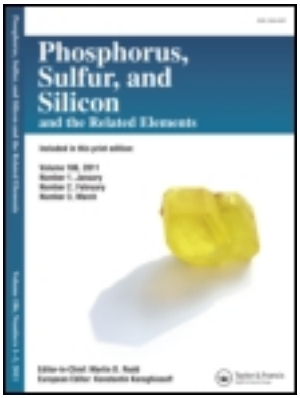

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Pyridazine Derivatives and Related Compounds, Part 21:[1] Synthesis of Different Heterocycles from 2-Methyl-4*H*-pyridazino[4′,3′:4,5]thieno[3,2-*d*]-1,3-oxazin-4-one

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*Starting with ethyl 5-amino-3,4-diphenylthieno[2,3-c]pyridazine-6-carboxyl-ate, the syntheses of 2-methyl-8,9-diphenyl-4H-pyridazino[4′,3′:4,5]thieno[3,2-d]-1,3-oxazin-4-one (**1**), 7-amino-6-methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido-[4′,5′:4,5]thieno[2,3-c]pyridazine (**3**), and some related compounds are described.*

INTRODUCTION

The pyrimidine ring is a frequent partner in polycyclic heterocyclic systems of biological significance.[2] Compounds containing a fused pyrimidine ring make up a broad class that has attracted attention in the past few years owing to its wide range of biological activity. Many potential drugs have been modeled on these compounds, particularly in cancer and virus research.[3] On the other hand, thienopyridazines have also attracted attention because of their promising biological activities.[4] This prompted us to consider new synthetic routes leading to substituted pyrimidothieno-pyridazine. Amino esters serve as good synthons for the formation of a pyrimidine ring.[5]

RESULTS AND DISCUSSION

Ethyl 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate was used as the starting material because it has suitable substituents for building other heterocyclic rings. The initial synthesis of a pyrimidine ring could be achieved via the preparation of 2-methyl-8,9-diphenyl-4*H*-

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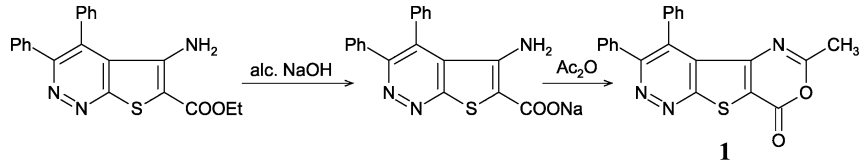
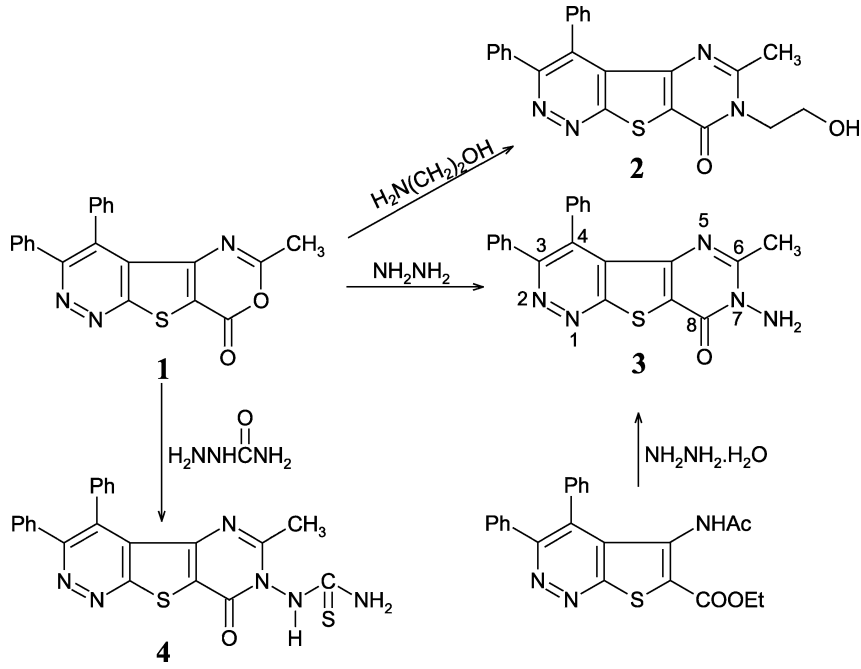
pyridazino-[4′,3′:4,5]thieno-[3,2-*d*]-1,3-oxazin-4-one[6] (**1**) as a key starting material (Scheme 1).[2]



