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Research Article

A NOVEL METHOD FOR THE REDUCTION OF AZIDES TO AMINES USING POLYMER SUPPORTED FORMATE AND MAGNESIUM

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ABSTRACT

A novel and efficient method for the reduction of both aliphatic and aromatic azides to corresponding amines using recyclable polymer supported formate as hydrogen source and inexpensive magnesium powder as catalyst in methanol at room temperature is described. It reduces a variety of aliphatic and aromatic azides to corresponding amines in presence of various sensitive functional groups such as halogens, carbonyl, ester, amide, methoxy, carboxyl, phenol and hydroxyl, which are compatible with the present system.

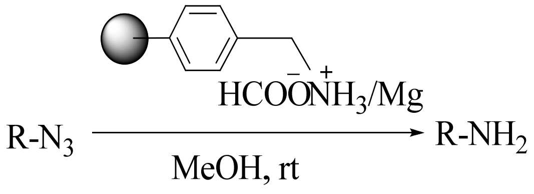
Keywords: Azides, Polymer supported formate, Magnesium, Amines, Catalytic transfer hydrogenation.

INTRODUCTION

Reduction of azide to an amine constitutes synthetically important functional group transformation in organic synthesis. Since, many azides can be prepared with regio- and stereo-control, subsequent reduction permits a controlled introduction of the amine function. It has been widely used for the preparation of nitrogen containing heterocycles[1], carbohydrate[2] and in nucleoside chemistry. There are many methods available in the literature for the conversion of azides to amines[3-8]. However, despite their potential utility these methods often suffer from certain inconveniences such as, incompatibility with other functionalities and protecting groups, use of expensive and hazardous reagents, drastic reaction conditions, longer reaction time and tedious product isolation procedure. Most of the catalytic transfer reductions have been achieved by the use of expensive and pyrophoric catalysts like Pd/C, Ru/Ca, Pd/$CaCO_3$, Ru/C and Raney Ni[9-11].

A mild and efficient catalytic transfer hydrogenation system could be developed if the hydrogen donor is immobilized on a solid support. Polymer supported reagents, catalysts and scavengers are ubiquitous through out the fields of combinatorial chemistry, organic synthesis and catalysis[12-20] which are environmentally benign. The utility and power of such reagents has been exquisitely demonstrated by the groups of Ley and others in synthesizing several complex natural products by multi-step sequences requiring many different kinds of hydrogenised reagents which can be removed by simple filtration. However in view of the rapid development in the field of polymer supported chemistry over the last few years, there is a pressing need for the proper exploitation of functionalized polymer supported reagents in organic synthesis. Recently, Gowda *et al*. reported the application of polymer supported formate as hydrogen donor for the removal of some commonly used protecting groups in peptide synthesis[21] and also for the functional group transformations in organic synthesis[22-24].

Thus, the present study discuss the transfer hydrogenation of azides to corresponding amines using low cost magnesium powder as catalyst and recyclable polymer supported formate as hydrogen source in methanol media at room temperature (Scheme-1)



R=alkyl or aryl

Scheme 1

MATERIALS AND METHODS

The IR spectra were recorded on Shimadzu FTIR-8300 spectrometer. The melting points were determined by using Thomas–Hoover melting point apparatus and are uncorrected. Thin-layer chromatography was carried out on silica gel plates obtained from E-Merck (India) Ltd. The substrates were either commercial products and were used as purchased or were prepared according to literature procedures. Aminomethyl polystyrene was purchased from Advanced Chemtech (1% DVB cross-linked, 100–200 mesh, 2 mmol/g). Magnesium metal powder was purchased from HiMedia laboratories Pvt. Ltd., Mumbai (India). All the solvents used were of analytical grade or were purified according to standard procedures. The azides were either commercially available and were used as purchased or were prepared according to procedures.

Preparation of polymer supported formate

The polymer-supported formate was prepared by washing (aminomethyl) polystyrene (2 mol/g) with an excess of 50% solution of formic acid in dichloromethane and washed thoroughly, successively with dichloromethane, ether and dried under vacuum. The resulting (aminomethyl) polystyrene formate is used directly for catalytic reduction[21].

General procedure for the reduction of azides to amines using polymer supported formate and magnesium

