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Synthesis of Guanidino-1,3,5-triazines Using DMF

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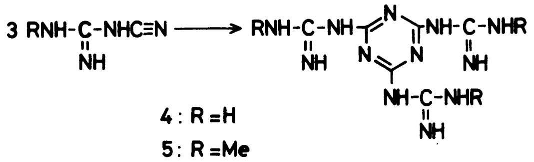
Synopsis. 2,4,6-Triguanidino-1,3,5-triazine and 2,4,6-tris(3-methylguanidino)-1,3,5-triazine were synthesized in 42 and 52% yields, respectively, by the cyclotrimerization of cyanoguanidine and 1-methyl-3-cyanoguanidine using DMF as a solvent in the presence of hydrogen chloride. 1-Phenyl-3-cyanoguanidine, 1,2-dimethyl-3-cyanoguanidine, and 2-imidazolidinylidenecyanamide, however, were cyclodimerized to the corresponding guanidino-1,3,5-triazines in a similar manner.

Our previous papers[1–3] described that 2,4-diamino-6-guanidino-1,3,5-triazine (**1**), 2-amino-4,6-diguanidino-1,3,5-triazine (**2**) and 1-amidino-2,4,6-triguanidino-dihydro-1,3,5-triazine (**3**) were prepared by a reaction of cyanoguanidine using phenol or pyridine–nitrobenzene as a solvent in the presence of hydrogen chloride. Especially 2,4,6-triguanidino-1,3,5-triazine (**4**) was not formed directly through the above reaction, but was produced quantitatively upon an elimination reaction of cyanamide from **3** in an alkaline solution.

In this paper, we wish to report a convenient method of synthesizing **4** by the cyclotrimerization of cyanoguanidine using DMF as a solvent, together with the reaction of substituted cyanoguanidines in DMF.

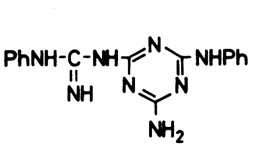
The reaction of cyanoguanidine in the presence of equimolar hydrogen chloride in DMF gave **4** and **1** in 42 and 8% yields, respectively. However, **2**, **3** and cyanamide were not detected in this reaction, and **3** did not release cyanamide under the conditions of this reaction. These results suggest that **4** was formed by the cyclotrimerization of cyanoguanidine.

The reaction was extended to substituted cyanoguanidines. Consequently, 2,4,6-tris(3-methylguanidino)-1,3,5-triazine (**5**) was obtained in 52% yield by the cyclotrimerization of 1-methyl-3-cyanoguanidine. The structure of **5** was established by its acid hydrolysis, which gave cyanuric acid and methylguanidine in 69 and 58% yields, respectively. The reaction of 1-phenyl-3-cyanoguanidine, however, did not afford the expected 2,4,6-tris(3-phenylguanidino)-1,3,5-triazine, and provided only the normal type of 3-phenylguanidino-1,3,5-triazines,[3] which was 2-amino-4-anilino-6-(3-phenylguanidino)-1,3,5-triazine (**6**) by the cyclodimerization of the starting material, in 21% yield. **6** was confirmed with an authentic sample.[3] In a similar manner, 1,2-dimethyl-3-cyanoguanidine and 2-imidazolidinylidenecyanamide were also cyclodimerized and deposited 1-methyl-2-methylamino-4-imino-6-(2,3-dimethylguanidino)-1,4-dihydro-1,3,5-triazine (**7**) and 2-amino-4-(4,5-dihydro-1*H*-imidazol-2-ylamino)-6,7-dihydroimidazo[1,2-*a*][1,3,5]triazine (**8**) from the DMF solution in 41 and 67% yields, respectively. **7** and **8** were also obtained in a phenol solvent in 81 and 71% yields, respectively, upon a treatment of the solution.[3] The structure of **7** was established by an elemental analysis, the mass spectrum and acid hydrolysis. This gave 1-methyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione, 1,3-dimethylguanidine, methylamine and ammonia. The structure of **8** was also established by an elemental analysis, its mass spectrum and acid hydrolysis, giving 6,7-dihydroimidazo[1,2-*a*][1,3,5]triazine-2,4-diol (**9**), 4,5-dihydro-1*H*-imidazol-2-amine and ammonia. These results suggest that the cyclotrimerization of cyanoguanidines using DMF has a limitation.



4: R=H

5: R=Me



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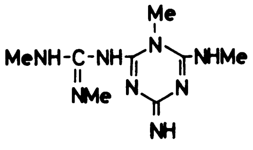

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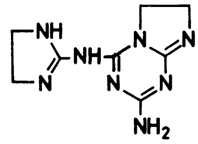

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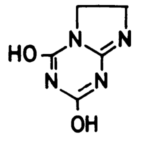

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Experimental

2,4,6-Triguanidino-1,3,5-triazine (4). Hydrogen chloride (8.75 g, 0.24 mol) was introduced into a stirred solution of cyanoguanidine (16.81 g, 0.20 mol) in 155 ml of DMF at room temperature. The solution was stirred at 80 °C for 110 min and then evaporated under reduced pressure. 2-Propanol was added to the oily residue and the resulting precipitate was collected by filtration. The precipitate was dissolved in water. After removing the insoluble material, the solution was adjusted to pH 13.6 with an aqueous sodium hydroxide solution. Then, the precipitate, the free state of **4**, was filtered off and washed with water. The yield was 0.69 g (3%). After the filtrate was made acidic with 6 mol dm^{-3} of nitric acid, the precipitate, **4** nitrate (8.51 g, 29%), was filtered off. The filtrate was concentrated to yield **1** nitrate (6.12 g, 21%) and the nitrate of the mixture. The mixture was separated to **1** (0.54 g, 1%; insoluble to the aqueous ammonia solution) and amidinourea (2.28 g, 3%; insoluble to the acetic acid solution) as the picrates. The filtrate of 2-propanol solution was concentrated to yield amidinourea (6.53 g, 10%) and guanidine (3.51 g, 6%) as the picrates.

