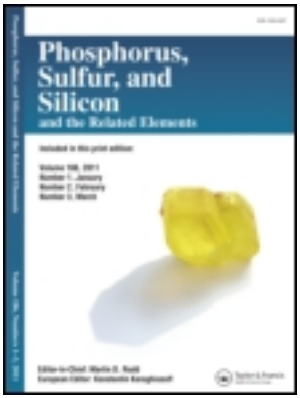


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# Pyridazine Derivatives and Related Compounds. Part 11: [1]Synthesis of Some Pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazines

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# PYRIDAZINE DERIVATIVES AND RELATED COMPOUNDS. PART 11: [1]SYNTHESIS OF SOME PYRIMIDO[4′,5′:4,5]THIENO[2,3-*c*]PYRIDAZINES

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*3-Substituted pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine-2,4-di-ones and 3-amino-2-methylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine-4-ones were synthesized starting from ethyl 5-aminothieno[2,3-c] pyridazine-6-carboxylate **1**. Reaction of amino ester **1** with phenyl isothiocyanate affords thiourea derivative **10** which undergo further transformation to the related fused heterocyclic systems.*

Pyridazine derivatives and heterocyclic-annelated pyridazines continue to attract interest due to a wide spectrum of biological activities.[2,3] In particular, some thienopyridazines have been reported to possess considerable antiasthmatic[4] and fibrinolytic activities.[5] As a continuation of our previous work on the synthesis and biological properties of fused systems of pyridazine and different heterocycles, we have been interested in the synthesis and biological properties of thieno[2,3-*c*]-pyridazine derivatives. In this article we report our results on the annulation of the pyrimidine ring to a preformed thieno[2,3-*c*]pyridazine system employing an amino ester as a conveniently accessible precursor and evaluate their antimicrobial activities.

Our synthesis began with the preparation of ethyl 5-amino-3,4-diphenyl-thieno[2,3-*c*]pyridazine-6-carboxylate **1**, which was obtained from the reaction of 3-chloro-4-cyanopyridazine or 4-cyanopyridazine-3-thione with ethyl mercapto-acetate or ethyl chloro(bromo)acetate, respectively.[6]

Boiling a solution of **1** and ethoxycarbonyl chloride in acetone, **2** (95%) was obtained. This last compound was cyclized to **3** with hydrazine

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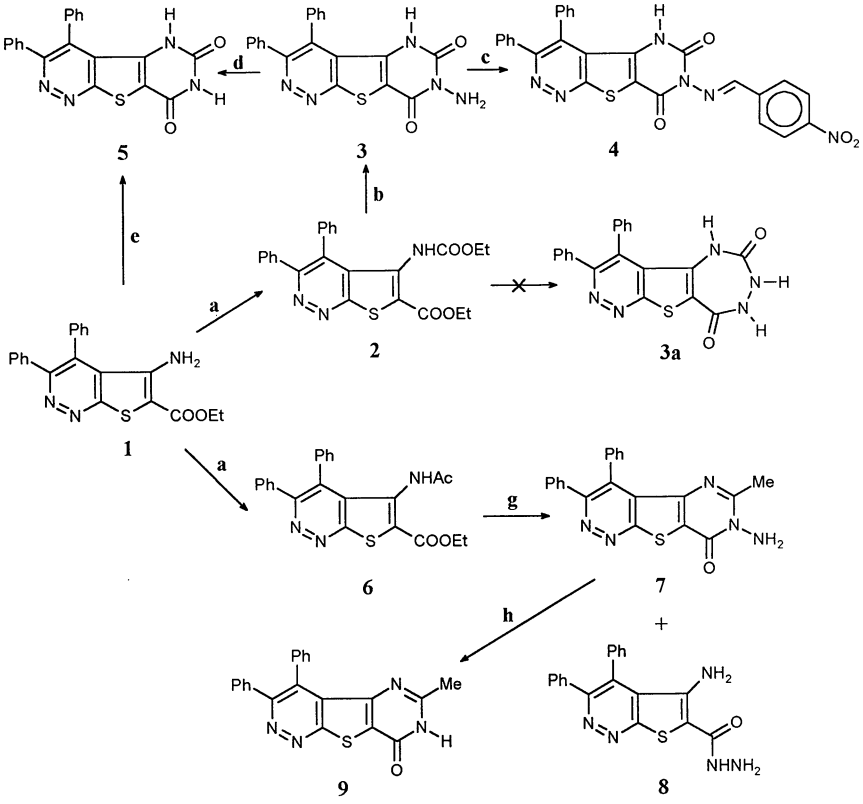
hydrate. From the elemental analysis and IR spectra, the compound **3** would be 3-amino-8,9-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine-2,4-dione or the isomeric triazepinedione **3a** resulting from the ring expansion (Scheme 1). The $^1$H NMR spectra showed that the correct structure is the aminopyrimidinedione. According to the literature,[7] 3-aminopyrimidine-4-ones show a signal at about $\delta$ 6.0–5.0 ppm (s or bs, 2H, 3-$NH_2$), in the $^1$H NMR spectra, which disappears with the addition of deuterium oxide. In the isomeric triazepinones, the signals for the protons of the system —CONHNHCO— appear at values of >8.0 ppm[8] as two different signals (s or bs). The $^1$H NMR spectra of **3** shows a signal at about 5.56 (bs, 2H), which was assigned to the 3-amino




