

Simple methods for the preparation of cryptands

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Abstract

Three new one-step methods for the preparation of cryptands are described. The first method is the reaction of available oxaalkylenediamines with the diiodide derivative of an oligoethylene glycol. This process works well to prepare cryptands containing two propylene units in one of the cryptand bridges. The second method allows the preparation of aliphatic cryptands such as [2.2.1], [2.2.2] and [3.3.2] in excellent yields by treating the ditosylate derivatives of the oligoethylene glycols with the available oligoethyleneoxydiamines. The third method provides unsymmetrical cryptands by the reaction of a tetraalcohol, prepared from diethanolamine and a dichloride or a diacid dichloride followed by reduction, and two moles of a dihalide or ditosylate. These new methods allow the synthesis of all types of cryptands in one-step from inexpensive starting materials.

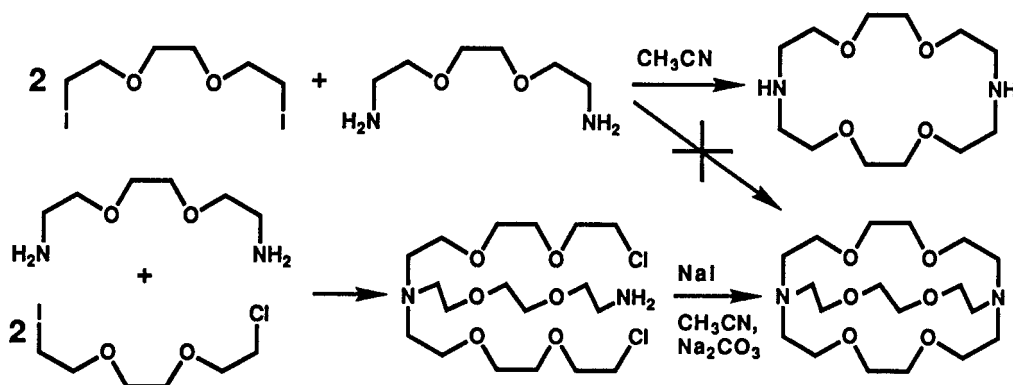
INTRODUCTION

The scientific world is fascinated by the discovery and exciting chemical properties of buckminsterfullerene (ref. 1,2). This molecule can easily be studied because of its availability. Buckminsterfullerene, composed of only carbon atoms, is prepared by a one-step reaction in burning graphite. Other three dimensional molecules, such as the calixerenes, can be prepared by one-step processes (ref. 3-5). Many of these molecules can be purchased so that their unique interactions with metal ions and other chemical properties can easily be studied.

The cryptands likewise have interesting chemical properties. However, they are not readily available. These interesting compounds were first prepared over twenty years ago in the Jean-Marie Lehn laboratory (ref 6-8). Cryptands are three dimensional molecules with two nitrogen atoms connected by three bridges composed of ethyleneoxy units. This arrangement allows the molecule to completely encapsulate a metal ion. Because of their unique and selective complexing properties (ref. 9), cryptands are of great interest to chemists worldwide. Improved methods for their preparation are needed to make these materials readily available for the study of their unique properties and for potential large-scale use.

Preparation of the first cryptands required many steps (ref. 6-8). Newkome and coworkers prepared certain pyridine-containing cryptands in low yields by a one-step 3:2 cyclization of dihalopyridines with triethanolamine (ref. 10,11). Kulstad and Malmsten attempted the preparation of cryptand [2.2.2] by a one-step 2:1 cyclization of 1,8-diiodo-3,6-dioxaoctane and

its diamine analog (ref. 12). Unfortunately, they only isolated 1,10-diaza-18-crown-6 as shown below. They were able to prepare [2.2.2] in a 6% yield by a two-step reaction from the chloro-



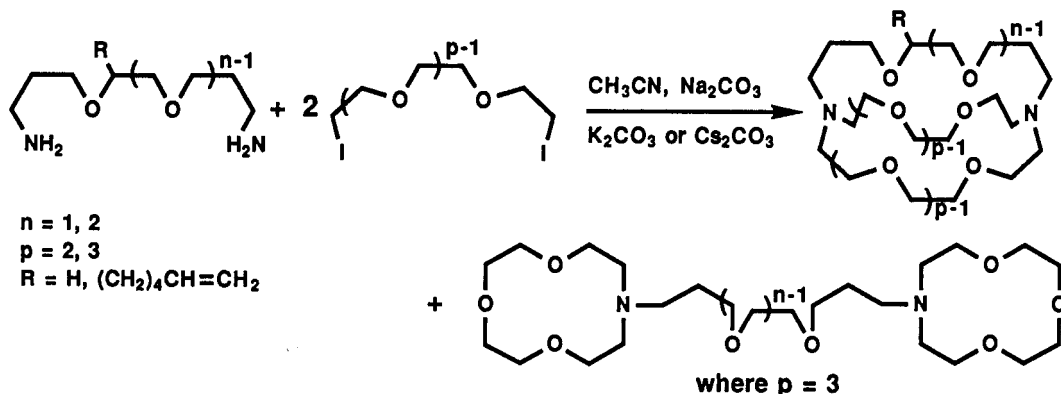
iodo compound as shown. This is not a viable method to prepare [2.2.2] because the chloroiodo starting material is not available and would require an extra step. Others have had success in preparing cryptands containing rigid aromatic groups by one-step processes, but often extra steps were needed to remove the metal ion (ref. 10,11,13-15).

