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An efficient and practical method for the synthesis of mono-*N*-protected α,ω-diaminoalkanes

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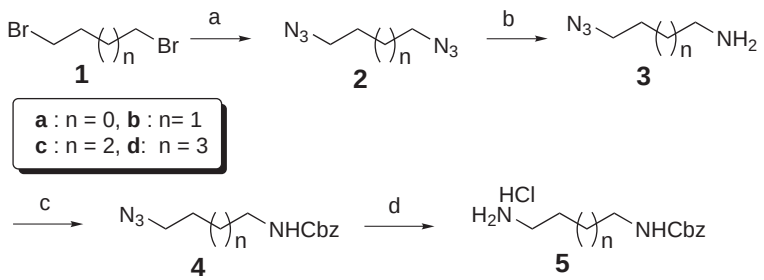
Abstract—The large-scale synthesis of mono-*N*-protected (Cbz, Boc, Ts, and Ns) α,ω-diaminoalkanes (the number of carbon atoms = 3, 4, 5 and 6) are accomplished in 81–94% yield by the protection of amine and subsequent reduction of an azido group from α,ω-azido alkyl amines. α,ω-Azido alkyl amines are prepared efficiently by the partial reduction of α,ω-diazidoalkanes which are obtained from the corresponding dibromoalkanes.

Polyamines such as putrescine, spermidine and spermine and their derivatives have attracted considerable interest in recent years due to their biological functions and pharmacological properties.[1] As well as medicinal chemistry, these amines have been used in supramolecular chemistry. For example, they form stable host–guest complexes with cucurbituril, a synthetic receptor.[2] Taking advantage of this fact, we have been studying self-assembly of interlocked structures such as rotaxanes, polyrotaxanes and molecular necklaces using cucurbituril as a molecular 'bead' and diamines and polyamines as molecular 'strings'.[3] These rotaxanes are potentially useful in the construction of molecular switches, memories and machines.[3g,4] However, development of such rotaxanes with functions requires elaborated polyamine-based molecular 'strings'. In our efforts to synthesize polyamine-based molecular 'strings' we decided to develop an efficient and practical route to mono-*N*-protected diaminoalkanes.

Despite many reported methods in the mono-protection of diamines,[5] however, mono-selective protection of diamines is still difficult and inefficient because of the concomitant generation of unprotected and diprotected by-products. Furthermore, these direct mono-protection methods are not economical because starting materials α,ω-diaminoalkanes and protecting reagents such as CbzCl and $(Boc)_2O$ are expensive. Although an azido group has been used as a primary amine genitor in organic synthesis,[6] little attention has been paid to the idea that azidoamines would provide an efficient synthetic route to mono-*N*-protected diaminoalkanes. Here



Scheme 1. Reagents and conditions: (a) NaN_3, DMF (H_2O), 80°C, 20 h; (b) Ph_3P, Et_2O/EtOAc –5% HCl, rt, 24 h; (c) CbzCl, NaOH, THF–H_2O, 2 h at 0°C and 3 h at rt; (d) Ph_3P, THF (H_2O), rt, 24 h, then HCl.

Keywords: mono-protection; α,ω-diaminoalkanes; azides; reduction.

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Table 1. Synthesis of compounds **2**, **3** and **5**

Compound	*n*	Yield (%)[a]	Compound	*n*	Yield (%)[a]
2a	0	97	**3c**	2	67
2b	1	98	**3d**	3	60
2c	2	99	**5a**	0	85
2d	3	99	**5b**	1	86
3a	0	90	**5c**	2	95
3b	1	88	**5d**	3	94

[a] Yields of pure, isolated products.

we report efficient preparation of mono-*N*-protected diaminoalkanes from diazidoalkanes via azidoamine (Scheme 1).

