

The Synthesis of 1,2,5-Thiadiazolo[3,4-*d*]pyridazines

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A number of previously unreported 1,2,5-thiadiazolo[3,4-*d*]pyridazines in this relatively unexplored ring system have been reported, characterized and screened for antibacterial and antifungal activity.

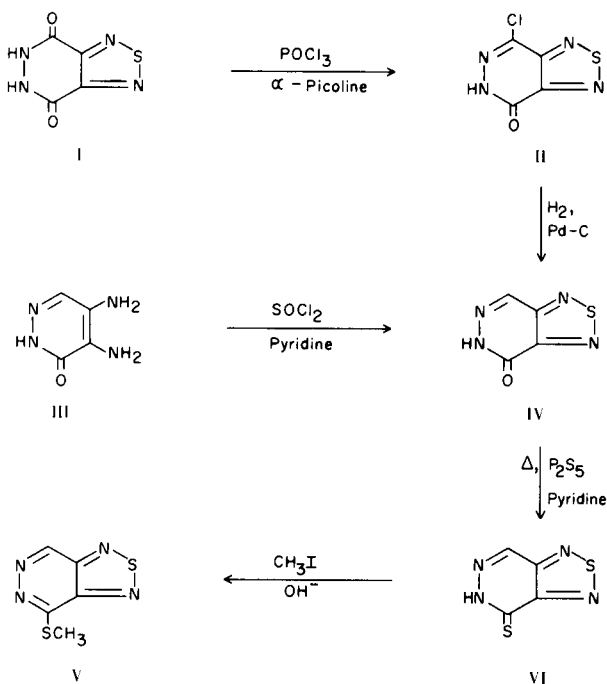
The 1,2,5-thiadiazolo[3,4-*d*]pyridazine ring system has been almost completely ignored. Prior to this work, only 1,2,5-thiadiazolo[3,4-*d*]pyridazine-4,7-dione (I) had been reported and characterized by Sekikawa (3). Dury (4) had mentioned this heterocyclic ring system but without experimental details. We have selected 1,2,5-thiadiazolo[3,4-*d*]pyridazine-4,7-dione (I) previously reported by Sekikawa (3) as the key intermediate in the synthesis of most of the new 1,2,5-thiadiazolo[3,4-*d*]pyridazines.

Compound I was allowed to react with refluxing phosphorus oxychloride and α -picoline. The product was exclusively 7-chloro-1,2,5-thiadiazolo[3,4-*d*]pyridazin-4-one (II) (67%). Attempts to isolate the 4,7-dichloro-1,2,5-thiadiazolo[3,4-*d*]pyridazine were unsuccessful.

