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PREPARATION OF DIAMINO ETHERS AND POLYAMINES

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I. INTRODUCTION

Diamino ethers and polyamines are used in macrocyclic chemistry and in the chemistry of natural products. In macrocyclic chemistry, diamino ethers and polyamines serve as starting materials for syntheses of macrocyclic and macropolycyclic compounds.[1,2] However, preparation of such open chain starting materials often is more difficult than subsequent ring closure reactions.[5] For example, preparation of triaza-18-crown-6 was accomplished by four different routes (methods A-D, Figure I). Each route required a different strategy to prepare the starting materials and the final macrocycle.

As shown in Figure I, preparation of the starting materials needed for ring closure required many steps. Where starting reagents are expensive, alternate routes to prepare them must be devised. Indeed, access to important open chain polyamines and diamino ethers by shorter and more convenient methods is being studied. Preparation of the triaza diether shown in method C is one example of a convenient route to an important starting material. Each year, more and more diamino ethers become commercially available. Some diamino ethers

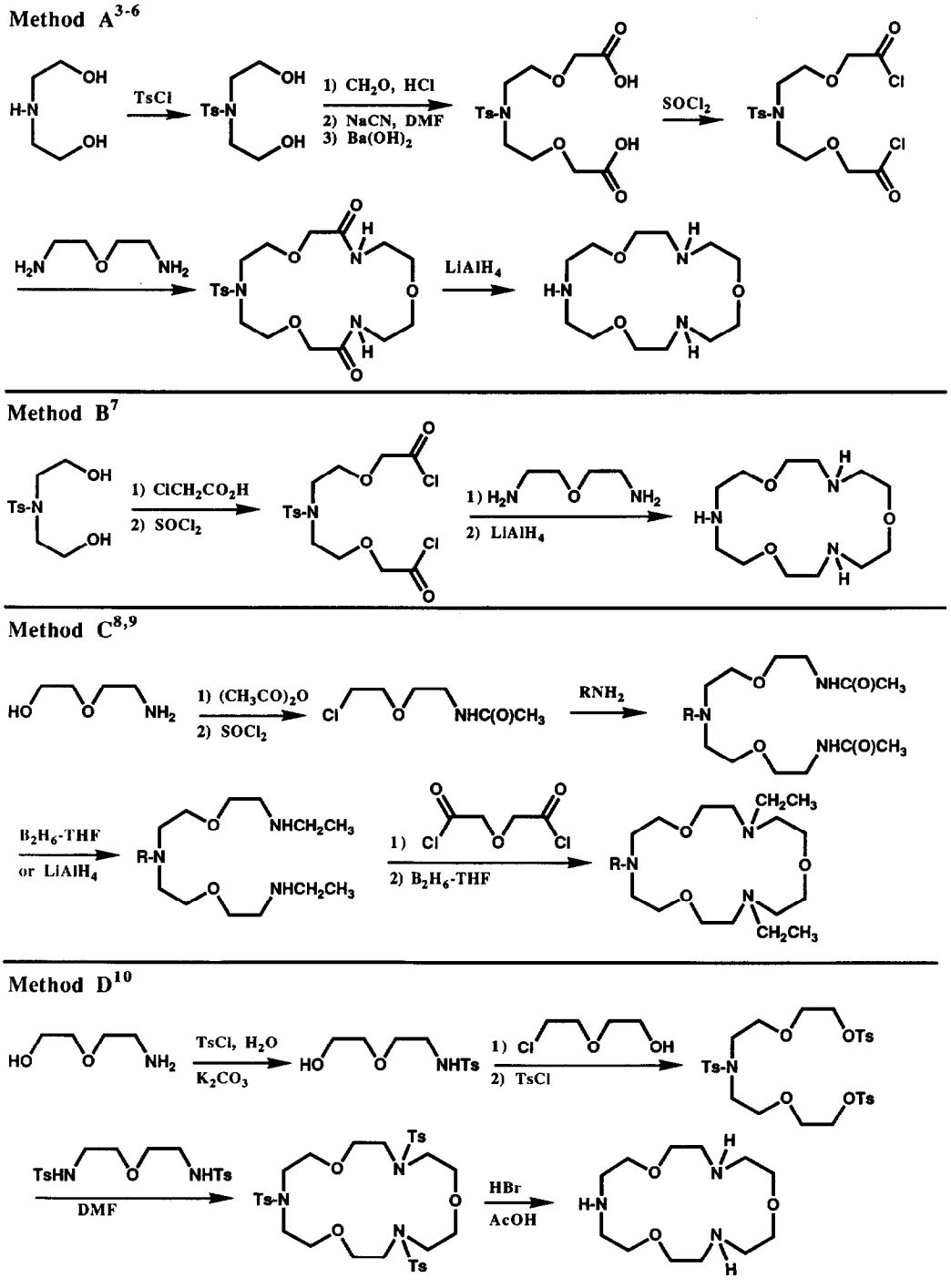


FIGURE 1. Methods for the Preparation of Triaza-18-Crown-6

include 1,5-diamino-3-oxapentane (Aldrich, Fluka); 1,8-diamino-3,6-dioxaoctane (Fluka); and some mixed oligo(ethyleneoxy)dipropylamines-$H_2N(CH_2)_3(OCH_2CH_2)_nO(CH_2)_3NH_2$- (Aldrich, Tokyo Kassei).

Many polyamines are now available from Aldrich, Fluka, Pfaltz and Bauer, Sigma, and TCI chemical companies. The available compounds include tri- and tetraamines with a mix of ethylene, trimethylene, and tetramethylene units between the nitrogen atoms. Of particular interest are those where the internal amines are tertiary and the terminal ones are secondary. These compounds can be used in ring closures to peraza-crowns without the need to protect the internal amines. It has to be mentioned that some of the available polyamines are of technical quality, which means they are somewhat impure. For example, triethylenetetraamine, which in 1989 was listed as 95% pure, was sold in 1991 as only 60% pure.

Numerous natural polyamines are available, such as putrescine, spermine and spermidine. The chemistry of these and related compounds has some recent developments[11,12] and their preparation is not straightforward.[13,14] The polyamines are ubiquitous in nature since they are synthesized in animal and bacterial cells. Most often the polyamines are conjugates with carbohydrates, steriods, and phospholipids, and exist as structural subunits in various antibiotics and plant alkaloids. Since the polyamines are found in so many cells, relevent synthetic reactions may be of physiological utility. Continued interest in the biochemistry and pharmacology of spermine and spermidine increases the need for their analogs for biological investigations. Polyamine levels in physiological fluids and in biopsy materials have been shown to be valuable guides for the evaluation of the pathogenesis of haematological diseases, as well as for monitoring the protracted course of the disease with or without chemotherapeutic treatment.[15-23]

More recently, awareness has grown that the polyamine biosynthetic pathway provides a useful target for the design of inhibitors that have value as pharmacological agents. It seems likely that certain polyamine analogs may have therapeutic application, particularly in cancer and other proliferative diseases and in the treatment of plant diseases.

Current literature about polyamines[15-23] indicate the following:

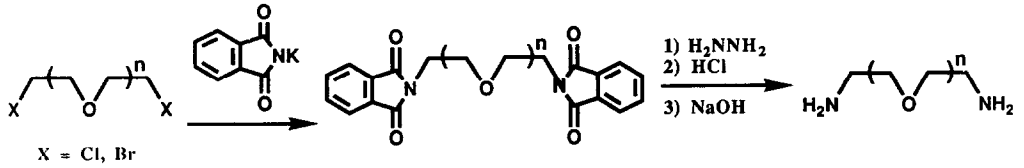
1. Polyamines have been linked to certain vival diseases, so that the proper design of polyamine inhibitors could produce important new medicinal compounds.
2. Polyamines may play essential roles in the growth process.
3. Diamine-polyamine biosynthesis and activation are essential processes in DNA replication in lymphocytes and in bone marrow cells.
4. Some siderophores, the microbial ferric ion transport agents, are polyamino derivatives of catechol.

Clearly, convenient synthetic routes to diamino ethers and polyamines on a big scale are of value to chemists and biochemists. These materials can be prepared by enzymatic or chemical means or a combination thereof. Even though enzymatic reactions to form polyamines are important[24], this report covers only synthetic methods. A brief review of the preparation

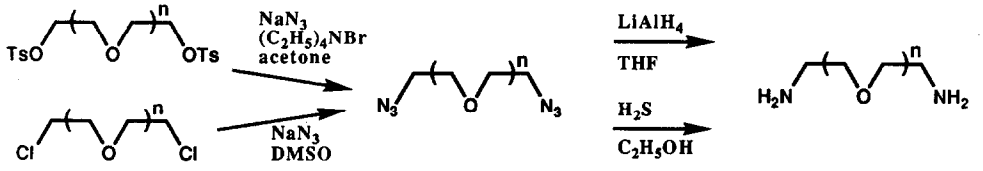
of certain polyoxapolyamines was recently published as part of a larger review of aza-crown ethers.[1] Books are available that deal with the chemistry of amines.[25-31] However, there is no comprehensive treatment on the synthesis of diamino ethers and polyamines. This review covers the synthesis of these important compounds.

II. DIAMINOALIPHATIC ETHERS

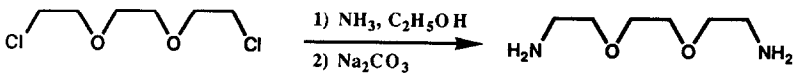
A modified Gabriel synthesis, by reaction of potassium phthalimide with a dihalide followed by hydrazine and hydrolysis, was one of the first routes to the diamino ethers.[32-35] Krakowiak and Kotelko used this method to prepare a variety of diamino ethers containing both ethylene and trimethylene connecting groups.[36,37]



The reduction of diazide-substituted ethers to form diamino ethers has been reported by a number of workers.[38-41] The starting diazido ethers were prepared by treatment of either the ditosylate or dichloro derivatives of the oligoethylene glycols with sodium azide. The reduction of the diazide can be done with lithium aluminum hydride or hydrogen sulfide in ethanol as shown. In these reactions (overall yields 65-85%) care must be taken because the diazide can be explosive.



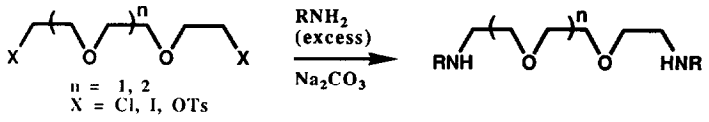
A more direct approach to 1,8-diamino-3,6-dioxaoctane was reported in 1974 by King and Krespan.[42] They treated 1,8-dichloro-3,6-dioxaoctane with ethanolic ammonia and sodium carbonate in an autoclave to give the diamine in a 71% yield.[42] Their reaction was similar



to that for the preparation of the 1,7-diamino-4-oxaheptane by Wiley.[43] The ditosylate derivative of triethylene glycol has been used in place of the dichloride for the above reaction. In this case, 30% aqueous ammonium hydroxide was used. The yields were lower, but an autoclave was not necessary.[44] This route to diamino ethers is probably not general. It is likely that the reaction of 1,5-dichloro-3-oxapentane with ammonia would give morpholine

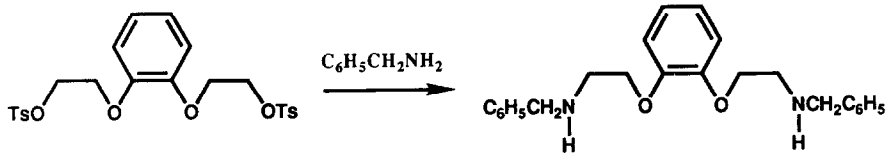
not the desired 1,5-diamino-3-oxapentane.[40,45]

The above procedure is also convenient for preparation of N,N'-dialkyl (or ditosyl) derivatives of 1,8-diamino-3,6-dioxaoctane and higher homologs. The procedure involves reaction of the readily available dihalide or ditosylate derivatives of the oligoethylene glycols with an excess of alkyl or arylamine.[46-49] This process is not possible for



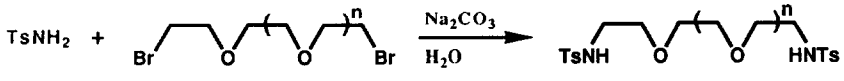
preparation of the diamine derivatives of diethylene glycol, since the reaction of an amine with the dihalide yields only N-alkylmorpholine as mentioned above.[40,45] Gokel and co-workers used the more reactive diiodide in this reaction to prepare some N,N'-dialkyldiamino ethers in 70-85% yields.[40] Bradshaw and Krakowiak[46] have optimized the reaction with the dichloride using only a 4-fold excess of the amine in the presence of sodium carbonate and a Dean-Stark apparatus (for removal of water) to obtain an 82% yield of the N,N'-dibenzyl derivatives. Recently, Gokel and co-workers also used 1,8-dichloro-3,6-dioxaoctane in excess benzylamine to prepare 1,10-dibenzyl-4,7-dioxa-1,10-diazadecane.[47]

A benzo-substituted diaminoether was obtained by Pedersen and Brumels in a similar manner from the ditosylate derivative of bis(2-hydroxyethoxy)benzene and benzylamine.[50] They



also isolated the benzoaza-9-crown-3 macrocycle as a byproduct unless an excess of benzylamine was used.

