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Glucose promoted facile reduction of azides to amines in aqueous alkaline conditions

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Abstract:

A quick and efficient method for reduction of azides to amines in water using D-glucose and KOH as a green reagent is reported. The protocol is simple, inexpensive, scalable, and can be applied to different aromatic, heteroaromatic and sulphonyl azides. A high level of chemoselectivity is observed for azide reduction in presence of other reducible functionalities like cyano, nitro, ether, ketone, amide and acid. The reaction gets completed in short time (5-20 minutes), and furnishes the amines in high yield (85-99%). Unlike conventional hydrogenations, this reduction protocol does not require any metal catalyst, elaborate experimental setup or use of high-pressure equipment.

Introduction:

Organic azides are versatile and useful synthons which find wide applications in the synthesis of heterocycles.[1,2] They can be prepared with good regio, stereo, and enantioselectivity and their transformation to amines provides an access to a variety of organic intermediates, particularly useful in the synthesis of pharmaceuticals, carbohydrates and nucleosides.[3, 4] Although there are several methods available in the literature for preparation of amines, their synthesis through reduction of azides is one of the important protocols since azides can be easily prepared[5-8] from halides and sulfonates. A number of reagents have been developed over the years to bring about this reductive transformation, and can be typically classified as: (i) hydride donors[9] such as $LiAlH_4$ or $NaBH_4$; (II) H_2 gas or its source in the presence of transition metals and their oxides (MOs) as catalyst;[10-12] (iii) low-valent metal ions[13] such as $SnCl_2$, $CrCl_2$, $TiCl_3$ / boranes[14, 15] / silanes;[16] (iv) phosphine reagents[17] as in Staudinger reaction; (v) sulphur reagents[18] e.g thiolates etc. Though useful, these methods suffer from limitations with regard to chemo-selectivity in presence of other reducible functionalities, use of transition metals, harsh reagents, and cost efficiency. Thus, it is highly desirable to develop reduction protocols for azides which are transition metal free, chemoselective, and do not involve toxic hydrogen source.

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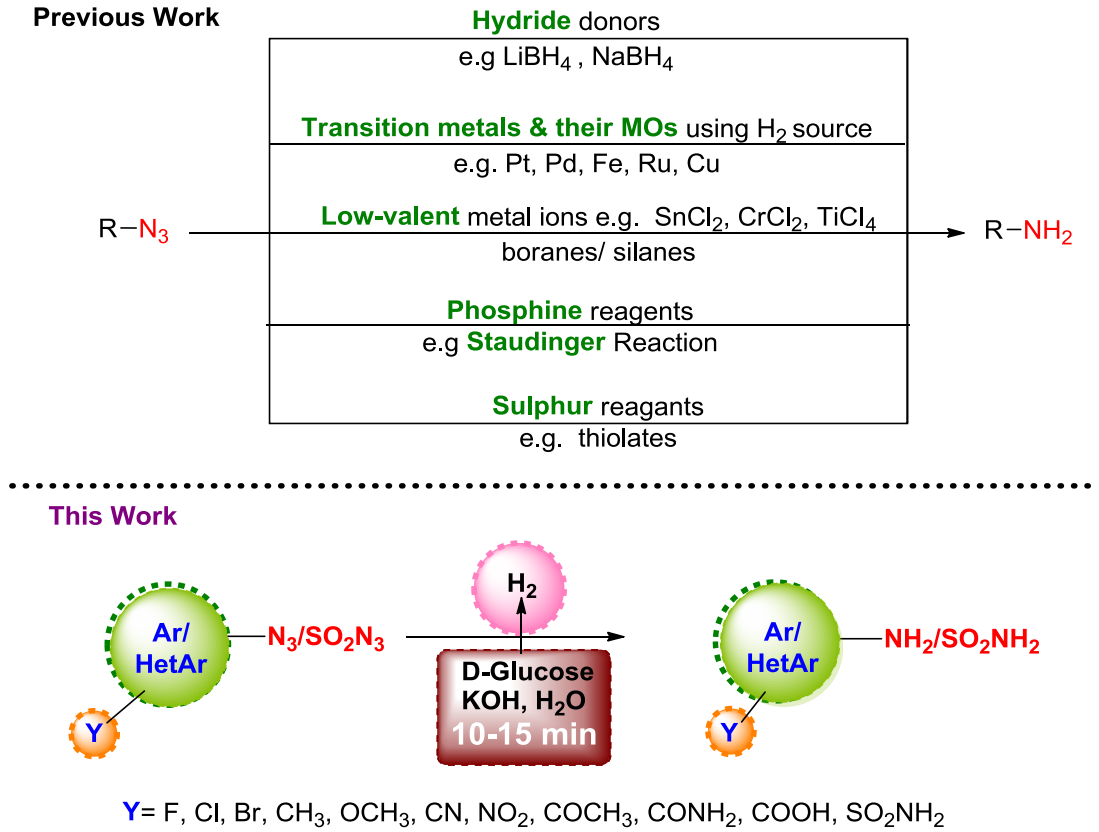
Carbohydrates are chiral organic molecules readily available from natural and renewable resources. They are inexpensive, eco-friendly, compatible with biological systems, and soluble in water. All these properties encouraged us to explore their capability as a hydrogen source for reduction of azides. Continuing our efforts towards greener and economical chemical protocols,[19-22] we herein report the reduction of aromatic, heteroaromatic and sulfonyl azides to the corresponding amines using D-glucose and KOH in aqueous conditions.