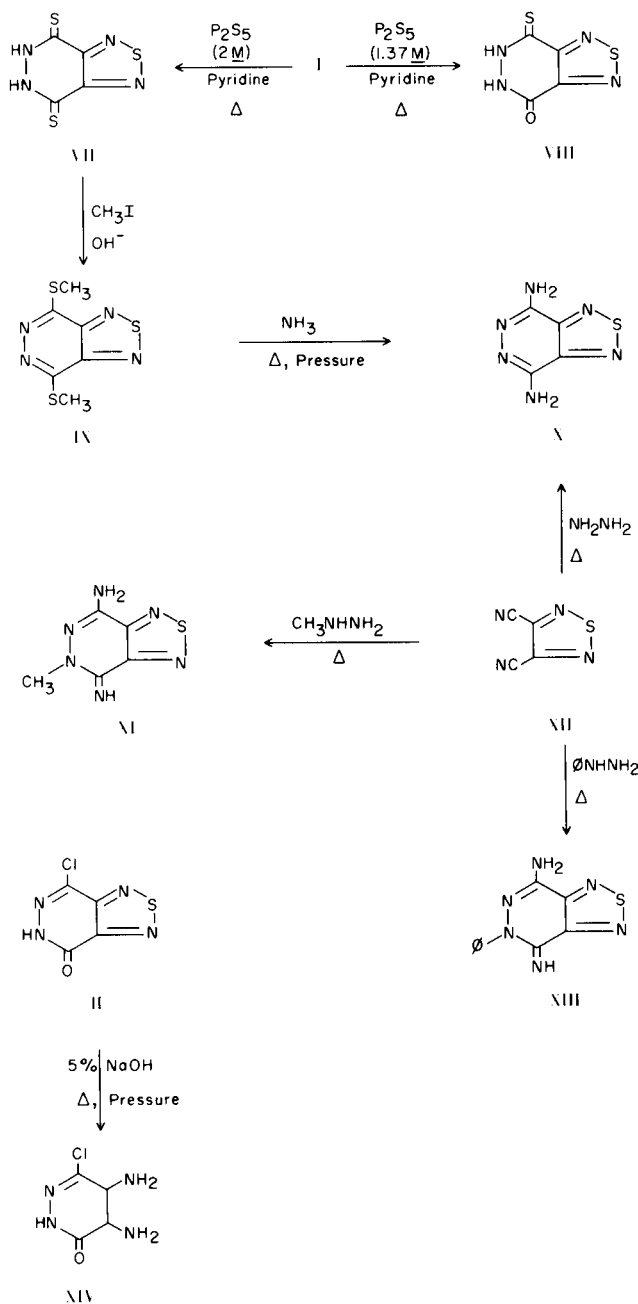
Compound II was catalytically dechlorinated in the presence of 10% palladium on charcoal. The solvent was methanol to which less than 1% of concentrated ammonium hydroxide had been added. 1,2,5-Thiadiazolo[3,4-*d*]pyridazin-4-one (IV) was obtained in 77% yield by this method. Compound IV was also obtained in 50% yield by allowing 4,5-diamino-3-pyridazone (III) (5) to react with thionyl chloride. The product was shown to be identical with that obtained by Method A. Compound IV was thiated with phosphorus pentasulfide in pyridine solution to give 1,2,5-thiadiazolo[3,4-*d*]pyridazine-4-thione (VI) in 32% yield. Compound VI was methylated with methyl iodide in alkali to give 4-methylthio-1,2,5-thiadiazolo[3,4-*d*]pyridazine (V) in 64% yield. The above transformations are outlined in Flow Sheet I.

Compound I could be converted into 1,2,5-thiadiazolo[3,4-*d*]pyridazin-4-one-7-thione (VIII) with ~ 1.3 moles of phosphorus pentasulfide (pyridine) per mole of I in 76% yield. When one mole of compound I was allowed to react with two moles of phosphorus pentasulfide in pyridine solution, 62% of 1,2,5-thiadiazolo[3,4-*d*]pyridazine-4,7-dithione (VII) was obtained. Compound VII was smoothly converted into 4,7-bis(methylthio)-1,2,5-thiadiazolo[3,4-*d*]pyridazine (IX) in 59% yield. Since the methylthio group is generally a good leaving group in pyridazines and related nitrogen heterocycles, we allowed IX to react with ethanolic ammonia under heat and pressure to give 4,7-diamino-1,2,5-thiadiazolo[3,4-*d*]pyridazine (X) in 56% yield. Compound X was also obtained by direct cyclization of 3,4-dicyano-1,2,5-thiadiazole (XII) (6) with hydrazine in 69% yield. The products X were shown to be identical by Methods A or B. Compound XII when treated with methylhydrazine or phenylhydrazine gave respectively, 7-amino-4-imino-5-methyl-1,2,5-thiadiazolo[3,4-*d*]pyridazine (XI) (85%) and 7-amino-4-imino-5-phenyl-1,2,5-thiadiazolo[3,4-*d*]pyridazine (XIII) (92%). When attempts were made to hydrolyze the chlorine atom of II to give I, the thiadiazole ring was opened

Flow Sheet I



Flow Sheet II



with the loss of sulfur to give 3-chloro-4,5-diaminopyridazin-6-one (XIV) in 86% yield. These transformations are outlined in Flow Sheet II. The spectral data reported in the Experimental are consistent with the structures reported and is confirmatory evidence for the structures of the 1,2,5-thiadiazolo[3,4-d]pyridazines proposed. However, the synthetic routes are so well known as to make the confirmatory evidence almost unnecessary.

The compounds were screened against several bacteria and fungi with no significant activity being observed (7).

