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A Convenient New Route to Tetradentate and Pentadentate Macrocyclic Tetraamide Ligands

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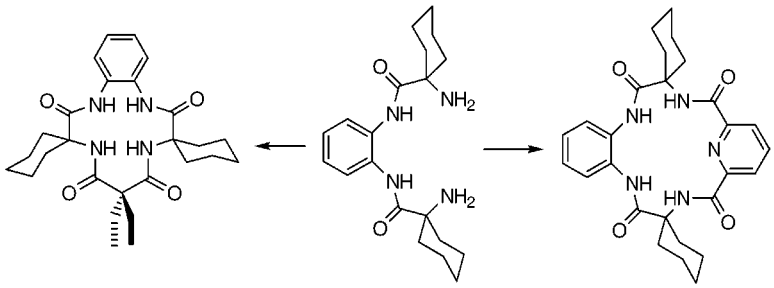
ABSTRACT



A crucial diamide diamine intermediate in the synthesis of tetradentate macrocyclic tetraamide ligands protected against oxidative decomposition has been synthesized without the use of potentially hazardous organic azide intermediates. This intermediate has also been used to synthesize a new class of pentadentate macrocyclic tetraamide ligands.

Since the potential importance to inorganic chemistry of macrocyclic tetraamide ligands protected against oxidative decomposition was first demonstrated,[1] these ligands have been used to synthesize a variety of rare or unprecedented oxidation states, geometries, and spin states of chromium, manganese, iron, cobalt, nickel, and copper.[1,2] When a two-step route to these macrocycles that did not involve organic azides was developed,[3] transition metal complexes of these ligands suddenly had the potential to become valuable homogeneous catalysts.[4] Recent work has demonstrated the utility of these catalysts in the important emerging field of green chemistry (bleaching and pulp and paper applications).[5]

We have been working to produce expanded macrocyclic tetraamide ligands for possible use with lanthanides and for multimetallic applications. In the process of solving difficulties we encountered in synthesizing a new class of tractable pentadentate macrocyclic tetraamide ligands, we have gener-

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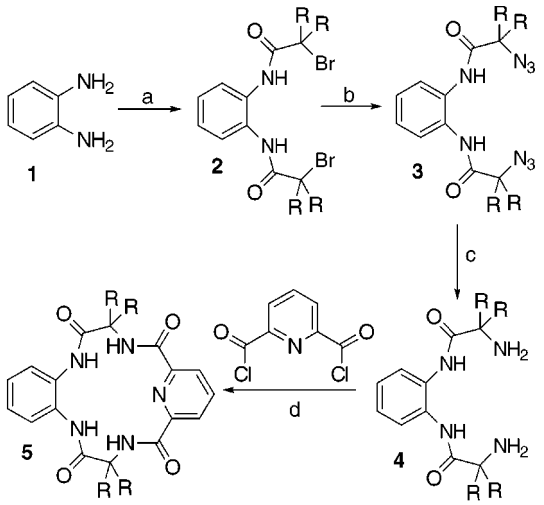
ated a valuable, convenient new method for synthesizing tetradentate macrocyclic tetraamide ligands.

Our synthesis of **5** (R = Me) proceeded by an organic azide route to the diamide diamine intermediate **4** (Scheme 1). This route to **4** was known from prior work.[1b,2f]

Scheme 1. Synthesis of an Intractable Macrocycle via an Old Azide Route[a]



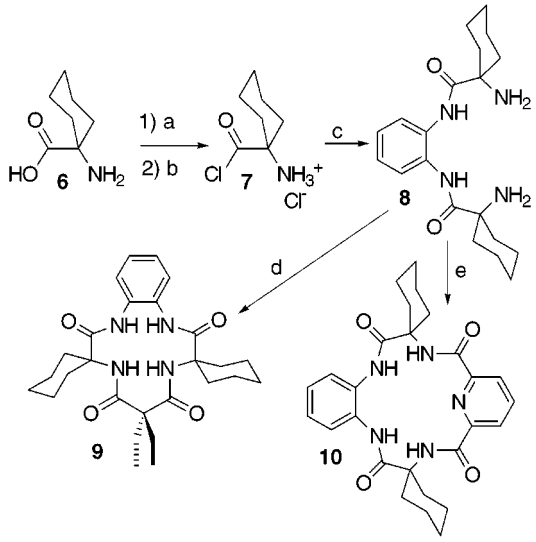
[a] Legend: (a−c) 2-bromoisobutyryl bromide, then NaN_3, then H_2, Pd/C (see refs 1b and 2f); (d) product quite insoluble, yield undetermined, product identified by FAB MS.

