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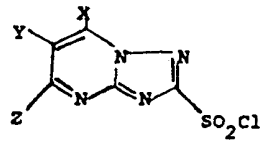
(54) Intermediate 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chlorides

(57) 1,2,4-Triazolo[1,5-a]pyrimidine-2-sulfonyl chlorides of the formula



(I)

wherein X, Y and Z independently represent hydrogen, alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, aryl or substituted aryl or two adjacent substituents selected from X, Y and Z are joined together in a cyclic structure, with the proviso that when Y is hydrogen, X and Z may not simultaneously be alkyl, are intermediates in the preparation of N-aryl substituted 1,2,4-triazolo[1,5-a]pyrimidine-2-sulphonamides.

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Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

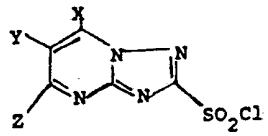
The date of filing shown above is that provisionally accorded to the application in accordance with the provisions of Section 15(4) of the Patents Act 1977 and is subject to ratification or amendment.

SPECIFICATION

1,2,4-Triazolo[1,5-a]pyrimidine-2-sulfonyl chlorides

The present invention relates to certain 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chlorides. These compounds are useful in the preparation of the N-aryl substituted 1,2,4-triazolo[1,5-a]-pyrimidine-2-sulfonamides which are described in British Patent Specification No. 2149792 out of which this Application is divided.

The present invention provides 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chlorides of the general formula:–



wherein X, Y and Z independently represent hydrogen, alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, aryl, substituted aryl or two adjacent substituents selected from X, Y and Z are joined together in a cyclic structure, with the proviso that when Y is hydrogen, X and Z may not simultaneously be alkyl.

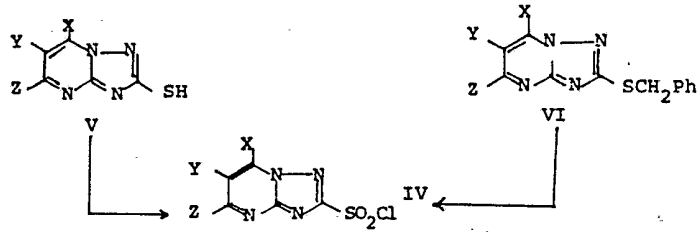
Preferred embodiments include those where X, Y and Z independently represent hydrogen, halo, C_1–C_4 alkyl or C_1–C_4 alkoxy.

Particularly preferred embodiments of the present invention include those where:–

(1) X is methyl and Y and Z are hydrogen
(2) Y is methyl and X and Z are hydrogen
(3) Z is methyl and X and Y are hydrogen
(4) Y is chlorine and X and Z are hydrogen

The sulfonyl chlorides of the present invention may be prepared according to routes outlined in Scheme I. Mercaptan V may be converted to sulfonyl chloride IV by treatment with Cl_2 in an aqueous acidic medium. Generally the medium would be aqueous acetic acid or aqueous HCl. The temperature of the reaction mixture is generally maintained between −20°C and 25°C during the course of the chlorine addition. Most preferably, temperature ranges between −20°C and 0°C are employed to minimize unwanted side reactions such as hydrolysis of IV to the corresponding sulfonic acid. Alternatively, the mercaptan V may be suspended ina two phase system of aqueous acid (i.e., HCl) and an organic solvent (i.e., CH_2Cl_2) and treated with sodium hypochlorite. This serves to convert V to the sulfonyl chloride IV in a reproducibly good yield. The solubility of the product in the organic phase serves to protect it from hydrolysis to the sulfonic acid. Again, temperatures in the range of −20°C to 25°C are employed with temperatures in the range of −5°C to 5°C being most generally used.

SCHEME I.



As an alternative, it is sometimes preferred to prepare sulfonyl chloride IV from benzyl sulfide VI (Scheme I). Reaction conditions as described above for the conversion of V to IV are operable. This procedure yields by-products containing benzyl residues which are generally removed by washing the product with water and/or an appropriate organic solvent and drying *in vacuo*.

Compounds of general structure V or VI may be prepared by routes illustrated in Scheme II. Some derivatives of structures V and VI are known materials (i.e., V, X=Z=Me, Y=H and VI, X=Z=Me, Y=H) prepared by methods described in *J. Med. Chem., 25,* 420 (1982). Compound IV is prepared directly by reaction of a 1,3-diketone with commercially available 3-amino-5-mercapto-1,2,4-triazole VII in glacial acetic acid as a solvent. Generally the reaction is performed at reflux. Alternatively, VII may be benzylated with benzyl chloride using an alkali earth metal alkoxide (i.e., NaOH) as a base to yield known benzyl sulfide VIII (*J. Heterocycl. Chem., 12,* 1187 (1975)). Benzyl sulfide VIII can be condensed with not only 1,3-diketones but also β-keto esters, malonic esters, malonaldehyde, β-ketoaldehydes or α-formyl esters or derivatives thereof

(i.e., acetals or enol ethers) to yield products of type VI as illustrated in Table A. Generally these reactions can be carried out under acidic conditions (i.e., glacial acetic acid as a solvent) or basic conditions (i.e., NaOR in ROH wherein R is C_1 to C_4 alkyl). In cases where the X, Y and Z substituents in VI are derived from a 1,3-diketone, compound VI may be prepared by benzylation of IV using an appropriate base (i.e., NaOH) and benzyl chloride in a variety of solvents (i.e., H_2O, CH_3OH, EtOH, THF, dioxane, CH_3CN, DMF or DMSO or combinations of the aforementioned).

SCHEME II.

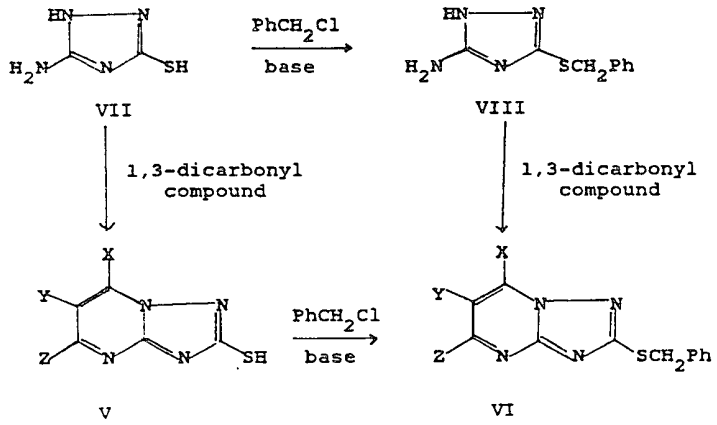
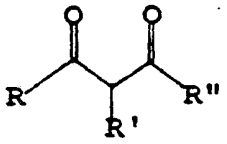
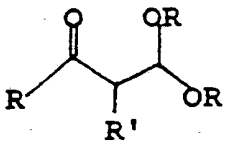
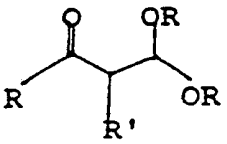
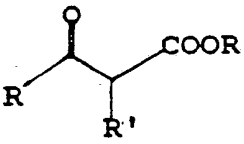
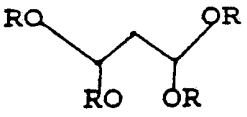
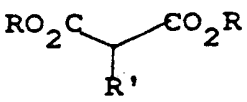


