The Synthesis of 3,5-Dimethylpyrazol-1-yl-*v*-triazolo[4,5-*d*]pyridazines and Substituted 3,5-Dimethylpyrazol-1-ylimidazo[4,5-*d*]pyridazines

Randall E. Draper (1) and Raymond N. Castle (2)

Department of Chemistry, Brigham Young University, Provo, Utah 84602

Received August 30, 1982

The synthesis of 4-(3,5-dimethylpyrazol-1-yl)-*v*-triazolo[4,5-*d*]pyridazine, 4-(3,5-dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridazine and several *S*-substituted derivatives of 4-(3,5-dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridazine-2-thiol is reported. These syntheses were carried out to provide a variety of interesting compounds for biological screening.

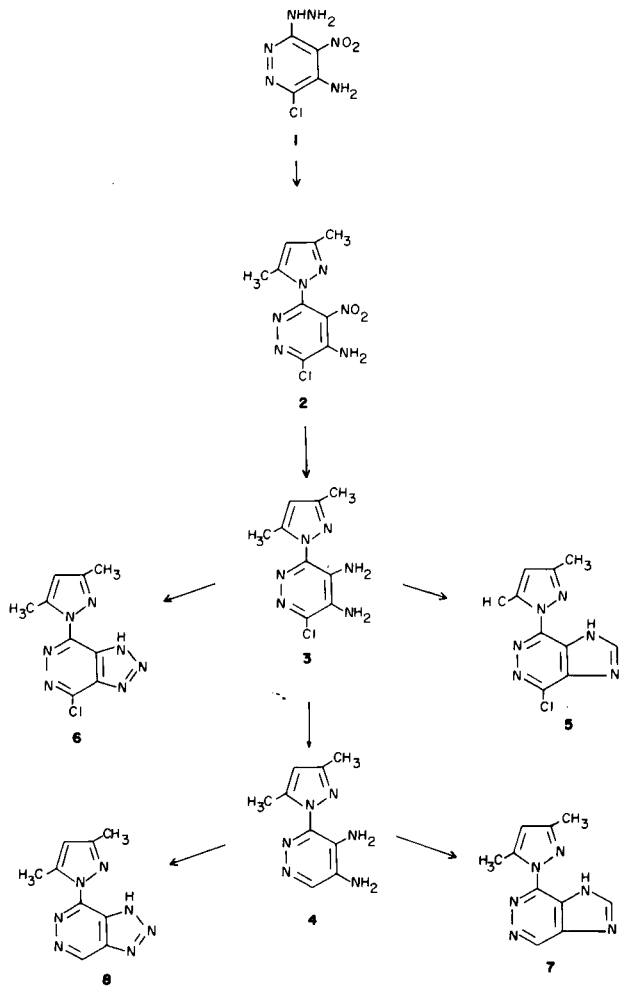
J. Heterocyclic Chem., **20**, 193 (1983).

Recent investigation has demonstrated significant biological activity in derivatives of 3,5-disubstituted pyrazoles, such as the hypoglycemic activity of sulfonylurea derivatives of 3,5-dimethylpyrazole (3). Of more particular interest is the hypotensive activity displayed by a variety of 3-(1-pyrazolyl)pyridazine derivatives, some of which also influence prostaglandin metabolism (4). Additionally, certain substituted imidazo[4,5-*d*]pyridazines have shown CNS depressant, diuretic and monoamine oxidase inhibitory activity (5) as well as *in vitro* antitumor activity (6).

In an effort to capitalize on the biological potential of these heterocyclic systems as well as exploit the availability of the versatile compound 3-chloro-6-hydrazino-5-nitropyridazin-4-amine (**1**) to provide interesting compounds for biological testing, we undertook the synthesis of the compounds herein described.

Thompson and Castle (7) have reported the synthesis of compound **1** from 3,6-dichloro-5-nitropyridazin-4-amine and hydrazine in absolute ethanol. When allowed to react with 2,4-pentanedione in hot acidified aqueous ethanol, compound **1** gave 3-chloro-5-nitro-6-(3,5-dimethylpyrazol-1-yl)pyridazin-4-amine (**2**) in 88% yield (Scheme I). Reduction of the nitro compound **2** with hydrogen, using Raney nickel as a catalyst, in absolute ethanol gave the diamine **3** in 90% yield. This intermediate was then reacted in several ways: with hydrogen over palladium on charcoal in ethanol; with triethyl orthoformate (8); and with nitrous acid (9) to give the dechloro compound **4** (98%), the imidazopyridazine **5** (46%), and the triazolopyridazine **6** (95%), respectively. Compound **4** was similarly reacted with triethyl orthoformate and nitrous acid to give the dechloro analogs **7** and **8** in 57% and 90% yields, respectively.

Scheme I

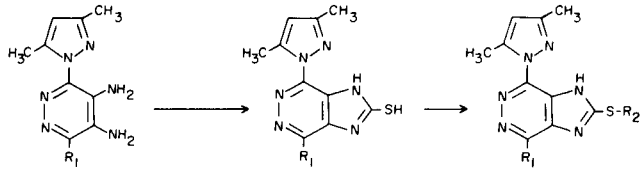


Reaction of the diamines **3** and **4** with carbon disulfide in dry pyridine containing crushed sodium hydroxide (10) gave ring closure to the expected 7-chloro-4-(3,5-dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridazine-2-thiol (**9**) and corresponding dechloro thiol (**10**) in respective yields of 64% and 93% (Scheme II). The thiols **9** and **10** were in turn reacted with methyl iodide and a variety of substituted benzyl or unsubstituted picolyl halides in either aqueous potassium hydroxide or *N,N*-dimethylformamide containing potassium *t*-butoxide to give the expected *S*-substituted thioimidazopyridazines **11-29** (Scheme II) (Table I).

