Chapter I
INTRODUCTION

Radical chemistry dates back to 1900 when Gomberg investigated the formation and reactions of the triphenylmethyl radical. In the 1920's Paneth showed that less stabilized alkyl radicals also exist and measured the lifetime of these radicals in gas phase. Organic synthesis with radicals began in 1937 when Hey and Waters described the phenylation of aromatic compounds by benzoyl peroxide as a radical reaction. In the same year, Kharasch recognized that the *anti*-Markovnikov addition of hydrogen bromide to alkenes proceeds *via* a radical chain process. In the following years, Mayo, Walling and Lewis discovered the rules of radical copolymerization reactions.[1]

In this research only C-centered radicals are discussed. The majority of free radical reactions which are of interest to the synthetic organic chemists are chain processes and involve three major steps: (1) radical initiation; (2) chain propagation (electron, group or atom transfer; addition, elimination, *etc.*) and (3) termination.

The success of radical reactions for a synthetic application is dependent on the "controlled generation" of the radical itself. This can be accomplished by deriving the radical from a "disciplinary group" to deal with otherwise unruly nature of radicals. The disciplinary group also produces the chain propagating radical. Further, some disciplinary effects can also be produced by the "reagent" which finally transfers an atom (H) or a group in the chain termination step. Undisciplined radicals attack at random and give many products and therefore are not useful for organic synthesis.[2]

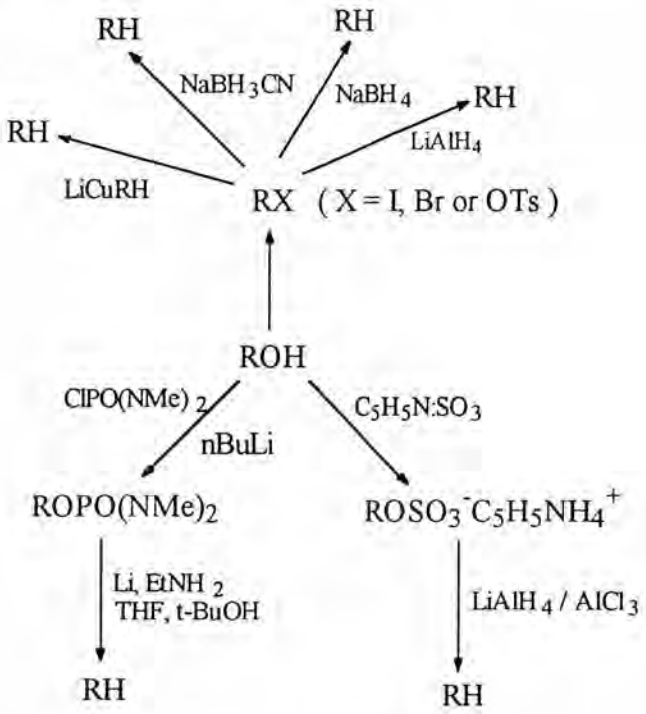
For many years, free radical species have been known to be intermediates in a large number of chemical reactions. Their use for the synthesis of special chemicals has been limited, due to lack of selectivity. However in recent years many well designed radical reactions which give high yields of desired products have been discovered. For instance, Barton-McCombie reaction is a method for selective

replacement of hydroxyl groups by hydrogen, which was discovered by D. H. R. Barton and S. W. McCombie in 1975.[3]

1.1 Deoxygenation of alcohols

Reactions for the selective replacement of hydroxyl groups by hydrogen are very important in many areas of natural product chemistry, particularly in the chemistry of carbohydrates and aminoglycosides. For instance, deoxyaminoglycoside antibiotics show enhanced biological activity because various bacteria cannot deactivate the antibiotics by *O*-acylation or *O*-phosphosylation.

