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Efficient preparation of 1,4,8-trimethylcyclam and its conversion into a thioalkyl-pendant pentadentate chelate

Jason A. Halfen*[a] and Victor G. Young, Jr.[b]

[a] *Department of Chemistry, University of Wisconsin-Eau Claire, Eau Claire, WI 54702, USA. E-mail: halfenja@uwec.edu; Fax: 715-836-4979; Tel: 715-836-4360*

[b] *Department of Chemistry, University of Minnesota, 207 Pleasant St. S.E., Minneapolis, MN 55455, USA. E-mail: young@chem.umn.edu; Fax: 612-626-7541; Tel: 612-625-6897*

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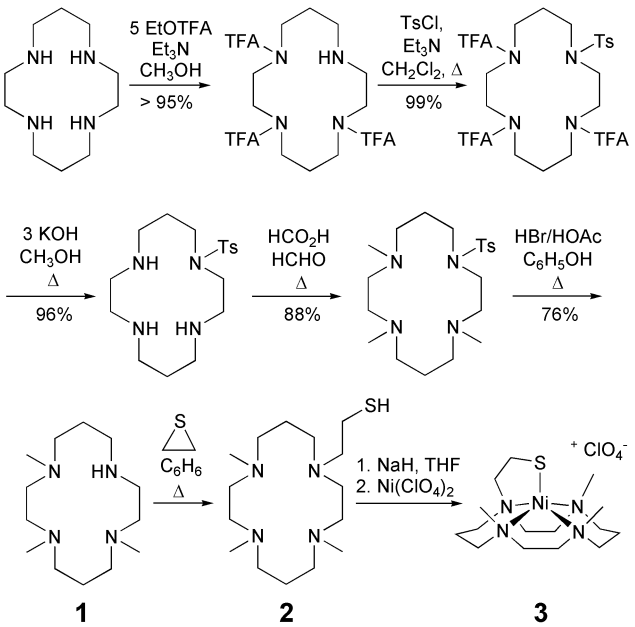
A facile synthesis of 1,4,8-trimethylcyclam and a thioalkyl-pendant derivative are reported, and the X-ray crystal structure of a nickel(II) complex illustrates structural consequences of appending the thiolate donor onto the macrocycle.

Tetraazamacrocycles such as 1,4,8,11-tetraazacyclotetradecane (cyclam) have a long history in synthetic inorganic chemistry and a burgeoning significance in medicinal chemistry.[1,2] Selective derivatization of the secondary amines in cyclam is a key step in the development of new ligands for transition metals and new bioactive agents alike.[3] Statistical methods using large excesses of cyclam in conjunction with yield-limiting quantities of electrophiles have been used to mono-alkylate cyclam, although the use of expensive, excess macrocycle renders these methods unattractive for large-scale use.[4] Selective protection methods have been used to generate cyclam macrocycles possessing less than four BOC or tosyl protecting groups; however, yields are often modest and pure macrocycles are usually isolated only after chromatographic purification.[5] Recent synthetic advances, taking advantage of the reactivity of cyclic bisaminal derivatives, have provided access to stereochemically well-defined difunctionalized cyclams.[6] However, facile routes to trialkylcyclams, which could serve as precursors to new pentadentate ligands or bioactive agents, have yet to be described. Herein we report an efficient, rapid synthesis of 1,4,8-trimethylcyclam (**1**, Scheme 1) that proceeds in excellent overall yield and, of equal significance, completely avoids tedious chromatographic purifications of synthetic intermediates. 1,4,8-Trimethylcyclam (**1**) has been prepared previously by rigorous methylation of a (1,8-dimethylcyclam)nickel(II) complex, although the yield of **1** is moderate and the reaction conditions are hazardous, as significant amounts of cyanide are required for demetallation of the macrocyclic product.[7] An alternate route to **1** involving cyclization of selectively *N*-methylated precursors has also been described, although chromatographic purification of several species is required to obtain pure product.[8] The utility of **1** is illustrated by its conversion into pentadentate chelate **2**, which contains a pendant thioalkyl group. The X-ray crystal structure of a mononuclear Ni(II) complex (**3**) of pentadentate **2** is also reported, illustrating structural perturbations caused by attaching the thiolate donor to the macrocyclic ligand.