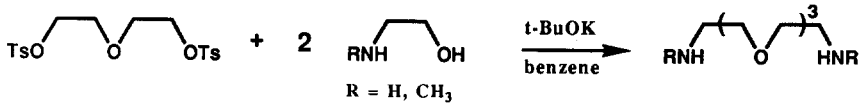
The N,N'-ditosyldiamino ethers can be prepared in a one-step reaction with p-toluenesulfonamide and the appropriate dihalide. This procedure is certainly easier than the three-step method of first forming the diamine and then reacting it with tosyl chloride.[33,35,38] In the new method, the tosylamide, in saturated aqueous sodium carbonate, was added to 1,8-dibromo-3,6-dioxaoctane (or to its next higher homolog) to give a high yield of the N,N'-ditosyldiamine.[51] The reaction of 1,8-dichloro-3,6-dioxaoctane with p-toluenesulfonamide in a different solvent gave a low yield of 1,10-ditosyl-1,10-diaza-18-



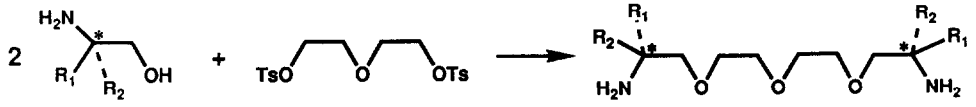
crown-6 rather than the open chain N,N'-ditosyldiamine.[52] Similar results were reported by

Pappalardo and co-workers for the reaction of p-toluenesulfonamide and 1,8-diiodo-3,6-dioxaoctane in DMF, except that they also isolated N-tosylaza-9-crown-3 in addition to the 1,10-ditosyldiaza-18-crown-6.[53]

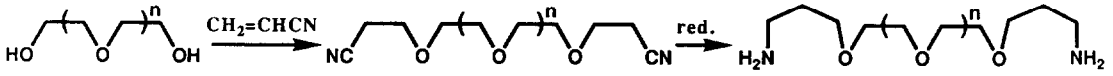
Böhmer and co-workers treated 2-aminoethanol with a ditosylate using potassium t-butoxide as the base to form the diamino ether in a 30% yield.[54] They also prepared the

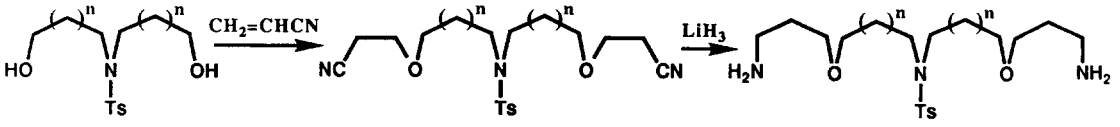


N,N'-dimethyl derivative. Sutherland and co-workers used this technique to prepare a chiral diamino ether in high yields.[55] Secondary amines were prepared in much the same fashion.



In contrast to the above work, mixed oligoethylene- and trimethylene-containing diamino ethers have been prepared by simple addition of acylonitrile to various oligoethylene glycols in the presence of alkali catalysts followed by reduction of the dinitrile product.[56-58] This reaction takes place at room temperature when a reactive catalyst such as sodium metal, sodium methoxide or sodium or potassium hydroxide is used. Other functional groups such as dialkylamino, halogen or an extra cyano group do not interfere with this reaction. This

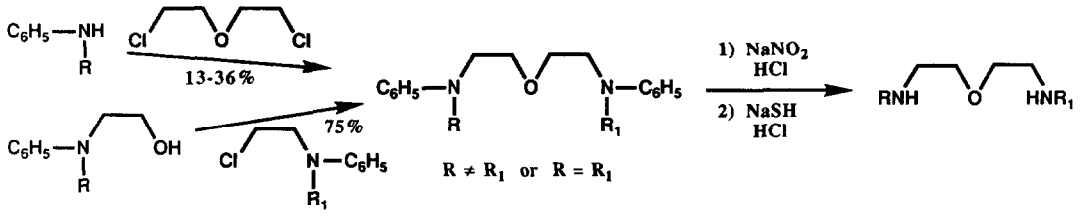




cyanoethylation process also was used for the preparation of triaminoethers with trimethylene bridges as shown above.[57] Reduction to the amine groups can be carried out with Ni and NH_3,[59,60] Ru and NH_4OH,[61] $NaBH_4$ and Ni,[62] and AlH_3 (prepared <u>in situ</u> from $LiAlH_4$ and H_2SO_4).[57] Reducing agents such as $LiAlH_4$ gave complex mixtures presumably from base catalyzed elimination of β-alkoxynitriles or from partial reduction of the dinitrile. The tosyl group, which was stable to reduction, can be removed from the product by lithium aluminum hydride in THF or by the use of sulfuric acid.[57]

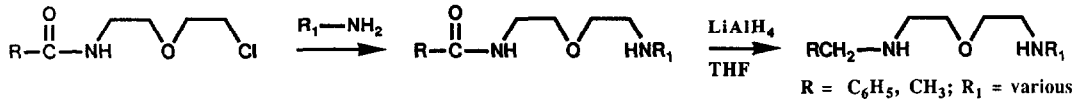
Boon prepared the 1,5-bis[methylamino or ethylamino]-3-oxapentanes by two methods as

shown.[45] The initial diamino ether contained phenyl protecting groups that required a

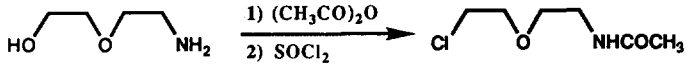


two-step method for removal. N-phenylmorpholine was isolated as a byproduct when the dichloride was reacted with aniline (R = H). The second method shown above allows the preparation of unsymmetrical analogs where the R groups on each nitrogen are different.[45]

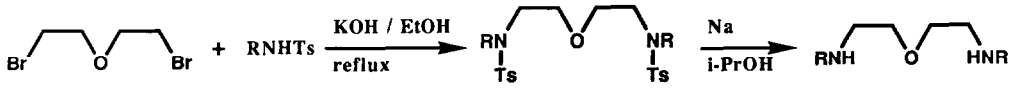
Recently, Bradshaw and co-workers reported the synthesis of N,N'-dialkyldiamino ethers with ethyl or benzyl on one amine nitrogen and any alkyl group (including ethyl or benzyl) on the other amine nitrogen.[63] The overall yields for these reactions were not high because



the primary amine also reacts with two equivalents of alkyl chloride to give the unwanted N,N,N'-trialkyl-substituted products. Even so, this procedure is important because it is a convenient way to prepare these unsymmetrically substituted N,N'-dialkyldiamines. The key building blocks, N-[2-(2-chloroethoxy)ethyl]acetamide and its benzamide analog, were prepared from available 2-(2-aminoethoxy)ethanol in high yields.[8,9,63]

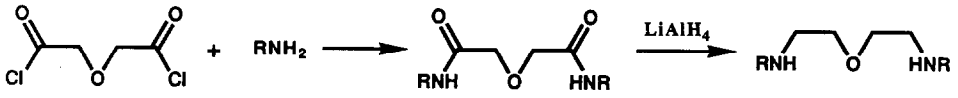


N-Tosyl substituted amines have also been used to prepare secondary diamino ethers. Petranek and Ryba treated N-tosylbenzylamine or the aniline analogue with the dibromo derivative of diethylene glycol to form the bis(N-tosylamino) derivatives.[64] The tosyl blocking groups were removed by sodium in isopropyl alcohol. An N,N'-dimethyldiamino ether was prepared by Krakowiak and Kotelko[65], who tosylated 1,5-diamino-3-oxapentane, subsequently



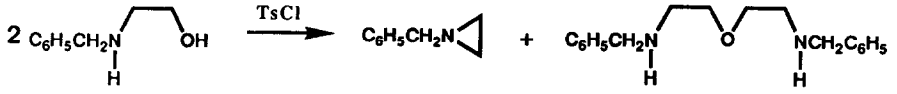
alkylated the N,N'-ditosyl derivative in base, and removed the tosyl group by HBr/phenol in acetic acid.

An excellent way to prepare the N,N'-dialkyl derivatives of 1,5-diamino-3-oxapentane involves the formation of a bisamide followed by reduction with lithium aluminum hydride.[65,66]

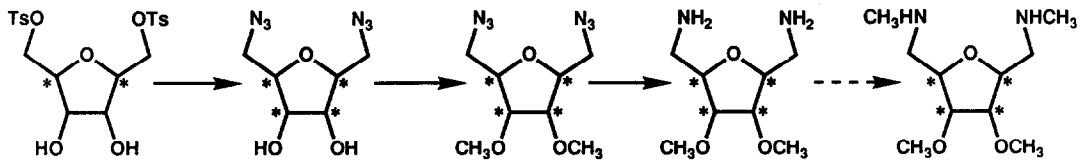


Diamines with a wide variety of alkyl substituents from methyl to 3-(N,N-diethylamino)propyl were prepared in moderate yields. Variants of this procedure have involved borane as the reducing agent.[40,67] Gokel and co-workers also prepared the N,N'-dialkyldiamino ether by treating the diamine with an acid chloride followed by reduction of the resulting bisamide.[40] This method is reasonably good for preparation of these diamines, but the starting 1,5-diamino-3-oxapentane is several times more expensive than diglycolyl dichloride used in the above procedure.

N,N'-Dibenzyl-1,5-diamino-3-oxapentane was prepared in a low yield by a one-step synthesis from N-benzylethanolamine.[63] The main product was the N-benzylaziridine.

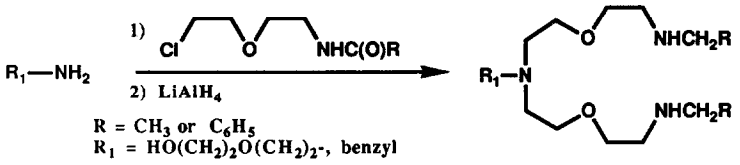


Lehn and Potvin have prepared an interesting chiral diamino ether based on the N,N'-dimethyl-1,5-diamino-3-oxapentane structure.[68] Starting with a ditosylate derivative of D-mannitol, they were able to produce the 2,5-anhydro-1,6-di-C-(N-methyl)amino-1,6-dideoxy-3,4-di-O-methyl-D-mannitol as shown (* = optically active center).

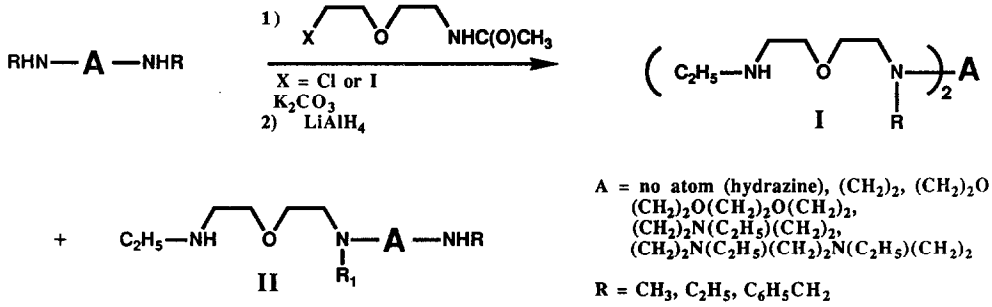


Diamino ethers containing additional amine groups in the chain have been prepared. These polyamino ethers contain terminal NHC_2H_5 or $NHCH_2C_6H_5$ functions.[8,9,63,69] The procedure used the reaction of N-[2-(2-chloroethoxy)ethyl]acetamide[9] or its benzamide analog with an amine, diamine, or polyamine and the subsequent reduction of the amide functions as shown in the following two schemes. When the reaction to form tetraamine I (excluding any amine groups in A) was run with an excess of N-[2-(2-chloroethoxy)ethyl]acetamide in toluene or DMF, mostly the diadduct (I) was formed. A greater amount of the monoadduct (II) was formed when the acetamide derivative was the limiting starting material.[8,63,69] It was possible to prepare higher order polyoxa amines if the polyamino products were further treated with N-[2-(2-chloroethoxy)ethyl]acetamide followed by reduction.[8]

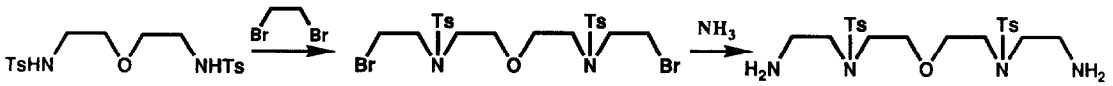
Triamines



Tetraamines and Polyamines

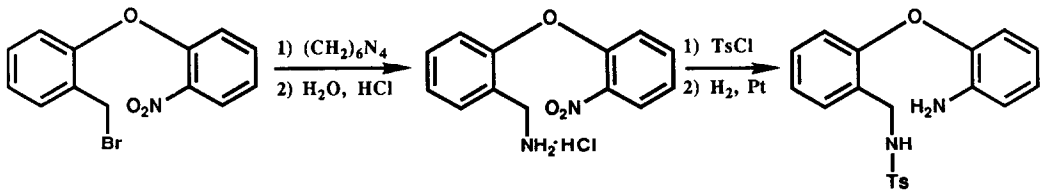


Lehn and co-workers prepared a tetraamino ether similar to those shown above except that the two internal amines contained tosyl groups.[70] They treated an excess of 1,2-dibromoethane with N,N'-ditosyl-1,5-diamino-3-oxapentane to form an open chain dibromide as shown. An excess of the dibromide suppressed the formation of a nine-membered ring. The

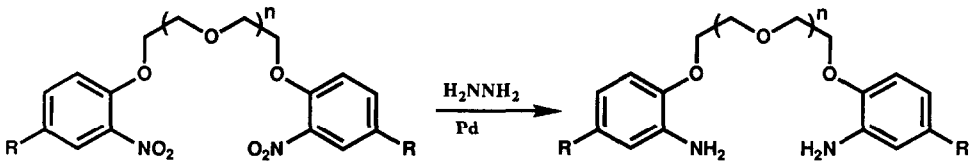


oxadiaza dibromide was then treated with ammonia to form the product.

