Methods for Controlling the Regioselection in the Reaction of 3-Amino-5-benzylthio-1,2,4-triazole with Acetylacetaldehyde Dimethyl Acetal

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The reaction of 3-amino-5-benzylthio-1,2,4-triazole with acetylacetaldehyde dimethyl acetal affords 2-benzylthio-5-methyl-1,2,4-triazolo[1,5a]pyrimidine or 2-benzylthio-7-methyl-1,2,4-triazolo[1,5a]pyrimidine regioselectively depending on the reaction conditions.

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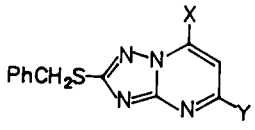
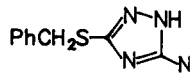
Recently we have reported the discovery of a new class of herbicides which contain the 1,2,4-triazolo[1,5-*a*]pyrimidine ring system as a central structural element [2]. These materials disrupt the biosynthesis of the branched chain amino acids by inhibiting acetolactate synthetase (EC 4.1.3.18). As part of that research effort we have needed a number of intermediate 2-benzylthio-1,2,4-triazolo[1,5-*a*]-pyrimidines (*e.g.* **1**) substituted in the 5-, 6- and 7-positions with a variety of substituents. This report details our efforts to develop syntheses of 2-benzylthio-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**1a**) and 2-benzylthio-7-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**1b**).

The most straightforward approach to **1** involves the reaction of 3-amino-5-benzylthio-1,2,4-triazole (**2**) with acetylacetaldehyde dimethyl acetal (**3**). The reaction of a number 3-amino-1,2,4-triazoles with **3** is reported to yield mixtures of isomeric 5- and 7-methyl 1,2,4-triazolo[1,5-*a*]-pyrimidines [3]. The selectivity in these reactions generally favors the formation of the 5-methyl isomer to a modest extent (2-3:1) [4]. In fact we have observed poor selectivity (2:1) in favor of the formation of **1a** in the reaction of **2** with **3** under standard conditions (*i.e.* glacial acetic acid at reflux). We have now found sets of reaction conditions which allow for the regiospecific synthesis of **1a** and the highly regioselective synthesis of **1b**.



1

a: X = H, Y = Me
b: X = Me, Y = H



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We have observed that the reaction of **2** with acetal **3** yields exclusively the 5-methyl isomer **1a** in the presence of sodium ethoxide. Compound **1a** precipitated (74% yield) from the reaction mixture obtained by addition of a solution of one equivalent of **3** in ethanol to a solution of one equivalent of **2** in ethanol containing one-half of an equivalent of sodium ethoxide. None of the isomeric 7-methyl isomer **1b** could be detected in the reaction. The structure of **1a** was assigned on the basis of the comparison of ^{1}H nmr spectral data to that of known model compounds [5]. Final confirmation of the structure was made by a single crystal X-ray analysis [1c]. Tables 1 and 2 contain the atomic coordinates, bond lengths and bond angles for **1a**. A stereoscopic drawing of **1a** is presented in Figure 1.

The mechanism to account for the regioselection in this base catalyzed formation of **1a** is unclear. The regiochemistry can be established in two ways. Mechanisms initiated by reaction of the exocyclic nitrogen of **2** with the ketone carbonyl group in **3** or the reaction of the anion of **2** with a product of base catalyzed elimination of methanol from **3** will lead ultimately to the production of **1a**. We favor the later mechanism due to the base catalyzed nature of the reaction.

For the synthesis of **1b** we began by considering a mechanistic explanation for the lack of high degrees of regiocontrol in the reaction of aminoazoles with **3** under standard conditions as described in the literature [3]. As applied to the present example it is illustrated in Scheme I. It is reasonable to assume that the first step in the reaction of **2** with **3** produces intermediate(s) **4** and/or **5**. Direct ring closure of **4** and **5** produce **1a** and **1b** respectively. However, it has been suggested that the direct ring closures of **4** and **5** are slow in relation to their reaction

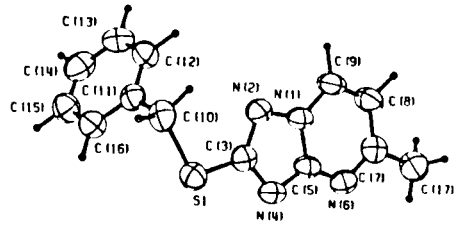

Figure 1. ORTEP drawing of **1a**.