The starting materials, α,ω-diazidoalkanes **2** are easily prepared from the corresponding dibromoalkanes **1**. 1,4-Diazidobutane **2b** ($n=1$) is reacted with triphenylphosphine in ether/ethyl acetate in the presence of 5% HCl.[7] The initially formed azidoamine is protonated by the acid to migrate into the aqueous layer. As a result, the over-reduction to diamine is prevented. After the organic layer is discarded, the aqueous layer is washed with methylene chloride to remove the remaining triphenylphosphine oxide and non-ionic organic components. Addition of a base to the aqueous layer followed by extraction with methylene chloride gives azidoamine **3b** in 88% yield, which contains virtually no diamine. Other azidoamines **3a**, **3c** and **3d** ($n=0$, 2 and 3, respectively) are also easily prepared from diazides **2a**, **2c** and **2d**, respectively.[8] Eventually we can prepare highly pure azidoamines by acid–base extractions.[9] The yields of azidoamines with shorter alkyl chains ($n=0$, 1) are higher than those with longer chains ($n=2$, 3). The somewhat lower isolation yields of the latter may be due to their higher solubilities in methylene chloride used to remove triphenylphosphine oxide and non-ionic organic components.

After a protective group is introduced to the amine group of the azidoamines, the azido group is transformed into a primary amine to produce mono-*N*-protected diaminoalkanes. Among many protective groups we first chose the benzyloxycarbonyl (Cbz) group, which is stable under basic and most acidic conditions.[10] A Cbz group is introduced to azidoamines **3** by the reaction with CbzCl in THF–H_2O in the presence of NaOH. The Cbz-protected aminoazides **4** are obtained quantitatively, and can be used in reduction of azide without further purification. The crude azides **4** are reduced to amines using triphenylphosphine in wet THF. Isolation of the mono-Cbz-protected diamines **5** as a hydrochloride salt is readily accomplished in 85–95% yields by treatment with conc. HCl (Table 1).[11]

Recognizing the advantages of this synthetic approach, we studied the introduction of other protective groups to the aminoazides. For example, 4-azidobutylamine **3b** was reacted with $(Boc)_2O$, TsCl and NsCl to give the corresponding protected aminoazides **6** quantitatively. The protected amino-azides **6** are reduced to mono-*N*-protected diaminoalkanes **7** using triphenylphosphine in wet THF, which are isolated in 81–90% yields as hydrochloride salts by treatment with conc. HCl (Scheme 2).

Although monoprotected diamines such as **5** and **7** have been widely used in organic synthesis, particularly polyamine synthesis,[1b,1e,12] their synthetic utilities in supramolecular chemistry are further demonstrated by our recent syntheses of DNA binding rotaxanes[13] and rotaxane-terminated dendrimers.[14] In the former, a cucurbituril 'bead' is threaded on desymmetric polyamine 'strings', while in the latter a cucurbituril 'bead' is threaded on each and every terminal diaminobutane unit of the dendrimers. In both cases, the key synthetic step involves regioselective monofunctionalization of the diaminoalkane, which was easily achieved using the monoprotected diaminoalkanes presented here.

In conclusion, large quantities of mono-*N*-protected diaminoalkanes can be easily prepared from azidoaminoalkanes, which are obtained efficiently by the desymmetric reduction of diazidoalkanes. No chromatography is needed in this procedure. Separation of the desired products can be achieved by simple acid–base extractions and crystallization. Thus, this is a highly efficient, economical and practical method for preparing mono-*N*-protected diaminoalkanes. Azidoaminoalkanes and mono-*N*-protected diaminoalkanes should be useful in the preparation of polyamines and their derivatives, which are important in medicinal chemistry as well as supramolecular chemistry.

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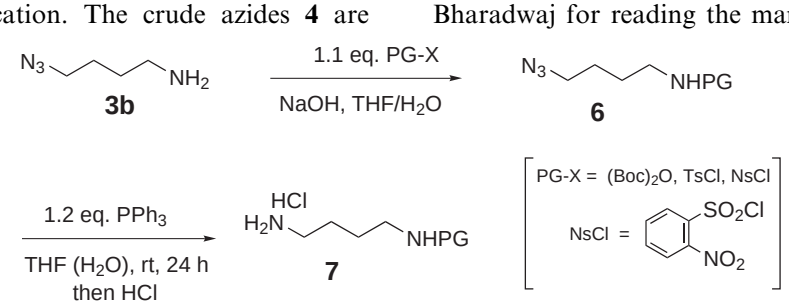

Scheme 2. 81% for PG = Boc (**7a**); 88% for PG = Ts (**7b**); 90% for PG = Ns (**7c**).

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