Scheme 1

The synthesis of **1** begins with 1,4,8-tris(trifluoroacetyl)cyclam, the preparation of which from cyclam and ethyl trifluoroacetate (EtOTFA) was described recently.[9] Tosylation of this triamide (TsCl, Et_3N, CH_2Cl_2, Δ) provides 1-(*p*-toluenesulfonyl)-4,8,11-tris(trifluoroacetyl)-cyclam as a tan solid. Characterization of this material by ^1H NMR is complicated by the hindered rotation of the three trifluoroacetamide groups. However, these groups are readily hydrolyzed (KOH, CH_3OH, Δ), affording 1-(*p*-toluenesulfonyl)-cyclam as an oil, which exhibits the expected set of NMR spectroscopic features. Specifically, the ^1H NMR spectra of this species and subsequent C_1-symmetric cyclams exhibit two high field quintets, arising from the middle $–CH_2–$ groups of the two propylene linkages in the cyclam macrocyclic ring. Permethylation of 1-(*p*-toluenesulfonyl)-cyclam (H_2CO, HCO_2H, Δ) followed by detosylation (HBr/HOAc, C_6H_5OH, Δ) provides the hydrobromide salt of 1,4,8-trimethylcyclam (**1**) as a white solid, from which the free base macrocycle can be readily liberated using a basic aqueous workup. Thus, the overall yield of **1** from commercially available cyclam is 60%, and can be rapidly accessed on a preparative scale without the need for chromatographic purification at any point in its synthesis.†

1,4,8-Trimethylcyclam is a valuable precursor for the preparation of chelates of potential utility in synthetic inorganic and medicinal chemistry investigations. For example, reaction of **1** with excess thirane (C_6H_6, Δ) affords thioethyl-pendant ligand **2** (Scheme 1). This ligand has been described previously, albeit in modest yield and with little exploration of its coordination chemistry.[10] To confirm the structure and composition of **2**, its complex with Ni(II) was prepared by deprotonation of the ligand (NaH, THF), followed by reaction with hydrated $Ni(ClO_4)_2$. The green crystalline material thus obtained, **3**, was subjected to crystallographic characterization.

The X-ray crystal structure of **3** (Fig. 1) confirms the presence of pentadentate chelate **2**, which encapsulates a central Ni(II) ion.‡ The geometry of the metal is best described as distorted square-pyramidal (τ = 0.43)[11] in which the Ni(II) ion is displaced from the mean plane of the four amines toward the pendant thiolate ligand by 0.38 Å. Relevant to the structure of **3** is that of a pentacoordinate Ni(II)-cyclam complex in which the macrocyclic ligand bears two pendant thioether donors.[12] Predictably, the axial Ni–S distance in that complex, 2.393 Å, is longer than the Ni–S distance in **3**, a difference that is rooted in the divergent nature of their sulfur ligands (thioether *vs.* thiolate). The structure of **3** is also related to that of

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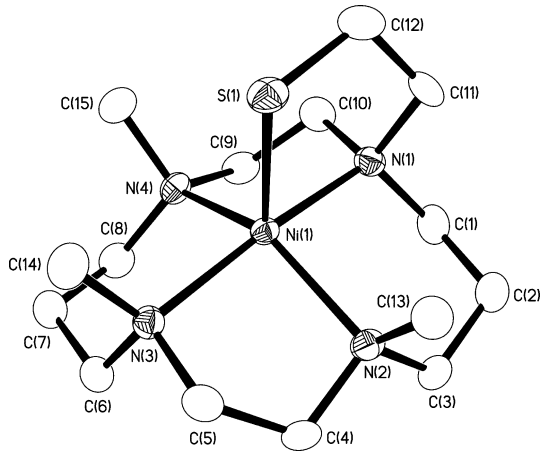

Fig. 1 Thermal ellipsoid representation (50% probability boundaries) of the cationic portion of the X-ray crystal structure of **3** with hydrogen atoms omitted for clarity. Significant interatomic distances (Å) and angles (°) include: Ni–N1, 2.117(2); Ni–N2, 2.148(3); Ni–N3, 2.129(3); Ni–N4, 2.166(3); Ni–S1, 2.2785(9); N1–Ni–N3, 172.59(10); N1–Ni–N2, 93.46(9); N3–Ni–N2, 84.91(9); N1–Ni–N4, 84.66(10); N3–Ni–N4, 92.76(9); N2–Ni–N4, 146.94(10); N1–Ni–S1, 88.48(7); N3–Ni–S1, 98.91(7); N2–Ni–S1, 106.83(7); N4–Ni–S1, 106.11(7).