In a similar manner, a cyanoguanidine–acetone adduct (hydrochloride)[4] used as a starting material gave **4** (42%) and **1** (8%) at 80 °C after 30 min, or gave **4** (40%) and **1** (1%) at room temperature after 5 d.

2,4,6-Tris(3-methylguanidino)-1,3,5-triazine (5). Hydrogen chloride (3.65 g, 0.1 mol) was introduced into a stirred solution of 1-methyl-3-cyanoguanidine[5] (9.81 g, 0.1 mol) in 70 ml of DMF below 10 °C. The solution was stirred at 80 °C for 3 h. After cooling, a precipitate was filtered off and washed with 2-butanone. The yield of **5** was 7.31 g, (52%). Recrystallization from a dilute hydrochloric acid provided pure **5** as the hydrochloride: mp 313 °C; Found: C, 25.39; H, 5.28; N, 39.39; Cl, 24.82%. Calcd for $C_9H_{18}N_{12}\cdot 3HCl\cdot H_2O$: C, 25.63; H, 5.50; N, 39.86; Cl, 25.22%. IR (KBr) 810 cm^{-1} (1,3,5-triazine ring). Recrystallization from a dilute nitric acid provided pure **5** as the nitrate: mp 265.5 °C (dec). Found: C, 21.63; H, 4.51, N. 42.25%. Calcd for $C_9H_{18}N_{12}\cdot 3HNO_3\cdot H_2O$; C, 21.56; H, 4.62; N, 41.91%. IR (KBr) 810 cm^{-1} (1,3,5-triazine ring).

2-Amino-4-anilino-6-(3-phenylguanidino)-1,3,5-triazine (6). Hydrogen chloride (18.60 g, 0.51 mol) was introduced into a stirred solution of 1-phenyl-3-cyanoguanidine[6] (80.09 g, 0.50 mol) in 386 ml of DMF at room temperature. The solution was stirred at 80 °C for 3 h, and then concentrated under reduced pressure to give *N*-(phenylamidino)urea as the picrate (76.58 g, 38%). After filtering off, the filtrate was extracted with water, and then the oily residue was dissolved in acetone. The acetone solution was evaporated to dryness and the residue was recrystallized from methanol to give 9.47 g (10%) of **6** as the hydrochloride.[3] The extracted solution was made alkaline with ammonia, and the resulting precipitate was recrystallized from a dilute nitric acid to give 11.29 g (11%) of **6** as the nitrate.[3]

1-Methyl-2-methylamino-4-imino-6-(2,3-dimethylguanidino)-1,4-dihydro-1,3,5-triazine (7). In a similar manner as for the preparation of **5**, **7** was obtained from 1,2-dimethyl-3-cyanoguanidine.[5] The yield was 41%. Recrystallization from water provided pure **7** as the hydrochloride: mp 245—246 °C; IR (KBr) 780 cm^{-1} (1,3,5-triazine ring). Found: C, 30.30; H, 7.00; N, 36.32; Cl, 11.90%. Calcd for $C_8H_{16}N_8\cdot HCl\cdot 3H_2O$: C, 30.53; H, 7.36; N, 35.60; Cl, 11.26%. MS Found: m/z 244. Calcd for $C_8H_{16}N_8$: M, 244.

*2-Amino-4-(4,5-dihydro-1*H*-imidazol-2-ylamino)-6,7-dihydroimidazo[1,2-*a*][1,3,5]triazine (8).* In a similar manner, **8** was obtained from 2-imidazolidinylidenecyanamide[7] in 64% yield. Recrystallization from 0.5 mol dm^{-3} of hydrochloric acid provided pure **8** as the hydrochloride: mp 337 °C. IR (KBr) 780 cm^{-1} (1,3,5-triazine ring). Found: C, 34.88; H, 5.35; N, 41.42; Cl, 13.11%. Calcd for $C_8H_{12}N_8\cdot HCl\cdot H_2O$: C, 34.98; H, 5.49; N, 40.79; Cl, 12.91%. MS Found: m/z 220. Calcd for $C_8H_{12}N_8$: M, 220.

Acid Hydrolysis. By the same procedure described in our previous paper,[8] **5** was refluxed in 6 mol dm^{-3} of hydrochloric acid for 133 h and gave unreacted **5** (6%), cyanuric acid (69%), methylguanidine as the picrate (58%). Ammonia was detected in the solution.

In a similar manner, **7** was refluxed for 10 h and gave 1-methyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione[9] (15%. mp 285—286 °C; MS m/z 143), 1,3-dimethylguanidine (96%) and methylamine (4%). Ammonia was also detected in the solution.

In a similar manner, **8** was refluxed for 48 h and gave 4,5-dihydro-1*H*-imidazol-2-amine[10] (77%) and **9**[11,12] (70%). Ammonia was also detected in the solution. By a Hinsberg test, **9** was confirmed to be the tertiary amine. Recrystallization from a dilute hydrochloric acid provided pure **9** as the hydrochloride: mp 302 °C (dec). (Found: C, 28.32; H, 4.34; N, 27.07; Cl, 16.63%. **9**: MS m/z 154).

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