Table 1

S-Substitution of 7-Chloro-4-(3,5-dimethylpyrazol-1-yl)imidazo[4,5-*d*]-pyridazine-2-thiol and 4-(3,5-dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridizine-2-thiol

Scheme II



3, R_1 = Cl; **4**, R_1 = H — **9**, R_1 = Cl; **10**, R_1 = H — **11-29**

	R_1	R_2
11	Cl	CH_3
12	Cl	*m*-chlorobenzyl
13	Cl	*o*-chlorobenzyl
14	Cl	*p*-chlorobenzyl
15	Cl	*m*-nitrobenzyl
16	Cl	*o*-nitrobenzyl
17	Cl	*p*-nitrobenzyl
18	Cl	3-picolyl
19	Cl	2-picolyl
20	H	CH_3
21	H	*m*-chlorobenzyl
22	H	*o*-chlorobenzyl
23	H	*p*-chlorobenzyl
24	H	*m*-nitrobenzyl
25	H	*o*-nitrobenzyl
26	H	*p*-nitrobenzyl
27	H	3-picolyl
28	H	2-picolyl
29	H	4-picolyl

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were obtained on a Beckmann Acculab 2 spectrophotometer. The ir spectral data are recorded in reciprocal centimeters (cm^{-1}). The ^1H nmr spectra were obtained on a Varian EM 390 spectrometer or a JEOL FX 90Q spectrometer in the indicated solvents. Chemical shifts are reported in ppm from TMS as an internal reference and are given in δ units. Mass spectra were obtained on a Hewlett-Packard model 5980A mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

3-Chloro-5-nitro-6-(3,5-dimethylpyrazol-1-yl)pyridazin-4-amine (**2**).

Compound **1** (9.5 g, 47 mmoles) was dissolved in 400 ml of 1:1 ethanol/water to which 8 ml of 10% hydrochloric acid had been added. The stirred solution was brought to near-boiling and 2,4-pentanedione (5 g, 50 mmoles) in 20 ml ethanol was added in a single aliquot. The dark red reaction mixture was observed to turn light orange as the reaction proceeded at reflux. After 15 minutes, ethanol was allowed to boil off until crystals began to form, whereupon the solution was allowed to cool. Crystallization occurred rapidly and yielded, after filtration and washing with small portions of cold ethanol, 11 g (88%) of fluffy yellow needles, mp 190-203°. An analtyical sample was obtained by recrystallization from water/ethanol to give yellow needles, mp 198-200°; ir (potassium bromide): 1330 and 1490 (NO_2), 1570 and 1615 (C=N); 3290 (NH_2), 1395 (CH_3), 1070 (C-N); nmr (DMSO-d_6): 1.90 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 6.08 (s, 1H, pyrazolyl), 7.75 (broad s, 2H, NH_2), ms: 270 (M^+, ^{37}Cl, 2.3), 268 (M^+, 6.3), 253 (M-OH, ^{37}Cl, 33.9), 251 (M-OH, 100).

Anal. Calcd. for $C_9H_9ClN_6O_2$ (268.66): C, 40.24; H, 3.38; Cl, 13.20; N, 31.28. Found: C, 40.36; H, 3.55; Cl, 13.09; N, 31.10.

6-Chloro-3-(3,5-dimethylpyrazol-1-yl)pyridazine-4,5-diamine (**3**).

The crude compound **2** (20.4 g, 76 mmoles) was partially dissolved in 600 ml of absolute ethanol containing about 4 g of Raney nickel T-1 (11) and stirred vigorously overnight at room temperature in the presence of hydrogen (1 atmosphere). During the course of the reaction, 5.5 liters of hydrogen were taken up and compound **2** dissolved completely. The catalyst was then removed by filtration through a Celite pad and ethanol was removed *in vacuo* (about 500 ml) until crystals began to form. Crystallization was permitted to continue overnight and gave, after collection by filtration and washing with cold water, 12.9 g of white flakes. Subsequent *in vacuo* concentration of the mother liquor afforded second and third crops of 2.7 g and 0.7 g, respectively, yielding a total of 16.3 g (90%) of the diamine, mp 225-226°. Recrystallization of a small amount of the product from water/ethanol gave white flakes of analytical purity, mp 225-226°; ir (potassium bromide): 1650 (C=N), 3320 and 3400 (NH_2); nmr (DMSO-d_6): 2.27 (s, 6H, $2CH_3$), 5.86 (s, 2H, NH_2), 6.06 (s, 1H, pyrazolyl), 6.13 (s, 2H, NH_2); ms: (M^+, ^{37}Cl, 32.6), 238 (M^+, 100), 203 (M-Cl, 20.7).

Anal. Calcd. for $C_9H_{11}ClN_6$ (238.68): C, 45.29; H, 4.69; Cl, 14.85; N, 35.21. Found: C, 45.44; H, 4.63; Cl, 15.02; N, 35.04.

3-(3,5-Dimethylpyrazol-1-yl)pyridazine-4,5-diamine (**4**).

