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The Photolytic Deprotection of Aliphatic Ketones from Tosylhydrazones

Joseph Patapas

A Thesis
in
the Department
of
Chemistry and Biochemistry

Presented in Partial Fulfillment of the Requirements
For the Degree of Master of Science at
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ABSTRACT

The Photolytic Deprotection of Aliphatic Ketones from Tosylhydrazones

Joseph Patapas

Ketones are amongst the most important and versatile groups of chemicals known, with applications in industry as solvents and starting materials, as well as playing an important role in biological and medicinal applications. With their importance for synthetic chemists, the search for means of protecting ketones is ongoing.

Tosylhydrazones have been suggested as such a means because they are easily formed through a simple condensation reaction between the ketone and p-tolysulfonylhydrazine, and they are resistant to many chemical conditions. Despite this, tosylhydrazones have seen little use as a protecting group, largely due to the difficulty of removing them.

This study investigated the deprotection of ketones from tosylhydrazones by irradiating a solution of the tosylhydrazone with visible light, in the presence of chloranil. In addition to ketone, a precipitate byproduct and nitrogen gas was produced. Depending on the experimental procedure, ketone was regenerated quantitatively.

The effect of several factors on the rate of ketone regeneration were investigated, among them were light intensity, solvent, initial concentrations of tosylhydrazone and chloranil and secondary reaction products.

Several factors elucidating to the reaction mechanism were probed. The first was the source of oxygen in the regenerated ketone, with three sources probed (air, water and the tosyl group). The second factor was the participation of a tosylhydrazone radical cation, with investigations into its independent generation and trapping, and computational studies on the tosylhydrazone and its radical cation. The final factor investigated was the nature of the secondary reaction products. A reaction mechanism was proposed based on experimental and computational data.

Acknowledgements

At the risk of sounding like I'm giving an Academy Award acceptance speech, I would like to express my deepest appreciation to my current supervisor Dr. Heidi Muchall and my previous supervisor Dr. Tim Gadosy, for their encouragement, advice, support, and patience. I have received the best training possible, and for this I am forever grateful. I would also like to extend my appreciation to Dr. Peter Bird and Dr. Gilles Peslherbe for sitting on my committee.

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I would like to say cheers to my closest friends: Alvira, Ann, Cyril, Dirk, Julie, Marika, Nabil, Phil and Raph. The last few years have been memorable thanks to you guys. Thanks for great moments, inane and insane conversation and wonderful experiences. Though many of us will soon be far away from home, I know our friendships will endure and there are more good times to come.

Last but not least, I want to thank my parents who supported me emotionally and financially. Thanks for your love and support, and for always encouraging me when things looked bleak. I hope I have made you proud.

This thesis is dedicated to my parents:

Carolyn Corbett-Patapas & Victor Patapas

For nurturing a young child's curiosity about the world,

and encouraging him to explore the universe in which he lived

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List of Schemes

List of Abbreviations

Å	Angstrom
amu	Atomic mass units
arom	Aromatic
as	Asymmetric
BET	Back electron transfer
d	Doublet
EDA	Electron donor-acceptor
GC	Gas chromatography
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
IC	Internal conversion
IR	Infrared
ISC	Intersystem crossing
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
MG	Methylene green
MS	Mass spectrometer
NMR	Nuclear magnetic resonance
oop	Out of plane
s	Singlet
sm	Symmetric

t	Triplet
TAP	Triarylpyrylium salt
TBAHFP	Tetrabutylammonium hexafluorophosphate
TBME	Tert-butyl methyl ether
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxy
TLC	Thin layer chromatography
Ts	Tosyl group
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible

1 INTRODUCTION

1.1 Fundamental Concepts of Photochemistry

1.1.1 Absorption of Light and Molecular Excitation

Photochemistry arises because certain molecules are able to absorb visible, ultraviolet, and in some cases, infrared light of a specific wavelength. The ability of a molecule to absorb light in the ultraviolet-visible region of the electromagnetic spectrum is determined by its chromophores.[1] Upon absorption of a photon, one electron from the highest occupied molecular orbital (HOMO) of the molecule is transferred to the lowest unoccupied molecular orbital (LUMO).[2] Prior to this transfer the molecule is said to be in the ground state, and in the excited state once the transfer has occurred (Figure 1.1). Only in the excited state can photochemical reactions take place.[1]

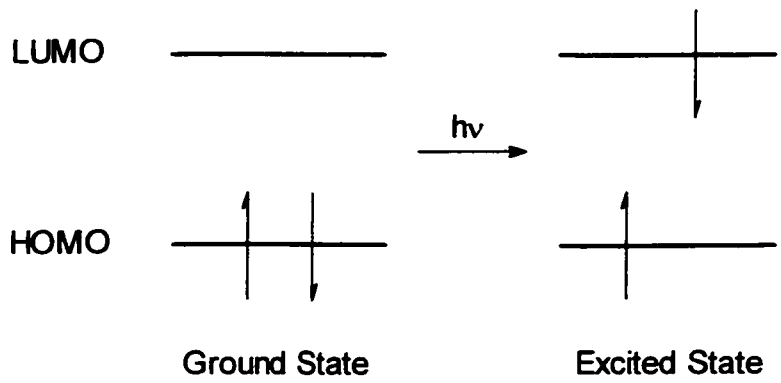
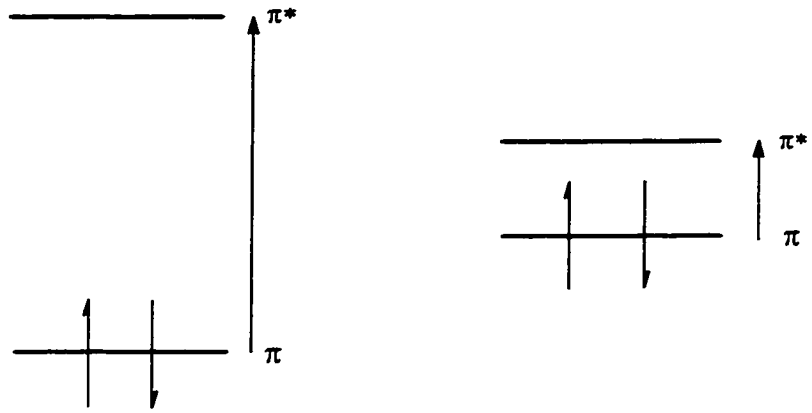


Figure 1.1: Electronic configurations of a molecule upon excitation

The exact wavelength of light needed to effect the transition from ground state to excited state is largely determined by the energy gap between the HOMO and the LUMO. Molecules with a smaller energy gap are excited by light with less



1,3-Butadiene: Large energy gap
λ_{max} = 217 nm

β-Carotene: Small energy gap
λ_{max} = 455 nm

Figure 1.2: Comparison of energy gaps of compounds with high and low levels of conjugation

energy and longer wavelengths (λ) than molecules with larger energy gaps (Figure 1.2).[3] If the incident light is not of the wavelength corresponding to the energy gap, then excitation of the electron does not occur.[1] Small energy gaps are often found in molecules with atoms containing nonbonding electrons (such as nitrogen and oxygen) and having a high level of conjugation (alternating single and multiple bonds with overlapping p orbitals). The compound β-carotene contains eleven double bonds in conjugation, whereas 1,3-butadiene has only two double bonds in conjugation. This results in β-carotene having a smaller energy gap than 1,3-butadiene and absorbing light of a longer wavelength (λ_{max} = 455nm for β-carotene, λ_{max} = 217nm for 1,3-butadiene).[2] The wavelength of light absorbed results in the color of the compound observed. 1,3-Butadiene appears colorless because it absorbs light in the ultraviolet region, whereas β-carotene

appears orange due to absorption in the blue region of the visible spectrum. This demonstrates that colored compounds have smaller energy gaps and are excited by absorbing lower energy light than their colorless counterparts.[2,3]

1.1.2 Fate of the Electronically Excited Molecule

The terms "ground state" and "excited state" are often in reference to the electronic ground and excited states. Energy absorbed by a molecule may contribute to vibrational and rotational excitation as well. The energy levels for vibrational and rotational excitations are very close; ground state molecules are a collection of species with different rotational and vibrational levels. Electronic excitation can occur from any of these levels and excited molecules are created with different rotational and vibrational levels (Figure 1.3).[1]

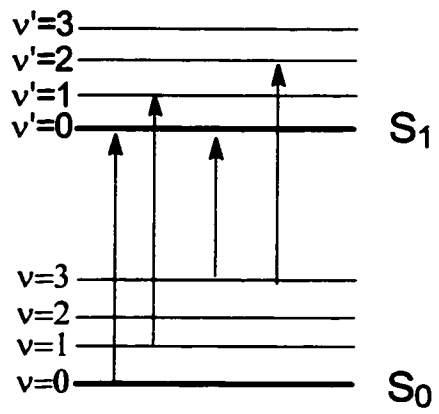


Figure 1.3: Excitation from the ground state (S_0) to excited state (S_1) occurring between different vibrational levels (v)

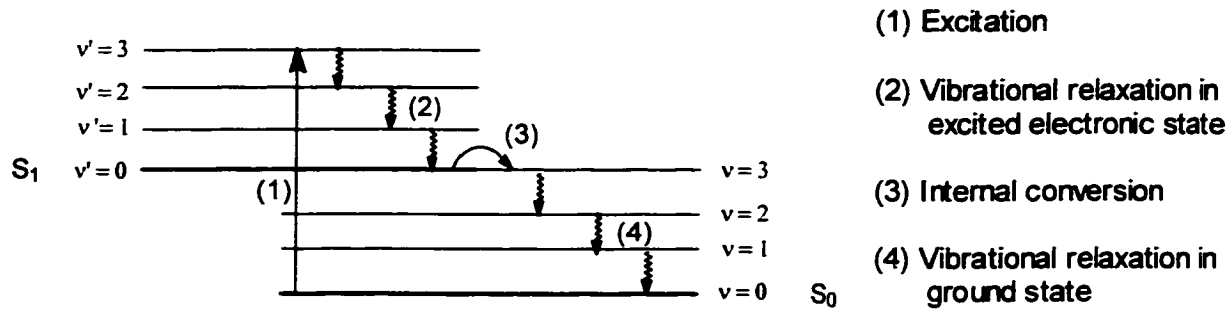


Figure 1.4: Relaxation to ground state via non-radiative heat loss

If a chemical reaction does not occur once the molecule is in the excited state, then the molecule quickly reverts back to the ground state. This is known as internal conversion.[4] There are several processes that can occur to accomplish this, the first is via non-radiative heat loss (Figure 1.4).[1,4,5] The excited molecule will relax to the lowest vibrational and rotational level in the excited state. This process called vibrational relaxation (or rotational relaxation in the case of the rotational energy levels) releases heat corresponding to the energy difference between vibrational (or rotational) states. Internal conversion then occurs and the process continues through the vibrational and rotational levels of the ground state. In the end the energy released via heat is equal to the energy difference between the initial level in the excited state and the final level in the ground state.[1,5]

An alternative to non-radiative heat loss is the emission of a photon, a process known as fluorescence.[1,4,5] This can occur instantly (Figure 1.5), emitting a photon of energy equal to that of the absorbed photon, or after a series of relaxations to a lower vibrational and rotational level (Figure 1.6), in which the photon emitted will have less energy than the photon absorbed.

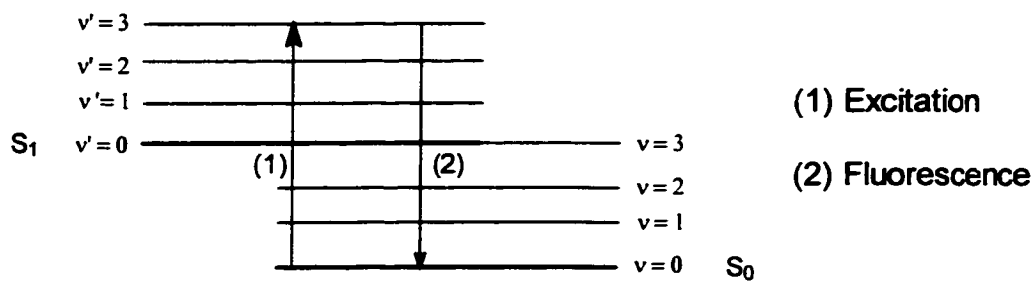


Figure 1.5: Direct fluorescence without vibrational relaxation

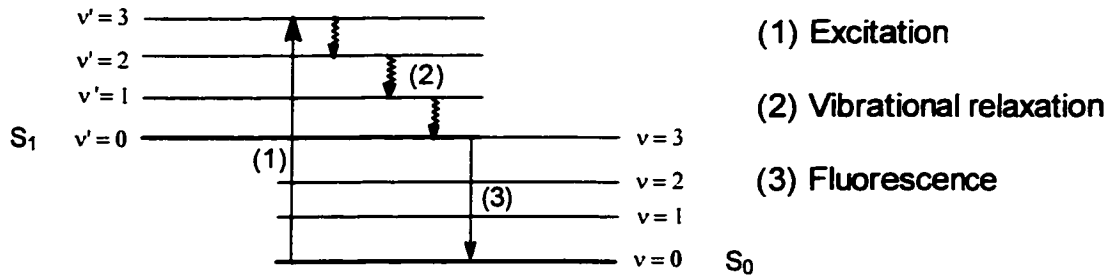


Figure 1.6: Fluorescence after vibrational relaxation cascade to the lowest electronically excited singlet state

The third process for the return of an excited electron back to the ground state involves the electron inverting its spin, and is known as intersystem crossing.[1,4,5] In the ground state most molecules have all their electrons paired with opposite spin. The molecule is said to be in the singlet state or has a multiplicity of one.[1] Upon excitation the excited electron usually maintains its spin number, and the excited molecule maintains its multiplicity. Sometimes the excited electron will invert its spin and the molecule is in the triplet state or has a multiplicity of three (Figure 1.7).[1,5] The triplet excited state of a molecule is

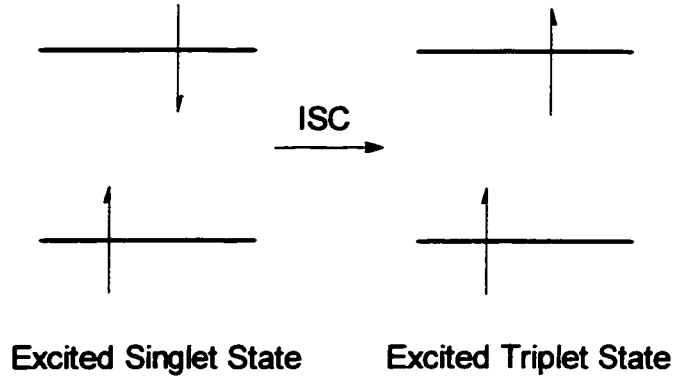


Figure 1.7: Electronic configurations of the excited singlet and triplet states

thermodynamically favored since the lowest vibrational/rotational level of the excited triplet state is lower in energy than the lowest vibration/rotational level of the excited singlet state.

Once in the excited triplet state, the molecule can either loose energy thermally (vibrational/rotational relaxation), undergo a photochemical reaction, or emit a photon.[1,5] The luminescent process going from the excited triplet state to the singlet ground state is referred to as phosphorescence (Figure 1.8). Analogous to fluorescence, phosphorescence exhibits two major differences. First

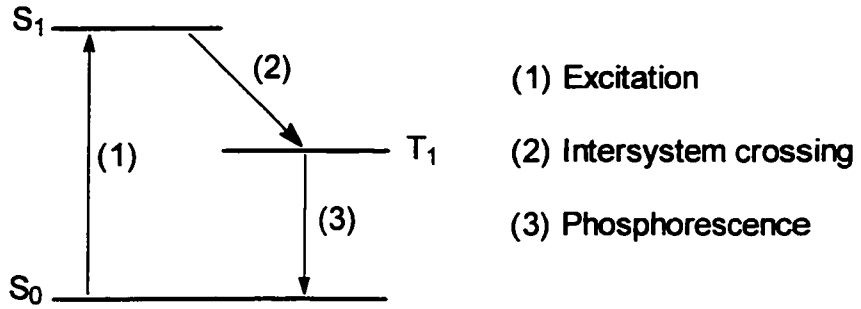


Figure 1.8: Representation of the processes leading to phosphorescence

the photon emitted always has less energy than the photon absorbed, due to energy being lost in the transition between multiplicities. Second, the lifetime of an excited triplet state molecule is longer than that of an excited singlet state molecule, resulting in longer time for phosphorescence to occur ($t \sim 10^{-8}$ seconds for fluorescence, $t \sim 10^{-4} - 10$ seconds for phosphorescence). It is this long lifetime of the excited triplet state that allows many photochemical processes to occur. [1]

1.1.3 Photosensitization

Many photochemical reactions are photosensitized. Photosensitization involves a photosensitizer (sometimes called a sensitizer in the literature), a compound that in some manner facilitates the reaction.[1,4,6] The photosensitizer can be either a free molecule in solution or covalently tethered to the reactant molecule itself,[7] (A molecule is said to be self-sensitizing, if it contains a chromophore that absorbs light and engages in a photoreaction by itself)[8] and will usually exhibit a high level of conjugation, such as in a dye or pigment.[2] A criterion that needs to be met by a photosensitizer is the ability to undergo intersystem crossing from the excited singlet state to the excited triplet state, since the reactant molecule is incapable of doing so due to the large gap between the excited singlet and triplet states. The relatively long lifetime of the excited triplet is required for the necessary interactions between photosensitizer and reagent to take place.[1,9]

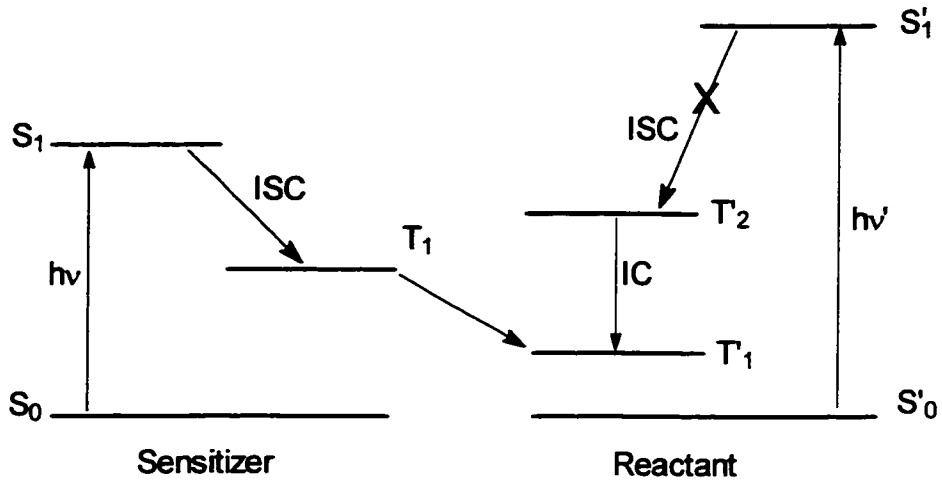
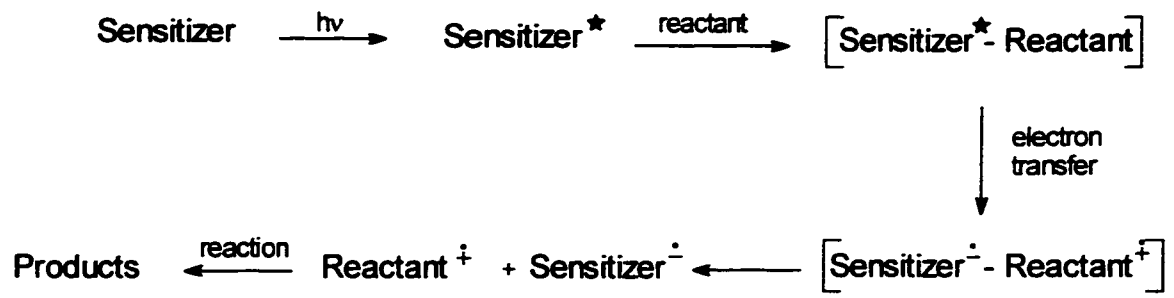


Figure 1.9: Photosensitized excitation process of a reactant molecule

There is some ambiguity in the literature as to what is a photosensitized reaction. The generally accepted definition is that of a reaction in which one molecule absorbs a photon, enters the excited singlet state, undergoes intersystem crossing to the excited triplet state, and transfers that energy to a reactant molecule which is then excited to the triplet state (Figure 1.9). The sensitizer molecule reverts to the singlet ground state while the reactant molecule engages in a photochemical reaction.[1,4-6,8,9] In solution, often the two species will interact forming a charge transfer complex which dissociates once electron transfer is completed.[1,8]

Though there is consensus that this constitutes a photosensitized reaction (sometimes referred to as triplet sensitization), other types of reactions are also referred to as "photosensitized". One such reaction is known as photoinduced electron transfer or photooxidation/photoreduction reaction (Scheme 1.1).[1,5,9] This

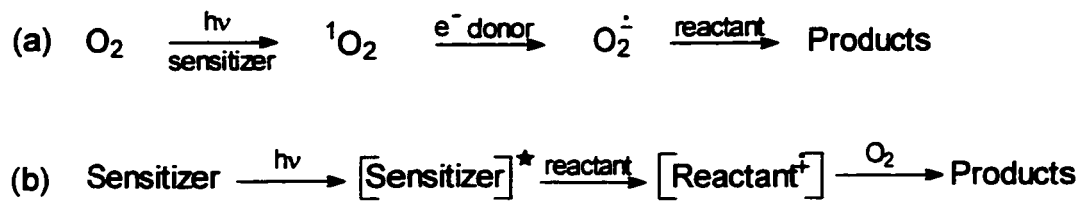


Scheme 1.1: Photoinduced electron transfer

reaction occurs because a molecule in the excited state is both a better oxidant and a better reductant.[9] The ability to reduce arises from the lone electron that was promoted to what was once the antibonding orbital, and now is located in a high energy position. The ability to oxidize arises from the creation of a "hole" in what was once the HOMO of the ground state species. What determines whether an excited species oxidizes or reduces is the redox potential of the photosensitizer, the donor or acceptor species involved in the reaction, and the singlet energy of the photosensitizer.[1,9]

Photooxygenation, a second photochemical process that is often classified as a photosensitized reaction, is a photochemical reaction involving molecular oxygen (Scheme 1.2).[1,8] Photooxygenation has three classes; the first is not sensitized, the second involves a singlet oxygen sensitizer (a molecule that upon irradiation generates singlet oxygen) and the third class is initiated by the sensitizer absorbing light, entering the excited state and oxidizing a substrate. This class of photooxygenation can therefore also be considered a photooxidation

since the radical cation substrate subsequently reacts with oxygen, generating the products.[8]



Scheme 1.2: Photooxygenation processes: (a) class 2 photooxygenation, (b) class 3 photooxygenation

1.2 Protecting Groups

Often in organic synthesis a molecule will have multiple functional groups. At times, one functional group will interfere with an intended reaction with another functional group located elsewhere in the molecule. When such a situation arises it can sometimes be remedied with the insertion of a protecting group. The protection process involves converting the interfering functional group into an inert or less reactive form, allowing the reaction to take place unimpeded. Once the desired reaction has occurred, the protecting group is removed and the original functionality of the molecule is re-established.[10]

There are certain criteria that must exist for an ideal protecting group. First, it should be easily introduced to the molecule, reacting selectively and giving a high yield of protected substrate. Ideally the protective group should form a crystalline derivative, without any new chiral centers, which can easily be separated from any side products. The protective group should be stable throughout the reaction sequence, a result of having a minimum of additional functionality. Upon completion of the desired modification, the protective group should be easily removable by readily available, preferably non-toxic reagents, which do not affect any of the functional groups on the molecule. Finally, the protecting group should be easily separated from the molecule once deprotection has occurred.[8,10] Very few protecting groups satisfy all the aforementioned criteria, especially for larger molecules with a multitude of different functional groups. Thus synthetic chemists are often required to employ a combination of different protective methods. It is for this reason why new and more efficient

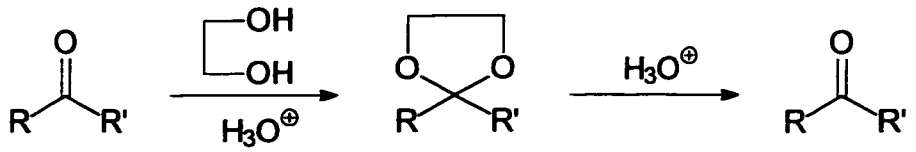
protection/deprotection methods are being developed and becoming available for use on many different functional groups.[10]

1.2.1 Protecting Groups for Ketones

The carbonyl group is one of the most important functional groups, making ketones one of the most important and versatile chemicals known.[11] Ketones are used industrially as solvents and as starting materials for a wide variety of products. In nature many substances required for living systems are ketones, and thus ketones play a significant role in biological and medicinal applications.[12]

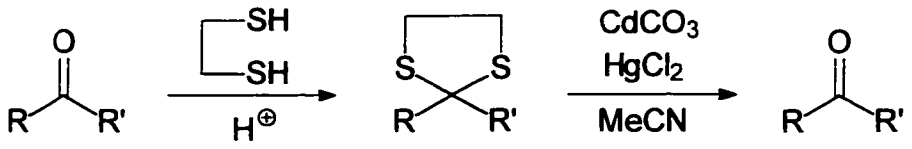
The versatility and practicality of ketones arises partially due to their rich chemistry. Ketones are sensitive to attack from various reagents, most notably moderate to strong nucleophiles (amines, carbenes, alcohols, organometallics, etc), reducing agents (hydridic, acidic, basic, or catalytic), and some oxidants such as potassium permanganate.[2,3,12] As a result of the importance of ketones and their susceptibility to different reagents, much work has gone into developing protective groups for the carbonyl moiety.

Ketones are most commonly protected by converting the carbonyl group to a ketal or a thioketal.[10,11] While both acyclic and cyclic ketals and thioketals can be formed, the cyclic versions are more common. Converting the carbonyl group to a ketal involves treating the ketone with either an alcohol or a diol (often ethylene glycol) in the presence of an acid catalyst (Scheme 1.3).[2,10,11] Removal of the ketal is accomplished by reaction with aqueous acid. The ketals are stable to most oxidants; aqueous and non-aqueous bases; reduction by hydrides,



Scheme 1.3: Formation and removal of a ketal from a ketone

catalysts and sodium in ammonia; and nucleophiles, including organometallic reagents,[11] though organolithium compounds and Grignard reagents have been known to cleave ketals under specific conditions.[11,13,14] Though a ketal is affective protection for many chemical processes, it finds its limitations in the use of acid in both the introduction and removal of the protecting group. Any moieties sensitive to acids can undergo unwanted modification.[11,12] In addition, should the process from which the carbonyl is being protected involve acidic conditions, then the protecting group can be prematurely cleaved and thus rendered useless for that process.



Scheme 1.4: Formation and removal of a dithioketal from a ketone

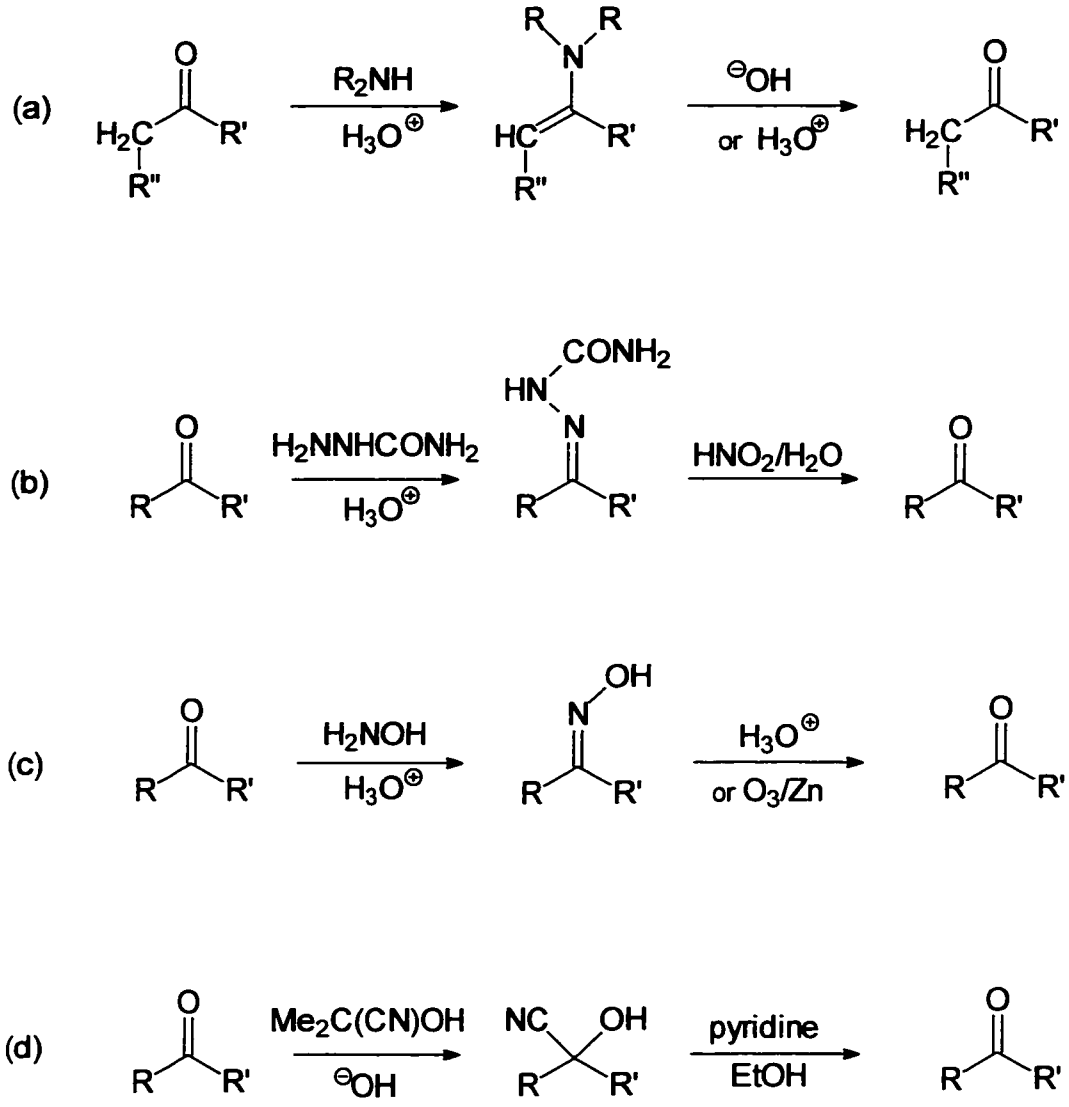
Thioketals are the sulfur derivatives of ketals,[11] and by analogy protection occurs by treatment with a thiol or dithiol (Scheme 1.4). The removal of the thioketal protecting group is accomplished under neutral conditions by mercury and cadmium salts in acetonitrile.[2,3,11] Like their oxygen counterparts, dithioketals

are stable under alkaline conditions, to nucleophilic attack and to hydride reduction.[11] Unlike the ketal method, dithioketals are stable under acidic conditions, but undergo hydrogenolysis by Raney nickel, and are cleaved by sodium in ammonia, and a wide range of oxidants. Since the removal of the dithioketal protecting group occurs under neutral conditions, there is little chance of unwanted modification of the molecule by the deprotection process. However, as was stated in Section 1.2, an ideal protecting group should be removable with readily available, non-toxic reagents. Both mercury and cadmium are highly toxic and pose serious health and environmental risks when used.

A wide variety of other protective groups exist for ketones but are seldom used, largely in part to the difficulty of their removal. One such method is to convert the ketone, often an α,β-unsaturated ketone in a steroid, to an enamine (Scheme 1.5a).[11] Enamines are stable to lithium aluminum hydride, Grignard and other organometallic reagents. Cleavage occurs upon treatment with dilute aqueous base or acid, though strong acids can result in rearrangements.

Semicarbazones are also used in the steroid field and can be used to protect against sodium borohydride,[11,15] lithium borohydride,[11,16] some oxidants[11] and alkaline ester hydrolysis (Scheme 1.5b).[11,17] Hydrolysis under stringent, acidic conditions or by nitrous acid result in the regeneration of the carbonyl group.[11,18]

Oximes have been found to have similar protective capabilities as semicarbazones, though they are harder to cleave (Scheme 1.5c).[11,18] Hydrolysis under acidic conditions, or oxidation with ozone are used to restore the original ketone.[11]

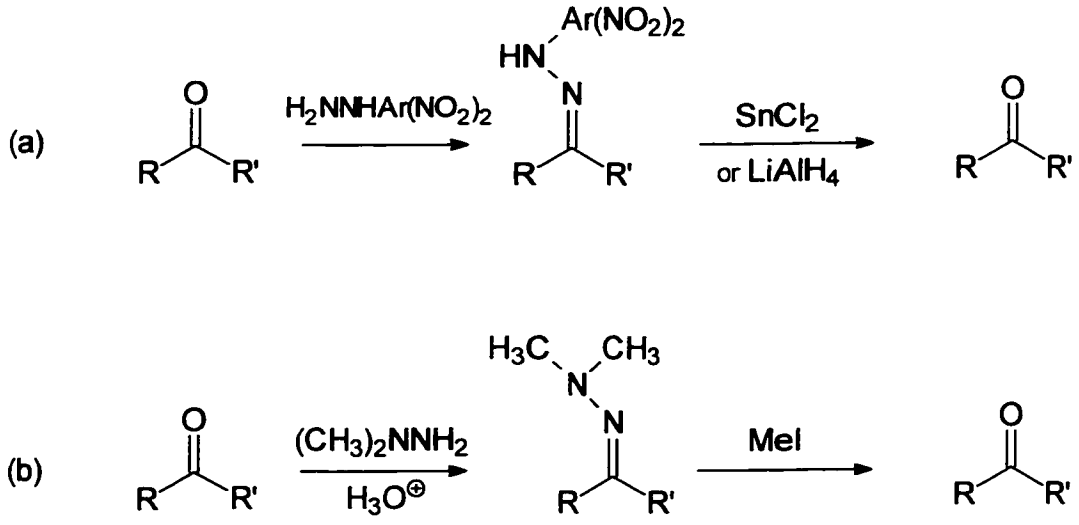


Scheme 1.5: Various protection/deprotection regimes for ketones: (a) enamines, (b) semicarbazones, (c) oximes, (d) cyanohydrins

Cyanohydrins are used to protect saturated ketones over α,β-unsaturated ketones selectively, using base catalyzed exchange with acetone cyanohydrine (Scheme 1.5d). Stable to mild acidic conditions, the unprotected α,β-unsaturated carbonyl can be converted to ethers and ketals by conventional methods, then the

saturated carbonyls can be deprotected and brominated. Cleavage is accomplished with mild alkaline conditions, such as pyridine in ethanol.[11]

Substituted hydrazones can be employed as protective groups, the most common being 2,4-dinitrophenylhydrazones and N,N-dimethylhydrazones (Scheme 1.6).[11] Due to considerable difficulty in cleavage, a result of the hydrolysis equilibrium constant that favors retention of the hydrazone grouping, 2,4-dinitrophenylhydrazones have seen little use. Studies have found this method resistant to acid ester hydrolysis, oxidation of hydroxyl groups to ketones and bromination. Cleavage is accomplished by a variety of reduction methods involving chromous chloride, stannous chloride, lithium aluminum hydride or sodium hydrosulfite. N,N-dimethylhydrazones have more potential as an effective protecting group due to relatively easy cleavage under mild conditions with methyl



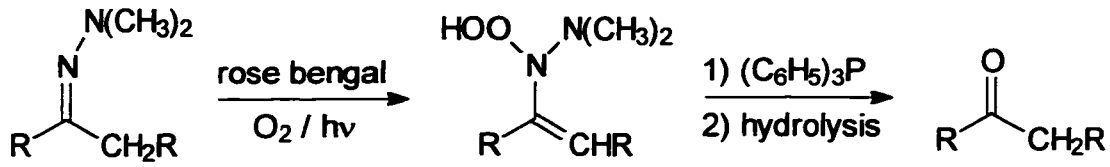
Scheme 1.6: Substituted hydrazones as protection/deprotection regimes: (a) 2,4-dinitrophenylhydrazones, (b) N,N-dimethylhydrazones

iodide. This method has been found to be effective protection against enolate alkylation, alkaline hydrolysis, metal hydride reduction, hydroboration and some oxidation.[11,19]

1.2.2 Photoremovable Protecting Groups for Ketones

In light of the difficulties that arise when devising a protection/deprotection process, new and unique methods were sought out by synthetic chemists.[8] One of these methods was the use of photochemically removable protecting groups. Though relatively new, much work has been done in this area, and these methods show great promise. The benefit of using photochemical reactions as a protection/deprotection method, is that potentially useful protecting groups, which meet the established criteria except that they are difficult to remove chemically, can now realize their potential since they can be removed through photolysis. As an additional advantage, photochemical reactions often take place under mild or neutral conditions. This means that the removal of the protecting group is nondestructive, even for relatively unstable molecules.[8]

A wide array of photolabile protecting groups have been devised for a number of functional groups, such as alcohols, nitrates, diols, carboxylic acids, amines and amides to name a few. However there is little in the literature pertaining to photoremovable protecting groups for the carbonyl functionality found in ketones and aldehydes. Of the ones that are found in literature, none have become important synthetic tools.[8]



Scheme 1.7: Photochemical deprotection of a ketone using the N,N-dimethylhydrazone method

One of the earliest of these methods to be published, involves protecting the ketone by converting it to an N,N-dimethylhydrazone.[8,20] The deprotection process is a dye-sensitized photooxygenation reaction (Scheme 1.7). In the presence of Rose Bengal, a singlet oxygen generating dye, the hydrazone dissolved in either methanol, tetrahydrofuran, or dichloromethane is irradiated with visible light, producing a hydroperoxide. This hydroperoxide is reduced with triphenylphosphine and then hydrolyzed to produce the parent carbonyl compound.[20] Although this method was shown to work with a variety of ketones containing different substituents, several factors limit its use. First, the yields were modest, ranging from 48% for 2,6-dimethyl-5-hydroxy-3-heptanone to 88% for ethyl 4-oxopentanoate. Second, this method requires long periods of irradiation, over eight hours in some cases, and reduction with triphenylphosphine requires reaction overnight. Other established methods work much faster. Finally the reaction often needs to be carried out at temperatures as low as -78°C. These factors make this method cumbersome and impractical compared to the established non-photolytical deprotection methods. It is not surprising that this method has found little use.

