TRIFLUOROETHYL ENOL ETHERS, DIENOL ETHERS, AND ACETALS: AN INVESTIGATION OF THEIR PREPARATIONS, REACTIVITIES, AND SYNTHETIC APPLICATIONS

by

Carl Wild

Dissertation submitted to the Faculty of the

Virginia Polytechnic Institute and State University

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

APPROVED:

H.C. Dorn, Chairman

M. Hudlicky

H.M. Bell

J.M. Tanko

D.G.I. Kingston

September, 1988

Blacksburg, Virginia

TRIFLUOROETHYL ENOL ETHERS, DIENOL ETHERS, AND ACETALS: AN INVESTIGATION OF THEIR PREPARATIONS,REACTIVITIES, AND SYNTHETIC APPLICATIONS

by

Carl Wild

Committee Chairman: Harry C. Dorn
Chemistry

(ABSTRACT)

The major portion of this work details our investigation of trifluoroethoxy (TFE) substituted compounds with particular emphasis given to their preparation and possible applications. The three types of compounds studied were trifluoroethoxy substituted ketals, enol ethers, and dienol ethers.

The ketal and enol ether work involved developing methodology for the large scale preparation of these structures as well as studies detailing their behavior. For the TFE ketals, preparation involved an acid catalyzed alcohol exchange reaction. Applications included their use as non-complexing/acid stable carbonyl protecting groups.

The TFE enol ether work also involved preparation and applications studies. These structures were synthesized from propargyl ketones via a conjugate addition reaction. The applications were synthetic in nature mainly involving utilization of these compounds in cycloaddition and conjugate addition reactions.

The last portion of this work involved our investigation into behavior of trifluoroethoxy substituted dienol ethers (substituted 1-trifluoroethoxy-3-trialkylsiloxy-1,3-butadienes). Their preparation was accomplished by a method similar to that used by Danishefsky in his synthesis of the 1-methoxy analogs. The applications portion of this study focused on the use of these compounds as 4 carbon synthons in [4+2] cyclcoaddition reactions. Information gained from these studies provided insight into the effect the electron withdrawing trifluoroethoxy group has on the reactivities of structures into which in has been incorporated.

Dedication

This thesis is dedicated to the memory of

Dave

Acknowledgements

During my time at Tech, I've received the help and support of many individuals. I owe a debt of thanks to these people because without their assistance this work would never have been completed.

Much of the credit must go to . In my opinion, he has been the ideal research director: part friend, part teacher, and part advisor. I sincerely hope that this is only the beginning of our association. also deserves a large vote of thanks. always made time to listen and help. It isn't often that you find an individual who will so readily give of his time. I would also like to thank the rest of my research colleagues: , , , , , , and .

A person would have a difficult time making it through graduate school without friends. I consider myself lucky in this respect. While at VPI, I've made friendships that I hope will last for life. , , , , , , and all deserve special credit. Without their help, I never would have finished when I did: It would have been a year sooner! Also, I want to wish the guys on FUBAR good luck. Maybe next year we can beat the Seal Clubbers. I would also like to thank the faculty and staff of the chemistry department at VPI & SU.

Most importantly, I must thank for the enormous amount of help she has provided. Without her, none of this would ever have been accomplished. She is without doubt the most remarkable person I have ever met or even hope to meet. I still haven't figured out why she puts up with me but I'm glad that she does. Thanks for everything.

TABLE OF CONTENTS

LIST FO FIGURES

LIST OF SCHEMES

LIST OF SCHEMES (cont.)

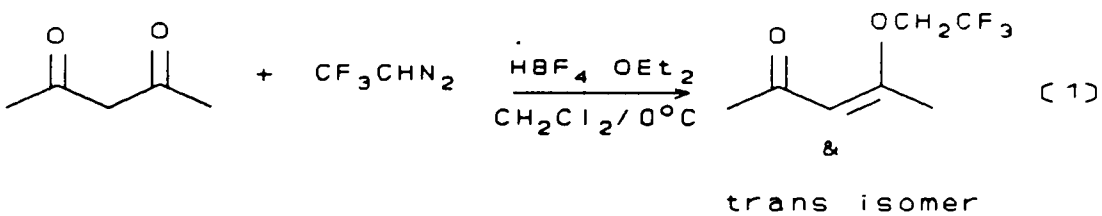
LIST OF SCHEMES (cont.)

