DEVELOPMENT IN GREEN WOLFF-KISHNER REACTION

A MSc Dissertation report by:

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APRIL 2022

DEVELOPMENT IN GREEN WOLFF-KISHNER REACTION

Submitted in Partial Fulfillment

Of

The Degree Of M.Sc (Organic Chemistry)

By

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To the

School Of Chemical Sciences

Goa University

Goa 403206

APRIL 2022

DECLARATION

I declare that the literature review titled “**Development in Green Wolff-Kishner Reaction”** has been carried out by me in the Chemistry Department, School Of Chemical Sciences, Goa University, The information derived from the literature has been duly acknowledged in the text and a list of references is provided.

NIKHIL N. HUNDRE

CERTIFICATE

This is to certify that the literature review entitled:” **Development in Green Wolff-Kishner Reaction** “submitted by the student is the record of research work carried out by the candidate during the academic year 2021-2022 under my supervision in the partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

DR. Kashinath Dhumaskar
(project guide)

DR.Vidhyadatta Verenkar
(Dean, of SCS, Goa University)

ACKNOWLEDGEMENT

I would like to express my special thanks of gratitude to my teacher Dr Kashinath Dhumaskar as well as our dean Dr Vidhyadatta M. Shet Verenkar and vice-dean Dr Rajendra N.Sirsat who gave me the opportunity to this wonderful project on the topic'' DEVLPOMENT IN GREEN WOLFF-KISHNER REACTION'' which also helped me in doing a lot of research and I came to know about so many new things I am really thankfull to them.

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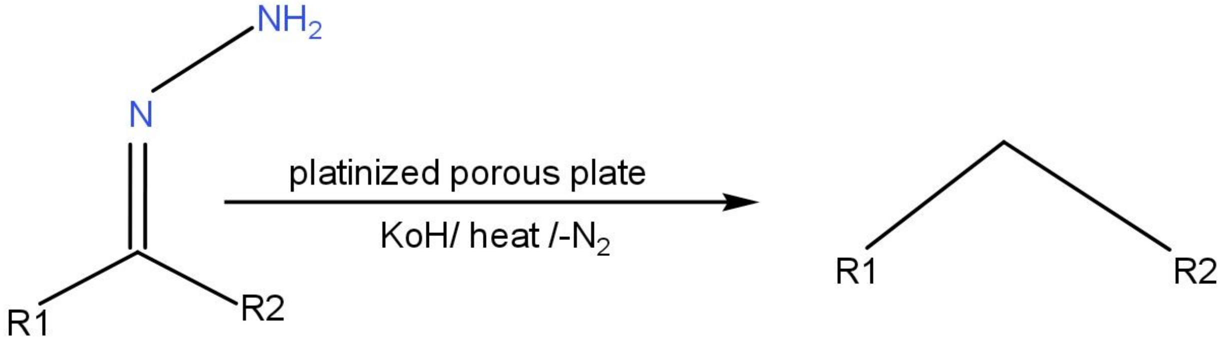
ABSTRACT

Wolff-Kishner is one of the important organic reaction to reduce carbonyl group to alkanes.In traditional Wolff-Kishner reaction uses very harsh and toxic condition. Efforts have been made to replace with more greener solvents .This review focuses on making the reader aware of this development toward green Wolff-Kishner reaction.

