5-2014

Reduction of ketoximes to amines by catalytic transfer hydrogenation using Raney Nickel and 2-propanol as hydrogen donor

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Recommended Citation

Reduction of Ketoximes to Amines by Catalytic Transfer Hydrogenation Using Raney Nickel® and 2-Propanol as Hydrogen Donor

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General Abstract

The reduction of ketoximes to amines is a valuable organic reaction and has been explored in our study *via* catalytic transfer hydrogenation (CTH) with a Raney Nickel® catalyst and 2-propanol as hydrogen donor. This reduction, while novel in our particular method, is not a new reaction. Traditionally, the conversion to amines takes advantage of classical hydrogenation techniques employing a metal catalyst and molecular hydrogen $(H_{2(g)})$,[1] which while successful in producing their intended products, are not particularly efficient. Molecular hydrogen must be stored in pressure vessels, and as it is gaseous in nature and highly flammable in air, is inherently more difficult to handle. On the other hand, hydrogen donors, such as 2-propanol, are typically inexpensive liquids that are much safer to use since $H_{2(g)}$ containment is avoided. Hydrogen donors in excess can often be used as the reaction solvent,[2] and 2-propanol, in particular, is a relatively clean material.[3] The production of a "metal sludge" in the presence of Raney Nickel® is also avoided, [4,5,6] so that the metal catalyst may be used repeatedly in hydrogenation reactions.

Previously, our laboratory performed reductions of aromatic alcohols,[4] epoxides [7] aldehydes, [5] ketones, [8] aryl ketones, [9] iodolactones, [10] nitriles, [11] and aldoximes [12] by CTH. After studies with aldoximes proved more complicated than originally anticipated, the extension of CTH to ketoximes drew greater interest and became the next logical step in the succession of CTH work. In this research, ketoximes successfully underwent hydrogenolysis and hydrogenation under catalytic

transfer conditions with Raney Nickel® and 2-propanol as hydrogen donor. One ketoxime was reduced to its primary amine when 2% KOH was included in the reaction; KOH was explored as a method of synthetic control as its addition to the reaction scheme seemed to poison the nickel catalyst. In the absence of KOH *N*-isopropyl-secondary-amines were obtained in good yields.

Introduction

   Traditional methods of hydrogenation, utilizing a metal catalyst and hydrogen gas, are effective and appropriate ways to synthesize amines through reductive amination. This amination method involves the formation of an amine from a carbonyl through an imine intermediate as shown in the examples in Figure I where the carbonyls are ketones.[13]   The imine intermediates, which include ketoximes in part b, are characterized by carbon-nitrogen double bonds (C=N).

(a)

(b)
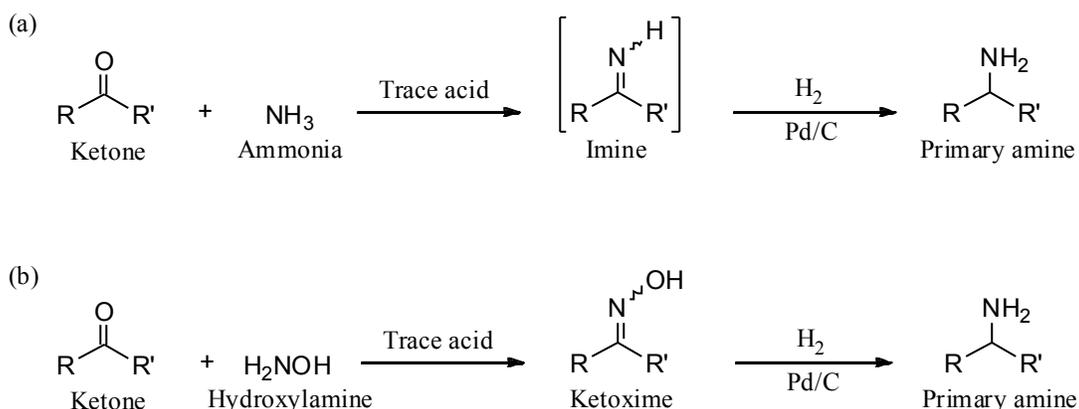
Figure I: Ketone conversions to amines through reductive amination with
(a) ammonia and (b) hydroxylamine as starting materials [13]

This method of reductive animation is successful in reducing carbonyls to amines via imine intermediates. However, in using molecular hydrogen as the reductant in these reactions, there is inherent difficulty in handling the gas so that while this method of hydrogenation is widely used, the pursuit of alternative methods of adding hydrogen to reactions has drawn interest.

