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13. ABSTRACT *(Maximum 200 words)*

Two synthetic routes to 5-substituted-1,3-diazacyclohexane derivatives **1** are reported. The first method involves treatment of 1,3-diaminopropan-2-ol **2** with paraformaldehyde to yield 5-hydroxy-1,3-diazacyclohexane **3**. A second method is based on the condensation of 2-bromo-2-nitro-1,3-propanediol with t-butylamine and formaldehyde to yield 1,3-di(t-butyl)-5-bromo-5-nitro-1,3-diazacyclohexane **22**. Functional group manipulations of **3** and **22** provide a number of novel 1,3-diazacyclohexanes functionalized at the 5-position.

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SYNTHESIS AND CHARACTERIZATION OF 5-SUBSTITUTED-1,3-DIAZACYCLOHEXANE DERIVATIVES

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Abstract:
Two synthetic routes to 5-substituted-1,3-diazacyclohexane derivatives **1** are reported. The first method involves treatment of 1,3-diaminopropan-2-ol **2** with paraformaldehyde to yield 5-hydroxy-1,3-diazacyclohexane **3**. A second method is based on the condensation of 2-bromo-2-nitro-1,3-propanediol with t-butylamine and formaldehyde to yield 1,3-di(t-butyl)-5-bromo-5-nitro-1,3-diazacyclohexane **22**. Functional group manipulations of **3** and **22** provide a number of novel 1,3-diazacyclohexanes functionalized at the 5-position.

Introduction

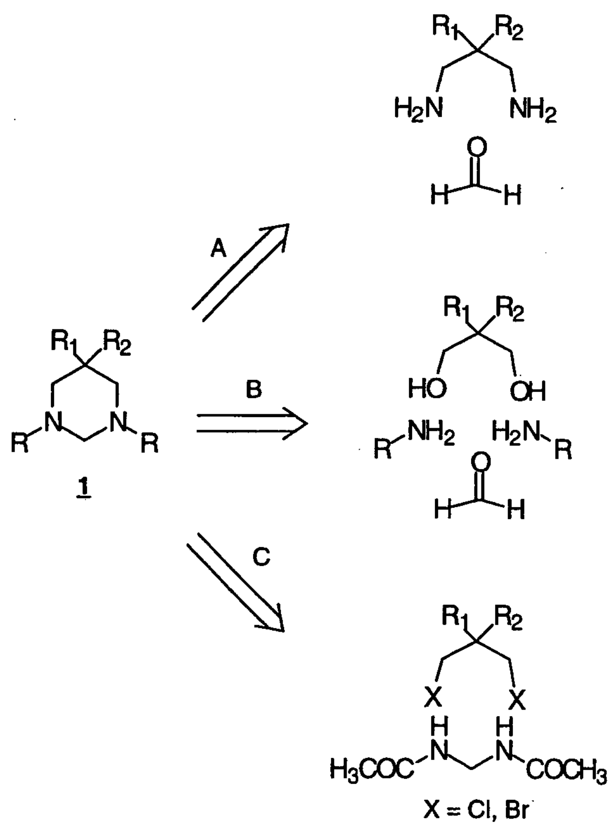
The design and synthesis of small[1] and medium-ring[2] nitrogen-containing heterocycles have been investigated in these laboratories as part of a continuing program to prepare novel high density energetic materials with improved sensitivity properties.[3] The chemistry of 1,3-diazacyclohexanes has attracted considerable interest in recent years, since appropriately functionalized compounds of this ring system, either serve as crucial synthetic precursors or are themselves important members of this class of materials. Examples include 1,3,5-trinitro-1,3-diazacyclohexane and 1,3,5,5-tetranitro-1,3-diazacyclohexane whose syntheses were achieved by the nitrolysis of the Mannich condensation product from nitromethane, formaldehyde and t-butylamine[4-7] as well as by the cyclocondensation of a nitroguanidine.[8] While the parent 1,3-diazacyclohexane,[9] 5-hydroxy-1,3-diazacyclohex-1-ene[10] and more recently 5-exomethylene-1,3-dialkyl-1,3-diazacyclohexane[11] have been reported, general methods for the syntheses of 1,3-diazacyclohexanes derivatives which have been functionalized at the 5-position with other than C-nitro groups, are lacking. In this report, we describe three such approaches to 5-substituted 1,3-diazacyclohexanes that allow for the incorporation of various substituents at the 1,3 and 5-positions. These approaches provide access to the hither-to-fore unknown 1,3-disubstituted 1,3-diazacyclohexan-5-ones or their surrogate equivalents which are key intermediates for the introduction of a variety of substituents at the 5-positon. Additionally, the facile synthesis of a new energetic material, 1,3-dinitro-5-

nitrato-1,3-diazacyclohexane **17**, as well as the chemistry leading to a number of related 5-substituted derivatives of this ring system are described.

Results and Discussion

The construction of the 1,3-diazacyclohexane ring system has been achieved by three pathways. These approaches are depicted below in scheme 1. In our first method,

