# A New and Improved Synthesis of 6-Aryl-1,2,4-triazolo[4,3-*b*]pyridazines



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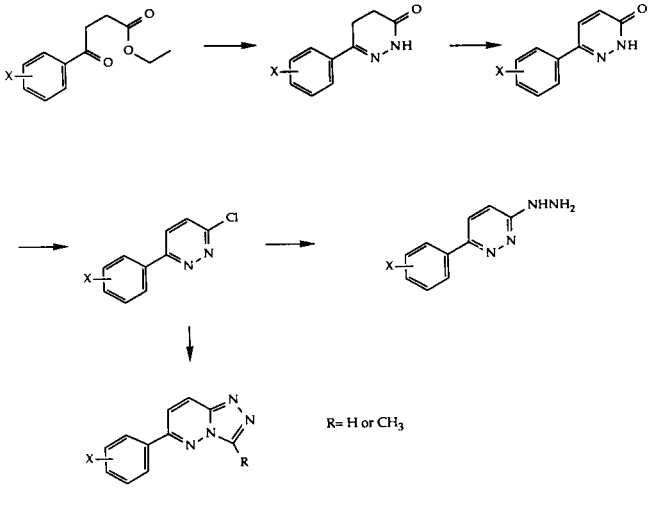
Received October 8, 1987

A new and improved synthesis of 6-aryl-1,2,4-triazolo[4,3-*b*]pyridazines is described. This methodology provides the title compounds under mild conditions and in high yields. The first step comprises the condensation of an aryl methyl ketone with a 4-amino-1,2,4-triazole in toluene heated at reflux. The second step involves the condensation of that imine and *t*-butoxybis(dimethylamino)methane in tetrahydrofuran at ambient temperature. The third step constitutes the pyridazine ring closure to the title compounds in acetic acid heated at reflux.

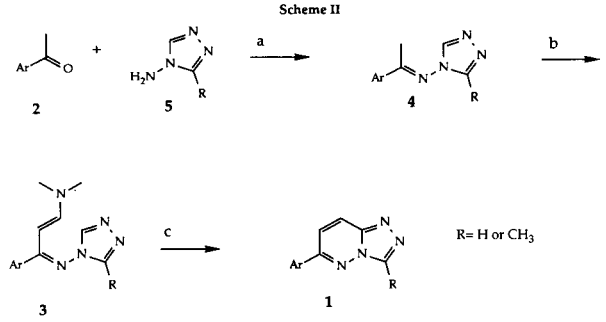
*J. Heterocyclic Chem.*, **25**, 827 (1988).

Several years ago 6-(substituted-phenyl)-1,2,4-triazolo-[4,3-*b*]pyridazines **1** were developed in these laboratories as non-benzodiazepine anxiolytic agents [1]. That synthesis entails the cyclization of both the five- and six-membered rings of triazolo[4,3-*b*]pyridazines **1** (see Scheme I). The six-membered ring is formed as a dihydropyridazinone which must be oxidized to a pyridazinone in a separate step. This oxidation limits the functional groups available as substituents on the phenyl ring. Depending upon the method employed to close the triazole ring, the previous synthesis requires six or more steps from the appropriate benzaldehydes. Continued interest in anxiolytic agents led to a new and improved synthesis of 6-aryl-1,2,4-triazolo[4,3-*b*]pyridazines **1**. The present three-step synthesis takes advantage of aryl methyl ketones **2** and substituted triazoles **5**, hence only the six-membered ring must be closed (see Scheme II). The use of a functionalized methylene group in enamines **3** allows the direct construction of the pyridazine moiety of triazolo[4,3-*b*]-pyridazines **1**. Without an oxidation step, both heteroaryl and electron-rich phenyl groups are easily incorporated substituents in the products.

Scheme I



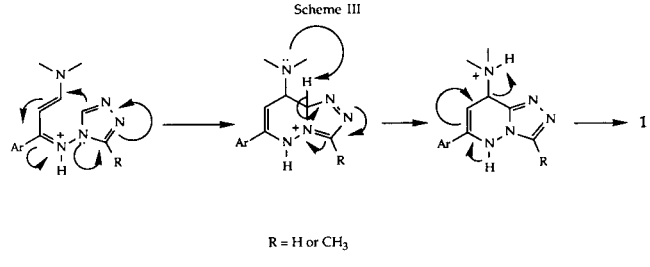

Scheme II




[a] *p*-Toluenesulfonic acid in toluene, 110°. [b] *t*-Butoxybis(dimethylamino)methane in tetrahydrofuran, 23°. [c] Acetic acid, 117°.

The synthetic pathway to 6-aryl-1,2,4-triazolo[4,3-*b*]-pyridazines **1** is outlined in Scheme II. Aryl methyl ketones **2a-h** [2,3] were converted to imines **4a-i** in 86 to 97% yield by treatment with either 4-amino-1,2,4-triazole or 4-amino-3-methyl-1,2,4-triazole [6] and catalytic *p*-toluenesulfonic acid in toluene heated at reflux. The active methyl groups of imines **4a-i** were dimethylaminomethylenated in 90 to 98% yield with *t*-butoxybis(dimethylamino)methane in tetrahydrofuran at 23° to provide enamines **3a-i**. Enamines **3a-i** were cyclized to 6-aryl-1,2,4-triazolo[4,3-*b*]pyridazines **1a-i** in 85 to 99% yield in acetic acid heated at reflux [7]. Scheme III provides a mechanistic rationale for closure of the pyridazine ring.

