The Synthesis and Dimroth-Type Rearrangement of 5,7-Bis(dimethylamino)-3-(methylthio)-*s*-triazolo[4,3-*a*]-*s*-triazine

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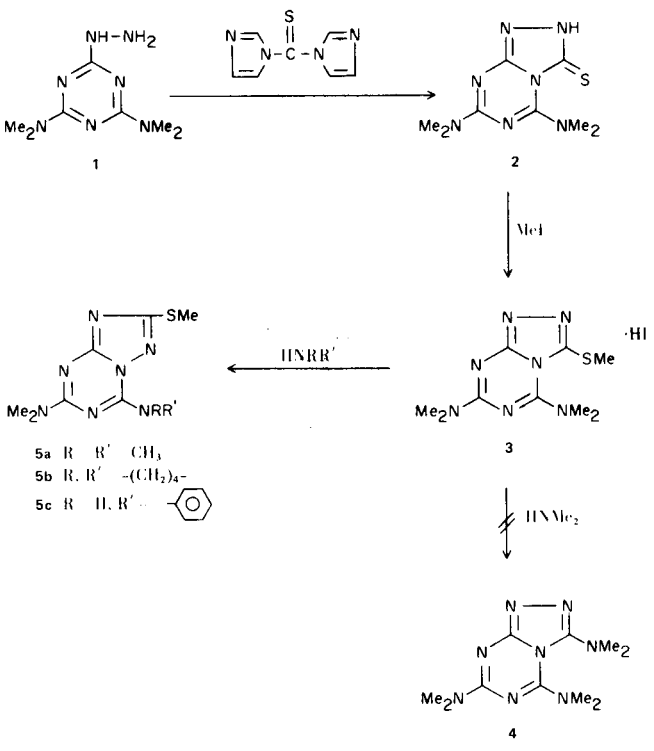
Since the discovery of the highly active insect sterilant, 2,4,6-tris(dimethylamino)-*s*-triazine (2), we have synthesized and screened over 300 additional *s*-triazine derivatives (3) as well as a variety of other dimethylamino-substituted heterocyclic compounds (4). To further study new *s*-triazine derivatives, we attempted a synthesis of 3,5,7-tris(dimethylamino)-*s*-triazolo[4,3-*a*]-*s*-triazine (**4**), a bicyclic compound incorporating the *s*-triazine ring.

Our approach to **4** is outlined in Scheme 1. Treatment of the readily available 2-chloro-4,6-bis(dimethylamino)-*s*-triazine (5) with hydrazine provided **1** which was condensed with 1,1′-thiocarbonyldiimidazole to give the bicyclic thione **2**. Alkylation of **2** with methyl iodide provided the HI salt **3**.

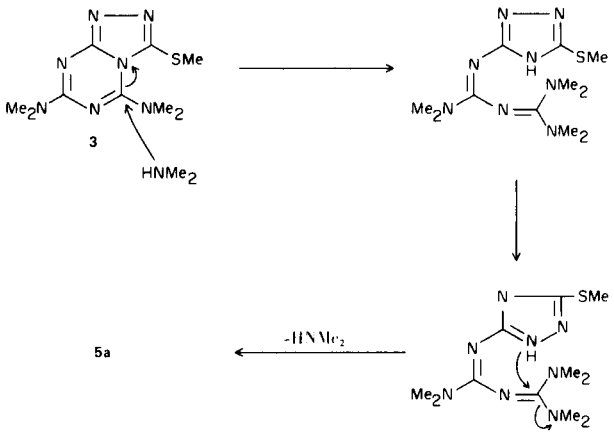
SCHEME 1



We have frequently employed alkyl mercaptans as leaving groups for the addition of amines to heterocycles (4a,6), but in this case, reaction of **3** with excess anhydrous dimethylamine in absolute ethanol at 85° gave an 88% yield of a new compound (**5a**) whose nmr spectrum indicated that the *s*-methyl group had been retained (δ 2.61) and that the molecule still contained two dimethylamino groups (δ 3.17 and 3.47; nmr of **3** as its free base has δ 2.72 (3H), 3.04 (6H), and 3.22 (6H)). The elemental analysis of this compound confirmed that it was an isomer of the free base of **3**. The most probable explanation of this isomerization seemed to be a Dimroth-type rearrangement of the *s*-triazolo[4,3-*a*]-*s*-triazine system (7,8, Scheme 1).

That the product was indeed 5,7-bis(dimethylamino)-2-(methylthio)-*s*-triazolo[2,3-*a*]-*s*-triazine (**5a**) was confirmed by a single-crystal X-ray diffraction analysis.

SCHEME 2



Base-catalyzed Dimroth rearrangements generally occur through attack on the six-membered ring by hydroxide ion, ring opening, and finally condensation of the newly formed carbonyl group with a different nitrogen in the five-membered ring (7). Since no water was present in

our case, it appears that dimethylamine must have effected the ring-opening to an unsaturated guanidine as shown in Scheme 2.