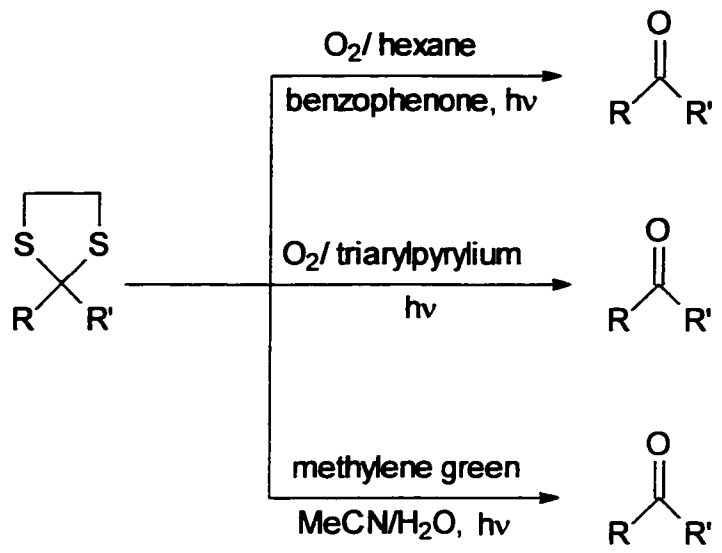
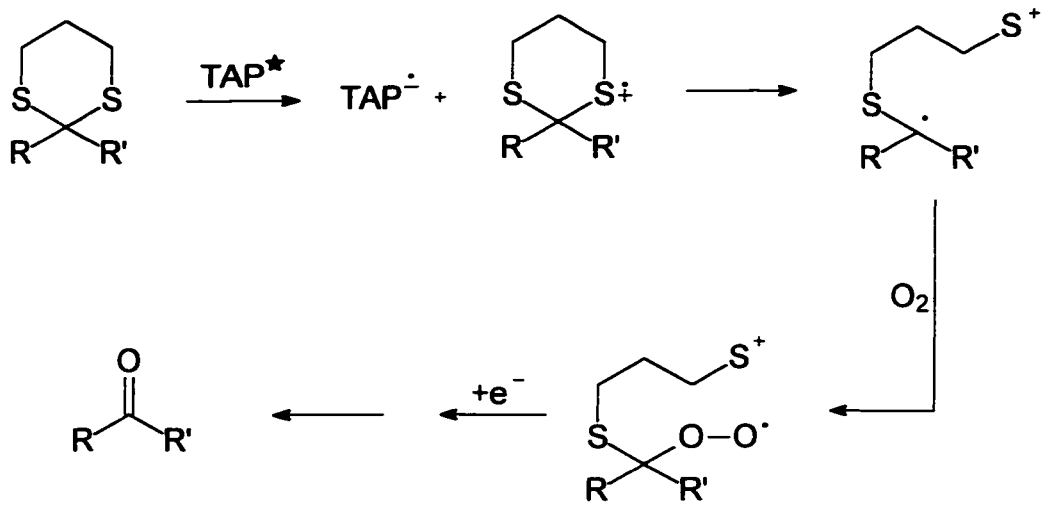


Figure 1.10: Photolytic deprotection methods involving dithioketals

A second general method devised involves the photolytic deprotection of a dithioketal (Figure 1.10).[8] Three different variations of this general method have been reported in literature. The first involved irradiating an oxygen saturated hexane solution of the dithioketal containing the triplet sensitizer benzophenone.[8] Although yields were still moderate (60-80%), there was some improvement over the dimethylhydrazone method. In addition the reaction occurs over a shorter time (2-5 hours) and at ambient temperature.[21] The limiting factor for this method is the solubility of the ketone in hexane.

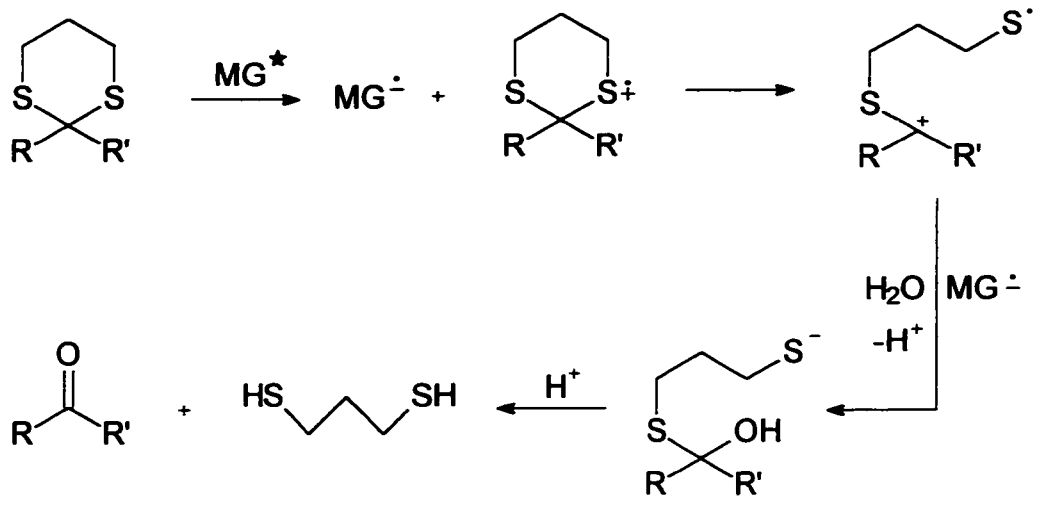
The second photolytic procedure regenerates the parent carbonyl compound from a dichloromethane solution of the dithioketal containing a triarylpyrylium salt. Upon irradiation the triarylpyrylium salt enters the excited state, oxidizes the dithioketal, forming a radical cation intermediate (Scheme 1.8). The radical cation undergoes a carbon-sulfur bond cleavage, forming a carbon-



Scheme 1.8: Deprotection mechanism in the triarylpyrylium (TAP) salt/dithioketal method[22]

centered radical which reacts with molecular oxygen to produce a peroxide radical intermediate that subsequently rearranges into the parent carbonyl compound.[22] Although this method was found to have high yields for some carbonyl compounds (benzophenone derivatives up to 95%), yields for many others, including most aldehydes and acetophenone derivatives, were low (less than 15%). As well, some researchers believe that the formation of singlet oxygen would likely lead to the formation of extensive byproducts, resulting in low yields.[23]

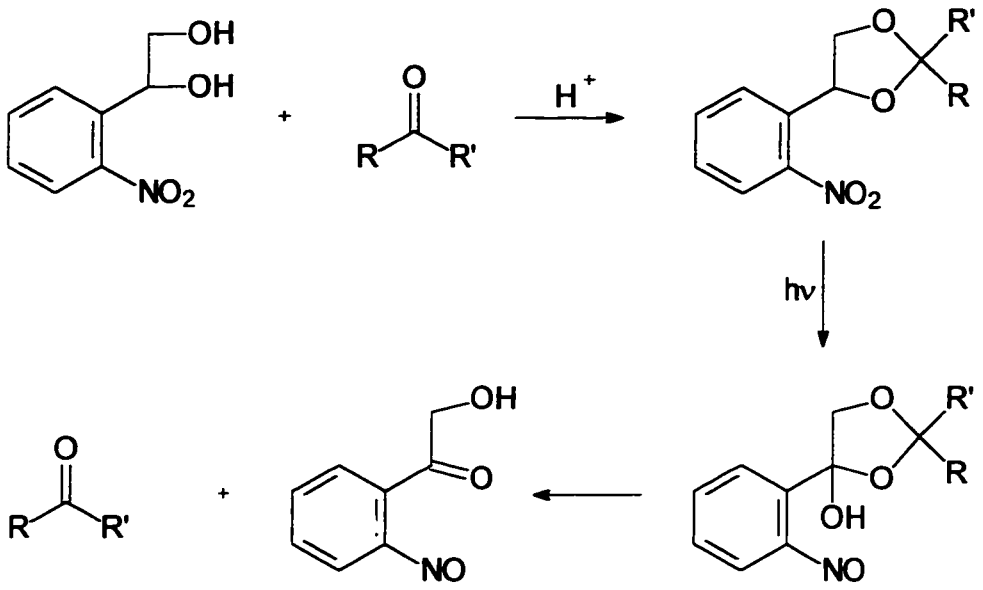
The third procedure involving dithioketals, is a photoinduced hydrolysis in a solution of water and acetonitrile, with methylene green as a sensitizer. Methylene green upon absorption of visible light oxidizes the dithioketal, producing a radical cation (Scheme 1.9). Cleavage of the sulfur-carbon bond occurs, producing a carbon-centered cation, which upon hydrolysis and rearrangement forms the



Scheme 1.9: Deprotection mechanism in the methylene green(MG)/dithioketal method[24]

corresponding carbonyl compound. This method has proven to have high yields, in excess of 90% over a three to four hour period of irradiation under nitrogen, but lower yields were obtained when oxygen was present.[24,25]

Possibly the most practical photolytic protection/deprotection regime for carbonyl compounds is the o-nitrobenzyl ketal method. By reacting a ketone or aldehyde with o-nitrophenylethylene glycol in the presence of a catalytic amount of acid, the corresponding ketal is formed.[8,26-28] Unlike the methods previously mentioned, no additional reagents are required for the deprotection step. This is due to the o-nitrobenzyl group undergoing a well-established photochemical reaction either in solution or in crystalline form (Scheme 1.10). Upon absorbtion of light, an o-nitrobenzylic shift occurs, resulting in a nitrosophenyl hemiketal. This intermediate then decomposes into the free carbonyl compound and α-hydroxy-o-

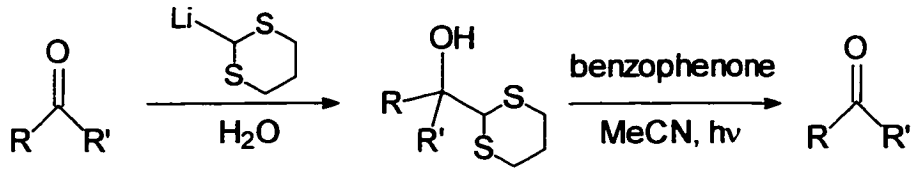


Scheme 1.10: Protection and deprotection of a ketone involving the o-nitrobenzyl ketal method[26]

nitrosoacetophenone. The literature reports a high degree of success in protecting a variety of ketones, except those where the carbonyl is sterically hindered.[26-28] In addition it has been reported that recovery of the deprotected ketones was equally high, with the exception of ketones that were known to be photoreactive themselves.[27] Though pragmatic in many ways, this method does have certain limitations. The protected compound can not be stored indefinitely since the nitrobenzyl group readily absorbs light and decomposes; other protection methods allow the protected compound to be stored easily. As well, it is the opinion of some researchers, that the nitro group itself is a limiting factor in the use of this method. Often carbonyls are protected to avoid reaction with organometallic

compounds or hydrides, and the presence of a nitro group limits the viability of this method.[23]

The most recent method investigated for ketone protection involves the use of 2-lithio-1,3-diethane as a photoremovable protective agent. It was shown that 2-lithio-1,3-diethane adds to carbonyls to produce 2-(1-hydroxyalkyl)-substituted dithianes in quantitative yields. Irradiation of these dithiane carbonyl adducts in the presence of benzophenone regenerates the original carbonyl compound (Scheme 1.11).[23,29] Though this method does seem to be promising, giving high yields of deprotected aromatic carbonyls, it was found that aliphatic compounds, such as propanone and heptanone, gave low yields (less than 40%) of deprotected compound.[23]



Scheme 1.11: Protection and deprotection of a ketone involving the 2-(1-hydroxyalkyl) dithiane method

1.3 Tosylhydrazones

Tosylhydrazones (Figure 1.11), also sometimes referred to as sulfonylhydrazones, toluene-p-sulfonylhydrazones and arenesulfonylhydrazones, have been cited in the literature as far back as the 1920's, though they did not receive much attention until the pioneering work of Bamford and Stevens in 1952.[30] Soon after, the potential applications for tosylhydrazones, first as a synthetic intermediate compound then as a protective grouping for carbonyls, were recognized.

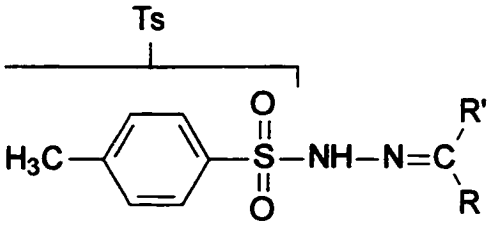


Figure 1.11: Generic structure of p-tosylhydrazone

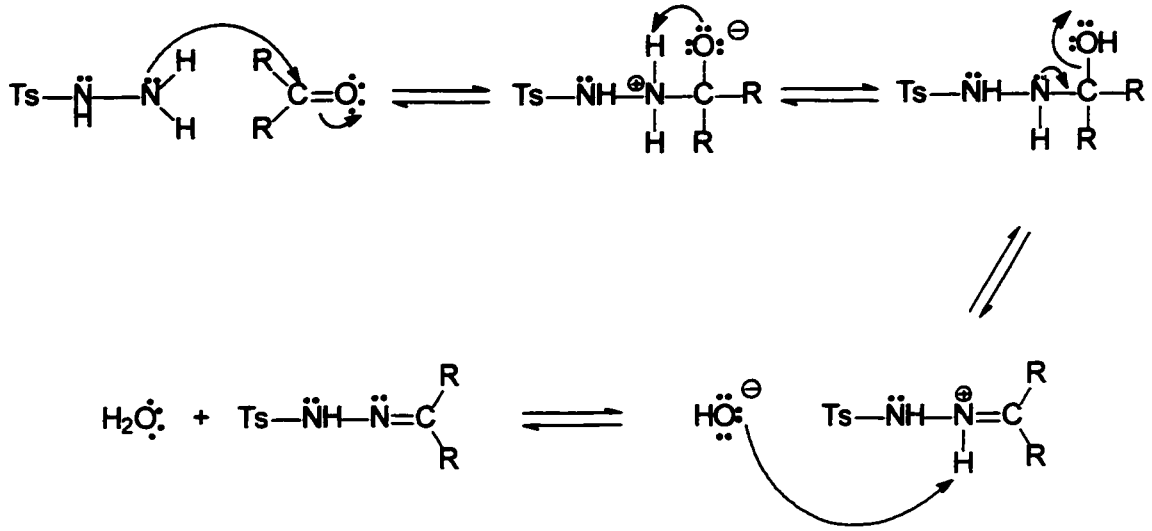
Tosylhydrazones exhibit several characteristics that render them convenient to use. They form easily and under mild conditions, usually in high yields.[31] They are easily crystallized, allowing for easy isolation, purification and characterization not only for the hydrazone itself but also for the parent carbonyl compound.[32] Possibly the most advantageous characteristic of tosylhydrazones is their relative stability under ambient conditions.[31] Compounds structurally akin to tosylhydrazones, such as phenylhydrazones, have shown to be reactive when exposed to light, water and air.[33] While non-reactive with air and resistant to hydrolysis because of equilibrium constants that favor retention of the

tosylhydrazine moiety by the carbonyl parent compound,[11,34] certain tosylhydrazones have been known to be photochemically reactive. In these tosylhydrazones the carbon-nitrogen double bond was conjugated with another π system.[35] Thus most tosylhydrazones are unchanged by exposure to light and can be stored indefinitely.

Despite this stability, research into tosylhydrazones has shown that they have a rich chemistry under certain conditions. This chemistry can be varied between different tosylhydrazones, particularly between those derived from ketones and those derived from aldehydes, as well as between those from saturated carbonyl compounds and α,β-unsaturated carbonyl compounds.[11,30,35]

1.3.1 Formation of Tosylhydrazones

The most common method for tosylhydrazone preparation involves a condensation reaction between a carbonyl compound and p-tosylhydrazine, which is commercially available.[36] This reaction is usually conducted in methanol or ethanol, however it has been found that the preparation of tosylhydrazones derived from aldehydes and some ketones is more efficient if conducted in diethyl ether or tetrahydrofuran.[37] In older literature the condensation reaction is catalyzed with aqueous acid, usually hydrochloric acid.[30] Although acid catalysis is necessary for the formation of many hydrazones, including phenylhydrazones, the protons found on tosylhydrazine are sufficiently acidic that the addition of acid is not needed for the condensation reaction to occur.[34] The mechanism for the



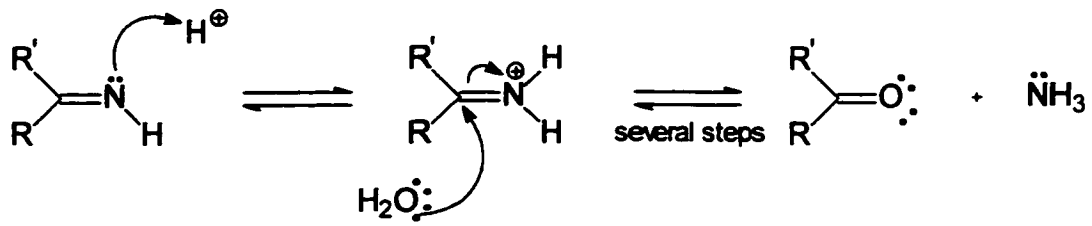
Scheme 1.12: Mechanism of the formation of a tosylhydrazone

condensation of a ketone with a hydrazine has been well known for some time (Scheme 1.12).[2,3,34]

Recently a new method has been proposed for the formation of tosylhydrazones, in the absence of not only catalyst, but solvent as well. This method, which can also be adapted to form oximes and semicarbazones, involves irradiating a paste composed of carbonyl compound, tosylhydrazine and a few drops of methanol, with microwaves. Extraction with dichloromethane afforded good yields of tosylhydrazone.[38]

1.3.2 Effects of Acidic and Alkaline Conditions on Tosylhydrazones

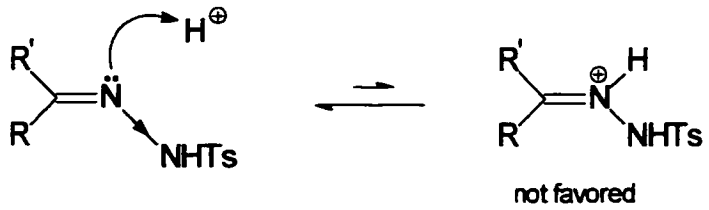
In many cases, a compound with a carbon-nitrogen double bond will hydrolyze into a carbonyl compound and an amine upon treatment with an aqueous acid.[39] An imine, for example, is easily hydrolyzed to a ketone and



Scheme 1.13: Hydrolysis of an imine[34]

ammonia (Scheme 1.13).[33] with initial protonation of the electron lone pair on the imine nitrogen. [2,3]

Hydrazones, and particularly tosylhydrazones, do not undergo such hydrolysis readily, as they are resistant to protonation by acids. The electron withdrawing nature of the group adjacent to the imine-like nitrogen greatly reduces its basicity (Scheme 1.14), and makes protonation unfavorable.[11,34]

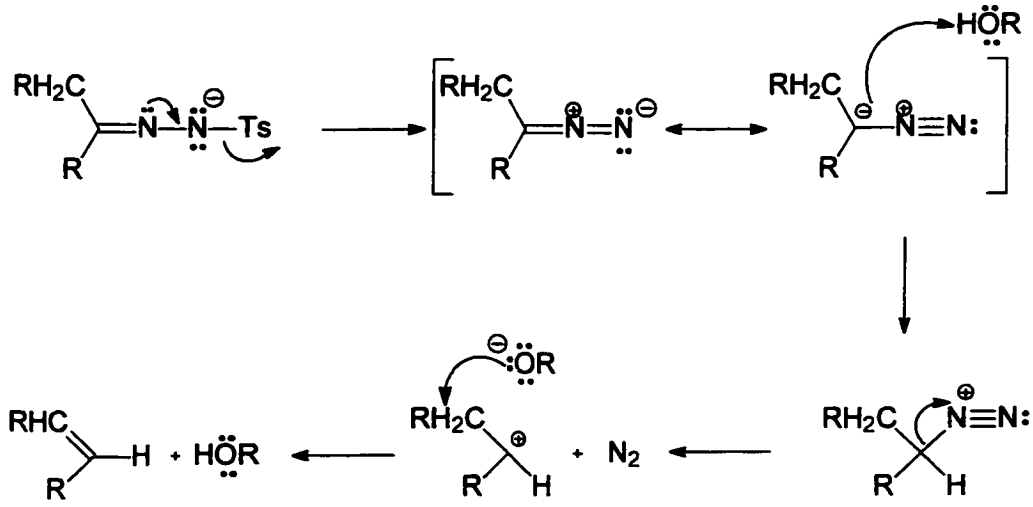


Scheme 1.14: Substituted hydrazone resistance to protonation[34]

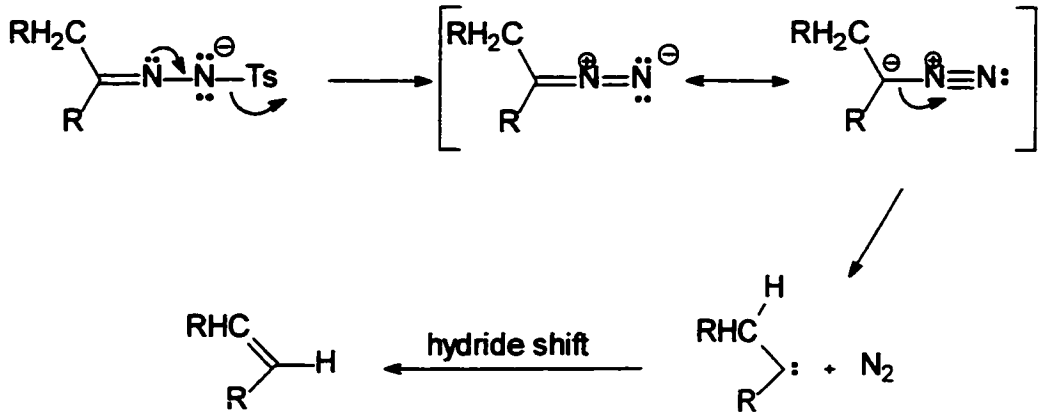
Although resistant to acids, tosylhydrazones are susceptible to bases. This was shown initially by Bamford and Stevens, and has been widely cited.[30,40-50] The same phenomenon that renders the imine-like nitrogen resistant to protonation, makes the hydrogen atom on the amine-like nitrogen acidic, and thus easily removed under alkaline conditions.[2,3] Removal of this proton results in the

formation of a tosylhydrazone anion (or with a counterion, a tosylhydrazone salt).[30,40-50] Though stable at ambient temperature, heating of this salt in solution will cause it to decompose rapidly.[30,40-43,45-48,50]

It has been shown that there are two possible reaction pathways for the decomposition of a tosylhydrazone salt, and the type of solvent present determines the pathway taken. In all cases, the tosylhydrazone salt will decompose by expulsion of a p-toluenesulfinate anion (CH_3-C_6H_4-SO_2^-) to a diazo compound.[30,40-50] In protic solvents this is protonated to form a diazonium ion.[30,40-42,50] The loss of a molecule of nitrogen results in a carbocation that can either a) lose a proton to form an olefin (Scheme 1.15)[30,40,42] b) react with a solvent molecule to form an ether,[42,50] or c) undergo a Wagner-Meerwein rearrangement.[41,42] In aprotic solvents, the diazo compound loses a molecule of nitrogen, forming a carbene intermediate (Scheme 1.16). This carbene can rearrange to form an olefin, or react with nucleophiles present to form side products.[44-48,50]



Scheme 1.15: Decomposition of a tosylhydrazone salt in a protic solvent



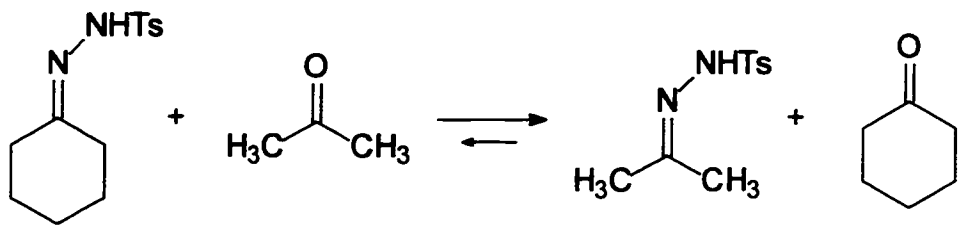
Scheme 1.16: Decomposition of a tosylhydrazone salt in an aprotic solvent

As is obvious from Schemes 1.15 and 1.16, the major product from both pathways is an alkene, and so tosylhydrazones were used in alkene synthesis. Alkene groups, that would otherwise be difficult to form, could be easily synthesized, including double bonds in terpenes and steroids.[30,43-46,48,51] Adding stoichiometric amounts of butyllithium produced olefins without side products from skeletal rearrangement.[52-55] Tosylhydrazone salts are also a convenient source for diazo compounds, which can be isolated.

1.3.3 Regeneration of the Carbonyl Moiety from Tosylhydrazones

While tosylhydrazones have been employed in reactions such as alkylation of carbonyl compounds,[56-61] relocation of carbonyl moieties,[49,62,63] and the syntheses of cyclopropanes,[44] pyrazoles,[64,65] alcohols,[54] ethers,[50,54] carboxylic acids,[54] and silanes[66,67] their potential use as a protective group has not been fully realized largely due to the difficulty in regenerating the carbonyl moiety.[11] Many different attempts have been made with varying degrees of success.

One of the earliest and simplest methods was to expose the tosylhydrazone to excess amounts of acetone.[68] An equilibrium will occur in which acetone will exchange with the tosylhydrazone, liberating the protected carbonyl compound (Scheme 1.17). Though simple, this method was found to give only moderate yields (60-85%) for ketones, and very low yields for aldehydes (approximately 5%). The addition of boron trifluoride etherate, with water rather than acetone as solvent, resulted in a substantial increase in yields (85-97%), however the exchange of larger, more complex carbonyl compounds required exceedingly long reaction times (as long as 48 hours).[69] These factors required a more efficient method of carbonyl regeneration to be found.



Scheme 1.17: Acetone exchange with a tosylhydrazone liberating a protected ketone

A variety of different oxidative procedures have been probed.[32,70-76] First attempts were made to oxidize the tosylhydrazone with acetates of mercury (II), thallium (III) or lead (IV).[70,71] Though the reaction was fast and had high yields, the reagents were both expensive and highly toxic. Sodium hypochlorite, common bleach, was suggested as an inexpensive and less toxic alternative.[32] It was found however, that this reaction gave modest yields for ketones (60-70%) and failed completely to regenerate aldehydes. Sodium peroxide was also suggested,

however much like sodium hypochlorite, yields were low and the method worked only for ketones.[72] Benzeneseleninic anhydride regenerated a wide array of carbonyl compounds, but in many cases had low yields or required long reaction times (up to 3 days).[73] N-bromosuccinimide in methanol was found to be an effective method for the regeneration of most carbonyl compounds under mild conditions, though some tosylhydrazones gave unwanted side products rather than the ketone.[74] Aqueous bromine in the presence of sodium hydrogen carbonate and hexamethylphosphoric triamide gave modest to good yields (69-82%) for numerous tosylhydrazones.[75] Yet the presence of bromine itself can be a limiting factor since other substituents could potentially react with a halogen. A method that gave quantitative yields for all reported tosylhydrazones was oxidation by peroxysulfur intermediates, generated by the reaction of 2-nitrobenzenesulfonyl chloride and superoxide. Though efficient, this method is cumbersome in that it must be performed in a dry argon atmosphere for over 5 hours at a temperature of -30°C.[76]

A recently published method for carbonyl regeneration was found to occur under mild, neutral and solvent-free conditions.[77] Bandgar and Makone found that treating a tosylhydrazone with hexamethylenetetramine-bromide and N-bromosuccinimide with a few drops of water resulted in the regeneration of the parent carbonyl compound, in good to excellent yields. This method was reported to work equally well for both ketones and aldehydes, without interference from carbon-carbon double bonds or hydroxyl groups. However, this method has been shown to work only for low concentrations of tosylhydrazones (1.0 mmol).

1.4 Chloranil

Chloranil (Figure 1.12), also known as 2,3,5,6-tetrachloro benzoquinone, is a yellow crystalline, synthetic benzoquinone first reported in literature in the 1850's.[78] Since then a number of practical applications have been identified for chloranil, amongst them a role in the manufacture of electrodes for pH measurements, use as a fungicide and as a fungicidal seed protectant and use as an oxidizing agent in organic synthesis, especially for dye intermediates and as a vulcanization agent.[79] It was this electron-accepting property which opened a realm of possible applications for chloranil in a number of chemical fields.

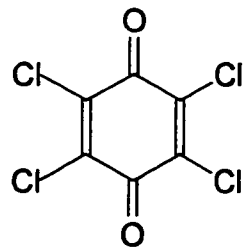


Figure 1.12: Structure of chloranil

1.4.1 Ground State Chloranil

The chloranil molecule is an almost planar, alicyclic compound, with a conjugate bond system, as shown in Figure 1.12.[80] This conjugated system gives chloranil (as well as other p-benzoquinones) a positive electron affinity.[81-84] As a result, ground state chloranil readily accepts electrons from strong aromatic electron-donors to form a long-lived radical anion.[83-86]

The transfer of an electron from an aromatic donor compound to chloranil arises from the formation of a ground state electron donor-acceptor (EDA)

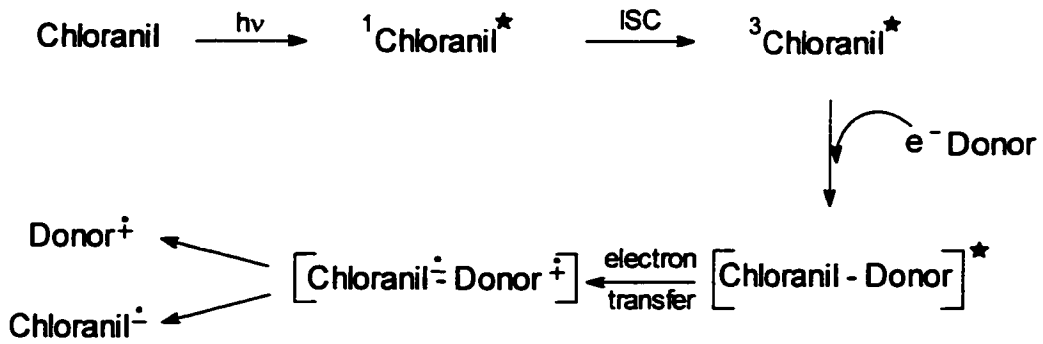
complex.[82,84,86,87] In the presence of a suitable aromatic electron-donor (such as toluene, xylene or durene), chloranil will arrange itself so that it lies on top of the electron-donor species, forming the relatively short-lived EDA complex. This formation is possible due to the planar nature of the molecules, and as a result, their π systems experience optimal overlap, enabling the electron transfer to occur.[84] Once this transfer has occurred (on the order of 1-10 ns), the radical ion pair quickly separates and diffuses in solution.[88-91]

1.4.2 Excited State Chloranil

Although the formation of EDA complexes by chloranil explains the observed oxidation of aromatic electron-donating species, it does not explain all the observed oxidations in which chloranil is involved. Many cases are cited where chloranil needs to be irradiated in order for oxidation to occur.[83,84,92-94] In addition non-aromatic species are known to be oxidized by chloranil,[83,92,94] and in some cases a lone pair electron is removed as opposed to a π electron.[94] As well, spectral analysis shows the presence of absorption bands in the visible region, which were not present in the spectra of ground state chloranil, the electron-donating species, the EDA complex or the radical ion pair. Chloranil in the excited state could account for these discrepancies.[84,95,96]

Laser flash photolysis and steady state irradiation studies revealed that chloranil readily absorbs light at a wavelength of 355 nm, resulting in an $n \rightarrow \pi^*$ transition.[97,98] Once in the excited singlet state, intersystem crossing (ISC) readily occurs and the relatively long lived excited triplet state of chloranil is formed. The

time required for absorption and intersystem crossing was found to be on the order of 50 ps, and the quantum yield of this process to be near unity.[84,99] Triplet chloranil, being long lived, exists for 1-10 μs before phosphorescing back to the ground state or being quenched by oxygen,[84,95,99] and can interact with an electron-donating species to form an excited charge transfer complex, or an exciplex (Scheme 1.18).[83,84] In the same way that EDA complexes allow the π systems of the two species to interact, in an exciplex the HOMO of the electron-donor species will interact with the π system of chloranil. In triplet chloranil the transition of one electron from the n orbital to the π^* orbital has left a vacancy in what was once the HOMO of chloranil.[100] This vacancy renders triplet chloranil a better oxidant than the ground state.[9] The result of the electron transfer is the formation of the radical cation of the electron-donor species and the radical anion of chloranil. This radical ion pair quickly dissociates in solution as free radical ions.[88-91]



Scheme 1.18: Interaction of excited chloranil with an electron donating species, producing a radical ion pair via an exciplex

The tendency for chloranil in the triplet state to form exciplexes and to act as a one-electron acceptor is well documented.[83,84,87-95,99] Spectral analysis has shown that upon appropriate irradiation, absorption bands characteristic to excited triplet chloranil become evident. These bands, around 380 nm, 480 nm and 500-530 nm (variations arising with different solvents), were found to decrease in intensity when an electron-donor species was present and an absorption band in the near infrared region (780-900 nm), attributed to the exciplex, would appear and increase in intensity.[84,94-96,100] The exciplex absorption band would then decrease in intensity (nanosecond time scale) as the characteristic absorption bands for the chloranil radical anion form at 325 nm, 430 nm and 450 nm.[84,92,94,96] These changes in the absorption spectrum support the notion of excited triplet chloranil proceeding to the radical anion form via exciplex formation.

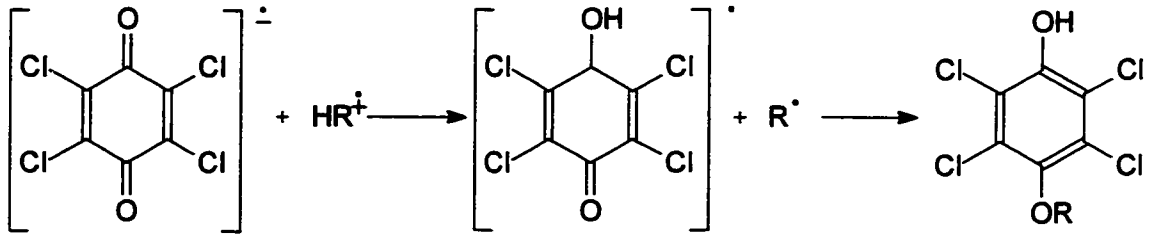
1.4.3 Chloranil Radical Anion

The radical anion of chloranil has been demonstrated to be a stable and long lived species.[81,82,84,86,95,99] In acetonitrile solution and in the presence of a counter ion, the radical anion has been known to remain stable for up to 4 hours.[99] This stability and long life is due to the conjugated system, which allows the radical electron to be delocalized across the molecule.[82] Despite this, the radical anion does decay, and this can proceed via one of two pathways; either by back electron transfer or by proton abstraction.

The simpler of the two processes is back electron transfer (BET), the return of an electron from the chloranil radical anion to the radical cation, regenerating

the neutral species that existed prior to the initial electron transfer.[91,92,101] Often BET is viewed as an undesired, energy wasting reversal of the electron transfer process, and steps are taken to reduce it. However if the radical cation species, generated during the initial charge transfer, reacts quickly with another reagent or undergoes some other rapid internal alteration, the BET process can insert an electron into cationic species and generate a neutral product as well as regenerate neutral ground state chloranil.[101]

The second process, proton abstraction, does not lead back to neutral ground state chloranil but rather a new product (Scheme 1.19).[93,95] The proton can be abstracted from a solvent molecule, but more often comes from the radical cation species. This will convert the chloranil radical anion to a neutral semiquinone radical, and the radical cation species into a neutral radical species. The semiquinone radical can combine with the second radical species generated, or with a fragment of that radical.[92] This process ends with chloranil being consumed and new adducts containing chloranil being formed.



Scheme 1.19: Quenching of the chloranil radical anion through proton abstraction from a radical cationic species

2 Objectives

The existing protecting methods for carbonyl compounds are limited in that they involve harsh conditions, toxic reagents, cumbersome procedures, or low yields.[10,11] This has made the search for an alternative protection/deprotection procedure an important topic in research. Tosylhydrazones have the potential to be effective protecting groups for carbonyl compounds in that they are formed easily, under mild conditions and in high yields, are largely non-reactive and can be stored indefinitely.[31,32] Despite these desirable characteristics, tosylhydrazones have not been widely employed as a protective group, due largely in part to the difficulties surrounding the deprotection process. Reaction conditions for the removal of tosylhydrazones often proved to be too harsh for sensitive functional groups or involved toxic and/or expensive reagents.[11,32,71-79] Photochemical reactions can occur under mild conditions, often with little or no additional reagents required. This makes photochemically removable protecting groups a viable alternative to conventional protecting groups.