Scheme 1

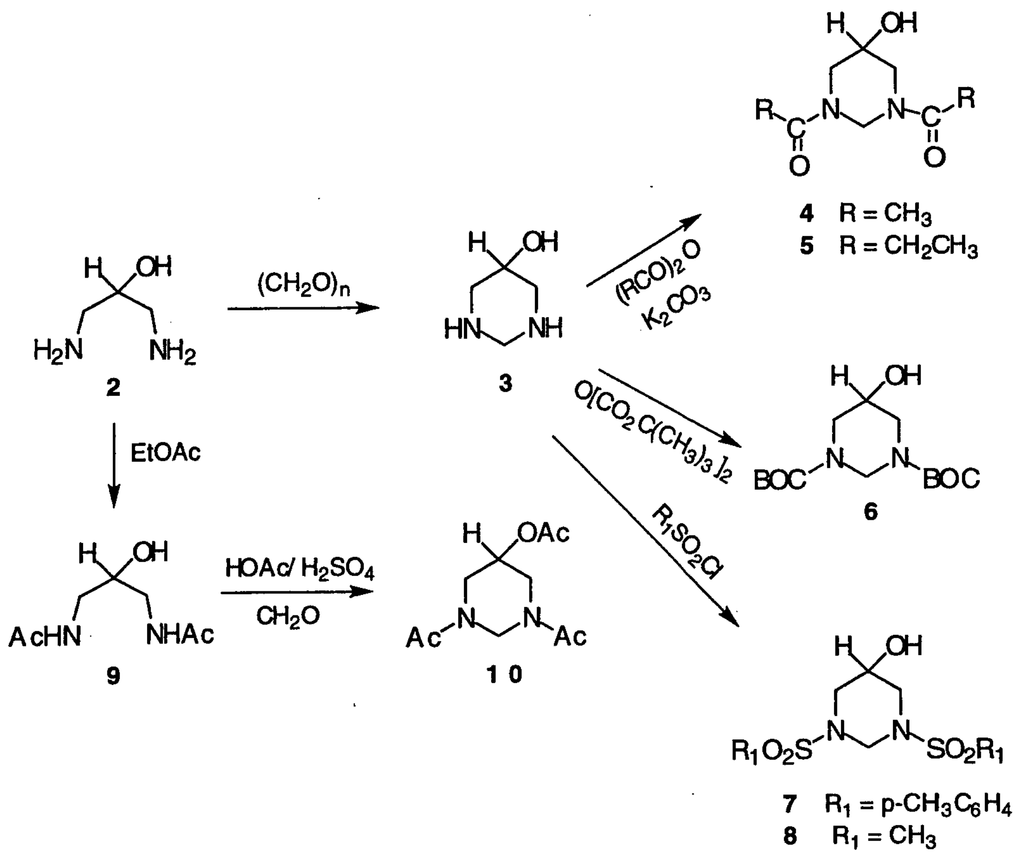


the ring closure reaction of 2,2-substituted-1,3-diaminopropane with formaldehyde gave the 5,5-substituted 1,3-diazacyclohexane ring which was further derivatized in the 1,3-positions by a variety of reagents. The second method involved the reaction of readily available 2-bromo-2-nitropropan-1,3-diol with t-butylamine and formaldehyde to give the 1,3-diazacyclohexane ring in one step. The reaction of methylenebisacetamide with with 3-chloro-2-chloromethyl-2-propene **27** was the basis of our third method to construct the 1,3-diazacyclohexane ring structure.

The synthesis of 5-substituted 1,3-diazacyclohexanes by method A described above is elaborated in Scheme 2. Treatment of 1,3-diaminopropan-2-ol **2** with paraformaldehyde in methanol solution affords 5-hydroxy-1,3-diazacyclohexane **3** in 88% yield as a water-soluble hygroscopic colorless crystalline solid.[12] In refluxing 1,2-dichloroethane **3** reacts with acetic anhydride to yield the completely acetylated derivative **10** or with acetic anhydride in potassium carbonate to yield the selectively diacetylated 1,3-derivative **4**. Similarly, propionic anhydride and di-*tert*-butyl dicarbonate convert **3** to the corresponding dipropionyl and di-BOC derivatives, **5** and **6**, respectively. Reduced water solubility and ease of isolation of products derived from the propionyl and butoxycarbonyl derivatives make them in some instances preferable to the acetyl derivatives as reactants. The reaction of **3** with *para*-toluenesulfonyl chloride in presence of potassium carbonate gave 1,3-ditosyl-5-hydroxy-1,3-diazacyclohexane **7** in excellent yield. Analogous reaction of **3** with methanesulfonyl chloride gave the corresponding 1,3-di(methanesulfonyl)-5-hydroxy-1,3-diazacyclohexane, **8**. 1,3-Diamino-2-propanol **2** was also conveniently acetylated in refluxing ethyl acetate to give 1,3-diacetaminopropan-2-ol **9**. The latter on treatment with formaldehyde in acetic acid containing sulfuric acid undergoes a Mannich ring-closure to also produce **10**, albeit in rather poor yield.[13] Selective hydrolysis of **10** by aqueous potassium carbonate also readily affords **4**.

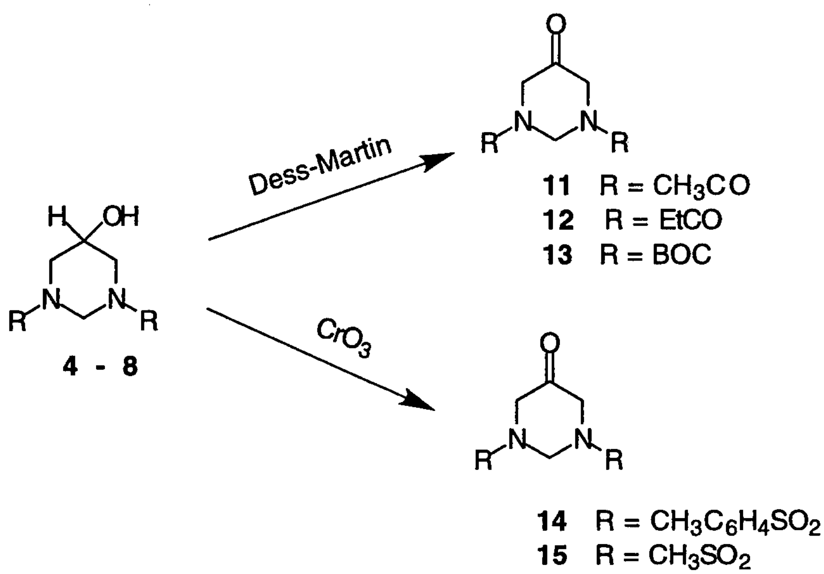
With 5-hydroxy-1,3-diazacyclohexane **3** and related compounds readily available, the synthesis of 5-keto derivatives was investigated as potential key intermediates for the further functionalization of the 1,3-diazacyclohexane ring system at the 5-position.

Scheme 2



However, attempts to transform the 5-hydroxyl group in either **4** or **5** to the corresponding ketone by various oxidation procedures were unsatisfactory. In our hands, when these materials were subjected to PCC, Jones reagent, Swern oxidation conditions and acetyl nitrate supported on montmorillonite[14] no ketone could be isolated and there was evidence of hydrolytic instability of the aminal group leading to the water-soluble ring-opened products. This view is at least partially strengthened by the finding, outlined in Scheme **3,** that 1,3-ditosyl- and 1,3-dimesyl-1,3-diazacyclohexane-5-ol derivatives **7** and **8,** water-insoluble materials, were readily converted by oxidation with Jones reagent to the corresponding ketones **14** and **15.** Although ketones **14** and **15** were found to readily form stable hydrates, the ketone forms were easily recovered by dehydration of the hydrate using azeotropic distillation with benzene or toluene. Reaction of ketone **14** with ethylene glycol in the presence of acid readily convertd it to the ketal derivative, 1,4-dioxa-7,9-ditosyl-7,9-diazaspiro[4.5]decane **16**.

Scheme 3



We now report that the Dess-Martin procedure[15] cleanly oxidizes diacylated 5-hydroxy 1,3-diazacyclohexanes to ketones in excellent yields using the preformed 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one periodinane reagent in methylene chloride solution. To avoid hydrate formation, product isolation was simplified by a non-aqueous work-up. Addition of ethyl ether to the reaction mixture precipitated the iodobenzoic acid and the organic layer was passed through a short column of silica gel. Elution with ethyl acetate afforded the corresponding ketones **11, 12** and the di-BOC derivative **13** in yields of 87%, 83% and 100%, respectively.

It is well-established that cyclic polynitramines are important energetic materials.[16] With reasonable quantities of these acylated ketones and related 5-hydroxy-1,3-diazacyclohexane compounds in hand, attention turned toward further functionalization of the ring system with a view towards preparing new high energy density materials. 5-Hydroxy-1,3-diazacyclohexane **3**, when treated with 100% HNO_3

and P_2O_5, produces the 1,3-dinitro-5-nitrato-1,3-diazacyclohexane **17**, in 80% yield. X-ray crystallographic analysis confirms this structure and the crystal density is found to be 1.76 g/cc^3. The ORTEP diagram for **17** is shown in Figure 1.