Numerous methods have been developed for the deoxygenation of alcohols. Conventional syntheses involve the reduction of suitable alcohol derivatives such as tosylate, mesylate, sulfate, *O*-alkylisourea *etc*, or by using the nucleophilic replacement of the hydroxy group by halogen or thiolate with subsequent reductive dehalogenation or desulfurisation. The majority of these procedures requires the conversion of the alcohol component to an activated derivative and subsequent reduction with a metal hydride reducing agent. Those general methods can be summarized as shown in Scheme 1.1[4]



Scheme 1.1 Representative procedures for the deoxygenation of alcohols.

Various types of metal hydrides used for increasing a reducing property had been develop. In 1973 S. Masamune *et al.*[5] have found "lithium dialkyl cuprate" as a reducing agent for removal of halo and tosyloxy or mesyloxy group. The yields of reduced products were excellent and the reactions were completed within 2 hr at room temperature. Primary and secondary mesylates underwent equally smooth reductive cleavage to achieve a 96% yield of product.

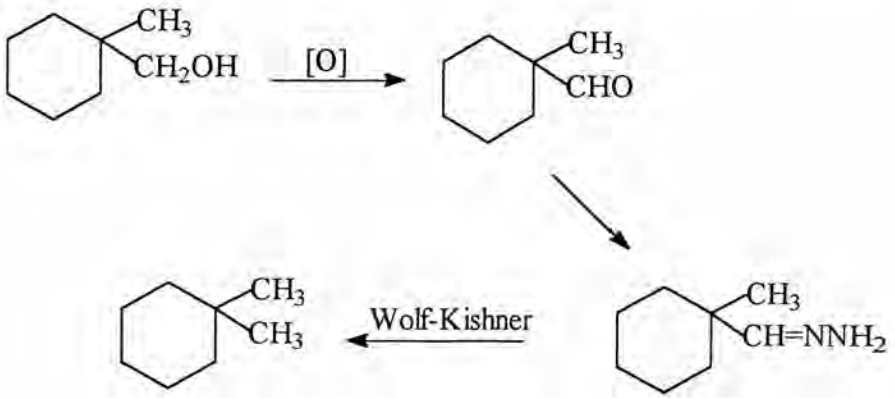
$$CH_3(CH_2)_6CH_2Br \xrightarrow[25^0\,C,\,1\,hr]{LiCu(CH_3)_2,\,THF} C_8H_{18}$$

In 1976 S. Krishnamurthy and H. C. Brown have brought "lithium triethylborohydride" (super hydride) as an exceptionally powerful nucleophilic reducing agent. They tested the effectiveness of this reagent for the reduction of representative alkyl tosylates to the corresponding alkanes. Tosylates of primary alcohols such as *n*-octyl tosylate is rapidly converted into *n*-octane in 96%yield.

$$CH_3(CH_2)_6CH_2OTs \xrightarrow[25^0\,C,\,15\,min]{LiEt_3BH,\,THF} CH_3(CH_2)_6CH_3$$

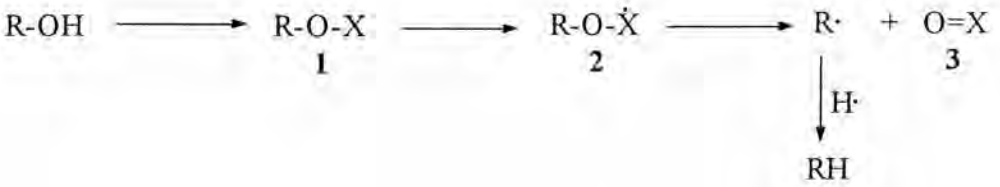
This procedure works satisfactorily with relatively unhindered primary alcohols, the results are however less favorable for the more hindered alcohols.[6]

Although these reactions, in principle ionic in nature, can be applied successfully to simple, sterically unhindered alcohols. In fact the usual procedure for the deoxygenation of such hindered alcohol involves the oxidation of the alcohol to the aldehyde followed by Wolf-Kishner reduction of the hydrazone derivative of the aldehyde.