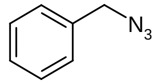
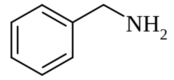
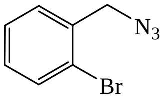
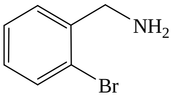
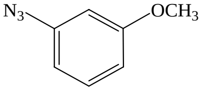
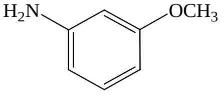
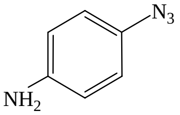
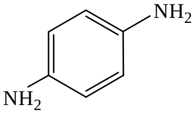
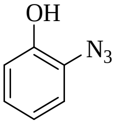
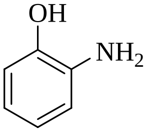
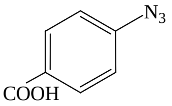
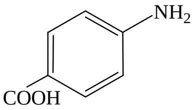
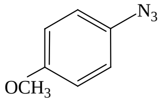
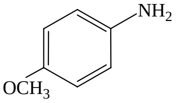
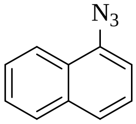
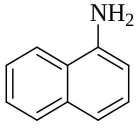
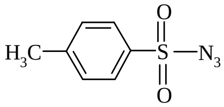
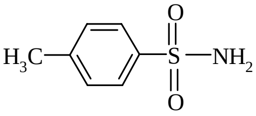
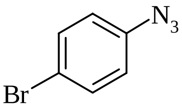
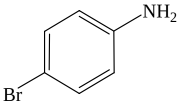
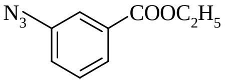
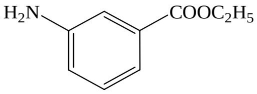
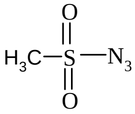
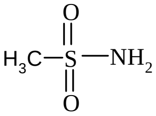
To a solution of azide (1 mmol) in methanol (15 mL) taken in a round bottomed flask and polymer supported formate (1 g) and magnesium (1 mmol) were added. The suspension was stirred for the specified time at room temperature. After consumption of the starting material, as monitored by TLC, the reaction mixture was filtered and washed thoroughly with methanol. The combined washings and filtrate were evaporated under reduced pressure. The crude product was found to be analytically pure in most cases. Where necessary, the crude product was taken into organic layer and washed with saturated sodium chloride.

For recycling purposes, the residue containing polymer supported formate and the catalyst was washed thoroughly and successively with DMF, dichloromethane, 50% solution of formic acid in dichloromethane, dichloromethane and ether. Thus activated resin along with the catalyst was dried under vacuum and used as such for further reduction reactions.

RESULTS AND DISCUSSION

Azides with a variety of substituents were reduced to corresponding to amines as illustrated in **Table 1**. The reaction was completed in 2-6 hrs at rt and products obtained in high yield (90-95%). It is worth to note that, our system selectively reduced azides to the corresponding amines in presence of other sensitive functional groups such as halogen, alkene, nitrile and carbonyl groups which are susceptible to reduction under transfer hydrogenation conditions. In addition many other functional groups such as ester, amide, methoxy, acid and hydroxyl groups are also compatible with the present system.

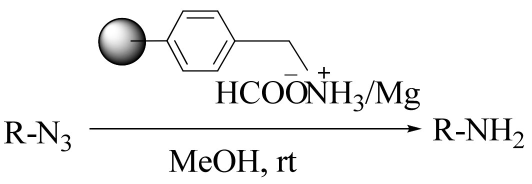
Table 1: Reduction of azides to amines using polymer supported formate and magnesium.

Azide	**Time (hr)**	**Amine**	**Yield (%)[a]**	**m.p. ºC**	
				Found	**Lit.**
	2		95	182-184[b]	184-185[26]
	3		92	109-110[b]	110-112[25]
	5		93	248-249[b]	251[26]
	6		95	144-146	145-147[26]
	5		95	172-174	174[25]
	5		90	185-186	187[25]
$CH_3\text{-}(CH_2)_5\text{-}N_3$	2	$CH_3\text{-}(CH_2)_5\text{-}NH_2$	90	129-130[b]	131-132[26]
	5		92	58-60	57[26]
	4		90	49-52	50[26]
	1.5		95	156-159	156-158[26]
	5		93	64-65	62-64[25]
	4		95	170-172	169-172[25]
 $H_3C{-}S(=O)_2{-}N_3$	2	 $H_3C{-}S(=O)_2{-}NH_2$	90	86	85-89[26]

[a] Isolated yields are based on single experiment and the yields were not optimized

[b] Boiling point.

A mixture of azide, (aminomethyl) polystyrene formate and magnesium in methanol was shaken well at room temperature. After completion of the reaction, mixture was filtered and washed thoroughly with methanol, the filtrate was evaporated under vacuum. The crude product isolated, was of good yield and purity for most cases. The water soluble aromatic amines were produced with excellent yields (entries 1 and 6). (Aminomethyl) polystyrene formate was regenerated and reused for the next set of hydrogenolysis up to ten cycles before there was an appreciable change in reaction yield and purity **(Table 2)**. All the products were characterized by comparison of their TLC, m.p, and IR with the authentic samples. The disappearance of strong stretching band near 2110 cm^{-1} due to the $N=N^{+}=N^{-}$ of $^{-}N_3$ and the appearance of two strong bands near 3500-3300 cm^{-1} of $-NH_2$ stretching (due to primary amine) in the IR spectra clearly indicated the conversion.



R=alkyl or aryl

Table 2: Recycling of polymer-supported formate for the reduction of benzyl azide

Cycles	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Time/hr	2.0	2.0	2.0	2.5	2.5	2.5	3.0	3.0	3.5	4.0
Yield/%	98	96	96	94	93	92	92	92	91	90

A control experiment was carried out using azides with polymer supported formate, but without magnesium which did not yield the desired product. This clearly indicates the requirement of magnesium to catalyze the reduction reaction. Further, reduction of azides was also attempted only with magnesium and methanol but without polymer supported formate. Even after long duration we could not obtain any reduced product. This confirms that methanol serves only as solvent and not as hydrogen source.

CONCLUSION

In summary, we have developed magnesium catalyzed transfer hydrogenation of both aliphatic and aromatic azides to corresponding amines using polymer supported formate as the source of hydrogen. The method is operationally simple, easiness of separation of the polymer-support and recyclability. The major advantages of this method are clean work up, high yields, environmentally benign conditions and the enhanced chemo-selectivity.

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