Table 1

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

Atom	x/a	y/b	z/c	Atom [a]	x/a	y/b	z/c
S1	636(2)	8188(0)	5887(2)	H(C8)	-6763	10330	942
N1	-3282(6)	9347(1)	3102(5)	H(C9)	-6705	9532	-196
N2	-2860(6)	8878(1)	2884(5)	H(C10)	-2893	7977	2090
C3	-748(8)	8764(1)	5020(7)	H(C10)	-833	7529	3459
N4	196(6)	9116(1)	6537(5)	H(C12)	-3376	8378	-521
C5	-1418(7)	9485(2)	5307(7)	H(C13)	-1682	8624	-1827
N6	-1402(7)	9929(1)	5965(6)	H(C14)	2699	8457	405
C7	-3326(9)	10226(2)	4388(8)	H(C15)	5338	8015	3849
C8	-5296(8)	10087(2)	2122(7)	H(C16)	3686	7768	5169
C9	-5262(8)	9645(2)	1476(7)	H(C17)	-3849	10994	3878
C10	-978(8)	7904(1)	3275(7)	H(C17)	-1718	10777	6671
C11	25(8)	8061(1)	2430(7)	H(C17)	-4835	10751	4743
C12	-1484(8)	8306(2)	432(8)				
C13	-513(10)	8445(2)	-308(7)				
C14	1964(10)	8347(2)	935(9)				
C15	3485(8)	8102(2)	2914(8)				
C16	2534(9)	7958(2)	3665(7)				
C17	-3334(8)	10716(2)	5111(7)				

[a] Hydrogen parameters were not refined.

with an additional molecule of **2** to form an intermediate such as **6** [3,4]. Consequently the regiochemical outcome of this reaction is determined by the selectivity in the conversion of **6** to **1a** and/or **1b**. This proposal is consistent with the modest regioselection in favor of the 5-methyl isomer observed in these reactions.

Scheme I

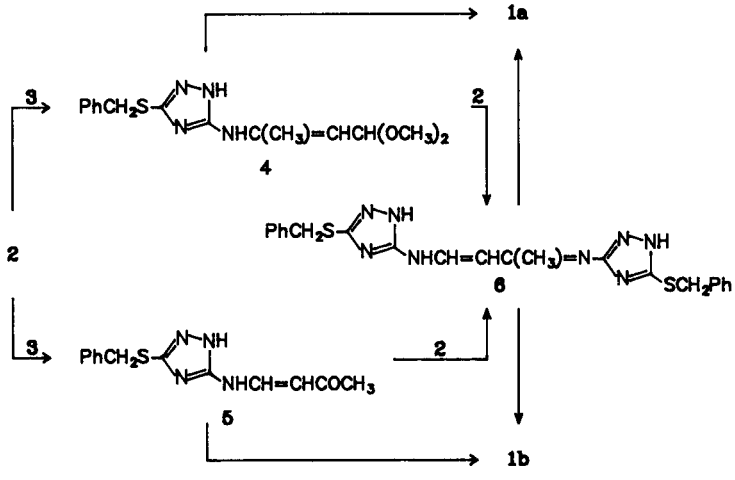

Table 2

Bond Lengths (Å) and Bond Angles (°) for **1a**
(See Figure 1 for Atom Numbering)

Bond Lengths		Bond Angles	
S1- 3	1.733(5)	10-S1- 3	101.9(2)
S1-10	1.811(4)	5- 1- 2	110.4(3)
1- 2	1.372(5)	9- 1- 2	127.8(3)
1- 5	1.376(5)	9- 1- 5	121.7(4)
1- 9	1.354(6)	3- 2- 1	100.7(3)
2- 3	1.339(6)	2- 3-S1	123.3 (3)
3- 4	1.350(6)	4- 3-S1	120.1 (3)
4- 5	1.328(6)	4- 3- 2	116.4(4)
5- 6	1.343(6)	5- 4- 3	103.5(3)
6- 7	1.328(7)	4- 5- 1	108.9(4)
7- 8	1.412(6)	6- 5- 1	122.1(4)
7-17	1.488(7)	6- 5- 4	129.0(4)
8- 9	1.347(7)	7- 6- 5	116.8(4)
10-11	1.502(10)	8- 7- 6	122.0(5)
11-12	1.380(6)	17- 7- 6	117.0(4)
11-16	1.391(10)	17- 7- 8	120.9(5)
12-13	1.381(11)	9- 8- 7	120.6(5)
13-14	1.366(12)	8- 9- 1	116.7(4)
14-15	1.369(7)	11-10-S1	113.8(3)
15-16	1.379(11)	12-11-10	121.8(6)
		16-11-10	120.0(4)
		16-11-12	118.3(7)
		13-12-11	120.5(6)
		14-13-12	120.6(5)
		15-14-13	119.7(8)
		16-15-14	120.3(7)
		15-16-11	120.6(4)

If the conditions for the reaction of **2** with **3** could be altered to make the direct ring closure of intermediates **4** and **5** fast in comparison to the formation of **6**, the regiochemical outcome of the reaction could be effected. It is reasonable to assume that the reaction of **2** to form **5** is faster than the formation of **4** [3,4]. The selective formation of 7-methyl isomer **1b** would be the outcome if the first step in the sequence was rate determining.

