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By

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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

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ABSTRACT

JOSHUA PELTAN: One-Pot Synthesis of Disubstituted Primary Amines from Nitriles Via Grignard Addition and Metal-Alcohol Reduction

(Under the direction of Dr. Daniell Mattern)

The process of developing a working base case procedure for a novel one-pot-two-step synthesis of primary amines from Grignard reagents, nitriles, sodium metal or alkali metal loaded silica gel, and alcohol is described. Initial steps towards applying the process broadly are detailed. The process has the potential to be an affordable, convenient, safer, greener, and more accessible alternative to exiting methods of accomplishing the same transformation. The reaction scheme has been proven to provide yields and purity comparable to existing methods for certain pairs of substrates; however, its utility as a general-purpose method for transforming arbitrary pairs of Grignard reagent and nitrile to their corresponding branched primary amine has yet to be demonstrated. Recommendations for further investigation are given.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

BHA	Benzhydrylamine
BHI	Benzhydrylimine
iPrOH	Isopropanol
MeOH	Methanol
mmol	Millimole
M-SG	Alkali metal on silica gel
Na	Sodium
NaOH	Sodium Hydroxide
NaK	Sodium-potassium alloy
NaK-SG	Sodium-potassium alloy absorbed on silica gel
Na-SG	Sodium absorbed on silica gel
n-BuOH	1-Butanol
n-PrOH	1-Propanol
t-BuOH	Tertiary butanol
X	A halogen

Introduction and Background

A variety of methods exists to prepare disubstituted primary amines from nitriles and Grignard reagents. The adduct formed by the addition of a Grignard reagent to a suitable nitrile can be reduced in-situ either by refluxing with lithium aluminum hydride (LAH) or by reaction with lithium metal in liquid ammonia [1][2]. These methods avoid the need to isolate the imine intermediate prior to reducing to the desired amine [3][4]. While these methods are significantly less cumbersome than synthetic routes involving isolation of an intermediate, they are not ideal due to the safety and environmental hazards associated with pyrophoric compounds, cryogenic ammonia, and toxic lithium salts; additionally, specialized equipment is required to safely generate and handle cryogenic ammonia. The method explored in this study replaces hazardous cryogenic ammonia with anhydrous alcohol and replaces the toxic and pyrophoric reducing agents with non-pyrophoric and non-toxic sodium absorbed on silica gel (Na-SG) [5]. Alternatively, Na-SG can be substituted by sodium metal (Na) to reduce the procedure cost at the expense of some of the safety benefits provided by Na-SG. The convenience of other one-pot methods is maintained while reducing environmental and safety hazards and providing acceptable yields. Additionally, this reaction scheme should be more accessible to researchers due to the lack of specialized equipment and reagents. It can be viewed as a low-tech extension of traditional Grignard chemistry.

Previous work has shown that Grignard-nitrile adducts can be readily converted to their corresponding imines via addition of an excess of anhydrous methanol [6]. It has also been shown that solutions of relatively pure secondary imines in alcohol can be reduced to their

corresponding amines by refluxing with sodium metal [7]. However, an extensive literature search failed to produce prior reports of the metal-alcohol reduction of primary imines, the metal-alcohol reduction of imines produced in-situ via the decomposition of Grignard-nitrile adducts, or the use of alkali metals absorbed on silica gel to reduce imines.

Absorbing alkali metals onto silica gel produces a black powder (M-SG) which maintains most of the reducing power of pure alkali metals. To produce these M-SG reducing agents, sodium, potassium, or sodium-potassium alloy (NaK) is combined with silica gel and heated under an inert atmosphere. Three distinct types are produced depending on the temperature used during manufacture. Stage 0 NaK-SG is the most reactive and is produced by combining silica gel and liquid NaK at ambient temperature. Stage I M-SG is produced by heating stage 0 M-SG, or silica gel and an alkali metal, to 150 °C. Stage II M-SG is produced by increasing the temperature to 400 °C. Since stage 0 NaK-SG is air sensitive, it does not provide major benefits to laboratory chemists and is not commercially available in small quantities. Stage I M-SG is not reactive to oxygen under ambient conditions; however, it quickly reacts with atmospheric moisture. Stage II M-SG reacts only slowly with atmospheric humidity. While stage II powders of Na-SG are less reducing than stage 0 or I, they can be easily handled under ambient conditions and stored in screw-cap bottles [5].