The objective of this project is to devise a method to deprotect photochemically, ketones that have been protected by conversion to a tosylhydrazone. Sixteen ketones: cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, 2-pentanone, 2-hexanone, 2-heptanone, acetylmalononitrile, acetoacetamide, ethyl acetoacetate, acetylbutyrolactone, 3-acetyl-propanol, 1-acetonaphthone, 2-acetonaphthone, 3-methoxyacetophenone and 4-methoxyacetophenone (Figure 2.1), are to be converted to tosylhydrazones. The deprotection of these ketones is to be investigated, with

emphasis placed on the deprotection of cyclopentanone and 2-heptanone as examples of cyclic and acyclic ketones, respectively. Preliminary investigations into the deprotection of the functionalized ketones and aromatic ketones are to be conducted to elucidate the effect of substituents on the deprotection process.

Two aspects of the photochemical deprotection of ketones from tosylhydrazones are to be the focus. The first is the efficiency of deprotection, with

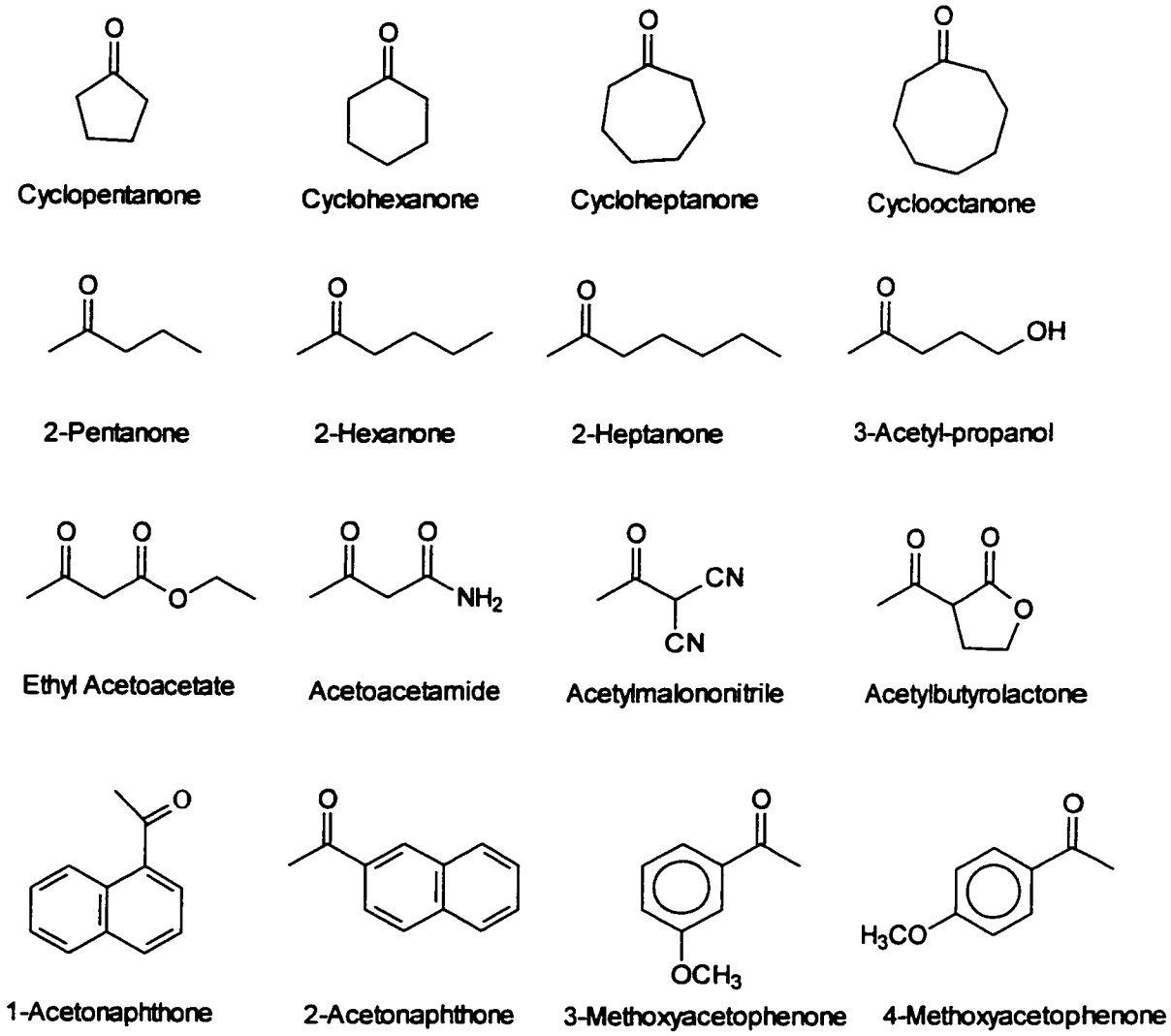


Figure 2.1: Ketones to be protected by conversion to tosylhydrazones

emphasis on the effects on deprotection by solvent, concentrations and light intensity. The second is an examination of factors that can help elucidate the reaction mechanism, with three areas to be examined. First the source of the oxygen atom in the regenerated ketone, with three possible sources to be probed (water in the solvent, oxygen atoms on the tosyl group and oxygen in the air). Second, the confirmation of the participation of a radical cation through independent generation and trapping. The role of a radical cation in the mechanism is to be investigated further through computational studies of its generation and reaction. Third, the determination of the identity of all reaction products.

3 RESULTS AND DISCUSSION

3.1 Protection of Ketones: Formation of Tosylhydrazones

Tosylhydrazone formation was accomplished by reacting the appropriate ketone with p-tolysulfonylhydrazine, a well-established reaction in tosylhydrazone synthesis.[36] Upon recrystallization from ethanol the purity of the tosylhydrazones was determined by melting point, gas chromatography and thin layer chromatography, while nuclear magnetic resonance spectroscopy was used to elucidate structural characteristics of the products, such as cis/trans isomerism.

Seven aliphatic ketones were protected by conversion to tosylhydrazones: 2-butanone, 2-pentanone, 2-hexanone, 2-heptanone, cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone, as were nine functionalized ketones: ethyl acetoacetate, acetoacetamide, 3-acetyl-1-propanol, acetylmalononitrile, 2-acetylbutyrolactone, 1-acetonaphthone, 2-acetonaphthone, 3-methoxyacetophenone and 4-methoxyacetophenone. All tosylhydrazones were obtained in good yields (87% - 95%), although optimization of the yields was not attempted.

3.1.1 Determination of Purity of Tosylhydrazones

Gas chromatography was used to determine whether residual ketone was contaminating the tosylhydrazone product. In most cases ketone was not detected, however if ketone was present, it was removed by repeated recrystallization. Elution times for the various ketones can be found in Appendix I in Table A.1.

Contamination by p-tolysulfonylhydrazine was determined by two means; melting point and thin layer chromatography. The presence of residual starting material would result in a depressed melting point for the tosylhydrazone, as well as an increased melting point range.[102] Development of a TLC plate could easily identify contamination by p-tolysulfonylhydrazine, since the R_f values for tosylhydrazones are distinct from the R_f value of p-tolysulfonylhydrazine. As with residual ketone, residual p-tolysulfonylhydrazine was rarely present, and removal was accomplished by further recrystallization. It was not possible to detect residual ketone by TLC, since they are highly soluble in the chosen mobile phase and would be carried with the solvent front. The R_f values are listed in Appendix I in Table A.2.

3.1.2 Structural Characterization of Tosylhydrazones

The chemical shifts for the protons and carbon atoms of the p-tolysulfonylhydrazine part of the tosylhydrazones were almost identical on each spectrum, with a deviation no greater than 0.02 ppm for proton NMR and 1.00 ppm for ^{13}C NMR.

Tosylhydrazones of cyclic ketones did not exhibit any cis/trans isomerism, due to the symmetry of the parent ketones. Despite this symmetry, none of the carbon atoms, or the protons bonded to them, were identical on the proton and ^{13}C NMR spectra. The carbon ring lies within the plane of the molecule, bringing the lone pair electrons of the hydrazone nitrogen into proximity with certain protons, as shown in Figure 3.1. This results in greater deshielding of the proximal

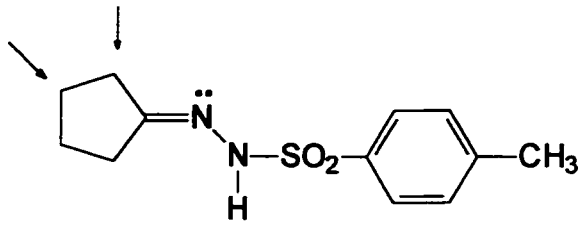


Figure 3.1: Structure of cyclopentanone tosylhydrazone depicting carbon atoms proximal to lone pair electrons on nitrogen (arrows)

protons and carbon atoms, and the NMR spectra show signals from the proximal atoms further downfield to their distal counterparts. The proton NMR spectrum of cyclopentanone tosylhydrazone in Figure 3.2 demonstrates this. The two pentets and the two triplets partially overlapping, indicate four sets of unequal protons on the carbon ring. If the proximal and distal protons were equivalent, then there would be only one pentet and one triplet.

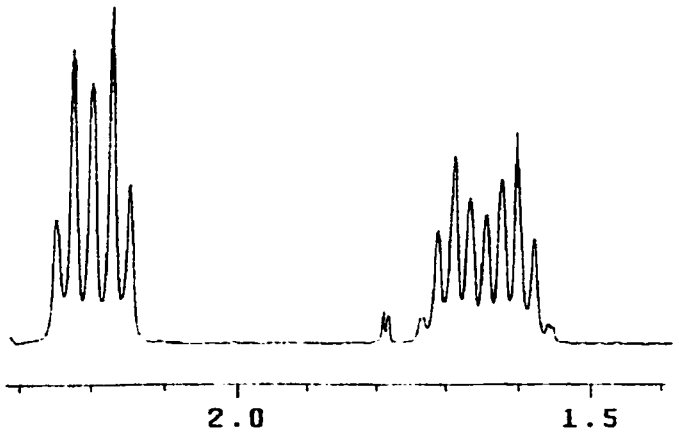


Figure 3.2: Partial proton NMR spectrum of cyclopentanone tosylhydrazone depicting peaks from protons on carbon ring

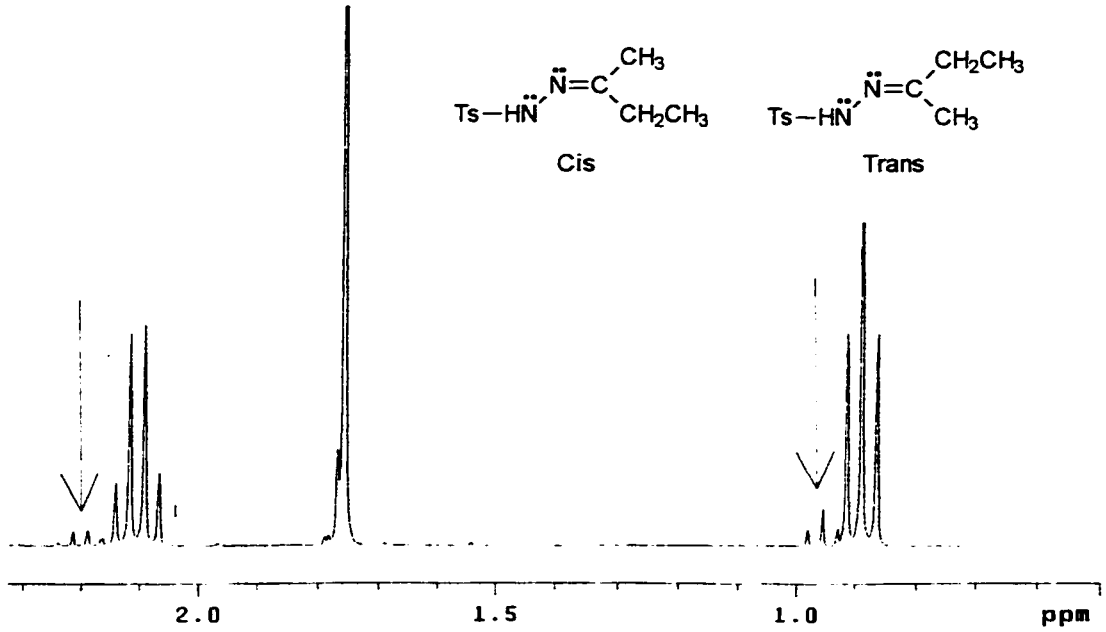


Figure 3.3: Partial proton NMR spectrum of 2-butanone tosylhydrazone depicting smaller secondary signal from trans isomer (arrows)

In contrast to the cyclic ketones, the tosylhydrazones of linear ketones exhibit cis/trans isomerism. Lipton and Shapiro report that tosylhydrazones from asymmetrical ketones will produce a mixture of tosylhydrazone isomers, with cis as the major form.[55] The cis isomer becomes more abundant as the parent ketone becomes larger or branched.

On both the proton NMR and ^{13}C NMR spectra of the linear ketone tosylhydrazones, small signals with identical splitting patterns to the signals from the protons on the carbon chain, were present slightly downfield from the main peak, as shown in the proton NMR spectrum of 2-butanone tosylhydrazone in Figure 3.3. These signals were not due to residual ketone contamination, as the chemical shifts are not the same as that of the parent ketone. These were

attributed to the trans isomer, as the trans isomer would have the bulk of the carbon chain proximal to the hydrazone nitrogen's lone pair electrons, resulting in greater deshielding and the observed chemical shifts. Lipton and Shapiro reported that the ratio between the cis and trans isomers was 83:17 in the case of 2-butanone tosylhydrazone.[55] Integration of the proton NMR signals indicate that the cis/trans ratio is 88:12 for 2-butanone tosylhydrazone, with similar values for other linear ketone tosylhydrazones. Cis/trans isomerism was not observed for tosylhydrazones of asymmetrical functionalized ketones.

3.1.3 Conclusion: Formation of Tosylhydrazones

The synthesis of the tosylhydrazones was uncomplicated and afforded good yields. The purity of the tosylhydrazones was determined by several means; gas chromatography for contamination by ketone, and melting point depression and TLC for contamination by p-tolysulfonylhydrazine. If contaminant was present, it was removed by further recrystallization.

The tosylhydrazones of linear ketones exhibited cis/trans isomerism, as evident from the proton and ^{13}C NMR spectra, with cis being the dominant isomer (88%). No cis/trans isomerism was detected for the tosylhydrazones of the asymmetrically functionalized ketones.

3.2 Photolysis of Tosylhydrazones: Ketone Deprotection

For the study of the photolytic deprotection of ketones in chloroform, tosylhydrazone concentrations were set at 25.0 mM, and each solution contained 65.0 mg (2.64 mM) of chloranil. These were standard concentrations and were used for all experiments unless otherwise specified. In all solutions, 1 mL of tert-butyl methyl ether (TBME) was added as an internal standard for quantitative GC measurements. These solutions were exposed to a high intensity Hg/Xe lamp for 4 hours at ambient temperature and pressure, in a Pyrex 100 mL volumetric flask. The summary of the results from these experiments found in Table 3.1.

As can be seen from this summary, the amount of ketone obtained after 4 hours of irradiation varies between 23% and 31%. These results are similar to the results obtained in an earlier study, in which the photolysis of tosylhydrazones was examined when dichloromethane was used as the solvent.[103] The results of

Table 3.1: Regenerated ketone from chloroform solution after 4 hours

Ketone Regenerated	Percent Yield
Cyclopentanone	26.1%
Cyclohexanone	26.9%
Cycloheptanone	29.8%
Cyclooctanone	29.6%
2-Pentanone	23.7%
2-Hexanone	27.9%
2-Heptanone	30.4%

Table 3.2: Regenerated ketone from dichloromethane solution after 4 hours

Ketone Regenerated	Percent Yield[103]
Cyclopentanone	22.0%
Cyclohexanone	< 7.0%
Cycloheptanone	23.5%
2-Hexanone	18.5%
2-Heptanone	27.2%

this study are shown in Table 3.2, and after 4 hours of irradiation the amount of ketone regenerated varied between 18% and 28% for some of the tosylhydrazones examined in this study.

Looking at the plot of the formation of cyclopentanone with respect to time shown in Figure 3.4 and the plots of the formation of the other ketones found in Appendix III (error bars represent absolute error), one can see an obvious trend

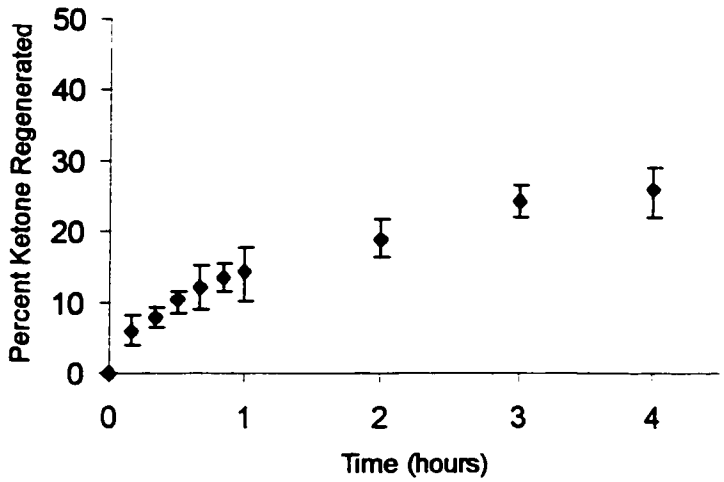


Figure 3.4: Regeneration of cyclopentanone over 4 hours of irradiation

found in all the tosylhydrazones studied. Within the first hour of irradiation, the majority of ketone that will be regenerated is formed. However, the amount of ketone generated during any subsequent one-hour time interval drastically decreases and eventually the amount of new ketone being regenerated during each time interval approaches zero. This slowing of the deprotection process was seen in all cases, for all tosylhydrazones, both when chloroform and dichloromethane were used as solvents.

In addition to the formation of ketone, which remains in solution, a white precipitate formed upon photolysis of all tosylhydrazones. It was visible after as little as 15 minutes of irradiation, and was present in every tosylhydrazone photolysed, both when chloroform and dichloromethane were used as solvent.

Different factors affected the rate in which ketone was regenerated. Each of these factors were examined and their effects are discussed.

3.2.1 Variations in Amounts of Chloranil: Effect on Ketone Formation

It was surmised that chloranil was essential for the photolytic deprotection reaction to take place since it was known to be a good oxidizer[83-94], and this was believed to be the first step in the reaction process. To further investigate this, cyclopentanone and 2-heptanone solutions were irradiated without the presence of chloranil. In both cases, after the standard irradiation time, there was no ketone or precipitate formed. Even after an additional 6 hours of irradiation, there was no evidence that the deprotection reaction was taking place. From these

observations it was concluded that chloranil is essential for the reaction to take place.

Knowing the necessity of chloranil, the effects of the quantity of chloranil on the formation of ketone were examined. Nine solutions, of equal concentration of cyclopentanone tosylhydrazone and variable concentrations of chloranil, were irradiated for one half hour and the amount of regenerated ketone was determined. The results of these measurements are shown in Figure 3.5. This graph clearly shows that the amount of chloranil present has little effect on the amount of ketone regenerated. For all solutions containing more than 0.05 g of chloranil, the amount of ketone regenerated was slightly more than 11%. However measurements show that when there is less than 0.05 g of chloranil in the solution there is a decrease in the amount of ketone that is formed. These measurements show a decrease from 11.2% when 0.05 g of chloranil is used to 8.73% when

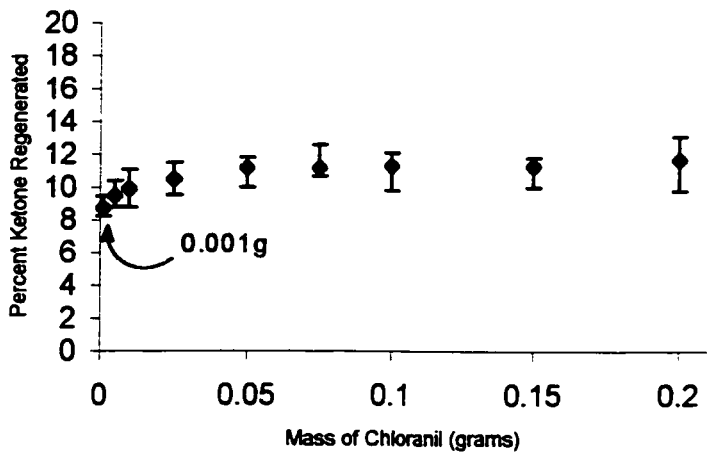


Figure 3.5: Plot of percent ketone formed after 0.5 hours versus mass of chloranil used

there is only 0.001 g of chloranil. From this information it can be concluded that a catalytic amount of chloranil is needed to affect the reaction.

3.2.2 Effect of Solvent on Ketone Formation

Studies have shown that solvents play a role in the separation of the radical ion pair formed in a chloranil charge transfer complex.[84] More polar solvents, such as acetonitrile, favour separation of the radical ion pair, while less polar solvents, such as chloroform, favour back-electron transfer to the neutral starting species.

The formation of cyclopentanone in acetonitrile, dichloromethane and chloroform over 4 hours is shown in Figure 3.6. There is little difference between the amount of ketone regenerated in acetonitrile and chloroform. This suggests that solvent is not a major factor in ketone regeneration, and that separation of the radical ion pair is not the rate limiting step. Yields were lower when

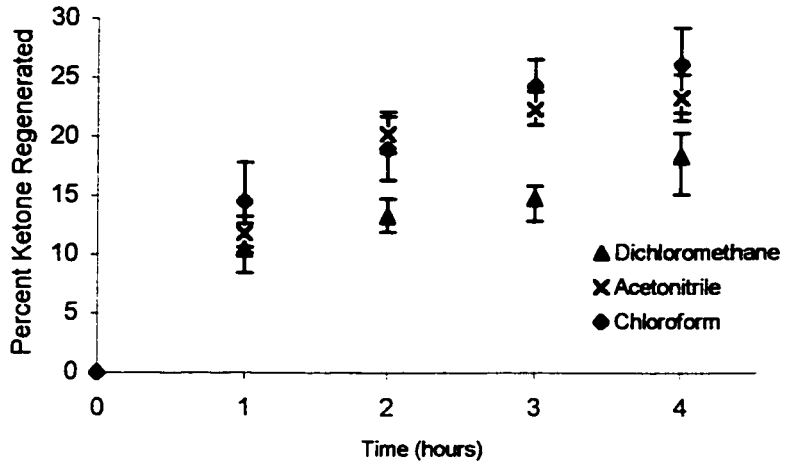


Figure 3.6: Regeneration of cyclopentanone in different solvents

dichloromethane was used, similar to the results obtained from the study summarized in Table 3.2.[103]

The lower yields obtained when dichloromethane was used can be explained, in part, to degradation of chloranil upon irradiation. Using UV-Vis spectroscopy it was found that, when in small concentrations (μM) and dissolved in dichloromethane, exposure to light results in chloranil degradation. The UV-Vis absorption spectra of chloranil in dichloromethane, at different time intervals, are depicted in Figure 3.7. This figure shows that the absorption bands are changing over time, with exposure to high intensity light, indicating a photochemical reaction is occurring involving chloranil.

The degradation of chloranil was not only observed when the solution was exposed to the Hg/Xe lamp but also when exposed to ambient light. Though the

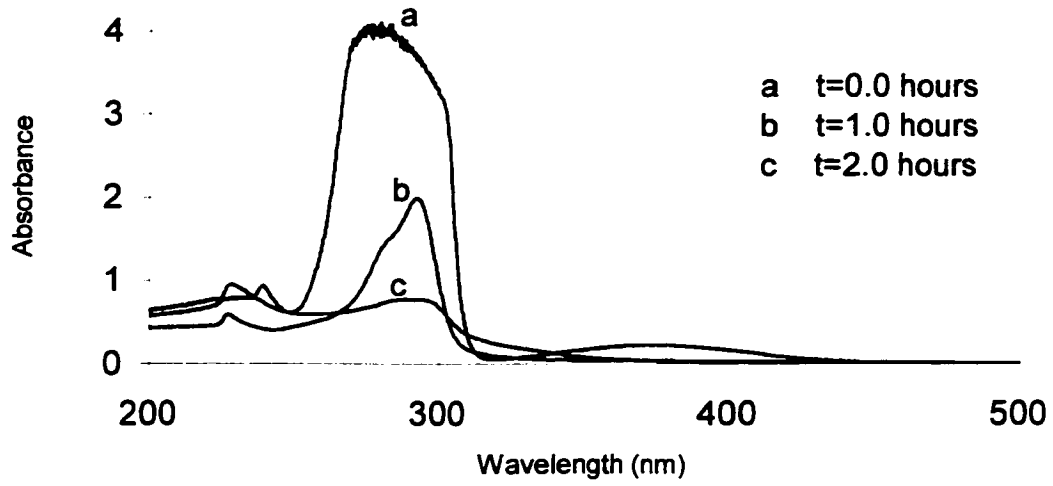


Figure 3.7: UV-Vis absorption spectra of chloranil in dichloromethane depicting degradation over time

degradation occurred at a slower rate, the changes in the absorption spectrum that were observed over time were similar to those in Figure 3.7.

In contrast to dichloromethane, chloroform does not degrade chloranil in the same manner. UV-Vis absorption spectroscopy experiments did not show any significant changes in the absorption spectrum of a chloranil solution in chloroform after extended periods of irradiation.

3.2.3 Effect of Light Intensity on Ketone Formation

Literature documents the fact that chloranil is capable of oxidizing aromatic species from the ground state.[82,84,86,87] With an aromatic component, it is possible that ground state chloranil can oxidize a tosylhydrazone and deprotect a ketone without irradiation.

Evidence was found which suggested that the deprotection reaction continued after irradiation of the tosylhydrazone-chloranil solution had ceased. Solutions in which the precipitate had been filtered would generate new precipitate when the solution was allowed to stand overnight.

To probe this possibility, experiments with variations of light were conducted. Three identical tosylhydrazone-chloranil solutions were irradiated for 4 hours with different light intensities. One solution was irradiated with the Hg/Xe lamp, the second solution was left on the bench top exposed to ambient light, and the third solution was placed in the dark. If the reaction is photochemical in nature, then it is expected that the regeneration of ketone will decrease with decreased

light intensity and no ketone should form from the solution that was placed in the dark.

The results are summarized in Figure 3.8. From this graph it can be seen that there is a decrease in the amount of ketone regenerated with decreasing light intensity. The cyclopentanone tosylhydrazone solution that was exposed to the Hg/Xe lamp regenerated 26.1% of the ketone. A solution of 2-heptanone tosylhydrazone in a similar experiment regenerated 30.4% of the ketone. The second set of solutions as exposed only to ambient light, regenerated 15.4% of cyclopentanone with 20.5% of 2-heptanone being regenerated in the corresponding experiment. For both ketones studied, the solutions that were left in the dark did not regenerate any ketone. These results confirm that the observed reaction is photochemical in nature, and that excitation of chloranil is required for the reaction to occur.

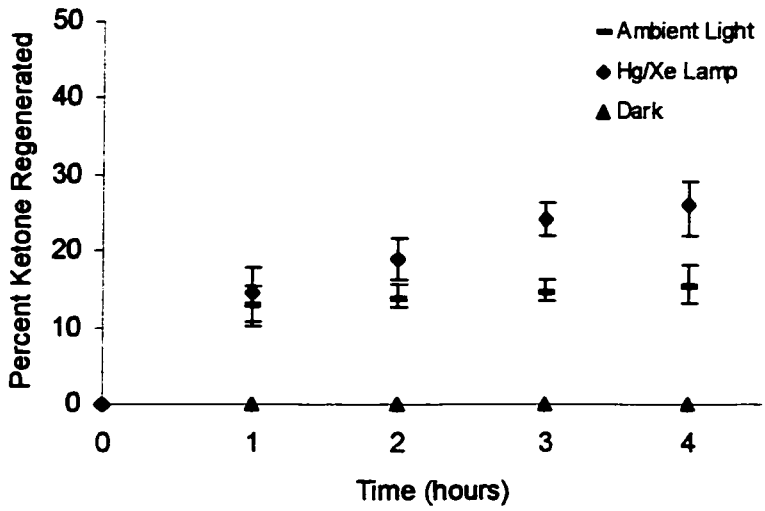


Figure 3.8: Effect of light intensity on cyclopentanone formation

3.2.4 Effect of Precipitate on Ketone Formation

Due to a decrease in the rate of ketone formation coinciding with the appearance of precipitate, it was hypothesized that this byproduct was retarding formation of the ketone. To probe this, experiments were done in which the precipitate was removed. Cyclopentanone tosylhydrazone and 2-heptanone tosylhydrazone solutions of standard concentrations were irradiated under standard conditions. After each hour the precipitate was filtered, and the filtrate was irradiated further.

The graph in Figure 3.9 shows the results for cyclopentanone tosylhydrazone. Like in previous experiments, the first hour produced around 17% of the deprotected ketone, but hourly filtration enables further ketone formation. After 10 hours the amount of ketone produced was close to 90%. The measurements taken at subsequent time intervals show little or no further generation of ketone. In addition no further precipitate was observed. Similar

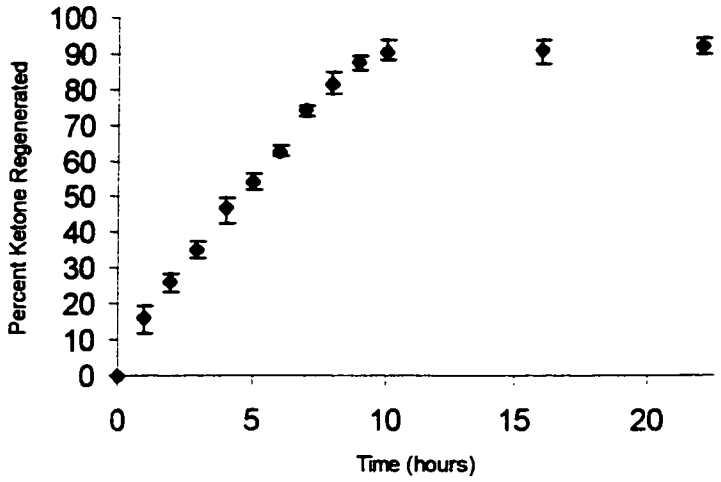


Figure 3.9: Deprotection of cyclopentanone over time with filtration of precipitate

patterns were observed for 2-heptanone tosylhydrazone. When precipitate was added to the initial tosylhydrazone solution (1:1 ratio with respect to tosylhydrazone), ketone formation was reduced to 9.2% after 4 hours. This confirms that the precipitate is the source of the hindrance in ketone regeneration.

Several possible explanations as to how the precipitate retards ketone formation were probed individually. These are: 1) Light absorption by the precipitate. The UV-Vis spectrum of the precipitate (Figure 3.10) shows absorption between 200 and 320 nm. As discussed in Section 1.4, the absorption band critical for the photochemistry of chloranil has a maximum at 355 nm.[97,98] Additionally, the absorption band of the precipitate falls within the cutoff wavelength of Pyrex glass (320 nm), thus it can not be interfering with the excitation of chloranil by absorbing light.

2) Scattering of the incident light by the precipitate. Irradiation experiments of a tosylhydrazone-chloranil solution, with a 10% ethanol-chloroform solvent

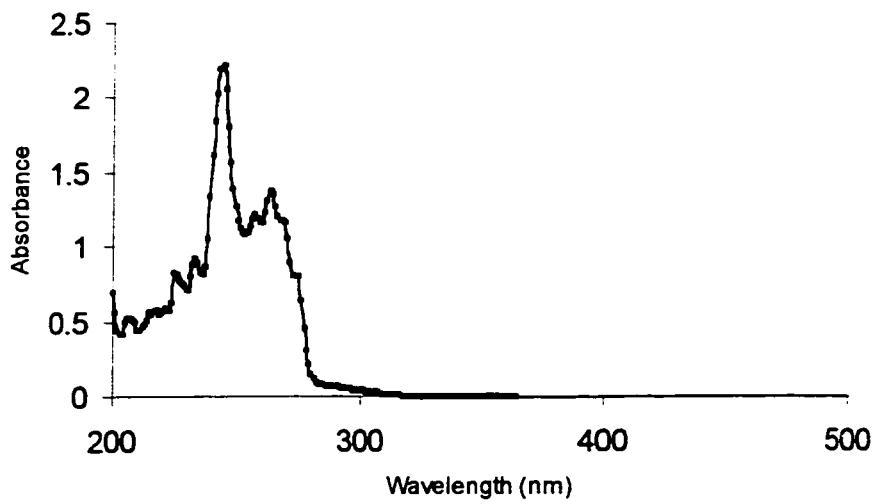


Figure 3.10: UV-Vis spectrum of the precipitate

mixture, resulted in no precipitate being formed. Mass spectrometry studies showed that the byproduct (m/z 373.2) was present in solution (Figure 3.11). The mass spectrum of the precipitated byproduct will be discussed further in Section 3.5. GC analysis indicated that the amount of ketone formed was similar to the amount when pure chloroform was used. The graph in Figure 3.12 shows that 13.8% of cyclopentanone is regenerated within the first hour of irradiation and 24.6% is regenerated after four hours. Upon removal of the solvent mixture, the colorless precipitate byproduct was recovered. Since ketone formation was hindered even when the byproduct remained in solution, scattering of light was ruled out.

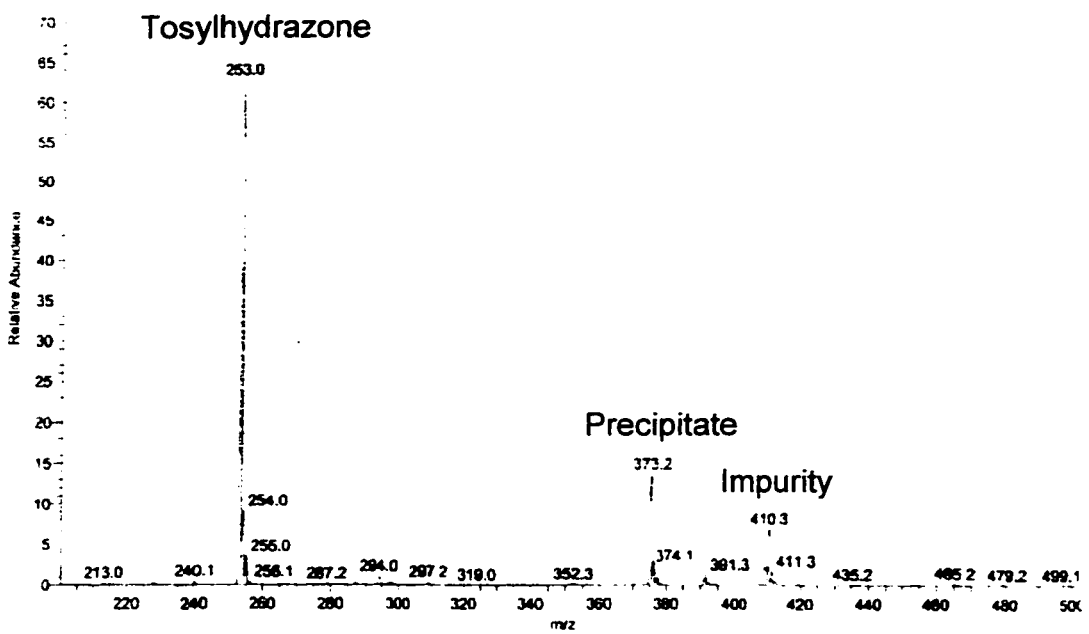


Figure 3.11: Mass spectrum of tosylhydrazone solution after irradiation for 2 hours, depicting cyclopentanone tosylhydrazone peak (m/z 253.0) and precipitate peak (m/z 373.2)

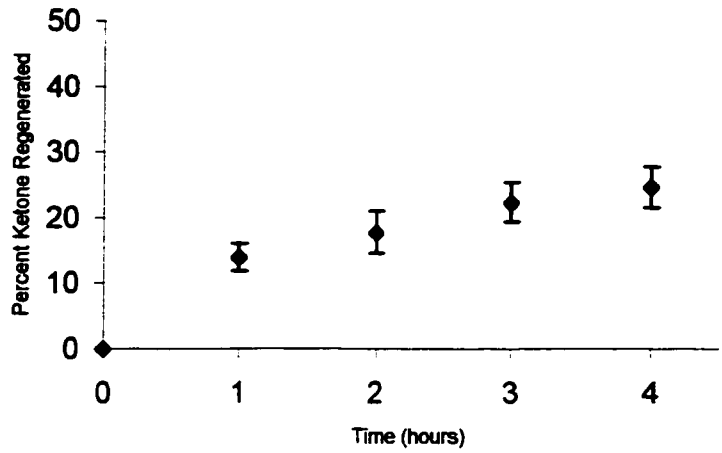


Figure 3.12: Regeneration of cyclopentanone in a 10% ethanol-chloroform solution

3) Competitive complexing of chloranil by the precipitate. Chloranil is known to complex with aromatic species.[82,84,86,87] Spectroscopic studies of the precipitate (discussed in Section 3.5) show that it contains two aromatic groups. A competitive complexing between chloranil and the precipitate would prevent formation of a complex between chloranil and tosylhydrazone, thus preventing the deprotection reaction from occurring. The addition of an excess of chloranil would remedy such a situation, however upon saturation of solution with chloranil, no change in the deprotection pattern was observed. This shows that competitive complexing of precipitate with chloranil is not causing the observed impedance of ketone formation.

4) Competitive oxidation of the precipitate by excited state chloranil. Cyclic voltammetry studies of tosylhydrazones and the precipitate (Section 3.4.1) have shown that the oxidation potentials of cyclopentanone tosylhydrazone and the

precipitate are 2.31V and 0.30V respectively. This indicates that oxidation of the precipitate by the excited state chloranil will occur more readily than that of the tosylhydrazone. The cyclic voltammogram of the precipitate also indicated that, in contrast to oxidation of the tosylhydrazone, oxidation of the precipitate is reversible. The most likely explanation for reduced ketone regeneration due to the precipitate byproduct, then, is that of preferred oxidation of the precipitate by excited state chloranil and rapid back electron transfer.

