

Michael D. Coburn\* and Donald G. Ott

University of California, Los Alamos National Laboratory,  
 Los Alamos, NM 87545, USA  
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Treatment of 1,3-diaminoguanidine monohydrochloride (**1**) with 2,4-pentanedione (**2**) in alcohols under carefully controlled conditions gave 3,6-diamino-1,2-dihydro-1,2,4,5-tetrazine monohydrochloride (**3**) in 45-50% yields along with 3,5-dimethyl-1*H*-pyrazole (**4**) and its hydrochloride **5**. Oxidation of **3** with sodium perborate produced 3,6-diamino-1,2,4,5-tetrazine (**6**) in quantitative yield.

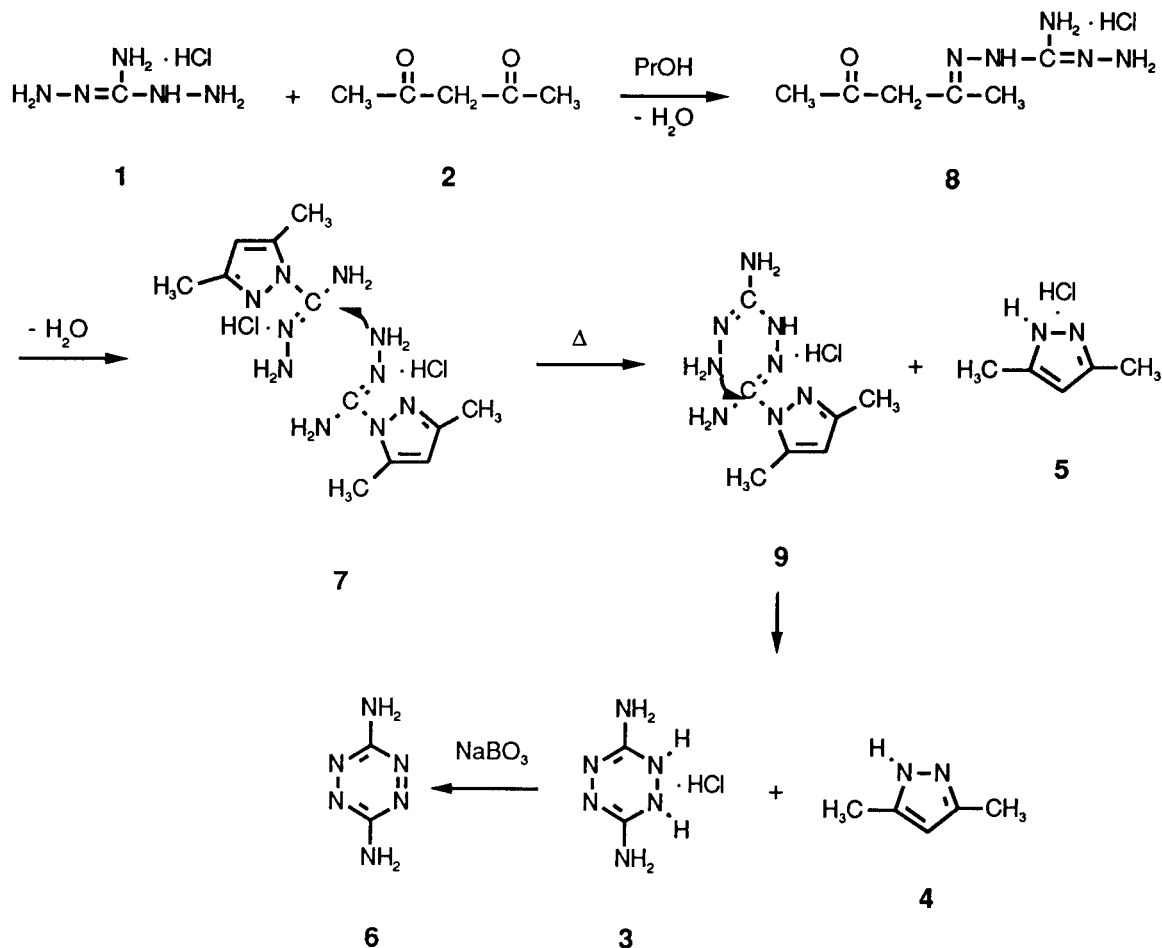
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3,6-Diamino-1,2,4,5-tetrazine (**6**) was synthesized unequivocally for the first time by Lin, Lieber, and Horwitz [1]. However, the yields of this preparation and of the less tedious alternate routes developed by these authors are very low (10-13%). Attempts in this laboratory to improve the yields of these methods by varying reaction conditions have been fruitless.