Reaction Scheme Overview

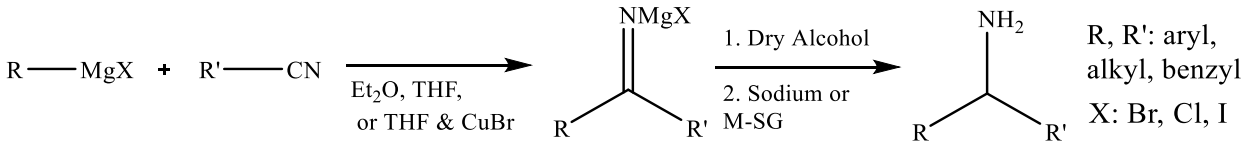


Figure 1. Overview of generalized reaction scheme

The generalized reaction sequence reported on here can be seen in the figure above. In the first step, a Grignard reacts with a nitrile in an ethereal solvent to form an intermediate complex. This rate of this reaction is highly dependent on the substrate structures. Sterically hindered substrates react slowly; however, the reaction rate can be improved by the addition of a small amount of copper(I) bromide (CuBr) as a catalyst [2]. Once the first reaction is complete, the Grignard-nitrile complex is decomposed to a primary imine and an alkoxide salt by the addition of an anhydrous alcohol. Finally, either metallic sodium or an alkali metal on silica gel is added to reduce the imine to the corresponding primary amine. The alcohol acts as a proton source both for the decomposition reaction and for the reduction. Metallic sodium or M-SG act as electron sources. All reaction steps are performed in a vessel without isolating, purifying, or concentrating the intermediate products. Once all reaction steps have been completed, a single workup is used to isolate the desired primary amine.

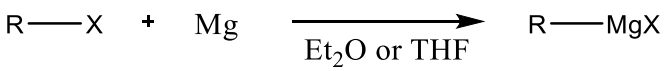


Figure 2. Synthesis of Grignard reagents

Although a wide variety of Grignard reagents are commercially available, there are several reasons why one might choose to prepare them in situ. While many common Grignard

reagents can be acquired affordably, more obscure ones are either exorbitantly priced or not purchasable. Additionally, they are liable to degrade during storage due to the ingress of moisture. To prepare a Grignard reagent, an organic halide is combined with metallic magnesium in diethyl ether or tetrahydrofuran. This reaction is shown above in figure 2. Although simple on paper, this process is prone to failure and variability due to its sensitivity to moisture and oxidation on the magnesium surface.

Chapter 1: Reaction Feasibility and Troubleshooting

As the synthetic method investigated in this work was previously untested, the initial phase sought to determine if the proposed sequence of reactions is capable of producing a primary amine product. Subsequent phases focused on improving reaction methodology and determining if a wide range of disubstituted products could be produced. Initial naïve attempts to complete the entire synthetic pathway from raw nitrile and organic halogen substrates failed to produce any isolatable amine products. The absence of published reaction parameters for the metal-alcohol reduction step combined with a lack of practical experience with air and moisture sensitive processes made this direct approach unworkable. Therefore, a sequential approach was developed to narrow the number of potential sources of failure. The first section of this approach investigated the production and decomposition of the Grignard-nitrile complex. The second part investigated the metal-alcohol reduction of pure isolated imine. The third step investigated the reduction of crude imine produced by decomposing a Grignard-nitrile complex. Finally, the lessons learned were combined into a working albeit non-optimal reaction procedure.

Preparation of Grignard-Nitrile Complex and Isolation of Pure Free Imine

For this portion of the feasibility investigation, formation of the Grignard-nitrile complex, decomposition with alcohol, and isolation were combined due to difficulty in analyzing the crude complex. Benzhydrylimine (BHI) was used as a model imine due to the availability of a published synthetic procedure and experimental spectra. A scaled-down version of the procedure published in *Organic Syntheses* was used. The synthetic pathway can be seen in figure 3 below.

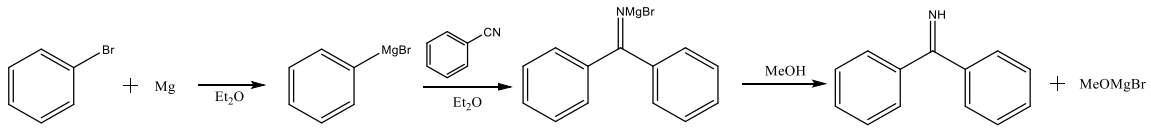


Figure 3. Synthesis of benzhydrylimine

Bromobenzene was added to a flask containing dry ether under an inert atmosphere to produce phenylmagnesium bromide. This was subsequently reacted with benzonitrile to give a complex which was decomposed using an excess of dry methanol. An insoluble methoxide salt was removed by filtration, and the ether solvent was removed under vacuum. Finally, the pure imine was isolated via Kugelrohr distillation under vacuum [8].