3.2.5 Reaction Order With Respect to Tosylhydrazone

The determination of the order of reaction with respect to tosylhydrazone was accomplished through two different means. The first method was to compare the consumption of tosylhydrazone, through the formation of ketone, with respect to time. The second method used involves comparing the amount of ketone formed with respect to initial concentration of tosylhydrazone.

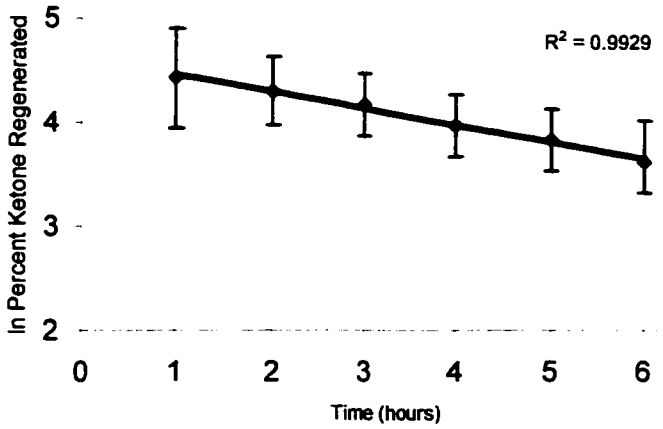


Figure 3.13: Plot of natural log of concentration of remaining cyclopentanone versus time

With the values that were obtained from the filtering of precipitate experiments of cyclopentanone tosylhydrazone and 2-heptanone tosylhydrazone, the amount of tosylhydrazone remaining at each time interval was determined. These values were plotted with respect to time, and the order of reaction for the tosylhydrazone was determined. A plot of the natural log of concentration against time gave a straight line with a negative slope, as shown in Figure 3.13. This suggests first order kinetics with respect to the tosylhydrazone, and the negative slope is expected since consumption of the reagent is monitored.

To corroborate this finding, a second experiment was conducted on solutions with different initial concentrations of cyclopentanone tosylhydrazone. These solutions were irradiated for one half hour, at which time the amount of ketone formed was measured. The graph that was obtained from this experiment is shown in Figure 3.14. For a first order reaction, doubling the hydrazone concentration leads to a doubling of ketone concentration and therefore a straight

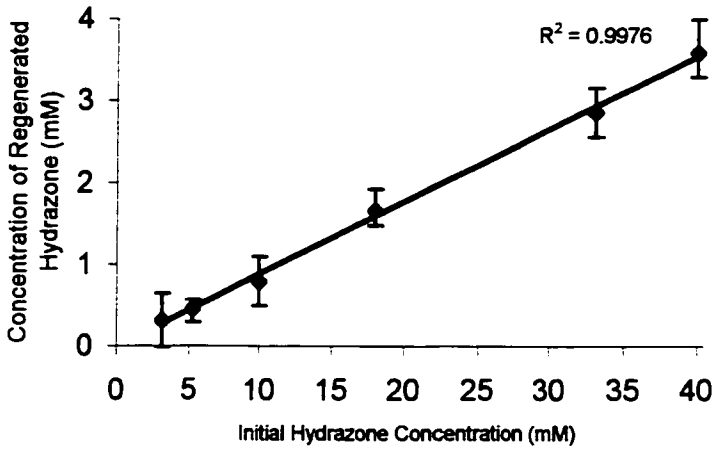


Figure 3.14: Concentration of regenerated ketone after half hour of irradiation versus initial concentration of hydrazone

line. This clearly demonstrates that the reaction order is one with respect to the tosylhydrazone.

3.2.6 Photolysis of Functionalized Tosylhydrazones

Five functionalized ketones: acetylmalononitrile, acetoacetamide, ethyl acetoacetate, acetylbutyrolactone, and 3-acetyl-propanol, and four aromatic ketones: 1-acetonaphthone, 2-acetonaphthone, 3-methoxyacetophenone and 4-methoxyacetophenone were protected by conversion to tosylhydrazones. Like the aliphatic counterparts, all were obtained in good yields (80-95%). The tosylhydrazine reacted selectively with the carbonyl group in ketones with functionality containing additional carbon-oxygen double bonds.

The photolytic deprotection of the functionalized ketones was conducted in a similar manner as the deprotection of the aliphatic ketones, with similar concentrations and reaction conditions. The results of these studies are summarized in Table 3.3. These results show that the functionalized ketones are

Table 3.3: Regeneration of functionalized ketones after 4 hours

Ketone Regenerated	Percent Yield
Acetoacetamide	22.5%
Acetylbutyrolactone	19.3%
Acetylmalononitrile	10.6%
Ethyl Acetoacetate	17.9%
3-Acetyl-1-Propanol	NA

regenerated between 10.5% and 22.5% after four hours of irradiation. Acetoacetamide tosylhydrazone was insoluble in chloroform and needed to be irradiated in a 50% ethanol-chloroform mixture. Quantitative results could not be obtained for 3-acetyl-1-propanol, as the GC column was not ideal for alcohol analysis, however 3-acetyl-1-propanol was detected upon irradiation. The ketone regeneration patterns were the same as those of the aliphatic ketones, with the majority being formed within the first hour and precipitate formation hindering further ketone formation.

Preliminary studies were conducted on the deprotection of the aromatic ketones. Qualitative experiments were conducted in which tosylhydrazone-chloranil solutions were irradiated for one hour, at which time GC analysis was performed to determine if the ketone was present in solution. In all cases the ketone was detected after irradiation and the precipitate was present. Further experimentation revealed that chloranil was not required by these tosylhydrazones to regenerate the ketone. When chloranil was present, the ketone peak area on a gas chromatogram from an irradiated tosylhydrazone solution was approximately twice that of the ketone peak area of a similar tosylhydrazone solution without chloranil. This indicates that two reactions are occurring: the first is a chloranil oxidation of the tosylhydrazone, similar to oxidation of an aliphatic ketone derived tosylhydrazone, and the second is a self-sensitized reaction.

Bellesia and co-workers demonstrated that tosylhydrazones with π systems in conjugation to the carbon-nitrogen double bond, such as acetophenone and

benzalacetone, are photoreactive.[35] However, in none of their experiments was ketone reported to be regenerated and the dominant product was a dimer of the imine of the aromatic ketone.

Gravel and co-workers demonstrated that substituted aromatic compounds could photochemically decompose without the need of any photosensitizing compound.[8,26-28] The o-nitrobenzyl ketal method of photolytic deprotection for ketones was designed using this technique, and is discussed in Section 1.2.2. Absorption of light by the aromatic portion of the tosylhydrazones could result in ketone regeneration as shown by Gravel.

No further studies were conducted on tosylhydrazones of aromatic ketones and the exploration of this phenomenon has been designated for a future project.

3.2.7 Conclusion: Ketone Deprotection

Irradiation of a tosylhydrazone in chloroform solution in the presence of chloranil, regenerates the starting ketone and produces a colorless precipitating byproduct. The yields varied between 23.7% and 30.4% for aliphatic ketones and 10.6% and 22.5% for functionalized ketones, after 4 hours of irradiation. The amount of chloranil present was shown to have little effect on the yields.

The majority of ketone was found to regenerate within the first hour of irradiation, however little additional ketone was regenerated with further irradiation. The reduced ketone formation was attributed to formation of the precipitate byproduct. Hourly filtration of the precipitate resulted in 90% regeneration of the ketone after 10 hours of irradiation. Both absorption and

scattering of light by the precipitate were ruled out as the cause of interference with ketone formation. Preferential oxidation of the precipitate over the tosylhydrazone by chloranil was attributed to this phenomenon.

The polarity of the solvent was shown to have little effect on the regeneration of ketone. Similar yields were obtained when acetonitrile and chloroform were used. Lower yields were obtained with dichloromethane, attributed to the degradation of chloranil in this solvent. These similarities indicate that separation of the radical ion species is not the rate limiting step.

Light intensity was shown to effect the amount of ketone regenerated in a given time. Irradiation with a high intensity Hg/Xe lamp regenerated more ketone than when a similar solution was exposed to ambient light. In addition, a solution that was kept in the dark did not regenerate any ketone within an identical time period. This demonstrates that the reaction is photochemical.

The order of reaction with respect to tosylhydrazone was determined in two independent experiments. Both the consumption of tosylhydrazone, measured through the formation of ketone, with respect to time, and the formation of ketone with respect to the initial amount of tosylhydrazone show the reaction order with respect to tosylhydrazone to be one.

3.3 Oxygen Atom Source in Regenerated Ketone

An investigation into the source of the oxygen atom in the regenerated ketone was conducted. Three possible sources of oxygen were identified: (a) water found in the solvent, (b) the oxygen atom on the tosyl moiety, and (c) molecular oxygen in the air. Each of these possibilities was probed individually by systematically removing them, and observing the effect on the formation of ketone.

3.3.1 Water as Oxygen Atom Source

Compounds containing carbon-nitrogen double bonds are, in principle capable of undergoing hydrolysis. Imines are one such category of compound, and hydrolyze readily to ketones and amines.[34] Substituted hydrazones, on the other hand, are resistant to simple hydrolysis, [11,34] yet regeneration of the carbonyl compound via "photolytic hydrolysis" has been observed.[33]

Work by Binkley on the photochemistry of phenylhydrazones shows that the nitrogen-nitrogen single bond will homolyze upon irradiation with a 450 W high-pressure quartz mercury-vapor lamp, and that subsequent hydrogen abstraction will form aniline and an imine.[33] This imine is easily hydrolyzed into a carbonyl compound, resulting in an overall "photolytic hydrolysis" of a substituted hydrazone. Conversely, Bellesia and co-workers probed the effects of light on tosylhydrazones, and their results did not show carbonyl formation upon irradiation.[35] Their work also showed that tosylhydrazones of conjugated carbonyl compounds, such as acetophenone and benzalacetone, were photoreactive,

whereas tosylhydrazones of unconjugated species, such as acetone, were not. Neither Binkley nor Bellesia et al. used a photosensitizer.

To investigate the possibility of water as the oxygen source, experiments were conducted with hydrazone-chloranil solutions, prepared from chloroform that was dried via simple distillation. The amount of ketone regenerated in each sample taken was plotted against time; results for cyclopentanone can be seen in Figure 3.15. The amount of cyclopentanone that was obtained after irradiating the dry solution for 4 hours was 27.4%. This is in comparison with 26.1% for the solution that was not dried. The dry 2-heptanone tosylhydrazone solution regenerated 31.4% as compared to 30.4% for the solution that was not dried in a similar experiment. The values are not markedly different and the data points for the dry solutions fall within the error bars for the solutions that are not dried. This indicates that water is not the oxygen source in the regenerated ketone.

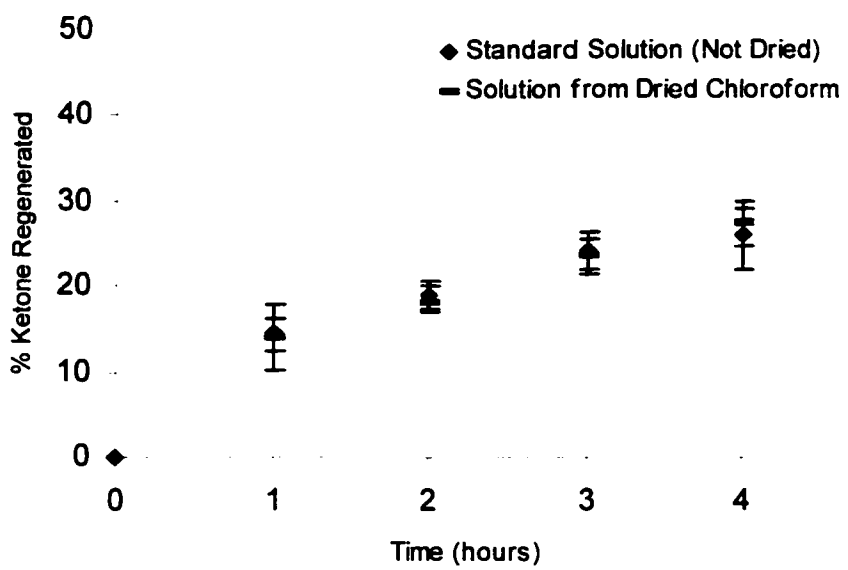
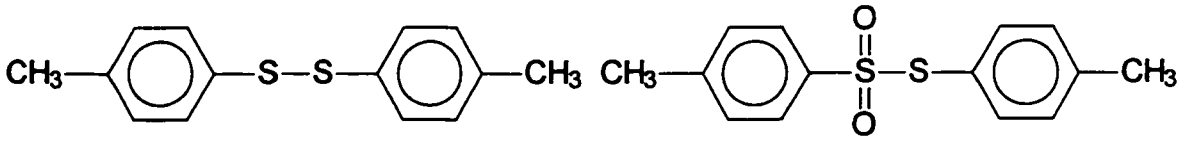


Figure 3.15: Effect of water in solution on the regeneration of cyclopentanone

3.3.2 Tosyl Group as Oxygen Atom Source

Wilt and co-workers, while studying the thermal decomposition of aldehyde tosylhydrazones, found that small amounts of aldehyde, p-tolyl disulfide and p-tolyl p-toluenethiosulfonate were produced as side products (Figure 3.16).[48] They attributed this side reaction as a result of an oxidation-reduction reaction between the p-toluenesulfinate ion and the carbene formed upon fragmentation of the molecule, rendering the tosyl group the source of oxygen in the regenerated ketone.



(a) (b)

Figure 3.16: Structure of p-tolyl disulfide (a) and p-tolyl p-toluenethiosulfonate (b)

To investigate this further, the phenylhydrazone analogues of cyclopentanone tosylhydrazone and 2-heptanone tosylhydrazone were synthesized. Chloroform solutions of these phenylhydrazones, containing chloranil, were irradiated. The amount of regenerated ketone was plotted against time, and the results are shown in Figures 3.17 and 3.18. After 4 hours, the amount of ketone obtained from irradiation of the phenylhydrazone solutions were 16.0% (cyclopentanone) and 17.2% (2-heptanone). This compared to 26.1% for cyclopentanone tosylhydrazone and 30.4% for 2-heptanone tosylhydrazone. Clearly, one observes a decrease in the amount of ketone produced, however if

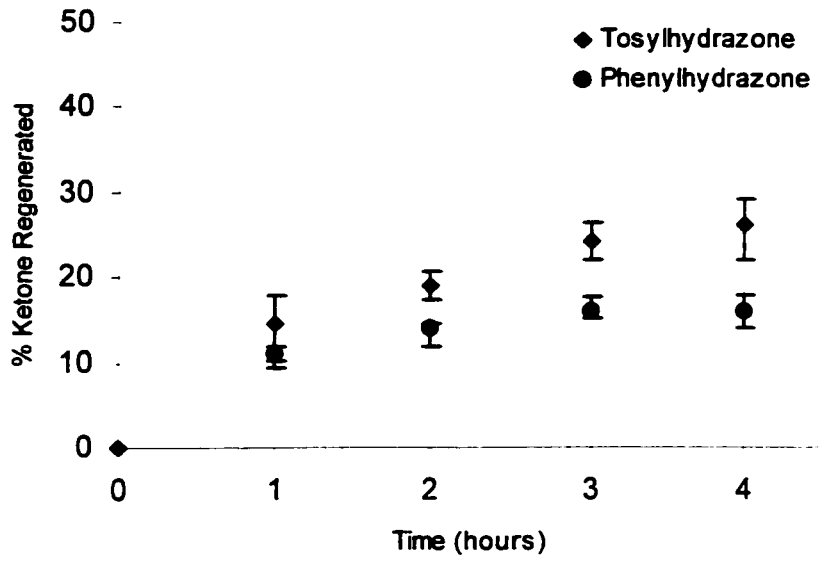


Figure 3.17: Cyclopentanone formation from its tosylhydrazone and phenylhydrazone

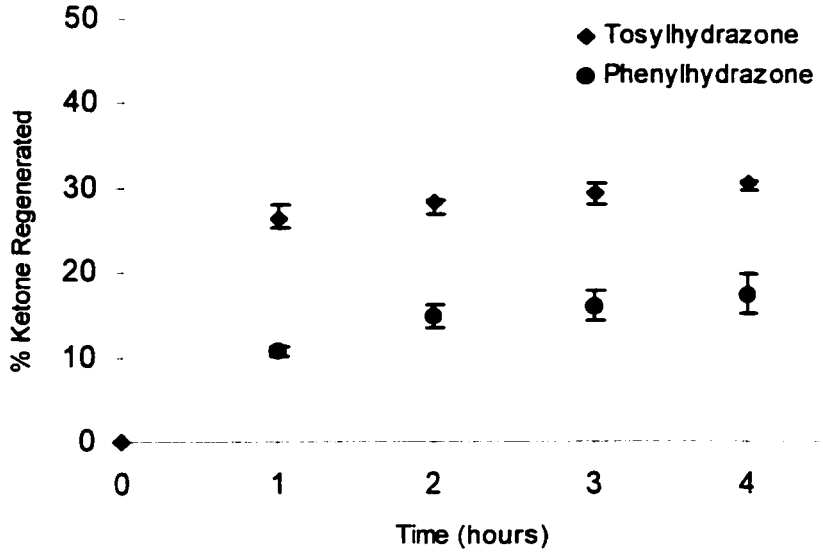


Figure 3.18: 2-Heptanone formation from its tosylhydrazone and phenylhydrazone

the tosyl group were the oxygen atom source it would be expected that there would not be any ketone formed upon irradiation of the phenylhydrazone-chloranil solutions. In Section 3.2.4 the effect of the precipitate product on the formation of ketone from tosylhydrazones was discussed. The precipitate was shown to be involved in a slowing in the regeneration of ketone. In the case of phenylhydrazones, the byproduct produced was black, and this dark byproduct would have prevented light from reaching chloranil, resulting in the observed decrease in ketone regeneration. From this it was concluded that the tosyl group was not the source of the oxygen atom in the regenerated ketone.

Binkley's work,[33] demonstrating that phenylhydrazones can undergo photochemical reactions that ultimately result in the formation of ketones, can provide a possible argument to the above conclusion, provided the phenylhydrazones in the above study yield ketone through "photolytic hydrolysis". Yet this is unlikely, as Binkley's reactions were slow and had low yields.

In addition, the byproduct from the tosylhydrazone would show evidence of an oxidation-reduction reaction. Should an oxidation-reduction reaction be taking place, then p-tolyl disulfide, p-tolyl p-toluenethiosulfonate, or some other similar compound would be present after irradiation. The precipitate byproduct was analyzed; it was comprised largely of the tosyl portion of the tosylhydrazone with the SO_2 portion of the tosyl group intact. The precipitate is described in further detail in Section 3.6. Thus an oxidation-reduction reaction did not take place, and the oxygen atom source was not the tosyl group.

3.3.3 Oxygen Gas as Oxygen Atom Source

It is well established that molecular oxygen as a ground-state diradical reacts with organic radicals to produce species containing peroxide bonds.[104,105] It is also well established that chloranil, upon irradiation, becomes an excellent oxidizer and produces a radical cation upon oxidizing an organic species.[83-94] This being the case, it is possible that the radical cation formed upon oxidation of the tosylhydrazone by chloranil, will react with molecular oxygen, producing a peroxide radical cation that decomposes regenerating the ketone.

Experiments were conducted in which the tosylhydrazone-chloranil solutions were degassed through freeze-pump-thaw cycles, to remove any traces of oxygen. The plots of regenerated ketone against time for cyclopentanone tosylhydrazone and 2-heptanone tosylhydrazone are shown in Figurers 3.19 and 3.20, respectively. After 4 hours of irradiation, one does not observe the formation

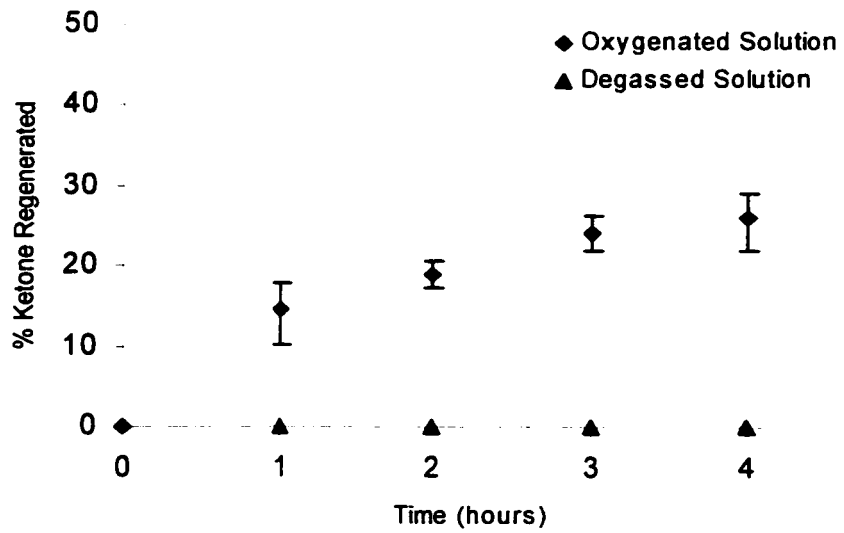


Figure 3.19: Cyclopentanone formation with molecular oxygen present and absent

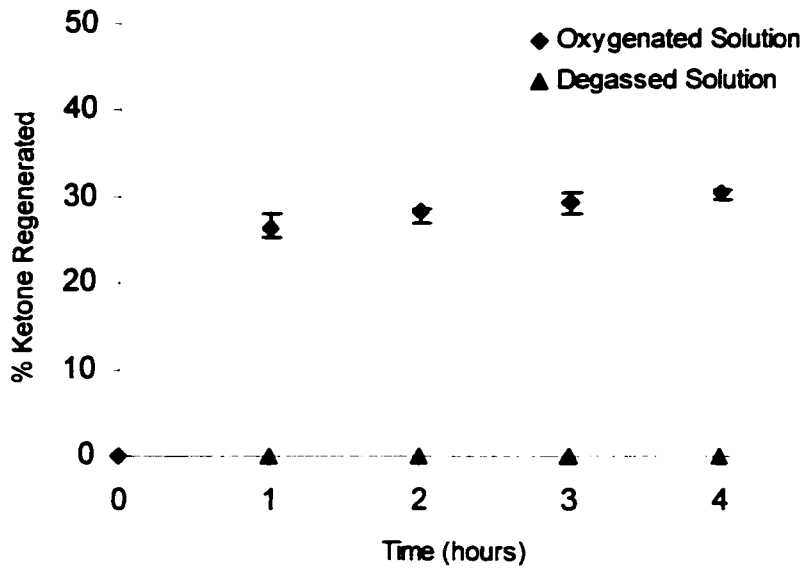


Figure 3.20: 2-Heptanone formation with molecular oxygen present and absent

of ketone in the degassed solutions. This was found to be consistent and reproducible with respect to both tosylhydrazones studied. From this observation it was concluded that the source of the oxygen atom was molecular oxygen.

3.3.4 Conclusion: Oxygen Atom Source in Regenerated Ketone

Three possible sources of oxygen in the regenerated ketone were identified, and systematically probed and eliminated. Water as the source was eliminated after experiments involving dried chloroform gave similar yields of deprotected ketone as solutions made from solvent that was not dried.

The tosyl group as the source was eliminated upon experiments involving the photolysis of the corresponding phenylhydrazones. The formation of ketone upon photolysis of these oxygen atom free compounds indicates that the tosyl group is not the oxygen atom source. In addition, the precipitate byproduct

contains tosyl groups with the SO_2 moiety intact, and will be discussed further is Section 3.5.

Degassing the solution through freeze-pump-thaw cycles was found to halt the regeneration of ketone upon irradiation. From this it was concluded that molecular oxygen is the source of the oxygen atom in the regenerated ketone.

3.4 Role of the Radical Cation

With experimental evidence that photochemically activated chloranil is crucial for the regeneration of ketones from tosylhydrazones, and numerous citations in the literature about excited triplet chloranil's ability as a one-electron oxidant[83-94], it is expected that a tosylhydrazone radical cation is involved in the reaction mechanism. To understand the reaction mechanism, the generation of a tosylhydrazone radical cation needed to be proven. If the tosylhydrazone radical is generated, investigation into where in the molecule is oxidation occurring, the changes in geometry upon oxidation, and the location where the radical electron resides in the radical cation molecule needs to be conducted.

The question of the possible generation of a tosylhydrazone radical cation was probed via two different methods: (1) independent generation of the radical cation electrochemically, (2) capturing the radical cation from chemical generation using a radical trap.

3.4.1 Electrochemical Oxidation of Tosylhydrazones

Using cyclic voltammetry, the presence of an oxidizable species results in a change in current when the oxidation potential is applied to the solution.[106] If the oxidation process is reversible, that is the oxidized species can be reduced, then the reversal of the potential results in another change in current, opposite to the change in current caused by oxidation. In the case of an irreversible oxidation, the cyclic voltammogram exhibits only an oxidation peak and no corresponding reduction peak when the potential is reversed.[106,107]

The analysis of the cyclic voltammogram between the potentials of –0.50V and 3.00V of a 0.50M solution of the supporting electrolyte, tetrabutylammonium hexafluorophosphate (TBAHFP), resulted in no oxidation or reduction peaks being observed (Appendix IV, Figure A.18) except for the oxidation of acetonitrile beginning at 1.50V and trace water at 2.07V. Knowing that TBAHFP will not interfere with the oxidation or reduction measurements, the voltammogram of a 50.0mM solution of cyclopentanone tosylhydrazone was obtained. Shown in Figure 3.21, the oxidation potential of cyclopentanone tosylhydrazone, taken at the maximum of the anodic current peak (5.31μA), appears at 2.31V. This voltammogram also shows that the oxidation of the tosylhydrazone is irreversible, since no reduction peak is observed along the negative scan.

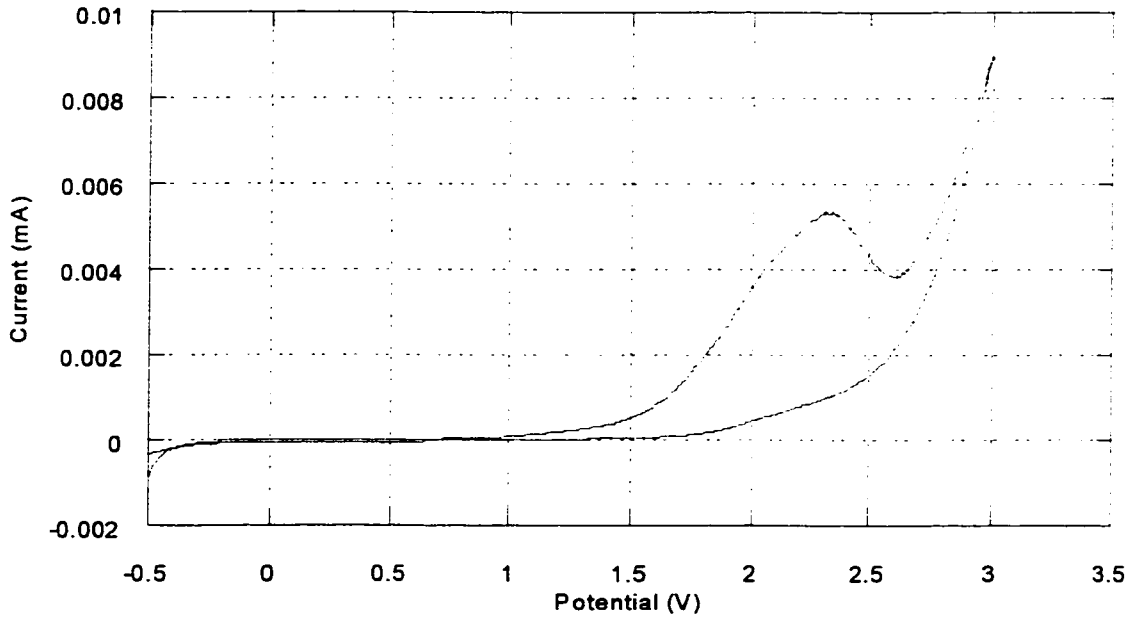


Figure 3.21: Cyclic voltammogram of a cyclopentanone tosylhydrazone solution

To ascertain further that the oxidation peak arises from oxidation of the tosylhydrazone, concentration studies were performed, as solutions with higher concentration are expected to generate a larger current at the oxidation potential. Solutions with tosylhydrazone concentrations of 10.0mM and 25.0mM were tested, the results of which are shown in Figure 3.22. As was expected, the current generated increased with increased concentration of the tosylhydrazone, with the 10.0mM solution generating a current of 2.85μA and the 25mM solution generating a current of 3.43μA.

With the consumption of the tosylhydrazone, the oxidation peak decreases over time. Figure 3.23 shows the voltammogram of a 50.0mM solution before and

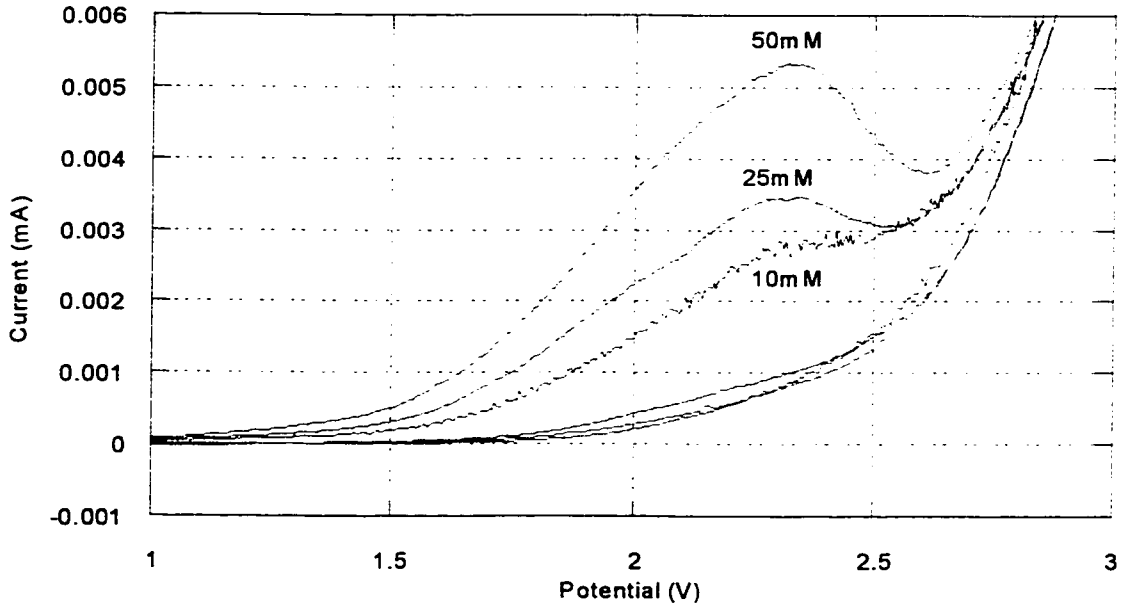


Figure 3.22: Partial cyclic voltammogram of cyclopentanone tosylhydrazone solutions of different concentrations

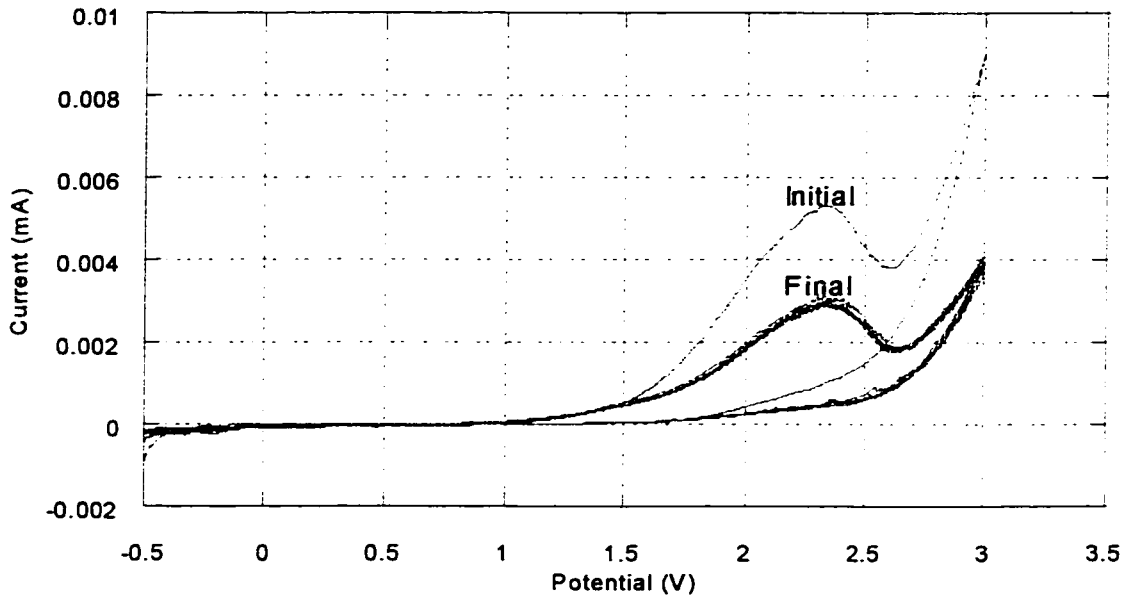


Figure 3.23: Cyclic voltammogram of cyclopentanone tosylhydrazone solution before and after running the voltammeter between –0.05V and 3.00V for 2 hours

after 2 hours elapsed. Running the voltammeter between the –0.50V and 3.00V, the current at the oxidation potential decreased from 5.31μA initially to 2.88μA at the end 2 hours. These experiments demonstrated that the oxidation of cyclopentanone tosylhydrazone was irreversible (a reduction peak was not present) and upon oxidation, the tosylhydrazone was being converted to another compound.

After the elapsed time of 2 hours, a small, but detectable current (0.00V, 0.16μA) was generated by the reduction of a species that was not initially present, indicating a reaction product. To determine whether this new reduction peak was caused one of the products of tosylhydrazone photolysis, cyclic voltammograms were obtained for cyclopentanone and the precipitate.

Ketones can not be oxidized except under very rigorous conditions,[2,3] but can be reduced, and the radical anion can be oxidized to the ketone. Thus the voltammogram of cyclopentanone should show a reduction peak followed by an oxidation peak and these signals should not decay with time. The voltammogram obtained for cyclopentanone did not show any oxidation or reduction peaks between the potential of 3.50V and –0.50V. Widening of this range to 3.50V and –2.00V revealed that reduction occurs for cyclopentanone at –1.58V while the corresponding oxidation occurs at –1.20V (Appendix IV, Figure A.20). Since these redox reactions occur well outside the potential range used in the previous experiments, cyclopentanone can not be the source of the observed reduction peak.

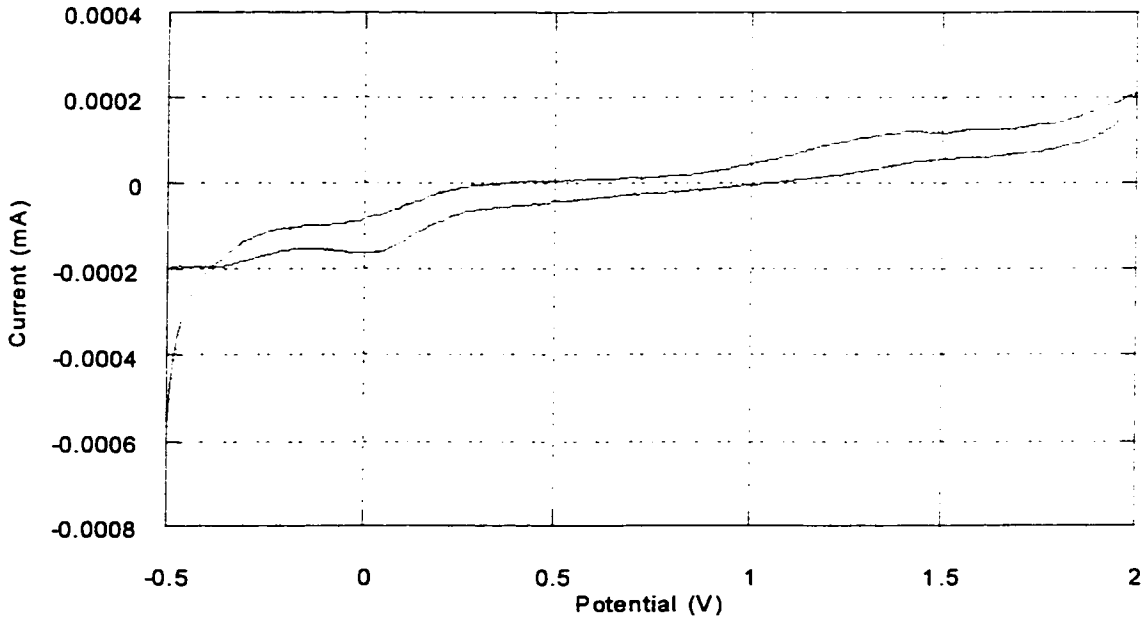


Figure 3.24: Cyclic voltammogram of a 10.0mM precipitate solution

The voltammogram for the precipitate on the other hand, shown in Figure 3.24, depicts a reduction peak at 0.01V and an oxidation peak at 0.30V. From this data it seems clear that the reduction peak, observed after 2 hours of the tosylhydrazone electrolysis is due to the presence of the precipitate product. Unlike tosylhydrazone and like cyclopentanone, the redox reactions of the precipitate are reversible, and so oxidation does not result in a change in concentration and thus there is no change in the cyclic voltammogram over time (Appendix IV, Figure A.21). What is also different from this voltammogram as opposed to the tosylhydrazone voltammogram, is that through this range of potential the precipitate is oxidized and reduced twice. The first time as noted above and a second time with oxidation occurring at 1.43V along the positive scan and reduction at 1.37V along the negative scan.