In an unsuccessful effort to prepare 1-aminoamidino-3,5-dimethyl-1*H*-pyrazole (**7**), Dickenson, Jacobsen, and Gillis heated 1,3-diaminoguanidine monohydrochloride (**1**) with 2,4-pentanedione (**2**) in refluxing ethanol for seven

hours to give an unidentified white solid that was converted to **6** in 10% yield when treated with base [2]. We repeated this experiment with essentially the same results; however, the <sup>1</sup>H-nmr spectrum of the filtrate, obtained after removal of the white solid, contained three methyl peaks at  $\delta = 2.22, 2.40,$  and  $2.54$ . The filtrate was heated under reflux an additional eight hours, during which time more of the white solid precipitated and the peaks at  $\delta = 2.22$  and  $2.54$  decreased with respect to the peak at  $\delta = 2.40$ . After a total of 36 hours at reflux, the reaction was complete as shown by the disappearance of the peaks at  $\delta$

Scheme A



= 2.22 and 2.54. The product remaining in solution was identified as a mixture of 3,5-dimethyl-1*H*-pyrazole (**4**) and its hydrochloride **5** by comparison of the <sup>1</sup>H- and <sup>13</sup>C-nmr spectra of the free base with those of an authentic sample. The elemental analysis as well as the <sup>1</sup>H- and <sup>13</sup>C-nmr spectra of the white solid are consistent with the structure of 3,6-diamino-1,2-dihydro-1,2,4,5-tetrazine monohydrochloride (**3**). The reflux time for complete reaction was reduced to six hours by increasing the concentration of reactants and employing higher-boiling alcohols as solvents.

In a more careful study of this reaction, **1** and **2** were mixed in 1-propanol and allowed to stir overnight at ambient temperature. After this time, the initially insoluble **1** had all dissolved to give a clear, yellow solution. The <sup>1</sup>H- and <sup>13</sup>C-nmr spectra of the product in solution were consistent with the structure of **7**; however, all attempts to isolate this compound in pure form failed. Heating the solution thus obtained under reflux for six hours gave **3** as a white precipitate. After recrystallization from 2-propanol/water, analytically pure **3** was obtained in 45-50% yields, which are considerably higher than those obtained by heating the mixture immediately after mixing the reactants. Furthermore, it was found that equivalent yields of **3** could be obtained when 2-propanol was used as the reaction solvent, although the intermediate **7** separated as a sticky semi-solid instead forming a clear solution as it did in 1-propanol.

Although the conversion of **3** to **6** can be accomplished in around 80% yield by treating a solution of **3** with base followed by oxidation with hydrogen peroxide, we found that sodium perborate will neutralize the hydrogen chloride of **3** and oxidize the free base immediately to **6** in quantitative yield. The **6** that precipitated from the latter reaction mixture was found to be analytically pure and identical in all respects with an authentic sample [1].