Catalytic transfer hydrogenation of organic molecules utilizing organic hydrogen donors as opposed to molecular hydrogen was proposed by Braude, Linstead, *et. al*. in 1952.[14] Though a novel approach to hydrogenation synthesis with its mild reaction conditions and use of accessible hydrogen donors, early uses of CTH resulted in poor product yields and required lengthy reaction times, so that utilizing molecular hydrogen was actually a more desirable method. But, upon reexamination of CTH and exploration of various hydrogen donors and catalysts, hydrogen transfer grew in popularity as it was used to optimize various synthetic reactions. Additionally, CTH offered the selectivity lacking in traditional hydrogenation methods as it utilized hydrogen donors that competitively adsorbed onto the catalytic surface.[6]

In CTH, reactions employ a hydrogen donor in the presence of a metal catalyst in order to carry out hydrogenation. Typical catalysts are homogenous or heterogeneous complexes of transition metals, generally those in groups 8-10 (cobalt, ruthenium, palladium, nickel, platinum),[15] and typical hydrogen donors for nickel complexes, which we have used in our research, are alcohols, such as ethanol and 2-propanol, and formic acid derivatives.[16] When hydrogen donors are introduced to reactions, they undergo oxidation, thus releasing molecular hydrogen to be adsorbed upon the surface of the metal catalyst, as shown in Figure II. This molecular hydrogen is then available for hydrogenating the reactant.
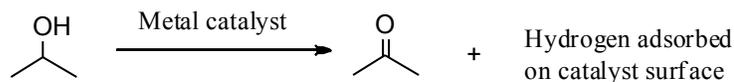
Figure II: Example of hydrogen donor oxidation to yield molecular hydrogen

In our research, we have utilized Raney Nickel® and 2-propanol as hydrogen donor in the hydrogenation of a variety of functional groups including aromatic alcohols,[4] epoxides [7] aldehydes, [5] ketones, [8] aryl ketones, [9] iodolactones, [10] and nitriles.[11] Several years ago Dan Zuidema, working in Mebane's laboratory, attempted to apply CTH with Raney Nickel® and 2-propanol to the reduction of aldoximes to primary amines which can be accomplished with traditional hydrogenation methods employing $H_{2(g)}$.[12] Much to their surprise they discovered that under the CTH reaction conditions the aldoximes were dehydrated to nitriles as shown in Figure III.
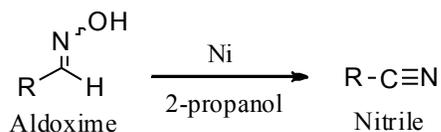

Figure III: Aldoxime reaction scheme

Nitriles are valuable synthetic intermediates since they can be easily transformed into other useful functional groups. Mebane and his former research students exploited

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this result into several "green chemistry" methods to prepare nitriles, amides and ethyl esters.[17,18,19,20]

Once that avenue of synthetic research was completed, the next logical step in our CTH work was to explore what would happen if ketoximes were placed under the same CTH conditions. As shown in Figure IV, aldoximes and ketoximes differ in structure only by the one –R group present in ketoximes that are absent in aldoximes.
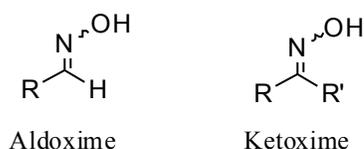
Figure IV: General aldoxime and ketoxime structures

Since aldoximes have an available hydrogen (–H) on the carbon of the carbon-nitrogen bond (C=N), which is close in proximity to the hydroxyl group (–OH), they are susceptible to water loss as was demonstrated in our previous research.[12] However, since an –R group takes the place of that available –H in ketoximes, we assumed that dehydration would not occur so that hydrogenation was more likely to take place.

