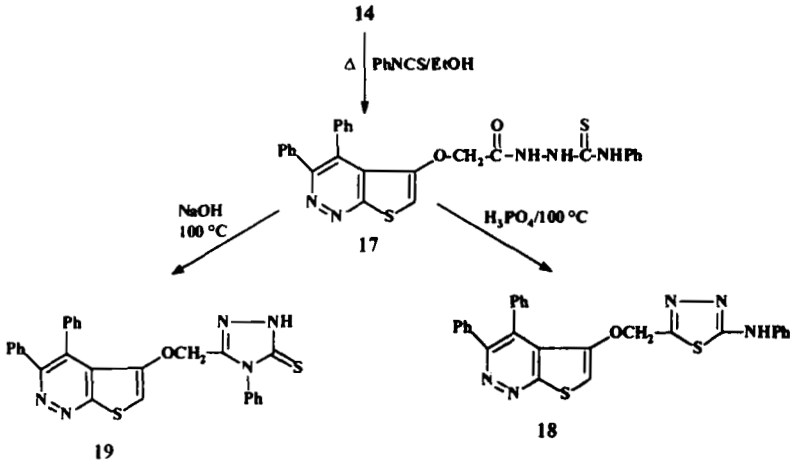
Compound 4 was reacted with ethyl chloroacetate in dimethyl-formamide in the presence of anhydrous K_2CO_3 to give (4,5-diphenylthieno[2,3-c]pyridazin-3-yloxy)acetate (12) which proved to be a versatile synthon for some thieno[2,3-c] pyridazines attached to other biologically active residues. For example, heating 12 in a mixture of hydrochloric and acetic acid afforded (4,5-diphenylthieno[2,3-c]pyridazin-3-yloxy)acetic acid (13). Refluxing **12** with hydrazine hydrate in ethanol gives the carbo-



SCHEME 3

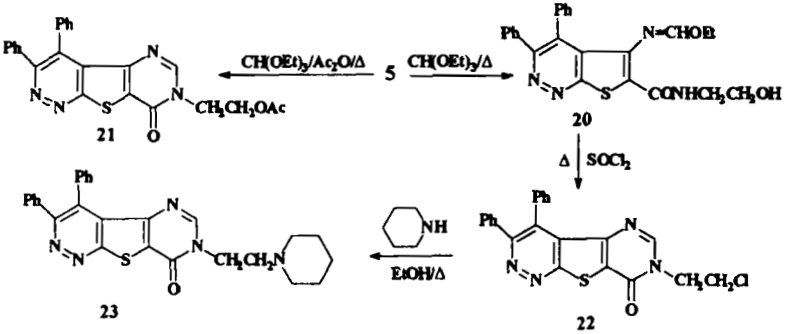
hydrazide derivative 14. On treatment of the latter compound in glacial acetic acid with sodium nitrite solution at room temperature produced the carbazide derivative 15 which underwent a Curtius rearrangement upon refluxing in absolute ethanol to give ethyl carbamate 16. The carbohydrazide 14 also reacts with phenyl isothiocyanate in refluxing ethanol to give 1-(4,5-diphenylthieno[2,3-c]pyridazine-3-yloxy)acetyl-4-phenylthiosemicarbazide (17). The latter compound upon heating with orthophosphoric acid and 2 N aqueous sodium hydroxide solution at 100 °C, respectively, afforded 3-(4,5-diphenylthieno[2,3-c]pyridazin-2-yloxy) methyl-5-phenylamino-1,2,4-thiadiazole (18) and 3-(4,5-diphenylthieno [2,3-c]pyridazin-3-yloxy)methyl-4-phenyl-1,2,4-triazole-5-(1H)thione (19) (Scheme 4).