To confirm the production of BHI, ^{1}H and ^{13}C NMR spectra were compared with those found in the literature. Figures 4 and 5 show both experimental and literature spectra. The experimental product spectra are on the left half of the figures. Since BHI lacks distinctive proton peaks outside of the aromatic region, the ^{13}C spectrum is the most diagnostic. Aside from a few additional impurity peaks, the experimental and reference spectra are a perfect match. The proton spectra, while not enough to conclusively identify the compound, gives good confirmation of the findings of the ^{13}C spectrum. Additionally, the proton spectrum shows that the product is of high purity due to the low total integration of impurity peaks outside of the aromatic region.

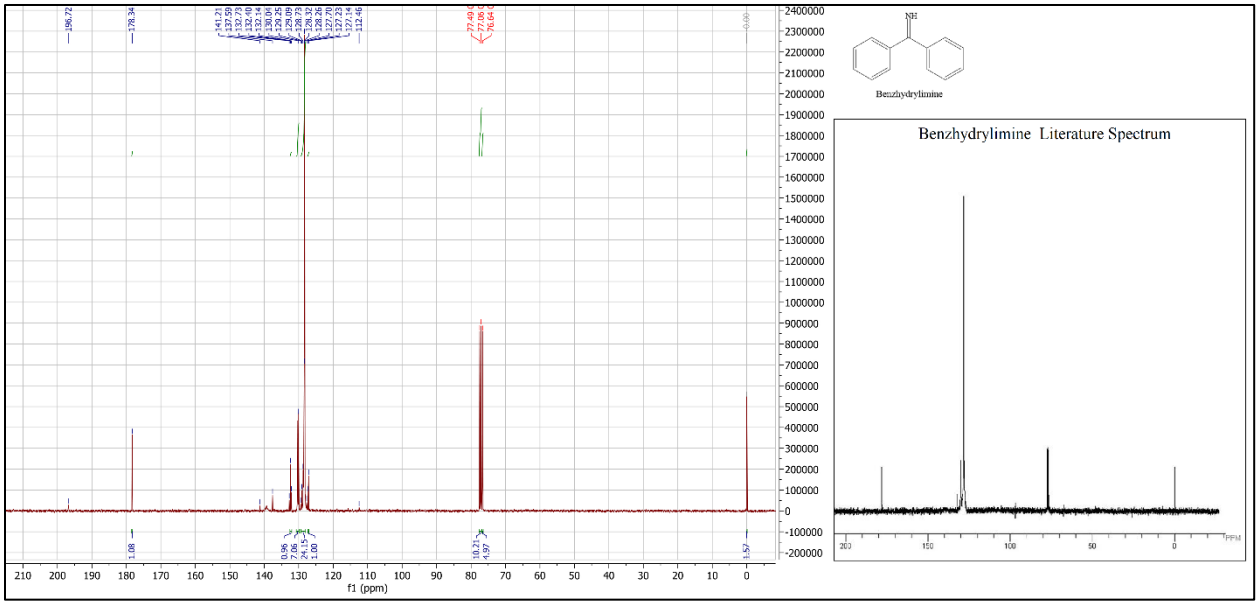


Figure 4. Comparison of experimental and literature 13C NMR spectra from Sigma [9]