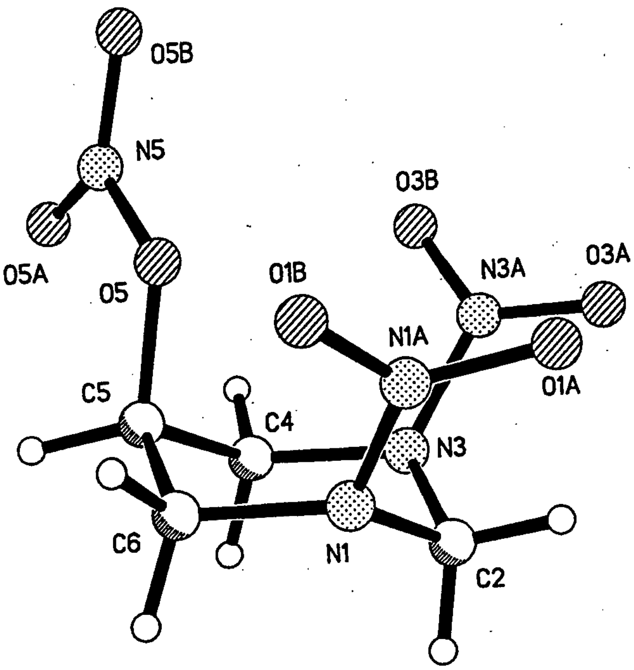
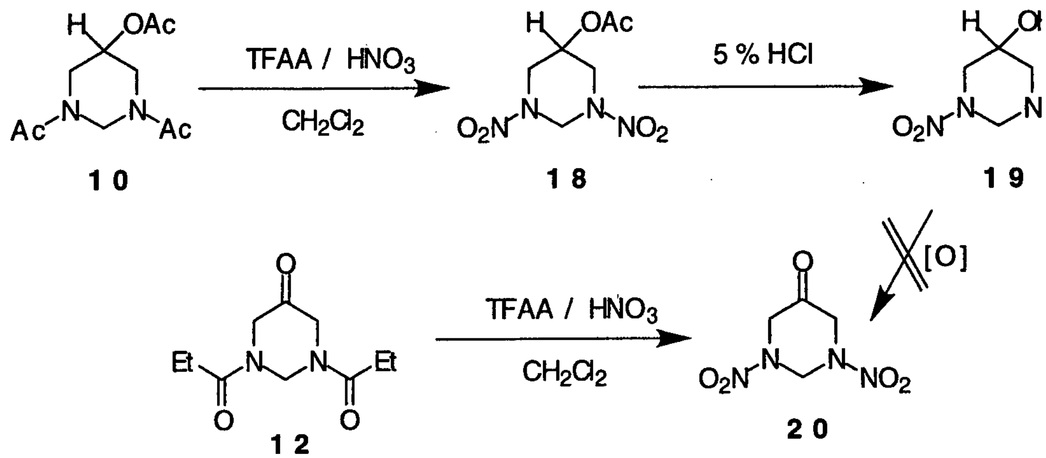


Figure 1. The ORTEP diagram for **17** showing the numbering scheme and an edge-on view of the molecular structure.[1] The figure was drawn using experimentally determined coordinates and thermal ellipsoids represented at the 20% probability level.

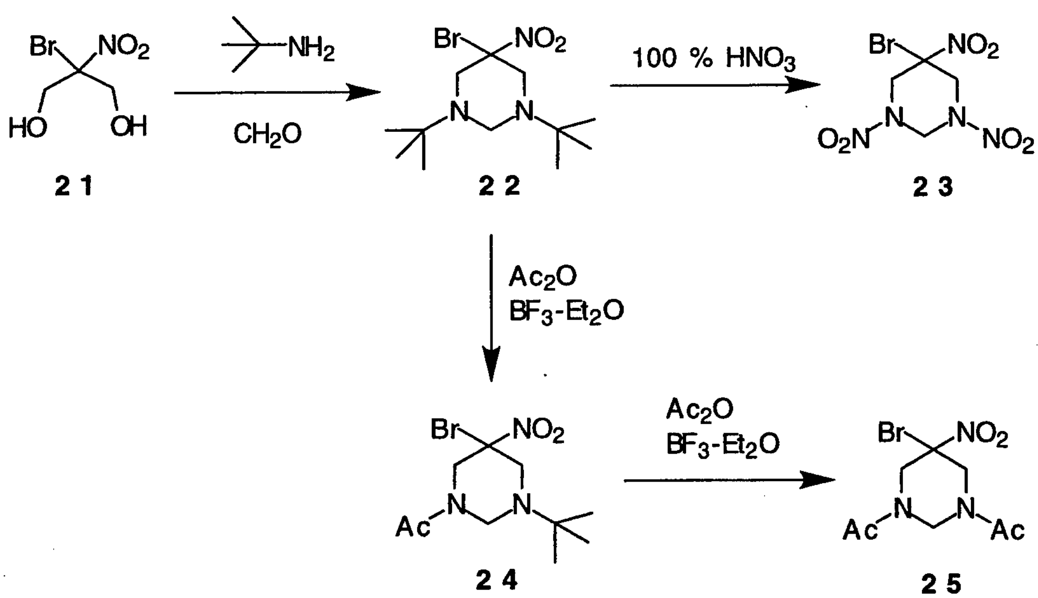
When compound **10** was subjected to nitrolysis using either nitric acid and trifluoroacetic anhydride in methylene chloride or nitric acid and P_2O_5 the N-acetyl groups were replaced by nitro groups to give the dinitramino acetate **18**. Hydrolysis of **18** with 5% HCl readily furnished the dinitramino alcohol **19.** Attempts to oxidize the dinitramino alcohol **19** to the desired dinitramino ketone **20** were unsuccessful (Jones, Dess-Martin), perhaps due to the instability of the product during the work-up, but the dinitramino ketone **20** could be prepared from the 1,3-dipropionyl ketone **12**. Thus, treatment of the 1,3-dipropionyl ketone **12** with nitric acid and trifluoroacetic anhydride in methylene chloride furnished the desired nitrolysis product, 1,3-dinitro-1,3-diazacyclohexan-5-one **20**. These transformations are summarized in Scheme 4.

Scheme 4



A second pathway (Method B, Scheme 1) to access this ring system, based on the condensation of 2-bromo-2-nitro-1,3-propanediol **21** with t-butylamine and formaldehyde to yield 1,3-di(t-butyl)-5-bromo-5-nitro-1,3-diazacyclohexane **22**, was examined and is shown in Scheme 5.

Scheme 5



Compound **22** was obtained in 81% yield as a pale yellow crystalline solid. The nitrolysis of **22** with 100% nitric acid gave a 54% yield of 1,3,5-trinitro-5-bromo-1,3-diazacyclohexane **23.** Further transformations involving acylative dealkylation of **22** by reaction with acetic anhydride and BF_3-etherate to afford the corresponding 1-acetyl-3-t-butyl-5-bromo-5-nitro-1,3-diazacyclohexane **24** and 1,3-diacetyl-5-bromo-5-nitro-1,3-diazacyclohexane **25** have been successfully carried out.[17] The details of this chemistry are reported elsewhere in this journal.[17]

In conclusion, two general approaches to the synthesis of 5-keto-1,3-diazacyclohexane and related 1,3-diazacyclohexanes, all versatile intermediates for further functionalization of the 1,3-diazacyclohexane ring system at the 5-position, have been developed. A number of 5-substituted 1,3-diazacyclohexanes including new energetic materials have been prepared.