The presence of the regenerated cyclopentanone was confirmed through GC analysis. After 2 hours electrolysis between 1.00V and 3.00V, the solution was mixed with water and extracted with chloroform. Cyclopentanone was detected through its retention time and compared with a known sample. Though this method was not quantitative as numerous extractions would be required to remove all cyclopentanone from the aqueous phase, it proved that the ketone was regenerated in the electrochemical oxidation of the tosylhydrazone.

3.4.2 Trapping the Tosylhydrazone Radical Cation

Radical trap experiments were performed to support the idea of a tosylhydrazone radical cation further. The compound chosen was 2,2,6,6-

tetramethylpiperidin-1-oxy, or TEMPO, a common radical trap that has long been used to trap carbon-centered radicals.[108-110] The reaction between carbon-centered radicals and TEMPO is very fast, with a second order rate constant of approximately 10^{10} $M^{-1}s^{-1}$ in acetonitrile.[109-111] This being the case, it is expected that upon oxidation by chloranil, the tosylhydrazone radical cation will quickly react with TEMPO, thus halting further progression of the reaction. Neither ketone nor the precipitate should be observed.

A cyclopentanone tosylhydrazone-chloranil solution was prepared with standard concentrations and TEMPO was added in equal concentration to the tosylhydrazone. This solution was irradiated for 15 minutes, at which time a sample was injected into the mass spectrometer.

The first indication that a reaction was occurring was a definitive color change in the solution. Prior to irradiation, the pale yellow color of the tosylhydrazone-chloranil solution was masked by the vivid red-orange color of TEMPO. After irradiation for a short period of time the solution turned dark blue. This color change coincides with the presumed formation of adduct.

The mass spectrum obtained for the irradiated tosylhydrazone-TEMPO solution is shown in Figure 3.25. At m/z 253.0, the M+1 peak for the unreacted tosylhydrazone is the most intense peak present (the M+1 peak was confirmed for cyclopentanone tosylhydrazone, Appendix V). The second most intense peak (relative abundance 65%) occurs at 408.2 m/z and belongs to the adduct (TEMPO 156 g/mol, cyclopentanone tosylhydrazone 252 g/mol).

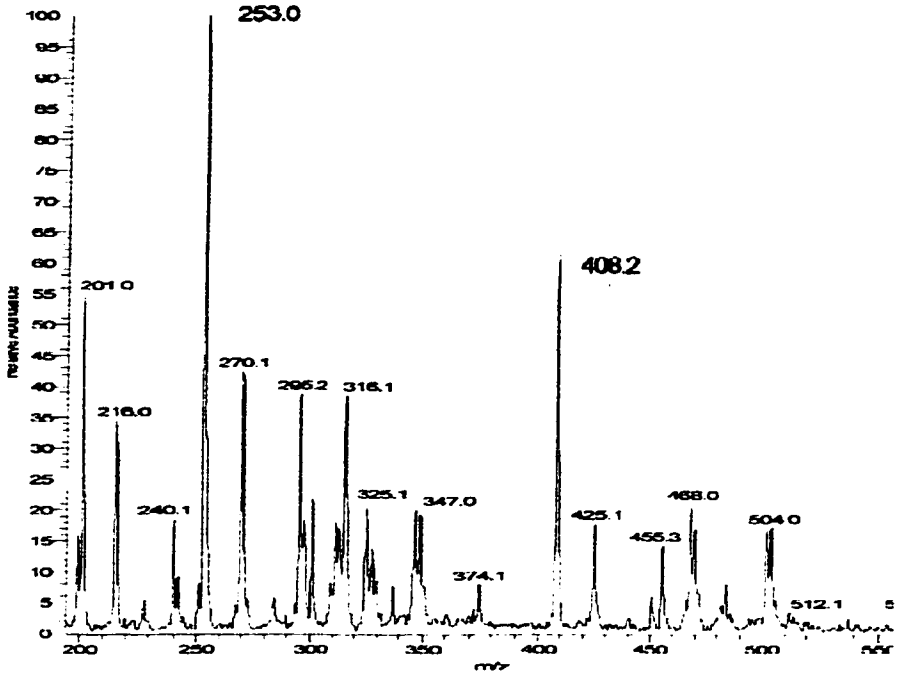


Figure 3.25: Partial mass spectrum of a cyclopentanone tosylhydrazone-TEMPO solution

This data seem to confirm the presence of the tosylhydrazone radical cation after irradiation for a short period of time. To confirm that the adduct detected is not a result of a reaction between TEMPO and the neutral tosylhydrazone, a cyclopentanone tosylhydrazone-TEMPO solution without chloranil was prepared and irradiated for one hour, upon which time a mass spectrum was obtained. This solution did not change color from red to blue; a first indication that the adduct was not forming. Accordingly, m/z 408 for the adduct was not present in the mass spectrum (Appendix V).

These experiments also provided additional information on the tosylhydrazone radical cation and the reaction mechanism for ketone formation.

The fact that the tosylhydrazone radical cation was captured by TEMPO and the adduct detected, points to a carbon-centered radical. TEMPO reacts with carbon-centered radicals, but not oxygen-centered or nitrogen-centered radicals.[108-110] Coupling between TEMPO, which is a nitroxyl radical, and a carbon centered radical result in a carbon-oxygen bond, which is substantially stronger than an oxygen-oxygen bond or a nitrogen-oxygen bond, which would form with oxygen-centered or nitrogen-centered radicals, respectively.[112,113] The location of the radical is further discussed in Sections 3.4.5.

Throughout the TEMPO experiments, a precipitate was not detected. This was expected, since the reaction of the tosylhydrazone radical cation and TEMPO halts the regeneration of the ketone. This indicates that the precipitate is a product of the fragmentation of the tosylhydrazone molecule, occurring after reaction with molecular oxygen. This and other aspects of the proposed mechanism will be elaborated in Section 3.6.

3.4.3 Location of Oxidation of Tosylhydrazone

It is well established that chloranil is a one electron oxidizer, and will remove one electron from the HOMO of the tosylhydrazone.[83-94] Two possibilities were proposed for the location of the HOMO. The HOMO could be either π-type and involve the aromatic π system or the carbon-nitrogen double bond, or n-type and involve a non-bonding basin, such as the lone pair electrons on the nitrogen atoms.

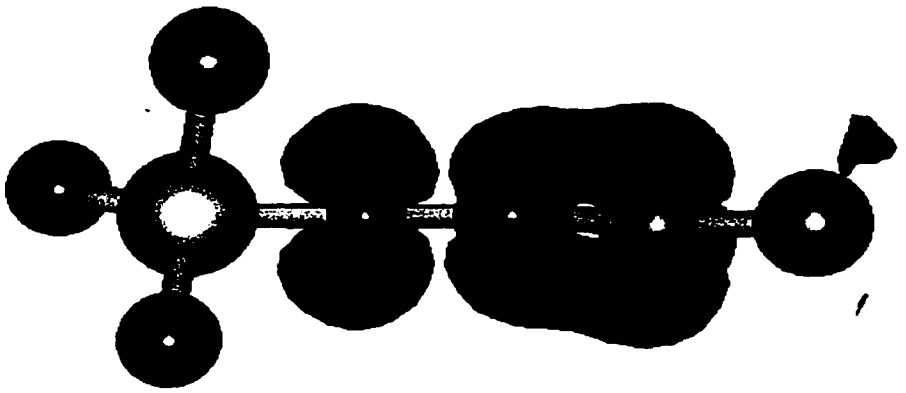


Figure 3.26: π-Type HOMO of acetone methyl sulfone hydrazone (H atoms omitted)

Determining the HOMO character is of interest because removal of an electron from different types of orbitals will have different effects on the geometry of the molecule. With electron removal from a π-type orbital there will be significant changes in the molecular geometry, most notably changes in bond length. Removal of a π-type electron will reduce the electron density in the overlapping π orbitals in multiple bonds, which will result in a lengthening of the bond. In addition to this, where the π orbitals are out of phase, the removal of an electron would lead to a shortening of the bond. Changes in bond length can be significant in understanding a reaction mechanism, as longer bonds are weaker than shorter bonds, and locations where bonds elongate upon oxidation are possible sites for fragmentation of the molecule.[102,114] Removal of an electron from an n-type orbital, on the other hand, does not lead to dramatic changes in

geometry. Usually only small changes in bond angles are observed upon electron removal from an n-type orbital. [102,114]

At the semi-empirical level, the HOMO is π type, depicted in Figure 3.26 for acetone methyl sulfone hydrazone (H atoms omitted), a simplified model, but results hold true for all tosylhydrazones investigated. It can be seen that the largest contributions to the HOMO are on the hydrazone carbon, the hydrazone nitrogen and the amine-like nitrogen atoms ($\pi_{C=N-N}$). The contribution from the two hydrazone atoms are in phase, those of the two nitrogen atoms are out of phase. Upon oxidation there should be discernible changes in the bonds of the C=N–N group.

3.4.4 Geometric Changes as a Result of Oxidation

Changes in the geometry of cyclopentanone tosylhydrazone and its optimized radical cation are shown in Table 3.4. For most of the bonds there is an agreement between the calculated bond length and the literature values,[114] and there is very little difference between the ground state bond lengths and the bond lengths in the radical cation. There are however two notable exceptions: the bond length of the C=N and the N–N bond.

Upon oxidation, as expected, there was an increase in the length of the carbon-nitrogen double bond, from 130.9 pm to 137.2 pm. The length of the hydrazone bond after oxidation had a value approximately midway between the length of the carbon-nitrogen double bond and the carbon-nitrogen single bond, valued at 147.2 pm.[114]

Table 3.4: Bond lengths in cyclopentanone tosylhydrazone and its radical cation

Bond	Bond Length in Ground State (pm)	Bond Length in Radical Cation (pm)	Literature Value of Bond Length[114] (pm)
C – C	152.7	151.1	154.1
C = N	129.9	137.2	134.2
N – N	139.3	134.3	145.0
N – S	168.1	162.9	168.3
S = O	144.6	143.0	143.2
S – Ar	169.3	170.1	169.2
Ar – C	148.4	147.9	149.9
Aromatic	139.7	138.0	139.5

The other notable change in bond length occurred in the nitrogen-nitrogen bond. This bond shortened from 140.2 pm prior to oxidation, to 134.3 pm after oxidation. This change in bond length occurred due to the same factors that lengthen the hydrazone bond. Section 3.4.3 discussed the contributors to the HOMO, which included contributions from both nitrogen atoms. These contributions were out of phase with one another, resulting in destructive interference and were manifested as a node between the two nitrogen atoms. The removal of one electron from the HOMO reduced the destructive interference and the node became smaller, resulting in the two nitrogen atoms coming closer together.

3.4.5 Location of Unpaired Electron: Spin Density Calculation

The results from a spin density calculation for the 2-heptanone tosylhydrazone radical cation is shown in Figure 3.27. It shows the greatest probability (green shading) of finding the unpaired electron on both the hydrazone carbon and the amine-like nitrogen atom (the induced contribution on the hydrazone nitrogen is depicted in pink).

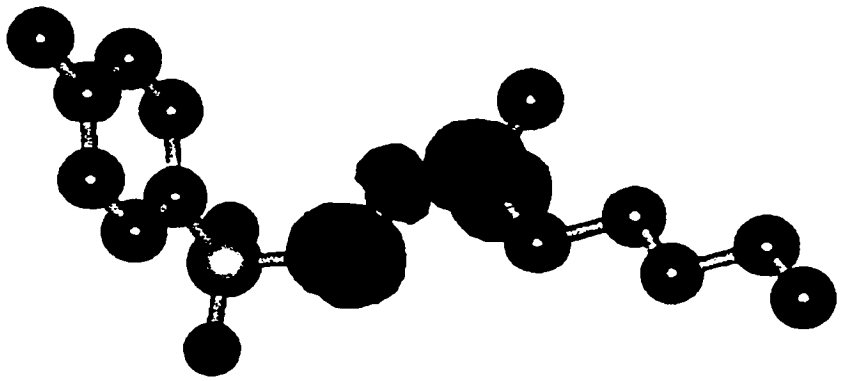
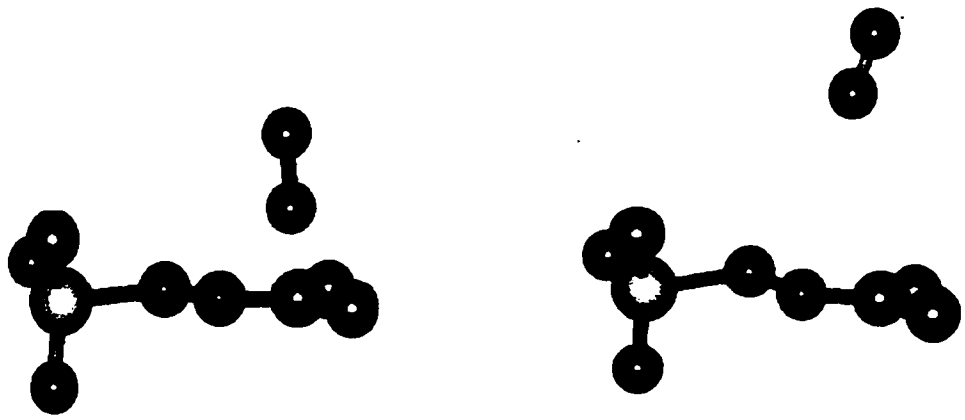


Figure 3.27: Spin density for the 2-heptanone tosylhydrazone radical cation (H atoms omitted)

3.4.6 Oxygen Attack on Tosylhydrazone Radical Cation

Data from spin density calculations suggested that the attack of molecular oxygen should occur on either the hydrazone carbon or the amine-like nitrogen atom of the radical cation. Several optimizations were run with different relative orientations of a simplified tosylhydrazone radical cation and an oxygen molecule in close proximity. The interaction between oxygen and the simplified radical cation was observed.

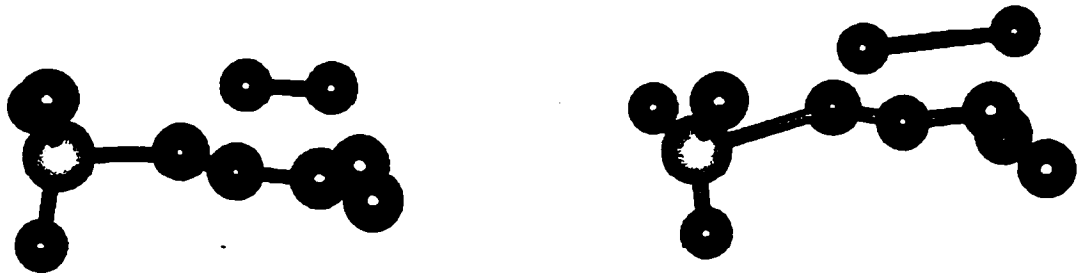


(a) (b)

Figure 3.28: Perpendicular attack by oxygen on simplified tosylhydrazone radical cation model; (a) before optimization, (b) after optimization

Product formation seems to be dependant on the angle of attack. If the oxygen molecule approaches the radical cation at a perpendicular angle, it is repelled (Figure 3.28). The oxygen molecule needs to be close to parallel to the C=N–N moiety for the reaction to occur. Although spin density calculations showed that there is equal probability of finding the radical electron on the hydrazone carbon or on the amine-like nitrogen, attack by molecular oxygen on nitrogen results in repulsion, regardless of the angle of attack.

Figure 3.29a shows the starting orientation for a successful attack. When the oxygen molecule approaches the radical cation along this trajectory, the hybridization of the hydrazone carbon atom changes from sp^2 to sp^3 and the geometry changes from planar to tetrahedral (Figure 3.29b), indicating C–O bond formation.



(a) (b)

Figure 3.29: Parallel attack by oxygen on a simplified tosylhydrazone radical cation model (H atoms omitted); (a) before optimization, (b) after optimization

In some instances there seemed to be interactions between an oxygen atom and the amine-like nitrogen atom. This suggests that ketone deprotection might involve a cyclization between the tosylhydrazone radical cation and molecular oxygen.

3.4.7 Conclusion: Role of the Radical Cation

Electrochemical studies have shown that the tosylhydrazone radical cation can be generated independently, with a maximum anodic current peak at 2.31V. The electrochemical oxidation is irreversible. Correspondingly a decrease of the anodic current peak over time demonstrated that the tosylhydrazone is consumed upon oxidation. The detection of ketone and the precipitate byproduct indicated that the electrochemical oxidation has similar results to photochemical oxidation by chloranil.

Adding TEMPO to the tosylhydrazone-chloranil solution resulted in the formation of a TEMPO-tosylhydrazone adduct upon irradiation. The presence of

the adduct supports the hypothesis that the tosylhydrazone is oxidized to a radical cation upon irradiation in the presence of chloranil. As well it supports a carbon centered radical in that TEMPO forms stable adducts with such radicals. Neither ketone nor the precipitate byproduct were detected, indicating that formation of the adduct halts the reaction.

Computational studies show that the HOMO of the simplified hydrazone is π type ($\pi_{C=N-N}$). Calculations of the bond lengths of the tosylhydrazone and the tosylhydrazone radical cation show that upon oxidation the carbon-nitrogen double bond lengthens from 130.9 pm to 137.2 pm, while the nitrogen-nitrogen bond shortens from 140.2 pm to 134.3 pm. The lengthening of the carbon-nitrogen bond suggests possible fragmentation of the molecule along this bond. Spin density calculations on the radical cation indicate the greatest probability of finding the unpaired electron on the hydrazone carbon or on the amine-like nitrogen atom.

Optimizations with different relative orientations of a simplified tosylhydrazone radical cation and an oxygen molecule in close proximity showed product formation (C–O bond formation with change in hybridization on carbon) upon "parallel" attack on carbon, which attack on nitrogen resulted in repulsion of O_2.

3.5 Secondary Reaction Products

As discussed in Section 3.2, upon irradiation of a tosylhydrazone a colourless precipitate was formed in addition to ketone. This precipitate formed whenever ketone was obtained from the tosylhydrazone in a chloroform or dichloromethane solution, and was suspended in the solvent. Further ketone formation was hindered as a result of the presence of the precipitate. Identifying the precipitate is necessary in clarifying the mechanism.

3.5.1 Physical Properties of the Precipitate

Filtration of the precipitate revealed that it was a colourless powder-like substance, comprised of small particles that gave flakes upon drying. When heated, the substance decomposes at 176°C with release of a gas. The Lassaigne's sodium fusion test was conducted and gave a positive result for sulphur and nitrogen.[116] Positive results were also obtained for tests for secondary amines and for nitrogen atoms bonded to oxygen atoms.[117]

The precipitate is soluble in methanol, ethanol, acetone and acetonitrile/water mixture, yet insoluble in water or acetonitrile by themselves. It is also insoluble in chloroform, dichloromethane, carbon tetrachloride, ethyl acetate, hexane and toluene. The insolubility of the precipitate in non-polar solvents indicates that it contains polar functional groups, however its insolubility in highly polar water indicates that there is a significant non-polar component to the precipitate.[102]

3.5.2 NMR Spectra for the Precipitate

The ^1H NMR shows two independent tosyl groups in the molecule (Figure 3.30). The methyl groups are indicated by two singlets (δ 2.92 and 2.40 ppm, 3 H each). The aromatic region shows three signals, two doublets at δ 7.12 and 7.73 ppm (2 H each) and a multiplet for 4 H at 7.46 ppm that resolves into two more doublets upon addition of D_2O (Figure 3.31). Two broad signals at δ 9.22 ppm (1 H) and 4-5 ppm are attributed to protons on nitrogen and oxygen respectively, and disappear upon deuterium exchange. The latter signal was not integrated as it was attributed, at least in part, to water in the solvent.

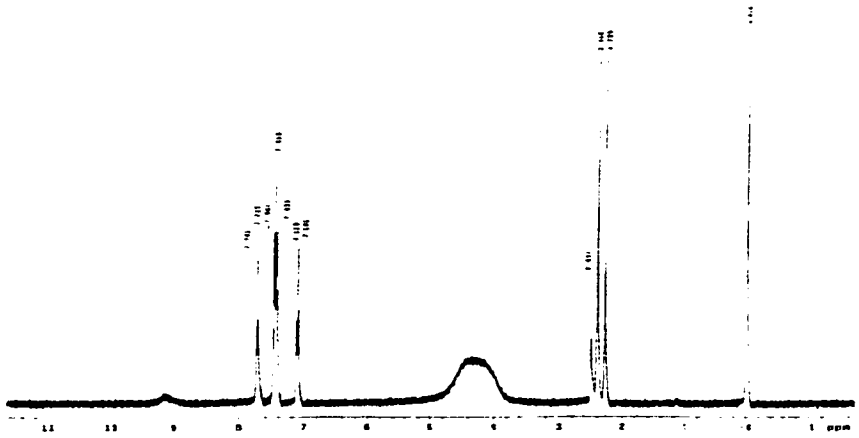


Figure 3.30: Proton NMR spectrum of precipitate

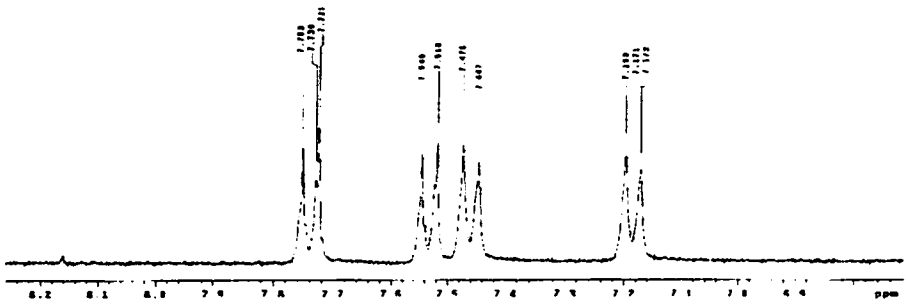


Figure 3.31: Aromatic region of the proton NMR spectrum of the precipitate upon addition of D_2O

In accord with the above analysis, the ^{13}C NMR spectrum only shows signals belonging to the two independent tosyl groups, two methyl signals and eight signals from aromatic carbons (Appendix VI).

The ^{15}N NMR (Appendix VI, Figure A.27) shows two signals (δ 60.5 and 116.5 ppm, referenced to urea: 77.0 ppm), in accord with the elemental analysis (Section 3.5.4) that indicates the precipitate contains two nitrogen atoms. ^{15}N NMR spectra were also obtained for cyclopentanone tosylhydrazone (two signals, δ 64.1 and 178.4 ppm), p-tolysulfonylhydrazine (two signals, δ 57.6 and 84.8 ppm), and N,N-dimethyl hydroxylamine hydrochloride (one signal, δ 102.4 ppm). The signal on the precipitate spectrum at 60.5 ppm is attributed to an amine nitrogen (similar signals found on tosylhydrazone and tolysulfonylhydrazine spectra). The signal at 116.5 ppm is more deshielded than an amine, yet less deshielded than a hydrazone. This signal is more deshielded that N,N-dimethyl hydroxylamine hydrochloride yet still within the range of hydroxylamines.[118] From this, and from data obtained from the proton NMR spectrum, this signal is attributed to a hydroxylamine.

3.5.3 Mass Spectrum of the Precipitate

The spectrum shown in Figure 3.32 reveals the most prominent peak at m/z 373.3 and this value was taken as the M+1 value of the molecular mass of the precipitate. This value can not be the M^+ value because according to the "nitrogen rule" an odd number for the molecular mass indicates the presence of an odd number of nitrogen atoms in the molecule.[118] Elemental analysis

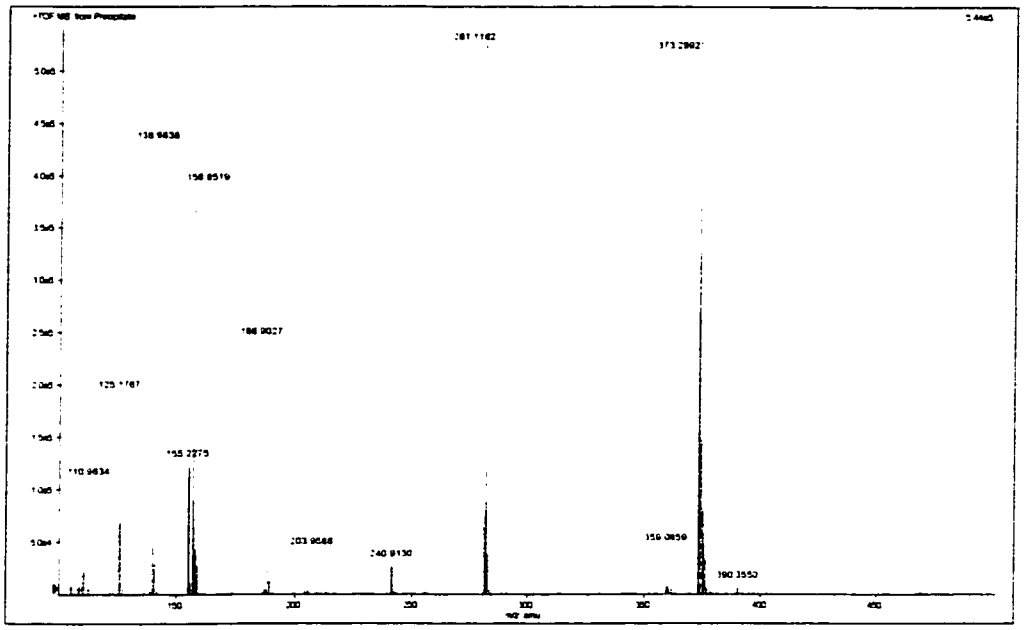


Figure 3.32: Mass spectrum of the precipitate

Table 3.5: Mass spectrum peaks and assigned fragments of the precipitate

m/z	Assignment
373.3	M + 1
281.1	M – C_7H_7
186.9	$C_7H_7SO_2NO$ + 1
156.9	$C_7H_7SO_2$ + 2
155.2	$C_7H_7SO_2$
139.0	C_7H_7SO
125.2	C_7H_7S + 2

(Section 3.5.4) shows the molecule to have two nitrogen atoms, and this was supported by ^{15}N NMR studies (Section 3.5.2). Table 3.5 summarises the masses and assigns fragments.

The second abundant fragment occurs at m/z 281.1. This value is 91 au less than the mass of the precipitate molecule, corresponding to a loss of a methyl-substituted aromatic ring.

Several fragments occur due to the tosyl group and its cleavage from the rest of the molecular ion. The peak at m/z 155.2 occurs due to the tosyl cation cleaving from the molecular ion. The more stable tosyl radical would abstract a proton, becoming a neutral closed-shelled species, and upon protonation would appear on the spectrum. The peak at m/z 156.9 supports this conclusion. Loss of one of the tosyl group's oxygen atoms results in a peak at m/z 139.0 and the loss of the second oxygen atom results in the M+2 peak at m/z 125.2. The peak at m/z 186.9 corresponds to the M+2 value of the tosyl group plus one nitrogen atom and one oxygen atom. These fragmentation patterns are similar to the fragmentation patterns for p-tolysulfonylhydrazine in literature.[119]

3.5.4 Elemental Analysis of the Precipitate

The results of the elemental analysis are summarised in Table 3.6. The molecular formula was found to be $C_{14}H_{16}N_2O_6S_2$ (372 g/mol) These results are in agreement with the findings of the NMR study, which indicates the presence of fourteen carbon atoms from two tosyl groups in the precipitate. The presence of two sulphur atoms is evidence that the precipitate arises from the tosyl portion of the tosylhydrazone molecule. The finding of two nitrogen atoms is in agreement with the "nitrogen rule" as outlined in Section 3.6.3.

Table 3.6: Results from elemental analysis of the precipitate

Element	Percent Mass	Percent Deviation	Number of Atoms
Carbon	45.616%	0.988%	14
Hydrogen	5.194%	1.371%	16
Nitrogen	7.482%	2.500%	2
Sulfur	15.295%	2.976%	2
Oxygen	26.413%	-	6

3.5.5 Infrared Spectrum of the Precipitate

The IR spectrum is shown in Figure 3.33 and the band assignments for the various functional groups are summarised in Table 3.7.

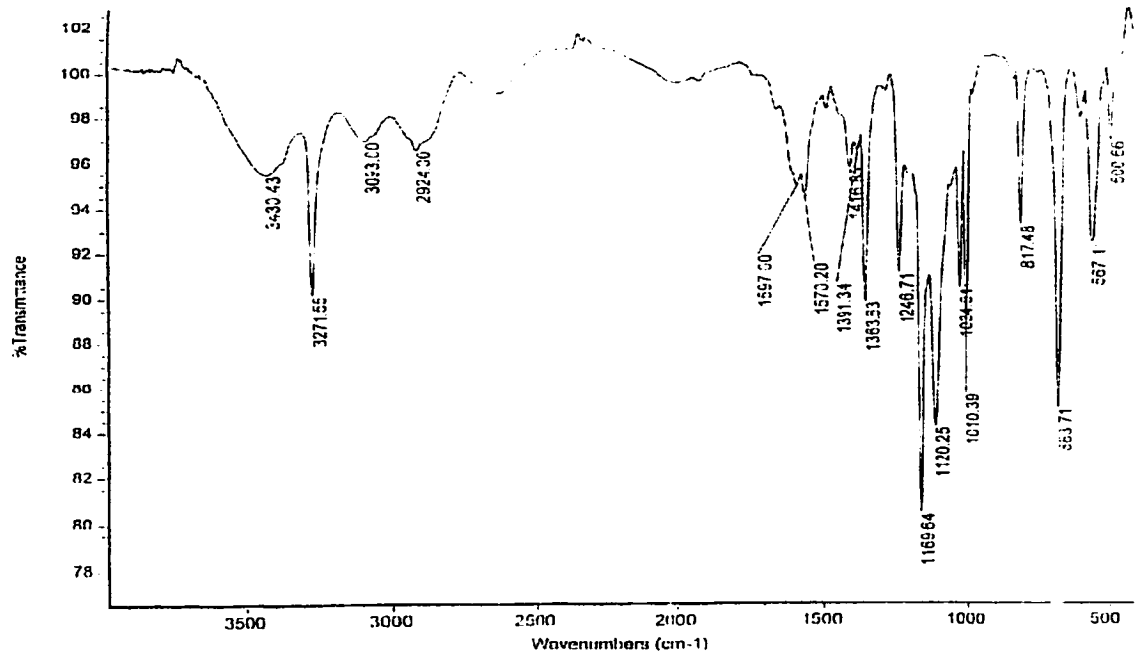
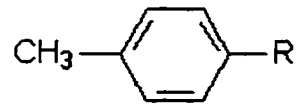
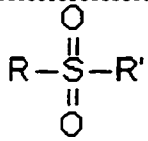


Figure 3.33: Infrared spectrum of precipitate, neat in KBr

Table 3.7: Assignment of the infrared bands of the precipitate

Vibration	Wavenumber (cm^{-1})	Structural Feature[118,120,121]
$\nu(O-H)$	3430	ROH
$\nu(N-H)$	3272	R_2NH
$\sigma(N-H)$	1597	
$\nu(=C-H)_{arom}$	3093	
$\nu(C-H)$	2924	
$\nu(C=C)_{arom}$	1417,1570	
$\sigma(=C-H)_{oop}$	817	
$\sigma(C=C)_{oop}$	684	
$\nu_{as}(SO_2)$	1364	
$\nu_s(SO_2)$	1170	
$\nu(N-O)$	1010	R_2NOH

Several absorption bands on the IR spectrum of the precipitate are due to the tosyl group, and the corresponding bands can also be found in the tosylhydrazone spectrum. In addition, and providing valuable structural information, the spectrum of the precipitate clearly shows bands at 3430 and 3272 cm^{-1}. The band at 3272 cm^{-1} is attributed to an N-H stretch and points, together with the band at 1597 cm^{-1}, to a secondary amine (primary amines exhibit two absorption bands in the N-H stretching region).

The broad and shallow absorption band at 3430 cm^{-1} corresponds to the O-H stretching frequency of a hydroxyl group. Initially this band was attributed to water, however subsequent drying of the sample did not eliminate the band. The shape and intensity of the absorption band are attributed to intramolecular bonding, as normally a hydroxyl group would produce a stronger band.[120] Any hydroxyl group in the linkage of the precipitate would be in close proximity to the sulfone group, a hydrogen bond acceptor. The formation of a hydrogen bond between the hydroxyl group and sulfone group would account for the observed absorption band (Figure 3.34). An absorption band at 1010 cm^{-1} corresponds with the stretching frequency of hydroxylamines,[121] which concurs with NMR data.

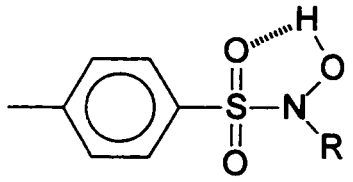


Figure 3.34: Intramolecular H-bonding between hydroxyl and sulfone groups

A broad yet shallow absorption band occurs at 2633 cm^{-1} and could be due to the stretching frequency of a secondary amine salt ($R_2NH_2^+$).[118,120] Such a salt could be generated through the loss of the hydroxylic proton, which is accepted by the amine group. This absorption band was reproducible on subsequent precipitate IR spectra and not present on the tosylhydrazone spectrum, where there are no proton-donating groups.

3.5.6 Possible Structure of the Precipitate

From the data obtained (Sections 3.6.1 - 3.6.5) three possible structures for the precipitate were determined. All three structures contained two tosyl groups with a linkage comprised of two nitrogen atoms, two oxygen atoms and two protons. The three possible structures are depicted in Figure 3.35.

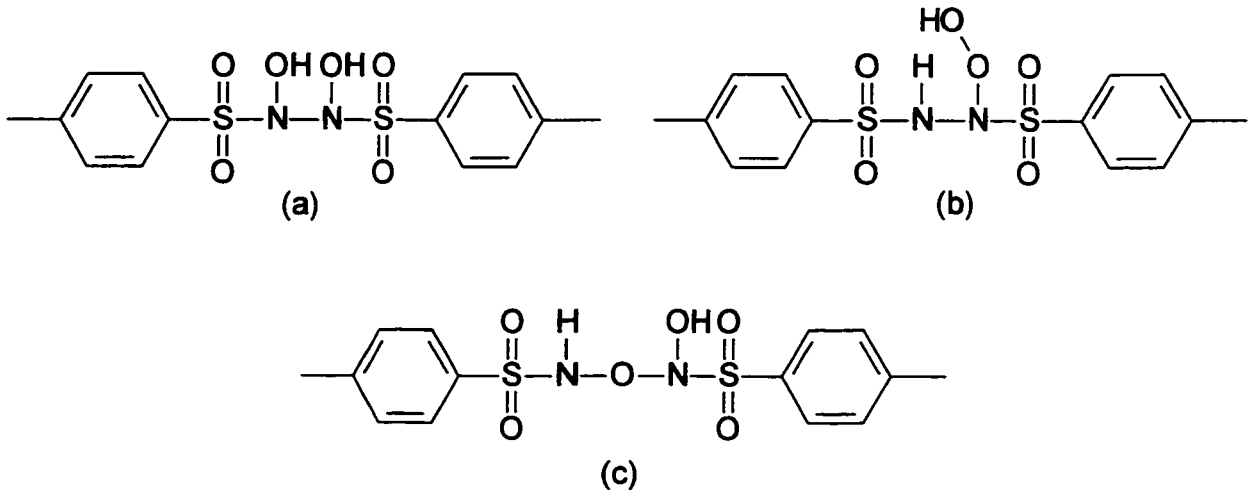


Figure 3.35: Possible molecular structures for the precipitate

One structure (Figure 3.35a) that has been ruled out, has two tosyl groups linked by two nitrogen atoms, where each nitrogen atom is bonded to a hydroxyl group. Though this structure does account for all the atoms determined in the elemental analysis, the symmetry of the molecule contradicts the findings of the NMR study. In addition the IR spectrum clearly shows an amine absorption band, a functional group not present in this proposed structure.

The second structure has the linkage comprised of two nitrogen atoms, with one bonded to a proton, the other to a hydroperoxide group (Figure 3.35b), a structure that does concur with the spectroscopic data given above. However, the

peroxide group should give rise to additional bands in the region between 1176 cm^{-1} and 1198 cm^{-1}, rendering this region more complex than it appears on the spectrum.[118,120]

The third possible structure, shown in Figure 3.35c, has the tosyl groups joined by a nitrogen analogue to an ether linkage. One nitrogen atom is bonded to a hydroxyl group the other bonded to a proton. This structure fits all the spectroscopic data.

3.5.7 Formation of Gas

Gas trap experiments were conducted and the changes in gas volume were measured with a manometer. Oxygen was consumed during the reaction (Section 3.3.3) thus a decrease in gas volume was expected. These experiments showed that for every two moles of ketone regenerated, one mole of gas was consumed.

The reaction determined thus far is summarised by the equation in Scheme 3.1. Balancing of the oxygen atoms indicate that for every mole of ketone regenerated (or tosylhydrazone consumed), one mole of molecular oxygen was consumed. This apparent contradiction of the results from the gas trap experiments can be explained if for every two moles of ketone regenerated (and

$$\underset{2 \times C_{12}H_{16}N_2O_2S}{2\ \text{Tosylhydrazone}} + 2\,O_2 \longrightarrow \underset{C_{14}H_{16}N_2O_6S_2}{\text{Precipitate}} + \underset{2 \times C_5H_8O}{2\ \text{Ketone}}$$

Scheme 3.1: Oxygen-balanced equation for cyclopentanone deprotection

consumption of O_2), one mole of gas was produced. Scheme 3.1 shows that every atom from the tosylhydrazone is accounted for except for one nitrogen. The oxygen-balanced equation shows two nitrogen atoms unaccounted for and suggests N_2 was released.