EXPERIMENTAL

All melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. The nmr were recorded on a Varian A-60-A with the standard and conditions indicated for each compound. The ir spectra were recorded in potassium bromide discs with a Perkin-Elmer 337 Spectrophotometer. The uv spectra were determined with a Cary 14R spectrophotometer in the solvent indicated.

7-Chloro-1,2,5-thiadiazolo[3,4-d]pyridazin-4-one (II).

To a mixture of 5.0 g. (0.0294 mole) of 1,2,5-thiadiazolo[3,4-d]pyridazin-4,7-dione (I) (3) and 150 ml. of phosphorus oxychloride was added slowly 20 ml. of freshly distilled α -picoline at room temperature. The mixture was heated under reflux for 3 hours. During the early stages of reflux the white solid dissolved and the solution became cherry red. About 90% of the excess phosphorus oxychloride was then removed under reduced pressure and the dark syrup was allowed to stand overnight. The mixture was then poured cautiously into 150 g. of crushed ice maintaining the temperature near 0° . The beige colored solid which separated was filtered quickly from the acid solution, washed thoroughly with chilled water and air dried, giving 3.75 g. (yield 67%) of crude product. Repeated recrystallization from petroleum ether ($90-120^\circ$) gave white needles m.p. $214-215^\circ$; uv λ max (95% ethanol), 202 (ϵ , 22,140), 248 (ϵ , 13,520), 267 (sh) (ϵ , 5,480), 276 (sh) (ϵ , 3,920), 327 m μ (ϵ , 6,270); ir cm^{-1} : 3250(m), 3190(m), 3160(m), 1695(s), 1420(s), 1290(s), 1170(s), 995(s), 855(s).

Anal. Calcd. for $C_4H_1ClN_4OS$: C, 25.47; H, 0.54; N, 29.71. Found: C, 25.85; H, 0.52; N, 29.57.

1,2,5-Thiadiazolo[3,4-d]pyridazin-4-one (IV).

Method A.

4,5-Diamino-3-pyridazinone (III) (1.0 g., 0.013 mole) was added slowly to 20 ml. of thionyl chloride at room temperature. After the addition of the pyridazinone was complete, 2 ml. of dry pyridine was added to the reaction mixture. The resulting mixture was then refluxed overnight and an aliquot was subjected to tlc with ethyl acetate-silica gel in order to monitor the progress of the reaction. The reaction mixture was then evaporated to dryness under reduced pressure, followed by boiling for 10 minutes with 25 ml. of a 1% sodium hydroxide solution to remove residual pyridine. Glacial acetic acid was added dropwise until the solution was neutral to universal indicator paper, then evaporated to dryness on a rotary evaporator. The yellow powder was dissolved in a minimum amount of 70% ethanol and allowed to stand overnight in the refrigerator. Filtration and drying gave 0.985 g. (50%) of crude product. Recrystallization from 95% ethanol (*Norite*) gave white fluffy needles m.p. $218-219^\circ$; uv λ max (95% ethanol), 243 (ϵ , 10,690), 267 (sh) (ϵ , 2,460), 327 m μ (ϵ , 4,550); ir cm^{-1} : 3210(m), 3060(m), 1675(s), 1275(s), 910(s), 830(s); nmr (deuterium oxide/sodium deuterioxide/DDS) δ 8.90 (singlet C₇H).

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.17; H, 1.31; N, 36.37. Found: C, 31.41; H, 1.37; N, 36.23.

Method B.

7-Chloro-1,2,5-thiadiazolo[3,4-d]pyridazin-4-one (II) (1.0 g., 0.0058 mole), 150 ml. of methanol and 1 ml. of concentrated ammonium hydroxide were mixed together. To this was added 0.50 g. of 10% palladium on charcoal. The solution was hydrogenated at room temperature under atmospheric pressure for 14 hours. The solution was warmed, filtered and evaporated to

dryness to give 0.628 g. (77%) of a yellow compound. Repeated recrystallization from 95% ethanol gave white fluffy needles, m.p. 218-219°. No depression of m.p. was observed upon admixture with the product obtained from Method A. The ir and uv spectra were identical with those of the compound synthesized by Method A.

1,2,5-Thiadiazolo[3,4-*d*]pyridazine-4-thione (VI).