Those mentioned reactions have limitations and disadvantages as soon as complex, polyfunctional compounds with sterically hindered OH groups are present. The main reasons for this are that reactants and intermediates in ionic reactions are highly solvated and that S_N reactions only take place in low yields, if at all, owing to steric hindrance and dipole repulsion. In addition, rearrangements and eliminations are common side reactions when carbocations appear as intermediates.

Radical reactions can be an alternative to ionic reactions. Radicals are not solvated and thus less susceptible to steric factors. Moreover, radical reactions may be highly chemoselective and able to take place under neutral conditions. Therefore, they are ideally suited for application to sensitive polyfunctional compounds. Radical deoxygenation, *i.e.* the homolytic cleavage of a C-O bond, can be realized according to Scheme 1.2 in which a suitable alcohol derivative **1** is converted to an intermediate radical **2**, which then fragments by β cleavage into an alkyl radical R• and a carbonyl compound **3**. The alkyl radical R• further reacts with a hydrogen donor yielding the corresponding hydrocarbon.[7]

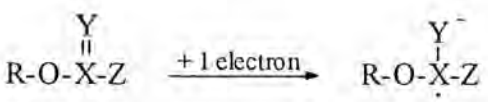


Scheme 1.2 The general mechanism of radical deoxygenation

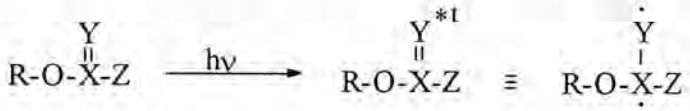
The intermediate radical **2** can be produced in three different ways:

a) By addition of a radical onto a CO or heterocarbonyl group

b) By electron transfer to an activated double bond with formation of a radical ion

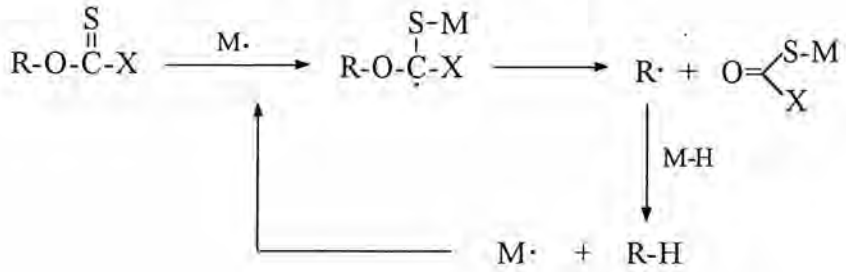


c) By photolytic excitation of a π system forming the triplet state



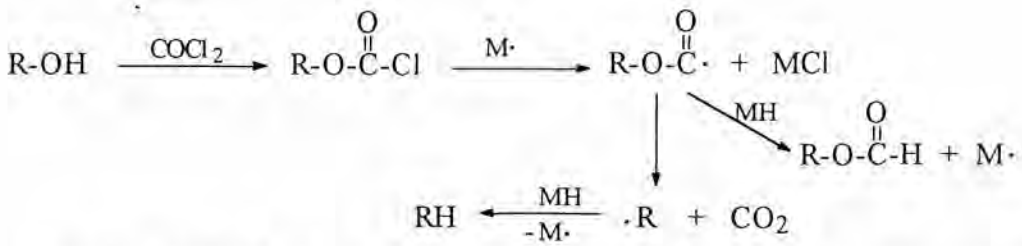
There are four types of intermediate radical **2** which usually prepared for alcohol derivatives.

i) Deoxygenation *via O*-alkylthiocarbonyl derivatives



The Barton deoxygenation method occurs at the reflux temperature of toluene. In this process, a radical M· capable of forming a stable bond to sulfur should react with an *O*-alkylthiocarbonyl compound to form an intermediate radical, which then fragments into an alkyl radical and carbonyl compound. The driving force of the reaction would be the energy gained by the transition from a C=S to a C=O double bond. This process suitable for sterically hindered polyfunctional compounds and alcohol derivatives are obtainable in high yield under neutral conditions. Fuctional groups such as ester and ketone, double and triple bonds, epoxide, tosylate and mesylate *etc.* are unaffected under this reaction conditions. Halogen and isocyanide groups, in contrast, are reduced by tributyltin hydride.