SCHEME 1

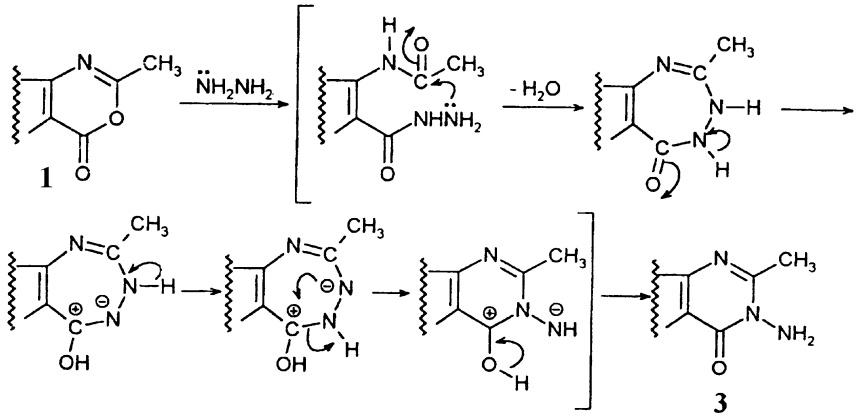
Treatment of **1** with ethanolamine, hydrazine hydrate, or thiosemicarbazide, or all of these, gave the corresponding tricyclic 7-substituted 6-methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4′,5′:4,5]thieno[2,3-*c*] pyridazine derivatives **2–4** as illustrated (Scheme 2):



SCHEME 2

The structures of compounds **2–4** were established on the basis of elemental analyses as well as spectroscopic data. Compound **3** also was obtained by condensing ethyl 5-acetylamino-3,4-diphenylthieno[2,3-*c*]pyrid-azine-6-carboxylate with hydrazine hydrate, as previously described.[6]

Mechanistically, the formation of 7-amino derivative **3** probably involves a nucleophilic ring opening of an oxazinone ring with a hydrazine hydrate to form a carbohydrazide intermediate. Then follows an intramolecular nucleo-philic cyclization of the hydrazido primary amino group to give the acetamido carbonyl group. The latter forms a triazepin intermediate, which rearranges to the product **3** (Scheme 3).[1]

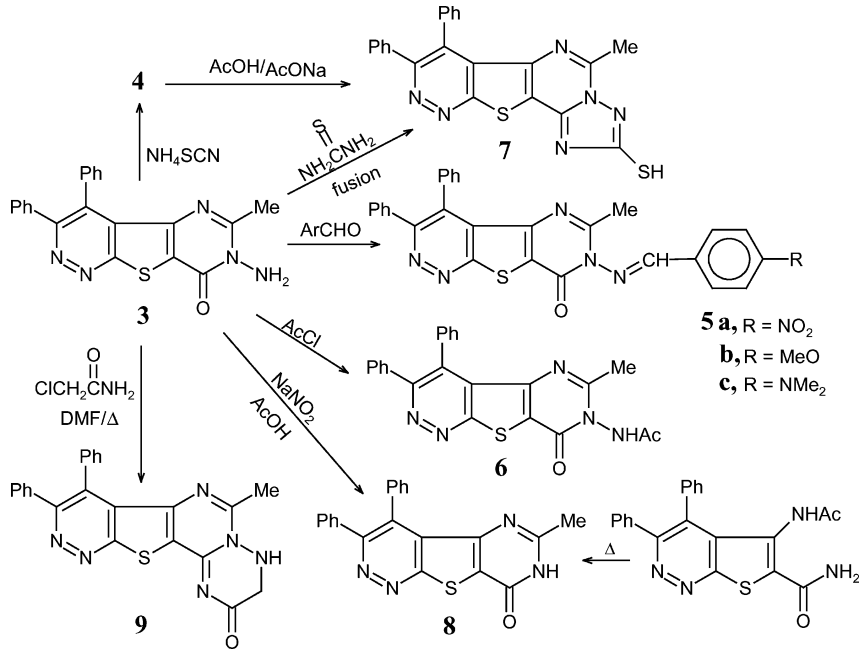


SCHEME 3

The reactivity of the 7-amino group in compound **3** was tested through its ease of reactions with aromatic aldehydes *p*-nitrobenzaldehyde, *p*-methoxy-benzaldehyde, and *p*-N,N-dimethylaminobenzaldehyde, which gave the corresponding arylideneamino derivatives **5a–c**. Acetylation of 7-amino derivative **3** using acetyl chloride in pyridine yielded N-acetylamino derivative **6**. The structure of **6** was elucidated from elemental analysis and spectral data. The IR spectrum showed peaks at 3200, 1690, and 1660 cm^{-1} due to NH and two C=O groups, respectively. The mass spectra recorded a molecular ion peak at *m/z* 427.