In the past, ketoximes have been successfully hydrogenated to amines via traditional hydrogenation methods with molecular hydrogen and a metal catalyst.[21] However, ketoxime reduction via CTH has not been done before, making our area of research a novel application towards amine synthesis. We chose 2-propanol as

hydrogen donor, since it is cheap and easy to handle. It is also fairly volatile so that it can be easily removed from a reaction scheme when end products must be isolated. Raney Nickel® is a heterogeneous catalyst, produced by leaching nickel from a nickel-aluminum alloy, which was donated to us from W.R. Grace Company in Chattanooga. This leaching leads to a skeletal structure of the alloy,[21] thus increasing the overall surface area upon which hydrogen donated from oxidation of the donor can be loaded.

Our approach to the hydrogenation of ketoximes can be separated into two parts: reactions where KOH is absent and those in which KOH is used. Little is known about the mechanism of how KOH contributes to selectivity in a reduction reaction,[22] but our previous research suggests that the addition of KOH poisons the metal catalyst after the addition of one mole of $H_2(g)$ so that the reaction stops when an imine intermediate is produced. The optimum amount of base needed to produce this imine was determined to be 2% KOH.[11] However, when KOH is absent from the reaction, the imine intermediate is further reduced to an *N*-isopropyl-secondary-amine. These reactions are further discussed in the remainder of the paper.

Results and Discussion

When KOH is absent from the reaction, ketoximes can be reduced to 2°

amines solely in the presence of 2-propanol and Raney Nickel® as shown in
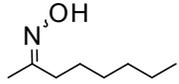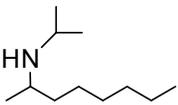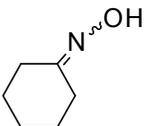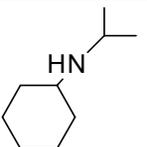
Figure V.
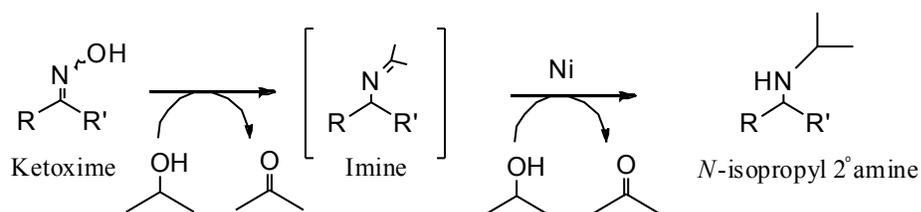
Figure V: Ketoxime reduction in the absence of KOH

Ketoximes are first reduced to imine intermediates when hydrogenolysis of the

nitrogen-oxygen bond (N-O) occurs to produce a temporary primary amine which

then condenses with acetone produced in the oxidation of 2-propanol. This imine

intermediate is then further reduced to an *N*-isopropyl-secondary-amine when

hydrogen cleaved in the oxidation of 2-propanol to acetone continues to add to the

reaction. This specific reaction scheme provides potential product variation, since

different hydrogen donors could condense with ketoximes and undergo further

reduction as 2-propanol did.

Under CTH conditions with Raney Nickel® and 2-propanol, six ketoximes

were successfully reduced to their *N*-isopropyl-secondary-amines in varying reaction

times and overall yields as shown in Table I.