ii) Deoxygenation *via* chloroformates

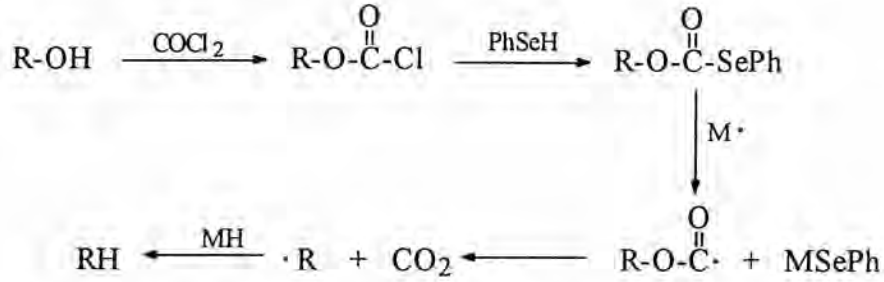


The reduction of chloroformates to hydrocarbons was first described by Kuivila and Walsh[8] in 1966 for the benzyl ester. The reaction, which takes place at

room temperature, only gives the hydrocarbon in poor yield, the main product being the corresponding formyl derivative. Later Jackson[9] in 1977 had developed this reduction to be in excellent yield, which carried out at higher temperatures (140-160°C) and with tri-*n*-propylsilane as a reducing agent. However deoxygenation of alcohols *via* chloroformates is limited to simple primary and secondary aliphatic alcohols, because large quantities (50-110%) of $(BuO)_2$ radical starter are required for high yields to be obtained. Moreover, it has some side reactions with some complicated molecules.

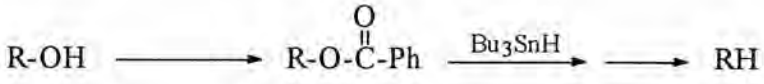
iii) Deoxygenation *via* phenylselenocarbonate

The process for the deoxygenation of primary and secondary alcohols, developed by Pfenniger, *et al.* [10] has a mechanism to the chloroformate method that has the advantage of very short reaction times (2-60 min) and need radical starter (AIBN). This is due to the high affinity of Sn and Se.



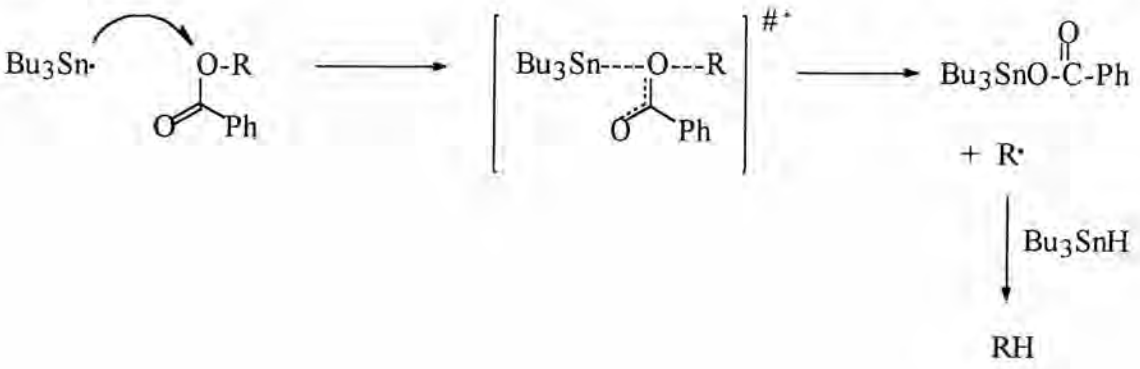
Many functional groups such as ester and α,β-unsaturated ketone groups are not affected under these reaction conditions. Tertiary alcohols can be deoxygenated *via* selenocarbonated but the preparation of the derivatives can only be achieved in unsatisfactory yield.