TABLE A

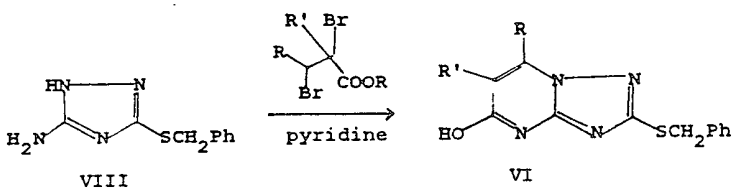
1,3-Dicarbonyl Compound or Derivative	Reaction Conditions	Compound of Formula V or VI X	Y	Z
	acid	R	R'	R"
	acid	H	R'	R
	base	R	R'	H
	acid	OH*	R'	R
	acid	H	H	H
	base	OH	R'	OH

*In this structural representation, as well as others bearing OH groups at 5- or 7-positions of the 1,2,4--triazolo[1,5-a]pyrimidine, the enol form has been depicted. Clearly this is the equilibrium with the various keto forms.

In instances where the 1,3-dicarbonyl compound is unsymmetrical, the possibility of obtaining two different isomers from condensation with VIII exists. In general, under acidic conditions the exocyclic nitrogen in VIII is the first to condense with the 1,3-dicarbonyl compound. Under basic conditions the endocyclic nitrogen in VIII is sometimes more reactive. Consequently, in situations where a clear difference in reactivity of the two carbonyl functionalities in the 1,3-dicarbonyl compound exists, some measures of regiochemical control may be achieved by choice of reaction conditions (i.e., entries 2 and 3 in Table A).

To prepare the alternative regioisomer to that depicted in entry 4 in Table A (i.e., VI, X=R, Y=R' and Z=OH) a route illustrated in Scheme III was followed. Compound VIII was condensed with 2,3-dibromocarboxylic acid esters to yield VI (X=R, Y=R', Z=OH). The reaction is generally carried out in refluxing pyridine.

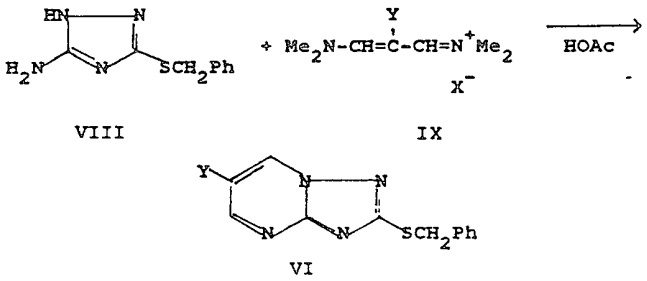
SCHEME III.



VIII VI

An additional route to compounds of type VI involves condensation of compound VIII with methanaminium compounds of type IX as illustrated in Scheme IV. The condensation is usually carried out by reaction in refluxing glacial acetic acid and is useful in the synthesis of a number of 6-substituted 1,2,4-triazolo[1,5-a]pyrimidines.

SCHEME IV.

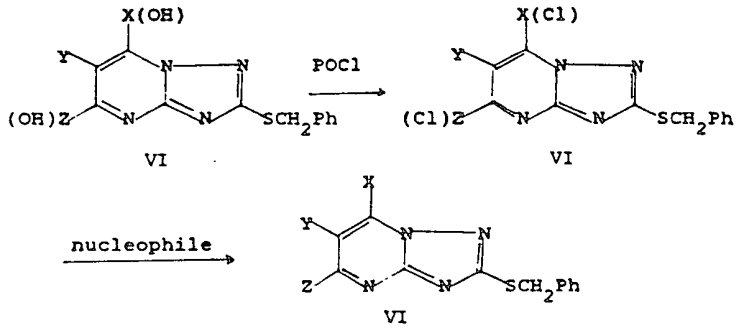


VIII IX

VI

In the synthetic routes listed above, compounds of type VI where X and/or Z is OH are capable of undergoing further transformation (Scheme V). For example, treatment of compound VI (X and/or Z=OH) with phosphorus oxychloride yields VI (X and/or Z=Cl). The reaction is generally carried out at reflux in neat phosphorus oxychloride or with phosphorous oxychloride in a solvent (i.e. CH_3CN). Compound IV (X and/or Z=Cl) can be further reacted with nucelophiles (i.e., $NaOCH_3$, MeMgBr) to yield VI (X and/or Z=OCH_3 or CH_3, respectively). In addition compound VI (x and/or Z=Cl) may be reduced to afford VI (X and/or Z=H). An effective reducing agent for this type of transformation is zinc–copper couple in the pressure of acid.

SCHEME V.



VI VI

VI

Using the routes illustrated above or minor variations based on the principles illustrated above the novel compounds of this invention can be prepared.

The invention is further illustrated by the following Examples. Examples 1 to 28 illustrate the preparation of the starting compounds used in the preparation of the compounds of the invention. Examples 48 to 54 also illustrate the preparations of starting compounds useful in preparing the compounds of the invention.

Example 1—Preparation of 2-benzylthio-6,7-cyclopentano-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 51.6 g (0.250 mol) of 3-amino-5-benzylthio-1,2,4-triazole and 31.5 g (0.250 mol) of 2-acetylcyclopentanone in 600 ml of HOAC was heated at reflux for 9.5 hours. The solvent was removed by evaporation, and the brown solid residue was recrystallized from EtOH to yield a light brown solid. A second recrystallization from EtOH gave 45.4 g (61 percent) of the desired product as a light brown solid, m.p. 157°–158.5°C: ^1H NMR ($CDCl_3$) δ7.0–7.6 (5H, m), 4.51 (2H, s), 3.29 (2H, t), 2.97 (2H, t), 2.0–2.7 (5H, m including s at 2.52); IR ($CHCl_3$)

1621, 1343 and 1290 cm^{-1}.