$[(Me_4cyclam)Ni(SPh)]PF_6$ (**4**) in which a distorted square pyramidal Ni(II) ion is bound by a tetramethylcyclam ligand and an axial benzenethiolate donor.[13] The Ni–S distance in **4** (2.347 Å) is longer than that found in **3**, and the pentacoordinate Ni(II) ion in **4** exhibits a smaller trigonal distortion (τ = 0.25).[11] Both of these geometric differences are ascribed to the thiolate donor being covalently tethered to the macrocyclic ligand in **3**, a condition that is absent in **4**.

Compounds **1** and **2** are two examples of selectively alkylated cyclams that can be prepared using the general methodology described herein. The structural differences between **3** and **4** suggest that pentadentate ligands derived from 1,4,8-trimethylcyclam may provide access to metal complex structures or reactions that are inaccessible without covalent attachment of the fifth donor to the macrocyclic ring.

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Notes and references

† Synthesis of **1**: 1,4,8-tris(trifluoroacetyl)cyclam (2.51 g, 5.23 mmol), *p*-toluenesulfonyl chloride (1.25 g, 6.56 mmol) and Et_3N (0.80 ml, 5.8 mmol) were combined in CH_2Cl_2 (30 ml) and refluxed 18 h. The mixture was evaporated, the residue partitioned between H_2O and CH_2Cl_2, the organic phase separated, dried and evaporated to provide 1-tosyl-4,8,11-tris(trifluoroacetyl)-cyclam (3.34 g, 99%). This material and KOH (1.24 g, 22.1 mmol) were combined in CH_3OH (30 ml) and refluxed for 1.5 h. The mixture was evaporated, the residue partitioned between aq. NaOH and CH_2Cl_2, the organic phase separated, dried and evaporated to provide 1-tosylcyclam (1.72 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H), 7.24 (d, 2H), 3.16 (t, 2H) 3.11 (t, 2H), 2.78 (t, 2H), 2.69 (m, 10H), 2.36 (s, 3H), 1.72 (quint, 2H), 1.65 (quint, 2H) ppm. 1-Tosylcyclam (2.35 g, 6.82 mmol), HCO_2H (90%, 10 ml) and HCHO (37%, 8 ml) were refluxed for 4 h. The solution was cooled and made basic by addition of KOH. The mixture was extracted with CH_2Cl_2, the extracts dried and evaporated to provide 1-tosyl-4,8,11-trimethylcyclam (2.32 g, 88%). ^{1}H NMR δ 7.65 (d, 2H), 7.27 (d, 2H), 3.20 (dt, 4H), 2.70 (m, 6H), 2.60 (t, 2H), 2.49 (t, 2H), 2.41 (m, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H), 2.17 (s, 3H), 1.84 (quint, 2H), 1.66 (quint, 2H) ppm. 1-Tosyl-4,8,11-trimethylcyclam (2.32 g, 6.00 mmol) and phenol (1.34 g, 14.2 mmol) were combined in 33% HBr/HOAc (60 ml) and heated to 100 °C for 16 h. The mixture was filtered, the solid washed with Me_2CO and Et_2O and then dissolved in aqueous KOH to liberate the free macrocyclic base. The mixture was extracted with CH_2Cl_2, and the extracts dried and evaporated to provide 1,4,8-trimethylcyclam, **1**, as a colorless oil (1.10 g, 76%). ^{1}H NMR δ 2.66 (t, 2H), 2.61 (t, 2H), 2.44 (t, 2H), 2.39 (m, 6H), 2.35 (t, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 1.68 (quint, 2H), 1.56 (quint, 2H) ppm.