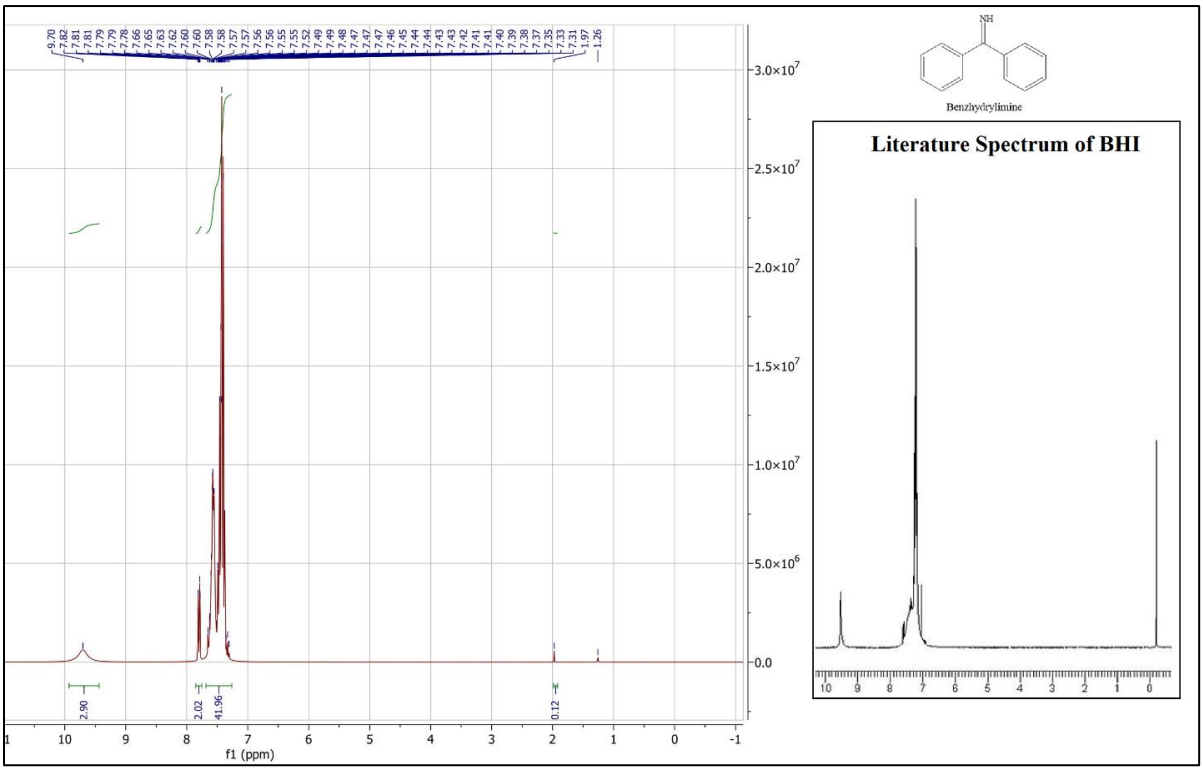


Figure 5. Comparison of experimental product and literature 1H NMR spectra from Sigma [9]

Reduction of Isolated Benzhydrylimine to Benzhydrylamine

Building on a published procedure for reducing an isolated secondary imine with sodium and ethanol, several combinations of electron sources and alcohols were tested to determine if any could produce the desired amine product [7]. For each run, approximately four equivalents of electrons were supplied for each imine. This represents a 100% electron excess. Additionally, each run used the same molar ratio of alcohol to imine of about 25. The results of this experiment are summarized in table 1 below.

Table 1. Yield comparison for various combinations of alcohol and electron source

	Na (metal)	Na-SG(II)	NaK-SG(I)
Methanol			0%
Ethanol		16%	
n-Propanol	74%	48%	0%
Isopropanol	0%		
n-Butanol	68%		
t-Butanol	53%	39%	

The grey cells in table 1 are combinations that were not tested and the cells with 0% yield are from reactions that produced no benzhydrylamine (BHA). While some of the low yields can likely be attributed to poor recovery method, water contamination in the alcohols, and degradation of the M-SG, it appears that sodium metal and longer unbranched alcohols give higher yield. This observation led to n-propanol (n-PrOH) being the standard proton source for

subsequent experiments. Sodium metal was used more often than M-SG simply due to the lower cost of metallic sodium compared to M-SG.

The identity and approximate purity of the products were determined using NMR spectroscopy. For the sake of brevity, only one example will be included. Figure 6 shows the comparison of literature and experimental ^{1}H NMR spectra. The spectrum on the left is from the product and it is an exact match to the reference spectra except for a few additional impurity peaks in the reference.