Analysis:

Calculated for $C_{16}H_{16}N_4S$:	C, 64.84; H, 5.44; N, 18.90; S, 10.82.
Found:	C, 64.88; H, 5.47; N, 18.98; S, 10.72.

Example 2—Preparation of 2-benzylthio-5,6,7-trimethyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 51.6 g (0.250 mol) of 3-amino-5-benzylthio-1,2,4-triazole and 28.5 g (0.250 mol) of 3-methyl-2,4-pentanedione in 350 ml of glacial acetic acid was heated at reflux for 17 hours. Upon cooling to room temperature, the reaction mixture was poured onto ice. The pale yellow solid which separated was collected by filtration, washed with water and dried *in vacuo* to yield 67.1 g (94%) of the desired product as a pale yellow solid, m.p. 133.5°–135°C. The IR and ^1H NMR spectra were consistent with the assigned structure.

Analysis:

Calculated for $C_{15}H_{15}N_4S$:	C, 63.35; H, 5.67; N, 19.70; S, 11.27.
Found:	C, 63.07; H, 5.48; N, 19.71; S, 11.09.

Example 3—Preparation of 2-benzylthio-6-chloro-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 6.52 g (31.6 mmol) of 3-amino-5-benzylthio-1,2,4-triazole and 9.09 g (31.6 mmol) of 1,3-bis(dimethylamino)-2-chlorotrimethinium perchlorate in 100 ml of glacial acetic acid was heated at reflux for 19 hours. After cooling to room temperature, the solution was poured into 300 ml of water. The solid which separated was collected by filtration, washed with water and dried *in vacuo* to yield 4.12 g (48%) for the desired product as a brown solid, m.p. 119.5°–135°C (decomposition). IR and ^1H NMR spectra were consistent with the assigned structure.

Analysis:

Calculated for $C_{12}H_9ClN_4S$:	C, 51.90; H, 3.20; N, 20.24.
Found:	C, 51.87; H, 3.42; N, 19.81.

Example 4—Preparation of 2-benzylthio-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 2.0 g (9.6 mmol) of 3-amino-5-benzylthio-1,2,4-triazole and 2.3 ml (9.6 mmol) of malonaldehyde bis(diethylacetal) in 20 ml of glacial acetic acid was heated at reflux for 17 hours. After cooling to room temperature, the solvent was removed by evaporation at reduced pressure. The brown solid residue was recrystallized from isopropyl alcohol to afford 0.4 g (17%) of the desired product as a light brown crystalline solid, m.p. 104°–106°C. IR and ^1H NMR spectra were consistent with the assigned structure.

Analysis:

Calculated for $C_{12}H_{10}N_4S$:	C, 59.52; H, 4.13; N, 23.13.
Found:	C, 59.19; H, 4.09; N, 22.73.

Example 5—Preparation of 2-benzylthio-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of sodium ethoxide in EtOH was prepared by dissolving 0.54 g (24 mg-atoms) of sodium metal in 120 ml of anhydrous EtOH, and 10.0 g (48 mmol) of 3-amino-5-benzylthio-1,2,4-triazole was added. After stirring for 15 minutes at room temperature, 6.4 ml (6.35 g, 48.4 mmol) of acetylacetaldehyde dimethyl acetal dissolved in 100 ml of absolute EtOH was added dropwise. After the addition was complete the reaction mixture was stirred at room temperature for 68 hours. The product which separated from solution was collected by filtration and dried to give 10.1 g (83%) of tan solid, m.p. 128.5°–130°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:

Calculated for $C_{13}H_{12}N_4S$:	C, 60.94; H, 4.68; N, 21.86.
Found:	C, 60.69; H, 4.61; N, 21.85.

Example 6—Preparation of 2-benzylthio-5-hydroxy-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine

Ethyl 2,3-dibromobutyrate (1.33 g, 48.5 mmol) was added dropwise over 15 minutes to a solution of 10 g (49 mmol) of 3-amino-5-benzylthio-1,2,4-triazole in 20 ml of pyridine heated to

65°C. After the addition was complete, the reaction mixture was heated at 65°C for 20 hours, cooled to room temperature and filtered. The filtrate was concentrated by evaporation at reduced pressure. The residue was triturated with methanol to separate 1.64 g (13%) of the desired product as a colorless crystalline solid, m.p. 219°–220°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{12}N_4OS$: C, 57.37; H, 4.41; N, 20.60.
Found: C, 56.86; H, 4.41; N, 20.72.

Example 7—Preparation of 2-benzylthio-5-methoxy-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 2.67 g (9.80 mmol) of 2-benzylthio-5-hydroxy-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine in 50 ml of phosphorous oxychloride was heated at reflux for 3 hours. The excess phosphorous oxychloride was removed by evaporation at reduced pressure. The residue was partitioned between CH_2Cl_2 and cold water. The organic phase was separated, dried ($MgSO_4$) and concentrated by evaporation at reduced pressure. The resulting solid was added to 50 ml (0.22 mol) of a 25 weight percent solution of sodium methoxide in methanol. The resulting suspension was stirred at room temperature for 30 minutes, diluted with 50 ml of water and filtered. The solid collected was dried *in vacuo* to yield 1.41 g (41%) of the desired product as a light brown solid, m.p. 112.5°–115°C. IR and ^1H NMR spectra were consistent with the assigned structure.

Example 8—Preparation of 2-benzylthio-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 50 g (0.24 mol) of 3-amino-5-benzylthio-1,2,4-triazole in 500 ml of glacial acetic acid was added dropwise over 3–4 hours to a solution of 34.0 g (0.25 mol) of acetylacetaldehyde dimethyl acetal in 500 ml of glacial acetic acid heated at 100°C. After the addition was complete the reaction mixture was heated at reflux overnight, cooled to room temperature and poured into an ice-water mixture. The solid which separated was collected by filtration and recrystallized from ethanol to yield 27 g (41%) of the desired product as a solid, m.p. 102°–104°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{12}N_4S$: C, 60.94; H, 4.68; N, 21.85.
Found: C, 60.81; H, 4.68; N, 21.74.

Example 9—Preparation of 2-benzylthio-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine

A suspension of 14.4 g (0.124 mol) of 3-amino-5-benzyl-1,2,4-triazole and 30.0 g (0.124 mol) of 1,3-bis(dimethylamino)-2-methyltrimethinium perchlorate in 500 ml of glacial acetic acid was heated at reflux for 63 hours. The reaction mixture was subjected to the work-up described in Example 5 to yield 13.9g (68%) of the desired product as a brown solid, m.p. 254°–256°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_6H_6N_4S$: C, 43.35; H, 3.61; N, 33.72.
Found: C, 42.71; H, 3.49; N, 33.26.

