Sodium Amalgam: A Highly Efficient Reagent for the Detosylation of Azathiacrown Ethers

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Abstract: A simple, nearly quantitative method is demonstrated for the deprotection of tosylated mixed azathiacrown ethers using sodium amalgam. Four macrocycles, containing differing numbers of amino groups and ring sizes, were prepared using traditional cyclization procedures and the described deprotection technique. Three of the macrocycles, [12]aneNS$_3$, [14]aneNS$_3$, and [15]aneN$_2$S$_3$, were reported previously, though either in low yields, only in protected form, or using hazardous precursors, while the fourth, [18]aneN$_3$S$_3$, is a new ionophore.

Key words: supramolecular chemistry, crown compounds, macrocycles, ligands, reductions

The broad field of macrocyclic chemistry[1] is advanced, in large part, through the preparation of new macrocyclic receptors or the discovery of more efficient routes to existing macrocycles. For example, over the past three decades, the coordination chemistry of homoleptic thiacrown ethers has been extensively studied due to improved procedures in their synthesis.[2] These sulfur-containing host structures are of interest because of their selectivity in forming complexes with heavy-metal ions. In contrast, the nitrogen-containing azacrown ethers (e.g., cyclam and cyclen) have an affinity for cations of more intermediate hardness, namely transition-metal ions. A wide range of synthetic tools has been developed for their successful elaboration and, indeed, as a class, these are some of the most well-studied ionophores.[3] Substantially fewer reports, however, have been published on the synthesis and coordination chemistry of the heteroleptic, mixed-donor azathiacrown ethers, macrocycles that contain a combination of N and S donor atoms.[4] This is reflective of the comparatively low-yielding synthetic procedures involved in their preparation. As such, the development of general synthetic avenues that lead to the preparation of azathiacrown ethers will provide a platform for their more thorough study as metal-chelating agents.

A particularly attractive synthetic route to azathiacrown ethers involves the cyclization of oligoethylene or propylene dithiols with N-tosylated acyclic precursors to produce N-protected azathiacrown ethers. These reactions take advantage of the commercial availability of a range of dithiols, the nucleophilicity of the thiolate functionality and proven methods for synthesizing the requisite N-protected compounds on large scale. In addition, the product crown is often highly crystalline allowing for its facile purification. However, this approach is limited by the apparent difficulty of removing the tosyl protecting group in the presence of thioether functionalities. Classically, the detosylation of amines is accomplished through the treatment of the protected amine with strong acids (e.g., 30% HBr–CH_3COOH, concd H_2SO_4) or lithium aluminum hydride at elevated temperatures for extended reaction periods. Attempts by several different groups to use these methods on N-tosylated azathiacrown ethers resulted in yields of deprotected targets that are either low (10%),[5] unreported,[6,7] or in no product formation at all.[8] Further, as noted by McAuley and Subramanian,[9] not only did conventional acid and base hydrolysis fail to deprotect the singly tosylated simplest azathiacrown ether, 1-(*p*-tolylsulfonyl)-1-aza-4,7-dithiacyclononane, but reductive hydrolysis (sodium/1-butanol) and reductive elimination with either sodium naphthalenide or the milder sodium anthracenide also failed, with the latter giving product in 0–5% yield.

As a result of our recent interest in the coordination of transition- and heavy-metal ions,[10] we sought an improved procedure for the detosylation of amines in the presence of C–S bonds. Sodium amalgam has been used as a comparatively mild, reductive desulfonylation agent for aryl and alkyl sulfones[11] and a detosylation agent for polyamines[12] and azaoxacrown ethers,[13] but to the best of our knowledge, not in the deprotection of tosylated azathiacrown ethers. We report here on the use of sodium amalgam as a general detosylation agent for N-tosylated azathiacrown ethers.

Due to their lack of commercial availability, the starting point for our investigation was the synthesis of a series of N-tosylated azathiacrown macrocycles. Four protected macrocycles were prepared with varying numbers of amino groups and ethylene or propylene linkages between the heteroatoms. Three of these crowns were chosen because they were previously described in the literature, 10-(*p*-tolylsulfonyl)-1,4,7-trithia-10-azacyclododecane (**1**),[5] 11-(*p*-tolylsulfonyl)-1,4,7-trithia-11-azacyclotetradecane (**2**),[7] and 10,13-bis(*p*-tolylsulfonyl)-1,4,7-trithia-10,13-diazacyclopentadecane (**3**),[8] but they were either deprotected in poor or unreported yields, or not at all. Compound **4** is a new macrocycle that further demonstrates the utility of the deprotection method described herein.