(**a**) ClCOOEt, anhyd. $K_2CO_3$, reflux; (**b**) $NH_2NH_2H_2O$, reflux; (**c**) p-$NO_2C_6H_5CHO$, ethanol, reflux; (**d**) $NaNO_2$/AcOH/45-50°C; (**e**) Urea, 180°C; (**f**) AcCl, dry pyridine; (**g**) $NH_2NH_2.H_2O$, ethanol, reflux; (**h**) $NaNO_2$/AcOH/45-50°C.

**SCHEME 1**

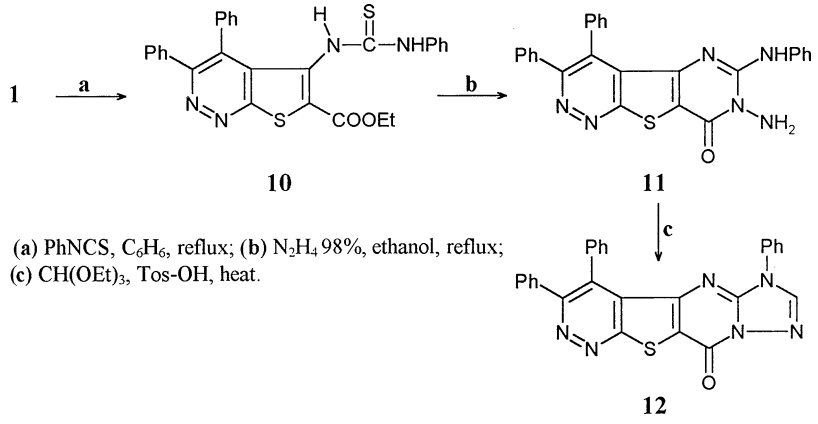
group. However, compound **3** does not show any expected signal for the proton of the group —N(1)H—CO—. This proton seems to interchange very easily with the protons of water in the solvent dimethylsulfoxide-$d_6$ (DMSO-$d_6$). The structure **3** for this compound was confirmed by the preparation of the *p*-nitrobenzylidene derivative **4** (60%). The structure of compound **3** was also confirmed by the fact that **3**, on treatment with sodium nitrite in 50% acetic acid, undergoes smooth by deamination to give 8,9-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine-2,4-dione **5**, which is identical to the product obtained by treatment of the aminoester **1** with urea at 180°C.

The reaction of **1** with either with acetyl chloride or acetic anhydride at reflux temperature led to the formation of the monoacetyl derivative **6**. Compound **6** on heating with hydrazine hydrate in ethanol produced 3-amino-2-methyl-3,4-dihydro-4-oxo-8,9-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine **7**, along with amino carbohydrazide **8**. The formation of **8** is probably due to the simultaneous partial deacetylation of **6** with hydrazine hydrate while it is being converted into the corresponding carboxyhydrazide, and subsequent ring closure is effected. Compound **7**, on treatment with sodium nitrite in 50% acetic acid, underwent deamination to give 2-methyl-3,4-dihydro-4-oxo-8,9-diphenylpyrimido-[4′,5′:4,5]-thieno[2,3-*c*]pyridazine **9**. It was found to be identical (m.p., mixed m.p., and super imposable IR) with an authentic sample synthesized unambiguously.[9]

On the other hand, we employed compound **1** as a starting material to synthesize other heterocyclic systems. Reaction with phenylisothiocyanate in toluene resulted in thiourea derivative **10**. Upon treatment with hydrazine hydrate (98%), **10** undergoes cyclization to 3-amino-2-anilino-4-oxo-8,9-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine **11**. Compound **11** in turn could be transformed to other fused heterocyclic systems. Reaction with triethylorthoformate in the presence of catalytic amounts of *p*-toluenesulfonic acid affords the tetracyclic compound **12** (Scheme 2). The most salient features of IR and $^1$H NMR spectra are given in the Experimental section below.