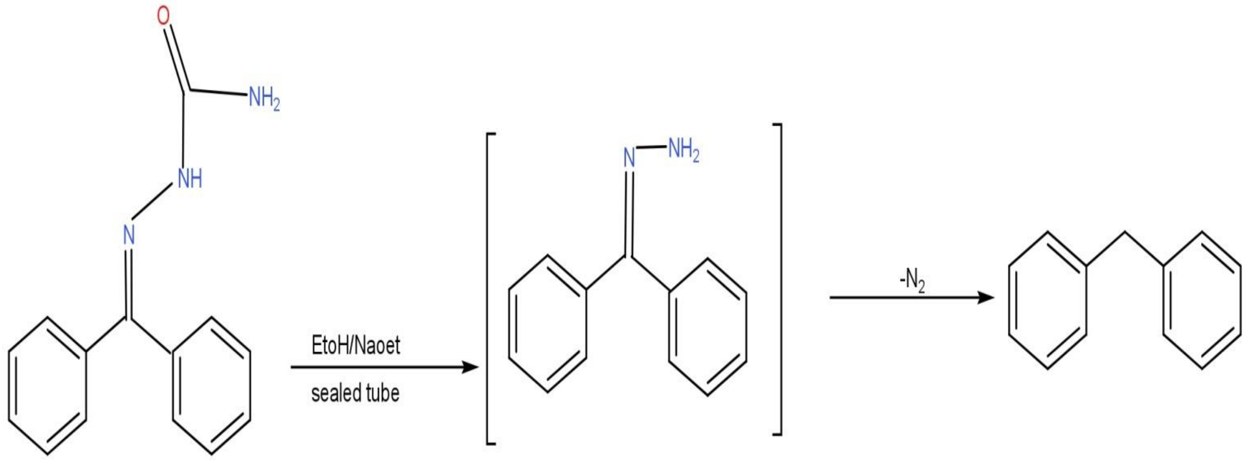
INTRODUCTION

Organic reactions plays a very important roles in industry and one of the important reaction is the Wolff -Kishner reduction which converts carbonyl functionalities into methylene groups .it was first reported independently by Russian scientist Nikolai matveevich kishner in 1911 and German chemist Ludwing wolff in 1912[1]. Nikolai matveevich kishner found, that addition of the preformed hydrazone to hot potassium hydroxide containing crushed platinized porous plate led to the formation of the corresponding hydrocarbon[2].

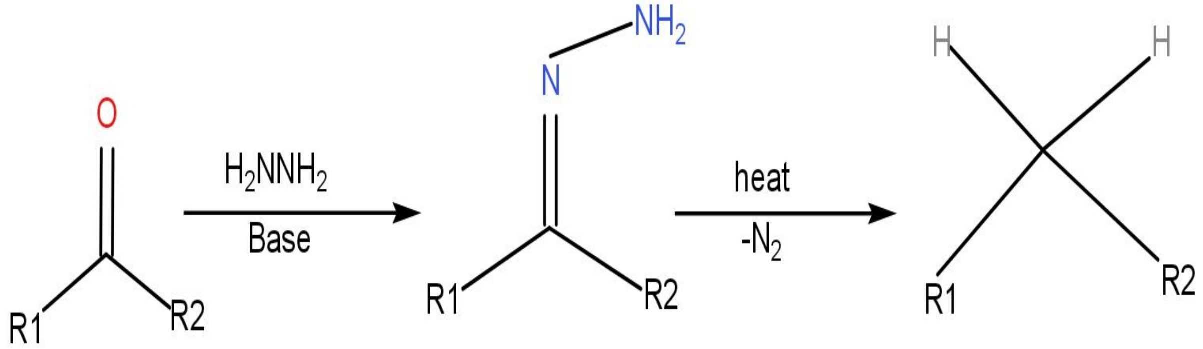


Scheme 1- Reduction of hydrazone to alkane in presence of platinized porous plate.

Later accomplished the same by result by heating the ethanol solution of Wolff semicarbazones or hydrazones in a sealed tube to 108 Celsius in presence of sodium ethoxide. the method developed by krishner has the advantage of avoiding the requirement of a sealed tube, but both the methodologies suffered from unreliability when applied to many substrates, these disadvantages promoted the development of Wolff's procedure, wherein the use of high – boiling solvents such as ethylene glycol and triethylene glycol were implemented to allow for the higher temperatures required for the reaction while avoiding the need of a sealed tube.[3,4]



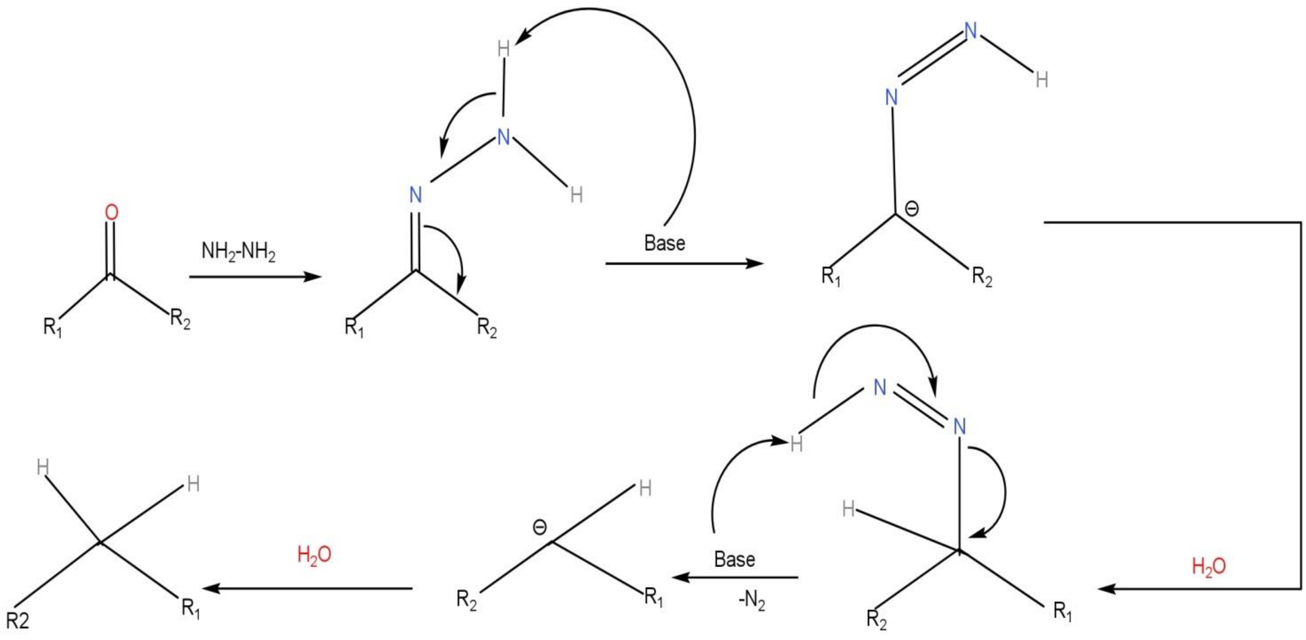
Scheme 2-Reduction of hydrazone in sealed tube in presence of sodium ethoxide.