Only a few of the many aromatic diamino ethers used to prepare macrocycles will be mentioned here. A reduction has been used to prepare aromatic diamines from nitro- and azide-containing ethers. The preparation of an aromatic diamine by known methods was reported by Glinka,[71] who treated an aromatic nitro halide with hexamethylenetraamine followed by hydrolysis to give an aromatic nitro amine. The nitro amine was first tosylated, and then the nitro groups were reduced as shown.[71] A palladium-catalyzed hydrazine or amalgamated



aluminum reduction of some bisnitro aromatic compounds appears to be a good method for the preparation of dianiline-substituted ethers.[44,72,73]



Other polyamino ethers can be prepared by the techniques discussed in the next section. For example, 1,5-diamino-3-oxapentane derivatives can react with compounds that extend each end by the 2-aminoethyl, 3-aminopropyl or 4-aminobutyl units.

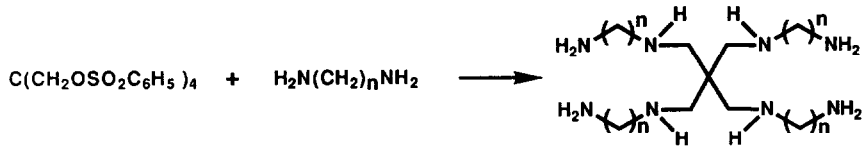
III. POLYAMINES

Preparation of polyamines requires the use of building blocks to extend the polyamine chain. Often, protecting groups must be employed for the amine units already in the starting oligoalkenepolyamine. This section covers the conventional routes to the polyamines and the many building block reactions that are used to extend the polyamine chain. The various methods used to protect the amine units in the starting oligoalkenepolyamines will be discussed in the next section.

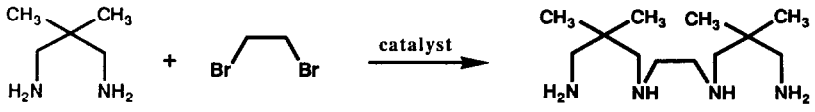
III.A. CONVENIENT ROUTES TO POLYAMINES

Amine preparative methods are found in textbooks and in monographs devoted to this subject.[25-31] Only the most important typical methods will be presented here for the preparation of amines that are useful for the preparation of the polyamines. The most convenient route to terminal diamines from readily available dihalogen compounds is the Gabriel synthesis using phthalimide, as mentioned above. Hydrazine hydrate cleavage of the imide,[34,74] instead of acid hydrolysis, has greatly improved this synthetic method. The reaction of alkyl halides or tosylates in the Delepine reaction with hexamethylenetetramine[75] and the Hofmann reaction with liquid ammonia[76] are often employed to prepare the bis terminal primary amines. These last two reactions have limited application. Hexamethylenetetraamine is a poor nucleophile and will react only with very reactive alkyl halides such as the benzylic, pyridylic, or allylic halides (or tosylates). Reactions with liquid ammonia require special equipment which is not available in many laboratories.

Although a large number of polyamines are now available, there is still a need to modify them or to make longer chains with more amine groups. The most common procedure to form higher order polyamines involves a large excess of the primary amine and a dihalide or ditosylate.[76-79] The use of excess primary amine reduces the problem of disubstitution on the amine, and the excess of primary amine is easy to remove by distillation. However, some side products can distill with the desired product, and other techniques for separation are important. This method was used to build a complicated polyamine by reaction of pentaerythritol tetrabenzenesulfonate (or tetrabromide) with ethylene or trimethylene diamine.[80-83] Barefield and co-workers prepared an interesting linear polyamine by using

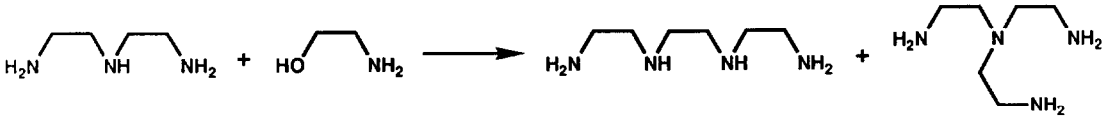


a large excess of the primary amine as shown in the following example.[58] Many other polyamines have been prepared by this standard nucleophilic displacement reaction.[84]



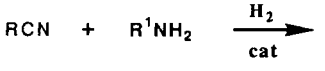
Oligoethylenepolyamines are traditionally prepared by the reaction of ammonia with 1,2-dichloroethane. The products of this reaction include ethylenediamine, diethylenetriamine, piperazine, and higher linear, branched and cyclic homologs. Polymerization of aziridine also has found some application for the preparation of the oligoethylenepolyamines, although mixtures of products were observed.[85-87] The polymerization of N-alkylaziridine gave fewer byproducts and more of the linear polyamines.[88]

A liquid phase supported phosphate-catalyzed process of converting ethanolamine and ethylenediamine to the oligoethylenepolyamines was patented by Texaco in 1977.[89] The catalysts were boron phosphate, strontium hydrogen phosphate, the lanthanide hydrogen phosphates, and others. The reaction of ethanolamine and ethylenediamine leads initially



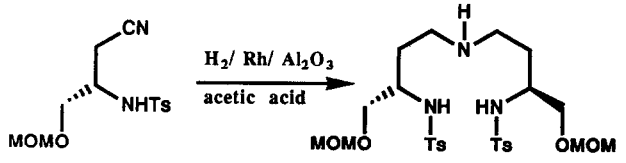
to diethylenetriamine. Subsequent reactions occur on both the primary and secondary amines to form linear and branched polyamines.

There could be future syntheses of the polyamines by reductive coupling of nitriles and amines. Indeed, nearly 70 years ago, von Braun and co-workers reported that nitriles were reduced to primary, secondary, and tertiary amines.[90] Kindler and Hesse[91] also reported that hydrogenation of a nitrile in the presence of an amine would give a secondary amine. Presently, selective catalysts exist to enable this reductive coupling reaction to give either secondary or tertiary amines.[92-94]

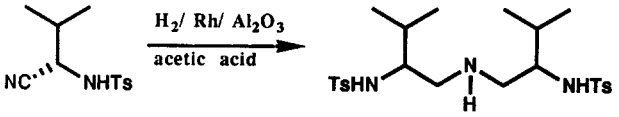


Galan and co-workers recently reported the reductive dimerizations of tosylaminonitriles in a 70% yield.[94] Presumably one nitrile was reduced and then reductively

coupled to the other nitrile.



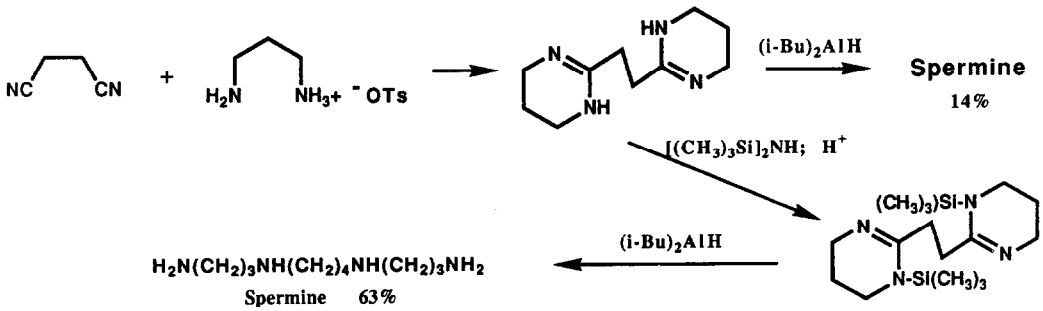
MOMO = CH_3OCH_2O



Other examples of the reductive coupling of amines to nitriles have been published. In general, the yields are not high.[95] The reaction of the appropriate primary diamines and nitriles can be a laboratory route to polyamines with tri- or tetramethylene bridges.

$$2\ (CH_3)_2NCH_2CH_2CN + H_2N(CH_2)_8NH_2 \xrightarrow[\text{coupling}]{\text{reductive}} (CH_3)_2N(CH_2)_3NH(CH_2)_8NH(CH_2)_3N(CH_3)_2$$

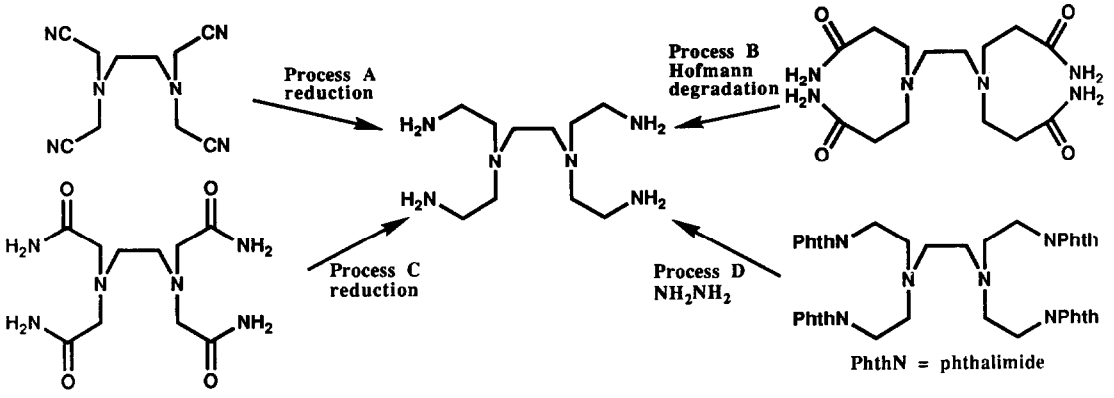
Succinonitrile was treated with the mono p-toluenesulfonic acid salt of 1,3-propanediamine at 140°C to give 1,2-bis(2-tetrahydropyrimidyl)ethane in a 95% yield.[96] This material was reduced with diisobutylaluminum hydride (DIBAH) to give spermine in a low yield. Yamamoto



and Maruoka reported that the conversion of the bistetrahydropyrimidyl compound to spermine was facilitated by treatment with hexamethyldisilazane followed by DIBAH to give a 63% yield of spermine.[97]

Often more than one pathway is possible for preparation of a particular polyamine and the best method is not always the shortest. For example, there are five or more possible methods to prepare N,N,N',N'-tetrakis(2-aminoethyl)ethylenediamine. Four methods are shown below. The starting materials for these reactions have been known for twenty years and can

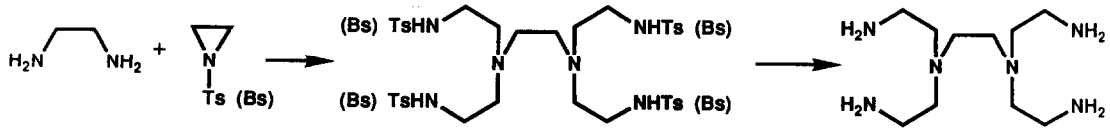
be prepared in one or two steps.



α-Substituted-nitriles, such as the α-aminonitriles, are useful intermediates for the preparation of many compounds including α-aminoacids, aldehydes, ketones, enamines, and the ρ-diamines.[98] Reduction of nitriles is complicated by small differences between the rates of hydrogenation and hydrogenolysis (substitution of cyanide by hydride),[99] and many unexpected products are formed.[94,99] For example, the catalytic hydrogenation of nitriles usually leads to a mixture of primary, secondary and tertiary amines as mentioned above. A specific catalyst can give pure products. Recently, the tetranitrile shown above (Process A) was reduced in high pressure hydrogen in an 85% yield using Raney Ni which has been specially activated with cobalt, chromium, or molybdenum in a continuous process.[100] On the other hand, other reducing agents, such as borane or sodium borohydride/Co(II), gave none of the hexaamine product, but in the case of borane, derivatives of piperazine were obtained.[101] Thus, in this case, partial decyanation occurred.

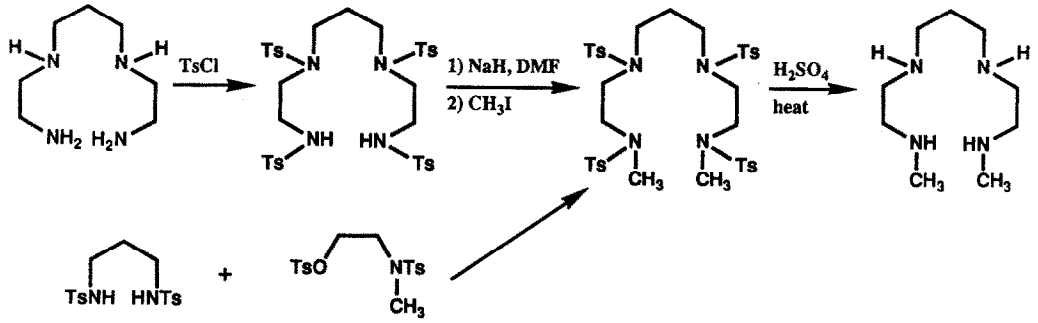
The Hofmann rearrangement to form the hexaamine (Process B) gave yields of 10-40%.[101,102] However, this rearrangement is sensitive to reaction conditions so that results were not reproducible. Processes C and D are currently being investigated as routes to this important hexaamine.[101]

For a small-scale laboratory synthesis of this unusual hexaamine, other (longer) routes were introduced. For example, the tosylamide or benzenesulfonamide derivatives of aziridine reacted with ethylenediamine to produce the tetrasulfonamide of the desire hexaamine as shown below.[103] This five step process was found by others to effectively produce the desired product.[104-107]



Paoletti and co-workers used N-tosyl protecting groups to prepare a tetraamine

containing only secondary amine functions.[108] The second reaction sequence shows another



strategy to prepare these compounds.