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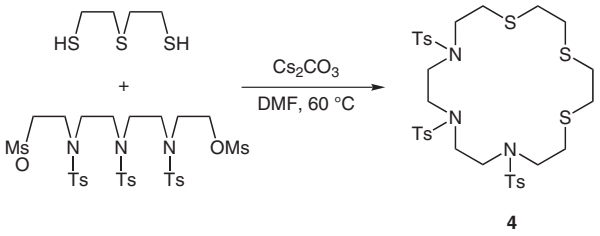
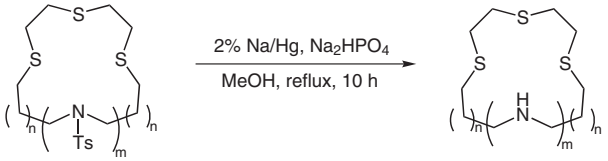


Scheme 1



1 n = 0, m = 1
2 n = 1, m = 1
3 n = 0, m = 2
4 n = 0, m = 3

5 n = 0, m = 1
6 n = 1, m = 1
7 n = 0, m = 2
8 n = 0, m = 3

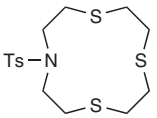
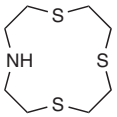
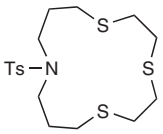
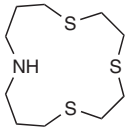
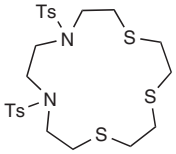
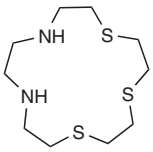
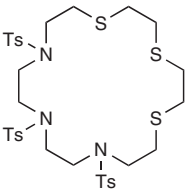
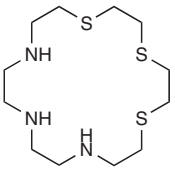
Scheme 2

Crowns **2** and **3** were prepared from the combination of the appropriate tosylated precursors with bis(2-mercaptoethyl) sulfide in the presence of Cs_2CO_3 using literature procedures. Yields were consistent with those reported previously (60% for **2**; 50% for **3**). Likewise, compounds **1** and **4** (see Scheme 1) were synthesized in an analogous fashion. As outlined in Scheme 2, the detosylations of **1**–**4** were achieved by treatment with 2% sodium amalgam in a buffered methanolic mixture. Yields for all four crowns tested were excellent with products realized in greater than 95% yield without the need for additional purification in the form of column chromatography or recrystallization. The individual results are summarized in Table 1. In all cases, the reactions were run overnight (ca. 10–14 hours) and found to be complete even with substrates that are poorly soluble in methanol, such as **3**.

In summary, sodium amalgam is a highly efficient, general reagent for the deprotection of N-tosylated azathiacrown ethers, thereby providing convenient access to a class of macrocycles that are relatively little studied.

Melting points were determined with an analog Mel-Temp melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 270 MHz spectrometer at 295 K in $CDCl_3$ or DMSO-d_6. High resolution mass spectra were acquired at the Mass Spectrometry Facility of the University of Texas at Austin. Sodium amalgam (2%) was prepared by the modification[14] of a published procedure in which mercury is added to sodium metal under an inert atmosphere.[15] In our hands, the amalgam was safely prepared, of reproducible consistency, air stable, and easily handled. The protected macrocycles **1**,[5] **2**,[7] and **3**[8] were prepared by procedures similar to those reported previously. The characterization of **1** and **2** was consistent with the literature data. As spectroscopic data for **3** were not reported previously, these are included here. Macrocycles **5**[16] and **6**[7] were prepared using alternate synthetic methods by van de Water et al. and Chak et al., respectively. Characterization data for **5** and **6** in this work are consistent with that reported in the literature. The coordination chemistry of compound **7** was previously investigated,[4,17] however, the synthetic procedures and spectral characterization of the free ligand, to the best of our knowledge, have yet to be reported. As such, we include it here.

Table 1 Detosylation Yields for **1**–**4**

Entry	Substrate	Product	Isolated Yield (%)
1			98
2			98
3			99
4			96

10,13-Bis(*p*-tolylsulfonyl)-1,4,7-trithia-10,13-diazacyclopentadecane (3)

The synthesis of **3** was accomplished via the procedure of Blake et al.;[8] mp 250–252 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 2.42 (s, 6 H, Ar-CH_3), 2.71 (m, 8 H, CH_2S), 3.25 (t, J = 7.5 Hz, 4 H, SCH_2CH_2N), 3.33 (s, 4 H, NCH_2CH_2N), 7.32 (d, J = 8.0 Hz, 4 H, Ar-H), 7.73 (d, J = 8.0 Hz, 4 H, Ar-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.55, 30.29, 31.82, 32.04, 47.69, 50.35, 127.31, 130.57, 136.82, 144.06.

HRMS–CI: m/z $[M + H]^+$ calcd for $C_{24}H_{35}N_2O_4S_5$: 575.1200; found: 575.1194.