Compound **3** (6.8 g, 28 mmoles) was dissolved in 200 ml of absolute ethanol containing 3 ml of 85% ammonium hydroxide. Palladium on charcoal (5%, 0.5 g) was added as a catalyst. The solution was hydrogenated at atmosphereic pressure until uptake of hydrogen had ceased (4 hours). The catalyst was then removed by filtration through Celite. The solution was evaporated *in vacuo* to dryness, affording a white solid which turned yellow upon exposure to air. The solid was then extracted with chloroform. Evaporation of the chloroform gave 5.7 g (98%) of the yellow, oily semi-solid compound **4**. An analytical sample of this intermediate was not prepared; rather the crude compound was used directly to synthesize compounds **7**, **8**, and **10** after adequate spectral data were obtained; ir (potassium bromide): 1650 (C=N), 3250-3670 (NH_2); nmr (deuteriochloroform): 2.10 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 4.77 (broad s, 4H, $2NH_2$), 5.83 (s, 1H, pyrazolyl), 8.13 (broad s, 1H, H-7); ms: 204 (M^+, 100), 187 (M-NH_3, 18), 95 (pyrazolyl, 24).

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridazine (**5**).

Compound **3** (2.1 g, 8.8 mmoles) was refluxed in 100 ml of ethyl orthoformate. A short condensor was employed to permit the escape of the ethanol formed as a by-product of the reaction. After four hours, the reaction mixture was distilled to dryness under aspirated vacuum. The light brown solid remaining in the reaction flask was dissolved in a minimum volume of hot ethanol, to which hot water was then added until the solution became slightly cloudy. Crystallization began as the solution cooled and was allowed to continue overnight. The crystals were collected and washed with cold water/ethanol. This afforded 1.0 g (46%) of analytically pure yellowish plates, mp 253-254°; ir: 1560 and 1590 (C=N), 3210 (NH); nmr (DMSO-d_6): 2.30 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 6.23 (s, 1H, pyrazolyl), 8.67 (s, 1H, H-2); ms: 250 (M^+, ^{37}Cl, 32), 248 (M^+, 100), 213 (M-Cl, 63).

Anal. Calcd. for $C_{10}H_9ClN_6$ (248.68): C, 48.30; H, 3.65; Cl, 14.26; N, 33.80. Found: C, 48.26; H, 3.87; Cl, 14.14; N, 33.66.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-*v*-triazolo[4,5-*d*]pyridazine (**6**).

Compound **3** (1.7 g, 7 mmoles) was dissolved with warming in 30 ml of water containing 1 ml of concentrated sulfuric acid, then cooled to 10°. A solution of 0.5 g (7 mmoles) of sodium nitrite in 2 ml of water was added dropwise to the stirred solution. A white precipitate formed immediately. This was collected, washed with water, and dried, yield 1.7 g (95%) of white microcrystals. The triazole decomposed on heating in organic

solvents, so the analytical sample was prepared by washing the product well with cold water followed by vacuum drying at room temperature, mp >300° (darkens at 160°); ir (potassium bromide): 1570 and 1590 (C=N); nmr (deuteriochloroform): 2.40 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 6.17 (s, 1H, pyrazolyl); ms: 251 (M^+, ^{37}Cl, 33), 249 (M^+, 100), 221 (M-N_2, 33).

Anal. Calcd. for $C_9H_8ClN_7$ (249.66): C, 43.30; H, 3.23; Cl, 14.20; N, 39.27. Found: C, 43.37; H, 3.40; Cl, 13.96; N, 39.10.

4-(3,5-Dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridazine (**7**).

With the exception that reflux was permitted to continue overnight, compound **7** was prepared by the same procedure as compound **5**. Thus, 0.67 g (3.3 mmoles) of **4** in 40 ml of ethyl orthoformate gave 0.40 g (57%) of long colorless needles, mp 233-235°. Recrystallization from water/ethanol afforded an analytical sample, mp 233-235°; ir (potassium bromide): 1570 and 1600 (C=N), 1385 (CH_3), 3400 (NH); nmr (DMSO-d_6): 2.18 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 6.10 (s, 1H, pyrazolyl), 8.53 (s, 1H, H-2), 9.43 (s, 1H, H-7); ms: 214 (M^+, 100), 197 (M-NH_3, 55), 95 (pyrazolyl, 66).

Anal. Calcd. for $C_{10}H_{10}N_6 \cdot \frac{1}{4}H_2O$ (218.73): C, 54.91; H, 4.84; N, 38.42. Found: C, 55.18; H, 4.81; N, 38.91.

4-(3,5-Dimethylpyrazol-1-yl)-*v*-triazolo[4,5-*d*]pyridazine (**8**).

Compound **8** was prepared in the same manner as described for compound **6**. Precipitate formation took 20 minutes and the reaction mixture was allowed to stir for 3 hours at room temperature after all reagents were combined. Thus, 0.40 g (2.0 mmoles) of compounds **4** and 0.16 g (2.0 mmoles) of sodium nitrite yielded 0.39 g (90%) of compound **8**. The analytical sample was prepared similarly as **6** mp 242-243°; ir (potassium bromide): 1570 and 1590 (C=N); nmr (deuteriochloroform): 2.40 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 6.12 (s, 1H, pyrazolyl), 9.74 (s, 1H, H-7); ms: 215 (M^+, 100), 187 (M-N_2, 14).