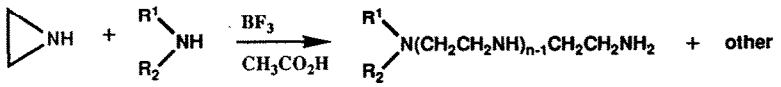
It is often easier to build a new molecule from simpler materials than to modify an already prepared compound. Methods that allow formation of polyamines from shorter moieties are of great interest. The syntheses of polyamines with terminal 2-aminoethyl, 3-aminopropyl or 4-aminobutyl units has developed in recent years. These types of compounds are important for the synthesis of cyclams that are similar to natural spermine and spermidine alkaloids.[109,110] Indeed, much of the interest in open-chain polyamines has focused on their use in the preparation of biologically active compounds including the peraza-crowns. Some of these processes are discussed in the next sections.

III.B. LONGER POLYAMINES BY EXTENSION OF THE POLYAMINE CHAIN

Some useful techniques are available to extend the polyamine chain on one or both sides to produce different types of polyamines with new ethylene, trimethylene or tetramethylene bridges. These techniques allow the preparation of modified polyamines from shorter, commercially available polyamine chains.

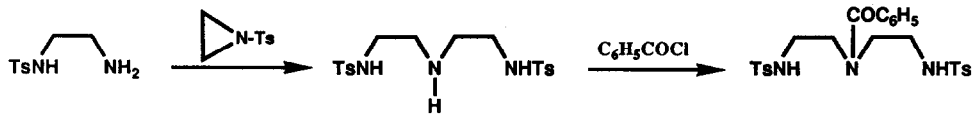
III.B.1. EXTENSION BY THE 2-AMINOETHYL UNIT.

Nucleophilic ring opening of the aziridine molecule is a laboratory method for extension of the polyamine chain. Most of the aziridines used have electron-withdrawing groups [RC(O), RSO_2, Ar, etc.] on the aziridine ring nitrogen. Other aziridines require more vigorous conditions for ring opening as shown below. Separations of the polyamine

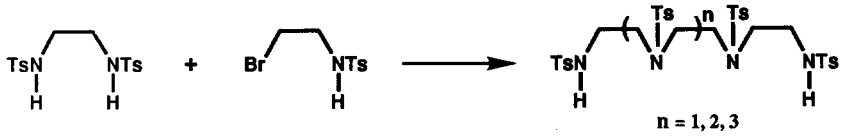


was done by distillation.[87,88] N-Tosylaziridine, which is not commercially available, has been used the most since the product has the reactive N-tosylamine groups on the terminal positions. Other examples of this reaction were presented above for the formation of N,N,N',N' tetrakis(2-aminoethyl)ethylenediamine. Martin and Bulkowski also have used N-tosylaziridine to prepare diethylene triamine with a different protecting group on the middle

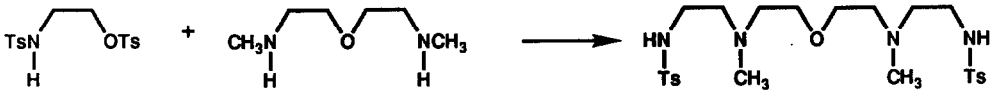
nitrogen. This type of reagent is helpful in producing macrocycles with selective functional groups.[111]



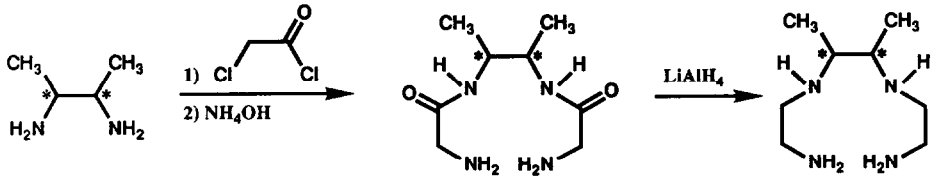
A similar type of reaction was observed with N-tosyl-2-bromoethylamine.[112] Its reaction with N,N'-ditosylethylenediamine gave mainly the desired pertosyltriethylenetetraamine but some pertosyltetraethylenepentaamine and pentaethylenehexaamine were also isolated. Opfeew



and Popkov found that 2-(N-tosylamino)ethyl tosylate, on the other hand, added only once to each amine group of N,N'-dimethyl-3-oxa-1,5-pentanediamine to give the dimethyl ditosyl tetraamine as shown.[113]



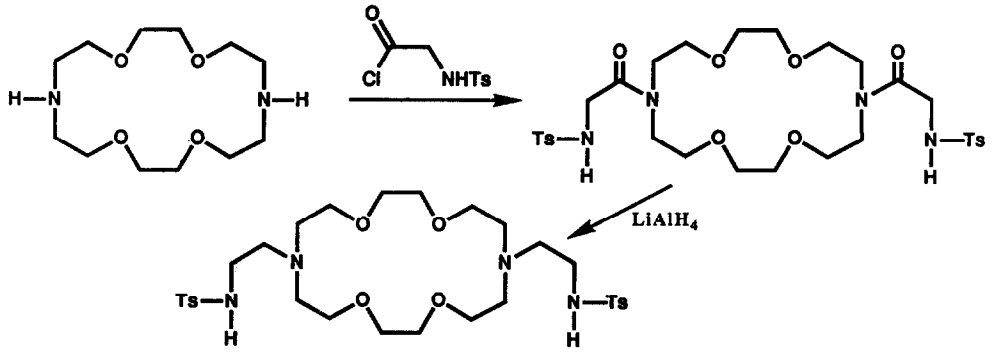
Inexpensive chloroacetyl chloride is a convenient building block for polyamine chain extension. Goto and co-workers prepared a chiral dimethyl-substituted triethylenetetraamine using chloroacetyl chloride.[114] These same workers prepared similar chiral tetraamines



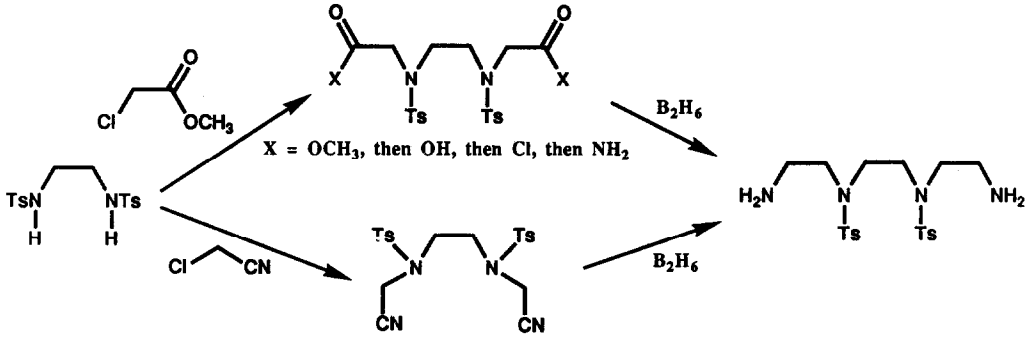
containing alkyl groups substituted on some of the carbon atoms.

N-Tosylaminoacetyl chloride has also been used to add 2-aminoethyl groups to a polyamine chain.[115] The process required reduction of the amide moieties as well as removal of the N-tosyl groups. The latter reaction is often difficult. The formation of bis-2-(N-tosylamino)ethyl-substituted 1,10-diaza-18-crown-6 (see top of next page) is an example of this process.[115]

Lehn and co-workers recently published the synthesis of triethylenetetraamine containing tosyl groups on the two center amine functions. They used the reaction of N,N'-ditosylethylenediamine with methyl chloroacetate or chloroacetonitrile followed by reduction

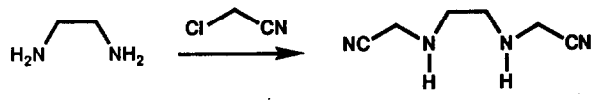


of the resulting diamide or dinitrile.[116] The sequence with chloroacetonitrile requires

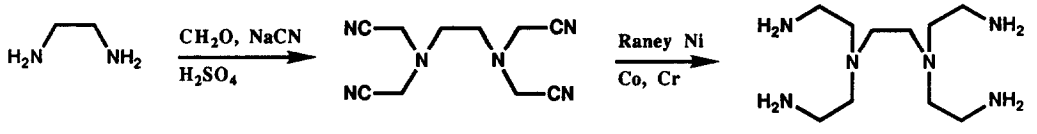


only two steps and gave a 76% overall yield of the tetraamine in contrast to the low-yield five-step process used previously to prepare these types of compounds.[117]

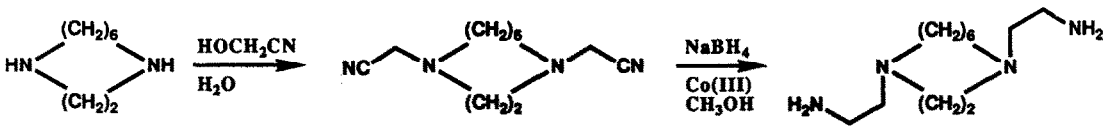
Overman and Burk reported that chloroacetonitrile reacted with amines to give the N-cyanomethylamines.[118] It is interesting that ethylene diamine reacted with an excess of chloroacetonitrile under the usual conditions (CH_3CN, K_2CO_3) to give the N,N'-bis(cyanomethyl)ethylenediamine and no tetrakis(cyanomethyl)ethylenediamine.[101]



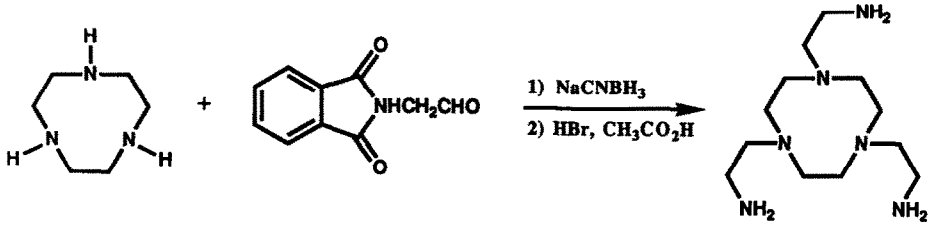
Formaldehyde and sodium cyanide react with ethylenediamine and acid to form EDTA. In this case, the four cyano groups were converted to the carboxylic acids. It is possible to separate the tetranitrile and convert it to the hexaamine as shown.[100,119] Vögtle and co-workers treated



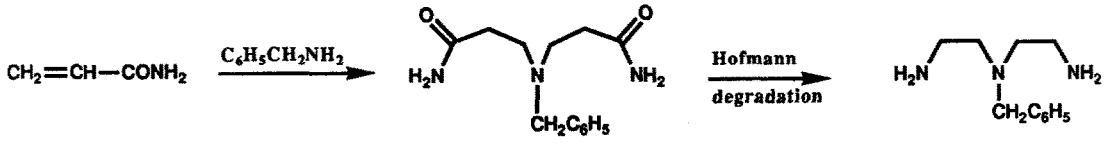
hydroxyacetonitrile with secondary amines at room temperature to give good yields of a bisnitrile, which was reduced with $NaBH_4$ and Co(II).[120]



2-Aminoethyl side chains can be added by use of phthalimide derivatives of 2-bromoethylamine or aminoacetaldehyde. Indeed, reaction of an amine with inexpensive N-(2-bromoethyl)phthalimide is one of the most important methods for introduction of 2-aminoethyl units. As reported by Sargeson and co-workers, the reaction of the phthalimide-substituted acetaldehyde with a secondary amine requires sodium cyanoborohydride to effect the reductive alkylation of the amine as shown.[121,122]

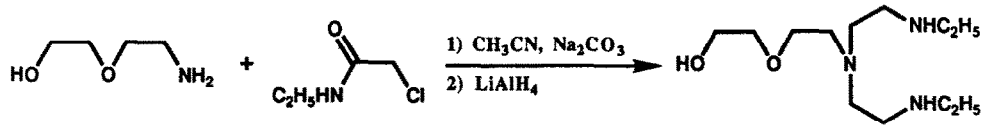


Amines undergo a Michael addition to acrylamide to form an aminoamide. A primary amine adds to two acrylamides to form a diamide. The diamide can be transformed to a bisprimary amine by the Hofmann amide rearrangement,[123] which requires sodium hypobromite or hypochlorite. The latter reagent is recommended.[124,125] Another example of this route to

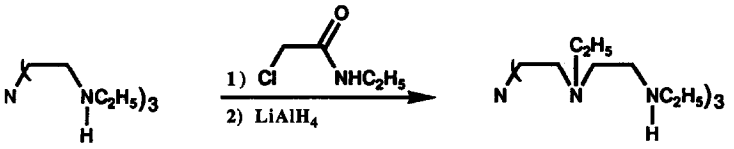


prepare polyamines is shown above for the preparation of the tetrakis(2-aminoethyl)ethylenediamine.[102]

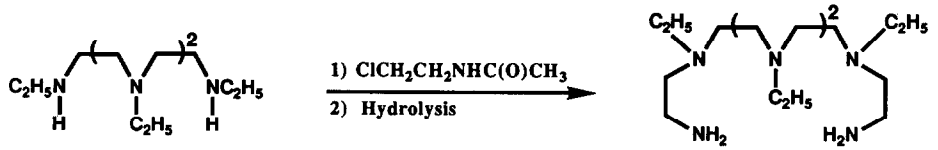
N-Alkylchloroacetamide is a readily available and convenient reagent that introduces 2-(N-alkylamino)ethyl groups onto an amine system.[126] Bradshaw and co-workers prepared an



interesting tri-terminal secondary amine by this procedure. Tris(2-ethylaminoethyl)amine was treated with N-ethylchloroacetamide in acetonitrile in the presence of anhydrous sodium carbonate to give the triamide, which was reduced to the tri-terminal secondary amine.[101] The same type of reaction with chloroacetamide (without the N-alkyl group) gave only average yields of the bis(2-aminoethyl) products.[127] Crnic and Glincic used N-(2-chloroethyl)-

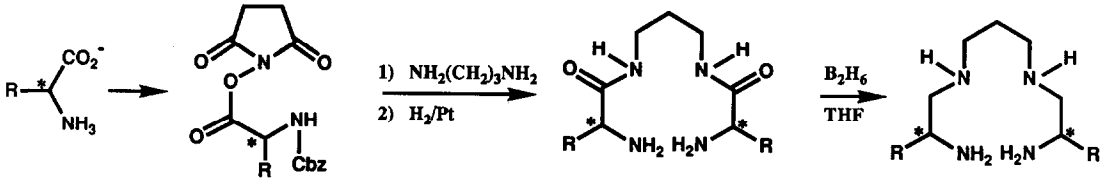


acetamide [$Cl(CH_2)_2NHC(O)CH_3$] rather than chloroacetamide to introduce N-(2-aminoethyl) substituents at the end of a polyamine.[128] This reaction must be carried out in acid



media since base causes the starting material to cyclize to 2-oxazoline.[129] These types of cyclizations are difficult to avoid so it is best to use reagents that do not cause cyclization.