Scheme 3- General Wolff-Kishner reduction

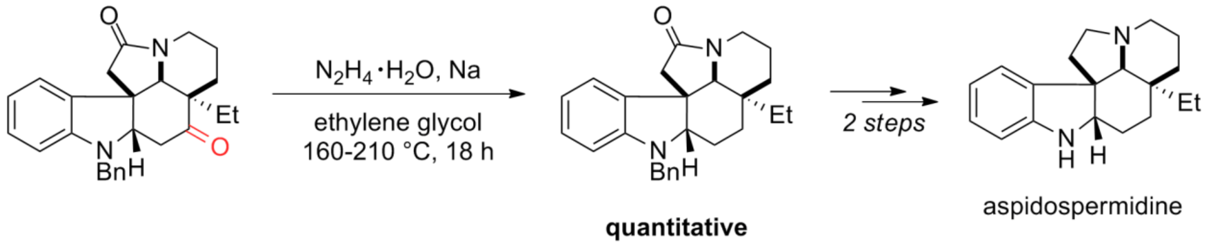
The mechanism of the Wolff–Kishner reduction has been studied by Szmant and coworkers.[5,6,7,8] According to Szmant's research, the first step in this reaction is the formation of a hydrazone anion by deprotonation of the terminal nitrogen by MOH. If semicarbazones are used as substrates, initial conversion into the corresponding hydrazone is followed by deprotonation[1]. A range of mechanistic data suggests that the rate-determining step involves formation of a new carbon–hydrogen bond at the carbon terminal in the delocalized hydrazone anion. This proton capture takes place in a concerted fashion with a solvent-induced abstraction of the second proton at the nitrogen terminal. Szmant’s finding that this reaction is first order in both hydroxide ion and ketone hydrazone supports this mechanistic proposal[9]. Several molecules of solvent have to be involved in this process in order to allow for a concerted process. A detailed Hammett analysis[5] of aryl aldehydes, methyl aryl ketones and diaryl ketones showed a non-linear relationship which the authors attribute to the complexity of the rate-determining step. Mildly electron-withdrawing substituents favor carbon-hydrogen bond formation, but highly electron-withdrawing substituents will decrease the negative charge at the terminal nitrogen and in turn favor a bigger and harder solvation shell that will render breaking of the N-H bond more difficult. The exceptionally high negative entropy of activation values observed can be explained by the high degree of organization in the proposed transition state.

It was furthermore found that the rate of the reaction depends on the concentration of the hydroxylic solvent and on the cation in the alkoxide catalyst. The presence of crown ether in the reaction medium can increase the reactivity of the hydrazone anion **1** by dissociating the ion pair and therefore enhance the reaction rate. The final step of the Wolff–Kishner reduction is the collapse of the diimide anion **2** in the presence of a proton source to give the hydrocarbon via loss of dinitrogen to afford an alkyl anion **3**, which undergoes rapid and irreversible acid-base reaction with solvent to give the alkane. Evidence for this high-energy intermediate was obtained by Taber via intramolecular trapping. The stereochemical outcome of this experiment was more consistent with an alkyl anion intermediate than the alternative possibility of an alkyl radical. The overall driving force of the reaction is the evolution of nitrogen gas from the reaction mixture.



