Controlling Substitution Patterns on the 1,2,4-Triazolo[1,5-*a*]-pyrimidine Ring. Selective Removal of Chlorine at the 7-Position

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A highly effective method for the selective removal of chlorine from the 7-position of the 1,2,4-triazolo[1,5-*a*]pyrimidine ring in the presence of chlorine at the 5- or 6-positions is reported. The method involves treatment of the appropriate substrate with zinc-copper couple in the presence of acetic acid in methanol-tetrahydrofuran. The method enables the construction of a variety of substitution patterns in key intermediates for the 1,2,4-triazolo[1,5-*a*]pyrimidine sulfonanilide herbicides.

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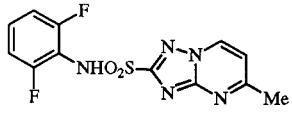
The triazolopyrimidine sulfonanilides are among several classes of new herbicides which act by inhibiting the branched-chain amino acid biosynthetic pathway at acetolactate synthase (EC 4.1.3.18) [2]. Flumetsulam (**1**) and metosulam (**2**) are representative members of this class [3,4]. In most instances, synthesis of the triazolo[1,5-*a*]-pyrimidinesulfonanilide proceeds through the 2-alkylthio (*i.e.*, 2-benzylthio) or 2-mercapto substituted triazolo-[1,5-*a*]pyrimidine. Controlling the substitution pattern on the triazolo[1,5-*a*]pyrimidine ring is critically important to successful completion of systematic structure-activity studies [5]. Previous reports from this laboratory describe approaches based on regioselection in the reaction of 3-amino-5-benzylthio-1,2,4-triazole with unsymmetrically substituted 1,3-dicarbonyl compounds [6,7]. This report outlines an approach to this problem based on selective manipulation of functional groups on the triazolo[1,5-*a*]-pyrimidine ring.



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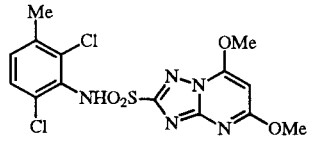


2

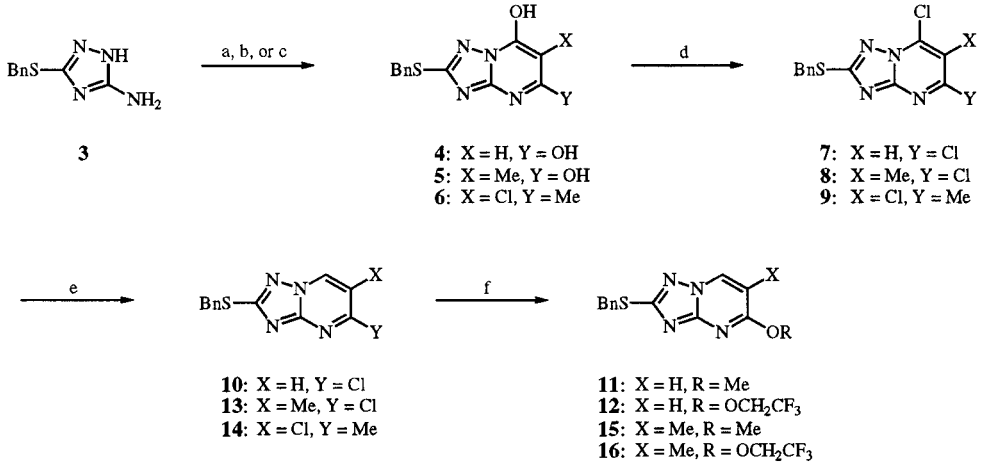
The syntheses of the required substrates for this study are outlined in Scheme I. The aminotriazole **3** [8,9] is condensed with the appropriate β-ketoester to afford the 7-hydroxytriazolopyrimidines **4**, **5** and **6** in good yield. The hydroxy compounds are converted to the corresponding chloro compounds (*i.e.*, **7**, **8** and **9**) by treatment with phosphorus oxychloride in greater than 80% yield in each instance.