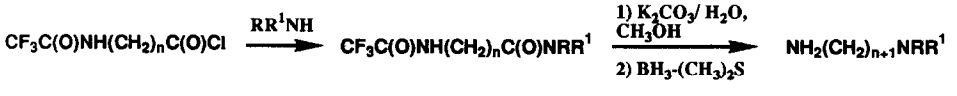
The inexpensive aminoacids have been used for the synthesis of chiral polyamines. These chiral materials are then used in the synthesis of peptides or other natural products. Burrows and co-workers recently published on the use of L-phenylalanine, L-leucine and L-valine to prepare chiral polyamines.[109,130] This synthesis (shown below) produced the chiral amines in overall yields of 37-62%. These chiral tetraamines were used to prepare macrocycles.



R = $CH_2C_6H_5$, $CH_2CH(CH_3)_2$, $CH(CH_3)_2$, H

Cbz = $CO_2CH_2C_6H_5$

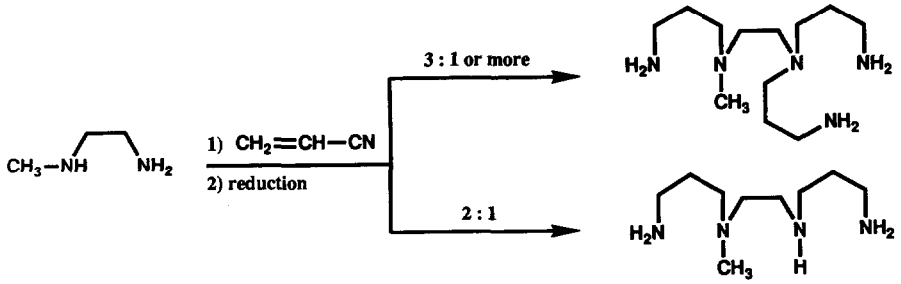
Nordlander and co-workers reported that N-(trifluoroacetyl)glycyl chloride (n = 1), prepared from N-(trifluoroacetyl)glycine and oxalyl chloride, reacted with primary and secondary amines to form an amide. The trifluoroacetyl group easily can be removed in a



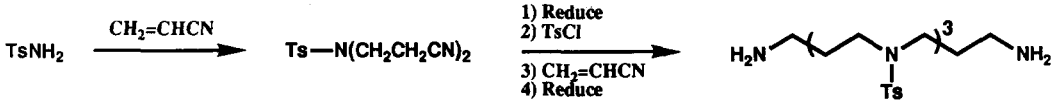
weak base followed by reduction with BH_3-$(CH_3)_2S$ to give the new aminoethylamine compound.[131] This process can be used to form the aminopropyl- and aminobutylamines when n = 2 or 3.

III.B.2. EXTENSION BY THE 3-AMINOPROPYL UNIT

The polyamines containing trimethylene units are important natural amines. The Michael addition of amines to acrylonitrile has been studied extensively. The reaction between a primary amine and acrylonitrile can be controlled by the stoichiometric ratios of the two reactants to produce mono- or disubstituted cyanoethylamines. Multiple additions are possible when polyamines are used. The products usually can be separated by distillation. The oligocyanoethylamine products can be reduced to the desired polyamines as shown.[58]



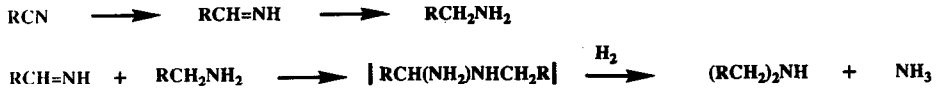
Vögtle and co-workers used this addition-reduction sequence to obtain a variety of polyamines containing primary amine functions at the ends of a polyamine chain as shown below.[120] In another example, Edwards and co-workers treated crotonitrile with 1,8-diamino octane followed

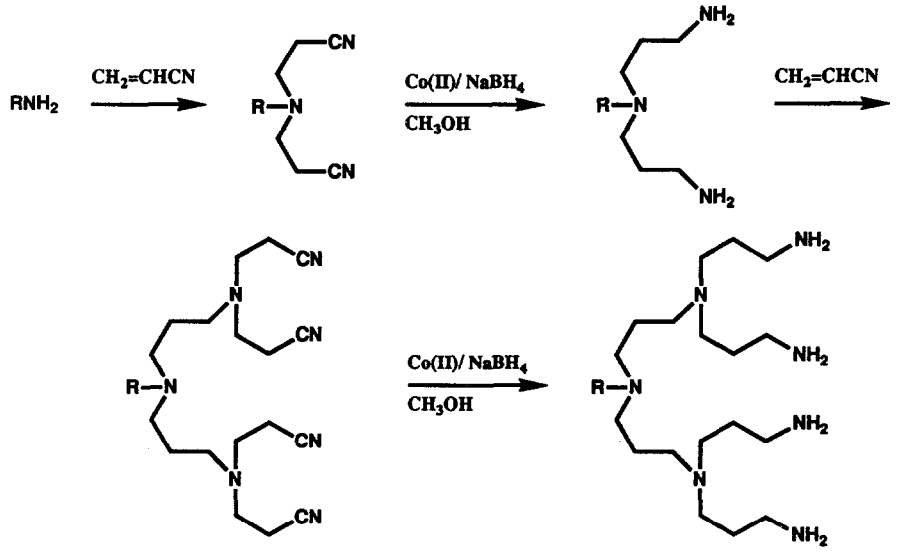


by reduction to give 1,16-diamino-3,14-dimethyl-4,13-diazahexadecane.[95] The "cascade"

polyamine compounds were made by this process from a primary amine and successive additions of acrylonitrile followed by reductions as shown at the top of the next page.[120]

Reduction of the nitrile group is not straightforward. Hydrogenation of a nitrile results in a mixture of primary, secondary, and tertiary amines. Reduction of the nitrile gives the aldimine, which can be further reduced to the primary amine or which undergoes condensation with an amine to yield other products.[132] The aldimine is easily hydrolyzed to





give an aldehyde, which reacts with an amine under reducing conditions to give a secondary amine.[133] Tertiary amines can be produced in these reactions by a similar process.[134]

Secondary Amines

$$RCH{=}NH + H_2O \longrightarrow RCHO + NH_3$$

$$RCHO + RCH_2NH_2 \longrightarrow H_2O + RCH{=}NCH_2R \xrightarrow{H_2} R(CH_2)_2NH$$

Tertiary Amines

$$RCH{=}NH + RCH_2NHCH_2R \rightleftharpoons \left|RCH(NH_2)N(CH_2R)_2\right| \xrightarrow{H_2} (RCH_2)_3N + NH_3$$

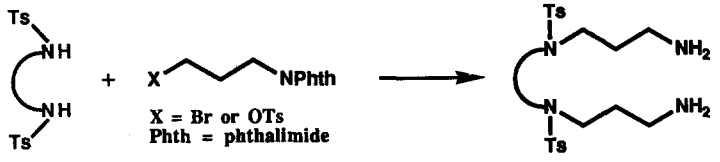
The difficulty in isolating pure products in these reductions is compounded where the polynitrile has a structure capable of forming five- and six-membered rings upon reduction. In those cases, cyclic products predominate. This is especially true with polynitriles such as tris(cyanomethyl)amine, bis(cyanomethyl)amine and ethylenediaminetetraacetonitrile. Thus, bis(cyanomethyl)amine forms mainly the piperazine on hydrogenation. Tris(cyanomethyl)amine forms very little of the open chain tris(2-aminoethyl)amine on hydrogenation under standard conditions.[100]

Special reaction conditions can favor the formation of a primary amine on hydrogenation of a nitrile. If acetic anhydride is present, the reduced amine is acylated as fast as it forms and gives an acetamide in high yields. In aqueous solutions containing phenylhydrazine, the primary amine is produced, since the aldehyde product of hydrolysis of the intermediate aldimine is removed as the phenylhydrazone. A large excess of ammonia also favors the formation of the primary amine by repressing its reaction with the aldimine.[100]

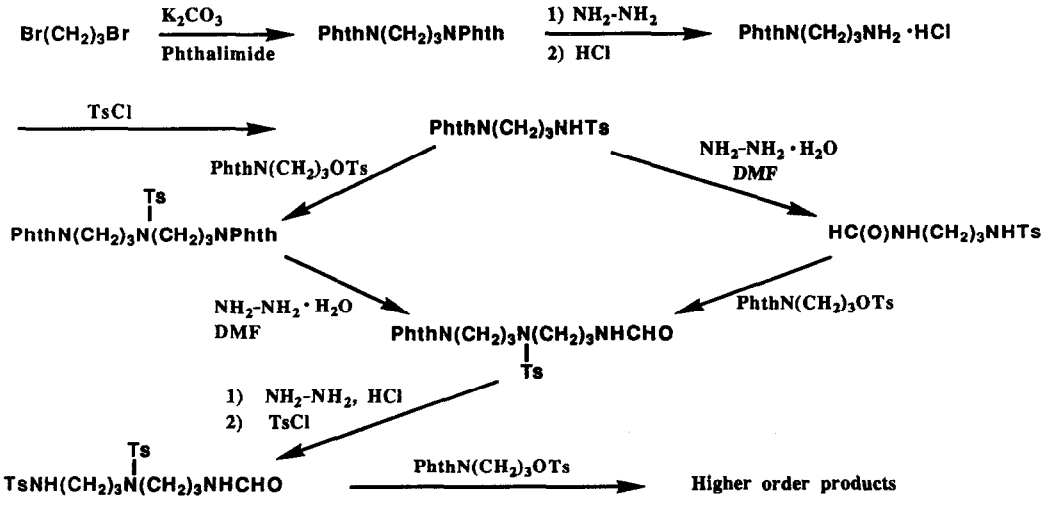
The catalyst is the most important variable in the hydrogenation reaction. By

choosing the correct catalyst, one can obtain primary amines with high selectivity or a product where secondary or tertiary amines prevail.[92] Catalysts based on Co,Ni and Ru produce mainly primary amines. Cu and Rh catalysts are used to give secondary amines on hydrogenation of a nitrile, while Pt and Pd catalysts give tertiary amines in high selectivity.[93,135-141] The most used laboratory reducing agents for the nitriles are BH_3, $LiAlH_4$, or $NaBH_4$/Co(II).[120,135]

Iwata and Kuruhara have reported that N-(3-bromopropyl)phthalimide (commercially available) or its tosylate analog are excellent synthons for the preparation of polyamines containing propylene bridges.[142,143] These authors also prepared a N-[3-(N'-tosylamino)-



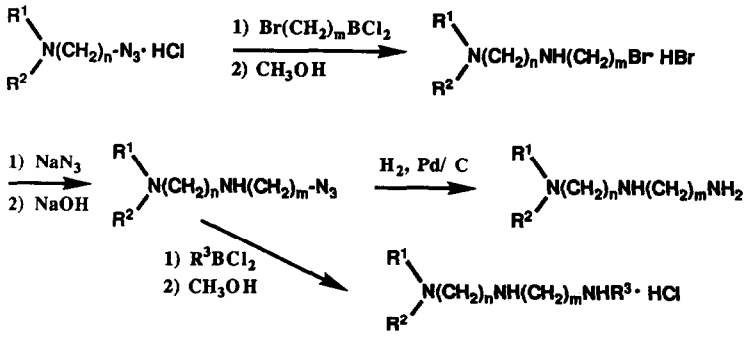
propyl]phthalimide, which can be treated with hydrazine to form 1-(*N*-formyl)-3-(*N*-tosyl)propanediamine.[142,143] This latter compound can be combined with the 3-phthalimidopropyl tosylate to form formyl-protected 7-phthalimido-4-tosyl-4-aza-1,7-heptanediamine (see Scheme below). The process can be repeated by reaction with hydrazine, treatment with tosylchloride, and reaction again with 3-phthalimidopropyl tosylate to form the tripropylene tetraamine type compound. In this way, polyamines with several propylene bridges can be constructed. The final products will have terminal tosylamides and formyl groups that can be removed to form the polyamines.