10,13,16-Tris(*p*-tolylsulfonyl)-1,4,7-trithia-10,13,16-triazacyclooctadecane (4)

To a stirring mixture of Cs_2CO_3 (6.33 g, 19.4 mmol) in DMF (400 mL) at 60 °C was added over 12 h a solution containing bis(2-mercaptoethyl)sulfide (1.58 g, 9.25 mmol) and *O*,*O*′-dimesyl-*N*,*N*′,*N*″-tritosyl-*N*,*N*″-bis(2-oxyethyl)diethylenetriamine[18] (7.50 g, 9.25 mmol) in DMF (250 mL). Once all the reagents had been added, the reaction mixture was stirred for an additional 6 h at 60 °C. The DMF was then removed in vacuo and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was collected and dried over $MgSO_4$. Following filtration and evaporation of the solvent, the crude reaction mixture was purified by column chromatography (silica gel, $CHCl_3$ as eluent) to afford **4** (2.39 g, 34% yield) as a white crystalline solid; mp 156–158 °C.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.44 (s, 9 H, Ar-CH_3), 2.73–2.85 (m, 12 H, CH_2S), 3.24 (t, J = 7.4 Hz, 4 H, SCH_2CH_2N), 3.38 (s, 8 H, NCH_2CH_2N), 7.32 (m, 6 H, Ar-H), 7.73 (m, 6 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.68, 31.26, 32.77, 33.18, 50.66, 51.32, 52.11, 127.51, 130.07, 134.18, 134.91, 143.96, 144.27.

HRMS–CI: *m/z* $[M + H]^+$ calcd for $C_{33}H_{46}N_3O_6S_6$: 772.1711; found: 772.1699.

Detosylation of Protected Azathiacrown Ethers: [12]aneNS$_3$; Representative Procedure (5)

To a 100-mL round-bottomed flask containing **1** (1.00 g, 2.65 mmol), Na_2HPO_4 (3.01 g, 21.2 mmol), and 2% Na/Hg (30.4 g, 26.5 mmol Na) was added 30 mL of anhyd MeOH. The mixture was then stirred at reflux overnight under an Ar atmosphere. Prior to workup, the reaction mixture was checked by TLC to verify that no starting material remained. After the mixture was cooled to r.t., the methanolic slurry was decanted from the Hg. The Hg was then washed with MeOH and CH_2Cl_2 successively (20 mL each), followed each time by decanting of the solvent. The decantate and washings were combined and the solvent removed by rotary evaporation. The resultant mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was collected and dried with $MgSO_4$. Following filtration of the drying agent, the filtrate was evaporated to give pure **5** (0.582 g, 98% yield) as a white crystalline solid.

Compounds **6–8** were prepared in an identical fashion as for **5** with the yields and amounts of reagents noted below. The amount of amalgam used is 10 equiv. Na per 1 equiv. of tosylated amine with buffer and MeOH amounts scaled accordingly.

[14]aneNS$_3$ (6)

Compound **2** (0.36 g, 0.89 mmol), 2% Na/Hg (10.1 g, 8.4 mmol Na), Na_2HPO_4 (2.52 g, 17.7 mmol), CH_3OH (10 mL); yield: 0.22 g (98%).

[15]aneN$_2$S$_3$ (7)

Compound **3** (1.00 g, 1.74 mmol), 2% Na/Hg (40.0 g, 34.8 mmol Na), Na_2HPO_4 (3.95 g, 27.8 mmol), CH_3OH (40 mL); yield: 0.46 g (99%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.69–2.90 (m, 20 H, CH_2S, CH_2N), 1.80 (s, 2 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.75, 33.41, 33.51, 48.75, 49.24.

HRMS–CI: *m/z* $[M + H]^+$ calcd for $C_{10}H_{23}N_2S_3$: 267.1023; found: 267.1025.

[18]aneN$_3$S$_3$ (8)

Compound **4** (1.00 g, 1.30 mmol), 2% Na/Hg (44.7 g, 38.9 mmol Na), Na_2HPO_4 (4.41 g, 31.1 mmol), CH_3OH (45 mL); yield: 0.39 g (96%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.64–2.88 (m, 24 H, CH_2S, CH_2N), 1.88 (s, 3 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.48, 32.87, 33.21, 48.84, 48.84, 49.11.

HRMS–CI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{28}N_3S_3$: 310.1445; found: 310.1446.

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(14) In our procedure, the reaction was performed without external heat under an argon atmosphere with the reaction apparatus placed in an oil bath. After initiating the reaction by addition of a small amount of mercury to the sodium metal, the remaining mercury was immediately and quickly added (approx. 10–15 s total addition time) via an addition funnel with rapid stirring at room temperature. The amounts of reagents and reaction workup were as reported in ref. 15.
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