There are several reports in the literature of removal of chlorine at the 5- and 7-positions of the 1,2,4-triazolo-[1,5-*a*]pyrimidine ring by catalytic hydrogenation [10,11,12]. In the hydrogenation of 5,7-dichloro-1,2,4-triazolo[1,5-*a*]pyrimidine using 5% palladium on carbon in ethanol, the only reported product was 5-chloro-1,2,4-triazolo[1,5-*a*]pyrimidine after one equivalent of hydrogen had been consumed [11]. However, the modest yield of this product (50%) in comparison to the yield of 1,2,4-triazolo[1,5-*a*]pyrimidine after two equivalents of hydrogen had been consumed (80%) raises a question regarding the selectivity of this reaction.

Subjecting **7** to catalytic hydrogenation conditions failed owing to the presence of divalent sulfur. In addition, attempts to reduce **7** with zinc in acetic acid also failed. We ultimately found that treatment of **7** with zinc-copper couple [13] in the presence of acetic acid in methanol-tetrahydrofuran gave the product from selective removal of the chlorine at the 7-position (**10**) in 81% yield. To verify that the chlorine at the 7-position was removed, **10** was treated with sodium methoxide in methanol to afford **11** in 83% yield. The structure of **11** was established by single crystal X-ray analysis (Figure 1). Tables 1 and 2 contain the atomic coordinates, bond lengths and bond angles for **11**. Compound **10** also reacted with sodium 2,2,2-trifluoroethoxide in tetrahydrofuran to afford **12** in 75% yield. In a similar manner, **8** and **9** were treated with zinc-copper couple to afford **13** and **14** in 74% and 83% yields respectively. Compound **13** was treated with sodium methoxide in methanol and sodium 2,2,2-trifluoroethoxide in tetrahydrofuran to afford **15** in 65% yield and **16** in 73% yield.

The reduction of 6,7-dichloro and 5,7-dichloro-1,2,4-triazolo[1,5-*a*]pyrimidines with zinc-copper couple is highly selective for removal of the chlorine at the 7-position. This selectivity enables the efficient construction of specific substitution patterns on the triazolopyrimidine ring. Specific substitution patterns are critical to modulating the biological properties of the triazolopyrimidine sulfonanilide herbicides derived from these intermediates [5].

Scheme I



3

4: X = H, Y = OH
5: X = Me, Y = OH
6: X = Cl, Y = Me

7: X = H, Y = Cl
8: X = Me, Y = Cl
9: X = Cl, Y = Me

10: X = H, Y = Cl
13: X = Me, Y = Cl
14: X = Cl, Y = Me

11: X = H, R = Me
12: X = H, R = OCH_2CF_3
15: X = Me, R = Me
16: X = Me, R = OCH_2CF_3

(a) $CH_2(COOMe)_2$, NaOMe, MeOH, reflux; (b) $MeCH(COOMe)_2$, NaOMe, MeOH, reflux; (c) MeCOCHClCOOEt, AcOH, 100°; (d) $POCl_3$; (e) Zn-Cu, AcOH, MeOH, Tetrahydrofuran; (f) NaOMe, MeOH or $NaOCH_2CF_3$, Tetrahydrofuran.

Table 1

Atomic Coordinates (x 10^4) for **11** [a]. Standard Deviations are Given in Parentheses
(See Figure 1 for Atom Numbering)

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
S(1)	2979(2)	8790(2)	9753(3)	H(20)	-904	6141	14026
N(2)	925(5)	7322(6)	12052(8)	H(21)	617	5653	12593
N(3)	1776(6)	7248(6)	11117(8)	H(22)	4073	7607	8384
C(4)	1981(6)	8338(8)	10872(9)	H(23)	3103	6881	9121
N(5)	1349(6)	9087(5)	11552(8)	H(24)	5533	8647	10623
C(6)	684(7)	8435(7)	12313(10)	H(25)	6963	7977	12268
N(7)	-123(6)	8750(5)	13139(7)	H(26)	6865	6169	13365
C(8)	-655(7)	7936(8)	13692(9)	H(27)	5401	4854	12504
C(9)	-445(7)	6766(7)	13513(10)	H(28)	3901	5521	10870
C(10)	359(7)	6486(7)	12678(10)	H(29)	-1006	9776	14942
C(11)	3705(7)	7483(7)	9382(11)	H(30)	-2376	9339	15524
C(12)	4580(7)	7112(9)	10502(11)	H(31)	-2239	9574	13723
C(13)	5458(8)	7812(7)	10994(12)				
C(14)	6290(8)	7467(11)	11999(14)				
C(15)	6271(10)	6416(13)	12579(12)				
C(16)	5416(10)	5714(9)	12100(14)				
C(17)	4569(8)	6050(9)	11118(12)				
O(18)	-1455(4)	8139(4)	14613(7)				
C(19)	-1752(7)	9304(7)	14811(11)				