Example 10—Preparation of 2-benzylthio-6-chloro-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine

To a suspension of 153 g (0.74 mol) 3-amino-5-benzylthio-1,2,4-triazole in 250 ml of glacial acetic acid was added 100 g (0.74 mol) of 3-chloro-2,4-pentanedione in a dropwise manner. The reaction mixture was heated at reflux for 18 hours and cooled to room temperature. The reaction mixture was poured over ice and the oil which separated solidified upon stirring. The solid was collected by filtration and recrystallized from methanol to yield 116 g (79%) of the desired product as an off white solid, m.p. 164°–166°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_{13}ClN_4S$: C, 55.16; H, 4.30; N, 18.38.
Found: C, 55.11; H, 4.30; N, 18.34.

Example 11—Preparation of 2-benzylthio-6-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine

This material was prepared in 28% yield from 3-amino-5-benzylthio-1,2,4-triazole and 1,3-bis(dimethylamino)-2-ethoxytrimethinium perchlorate following the general procedure described in

Example 3. The desired product was isolated as a solid, m.p. 139–140°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_{14}N_4OS$: C, 58.73; H, 4.89; N, 19.57.
Found: C, 58.68; H, 4.64; N, 19.58.

Example 12—Preparation of 2-benzylthio-5-isopropyl-1,2,4-triazolo[1,5-a]pyrimidine
This material was prepared in 96% yield from 3-amino-5-benzylthio-1,2,4-triazole and 4-methyl-3-oxopentanal following the general procedure described in Example 5. The desired product was isolated as a solid, m.p. 65°–66°C. IR and ^{1}H NMR were in agreement with the assigned structure.

Analysis:
Calculated for $C_{15}H_{16}N_4S$: C, 63.36; H, 5.63; N, 19.71.
Found: C, 63.00; H, 5.62; N, 19.62.

Example 13—Preparation of 2-benzylthio-5,6-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine
A solution of 5.0 g (24 mmol) of 3-amino-5-benzylthio-1,2,4-triazole and 5.0 g (41 mmol) of the sodium salt of 2-methyl-3-oxobutanal in 200 ml of glacial acetic acid was heated at reflux overnight. The solution was cooled to room temperature and the reaction mixture was concentrated by evaporation at reduced pressure. The residue was combined with ice and H_2O to separate a tan solid. The solid was collected by filtration, dried and carefully recrystallized from ethyl acetate to yield 3.53 g (54%) of the desired product as a crystalline solid, m.p. 147°–149°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_{14}N_4S$: C, 62.10; H, 5.18; N, 20.72.
Found: C, 61.58; H, 5.18; N, 20.45.

Example 14—Preparation of 2-benzythio-6-chloro-7-hydroxy-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine
A solution of 16 g (77 mmol) of 3-amino-5-benzylthio-1,2,4-triazole and 10.6 g (77 mmol) of ethyl 2-chloroacetoacetate in 150 ml of glacial acetic acid was heated at 100°C for 17 hours. Upon cooling to room temperature the solid which separated was collected by filtration. The filtrate was diluted with ice water to separate an additional quantity of solid. The solids were combined and dried to yield 14.0 g (60%) of the desired product as a solid, m.p. 258°–260°C. IR and ^{1}H NMR were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{11}ClN_4OS$: C, 50.89; H, 3.58; N, 18.27.
Found: C, 50.51; H, 3.36; N, 18.67.

Example 15—Preparation of 2-benzylthio-6,7-dichloro-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine
This material was prepared in 68% yield from 2-benzylthio-6-chloro-7-hydroxy-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine and phosphorus oxychloride following the general procedure described in Example 20. The desired product was isolated as a solid, m.p. 103°–105°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{10}Cl_2N_4S$: C, 48.00; H, 3.07; N, 17.23.
Found: C, 47.40; H, 3.00; N, 17.43.

Example 16—Preparation of 2-benzylthio-6-chloro-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine
This material was prepared by reduction of 2-benzylthio-6,7-dichloro-5-methyl-1,2,4-triazolo-[1,5-a]pyrimidine with zinc–copper couple following the general procedure described in Example 19. The desired product was isolated in 88% yield as a solid, m.p. 160°–161°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{11}ClN_4S$: C, 53.56; H, 3.56; N, 19.27.
Found: C, 53.30; H, 3.79; N, 19.28.

Example 17—Preparation of 2-benzylthio-5,7-dihydroxy-2,4-triazolo[1,5-a]pyrimidine

A solution of 125 g (0.58 mol) of a 25% solution of sodium methoxide in methanol dissolved in 100 ml of absolute ethanol was treated with 66.3 ml (0.29 mol) of dimethyl malonate followed by 60.0 g (0.29 mol) of 3-amino-5-benzylthio-1,2,4-triazole. The resulting solution was heated at reflux for 5 days. On cooling to room temperature the solid which had separated was collected by filtration, washed with cold ethanol and dissolved in 1000 ml of water. The resulting yellow solution was acidified with concentrated HCl to precipitate a solid. The solid was collected by filtration and dried to yield 70.1 g (82%) of the desired product as a white solid, m.p. 199°–210°C (decomposition). IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{12}H_{10}N_4O_2S \cdot H_2O$: C, 49.30; H, 4.14; N, 19.16.
Found: C, 48.70; H, 3.89; N, 18.83.

Example 18—Preparation of 2-benzylthio-5,7-dichloro-1,2,4-triazolo[1,5-a]pyrimidine

A suspension of 70.0 g (0.24 mol) of 2-benzylthio-5,7-dihydroxy-1,2,4-triazolo[1,5-a]pyrimidine and 67.0 ml (0.72 mol) of phosphorous oxychloride in 600 ml of acetonitrile was heated at reflux for 3 hours. The resulting orange solution was stirred at room temperature overnight (17 hours). The solution was filtered and the filtrate was concentrated by evaporation at reduced pressure. The residue was partitioned between cold water and methylene chloride, and the organic phase was separated and dried ($MgSO_4$). The organic phase was concentrated to induce crystallization. The desired product was collected by filtration to yield 98.0 g (81%) of solid, m.p. 97°–100°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated 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.