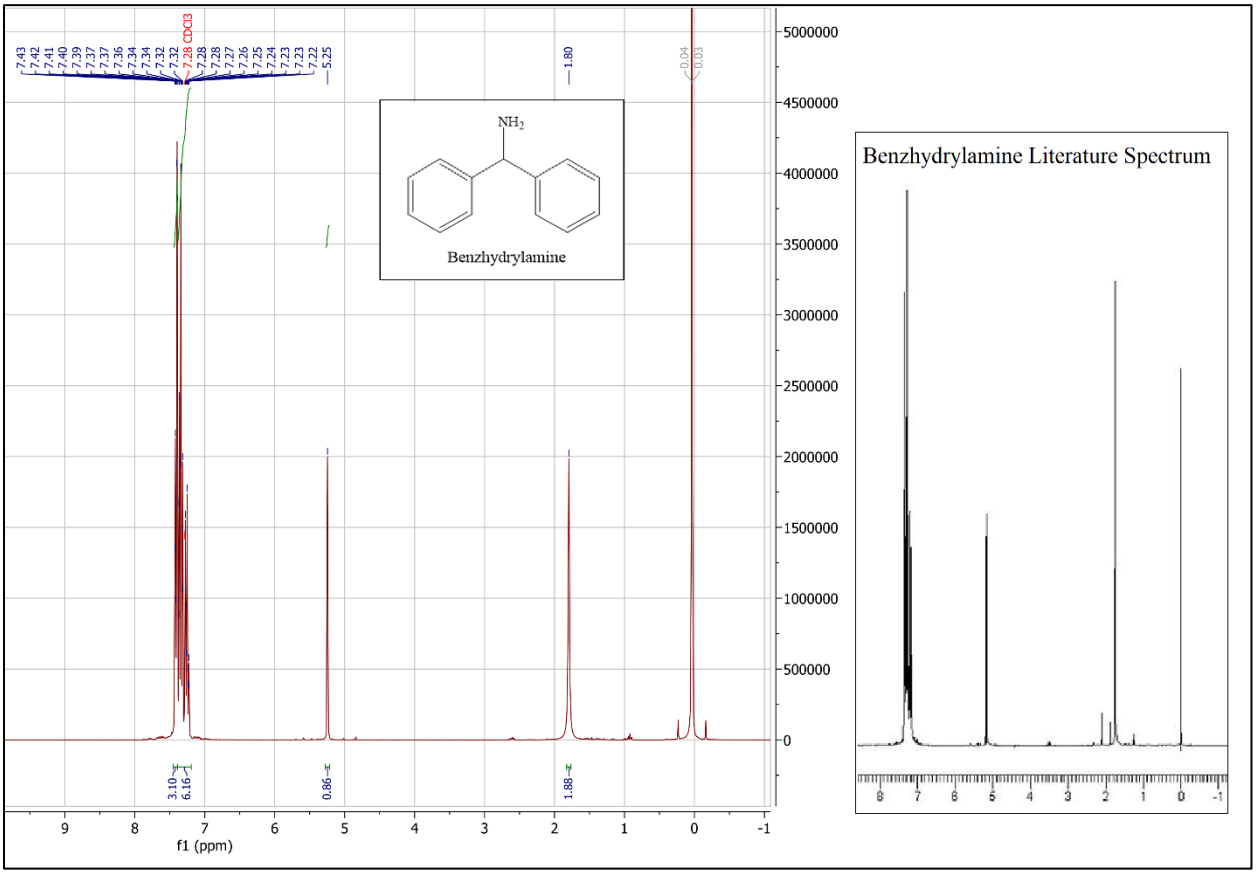


Figure 6. Comparison of experimental product 1H spectrum to reference from Sigma

Reduction of Crude Imine Formed by the Decomposition of a Grignard-Nitrile Adduct

Before proceeding to the complete synthetic procedure, a series of tests were performed to ensure that the metal-alcohol reduction of purified BHI is not a special case and that impure imine can also be reduced using the same reagents. Additionally, working with the adduct as a starting point allowed a larger batch of adduct to be prepared and split among many reduction trials. In addition to saving time, larger Grignard synthesis and addition reactions tend to have better yields in a practical laboratory setting due to the reagents consumed by what is essentially a fixed rate of moisture ingress, for a given apparatus, constituting a lower fraction of the total amount of reactive substance. However, one major disadvantage of this strategy is that the uncertainty associated with measuring yield will be higher than in batches where reagents are measured individually.

The Grignard-nitrile adduct was prepared in the same way as described above, except instead of decomposing with anhydrous methanol, the solvent was removed under vacuum and inert gas was reintroduced once dry. This resulted in a yellow-colored solid which could easily be broken up into powder for use in subsequent experiments. To estimate yield, an effective nitrile concentration was determined by dividing the mass of the nitrile used by the total mass of the solid produced. Assuming that the concentration of the adduct is constant throughout the material, this should produce a relatively accurate yield based on the nitrile.

A mass equivalent to about 1.5 millimoles of nitrile was reconstituted with ether before being decomposed with 25 molar equivalents of n-PrOH. The newly formed imine was then reduced using 4.5 equivalents of metallic sodium to give a 69% yield. Additionally, another

portion of crude adduct equivalent to 1.5 mmol of nitrile was reconstituted with ether and reduced with a large excess of LAH. This resulted in a yield of 61%. While there are several sources of unaccounted for error, this comparison shows that the sodium-alcohol reduction of crude Grignard-nitrile adducts performs similarly well to better established reducing agents.