[a] Cell dimensions are: a = 11.792(3)Å; b = 11.934(3)Å; c = 9.383(3)Å. Hydrogen parameters were not refined.

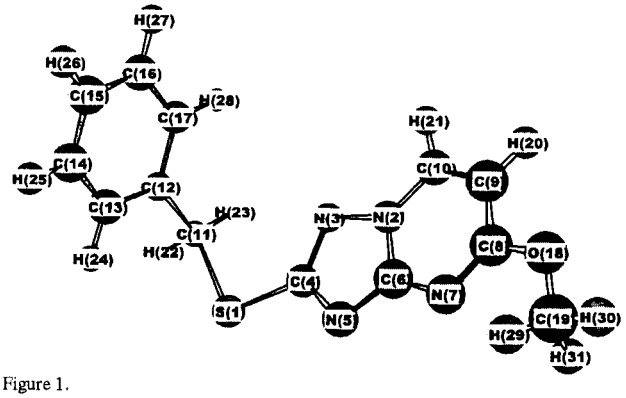


Figure 1.

Table 2

Bond Length (Å) and Bond Angles (°) for **11**
(See Figure 1 for Atom Numbering)

Bond Lengths		Bond Angles	
S(1)-C(4)	1.728(8)	C(11)-S(1)-C(4)	101.7(4)
S(1)-C(11)	1.826(9)	C(6)-N(2)-N(3)	110.0(6)
N(2)-N(3)	1.390(10)	C(10)-N(2)-N(3)	129.2(7)
N(2)-C(6)	1.384(11)	C(10)-N(2)-C(6)	120.8(7)
N(2)-C(10)	1.361(11)	C(4)-N(3)-N(2)	101.3(6)
N(3)-C(4)	1.347(11)	N(3)-C(4)-S(1)	123.1(6)
C(4)-N(5)	1.356(11)	N(5)-C(4)-S(1)	120.6(7)
N(5)-C(6)	1.351(11)	N(5)-C(4)-N(3)	116.3(7)
C(6)-N(7)	1.331(11)	C(6)-N(5)-C(4)	103.6(6)
N(7)-C(8)	1.289(11)	N(5)-C(6)-N(2)	108.8(7)
C(8)-C(9)	1.430(12)	N(7)-C(6)-N(2)	122.8(7)
C(8)-O(18)	1.354(10)	N(7)-C(6)-N(5)	128.3(8)
C(9)-C(10)	1.322(12)	C(8)-N(7)-C(6)	114.7(7)
C(11)-C(12)	1.478(13)	C(9)-C(8)-N(7)	126.4(8)
C(12)-C(13)	1.379(13)	O(18)-C(8)-N(7)	120.7(8)
C(12)-C(17)	1.394(15)	O(18)-C(8)-C(9)	112.8(7)
C(13)-C(14)	1.367(16)	C(10)-C(9)-C(8)	117.2(8)
C(14)-C(15)	1.369(19)	C(9)-C(10)-N(2)	118.1(7)
C(15)-C(16)	1.358(17)	C(12)-C(11)-S(1)	115.5(7)
C(16)-C(17)	1.362(16)	C(13)-C(12)-C(11)	121.1(9)
O(18)-C(19)	1.449(10)	C(17)-C(12)-C(11)	122.5(8)
		C(17)-C(12)-C(13)	116.4(9)
		C(14)-C(13)-C(12)	121.6(9)
		C(15)-C(14)-C(13)	121.0(10)
		C(16)-C(15)-C(14)	118.1(11)
		C(17)-C(16)-C(15)	121.6(11)
		C(16)-C(17)-C(12)	121.1(9)
		C(19)-O(18)-C(8)	116.3(6)

EXPERIMENTAL

General Methods.