Scheme III




In conclusion the present three-step sequence delivers 6-aryl-1,2,4-triazolo[4,3-*b*]pyridazines **1a-i** in 72 to 94% overall yield under mild conditions.

## EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Thin layer chromatography was performed with Merck silica gel 60 F254 0.25 mm plates. Proton nuclear magnetic resonance spectra (nmr) were recorded on either a Nicolet NT-300 WB or a General Electric QE-300 Fourier transform nuclear magnetic resonance spectrometer. Chemical shifts are reported as $\delta$ in units of parts per million relative to an internal standard of tetramethylsilane in deuteriochloroform. Coupling constants are reported in Hertz (Hz), multiplicities are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Infrared spectra (ir) were recorded with a Nicolet 7199 Fourier transform spectrometer. Ultraviolet spectra (uv) were recorded on a Hewlett-Packard 8450A diode array spectrophotometer. Low resolution mass spectra (ms) were obtained with a Varian MAT CH7, a Finnigan TSQ 4500, or a Vestec Thermospray interfaced with a Hewlett-Packard 5970 mass spectrometer.

General Procedure for the Synthesis of Imines **4a-g** as Demonstrated for (*E*)-*N*-[1-(4-Methoxyphenyl)ethylidene]-4*H*-1,2,4-triazol-4-amine (**4a**).

A mixture of 4'-methoxyacetophenone (6.61 g, 44.0 mmoles), 4-amino-1,2,4-triazole (6.18 g, 73.5 mmoles), and *p*-toluenesulfonic acid (0.40 g, 2.3 mmoles) in toluene (120 ml) was heated at reflux for 4.5 hours with azeotropic removal of water. The solvent was removed *in vacuo* and the resulting solid was partitioned between dichloromethane (140 ml) and aqueous sodium bicarbonate (40 ml). The aqueous phase was extracted with dichloromethane (5 x 10 ml). The combined organic phases were dried with magnesium sulfate and concentrated. The white solid was recrystallized from ethanol and the mother liquor was purified by silica gel chromatography with 95:5 dichloromethane-methanol as eluant to afford 9.00 g (94%) of imine **4a** as white needles, mp 167.5-169.5°; Rf 0.30 (95:5 dichloromethane-methanol); ir (chloroform): 3119, 1612, 1591, 1513, 1498, 1258, 1177, 841 $cm^{-1}$; nmr: $\delta$ 8.22 (s, 2H, triazole H's), 7.92 (d, J = 8.9, 2H, C(2')- and C(6')-H's), 6.99 (d, J = 9.0, 2H, C(3')- and C(5')-H's), 3.89 (s, 3H, $OCH_3$), 2.34 (s, 3H, $CH_3$); uv: $\lambda$ max 220 (12,000), 287 (19,000); ms: m/e 216 $M^+$, 148 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 60.97; H, 5.49; N, 25.86.

(*E*)-*N*-(1-Phenylethylidene)-4*H*-1,2,4-triazol-4-amine (**4b**).

This compound was obtained after 4.5 hours as white plates (ethanol) in 96% yield, mp 137.5-139°; Rf 0.29 (95:5 dichloromethane-methanol); ir (chloroform): 3125, 1618, 1442, 1371, 1168, 858, 768 $cm^{-1}$; nmr: $\delta$ 8.28 (s, 2H, triazole H's), 7.94 (m, 2H, C(3')- and C(5')-H's), 7.52 (m, 3H, C(2')-, C(4')-, and C(6')-H's), 2.42 (s, 3H, $CH_3$); uv: $\lambda$ max 251 (15,000); ms: m/e 187 M + $H^+$, 118 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_9H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.58; H, 5.23; N, 30.41.

(*E*)-*N*-[1-[3-(Trifluoromethyl)phenyl]ethylidene]-4*H*-1,2,4-triazol-4-amine (**4c**).

This compound was obtained after 20 hours as yellow needles (dichloromethane-hexane) in 91% yield, mp 120.5-122°; Rf 0.30 (95:5 dichloromethane-methanol); ir (chloroform): 3110, 1632, 1500, 1350, 1275, 1130, 1118, 1065 $cm^{-1}$; nmr: $\delta$ 8.34 (s, 2H, triazole H's), 8.23 (s, 1H, C(2')-H), 8.14 (d, J = 7.9, 1H, C(4')- or C(6')-H), 7.83 (d, J = 7.5, 1H, C(6')- or C(4')-H), 7.67 (t, J = 7.9, 1H, C(5')-H), 2.51 (s, 3H, $CH_3$); uv: $\lambda$ max 245 (14,000); ms: m/e 255 M + $H^+$, 186 M+ $-C_2H_2N_3$.

*Anal.* Calcd. for $C_{11}H_9F_3N_4$: C, 51.97; H, 3.57; F, 22.42; N, 22.04. Found: C, 51.80; H, 3.40; F, 22.30; N, 22.03.

(*E*)-*N*-[1-(3-Nitrophenyl)ethylidene]-4*H*-1,2,4-triazol-4-amine (**4d**) [8].