Unfortunately, **5** (R = Me) is sparingly soluble in DMSO and DMF and is insoluble in other common lower boiling organic solvents. Conceptually, greater organic solubility could be designed into the molecule in three places: by varying the aromatic ring substituents, by varying the R groups, or by varying the substituents on the pyridine ring. Increasing the size of the R groups destroys the viability of the azide route. Efforts to synthesize **5** (R = Pr) via the azide route were thwarted by considerable elimination.

In the redesign of the synthesis, we recognized that it is desirable to employ highly reactive acylating agents with 1,2-phenylenediamines, since the production of benzimidazoles can be a competing side reaction even with acid chlorides.[6] Indeed, 1,2-phenylenediamines that are even weakly deactivated by other substituents on the benzene ring often yield benzimidazoles exclusively when acylation is attempted with reagents less active than acid chlorides.[6] This factor renders much of the protected amino acid coupling technology developed for biochemistry inapplicable to macrocyclic systems such as **5**, **9**, and **10**. Clearly, **5**, **9**, and **10** are conceptually composed of 1,2-phenylenediamine, 2 equiv of an amino acid, and either 2,6-pyridinedicarboxylic acid or diethylmalonic acid.

Our new method of synthesizing these crucial diamide diamine intermediates, **4** and **8**, is derived from the antibiotic synthesis patent literature,[7] and it allows us to generate a very reactive acylating agent (the acid chloride), using the proton as a protecting group. As an example (Scheme 2),

Scheme 2. Synthesis of a Key Diamide Diamine Intermediate and Its Conversion to Tractable Macrocycles[a]



[a] Legend: (a) PCl_5 (1 equiv), 2-oxazolidone (2 equiv), MeCN, room temperature, 12 h; (b) **6** is added to the PCl_5/2-oxazolidone mixture and stirred, room temperature, 12 h, 92%; (c) solution of 1,2-phenylenediamine and pyridine (2.2 equiv) slowly added (2 h) to suspension of acid chloride (2 equiv), CH_2Cl_2, room temperature, 12 h, 42%, see ref 8; (d) diethylmalonyl dichloride, CH_2Cl_2, 25% (procedure similar to that in refs 1b and 2f); (e) 2,6-pyridinedicarbonyl dichloride, THF, 55%, see refs 9 and 13.

PCl_5 was stirred with 2-oxazolidone, followed by the addition of 1-amino-1-cyclohexanecarboxylic acid (**6**). The resulting salt, **7**, is easily isolated by filtration and is used as is, even though it is slightly contaminated with 2-oxazolidone. Slow addition of 1,2-phenylenediamine yields the diamide diamine product **8**.[8] Addition of diethylmalonyl dichloride gives **9** in 25% yield (the NMR, electrospray MS, and IR data for this compound are identical with the data for the same compound produced by the patented method[3,4d]).

It should be noted that this synthetic method holds great promise for introducing chirality into the macrocyclic tetraamide ligands via α-disubstituted amino acids bearing different R groups. Furthermore, recent research has revealed that although the metalated macrocyclic tetraamide ligands are extraordinarily robust under oxidizing conditions, high-valent iron-oxo species formed from these macrocycles

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(8) Characterization of **8**: ^1H NMR (in $CDCl_3$) δ 1.3−2.2 (m, 20H, cyclohexane H), 2.15 (br s, 4H, amine H), 7.15 (m, 2H, aromatic H), 7.65 (m, 2H, aromatic H), 9.95 (s, 2H, amide H); ^{13}C NMR (in $CDCl_3$) δ 21.4 (cyclohexane C-3 or C-4), 25.0 (cyclohexane C-3 or C-4), 34.5 (cyclohexane C-2), 58.0 (cyclohexane C-1), 124.4 (aromatic C-3 or C-4), 125.6 (aromatic C-3 or C-4), 130.5 (aromatic C-1), 176.5 (carbonyl C); NMR assignments confirmed by CH correlation spectra, edited DEPT, and 2D COSY NMR; IR (Nujol) $\bar{\nu}$ (cm^{-1}) 3409, 3324, 3201, 1654, 1590; electrospray MS (positive ion mode) *m/z* 358.49 (M + 1, 100%). Anal. Calcd for diamide diamine: C, 67.01; H, 8.44; N, 15.63. Found: C, 66.95; H, 8.40; N, 15.56.

ultimately decompose slowly via intramolecular hydrogen atom abstraction from the methylene carbon of the diethylmalonamide unit.[4a] Substitution chemistry at this site has already generated even more robust catalyst systems.[4c] The prior non-azide route involves coupling 2 equiv of amino acid with diethylmalonyl dichloride to generate a diamide dicarboxylic acid, which is then coupled with a 1,2-phenylenediamine derivative to yield product.[3] Large amounts of pyridine solvent are used in both steps. Our new synthetic route promises to make the systematic exploration of the effect of varying the malonamide groups more efficient and more economical. We anticipate that the prior method and our new method will ultimately be complementary in terms of commercial applicability; i.e., each method appears to have complementary strengths and limitations.