Example 19—Preparation of 2-benzylthio-5-chloro-1,2,4-triazolo[1,5-a]pyrimidine

A zinc–copper couple was prepared following the procedure of Bradley (*J. Org. Chem., 31,* 626 (1966)) by stirring 1.0 g of copper sulfate in 20 ml of water with 15.0 g of zinc dust for 2 hours. The couple was collected by filtration, washed with acetone and dried overnight under vacuum at 100°C. To a solution of 33.0 g (106 mmol) of 2-benzylthio-5,7-dichloro-1,2,4-triazolo[1,5-a]pyrimidine in 12.5 ml (213 mmol) of acetic acid, 50 ml of methanol and 300 ml of tetrahydrofuran was added 20.5 g of Zn–Cu couple. The mixture was stirred overnight at 22°–23°C. When the reaction was complete (TLC analysis) the reaction mixture was filtered through celite and the filtrate was concentrated by evaporation at reduced pressure. The residue was triturated with hexane to separate a solid. The solid was collected by filtration to yield the desired product as 26.5 g (92%) of orange solid, m.p. 125°–127°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{12}H_9ClN_4S$: C, 52.08; H, 3.25; N, 20.25.
Found: C, 51.76; H, 3.00; N, 20.27.

Example 20 –Preparation of 2-benzylthio-5-methoxy-1,2,4-triazolo[1,5-a]pyrimidine

A mixture of 6.0 g (22 mmol) of 2-benzylthio-5-chloro-1,2,4-triazolo[1,5-a]pyrimidine in 25 ml of methanol was treated with 5.0 g (23.8 mmol) of a 25% solution of sodium methoxide in methanol. After stirring for 1.5 hours the reaction mixture was diluted with 100 ml of water and neutralized with 3N HCl (aq). The solid which separated was collected by filtration, washed with water and dried to afford 5.0 g (84%) of the desired product as a white solid, m.p. 126°–128°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.41; N, 20.58.
Found: C, 57.21; H, 4.42; N, 20.13.

Example 21—Preparation of 2-benzylthio-5-(2,2,2-trifluoroethoxy)-1,2,4-triazolo[1,5-a]pyrimidine

A solution of sodium 2,2,2-trifluoroethoxide in tetrahydrofuran was prepared by the addition of 1.1 g (48 mg-atom) of sodium metal to a solution of 3.5 ml (48 mmol) of 2,2,2-trifluoroethanol in 100 ml of tetrahydrofuran. To this solution was added 7.0 g (25 mmol) of 2-benzylthio-5-chloro-1,2,4-triazolo[1,5-a]pyirmidine, and the reaction mixture was stirred for 30 minutes and concentrated by evaporation at reduced pressure to approximately one quarter of the original volume. Pentane (200 ml) was added to induce crystallization. The solid which separated was collected by filtration to yield 6.42 g (75%) of the desired product as a light yellow wolid, m.p. 114°–118°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_{11}F_3N_4OS$: C, 49.40; H, 3.23; N, 16.46.
Found: C, 49.63; H, 3.09; N, 16.70.

Example 22—Preparation of 2-benzylthio-5-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine

This material was prepared by heating 2-benzylthio-5-(2,2,2-trifluoroethoxy)-1,2,4-triazolo[1,5-a]pyrimidine in boiling ethanol. The hot mixture was filtered and the filtrate was concentrated. The crude product was recrystallized from isopropanol to yield the desired product as a solid, m.p. 115°–117°C. IR and ^{1}HNMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_{14}N_4OS$: C, 58.73; H, 4.89; N, 19.31; S, 11.20.
Found: C, 57.90; H, 4.69; N, 19.30; S, 10.79.

Example 23—Preparation of 2-benzylthio-5,7-dihydroxy-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine

This material was prepared in 80% yield from 3-amino-5-benzylthio-1,2,4-triazole and dimethyl 2-methyl malonate following the general procedure described in Example 17. The product was isolated as a solid, m.p. 260°–272°C (decomposition). IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.16; N, 19.44.
Found: C, 53.48; H, 4.07; N, 19.53.

Example 24—Preparation of 2-benzylthio-5,7-dichloro-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine

This material was prepared in 97% yield from the reaction of 2-benzylthio-5,7-dihydroxy-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine and phosphorus oxychloride following the general procedure described in Example 18. The product was isolated as a solid, m.p. 121°–123°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{10}Cl_2N_4S$: C, 48.01; H, 3.08; N, 17.23.
Found: C, 47.65; H, 3.11; N, 17.70.

Example 25—Preparation of 2-benzylthio-5-chloro-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine

This material was prepared in 32% yield by reduction of 2-benzylthio-5,7-dichloro-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine with zinc–copper couple following the general procedure described in Example 19. The desired product was isolated as a solid, m.p. 179°–181°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{13}H_{11}ClN_4S$: C, 53.70; H, 3.79; N, 19.28.
Found: C, 53.33; H, 3.73; N, 19.53.

Example 26—Preparation of 2-benzylthio-5-methoxy-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine
This material was prepared in 64% yield by reaction of 2-benzylthio-5-chloro-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine with sodium methoxide following the general procedure described in Example 20. The desired product was isolated as a solid, m.p. 145°–146°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_{14}N_4OS$: C, 58.73; H, 4.89; N, 19.58.
Found: C, 58.34; H, 4.84; N, 19.67.

Example 27—Preparation of 2-benzylthio-6-ethoxycarbonyl-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine
A solution of 15 g (73 mmol) of 3-amino-5-benzylthio-1,2,4-triazole and 15.0 g (80.0 mmol) of ethyl ethoxymethyleneacetoacetate in 250 ml of glacial acetic acid was heated at reflux for 60 hours. After cooling the volume of the reaction was reduced to approximately one quarter of the oroginal volume by evaporation at reduced pressure. The resulting residue was poured into water, and the solid which separated was collected by filtration, washed with water and dried to yield 7.88 g (33%) of the desired product as a solid, m.p. 98°–99°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.87; N, 17.07.
Found: C, 58.51; H, 4.89; N, 17.03.

Example 28—Preparation of 2-benzylthio-6-(4-nitrophenyl)-1,2,4-triazolo[1,5-a]pyrimidine
This material was prepared from 3-amino-5-benzylthio-1,2,4-triazole and 1,3-bis(dimethylamino)-2-(4-nitrophenyl)-trimethinium perchlorate following the general procedure described in Example 3. The desired product was isolated as a solid, m.p. 195°–199°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Example 29—Preparation of 6,7-cyclopentano-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride
Chlorine gas was bubbled into a suspension of 4.45 g (15.0 mmol) of 2-benzylthio-6,7-cyclopentano-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine in 30 ml of HOAC–H_2O (1:1, v/v) cooled to −4°C. After 30 minutes the addition was stopped and the reaction mixture was stirred for 30 minutes maintaining the temperature below 5°C. The reaction mixture was filtered and the collected solid was dried under vacuum to yield 3.46 g (85 percent) of the desired sulfonyl chloride as a cream colored solid which was used directly without further purification: IR ($CHCl_3$) 1627, 1551, 1398 and 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ3.50 (2H, broad t), 3.18 (2H, broad t) and 2.2–2.8 (5H, m including s at 2.68).