iv) Deoxygenation *via* benzoate



This method is thus particulally limited to benzyl, allyl- and α-keto-alcohols, but only succeeds with alcohols that bare a radical stabilizing substituent in the α-position to the hydroxy group. This difference in reaction behaviour of benzoates,

compared with chloroformates and selenocarbonates, is attributed by Khoo and Lee[11] to a fundamentally different reaction mechanism. The tin radical, generated as usual from a tin hydride and initiator, attacks at the ether oxygen with cleavage to the alkyl radical. The reaction is thus particularly easy when stabilized alkyl radicals can be formed.

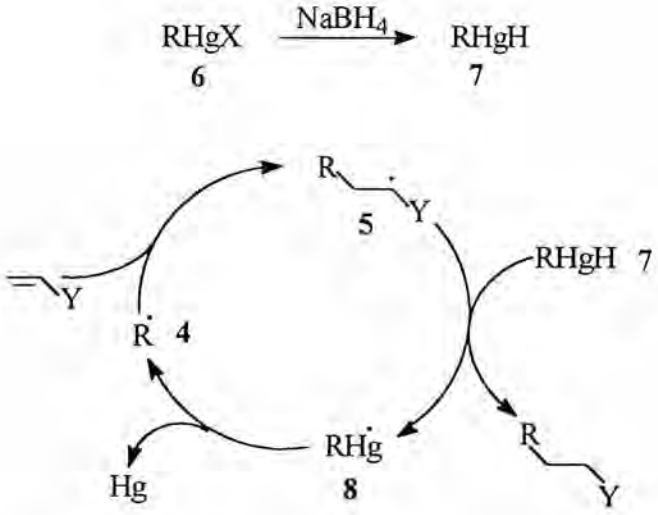


The general applicability of the method is further limited because, under the reaction conditions, side reactions occur such as the addition of tributyltin hydride on terminal double bonds or isomerizations.

According to previous methods reported, organostannane as a chain carrier and hydrogen radical donors was usually used in a chain reaction. Although that method gave good yields and found in many application, the problems associated with the price, toxic waste and removal of tin residues results in unacceptable for phramaceutical applications.[12]

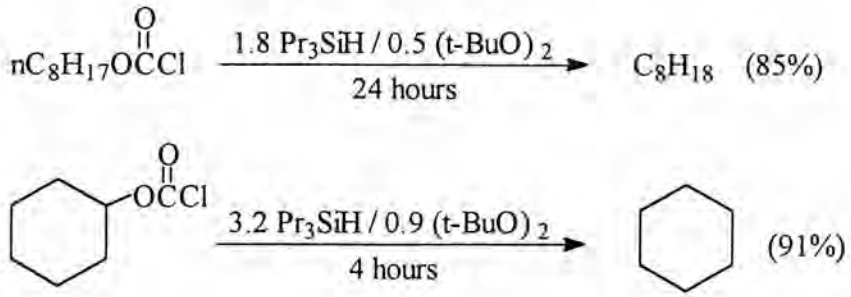
Therefore, various attempts have been made to replace tin hydrides. In 1987, Lusztyk and his colleagues discovered the use of trialkylgermanium hydrides instead of trialkyltin hydrides, but corresponding germyl radicals are less reactive than stannyl radicals. In addition, the cost of germanium hydrides was higher compared with trialkyltin hydrides. The concentration of the reagents required for carrying out the reaction was also necessary to be used in higher concentration than in the case of trialkyltin hydrides.[13] Nonetheless, the germane, on the other hand, is good for the reaction in which radicals undergo relatively slow rearrangements compared with tin hydride they was proved to be too reactive. In such cases, tri-*n*-butylgermanium hydride may offer a variable alternative, since it is less reactive than tin hydride.[14]