When two systems, each containing a nitrogen-nitrogen bond, react with one another, the end result is the release of nitrogen gas and a linking of the two systems.[112,113] In the presence of heteroatoms rearrangement can also occur. The apparent dimer nature of the precipitate suggests this and the release of nitrogen gas is in accord with the results from the gas trap experiment.

3.5.8 Conclusion: Secondary Reaction Products

The mass spectrum revealed that the precipitate has a mass of 372.3 g/mol. In accordance with the "nitrogen rule" (even number of nitrogen), the peak at 373.3 m/z was determined to be the M+1 signal. The fragmentation pattern of the precipitate was similar to that of p-tolysulfonylhydrazine in the literature, indicating similarities in structure.

The elemental analysis, along with the molecular mass obtained from the mass spectrum, determined the molecular formula of the precipitate to be $C_{14}H_{16}N_2O_6S_2$.

The precipitate byproduct (a colourless solid, melting point 176°C) was determined by ^1H and ^{13}C NMR to be comprised of two unequal tosyl groups. ^{15}N NMR determined two unequal nitrogen atoms, one assigned to an amine, the other to a hydroxylamine.

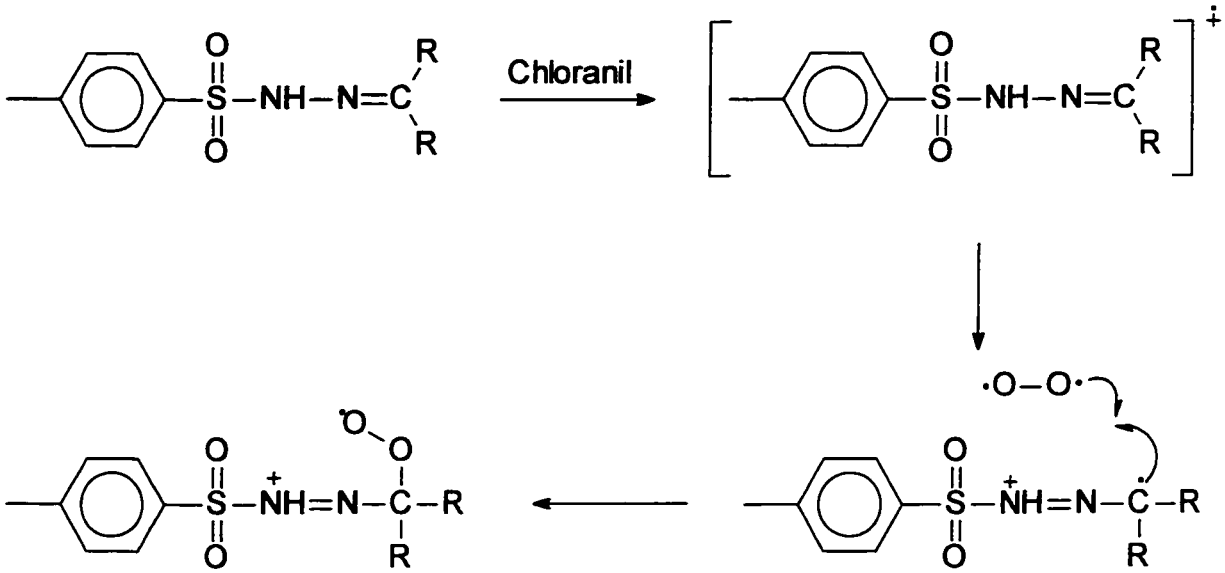
The infrared spectrum of the precipitate showed absorption bands characteristic of a tosyl group, as well as bands associated with secondary amines. A shallow absorption band in the region of hydroxyl absorption was attributed to a hydrogen bonded hydroxyl group. Absorption bands characteristic of a hydroxylamine were also observed.

The structure for the precipitate that fits all the spectroscopic data is one with two tosyl groups that are linked together by two nitrogen atoms, two oxygen atoms and two protons. The linkage was determined to be composed of an oxygen atom between two nitrogen atoms, in an ether-like formation. One nitrogen atom is bonded to a hydroxyl group while the other is bonded to a proton.

The precipitate and ketone account for all of the atoms in the tosylhydrazone + O_2, except for one nitrogen atom. Gas trap experiments have shown the overall consumption of one mole of gas, which is explained as the consumption of two moles of O_2 and formation of one mole of N_2 for every mole of tosylhydrazone.

3.6 Putting it Together: Partial Reaction Mechanism

From the experimental data, part of the reaction mechanism has been determined (Scheme 3.2). Upon irradiation, chloranil is excited to the triplet state. In the excited triplet state, it is an excellent one electron oxidizer and removes an electron from the HOMO of the tosylhydrazone. Oxidation takes place in the π system at the carbon-nitrogen double bond. The tosylhydrazone radical cation, can be described as a carbon-centered radical with a nitrogen centered charge.

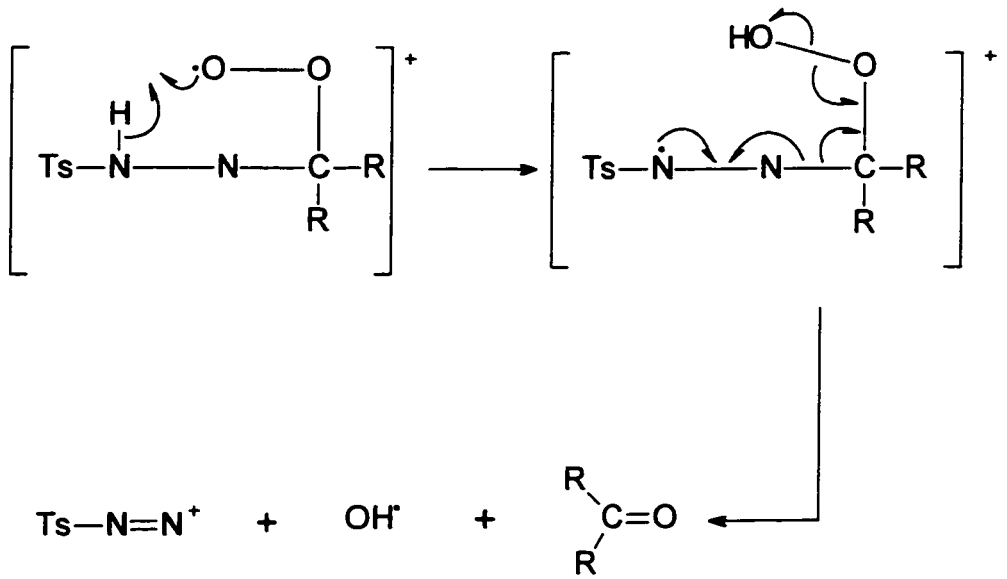


Scheme 3.2: Partial reaction mechanism determined from experimental data

Molecular oxygen, a diradical species, is known to react with carbon centered radicals to produce peroxy radical species.[105] This peroxy radical could decompose via homolysis of the peroxide bond and the carbon-nitrogen bond, regenerating the protected ketone species.

Though a complete mechanism is not known, experimental data and theory can infer to the possible missing steps. The homolysis of the peroxide bond will generate a new oxygen centered radical. The type of radical generated depends on how the peroxy radical was interacting with other functionalities prior to homolysis. Computer modeling studies have shown that the peroxy radical will interact with the amine-like nitrogen atom, and there are several possible ways.

The first is the abstraction of the ammonium proton, which would result in the formation of a hydroxyl radical upon homolysis (Scheme 3.3) and a number of products would be expected. Hydroxyl radicals are highly electrophilic, and will react with a number of different functional groups, including aromatic compounds. In addition, small sized radicals, such as the hydroxyl radical, can diffuse quickly away from the site of generation, and would encounter tosylhydrazone molecules

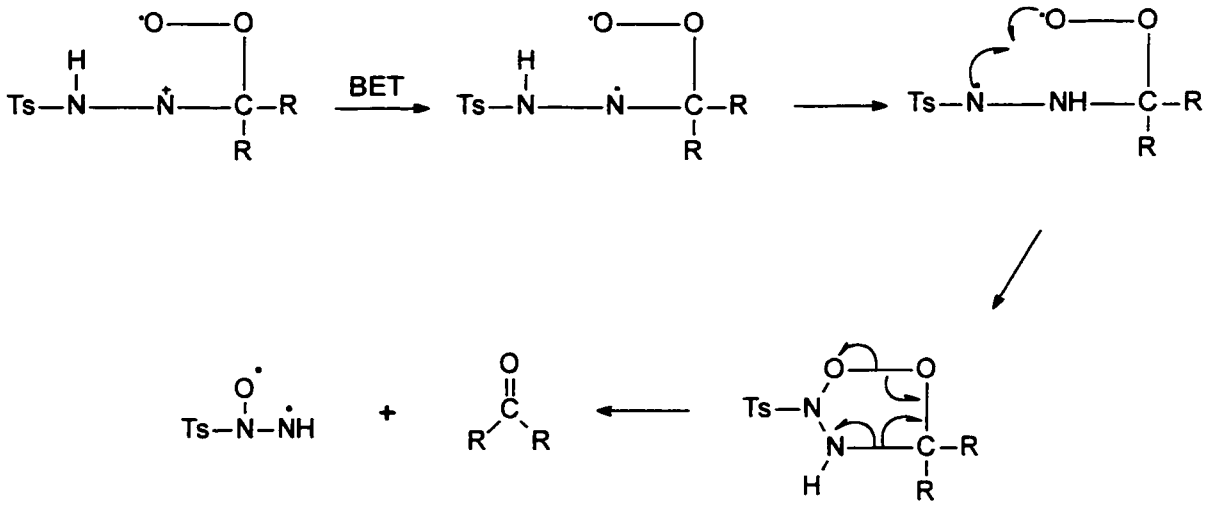


Scheme 3.3: Fragmentation of the tosylhydrazone-peroxy radical as a result of proton abstraction

in various stages of reaction. The hydroxyl radical would react with these molecules and several different product species would be observed. Since only ketone and the precipitate were observed, it is improbable that hydroxyl radicals form.[104,105,112,113,122,123]

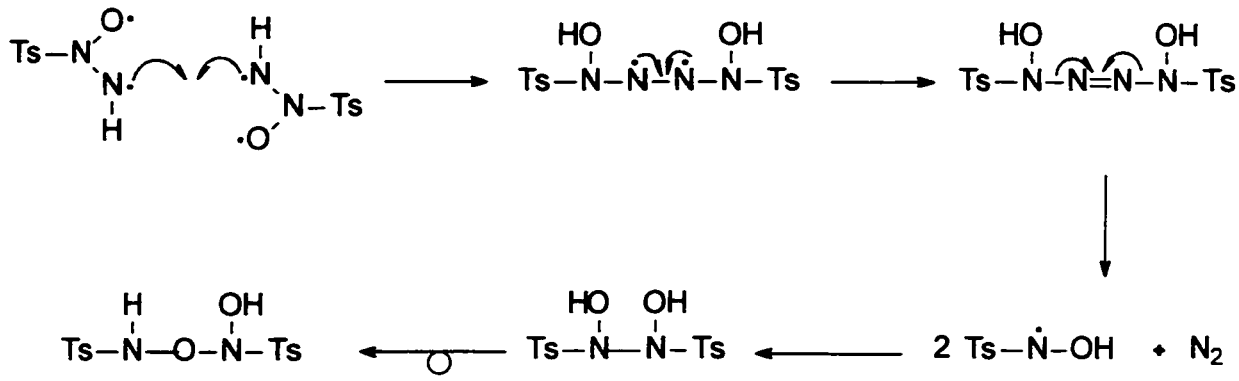
The second possibility is that cyclization occurs, yielding a cyclic peroxide. Cyclization would take place in a diradical species, and this could be generated through back electron transfer from the radical anion state chloranil.[105] BET must occur since neutral products are being generated and chloranil is not consumed in any reactions.

In the cyclic peroxide species (Scheme 3.4), homolysis would occur at the peroxide bond and the carbon-nitrogen bond, forming the ketone and the diradical species. Dimerization of this diradical species with subsequent hydrogen shift to the oxygen atoms would result in a 2-tetrazene (Scheme 3.5). Hydroxy-



Scheme 3.4: Fragmentation of the tosylhydrazone-peroxy radical via cyclization into a five-member ring

substituted 2-tetrazenes decompose readily with loss of N_2. If the two nitrogen centered radical fragments recombine, they can rearrange into the precipitate molecule.[104,105,112,113]



Scheme 3.5: Proposed mechanism for precipitate formation via dimerization of tosylhydrazone diradical fragment

4. Conclusion and Future Work

4.1 Conclusion

This study has shown that the reaction between aliphatic ketones and p-tolysulfonylhydrazine produces tosylhydrazones in quantitative yields. These tosylhydrazones are efficient protecting groups in that their formation process is simple and efficient, and that they are highly stable and can be stored indefinitely. These findings concur with the literature with respect to the facile formation and stability of tosylhydrazones.

The deprotection of ketones was shown to occur in solution, when chloranil was present, upon irradiation with light at 355 nm. An approximate 23% to 31% yield was obtained for aliphatic ketones after 4 hours of irradiation and between 10% and 23% for functionalized ketones. Preliminary studies on the tosylhydrazones of aromatic ketones show that deprotection occurs without the presence of chloranil.

The formation of a secondary byproduct was shown to hinder ketone formation. Upon hourly filtration of the precipitous byproduct, ketone continued to be regenerated, with 90% regeneration after 10 hours. Several possible causes were ruled out, including absorption or scattering of light by the byproduct. Oxidation of the precipitate preferentially over the tosylhydrazone by chloranil was attributed to this discrepancy.

Measurements of tosylhydrazone consumption as a function of time and initial tosylhydrazone concentration was used to determine a first order of reaction with respect to the tosylhydrazone.

Results from experiments conducted in chloroform were compared with results obtained when acetonitrile and dichloromethane were used. There was little difference in yields between chloroform and acetonitrile, indicating that separation of the radical ion species is not the rate limiting step. A slightly lower yield was obtained from dichloromethane, which was attributed in part to the degradation of chloranil.

The concentration of chloranil was found to have little effect on the amount of ketone regenerated. Only catalytic amounts of the photosensitizer were necessary for ketone regeneration.

The intensity of light was found to have an effect on the amount of ketone regenerated during a particular time period. Solutions exposed to a high intensity Hg/Xe lamp regenerated more ketone than a solution exposed only to ambient light. Solutions that remained in the dark did not regenerate any ketone at all, proving the reaction is photosensitized.

The source of the oxygen atom in the regenerated ketone was found to be atmospheric molecular oxygen. Two other possible sources, water present in the solvent, and oxygen atoms on the tosyl group, were discarded. The removal of all oxygen gas and conducting the reaction under nitrogen resulted in the complete halting of ketone formation. Venting the degassed solution and re-exposing it to air caused ketone formation to commence.

The formation of the tosylhydrazone radical cation was demonstrated via two methods: electrochemical oxidation of the tosylhydrazone, and trapping of the radical cation with TEMPO, with the mass of the adduct showing on a mass

spectrum. The electrochemical oxidation method was able to produce ketone, whereas the TEMPO trapping experiment caused the reaction sequence to stop.

Computational studies show that the HOMO of the tosylhydrazone is π type ($\pi_{C=N-N}$). Calculations show that upon oxidation the C=N bond lengthens, while the N–N bond shortens. This suggests fragmentation occurs along the former carbon-nitrogen double bond in the radical cation. Spin density calculations on the tosylhydrazone radical cation show the greatest probability of finding the unpaired electron on the hydrazone carbon or the amine-like nitrogen.

Optimization of a simplified tosylhydrazone radical cation and an oxygen molecule in close proximity and at different relative orientations show "parallel" attack result in product formation (indicated by C–O bond formation and change in carbon hybridization). Perpendicular attack and/or attack on the nitrogen resulted in repulsion of the O_2 molecule.

Further reaction products were determined to be N_2 gas and a precipitate comprised mostly of two tosylhydrazine portions of the tosylhydrazone. The molecular mass of the precipitate was determined by mass spectrometry to be 372.2 g/mol, and the molecular formula from an elemental analysis to be $C_{14}H_{16}N_2O_6S_2$. Spectroscopic data indicated that the structure for the precipitate is one with two tosyl groups that are linked together by two nitrogen atoms, two oxygen atoms and two protons. The linkage was determined to be composed of an oxygen atom between two nitrogen atoms, in an ether-like formation. One nitrogen atom is bonded to a hydroxyl group while the other is bonded to a proton.

From the data obtained, a mechanism was proposed. Upon excitation, chloranil oxidizes the π system of the tosylhydrazone, generating a tosylhydrazone radical cation. Perpendicular attack by molecular oxygen on the radical cation results in the formation of a peroxy radical. Cyclization of the peroxy radical into a five-member ring occurs, followed by homolysis at the peroxide bond and the carbon-nitrogen bond, producing the ketone and a diradical species. Dimerization of this diradical species with subsequent hydrogen shift to the oxygen atom would result in a hydroxy-substituted 2-tetrazene. Decomposition of the 2-tetrazene releases N_2 and recombination and rearrangement of the remaining fragments produce the precipitate molecule.

4.2 Future Work

Future work will primarily focus on the reaction mechanism, particularly the fragmentation of the tosylhydrazone molecule, and rearrangements of these fragments into the products. In addition to further theoretical calculations, a number of experiments can be performed.

Back electron transfer (BET), though an energy wasting reversal process when oxidizing the tosylhydrazone, is a necessary step in the formation of the final products. Studies have shown that BET can be hindered by the presence of an electrolyte such as TBAHFP.[92] Photolysis experiments could be conducted with the presence of the electrolyte in solution, to determine if the slowing of BET has any effect on the rate and efficiency of ketone regeneration. Additionally, the effects of BET the on formation of the precipitate can be studied this way.

A number of metal ions, such as Co^{2+}, are known to react with peroxy radicals to generate peroxide molecular products.[112] Using cobalt, or another suitable metal ion, the detection of the peroxide molecular product, or products resulting from the peroxide decomposition, might elucidate the cyclization step of the proposed mechanism.

Conducting the photochemical deprotection reaction in the presence of labeled oxygen would make detection of oxygen atoms in a molecule easier. The structure of secondary products can be confirmed this way, and intermediates would be easier to identify.

Cacchi and co-workers devised a simple method for N-alkylation of tosylhydrazones through phase-transfer catalysis.[124] If the reaction mechanism for deprotection involves a proton shift between nitrogen atoms, then replacing this proton with a methyl group would alter the mechanism and final products. Observing the final products from this reaction would verify if a proton shift does indeed occur.

The introduction discussed the chemistry of tosylhydrazones. Though resistant to many different reagents and reaction conditions, tosylhydrazones are susceptible to bases. Most of the reactions tosylhydrazones can undergo first involve treatment with a base to abstract the amine-like proton. Often new protecting groups for carbonyl compounds are sought after, for protection against organometallic compounds, such as Gringard reagents. A protecting group with labile protons, such as a tosylhydrazone, would be useless. The method for N-alkylation by Cacchi and co-workers provides a means of possibly rendering

tosylhydrazones effective protection against organometallic compounds.[124] New studies into this possibility can be conducted.

Only preliminary experiments have been conducted in the deprotection of aromatic ketones that have been converted into tosylhydrazones. Early result show deprotection occurs both with and without the presence of chloranil, however irradiation of the solution with chloranil regenerated larger amounts of ketone. A complete study into aromatic deprotection needs to be conducted.

5. EXPERIMENTAL

5.1 Melting Points

The melting points of all solids were measured using a Gallenhamp electro-thermal melting point apparatus. All values are uncorrected.

5.2 Thin Layer Chromatography

TLC analysis was performed on 3 cm X 10 cm polyester plate coated with aluminum oxide (Aldrich). The mobile phase was ethyl acetate. Samples were dissolved in 99% ethanol before spotting. Visualization of the TLC plate was accomplished using a 4 W UV lamp (Ultra-Violet Products Inc. Model: UVSL-25).

5.3 Gas Chromatography

Gas chromatography analysis was accomplished with a Hewlett-Packard GC (Model 5790A, Flame Ionization Detector) equipped with a 50 m Quardrex capillary column, with an internal diameter of 0.25 mm. The integrator was a Hewlett-Packard 3390A series integrator. Helium (ultra high purity) was used as carrier gas while hydrogen (ultra high purity) and compressed air (extra dry) were used as fuel gases for the detector. The oven temperature was set at 80°C for experiments involving 2-pentanone, 100°C for experiments involving all other aliphatic ketones and 175°C for experiments involving aromatic ketones. Injector and detector temperatures were set at 200°C for all experiments involving aliphatic ketones and 225°C for experiments involving aromatic ketones.

5.4 Nuclear Magnetic Resonance

NMR spectra were run on a Varian Unity Innova 300 MHz NMR. All samples were measured in deuterated dimethyl sulfoxide, containing 1% tetramethylsilane. ^{1}H (300 MHz) spectra were obtained after 16 scans, and chemical shifts were referenced to tetramethylsilane (0.0 ppm). ^{13}C (75 MHz) spectra were obtained after 2 000 scans, and chemical shifts were referenced to dimethyl sulfoxide (39.51 ppm). Dimethyl sulfoxide was chosen as the reference because the signal was more intense than that of tetramethylsilane on those spectra. ^{15}N (30 MHz) spectra were obtained after 10 000 scans, and urea was used as an external standard for referencing chemical shifts (77.00 ppm). Signals in ^{1}H spectra are given as s (singlet), d (doublet), t (triplet), m (multiplet).

5.5 Ultraviolet-Visible Spectroscopy

UV-Vis spectra were obtained on a Varian Cary 100 Bio Model UV-Vis Spectrophotometer, coupled to Cary WinUV Scan Application Software. The scan range was 190 nm to 900 nm and the scan rate was 100 nm/min. Hellma 10 mm path length quartz glass cuvets were used for all liquid samples.

5.6 Infrared Spectroscopy

Infrared spectra were obtained using a Nicolet Magna-IR Spectrophotometer 550, with a DTGS KBr detector, coupled to OMNIC FTIR software version 2.0. The samples were scanned in form of KBr pellets. The scanning range was 400 cm^{-1} to 4000 cm^{-1}, 32 scans per sample.

5.7 Mass Spectrometry

Mass spectral analysis was performed on a ThermoFinnigan SSQ 7000 single quadrupole MS (typical operating conditions: needle voltage, 4.50 kV; spray current, 2.30 mA; capillary temperature, 220°C for TEMPO experiments, 150°C for all other experiments; electron multiplier, 1450 V). The mass range was scanned from 200-500 m/z at 1 s/scan in positive ion mode. Ultra pure N_2 (Praxair) was used as a nebulizer gas. Data analysis was performed using Xcalibur software (ThermoFinnigan).

5.8 Elemental Analysis

Elemental analysis was conducted at the Laboratoire d'Analyse Élémentaire at the Université de Montréal on a Fisons Instruments SPA, model EA 1108.

5.9 Cyclic Voltammetry

Cyclic voltammograms were obtained with a Radiometric Analytical Voltalab model PG2-301, coupled to Voltamaster 4.0 software version 1.2 beta. Platinum working and counter electrodes were used, referenced to a standard calomel electrode. The scanning range was –0.5 V to 3.0 V to –0.5 V for experiments involving cyclopentanone tosylhydrazone, 2.0 V to –2.0 V to 2.0 V for experiments involving cyclopentanone, and –0.5 V to 2.0 V to –0.5 V for experiments involving the precipitate. The scan rate was set at 100 mV/s for all experiments.

5.10 Computational Analysis

Computational studies were conducted using HyperChem6. The level of theory employed was semi-empirical PM3. The convergence limit in the SCF was set at 0.01. The termination limit was RMS gradient of 0.01 kcal/(Å mol). Isosurface was set at 0.04.

5.11 Materials

All chemicals used, except solvents, gases, tosylhydrazones and phenylhydrazones were purchased from Aldrich Chemical Company, and were used without any further purification. Ethanol (99%) was purchased from Commercial Alcohols Incorporated. Dichloromethane, ethyl acetate and methanol (reagent grade) were purchased from Anachemia Science. Hydrochloric acid, acetonitrile and methanol (HPLC grade) were purchased from Fisher Scientific. Chloroform was purchased from EM Science (Omnisolv). Chloroform was dried over 4 Å, 8-12 mesh molecular sieves (Aldrich). All gases were purchased from Praxair Incorporated. Tosylhydrazones were synthesized as described below.

5.12 Preparation of Tosylhydrazones

The tosylhydrazones of cyclic ketones were synthesized by reacting equal molar amounts of ketone with p-toluenesulfonhydrazide (p-tosylhydrazine). The ketone was added quickly to a magnetically stirred slurry of p-tolysulfonylhydrazide in ethanol. The mixture was allowed to stir for 3 hours, and the tosylhydrazone product was collected by suction filtration. The collected solid

was recrystallized from 99% ethanol and dried at ambient temperature and pressure.[36]

All other tosylhydrazones were synthesized in the following manner. Equal molar amounts of ketone and p-toluenesulfonhydrazide were dissolved in ethanol, and magnetically stirred for 6 hours, after which time the flask was placed in the freezer overnight. Excess solvent was removed using a rotary evaporator. The solid was collected by suction filtration, recrystallized from 99% ethanol, and dried at ambient temperature and pressure.

5.13 Preparation of Phenylhydrazones

Cyclopentanone phenylhydrazone was synthesized according to a modified literature procedure.[125] Cyclopentanone (3.00 mL, 2.85 g, 33.9 mmol) and phenylhydrazine (3.30 mL, 3.62 g, 33.5 mmol) were heated under reflux in 95% ethanol for 5 hours. Concentration by rotary-evaporation, collection by suction filtration and recrystallization from ethanol afforded fine colorless crystals (1.53 g, 26.2%). The purity of the product was determined by TLC and GC. The product was stored under vacuum in the dark.

5.14 Analysis of Tosylhydrazones

Cyclopentanone p-Tosylhydrazone: Reaction of cyclopentanone (5.30 mL, 5.00 g, 59.4 mmol) with p-tosylhydrazine (11.5 g, 61.6 mmol) resulted in the known tosylhydrazone (13.9 g, 91.2%; literature value, 85.0%)[36]. Recrystallization afforded small, colorless, crystalline granules. Melting point 178-180°C (literature

value, 185-186.5°C)[36]. ^{1}H-NMR δ 1.55-1.75 (complex m, 2 H), 1.93-2.08 (complex m, 2 H), 2.17 (t, 2 H), 2.23 (t, 2 H), 2.38 (s, 3 H), 7.39 (d, 2 H), 7.72 (d, 2 H), 9.96 (s, 1 H). A complex multiplet is depicted in Figure 3.2 in Section 3.1.2. ^{13}C-NMR δ 21.00, 24.25, 24.38, 28.56, 32.80, 127.45, 129.39, 136.49, 143.01, 168.22.

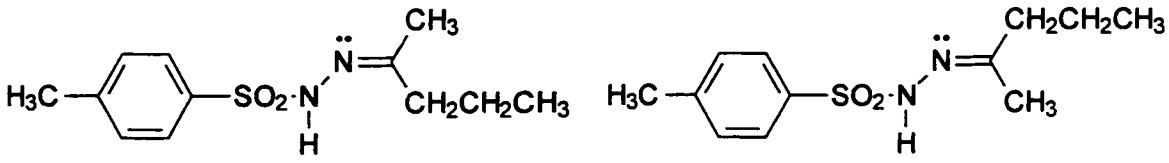
Cyclohexanone p-Tosylhydrazone: Reaction of cyclohexanone (8.00 mL, 7.58 g, 77.2 mmol) with p-tosylhydrazine (14.4 g, 77.2 mmol) resulted in the known tosylhydrazone (19.0 g, 92.2%; literature value, 88.0%)[36]. Recrystallization afforded colorless prisms. Melting point 147-148°C (literature value, 148–150°C)[36]. ^{1}H-NMR δ 1.51 (complex m, 6 H), 2.07 (t, 2 H), 2.26 (t, 2 H), 2.37 (s, 3 H), 7.38 (d, 2 H), 7.73 (d, 2 H), 10.10 (s 1 H). ^{13}C-NMR δ 20.98, 24.83, 25.47, 26.69, 27.35, 34.63, 127.49, 129.28, 136.44, 142.90, 162.15.

Cycloheptanone p-Tosylhydrazone: Reaction of cycloheptanone (9.50 mL, 9.03 g, 80.5 mmol) and p-tosylhydrazine (15.0 g, 80.8 mmol) resulted in known tosylhydrazone (20.5 g, 90.9%; literature value, 92.0%)[36]. Recrystallization afforded colorless, elongated prisms. Melting point 148-150°C (literature value 149.5-151°C)[36]. ^{1}H-NMR δ 1.24 (m, 2 H), 1.30-1.44 (complex m, 4 H), 1.52-1.70 (complex m, 4 H), 2.13 (t, 2 H), 2.31 (t, 2 H), 2.37 (s, 3 H), 7.37 (d, 2 H), 7.72 (d, 2 H), 9.98 (s, 1 H). ^{13}C-NMR δ 20.98, 22.86, 24.54, 26.23, 26.56, 27.84, 35.39, 127.40, 129.27, 136.50, 142.90, 164.43.

Cyclooctanone p-Tosylhydrazone: Reaction of cyclooctanone (5.07 g, 39.6 mmol) and p-tosylhydrazine (7.38 g, 40.2 mmol) resulted in known tosylhydrazone (10.3 g, 87.9%; literature value, 83.0%)[36]. Recrystalization afforded large, colorless granules. Melting point 135-138 °C (literature value 136-139°C)[36]. ^{1}H-

NMR δ 1.24 (m, 2 H), 1.30-1.44 (complex m, 4 H), 1.52-1.70 (complex m, 4 H), 2.13 (t, 2 H), 2.31 (t, 2 H), 2.37 (s, 3 H), 7.37 (d, 2 H), 7.72 (d, 2 H), 9.98 (s, 1 H). ^{13}C-NMR δ 20.98, 22.86, 24.54, 24.98, 26.23, 26.56, 27.84, 35.39, 127.40, 129.27, 136.50, 142.90, 164.43.

2-Pentanone p-Tosylhydrazone: Reaction of 2-pentanone (6.60 mL, 5.36 g, 62.2 mmol) with p-tosylhydrazine (11.6 g, 62.2 mmol) afforded tosylhydrazone product (13.8 g, 87.2%; literature value 84.0%)[37]. Recrystallization afforded a colorless powder. Cis and trans isomers (Figure 5.1) were present in a 82:18 ratio. Melting point 84-87°C (literature value 86-88°C)[37]. ^{1}H-NMR δ 0.72 (t, 3 H, cis isomer), 0.87 (t, 3 H, trans isomer), 1.36 (m, 2 H, cis isomer), 1.48 (m, 2 H, trans isomer), 1.75 (s, 3 H, cis isomer), 1.76 (s, 3 H, trans isomer), 2.05 (t, 2 H, cis isomer), 2.28 (t, 2 H, trans isomer), 2.37 (s, 3 H), 7.38 (d, 2 H), 7.72 (d, 2 H), 9.92 (s, 1 H). ^{13}C-NMR δ 13.24, 16.28, 18.77, 20.98, 32.29, 127.48, 129.22, 136.35, 142.93, 158.78.



Cis Isomer Trans Isomer

Figure 5.1: Structure of cis and trans isomers of 2-pentanone tosylhydrazone

2-Butanone p-Tosylhydrazone: Reaction of 2-butanone (5.50 mL, 4.43 g, 61.4 mmol) and p-tosylhydrazine (11.6 g, 62.1 mmol) resulted in known tosylhydrazone (12.3 g, 84.2%; literature value, 85.0%)[42]. Recrystallization

afforded colorless, medium to large granules. Cis and trans isomers were present in an 88:12 ration (literature value 85:15)[55]. Melting point 121-122°C (literature value 123-124°C)[42]. ^{1}H-NMR δ 0.89 (t, 3 H, cis isomer), 0.95 (t, 3 H, trans isomer), 1.76 (s, 3 H, cis isomer), 1.77 (s, 3 H, trans isomer), 2.10 (m, 2 H, cis isomer), 2.21 (m, 2 H, trans isomer), 2.38 (s, 3 H), 7.38 (d, 2 H), 7.73 (d, 2 H), 9.91 (s, 1 H). ^{13}C-NMR δ 10.33, 16.27, 21.00, 31.10, 127.54, 129.22, 136.30, 142.98, 159.90.

2-Hexanone p-Tosylhydrazone: Reaction of 2-hexanone (9.50 mL, 7.71 g, 77.0 mmol) with p-tosylhydrazine (14.4 g, 77.2 mmol) afforded the tosylhydrazone product (19.1 g, 92.5%; literature value, 85.0%)[37]. Recrystallization afforded a colorless, sticky powder. Cis and trans isomers were present in a 92:8 ratio. Melting point 70.5-72°C (literature value 74-76°C)[37]. ^{1}H-NMR δ 0.76 (t, 3 H, cis isomer), 0.89 (t, 3 H, trans isomer), 1.09 (m, 2 H, trans and cis isomers), 1.32 (m, 2 H, trans and cis isomers), 1.75 (s, 3 H, cis isomer), 1.76 (s, 3 H, trans isomers), 2.07 (t, 2 H, cis isomer), 2.19 (t, 2 H, trans isomer), 2.38 (s, 3 H), 7.37 (d, 2 H), 7.72 (d, 2 H), 9.91 (s, 1 H). ^{13}C-NMR δ 13.62, 16.29, 20.97, 21.33, 27.48, 37.41, 127.49, 129.19, 136.16, 142.91, 158.83.

2-Heptanone p-Tosylhydrazone: Reacting 2-heptanone (7.60 mL, 6.23 g, 54.6 mmol) with p-tosylhydrazine (10.2 g, 54.6 mmol) afforded the tosylhydrazone product (13.4 g, 86.7%; literature value 80.0%)[37]. Recrystallization afforded medium sized, colorless granules. Cis and trans isomers were present in a 95:5 ratio. Melting point 75-77°C (literature value 77-79°C)[37]. ^{1}H-NMR δ 0.77 (t, 3 H, cis isomer), 0.87 (t, 3 H, trans isomer), 0.98-1.41 (complex m, 6 H, trans and cis

isomers), 1.75 (s, 3 H, cis isomer), 1.76 (s, 3 H, trans isomer), 2.37 (s, 3 H), 7.37 (d, 2 H), 7.72 (d, 2 H), 9.91 (s, 1 H). ^{13}C-NMR δ 13.80, 16.30, 20.40, 21.81, 25.02, 30.39, 37.66, 127.49, 129.19, 136.35, 142.90, 158.79.

Acetoacetamide p-Tosylhydrazone: Reaction of acetoacetamide (5.00 g, 49.5 mmol) and p-tosylhydrazine (9.00 g, 48.4 mmol) afforded the desired tosylhydrazone (12.5 g, 95.7%). Recrystallization afforded a colorless powder. Melting point 138-139°C. ^{1}H-NMR δ 1.83 (s, 3 H), 2.37 (s, 3 H), 2.97 (s, 2 H), 6.99 (s, 2 H), 7.38 (d, 2 H), 7.75 (d, 2 H), 10.17 (s, 1 H). ^{13}C-NMR δ 16.90, 21.06, 44.81, 127.54, 129.44, 136.45, 143.18, 155.00, 170.26.

Ethyl Acetoacetate p-Tosylhydrazone: Reaction of ethyl acetoacetate (5.00 mL, 5.11 g, 39.2 mmol) and p-tosylhydrazine (7.30 g, 39.3 mmol) afforded the desired tosylhydrazone (9.46 g, 80.8%; literature value 65.0%)[30]. Recrystallization generated yellow granules. Melting point 101-102°C (literature value 105°C)[30]. ^{1}H-NMR δ 1.83 (s, 3 H), 2.37 (s, 3 H), 3.20 (s, 2 H), 4.02 (s, 1 H), 7.38 (d, 2 H), 7.72 (d, 2 H), 10.27 (s, 1 H). ^{13}C-NMR δ 16.83, 21.00, 43.66, 127.50, 129.38, 136.27, 143.20, 152.91, 169.19.

3-Acetyl-1-Propanol p-Tosylhydrazone: Reaction of 3-acetyl-1-propanol (5.00 mL 5.04 g, 49.3 mmol) and p-tosylhydrazine (9.00 g, 48.4 mmol) afforded the desired tosylhydrazone (11.6 g, 86.9%). Recrystallization afforded colorless granules. Melting point 117-120°C. ^{1}H-NMR δ 1.50 (m, 2 H), 1.77 (s, 3 H), 2.12 (t, 2 H), 2.38 (s, 3 H), 3.31 (t, 2 H), 4.44 (s, 1 H), 7.38 (d, 2 H), 7.73 (d, 2 H), 9.93 (s, 1 H). ^{13}C-NMR δ 16.60, 21.01, 28.90, 34.61, 66.10, 127.53, 129.26, 136.38, 142.99, 159.04.

2-Acetylbutyroloactone p-Tosylhydrazone: Reaction of 2-acetylbutrolactone (1.00 mL 1.19 g, 9.25 mmol) and p-tosylhydrazine (1.70 g, 9.14 mmol) afforded the desired tosylhydrazone (2.44 g, 90.0%). Recrystallization afforded a colorless powder. Melting point 137-138 °C. ^{1}H-NMR δ 1.87 (s, 3 H), 2.20 (m, 2 H), 2.38 (s, 3 H), 3.56 (t, 1 H), 4.19 (t, 2 H), 7.40 (d, 2 H), 7.73 (d, 2 H), 10.35 (s, 1 H). ^{13}C-NMR δ 15.69, 21.03, 25.91, 47.62, 66.83, 127.52, 129.41, 136.00, 143.33, 153.47, 175.44.