1,2,5-Thiadiazolo[3,4-*d*]pyridazin-4-one (IV) (3.0 g., 0.02 mole) was dissolved in 150 ml. of dry pyridine and the mixture was heated under reflux with stirring. Phosphorus pentasulfide (6.33 g., 0.029 mole) was added slowly and the mixture heated in an oil bath at 125-130° for 6 hours. The excess pyridine was removed under reduced pressure and 150 ml. of ice water was added to replace the pyridine. The mixture was warmed on a steam bath for 30 minutes and a small amount of ammonium hydroxide (28%) was added to dissolve the suspended solids. The solution was then heated to boiling, treated with *Norite* and filtered. The dark red filtrate was acidified with concentrated hydrochloric acid to pH ~ 1 and allowed to cool in the refrigerator overnight. After subsequent filtration and drying the solid residue amounted to 1.06 g. (32%), m.p. 180-182° dec. Purification of a sample for analysis was accomplished by acid-base precipitation. A pumpkin yellow powder was obtained; uv λ max (95% ethanol) 204 (ϵ , 13,890), 210 (sh) (ϵ , 13,320), 324 m μ (ϵ , 5,710); ir cm^{-1} : 3330(s), 3200(s), 2960(s), 1645(s), 1595(s), 1490(s); nmr (deuterium oxide/sodium deuterioxide/DDS) δ 8.15 (singlet C₇H).

Anal. Calcd. for C₄H₂N₄S₂·H₂O: C, 25.54; H, 2.14; N, 29.79. Found: C, 25.67; H, 1.93; N, 29.91.

4-Methylthio-1,2,5-thiadiazolo[3,4-*d*]pyridazine (V).

Methyl iodide (4.26 g., 0.003 mole) in 10 ml. of ethanol was added in portions to 0.5 g. (0.0029 mole) of 1,2,5-thiadiazolo[3,4-*d*]pyridazine-4-thione (VI) dissolved in a mixture of 10 ml. of 10% potassium hydroxide and 5 ml. of 28% ammonium hydroxide. The mixture was stirred for 5 hours at room temperature, cooled in ice, and the product was collected by filtration, washed with ice water and dried over phosphorus pentoxide in a desiccator. The yield of crude product was 0.345 g. (64%). The product was recrystallized from ethanol-water (*Norite*), light tan crystals, m.p. 148-150°; uv λ max (95% ethanol) 218 (ϵ , 9,390), 238 (sh) (ϵ , 6,410), 260 (ϵ , 3,790) 301 m μ (ϵ , 1,310); nmr (deuterium oxide/sodium deuterium/DDS) δ 3.32 (singlet C₇H), δ 2.64 (singlet -SCH₃).

Anal. Calcd. for C₅H₄N₄S₂: C, 32.61; H, 2.19; N, 30.44. Found: C, 32.62; H, 2.44; N, 30.64.

1,2,5-Thiadiazolo[3,4-*d*]pyridazin-4-one-7-thione (VIII).

1,2,5-Thiadiazolo[3,4-*d*]pyridazine-4,7-dione (I) (4.13 g., 0.024 mole) was added to 200 ml. of dry pyridine and the mixture was heated under reflux. Phosphorus pentasulfide (7.33 g., 0.033 mole) was added slowly (Caution! Frothing occurs.) in small portions to the boiling solution. The mixture was then heated for 4 hours and allowed to cool several degrees. The excess pyridine was removed under reduced pressure. The black syrupy residue was added to 250 ml. of ice and water. The mixture was digested on a steam bath for 1 hour followed by the addition of a few sodium hydroxide pellets to bring all the solids into solution. The solution was treated with *Norite* and the volume reduced to ~ 60 ml. by rotary evaporation. The solution was then acidified with concentrated hydrochloric acid to ~ pH 1, and allowed to stand in the refrigerator overnight. The orange colored compound was filtered and dried to give 3.4 g. (76%) of crude product, m.p. 238-239° dec. An analytical sample was prepared by acid-base

(*Norite*) precipitation; uv λ max (0.1 *N* sodium hydroxide) 266 m μ (ϵ , 19,150); ir cm^{-1} : 3326(s), 1632(s), 1548(s), 1293(s), 856(s).