All melting points are uncorrected. The ^{1}H nmr chemical shifts are expressed as delta values (ppm) relative to tetramethylsilane internal standard. Significant nmr data are tabulated in order: number of protons, multiplicity, (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant(s) in hertz.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. 3-Amino-5-benzylthio-1,2,4-triazole (**3**) [8] was prepared in 83% yield following a previously described general procedure [9]. Zinc-copper couple was prepared by the method of Brady [13].

Preparation of 2-Benzylthio-5,7-dihydroxy-1,2,4-triazolo[1,5-*a*]-pyrimidine (**4**).

A mixture of 125 g (0.58 mole) of a 25% solution of sodium methoxide in methanol, 66.3 ml (76.6 g, 0.580 mole) of dimethyl malonate and 60.0 g (0.291 mole) of **3** was heated at reflux for 5 days. After cooling to room temperature, the precipitate that formed during the course of the reaction was collected by filtration, washed with cold ethanol and dissolved in 1 l of water. The resulting clear yellow solution was acidified with concentrated aqueous hydrochloric acid. The solid that separated was collected by filtration and dried to afford 70 g (82%) of the hydrate of **4** as a white solid, mp 199-210°: ^{1}H nmr (dimethyl-d_6 sulfoxide) 7.4 (6H, m); 4.4 (2H, s); ir (potassium bromide); 1760, 1630, 1560, 1280, 1220 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_4O_2S \cdot H_2O$: C, 49.31; H, 4.14; N, 19.17. Found: C, 48.70; H, 3.89; N, 18.83.

Preparation of 2-Benzylthio-5,7-dihydroxy-6-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**5**).

A mixture of 250 g (1.16 moles) of 25% sodium methoxide in methanol, 132.6 ml (146 g, 0.996 mole) of dimethyl 2-methylmalonate and 120 g (0.582 mole) of **3** was heated at reflux for 4 days. After cooling to room temperature, the precipitate that formed during the course of the reaction was collected by filtration, washed with cold ethanol and dissolved in 1 l of water. The resulting clear yellow solution was acidified with concentrated aqueous hydrochloric acid. The solid that separated was collected by filtration and dried to afford 127 g (76%) of **5** as a white solid, mp 260-272° slow dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): 7.4-7.7 (5H, m), 4.45 (2H, s), 1.90 (3H, s); ir (potassium bromide): 2600-3500, 1600-1800, 1400 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.16; H, 4.19; N, 19.43. Found: C, 53.48; H, 4.07; N, 19.53.

Preparation of 2-Benzylthio-6-chloro-7-hydroxy-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**6**).

A solution of 16 g (78 mmoles) of **3** and 10.6 g (64.4 mmoles) of ethyl 2-chloroacetoacetate in 150 ml of glacial acetic acid was heated at 100° for 17 hours. After cooling to room temperature, the solid that separated was collected by filtration. The filtrate was diluted with 300 ml of ice water and the solid that separated was collected by filtration. The combined solids were washed with water and dried under vacuum to afford 14.0 g (71%) of **6** as a white solid, mp 258-260°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 7.4-7.7 (5H, m), 4.4 (2H, s), 2.43 (3H, s); ir (potassium bromide): 2600-3100, 1720, 1640, 1560, 1280, 1240 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClN_4OS$: C, 50.90; H, 3.61; N, 18.27. Found: C, 50.51; H, 3.36; N, 18.67.

Preparation of 2-Benzylthio-5,7-dichloro-1,2,4-triazolo[1,5-*a*]-pyrimidine (**7**).

A suspension of 70.0 g (0.239 mole) of the hydrate of **4** and 67.0 ml (110 g, 0.717 mole) of phosphorus oxychloride in 600 ml of acetonitrile was heated at reflux for 3 hours. The orange

homogeneous solution was cooled to room temperature and concentrated under vacuum on a rotary evaporator. The residue was partitioned between dichloromethane and ice water, and the organic layer was separated and dried (magnesium sulfate). Concentration under vacuum on a rotary evaporator gave 98.0 g (81%) of **7** as a white solid, mp 97-100°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 7.90 (1H, s), 7.2-7.7 (5H, m), 4.60 (2H, s); ir (potassium bromide): 3060, 1590, 1480, 1350, 1280, 1100, 850 cm^{-1}.