Anal. Calcd. for $C_9H_9N_7$ (215.22): C, 50.23; H, 4.22; N, 45.56. Found: C, 50.11; H, 4.45; N, 45.45.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridazine-2-thiol (**9**).

Compound **3** (4.8 g, 20 mmoles), excess carbon disulfide (18 ml, 300 mmoles), crushed sodium hydroxide (1.6 g, 40 mmoles) and 50 ml of dry pyridine were combined in a flask fitted with condenser and heated in an 80° oil bath with stirring. Before heating the mixture was brown. Within minutes of initiation of heating, the mixture began to turn yellow and a yellow solid began to appear. After 3 hours, heating was stopped and the solvent and unreacted carbon disulfide were removed *in vcacuo* from the reaction mixture, leaving a yellow amorphous residue. This residue was dissolved in 200 ml of water and filtered. The filtrate was first neutralized, then made acidic (*p*H 3) by dropwise addition of concentrated hydrochloric acid, whereupon a buff-colored precipitate formed. This was collected by filtration and washed with copious amounts of water, thus yielding, after drying, 3.6 g (64%) of the thiol, mp >300°. An analytical sample was recrystallized from hot acetone to give flocculent white needles, mp > 300°; ir (potassium bromide): 1565 and 1590 (C=N), 3390 (NH), nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.25 (s, 1H, pyrazolyl); ms: 2.82 (M^+, ^{37}Cl, 36), 280 (M^+, 100), 245 (M-Cl, 18).

Anal. Calcd. for $C_{10}H_9ClN_6S$ (280.74): C, 42.78; H, 3.23; Cl, 12.63; N, 29.94; S, 11.42. Found: C, 42.59; H, 3.49; Cl, 12.71; N, 29.67; S, 11.17.

4-(3,5-Dimethylpyrazol-1-yl)imidazo[4,5-*d*]pyridazine-2-thiol (**10**).

Compound **4** (5.8 g, 28 mmoles) and 2.3 g (60 mmoles) of crushed sodium hydroxide were added to 200 ml of dry pyridine. Excess carbon disulfide (25 ml, 420 mmoles) was added and the mixture was stirred and refluxed at 80° overnight. On termination of the reaction, sufficient aqueous sodium hydroxide solution (10%) was added to bring the white preciptiate which had formed as the reaction progressed into solution. The solution was filtered through Celite, then acidified to *p*H 3 by dropwise addition of 10% hydrochloric acid. The pinkish-white precipitate that formed upon acidification was collected, washed with copious amounts of water, and dried *in vacuo*. This afforded 6.5 g (93%) of compound **10**. The analytical sample was obtained by recrystallization from acetone/water, which gave a fibrous white precipitate, mp >300°; ir (potassium bromide): 1565 and 1605 (C=N), 3405 (NH); nmr (DMSO$_6$): 2.33 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 6.23 (s, 1H, pyrazolyl), 9.10 (s, 1H, H-7); ms: 246 (M^+, 100), 95 (pyrazolyl, 46).

Anal. Calcd. for $C_{10}H_{10}N_6S$ (246.29): C, 48.77; H, 4.09; N, 34.12; S, 13.02. Found: C, 48.66; H, 4.31; N, 34.35; S, 12.80.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-methylthioimidazo[4,5-*d*]pyridazine (**11**).

Compound **9** (0.5 g, 2 mmoles) was dissolved in 5 ml of 1*N* potassium hydroxide. Methyl iodide (0.28 g, 2 mmoles) was added and the mixture was allowed to stir for 3 hours at room temperature. The pink reaction mixture was filtered and the filtrate neutralized with glacial acetic acid, whereupon a pale pink precipitate (0.5 g, 95%) formed. Recrystallization from acetone gave pinkish flocculent needles, mp 209°; ir (potassium bromide): 1565 and 1590 (C=N); nmr (acetone-d_6): 2.28 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.85 (s, 3H, SCH_3), 6.18 (s, 1H, pyrazolyl); ms: 296 (M^+, ^{37}Cl, 28), 294 (M^+, 70), 95 (pyrazolyl, 100).

Anal. Calcd. for $C_{11}H_{11}ClN_6S$ (294.77): C, 44.82; H, 3.76; Cl, 12.03; N, 28.51; S, 10.88. Found: C, 44.88; H, 3.80; Cl, 12.28; N, 28.31; S, 10.90.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(3-chlorobenzylthio)imidazo-[4,5-*d*]pyridazine (**12**).

Compound **9** (1.0 g, 3.6 mmoles) was dissolved in 25 ml of *N,N*-dimethylformamide to which potassium *t*-butoxide had been added in slight excess (0.42 g, 3.7 mmoles). When **9** was completely dissolved, *m*-chlorobenzyl chloride (0.60 g, 3.7 mmoles) was added and the mixture was stirred at about 50° for four hours. The mixture was then poured into 200 ml of water, and the resulting flocculent tan precipitate was collected and washed well with water. This afforded 1.1 g (75%) of the desired product. The analytical sample was prepared by recrystallization from ethyl acetate, which gave beige microcrystals, mp 151-156°; ir (potassium bromide): 1575 and 1600 (C=N), 2490 (aromatic), 3385 (NH); nmr (DMSO-d_6): 2.34 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 6.24 (s, 1H, pyrazolyl), 7.27-7.75 (m, 4H, *m*-aromatic); ms: 406 (M^+, ^{37}Cl, 41), 404 (M^+, 59), 125 (chlorobenzyl, 100).

