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Facile Synthesis of Substituted Nitrilotriacetamides

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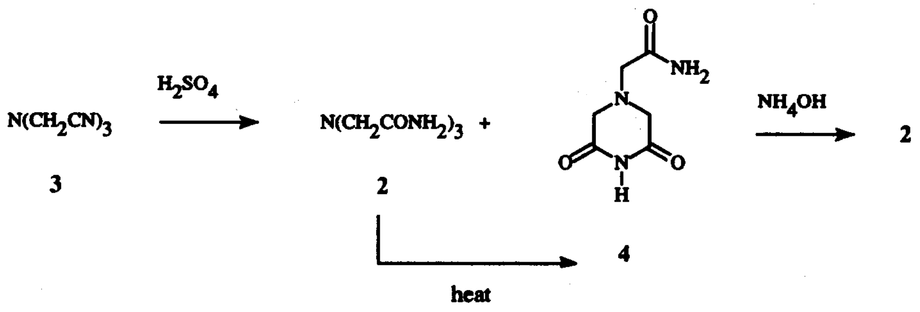
Abstract: Ligands which contain multiple amide groups represent interesting possibilities as chelating agents. We report here a facile synthesis and crystal structure of nitrilotriacetamide, 2, a neutral tetradentate ligand which we have been studying for metal complexation. Also described herein is a divergent synthesis of the mono-, di- and trimethylated and dimethyl-monoalkyl derivatives of 2.

Both nitrilotriacetic acid, 1, and the amide functional group are ubiquitous ligands for metal coordination, yet there are only two reports of a metal complex of nitrilotriacetamide, 2, the triamide derivative of nitrilotriacetic acid, in the literature.[2] One reason could be the negligible solubility of 2 in solvents other than water and DMSO. Another reason may be the difficulty in preparing pure 2. As part of our program to design and study novel amide chelating ligands, we require significant amounts of 2. We are also interested in the N-methyl, N,N'-dimethyl, and N,N',N"-trimethyl derivatives of 2 not only for their potentially greater solubility in organic solvents but also because of the increased electron donation of the methyl group to the amides.

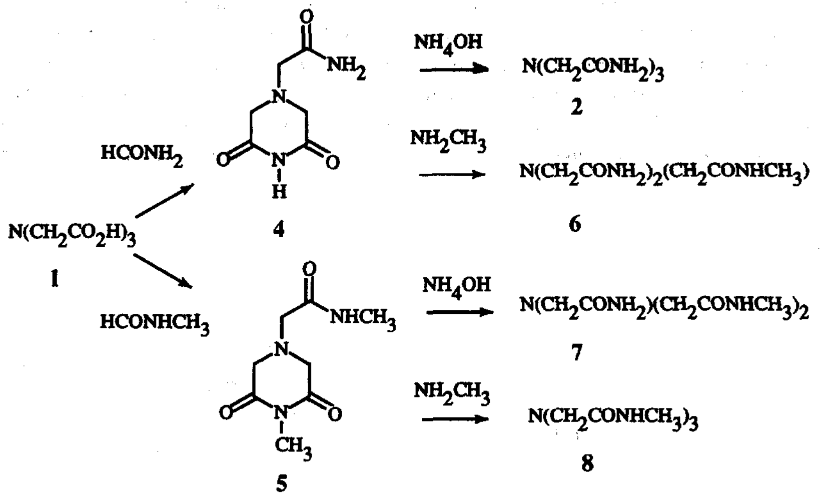
Scheme 1



We have prepared 2 from nitrilotriacetonitrile, 3, in concentrated sulfuric acid containing 5 molar equivalents of water (Scheme 1). While the hydrolysis stops at the amide under these conditions[3], the reaction is exothermic and typically some cyclization of 2 to form 3,5-dioxo-1-piperazineacetamide, 4, invariably occurs. This cyclization was confirmed by heating pure 2 in concentrated H_2SO_4 at 70 °C for 12h gave an equilibrium mixture from which 4 was isolated in 44% yield. Further support for this mechanism is found in work by Svedaite, who prepared derivatives of 3,5-dioxopiperazine by heating amine diacids in the presence of formamide.[4] Neutralization of the acid and ring opening with excess NH_4OH gave the desired product, 2, in virtually quantitative yield.[5] Purification of 2 from the $(NH_4)_2SO_4$ by-product was accomplished with difficulty by selective precipitation of the triamide from aqueous solution or by drying the sample, extracting 2 with DMSO, and solvent removal by vacuum distillation. In order to overcome the problems with isolation and purification, and to obtain the N-alkylated derivatives of 2, we devised the divergent synthesis of these compounds shown in Scheme 2.

It is known that 4 can be prepared by the transamidation reaction between nitrilotriacetic acid, 1, and formamide.[5] We prepared 4 and its N,N'-dimethyl derivative 5 from nitrilotriacetic acid in either formamide or N-methyl formamide at 150-60 °C. Recrystallization from isopropanol-water gave 4, mp 215-16.5 °C, and 5, mp 111-12 °C, in 46% and 59% yield, respectively.[6] Ammonolysis of 4 or 5 with 30% NH_4OH at room temperature provided 2 (mp 209-10 °C, 84% recrystallized from isopropanol-water) and N,N'-dimethyl derivative 7 (mp 158-9 °C, 80% recrystallized from isopropanol-THF), respectively. Alternatively, nucleophilic ring opening of 4 and 5 with 40% aqueous methyl amine provided N-methyl derivative 6 (mp 146-7 °C, 61% recrystallized from THF) and N,N',N"-trimethyl derivative 8 (mp 155-8 °C, 87% recrystallized from isopropanol-THF). As expected, the methylated compounds 5-8 show enhanced solubility in organic solvents including methanol, ethanol, isopropanol, chloroform and warm THF with little loss of water solubility.