One approach to effecting this change in relative reaction rates to test the validity of the mechanism in Scheme I is to add **2** slowly to a reaction mixture containing **3**. Keeping the concentration of **2** low should suppress the formation of **6**. Indeed we have now found that this slow addition procedure yields a 5:1 mixture of **1b** to **1a**. A pure sample of **1b** was isolated in 63% yield by a simple recrystallization.

We have developed syntheses of **1a** and **1b** which are amenable to the production of sizeable quantities of these materials. Some of the mechanistic principles presented in this report may be useful in predicting the regiochemical outcome of other reactions of aminoazoles with 1,3-dicarbonyl compounds or their derivatives. Future reports will describe the use of these intermediates in the synthesis of biologically active materials [6].

EXPERIMENTAL

General Methods.

All melting points are uncorrected. The ^{1}H nmr chemical shifts are expressed as delta values (ppm) relative to TMS 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 (**2**) [7] was prepared in 83% yield following a previously described general procedure [8].

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

Sodium (9.20 g, 0.400 g-atom) was dissolved in 800 ml of absolute ethanol and 165 g (0.800 mole) of **2** was added. After stirring for 10 minutes, a solution of 118 ml (106 g, 0.800 mole) of acetylacetaldehyde dimethyl acetal in 80 ml of absolute ethanol was added dropwise over 1 hour. After the addition was complete, the red solution was stirred at room temperature for 72 hours. The solid which separated was collected by filtration, washed with ethanol and dried under vacuum to afford 151 g (74%) of **1a** as a red-brown crystalline solid, mp 130-131°; ir (chloroform): 1620, 1529, 1343, 1265 cm^{-1}; ^{1}H nmr (deuteriochloroform) δ 8.46 (1 H, d, J = 7.5 Hz), 7.1-7.7 (5 H, m), 6.79 (1 H, d, J = 7.5 Hz), 4.49 (2 H, s), 2.62 (3 H, s).

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 61.01; H, 4.57; N, 21.87.

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

A solution of 50 g (0.24 mole) of **2** in 500 ml of glacial acetic acid was added dropwise over 6.5 hours to a stirred solution of 34 g (0.26 mole) of acetylacetaldehyde dimethyl acetal in 500 ml of glacial acetic acid at 100°. The resulting solution was heated at 95° for 17 hours, cooled to room temperature and poured onto an ice-water mixture. The solid which separated was collected by filtration, washed with water and dried under vacuum to afford 47.6 g (77%) of a crude mixture of **1b** and **1a** (5:1) as determined by ^{1}H nmr. The crude product was recrystallized from ethanol to afford 39 g (63%) of **1b** as golden needles, mp 103-104°; ir (potassium bromide): 1615, 1550, 1355, 1305 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.59 (1 H, d, J = 4.8 Hz), 7.2-7.6 (5 H, m), 6.85 (1 H, d, J = 4.8 Hz), 4.55 (2 H, s), 2.79 (3 H, s).

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.81; H, 4.68; N, 21.74.

Single Crystal X-ray Analysis of **1a**.

A representative crystal was surveyed and a 1-Å data set (maximum sin $\theta/\lambda = 0.5$) was collected on a Syntex P1 diffractometer. The diffractometer was equipped with a graphite monochrometer and copper radiation ($\lambda = 1.5418$ Å). Atomic scattering factors were taken from the "International Tables for X-ray Crystallography" [9], except hydrogen which was taken from Stewart, Davidson and Simpson [10]. All crystallographic calculation were facilitated by the CRYM system [11]. All diffractometer data were collected at room temperature.

A trial structure was obtained by direct methods using the MULTAN program [12]. This trial structure refined routinely. 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 0.0 of their corresponding standard deviation. A final difference Fourier revealed no missing or displaced electron density. The refined structure was plotted using the ORTEP computer program of Johnson [13].

Supplementary Material Available.

Complete experimental details and data for the single crystal X-ray analysis of **1a** is available from one of the authors (JB).

REFERENCES AND NOTES

[1a] Dow Chemical U.S.A. [b] Current address: Chemical and Agricultural Products Department, Abbott Laboratories, North Chicago, IL 60064. [c] Address all correspondence to this author. [d] North Carolina State University. Address correspondence regarding the X-ray structure of **1a** to this author at Central Research, Pfizer Inc., Groton, CT 06340.

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[5] The coupling constants for the hydrogens in the 6- and 7- positions in **1a** and the 5- and 6-positions in **1b** are 7.5 and 4.8 Hz respectively. This is in agreement with expected values based on observations described in reference [3].

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