Experimental

Melting points are uncorrected. 1,3-Diaminopropan-2-ol was used as obtained from Aldrich Chemical Co. The ^1H and ^{13}C nmr spectra were recorded at 300 MHz and 75 MHz, respectively, in either deuteriochloroform or deuterioacetone solution with tetramethylsilane as the internal reference. In the case of spectra measured in D_2O solution, an external capillary of tetramethylsilane was used as the reference.

WARNING: Although no problems were encountered in this work, compound **17** is potentially an energetic material and appropriate precautions should be taken in the handling of this material.

5-Hydroxy-1,3-diazacyclohexane (3). A solution of 1,3-diaminopropan-2-ol **(2)** (0.64 g, 7.10 mmole) and paraformaldehyde (0.2 g, 6.67 mmole) in methanol (10 mL) was heated under reflux for 48 h followed by removal of the solvent in vacuum. The resulting solid residue was recrystallized from acetonitrile to afford 0.60 g (88%) of pure **3** as a colorless crystalline solid; mp 99-102 °C. ^1H NMR (D_2O) δ 1.93 (dd, J=13.27 Hz, 7.78 Hz, 2H), 2.40 (dd, J= 13.27 Hz, 3.66 Hz, 2H), 2.78 (d, J=12.82 Hz, 1H), 2.90 (m, 1 H), 2.98 (d, J = 12.82 Hz, 1H); ^{13}C NMR (D_2O) δ 49.5, 59.2, 63.9. HRMS (FAB) Calc. for $C_4H_{11}N_2O$ (MH^+) 103.0871. Found m/z 103.0871

1,3-Diacetyl-5-hydroxy-1,3-diazacyclohexane (4). **Method 1. From the acetylation of (3).** Acetic anhydride was added dropwise to a stirred solution of **3** (4.26 g, 41.8 mmole) and potassium carbonate (11.7 g, 85.3 mmole) in water (50 mL) maintained at 0

2.98 (d, J = 12.82 Hz, 1H); ^{13}C NMR (D_2O) δ 49.5, 59.2, 63.9. HRMS (FAB) Calc. for $C_4H_{11}N_2O$ (MH^+) 103.0871. Found m/z 103.0871

1,3-Diacetyl-5-hydroxy-1,3-diazacyclohexane (4). Method 1. From the acetylation of (3). Acetic anhydride was added dropwise to a stirred solution of **3** (4.26 g, 41.8 mmole) and potassium carbonate (11.7 g, 85.3 mmole) in water (50 mL) maintained at 0 °C. Upon completion of the addition, the reaction mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was taken up in methylene chloride and dried over magnesium sulfate. Removal of the solvent gave 6.43 g (83%) of a solid. Recrystallization from ethyl acetate afforded **4** as a colorless crystalline solid; mp 102.5-104.5 °C. The molecular structure of **4** was confirmed by an X-ray structure determination.[18] ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.27 (s, 3H), 3.42 (dd, J= 13.73 Hz, 2.29 Hz, 1H), 3.57 (dd, J= 13.73 Hz, 2.75 Hz, 1H), 3.70 (dd, J = 13.73 Hz, 4.58 Hz, 1H), 3.88 (m, 1 H), 3.99 (s, br, 1H), 4.09 (dd, J= 13.73 Hz, 4.58 Hz, 1H), 4.54 (d, J = 12.82 Hz, 1H), 5.59 (d, J= 12.81 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.2, 47.7, 51.9, 56.4, 63.9, 170.5, 171.0. HRMS (FAB) Calc. for $C_8H_{14}N_2O_3$ (MH^+) 187.1084. Found m/z 187.1083

Method 2. From hydrolysis of (10). A solution of **10** (63 mg, 0.28 mmole) dissolved in ethanol (2.5 mL) containing 10% potassium carbonate (2.5 mL) was heated under reflux for 1.5 h followed by removal of the solvent in vacuum. The residue was taken up in methylene chloride and dried over magnesium sulfate. Removal of the solvent gave 29 mg (56%) of a colorless solid which was identical with that isolated from the acetylation of (3).

1,3-Dipropionyl-5-hydroxy-1,3-diazacyclohexane (5). To a stirred solution of **3** (3.25 g, 31.9 mmole) and potassium carbonate (13.89 g, 100.5 mmole) in water (50 mL) maintained at 0 °C was added propionic anhydride dropwise. Upon completion of the addition, the reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was taken up in methylene chloride and dried over magnesium sulfate. Removal of the solvent gave a colorless solid (6.10 g, 89%) which after recrystallization from ethyl acetate afforded **5** as a colorless crystalline solid; mp 141-143 °C. The molecular structure of **5** was confirmed by an X-ray structure determination.[18] ^1H NMR ($CDCl_3$) δ 1.12 (q, 6H), 2.67-2.71 (m, 4H), 3.65 (m, 3H), 3.88(m, 2H), 4.26 (s, 1H) 4.80 (d, J = 13.73 Hz, 1H), 5.37 (d, J = 13.73 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.2, 26.0, 26.3, 48.0, 51.0, 55.6, 63.8, 173.4, 174.1; HRMS (FAB) Calc. for $C_{10}H_{19}N_2O_3$ (MH^+) 215.1396. Found m/z 215.1394.

1,3-Di(t-butoxycarbonyl)-5-hydroxy-1,3-diazacyclohexane (6). To a stirred solution of **3** (0.61 g, 5.98 mmole) and potassium carbonate (2.50 g, 18.1 mmole) in water (30 mL) maintained at 0°C was added dropwise a solution of di-tert-butyl dicarbonate in tetrahydrofuran (20 mL). On completion of the addition, the reaction mixture was stirred at room temperature overnight. The separated aqueous layer was extracted with methylene chloride (2 x 30 mL) and the combined organic layers were washed with water and dried over magnesium sulfate. Removal of the solvent gave a colorless solid (1.54 g, 85%) which after recrystallization from ethyl acetate and hexanes afforded **6** as a colorless crystalline solid; mp 127-129 °C. ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 18H), 3.24 (m, br, 3H), 3.77 (m, br, 3H), 4.90 (m, br, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 49.3, 57.0, 63.3, 80.6, 154.3. Anal. Calcd for $C_{14}H_{26}N_2O_5$: C, 55.61; H, 8.67; N, 9.26. Found: C, 55.68; H, 8.84; N, 9.13.

1,3-Di(4-toluenesulfonyl)- 5-hydroxy-1,3-diazacyclohexane (**7**). To a stirred solution of **3** (1.00 g, 9.80 mmole) in water (10 mL) containing potassium carbonate (2.70 g, 20 mmole) was added a solution of tosyl chloride (3.74 g, 20 mmole) in THF (10 mL). The reaction mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue was taken up in chloroform (100 mL), washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent gave a colorless solid which after recrystallization from ethanol afforded 2.95 g (73%) of **7** as a crystalline solid; mp 182-183 °C. ^{1}H NMR ($CDCl_3$) δ 1.94 (d, J= 8.2 Hz, 1H), 2.44 (s, 6H), 3.18 (dd, J= 13.28 Hz, 5.49 Hz, 2H), 3.25 (dd, J= 13.28 Hz, 3.66 Hz, 2H), 3.53 (m, 1H), 4.48 (d, J= 12.36 Hz, 1H), 4.78 (d, J= 12.36 Hz, 1H), 7.34 (d, J= 8.24 Hz, 4H), 7.73 (d, J = 8.24 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.5, 50.8, 60.6, 62.0, 127.6, 129.9, 135.1, 144.3; HRMS (FAB) Calc. for $C_{18}H_{22}N_2O_5S_2$ (MH^+) 411.1048. Found m/z 411.1058.