Reaction of the diamide diamine intermediate **8** with 2,6-pyridinedicarbonyl dichloride yields a new class of pentadentate tetraamide macrocycles in a remarkable 55% yield (Scheme 2).[9] Just as one class of the tetradentate macrocyclic tetraamide ligands appears to be templated by a hydrogen bond analogous to the β-turn seen in protein folding,[1b,2e,10] it is possible that the new pentadentate tetraamide macrocycle may be templated by a hydrogen bond involving the pyridine that is analogous to hydrogen bonds seen with amides derived from 2,6-pyridinedicarboxylic acid for catenanes[11] and helical supramolecular arrays.[12] This new pentadentate tetraamide macrocycle, **10**, has been characterized by ^{1}H NMR, ^{13}C NMR, C−H correlation spectra, edited DEPT, 2D COSY, 2D NOESY, IR, and electrospray MS.[13] The new pentadentate macrocycles show cross-peaks in the 2D NOESY spectra for the amide protons, indicating that they are in close proximity to each other. Not only is the geometric proximity of the amide protons consistent with a hydrogen bond template in the final coupling reaction, the pentadentate tetraamide macrocycles do not exhibit a change in the ^{1}H NMR in the presence of strong acids, indicating that the pyridine ring is extraordinarily difficult to protonate.

Not only is **10** stable in concentrated acid, it is also base-stable. Addition of 4 equiv of LDA removes the amide protons and generates a lithiated tetraanion which we have characterized by NMR in THF-d_8 and DMSO-d_6. Addition of water to the lithiated tetraanion quantitatively regenerates **10**. We are surveying the reactivity of the lithiated tetraanion with transition metals and with the lanthanide series of trications. Coordinating the organic amido-*N* ligand to a lanthanide series trication would not only have significant implications for the fundamental coordination chemistry of the lanthanides but could also, depending on hydrolytic stability, have significance to the field of MRI contrast agents.

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(9) Synthesis of **10**: compound **8** (0.615 g, 0.00172 mol) was dissolved in anhydrous THF (7.5 mL) and triethylamine (0.7 mL, 0.00502 mol). 2,6-Pyridinedicarbonyl dichloride (0.352 g, 0.00173 mol) was dissolved in anhydrous THF (8.2 mL). Each solution was added to a common pool of THF (75 mL) via syringe pump (1.5 h). The reaction mixture was stirred (24 h) and then filtered, saving the filtrate. The filtrate was taken to dryness under reduced pressure. The resultant solid was washed with distilled water, filtered, and pumped to dryness. The solid was then washed with methylene chloride, filtered, and dried under vacuum oven (~40 °C). Net yield: 0.465 g, 0.000 949 mol, 55.4%. The macrocycle is recrystallized in high yield by vapor diffusion of hexanes into a THF solution.

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(13) Characterization of **10**: ^{1}H NMR (in DMSO-d_6) δ 1.3 (s, 2H, cyclohexane H), 1.7 (s, 10H, cyclohexane H), 2.0 (d, 4H, cyclohexane H), 2.8 (m, 4H, cyclohexane H), 7.2 (m, 2H, benzene H), 7.45 (m, 2H, benzene H), 8.18 (m, 3H, pyridine H), 9.34 (s, 2H, amide H), 9.72 (s, 2H, amide H); ^{13}C NMR in (DMSO-d_6) δ 23.8 (cyclohexane C-2 or -3), 25.7 (cyclohexane C-4), 31.8 (cyclohexane C-2 or -3), 61.9 (cyclohexane C-1), 124.0 (pyridine C-4), 125.5 (benzene C-4 and C-5), 128.0 (benzene C-3 and C-6), 131.6 (benzene C-1 and C-2), 140.4 (pyridine C-3 and C-5), 149.6 (pyridine C-2 and C-6), 163.8 (carbonyl C), 171.8 (carbonyl C); NMR assignments confirmed by CH correlation spectra, edited DEPT, 2D COSY NMR, and 2D NOESY NMR; IR (Nujol) $\bar{\nu}$ (cm^{-1}) 3496, 3349, 3222, 1691, 1654; electrospray MS (negative ion mode) *m*/*z* 489.58 (M − 1, 100%).