Scheme 1 Various methods for reduction of azides to amines.

Results and Discussion:

The aim to develop a transition metal-free reduction of azides motivated us initially to investigate the reaction of 4-azidobenzonitrile (**1a**) with 2 equiv. of D-glucose and KOH in DMF at 110 °C. As desired, 4-aminobenzonitrile (**2a**) was formed (Scheme 1), albeit in moderate yield (72%) (Table 1, entry 1). In a quest to improve the yield of product, reaction conditions were optimized. Screening of solvents showed that switching from DMF to DMSO (Table 1, entry 2) dropped the yield of **2a** to 30% along with formation of other undesired products. Further, either no conversion or trace conversions took place in 1,4-dioxane, toluene, [Bmim]PF_6, and *N*-methyl-2-pyrrolidone as solvents. In DMF: H_2O (1:1), the yield of **2a** increased to 80% (Table 1, entry 3). To eliminate

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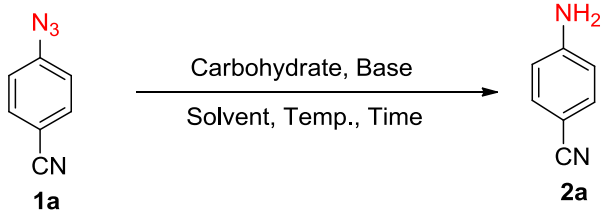
the use of organic solvent completely, we treated **1a** with 2 equiv. of D-glucose and KOH in minimum amount of water at 110 °C in a pressure tube. We found that the reaction completed in ten minutes, and was indicated by a change in color of the reaction mixture from yellow to brown (Table 1, entry 4). Next, we optimized the conditions with respect to base, catalyst, and temperature in water. Use of other inorganic bases like NaOH and K_2CO_3 gave lower yields of **2a** (Table 1, entries 5 and 6). Similar low yields were seen with Na_2CO_3, NaO^{t}Bu, KO^{t}Bu, and CH_3COONa. Control reaction in the absence of base did not yield any product even after prolonged heating for 24 h (Table 1, entry 7). Reducing the amount of KOH to 1 equiv., or raising it to 5 equiv. resulted in incomplete conversion. However, with 3 equiv. of KOH, **2a** was formed in almost 99% yield (Table 1, entry 8). Optimizing the temperature revealed that reaction performed equally well at 85 °C (Table 1, entry 9), and conversion was complete in ten minutes. Amount of D-glucose was also varied (1-3 equiv.), and it was found that 2 equivalents were necessary and sufficient for the reaction (Table 1, entry 10). To establish the role of sugars in promoting the reaction, other sugars such as maltose, fructose, D-mannose, sucrose and cellulose were tested (Table 1, entries 11-15); of which only D-mannose was found to be effective. Further, no conversion took place in the absence of added sugar (Table 1, entry 16).

Table 1 Optimization of reaction conditions for reduction of **1a**



1a **2a**

Entry	Carbohydrate (equiv.)	Base (equiv.)	Temp (° C)	Solvent	Time	Yield[b] (%)
1.	D-Glucose (2)	KOH (2)	110	DMF	10 min	72%
2.	D-Glucose (2)	KOH (2)	110	DMSO	10 min	30%
3.	D-Glucose (2)	KOH (2)	110	DMF:Water (1:1)	10 min	80%
4.	D-Glucose (2)	KOH (2)	110	Water	10 min	90%