Anal. Calcd. for $C_{12}H_8Cl_2N_4S$: C, 46.32; H, 2.59; N, 18.00. Found: C, 46.43; H, 2.57; N, 18.08.

Preparation of 2-Benzylthio-5,7-dichloro-6-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**8**).

A suspension of 153 g (0.531 mole) of **5** and 186 ml (306 g, 2.00 moles) of phosphorus oxychloride in 2 l of acetonitrile was heated at reflux for 28 hours. The resulting homogeneous was filtered and concentrated under vacuum on a rotary evaporator. The residue was partitioned between dichloromethane and ice water, and the organic layer was separated and dried (magnesium sulfate). Concentration under vacuum on a rotary evaporator gave a residue that crystallized upon trituration with hexane. The solid was collected and dried under vacuum to afford 147 g (85%) of **8** as a yellow solid, mp 121-123°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 7.5 (5H, m), 4.6 (2H, s), 2.58 (3H, s); ir (potassium bromide): 1610, 1490, 1370, 1290, 1040 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_4S$: C, 48.01; H, 3.10; N, 17.23. Found: C, 47.65; H, 3.11; N, 17.17.

Preparation of 2-Benzylthio-6,7-dichloro-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**9**).

A suspension of 45.0 g (0.147 mole) of **6** in 1 l of phosphorus oxychloride was heated at reflux for 17 hours. After cooling to room temperature, the resulting orange solution was concentrated under vacuum on a rotary evaporator. The residue was partitioned between dichloromethane and ice water, and the organic layer was separated and dried (magnesium sulfate). Concentration under vacuum on a rotary evaporator gave a residue that crystallized. The solid was collected and dried to afford 39.6 g (83%) of **9** as a white solid, mp 95-98°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 7.4-7.6 (5H, m), 4.62 (2H, s), 2.85 (3H, s); ir (potassium bromide): 1600, 1460, 1370, 1280 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_4S$: C, 48.01; H, 3.10; N, 17.23. Found: C, 47.45; H, 3.00; N, 17.43.

Preparation of 2-Benzylthio-5-chloro-1,2,4-triazolo[1,5-*a*]-pyrimidine (**10**).

A solution of 33.0 g (106 mmoles) of **7**, 12.5 ml (13.1 g, 218 mmoles) of acetic acid and 50 ml of methanol in 300 ml of tetrahydrofuran was treated with 20.5 g of zinc-copper couple. A mild exothermic reaction ensued and the temperature of the reaction mixture was maintained between 22 and 28° with an ice bath. After the exothermic reaction subsided, the reaction mixture was stirred at room temperature overnight, and the progress of the reaction was monitored by tlc (silica gel, ethyl acetate-hexane eluent, 1:1, v/v). When the reaction was complete the reaction mixture was filtered through celite and concentrated under vacuum. The residue was crystallized by trituration with hexane. The solid was collected by filtration and dried under vacuum to afford 26.5 g (90%) of **10** as a yellow solid, mp 125-127°; ^{1}H nmr (deuteriochloroform): 8.71 (1H, d), 7.3-7.7 (5H, m), 7.12 (1H, d), 4.51 (2H, s); ir (potassium bromide): 3080, 1600, 1490, 1330, 1280, 1260 cm^{-1}.

Anal. Calcd. for $C_{12}H_9ClN_4S$: C, 52.08; H, 3.28; N, 20.25. Found: C, 51.76; H, 3.00; N, 20.27.

Preparation of 2-Benzylthio-5-methoxy-1,2,4-triazolo[1,5-*a*]-pyrimidine (**11**).