A similar building block containing a t-butoxycarbonyl protecting group rather than the phthalimide, namely 1-bromo-3-(t-butoxycarbonylamino)propane [t-BuOC(O)NH$(CH_2)_3$Br],has been

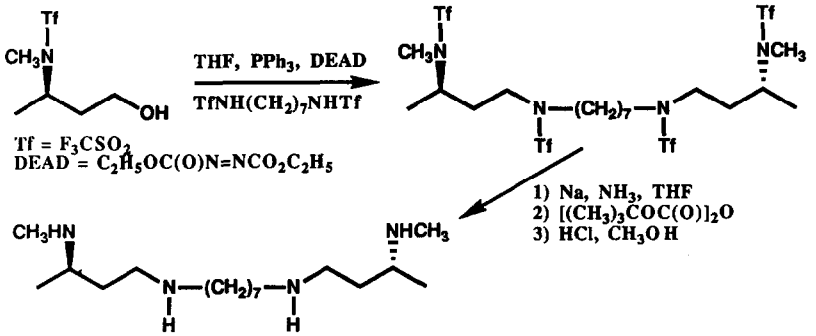
used for the preparation of argiotoxins.[144]

Brown and co-workers have shown that the azide function can be converted to give a primary or secondary amine by reduction or reductive alkylation using various borane reductants.[145] The azides are readily prepared from available alkyl halides and the dichloroboranes by the hydroboration of allyl or butenyl halides. Carboni and coworkers



reported that this process can be repeated with ethylene or trimethylene units to give longer polyamines with ethylene or trimethylene bridges.[14]

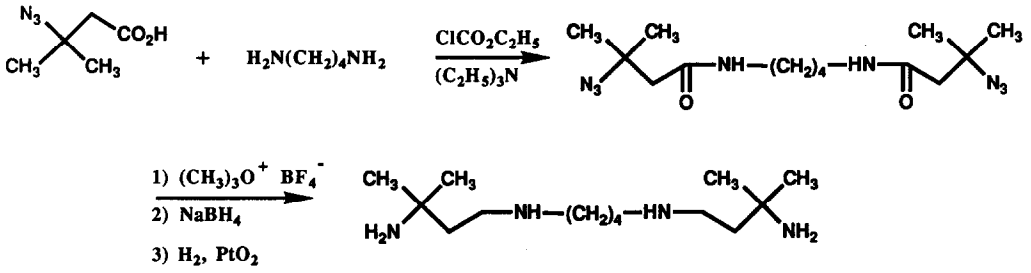
Edwards and co-workers[146] used the Mitsunobu process[147] to prepare a chiral bissecondary amine. Chiral 3-(N-methyltrifluoromethanesulfonamido)-1-butanol was treated with 1,7-bistrifluoromethanesulfonamidoheptane to form the bistrifluoromethanesulfonyl-protected chiral diamines as shown below. The sulfonyl groups were reductively removed without loss of chirality, and the product was converted to the bis-t-butoxycarbonyl-protected diamine for isolation and purification. The t-butoxycarbonyl protecting groups were removed by hydro-



chloric acid. When the p-toluenesulfonyl group instead of the trifluoromethanesulfonyl unit was used to protect the amine functions, product yields were lower and some additional byproducts were observed. This process with the trifluoromethanesulfonyl protecting group has been used to prepare other polyamines.

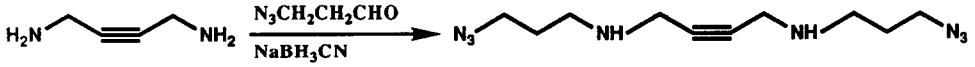
Many special coupling agents have been developed to convert amino acids into peptides.

In a sequence similar to the one above, Nagarajan and Ganem condensed 3-azido-3-methylbutanoic acid (prepared from the reaction of sodium azide and 3,3-dimethylacrylic acid) with putrescine using ethyl chloroformate as the coupling agent to form a diaminodiamide product.[137] The amide and azide moieties were reduced in two steps as shown to form tetramethyl-substituted spermine in a 27% overall yield. The same authors also used 3-azido-3-methylbutyric acid to form a bisimine intermediate, which was reduced in one step along



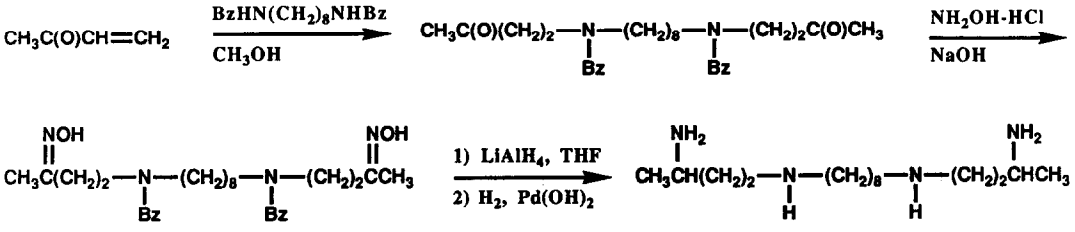
with the two azide functions by use of hydrogen and platinum oxide. This process was not useful for the preparation of spermidine because reductive amination of 3-azido-3-methyl-1-butanol and putrescine did not give the pure 2:1 adduct as needed.

Nagarajan and Ganem recently reported a way to prepare a tetraamine with either a 2-butene or a 2-butyne bridge between the central amine groups.[148] 2-Butyne-1,4-diamine was treated with 3-azidopropanal in the presence of sodium cyanoborohydride. The resulting

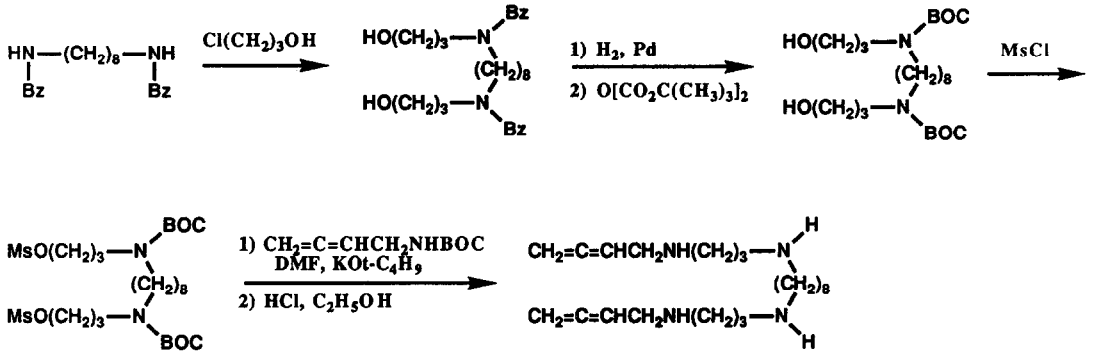


butyne-containing diaminodiazide was reduced by triphenylphosphine to the tetraamine with the butyne moiety, or with diborane to give the tetraamine with a tetramethylene bridge.

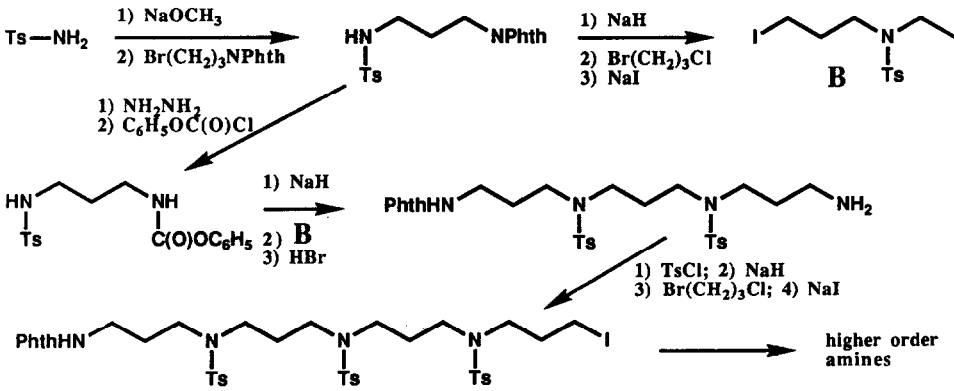
Edwards and co-workers have reported an interesting series of reactions that start with methyl vinyl ketone to give a tetraamine containing two trimethylene bridges and two secondary and two primary amine functions.[95] The unsaturated ketone was treated with N,N'-dibenzyl-1,8-octanediamine followed by hydroxylamine to form a bisoxime. The oximes were reduced with $LiAlH_4$ and the benzyl groups were reductively cleaved to give the tetraamine as shown below.



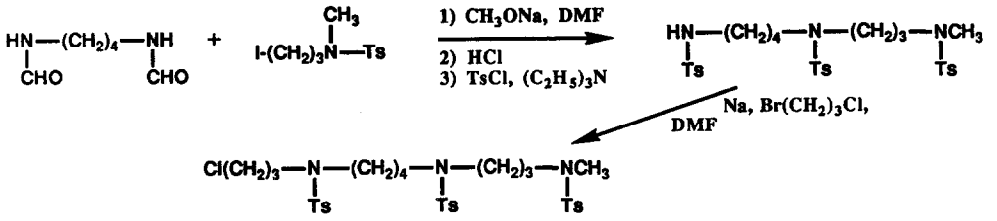
3-Chloro-1-propanol was used to give a similar tetraamine. The same researchers first combined 3-chloro-1-propanol with N,N'-dibenzyl-1,8-octanediamine, and the benzyl groups were removed. The diaminodiol product was treated with di-t-butyl dicarbonate to protect the amine functions. The resulting diol was mesylated and treated with a protected allenyl amine to form the protected tetraamine. The protecting groups were removed with hydrochloric acid to form the bisallenyl tetrasecondaryamine as shown.[95]



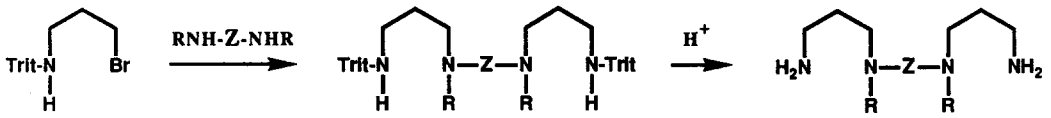
Kramer and co-workers have used 1-bromo-3-chloropropane to prepare a number of polyamines, some with up to eleven nitrogens in the chain.[149,150] The reaction of 1-Bromo-3-chloropropane with an amide salt followed by sodium iodide gave a 3-iodopropyl amide (B in the following sequence). The reactive 3-iodoamide building blocks are used to prepare long chain polyamines where the amine functions were separated by trimethylene units.[149,150] The process can be repeated to form long chain polyamines. The same research group also used the acetamide moiety instead of phthalimide in intermediate B.[151]



Similar building blocks but containing tetramethylene and trimethylene units were prepared as shown below.[152] A branched building block was prepared with the N-butoxycarbonyl derivative of 1-iodo-3-methyl-3-butanamine.[153]



Krakowiak and co-workers have reported that diamines readily react with 3-bromo-N-trityl-1-propanamine to give N,N'-ditritylpolyaza compounds in yields of 50-80%.[154] Without the diamine, the starting N-tritylbromide reacts to form N-tritylazetidine. The



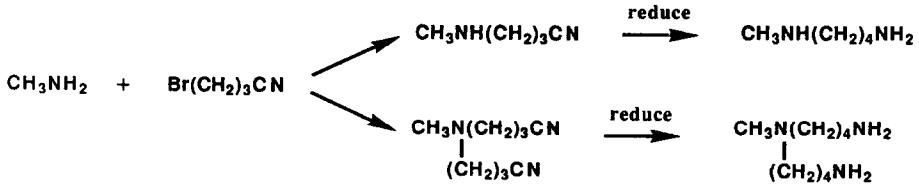
trityl groups were easily removed in acid. This process makes possible the preparation of new α,ω-diamines needed for the synthesis of new cryptands and polyaza-crowns.

Murahashi and co-workers used the paladium catalyzed reaction of azetidine with a diamine to prepare polyamines containing 3-aminopropyl units. For example, an excess of 1,3-propanediamine was treated with azetidine to give N-(3-aminopropyl)-1,3-propanediamine in a 73% yield.[155]

III.B.3. EXTENSION BY THE 4-AMINOBUTYL UNIT

Many natural polyamines have tetramethylene units between the amine nitrogen. This section describes some of the ways to prepare polyamines with 4-aminobutyl functions on one or both ends.