Compounds 5 and 6 were used as key intermediates for synthesizing some new pyimidothieopyridazines with anticipated biological activities. Thus, reaction of 5 with triethyl orthoformate (neat) for a prolonged time and triethyl orthoformate in acetic anhydride, respectively, furnished 4,5-diphenyl-3-ethoxymethylene-amino-2-[N-(2-hydroxyethyl)]car-



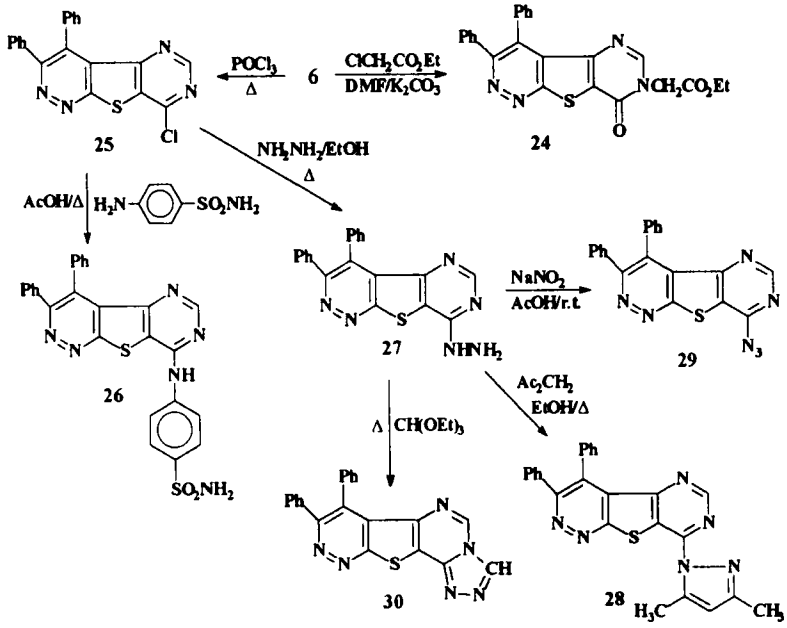
SCHEME 4

bamoylthieno[2,3-c]pyriazine (20) and 7-(2-acetoxyethyl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (21). Upon heating compound 20 with excess thionyl chloride, cyclization, followed by chlorination of the hydroxyl group, occurs to give 7-(2-chloroethyl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (22). The reaction of 22 with piperidine in refluxing ethanol gives 7-(2-piperidinoethyl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c] pyridazine (23) (Scheme 5).



SCHEME 5

The interaction of 6 with ethyl chloroacetate in dimethylformamide in the presence of anhydrous K_2CO_3 furnished the N-alkylated product 24 while its fusion with phosphorous oxychloride produced the chlorinated compound 25. When compound 25 was allowed to react with 4-aminobenzene sulphonamide in acetic acid or hydrazine hydrate in ethanol, 4-(3,4-diphenylpyrimido [4′,5′:4,5]thieno[2,3-c]pyridazin-8-yl)aminobenzenesulphonamide (26) or 8-hydrazino-3,4-diphenylpyrimido[4′,5′:4,5] thieno[2,3-c]pyridazine (27) was obtained. Treatment of 27 with acetyl acetone in refluxing ethanol, sodium nitrite in acetic acid, and/or triethyl orthoformate, respectively, furnished 8-(3,5-dimethylpyrazol-4-yl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (28), 8-azido-3,4-diphenyl-primido[4′,5′:4,5]thieno[2,3-c]pyridazine (29) and 3,4-diphenyl-s-triazolo[4″,3″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (30) (Scheme 6).



SCHEME 6

The chemical structure of all the synthesized compounds was confirmed by elemental and spectral analyses.

EXPERIMENTAL

All melting points were uncorrected and measured on a Fisher-John apparatus. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyser. IR spectra were recorded on a Pye Unicam SP-100 spectrophtometer using the KBr wafer technique. ^{1}HNMR spectra were recorded on a Varian EM-390 90 MHz ^{1}H NMR spectrometer in suitable deuterated solvents using TMS as internal standard (compound 12 was recorded on a Jeol LA 400 MHz FT-NMR spectrometer). MS spectra were recorded on Jeol-JMS-600 apparatus.

3-Amino-4,5-diphenylthieno[2,3-c]pyridazine-2-carboxylic Acid (2)

Ethyl 3-amino-4,5-diphenylthieno[2,3-c]pyridazine-2-carboxylate (1)[5] (0.01 mol) was refluxed for 2 hours with ethanolic sodium hydroxide solution (20 ml, 4%). The reaction mixture was cooled and acidified with acetic acid, and a solid product was precipitated. It was filtered, washed with water and recrystallized from ethanol to give 2, (83%), mp 237–239 °C. IR: 3490, 3400 cm^{-1} (NH_2) and 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{19}H_{13}N_3O_2S$:	C: 65.69, H: 3.77, N: 12.09, S: 9.22
Found:	C: 65.43, H: 3.69, N: 11.88, S: 9.11

