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COMMUNICATION

Marilyn M. Olmstead, Alan L. Balch, Josep M. Poblet, Luis Echegoyen *et al.*

Reactivity differences of $Sc_3N@C_{2n}$ (2*n* = 68 and 80). Synthesis of the first methanofullerene derivatives of $Sc_3N@D_{5h}$-C_{80}

175 YEARS

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Journal Name

COMMUNICATION

A new way to do an old reaction: highly efficient reduction of organic azides by sodium iodide in the presence of acidic ion exchange resin

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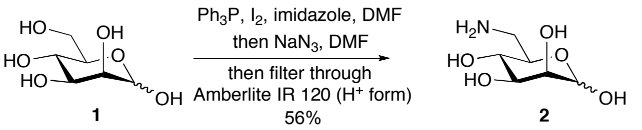
Kajitha Suthagar,[a] and Antony J. Fairbanks*[a,b]

Organic azides are readily reduced to the corresponding amines by treatment with sodium iodide in the presence of acidic ion exchange resin. The process, optimal when performed at 40 °C and 200 mbar pressure on a rotatory evaporator, is extremely efficient, clean, and tolerant of a variety of functional groups.

Azide is a highly versatile functional group,[1] which has surged in prominence over recent years due to the burgeoning utility of the the Cu-catalysed[2] and strain-promoted[3] Huisgen cycloadditions, and the highly useful Staudinger ligation;[4] all processes which have found wide application under biocompatible conditions.[5] More long-standing interest has centred on the highly useful reduction of azides to amines; one of their most effective means of amine synthesis. Indeed the literature abounds with different methods of azide reduction.[6-11] Although it may appear that sufficient synthetic methods already exist for this highly useful functional group interconversion, each of the above methods has limitations, either with respect to other functional group tolerance, or associated issues of product purification, for example removal of the phosphine oxide by-product from the Staudinger reduction. Occasionally situations still arise in which the more traditional methods of azide reduction do not work well.[12] During investigations into the use of a series a carbohydrate-based azides for the production of sugar-sulfamides,[13] we unexpectedly observed the *in situ* reduction of an intermediate azide. During this process (Scheme 1) mannose **1** was first subjected to an Appel reaction. Following removal of the triphenylphosphine and triphenylphosphine oxide (by washing with dichloromethane), the crude material was carried through to the next step of azide displacement. At the end of that process the reaction product was dissolved in water and filtered through a column of acidic ion exchange resin (Amberlite IR 120, H^+ form) to remove residual imidazole. Surprisingly analysis of the final reaction product revealed the complete absence of any azide functionality; the major product was purified and identified as 6-amino mannose **2**.[14]



Scheme 1. Unexpected azide reduction and direct production of 6-amino mannose.

We reasoned that the azide must have been reduced by residual iodide, which was either left over from the Appel reaction or produced during the nucleophilic substitution process. However, we were intrigued by the ease and efficiency with which the azide reduction had occurred. A search of the literature revealed several reports of the reduction of azide by iodide, but in all cases such reactions had required the use of strong Lewis acids, for example $BF_3.OEt_2$,[15] $FeCl_3$[16], $CeCl_3$[17] or Al or Gd triflates.[18]

Intrigued by the apparent simplicity and efficiency of the iodide-mediated reduction process in the absence of strong Lewis acids, we undertook a series of investigations to further probe this unexpectedly facile reaction. Our motivation was to arrive both at an optimised procedure in terms of practicality, and to investigate reaction scope with respect to applicability to a variety of different substrates.

In order to arrive at an optimised procedure, azide **3a** was used as a substrate for variation of reaction parameters (Table 1). In previously reported procedures[15-18] typically nine equivalents of sodium iodide had been used, although from a redox perspective only two equivalents of iodide should be required. Studies therefore commenced with the use of two equivalents of iodide. In addition to iodide, the reduction of an azide to an amine additionally requires two protons. Reasoning that acidic ion exchange resin, which may be separated from polar reaction products simply by filtration, may be the most practically convenient proton source, we selected Amberlite IR

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[a] Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand. Email: antony.fairbanks@canterbury.ac.nz
[b] Biomolecular Interaction Centre, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand.

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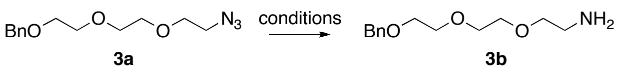
120 (H^+ form) as the source of acid. Reactions were performed in CD_3OD to enable monitoring of reaction progress by 1H NMR (Table 1).