Example 30—Preparation of 5,6,7-trimethyl-1,2,4-triazolo[1,5a]pyrimidine-2-sulfonyl chloride
Chlorine was bubbled into a suspension of 28.4 g (0.100 mol) of 2-benzylthio-5,6,7-trimethyl-1,2,4-triazolo[1,5-a]pyrimidine in 200 ml of glacial acetic acid-H_2O (1:1, v/v) and cooled to −5°C. The chlorine addition continued over 35 minutes and the temperature of the reaction mixture never exceeded 5°C. After the addition was complete, the reaction mixture was stirred for 5 minutes and filtered. The solid collected was washed twice with H_2O and dried *in vacuo* to yield 24.3 g (93%) of the crude sulfonyl chloride as a pale yellow solid. The IR and ^{1}H NMR were consistent with the assigned structure. The crude sulfonyl chloride was used in subsequent transformations without further purification.

Example 31—Preparation of 6-chloro-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride
A suspension of 3.75 g (13.5 mmol) of 2-benzylthio-6-chloro-1,2,4-triazolo[1,5-a]pyrimidine in 40 ml of AcOH–H_2O (1:1, v/v) was cooled to −10°C and chlorine gas was bubbled into the reaction mixture for 10 minutes. After the addition was complete, the reaction mixture was stirred for 10 minutes and diluted with 25 ml of H_2O. The mixture was filtered and the filtrate was extracted with CH_2Cl_2. The organic phase was evaporated at reduced pressure to afford 2.14 g of the crude sulfonyl chloride as a liquid. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Example 32—Preparation of 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride
A suspension of 8.0 g (33 mmol) of 2-benzylthio-1,2,4-triazolo[1,5-a]pyrimidine in 60 ml of HOAc–H_2O (1:1, v/v) was cooled below 0°C and chlorine gas was bubbled into the reaction mixture for 15 minutes. The temperature of the reaction mixture was maintained below 10°C

during the course of the addition. After the addition was complete, the reaction mixture was stirred for 15 minutes, diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated at reduced pressure to yield 5.74 g of the desired crude product as a brown oil. IR and ^1H NMR were in agreement with the assigned structure.

Recrystallization from EtOAc gave an analytical sample, m.p. 105°–109°C.

Analysis:
Calculated for $C_5H_3ClN_4O_2S$: C, 27.45; H, 1.32; N, 25.62.
Found: C, 28.91; H, 1.52; N, 25.79.

Example 33—Preparation of 5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonylchloride

A suspension of 2.77 g (10.8 mmol) of 2-benzylthio-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine in 40 ml of AcOH–H_2O (1:1, v/v) was cooled to −10°C and chlorine gas was bubbled into the solution for 10 minutes. After the addition was complete, the reaction mixture was stirred for 5 minutes, diluted with H_2O (25 ml) and filtered. The solid collected was dried *in vacuo* to yield 1.17 g of the desired sulfonyl chloride. IR and ^1H NMR were in agreement with the assigned structure.

An additional quantity of the product contaminated with by-products containing benzyl residues was obtained by extraction of the filtrate with CH_2Cl_2 and evaporation of the organic phase at reduced pressure.

Example 34—Preparation of 5-methoxy-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

A suspension of 1.41 g (4.93 mmol) of 2-benzylthio-4-methoxy-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine in 40 ml of AcOH–H_2O (1:1, v/v) was cooled to −20°C, and chlorine gas was bubbled into the reaction mixture for 5 minutes. After the addition was complete, the reaction mixture was stirred for 10 minutes, diluted with H_2O (20 ml) and filtered. The solid collected was dried *in vacuo* to yield 0.63 g of the desired crude sulfonyl chloride as a colorless solid. IR and ^1H NMR were in agreement with the assigned structure.

Example 35—Preparation of 5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

A suspension of 3.52 g (13.7 mmol) of 2-benzylthio-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine in 40 ml of AcOH–H_2O (1:1, v/v) was cooled to −10°C, and chlorine gas was bubbled into the reaction mixture for 10 minutes. After the addition was complete, the reaction mixture was stirred for 10 minutes, diluted with H_2O and filtered. The solid collected was dried *in vacuo* to yield 0.46 g of the desired sulfonyl chloride as a tan solid. IR and ^1H NMR spectra were in agreement with the assigned structure.

An additional quantity (2.2 g) of crude sulfonyl chloride contaminated with by-products containing benzyl residues was obtained by extraction of the filtrate with CH_2Cl_2 and evaporation at reduced pressure.

Example 36—Preparation of 6-methyl-1,2,4-triazolo[1,5-a]pyrimide-2-sulfonyl chloride

A suspension of 10.0 (60 mmol) of 2-benzylthio-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine in 260 ml of methylene chloride, 100 ml of water and 17 ml of concentrated HCl was cooled to −5°C and treated with 284 ml (197 mmol) of 5.25% aqueous sodium hypochlorite (commercial bleach) by dropwise addition. After the addition was complete the reaction mixture was stirred for 20 minutes at 0°C and filtered. The organic layer was separated and the aqueous layer was extracted twice with methylene chloride. The combined organic phases were dried ($MgSO_4$) and evaporated at reduced pressure to yield 7.0 g (50%) of the desired product as a solid, mp 106–108°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_6H_5ClN_4O_2S$: C, 30.96; H, 2.15; N, 24.08
Found: C, 31.00; H, 2.23; N, 23.91

Example 37—Preparation of 6-chloro-5,7-dimethyl-1,2,4-triazol[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 50% yield from 2-benzylthio-6-chloro-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Examples 29–35. The product was isolated as a pale yellow solid, mp 131–133°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Example 38—Preparation of 6-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 82% yield from 2-benzylthio-6-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Examples 29–35. The product was isolated as

a solid, mp 134–137°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:

Calculated for $C_7H_7ClN_4O_3S$:	C, 31.96; H, 2.66; N, 21.31.
Found:	C, 32.64; H, 2.36; N, 21.30.