1,3-Dimesyl-5-hydroxy-1,3-diazacyclohexane (**8**). To a stirred solution of **3** (0.34 g, 3.33 mmole) in water (10 mL) containing potassium carbonate (1.33 g, 9.62 mmole) was added methanesulfonyl chloride (0.88 g, 7.68 mmole) dropwise. The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was taken up in acetone (100 mL), washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent gave a colorless semi-solid which after recrystallization from acetone / hexanes afforded **8** as a colorless crystalline solid (0.50 g, 58%) of **8**; mp 156-157 °C. The molecular structure of **8** was confirmed by an X-ray structure determination.[18] ^{1}H NMR (acetone-d_6) δ 3.04 (s, 6H), 3.46 (dd, J= 13.73 Hz, 5.50 Hz, 2H), 3.58 (dd, J= 13.73 Hz, 3.21 Hz, 2H), 3.95 (m, 1H), 4.71 (d, J= 13.27 Hz, 1H), 4.90 (d, J= 13.28 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 39.2, 51.4, 60.3, 62.9; HRMS (FAB) Calc. for $C_6H_{15}N_2O_5S_2$ (MH^+) 259.0422. Found m/z 259.0420.

1,3-Diacetaminopropan-2-ol (**9**). A solution of 1,3-diaminopropan-2-ol **2** (10.50 g, 116.5 mmole) in ethyl acetate (50 mL) was heated under reflux for 48 h. Removal of the solvent in vacuum afforded 17.33 g (85%) of an oil which solidified on standing. Recrystallization from ethyl acetate-hexanes gave a colorless solid; mp 92-94 °C. ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 6H), 3.31 (m, 4H), 3.77 (m, 1H),), 4.75 (s, br, 1H), 6.86 (t, br, 2H); ^{13}C NMR ($CDCl_3$) δ 23.1, 43.0, 70.3, 171.9. HRMS (FAB) Calc. for $C_7H_{15}N_2O_3$ (MH^+) 175.1083. Found m/z 175.1082.

1,3-Diacetyl-5-acetoxy-1,3-diazacyclohexane (10). Method 1. From the acetylation of 3. Acetic anhydride (5.0 mL, 53 mmole) was added dropwise to a stirred solution of 5-hydroxy-1,3-diazacyclohexane (3) (1.06 g, 10.4 mmole) in 1,2-dichloroethane (30 mL) while the temperature was maintained at 0 °C. Upon completion of the addition, the reaction mixture was heated under reflux for 48 h followed by removal of the excess acetic anhydride in vacuum. The residue, a clear oil, slowly solidified on standing and was recrystallized from methylene chloride - ether to give 1.74 g (73%) of pure **10** as colorless cubic crystalline material; mp 87-89 °C. The molecular structure of **10** was confirmed by an X-ray structure determination.[18] ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.09 (s, 3H), 2.28 (s, 3H), 3.35 (dd, J= 14.19 Hz, 2.29 Hz, 1H), 3.68 (dd, J= 14.19 Hz, 2.29 Hz, 1H), 3.84 (m, 1 H), 4.40 (m, 1 H), 4.46 (d, J= 13.27 Hz, 1H), 4.84 (m, 1 H), 5.77 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.2, 44.3, 49.3, 56.2, 65.7, 169.7, 169.9 170.0. HRMS (FAB) Calc. for $C_{10}H_{16}N_2O_4$ (MH^+) 229.1188. Found m/z 229.1186.

Method 2. From the Mannich condensation of (9) with formaldehyde. A solution of 1,3-diacetaminopropan-2-ol **9** (2.84 g, 16.3 mmole) and 37% aqueous formaldehyde (1.33 g, 16.4 mmole) in acetic acid (20 mL) containing 3 drops of concentrated sulfuric acid was heated at 100 °C for 20 h. After removal of the solvent at reduced pressure, the residue was taken up in methylene chloride (50 mL) and the organic layer was washed successively with water, saturated sodium bicarbonate, water and then dried over magnesium sulfate. Removal of the solvent afforded 80 mg (2%) of a clear oil which solidified on standing. This material, much of which was likely lost due to its water solubility, was identical with that isolated from method described above.

1,3-Diacetyl-1,3-diazacyclohexan-5-one (11). Method 1. From the diacetamido alcohol **4** (0.51 g, 2.74 mmole) using the same procedure as that employed to prepare **12** there was obtained 0.44 g (87%) of **11** as a colorless oil. Recrystallization from acetone-hexanes afforded a colorless solid. HRMS (FAB) Calc. for $C_8H_{13}N_2O_3$ (MH^+) 185.0926. Found m/z 185.0923.

Method 2. From ozonolysis of 28: Compound **27** (2.5 g, 13.7 mmol) was dissolved in methanol (250 mL) and cooled to -78 °C. A mixture of ozone in oxygen was bubbled into the solution for one hour, and then oxygen was run into it until the blue color completely disappeared. The solution was then flushed with nitrogen gas while slowly warming up to room temperature. The solution was then treated with Pd(10%/C) and hydrogen gas overnight, to destroy the ozonide,. The suspension was then filtered and the filtrate was concentrated to get a colorless oil. The oil was dissolved in THF (10 mL) and then slowly poured into ethyl ether (50 mL). The 1,3-diacetyl-1,3-diazacyclohexan-5-one was collected (1.9 g, 75% yield) as a precipitate. The precipitate is hygroscopic and was kept in a desiccator. ^{1}H NMR ($CDCl_3$), δ 5.24 (s, 2H), 4.40 (s, 2H), 4.20 (s, 2H), 2.32 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$), δ 199.0, 169.5, 169.2, 55.5, 54.9, 52.3, 21.2. HRMS (EI) Calc. for $C_8H_{12}N_2O_3$ (M^+) 184.0848. Found m/z 184.0846.

Alternatively, the dangerous ozonide can be destroyed by addition of dimethylsulfide. However, the by-product is DMSO that remains with the product can not be separated easily.

1,3-Dipropionyl-1,3-diazacyclohexan-5-one (12). To a stirred solution of alcohol **5** (0.55 g, 2.57 mmole) in methylene chloride (20 mL) was added the preformed 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one Dess-Martin periodinane reagent (3.47 g, 8.18 mmole) and the resulting mixture was stirred at room temperature for 5 h. Ethyl ether (100 mL) was added and the resulting solid was removed by filtration. The filtrate was passed through a short silica gel column and the product was eluted with ethyl acetate. Removal of the solvent gave a yellow oil (0.45 g, 83%). Recrystallization from acetone-hexanes afforded a colorless solid; mp 95-97 °C. ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 6H), 2.32 (q, 2H), 2.58 (q, 2H), 4.21 (s, 2H) 4.38 (s, 2H), 5.27 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 8.7, 8.9, 26.4, 52.5, 54.4, 54.7, 172.4, 172.8, 199.8; HRMS (FAB) Calc. for $C_{10}H_{17}N_2O_3$ (MH^+) 213.1239. Found m/z 213.1239.