This compound was obtained after 24 hours as tan needles (ethanol) in 97% yield, mp 189.5-191.5°; Rf 0.23 (95:5 dichloromethane-methanol); ir (chloroform): 3146, 3110, 3083, 1616, 1526, 1495, 1350, 1061, 742 $cm^{-1}$; nmr: $\delta$ 8.79 (t, J = 1.9, 1H, C(2')-H), 8.43 (dm, J = 8.1, 1H, C(4')- or C(6')-H), 8.33 (s, 2H, triazole H's), 8.32 (dm, J = 8.1, 1H, C(6')- or C(4')-H), 7.73 (t, J = 8.0, C(5')-H), 2.54 (s, 3H, $CH_3$); uv: $\lambda$ max 239 (22,000); ms: m/e 232 M + $H^+$, 163 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_{10}H_9N_5O_2$: C, 51.95; H, 3.92; N, 30.29. Found: C, 51.91; H, 3.83; N, 30.54.

(*E*)-*N*-[1-(2-Thienyl)ethylidene]-4*H*-1,2,4-triazol-4-amine (**4e**).

This compound was obtained after 18 hours as white needles (ethanol-hexane) in 94% yield, mp 156-158°; Rf 0.47 (90:10 dichloromethane-methanol); ir (chloroform): 3128, 3072, 1592, 1498, 1421, 1061, 754, 623 $cm^{-1}$; nmr: $\delta$ 8.25 (s, 2H, triazole H's), 7.64 (br d, J = 3.8, 1H, C(3')-H), 7.61 (br d, J = 5.0, 1H, C(5')-H), 7.17 (dd, J = 4.0 and 4.9, 1H, C(4')-H), 2.42 (s, 3H, $CH_3$); uv: $\lambda$ max 266 (11,000), 300 (12,000); ms: m/e 193 M + $H^+$, 124 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.14; S, 16.68. Found: C, 49.82; H, 4.13; N, 28.94; S, 16.71.

(*E*)-*N*-[1-(3-Pyridyl)ethylidene]-4*H*-1,2,4-triazol-4-amine (**4f**).

This compound was obtained after 21 hours as tan crystals (ethanol) in 92% yield, mp 140.5-142°; Rf 0.27 (90:10 dichloromethane-methanol); ir (chloroform): 3094, 2980, 2932, 1609, 1592, 1499, 1370, 1293, 1174, 1062, 711, 630 $cm^{-1}$; nmr: $\delta$ 9.15 (d, J = 2.2, 1H, C(2')-H), 8.79 (dd, J = 1.3 and 4.8, 1H, C(6')-H), 8.34 (s, 2H, triazole H's), 8.24 (td, J = 1.9 and 8.1, 1H, C(4')-H), 7.47 (dd, J = 4.9 and 8.1, 1H, C(5')-H), 2.51 (s, 3H, $CH_3$); uv: $\lambda$ max 239 (12,000), 267 (8,000); ms: m/e 187 $M^+$, 119 $M^+ - C_2H_2N_3$, 105 $M^+ - C_2H_2N_4$, 78 $C_5H_4N^+$.

*Anal.* Calcd. for $C_9H_9N_5$: C, 57.74; H, 4.85; N, 37.41. Found: C, 57.88; H, 4.87; N, 37.54.

3-Methyl-(*E*)-*N*-[1-[3-(methylthio)phenyl]ethylidene]-4*H*-1,2,4-triazol-4-amine (**4g**).

This compound was obtained after 20 hours as a tan powder (ethyl acetate-hexane) in 86% yield, mp 90-91°; Rf 0.34 (90:10 dichloromethane-methanol); ir (potassium bromide): 3082, 2987, 2930, 1610, 1563, 1526, 1500, 1370, 1208, 780 $cm^{-1}$; nmr: $\delta$ 8.12 (s, 1H, triazole H), 7.85 (s, C(2')-H), 7.68 (td, J = 2.1 and 6.4, 1H, C(4')- or C(6')-H), 7.43 (m, 2H, C(5')-and C(6')- or C(4')-H), 2.54 (s, 3H, $CH_3$), 2.42 (s, 3H, triazole $CH_3$), 2.36 (s, 3H, $SCH_3$); uv: $\lambda$ max 248 (25,000); ms: m/e 247 M + $H^+$, 164 $M^+ - C_3H_4N_3$.

*Anal.* Calcd. for $C_{12}H_{14}N_4S$: C, 58.51; H, 5.73; N, 22.74; S, 13.02. Found: C, 58.58; H, 5.66; N, 22.79; S, 12.86.

General Procedure for the Conversion of Imines **4a-g** to Enamines **3a-g** as Demonstrated for (*E,E*)-*N*-[3-(Dimethylamino)-1-(4-methoxyphenyl)-2-propenylidene]-4*H*-1,2,4-triazol-4-amine (**3a**).