Anal. Calcd. for C₄H₂N₄OS₂·½H₂O: C, 24.62; H, 1.55; N, 28.72. Found: C, 24.40; H, 1.37; N, 28.38.

1,2,5-Thiadiazolo[3,4-*d*]pyridazine-4,7-dithione (VII).

1,2,5-Thiadiazolo[3,4-*d*]pyridazine-4,7-dione (I) (7.88 g., 0.0463 mole) was heated with 200 ml. of dry pyridine while stirring. To the refluxing solution was added slowly (Caution! Frothing occurs.) in small portions 20.67 g. (0.093 mole) of phosphorus pentasulfide. The solution was heated under reflux for 6 hours. The excess pyridine was removed by distillation under reduced pressure. The black tar-like residue was added slowly to 200 ml. of ice and water. The solution was digested on a steam bath for 1 hour followed by the addition of a few pellets of sodium hydroxide to dissolve the few remaining suspended solids. The dark solution was treated with *Norite*, filtered, and acidified to ~ pH 1 with hydrochloric acid. The dark red product was refrigerated overnight, filtered and dried over phosphorus pentoxide giving 5.78 g. (62%) of crude material, m.p. 224° dec. An analytical sample was prepared by repeated reprecipitation (acid-base) (*Norite*), to give a dark red powder; uv λ max (0.1 *N* sodium hydroxide) 256 (ϵ , 25,770), 292 (sh) m μ (ϵ , 5,320); ir cm^{-1} : 3320(s), 1625(s), 1530(s), 1475(s), 1300(s), 1250(s).

Anal. Calcd. for C₄H₂N₄S₃: C, 23.75; H, 1.00; N, 27.70. Found: C, 23.53; H, 0.89; N, 28.04.

4,7-Bis(methylthio)-1,2,5-thiadiazolo[3,4-*d*]pyridazine (IX).

Methyl iodide (9.94 g., 0.07 mole) in 50 ml. of ethanol was added portionwise to 6.85 g. (0.034 mole) of 1,2,5-thiadiazolo[3,4-*d*]pyridazine-4,7-dithione (VII) dissolved in a mixture of 20 ml. of 10% potassium hydroxide and 10 ml. of 28% ammonium hydroxide. During the addition a yellow green precipitate began to separate. Stirring was continued for 12 hours at room temperature. The reaction mixture was cooled in ice, the solid was collected, washed with 30 ml. of cold ethanol, dried in a vacuum desiccator and recrystallized from 95% ethanol to give 4.57 g. (59%) of yellow prisms, m.p. 220-221°. An analytical sample was recrystallized from petroleum ether (90-120°); uv λ max (95% ethanol) 238 (ϵ , 15,920), 302 m μ (ϵ , 3,040); ir cm^{-1} : 1625(m), 1385(s), 1290(s), 860(s); nmr (deuteriochloroform/TMS) δ 2.80 (S-CH₃ singlet).

Anal. Calcd. for C₆H₆N₄S₃: C, 31.28; H, 2.63; N, 24.33. Found: C, 31.64; H, 2.75; N, 24.27.

4,7-Diamino-1,2,5-thiadiazolo[3,4-*d*]pyridazine (X).

Method A.

A mixture containing 0.250 g. (0.0011 mole) of 4,7-bis-(methylthio)-1,2,5-thiadiazolo[3,4-*d*]pyridazine (IX) in 50 ml. of absolute ethanol saturated with ammonia at 0-5° was heated in a glass pressure bottle at 150° for 16 hours. The orange solution was evaporated to dryness giving 0.102 g. (56%) of a pale orange residue. The residue was recrystallized from 95% ethanol to give an analytical sample consisting of pale orange crystals of 4,7-diamino-1,2,5-thiadiazolo[3,4-*d*]pyridazine m.p. 268° dec.; uv λ max (95% ethanol), 206 (ϵ , 11,450), 259 m μ (ϵ , 13,060); ir cm^{-1} : 3290(m), 3050(m).

Anal. Calcd. for C₄H₄N₆S: C, 28.57; H, 2.40; N, 50.00. Found: C, 28.14; H, 2.23; N, 49.86.