There is great interest in the chemistry of the cryptands. More than 900 papers concerning the aliphatic cryptands have been published in the past 24 years (ref. 16). Only 4 cryptands can be purchased and they are very expensive. Obviously new synthetic methods are needed to make these materials available for large scale applications.

NEW ONE-STEP METHODS

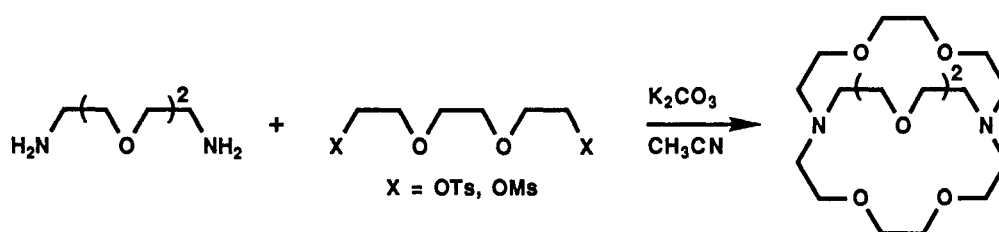
The most convenient method to prepare cryptands would be the one-step process tried by Kulstad and Malmsten (ref. 12) shown above. Although they were unsuccessful, we repeated their work and found that some [2.2.2] was produced when K_2CO_3 , Cs_2CO_3 or $MgCO_3$ was used as the base (ref. 17,18). There were so many side products in this reaction that we prepared other cryptands by this process before we discovered how to make [2.2.2].

Using the Kulstad-Malmsten approach, we prepared a series of cryptands where one bridge contained two propylene moieties (ref. 17,18) as shown below. Cryptand [2Pr₂-2-2] (Pr stands for a propylene unit) was isolated in a 31% yield; [2Pr₂-3-3], 19%; and [3Pr₂-2-2], 34%. This process also worked well to form cryptands with one *m*-phenylene group (21%), one bridge containing two propylene units and nitrogen (17%) or sulfur (38%) heteroatoms, or where one or more bridges contained the tetraethyleneoxy unit (33%). A bis(aza-12-crown-4) by-product, where the two aza-12-crown-4 groups were connected by an alkaleneoxy unit, was also isolated when the diiodide derivative of tetraethylene glycol ($p = 3$) was used as a reactant (ref. 17, 18).



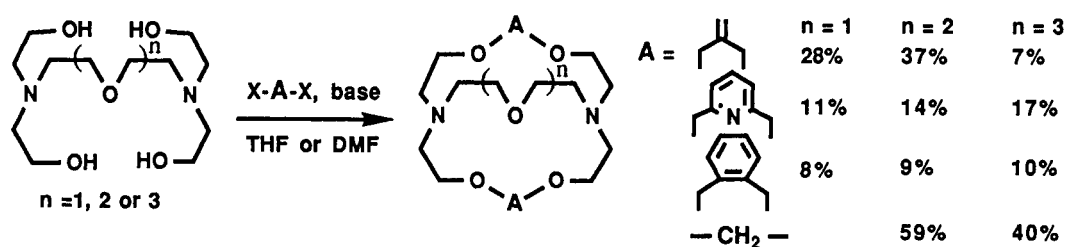
This bis(aza-12-crown-4) was the major product (26%) where large cavity cryptands were desired. The bis-crown by-product was not observed when $p = 2$ because of the difficulty in forming nine-membered rings. The cryptand and bis(aza-12-crown-4) by-product have the same molecular formulas and ^1H NMR spectra. They can be distinguished by their ^{13}C NMR spectra and by their silica gel TLC characteristics (ref. 17, 18). The TLC spot for the cryptand has considerable fronting while that for the bis-crown has the usual tailing.

Often, the leaving group is very important in determining the course of a nucleophilic substitution reaction. Even though treatment of the diiodide derivative of triethylene glycol with its diamine analog did not give useful yields of cryptand [2.2.2], the same reaction with the ditosylate derivative of triethylene glycol gave a 38% yield of [2.2.2] (ref. 19). Similar results were obtained using the dimesylate. The ditosylate is recommended because it can be purchased. Use of the



ditosylate also allows the preparation of [2.2.1], [3.2.2] (50%), [3.3.2] (40%) and other similar cryptands. This one-step method is simple and uses inexpensive starting materials. This process could become the method of choice for the preparation of the simple aliphatic cryptands. It is not clear at the present time why the ditosylate ester reacted to give a good yield of cryptand [2.2.2] and the diiodide did not.

Cryptands have also been prepared by a one-step process from specially prepared tetraalcohols as shown below (ref. 20, 21). As shown in the scheme, this method allowed the preparation in



excellent yields of two cryptands each containing a methylene unit in two bridges. The yields for product cryptands containing the (2-methylene)propylene unit were also good in two cases. The tetraalcohol starting materials were prepared in a 90% yield from diethanolamine and a dichloride or a diacid dichloride followed by reduction (ref. 21).

These three new one-step methods will make all types of cryptands available for complexation studies and for large scale applications. Specific details on these syntheses and on purification methods are available in the relevant papers.

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