Anal. Calcd. for $C_{17}H_{14}Cl_2N_6S$ (405.30): C, 50.38; H, 3.48; Cl, 17.49; N, 20.74; S, 7.91. Found: C, 50.54; H, 3.61; Cl, 17.31; N, 20.52; S, 8.09.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(2-chlorobenzylthio)imidazo-[4,5-*d*]pyridazine (**13**).

Compound **13** was prepared by the same method as described for compound **12**, thus, compound **9** (0.56 g, 2 mmoles), *o*-chlorobenzyl chloride (0.35 g, 2.2 mmoles) and potassium *t*-butoxide (0.25 g, 2.2 mmoles) gave **13** in quantitative yield (0.82 g). Recrystallization from ethyl acetate gave pale yellow microcrystals, mp 165°; ir (potassium bromide): 1565 and 1590 (C=N), 3000 (aromatic), 3365 (N-H); nmr (DMSO-d_6): 2.30 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.76 (s, 2H, CH_2), 6.22 (s, 1H, pyrazolyl), 7.24-7.85 (m, 4H, *o*-aromatic); ms: 406 (M^+, ^{37}Cl, 64), 404 (M^+, 77), 369 (M-Cl, 100).

Anal. Calcd. for $C_{17}H_{14}Cl_2N_6S$ (405.30); C, 50.38; H, 3.48; Cl, 17.49; N, 20.74; S, 7.91. Found: C, 50.41; H, 3.57; Cl, 17.61; N, 20.54; S, 8.00.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(4-chlorobenzylthio)imidazo-[4,5-*d*]pyridazine (**14**).

Compound **14** was prepared as was compound **12**, thus, compound **9** (0.56 g, 2 mmoles), *p*-chlorobenzyl chloride (0.35 g, 2.2 mmoles) and potassium *t*-butoxide (0.25 g, 2.2 mmoles) gave 0.68 g of **14** (84%). Recrystallization from ethyl acetate gave short beige needles, mp 187-189°; ir (potassium bromide): 1565 and 1590 (C=N), 2910 (aromatic), 3380 (N-H); nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 6.28 (s, 1H, pyrazolyl), 7.30-7.70 (m, 4H, *p*- aromatic); ms: 406 (M^+, ^{37}Cl, 41), 404 (M^+, 64), 125 (chlorobenzyl, 100).

Anal. Calcd. for $C_{17}H_{14}Cl_2N_6S$ (405.30): C, 50.38; H, 3.48; Cl, 17.49; N, 20.74; S, 7.91. Found: C, 50.35; H, 3.53; Cl, 17.37; N, 20.78; S, 8.00.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(3-nitrobenzylthio)imidazo-[4,5-*d*]pyridazine (**15**).

Compound **15** was prepared in the same manner as was compound **12**. Thus, 0.74 g (2.6 mmoles) of **9**, 0.45 g (2.6 mmoles) of *m*-nitrobenzyl chloride and 0.30 g (2.7 mmoles) of potassium *t*-butoxide yielded 0.80 g (74%) of the desired **15**. Recrystallization from ethyl acetate gave white microcrystals, mp 219°; ir (potassium bromide): 1345 and 1520 (NO_2), 1565 and 1595 (C=N), 3370 (NH); nmr (DMSO-d_6): 2.32 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 4.81 (s, 2H, CH_2), 6.28 (s, 1H, pyrazolyl), 7.52-8.30 (m, 4H, *m*-aromatic); ms: 417 (M^+, ^{37}Cl, 34), 415 (M^+, 83), 95 (pyrazolyl, 86).

Anal. Calcd. for $C_{17}H_{14}ClN_7O_2S$ (415.86): C, 49.10; H, 3.39; Cl, 8.53; N, 23.58; S, 7.71. Found: C, 48.87; H, 3.38; Cl, 8.43; N, 23.65; S, 7.66.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(2-nitrobenzylthio]imidazo[4,5-*d*]-pyridazine (**16**).

Compound **16** was prepared in the same manner as described for compound **12**. Thus, compound **9** (1.0 g, 3.6 mmoles), *o*-nitrobenzyl chloride (0.60 g, 3.7 mmoles) and potassium *t*-butoxide (0.42 g, 3.7 mmoles) reacted to give 1.2 g (79%) of compound **16**. Recrystallization from ethyl acetate gave yellow microcrystals, mp 227-229°; ir (potassium bromide): 1340 and 1520 (NO_2), 1565 and 1595 (C=N), 3080 (aromatic), 3330 (NH); nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 6.26 (s, 1H, pyrazolyl), 7.44-8.21 (m, 4H, *o*-aromatic); ms: 417 (M^+, ^{37}Cl, 19), 415 (M^+, 48), 280 (*m*-nitrobenzyl, 100).

Anal. Calcd. for $C_{17}H_{14}ClN_7O_2S$ (415.86): C, 49.10; H, 3.39; Cl, 8.53; N, 23.58; S, 7.71. Found: C, 49.31; H, 3.57; Cl, 8.32; N, 23.43; S, 7.89.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(4-nitrobenzylthio)imidazo[4,5-*d*]-pyridazine (**17**).