3-Amino-4,5-diphenylthieno[2,3-c]pyridazine (3)

Method A

Compound 2 (1 g) and H_3PO_4 (5 ml) were left overnight. The mixture was poured in to cold water and then treated with ammonium hydroxide solution (15 %). The product obtained was filtered off, washed with water, and recrystallized (ethanol) to afford 3 (73%), mp 217–219 °C. IR: 3400, 3300 cm^{-1} (NH_2) and 1600 cm^{-1} (C=NH). ^{1}H NMR ($CDCl_3$): δ 3.3 (s, 2 H, NH_2), 6.4 (s, 1 H, thiophene ring) and 7.1–7.4 (m, 10 H, ArH).

Anal. Calcd. for $C_{18}H_{13}N_3S$:	C: 71.26, H: 4.31, N: 13.85, S: 10.56
Found:	C: 70.97, H: 4.11, N: 13.73, S: 10.23

Method B

Compound 2 (1 g) and H_3PO_4 (5 ml) were heated at 50 °C for 2 hours and treated as the previous method to produce 3 (75%) which was identical with the compound obtained in method A in all aspects.

3-Hydroxy-4,5-diphenylthieno[2,3-c]pyridazine (4)

Compound 2 (1 g) and H_3PO_4 (5 ml) were heated for 2 hours at 100°C. After cooling, the mixture was treated as in the previous method for the synthesis of 3. The crude product was recrystallized (ethanol) to give 4 (64%), mp 230°C, Lit.[7], 230–231°C. IR: 3500, 2500 cm^{-1}(br. OH). ^1H NMR (DMSO-d_6): δ 6.9 (s, 1H, thiophene ring), 7.2–7.4 (m, 10 H, ArH) and 10.5(s, 1 H, OH).

Anal. Calcd. for $C_{18}H_{12}N_2OS$:	C: 71.03, H: 3.97, N: 9.20, S: 10.53
Found:	C: 70.88, H: 3.77, N: 8.99, S: 10.33

3-Amino-4,5-diphenyl-2-[N-(2-hydroxyethyl)]carbamoylthieno [2,3-c] pyridazine (5)

A mixture of 1 (2 g) and ethanolamine (8 ml) heated at 140–150°C for 2 hours. Upon cooling, the mixture was treated with ethanol (30 ml), and the product obtained was filtered off, washed with ethanol and recrystallized (ethanol-chloroform mixture) to yield 5 (91%), mp 274–276 °C. IR: 3450, 3350, 3200 cm^{-1} (NH_2, OH) and 1620 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 3.1–3.3 (m, 4 H, 2xCH_2), 4.7 (s, 1 H, OH), 5.7 (s, 2 H, NH_2), 7.2–7.5 (m, 10 H, ArH) and 7.9 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{18}N_4O_2S$:	C: 64.60, H: 4.04, N: 14.34, S: 8.21
Found:	C: 64.31, H: 4.21, N: 14.11, S: 8.03

3,4-Diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazin-8(7H)-one (6)

Compound 1 (2 g) and formamide (15 ml) were gently refluxed for 2 hours. Upon cooling, the precipitated formed was collected, washed with ethanol and recrystallized (acetic acid) to give 6 (71%), mp > 300 °C, Lit.[6]

>300 °C. IR: 1680 cm^{-1} (C=O). ^1H NMR (CF_3CO_2D): δ 7.2–7.5 (m, 10 H, ArH) and 8.2 (s, 1 H, CH pyrimidine).

Anal. Calcd. for $C_{20}H_{12}N_4OS$:	C: 67.40, H: 3.39, N: 15.72, S: 8.99
Found:	C: 67.11, H: 3.14, N: 15.53, S: 8.73

(4,5-Diphenylthieno[2,3-c]pyridazin-3-yl)phenylthiourea (7)

A mixture of 3 (0.92 g, 0.003 mol), phenyl isothiocyante (0.42 g, 0.003 mol) in absolute ethanol (20 ml) containing few drops of triethylamine was refluxed for 6 hours. Upon cooling, the solid product obtained was filtered off and recrystallized (acetic acid) to afford 7 (15%), mp > 300 °C. IR: 3350 cm^{-1} (NH). ^1H NMR (CF_3CO_2D): δ 6.5 (s, 1H, thiophene ring) and 7.1–7.6 (m, 15 H, ArH).