Table 1. Variation of reaction parameters for the for the reduction of azide **3a**



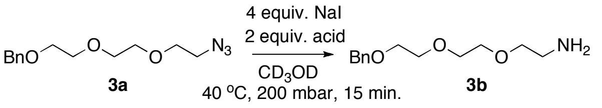
Entry	Iodide/ equiv.	Acid/ equiv.[a]	Solvent	Time	Temp /°C	Conversion /%[b]
1	2	2	CD_3OD	1 h	rt	0
2	4	2	CD_3OD	1 h	rt	20
3	4	0	CD_3OD	1 h	rt	0
4	4	2	CD_3OD	1 h	40	45
5	8	2	CD_3OD	1 h	rt	46
6	8	2	CD_3OD	16 h	rt	82
7	8	2	CD_3OD	1 h	40	50
8	10	2	CD_3OD	1 h	rt	65
9	10	2	CD_3OD	16 h	rt	94
10	12	2	CD_3OD	1 h	rt	100
11	12	2	CD_3CN	1 h	rt	90
12[c]	4	2	CD_3OD	0.25 h	40	100
13[d]	12	2	CD_3OD	1h	rt	100

[a] Equivalents calculated using a wetted bed volume (MeOH) for Amberlite IR120 of 1.8 mequiv./mL. [b] Assessed by 1H NMR [c] Performed at 200 mbar on a rotary evaporator. The reaction was complete when evaporated to dryness in approx. 15 minutes. [d] Reaction performed in the presence of six equivalents of I_2.

The use of 2 equivalents of sodium iodide and 2 equivalents of acid did not produce any amine after 1 h at room temperature (Entry 1). Increasing the number of equivalents of sodium iodide to 4 did result in the formation of some amine **3b**, but with a very modest 20% conversion (Entry 2). In the absence of added acid no reaction was observed at all (Entry 3). Performing the reaction at 40 °C accelerated the process (45% conversion after 1h, Entry 4). The use of a larger excess of iodide (ranging from 8 equivalents to 12 equivalents) and longer reaction times also further improved the efficiency of the process (entries 5-9). Indeed complete conversion of azide to amine was achievable in one hour at room temperature by using 12 equivalents of iodide (Entry 10). Changing the solvent from CD_3OD to CD_3CN had a minor effect of the reaction efficiency (90% conversion, Entry 11).

Although conditions had been arrived at which led to complete conversion of azide into product, the use of such a large excess (e.g. 12 equivalents) of iodide was undesirable. Additionally we were mindful of the original observation (Scheme 1) in which almost quantitative azide reduction had followed concentration of the crude reaction product on a rotatory evaporator. We therefore investigated whether performing the reaction under reduced pressure increased the efficiency of the process. Pleasingly it was found that, with only 4 equivalents of iodide and 2 equivalents of acid, simply performing the entire process on a rotary evaporator at 40 °C and 200 mbar pressure resulted in complete conversion to amine **3b** as soon as the solvent had been evaporated to dryness (approximately 15 minutes, Entry 12). The effect of the use of a rotary evaporator was investigated further. Firstly that the beneficial effect was not due to the removal of iodine from the reaction mixture was confirmed by an experiment in which 6 equivalents of I_2 were added to a reaction performed at atmospheric pressure (Entry 13); no change in either conversion or reaction time were observed, indicating that iodine did not inhibit the reaction. Secondly a series of experiments was performed at atmospheric pressure at increasing iodide concentration (Supporting information, Table S1). These experiments clearly indicated that increasing iodide concentration accelerated the reaction, implying that the rate determining step is perhaps bimolecular involving attack by iodide. Thus we conclude that the rotatory evaporator 'effect' is a concentration effect.