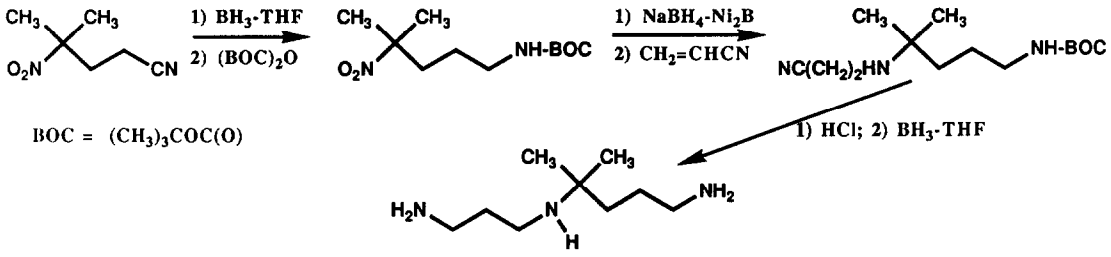
4-Halobutanenitrile appears to be a convenient reagent for introducing the 4-aminobutyl unit into polyamines. Reaction with primary amines gave mono- and diadducts



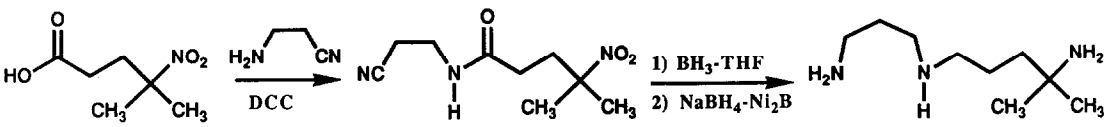
which were separated by chromatography.[136] Addition of 4-bromobutanenitrile to an alkylbenzylamine followed by reduction (cleavage of the benzyl group and reduction of the nitrile) gave N-alkyl-1,4-butanediamine.

Nitro compounds have been used to prepare certain polyamines. Garrido and co-workers reported an interesting syntheses of triamines from nitro-containing materials.[136] In the

first step, the cyano group of a nitro-substituted nitrile (prepared from 2-nitropropane and acrylonitrile) was selectively reduced and the resulting amine was protected. The nitro



group was then reduced and treated with acrylonitrile. The protecting group was removed and the cyano group was reduced to a triamine where the amine nitrogens were separated by trimethylene and tetramethylene units.[136] In a second reaction by the same authors, a nitrocarboxylic acid (prepared from 2-nitropropane and methyl acrylate) was coupled with 3-aminopropanenitrile. Sequential reduction of the amide, nitrile, and nitro groups gave a slightly different triamine as shown.



Other methods for introduction of 4-aminobutyl groups have been published.[154,156]

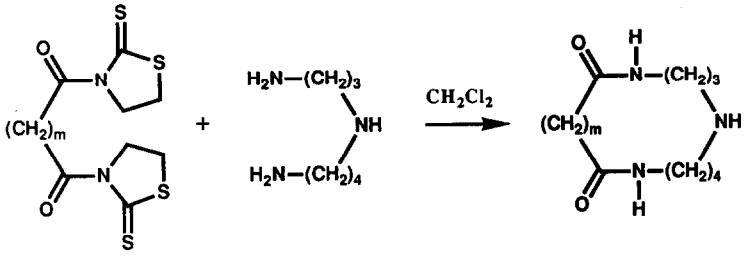
IV. SELECTIVE AMINE PROTECTING GROUPS

To accomplish specific syntheses, it is very important to protect selectively the various amine functions in a polyamine. From a synthetic point of view, selective protection allows the synthesis of longer polyamines or branched polyamines. For example, without protecting groups, acylation reactions of the polyamines with acid chlorides or anhydrides gives mixtures of products.[157,158] There are examples of the acylation of primary amines in the presence of secondary amines by means of bulky or aromatic acylating agents,[159-162] but one is not always assured of such selective acylations. Thus, selective methods to protect only primary or only secondary amines have been developed. Some of these methods will be discussed briefly here.

IV.A. PROTECTION OF PRIMARY AMINES

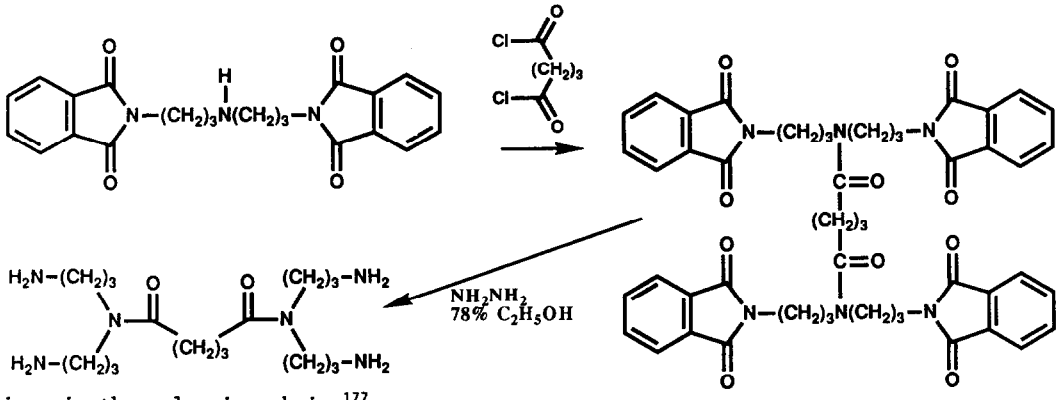
Protection of primary amines can be achieved by simple selective reagents in one step or by multi-step processes. Certain esters or acid coupling agents can be used to acylate only primary amines. Some of these processes utilize esters of 1-hydroxypiperidine,[163,164] various 3-acylthiazolidine-2-thione derivatives,[165-167] and esters derived from a carboxylic

acid and N,N'-dicarboxyldiimidazole.[168] The use of the 3-acylthiazolidine-3-thione to react with the terminal primary amines of spermidine, as reported by Nagao and co-workers, is shown below.[165] Interestingly, macrocyclic polyamines (the cyclams) and polyaminoethers (the



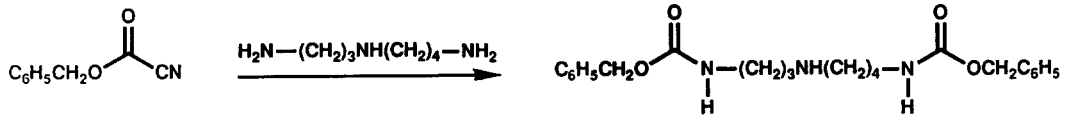
polyaza-crowns) can be prepared by the action of a diester with a polyamine where there are two terminal primaryamines.[168,169] In these cases, only the primary amines react to form the macrocyclic diamide.

Many reseachers have reported that primary amines react with phthalic acid or anhydride in the presence of secondary amines in the polyamine chain to form the phthalimide of the primary amines. The secondary amines can then react and the primary amines are recovered by use of hydrazine as shown below.[103,171-175] N-Ethoxycarbonylphthalimide (Nefkins' reagent[176]) also reacts selectively with primary amines in high yields and in the presence of secondary

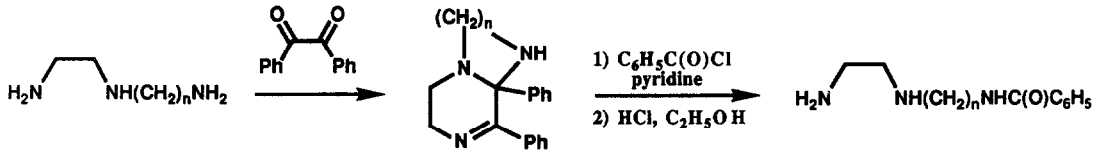


amines in the polyamine chain.[177]

Nitriles react with polyamines in the presence of $RuH_2(PPh_3)_4$ to give the amide in high yields.[178] Thus, spermidine reacted with acetonitrile to give N^1,N^8-diacetylspermidine in a 93% yield. Acyl cyanides react in the same manner under mild conditions.[179] It is noteworthy that the benzyloxycarbonyl protecting groups can be introduced selectively into polyamines by reaction with benzyl cyanoformate.[179] The benzyloxycarbonyl group can be removed under mild conditions.[180]



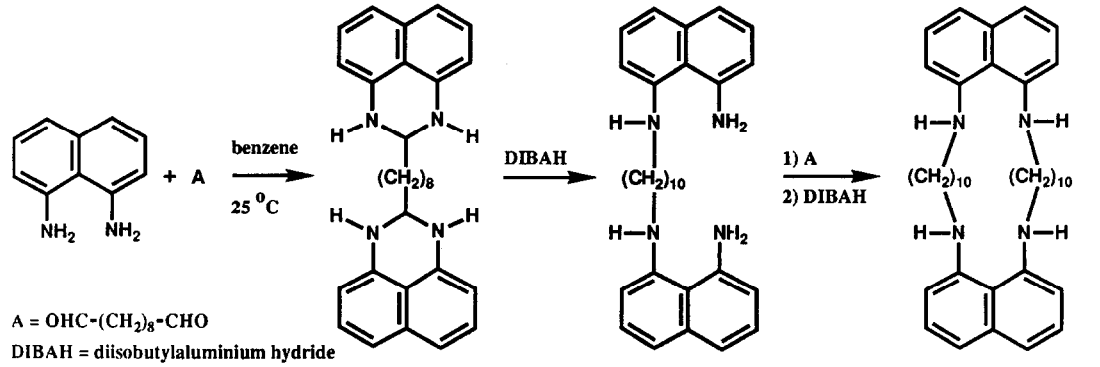
A very interesting monoacylation of a triamine by use of benzil as a protecting group was reported recently by Okawara and co-workers.[181] The amine-substituted tetrahydropyrazine molecule, formed by reaction of benzil and the triamine, was acylated and the resulting product was deprotected with acid as shown.



Other strategies are useful for protection of primary amines. Oxazolone can selectively protect primary over secondary amines.[182] Procedures are available to protect each type of amine group selectively so that reactions can be conducted on the desired amine groups in succession. The protecting groups are then selectively removed.[183,184]

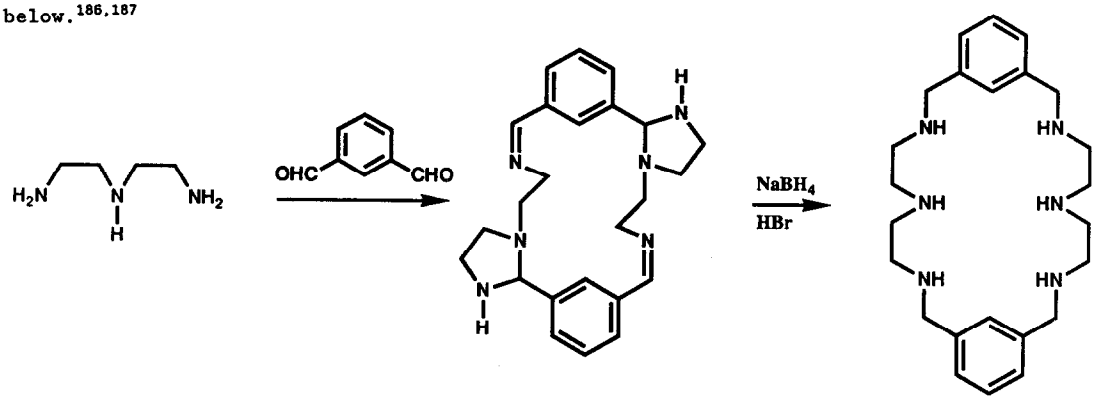
IV.B. PROTECTION OF SECONDARY AMINES

It is often important to protect secondary amines in order to carry out reactions on primary amine functions. One important new protection method for internal secondary amines is to form a 1,3-diazacyclohexane (hexahydropyrimidine) by reaction of a 1,3-diamine with an aldehyde or ketone. The diazacyclohexane is easily opened by hydrolysis. Even though the first attempt to protect internal amines of spermine by reaction with benzaldehyde was not successful,[11] this type of reaction has been used to form macrocyclic polyamines. Yamamoto and Maruoka prepared a series of perazacyclophanes by treating dialdehydes with 1,2- or 1,3-diamines to form the 1,3-diazacyclopentane or -hexane followed by reduction.[97] The resulting open chain polyamine was further treated with the dialdehyde followed by reduction to give the peraza macrocycle as shown. Similar syntheses of the perazacyclophanes by the reaction

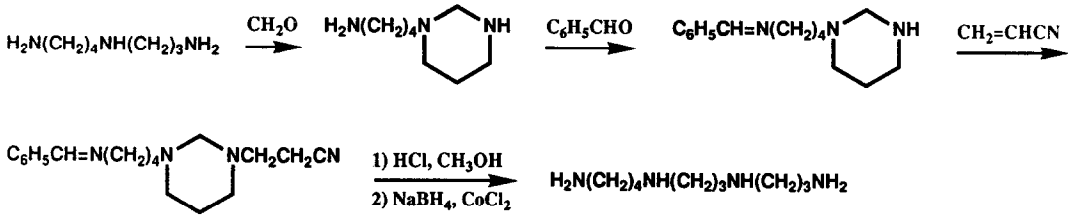


of rigid dialdehydes and polyamines via the diazacyclohexane or diazacyclopentane have been reported by many researchers.[185-190] The reaction of diethylenetriamine with

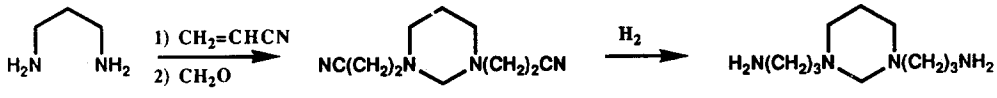
isophthaldialdehyde followed by reduction as reported by Menif and co-workers is shown below.[186,187]



The internal secondary amine of spermidine was successfully protected with formaldehyde to give a 95% yield of the 1,3-diazacyclohexane. This compound was acylated or alkylated by a variety of reagents and then reduced to form the desired polyamine.[191-195] An example of this route to a 3-aminopropyl derivative of spermidine is shown below.