Compound **17** was prepared in the same manner as described for compound **12**. Thus, compound **9** (0.56 g, 2 mmoles), *p*-nitrobenzyl bromide (0.44 g, 2 mmoles) and potassium *t*-butoxide (0.25 g, 2.2 mmoles) gave 0.67 g (80%) of compound **17**. Recrystallization from methylene chloride/hexane gave beige microcrystals, mp 232-234°; ir (potassium bromide): 1335 and 1510 (NO_2), 1565 and 1590 (C=N), 2920 (aromatic), 3300 (NH); nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 6.25 (s, 1H, pyrazolyl), 7.75-8.30 (m, 4H, *p*-aromatic); ms: 280 (*m*-nitrobenzyl, 100), 369 (M^+-NO_2, 2).

Anal. Calcd. for $C_{17}H_{14}ClN_7O_2S$ (415.86): C, 49.10; H, 3.39; Cl, 8.53; N, 23.58; S, 7.71. Found: C, 49.03; H, 3.53; Cl, 8.65; N, 23.49; S, 7.66.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(3-picolylthio)imidazo[4,5-*d*]-pyridazine (**18**).

Compound **9** (0.56 g, 2 mmoles) and 94% 3-picolyl chloride hydrochloride (0.35 g, 2.1 mmoles) were stirred at 45° in 5 ml of 1*N* potassium hydroxide. After five hours, the reaction mixture was acidified with glacial acetic acid. The resulting tan precipitate was collected, washed with water and cold ethanol, and dried to give 0.67 g (90%) of crude product, mp 190° dec. Recrystallization from ethanol/water gave tan microcrystals, mp 216 dec; ir (potassium bromide): 1575 and 1595 (C=N), 3000 (aromatic); nmr (acetone-d_6): 2.20 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 6.13 (s, 1H, pyrazolyl), 7.23-8.73 (m, 4H, picolyl); ms: 373 (M^+, ^{37}Cl, 44), 371 (M^+, 100).

Anal. Calcd. for $C_{16}H_{14}ClN_7S$ (371.85): C, 51.68; H, 3.79; Cl, 9.53; N, 26.37; S, 8.62. Found: C, 51.63; H, 3.99; Cl, 9.46; N, 26.16; S, 8.67.

7-Chloro-4-(3,5-dimethylpyrazol-1-yl)-2-(2-picolylthio)imidazo[4,5-*d*]-pyridazine (**19**).

Compound **19** was prepared in the same manner as compound **12**; therefore, compound **9** (1.0 g, 3.6 mmoles), 2-picolyl chloride hydrochloride (0.6 g, 3.7 mmoles) and potassium *t*-butoxide (0.84 g, 7.5 mmoles) yielded 1.0 g (75%) of **19**. Recrystallization from ethyl acetate afforded tan microcrystals, mp 186-187°; ir (potassium bromide): 1565 and 1590 (C=N), 2920 (aromatic), 3450 (NH); nmr (DMSO-d_6): 2.37 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 6.33 (s, 1H, pyrazolyl), 7.33-8.77 (m, 4H, picolyl); ms: 371 (M^+, 47), 281 (M-picolyl, ^{37}Cl, 36), 279 (M-picolyl, 100).

Anal. Calcd. for $C_{16}H_{14}ClN_7S$ (371.85): C, 51.68; H, 3.79; Cl, 9.53; N, 26.37; S, 8.62. Found: C, 51.44; H, 3.86; Cl, 9.37; N, 26.21; S, 8.49.

4-(3,5-Dimethylpyrazol-1-yl)-2-methylthioimidazo[4,5-*d*]pyridazine (**20**).

Compound **20** was prepared by the same method employed for compound **11**. Thus, compound **10** (0.5 g, 2 mmoles) and methyl iodide (0.35 g, 2.5 mmoles) gave 0.43 g (82%) of crude **20**, mp 190-202°. The analytical sample was recrystallized from ethanol, yielding white microcrystals, mp 205-207°; ir (potassium bromide): 1560 and 1590 (C=N), 2920 (aromatic), 3400 (NH); nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.75 (s, 3H, SCH_3), 6.20 (s, 1H, pyrazolyl), 9.40 (s, 1H, H-7); ms: 2.60 (M^+, 100), 245 (M-CH_3, 29).

Anal. Calcd. for $C_{11}H_{12}N_6S$ (260.32): C, 50.75; H, 4.65; N, 32.28; S, 12.32. Found: C, 50.42; H, 4.73; N, 32.56; S, 12.17.

4-(3,5-Dimethylpyrazol-1-yl)-2-(3-chlorobenzylthio)imidazo[4,5-*d*]-pyridazine (**21**).

Compound **21** was prepared in the same manner as compound **18**; thus compound **10** (1.0 g, 4.1 mmoles) and *m*-chlorobenzyl chloride (0.7 g, 4.1 mmoles) yielded 1.5 g (97%) of tan solid. This was recrystallized from ethyl acetate to give tan microcrystals, mp 191-193°; ir (potassium bromide): 1560 and 1590 (C=N), 3060 (aromatic); nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 6.25 (s, 1H, pyrazolyl), 7.24-7.73 (m, 4H, *m*-aromatic), 9.47 (s, 1H, H-7); ms: 372 (M^+, ^{37}Cl, 23), 370 (M^+, 58), 125 (chlorobenzyl, 100).

Anal. Calcd. for $C_{17}H_{15}ClN_6S$ (370.86): C, 55.06; H, 4.08; Cl, 9.56; N, 22.66; S, 8.64. Found: C, 54.93; H, 4.19; Cl, 9.37; N, 22.44; S, 8.78.