Anal. Calcd. for $C_{25}H_{18}N_4S_2$:	C: 68.45, H: 4.10, N: 17.77, S: 14.62
Found:	C: 68.11, H: 3.99, N: 17.53, S: 14.33

Ethyl (4,5-diphenylthieno[2,3-c]pyridazin-3-yl)aminomethylene cyanoacetate (8)

A mixture of 3 (0.92 g, 0.003 mol) and ethoxymethylene ethyl cyanoacetate (0.5 g, 0.003 mol) in absolute ethanol (20 ml) was heated under reflux for 5 hours. Upon cooling, the product obtained was filtered off and recrystallized (ethanol) to give 8 (56%), mp 213–215 °C. IR: 3100 cm^{-1} (NH), 2200 cm^{-1} (CN) and 1670 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 1.1–1.3 (t, 3 H, CH_3), 3.9–4.2 (q, 2 H, OCH_2), 7.1–7.8 (m, 12 H, 1H thiophene ring, 1H CH=C and 10 H, ArH) and 9.6 (s, 1 H, NH).

Anal. Calcd. for $C_{24}H_{18}N_4O_2S$:	C: 67.58, H: 4.25, N: 13.13, S: 7.51
Found:	C: 67.33, H: 4.13, N: 12.97, S: 7.31

3,4-Diphenylpyrido[2′,3′:4,5]thieno[2,3-c]pyridazin-8(5H)-one-7-carbonitrile (9)

Compound 8 (0.5 g) in diphenyl ether (10 ml) was heated under reflux for 2 hours. The precipitated formed after cooling was filtered off, washed with ethanol and recrystallized (dioxane) to give 9 (69%), mp > 300 °C.

IR: 3300 cm^{-1} (NH), 2200 cm^{-1} (CN) and 1620 cm^{-1} (C=O). ^1H NMR (CF_3CO_2D): δ 7.3–7.8 (m, 10 H, ArH) and 8.6 (s, 1H, pyridine ring).

Anal. Calcd. for $C_{22}H_{12}N_4OS$:	C: 69.46, H: 3.17, N: 14.72, S: 8.42
Found:	C: 69.32, H: 3.12, N: 14.53, S: 8.22

3-Acetoxy-4,5-diphenylthieno[2,3-c]pyridazine (10)

Compound 4 (0.5 g) and acetic anhydride (10 ml) were heated under reflux for 2 hours. Upon cooling, the precipitated formed was collected, washed with petroleum ether and recrystallized (ethanol) to afford 10 (83%), mp 173–175 °C. IR: 1750 cm^{-1}(C=O). ^1H NMR ($CDCl_3$): δ 3.4 (s, 3 H, CH_3), 6.9 (s, 1 H, thiophene ring) and 7.1–7.4 (m, 10 H, ArH).

Anal. Calcd. for $C_{20}H_{14}N_2O_2S$:	C: 69.34, H: 4.07, N: 8.08, S: 9.25
Found:	C: 69.13, H: 4.11, N: 8.13, S: 9.11

(3-Hydroxy-4,5-diphenylthieno[2,3-c]pyridazin-2-yl)phenylcarbinol (11)

A mixture of 4 (0.6 g, 0.002 mol), benzaldehyde (0.21 g, 0.002 mol) in ethanol (15 ml) containing few drops of piperidine was refluxed for 5 hours. The solid product obtained after cooling was filtered off and recrystallized (ethanol) to give 11 (74%), mp 273–275 °C. IR: 3100–2500 cm^{-1} (br. OH). ^1H NMR (CF_3CO_2D): δ 5.8 (s, 1 H, CH) and 7.2–7.7 (m, 15 H, ArH). MS: 410 (M^+).

Anal. Calcd. for $C_{25}H_{18}N_2O_2S$:	C: 73.15, H: 4.41, N: 6.82, S: 7.81
Found:	C: 72.97, H: 4.33, N: 6.77, S: 7.73

Ethyl (4,5-diphenylthieno[2,3-c]pyridazine-3-yloxy)acetate (12)

To a mixture of 4 (3 g, 0.01 mol) and ethyl chloroacetate (1.25 g, 0.01 mol) in dimethylformamide (20 ml), was added anhydrous K_2CO_3 (2 g). The reaction mixture was heated on a water bath for 4 hours, then cooled and diluted with water (50 ml). The solid was collected and recrystallized (ethanol) to yield 12 (71%), mp 164–166°C. IR: 1730 cm^{-1}(C=O). ^1H NMR ($CDCl_3$): δ 1.22–1.26 (t, 3 H, CH_3, J = 7.08), 4.15–4.2 (q, 2 H,

$COOCH_2$, J=7.08), 4.31(s, 2 H, OCH_2), 6.81(s, 1 H, thiophene ring) and 7.24–7.36 (m, 10 H, ArH).