Successful Test of Complete Synthetic Procedure

With most of the critical issues ironed out using the stepwise approach previously discussed and many lessons learned about each step of the process, a one-pot run from bromobenzene and benzonitrile to benzhydrylamine was conducted. Bromobenzene (1.5 mmol) was converted to phenylmagnesium bromide using 1.6 mmol of freshly shaven magnesium in ethyl ether under a nitrogen atmosphere. Benzonitrile (0.8 mmol) was then added and the mixture was refluxed for 24 hours. Anhydrous n-PrOH (20 mmol) was added, or 25 equivalents per nitrile, and 4.5 molar equivalents of sodium metal were added. Once the sodium had completely reacted, the mixture was quenched with a small amount of methanol followed by 5% sodium hydroxide (NaOH). The basic mixture was extracted three times with ethyl ether. The ether extracts were then combined in a separatory funnel extracted three times with 5% HCl. Non-basic contaminants were then removed from the acidic extracts by washing with three small portions of ethyl ether. The water layer was then basified to a pH of 12 using NaOH and extracted three times with ethyl ether. The ether was then removed on a rotary evaporator to give 82 mg of pure benzhydrylamine. This corresponds to a 56% yield based on the amount of nitrile.

Chapter 2: Assessment of Reaction Generality

Having proven that the metal-alcohol reduction of Grignard-nitrile complexes is possible in the specific case of benzhydrylamine, this chapter seeks to discover whether this holds for other products. For the synthetic method to be a truly useful extension of a classic organic reaction, it must be applicable for a wide range of substrates. Benzhydrylimine is sterically hindered and lacks acidic alpha hydrogens which might prevent some potentially unwanted side reactions from occurring. Side reactions could reduce yields, or worse, create unwanted products containing basic nitrogen which would render traditional acid-base workups all but useless. Additionally, it would be unwise to claim that metal-alcohol reduction works on a broad range of primary imines when it has only been shown on one substrate. Until proven otherwise, it cannot be said with great certainty that there is not something unique about the structure of BHI that helps facilitate metal-alcohol reduction.

Parallel Amine Synthesis Experiment

To improve throughput and more quickly cover product space, a salvaged Radleys Carousel 12 position reaction station was adapted to utilize standard 1” x 6” glass boiling tubes sealed by 24/40 rubber septa. This setup allows for up to 12 parallel reactions to be refluxed or run at room temperature under inert gas with stirring. The modification to use standard

laboratory equipment rather than the proprietary tubes the reaction station was originally intended to use resulting in significant cost savings; however, this new setup introduces more potential sources of error compared to using traditional glassware.

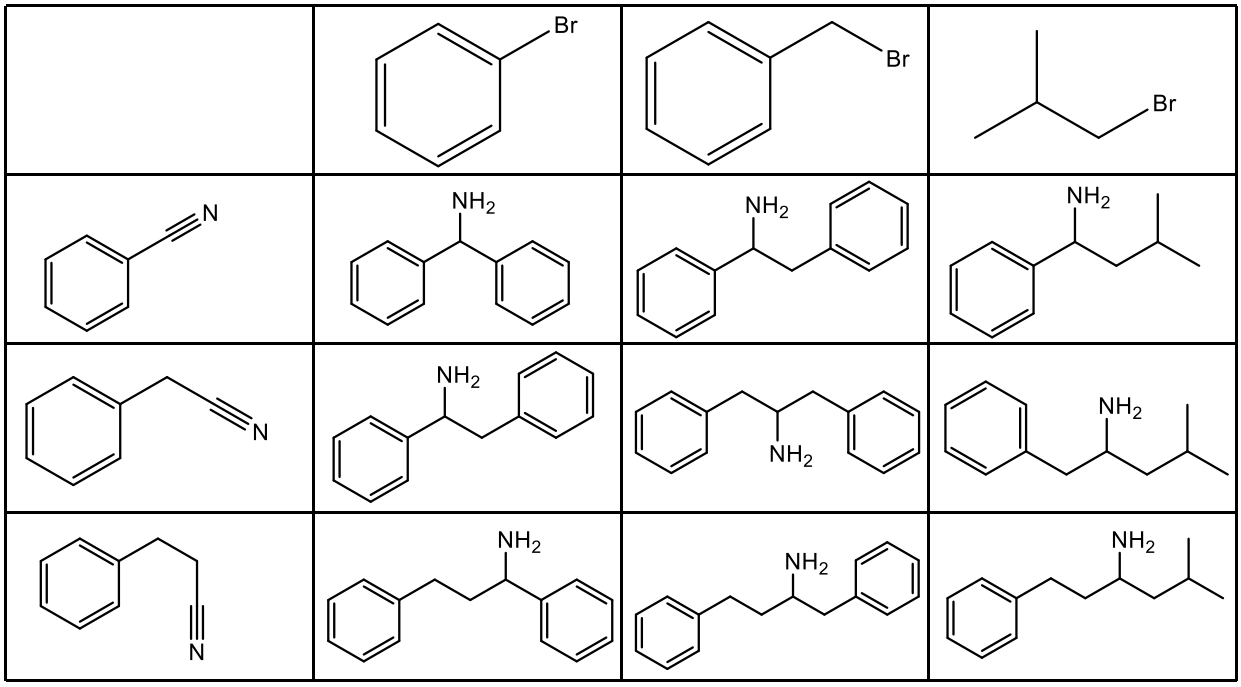
To test the generality of the synthetic procedure developed up to this point, an aryl, alkyl, and benzyl bromide and nitrile were selected for use in the procedure. All reactions were performed on a 1.5 mmol scale based on the nitrile. Other than the use of the parallel reaction station instead of a standard round bottom flask and condenser, the reaction procedure used was similar to what was described on page 11. The molar ratios of reagents remained the same, n-PrOH and sodium metal were used, and a unique pair of nitrile and bromide were used in each tube. An acid-base workup was used to isolate the products from the crude reaction mixtures. A table of the chosen substrates, their corresponding products, and their isolated product yields unadjusted for purity is shown below.