A suspension of imine **4a** (2.2850 g, 10.55 mmoles) and *t*-butoxybis-(dimethylamino)methane (7.0 ml, 34 mmoles) in dry tetrahydrofuran (100 ml) was stirred at 23° for four days. The volatiles were removed *in vacuo* and the resulting solid was partitioned between dichloromethane (45 ml) and aqueous sodium bicarbonate (20 ml). The aqueous phase was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried with magnesium sulfate and concentrated. The white solid was recrystallized from chloroform-hexane and the mother liquor was purified by silica gel chromatography with 95:5 dichloromethane-methanol as eluant to give 2.7305 g (95%) of enamine **3a**, mp 184-185.5°; Rf 0.40 (90:10 dichloromethane-methanol); ir (chloroform): 3131, 2941, 2915, 1623, 1604, 1507, 1465, 1243, 1062, 1024, 800 $cm^{-1}$; nmr: $\delta$ 8.25 (s, 2H, triazole H's), 7.51 (d, J = 8.6, 2H, C(2')- and C(6')-H's), 6.98 (d, J = 8.6, C(3')- and C(5')-H's), 6.81 (d, J = 12.8, 1H, C(3)-H), 4.77 (d, J = 12.8, 1H, C(2)-H), 3.86 (s, 3H, $OCH_3$), 2.97 (br s, 3H, $NCH_3$), 2.74 (br s, 3H, $NCH_3$); uv: $\lambda$ max 319 (32,000); ms: m/e 271 $M^+$, 203 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81. Found: C, 62.00; H, 6.24; N, 25.77.

(*E,E*)-*N*-[3-(Dimethylamino)-1-phenyl-2-propenylidene]-4*H*-1,2,4-triazol-4-amine (**3b**).

This compound was obtained after 22 hours as a white solid (chloroform-hexane) in 93% yield, mp 135.5-136.5°; Rf 0.26 (95:5 dichloromethane-methanol); ir (chloroform): 2983, 1622, 1529, 1399, 1359, 1289, 1105,

1065, 754 $cm^{-1}$; nmr: δ 8.26 (s, 2H, triazole H's), 7.54 (m, 5H, phenyl H's), 6.77 (d, J = 12.8, 1H, C(3)-H), 4.82 (d, J = 12.8, 1H, C(2)-H), 2.97 (s, 3H, $NCH_3$), 2.74 (s, 3H, $NCH_3$); uv: λ max 239 (12,000), 318 (33,000); ms: m/e 241 $M^+$, 173 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_{12}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02. Found: C, 64.56; H, 6.19; N, 29.07.

(*E,E*)-*N*-[3-(Dimethylamino)-1-[3-(trifluoromethyl)phenyl]-2-propenylidene]-4*H*-1,2,4-triazol-4-amine (**3c**).

This compound was obtained after 7 hours as a pale tan powder (chloroform-hexane) in 97% yield, mp 183-184.5°; Rf 0.25 (95:5 dichloromethane-methanol); ir (chloroform): 3103, 2917, 1622, 1535, 1398, 1321, 1278, 1164, 1121 $cm^{-1}$; nmr: δ 8.27 (s, 2H, triazole H's); 7.82 (s, 1H, C(2')-H), 7.77 (d, J = 8.3, 1H, C(4')- or C(6')-H), 7.74 (d, J = 8.8, 1H, C(6')- or C(4')-H), 7.61 (t, J = 7.7, 1H, C(5')-H), 6.69 (d, J = 12.9, 1H, C(3)-H), 4.87 (d, J = 12.8, 1H, C(2)-H), 3.00 (s, 3H, $NCH_3$), 2.76 (s, 3H, $NCH_3$); uv: λ max 231 (10,000), 320 (30,000); ms: m/e 309 $M^+$, 241 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_{14}H_{14}F_3N_5$: C, 54.37; H, 4.56; F, 18.43; N, 22.64. Found: C, 54.24; H, 4.60; F, 18.39; N, 22.46.

(*E,E*)-*N*-[3-(Dimethylamino)-1-(3-nitrophenyl)-2-propenylidene]-4*H*-1,2,4-triazol-4-amine (**3d**) [8].

This compound was obtained after 22 hours as a yellow powder (dichloromethane-hexane) in 98% yield, mp 190.5-192.5°; Rf 0.25 (95:5 dichloromethane-methanol); ir (chloroform): 3113, 3086, 1636, 1619, 1533, 1350, 1288, 1121 $cm^{-1}$; nmr: δ 8.42 (t, J = 1.8, 1H, C(2')-H), 8.36 (dm, J = 8.1, 1H, C(4')- or C(6')-H), 8.28 (s, 2H, triazole H's), 7.90 (dm, J = 8.8, 1H, C(6')- or C(4')-H, 7.69 (t, J = 7.9, 1H, C(5')-H), 6.70 (d, J = 12.8, 1H, C(3)-H), 4.91 (d, J = 12.9, 1H, C(2)-H), 3.01 (s, 3H, $NCH_3$), 2.79 (s, 3H, $NCH_3$); uv: λ max 219 (17,000), 259 (14,000), 319 (29,000); ms: m/e 287 M + $H^+$, 218 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.35. Found: C, 54.28; H, 4.77; N, 29.62.

(*E,E*)-*N*-[3-(Dimethylamino)-1-(2-thienyl)-2-propenylidene]-4*H*-1,2,4-triazol-4-amine (**3e**).