LIST OF TABLES

Introduction

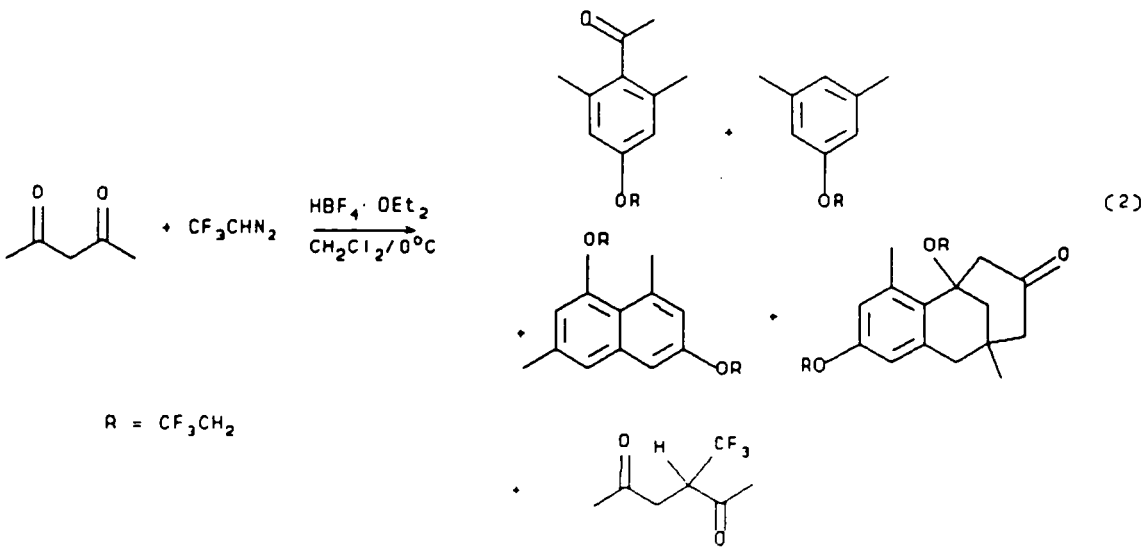
For the past several years, one area of active research in our laboratory has involved the reactivities of a number of trifluoroethoxy substituted compounds. Interestingly, this work had its origins in a project that in its early stages was analytical in nature.

Initial work in this area was carried out by Roy [1] and grew out of a series of observations he made concerning the action of 2,2,2-trifluorodiazoethane (TFD) on β-dicarbonyl containing structures in the presence of HBF_4OEt_2. In an attempt to convert 2,4-pentanedione (a β-diketone) into its cis and trans trifluoroethyl enol ethers, the reaction shown in equation 1 was carried out.



(1)

However, rather than forming the expected compounds, this reaction yielded a complex mixture of trifluoroethyl containing products. From this product mixture, Roy was eventually able to isolate and identify the series of compounds shown in equation 2.



(2)

As these results indicate, this initial observation regarding the behavior of β-diketones in the presence of TFD and HBF_4OEt_2 lead to the discovery of a novel acid catalyzed cyclization process.

In order to gain better insight into the processes that were occurring during this reaction, a study of trifluoroethoxy substituted compounds was undertaken. The work outlined in this dissertation details the course of this project.

Due to the limited number of trifluoroethoxy containing compounds available, the initial stage of this work involved development of the methodology necessary to produce these compounds on a preparative scale. Eventually, procedures for the preparation of trifluoroethyl (TFE) enol ethers, dienol ethers, and acetals were perfected. As these compounds became available, the second phase of the study was initiated, which involved determining the behavior of several of the TFE derivatives under a variety of conditions. The third stage of this work dealt for the most part with the reactivities of a number of TFE

enol and dienol ethers in an attempt to determine what role (if any) these types of structures play in Roy's acid-catalyzed condensation reaction.

This dissertation is divided into seven main sections, which include an introduction, four chapters and three appendices. Chapter 1 is mainly a literature survey on the different methods by which acetals, enol ethers, and dienol ethers are produced. Although not exhaustive, it does provide ample background on each of these three types of compounds. Chapters two to four are experimental in nature. Chapter two describes a new, preparative scale procedure for the formation of TFE ketals. It also includes the results of several studies designed to determine the ability of these functions to serve as acid stable carbonyl protecting groups. Chapter three deals with the preparation of TFE enol and dienol ethers. Included are observations relating to both successful and unsuccessful attempts to prepare these compounds. Chapter four details our investigation into the reactivities of TFE enol and dienol ethers. In this chapter, several experiments designed to give better insight into Roy's condensation reaction are described. The information and data presented in Appendix I outlines work which is similar but not directly related to that carried out in the rest of project. Appendix II contains ^{1}H NMR data for compounds utilized in a number of the experiments. Appendix III deals with work which is unrelated to materials presented in the first six sections. It contains information relating to the preparation of immobilized free radical precursors which found use in several Dynamic Nuclear Polarization (DNP) studies.