1,3-Di(t-butoxycarbonyl)-1,3-diazacyclohexan-5-one (13). A solution of the di-BOC derivative **6** (0.87 g, 2.88 mmole) and the preformed 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one Dess-Martin periodinane reagent (2.04 g, 4.81 mmole) in methylene chloride (30 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl ether (100 mL), poured into a saturated aqueous sodium bicarbonate solution containing excess sodium thiosulfate and stirred for 15 min. The separated organic layer was treated successively with 5% sodium bicarbonate, water and finally dried over magnesium sulfate. Removal of the solvent gave a viscous colorless oil (0.86 g, 100%) which solidified on standing; mp 65-66°C. ^{1}H NMR ($CDCl_3$) δ1.49 (s, 18H), 4.11 (s, 4H), 5.03 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 53.0, 55.9, 81.5, 153.5, 201.7.

1,3-Di(*p*-toluenesulfonyl)-1,3-diazacyclohexan-5-one (14). To a stirred solution of (7) (2.02 g, 4.93 mmole) in acetone (50 mL) maintained at 0 °C was added dropwise a mixture of CrO_3 (1.20 g, 12.0 mmole) in water (3 mL) containing concentrated sulfuric acid (1.5 mL). After the addition was complete the reaction mixture was stirred vigorously at room temperature for 2.5 h. Water was added to dissolve precipitated salts and the solution was extracted with methylene chloride (3 x 30 mL). The combined organic layers were washed with saturated sodium bicarbonate solution, water and dried over magnesium sulfate. Removal of the solvent in vacuum afforded 1.52 g (76%) of a colorless solid which was recrystallized from acetone-hexanes to give pure **14**; mp 148 °C (dec.). ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 6H), 3.65 (s, 4H), 4.89 (s, 2H), 7.34 (d, J = 8.24 Hz, 4H), 7.68 (d, J= 8.24 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 53.7, 59.3, 127.7, 130.1, 134.0, 144.9, 196.9; HRMS (FAB) Calc. for $C_{18}H_{20}N_2O_5S_2$ (MH^+) 409.0898. Found m/z 409.0892.

1,4-Dioxa-7,9-ditosyl-7,9-diazaspiro[4.5]decane (16): A mixture of ketone **14** (1.15 g, 2.82 mmole), ethylene glycol (0.55 g, 8.87 mmole) and p-toluenesulfonic acid monohydrate (~0.1 g) in benzene (50 mL) was heated under reflux for 20 h using a Dean-Stark apparatus to remove water. After cooling, the solution was washed with saturated sodium bicarbonate solution, water and dried over magnesium sulfate. Removal of the solvent afforded 1.15 g (90%) of a colorless solid which was recrystallized from acetone-hexanes to give pure **16** as a crystalline solid; mp 210 °C. (dec.) ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 6H), 3.13 (s, 4H), 3.79 (s, 4H), 4.63 (s, 2H), 7.30 (d, J= 8.24 Hz, 4H), 7.70 (d, J = 8.24 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 51.2, 60.0, 65.0, 101.5, 127.7, 129.6, 135.5, 143.8; HRMS (FAB) Calc. for $C_{20}H_{24}N_2O_6S_2$ (MH^+) 453.1154. Found m/z 453.1166.

1,3-Dimesyl-1,3-diazacyclohexan-5-one (15). To a stirred solution of **8** (0.26 g, 1.01 mmole) in acetone (10 mL) maintained at 0 °C was added dropwise a mixture of CrO_3 (0.35 g, 3.5 mmole) in water (0.75 mL) containing concentrated sulfuric acid (0.75 g). After the addition was complete the reaction mixture was stirred vigorously at room temperature for 4 h. Solid sodium bicarbonate was added and the mixture was stirred for 30 min. The solution was passed through a short silica gel column and the product was eluted with acetone. Removal of the solvent in vacuum afforded a colorless solid (1.52 g, 76%) which was recrystallized from acetone-hexanes to give pure **15**; mp 139 °C (dec.). ^{1}H NMR (acetone-d_6) δ 3.05 (s, 6H), 3.47 (s, 4H), 4.82 (s, 2H); ^{13}C NMR (acetone-d_6) δ 39.5, 55.2, 60.1, 198.4. (ketone); δ38.5, 54.9, 59.1, 89.1 (ketone monohydrate). HRMS (FAB) Calc. for $C_6H_{13}N_2O_5S_2$ (MH^+) 257.0266. Found m/z 257.0264.

1,3-Dinitro-5-nitrato-1,3-diazacyclohexane (17). To 100% nitric acid (5.0 mL) maintained between -5 °C to 0 °C was added P_2O_5 (~0.5 g) portionwise and after stirring for 20 min. at this temperature, 5-hydroxy-1,3-diazacyclohexane **3** (0.270 g, 2.65 mmole) was added cautiously in small portions. The resulting solution was stirred at 0 °C for 4 h and then poured on to ice (50 g) to give a precipitate that was collected by vacuum filtration, dried and recrystallized from ethanol-water to afford a white solid (0.50 g, 80%); mp 124-125.5 °C. The molecular structure of **17** was confirmed by an X-ray structure determination.[18] ^{1}H NMR (acetone-d_6) δ4.24 (d, J=15.56 Hz, 2H), 5.04 (dd, J= 15.56 Hz, ~1.5 Hz, 2H), 5.30 (d, J= 14.65 Hz, 1H), 5.64 (m, 1H), 6.97 (dd, J= 14.65 Hz, ~1.5 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 49.0, 61.8, 76.0. Anal. Calc. for $C_4H_7N_5O_7$: C, 20.26; H, 2.98; N, 29.53. Found: C, 20.23; H, 3.08; N, 29.46.

5-Acetoxy-1,3-dinitro-1,3-diazacyclohexane (18). To a stirred solution of trifluoroacetic anhydride (2.4 mL, 17 mmole) in methylene chloride (20 mL) was added 100% nitric acid (1.13 g, 18 mmol) at -5 °C and the mixture was stirred at this temperature for 0.5 h. A solution of **10** (0.36 g, 1.6 mmole) in methylene chloride (5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued over night. The solution was poured in cold water (50 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 X 30 mL) and the combined organic layers were treated successively with water, 5% sodium bicarbonate, water and finally dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a colorless solid (0.37 g, 100%) which was recrystallized from ethyl acetate and hexanes to furnish **18** as a colorless crystalline solid;

mp 118-119 °C. ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 3.70 (m, 2H), 4.85 (m, 2H), 4.96 (d, J= 14.65 Hz, 1H), 5.10 (m, 1H), 6.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 49.6, 60.7, 65.0, 169.6; Anal. Calc. for $C_6H_{10}N_4O_6$: C, 30.78; H, 4.30; N, 23.93. Found: C, 30.75; H, 4.58; N, 23.88.