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5.	D-Glucose (2)	NaOH (2)	110	Water	10 min	62%
6.	D-Glucose (2)	K_2CO_3 (2)	110	Water	10 min	54%
7.	D-Glucose (2)	-	110	Water	24 h	NR
8.	D-Glucose (2)	KOH (1-5)	110	Water	10 min	70[c], 99[d], 65[e]
9.	**D-Glucose (2)**	**KOH (3)**	**85**	**Water**	**10 min**	**99%**
10.	D-Glucose (1 & 3)	KOH (3)	85	Water	10 min	50% & 98%
11.	D-Maltose (2)	KOH (3)	85	Water	10 min	60%
12.	D-Fructose (2)	KOH (3)	85	Water	10 min	58%
13.	D-Mannose (2)	KOH (3)	85	Water	10 min	95%
14.	Sucrose (2)	KOH (3)	85	Water	10 min	NR
15.	Cellulose (2)	KOH (3)	85	Water	10 min	NR
16.	-	KOH (3)	85	Water	10 min	NR

[a]Reaction conditions: **1a** (1 mmol, 1 equiv.), D-Glucose (2 mmol, 2 equiv.), KOH (3 mmol, 3 equiv.) were taken in water (100 μL), and stirred for 10 min at 85 °C, [b]Yield of **2a** as determined by HPLC conversion, [c]1 equiv. KOH, [d]3 equiv. KOH, [e]5 equiv. KOH, NR= No Reaction

Next, we investigated the generality and scope of this reaction by reacting a range of azides under the optimized conditions in water. Though the azides were partly soluble in water at the beginning of the reaction; but as the reaction proceeded at 85 °C, the solution turned homogeneous. Notably, a rapid completion of reaction was observed in most cases (Table 2). Further, the work-up was simple and clean. The amines, partly soluble in water, could be easily isolated from the reaction mixture by extracting it with ethyl acetate. In most cases, the product was free from any associated impurities, and no column was required for further purification. The reduction of halogenated aryl azides yielded the corresponding amines **2c**-**2g** in high yields without suffering any dehalogenation (Table 2). In few cases (Table 2, compounds **2d**, **2j** and **2k**), the reaction was found to perform better in DMF: H_2O (0.5:1), though these reactions took longer time (18-120 min) to complete. High chemoselectivity with excellent yields was observed with 4-nitro and 3-nitrophenylazides as

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the azide group reduced exclusively in presence of nitro yielding the corresponding nitro anilines (**2h**, **2i**). Notably, even on using excess (6 equiv.) of D-glucose and KOH, azido group reduced selectively in presence of nitro. Aryl azides substituted with methoxy and methyl groups (**1j** and **1k**) were successfully reduced though much longer reaction times were required. 4-Azidoacetophenone, 4-azidobenzoic acid and 4-azidobenzamide gave the corresponding anilines (**2l-2n**) without reducing the carbonyl functionality. The methodology also worked very well for reduction of azides in presence of sulphonamide group (**1o**) as well as with 1-azidonaphthalene (**1p**). Further, the protocol was equally facile for heterocyclic azides, and clean reactions were observed in all the cases without affecting the heterocyclic ring (**2q-2s**). Unfortunately, the reaction did not work with alkyl azides, and no amine formation was seen with n-butyl azide as the substrate. In addition to aryl and heteroaryl azides, the sulphonyl azides (**1t-1v**) could also be reduced efficiently to the corresponding amines (**2t-2v**) in near quantitative yields within minutes. Reduction of biologically relevant azides, 5-phenylthiazol-2-azide (**1w**) and 5-(4-chlorobenzyl)thiazol-2-azide (**1x**) yielded the corresponding aminothiazoles (**2w**, **2x**) in 95 and 96% yields respectively. These compounds are known to display potent antifungal, antibacterial, antitubercular, and anticancer activities.[23] It is noteworthy to reiterate that the reaction time required for conversion of azides to amines is much lower compared to any of the previous methods discussed above in Scheme 1.

Table 2 Scope of reduction of azides to amines[a,b]

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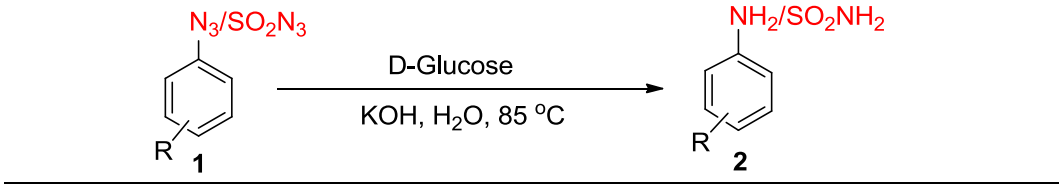
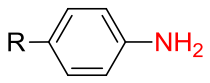
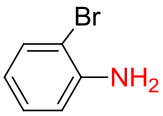
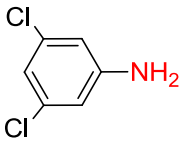