Chapter 1

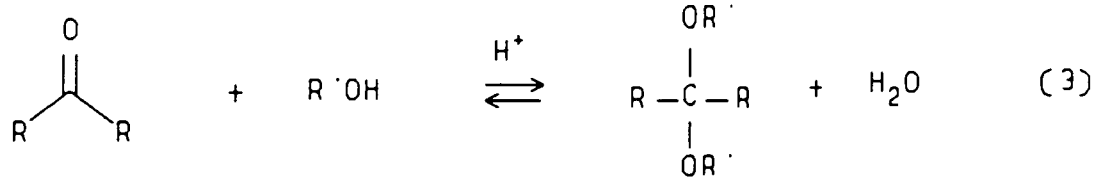
Section 1: Ketals

Introduction

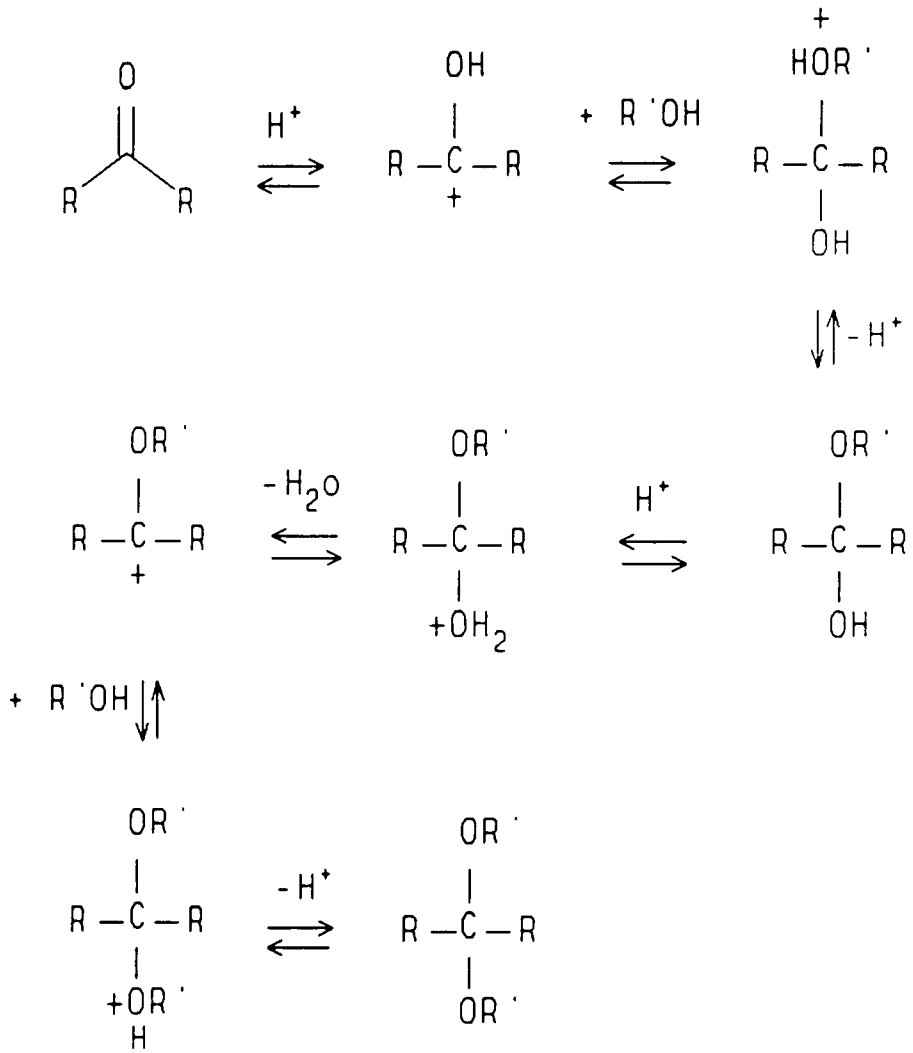
Acetals, ketals and related compounds have found many applications in synthetic organic chemistry. Much of the work in the areas of carbohydrate and steroid chemistry utilize ketals as both intermediate and target compounds [2-8]. Recent developments in the field of asymmetric synthesis include the use of various ketals in the stereospecific reduction of certain prochiral ketones [9-10]. However, the most common use for ketals involves the protection of the carbonyl function of aldehydes, ketones, and other types of carbonyl containing compounds [11].

Acid Catalyzed Preparation

Although ketals are generally prepared under acidic conditions, a variety of methods employing neutral or basic conditions have also been utilized [12]. The most common approach involves the acid catalyzed reaction of a carbonyl function with an alcohol or an alcohol source (e.g. an orthoester) [13]. The overall reaction is outlined in equation 3 while the mechanistic details are depicted in Scheme 1.1.



(3)



Scheme 1.1

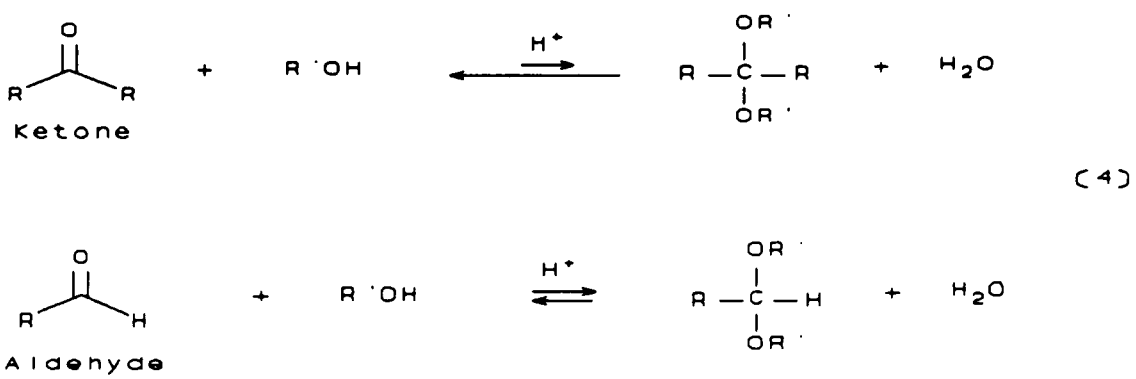
It can be seen that product formation in these types of reactions is under equililbrium control. In order to optimize ketal formation, the equilibrium must be shifted to the right. This can be accomplished in several ways utilizing both physical and chemical means. Of the physical techniques three are outlined below.

The first involves carrying out the reaction in a solvent which forms an azeotrope with water. The water-azeotropic mixture is then removed by distillation [14]. This approach works well as long as none of the desired reaction components are removed by this means.

A second method employs the use of agents which complex with water, often through the formation of hydrates. Compounds such as calcium sulfate [15], aluminum oxide [16], copper sulfate [17], and molecular sieves [18] have all been utilized in this respect.