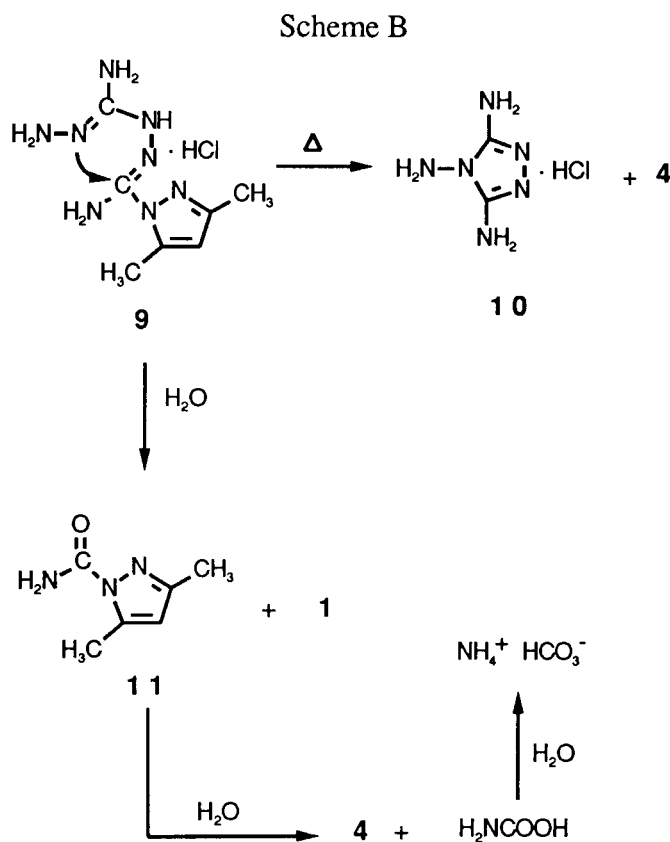
Based upon the observations reported thus far, we suggest the mechanism shown in Scheme A for the reaction of **1** with **2**. Thus, **1** condenses with **2** to form the hydrazone derivative **8**, which cyclizes with the elimination of water to form **7**. When the solution is heated, two molecules of **7** react as shown to displace **5** and form **9**, which cyclizes with the elimination of **4** to produce **3**.

Although the yield of **6** obtained in this two-step process is much greater than that reported previously, we were curious as to why the yield of **3** seems to be limited to 50%. Therefore, we initiated an effort to determine the fate of the remainder of the **7** with the ultimate goal of improving the yield of **3**.

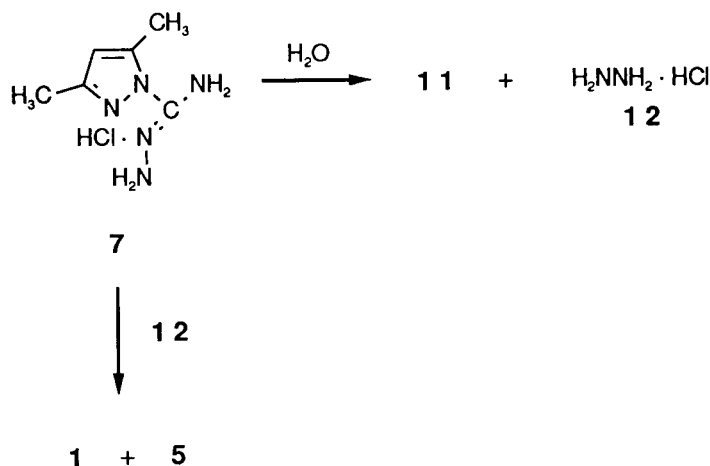
The <sup>13</sup>C-nmr spectrum of the solution of **7** in 1-propanol before heating showed only very small quantities of by-products; conversion of **1** and **2** to **7** is essentially quantitative. The white precipitate isolated following heating of the alcohol solution and before recrystallization was found

by <sup>13</sup>C-nmr to contain products other than **3**. Three major peaks were present (DMSO-d<sub>6</sub>): δ = 160.3, 154.6, and 150.3, in proportions of approximately 1:3:1, respectively. They were identified through spiking experiments as **1**, **3**, and 3,4,5-triamino-4*H*-1,2,4-triazole monohydrochloride (**10**) [3]. The formation of **10** is readily explained by an alternative ring-closure path for **9** (Scheme B). This compound was also found to be a major product in preparation of **6** from *S*-methylthiosemicarbazide hydroiodide [1]. There are several ways that **1** could be formed in the reaction mixture. Intermediate **9** could react with the water formed in the initial condensation of **1** and **2** to give **1** and 3,5-dimethyl-1-*H*-pyrazolecarboxamide (**11**). Reaction of **11** with more water might give **4** and carbamic acid, which would hydrolyze to ammonium bicarbonate (Scheme B). Although evidence for carbamate and bicarbonate was not entirely conclusive, because of the dependence of their chemical shifts on acidity, concentration, solvent, etc., it is reasonable to suggest that they are possible and likely by-products. Ammonium ion was observed in the solution after reaction by <sup>14</sup>N-nmr. Carbon dioxide was not found by <sup>13</sup>C-nmr in reactions carried out in sealed nmr tubes; subsequent spiking showed that it would have been observed if present.