‡ X-ray crystallographic data for **3**: $C_{15}H_{33}ClN_4NiO_4S$, M = 459.67, monoclinic, a = 8.3748(15), b = 14.505(3), c = 8.9820(16) Å, β = 113.659(3)°, V = 999.4(3) Å^3, T = 173 K, space group $P2_1$, Z = 2, μ(Mo K_α) = 1.237 mm^{-1}, 11765 reflections collected, 4729 unique (R_{int} = 0.0550) which were used in all calculations. The specimen was a non-merohedral twin with the twin law (by rows) [−0.03015, 0.00732, 0.91909/ 0.04477, −0.99794, 0.03830/ 1.08327, 0.01048, 0.02948], which corresponds to a 180 degree rotation about direct axis [1.00, 0.01, 0.95].[14] The reflections were integrated for both twin components with SAINT V6.35A.[15] Absorption correction was performed with TWINABS V1.05.[16] Redundant reflections were removed with STRIP-REDUNDANT.[17] 248 reflections were common to both twin components. Least-squares refinements were performed with SHELXL V6.10.[18] The final residuals for all data were $R1$ = 0.0433 and $wR2$ = 0.0728. CCDC 220192. See http://www.rsc.org/suppdata/cc/b3/b311520h/ for crystallographic data in .cif or other electronic format.

1 J. Reedijk, in *Comprehensive Coordination Chemistry*, **Vol. 2**. G. Wilkinson, Ed.; Pergamon Press, Oxford, 1987; L. F. Lindroy, in *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, 1989.
2 R. B. Lauffer, *Chem. Rev.*, 1987, **87**, 901. For a recent reference, see: G. J. Bridger, R. T. Skerlj, S. Padmanabhan, S. A. Martellucci, G. W. Henson, S. Struyf, M. Witvrouw, D. Schols and E. De Clercq, *J. Med. Chem.*, 1999, **42**, 3971.
3 F. Denat, S. Brandès and R. Guilard, *Synlett*, 2000, 561.
4 I. Meunier, A. K. Mishra, B. Hanquet, P. Cocolios and R. Guilard, *Can. J. Chem.*, 1995, **73**, 685.
5 For three BOC or Ts protecting groups, see: D. D. Dischino, E. J. Delaney, J. E. Emswiler, G. T. Gaughan, J. S. Prasad, S. K. Srivastava and M. F. Tweedle, *Inorg. Chem.*, 1991, **30**, 1265; S. Brandès, C. Gros, F. Denat, P. Pullumbi and R. Guilard, *Bull. Soc. Chim. Fr.*, 1996, **133**, 65.
6 R. Tripier, J.-M. Lagrange, E. Espinosa, F. Denat and R. Guilard, *Chem. Commun.*, 2001, 2728; G. Royal, V. Dahaoui-Gindrey, S. Dahaoui, A. Tabard, R. Guilard, P. Pullumbi and C. Lecomte, *Eur. J. Org. Chem.*, 1998, 1971; C. Bucher, G. Royal, J.-M. Barbe and R. Guilard, *Tetrahedron Lett.*, 1999, **40**, 2315.
7 E. K. Barefield, K. A. Foster, G. M. Freeman and K. B. Hodges, *Inorg. Chem.*, 1986, **25**, 4663.
8 J. S. Bradshaw, K. E. Krakowiak, R. M. Izatt and D. J. Zamecka-Krakowiak, *Tetrahedron Lett.*, 1990, **31**, 1077.
9 W. Yang, C. M. Giandomenico, M. Sartori and D. A. Moore, *Tetrahedron Lett.*, 2003, **44**, 2481.
10 D. Tschudin, A. Basak and T. A. Kaden, *Helv. Chim. Acta*, 1988, **71**, 100.
11 A. W. Addison, T. N. Rao, J. Reedjik, J. van Rijn and G. C. Verschoor, *J. Chem. Soc., Dalton Trans.*, 1984, 1349.
12 C. L. Schmid, M. Neuburger, M. Zehnder, T. A. Kaden, K. Bujno and R. Bilewicz, *Helv. Chim. Acta*, 1997, **80**, 241.
13 M. S. Ram, C. G. Riordan, R. Ostrander and A. L. Rheingold, *Inorg. Chem.*, 1995, **34**, 5884.
14 *GEMINI*, Bruker Analytical X-Ray Systems, Madison, WI, (2000).
15 *SAINT V6.35A*, Bruker Analytical X-Ray Systems, Madison, WI, (2002).
16 *TWINABS V1.05*, (*a*) G. Sheldrick, 2003; (*b*) R. Blessing, *Acta Cryst.*, 1995, **A51**, 33.
17 W. W. Brennessel and V. G. Young, Jr., *STRIP-REDUNDANT V1.2, A program to remove duplicated reflections from HKLF 5 files*, unpublished work (2002).
18 *SHELXTL V6.10*, Bruker Analytical X-Ray Systems, Madison, WI, (2000).