Table I. Transfer hydrogenation of ketoximes with Raney Nickel® and 2-propanol

Entry	Ketoxime	Product	Time[a] (min)	Yield[b] (%)
1	2-octanone oxime*	N-isopropyl-2-octanamine	180	80
2	cyclohexanone oxime	N-isopropylcyclohexanamine	105	66
3	3-heptanone oxime	N-isopropyl-3-heptanamine	280	81
4	2-nonanone oxime	N-isopropyl-2-nonanamine	131	76
5	5-nonanone oxime	N-isopropyl-5-nonanamine	225	80
6	2-decanone oxime	N-isopropyl-2-decanamine	180	90
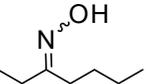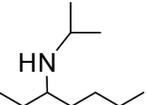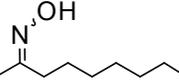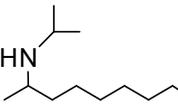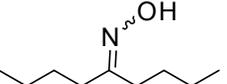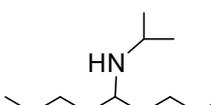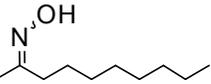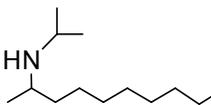
[a]Time to reach complete conversion under reflux as determined by GC-MS.
[b]Isolated yields. Product amines were confirmed by ^{1}H-NMR, ^{13}C-NMR, and GC-MS.
*Conversion completed before we started monitoring reactions by GC-MS. Based solely on NMR data which proved our intended amine had been produced.

Procedurally, 1 g of each oxime dissolved in 2-propanol (5 ml) was added dropwise to a mixture of Raney Nickel® (~5 g) in 2-propanol (20 ml) that was stirring and refluxing in a round-bottom flask. As recorded in Table I, reflux times varied between oximes and were determined based upon GC-MS analysis of samples

drawn at various points along the reactions. Workup consisted of decanting the 2-propanol layer from the nickel while hot, and the nickel was then refluxed and decanted with 3 x 20 ml of 2-propanol to remove all organic material from the reaction flask. The combined organic material underwent rotary evaporation to a constant mass to remove the 2-propanol layer, leaving the isolated racemic mixture of the amine product. ^{1}H,^{13}C-NMR spectroscopy confirmed the intended amine identity by comparing generated spectra to authentic amine spectra found in the Spectral Database for Organic Compounds (SDBS),[23] and GC-MS analysis further asserted our conclusions of amine identities.

Though six oximes were successfully converted to their *N*-isopropyl-secondary-amines, we did have difficulties reducing other oximes to their intended products. For example, when we attempted to reduce 2,4-dimethyl-3-pentanone oxime with a reflux time of 3 hrs, we obtained a complex mixture of signals in NMR analysis. Upon increasing the reflux time to 7.5 and 21 hrs, we still found no conclusive evidence that our intended *N*-isopropyl-secondary-amine product had been formed. As a fairly branched molecule when compared to other oximes we used in reductions, it is possible that the reduction of 2,4-dimethyl-3-pentanone oxime did not occur as efficiently as with other oximes due to steric hindrance. Its structure is shown in Figure VI. We chose not to further pursue analysis of the complex mixture we obtained.
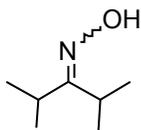
Figure VI: The structure of 2,4-dimethyl-3-pentanone oxime

Additionally, in our workups for the CTH reaction of 2,4-dimethyl-3-pentanone oxime, we only managed to obtain yields consistently less than 30%, leading us to also assume that our product was more volatile than we had originally anticipated. We do plan to further explore this reduction by changing reaction conditions. We also attempted to reduce benzophenone oxime, another molecule with extensive R-group branching off the central C=N bond. The CTH of this oxime resulted in a complex mixture that was determined not to be of synthetic value. We chose not to further pursue this reaction.

In addition to exploring various oximes under CTH conditions, we also pursued reductions of 2-octanone oxime with other hydrogen donors besides 2-propanol. When we used 2-butanol as hydrogen donor along with standard CTH procedures (3 hr reflux) and workup, NMR analysis indicated that we had produced the appropriate *N-sec*-butyl-2-octanamine but also high amounts of 2-octanol. In an attempt to isolate the amine product, we performed an extraction with HCl(aq) and NaOH to rid the reaction flask of any neutrals, including 2-octanol. When we analyzed the isolated amine product with NMR analysis, we found more peaks than