## ANTIMICROBIAL SCREENING

The synthesized compounds were evaluated for their antimicrobial activity by the agar diffusion techniques.[11] A 0.1% solution in dimethylformamide (DMF) was used. The test organisms were *Staphylococcus aureus NCTS* 4163, *Escherichia coli NCTC* 5933, and *Candida albicans* 3501. Inhibition zones against *E. coli* for **3**, 18 mm; **4**, 21 mm; **5**, 16 mm; **7**, **9**, **10**, 14 mm; and **11** and **12**, 17 mm. The other compounds




**SCHEME 2**

showed no inhibition zones against *E. coli*. The reference compound was *Streptomycin* (inhibition zone: 34 mm). DMF showed no inhibition zones. The minmum inhibitory concentrations (MICs) for compounds **3**, **4**, **7**, **9**, and **10** were 0.05, 0.0125, 0.025, 0.1, and 0.023 mg/ml, respectively. The MIC for *Streptomycin* was 0.006 mg/ml. None of the tested compounds was superior to *Streptomycin* in the test against *E. coli*. The compounds showed no inhibition against *S. aureus* and *C. albicans*.

## EXPERIMENTAL

All the melting points are 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 $^1H$ NMR spectra were observed on a Perkin-Elmer R 12 B spectrometer and chemical shifts ($\delta$) are in ppm relative to internal TMS. Reactions were routinely followed by thin layer chromatography (TLC) on silica gel $F_{254}$ aluminium sheets (Merck). The spots were detected by UV irradiation at 254–365 nm.

### Ethyl 5-Amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate 1

$Na_2CO_3$ (3.99 g, 37.64 mmol) was added to a solution of 3-chloro-4-cyano-5,6-diphenylpyridazine[6] (9.14 g, 31.36 mmol) and ethyl 2-mercaptoacetate (4.11 g, 37.64 mmol) in EtOH/THF (5:1) (600 ml). The reaction mixture was refluxed for 2.5 h. The reaction mixture was

collected by filtration while hot, concentrated and left to cool. The solid product formed was filtered off and recrystallized from ethanol to give **1** (10.82 g, 92%); m.p. 182–184°C (lit[10] m.p. 180–182°C).

## Ethyl 5-Ethoxycarbonylamino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate 2

To a solution of **1** (0.38 g, 1 mmol) in dry acetone (50 ml), anhydrous potassium carbonate (0.5 g) and ethoxycarbonyl chloride (0.11 g, 1 mmol) were added. The reaction mixture was refluxed for 5 h. After filtration, the solvent was removed in vacuo and the solid residue was recrystallized to give **2**, m.p. 117–118°C (ethanol), yield 0.27 g (60%) as yellow crystals. IR: 3330 and 3260 (NH), 1690 (multiple, C=O), 1630 (C=N), 1550 (C=C). $^1$H NMR (DMSO-$d_6$)$\delta$: 8.75 (s, 1H, CO–NH), 7.4 (s, 10H, 2Ph), 4.4–4.0 (m, 2H, $CH_2$), 3.8–2.45 (m, 2H, $CH_2$), 1.3 (t, 3H, $CH_3$), 1.2 (t, 3H, $CH_3$). Anal. Calcd for $C_{24}H_{21}N_3O_4S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.30; H, 4.60; N, 9.20.

## 3-Amino-8,9-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine-2,4-dione 3

A mixture of **2** (0.45 g, 1 mmol) and hydrazine hydrate (98%; 5 ml) was boiled for 4 h. Excess hydrazine was removed in vacuo and the solid residue recrystallized to give **3**, m.p. 206–207°C (ethanol), yield 0.22 g (56%) as pale brown crystals. IR: 3340 (w, NH), 3190 (s, NH), 1680 (m, C=O), 1640 (s, C=O), 1630 (C=N), 1520 (C=C). $^1$H NMR (DMSO-$d_6$) $\delta$: 7.4–7.0 (m, 10H, 2Ph), 5.56 (s, 2H, $NH_2$). No any signal was observed for –N(1)H–; this proton seems to interchange with the protons of the trace of water in the solvent. The signal at 5.56 (s) disappeared following the addition of deuterium oxide. Anal. Calcd for $C_{20}H_{13}N_5O_2S$: C, 62.00; H, 3.38; N, 18.08. Found: C, 61.80; H, 3.10; N, 17.90.