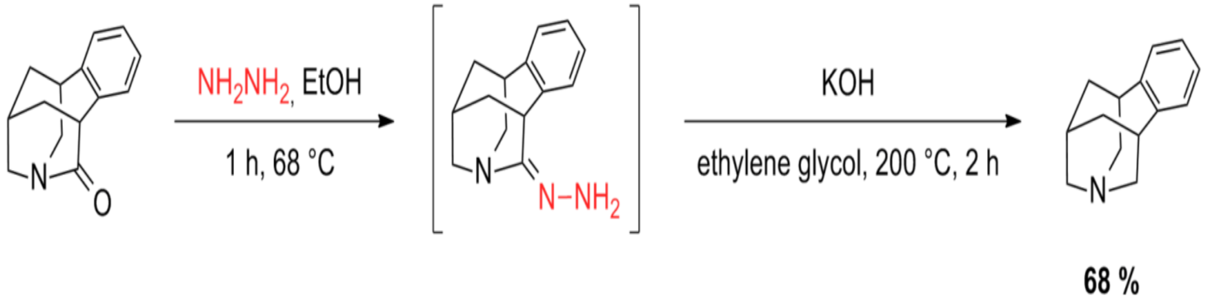
Scheme 4- general mechanism of Wolff-Kishner reduction

The Wolff–Kishner reduction has been applied to the total synthesis of scopadulcic acid B[10],aspidospermidine[11,12] and dysidiolide[13]. The Wolff–Kishner reduction is an effective tool in organic synthesis. For example, Ishibashi and coworkers employed the Huang Minlon modification of the Wolff–Kishner reduction as one of the final steps in their synthesis of (±)-aspidospermidine. Distillable material was removed after hydrazone formation at 160 °C and then heated to 210 °C overnight. The carbonyl group that was reduced in the Wolff–Kishner reduction was essential for preceding steps in the synthesis. The tertiary amide was stable to the reaction conditions and reduced subsequently by lithium aluminum hydride[12].



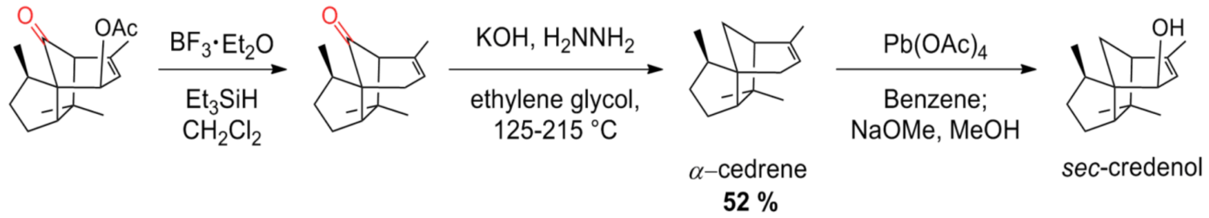
Scheme 5-Wolff-Kishner reduction of scopadulic acid B

Amides are usually not suitable substrates for the Wolff–Kishner reduction as demonstrated by the example above. Coe and coworkers found however that a twisted amide can be efficiently reduced under Wolff–Kishner conditions[14]. The authors explain this observation with the stereoelectronic bias of the substrate which prevents “anti–Bredt” iminium ion formation and therefore favors ejection of alcohol and hydrazone formation. The amide functionality in this strained substrate can be considered as isolated amine and ketone functionalities as resonance stabilization is prevented due to torsional restrictions. The product was obtained in 68% overall yield in a two step procedure.



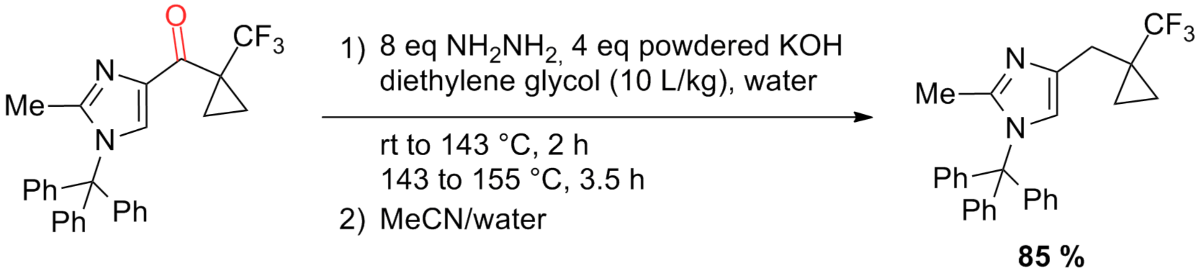
Scheme 6- Wolff-Kishner reduction of amides

In 2011, Pettus and Green reduced a tricyclic carbonyl compound using the Huang Minlon modification of the Wolff–Kishner reduction[15]. Several attempts towards decarbonylation of tricyclic allylic acetate containing ketone failed and the acetate functionality had to be removed to allow successful Wolff–Kishner reduction. Finally, the allylic alcohol was installed via oxyplumbation



