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A new synthesis for the title compound that gives an 80% overall yield was developed. Treatment of triaminoguanidine monohydrochloride (**1**) with 2,4-pentanedione (**2**) gave 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine (**3**) in 80-85% yield. Oxidation of **3** with nitric oxide or nitrogen dioxide to 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**4**) followed by ammonolysis of **4** gave 3,6-diamino-1,2,4,5-tetrazine (**5**) in quantitatively yields.

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In a previous communication [1] from this laboratory we reported a synthesis of 3,6-diamino-1,2,4,5-tetrazine (**5**) starting initially with 1,3-diaminoguanidine monohydrochloride and 2,4-pentanedione (**2**) that gave 45-50% yields, which was a significant improvement over earlier methods [2] that gave yields of 10-13%. We subsequently found a literature report [3] that triaminoguanidine nitrate reacts with **2** to give a 32% yield of 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine (**3**), which was oxidized with hydrogen peroxide in acetic acid to 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**4**) in 6% yield. We suspected that ammonolysis of **4** may be a superior alternate route to **5** if the yields of **3** and **4** could be significantly improved (Scheme 1).

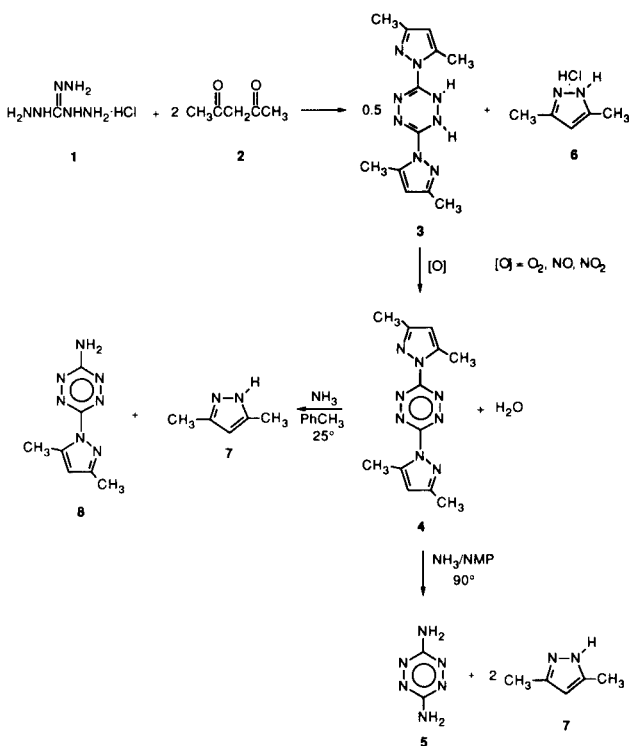
We optimized the reaction of triaminoguanidine monohydrochloride (**1**) with two equivalents of **2** in water at 70° for four hours to give **3** in 80-85% yields along with 3,5-dimethyl-1*H*-pyrazole hydrochloride (**6**). The use of organic solvents that have some solubility for **3** led to significantly lower yields. The mechanism of the tetrazine ring formation is probably similar to that given for the reaction 1,3-diaminoguanidine monohydrochloride with **2** [1].

For the oxidation of **3** to **4**, we desired a simple method that would leave the product with no interfering by-products in a solvent suitable for subsequent ammonolysis of **4** to **5**. The oxidation **3** to **4** with molecular oxygen at 500 psig was studied in 1,4-dioxane, 1,2-dichloroethane, sulfolane, and 1-methyl-2-pyrrolidinone (NMP). The reaction was found to be much faster in NMP than the other solvents, but still very slow (24 hours for complete conversion) at ambient temperature in this solvent. At 90° in NMP the reaction was complete in 0.5 hour, but significant hydrolytic by-products (~20%) were observed in the product by nmr analysis. These by-products were also observed in lesser amounts in the reactions run at ambient temperature.