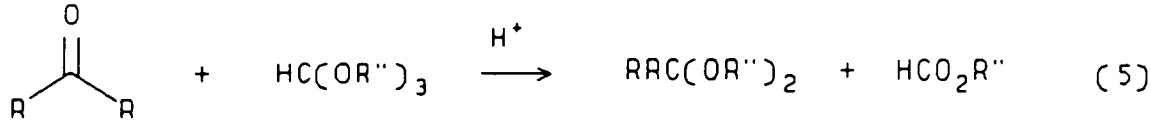
The third technique is similar to the first in that it involves azeotropic removal of water with an organic solvent, however, in this case the solvent is returned to the reaction mixture after its separation from the water. The most common apparatus used to accomplish this is the Dean-Stark adapter [19].

Most aldehydes react readily with alcohols under acidic conditions to yield acetals [20-25]. Ketones, however, are not as reactive as aldehydes and their reaction equilibria tend to lie considerably towards the left (eq 4).



The greater success of acetal formation relative to ketal formation, under these conditions, can be accounted for on a thermodynamic basis. On going from the carbonyl containing structure to the acetal or ketal, there is a gain of ~ 5 kcal/mole of bonding energy. In both cases, the majority of this gain is offset by entropic and steric factors. However due to the interaction between the substituents, there is usually greater steric crowding in the ketal product. This results in a larger offset of bond energy gains making the direct reaction of ketones with alcohols generally unfavorable. This is in contrast to the analogous reaction utilizing aldehydes which proceeds readily [26].

In order to overcome this problem, orthoesters are often utilized in reactions involving conversion of ketones to ketals (eq 5). There are several reasons why reactions with these



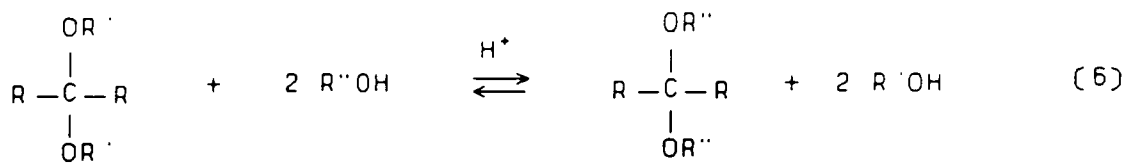
(5)

these compounds are successful while those with alcohols are not. These include, a more favorable entropy change as well as an added increase in bonding energy due to ester formation. Also the ability of orthoesters to act as water scavengers tends to shift the equilibrium towards product.

With both aldehydes and ketones, factors which tend to decrease the electrophilicity of the carbonyl center or the nucleophilicity of the alcohol tend to deactivate the various reactants towards ketal formation. For example, conjugation deactivates the carbonyl group towards nucleophilic attack [24,27], while electron withdrawing groups associated with the carbon-oxygen double bond tend to enhance ketal formation. However, these same functionalities hinder this process when associated with the alcohol [25,28,29].

Geometric and steric effects can also play an important role in ketal formation. It has been observed that five membered ring ketones react more slowly than their six membered analogs [30]. Also, alcohols and carbonyl functions possessing large or bulky groups encounter steric hinderance in these reactions.

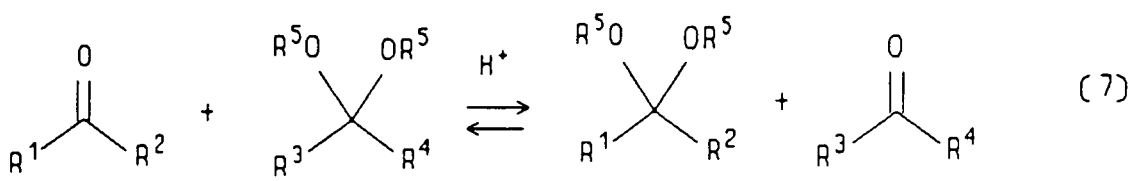
Although the acid catalyzed reaction described above utilizing either an alcohol or an orthoester as an alcohol source is the most common method by which ketals are prepared, several variations on this approach have been developed. One such method termed transacetalization, is outlined in equation 6.



(6)

This procedure is often referred to as an alcohol exchange reaction [31-33] and its equilibrium is shifted in the direction of product by using either a large excess of R"-OH and/or selectively removing R'-OH from the reaction mixture. If less than two equivalents of R"-OH are used in this type of reaction a mixed ketal may result [34].

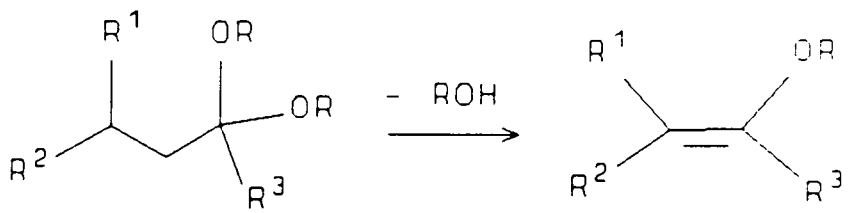
A variation of the transacetalization reaction involving exchange between a ketal and a carbonyl containing compound is shown in equation 7.