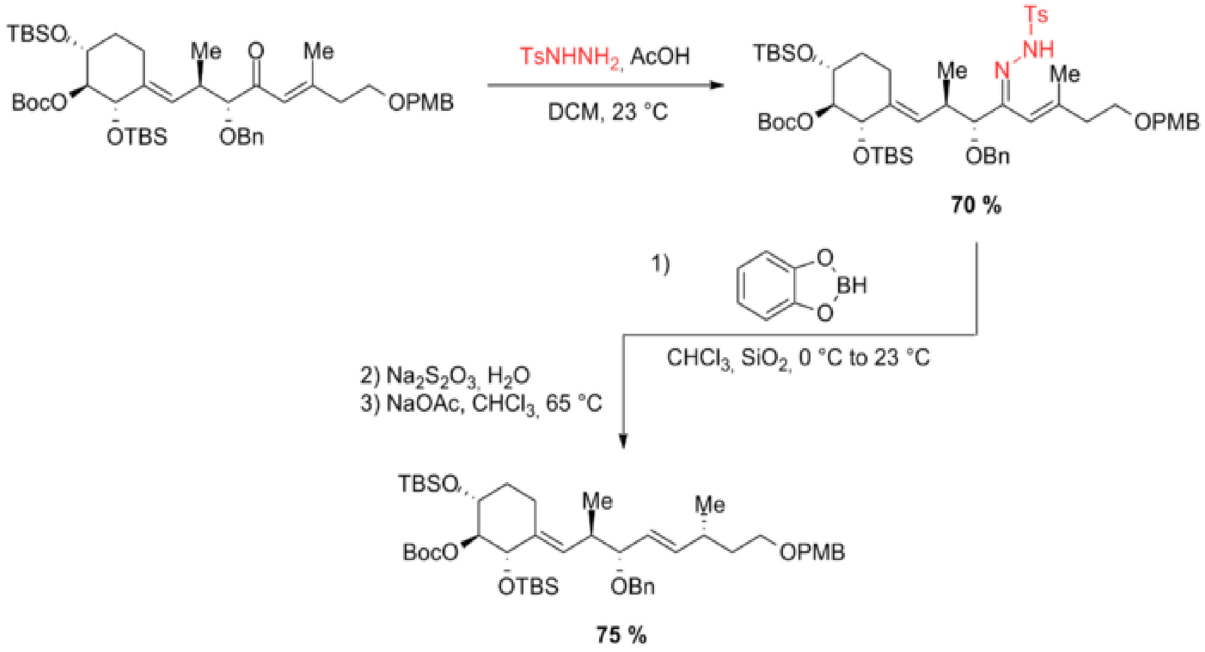
Scheme 7-Wolff –Kishner reduction of tricylic carbonyl compound.

The Wolff–Kishner reduction has also been used on kilogram scale for the synthesis of a functionalized imidazole substrate. Several alternative reduction methods were investigated, but all of the tested conditions remained unsuccessful. Safety concerns for a large scale Wolff–Kishner reduction were addressed and a highly optimized procedure afforded to product in good yield[16].



Scheme 8- Wolff-Kishner reduction of functionalised imidazole

McIntosh *et al.* used an allylic diazene rearrangement in their synthesis of the C_{21}–C_{34} fragment of antascomicin B[17]. The hydrazone was reduced selectively with catecholborane and excess reducing agent decomposed with sodium thiosulfate. The crude reaction product was then treated with sodium acetate and heated under reflux in chloroform to give the 1,4-*syn* isomer.



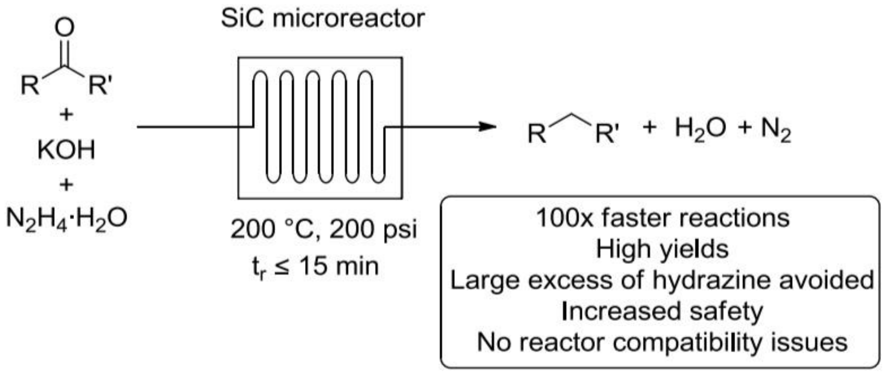
Scheme 9- Wolff-Kishner reduction of antacosmicin B

LITERATURE REVIEW

1.Rapid Wolff-Kishner Reductions in a Silicon Carbide Microreactor

Wolff-Kishner reductions are performed in a novel silicon carbide microreactor. Greatly reduced reaction times and safer operation are achieved, giving high yields without requiring a large excess of hydrazine. The corrosion resistance of silicon carbide avoids the problematic reactor compatibility issues that arise when Wolff-Kishner reductions are done in glass or stainless steel reactors. With only 10 nitrogen gas and water as by-products, this opens the possibility of performing selective, large scale ketone reductions without the generation of hazardous waste streams.