This compound was obtained after 23 hours as tan plates (dichloromethane-hexane) in 98% yield, mp 151-153°; Rf 0.41 (90:10 dichloromethane-methanol); ir (chloroform): 3123, 2918, 2820, 1621, 1432, 1397, 1291, 1120, 813 $cm^{-1}$; nmr: δ 8.23 (s, 2H, triazole H's), 7.40 (d, J = 3.7, 1H, C(3')-H), 7.22 (d, J = 12.7, 1H, C(3)-H), 7.15 (dd, J = 3.8 and 4.9, 1H, C(4')-H), 7.14 (dd, J = 0.7 and 5.2, 1H, C(5')-H), 4.78 (d, J = 12.8, 1H, C(2)-H), 2.99 (br s, 3H, $NCH_3$), 2.78 (br s, 3H, $NCH_3$); uv: λ max 220 (8,000), 259 (12,000), 330 (23,000); ms: m/e 248 M + $H^+$, 179 $M^+ - C_2H_2N_3$.

*Anal.* Calcd. for $C_{11}H_{13}N_5S$: C, 53.42; H, 5.30; N, 28.32; S, 12.96. Found: C, 53.55; H, 5.28; N, 28.31; S, 13.21.

(*E,E*)-*N*-[3-(Dimethylamino)-1-(3-pyridyl)-2-propenylidene]-4*H*-1,2,4-triazol-4-amine (**3f**).

This compound was obtained after 20 hours as tan crystals (dichloromethane-hexane) in 98% yield, mp 131.5-134.5°; Rf 0.15 (60:40 ethyl acetate-methanol); ir (chloroform): 3110, 2910, 1623, 1528, 1399, 1115 $cm^{-1}$; nmr: δ 8.78 (m, 1H, C(2')-H), 8.75 (dd, J = 1.7 and 4.8, 1H, C(6')-H), 8.28 (s, 2H, triazole H's), 7.90 (td, J = 2.0 and 7.8, 1H, C(4')-H), 7.44 (ddd, J = 0.6, 4.8, and 7.8, 1H, C(5')-H), 6.73 (d, J = 12.9, 1H, C(3)-H), 4.90 (d, J = 12.9, 1H, C(2)-H), 3.00 (s, 3H, $NCH_3$), 2.77 (s, 3H, $NCH_3$); uv: λ max 228 (10,000), 260 (10,000), 321 (29,000); ms: m/e 242 $M^+$, 174 $M^+ - C_2H_2N_3$, 82 $C_2H_2N_4^+$.

*Anal.* Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.09; H, 5.88; N, 34.82.

(*E,E*)-*N*-[3-(Dimethylamino)-1-[3-(methylthio)phenyl]-2-propenylidene]-3-methyl-4*H*-1,2,4-triazol-4-amine (**3g**).

This compound was obtained after 46 hours as a yellow syrup which solidified slowly to a yellow solid in 97% yield, mp 91.5-94°; Rf 0.20 (95:5 dichloromethane-methanol); ir (neat): 3101, 2920, 1620, 1526, 1395, 1285, 1113 $cm^{-1}$; nmr: δ 8.14 (s, 1H, triazole H), 7.39 (m, 3H, phenyl H's), 7.27 (m, 1H, phenyl H), 6.76 (d, J = 12.8, 1H, C(3)-H), 4.67 (d, J = 12.8, 1H, C(2)-H), 2.96 (s, 3H, $NCH_3$), 2.72 (s, 3H, $NCH_3$), 2.54 (s, 3H, triazole $CH_3$), 2.38 (s, 3H, $SCH_3$); uv: λ max 253 (17,000), 319 (30,000); ms: m/e 302 M + $H^+$, 219 $M^+ - C_3H_4N_3$.

*Anal.* Calcd. for $C_{15}H_{19}N_5S$: C, 59.77; H, 6.35; N, 23.24; S, 10.64. Found: C, 59.67; H, 6.35; N, 23.44; S, 10.31.

General Procedure for the Cyclization of Enamines **3a-g** to Triazolopyridazines **1a-g** as Demonstrated for 6-(4-methoxyphenyl)-1,2,4-triazolo-[4,3-*b*]pyridazine (**1a**).

Enamine **3a** (0.7223 g, 2.66 mmoles) was dissolved in hot acetic acid (25 ml) and this solution was heated at reflux for 6.5 hours. The cooled solution was poured into ice water (175 ml) at which point a precipitate formed. This solid was collected by vacuum filtration; the filtrate was concentrated and purified by silica gel chromatography with 95:5 dichloromethane-methanol as eluant to provide a total of 0.5101 g (85%) of triazolopyridazine **1a**. A sample was recrystallized from dichloromethane-hexane to give white needles, mp 190-192.5°; Rf 0.30 (95:5 dichloromethane-methanol); ir (potassium bromide): 3116, 1609, 1513, 1478, 1258, 1185, 818 $cm^{-1}$; nmr: δ 9.11 (s, 1H, C(3)-H), 8.14 (d, J = 10.0, 1H, C(8)-H), 7.93 (d, J = 8.9, 2H, C(2')- and C(6')-H's), 7.56 (d, J = 9.7, 1H, C(7)-H), 7.05 (d, J = 8.9, 2H, C(3')- and C(5')-H's), 3.90 (s, 3H, $OCH_3$); uv: λ max 258 (21,000), 315 (11,000); ms: m/e 227 M + $H^+$.

*Anal.* Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.64; H, 4.28; N, 24.77.