Reaction of **3** with pyrrolidine and with aniline supported the mechanism in Scheme 2. In each case the rearranged system was isolated, and in each case the dimethylamino group at position 7 had been replaced by the reactant amine (these reactions were run in open systems allowing dimethylamine to escape). Although we have not determined the full scope of this reaction, the method appears to offer considerable synthetic value for the preparation of *s*-triazolo[2,3-*a*]-*s*-triazines, particularly since syntheses of the latter system from aminotriazoles often suffer from the variety of products of competing reactions with various aminotriazole nitrogens (9). Furthermore, the availability of a wide variety of symmetrically and unsymmetrically substituted *s*-triazines (10) as suitable starting materials could make this the method of choice for the preparation of numerous derivatives of this system.

Dimroth rearrangements can also be acid catalyzed (7), and indeed we have found the rearrangement of **3** to occur in an acidic medium. An aqueous solution of **3** rearranged very slowly at 100°, but after 16 hours at 110° followed by neutralization, an 85:15 mixture of **5a** and **3** (free base) was obtained. Only a 53% yield was realized, however, and a highly insoluble, unidentified product was also formed.

X-ray Crystallographic Analysis of **5a**.

The structure (**5a**) was completely corroborated by a single-crystal X-ray diffraction analysis. Small crystals of the material were grown from an acetone-cyclohexane mixture, and X-ray intensity data were collected on an automatic diffractometer using MoKα X-rays. The diffraction pattern indicated the space group could be either C2/c (centric) or Cc (acentric), with four molecules per unit cell. Four molecules can fit into a C2/c cell only if each molecule possesses a 2-fold rotation axis or a center of symmetry, neither of which was considered likely in this case. Thus, the analysis of the data was begun with the assumption that the symmetry was Cc, and this proved to be correct.

The molecular structure of **5a** was obtained directly from the data by applying the symbolic addition procedure for noncentric crystals (11) to a set of 1358 intensities. The atomic identities and the positions of all 15 hydrogen atoms were confirmed by refinement of the model to an R-factor (agreement factor) of less than 0.05. The nonhydrogen atoms of the molecule are almost completely coplanar; none of the terminal methyl groups are rotated out of the plane by more than 10 degrees. The final stages of refinement are in progress, and complete structural details will be published later.

EXPERIMENTAL (12,13)

2,4-Bis(dimethylamino)-6-hydrazino-*s*-triazine (**1**).

A mixture of 2-chloro-4,6-bis(dimethylamino)-*s*-triazine (80.6 g.) (5), hydrazine hydrate (85%, 89 g.) and 95% ethanol (500 ml.) was refluxed for 2.5 hours. The solvent was removed *in vacuo* and the residue triturated with 150 ml. of water. The insoluble product was collected by filtration, washed with water, and recrystallized from 95% ethanol to give 74.2 g. (79%) of colorless crystals melting at 148.5-152.5°.

Anal. Calcd. for $C_7H_{15}N_7$: C, 42.64; H, 7.67; N, 49.72. Found: C, 42.73; H, 7.56; N, 49.64.

5,7-Bis(dimethylamino)-*s*-triazolo[4,3-*a*]-*s*-triazine-3(2*H*)thione (**2**).

A finely pulverized portion of **1** (28.4 g.) was rapidly added to a stirred solution of 1,1'-thiocarbonyldiimidazole (25.6 g.) (14) in acetonitrile (1 l.) An exothermic reaction occurred and a new solid began to separate almost immediately. The warm mixture was quickly heated to reflux, boiled two minutes (total reaction time *ca.* 11 minutes), then quickly chilled. The solid (**2**, 19.8 g., m.p. 181.5° dec.) was collected and washed with acetonitrile. By heating the filtrate on a steam bath for 1 hour, then cooling to 5°, an additional 2.7 g. of **2** was obtained (65% overall yield). A mass spectrum confirmed a molecular weight of 239. An analytical sample was recrystallized from acetonitrile, m.p. 191° dec.

Anal. Calcd. for $C_8H_{13}N_7S$: C, 40.15; H, 5.47; N, 40.97; S, 13.40. Found: C, 40.04; H, 5.50; N, 40.98; S, 13.39.

5,7-Bis(dimethylamino)-3-(methylthio)-*s*-triazolo[4,3-*a*]-*s*-triazine Monohydriodide (**3**).

A mixture of thione **2** (15 g.), methyl iodide (8.85 g.), and acetone (600 ml.) was refluxed for 45 minutes. Concentration of the reaction mixture and cooling provided 19.3 g. (82%) of crystalline **3**, m.p. 189-190.5°. Recrystallization from hexane-ethanol gave an analytical sample. The nmr spectrum (dimethyl sulfoxide-d_6) consisted of singlets at δ = 2.69 (S-CH_3, 3H) and δ = 3.12 (N(CH_3)$_2$, 6H) and a doublet centered at δ = 3.26 (N(CH_3)$_2$, 6H).