We were pleased to find nitric oxide to be an effective reagent for the oxidation of **3** to **4** in NMP. A 0.5 molar slurry of **3** in NMP under an excess of nitric oxide at 50 psig required one hour for complete conversion to **4** with no trace of by-products. Alternatively, nitric oxide could be bubbled rapidly through such a slurry of **3** in NMP for one hour to give a 99% yield of pure **4**.

Although nitric oxide is a suitable oxidant for the conversion of **3** to **4**, the reagent of choice for this oxidation is nitrogen dioxide because the reaction is essentially instantaneous, quantitative, clean, and nearly stoichiometric with this reagent, which is less expensive and more readily available than nitric oxide. When a one molar slurry of **3** was treated with an equimolar amount of nitrogen dioxide, approximately 70% conversion of **3** to **4** was observed. Some of the nitrogen dioxide probably reacted with the

Scheme 1



water formed in the oxidation to prevent complete conversion under these conditions. Complete conversion of **3** to **4** occurred when the slurry was treated with two molar equivalents of nitrogen dioxide. A sample of the gas that is formed during the reaction was trapped and shown by mass spectrometric analysis to be mostly nitric oxide.

The ammonolysis of **4** to **5** and 3,5-dimethyl-1*H*-pyrazole (**7**) was found to be quantitative when a slurry of **4** in NMP was heated in a pressure reactor with an excess of ammonia at 90° for six hours. Furthermore, a one-pot process for the conversion of **3** to **5** in NMP was developed. When the ammonolysis of **4** was performed at atmospheric pressure and ambient temperature in toluene, 3-amino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**8**) was obtained in quantitative yield (Scheme 1). Thus, **4** and **8** may be useful intermediates for the synthesis of unsymmetrically substituted 1,2,4,5-tetrazines.

EXPERIMENTAL

Guanidine hydrochloride (95%), hydrazine monohydrate (98%), and 2,4-pentanedione (99 + %) were purchased from the Aldrich Chemical Company. All nmr spectra were obtained on a JEOL GSX-270 spectrometer. Chemical shifts are relative to internal tetramethylsilane = 0 for the ¹H and ¹³C nmr spectra and to external nitromethane = 0 for the ¹⁵N nmr spectra. Microanalyses were performed at Los Alamos National Laboratory by M. J. Naranjo. All melting points were determined at 2°/minute with a Mettler FPI apparatus and are corrected.

Triaminoguanidine Monohydrochloride (**1**).

To a slurry of guanidine hydrochloride (19.1 g, 0.20 mole) in 1,4-dioxane (100 ml) was added hydrazine monohydrate (34.1 g, 0.68 mole) with stirring. The mixture was heated under reflux for 2 hours. After the mixture cooled to ambient temperature, the product was collected by filtration, washed with 1,4-dioxane, and dried to give 27.7 g (98%) of pure **1**, mp 230° (lit mp 228° [4]); ¹³C nmr (deuterium oxide): δ 160.8; ¹⁵N nmr (deuterium oxide): δ -290.1, -331.7.

Anal. Calcd. for CH₇ClN₆: C, 8.54; H, 6.45; N, 59.78. Found: C, 8.59; H, 6.69; N, 59.55.

3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine (**3**).

To a solution of **1** (7.03 g, 0.05 mole) in water (50 ml) was added 2,4-pentanedione (**2**) dropwise with stirring at 25°. After the mixture had stirred at 25° for 0.5 hour it was heated at 70° for 4 hours, during which time solid precipitated from solution. The product was filtered from the cooled mixture, washed with water, and dried to yield 5.77 g (85%) of pure **3**, mp 150° (lit mp 147-149° [3]); ¹H nmr (deuteriochloroform): δ 2.21 (s, 6H), 2.47 (s, 6H), 5.95 (s, 2H), 8.09 (bs, 2H); ¹³C nmr (deuteriochloroform): δ 13.4, 13.7, 109.8, 142.3, 145.8, 149.9; ¹⁵N nmr (deuteriochloroform): δ -92.6, -156.8, -182.6, -266.5.

3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**4**).