(7)

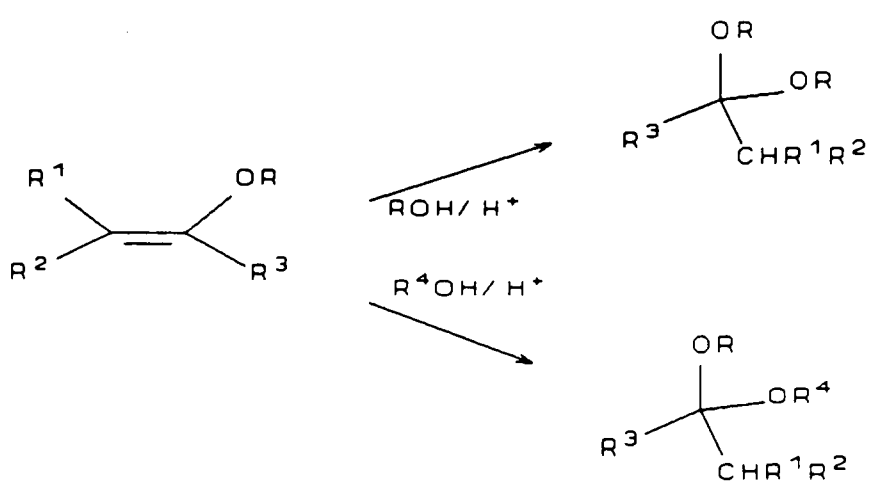
In this case, the ketal serves as the alcohol source in the derivatization of the carbonyl function [35-37]. Generally, these reactions require the presence of a small amount of alcohol or water to serve as a catalyst [31, 35, 38].

Another method of ketal formation involves enol ethers as intermediates. These compounds are related to ketals in that the loss of a molecule of alcohol from a ketal or acetal possessing an α hydrogen results in their formation (eq 8). In ketal formation, the reverse



(8)

reaction takes place resulting in the acid catalyzed addition of an alcohol to the vinyl ether double bond. Depending on the choice of starting enol ether and alcohol, either a mixed or symmetrical product may be obtained [39-42] (eq 9).



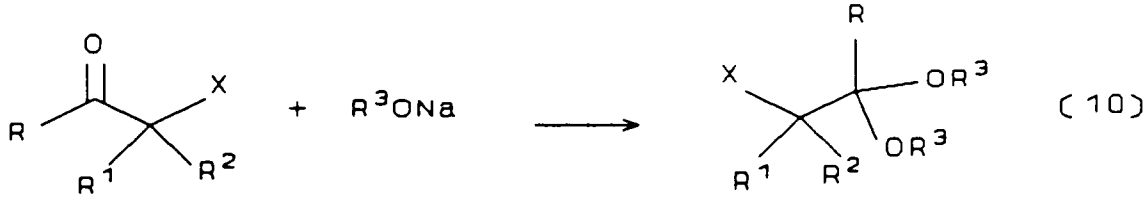
(9)

There are many factors which dictate the type of acid catalyst used in these reactions. Most often used in organic based ketalization reactions is p-toluenesulfonic acid (p-TsOH). The excellent solubility characteristics and relative acid strength of this compound are the chief reasons for this choice. Depending on the type of carbonyl function to be derivatized, other types of acids (both Lewis and Bronsted) are also used. Aldehydes react readily, and a weak acid will usually suffice as the catalyst. Ammonium chloride, ammonium nitrate, calcium chloride, and zinc chloride have all been used [43, 44]. Most ketones require a stronger acid in order to react. Mineral acids such as H_2SO_4 or HCl or strong organic acids are usually employed.

To this point we have discussed the formation of ketals under acidic conditions. However, these compounds can be formed in a variety of ways including base and metal catalyzed reactions, photochemical reactions, as well as formation under neutral condtions.

Base Catalyzed Preparation

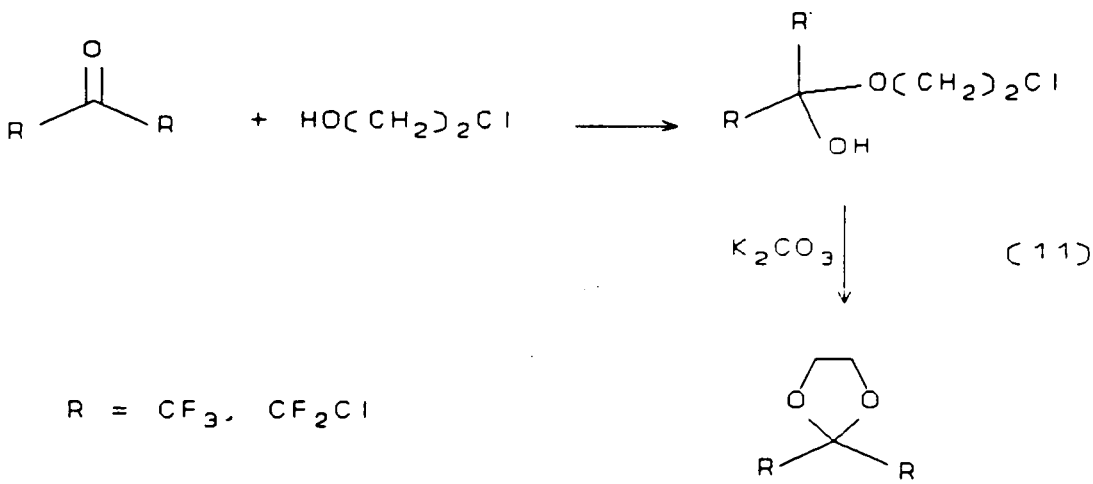
Base catalyzed ketalization is often utilized when the carbonyl function contains strong electron withdrawing groups [45]. In a mechanistic sense this is analogous to addition of a base (nucleophile) to the electropositive carbonyl carbon.