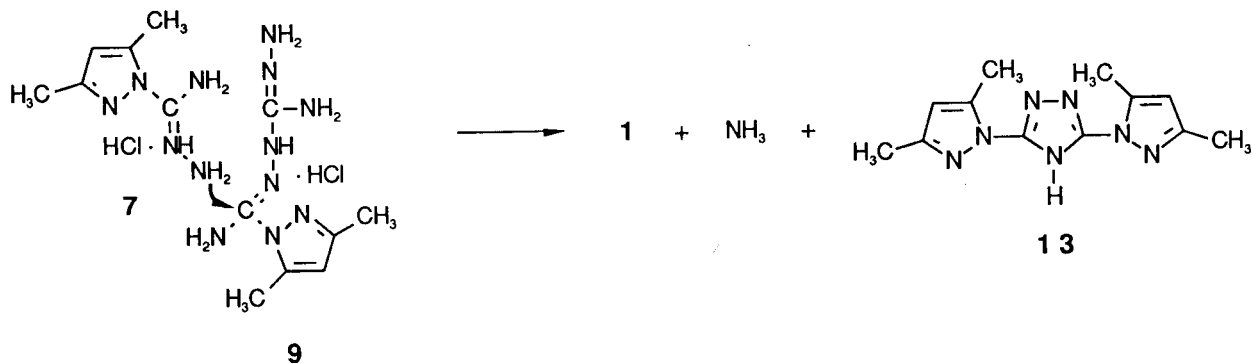
Water could also react with **7** to form **11** and hydrazine hydrochloride (**12**) that could then attack **7** to produce **1**



## Scheme C



## Scheme D



and **5** (Scheme C). A reaction in which an equivalent of **12** was intentionally added to a solution of **7** and then heated gave predominantly **1** and **5**, with very little **3** or **10**. Another pathway, which does not involve water, might be the reaction of the two intermediates **7** and **9** to expel **1**, **13**, and ammonia (Scheme D). Ammonia could also result from hydrolysis of **11**, **7** or **9**. Other dimethylpyrazole derivatives, such as **13**, are proposed because of additional, small nmr peaks in the methyl region.

From the overall reactions leading to **3** in Scheme A, it can be seen that only two moles of hydrochloric acid are available for the three moles of basic products. A reaction was carried out in which this additional mole of hydrogen chloride was added to a 1-propanol solution of **7** before heating in the usual manner. The  $^{13}\text{C}$ -nmr spectrum of the precipitated product showed only three peaks, none of which corresponded to **3**; one corresponded to **1**, and the other two probably to bicarbonate and carbamate.

1,3-Diaminoguanidinium nitrate (in place of the usual chloride salt) was used in one reaction carried out in 1-propanol. The yield of the dihydrotetrazine (as the nitrate salt) was much lower (about 30%), and there was a greater

proportion of both the **10** and regenerated diaminoguanidinium nitrate. The solution had become red, indicating that some oxidation to **6** had occurred (confirmed by a small peak in the nmr spectrum). The yield of the intermediate corresponding to **7** was not determined because of its insolubility in the alcohol.

An estimate of the material balance can be made by consideration of the relative intensities of the  $^{13}\text{C}$ -nmr peaks and the yield of **3**. The ratios observed in the  $^{13}\text{C}$ -nmr (1:3:1) for the three major products, **1**, **3**, and **10**, respectively, represent the relative moles of contained carbon. The 50% yield of **3** obtained following recrystallization also represents the amounts present in the crude mixture, since recovery of **3** is essentially quantitative. The ratio can then be roughly expressed as 16:50:16; that is, the three products contain approximately 80% of the guanidinium carbon present in the starting material. The remainder must have gone to various other products through reactions such as **7** or **9** with water or with each other.