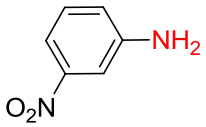
2a, (R = CN), 99%,10 min
2b, (R = H), 95%,15 min
2c, (R = Cl), 96%,10 min
2d[c], (R = F), 97%,18 min
2e, (R = Br), 94%,10 min



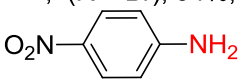
2f, 85%,10 min



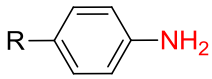
2g, 90%,10 min



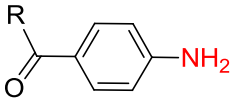
2h, 99%,5 min



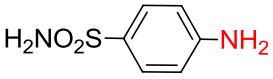
2i, 97%, 5 min



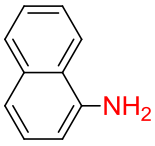
2j[c], (R = OCH_3), 87%,120 min
2k[c],(R = CH_3), 89%, 60 min



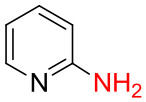
2l, (R = CH_3), 95%, 10 min
2m, (R = OH), 96%, 15 min
2n, (R = NH_2), 95%, 10 min



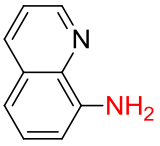
2o, 99%, 5 min



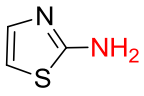
2p, 98%, 10 min



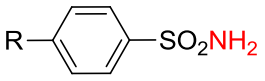
2q, 99%, 10 min



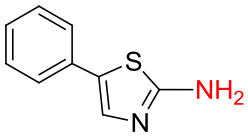
2r, 99%, 10 min



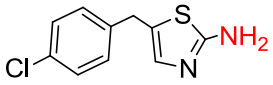
2s, 97%, 15 min



2t, (R = CH_3), 99%, 5 min
2u, (R = H), 95%,15 min
2v, (R = Cl), 96%,10 min



2w, 95%, 10 min



2x, 96%, 10 min

[a]Reaction conditions: **1** (1 mmol, 1 equiv.), D-Glucose (2 mmol, 2 equiv.), KOH (3 mmol, 3 equiv.) were taken in water (100 μL) in a pressure tube, and stirred at 85 °C, [b]isolated yield, [c]solvent was DMF: H_2O (0.5:1, 100 μL)

Next, the synthetic utility of the developed protocol was ascertained by carrying out the reaction on a gram scale. The reduction of 4-azidobenzonitrile (**1a**), 2-azidoquinoline (**1r**) and *p*-toluenesulphonyl azide (**1o**) starting from 10 mmol of these substrates under the optimized reaction conditions yielded the corresponding amines **2a, 2r** and **2o** in 95%, 93% and 97% yields respectively.

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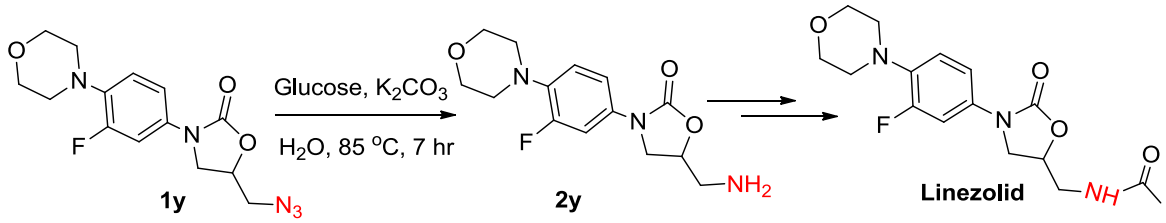
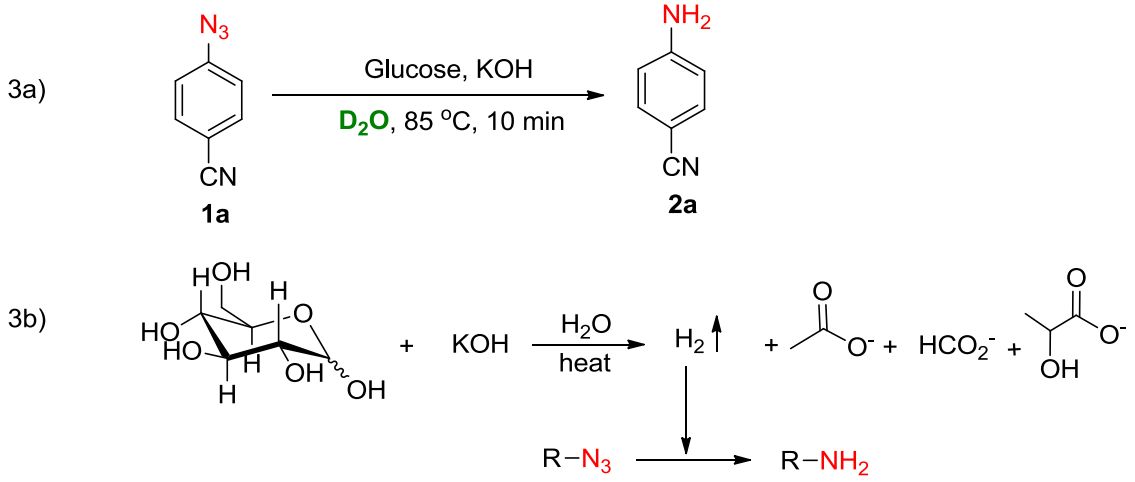
Further, we also applied this protocol successfully to 5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one (**1y)** which is an intermediate in the preparation of the antibiotic Linezolid. The azide could be reduced using the general reaction conditions and the desired amine (**2y**) was isolated in 50% yield. However, K_2CO_3 was used instead of KOH to avoid the ring opening of oxazolidinone. Increasing the amount of glucose to 3 mmol and K_2CO_3 to 5 mmol enhanced the yield of **2y** upto 60%.