(10)

X = electron withdrawing group

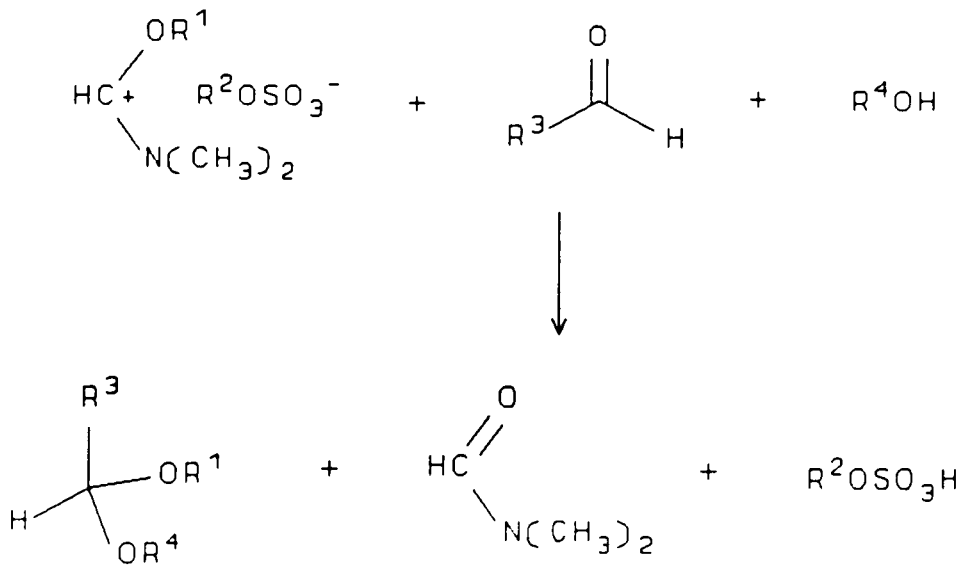
For example, alkoxides will add to ketones possessing an α-halo substituent to yield an α-hydroxy ketal (eq 10) [46-48]. If both α and β-halo substituents are present, epoxy ketals often form [49]. Other types of ketones and aldehydes which can stablize the hemi-ketal intermediate will undergo similar types of reactions [50]. These include α-fluoro ketones (eq 11).



Another type of base-mediated ketalization reaction involves compounds which contain activating groups β to the ketal function (e.g. carbonyl). In these cases, a transacetalization reaction can occur via a β-substituted enol ether intermediate (e.g. a β-keto enol ether) [51,52]. By this conjugate addition method, nucleophiles other than oxy-anions may be added to a given intermediate yielding mixed heteroatom acetals (e.g. oxy-thio or oxy-amino actetals).

Additional Methods of Preparation

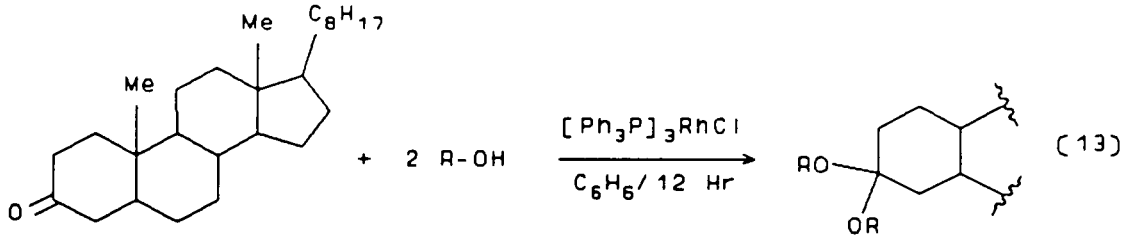
Ketal formation can take place under neutral conditions. In these cases, dimethyl formamide/ dialkyl sulfate adducts react with the carbonyl function of aldehydes and ketones to give the desired products [53, 54] (eq 12). Similar to this type of reaction, is the formation



(12)

of cyclic ketals from halogenated ketones and cyclic carbonates [55]. This procedure is carried out under neutral conditions and involves heating a haloketone with a cyclic carbonate containing at least one free hydroxy group.

In a number of instances, metals have been used as catalysts in ketalization reactions. One example involves the synthesis of cyclic ketals from diols. The reaction proceeds as the ketone or aldehyde is heated with a diol in the presence of the metal supported on carbon. Rhodium, iridium, palladium, and platinum have all been used [56]. Complexed metals have also found use as catalysts. $Rh_2(CO)_4Cl_2$ in methanol has been used to prepare the methyl acetals of α, β-unsaturated aldehydes [57]. $Rh(PPh_3)_3Cl$ under H_2 has been used in the selective ketalization of certain steroids [54] (eq 13).