Sodium methoxide (25%) in methanol (5.0 g, 24 mmoles) was added to a solution of 6.0 g (22 mmoles) of **10** in 25 ml of methanol. A mild exothermic reaction occurred, and the temperature of the reaction mixture was maintained at 30° with an ice bath. The progress of the reaction was monitored by tlc (silica gel, ethyl acetate-hexane eluent, 1:1, v/v). After 1.5 hours the reaction mixture was diluted with 100 ml of water and neutralized with 3*N* aqueous hydrochloric acid. The resulting solid that separated was collected by filtration, washed with water and dried under vacuum to afford 5.0 g (83%) of **11** as a white solid, mp 126-128°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 9.3 (1H, d, J = 5 Hz), 7.4-7.7 (5H, m); 6.8 (1H, d, J = 5 Hz), 4.45 (2H, s), 3.96 (3H, s); ir (potassium bromide): 3100, 1625, 1535, 1470, 1345, 1260 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.21; H, 4.42; N, 20.13.

Preparation of 2-Benzylthio-5-(2,2,2-trifluoroethoxy)-1,2,4-triazolo[1,5-*a*]pyrimidine (**12**).

Sodium metal (1.1 g, 48 mg-atoms) was dissolved in a solution of 3.5 ml (4.8 g, 48 mmoles) of 2,2,2-trifluoroethanol in 100 ml of dry tetrahydrofuran. Compound **10** (7.0 g, 25 mmoles) was added, and the resulting solution was stirred for 30 minutes at 30°. The solution was concentrated under vacuum on a rotary evaporator. Pentane was added to the residue to induce crystallization. The solid that separated was collected by filtration, washed with water and pentane, and dried under vacuum to afford 6.4 g (75%) of **12** as a light yellow solid, mp 114-118°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 9.37 (1H, d, J = 6 Hz), 7.4-7.7 (5H, m), 7.07 (1H, d, J = 6 Hz), 5.27 (1H, q, J = 9 Hz), 4.57 (2H, s); ^{19}F nmr (dimethyl sulfoxide-hexafluorobenzene): 92.7 ppm; ir (potassium bromide): 3020-3040, 1630, 1540, 1440, 1350, 1270, 1240, 1170 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}F_3N_4OS$: C, 49.41; H, 3.26; N, 16.46. Found: C, 49.63; H, 3.09; N, 16.70.

Preparation of 2-Benzylthio-5-chloro-6-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**13**).

A solution of 100 g (0.307 mole) of **8**, 24 ml (25 g, 0.42 mole) of acetic acid and 100 ml of methanol in 1.5 l of tetrahydrofuran was treated with 40.0 g of zinc-copper couple. A mild exothermic reaction ensued and the temperature of the reaction mixture was maintained between 22 and 28° with an ice bath. After the exothermic reaction subsided, the reaction mixture was stirred at room temperature for 20 hours, and the progress of the reaction was monitored by tlc (silica gel, ethyl acetate-hexane eluent, 1:1, v/v). When the reaction was complete the reaction mixture was filtered through celite and concentrated under vacuum. The residue was crystallized by trituration with hexane. The solid was collected by filtration and dried under vacuum to afford 66.5 g (74%) of **13** as a white solid, mp 180-181°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 9.17 (1H, s), 7.4-7.7 (5H, m), 4.53 (2H, s), 2.43 (3H, s); ir (potassium bromide): 1620, 1500, 1340, 1240, 1150, 1050 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClN_4S$: C, 53.70; H, 3.81; N, 19.27. Found: C, 53.33; H, 3.73; N, 19.53.

Preparation of 2-Benzylthio-6-chloro-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**14**).

A solution of 10.0 g (30.7 mmoles) of **9**, 1.0 ml (1.0 g, 17 mmoles) of acetic acid and 5 ml of methanol in 30 ml of tetrahydrofuran was treated with 2.0 g of zinc-copper couple. A mild exothermic reaction ensued and the temperature of the reaction mixture was maintained between 22 and 28° with an ice bath. After the exothermic reaction subsided, the reaction mixture was stirred at room temperature for 3 hours, and the progress of the reaction was monitored by tlc (silica gel, ethyl acetate-hexane eluent, 1:1, v/v). When the reaction was complete the reaction mixture was filtered through celite and concentrated under vacuum. The residue was crystallized by trituration with hexane. The solid was collected by filtration and dried to afford 7.9 g (88%) of **14** as a yellow solid, mp 160-161°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 8.87 (1H, s), 7.3-7.7 (5H, m), 4.55 (2H, s), 2.77 (3H, s); ir (potassium bromide): 1600, 1490, 1340, 1290 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClN_4S$: C, 53.70; H, 3.81; N, 19.27. Found: C, 53.30; H, 3.79; N, 19.28.