we had anticipated in the generated spectra, leading us to speculate that perhaps we had produced diastereomers of *N-sec*-butyl-2-octanamine. We also tried using cyclopentanol as a hydrogen donor with methanol as a cosolvent since cyclopentanol is not soluble with nickel. The reaction was carried out under CTH conditions with a 3 hr reflux. In looking at generated NMR spectra of the product after workup, we saw many more peaks than expected, one for which we could not find anything to account. This reaction was not pursued further. One last hydrogen donor explored with the reduction of 2-octanone oxime was ammonium formate. The standard 1 g of 2-octanone oxime was dissolved in a mixture of approximately 2 g of ammonium formate and 20 ml of methanol and Raney Nickel® and allowed to stir at room temperature under a condenser for 21 hrs. Since ammonium formate dissociates into $CO_2(g)$, $NH_3(g)$, and $H_2(g)$ in the presence of nickel, we ran the reaction without heat. In ^{13}C-NMR analysis of the product, most peaks could be attributed to 2-octanone, and a few other peaks could not be accounted for. The same reaction was run with heat for only 3 hrs to see if the same products were obtained. According to ^{13}C-NMR analysis, the major product was again 2-octanonone. The reaction was not pursued further.

Additionally, a sample of Raney Nickel® was reused six times in the CTH of 2-octanone oxime and was shown not to decrease in catalytic activity. Thus, we were able to conserve the amount of metal catalyst we used in reactions without sacrificing optimal reaction conditions.

With respect to reactions performed in the absence of KOH, future work will involve optimizing the reaction conditions for the CTH of 2,4-dimethyl-3-pentanone oxime and exploring other low-weight hydrogen donors.

When KOH is present, ketoximes can be reduced in the presence of Raney Nickel® and 2-propanol as shown in Figure VII.
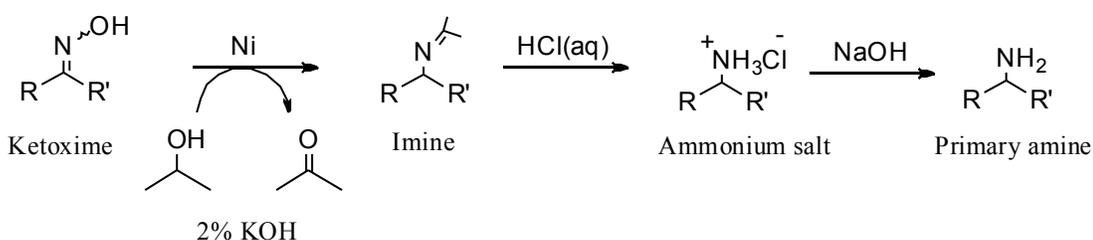
Figure VII: KOH inclusive reaction scheme for ketoxime reduction

The depicted ketoxime reduces to its primary amine but then immediately condenses with acetone, the oxidation product of 2-propanol, to give an imine. No further reduction takes place when KOH is present. In order to synthesize the primary amine, the imine can be hydrolyzed with aqueous HCl to create the ammonium salt, which is then basified with NaOH. This reaction scheme is valuable in that there are three steps in synthesis, which allows for three possible products: imine, ammonium salt, and primary amine. Thus, with KOH present, there is an increased method of control or selectivity in hydrogenating ketoximes.

With the inclusion of 2% KOH under CTH conditions with Raney Nickel®

and 2- propanol, one commercially available ketoxime was successfully reduced to its

primary amine. CTH of 2-octanone oxime gave 2-octanamine with an 83% isolated

yield after 60 minutes of reflux as demonstrated in Figure VIII.
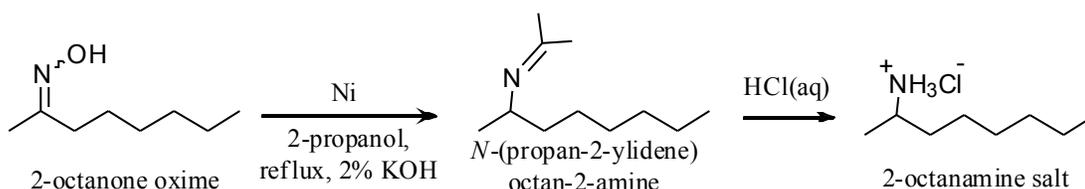
Figure VIII: Reduction of 2-octanone oxime with KOH