Scheme 2



Molecular and crystal structures have been determined for 2, 4 and 5 by single crystal x-ray diffraction. The crystallographic data for triamide 2 are as follows: triclinic, P1 bar, a = 9.590(3), b = 9.591(2), c = 9.918(3) Å, α = 87.73(2)°, β = 87.72(2)°, γ = 89.17(2)°, Z = 4, D_x = 1.37 g/cm^3 and R = 3.6% (2468 reflections). The structure of 2 is shown in Figure 1. The crystallographic data for imide 4 are as follows: orthorhombic, $Pca2_1$, a = 23.836(6), b = 6.351(2), c = 9.890(1) Å, Z = 8, D_x = 1.52 g/cm^3, R = 3.6% (1269 reflections). The crystallographic data for imide 5 are as follows: monoclinic, Cc, a = 11.409(1), b = 9.282(1), c = 10.187(1) Å, β = 112.80(1), Z = 4, D_x = 1.33 g/cm^3, R = 3.1% (947 reflections). We are currently using molecular modeling techniques to study the hydrogen bonding in these compounds and will report on that work, along with full crystallographic details, in due course.

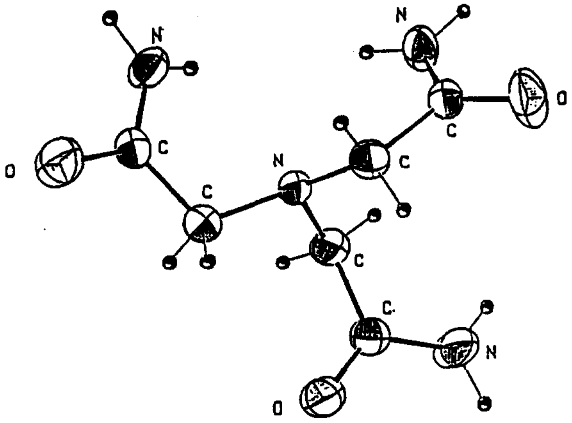
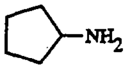
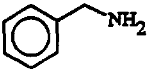
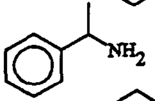
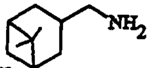
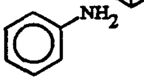


Figure 1. ORTEP plot of Nitrilotriacetamide 2. Thermal ellipsoids represent 50% probability.

Table 1. Ring Opening Reactions of 5 to Give N,N'-Dimethyl-N''-alkyl Nitrilotriacetamides

Amine	Time	Yield (%)	MP (°C)
CH_3NH_2	1 d	87[a]	155-8
	3 d	74[a]	81-4
$CH_3(CH_2)_{11}NH_2$	3 d	90[a]	92-4
	3 d	54[a]	131-3
	4 d	75[b]	43-50
	6 d	65[b]	70-77
	6 d	95[b]	156-60
	6 d	NR	

[a] Yield after recrystallization. [b] Yield after flash chromatography.

We have further examined our ability to open the piperazinedione ring with amine nucleophiles as a means of generating structurally unique ligands. Initial attempts using 4 were frustrated by the lack of solubility of this compound in organic solvents and the low solubility of many amines in water. We therefore concentrated our efforts on the dimethyl derivative 5. A series of primary amines, shown in Table 1, were examined. All reactions were run with a 4:1 ratio of amine to 5 in dry THF under nitrogen at 50 °C for 1-6 days with two exceptions. Pentylamine was used in a 2:1 ratio at room temperature, and methyl amine was used as a 40% aqueous solution (no THF) at room temperature. The products were isolated by solvent removal under vacuum followed by flash column chromatography on silica gel using 4:1 ethyl acetate to methanol as the eluant. All products were solids; some have been recrystallized. Yields are reported for homogeneous (tlc and ^{1}H NMR) samples.

As can be seen from Table 1, ring opening with aliphatic primary amines give excellent yields of nitrilotriacetamides, although α-branching decreases the yields somewhat. Aromatic amines such as aniline and secondary amines gave no product.

We have been studying 2 and its derivatives as ligands for metal complexation, and have recently reported the first isolable, crystalline complex involving two molecules of nitrilotriacetamide around a ten-coordinate lead.[2] In future papers we will report on complexes of 2 with cobalt and mercury.

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References and Notes

1. Undergraduate research fellow, University of Toledo Undergraduate Summer Research Participation program, 1990 and 1991.
2. Smith, D. A.; Sucheck, S.; Pinkerton, A. A. *J. C. S. Chem.Commun.* 1992, 367. The copper(II) complex with nitrilotriacetamide in solution has been reported, although no confirmation or details of the structure were given. L. Przyborowski, *Rocz. Chem.* 1970, *44*, 1883.
3. Liler, M., *Reaction Mechanisms in Sulfuric Acid and other Strong Acid Solutions*, Academic Press, New York, 1971, p. 189-96, 205-8.
4. Svedaite, I.; Cekuoliene, L; Kazlauskas, D. *Liet. TSR Mokslu Adak. Darb., Ser. B* 1983, 59. *Chem. Abstr.* 1984, *100*, 121,016.
5. British Patent #1,170,399, W. R. Grace, 1969.
6. All compounds were fully characterized by ^{1}H NMR, IR, low resolution MS and in some cases ^{13}C NMR and elemental analysis. Low yields of some compounds are attributed to isolation problems and high water solubility.

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