Table 2. Substrate pairs, corresponding products, and yields

	Bromobenzene	**Benzyl bromide**	**Isobutyl Bromide**
Benzonitrile	1,1-Diphenylmethylamine	1,2-Diphenylethylamine	3-Methyl-1-phenylbutan-1-amine
Yield:	39%	37%	23%
Benzyl cyanide	1,2-Diphenylethylamine	1,3-Diphenyl-2-aminopropane	4-Methyl-1-phenylpentan-2-amine
Yield:	21%	35%	25%
Hydrocinnamonitrile	1,3-Diphenylpropylamine	1,4-Diphenylbutan-2-amine	3-Methyl-1-phenethylbutylamine
Yield:	19%	21%	16%

Figure 7, shown below, is a visual representation of the relationship between the substrate pairs and corresponding products from table 2.

Table 3. Substrate pairs and corresponding product structures



As seen in table 2, the product yields are relatively low. Since the BHA yield is only 39%, and a previous reaction under the same conditions produced a 56% yield, it is unlikely due to structural effect alone. The more important line of inquiry is whether NMR data indicates the presence of the desired primary amine or any undesired side products. Unfortunately, the raw NMR data for three runs was corrupted, none of the samples were particularly pure, and experimental reference spectra do not exist for several compounds. Therefore, determining the composition of each sample from NMR spectra alone is difficult. Nonetheless, positive identification of one new product was possible. This result confirms that the one-pot reaction scheme does produce the desired product for cases other than the synthesis of BHA; however, it has yet to be determined if difficult-to-separate side products were produced.