Table 2. Variation of acid for the reduction of azide **3a**



Entry	Acid	Conversion / %[a]	pKa
1	Amberlite (IR-120 H^+)	100	-
2	HCl	100	-8.0
3	CF_3CO_2H	54	-0.25
4	AcOH	0	4.76

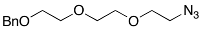
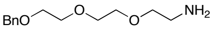
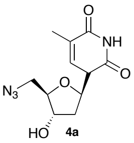
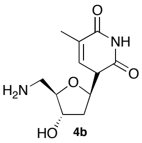
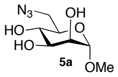
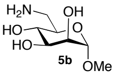
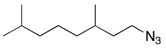
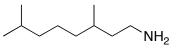
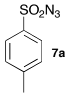
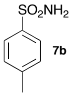
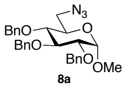
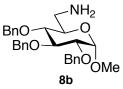
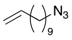
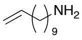
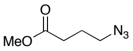
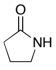
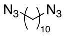
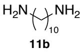
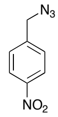
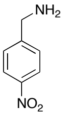
[a] Assessed by 1H NMR

A brief survey of the strength of the acid that was required for this process was undertaken (Table 2) using the optimised reaction conditions from above. Whilst the use of HCl resulted in complete conversion of azide **3a** to amine **3b** (Entry 2), the use of weaker acids was sequentially less effective: trifluororacetic acid gave only 54% conversion to **3b** (Entry 3), whilst the use of acetic acid did not result in any reaction (Entry 4). These results imply that a strong acid is essential, perhaps indicating that pre-protonation is required before subsequent attack by iodide. Given the ease with which ion exchange resin may be removed by filtration, Amberlite IR 120 (H^+ form) was used as the acid in all subsequent reactions. Additionally it may be recycled and re-used (Supporting Information Table S2).

The reaction scope was next investigated using a variety of different organic azides (Table 3). In contrast to the assessments of reaction conversion using 1H NMR, in these cases the amine products were isolated, and yields refer to quantities of materials produced following purification. Whilst MeOH was used as the solvent for reaction of the more polar substrates (Table 3, Entries 1-3), solubility issues necessitated the use of a less polar solvent system for the less polar azides; in these cases a $CHCl_3$/MeOH mixed solvent system was used (Table 3, Entries 4-10).

Azide reduction was found to be highly efficient; in all cases reaction reaction analysis indicated that the amines **3b-12b** were the sole reaction products. Good functional group tolerance was observed, for example the glycosidic linkages of nucleosides **4a/b** and glycosides **5a/b** and **8a/b**, the benzyl ethers of **8a/b**, and the alkene of **9a/b**. Double reduction of di-azide **11a** was efficiently achieved using a total of 4 equivalents of acid and 8 equivalents of sodium iodide (Entry 9). The reaction products could be purified very simply by ion exchange chromatography; the process involving the addition of more acidic ion exchange resin after the reaction was complete, and then elution on a column with 2.5 M ammonia in MeOH. In the case of reduction of ester **10a** (entry 8) it was found that the intermediate amine spontaneously cyclised to produce lactam **10b** during purification by ion exchange chromatography.

Table 3. Reaction Scope

Entry	Substrate	Product	Solvent	Yield /%
1	 **3a**	 **3b**	MeOH	89
2	 **4a**	 **4b**	MeOH	93
3	 **5a**	 **5b**	MeOH	91
4	 **6a**	 **6b**	$CHCl_3$: MeOH 3:2	85
5	 **7a**	 **7b**	$CHCl_3$: MeOH 3:2	95
6	 **8a**	 **8b**	$CHCl_3$: MeOH 3:2	93
7	 **9a**	 **9b**	$CHCl_3$: MeOH 3:2	87
8	 **10a**	 **10b**	$CHCl_3$: MeOH 3:2	quant.
9	 **11a**	 **11b**	$CHCl_3$: MeOH 3:2	92
10	 **12a**	 **12b**	$CHCl_3$: MeOH 3:2	quant.

In summary investigation into the formation of an anomalous reaction product has revealed that organic azides are readily reduced in polar solvents simply by treatment with four equivalents of sodium iodide in the presence of two equivalents of acidic ion exchange resin. The reaction is highly efficient when performed at 40 °C and 200 mbar on a rotary evaporator, due to a concentration effect, and complete conversion to product is observed as soon as the solvent has fully evaporated; typically within 15 minutes. Although other sources of strong acid may be used, the process is experimentally extremely simple as the ion exchange resin may then be used to directly purify the product. This highly practically rapid and clean procedure, which does not require the use of Lewis acids and/or transition metal salts in addition to iodide, may prove a useful addition to the methods of amine synthesis from azides where either functional group tolerance or product purification hamper the use of more common processes, such as catalytic hydrogenation or Staudinger reaction.

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