6-Phenyl-1,2,4-triazolo[4,3-*b*]pyridazine (**1b**) [9].

This compound was obtained after 9 hours as tan plates (dichloromethane-hexane) in 92% yield, mp 192-193°; Rf 0.28 (95:5 dichloromethane-methanol); ir (potassium bromide): 3155, 3054, 1604, 1541, 1483, 1447, 1335, 1007, 835, 771, 695 $cm^{-1}$; nmr: δ 9.15 (s, 1H, C(3)-H), 8.20 (d, J = 9.6, 1H, C(8)-H), 7.97 (m, 2H, phenyl H's), 7.61 (d, J = 9.8, 1H, C(7)-H), 7.57 (m, 3H, phenyl H's); uv: λ max 246 (27,000), 286 (8,000); ms: m/e 197 M + $H^+$.

*Anal.* Calcd. for $C_{10}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.29; H, 4.11; N, 28.68.

6[3-(Trifluoromethyl)phenyl]-1,2,4-triazolo[4,3-*b*]pyridazine (**1c**).

This compound was obtained after 10 hours as white needles (dichloromethane-hexane) in 92% yield, mp 137-138°; Rf 0.19 (95:5 dichloromethane-methanol); ir (potassium bromide): 3113, 3063, 1545, 1478, 1334, 1285, 1164, 1123, 1078, 802 $cm^{-1}$; nmr: δ 9.02 (s, 1H, C(3)-H), 8.27 (d, J = 9.8, 1H, C(8)-H), 8.27 (m, 1H, C(2')-H), 8.18 (d, J = 7.7, 1H, C(4')-or C(6')-H), 7.83 (d, J = 7.7, 1H, C(6')- or C(4')-H), 7.71 (t, J = 7.8, 1H, C(5')-H), 7.64 (d, J = 9.8, 1H, C(7)-H); uv: λ max 243 (28,000), 276 (7,000); ms: m/e 265 M + $H^+$, 245 $M^+$ -F.

*Anal.* Calcd. $C_{12}H_7F_3N_4$: C, 54.55; H, 2.67; F, 21.57; N, 21.21. Found: C, 54.56; H, 2.54; F, 21.62; N, 21.33.

6-(3-Nitrophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**1d**) [8].

This compound was obtained after 10 hours as a white powder (dichloromethane-methanol-hexane) in 99% yield, mp 237-238.5°; Rf 0.16 (95:5 dichloromethane-methanol); ir (chloroform): 3141, 3085, 1526, 1354, 1333, 808 $cm^{-1}$; nmr: δ 9.22 (s, 1H, C(3)-H), 8.88 (t, J = 1.9, 1H, C(2')-H), 8.43 (dm, J = 7.9, 1H, C(4')- or C(6')-H), 8.36 (dm, J = 8.1, 1H, C(6')- or (4')-H), 8.31 (d, J = 9.5, 1H, C(8)-H), 7.78 (t, J = 8.0, 1H, C(5')-H), 7.68 (d, J = 9.9, 1H, C(7)-H); uv: λ max 241 (35,000); ms: m/e 241 $M^+$.

*Anal.* Calcd. for $C_{11}H_7N_5O_2$: C, 54.77; H, 2.92; N, 29.03. Found: C, 54.43; H, 2.81; N, 29.14.

6-(2-Thienyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**1e**) [10].

This compound was obtained after 5 hours as brown plates (dichloromethane-hexane) in 97% yield, mp 162-163°; Rf 0.30 (94:6 dichloromethane-methanol); ir (chloroform): 3142, 3106, 3075, 3053, 1552, 1472, 1426, 1332, 952, 821, 717 $cm^{-1}$; nmr: δ 9.08 (s, 1H, C(3)-H), 8.12 (d, J = 9.5, 1H, C(8)-H), 7.70 (d, J = 3.6, 1H, C(3')-H), 7.55 (dd, J = 0.9 and 4.3, 1H, C(5')-H), 7.54 (d, J = 9.9, 1H, C(7)-H), 7.17 (dd, J = 3.9 and 4.9, 1H, C(4')-H); uv: λ max 262 (20,000), 318 (12,000); ms: m/e 203 M + $H^+$.

*Anal.* Calcd. for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70; S, 15.85. Found: C, 53.39; H, 2.90; N, 27.92; S, 15.84.

6-(3-Pyridyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**1f**) [11].

This compound was obtained after 28 hours as an orange powder (di-

chloromethane-methanol-hexane) in 91% yield, mp 202.5-204°; Rf 0.34 (90:10 dichloromethane-methanol); ir (chloroform): 3113, 3063, 3044, 1588, 1575, 1544, 1343, 1330, 1193, 1008, 958, 809, 705 $cm^{-1}$; nmr: δ 9.23 (dd, J = 0.7 and 2.4, 1H, C(2')-H), 9.20 (d, J = 0.7, 1H, C(3)-H), 8.81 (dd, J = 1.6 and 4.8, 1H, C(6')-H), 8.32 (ddd, J = 1.7, 2.3, and 8.1, 1H, C(4')-H), 8.28 (dd, J = 0.7 and 9.6, 1H, C(8)-H), 7.63 (d, J = 9.7, 1H, C(7)-H), 7.52 (ddd, J = 0.8, 4.8, and 8.0, 1H, C(5')-H); uv: λ max 239 (25,000); ms: m/e 198 M + H⁺.