On the other hand, compound **3**, when refluxed with ammonium thiocyanate in acetone, gave a product identified as an N-substituted thiourea **4** in the basis of m.p., mixed m.p., and super-imposable IR spectra. Upon fusion of compound **3** and thiourea at 150–160°C, cyclization occurred with a loss of ammonia to form the triazolopyrimidothienopyridazine **7**. An alternative route to **7** was found in heating **4** in glacial-acetic-acid-fused sodium acetate.

It was of interest to react 7-amino derivative **3** with nitrous acid, which yields 6-methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido [4′,5′:4,5]thieno-[2,3-*c*]pyridazine (**8**). Since the N-diazonium ion was generated as an intermediate, it decomposes with the ultimate



SCHEME 4

deamination and formation of dinitrogen monoxide.[7] Compound **8** was identical (m.p., mixed m.p., and super impossible IR) with an authentic sample synthesized unambiguously from 5-acetamido-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxamide, which under-went smooth cyclization to **8**.[8] A single example of a new heterocyclic system was made by treating the 7-amino derivative **3** with chloroacetamide at a refluxed temperature in dimethylformamide to produce the 6-methyl-8,9-diphenyl-3,4-dihydropyridazino[3″,4″:5′,4′] thieno[2′,3′:5,6]pyrimido[3,4-*b*]-1,2,4-triazin-2-one (**9**). Its mass spectrum showed an intense peak at $m/z = 424$ corresponding to the molecular ion. The most salient features of the IR, ^{1} H-NMR, and mass spectra are given in the Experimental section (Scheme 4).

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and were uncorrected. The IR spectra of the compounds were recorded on a Perkin-Elmer spectrophotometer model 1310 as potassium bromide pellets and frequencies are reported in cm^{-1}. The ^{1}H-NMR spectra were observed on a Perkin-Elmer R12B spectrometer and chemical shifts (δ) are in ppm relative to internal TMS. Mass spectra were

obtained at 70 eV by using a AEI MS 30 mass spectrometer. All reactions were monitored by thin layer chromatography and carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 366 nm).

2-Methyl-8,9-diphenyl-4*H*-pyridazino[4′,3′:4,5]thieno[3,2-*d*]1,3-oxazin-4-one (1)

A sample of ethyl 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate[6] (1.0 g, 2.66 mmol) was refluxed in ethanolic sodium hydroxide (30 mL, 4%) for 2 h. The solvent then was evaporated under reduced pressure and the residue was used without purification in the following reaction: The sodium salt was heated in acetic anhydride (10 mL) at reflux temperature for 2 h; the cooled mixture was poured into water (30 mL); and the solid product formed was filtered off, dried, and recrystallized (ethanol) to give **1** (0.7 g, 60.6%), m.p. 160–161°C. IR: 1762 (C=O), 1660 (C=N), 1555 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.45–7.10 (m, 10H, 2 Ph), 1.45 (s, 3H, CH_3). Anal. calcd for $C_{21}H_{13}N_3O_2S$: C, 67.90; H, 3.52; N, 11.31. Found: C, 67.80; H, 3.40; N, 11.10.

7-β-Hydroxyethyl-6-methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido-[4′,5′:4,5]thieno[2,3-*c*]pyridazine (2)

To a solution of compound **1** (0.5 g, 1.34 mmol) in *n*-butanol (15 mL) ethanolamine (0.1 g, 1.34 mmol) and sodium acetate (0.1 g) were added. The reaction mixture was refluxed for 8 h. Upon cooling, a precipitate formed and was filtered off, washed several times with water, dried, and recrystallized (ethanol) to give **2** (0.4 g, 71.8%), m.p. 260–261°C. IR: 3449 (OH), 1655 (C=O), 1631 (C=N) cm^{-1}; MS *m/z* (%): 414 (M^+, 9.5), 355 (M^+-N$(CH_2)_2$OH, 11.3, ion A), 327 (M^+-$CONCH_2CH_2OH$, 32.3), 286 (ion A-N = C–CH_3, 18.4). Anal. calcd for $C_{23}H_{18}N_4O_2S$: C, 66.64; H, 4.37; N, 13.51. Found: C, 66.50; H, 4.10; N, 13.30.

