

Facile entry into the 3*H*,9*H*-bis[1,2,4]triazolo-[1,5-*a*:5',1'-*d*]-[1,3,5]triazinium (5/6/5 tricyclic NNN) system

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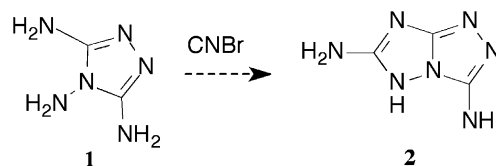
Abstract—A facile, one-pot reaction between 3,4,5-triamino-1,2,4-triazole (guanazine) and cyanogen bromide provides a new high-nitrogen example of the 3*H*,9*H*-bis[1,2,4]triazolo[1,5-*a*:5',1'-*d*][1,3,5]triazinium system, the 2,3,5,6-tetraamino-9-imino derivative (**3**) as a quaternary bromide salt.

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1. Introduction

In a previous limited-distribution US Government report,¹ we described a facile and unexpected formation of an example of the then unprecedented 3*H*,9*H*-bis[1,2,4]triazolo[1,5-*a*:5',1'-*d*][1,3,5]triazinium system from a one-pot reaction between 3,4,5-triamino-4*H*-1,2,4-triazole (guanazine, **1**) and cyanogen bromide. Anders and co-workers have since reported in the open literature about independent preparations of different derivatives of that system from the amination reactions of 9*H*-bis[1,3,4]thiadiazolo[3,2-*a*:2',3'-*d*][1,3,5]triazinium² and [1,3,4]thiadiazolo[2,3-*d*][1,2,4]triazolo[1,5-*a*][1,3,5]-triazinium³ derivatives, the former of which were prepared via a two-step sequence from reactions of thionyl halide, aldehydes, and pyridine to make 1-(haloalkyl)pyridinium halides followed by the reactions of these intermediates with 2-amino-1,3,4-thiadiazoles.⁴ Here we describe our alternative preparation of the 5/6/5 tricyclic 'NNN' system (using the nomenclature of Anders and co-workers³ for this trinuclear, that is, tricyclic, system).

Cyanogen bromide has been used as a carbon-insertion reagent between vicinal diamines to make aminoazoles, for example, with *C,C*-diamines to make 2-aminoimidazoles⁵ or *C,N*-diamines to make 3-amino-1,2,4-triazoles.⁶ Thus, CNBr might be similarly predicted to add

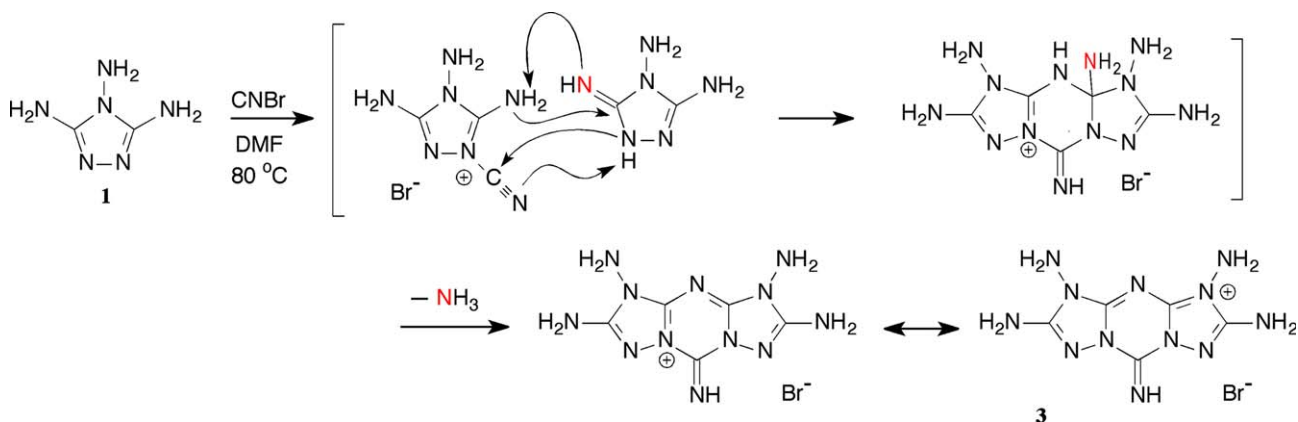


Scheme 1. Hypothetical cyclization of guanazine by cyanogen bromide.

to guanazine (**Scheme 1**), producing the 7*H*-1,2,4-triazolo[4,3-*b*][1,2,4]triazole system—as its 3,6-diamine **2** (or a guanidino tautomer)—a binuclear (bicyclic) skeleton, which had been prepared alternatively, by Potts and Hirsch,⁷ via the reaction of triaminoguanidine with cyanogen bromide, producing the 3,6,7-triamine.