In addition, organomercury hydride can play the role as hydrogen radical donor and then decomposes to mercury and alkyl radical. The advantages of the mercury method over the tin method are mild reaction conditions (room temperature, absence of light) and very short reaction time.[15] The alkyl radicals are formed by reaction of alkylmercury salts **6** (particularly halides and acetates) with boron or tin hydrides. Stereochemical[16], polarographic, and kinetic[17] studies suggest that an organomercury hydride **7** is formed, which, *via* hydrogen abstraction, gives the labile alkylmercury radical **8**. This decomposes spontaneously to mercury and an alkyl radical. The alkylmercury hydride **7** plays the role of the hydrogen donor, trapping the adduct radicals **5** prior to their polymerization.



Nowadays, the use of silicon hydrides seems to be attractive because of the relatively low molecular weight and elimination of toxicity and waste problems. The only exception remaining is whether the silicon-hydrogen bond must be weak enough to make it possible to generate the corresponding silicon radical needed to carry the radical chain.[18]

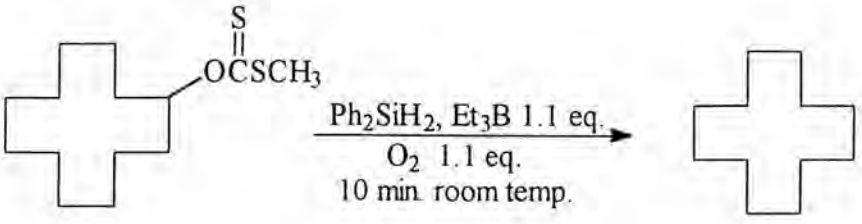
In 1977 R. A. Jackson, *et al.* introduced for the first time the use of organosilane as a reducing agent instead of organostannane. The chloroformate derivatives of secondary alcohols were selected and reduced to the corresponding alkane in excellent yields by reactions with tri-*n*-propylsilane (nPr$_3$SiH) in the presence of *t*-butyl peroxide at 140°C in a sealed ampoule.[9]



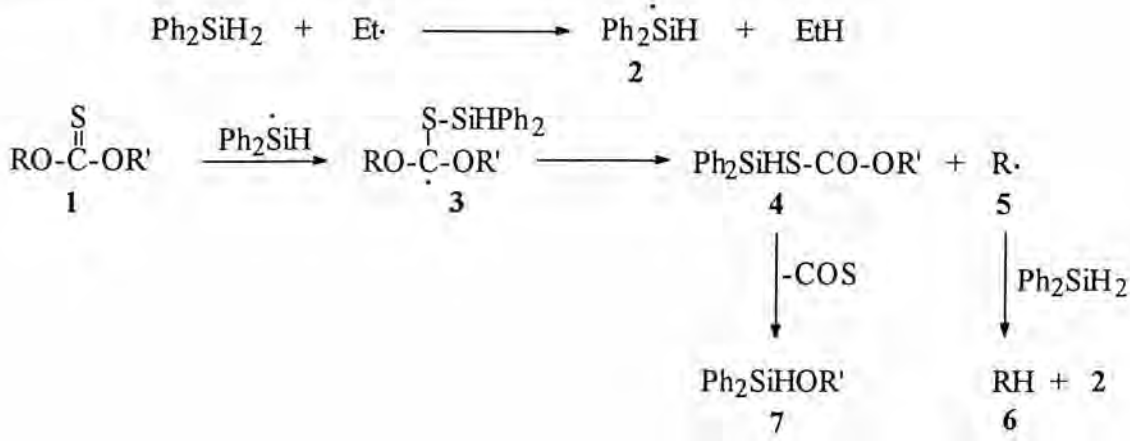
On the other hand, yields of hydrocarbons obtained from benzyl alcohol and 3-ethylpentan-3-ol were poor and phenol gave only trace amount of benzene.[19]