Anal. Calcd. for $C_{22}H_{18}N_2O_3S$:	C: 67.67, H: 4.64, N: 7.17, S: 8.21
Found:	C: 67.31, H: 4.43, N: 6.95, S: 8.12

(4,5-Diphenylthieno[2,3-c]pyridazin-3-yloxy)acetic acid (13)

Compound 12 (0.5 g) in a mixture of hydrochloric acid (1 ml) and acetic acid (10 ml) was refluxed for 2 hours. After cooling, the mixture was diluted with water (20 ml), and the precipitated formed was filtered off, washed with water and recrystallized (ethanol) to afford 13 (83%), mp 277–279 °C. IR: 3000–2500 cm^{-1} (br. OH) and 1690 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 4.5 (s, 2 H, OCH_2), 6.8 (s, 1 H, thiophene ring) and 7.3–7.7 (m, 10 H, ArH).

Anal. Calcd. for $C_{20}H_{14}N_2O_3S$:	C: 66.80, H: 3.89, N: 7.71, S: 8.84
Found:	C: 66.53, H: 3.64, N: 7.56, S: 8.64

The reaction of compound 12 with hydrazine hydrate: Formation of the carbohydrazide derivative (14)

A mixture of compound 12 (3.9 g, 0.01 mol) and hydrazine hydrate (0.6 ml, 85%) in ethanol (30 ml) was heated under reflux for 2 hours. Upon cooling, the solid product so formed was filtered off and recrystallized (ethanol) to give 14 (78%), mp 221–223 °C. IR: 3400, 3300 cm^{-1} (NH) and 1680 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 4.1 (s, 2 H, NH_2), 4.3 (s, 2 H, OCH_2), 7.1–7.4 (m, 11 H, ArH and thiophene ring) and 8.3 (s, 1 H, NH).

Anal. Calcd. for $C_{20}H_{16}N_4O_2S$:	C: 69.74, H: 4.68, N: 16.26, S: 9.30
Found:	C: 69.57, H: 4.42, N: 15.97, S: 9.11

Reaction of compound 13 with nitrous acid: Formation of the carboazide derivative (15)

To a well stirred solution of 14 (0.5 g) in glacial acetic acid (15 ml) was added at room temperature a solution of sodium nitrite (0.3 g in 5 ml water), and stirring was continued for two hours. The solid product obtained was filtered off, washed with water, air dried and used in the next

step without crystallization to give 15 (68%), mp 140 °C (dec.). IR: 2130 cm^{-1} (N_3) and 1720 cm^{-1} (C=O).

Anal. Calcd. for $C_{20}H_{13}N_5O_2S$:	C: 62.00, H: 3.38, N: 18.07, S: 8.27
Found:	C: 61.73, H: 3.23, N: 17.88, S: 8.13

Ethyl (4,5-diphenylthieno[2,3-c]pyridazin-3-yloxy)carbamate (16)

Compound 15 (0.5 g) in absolute ethanol (15 ml) was refluxed for 2 hours. After cooling, the precipitated formed was collected and recrystallized (aqueous ethanol) to afford 16 (86%), mp 157–159 °C. IR: 3400–3200 cm^{-1} (br. NH) and 1740 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 1.1–1.3 (t, 3 H, CH_3), 4.1–4.2 (q, 2 H, $COOCH_2$), 4.3 (s, 2 H, OCH_2), 6.8 (s, 1 H, thiophene ring), 7.3–7.6 (m, 10 H, ArH) and 7.8 (s, 1 H, NH).