## 3-(4-Nitrobenzilideneamino)-8,9-diphenylpyrimido-[4′,5′:4,5]thieno[2,3-*c*]pyridazine-2,4-dione 4

A mixture of **3** (1.00 g, 2.58 mmol), *p*-nitrobenzaldehyde (0.54 g, 3 mmol) and ethanol (20 ml) was boiled for 6 h. Solvent was removed in vacuo and the residual material was recrystallized to give **4** as brown crystals, m.p. 235–236°C (ethanol), yield 0.8 g (60%). IR: 3170 (bs, NH), 1685 (s, C=O), 1630 (w, C=O, C=N), 1540 (C=C). Anal. Calcd for $C_{27}H_{16}N_6O_4S$: C, 62.29; H, 3.09; N, 16.14. Found: C, 62.00; H, 2.90; N, 15.80.

## 8,9-Diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine-2,4-dione 5

### *Method A*

To a suspension of **3** (0.4 g, 1.03 mmol) in 50% acetic acid (30 ml) warmed to 45–50°C, sodium nitrite (0.4 g, 5.8 mmol) was added in portions. The reaction mixture was maintained at this temperature till the evolution of brown fumes ceased. The product that separated as a colorless solid on dilution with water was collected and further purified by dissolving in alkali and reprecipitating with acid. It was finally recrystallized from DMF as colorless granules, yield 0.3 g, (80%), m.p. 335–336°C. IR: 3160 (bs NH), 1680 (s, CO), 1635 (w, CO, C=N), 1550 (C=C). Anal. Calcd for $C_{20}H_{12}N_4O_2S$: C, 64.50; H, 3.24; N, 15.04. Found: C, 64.30; H, 3.00; N, 14.80.

### *Method B*

Compound **1** (1 g, 2.6 mmol) and urea (1.5 g, 25 mmol) were heated together at 180°C for 30 min. The reaction mixture became almost liquid. The temperature was then raised to 190°C, and it was further heated for 20 min at this temperature. The reaction product was cooled, dissolved in hot aqueous NaOH (2N), and filtered. The filtrate was acidified with acetic acid in hot condition, and the product was filtered and recrystallized from DMF to give **5** as colorless plates (0.4 g, 41%), m.p. 335–336°C. The compound is identical to that obtained according to Method A.

### *Ethyl 5-Acetylamino-3,4-diphenylthieno[2,3-c]-pyridazine-6-carboxylate 6*

Acetyl chloride (0.08 g, 1 mmol) was added to a solution of **1** (0.38 g, 1 mmol) in dry pyridine (10 ml). The reaction mixture was heated on water bath for 3 h, the cooled reaction mixture was poured into water (100 ml). The precipitated product was filtered, dried, and recrystallized, m.p. 147–148°C (ethanol), yield 0.38 g, (90%). IR: 3230 (NH), 1700, 1690 (C=O groups), 1640 (C=N), 1565 (C=C). $^1$H NMR (DMSO-$d_6$) $\delta$: 7.5–7.0 (s, 10H, 2Ph), 4.2–4.0 (m, 2H, $CH_2$), 1.8 (s, 3H, $CH_3$), 1.2 (t, 3H, $CH_3$). Anal. Calcd for $C_{23}H_{19}N_3O_3S$: C, 66.17; H, 4.59; N, 10.06. Found: C, 66.00; H, 4.40; N, 9.90.

### *3-Amino-2-methyl-3,4-dihydro-4-oxo-8,9-diphenylpyrimido-[4′,5′:4,5]thieno[2,3-c]-pyridazine 7 and 3-amino-4,5-diphenylthieno[2,3-c]pyridazine-2-carbohydrazide 8*

A mixture of **6** (3 g, 7.18 mmol) and hydrazine hydrate 80% (6 ml) was heated under reflux in ethanol (60 ml). Within 1 h, a crystalline

product started to separate. After refluxing for a further period of 1 h, the reaction mixture was cooled and **7**, which separated as a crystalline solid (0.5 g, 40%), was collected, m.p. 205–206°C (DMF). IR: 3500, 3310, 3180 (NH groups), 1660, 1640 (C=O), 1620 (C=N), 1530 (C=C). $^1$H NMR (DMSO-$d_6$)$\delta$: 9.89 (s, 2H, $NH_2$), 7.4–7.0 (m, 10H, 2Ph), 3.3 (s, 3H, $CH_3$). Anal. Calcd for $C_{21}H_{15}N_5OS$: C, 65.43; H, 3.92; N, 18.17. Found: C, 65.20; H, 3.80; N, 18.00.