In 1990 B. P. Robert and coworkers demonstrated simple, low molecular weight trialkylsilanes, Et_3SiH, in deoxygenation reaction. They have reported that 1- and 2- octyl methyl xanthates were carried out in sealed tubes at 115 °C with triethylsilane (2 eq.), together with 1,1-di-*t*-butylperoxycyclohexane initiator and *t*-dodecanethiol as a catalyst. The yields of octane were obtained in 82 and 92%, respectivly.[20]

In the same year D. H. R. Barton and his colleagues improved radical chain procedure for the deoxygenation of secondary and primary alcohols using diphenylsilane as a hydrogen atom donor and triethylborane-air as an initiator. In the deoxygenation of cyclododecyl *S*-methyl xanthate, dry air was injected into the solution at a rate of 10 mL/min.

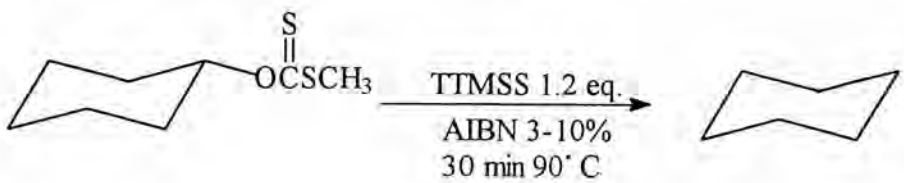


All the yields for the deoxygenation of secondary positions at room temperature are very satisfactory. The reactions involved are summerized in the scheme 1.3. The silyl radical **2**, generated from the ethyl radical, reacts with **1** to give the radical **3**, which fragments to **4** and radical **5** which is reduced by Ph_2SiH_2 to give **6** and radical **2** again. Intermediate **4** readily loses COS and affords 7. [21]



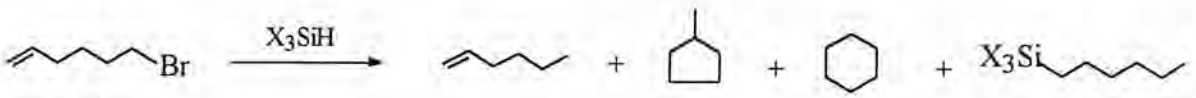
Scheme 1.3 Mechanism of radical deoxygenation *via* Ph_2SiH_2

In 1989 C. Chatgilialoglu and B. Giese exhibited, that *tris*(trimethylsilyl) silane: $(Me_3Si)_3SiH$ could be used for reductive reactions because its Si-H bond energy is low enough. This is probably due to the bonding interaction between β-silicon d orbitals and the semioccupied p orbital on the central silicon atom in the corresponding silyl radical.[22] Thus, the reaction of cyclohexyl *S*-methyl xanthate with TTMSS 1.2 eq and AIBN 3-10% as an initiator in toluene heated at 90°C for 30 min gave deoxygenated product, cyclohexane, 86% yield.[23]



In 1992 C. Chatgilialoglu *et al.* reported the use of *tris*(alkylthio)silanes as new reducing agents. A bond strength of 82-83 kcal mol^{-1} is predicted for $(MeS)_3Si-H$; this value is similar to the dissociation bond energy of trialkylgermanium hydrides. These results suggest that *tris*(alkylthio)silanes could be attractive alternatives

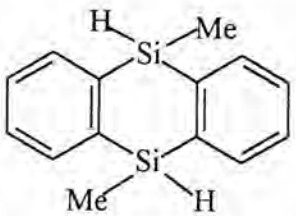
comparable to trialkylgermanium hydrides for a variety of radical chain reactions. Reaction of 5-hexenyl bromide with *tris*(methylthio)silane and *tris*(isopropylthio) silane in toluene at 75°C containing catalytic amounts of AIBN afforded the expected products together with the unexpected hydrosilylated product.[24]



$(MeS)_3SiH$ 4.7% 62% 1.3% 25%

In the same year D. H. R. Barton, *et al.* found that commercially available dialky phosphates can also be used in the deoxygenation reaction. Dimethylphosphite or diethylphosphite work equally well. These reactions, when initiated with benzoyl peroxide in boiling dioxane or toluene furnished the deoxygenated products normally in higher yield of more than 90%.[25]