Acetylmalononitrile p-Tosylhydrazone: Reaction of acetylmalononitrile (1.00 g, 8.20 mmol) and p-tosylhydrazine (1.50 g, 8.06 mmol) afforded the desired tosylhydrazone (1.87 g, 80.0%). Recrystallization afforded a colorless powder. Melting point 102°C. ^{1}H-NMR δ 1.76 (s, 3 H), 2.07 (s, 3 H), 2.41 (d, 1 H), 3.50 (t, 1 H), 7.38 (d, 2 H), 7.72 (d, 2 H), 9.91 (s, 1 H). ^{13}C-NMR δ 16.60, 21.08, 26.67, 28.88, 34.60, 66.08, 127.66, 129.36, 136.36, 142.99, 159.05.

3'-Methoxyacetophenone Tosylhydrazone: Reaction of 3'-methoxy-acetophenone (5.00 mL, 5.47 g, 36.4 mmol) with p-tosylhydrazine (6.79 g, 36.5 mmol) produced the desired tosylhydrazone (10.2 g, 87.9%). Recrystallization afforded colorless needles. Melting point 124-126°C. ^{1}H-NMR δ 2.16 (s, 3 H), 2.37 (s, 3 H), 3.75 (s, 3 H), 6.95 (d, 1 H), 7.11 (s, 1 H), 7.19 (d, 1 H), 7.29 (t, 1 H), 7.42 (d, 2 H), 7.81 (d, 2 H), 10.51 (s, 1 H). ^{13}C-NMR δ 14.37, 21.01, 55.03, 111.13, 115.09, 118.47, 127.63, 129.43, 136.13, 138.83, 143.40, 152.99, 159.11.

4'-Methoxyacetophenone Tosylhydrazone: Reacting 4'-methoxy-acetophenone (10.0 g, 66.6 mmol) with p-tosylhydrazine (12.4 g, 66.6 mmol) produced the desired tosylhydrazone (17.5 g, 82.8%; literature value, 79.0%)[126].

Recrystallization from a 1:1 methanol/propanol solution afforded small, colorless granules. Melting point 168.5-174°C (literature value 163-171°C)[126]. ^{1}H-NMR δ 2.13 (s, 3 H), 2.37 (s, 3 H), 3.76 (s, 3 H), 6.91 (d, 1 H), 7.41 (d, 2 H), 7.57 (d, 2 H), 7.80 (d, 2 H), 10.34 (s, 1 H). ^{13}C-NMR δ 11.12, 21.00, 55.19, 113.68, 127.42, 127.58, 129.39, 129.82, 136.25, 143.22, 153.15, 160.26.

5.15 Gas Chromatography Calibration Curves

Seven 100 mL chloroform solutions, with the concentrations of 5.00 mM, 15.0 mM, 25.0 mM, 35.0 mM, 45.0 mM and 55.0 mM, were made for each ketone. Each solution contained 1 mL of tert-butyl methyl ether (TBME) as an internal standard. Triplicate 2 μL aliquots of the respective concentrations were injected into the GC. For each run the peak area of the ketone was divided by the peak area of TBME, giving a value of ketone/TBME. The average ketone/TBME value for each concentration was determined. Plotting the average ketone/TBME value verses the concentration resulted in a straight line calibration curve. A calibration curve was obtained for each aliphatic ketone studied. Calibration curves are depicted in Appendix II.

5.16 Photolysis of Tosylhydrazones

A 100 mL chloroform solution, in a covered volumetric flask, containing tosylhydrazone, with a concentration of 25 mM, 65 mg of chloranil and 1 mL of TBME was irradiated, with stirring, with a 200 W Hg/Xe arc lamp (Oriel Instruments, Model 68811), located within a 120 cm X 60 cm X 50 cm enclosed

box. Solutions were irradiated for 4 hours. At appropriate time intervals (usually hourly), triplicate 2 μL samples were obtained and injected into the GC to determine the progress of ketone formation. When quantifying the amount of ketone regenerated over time, the moles regenerated were obtained from the calibration curve of the ketone of interest.

Variable Concentration of Chloranil Experiment: Nine 25 mM cyclopentanone tosylhydrazone solutions in 100 mL of chloroform, with 1mL of TBME and 0.001 g, 0.005 g, 0.010 g, 0.025 g, 0.050 g, 0.075 g, 0.100 g, 0.150 g, and 0.200 g of chloranil were irradiated for one half hour. Triplicate 2 μL samples were obtained and injected into the GC to determine the amount of ketone formed.

Precipitate Filtration Experiments: A 100 mL chloroform solution containing 25 mM tosylhydrazone, 65 mg chloranil and 1 mL TBME was irradiated with stirring. At hourly intervals, triplicate 2 μL aliquots were obtained and injected into the GC to determine the progress of ketone formation. At each hourly interval, gravity filtration was performed on the solution to remove precipitate that was formed.

Kinetic Order Study, Variable Concentration of Tosylhydrazone: Six 100 mL chloroform solutions, containing tosylhydrazone with concentrations of 2.50 mM, 5.00 mM, 10.0 mM, 20.0 mM, 30.0 mM and 40.0 mM, and each containing 65 mg of chloranil and 1 mL of TBME were irradiated for 30 minutes. Triplicate 2 μL aliquots of solution were obtained and injected into the GC to determine the amount of ketone formed.

Varying Light Intensity Experiments: Three 100 mL chloroform solutions, containing 25 mM of tosylhydrazone, 65 mg of chloranil and 1 mL of TBME were prepared. The first solution was exposed to the Hg/Xe lamp, the second solution was exposed to ambient light, and the third solution was placed in the dark, all for 4 hour periods. Hourly, triplicate 2 μL aliquots of solution were obtained and injected into the GC to determine the progress of ketone regeneration.

Formation of Ketone from Phenylhydrazone Solution: Phenylhydrazone experiments were conducted with similar solutions and under similar conditions as those for tosylhydrazones.

Formation of Ketone Under Anaerobic Conditions: A solution containing 25 mM of tosylhydrazone and 1 mL of TBME was prepared in 100 mL of chloroform. The solution was cooled with liquid nitrogen, air was pumped out of the reaction vessel and replaced with nitrogen gas. 65 mg of chloranil was then added to the solution via a solid-dropping funnel. The solution was irradiated with stirring for 4 hours. Upon hourly intervals, triplicate 2 μL aliquots were removed, via a rubber septum, and injected into the GC to analyze for ketone formation.

Trapping of the Radical Cation with TEMPO: A solution containing 0.63 g cyclopentanone tosylhydrazone, 65 mg chloranil and 0.39 g TEMPO in 100 mL of chloroform was irradiated with the Hg/Xe lamp for 15 minutes. 2 μL samples were injected into the MS to confirm the presence of adduct between cyclopentanone tosylhydrazone radical cation and TEMPO.

5.17 Solutions Used in Cyclic Voltammetry Experiments

Unless otherwise specified, solutions used in cyclic voltammetry contained 50 mM of analyte and 0.5 M of the supporting electrolyte tetrabutylammonium hexafluorophosphate (TBAHFP) in 25 mL HPLC grade acetonitrile. Solutions were purged with nitrogen gas for 20 minutes prior to each run.

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Appendix I: Chromatographic Data

Table A.1: GC elution times for different analytes

Analyte Compound	Elution Time (minutes)
Cyclopentanone	4.62
Cyclohexanone	5.56
Cycloheptanone	7.41
Cyclooctanone	9.95
2-Pentanone	4.14[a]
2-Hexanone	4.12
2-Heptanone	4.58
1-Acetonaphthone	11.68[b]
2-Acetonaphthone	14.39[b]
3-Methoxyacetophenone	7.16[b]
4-Methoxyacetophenone	8.69[b]
t-Butyl Methyl Ether	3.50
	3.37[a]
Chloroform	3.63
	3.67[a]
	3.86[b]

[a] Experiments involving 2-pentanone were conducted at lower GC temperatures, resulting in different elution times. See Experimental Section 5.12 for GC settings.

[b] Experiments involving aromatic ketones were conducted at higher GC temperatures, resulting in different elution times. See Experimental Section 5.12 for GC settings.

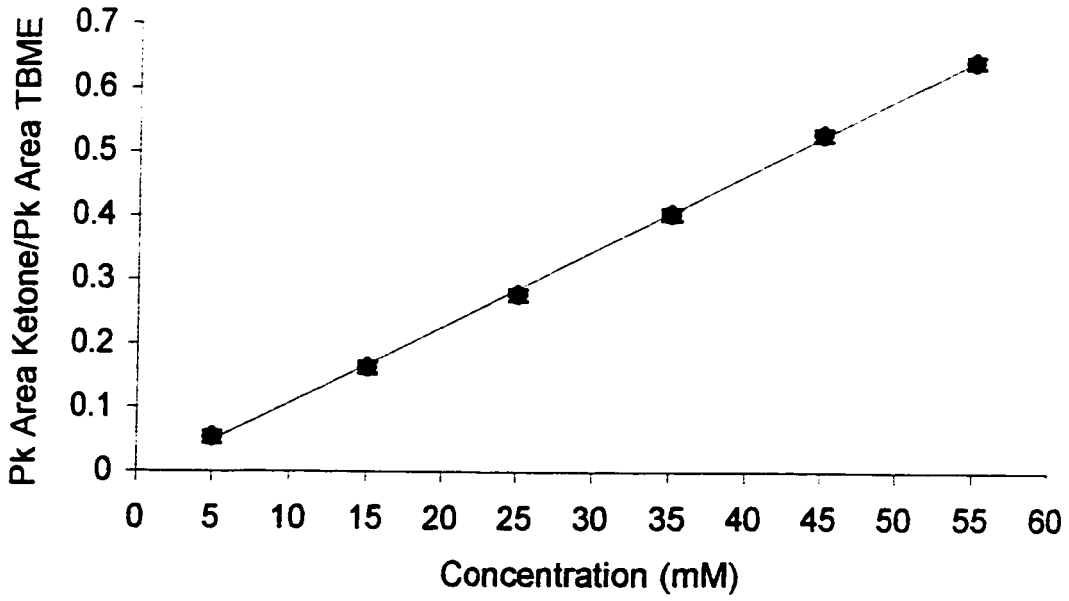
Table A.2: R_f values for TLC study

Analyte Compound	R_f value
Cyclopentanone Tosylhydrazone	0.905
Cyclohexanone Tosylhydrazone	0.920
Cycloheptanone Tosylhydrazone	0.886
Cyclooctanone Tosylhydrazone	0.898
2-Pentanone Tosylhydrazone	0.883
2-Hexanone Tosylhydrazone	0.889
2-Heptanone Tosylhydrazone	0.888
p-Tolysulfonylhydrazine	0.725
Cyclopentanone Phenylhydrazone	0.711
Phenylhydrazine	0.491

Appendix II: Calibration Curves

Table A.3: Raw data for cyclopentanone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0581	0.0543	0.0523	0.0549
15.0	0.163	0.162	0.169	0.164
25.0	0.278	0.286	0.274	0.279
35.0	0.403	0.420	0.395	0.405
45.0	0.530	0.533	0.524	0.529
55.0	0.652	0.631	0.649	0.644

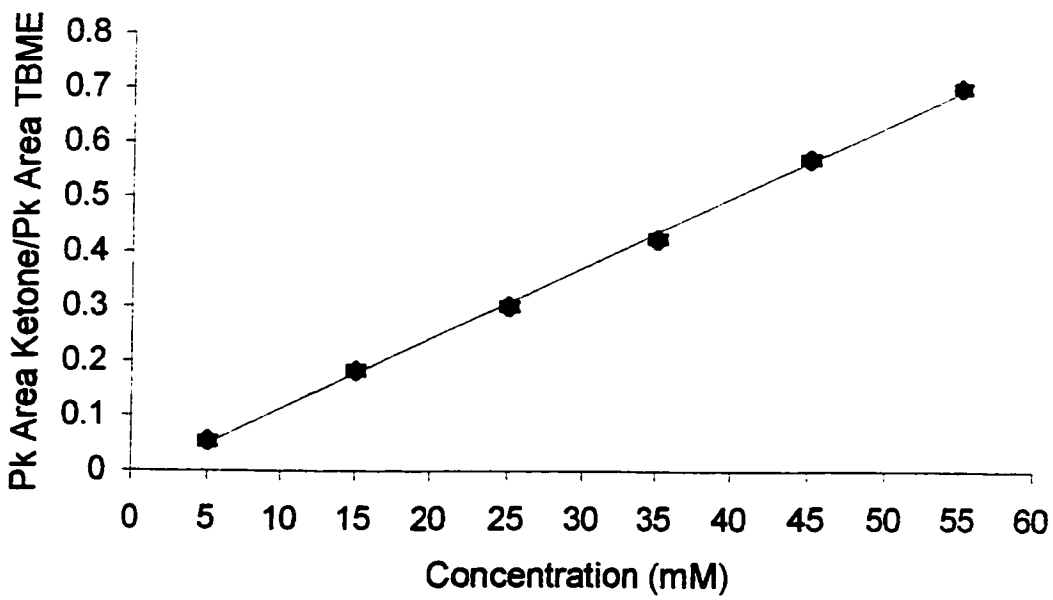


Equation of the line: $y = 0.0119x - 0.0111$ $R^2 = 0.9995$

Figure A.1: Cyclopentanone GC calibration curve

Table A.4: Raw data for cyclohexanone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0549	0.0567	0.0517	0.0544
15.0	0.197	0.178	0.176	0.184
25.0	0.294	0.296	0.313	0.301
35.0	0.433	0.424	0.418	0.425
45.0	0.554	0.587	0.572	0.571
55.0	0.697	0.708	0.698	0.701

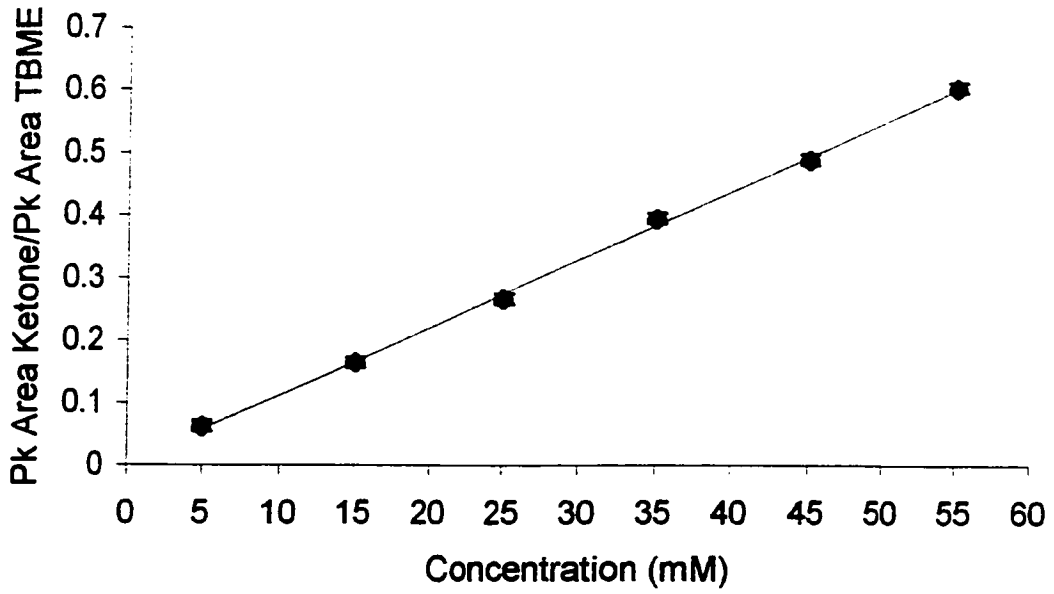


Equation of the line: $y = 0.0129x - 0.0145$ $R^2 = 0.9990$

Figure A.2: Cyclohexanone GC calibration curve

Table A.5: Raw data for cycloheptanone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0610	0.0649	0.0563	0.0607
15.0	0.174	0.162	0.156	0.164
25.0	0.277	0.251	0.269	0.266
35.0	0.398	0.403	0.382	0.394
45.0	0.483	0.475	0.507	0.488
55.0	0.594	0.608	0.607	0.603

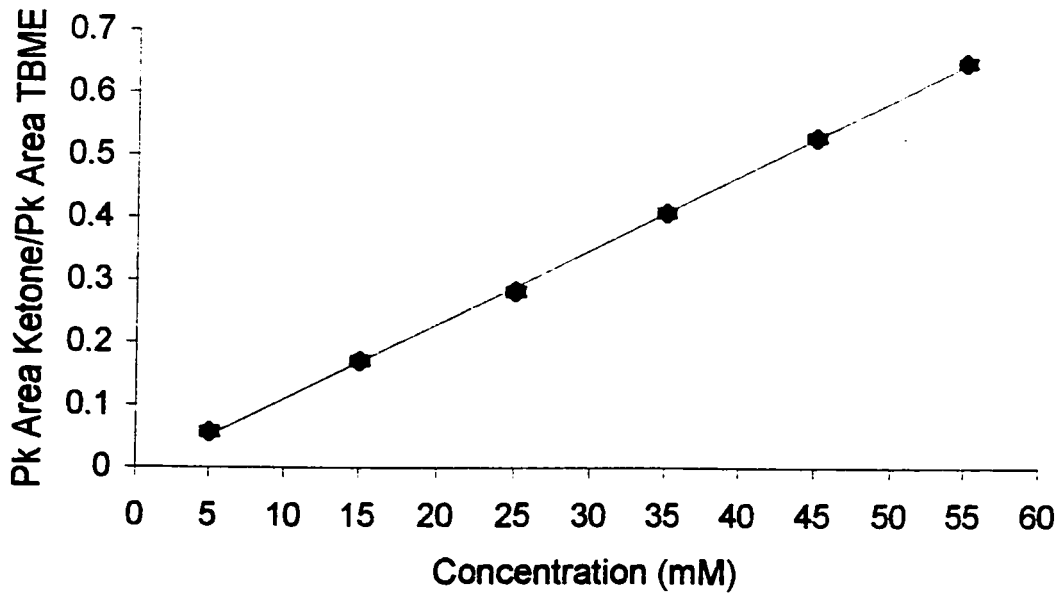


Equation of the line: $y = 0.0109x + 0.0026$ $R^2 = 0.9989$

Figure A.3: Cycloheptanone GC calibration curve

Table A.6: Raw data for cyclooctanone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0544	0.0607	0.0549	0.0567
15.0	0.164	0.184	0.164	0.171
25.0	0.301	0.266	0.279	0.282
35.0	0.405	0.394	0.425	0.408
45.0	0.571	0.488	0.529	0.529
55.0	0.603	0.701	0.644	0.649

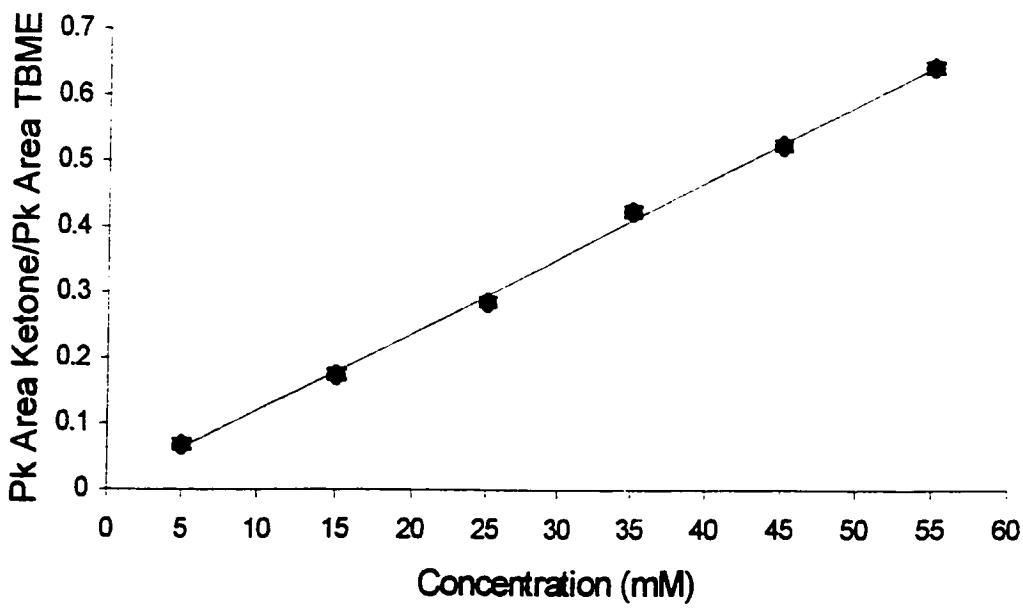


Equation of the line: $y = 0.0119x - 0.0074$ $R^2 = 0.9996$

Figure A.4: Cyclooctanone GC calibration curve

Table A.7: Raw data for 2-pentanone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0685	0.0681	0.0674	0.0680
15.0	0.174	0.172	0.179	0.175
25.0	0.284	0.287	0.285	0.286
35.0	0.423	0.426	0.423	0.424
45.0	0.529	0.519	0.523	0.524
55.0	0.639	0.648	0.642	0.643

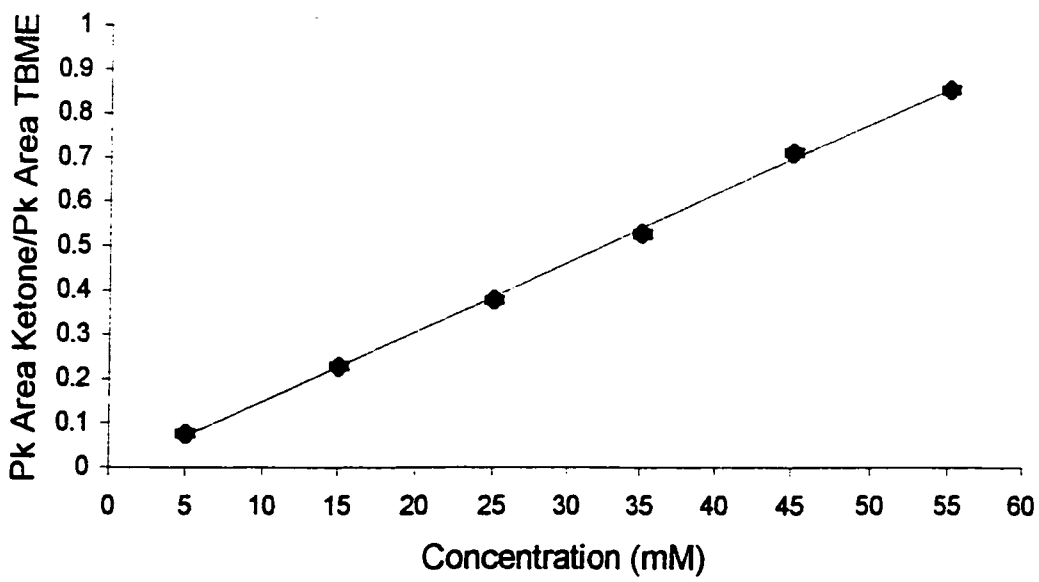


Equation of the line: $y = 0.0116x + 0.0053$ $R^2 = 0.9987$

Figure A.5: 2-Pentanone GC calibration curve

Table A.8: Raw data for 2-hexanone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0714	0.0833	0.0776	0.0774
15.0	0.226	0.230	0.232	0.229
25.0	0.374	0.384	0.380	0.379
35.0	0.519	0.539	0.529	0.529
45.0	0.709	0.718	0.714	0.713
55.0	0.861	0.841	0.866	0.856

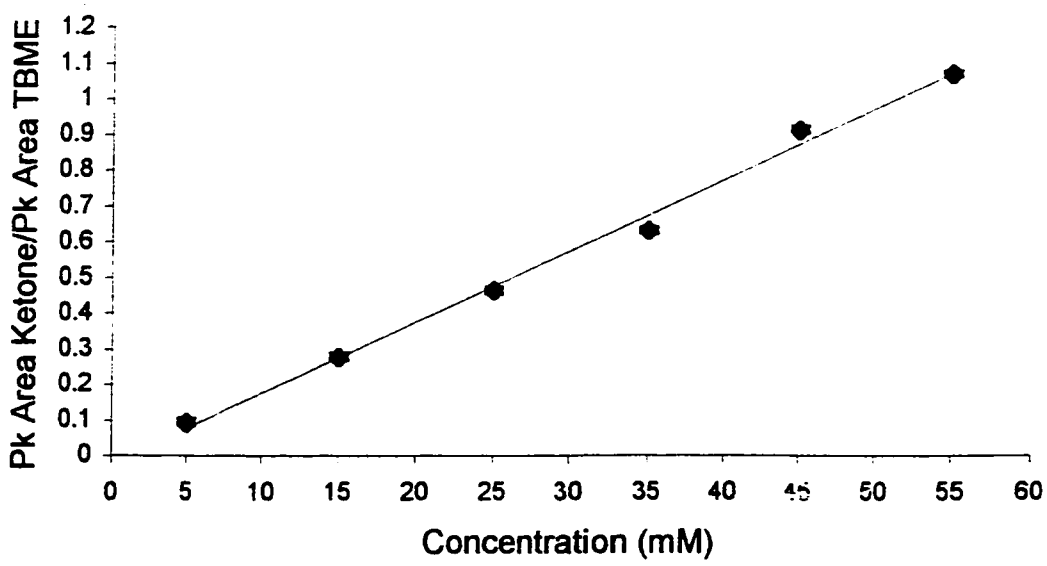


Equation of the line: $y = 0.0157x - 0.0071$ $R^2 = 0.9990$

Figure A.6: 2-Hexanone GC calibration curve

Table A.9: Raw data for 2-heptanone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0936	0.0909	0.0957	0.0933
15.0	0.279	0.277	0.277	0.278
25.0	0.463	0.464	0.462	0.463
35.0	0.623	0.630	0.640	0.631
45.0	0.914	0.912	0.913	0.913
55.0	1.12	0.997	1.09	1.07

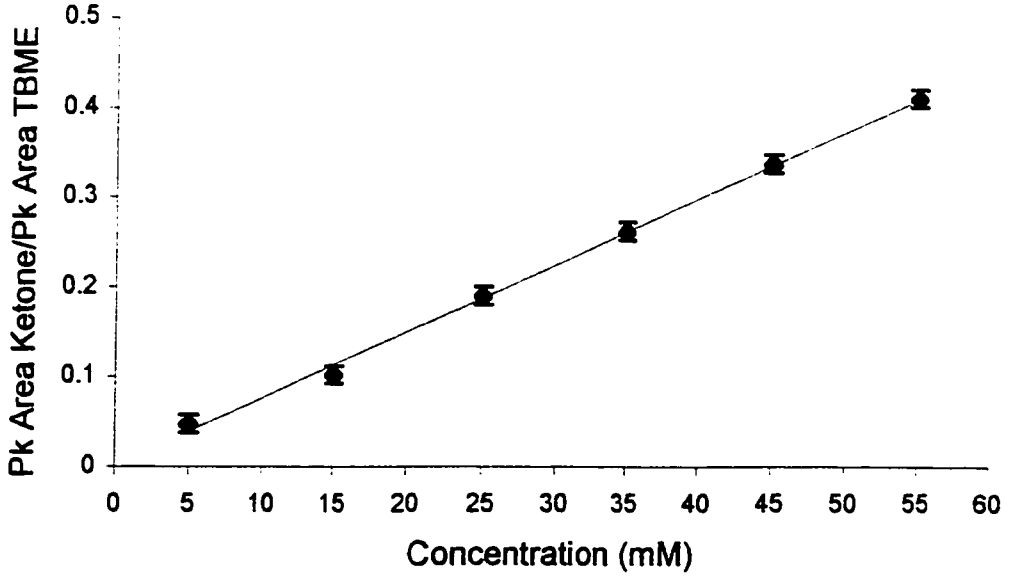


Equation of the line: $y = 0.0199x - 0.0216$ $R^2 = 0.9944$

Figure A.7: 2-Heptanone GC calibration curve

Table A.10: Raw data for ethyl acetoacetate GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0444	0.0501	0.0480	0.0475
15.0	0.100	0.105	0.101	0.102
25.0	0.198	0.187	0.185	0.190
35.0	0.268	0.258	0.260	0.262
45.0	0.339	0.332	0.340	0.337
55.0	0.415	0.400	0.415	0.410

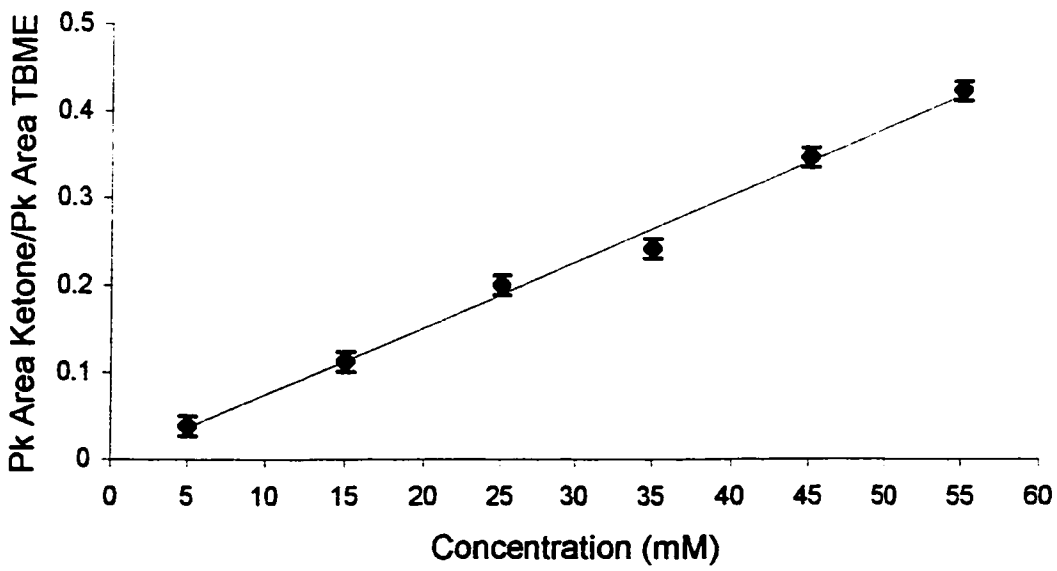


Equation of the line: $y = 0.0074x - 0.0028$ $R^2 = 0.9979$

Figure A.8: Ethyl acetoacetate GC calibration curve

Table A.11: Raw data for acetoacetamide GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0388	0.0380	0.0387	0.0385
15.0	0.104	0.115	0.120	0.113
25.0	0.204	0.197	0.202	0.201
35.0	0.248	0.237	0.244	0.243
45.0	0.351	0.340	0.350	0.347
55.0	0.421	0.428	0.423	0.424

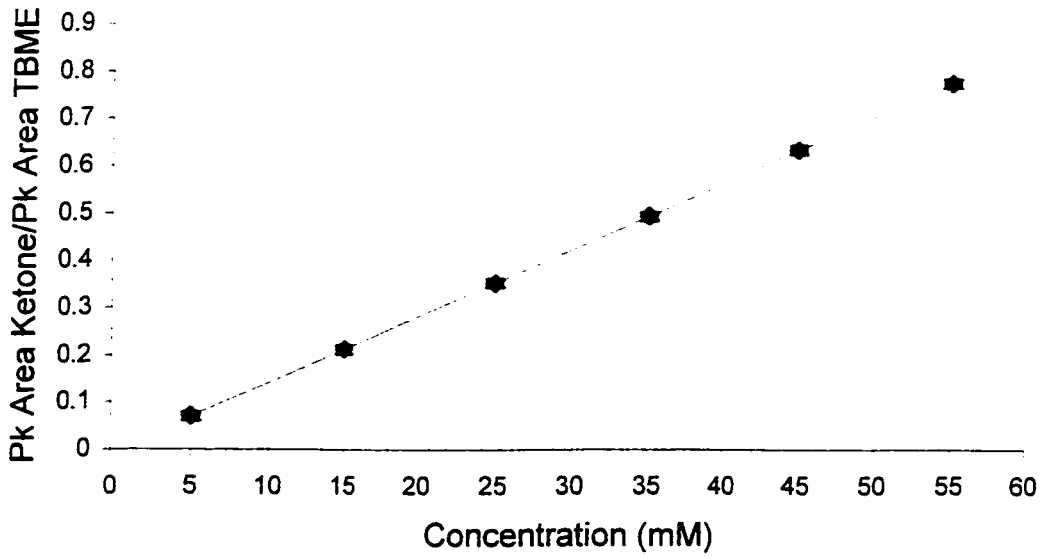


Equation of the line: $y = 0.0076x - 0.0012$ $R^2 = 0.9931$

Figure A.9: Acetoacetamide GC calibration curve

Table A.12: Raw data for acetylbutyrolactone GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0709	0.0747	0.0664	0.0706
15.0	0.215	0.209	0.211	0.212
25.0	0.354	0.356	0.349	0.353
35.0	0.499	0.490	0.492	0.494
45.0	0.633	0.636	0.636	0.635
55.0	0.781	0.774	0.776	0.777

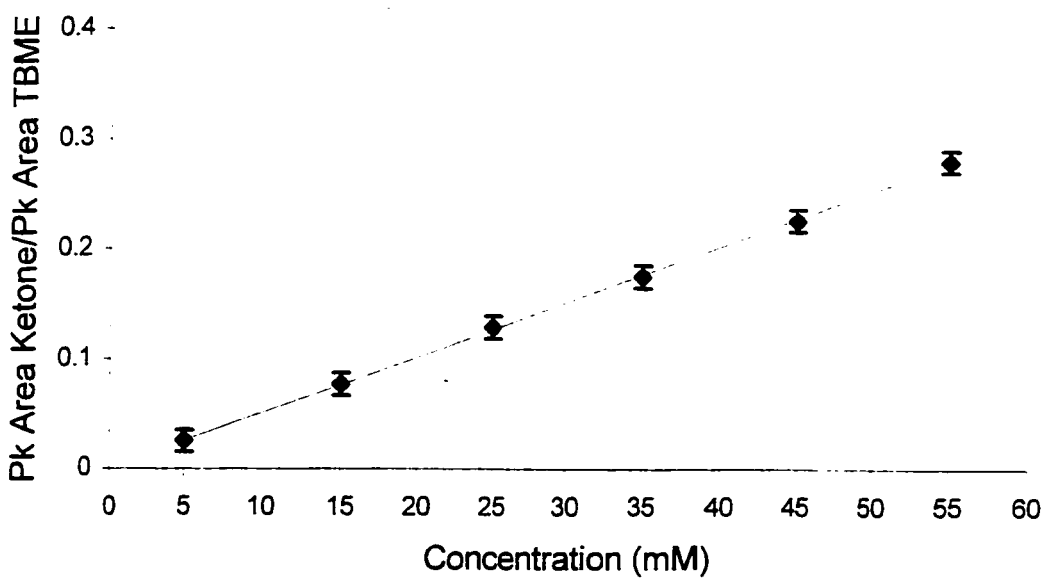


Equation of the line: $y = 0.0141x - 0.0010$ $R^2 = 0.9999$

Figure A.10: Acetylbutyrolactone GC calibration curve

Table A.13: Raw data for acetylmalononitrile GC calibration curve

Concentration (mM)	Peak Area Ketone/Peak Area TBME			Average
	Run #1	Run#2	Run#3	
5.00	0.0244	0.0261	0.0259	0.0255
15.0	0.0758	0.0778	0.0771	0.0769
25.0	0.135	0.126	0.125	0.129
35.0	0.172	0.174	0.178	0.175
45.0	0.235	0.220	0.223	0.226
55.0	0.296	0.294	0.250	0.280



Equation of the line: $y = 0.0005x + 0.0007$ $R^2 = 0.9996$

Figure A.11: Acetylmalononitrile GC calibration curve

Appendix III: Ketone Deprotection Data

Table A.14: Raw data for cyclopentanone deprotection experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	4.45	17.8	2.53	10.1	3.92	15.7	14.5
2.0	4.77	19.1	4.57	18.3	4.93	19.7	19.0
3.0	6.11	24.4	6.63	26.5	5.50	22.0	24.3
4.0	5.50	22.0	6.75	27.0	7.30	29.2	26.1

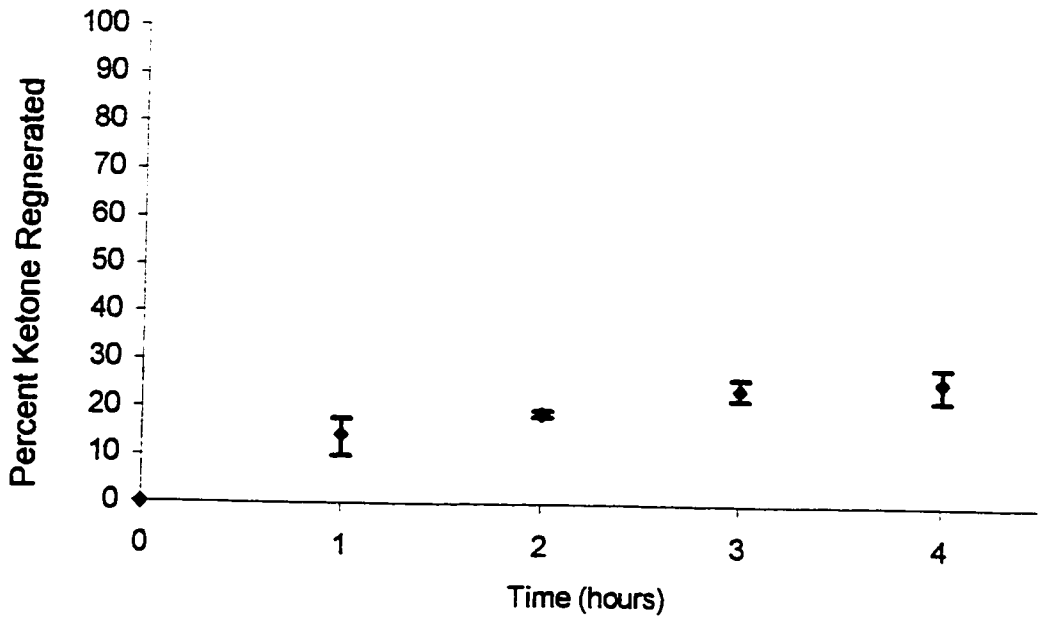


Figure A.12: Regeneration of cyclopentanone over time

Table A.15: Raw data for cyclohexanone deprotection experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	4.33	17.3	6.08	24.3	5.28	21.1	20.9
2.0	6.15	24.6	6.35	25.4	5.88	23.5	24.5
3.0	6.23	24.9	6.48	25.9	5.98	23.9	24.9
4.0	6.23	24.9	6.73	26.9	6.00	24.0	26.9