Preparation of 2-Benzylthio-5-methoxy-6-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**15**).

Sodium methoxide (25%) in methanol (5.0 g, 24 mmoles) was added to a solution of 5.5 g (19 mmoles) of **13** in 100 ml of methanol. A mild exothermic reaction occurred, and the temperature of the reaction mixture was maintained at 30° with an ice bath. The progress of the reaction was monitored by tlc (silica gel, ethyl acetate-hexane eluent, 1:1, v/v). After 20 minutes the reaction mixture was diluted with 100 ml of water and neutralized with 6*N* aqueous hydrochloric acid. The resulting solid that separated was collected by filtration, washed with water, dried under vacuum and recrystallized from 2-propanol to afford 3.5 g (65%) of **15** as a white solid, mp 145-146°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 9.13 (1H, s), 7.4-7.7 (5H, m), 4.53 (2H, s), 4.07 (3H, s), 2.17 (3H, s); ir (potassium bromide): 1635, 1520, 1465, 1350, 1270,1240, 1230 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57. Found: C, 58.34; H, 4.84; N, 19.67.

Preparation of 2-Benzylthio-6-methyl-5-(2,2,2-trifluoroethoxy)-1,2,4-triazolo[1,5-*a*]pyrimidine (**16**).

Sodium metal (5.2 g, 0.23 g-atom) was dissolved in a solution of 16.5 mL (22.7 g, 0.227 mole) of 2,2,2-trifluoroethanol in 250 ml of dry tetrahydrofuran. Compound **13** (60.0 g, 0.206 mole) was added, and the resulting solution was stirred for 30 minutes at 30°. The solution was concentrated under vacuum on a rotary evaporator. Pentane was added to the residue to induce crystallization. The solid that separated was collected by filtration, washed with water and pentane, and dried under vacuum to afford 53.0 g (73%) of **16** as pale yellow needles, mp 176-179°. An analytical sample of **16** was prepared by recrystallization from hexane to afford **16** as pale yellow needles, mp 179-181°; ^{1}H nmr (dimethyl-d_6 sulfoxide): 9.02 (1H, s), 7.2-7.4 (5H, s), 5.09 (2H, q, J = 8.9 Hz), 4.44 (2H, s), 2.14 (3H, s); ^{13}C nmr (dimethyl-d_6 sulfoxide): 164.6, 162.4, 153.2, 137.5, 135.8, 128.7, 128.3, 127.1, 126.2, 120.7, 109.9, 62.3 (q), 34.3, 12.0 ppm; ir (potassium bromide): 1625, 1510, 1420, 1340, 1260, 1220, 1160 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}F_3N_4OS$: C, 50.84; H, 3.70; N, 15.81. Found: C, 50.92; H, 3.71; N, 16.10.

Single Crystal X-ray Analysis of **11**.

A representative crystal was surveyed and a 1-Å data set (maximum sin θ/λ = 0.5) was collected on a Syntex P1 diffractometer. The diffractometer was equipped with a graphite monochrometer and copper radiation (λ = 1.5418Å). Atomic scattering factors were taken from the International Tables for X-ray Crystallography [14], except hydrogen which was taken from Stewart, Davidson and Simpson [15]. All crystallographic calculations were facilitated by the CRYM system [16]. All diffractometer data were collected at room temperature.

A trial structure was obtained by direct methods using the MULTAN program [17]. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The final cycles of full matrix least-squares refinement contained the scale factor, secondary extinction coefficient, coordinates, and anisotropic temperature factors in a single matrix. The shifts calculated in the final cycle were all less than 0.1 of their corresponding standard deviation. The R-index was 0.084. A final difference Fourier revealed no missing or misplaced electron density.

Supplementary Material Available.

Complete experimental details and data for the single crystal X-ray analysis of **7** is available from one of the authors (JB).

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