Anal. Calcd. for $C_{22}H_{19}N_3O_3S$:	C: 65.17, H: 4.72, N: 10.36, S: 7.90
Found:	C: 64.95, H: 4.63, N: 10.11, S: 7.73

1-(4,5-Diphenylthieno[2,3-c]pyridazin-3-yloxy)acetyl-4-phenylthiosemicarb- azide (17)

A mixture of 14 (1 g, 0.003 mol) and phenyl isothiocyanate (0.42 g, 0.003 mol) in absolute ethanol (20 ml) was gently refluxed for 2 hours. After cooling, the precipitated formed was filtered off, washed with ethanol and recrystallized (acetic acid) to give 17 (87%), mp 213–215 °C. IR: 3250, 3100 cm^{-1} (NH) and 1680 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ 4.5 (s, 2 H, OCH_2), 6.8 (s, 1 H, thiophene ring), 7.3–7.6 (m, 15 H, ArH), 8.4 (s, 1 H, NH) and 9.6 (s, 2 H, NH).

Anal. Calcd. for $C_{27}H_{21}N_5O_2S_2$:	C: 63.38, H: 4.13, N: 13.68, S: 12.59
Found:	C: 63.14, H: 4.02, N: 13.43, S: 12.39

3-(4,5-Diphenylthieno[2,3-c]pyridazin-3-yloxy)methyl-5-phenylamino-1,2,4-thiadiazole (18)

Compound 17 (0.5 g, 0.001 mol) and H_3PO_4 (5 ml) was heated on a steam bath for 3 hours. After cooling, the reaction mixture was diluted with

water (50 ml) and treated with ammonium hydroxide solution (15 %). The solid product formed was filtered off, washed with water, and recrystallized (methanol) to afford **18** (77%), mp > 300 °C. IR: 3200 cm^{-1} (NH). ^1H NMR (DMSO-d_6): δ 5.1 (s, 2 H, OCH_2), 6.8 (s, 1 H, thiophene ring), 7.3–7.8 (m, 15 H, ArH) and 10.3 (s, 1 H, NH).

Anal. Calcd. for $C_{27}H_{19}N_5OS_2$:	C: 65.70, H: 3.87, N: 14.18, S: 12.99
Found:	C: 65.43, H: 3.77, N: 13.96, S: 12.73

3-(4,5-Diphenylthieno[2,3-c]pyridazin-3-yloxy)methyl-4-phenyl-1,2,4-triazole-5(1H)thione (19)

Compound 17 (0.5 g, 0.001 mol) in an aqueous sodium hydroxide solution (2 N, 5 ml) was heated on a steam bath for 6 hours. Upon cooling, the reaction mixture was acidified with acetic acid, and the product formed was collected and recrystallized (ethanol) to give 19 (78%), mp 183–185 °C. IR: 3490 cm^{-1} (NH). ^1H NMR (DMSO-d_6): δ 4.5 (s, 2 H, OCH_2), 6.9 (s, 1 H, thiophene ring), 7.2–7.7 (m, 15 H, ArH) and 13.0 (s, 1 H, NH).

Anal. Calcd. for $C_{27}H_{19}N_5OS_2$:	C: 65.70, H: 3.87, N: 14.18, S: 12.99
Found:	C: 65.53, H: 3.81, N: 13.92, S: 12.69

4,5-Diphenyl-3-ethoxymethyleneamino-2-[N-(2-hydroxyethyl)] carbomylthieno[2,3-c]pyridazine (20)

A mixture of 5 (1 g) and triethyl orthoformate (10 ml) was gently refluxed for 6 hours. The excess triethyl orthoformate was removed under reduced pressure, and the precipitated formed was filtered off and recrysallized (benzene) to afford 20 (81%), mp 162–164 °C. IR: 3450–3200 cm^{-1} (br. NH and OH) and 1640 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 1.1–1.3 (t, 3 H, CH_3), 3.3–3.6 (m, 4 H, 2xCH_2), 4.2–4.4 (q, 2 H, OCH_2), 5.1 (s, 1 H, OH), 7.2–7.5 (m, 11H, 10 H, ArH and N=CH) and 8.1 (s, 1 H, NH).

Anal. Calcd. for $C_{24}H_{22}N_4O_3S$:	C: 64.55, H: 4.96, N: 12.54, S: 7.17
Found:	C: 64.33, H: 4.88, N: 12.23, S: 6.93

7-(2-Acetoxyethyl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c] pyridazine (21)

A mixture of compound 5 (1 g), triethyl orthoformate (2 ml) and acetic anhydride (10 ml) was heated under reflux for 2 hours. Upon cooling, the product formed was collected and recrystallized (ethanol) to give 21 (67%), mp 217–219 °C. IR: 1740 cm^{-1}(C=O) and 1675 cm^{-1} (C=O, pyrimidinone). ^1H NMR ($CDCl_3$): δ 2.1 (s, 3 H, CH_3), 3.2–3.5 (m, 4 H, 2xCH_2), 7.3–7.7 (m, 10 H, ArH) and 8.1 (s, 1 H, CH pyrimidine).