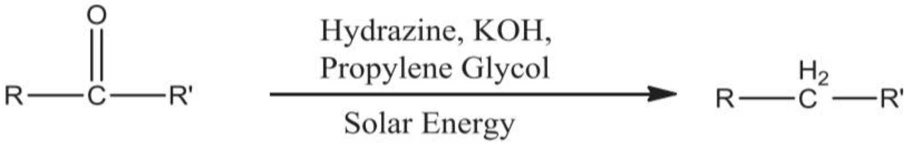
Despite these reports, there are many challenges 40 encountered in the Wolff-Kishner reduction. For instance, dangerous anhydrous hydrazine may be required. Pre-formation and isolation of thehydrazone intermediate is sometimes necessary, making formation of azine by-products a significantissue. From a scale-up point of view, there are many safety 45 hazards associated with accumulation of explosive gaseous hydrazine in the reactor headspace. Moreover, reactor compatibility can be problematic. Hydrazine decomposition can be catalyzed by metals, so contact with stainless steel should generally be avoided. Glass is also undesirable due to the ability of strong base to etch the surface at elevated temperatures. Many other methods for performing similar ketone and aldehyde reductions exist. The Clemmensen reduction, using stoichiometric zinc, is a complimentary acidic reaction.The use of silanes or borohydrides along with a Lewis acid is also common. These and most other methods all have large waste streams, making them particularly environmentally unfriendly and costly on large scale. For example, researchers at Eli Lilly recently performed a TFA-promoted triethylsilane reduction of a diaryl ketone to the corresponding methylene on 100 mol scale; however an alternative route was sought due to challenges associated with the disposal of the fluoride and silane waste.Catalytic reduction with hydrogen gas is the greenest method, but suffers from limited scope and functional group compatibility.While the Wolff-Kishner reduction uses inexpensive hydrazine as a reducing agent and generates only water and nitrogen gas as waste products, alternative reduction methods are often chosen due to issues with high temperatures, high pH, reactor incompatibility, the need for multiple stages, and potential decomposition of hydrazine. However, most flow reactors are prepared out of base-sensitive silicon or glass, thermally sensitive polymer tubing, or steel that may react with hydrazine. To overcome these materials limitations, we designed a microreactor prepared from sintered silicon carbide (SiC).and reason we chose silicon carbide is a ceramic material with exceptional chemical compatibility, temperature stability, and thermal conductivity. In chemical synthesis, Kappe and co-workers used a microwave vial made out of SiC to perform high temperature chemical reactions which would corrode typical Pyrex microwave vials. Industrial flow reactors constructed of SiC have recently been commercialized by Boostec and ESK allowing access to otherwise 'forbidden' chemistries on large scale. Microreactors prepared out of robust ceramic materials are known; however, to our knowledge, none have been generally applicable for fine chemical synthesis. As such, we wanted to design a universally corrosion resistant microreactor constructed of SiC for the purpose of small scale reaction development. Such reactors would facilitate development of chemistries that may otherwise be impossible in traditional glass or metal reactors, without needing to commit the large amounts of material necessary to operate industrial scale SiC reactors[18].



Scheme 10- Wolff-Kishner reduction in silicon carbide microreactor.

2.Wolff–Kishner reduction reactions using a solar irradiation heat source and a green solvent system

Due to the recognition of the irreversible damage done to the environment through man-made materials, scientists have attempted to transform synthetic procedures into environmentally favorable procedures. Since fossil fuels are used for electrical energy in the USA, the amount of electricity required to complete an experiment has become an environmental concern. Solar parabolic reflectors have been proposed as a means for minimizing the amount of electricity needed to perform chemical reactions. The ability to use the solar reflector as the sole heat source for synthetic reactions is being considered. Another area of environmental concern is the chemical solvent systems involved in synthetic reactions that are not friendly to the environment. The ability to exchange solvent systems for greener solvents is being considered. A comparative study was conducted using an electrical and solar heat source on a series of Wolff–Kishner reduction reactions performed in a green solvent system. The following generalized chemical reaction is representative:



Scheme 11- Wolff-Kishner reduction using solar energy and propylene glycol.

where R is a hydrocarbon chain and R’ is a hydrocarbon chain or hydrogen.