Method B.

To a solution of 4,5-dicyano-1,2,5-thiadiazole (6) (1.5 g., 0.0110 mole) in 50 ml. of 95% ethanol was added slowly, 15 ml. of hydrazine hydrate while cooling the reaction mixture in ice. After refluxing the mixture for 6 hours the product was obtained by evaporating the solvent under reduced pressure. Upon drying overnight in a vacuum dessicator over sodium hydroxide, 1.28 g. (69%) of a bright red product was obtained. Further recrystallization from 95% ethanol gave pale orange crystals, m.p. 268° dec., identical with the product prepared *via* Method A as shown by a comparison of the melting point and the uv and ir spectra.

7-Amino-4-imino-5-methyl-1,2,5-thiadiazolo[3,4-*d*]pyridazine (XI).

3,4-Dicyano-1,2,5-thiadiazole (6) (1.0 g., 0.0073 mole) was dissolved in 50 ml. of absolute ethanol. To this rapidly stirred and cooled mixture was added dropwise, 15 ml. of methylhydrazine reagent. The reaction mixture was refluxed for 5 hours. The black solution was evaporated to dryness under reduced pressure to give a black powder, 1.32 g. (85%). Repeated recrystallization from 95% ethanol (*Norite*) gave a black crystalline product, m.p. 209-210° dec.; uv λ max (95% ethanol), 210 (ϵ , 10,020), 268 μ (ϵ , 11,890); ir cm^{-1} : 3320(m), 3200(m), 1655(m), 1610(s), 1280(m), 850(s).

Anal. Calcd. for $\text{C}_5\text{H}_6\text{N}_6\text{S}$: C, 32.96; H, 3.33; N, 46.14. Found: C, 33.11; H, 3.14; N, 46.09.

7-Amino-4-imino-5-phenyl-1,2,5-thiadiazolo[3,4-*d*]pyridazine (XIII).

To a solution of (1.2 g., 0.0088 mole) of 3,4-dicyano-1,2,5-thiadiazole (7) in 50 ml. of absolute ethanol was added dropwise 10 ml. of phenylhydrazine reagent with stirring and cooling on ice. The reaction mixture was refluxed for 4 hours. This was followed by evaporation to dryness in a rotary evaporator, to give a deep red powder, 198 g. (92%). The analytical sample was prepared by repeated recrystallization from 95% ethanol (*Norite*) to give an orange-red crystalline compound, m.p. 204-205° dec.; uv λ max (95% ethanol), 204 (ϵ , 20,850), 258 μ (ϵ , 13,450); ir cm^{-1} : 3335(m), 3300(m), 1600(m), 1550(s), 1445(s), 1280(m), 851(m).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_6\text{S}$: C, 49.15; H, 3.31; N, 34.43. Found: C, 49.31; H, 3.40; N, 34.30.

3-Chloro-4,5-diaminopyridazin-6-one (XIV).

A solution containing 1.69 g. (0.00895 mole) of 4-chloro-1,2,5-thiadiazolo[3,4-*d*]pyridazin-7-one (II) and 50 ml. of 5% aqueous sodium hydroxide was heated in a pressure bottle at 80° for 1 hour. After cooling, the solution was neutralized with glacial acetic acid and the white crystalline solid that separated was filtered and dried to give 1.25 g. (86%) of crude product. Recrystallization from dilute ammonium hydroxide (*Norite*) gave the purified compound in the form of white fluffy needles, m.p. 336°. A Beilstein test was positive; uv λ max (95% ethanol) 209 (ϵ , 12,620), 232 (ϵ , 18,660), 278 (sh) (ϵ , 3,110), 316 μ (ϵ , 7,820); ir cm^{-1} : 3360(s), 1620(s), 1590(s), 1390(s), 905(s), 745(s); nmr (DMSO- d_6 /external TMS), (N_1 H singlet δ 12.36); (C_4 NH_2 singlet broad δ 5.28); (C_5 NH_2 singlet broad δ 5.07).

Anal. Calcd. for $\text{C}_4\text{H}_5\text{ClN}_4\text{O}$: C, 29.91; H, 3.14; N, 34.62. Found: C, 30.04; H, 3.03; N, 34.89.

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