Anal. Calcd. for $C_{24}H_{18}N_4O_3S$:	C: 65.14, H: 4.10, N: 12.66, S: 7.24
Found:	C: 64.95, H: 3.97, N: 12.41, S: 7.12

7-(2-Chloroethyl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c] pyridazine (22)

Compound 20 (1 g) in thionyl chloride (15 ml) was heated on a steam bath for two hours. The excess solvent was removed under reduced pressure and the residue was treated with aqueous sodium carbonate solution (10 %). The solid was filtered off, washed with water, and recrystallized (acetic acid) to give 22 (63%), mp 296–298°C. IR: 1680 cm^{-1}(C=O, pyrimidinone). ^1H NMR (CF_3CO_2D): δ 4.0–4.2 (t, 2 H, $ClCH_2$), 4.5–4.7 (t, 2 H, NCH_2), 7.4–7.8 (m, 10 H, ArH) and 8.5 (s, 1 H, CH pyrimidine). MS: 418 (M^+).

Anal. Calcd. for $C_{22}H_{15}ClN_4OS$:	C: 63.08, H: 3.60, N: 13.37, S: 7.65
Found:	C: 62.87, H: 3.53, N: 13.11, S: 7.43

7-(2-Piperdinoethyl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c] pyridazine (23)

A mixture of 22 (0.5 g) and piperidine (1 ml) in absolute ethanol (15 ml) was heated under reflux for 4 hours. Upon cooling, the precipitate formed was filtered off and recrystallized (acetic acid) to give 23 (77%), mp 252–254 °C. IR: 1675 cm^{-1} (C=O, pyrimidinone). ^1H NMR (CF_3CO_2D): δ

1.8–2.2 (m, 6 H, piperidine), 2.9–3.1 (m, 2 H, piperidine), 3.8–4.1 (m, 4 H, 2H piperidine and 2 H, CH_2), 4.6–4.8 (t, 2 H, CH_2), 7.2–7.6 (m, 10 H, ArH) and 8.6 (s, 1 H, pyrimidine ring).

Anal. Calcd. for $C_{27}H_{25}N_5OS$:	C: 69.35, H: 5.38, N: 14.97, S: 6.85
Found:	C: 69.02, H: 5.22, N: 14.88, S: 6.73

7-Ethoxycarbonylmethyl-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c] pyridazin-8-one (24)

A mixture of compound 6 (0.7 g, 0.002 mol), ethyl chloroacetate (0 25 g, 0.002 mol), anhydrous K_2CO_3 (0.5 g) and dimethylformamide (10 ml) was heated on a steam bath for 4 hours. Upon cooling, the mixture was diluted with water (20 ml), and the precipitated formed was filtered off, washed with water and recrystallized (ethanol) to afford 24 (78%), mp 213–215 °C. IR: 1740 cm^{-1} (C=O) and 1680 cm^{-1} (C=O, pyrimidinone). ^1H NMR ($CDCl_3$): δ 1.2–1.4 (t, 3 H, CH_3), 4.2–4.4 (q, 2 H, OCH_2), 4.7 (s, 2 H, N-CH_2), 7.2–7.5 (m, 10 H, ArH) and 8.1 (s, 1 H, CH pyrimidine).

Anal. Calcd. for $C_{24}H_{18}N_4O_3S$:	C: 65.14, H: 4.10, N: 12.66, S: 7.24
Found:	C: 64.93, H: 3.98, N: 12.73, S: 7.13

8-Chloro-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (25)

Compound 6 (2 g) in phosphorus oxychlroide (15 ml) was gently refluxed for 4 hours. The excess solvent was removed under reduced pressure, and the residue was poured into ice-cold water, and neutralized with aqueous sodium carbonate solution (10 %). The precipitated formed was filtered off, washed with water and recrystallized (ethanol-benzene mixture) to give 25 (83%), mp 203–205 °C, Lit.[6] 204–206 °C. IR: 1620 cm^{-1} (C=N). ^1H NMR (DMSO-d_6): δ 7.2–7.5 (m, 10 H, ArH)and 8.5 (s, 1 H, pyrimidine ring).