Scheme 2 Azide reduction step in synthesis of linezolid.

To identify the source of hydrogen and understand the mechanism, the reaction of **1a** was carried out in D_2O instead of water (Scheme 3a). A single non-deuterated product **2a** was obtained which indicated that hydrogens of amine were being provided by glucose which acted as a reducing agent in the reaction. Based on literature reports[24-26] and D_2O experiment, we believe that the reduction of azide to amine is mediated through a hot alkaline degradation of glucose which generates hydrogen *in situ* along with formation of lactate, acetate, formate and glycolate ions (Scheme 3b). To confirm this, a model reaction of **1a** was carried out in D_2O, and NMR analysis of the reaction mixture was performed (supporting info). The NMR data revealed that along with the formation of reduced product **2a**, lactate, acetate and formate ions were also being produced in the reaction. These findings support our proposed pathway for hydrogen generation in this reaction (Scheme 3b).



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Scheme 3 a) Reaction in D_2O; b) Proposed mechanism for reduction.

Conclusions

In conclusion, a highly efficient method for the reduction of aryl(heteroaryl)azides and aryl suphonyl azides to corresponding amines and sulphonamides employing D-glucose as the hydrogen source along with KOH in water is reported for the first time. The reagents are inexpensive, non-stinking and non-toxic. The protocol is highly chemoselective and challenging functional groups such as CN, NO_2, COR, and SO_2NH_2 are well tolerated. The reaction is a rapid and practical way of accessing amines from aryl, heteroaryl, and suphonyl azides under metal-free conditions. The present method compares favorably to most of the earlier literature reported procedures.

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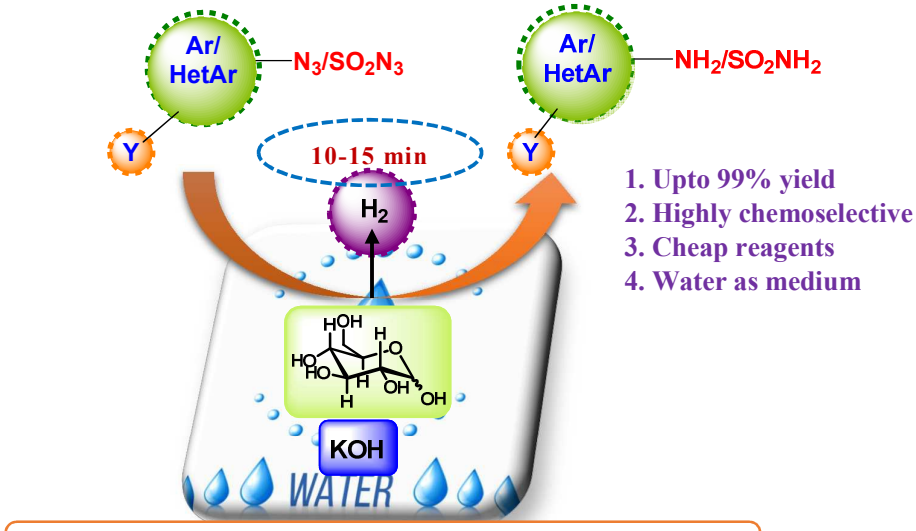

Y= F, Cl, Br, CH_3, OCH_3, CN, NO_2, $COCH_3$, $CONH_2$, COOH, SO_2NH_2