1,3-Dinitro-5-hydroxy-1,3-diazacyclohexane (19). A mixture of **18** (0.36 g, 1.54 mmole) and 5% HCl (20 mL) was heated under reflux for 4 h. Removal of the solvent under reduced pressure gave a colorless solid (0.29 g, 98%) which was recrystallized from ethyl acetate and hexanes to furnish **19** as a colorless crystalline solid; mp 102.5-104.5 °C. The molecular structure of **19** was confirmed by an X-ray structure determination.[18] ^{1}H NMR (acetone-d_6) δ 4.06 (dd, J=14.20 Hz, 2.29 Hz, 2H), 4.24-4.35 (m, 3H), 4.79 (m, 1H), 5.68 (d, J=14.64 Hz, 1H), 6.31 (d, J= 14.64 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 53.3, 61.2, 63.5. Anal. Calc. for $C_4H_8N_4O_5$: C, 25.01; H, 4.20; N, 29.16. Found: C, 25.21; H, 4.30; N, 28.79.

1,3-Dinitro-1,3-diazacyclohexan-5-one (**20**). To a stirred solution of trifluoroacetic anhydride (16 mL, 113 mmole) in methylene chloride (50 mL) was added dropwise 100% nitric acid (4.5 mL, 109 mmole) at –5 to 0 °C and the mixture was stirred at this temperature for 20 min. To this mixture ketone **12** (1.57 g, 7.41 mmole) was added in small portions and stirring was continued at 0 °C for 4 h. The reaction mixture was poured into excess hexane and stored in a freezer overnight. The resulting precipitate was collected by filtration to afford the product **20** (0.91 g, 65%) as a colorless solid; mp 90d °C. ^{1}H NMR (acetone-d_6) δ4.81 (s, 4H), 6.22 (s, 2H); ^{13}C NMR (acetone-d_6) δ57.3, 61.1, 195.7.

1,3-Di(t-butyl)-5-bromo-5-nitro-1,3-diazacyclohexane (22): To a stirred solution of 2-bromo-2-nitro-1,3-propanediol **21** (18.26 g, 91.3 mmole) in 100 mL of methanol at 0°C was added t-butylamine (13.40 g, 183 mmole) dropwise in 30 min. The mixture was stirred at this temperature for an additional 30 min. followed by the addition of 37% aqueous formaldehyde (07.46 g, 92.0 mmole) in one portion. The resulting mixture was stirred at ambient temperature for 48 h, cooled to 0°C and water (150 mL) was added. The resulting precipitate was collected by filtration and washed with water to yield give after recrystallization from ethanol-water 23.92 g of **22** as a pale yellow solid (81%), mp 93-94°C. The molecular structure of **22** was confirmed by an X-ray structure determination.[18] HRMS (FAB) Calc. for $C_{12}H_{25}BrN_3O_3$ (MH^+) 322.1130. Found m/z 322.1132. ^{1}H NMR ($CDCl_3$) δ1.10 (s, 18 H), 2.70 (d, J=11.9 Hz, 2H), 2.79 (d, J=9.16 Hz, 1H), 4.16 (m, 3H); ^{13}C NMR ($CDCl_3$) δ26.4, 53.9, 56.1, 63.3, 86.8

1,3,5-Trinitro-5-bromo-1,3-diazacyclohexane(23): Compound **22** (5.55 g, 17.2 mmole) was cautiously added in small portions during about 1h to a stirred solution of 65 mL of 100% nitric acid at 0°C. During the addition the temperature of the reaction mixture was always maintained lower than 5°C. On completion of the addition, the reaction mixture was allowed to warm to room temperature stirred over night and then poured onto 500g of ice. The resulting precipitate was collected by filtration, washed thoroughly with water and dried to give 2.78 g (54%) of **23**; mp 158-159 °C. The molecular structure of **23** was confirmed by an X-ray structure determination.[18] ^{1}H-NMR (acetone-d_6) δ5.01 (d, J=15.0 Hz, 2H), 5.40 (d, 14.7 Hz, 2H) 6.10 (d, J=14.6 Hz, 1H) 6.29 (d, 14.6 Hz, 1H); ^{13}C-NMR (acetone-d_6) δ55.2, 60.3, 83.1.

1-Acetyl-3-t-butyl-5-bromo-5-nitro-1,3-diazacyclohexane (24a/b): To a solution of **22** (0.41 g, 1.27 mmol) in acetic anhydride (5 mL) was added boron trifluoride diethyl etherate (0.4 mL) with stirring. The reaction mixture was stirred at room temperature for 24 h after which excess acetic anhydride was removed in vacuum and methylene chloride (50 mL) was added to the residue. The solution was washed successively with water (3 x 20 mL), brine (20 mL) and finally dried over anhydrous magnesium sulfate. Removal of the solvent gave 0.32 g (81%) of solid which was recrystallized from ethanol-water: mp 152-154d °C. The molecular structure of **24** was confirmed by an X-ray structure determination.[18] HRMS (FAB) Calc. for $C_{10}H_{19}BrN_3O_3$ (MH^+) 308.0610; Found m/z 308.0607. The NMR solution spectra of **24** shows it to be an equilibrium mixture of a major **24a** and minor **24b** rotomer in the ratio 2.5:1.

^{1}H NMR major rotomer **24a** ($CDCl_3$) δ1.12 (s, 9H), 2.25 (s, 3H), 2.92 (d, J = 12.81 Hz, 1H), 3.18 (d, J = 10.98 Hz, 1H), 3.65 (d, J = 14.65 Hz, 1H), 4.23-4.28 (m, 1H), 4.88-4.94 (m, 1H), 5.53-5.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ20.8, 26.4, 49.9, 54.2, 57.1, 57.4, 84.6, 168.5.

^{1}H NMR minor rotomer **24b** ($CDCl_3$) δ1.12 (s, 9H), 2.09 (s, 3H), 2.98 (d, J = 12.82 Hz, 1H), 3.31 (d, J = 13.65 Hz, 1H), 3.72 (d, J = 10.99 Hz, 1H), 4.17-4.23 (m, 1H), 4.66-4.71 (m, 1H), 5.55-5.61 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 21.0, 26.4, 49.9, 54.6, 62.2, 84.9, 167.9.

1,3-Di(acetyl)-5-bromo-5-nitro-1,3-diazacyclohexane (25): To a solution of **22** (0.30 g, 9.32 mmol) in acetic anhydride (5 mL) was added boron trifluoride dietherate (0.5 mL) and the mixture was stirred at 100 0°C for 3.5 h. Excess acetic anhydride was removed in vacuum and the residue was taken up in methylene chloride, washed with water and dried over magnesium sulfate. Removal of the solvent gave a brown oil which was purified by passage through a short column of silica gel using ethyl acetate to elute the material. The solvent was concentrated in vacuum and a colorless oil (0.20 g, 73%) obtained. Recrystallization from ethyl acetate / hexanes gave pure 1,3-di(acetyl)-5-bromo-5-nitro-1,3-diazacyclohexane **25** as a colorless solid. mp 116-118 °C. The molecular structure of **25** was confirmed by an X-ray structure determination.[18] HRMS (FAB) Calc. for $C_8H_{13}BrN_3O_4$ (MH^+) 294.0089. Found m/z 294.0081. ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 2H), 2.25 (s, 3H), 3.99 (d, J = 14.65 Hz, 1H), 4.13 (d, J = 14.65 Hz, 1H),4.69 (d, J = 13.27 Hz, 1H), 4.77 (d, J = 14.65 Hz, 1H), 5.15 (d, J = 14.19 Hz, 1H), 5.61 (d, J = 13.28 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ20.3, 20.9, 50.2, 54.9, 55.1, 83.6, 168.4, 168.9.