Anal. Calcd. for $C_{20}H_{11}ClN_4S$:	C: 64.08, H: 2.96, N: 14.95, S: 8.55
Found:	C: 63.91, H: 2.88, N: 14.66, S: 8.37

4-(3,4-Diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazin-8-yl) aminobenzene-sulphonamide (26)

Compound 25 (0.76 g, 0.002 mol) and 4-aminobenzenesulphonamide (0.35 g, 0.002 mol) in glacial acetic acid (15 ml) were heated under reflux for 4 hours. Upon cooling, the precipitated formed was collected and recrystallized (acetic acid) to afford 26 (84%), mp 261–263°C. IR: 3350–3250 cm^{-1} (br. NH). ^1H NMR (CF_3CO_2D): δ 7.2–7.6 (m, 14 H, ArH) and 8.6 (s, 1 H, CH pyrimidine).

Anal. Calcd. for $C_{26}H_{18}N_6O_2S_2$:	C: 61.16, H: 3.55, N: 16.45, S: 12.55
Found:	C: 60.92, H: 3.41, N: 16.13, S: 12.33

8-Hydrazino-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c] pyridazine (27)

Compound 25 (1 g) and hydrazine hydrate (85%, 1 ml) in ethanol (25 ml) were heated under reflux for 3 hours. After cooling, the product formed was filtered off and recrystallized (dioxaine) to give 27 (86%), mp 263–265 °C. IR: 3450, 3300, 3200 cm^{-1} (NH) and 1620 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): δ 7.2–7.5 (m, 10 H, ArH) and 8.4 (s, 1 H, CH pyrimidine).

Anal. Calcd. for $C_{20}H_{14}N_6S$:	C: 64.84, H: 3.80, N: 22.68, S: 8.65
Found:	C: 64.73, H: 3.71, N: 22.43, S: 8.44

8-(3,5-Dimethylpyrazol-4-yl)-3,4-diphenylpyrimido[4′,5′:4,5]thieno [2,3-c] pyridazine (28)

A mixture of compound 27 (0.5 g) and acetyl acetone (0.4 ml) in absolute ethanol (15 ml) was heated under reflux for 4 hours. The precipitated formed after cooling was filtered off and recrystallized (acetic acid) to give 28 (72%), mp 259–261 °C. IR: 1600 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): δ 2.6 (s, 3 H, CH_3), 2.8 (s, 3 H, CH_3), 6.5 (s, 1 H, pyrazolel), 7.4–7.8 (m, 10 H, ArH) and 9.2 (s, 1 H, CH pyrimidine).

Anal. Calcd. for $C_{25}H_{18}N_6S$:	C: 69.10, H: 4.17, N: 19.34, S: 7.37
Found:	C: 68.88, H: 4.07, N: 19.13, S: 7.15

8-Azido-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (29)

The compound **29** obtained by the reaction of 27 (0.5 g) and sodium nitrite (0.2 g) using similar conditions as for the synthesis of compound 15; yield (84%), mp 237 °C (dec.). IR: 3130 cm^{-1} (N_3). ^1H NMR (DMSO-d_6): δ 7.3–7.7 (m, 10 H, ArH) and 8.6 (s, 1 H, Pyrimidine).

Anal. Calcd. for $C_{20}H_{11}N_7S$:	C: 62.98, H: 2.90, N: 25.70, S: 8.40
Found:	C: 62.68, H: 2.87, N: 25.53, S: 8.19

3,4-Diphenyl-1,2,4-triazolo[4″,3″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-c] pyridazine (30)

A mixture of 27 (0.5 g) and triethyl orthoformate (10 ml) was heated under reflux for 3 hours. After cooling, the precipitate formed was filtered off and recrystallized (acetic acid) to afford 30 (87%), mp > 300 °C. IR: 1600 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): δ 7.3–7.7 (m, 10 H, ArH), 9.4 (s, 1 H, CH pyrimidine) and 9.7 (s, 1 H, CH triazole).

Anal. Calcd. for $C_{21}H_{12}N_6S$:	C: 66.30, H: 3.17, N: 22.09, S: 8.42
Found:	C: 66.11, H: 3.06, N: 21.85, S: 8.26

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