However, we discovered that the guanazine–cyanogen bromide reaction (**Scheme 2**) instead unexpectedly produced a tricyclic quaternary salt, 2,3,5,6-tetraamino-9-imino-3*H*,9*H*-bis[1,2,4]triazolo[1,5-*a*:5',1'-*d*][1,3,5]triazinium bromide (**3**).⁸ The product was characterized by X-ray crystallography⁹ (**Fig. 1**) as well as spectroscopically and by elemental analysis. That the charge in the triazininium ring is not evenly delocalized is indicated by an asymmetry of the tricyclic structure's bond lengths (**Fig. 2**) as well as the distinct absorptions seen in the ¹H and ¹³C NMR spectra at room temperature—three peaks for NH₂ and five different carbons—unlike one of Anders' symmetrical 'NNN' derivatives (their **9k**), which showed equivalent substituents according to

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Scheme 2. Cyclization of guanazine by cyanogen bromide.

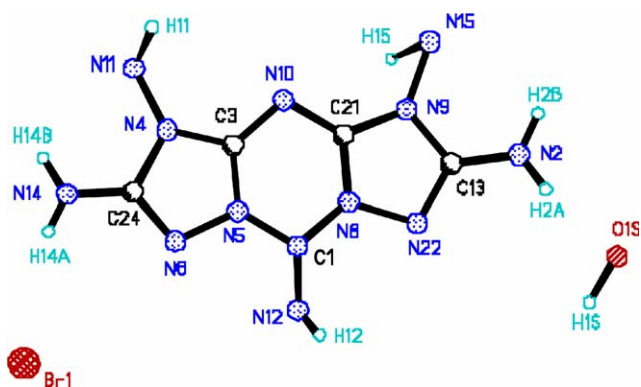


Figure 1. A drawing of 2,3,5,6-tetraamino-9-imino-3*H*,9*H*-bis[1,2,4]-triazolo[1,5-*a*:5',1'-*d*][1,3,5]triazinium bromide (**3**) hydrate.

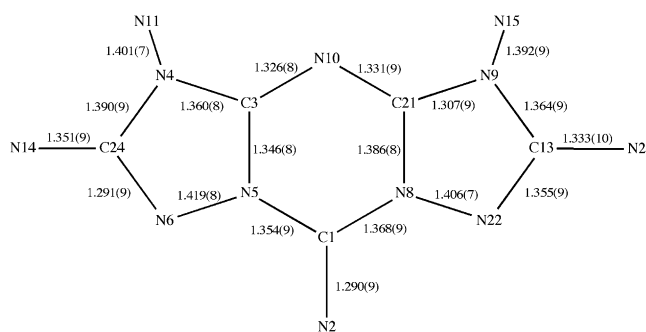


Figure 2. Bond lengths (Å) of non-hydrogen-bonds in the cation of **3**.

NMR.³ Also, interestingly, the ¹H NMR spectrum shows a temperature dependence, specifically, coalescence of the two N–NH₂ signals at an elevated temperature (333 K in DMSO-*d*₆), indicating an enhanced delocalization of the electron density.

The course of reaction leading to this product requires that CNBr must initially attack N¹ of guanazine, rather than the 4-amino substituent, analogous to the protonation of 4-amino-1,2,4-triazole at N¹.¹⁰ The cyano substituent links two guanazine rings (at N¹), which further cyclize via their 5-amino substituents—perhaps via an imine tautomer under the reaction conditions—

to form the 1,3,5-triazinium ring following the elimination of ammonia.

This formation of a fused triazoloquinazolinium quaternary salt is reminiscent of the unexpected cyclization by cyanogen bromide of 4-amino-3-(2-aminophenyl)-1,2,4-triazoles between the phenyl 2-amino substituent and N¹ of the triazole ring (rather than its 4-amino substituent). This produces 1,5-diamino-1*H*-1,2,4-triazolo[1,5-*c*]quinazolium bromides, reported by Jarvis and co-workers,¹¹ instead of the expected triazepines.