The filtrate after dilution with water was cooled thoroughly to get **8** as a colorless solid. It was collected and crystallized from ethanol as needles (0.25 g, 40%), m.p. 245–246°C. IR: 3450, 3320, 3260 (NH groups), 1640 (C=O), 1600 (C=N), 1530 (C=C). $^1$H NMR (DMSO-$d_6$) $\delta$: 9.4 (s, 1H, NH), 8.0–7.6 (d, 2H, $NH_2$), 7.4–7.0 (s, 10H, 2Ph), 4.2 (s, 2H, 5-$NH_2$). Anal. Calcd for $C_{19}H_{15}N_5OS$: C, 63.14; H, 4.18; N, 19.38. Found: C, 63.00; H, 4.10; N, 19.20.

### *3.4-Dihydro-2-methyl-4-oxo-8,9-diphenylpyrimido-[4′,5′:4,5]thieno[2,3-c]pyridazine 9*

A suspension of **7** (0.2 g) in 50% acetic acid (15 ml) was treated with sodium nitrite (0.2 g) at 45–50°C. Subsequent work up as described above gave **9** as colorless long needles (0.18 g, 94.7%), m.p. > 300°C (DMF). TLC chromatography in three solvent systems and IR spectra showed the compound to be same as that previously reported.[9]

### **N-***(6-Ethoxycarbonyl-3,4-diphenylthieno[2,3-c]pyridazin-5-yl)*-**N′***-phenylthiourea 10*

A solution of amino ester **1** (0.38 g, 1 mmol) and phenyl isothiocyanate (0.14 g, 1 mmol) in benzene (10 ml) was heated at reflux. After 2 h the mixture was cooled, and the solid was collected and dried, m.p. 130–131°C (benzene), yield 0.28 g (54%). IR: 3443, 3309 (NH), 1723 (C=O), 1665 (C=N), 1620, 1155 (C=S). $^1$H NMR (DMSO-$d_6$) $\delta$: 8.05, (s, 1H, NH), 7.84 (s, 1H, NH), 7.4–7.1 (m, 15H, 3Ph), 4.2 (q, 2H, $CH_2$), 1.2 (t, 3H, $CH_3$). Anal. Calcd for $C_{28}H_{22}N_4O_2S_2$: C, 65.86; H, 4.34; N, 10.97. Found: C, 65.70; H, 4.20; N, 10.80.

### *3-Amino-2-anilino-3,4-dihydro-4-oxo-8,9-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine 11*

Hydrazine hydrate 98% (3 ml) was slowly added to a stirred solution of thiourea derivative **10** (1 g, 1.95 mmol) in 15 ml of ethanol. The mixture was refluxed for 8 h and the solid crystallized on cooling was collected, repeatedly washed with water, and dried, m.p. 239–240°C (ethanol), yield 0.63 g, (70%). IR: 3501, 3319, 3176 (NH), 1655 (C=O), 1618 (C=N), 1491 (C=C). $^1$H NMR (DMSO-$d_6$) $\delta$: 9.3 (br s, 1H, NH),

7.4–7.0 (m, 15H, 3Ph), 4.1 (s, 2H, $NH_2$). Anal. Calcd for $C_{26}H_{18}N_6OS$: C, 67.51; H, 3.92; N, 18.17. Found: C, 67.30; H, 3.70; N, 18.00.

### *1,9,10-Triphenyl-5-oxo-[1,2,4]triazolo[2″,3″:1′,2′]pyrimido-[4′,5′:4,5]thieno-[2,3-c]pyridazine 12*

A suspension of **11** (2.7 g, 5.85 mmol) and *p*-toluenesulfonic acid (1.5 g, 8.72 mmol) in triethylorthoformate (45 ml) was refluxed under stirring for 18 h. The solid material was collected by filtration, washed with water, dried and recrystallized from DMF, the yield of **12** was 50%, m.p. > 300°C. IR: 3057 (NH), 1686 (C=O), 1545 (C=C). $^1$H NMR ($CDCl_3$)$\delta$: 7.66 (s, 1H, triazole), 7.35–7.05 (m, 15 H, 3Ph). Anal. Calcd for $C_{27}H_{16}N_6OS$: C, 68.62; H, 3.41; N, 17.78. Found: C, 68.30; H, 3.20; N, 17.60.

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