A. Oxidation of **3** with Nitric Oxide.

A slurry of **3** (6.80 g, 0.025 mole) in 1-methyl-2-pyrrolidinone (50 ml) was treated with nitric oxide through a gas dispersion tube in a 125-ml gas washing bottle at a rate of 500 ml/minute for one hour at ambient temperature. The mixture was poured into ice water (200 ml), and the red solid was collected by filtration,

washed with water, and dried to produce 6.70 g (99%) of pure **4**, mp 226° (lit mp 223-225° [3]); ¹H nmr (deuteriochloroform): δ 2.39 (s, 6H), 2.72 (s, 6H), 6.20 (s, 2H); ¹³C nmr (deuteriochloroform): δ 13.9, 14.7, 111.9, 143.8, 154.5, 159.3; ¹⁵N nmr (deuteriochloroform): δ -15.3, -85.5, -178.5.

B. Oxidation of **3** with Nitrogen Dioxide.

Into a 125-ml gas washing bottle, which was equipped with an open-ended tube in place of the gas dispersion tube, was placed **3** (13.6 g, 0.05 mole) and 1-methyl-2-pyrrolidinone (50 ml). Nitrogen dioxide (3.2 ml, 0.10 mole) was vaporized over 5-10 minutes from a graduated, conical test tube into the rapidly stirred slurry at ambient temperature. The yield of product, obtained as described above, was 13.3 g (99%), identical in all respects with that obtained in A.

3,6-Diamino-1,2,4,5-tetrazine (**5**).

A. Ammonolysis of **4**.

A 100-ml capacity pressure reactor equipped with a magnetic stirrer was charged with **4** (13.5 g, 0.05 mole) and 1-methyl-2-pyrrolidinone (50 ml). Ammonia (5 g, 0.3 mole) was introduced over 30 minutes at ambient temperature to the closed vessel. The pressure following the addition was about 60 psig. The pressure rose to around 150 psig as the reactor was heated to 90°. After 6 hours at 90°, the vessel was cooled to ambient temperature and opened. The mixture was diluted with 2-propanol (100 ml) and set aside overnight to allow complete precipitation of the product, which was collected by filtration, washed with 2-propanol, and dried to yield 5.60 g (100%) of pure **5**, identical in all respects with that reported previously [1,2].

B. One-Pot Process from **3**.

A slurry of **3** (13.6 g, 0.05 mole) in 1-methyl-2-pyrrolidinone (50 ml) was treated with nitrogen dioxide (0.10 mole) as described above. The resulting mixture was purged with dry nitrogen, transferred to the 100-ml pressure reactor, treated with ammonia (5 g, 0.3 mole), and worked up as described above. The yield of pure **5** was 5.38 g (96%).

3-Amino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**8**).

Ammonia was bubbled through a slurry of **4** (13.6 g, 0.05 mole) in toluene (250 ml) with rapid stirring at ambient temperature for 30 minutes. The resulting solid was collected by filtration, washed with toluene, and dried to yield 9.50 g (99%) of pure **8**, mp 218°; ¹H nmr (deuteriochloroform): δ 2.37 (s, 3H), δ 2.59 (s, 3H), 5.78 (s, 2H), 6.12 (s, 1H); ¹³C nmr (methyl sulfoxide): δ 12.3, 13.3, 108.4, 141.3, 150.1, 157.1, 163.1; ¹⁵N nmr (methyl sulfoxide): δ -7.2, -38.4, -80.5, -175.9, -302.2.

Anal. Calcd. for C₇H₈N₇: C, 43.97; H, 4.74; N, 51.28. Found: C, 43.59; H, 4.82; N, 51.31.

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REFERENCES AND NOTES

- [1] M. D. Coburn and D. G. Ott, *J. Heterocyclic Chem.*, **27**, 1941 (1990).
- [2] C.-H. Lin, E. Lieber and J. P. Horwitz, *J. Am. Chem. Soc.*, **76**, 427 (1954).
- [3] R. N. Butler, F. L. Scott and R. D. Scott, *J. Chem. Soc. (C)*, 2510 (1970).
- [4] R. Stolle, *Ber.*, **37**, 3548 (1904).