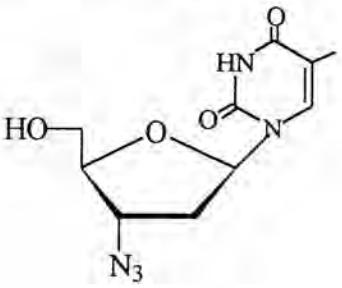
In 1996 M. Oba. and coworker discovered 9,10-dimethyl-9,10-dihydro-9-silaanthracenes containing Si-H groups. This reagent was regarded as a new type of reducing reagent.



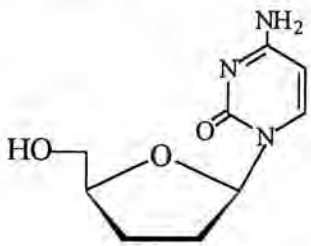
The abilities of hydrogen-donating in deoxygenation of aliphatic alcohols *via* *O*-thiocarbonyl derivatives with a novel silane induced by AIBN at 80°C was evaluated. It was found that the deoxygenation of cyclododecyl *N*-acetylthioxocarbamate and 4-fluorophenylthioxocarbonate occurred and afforded cyclododecane in 100 and 87% yields, respectively. On the other hand xanthate gave the products in a somewhat lower yield (19%).[26]

1.2 Application of Deoxygenation Reactions

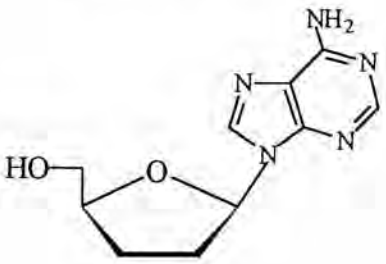
Since radical deoxygenation reactions can be carried out effectively under mild conditions, they are more applicable to sensitive biomolecules than the ionic processes. These reactions are becoming more and more important in the functional group manipulation of natural products. For instance, deoxygenated derivatives of nucleosides exhibiting replication of the human immunodeficiency virus is disrupted by certain deoxy nucleosides. Several compounds of this type are extensively studied because of their potential in the treatment of AIDS. The best known of these compounds are 3′-deoxythymidine (AZT, **1**), 2′,3′-dideoxycytidine (ddC, **2**), 2′,3′-dideoxyadenosine (ddA, **3**), 2′,3′-dideoxyinosine (ddI, **4**), and 2′,3′-didehydro-3′-deoxythymidine (d4T, **5**).[27] There are inhibitors of HIV reverse transcriptase (RT) after conversion into their corresponding 5′-triphosphates, which compete with natural substrates.[28] Furthermore, the value of deoxycarbohydrates is as part of cardenolides and antitumor products and sugars as the 'chiral pool' for enantioselective syntheses.[29]



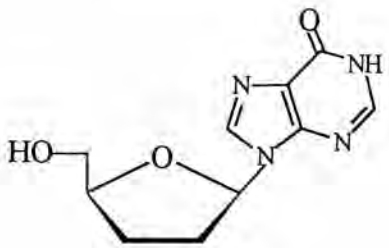
1 (AZT)



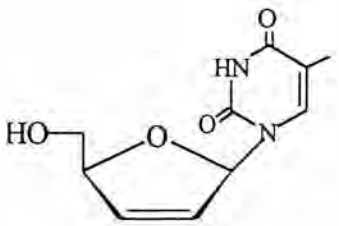
2 (ddC)



3 (ddA)



4 (ddI)



5 (d4T)

1.3 Goal of this Research

The goal of this research is mainly to deoxygenate alcohol derivatives *via* Barton-McCombie method which will lead to standard conditions in the deoxygenation reaction of a model alcohol. In addition, this developed methodology will apply to other alcohols, particularly for naturally occurring compounds.