In the course of elucidating this system, we have also developed a superior procedure for the preparation of guanazine (**1**). We employed the chemical scheme devised by Child:¹² the reaction between commercially available dimethylcyanamide and hydrazine produces guanazine in one pot (with dimethylamine as by-product). By conducting the reaction in 2-methoxyethanol solvent instead of with neat reactants, the reaction proceeds much more cleanly and the workup is facilitated.¹³ The other recent preparations of **1** suffer the disadvantage of requiring toxic heavy metal oxides (lead or mercury) for the conversion of thiosemicarbazide derivatives.¹⁴

2. Conclusions

A facile, one-pot preparation of **3** provides the 3*H*,9*H*-bis[1,2,4]triazolo[1,5-*a*:5',1'-*d*][1,3,5]triazinium system in a highly functionalizable form, that is, one with five nitrogenous substituents (NH or NH₂) that may be used for numerous chemical conversions or extensions of this trinuclear (tricyclic) high-nitrogen skeleton. A superior preparation of guanazine (**1**) is reported.

Acknowledgments

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retrieving the crystallographic data⁹ (Figs. 1 and 2) for publication.

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8. *Preparation of 3*: A mixture of 14.02 g (0.123 mol) of 3,4,5-triamino-1,2,4-triazole (**1**) and 7.60 g (0.072 mol) of cyanogen bromide in 200 mL DMF was heated in a water bath at 80–81 °C for 2.5 h. The mixture, which contained a considerable amount of solid, was then cooled to ambient temperature, and the solid was collected on a medium-porosity fritted-glass filter funnel, washed twice with 25-mL portions of DMF and finally thrice with 2-propanol. After drying at 70 °C, the yield of a light olive solid (**3**) was 13.36 g (0.042 mol, 68% based on **1**). Multiple crystallizations from water gave small colourless needles, the form analyzed by X-ray crystallography. A sample for elemental analysis was vacuum dried over P₄O₁₀. DSC: exotherm 290 °C (onset), 293 °C (peak). ¹H NMR (DMSO-*d*₆, 300 K) δ 6.06 (s, 4H), 7.32 (s, 2H), 7.41 (s, 2H), 7.63 (s, 1H). ¹H NMR (DMSO-*d*₆, 333 K) δ 5.95 (s, 4H), 7.21 (bs, 4H), 7.58 (s, 1H). ¹³C NMR (DMSO-*d*₆, 300 K): δ 136.5 (non-¹H-decoupled d, ²J_{CH} = 6.0 Hz), 147.7, 149.0, 154.05 (¹H-decoupled), 154.11 (¹H-decoupled). IR (KBr): 3396, 3316, 1721, 1661, 1602, 1268, 1120, 1061, 993, 815, 766, 722, 638 cm⁻¹. Anal. Calcd for C₅H₉N₁₂Br (%): C, 18.95; H, 2.86; N, 53.00; Br, 25.20. Found: C, 18.96; H, 3.09; N, 52.45; Br (by difference), 25.50.
9. *Single-crystal X-ray diffraction analysis of 3 hydrate*: C₅H₁₁BrN₁₂O, FW = 335.17, Orthorhombic, *C*cc2, *a* = 15.7916(11) Å, *b* = 25.510(2) Å, *c* = 6.2985(9) Å, α = 90°, β = 90°, γ = 90°, *V* = 2537.3(5) Å³, *Z* = 8, ρ_{calcd} = 1.755 Mg/m³, μ = 4.615 mm⁻¹, *F*(000) = 1344, *R*₁ = 0.0608 for 1618 observed (*I* > 2σ₁) reflections and 0.0621 for all 1675 reflections, Goodness-of-fit = 1.114, 188 parameters. The data were collected on a Bruker P4 four-circle diffractometer. The crystals were irradiated using graphite monochromated CuK_α source (λ = 1.54178). The corrections were applied for Lorentz, polarization and absorption effects using SADABS [Bruker (2000). SADABS v 2.03, Bruker AXS Inc., Madison, Wisconsin, USA]. The structure was solved and refined with the aid of the programs in the SHELXTL-plus system of programs [Bruker (2000). SHELXTL v 6.10. Bruker AXS Inc., Madison, Wisconsin USA]. The full-matrix least-squares refinement on *F*² included atomic coordinates and anisotropic thermal parameters for all non-H atoms. The H atoms were included using a riding model, except for the water hydrogens, which were refined with fixed associative distances. This structure was determined to be a two-component merohedral twin with a relative population ratio of 65:35.
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13. *Preparation of 1*: A solution of 140.27 g (2.00 mol) of dimethylcyanamide and 68.49 g (2.14 mol) of 98% hydrazine in 250 mL of 2-methoxyethanol was refluxed for 7 h and then allowed to stand at an ambient temperature overnight. The solid that formed was collected on a medium-porosity fritted-glass filter funnel, washed once with 2-propanol–2-methoxyethanol (4:1) and four times with 2-propanol, and then allowed to air-dry overnight. The yield of gray solid was 48.50 g (0.425 mol, 42.5%). Mp 255–258 °C dec; lit.¹² 262–263 °C dec.
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