Example 39—Preparation of 5-isopropyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 56% yield from 2-benzylthio-5-isopropyl-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Example 36. The product was isolated as a solid, mp 60–62°C. IR and ^{1}HNMR spectra were in agreement with the assigned structure.

Analysis:

Calculated for $C_8H_9ClN_4O_2S$:	C, 36.85; H, 3.45; N, 21.49.
Found:	C, 37.02; H, 3.49; N, 21.71.

Example 40—Preparation of 5,6-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 80% yield from 2-benzylthio-5,6-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Example 36. The product was isolated as a solid, mp 116–120°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Exact mass calculated for $C_7H_7ClN_4O_2S$:	245.9984
Found:	245.9981

Example 41—Preparation of 6-chloro-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 60% yield from 2-benzylthio-6-chloro-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Examples 29–35. The product was isolated as a solid, mp 99–101°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Example 42—Preparation of 5-methoxyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 57% yield from 2-benzylthio-5-methoxyl-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Examples 29–35. The product was isolated as a solid, mp 110–112°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:

Calculated for $C_6H_5ClN_4O_3S$:	C, 28.97; H, 2.01; N, 22.53.
Found:	C, 29.90; H, 2.23; N, 22.76.

Example 43—Preparation of 5-(2,2,2-trifluoroethoxy)-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 74% yield from 2-benzylthio-5-(2,2,2-trifluoroethoxy)-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Examples 29–45. The product was isolated as a solid, mp 91–96°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Exact mass calculated for $C_7H_4ClF_3N_4O_3S$:	315.9655
Found:	315.9650

Example 44—Preparation of 5-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 74% yield from 2-benzylthio-5-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Examples 29–35. The product was isolated as a solid, mp 91–96°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Example 45—Preparation of 5-methoxy-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 80% yield from 2-benzylthio-5-methoxy-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure outlined in Examples 29–35. The product was isolated as a solid, mp 154–157°C. IR and ^{1}H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_7H_7ClN_4O_3S$: C, 32.00; H, 2.67; N, 21.33.
Found: C, 32.35; H, 2.61; N, 21.45.

Example 46—Preparation of 6-ethoxycarbonyl-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 82% yield from 2-benzylthio-6-ethoxycarbonyl-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Example 36. The product was isolated as a solid, mp 65–69°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_9H_9ClN_4O_4S$: C, 35.47; H, 2.95; N, 18.39
Found: C, 36.04; H, 3.02; N, 18.27

Example 47—Preparation of 6-(4-nitrophenyl)-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

This material was prepared in 71% yield from 2-benzylthio-6-(4-nitrophenyl)-1,2,4-triazolo[1,5-a]pyrimidine following the general procedure described in Examples 29–35. The product was isolated as a solid, mp 159–167°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Example 48—Preparation of 2-benzylthio-5,6-cyclopentano-7-hydroxy-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 20.6 g (100 mmol) of 3-amino-5-benzylthio-1,2,4-triazole and 15 ml (16 g, 0.10 mol) of 2-carboethoxycyclopentanone in 110 ml of glacial acetic acid was heated at reflux for 23 hours. After cooling to room temperature the solid which separated from the reaction mixture was collected by filtration, washed with acetic acid and dried *in vacuo* to yield 22.4 g (75%) of the desired product as a colorless crystalline solid, m.p. 241°–243°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78; S, 10.75.
Found: C, 60.10; H, 4.66; N, 18.91; S, 10.72.

Example 49—Preparation of 2-benzylthio-7-chloro-5,6-cyclopentano-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 5.97 g (20.0 mmol) of 2-benzylthio-5,6-cyclopentano-7-hydroxy-1,2,4-triazolo[1,5-a]pyrimidine in 250 ml of phosphorus oxychloride was heated at reflux for 50 minutes. After cooling to room temperature the excess phosphorous oxychloride was removed by distillation at aspirator pressure. The residue was partitioned between ice cold water and methylene chloride. The organic phase was dried (Na_2SO_4) and evaporated at reduced pressure. The residue was chromatographed on silica gel eluting with EtOAc-hexane (1:1, v/v) to yield 3.72 g (59%) of the desired product as a yellow solid, m.p. 119°–120°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{15}H_{13}ClN_4S$: C, 56.87; H, 4.14; N, 17.68; Cl, 11.19; 2, 10.12.
Found: C, 56.91; H, 4.06; N, 17.83; Cl, 10.68; S, 9.65.

Example 50—Preparation of 2-benzylthio-5,6-cyclopentano-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 2.47 g (7.80 mmol) of 2-benzylthio-7-chloro-5,6-cyclopentano-1,2,4-triazolo[1,5-a]pyrimidine in 40 ml of dry tetrahydrofuran was cooled to 5°C and 5.9 ml (17 mmol) of 2.9 M methyl magnesium bromide in ether was added over 5 minutes. After the addition was complete the reaction mixture was warmed to room temperature and stirred overnight (17 hours). The reaction was quenched by addition of 10 ml of saturated aqueous ammonium chloride. The organic phase was separated, dried (Na_2SO_4) and evaporated at reduced pressure. The red oil residue was chromatographed on silica gel (HPLC) eluting with EtOAc-hexane (1:1, v/v) to yield 1.12 g (48%) of the desired product as a pale red solid, m.p. 109°–111°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90; S, 10.82.
Found: C, 64.99; H, 5.41; N, 18.16; S, 10.42.

Example 51—Preparation of 2-benzylthio-5,7-bis-(trifluoromethyl)-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 20.8 g (0.100 mol) of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione and 20.6 g (0.100 mol) of 3-amino-5-benzylthio-1,2,4-triazole in 150 ml of glacial acetic acid was heated at reflux for 14 hours. The solution was cooled to room temperature and poured over ice. The solid which separated was collected by filtration, washed with water and dried *in vacuo* to yield 35.5 g (94%) of the desired product as a pale yellow solid, m.p. 78.5°–80.5°C. IR, ^1H NMR and ^{19}F NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_8F_6N_4S$: C, 44.45; H, 2.13; N, 14.81; S, 8.48.
Found: C, 44.53; H, 2.15; N, 14.97; S, 8.39.

Example 52—Preparation of 2-benzylthio-5-methyl-7-trifluoromethyl-1,2,4-triazolo[1,5-a]pyrimidine

This material was prepared in 84% yield from 3-amino-5-benzylthio-1,2,4-triazole and 1,1,1-trifluoro-2,4-pentanedione following the general procedure described in Example 34. The product was purified by recrystallization from benzene-hexane to yield a tan solid, m.p. 83.5°–84.5°C. IR, ^1H NMR and ^{19}F NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{14}H_{11}F_3N_4S$: C, 51.85; H, 3.42; N, 17.27; S, 9.89.
Found: C, 51.73; H, 3.44; N, 18.01; S, 10.08.