*Anal.* Calcd. for $C_{10}H_7N_5$: C, 60.91; H, 3.58; N, 35.51. Found: C, 60.80; H, 3.59; N, 35.93.

3-Methyl-6-[3-(methylthio)phenyl]-1,2,4-triazolo[4,3-*b*]pyridazine (**1g**).

This compound was obtained after 23 hours as tan needles (dichloromethane-hexane) in 89% yield, mp 188-190.5°; Rf 0.34 (95:5 dichloromethane-methanol); ir (potassium bromide): 3080, 2914, 1609, 1577, 1546, 1520, 1483, 1466, 1378, 1338, 819, 788 $cm^{-1}$; nmr: δ 8.13 (d, J = 9.7, 1H, C(8)-H), 7.86 (s, 1H, C(2')-H), 7.71 (td, J = 1.4 and 7.5, 1H, C(4')- or C(6')-H), 7.52 (d, J = 9.9, 1H, C(7)-H), 7.46 (t, J = 7.7, 1H, C(5')-H), 7.41 (dm, J = 8.0, 1H, C(6')- or C(4')-H), 2.88 (s, 3H, C(3)-$CH_3$), 2.57 (s, 3H, $SCH_3$); uv: λ max 248 (34,000); ms: m/e 257 M + H⁺.

*Anal.* Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86; S, 12.51. Found: C, 60.78; H, 4.55; N, 21.51; S, 12.41.

6-[3-(1-Imidazolyl)phenyl]-3-methyl-1,2,4-triazolo[4,3-*b*]pyridazine (**1h**).

A mixture of 3'-(1-imidazolyl)acetophenone (1.2805 g, 6.88 mmoles), 4-amino-3-methyl-1,2,4-triazole (0.8326 g, 8.48 mmoles), and *p*-toluenesulfonic acid (0.15 g, 0.87 mmoles) in toluene (25 ml) was heated at reflux for 24 hours with azeotropic removal of water. The solvent was removed *in vacuo* and the resulting solid was partitioned between dichloromethane (40 ml) and aqueous sodium bicarbonate (20 ml). The aqueous phase was extracted with dichloromethane (6 x 15 ml). The combined organic phases were dried with sodium sulfate and concentrated. The white solid was recrystallized from dichloromethane-methanol-hexane and the mother liquor was purified by silica gel chromatography with a gradient of 8-15% methanol in dichloromethane as eluant to afford 1.7636 g of imine **4h** as white needles, mp 176-178°; Rf 0.21 (90:10 dichloromethane-methanol).

A suspension of imine **4h** (1.5290 g, 5.74 mmoles) and *t*-butoxybis(dimethylamino)methane (2.5 ml, 12 mmoles) in dry tetrahydrofuran (50 ml) was stirred at 23° for 16 hours. The volatiles were removed *in vacuo* and the resulting solid was partitioned between dichloromethane (30 ml) and aqueous sodium bicarbonate (12 ml). The aqueous phase was extracted with dichloromethane (3 x 6 ml). The combined organic layers were dried with sodium sulfate and concentrated. The yellow solid was recrystallized from dichloromethane-hexane and the mother liquor was purified by silica gel chromatography with a gradient of 10-20% methanol in dichloromethane as eluant to give 1.8117 g of enamine **3h** as a yellow powder, mp 182-184°; Rf 0.33 (85:15 dichloromethane-methanol).

Enamine **3h** (1.3267 g, 4.13 mmoles) was dissolved in hot acetic acid (25 ml) and this solution was heated at reflux for 24 hours. The cooled solution was poured into ice water (175 ml) at which point no precipitate formed. The reaction mixture was concentrated to a solid and partitioned between dichloromethane (40 ml) and 1*N* sodium hydroxide (10 ml). The aqueous phase was extracted with dichloromethane-methanol (90:10, 6 x 10 ml). The combined organic layers were dried with sodium sulfate and concentrated. The tan solid was recrystallized from dichloromethane-methanol-hexane and the mother liquor was purified by silica gel chromatography with 90:10 dichloromethane-methanol as eluant to provide a total of 1.001 g (83% over three steps) of triazolopyridazine **1h** as an orange solid, mp 227-230°; Rf 0.28 (90:10 dichloromethane-methanol); ir (chloroform): 3111, 3042, 1615, 1590, 1503, 1488, 1311, 1062, 811 $cm^{-1}$; nmr: δ 8.20 (d, J = 9.7, 1H, C(8)-H), 8.08 (t, J = 1.7, 1H), 7.97 (m, 2H), 7.70 (t, J = 7.8, 1H, C(5')-H), 7.59 (d, J = 9.7, 1H, C(7)-H), 7.59 (m, 1H), 7.40 (s, 1H), 7.28 (d, J = 0.9, 1H), 2.90 (s, 3H, C(3)-$CH_3$); uv: λ max 244 (36,000); ms: m/e 277 M + H⁺.

*Anal.* Calcd. for $C_{15}H_{12}N_6$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.06; H, 4.33; N, 30.36.

3-Methyl-6-[3-(trifluoromethyl)phenyl]-1,2,4-triazolo[4,3-*b*]pyridazine (**1i**).