A variety of different solvents - including dimethyl sulfoxide (DMSO), 1-methyl-2-pyrrolidinone (NMP), 1,4-dioxane, tetrahydrofuran, and acetonitrile - for the prepara-

Table  
NMR Spectral Data

Compound	Solvent	<sup>1</sup> H	Chemical Shifts (ppm)[a] <sup>13</sup> C	<sup>15</sup> N
<b>1</b>	DMSO H <sub>2</sub> O		160.3 162.5	26.5, 41.1, 66.6
<b>3</b>	DMSO H <sub>2</sub> O	6.75 (bs, 4 H); 9.16 (bs, 3 H)	154.6 156.7	
<b>4/5</b>	EtOH 1-PrOH DMSO	2.40 (s, 6 H); 6.29 (s, 1 H) 2.41 (s, 6 H); 6.30 (s, 1 H)	10.6, 107.0, 146.0 10.8, 107.1, 146.2 11.4, 105.7, 144.4	94.2
<b>6</b>	DMSO MeSO <sub>3</sub> H	6.72 (bs)	161.7 150.8	56.4, 303.5
<b>7</b>	EtOH 1-PrOH DMSO	2.22 (s, 3 H); 2.54 (s, 3 H); 6.19 (s, 1 H) 2.23 (s, 3 H); 2.56 (s, 3 H); 6.20 (s, 1 H)	12.8, 13.0, 111.6, 143.6, 153.3, 154.9 13.6, 112.0, 144.0, 153.5, 155.1 13.6, 13.7, 110.3, 142.5, 150.5, 154.3	43.0, 58.0, 139.9, 175.2, 268.2
<b>10</b>	DMSO H <sub>2</sub> O		150.2 150.1	22.5, 28.8, 146.1, 147.4
<b>11</b>	DMSO		13.6, 14.0, 110.0, 142.8, 149.5, 152.3	
<b>14</b>	DMSO		157.9	
Guanidinium bicarbonate	DMSO/H <sub>2</sub> O		159.3, 160.6	
Guanidinium carbonate	DMSO/H <sub>2</sub> O		159.6, 167.5	
Ammonium carbonate	DMSO/EG		150.6	0.0, 61.7

[a] Chemical shifts are relative to internal tetramethylsilane = 0 for <sup>1</sup>H and <sup>13</sup>C and to external 1 M <sup>15</sup>NH<sub>4</sub>NO<sub>3</sub> = 0 for <sup>15</sup>N.

tion of **3** were investigated and found to be ineffective. In DMSO and in NMP, intermediate **7** formed in excellent yields in solution; however, after heating the principal material observed in the  $^{13}\text{C}$ -nmr spectrum was **5** with only a very small yield of the desired **3**, along with similar amounts of **1**, **10**, and a few other unidentified materials. The total of all these small peaks appeared to account for the guanidinium carbon. All attempts to isolate pure **7** from these solutions failed.

Compound **11** was prepared in DMSO solution by reaction of **2** with semicarbazide hydrochloride (**14**) under the same conditions as for preparation of **7**. The  $^{13}\text{C}$ -nmr spectrum showed only peaks for **11** and for **4**. The latter was quite predominant and increased with time, indicating the ease of hydrolysis of **11** at ambient temperature. Probably the proton from the hydrochloric acid was more readily available to the pyrazole moiety, and it became a more effective leaving group than was the case with **7**. Another by-product that might be expected from the hydrolysis of **7**, in which **5** is eliminated rather than **1**, would be **14**. No evidence for this was found by  $^{13}\text{C}$ -nmr.

Various attempts were made to remove the water produced in formation of the intermediate **7**. Azeotropic distillation of the 1-propanol solvent at ambient temperature under reduced pressure before initial heating in conversion of **7** to **3** was carried out until the distillate was free of water ( $^1\text{H}$ -nmr). The yield of **3** after heating remained the same. Addition of magnesium sulfate to a reaction mixture containing **3** in 1-propanol failed to remove all of the water as judged from the weight of desiccant from the filtered solution and  $^1\text{H}$ -nmr. Addition of molecular sieve (Type 4A) to a mixture of **1** and **2** in 1-propanol prevented the reaction from occurring. Apparently, at least some water is needed for reaction to proceed, probably because of the extreme insolubility of **1** in anhydrous alcohol. Treatment of a reaction mixture carried out in DMSO as solvent with molecular sieve (Type 4A) appeared to remove some, but not all, of the water ( $^1\text{H}$ -nmr). It thus seems that the water produced in the reaction of **1** and **2** is very tightly bound to **7**.