Example 53—Preparation of 2-benzylthio-5,7-diphenyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 8.40 g (37.5 mmol) of dibenzoylmethane and 7.73 g (37.5 mmol) of 3-amino-5-benzylthio-1,2,4-triazole in 50 ml of glacial acetic acid was heated at reflux for 24 hours. Upon cooling to room temperature the solid which separated was collected by filtration and dried. The product was chromatographed on silica gel (HPLC) eluting with EtOAc-hexane (3:7, v/v) to afford 5.08 g (34%) of the desired product as a colorless solid, m.p. 122.5°–123.5°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{24}H_{18}N_4S$: C, 73.07; H, 4.60; N, 14.20; S, 8.13.
Found: C, 73.48; H, 4.54; N, 14.17; S, 7.97.

Example 54—Preparation of 2-benzylthio-5-methyl-7-phenyl-1,2,4-triazolo[1,5-a]pyrimidine and 2-benzylthio-7-methyl-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidine

A solution of 20.6 g (100 mmol) of 3-amino-5-benzylthio-1,2,4-triazole and 16.2 g (100 mmol) of benzoyl acetone in 100 ml of glacial acetic acid was heated at reflux for 14 hours. The solvent was removed by evaporation at reduced pressure and the residue was chromatographed on silica gel (HPLC) eluting with EtOAc-hexane (3:7, v/v) to afford 4.81 g (14%) of 2-benzylthio-7-methyl-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidine as a pale yellow wolid, m.p. 154°–155°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

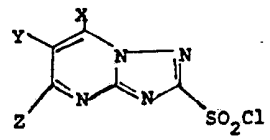
Analysis:
Calculated for $C_{16}H_{16}N_4S$: C, 68.65; H, 4.85; N, 16.85; S, 9.65.
Found: C, 68.76; H, 4.82; N, 16.98; S, 9.93.

Further elution afforded 22.8 g (69%) of 2-benzylthio-5-methyl-7-phenyl-1,2,4-triazolo[1,5-a]pyrimidine as a pale yellow solid, m.p. 110°–111°C. IR and ^1H NMR spectra were in agreement with the assigned structure.

Analysis:
Calculated for $C_{19}H_{16}N_4S$: C, 68.65; H, 4.85; N, 16.85; S, 9.65.
Found: C, 68.52; H, 4.75; N, 16.93; S, 9.61.

CLAIMS

1. A compound having the formula



(I)

wherein X, Y and Z independently represent hydrogen, alkyl, haloalkyl, alkoxy, haloalkoxy, halogen, aryl, substituted aryl or two adjacent substituents selected from X, Y and Z are joined together in a cyclic structure, with the proviso that when Y is hydrogen, X and Z may not simultaneously be alkyl.

2. A compound as claimed in claim 1 wherein X, Y and Z independently represent hydrogen, halo, C_1–C_4 alkyl or C_1–C_4 alkoxy.

3. A compound as claimed in claim 1 wherein X is methyl and Y and Z are hydrogen.

4. A compound as claimed in claim 1 wherein Y is methyl and X and Z are hydrogen.

5. A compound as claimed in claim 1 wherein Z is methyl and X and Y are hydrogen.

6. A compound as claimed in claim 1 wherein Y is chloro and X and Z are hydrogen.

7. A compound as claimed in claim 1 which is 6,7-cyclopentano-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride

8. A compound as claimed in claim 1 which is 5,6,7-trimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

9. A compound as claimed in claim 1 which is 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

10. A compound as claimed in claim 1 which is 5-methoxy-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

11. A compound as claimed in claim 1 which is 6-chloro-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

12. A compound as claimed in claim 1 which is 6-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

13. A compound as claimed in claim 1 which is 5-isopropyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

14. A compound as claimed in claim 1 which is 5,6-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

15. A compound as claimed in claim 1 which is 6-chloro-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

16. A compound as claimed in claim 1 which is 5-methoxy-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

17. A compound as claimed in claim 1 which is 5-(2,2,2-trifluoroethoxy)-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

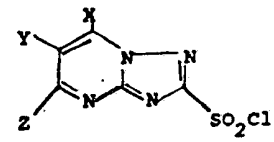
18. A compound as claimed in claim 1 which is 5-ethoxy-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

19. A compound as claimed in claim 1 which is 5-methoxy-6-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

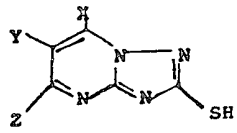
20. A compound as claimed in claim 1 which is 6-ethoxycarbonyl-7-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

21. A compound as claimed in claim 1 which is 6-(4-nitrophenyl)-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride.

22. A process for preparing a sulfonyl chloride of the formula 1

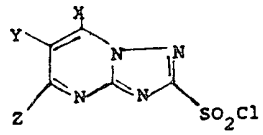


wherein X, Y and Z are as defined in claim 1 which comprises reacting a mercaptan of the formula

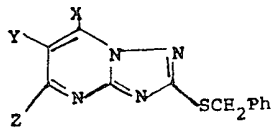


wherein X, Y and Z are as defined above either (a) with Cl_2 in an aqueous acidic medium or (b) with sodium hypochlorite in a two phase system of aqueous hydrochloric acid and methylene chloride at a temperature in the range of from −20°C to 25°C.

23. A process for preparing a sulfonyl chloride of the formula



wherein X, Y and Z are as defined in claim 1 which comprises reacting a benzyl sulfide of the formula



wherein X, Y and Z are as defined above, either (a) with Cl_2 in an aqueous acidic medium or (b) with sodium hypochlorite in a two phase system of aqueous hydrochloric acid and methylene chloride at a temperature in the range of from −20°C to 25°C.

24. A process as claimed in claim 22 or 23 wherein the reactions (a) as defined are carried out at a temperature in the range of from −20° to 0°C.

25. A process as claimed in any one of claims 22 to 24 wherein the reactions (a) as defined are carried out in aqueous acetic acid or aqueous hydrochloric acid.

26. A process as claimed in claim 22 or 23 wherein the reactions (b) as defined are carried out at a temperature in the range of −5°C to +5°C.

27. A process for preparing a sulfonyl chloride as claimed in claim 1 substantially as herein-before described with reference to any one of Examples 29 to 47.

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