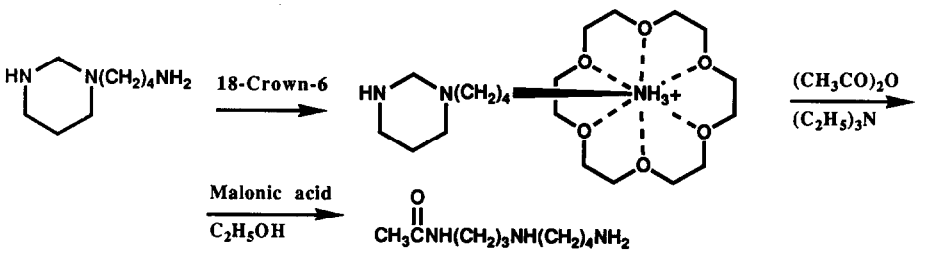
The 1,3-diamine functionality is important for this type of protection. Polyamines that have successive 1,3-diamine units react with formaldehyde to form mixtures of the diazacyclohexanes.[139] Dutasta and co-workers prepared 4,8-diaza-1,11-undecanediamine with protected internal amines by reaction of 1,3-propanediamine with 2 moles of acrylonitrile, followed by reaction with formaldehyde and reduction. The protected tetraamine was used



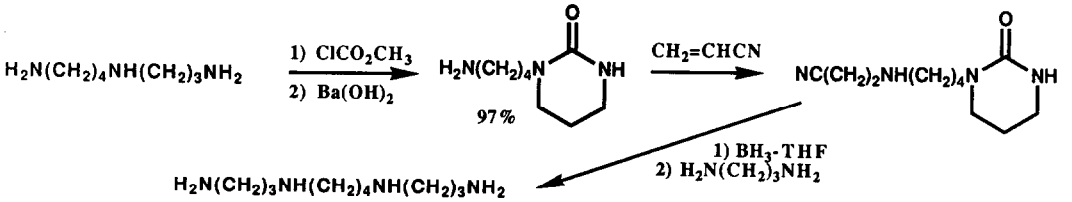
to make a macrocycle and then the diazacyclohexane rings were opened by acid. Many other natural polyamines contain 1,3-diamine units, including N-(3-aminopropyl)cadaverine and spermine. As shown by Chantrapromma and Ganem, spermine forms a bis(1,3-diazacyclohexane) structure that is capable of further reactions on the end amine groups.[196]

Tice and Ganem also devised a way to protect both the internal amine and the N^8 primary amine of spermidine.[195] The N^1 and internal amine were first blocked with formaldehyde and

then the N^8 amine was complexed with 18-crown-6. The N^1 amine was then acetylated and the methylene protecting group was removed as shown.



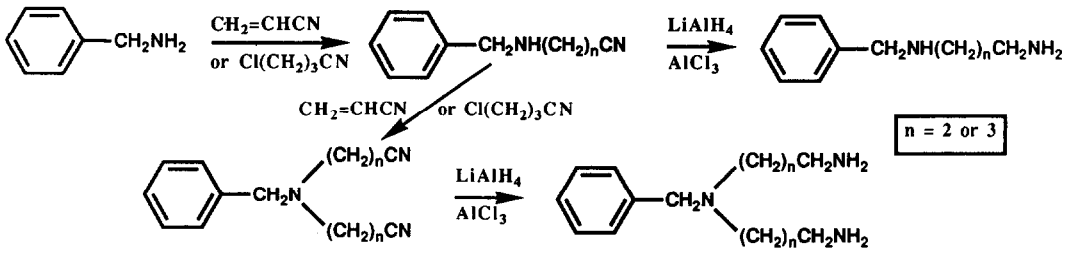
Internal secondary amines have also been protected through the formation of cyclic urea derivatives. The 1,3-diamine portion of spermidine reacted with methyl chloroformate to give the cyclic urea. The amide nitrogens of the urea are not reactive so that further reactions take place on the remaining primary amine. Such a process using acrylonitrile is shown below.[11] Cyclic ureas are resistant to hydrolysis so that "urea exchange" with



1,3-propanediamine allowed the isolation of the final product. Chantrapromma and co-workers used this method to prepare spermidine derivatives with three different substituents on the three nitrogen atoms.[197]

IV.C. MISCELLANEOUS METHODS

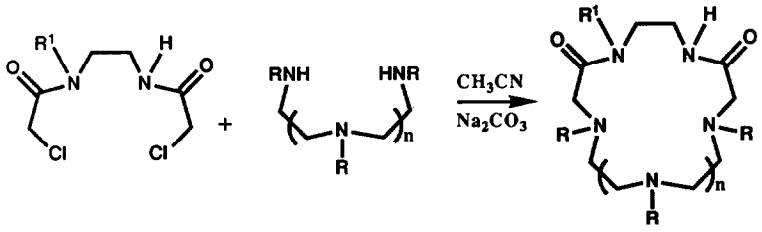
Often polyamines containing protecting groups on internal secondary nitrogens can be prepared. Bergeron and co-workers reported that benzylamine reacts with one or two moles of 4-chlorobutanenitrile or acrylonitrile to form mono or dicyano derivatives.[12,140,198]



The cyano groups were reduced with $LiAlH_4$ in the presence of $AlCl_3$ to give the benzyl

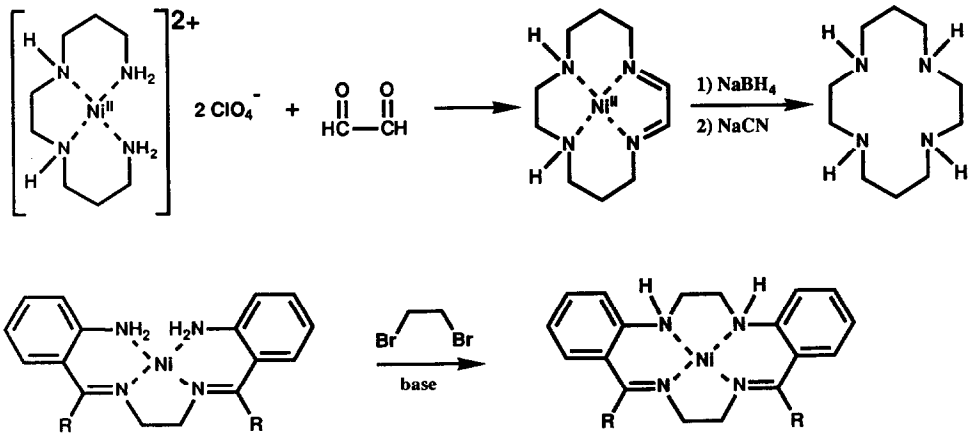
protected triamine. Benzyl groups are reductively cleaved with Pd/C.

Bradshaw and Krakowiak have shown that amide groups can be used to protect nitrogens. Bis-α-chloroamides react with primary amines or bissecondary amines to form macrocyclic diamides, which can be reduced to the macrocyclic polyamines. The amide



nitrogens of the bis-α-chloroamide are not reactive so that one or both can carry a hydrogen without need for protection.[127,199-204] This procedure with the bis-α-chloroamide should be useful for access to open chain polyamines.

Tri- and tetraamines complex with metal cations by wrapping themselves around the cation. Even though the cation coordinates to all nitrogens, the terminal primary amines are still reactive nucleophiles. Their reactivity is shown by the metal template synthesis of macrocyclic polyamines.[205-212] The peraza macrocycles were prepared without the need for

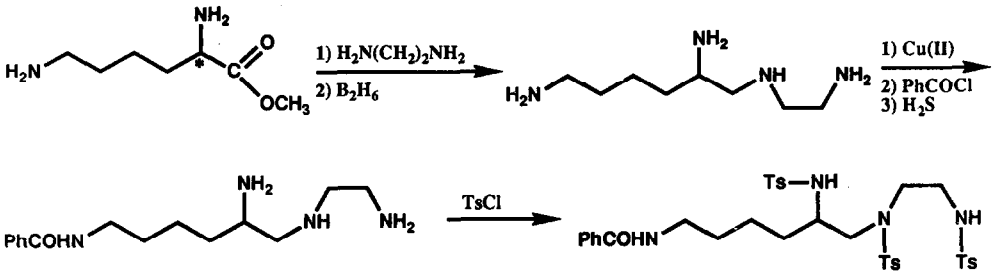


protection of the internal amine functions. These types of cyclizations have been studied by many researchers.[188,213-215]

Recently, N-monoalkylated macrocycles and linear tetraamines were prepared from their complexes with borane or with chromium ions. The metal ion coordinates only with three nitrogens, thus, alkylation took place on the fourth nitrogen.[216,217]

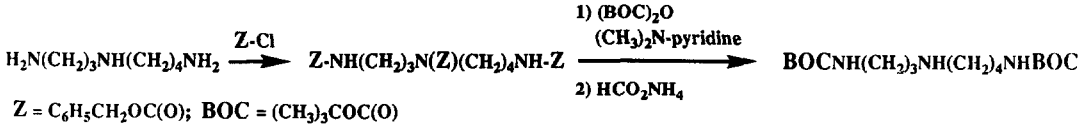
Craig and co-workers also have used metal ion complexation to protect amines in one part of a molecule while carrying out a reaction in another part.[218] The methyl ester of lysine was combined with ethylenediamine followed by reduction to give a new tetraamine. The

diethylenetriamine portion of the molecule was complexed with Cu(II) while the remaining

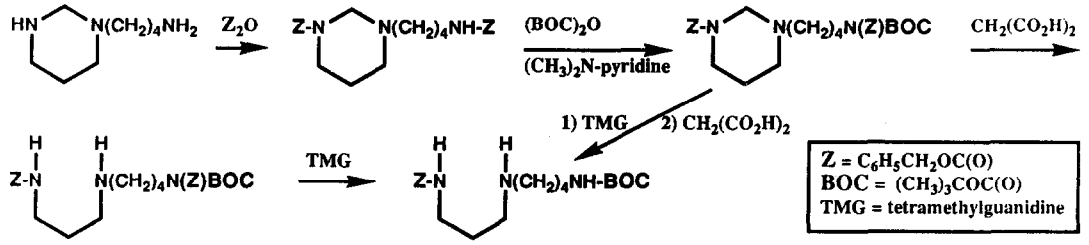


amine was benzoylated. A similar process was used by Kaden and co-workers to protect cyclam amine functions while an amine on a side arm was acylated.[219]

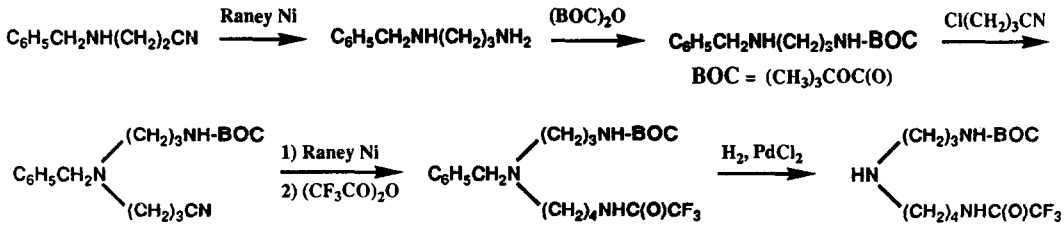
The many protecting groups available for amines[180] can be selectively removed to provide a variety of polyamines. For example, the terminal amines of spermidine can be protected by treatment of all amine groups with benzyloxycarbonylchloride(ZCl) followed by t-butylcarbonylanhydride $(BOC)_2O$. The benzyloxycarbonyl groups are then removed by catalytic transfer hydrogenation to leave the t-butoxycarbonyl protectors on the terminal nitrogens as shown.[220] Similar primary amine-protected spermidines were obtained by an aza-Wittig



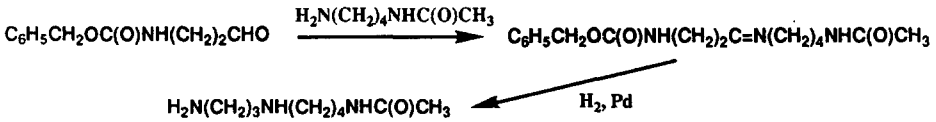
reaction[221] or by a five-step synthesis via the 1,3-diazacyclohexane protection route.[220]



The preparation of spermidine with the secondary amine unprotected was also accomplished from available 3-(benzylamino)propanenitrile as shown below.[222] This process was used by Bergeron and co-workers to prepare other selectively protected triamines.[222]



N^8-Acetyl spermidine was prepared from N-(2-formylethyl)benzyl carbamate and N-(4-aminobutyl)acetamide as reported by Boukouvalas and co-workers.[223] The resulting Schiff-base was reduced with $NaBH_4$ followed by hydrogenolysis to give the N^8-acetyl spermidine as



shown. The N^1-acetyl spermidine was prepared in a similar manner from N-(4-aminobutyl)benzyl carbamate and N-(2-formylethyl)acetamide. A few other multistep pathways have been used to prepare monoacylated spermidine. Although the processes look complicated, monoacetylation on each amine group is possible.[220,224]

Protecting a primary and secondary amine of spermidine allows the coupling of this material to other amines to form higher polyamines. Some of the protected spermidines that have been used are N^4-tosyl-N^8-phthaloylspermidine[225], N^4,N^8-di-t-butyloxycarbonylspermidine[226,227], N^4-tosyl-N^8-acetylspermidine[228], and N^4,N^8-ditosylspermidine.[229]

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