A mixture of 3'-(trifluoromethyl)acetophenone (1.15 ml, 7.55 mmoles), 4-amino-3-methyl-1,2,4-triazole (0.6304 g, 6.42 mmoles), and *p*-toluenesulfonic acid (0.20 g, 1.2 mmoles) in toluene (40 ml) was heated at reflux for 44 hours with azeotropic removal of water. The solvent was removed *in vacuo* and the resulting solid was partitioned between dichloromethane (45 ml) and aqueous sodium bicarbonate (15 ml). The aqueous phase was extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried with magnesium sulfate and concentrated. The white solid was recrystallized from ethanol-water and the mother liquor was purified by silica gel chromatography with 93:7 dichloromethane-methanol as eluant to afford 1.5135 g of imine **4i** as white needles, mp 68-72°; Rf 0.43 (90:10 dichloromethane-methanol).

A suspension of imine **4i** (0.7703 g, 2.87 mmoles) and *t*-butoxybis(dimethylamino)methane (1.5 ml, 7.3 mmoles) in dry tetrahydrofuran (30 ml) was stirred at 23° for 16 hours. The volatiles were removed *in vacuo* and the resulting solid was partitioned between dichloromethane (30 ml) and aqueous sodium bicarbonate (10 ml). The aqueous phase was extracted with dichloromethane (3 x 6 ml). The combined organic layers were dried with magnesium sulfate and concentrated. The tan solid was recrystallized from chloroform-hexane and the mother liquor was purified by silica gel chromatography with 95:5 dichloromethane-methanol as eluant to give 0.7174 g of enamine **3i** as a tan powder, mp 135-137°; Rf 0.20 (95:5 dichloromethane-methanol).

Enamine **3i** (0.5043 g, 1.56 mmoles) was dissolved in hot acetic acid (25 ml) and this solution was heated at reflux for 19 hours. The cooled solution was poured into ice water (175 ml) at which point a precipitate formed. This solid was collected by vacuum filtration; the filtrate was concentrated and purified by silica gel chromatography with 95:5 dichloromethane-methanol as eluant to provide a total of 0.3951 g (72% over three steps) of triazolopyridazine **1i**. A sample was recrystallized from dichloromethane-hexane to give white needles, mp 196-197.5°; Rf 0.31 (95:5 dichloromethane-methanol); ir (potassium bromide): 3117, 3062, 1525, 1417, 1337, 1315, 1275, 1168, 1126, 1082 $cm^{-1}$; nmr: δ 8.25 (s, 1H, C(2')-H), 8.18 (d, J = 9.6, 2H, C(8)-H and C(4')- or C(6')-H), 7.81 (d, J = 7.8, 1H, C(6')- or C(4')-H), 7.70 (t, J = 7.8, 1H, C(5')-H), 7.56 (d, J = 9.7, 1H, C(7)-H), 2.89 (s, 3H, C(3)-$CH_3$); uv: λ max 246 (27,000); ms: m/e 279 M + H⁺, 259 M⁺ -F.

*Anal.* Calcd. for $C_{13}H_9F_3N_4$: C, 56.12; H, 3.26; F, 20.48; N, 20.14. Found: C, 55.98; H, 3.07; F, 20.41; N, 20.22.

## REFERENCES AND NOTES

[1] J. D. Albright, D. B. Moran, W. B. Wright, Jr., J. B. Collins, B. Beer, A. S. Lippa and E. N. Greenblatt, *J. Med. Chem.*, **24**, 592, (1981).

[2] 3'-(1-Imidazolyl)acetophenone was prepared by the method of M. A. Khan and J. B. Polya, *J. Chem. Soc. C*, 85 (1970).

[3] 3'-(Methylthio)acetophenone was prepared in 86% overall yield from 3'-bromoacetophenone *via* i) conversion to the ethylene ketal under standard conditions [4], ii) metal-halogen exchange with 2 equivalent of *t*-butyllithium in tetrahydrofuran at −78° [5], iii) reaction with dimethyl disulfide between −78 and 23° [5], and iv) ketal hydrolysis with dilute hydrochloric acid in tetrahydrofuran.

[4] G. P. Schiemenz and H. Kaack, *Ann. Chem.*, 1480 (1973).

[5] D. Seebach and H. Neumann, *Chem. Ber.*, **107**, 847, (1974).

[6] H. Neunhoeffer, H.-K. Degen and J. J. Kohler, *Ann. Chem.*, 1120, (1975).

[7] For an example of an electrophilic attack at C(3) of a 1,2,4-triazole see: M. Gall, J. B. Hester, Jr., A. D. Rudzik and R. A. Lahti, *J. Med. Chem.*, **19**, 1057, (1976).

[8] This compound was initially prepared by Dr. D. W. Powell.

[9] No solid precipitated upon pouring the reaction mixture into water. Concentration *in vacuo* and isolation after silica gel chromatography gave **1b**.

[10] When cooled to room temperature a precipitate formed. A warmed solution was poured into water to give a precipitate which was processed in the usual manner.

[11] No solid precipitated upon pouring the reaction mixture into water. The product was isolated *via* extraction of the aqueous phase with 10% methanol in dichloromethane, followed by recrystallization.