Procedurally, 1 g (~7 mmol) of 2-octanone oxime dissolved in 2-propanol (5

ml) containing 2% KOH was added dropwise to a mixture of Raney Nickel® (~5 g)

in 2-propanol (20 ml) containing 2% KOH that was refluxing and stirring in a round-

bottom flask. The reaction was refluxed for 1 hr. Workup consisted of decanting the

2-propanol layer from the nickel while hot, and the nickel was then refluxed and

decanted with 3 x 20 ml of 2-propanol to remove all organic material from the

reaction flask. The combined organic material containing the product was subjected

to rotary evaporation to remove the 2-propanol used in extracting the imine product.

The imine was hydrolyzed by adding hot HCl(aq) (30 ml of 1M) to the flask, and the

mixture was heated and stirred for 30 min. The flask was then cooled in an ice bath,

and to free the base 30 ml of 1M NaOH was added to the flask. Then 20 ml of diethyl ether was added to dissolve the nonpolar amine. The nonpolar layer was extracted from the aqueous layer with 2 x 20 ml of ether, and K_2CO_3 was used to dry the nonpolar material collected to ensure all aqueous material had been removed. The contents of the flask were funnel-filtered into another flask, and the original flask containing the K_2CO_3 was washed with 20 ml of ether to ensure quantitative transfer. The organic matter underwent rotary evaporation to a constant to remove the ether layer, leaving the isolated amine product. ^{1}H,^{13}C-NMR spectroscopy confirmed the intended amine identity by comparing generated spectra to authentic amine spectra found in the Spectral Database for Organic Compounds (SDBS).[23]

Though 2-octanone oxime was the only oxime that was successfully converted to its primary amine, we did attempt to reduce other oximes in the presence of KOH. Cyclohexanone oxime, when subjected to standard reaction setup (1 hr reflux) and workup (including hydrolyzing the imine and basifying), was analyzed to see if its intended reduced amine had been produced. However, upon NMR analysis, only chloroform-D (NMR solvent) was shown to be present in the sample. Thus, we were led to assume that the cyclohexylamine we had attempted to produce must be more water-soluble than originally anticipated. We additionally tried to isolate the imine intermediate of the oxime after 1 hr reflux with standard setup and workup, but upon adding chloroform-D for sampling, the product generated heat and formed bubbles and a solid precipitate, leading us to conclude that not all of the KOH had been

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removed from the sample. The product underwent further extractions with ether, but when analyzed via NMR, a complex of signals was generated, so that we determined that 1 hr of reflux was not sufficient for full conversion to the imine. However, even upon the extension of reflux time to 3 hrs, NMR analysis showed some peaks indicative of the desired amine product but many other peaks as well. We chose not to further pursue isolation of cyclohexylamine.

Additionally, the imines of 2,4-dimethyl-3-pentanone oxime and 3-heptanone oxime were attempted to be isolated according to standard procedure. However, both imines, when analyzed via NMR spectroscopy, indicated complex mixtures of signals, where we were unable to determine what exactly had been produced in the reductions. Further isolation of the imines for those oximes was not pursued.

Future work will involve optimizing the reaction conditions for the CTH of ketoximes into their imine intermediates using Raney Nickel® and 2-propanol.

Experimental

General Methods

The ketoximes 2-octanone oxime and cyclohexanone oxime were purchased from Acros and used as received. All other oximes were purchased from Acros and Aldrich as their respective ketones and reacted with hydroxylamine in order to form their corresponding ketoximes, which we then used in our reactions. Raney® 2800 nickel catalyst was donated by W.R. Grace Company of Chattanooga and washed three times with 2-propanol prior to use. As reactions were refluxed, samples were taken at t=0 and at various points throughout the reflux and were analyzed on a ThermoFinnigan PolarisQ Ion Trap GC/MS to monitor the progress of the reaction. When GC-MS data indicated the reaction was complete, the reflux was stopped. Once the product was isolated, data was generated via ^{1}H, ^{13}C-NMR analysis on a JEOL 400 MHz FT-NMR for the sample. NMR data of the sample was compared to published spectra on the SDBS database to identify both the product as well as any impurities found within the sample. GC-MS data was also used to verify the product based upon our determination of possible fragmentation of the sample.