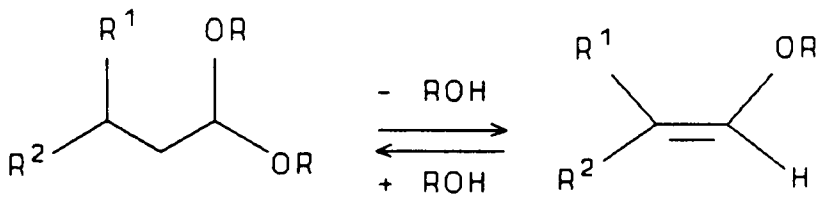


(13)

In several cases, photolytic catalysis of ketones has also proved possible. α-Aryloxyacetones form ketals with methanol, ethanol, and benzyl chloride on irradiation with hν light. The presence of a low concentration of an acid catalyst will sometimes increase yields [58]. Phenacyl halides undergo similar photo-induced reactions with yields which are component dependent. However, no acid catalyst is required in these photo-induced reactions [59].

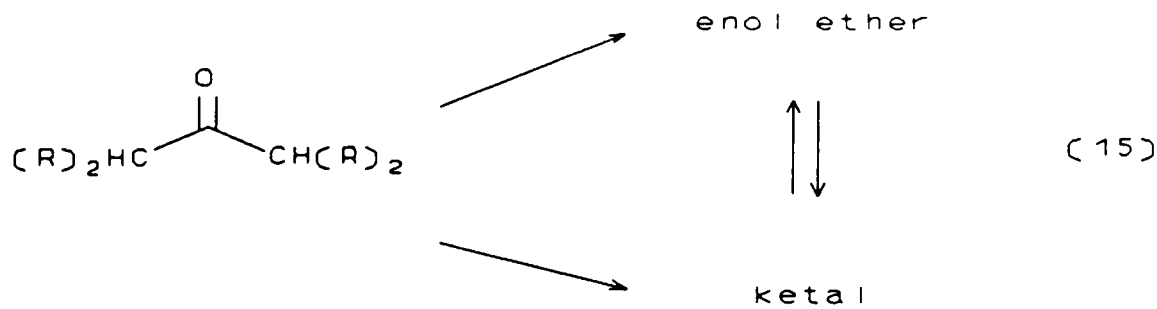
Section 2: Enol Ethers

In a formal sense, enol ethers (vinyl ethers) are related to ketals through the gain or loss of a molecule of alcohol (eq 14). Depending on the structure of the starting carbonyl



(14)

compound, enol ethers may in fact be formed during attempts at ketalization [60] (eq 15).



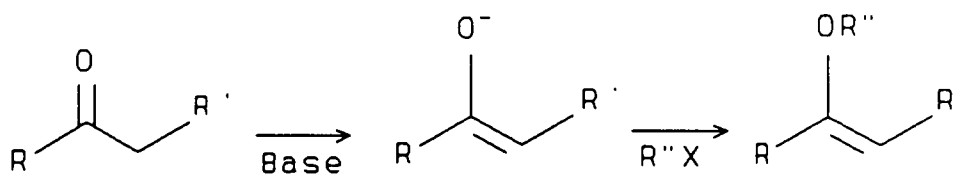
(15)

As was the case with ketals, enol ethers can be prepared from a number of precursors under a variety of conditions [61]. Specific examples are outlined below.

Base Catalyzed Preparation

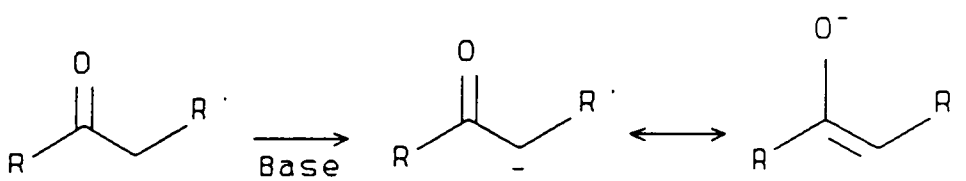
Under basic conditions, the most common method of formation of enol ethers involves the O-alkylation of a carbonyl containing compound. In principle, this is a two step process, which involves initial formation of the enolate anion followed by alkylation at oxygen [62-67] (eq 16). In practice, however, there are several factors which dictate the ultimate outcome

of this type of reaction.



(16)

The main obstacle encountered in preparing enol ethers by this methodology involves alkylation taking place, not at oxygen (O-alkylation), but at carbon (C-alkylation). This results from the ambident nature of the anion generated by base abstraction of an α proton from the carbonyl containing compound [68-69] (eq 17).



(17)

Of the several factors influencing the position at which alkylation occurs (O vs. C) the following are usually considered the most important [68]:

1) Acidity of the compound to be alkylated

2) Nature of the counter-ion/solvent system used in generating the anion.

3) Nature of the alkylating agent.