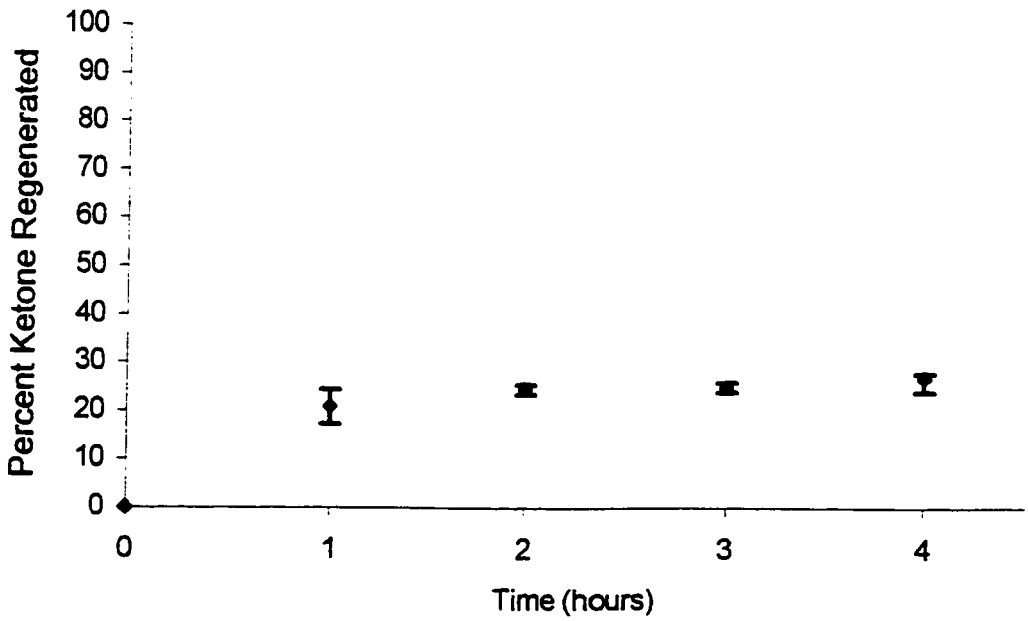


Figure A.13: Regeneration of cyclohexanone over time

Table A.16: Raw data for cycloheptanone deprotection experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	4.96	19.8	5.84	23.4	4.21	16.8	20.0
2.0	6.03	24.1	6.01	24.0	6.44	25.8	24.6
3.0	6.82	27.3	7.13	28.5	7.17	28.7	28.2
4.0	6.93	27.7	8.28	33.1	7.18	28.7	29.8

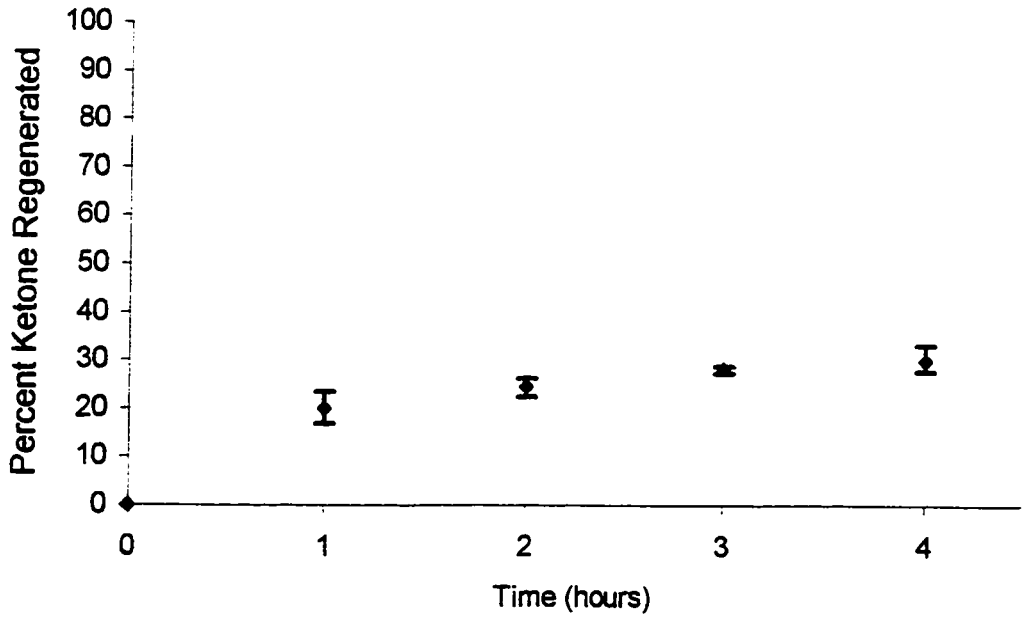


Figure A.14: Regeneration of cycloheptanone over time

Table A.17: Raw data for cyclooctanone deprotection experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	5.07	20.3	6.04	24.2	5.91	23.6	22.7
2.0	5.21	20.8	6.09	24.4	5.93	23.7	23.0
3.0	6.04	24.2	6.59	26.4	6.42	25.7	25.4
4.0	7.13	28.5	7.44	29.8	7.60	30.4	29.6

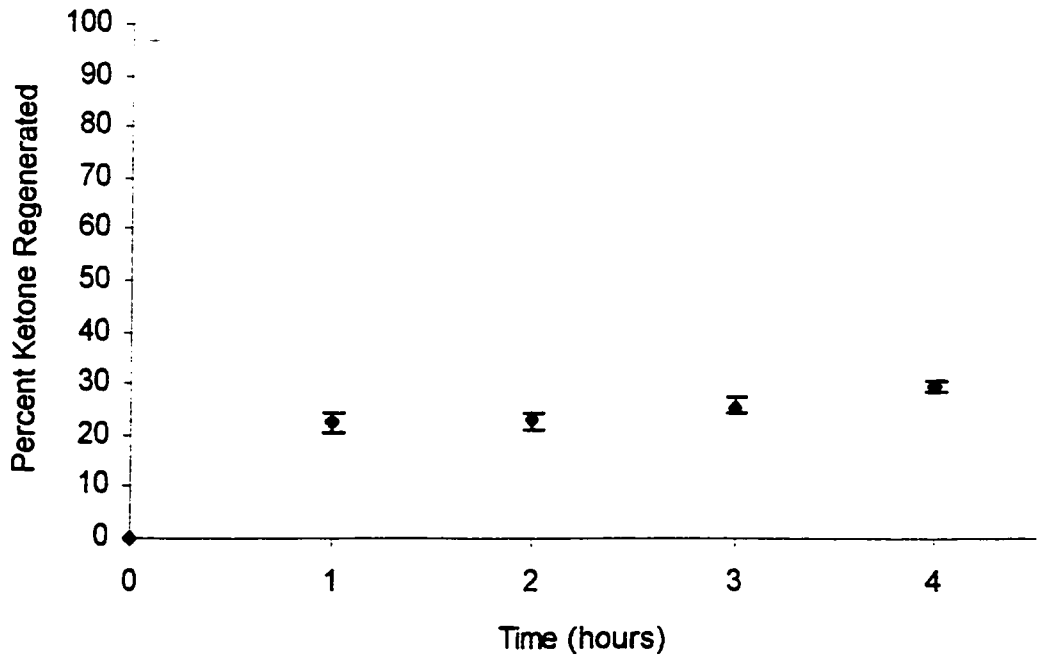


Figure A.15: Regeneration of cyclooctanone over time

Table A.18: Raw data for 2-pentanone deprotection experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	4.81	19.2	4.70	18.8	5.04	20.2	19.4
2.0	5.65	22.6	5.16	20.6	5.41	21.6	21.6
3.0	5.85	23.4	5.77	23.1	5.41	21.6	22.7
4.0	6.17	24.7	6.19	24.8	5.42	21.7	23.7

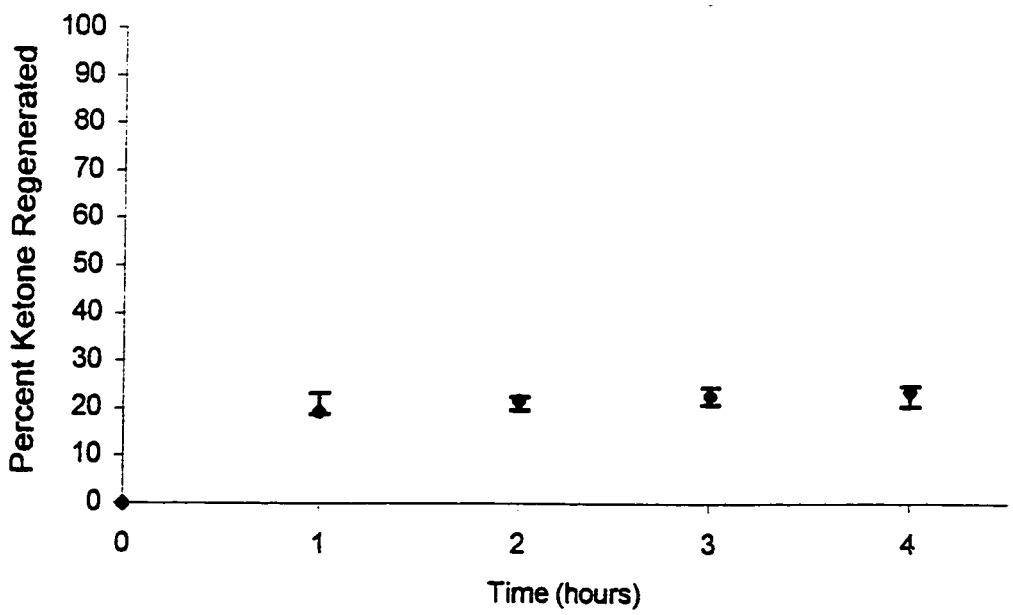


Figure A.16: Regeneration of 2-pentanone over time

Table A.19: Raw data for 2-hexanone deprotection experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	5.66	22.6	5.76	23.0	6.01	24.0	23.2
2.0	6.00	24.0	6.22	24.9	5.82	23.3	24.1
3.0	6.17	24.7	5.94	23.8	6.09	24.4	24.3
4.0	6.36	25.4	7.29	29.2	7.31	29.2	27.9

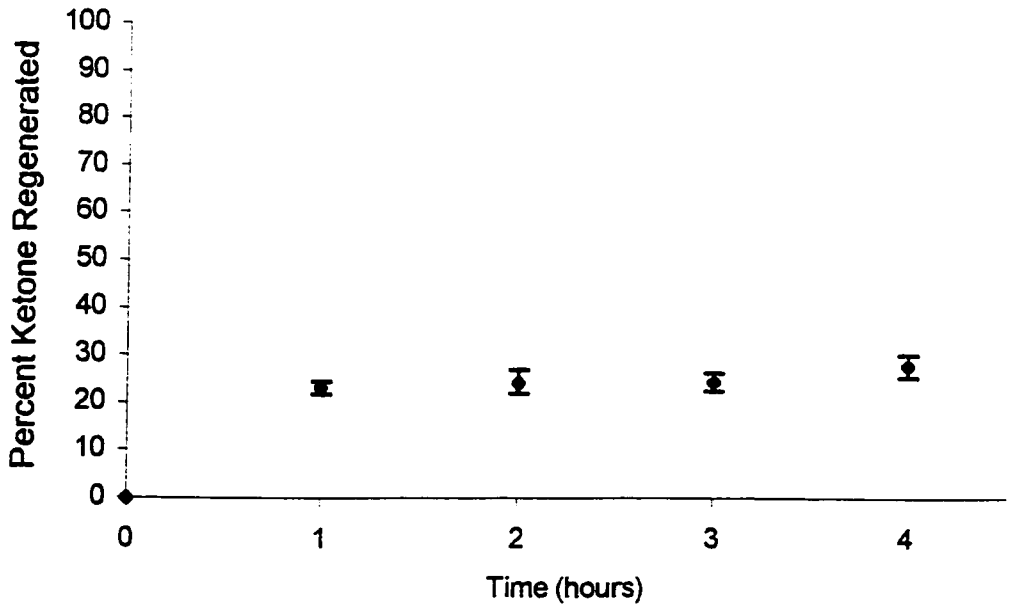


Figure A.17: Regeneration of 2-hexanone over time

Table A.20: Raw data for 2-heptanone deprotection experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	6.77	27.1	6.54	26.2	6.54	26.2	26.5
2.0	7.09	28.4	6.95	27.8	7.17	28.7	28.3
3.0	7.36	29.4	7.25	29.0	7.39	29.6	29.3
4.0	7.53	30.1	7.73	30.9	7.51	30.1	30.4

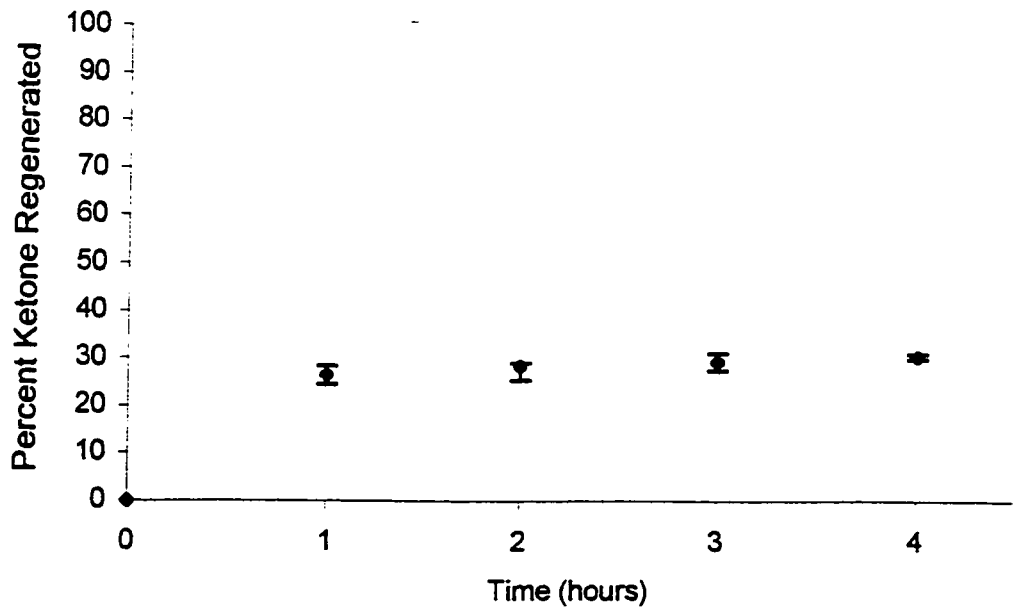


Figure A.18: Regeneration of 2-heptanone over time

Table A.21: Raw data for the cyclopentanone deprotection/precipitate filtering experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	4.00	16.0	4.17	16.7	4.08	16.3	16.4
2.0	6.41	25.6	6.53	26.1	6.55	26.2	26.0
3.0	8.76	35.0	9.49	37.9	8.00	32.0	35.0
4.0	10.9	43.6	11.3	45.2	12.9	51.6	46.8
5.0	13.8	55.2	13.8	55.1	13.0	52.0	54.1
6.0	15.4	61.5	15.5	62.0	16.3	65.0	62.8
7.0	19.1	76.4	17.9	71.4	18.8	75.1	74.3
8.0	20.7	82.8	20.2	80.5	20.5	82.0	81.8
9.0	21.2	84.8	21.9	87.6	22.6	90.3	87.6
10.0	22.2	88.8	23.1	92.4	22.7	90.7	90.6
16.0	22.4	89.6	22.8	91.2	23.1	92.4	91.1
22.0	23.0	92.0	23.1	92.4	23.2	92.8	92.4

Table A.22: Raw data for the 2-heptanone deprotection/precipitate filtering experiment

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	6.20	24.8	7.03	28.1	5.98	23.9	25.6
2.0	9.25	37.0	8.68	34.7	8.48	33.9	35.2
3.0	12.6	50.3	11.1	44.3	11.8	47.3	47.3
4.0	13.3	53.4	13.0	51.9	13.2	52.8	52.7
5.0	14.8	59.0	15.3	61.1	13.9	55.7	58.6
6.0	16.4	65.5	16.6	66.3	17.4	69.5	67.1
7.0	19.4	77.4	19.0	75.8	19.2	76.6	76.6
8.0	21.6	86.3	21.2	84.7	21.4	85.5	85.5

Table A.23: Raw data for cyclopentanone deprotection: exposure to ambient light

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	3.01	12.0	2.69	10.8	3.87	15.5	12.8
2.0	3.15	12.6	3.20	12.8	3.93	15.7	13.7
3.0	3.37	13.5	3.57	14.3	4.03	16.1	14.6
4.0	3.54	14.2	3.96	15.8	4.06	16.2	15.4

Table A.24: Raw data for 2-heptanone deprotection: exposure to ambient light

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	3.60	14.4	3.69	14.8	3.73	14.9	14.7
2.0	3.91	15.6	3.96	15.8	3.94	15.8	15.7
3.0	4.05	16.2	4.34	17.4	4.08	16.3	16.6
4.0	5.21	20.9	5.33	21.3	4.84	19.4	20.5

Table A.25: Raw data for the variable chloranil experiment

Mass Chloranil (g)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.001	2.06	8.25	2.25	8.98	2.24	8.96	8.73
0.005	2.58	9.47	2.42	9.67	2.33	9.31	9.48
0.010	2.56	9.40	2.53	10.1	2.53	10.1	9.87
0.025	2.90	10.6	2.50	10.0	2.73	10.9	10.5
0.050	2.98	10.9	2.75	11.0	2.95	11.8	11.2
0.075	2.83	11.3	2.68	10.7	2.90	11.6	11.2
0.100	2.73	10.9	2.73	10.9	3.03	12.1	11.3
0.150	3.22	11.8	2.75	11.0	2.75	11.0	11.3
0.200	3.06	11.3	2.70	10.8	3.28	13.1	11.7

Table A.26: Raw data for kinetics study: variable initial hydrazone concentration/ 30 minutes irradiation

Initial Concentration of Tosylhydrazone (mM)	Concentration of Regenerated Ketone (mM)			Average (mM)
	Run #1	Run #2	Run #3	
2.93	0.255	0.279	0.255	0.263
3.14	0.323	0.337	0.279	0.313
5.28	0.475	0.443	0.459	0.459
10.0	0.830	0.760	0.780	0.790
18.0	1.92	1.47	1.59	1.66
33.1	3.01	2.57	3.00	2.86
40.0	3.60	3.44	3.73	3.59

Table A.27: Raw data for cyclopentanone deprotection when solvent is dried

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	4.04	16.2	3.47	13.9	3.07	12.3	14.1
2.0	4.39	17.6	4.24	16.9	5.00	20.0	18.2
3.0	5.93	21.3	6.16	24.6	5.55	22.2	23.5
4.0	7.24	28.9	6.90	27.6	6.42	25.7	27.4

Table A.28: Raw data for 2-heptanone deprotection when solvent is dried

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	6.49	26.0	6.67	26.7	6.37	25.5	26.1
2.0	7.08	28.3	7.21	28.8	6.57	26.3	27.8
3.0	7.25	29.0	7.37	29.5	7.88	31.5	30.0
4.0	7.30	29.2	8.19	32.8	7.28	29.1	31.4

Table A.29: Raw data for cyclopentanone formation from cyclopentanone phenylhydrazone

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	2.82	11.3	2.89	11.6	2.57	10.3	11.1
2.0	3.56	14.2	3.29	13.2	3.63	14.5	14.0
3.0	3.91	15.6	3.82	15.3	4.18	16.7	15.9
4.0	3.76	15.0	3.83	15.3	4.46	17.8	16.0

Table A.30: Raw data for 2-heptanone formation from 2-heptanone phenylhydrazone

Time (hours)	Ketone Regenerated						Average Ketone Regenerated (%)
	Run #1		Run #2		Run #3		
	(mM)	%	(mM)	%	(mM)	%	
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.0	2.78	11.1	2.54	10.2	2.71	10.8	10.7
2.0	3.78	15.1	3.61	14.4	3.81	15.2	14.9
3.0	3.98	15.9	3.61	14.4	4.46	17.8	16.0
4.0	4.15	16.6	4.21	16.8	4.55	18.2	17.2

Appendix IV: Cyclic Voltammograms

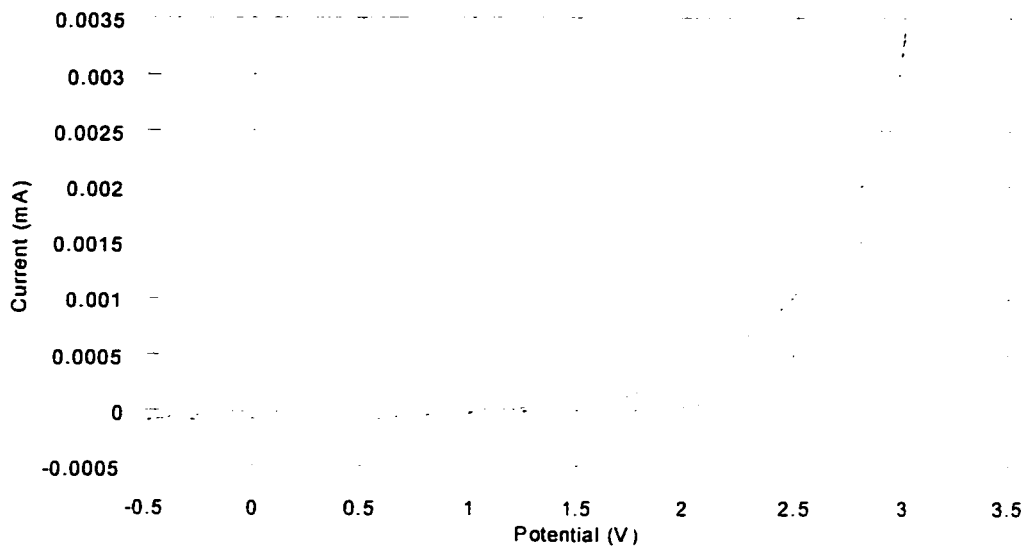


Figure A.19: Cyclic Voltammogram of TBAHFP solution

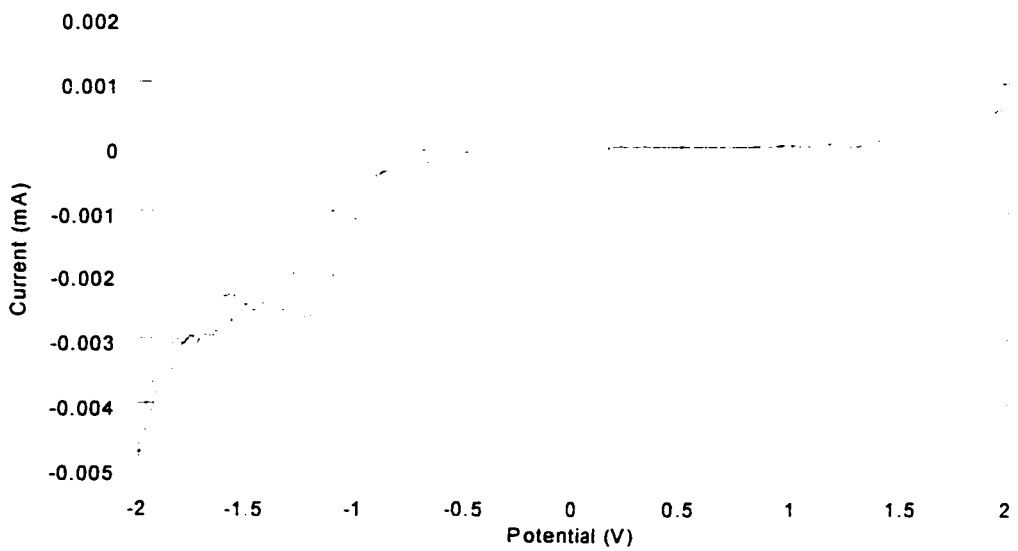


Figure A.20: Cyclic voltammogram of cyclopentanone

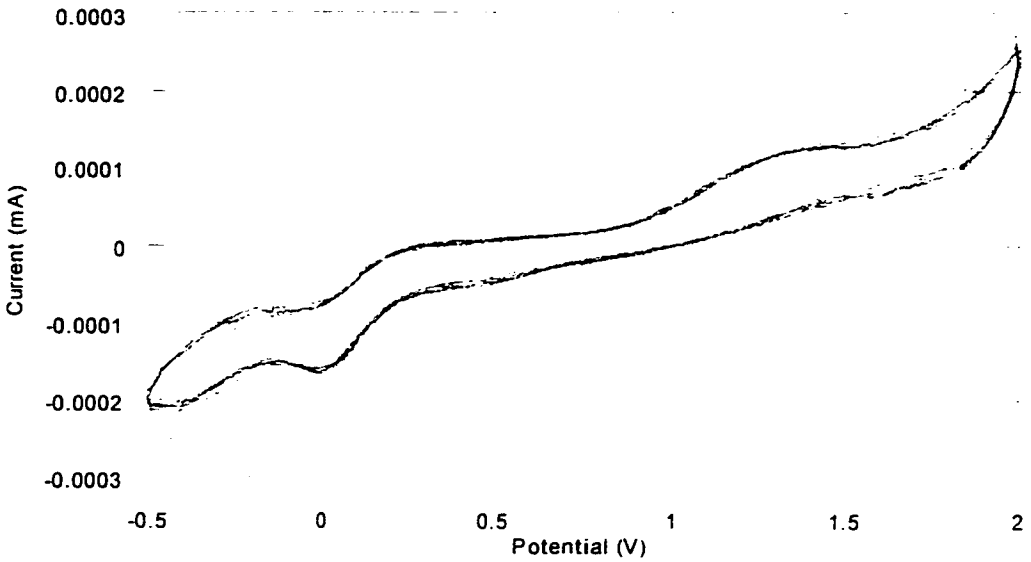


Figure A.21: Cyclic voltammogram of precipitate over 1 hour

Appendix V: Mass Spectra from Radical Trap Experiments

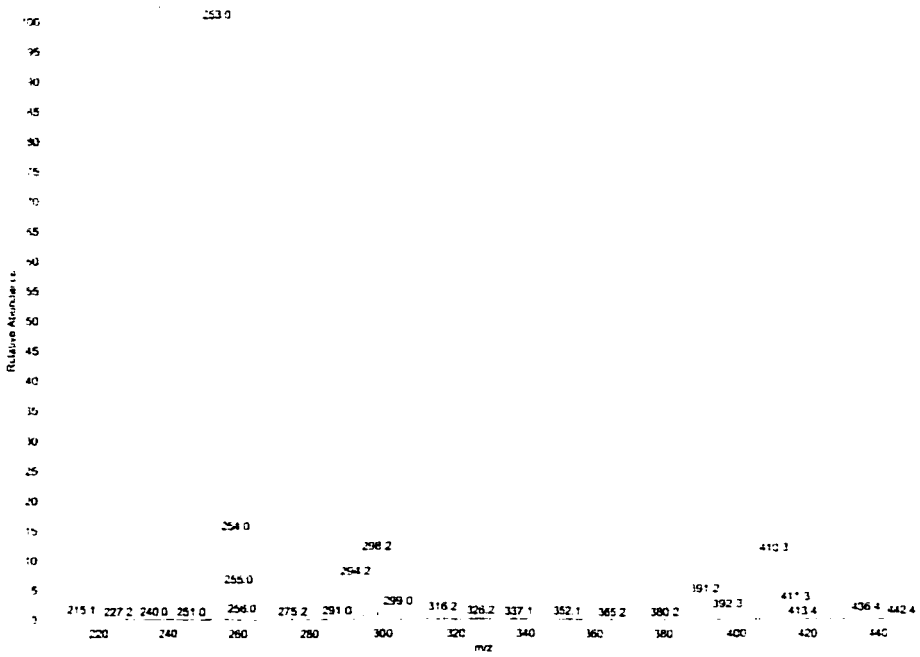


Figure A.22: Mass spectrum of cyclopentanone tosylhydrazone

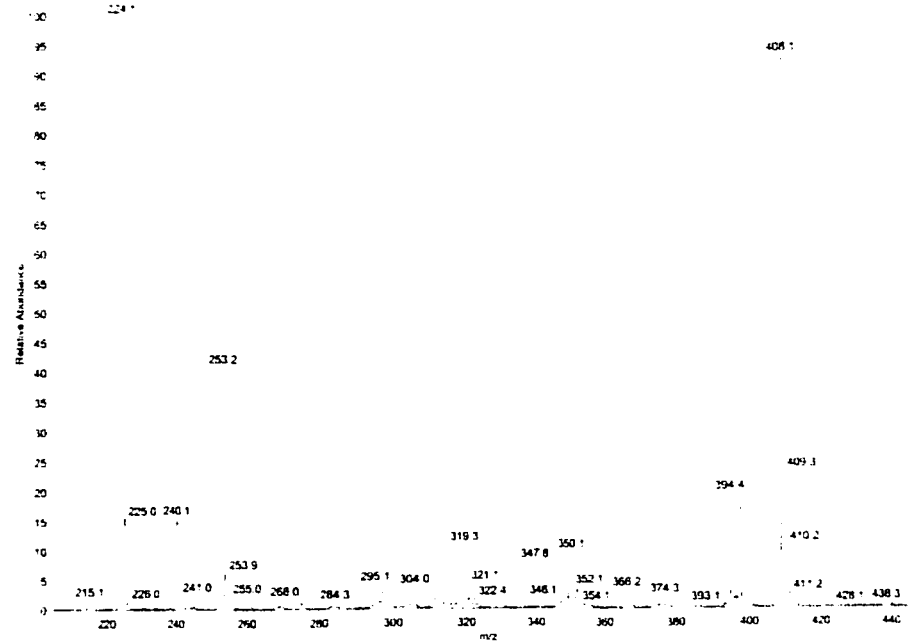


Figure A.23: Mass spectrum of irradiated cyclopentanone tosylhydrazone-TEMPO solution

Appendix VI: Precipitate ^{13}C-NMR and ^{15}N-NMR Data

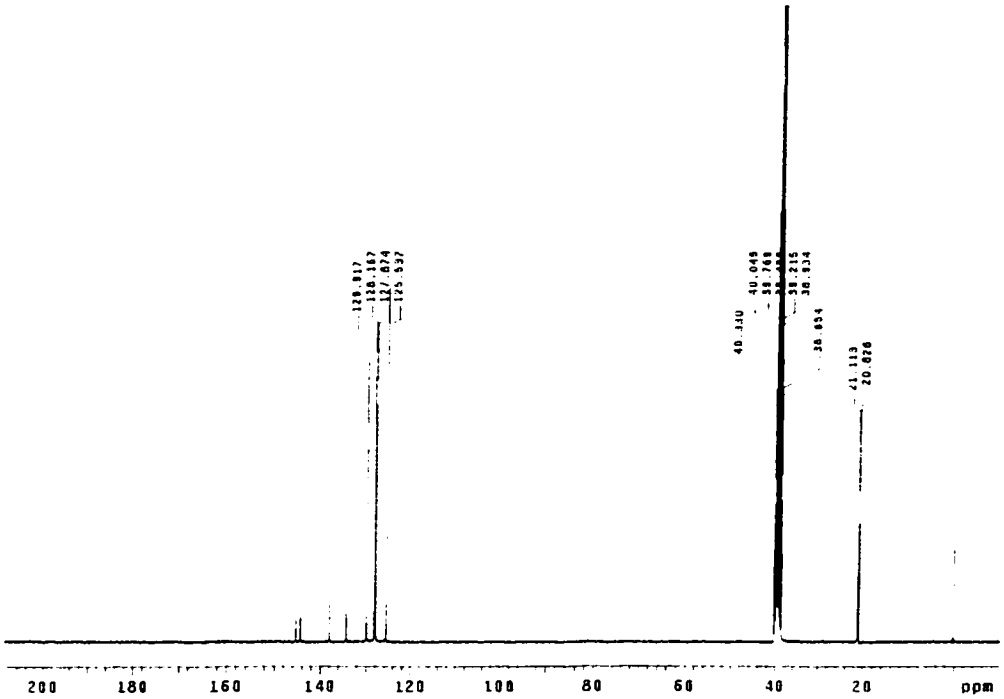


Figure A.24: ^{13}C-NMR spectrum

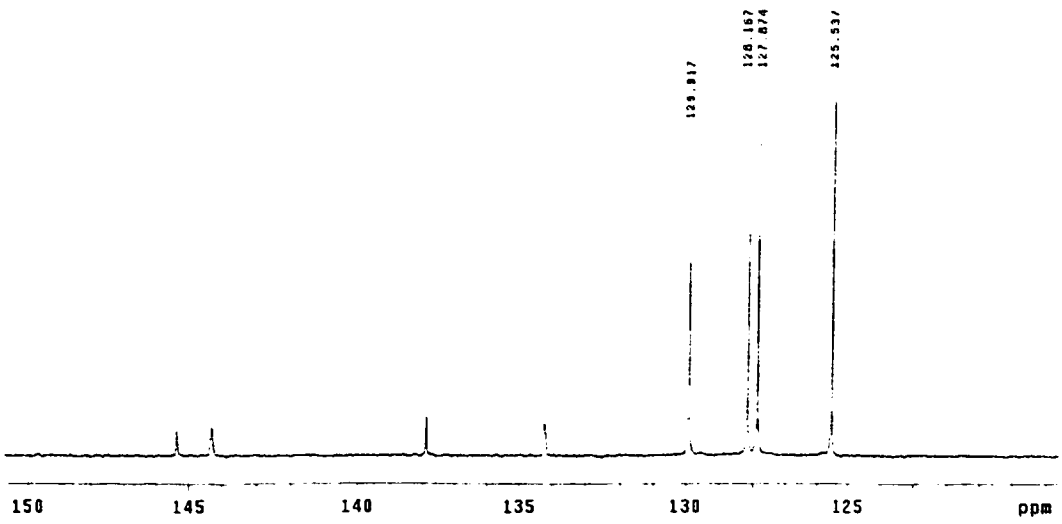


Figure A.25: Enlargement of the ^{13}C-NMR spectrum (δ 120 to 150 ppm)

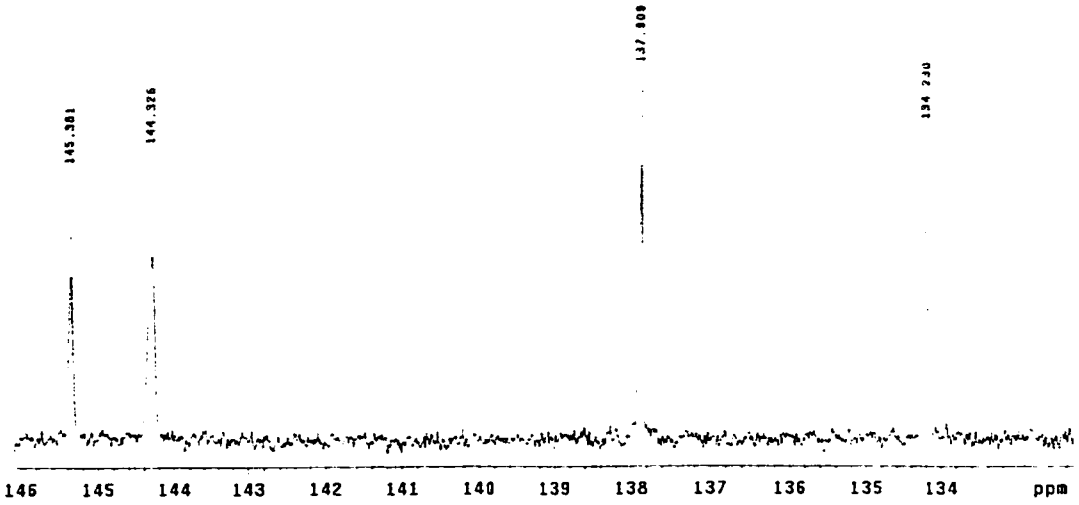


Figure A.26: Enlargement of the ^{13}C-NMR spectrum (δ 132 to 146 ppm)

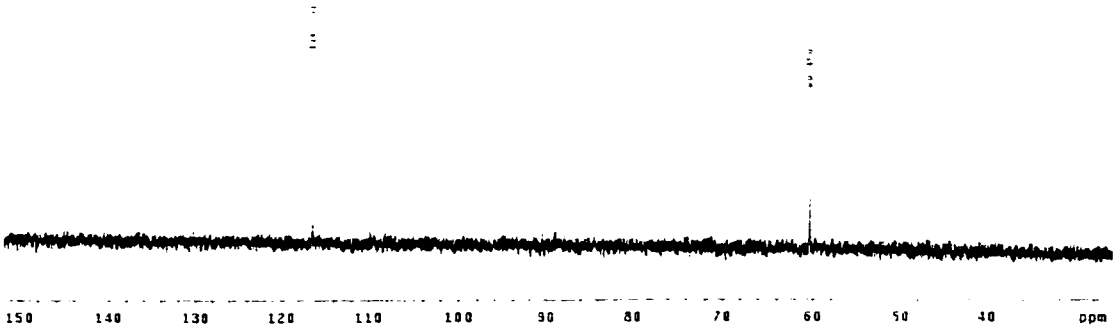


Figure A.27: Enlargement of the ^{15}N-NMR spectrum (δ 30 to 150 ppm)