The main aim of this experiment was to use a good ecofreindly source and green solvent for wolff kishner reaction so there are three devices in these studies use sunlight-collecting devices to collect energy from the sunlight and

use them as heat sources for chemical reactions. A recent publication examined three different solar reactors that could potentially be used for photochemical synthesis. The first solar reactor was *PROPHIS*, which is a line-focusing parabolic trough collector that is capable of following the sun by a three-dimensional tracking system. The *PROPHIS* solar collector works by collecting energy from the sun, and through a heat exchanger, transfers the energy to the reaction vessel . The second sunlight-collecting device that was examined was the *COMPOUND PARABOLIC COLLECTOR (CPC)* reactor. This system is capable of using part of the diffuse solar radiation; however, it is incapable of tracking the sun. The CPC reactor is run with a fixed slope of 50° to the position of the sun, and reaction mixtures are passed through the absorber tubes during the experiment. For overnight reactions, the reactor is covered with a plastic foil to help maintain heat to the system. The third sunlight-collecting device that has recently been examined was the *DOUBLE-SHEET FLAT BED* reactor. The main advantages of this solar collector are the simple design and ability to use direct and diffuse solar radiation. Like the CPC collector, this design is also non-mobile, and is at a fixed slope of 30° to the position of the sun. Due to the design of this collector, two major disadvantages were observed: reacting components were not properly mixed and the solution solidified overnight during the cold weather month.

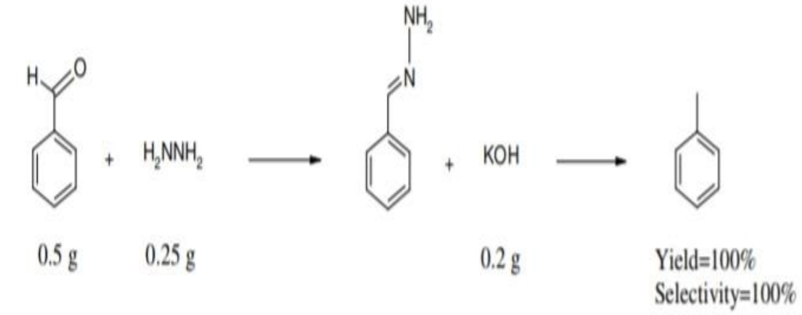
Most chemical reactions that are currently known must be performed in a chemical solvent system. Many chemical solvents involved in synthetic organic reactions are not friendly to the environment. For instance, Wolff–Kishner reduction reactions typically use a solvent system that is comprised of ethylene glycol or diethylene glycol (DEG). DEG has been observed in rat models to be metabolized in the liver into a hydrogen ion, NADH, and 2-hydroxyethoxyacetaldehyde. The enzyme alcohol dehydrogenase (ADH) then metabolizes 2-hydroxyethoxyacetaldehyde into the weak acid 2-hydroxyethoxyacetic acid (HEAA), which is partially filtered in the kidneys for elimination . Ethylene glycol, however, is very toxic and is metabolized into oxalic acid, which has toxic effects through contact and ingestion, targeting the kidneys, nerves, blood, and eyes . Because of this there is a need to attempt to exchange the current protocol for the Wolff– Kishner reduction reaction for a more green method. A more environmentally friendly solvent for Wolff–Kishner reduction reactions would be propylene glycol. Acute oral toxicity of propylene glycol is very low, and large quantities are required to cause health damage in humans. Furthermore, propylene glycol is metabolized in the human body into pyruvic acid, which is a normal part of the glucosemetabolism process . Yet another benefit of exchanging ethylene glycol for propylene glycol is the cost difference between the two solvents. Currently, the US dollar cost of propylene glycol is slightly less than the price of ethylene glycol per pound of chemical . Therefore, it is believed that propylene glycol could potentially be a replacement for more environmentally unfriendly solvents such as ethylene glycol.

The experiment was carried using light as heat source and In order to gather data on how much heat the solar dish could generate, several high-boiling organic compounds were tested to determine whether enough heat could be generated to get the organic solvents to boil.many wolff kishner reduction reaction on many molecules were carried out like acetophenone, propiophenone, isobutyrophenone, butyrophenone, benzophenone etc.the results obtained by using light as a heat source provided a reliable, efficient alternative heating source that produced similar results to its electrical counterpart study[19].

3.Glycerol as an alternative green medium for carbonyl compound reductions.