The dihydrotetrazine **3** on heating in DMSO solution was oxidized to **6**; dimethyl sulfide was the reduced product, which was evident in the nmr spectrum when the reaction was carried out in a sealed tube. The very low yield of **3** in this solvent was thus not a result of decomposition of the ring system following its formation. Solvation in DMSO and NMP must facilitate different pathways as compared to the alcohols. For example, perhaps the hydrogen chloride is not accessible to the pyrazole to facilitate its leaving, but more readily available to the aminoamino portion of the intermediate.

#### EXPERIMENTAL

1,3-Diaminoguanidine monohydrochloride (98%) and 2,4-

pentanedione (99+%) were purchased from the Aldrich Chemical Company and were used as received except that the 1,3-diaminoguanidine monohydrochloride was finely ground with a mortar and pestle prior to use. Authentic samples of 3,5-dimethyl-1*H*-pyrazole and 3,5-dimethyl-1*H*-pyrazolecarboxamide were also purchased from the Aldrich Chemical Company. All nmr spectra were obtained with a JEOL FX90Q spectrometer and are given in the Table; all ir spectra were obtained on a Perkin-Elmer 283 spectrometer.

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

To a slurry of finely divided 1,3-diaminoguanidine monohydrochloride (98%) (**1**, 128.0 g, 1.0 mole) in 2-propanol (1 l) was added 2,4-pentanedione (**2**, 100.0 g, 1.0 mole) with efficient mechanical stirring, and the mixture was allowed to stir at ambient temperature for 20 hours. The resulting mixture was heated under reflux for 8 hours during which time the initially formed sticky semi-solid dissolved and another solid crystallized from the solution. The solid was collected by filtration, washed with 2-propanol, and suspended in boiling 2-propanol (500 ml). Water (~400 ml) was added slowly to the boiling mixture to form a clear solution, which was chilled in the freezer to give pure **3** (34.8 g, 46%) as glistening plates, mp 194-195° dec; ir (potassium bromide): 3270, 3140, 2940, 2780, 1640, 1500, 1458, 1391, 1182, 1041, 890, 821, 683, 590, 418, 370  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_2\text{H}_7\text{ClN}_6$ : C, 15.95; H, 4.69; N, 55.82. Found: C, 16.13; H, 4.88; N, 55.44.

The filtrate from the reaction mixture was evaporated to dryness under reduced pressure to give another solid, which was dissolved in water (1 l) and treated with sodium hydroxide (20.0 g, 0.5 mole) dissolved in water (100 ml). The resultant mixture was extracted with ether (5 x 100 ml). The extracts were dried (magnesium sulfate) and evaporated to dryness to yield 3,5-dimethyl-1*H*-pyrazole (**4**) (92.1 g, 96%), mp 107°, identical in all respects with a commercial sample.

Reactions of **1** with **2** in other solvents were performed with 5 mmoles of each reactant in 5 ml of solvent.

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

To a stirred solution of **3** (30.1 g, 0.20 mole) in water (1 l) was added sodium perborate tetrahydrate (32.3 g, 0.21 mole). As the sodium perborate dissolved, the solution turned dark red and dark red crystals separated. The mixture was allowed to stir at ambient temperature for 2 hours then it was cooled to 0°. The product was collected by filtration, washed with ice water, and dried to give pure **6** (22.4 g, 100%), identical in all respects with an authentic sample [1], ir (potassium bromide): 3340, 3295, 3140, 1620, 1476, 1090, 1058, 920, 856, 825, 577, 480, 350  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_2\text{H}_4\text{N}_6$ : C, 21.43; H, 3.60; N, 74.97. Found: C, 21.27; H, 3.54; N, 74.61.

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#### REFERENCES AND NOTES

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