Anal. Calcd. for $C_9H_{15}N_7S$·HI: C, 28.36; H, 4.23; N, 25.72; S, 8.41. Found: C, 28.34; H, 4.05; N, 25.90; S, 8.19.

Free Base of **3**.

The free base was obtained by dissolving the hydriodide in a small volume of water, neutralizing the solution with sodium bicarbonate and extracting the aqueous phase with chloroform. Evaporation of the dried (magnesium sulfate) chloroform layer and recrystallization of the oily residue from ethyl acetate gave colorless needles, m.p. 138° with subsequent resolidification and remelting at 148-150°. The nmr spectrum (deuteriochloroform) contained a singlet at δ = 2.72 (S-CH_3, 3H) and two singlets ((CH_3)$_2$N groups) at δ = 3.04 (6H) and δ = 3.22 (6H).

Anal. Calcd. for $C_9H_{15}N_7S$: C, 42.68; H, 5.97; N, 38.71; S, 12.65. Found: C, 42.99; H, 5.69; N, 38.75; S, 12.45.

5,7-Bis(dimethylamino)-2-(methylthio)-*s*-triazolo[2,3-*a*]-*s*-triazine (**5a**).

A mixture of **3** (4.56 g.), anhydrous dimethylamine (1.5 g.) and absolute ethanol (20 ml.) was heated in a sealed tube at 85° for 6.25 hours. After allowing the mixture to stand for 16 hours at room temperature the solvent was removed. The solid residue was triturated with a small volume of dilute sodium bicarbonate

and the insoluble solid was extracted with chloroform. Evaporation of the solvent gave 2.66 g. (88%) of **5a**, m.p. 136-138.5°.

Both the ir spectrum and tlc mobility of this material were markedly different than those of the free base of **3**. The nmr spectrum (deuteriochloroform) contained a singlet at δ = 2.61 (S-CH_3, 3H) and two singlets ($(CH_3)_2N$ groups) at δ = 3.17 (6H) and δ = 3.47 (6H).

Anal. Calcd. for $C_9H_{15}N_7S$: C, 42.68; H, 5.97; N, 38.71; S, 12.65. Found: C, 42.68; H, 6.00; N, 38.89; S, 12.55.

Acid Catalyzed Rearrangement of **3**.

A sample of **3** (0.94 g.) in water (10 ml.) was heated in a sealed tube at 110° for 16 hours. The solution was made alkaline with sodium carbonate and extracted with chloroform (3 x 15 ml.). The combined chloroform portions were washed with brine, dried, and evaporated to give 0.33 g. (53%) of product, m.p. 117-129°. Although the ir spectrum was essentially identical to that of **5a**, the nmr spectrum indicated the presence of *ca.* 15% of unrearranged material. Recrystallization from hexane-ethyl acetate gave a sample melting at 130-133°. Nmr and tlc data indicated this material to be *ca.* 90% **5a**.

5-(Dimethylamino)-7-(1-pyrrolidinyl)-2-(methylthio)-*s*-triazolo[2,3-*a*]-*s*-triazine (**5b**).

A mixture of **3** (381 mg.), pyrrolidine (184 mg.), and absolute ethanol (12 ml.) was heated under reflux for 8 hours. Evaporation of the solvent under reduced pressure yielded a solid residue that was triturated with a small volume of aqueous sodium bicarbonate. Extraction of the water-insoluble product with chloroform and evaporation of the solvent gave 216 mg. (77%) of **5b**, m.p. 163-177°, *ca.* 95% pure by tlc. Recrystallization from hexane-ethyl acetate gave colorless needles, m.p. 186-192.5°. The nmr spectrum (deuteriochloroform) contained a singlet at δ = 2.60 (S-CH_3, 3H), a singlet at δ = 3.16 ($(CH_3)_2N$, 6H) and 2 multiplets (methylene protons of pyrrolidine) centered at δ = 1.96 (4H) and δ = 3.97 (4H).

Anal. Calcd. for $C_{11}H_{17}N_7S$: C, 47.28; H, 6.13; N, 35.09. Found: C, 47.16; H, 6.10; N, 35.23.

7-(Anilino)-5-(dimethylamino)-2-(methylthio)-*s*-triazolo[2,3-*a*]-*s*-triazine (**5c**).

A mixture of **3** (1.154 g.), aniline (0.734 g.) and absolute ethanol (30 ml.) was refluxed for 24.5 hours. The work-up procedure was essentially the same as for **5b** with the exception that moderate heating (80-90°) and reduced pressure (0.5 mm.) was used to remove excess aniline from the crude product. The oily residue was recrystallized from heptane-ethyl acetate to give 0.485 g. (53%) of colorless needles, m.p. 158-160°. A second recrystallization from heptane-ethyl acetate gave an analytical sample, m.p. 159.5-160.5°.

Anal. Calcd. for $C_{13}H_{15}N_7S$: C, 51.79; H, 5.02; N, 32.53. Found: C, 51.94; H, 4.87; N, 32.66.

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(13) Mention of a proprietary product or company does not imply endorsement by the U.S. Department of Agriculture.

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