Methylenebisacetamide (26): A literature procedure [20] was slightly modified. A mixture of acetamide (71.2 g, 1.2 mol), paraformaldehyde (18.0g, 0.6 mol), and acetic acid (14.4 g) were refluxed overnight. When cooled to room temperature a solid was formed which was collected by filtration, and washed with acetone to give the product as a white solid (36.1 g). ^1H NMR ($CDCl_3$) δ6.9 (br, 2H), 4.58 (t, 2H), 2.0 (s, 6H). The acetone wash after three days gave another 3.6 g of the product (total yield 51%). The product was identical to the one reported in the literature.[20]

5-Exomethylene-1,3-diacetyl-1,3-diazacyclohexane (28): To a suspension of sodium hydride (4.4 g, 183.2 mmol) in freshly dried THF (700 mL) was added methylenebisacetamide (10.0 g, 77.0 mmol). The suspension was stirred at room temperature under nitrogen for 30 min. A solution of 3-chloro-2-chloromethyl-1-propene (10.0 g, 80 mmol) in THF (50 mL) was slowly added to the suspension in 2 h. The resulting mixture was heated under reflux for 72 h. The reaction mixture was cooled to room temperature and the formed solid was removed by filtration and discarded. The filtrate was concentrated, the residue dissolved in methylene chloride (400 mL) and extracted with water (300 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give **27** (13.8 g, 98 % yield) as a yellow oil. ^1H NMR ($CDCl_3$) δ5.12 (s,1H), 5.10 (s, 2H), 5.08 (s, 1H), 4.24 (s, 2H), 4.13 (s, 2H), 2.3 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ169.30, 169.36, 136.36, 114.31, 54.72, 51.63, 47.45, 21.44, 21.06; LRMS (CI) 183 (MH^+).

5-Exomethylene-1,3-diazacylohexane (29): A mixture of **28** (0.97 g, 5.3 mmol), NaOH (1 g, 25 mmol) and water (5 mL) was heated overnight in an oil bath maintained at 110 °C. The reaction mixture was cooled to room temperature, excess solid NaOH was added, followed by methylene chloride (25 mL). The layers were separated and the organic layer was dried over solid sodium hydroxide / sodium sulfate. A small portion was concentrated under reduced pressure at room temperature to obtain 5-exomethylene-1,3-diazacyclohexane while the major portion was reacted further to obtain **31**. ^1H NMR ($CDCl_3$) δ3.47 (s, 1H), 3.58 (s, 2H), 4.67 (s, 2H).

1,3-Diamino-(2-methylene)-propane (30): This compound was prepared according to the literature procedure.[21]

1,3-Bis(trifluoroacetyl)-5-exomethylene-1,3-diazacyclohexane (31): To the bulk of the above solution of **29** was added trifluoroacetic anhydride (2 mL) and the mixture stirred at room temperature overnight. The mixture was then concentrated under reduced pressure and the residue was chromatographed on silica gel eluting with 40 % acetone/hexane to give **31** as a pale yellow oil. The NMR spectra indicated it to be a mixture of conformers with the major conformer having the trifluoroacetamide groups anti to each other. ^1H NMR ($CDCl_3$) δ4.32 (br s, 4H); 5.21-5.35 m, 4H); ^{13}C NMR ($CDCl_3$) δ49.32, 50.76, 55.38 CF_3 quartet 110.61, 114.41, 118.22, 122.05 J = 286 Hz; CF_3 quartet 110.77, 114.58, 118.39, 122.20 J = 286 Hz, 118.0, 133.4, 155.8 (q), 156.3 (q). HRMS (EI) Calc. for $C_9H_8N_2O_2F_6$ (M^+) 290.0490. Found m/z 290.0503.

24 h after which excess acetic anhydride was removed in vacuum and methylene chloride (50 mL) was added to the residue. The solution was washed successively with water (3 x 20 mL), brine (20 mL) and finally dried over anhydrous magnesium sulfate. Removal of the solvent gave 0.32 g (81%) of solid which was recrystallized from ethanol-water: mp 152-154d °C. The molecular structure of **24** was confirmed by an X-ray structure determination.[18] HRMS (FAB) Calc. for $C_{10}H_{19}$ BrN_3O_3 (MH^+) 308.0610; Found m/z 308.0607. The NMR solution spectra of **24** shows it to be an equilibrium mixture of a major **24a** and minor **24b** rotomer in the ratio 2.5:1.

^{1}H NMR major rotomer **24a** ($CDCl_3$) δ1.12 (s, 9H), 2.25 (s, 3H), 2.92 (d, J = 12.81 Hz, 1H), 3.18 (d, J = 10.98 Hz, 1H), 3.65 (d, J = 14.65 Hz, 1H), 4.23-4.28 (m, 1H), 4.88-4.94 (m, 1H), 5.53-5.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ20.8, 26.4, 49.9, 54.2, 57.1, 57.4, 84.6, 168.5.

^{1}H NMR minor rotomer **24b** ($CDCl_3$) δ1.12 (s, 9H), 2.09 (s, 3H), 2.98 (d, J = 12.82 Hz, 1H), 3.31 (d, J = 13.65 Hz, 1H), 3.72 (d, J = 10.99 Hz, 1H), 4.17-4.23 (m, 1H), 4.66-4.71 (m, 1H), 5.55-5.61 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 21.0, 26.4, 49.9, 54.6, 62.2, 84.9, 167.9.

1,3-Di(acetyl)-5-bromo-5-nitro-1,3-diazacyclohexane (25): To a solution of **22** (0.30 g, 9.32 mmol) in acetic anhydride (5 mL) was added boron trifluoride dietherate (0.5 mL) and the mixture was stirred at 100 0°C for 3.5 h. Excess acetic anhydride was removed in vacuum and the residue was taken up in methylene chloride, washed with water and dried over magnesium sulfate. Removal of the solvent gave a brown oil which was purified by passage through a short column of silica gel using ethyl acetate to elute the material. The solvent was concentrated in vacuum and a colorless oil (0.20 g, 73%) obtained. Recrystallization from ethyl acetate / hexanes gave pure 1,3-di(acetyl)-5-bromo-5-nitro-1,3-diazacyclohexane **25** as a colorless solid. mp 116-118 °C. The molecular structure of **25** was confirmed by an X-ray structure determination.[18] HRMS (FAB) Calc. for C_8H_{13} BrN_3O_4 (MH^+) 294.0089. Found m/z 294.0081. ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 2H), 2.25 (s, 3H), 3.99 (d, J = 14.65 Hz, 1H), 4.13 (d, J = 14.65 Hz, 1H),4.69 (d, J = 13.27 Hz, 1H), 4.77 (d, J = 14.65 Hz, 1H), 5.15 (d, J = 14.19 Hz, 1H), 5.61 (d, J = 13.28 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ20.3, 20.9, 50.2, 54.9, 55.1, 83.6, 168.4, 168.9.

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Supplementary Material Available:. Copies of the ^{1}H and ^{13}C NMR spectra of 3,4,5,6,7,8,9,10,12,13,14,15,16,17,18,19,20,22,23,24a/b,25. This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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18. X-ray crystallographic analysis and ORTEP diagrams are included in the supporting information for this article. Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Center. They can be obtained, on request, from the Director, Cambridge Crystallographic Center, 12 Union Road, Cambridge CB2 1EZ. UK.

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