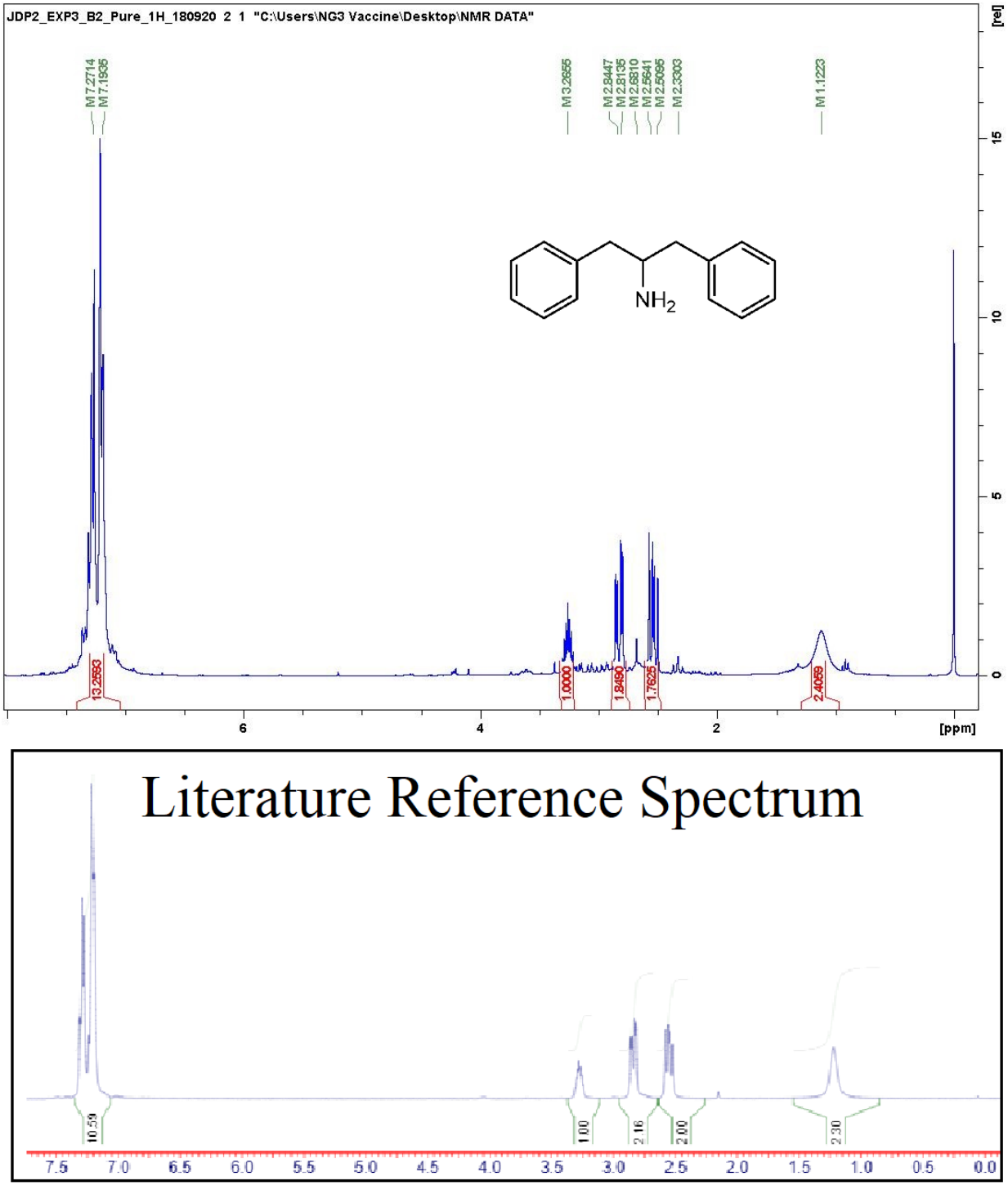


Figure 7. Experimental 1,3-diphenyl-2-aminopropane compared with literature spectrum from Enamine Ltd.

Clearly shown in figure 7, the 1H NMR spectrum for the experimental 1,2-diphenyl-2-aminopropane product is an excellent match to the reference spectrum in terms of chemical shifts, multiplicity, and integration. However, the additional peaks seen in the experimental spectrum indicate the presence of some contamination.

Conclusion and Recommendations for Future Investigation

The one-pot synthesis of primary amines from nitriles via Grignard addition followed by metal-alcohol reduction is a process that shows some promise and offers some potential benefits compared to existing synthetic techniques that accomplish the same transformation. The process uses more accessible, less hazardous, and greener reagents than other similar pathways; additionally, all of the byproducts pose little environmental risk. Initial experiments show that, with non-optimal reaction parameters, the synthetic scheme can produce at least some desired products with acceptable yields and purity. However, it has yet to be demonstrated whether it is broadly applicable to entire classes of substrate pairs or if it can compete with other methods in terms of either cost or effort.

Developing a base case for the process that gives any positive results was a significant hurdle to overcome. Without understating the effort and cost associated with continued investigation, there is a reasonable basis to assume that the ratio of reward to cost for further research will be higher than what has been realized thus far.

The primary objective of future research should be to determine if the reaction pathways can be reliably applied to a broad range of substrates. A secondary goal is to develop a more optimal process parameter in terms of either yield, purity, product unit cost, robustness, or convenience. As a first step towards determining the applicability of the reaction scheme for many substrates, the parallel synthesis of amines experiment should be repeated; however, more care should be paid to isolating pure products, identifying other organic compounds produced by

the process, and determining how much of each substrate or intermediate is consumed. This detailed level of analysis will help guide the process of increasing reaction efficiency. It is probable that many of the reactions performed already produced the desired amine product but resulted in too low purity to fully resolve the spectra. Additional analytical techniques such as GC-MS, LC-MS, or UV-VIS might prove to be useful tools in identifying products and refining the reaction procedure.

If the process is proven to be broadly applicable to substrate pairs, then work on optimization might be worthwhile. One potential technique is to generate response surface models to correlate process variables with parameters of interest for optimization, such as yield, purity, and product unit cost. Breaking the process up into individual steps would significantly reduce the number of runs required to generate a working model. Additionally, the use of commercially produced Grignard reagents would likely result in a significant reduction in process variability. Using a model compound for optimization would also reduce the amount of work needed to optimize; however, this approach risks overfitting the procedure for a specific compound or pair of substrates. It will be critical to understand what relationship there is between structure and optimal parameters if the procedure is to be both efficient and general.

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