4-(3,5-Dimethylpyrazol-1-yl)-2-(2-chlorobenzylthio)imidazo[4,5-*d*]pyridazine (**22**).

Compound **22** was prepared in the same manner as compound **18**; thus, compound **10** (1.0 g, 4.1 mmoles) and *o*-chlorobenzyl chloride (0.7 g, 4.1 mmoles) yielded 1.5 g (97%) of tan precipitate. Recrystallization from ethyl acetate afforded tan microcrystals, mp 178-181°; ir (potassium bromide): 1570 and 1595 (C=N), 3000 (aromatic), nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 6.25 (s, 1H, pyrazolyl), 7.24-7.74 (m, 4H, *o*-aromatic), 9.46 (s, 1H, H-7); ms: 372 (M^+, ^{37}Cl, 15), 370 (M^+, 37), 125 (chlorobenzyl, 100).

Anal. Calcd. for $C_{17}H_{15}ClN_6S$ (370.86): C, 55.06; H, 4.08; Cl, 9.56; N, 22.66; S, 8.64. Found: C, 55.03; H, 4.13; Cl, 9.83; N, 22.43; S, 8.55.

4-(3,5-Dimethylpyrazol-1-yl)-2-(4-chlorobenzylthio)imidazo[4,5-*d*]pyridazine (**23**).

Compound **23** was prepared by the same procedure as compound **18**. Thus, compound **10** (1.0 g, 4.1 mmoles) and *p*-chlorobenzyl chloride (0.7 g, 4.3 mmoles) gave 1.5 g (98%) of white solid. Recrystallization from ethyl acetate afforded white microcrystals, mp 181-183°; ir (potassium bromide): 1565 and 1595 (C=N), 2980 (aromatic); nmr (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 6.21 (s, 1H, pyrazolyl), 7.30-7.67 (m, 4H, *p*-aromatic), 9.45 (s, 1H, H-7); ms: 372 (M^+, ^{37}Cl, 16), 370 (M^+, 38), 335 (M-Cl, 83), 125 (chlorobenzyl, 100).

Anal. Calcd. for $C_{27}H_{15}ClN_6S$ (370.86): C, 55.06; H, 4.08; Cl, 9.56; N, 22.66; S, 8.64. Found: C, 54.88; H, 4.04; Cl, 9.32; N, 22.68; S, 8.70.

4-(3,5-Dimethylpyrazol-1-yl)-2-(3-nitrobenzylthio)imidazo[4,5-*d*]pyridazine (**24**).

Compound **24** was prepared by the same method as compound **12**. Thus compound **10** (1.0 g, 4.1 mmoles), *m*-nitrobenzyl chloride (0.7 g, 4.1 mmoles) and potassium *t*-butoxide (0.47 g, 4.2 mmoles) gave 1.44 g (92%) of white solid, mp 238-240°. Recrystallization from ethanol gave white microcrystals, mp 241-243°; ir (potassium bromide): 1345 and 1525 (NO_2), 1570 and 1660 (C=N), 2980 (aromatic), 3440 (NH); nmr (DMSO-d_6): 2.34 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 6.22 (s, 1H, pyrazolyl), 7.50-8.47 (m, 4H, *m*-aromatic), 9.40 (s, 1H, H-7); ms: 381 (M^+, 100).

Anal. Calcd. for $C_{17}H_{15}N_7O_2S$ (381.40): C, 53.54; H, 3.96; N, 25.71; S, 8.41. Found: C, 53.50; H, 4.05; N, 25.62; S, 8.36.

4-(3,5-Dimethylpyrazol-1-yl)-2-(2-nitrobenzylthio)imidazo[4,5-*d*]pyridazine (**25**).

Compound **25** was prepared by the same method as compound **12**. Thus, compound **10** (1.0 g, 4.1 mmoles), *o*-nitrobenzyl chloride (0.7 g, 4.1 mmoles) and potassium *t*-butoxide (0.47 g, 4.2 mmoles) gave 1.42 g (91%) of buff solid, mp 187-192°. Recrystallization gave a flocculent buff precipitate from ethanol, mp 194-201°; ir (potassium bromide): 1340 and 1520 (NO_2), 1565 and 1595 (C=N), 2980 (aromatic); nmr (DMSO-d_6): 2.28 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 6.14 (s, 1H, pyrazolyl), 7.32-8.13 (m, *o*-aromatic), 9.33 (s, 1H, H-7); ms: 381 (M^+, 32), 245 (nitrobenzyl, 100), 335 (M-NO_2, 30).

Anal. Calcd. for $C_{17}H_{15}N_7O_2S$ (381.40): C, 53.54; H, 3.96; N, 25.71; S, 8.41. Found: C, 53.37; H, 4.11; N, 25.67; S, 8.22.

4-(3,5-Dimethylpyrazol-1-yl)-2-(4-nitrobenzylthio)imidazo[4,5-*d*]pyridazine (**26**).

Compound **26** was prepared by the same method described for compound **12**. Thus, compound **10** (1.0 g, 4.1 mmoles), *p*-nitrobenzyl bromide (0.9 g, 4.2 mmoles) and potassium *t*-butoxide (0.47 g, 4.2 mmoles) gave 1.51 g (96%) of white solid, mp 241-245°. Recrystallization from ethanol gave white microcrystals, mp 247°; ir (potassium bromide); 1335 and 1510 (NO_2), 1560 and 1595 (C=N), 2920 (aromatic), 3440 (NH); nmr (DMSO-d_6): 2.25 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 6.10 (s, 1H, pyrazolyl), 7.53-8.20 (m, 4H, *p*-aromatic), 9.30 (s, 1H, H-7); ms: 381 (M^+, 100).