7-Amino-6-methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido [4′,5′:4,5]-thieno[2,3-*c*]pyridazine (3)

To a solution of compound **1** (0.5 g, 1.34 mmol) in ethanol (10 mL) was added hydrazine hydrate 85% (0.1 g, 1.99 mmol). The reaction mixture was refluxed for 30 min, and the solvent was evaporated under reduced pressure. The residue was treated with water (50 mL). A precipitate formed and was filtered off, dried, and recrystallized (ethanol) to give **3** (0.4 g, 7.71%), m.p. 190–191°C. IR: 3350, 3190 (NH_2), 1672 (C=O), 1620

(C=N)cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 10.2 (s, 2H, NH_2), 7.4–7.0 (m, 10H, 2 Ph), 6.8 (s, 3H, CH_3). Anal. calcd for $C_{21}H_{15}N_5OS$: C, 65.43; H, 3.92; N, 18.17. Found: C, 65.30; H, 3.70; N, 17.90.

N-(6-Methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido [4′,5′:4,5]thieno-[2,3-*c*]pyridazin-7-yl)thiourea (4)

Method A

To a solution of compound **1** (0.5 g, 1.34 mmol) in n-butanol (10 mL) was added to thiosemicarbazide (0.1 g, 1.34 mmol). The reaction mixture was refluxed for 6 h, and, upon cooling, a precipitate was filtered off, dried, and recrystallized (ethanol) to give **4** (0.4 g, 67.02%), m.p. 105–106°C. IR: 3421, 3058 (NH_2), 1681 (C=O), 1620 (C=N), 1550 (C=C), 1154 (C=S) cm^{-1}; MS *m/z* (%): 444 (M^+, 1.1), 372 (M^+-$NHCSNH_2$, 21), 428 (M^+-NH_2, 12.8), 384 (M^+-$CSNH_2$, 3.9), 327 (M^+-$CONNHCSNH_2$, 19.3). Anal. calcd for $C_{22}H_{16}N_6OS_2$: C, 59.43; H, 3.62; N, 18.90. Found: C, 59.20; H, 3.50; N, 18.70.

Method B

To a solution of compound **3** (0.5 g, 1.29 mmol) in dry acetone (10 mL) ammonium thiocyanate (0.1 g, 1.29 mmol) was added. The reaction mixture was refluxed for 4 h; the solvent was evaporated under reduced pressure and the residue was treated with water (50 mL). The precipitate was filtered off, dried, and recrystallized (ethanol) to give **4** (0.3 g, 56%). It was identical with that prepared by Method A.

7-Arylideneamino-6-methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido-[4′,5′:4,5]thieno[2,3-*c*]pyridazine 5a–c: General procedure

A mixture of compound **3** (0.5 g, 1.29 mmol) and the appropriate aromatic aldehyde (1.29 mmol) was refluxed in glacial acetic acid (10 mL) for 6 h, cooled, and poured into water (50 mL). The separated solid was filtered off, washed with water, dried, and recrystallized (ethanol) to give **5a–c**.

7-(*p*-Nitrobenzylideneamino)-6-methyl-8-oxo-3,4-diphenyl-7,8-dihydro-pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (5a)

Yield (0.4 g, 80%), m.p. 282–283°C. IR: 1699 (C=O), 1521, 1345 (NO_2) cm^{-1}. Anal. calcd for $C_{28}H_{18}N_6O_3S$: C, 64.85; H, 3.49; N, 16.20. Found: C, 64.60; H, 3.20; N, 16.00.

7-(*p*-Methoxybenzylideneamino)-6-methyl-8-oxo-3,4-diphenyl-7,8-di-hydropyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (5b)

Yield (0.4 g, 61.5%), m.p. >300°C. IR: 1681 (C=O), 1610 (C=N), 1550 (C=C) cm^{-1}. Anal. calcd for $C_{29}H_{21}N_5O_2S$: C, 69.16; H, 4.20; N, 13.90. Found: C, 68.90; H, 4.00; N, 13.70.

7-(*p*-N,N-Dimethylaminobenzylideneamino)-6-methyl-8-oxo-3, 4-di-phenyl-7,8-dihydropyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (5c)

Yield (0.5 g, 75.7%), m.p. > 300°C. IR: 1664 (C=O), 1610 (C=N), 1550 (C=C) cm^{-1}. Anal. calcd for $C_{30}H_{24}N_6OS$: C, 69.74; H, 4.68; N, 16.26. Found: C, 69.50; H, 4.40; N, 16.00.