Glycerol is the main by-product of oil and fat conversion in oleochemical production. The increased production and use of fatty acid derivatives over the past decade in the food, cosmetics, and drugs industries and in the synthesis of biofuel, i.e., biodiesel, has led to a growth in the supply of glycerol and a subsequent dramatic decrease in its price. Glycerol is a non-toxic, biodegradable, and recyclable liquid that is highly inert and stable, and compatible with many other non-toxic and non-irritating chemicals. These qualities make it ideal for use as a humectant, plasticizer, emollient, thickener, dispersing medium, lubricant, sweetener, bodying agent, antifreeze, and processing aid. Glycerol has been approved for food and drug use by many government agencies and is used as an ingredient or processing aid in cosmetics, toiletries, personal care, drugs, and food products. In addition, glycerol derivatives such as glycerol esters are also extensively used in many industries Glycerol is also a raw material in several chemical syntheses, including dendrimer and hyperbranched polyether and polyester production catalytic hydrogenolysis to propylene glycols, especially 1,3-propanediol, a high value chemical in the synthesis of polyesters, and catalytic oxidation to form important compounds such as dihydroxyacetone and glyceraldehydes The use of glycerol as an energy source for microorganism fermenting systems, yielding ethanol and hydrogen, was also reported. However, whether employed as a reactant or as an additive, glycerol is usually used as a highly refined and purified product. And as the amounts of glycerol generated by the biodiesel industry continue to grow, it is vital that economical ways of utilizing it be explored to further defray the cost of biodiesel production.

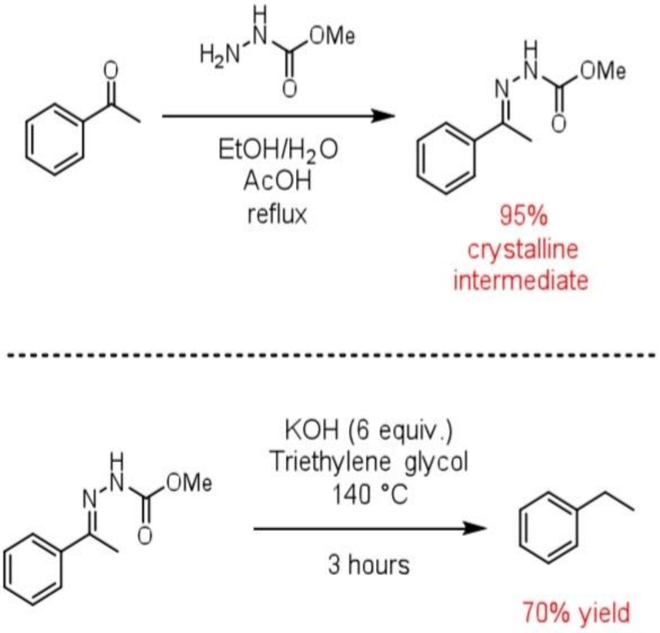
benzaldehyde can also be fully reduced to toluene with hydrazine in basic conditions via the Wolff-Kishner reaction. Although usually conducted at elevated temperatures (about 200 °C) for hours, it can also be performed under microwave irradiation at lower temperatures and in much shorter times. As noted above a solvent is also utilized to transport heat. In microwave assisted heating, solvent selection is even more crucial. Microwave heating has many applications in organic synthesis as it is clean and it substantially reduces reaction times. Microwave promoted organic synthesis is based on the ability of a solvent to absorb microwave energy and convert it into heat, an ability that increases with increasing dielectric constants. Therefore, glycerol's high dielectric constant and high boiling point make it an attractive solvent. The microwave assisted reduction of benzaldehyde to toluene was performed in two steps using a conventional microwave oven. First, benzaldehyde and hydrazine were dissolved in glycerol and heated in the microwave oven for 5 min from room temperature to about 110 °C. Then the reaction mixture was cooled to room temperature in an ice bath, and KOH was added. Finally, the mixture was again heated for 5 min in the microwave oven. The reaction conversion was complete after 10 min in the microwave. Again, the product was easily separated by extraction with diethyl ether and evaporation of the solvent under reduced pressure[20].



Scheme 12- Wolff-Kishner reduction of benzaldeyde to tolune in glycerol.

4. A hydrazine free wolff-kishner reaction in undergraduate laboratory

A Wolff–Kishner reaction that does not require hydrazine has been developed. The reaction sequence has two steps; formation of a carbomethoxyhydrazone from methyl hydrazinocarboxylate and 10 acetophenone, then decomposition of this intermediate by treatment with potassium hydroxide in triethylene glycol. Purification is by filtration through a plug of silica encased in the barrel of a plastic syringe. The reaction sequence can be completed within a day-long laboratory class (8 hours)[21].



Scheme 13- Hydrazine-free Wolff-Kishner reduction

CONCLUSION

Wolff-Kishner reaction is one of the important organic reaction to reduce carbonyl group to alkanes.the traditional Wolff-Kishner reaction uses very harsh condition and toxic solvents like ethylene glycol .Efforts have been made to replace this toxic solvent with more greener solvents like propylene glycol,glycerol and use of solar energy as a heat source is also promoted.

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