Raney Nickel® CTH of Ketoximes – General Procedure

Without KOH: To illustrate the hydrogenation of ketoximes in the sole presence of 2-propanol and Raney Nickel® the procedure for the CTH of 2-octanone oxime will be used. A mixture of 2-octanone oxime (1.008g, 7.05 mmol) dissolved in

5 ml of 2-propanol was added slowly and dropwise to a mixture of Raney Nickel® (~5 g) in 20 ml of 2-propanol that was refluxing and magnetically stirring in a round-bottom flask over a hotplate. The reaction was refluxed for 3 hrs while open to the atmosphere. Workup consisted of decanting the organic layer from the nickel while hot, and the nickel was then refluxed and washed with 3 x 20 ml of 2-propanol. The organic layers were combined and underwent rotary evaporation and high vacuum to remove 2-propanol from the product. Product yield was determined to be 0.960 g (79.6%). An aliquot of sample was taken, filtered through Celite® to remove any traces of nickel, and transferred to an NMR tube where it was combined with the NMR solvent deuterated chloroform (CDCl$_3$). ^{1}H, ^{13}C-NMR analysis confirmed the identity of the intended amine product.

With 2% KOH: To illustrate the hydrogenation of ketoximes in the presence of 2% KOH, the procedure of the CTH of 2-octanone oxime will also be used. A mixture of 2-octanone oxime (1.004 g, 7.02 mmol) dissolved in 2% KOH dissolved in 2-propanol (5 ml) was added slowly and dropwise to a mixture of Raney Nickel® (~5 g) in 2% KOH dissolved in 2-propanol (20 ml) that was refluxing and magnetically stirring in a round-bottom flask over a hotplate. The reaction was refluxed for 1 hr while open to the atmosphere. Workup consisted of decanting the organic layer from the nickel while hot, and the nickel was then refluxed and washed with 3 x 20 ml of 2-propanol. The organic layers were combined and subjected to rotary evaporation and high vacuum to yield a mass of 3.12 g of imine product. Then 30 ml of 1 M HCl

was added to the reaction flask, and the mixture was heated, magnetically stirred, and refluxed for 30 min while open to the atmosphere. The flask was then cooled in an ice bath, and when at room temperature, 30 ml of 1 M NaOH was added to the mixture. Then 20 ml of diethyl ether was added to the flask to dissolve the organic layer, which would have included the amine product. The nonpolar layer was extracted by 2 x 20 ml of diethyl ether, and K_2CO_3 was added to dry the mixture. The contents of the flask were funnel filtered into another flask, and the organic matter underwent rotary evaporation and high vacuum to give 0.980 g of product (82.6% yield). An aliquot of sample was taken, filtered through Celite® to remove any traces of nickel, and transferred to an NMR tube where it was combined with $CDCl_3$. ^1H, ^{13}C-NMR analysis confirmed the identity of the intended amine product when compared to published spectra.

Conclusion

Within this study, ketoximes were successfully reduced to their corresponding amines in good yields under catalytic transfer hydrogenation conditions with Raney Nickel® and 2-propanol as hydrogen donor. Without KOH in the reaction, six ketoximes were reduced to their *N*-isopropyl-secondary-amines, and when KOH was present, one ketoxime was reduced to its imine and was ultimately converted to its primary amine.

Under CTH conditions, ketoxime reduction utilized a hydrogen donor as opposed to molecular hydrogen so that reactions were run in more manageable conditions without need of pressure containment for hydrogen gas. Additionally, using a liquid donor as opposed to a gas eliminated the production of a metal sludge with Raney Nickel® so that the catalyst could be used repeatedly without loss of activity. Thus, with our application of CTH to ketoximes, we were able to perform our reductions with efficient and practical methods within safe hydrogenation conditions, therefore providing another desirable avenue for amine synthesis.

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