7-Acetylamino-6-methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido-[4′,5′:4,5]thieno[2,3-*c*]pyridazine (6)

A mixture of compound **3** (0.5 g, 1.29 mmol) and acetyl chloride (10 mL) was refluxed for 2 h. The cooled reaction mixture was poured into water (30 mL), and the precipitate formed was filtered off, dried, and recrystallized (ethanol) to give **6** (0.2 g, 36%), m.p. 146–147°C. IR: 3396 (NH), 1768 (C=O), 1730 (C=O), 1621 (C=N) cm^{-1}; MS *m/z*(%): 427 (M^+, 30), 384 (M^+-Ac, 12.8, ion A), 355 (ion A-N≡NH, 6.3 ion B), 327 (ion B-CO, 8.9, ion C), 286 (ion C–CH_3 CN, 13). Anal. calcd for $C_{23}H_{17}N_5O_2S$: C, 64.62; H, 4.01; N, 16.38. Found: C, 64.40; H, 3.90; N, 16.10.

2-Mercapto-5-methyl-7,8-diphenyl-1,2,4-triazolo[2″,3″:3′,4′]-pyrimido-[5′,6′:4,5]thieno[2,3-*c*]pyridazine (7)

Method A

A mixture of compound **3** (0.5 g, 1.29 mmol) and thiourea (0.1 g, 1.29 mmol) was heated at 150–160°C for 1 h. Methanol (30 mL) was added to the cooled reaction mixture, and the precipitate was filtered off, dried, and recrystallized (ethanol) to give **7** (0.4 g, 72.7%), m.p. >300°C. IR: 2400 (SH), 1620 (C=N), 1560 (C=C) cm^{-1}; MS *m/z* (%): 426 (M^+, 33), 385 (M^+ -CH_3CN, 12.3 ion A), 186 (ion A-substituted triazole, 6.9). Anal. calcd for $C_{22}H_{14}N_6S_2$: C, 61.95; H, 3.30; N, 19.70. Found: C, 61.70; H, 3.10; N, 19.60.

Method B

To a solution of **4** (0.5 g, 1.12 mmol) in acetic acid (10 mL) sodium acetate (0.1 g) was added. The reaction mixture was refluxed for 8 h, and the cooled solution was poured into water (100 mL). The precipitate was filtered off, dried, and recrystallized (ethanol) to give **7** (0.3 g, 58.02%). It was identical with that prepared by Method A.

6-Methyl-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4′,5′:4,5]-thieno[2,3-*c*]pyridazine (8)

A solution of sodium nitrite (0.38 g, 5.3 mmol) in water (10 mL) was added dropwise to a stirred solution of compound **3** (0.5 g, 1.29 mmol) in acetic acid (10 mL) at room temperature. The reaction mixture was stirred for 2 h, and the precipitate was filtered off, washed with water, dried, and recrystallized (acetic acid) to give **8** (0.4 g, 83.2%), m.p. >300°C. IR: 3400 (NH), 1690 (C=O), 1620 (C=N) cm^{-1}; MS *m/z* (%): 370 (M^+, 6.8), 342 (M^+-CO, 5.2, ion A), 286 (ion A-N=C-$NHCH_3$, 22.3); ^{1}H-NMR (DMSO-d_6): δ 8.3 (s, 1H, NH), 7.8–7.6 (m, 10H, 2 Ph), 1.8 (s, 3H, CH_3). Anal. calcd for $C_{21}H_{14}N_4OS$: C, 68.07; H, 3.81; N, 15.12. Found: C, 68.10; H, 3.60; N, 15.50.

6-Methyl-8,9-diphenyl-3,4-dihydropyridazino[3″,4″:5′,4′]-thieno-[2′,3′:5,6]pyrimido[3,4-*b*]-1,2,4-triazin-7-one (9)

A solution of compound **3** (0.5 g, 1.29 mmol) in dimethylformamide (10 mL) and 2-chloroacetamide (0.1 g, 1.29 mmol) was refluxed for 12 h. The cooled reaction mixture was poured into water (50 mL). The precipitate was filtered off, washed with water, dried, and recrystallized (ethanol) to give **9** (0.3 g, 54.4%), m.p. 196–197°C. IR: 3427 (NH), 1658 (C=O), 1610 (C=N), 1550 (C=C) cm^{-1}; MS *m/z* (%): 424 (M^+, 16.3), 395 (M^+-NH=CH_2), 35.6 ion A), 353 (ion A - NCO, 17.6). Anal. calcd for $C_{23}H_{16}N_6OS$: C, 65.07; H, 3.79; N, 19.79. Found: C, 64.80; H, 3.60; N, 19.70.

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