Anal. Calcd. for $C_{27}H_{15}N_7O_2S$ (381.40): C, 53.54; H, 3.96; N, 25.71; S, 8.41. Found: C, 53.45; H, 3.92; N, 25.87; S, 8.33.

4-(3,5-Dimethylpyrazol-1-yl)-2-(3-picolylthio)imidazo[4,5-*d*]pyridazine (**27**).

Compound **27** was prepared by the same method described for compound **12**. Thus, compound **10** (1.0 g, 4.1 mmoles), 94% 3-picolyl chloride hydrochloride (0.71 g, 4.2 mmoles) and potassium *t*-butoxide (1 g, 8.5 mmoles) gave 0.86 g (62%) yellow preciptiate. Recrystallization from ethanol/water yielded peculiar white hemispheres, mp 141-148°; ir (potassium bromide): 1565 and 1600 (C=N), 2980 (aromatic), 3400 (NH); nmr (DMSO-d_6): 2.29 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 6.16 (s, 1H, pyrazolyl), 7.48-8.64 (m, 4H, picolyl), 9.48 (s, 1H, H-7); ms: 337 (M^+, 100), 245 (M-picolyl, 49).

Anal. Calcd. for $C_{16}H_{15}N_7S \cdot \frac{1}{4}H_2O$ (341.90): C, 56.21; H, 4.53; N, 28.68; S, 9.38. Found: C, 56.29; H, 4.60; N, 28.88; S, 9.29.

4-(3,5-Dimethylpyrazol-1-yl)-2-(2-picolylthio)imidazo[4,5-*d*]pyridazine (**28**).

Compound **28** was prepared in the same way as compound **12**. Thus, compound **10** (1.0 g, 4.1 mmoles), 2-picolyl chloride hydrochloride (0.67 g, 4.1 mmoles) and potassium *t*-butoxide (1 g, 8.5 mmoles) yielded 1.0 g (72%) of yellow precipitate, mp 156°. Recrystallization from ethyl acetate/hexane gave white microcrystals, mp 163-164°; ir (potassium bromide): 1565 and 1595 (C=N), 2980 (aromatic), 3400 (NH); nmr (DMSO-d_6): 2.34 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 6.12 (s, 1H, pyrazolyl), 7.20-8.32 (m, 4H, picolyl), 9.32 (s, 1H, H-7); ms: 337 (M^+, 100), 245 (M-picolyl, 45).

Anal. Calcd. for $C_{16}H_{15}N_7S$ (337.40): C, 56.96; H, 4.48; N, 29.06; S, 9.50. Found: C, 56.84; H, 4.71; N, 28.93; S, 9.36.

4-(3,5-Dimethylpyrazol-1-yl)-2-(4-picolylthio)imidazo[4,5-*d*]pyridazine (**29**).

Compound **29** was prepared in the same manner as described for compound **12**. Thus, compound **10**, (1.0 g, 4.1 mmoles), 4-picolyl chloride hydrochloride (0.69 g, 4.1 mmoles) and potassium *t*-butoxide (1 g, 8.5 mmoles) yielded 0.94 g (68%) of white solid. Recrystallization from ethyl acetate gave white microcrystals, mp 145-147°; ir (potassium bromide): 1575 and 1605 (C=N), 3000 (aromatic), 3425 (NH), nmr (deuteriochloroform): 2.35 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.12 (s, 1H, pyrazolyl), 7.29-8.70 (m, 4H, picolyl), 9.39 (s, 1H, H-7); ms: 337 (M^+, 100), 245 (M-picolyl, 71).

Anal. Calcd. for $C_{16}H_{15}N_7S$ (337.40): C, 56.96; H, 4.48; N, 29.06; S, 9.50. Found: C, 57.12; H, 4.74; N, 28.75; S, 9.25.

REFERENCES AND NOTES

(1) Present address: School of Medicine, University of Utah, Salt Lake City, UT 84132 USA.

(2) To whom inquiries should be directed at: Department of Chemistry, University of South Florida, Tampa, FL 33620 USA.

(3) R. Soliman, *J. Med. Chem.*, **22**, 321 (1979).

(4) G. Szilagyi, E. Kasztreiner, L. Tardos, L. Jaszlits, E. Kosa, G. Cseh, P. Tolnay and I. Kovacs-Szabo, *Eur. J. Med. Chem.-Chim. Ther.*, **14**, 439 (1979).

(5) G. G. Ferguson, *Diss. Abstr. Int. B*, **30**, 4731 (1970).

(6) G. A. Gerhardt, D. L. Aldous, and R. N. Castle, *J. Heterocyclic Chem.*, **2**, 247 (1965).

(7) R. D. Thompson and R. N. Castle, *ibid.*, **18**, 1523 (1981).

(8) S. F. Martin and R. N. Castle, *ibid.*, **6**, 93 (1969).

(9) G. A. Gerhardt and R. N. Castle, *ibid.*, **1**, 247 (1964).

(10) H. Murakami and R. N. Castle, *ibid.*, **4**, 555 (1967).

(11) X. A. Dominguez, I. C. Lopez and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).