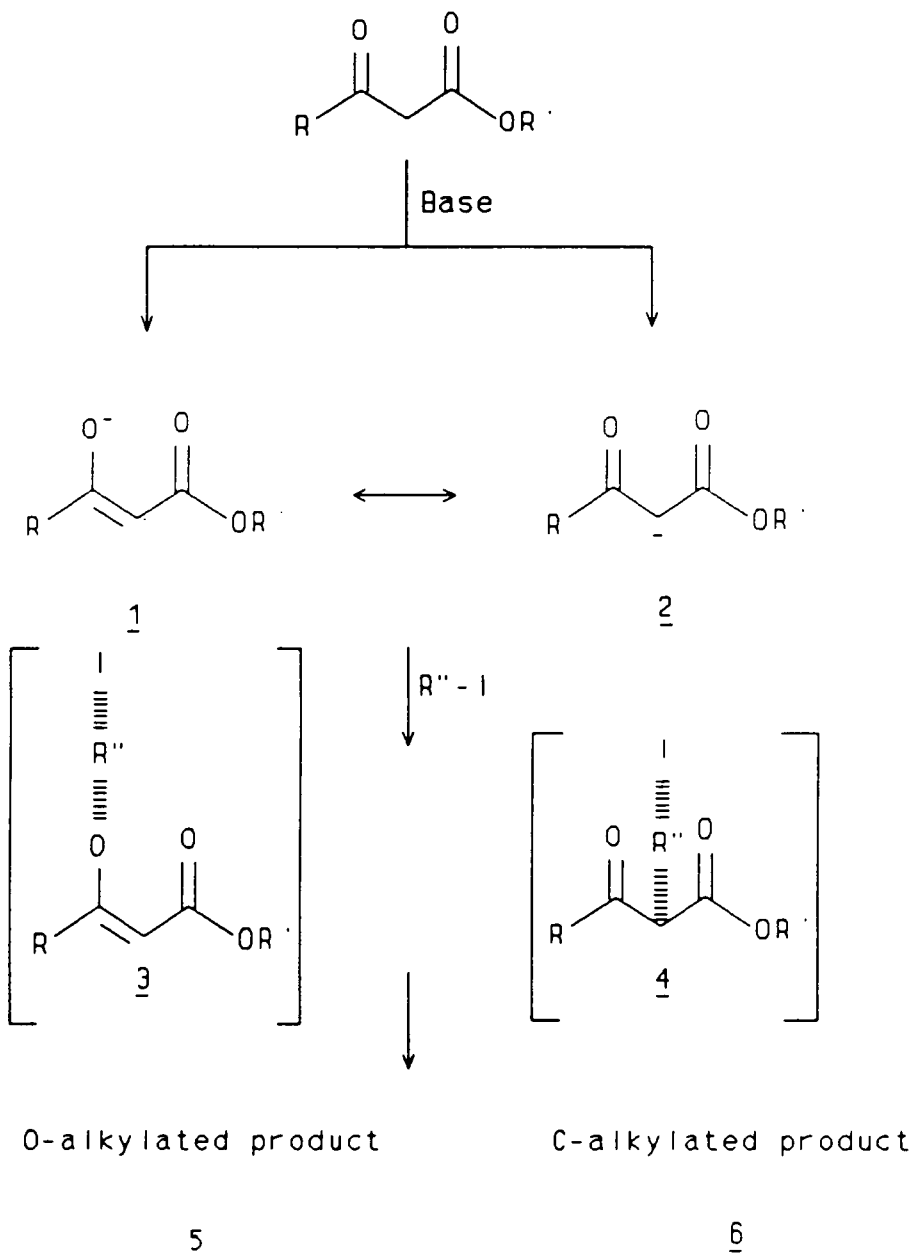
These will be discussed in turn.

1) Acidity of the compound to be alkylated.

The relative stability of an enolate anion along with the charge distribution within its structure can be useful parameters in predicting the type of alkylation which will occur in a given carbonyl containing structure will undergo. This type of information can often be correlated with the relative acidity of a compound making this physical property a general indicator of the course the reaction will follow [69, 70]. This is illustrated by example in the case of a β-ketoester (Scheme 1.2).

Following reaction with base, an anion, represented equally well by two resonance structures, forms. In structure 1 the negative charge is located on oxygen while in 2, this charge is located on carbon. The activation energy in proceeding from these structures to transition states 3, and 4 is directly related to the relative stability of both the enolate anion and the respective transition state structures. Since structures 3 and 4 both closely resemble the anions from which they are derived, their relative stabilities will resemble those of the anions. Also, the more acidic a given compound, the better its ability to accomodate an anionic form such as 1. This results in a lower energy barrier in proceeding from structures similar to 1 through states similar to 3 to form the O-alkylated product 5 [71].

This is the thermodynamic correlation between acidity and position of alkylation, and accounts for the observation that O-alkylation is most favored for those structures in which the enol form is relatively stable. This is a major reason that compounds which do not contain enolate stablizing groups, e.g. monoketones, esters, aldehydes, etc, tend to undergo a larger proportion of C-alkylation when compared to those structures that do, e.g. 1,3-dicarbonyl compounds, β-keto esters, phenols, β-cyanoketones, etc [72].

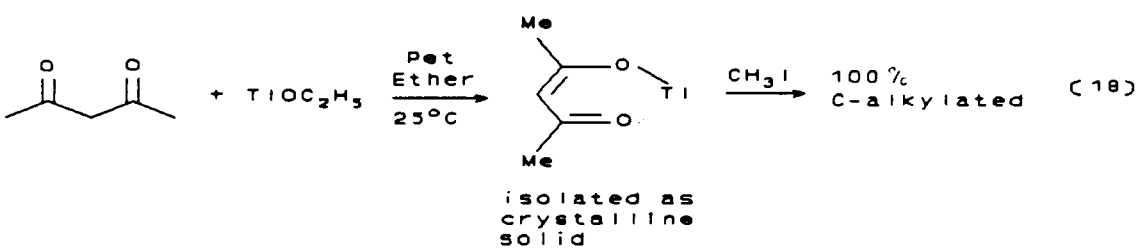


Scheme 1.2

2) Nature of the counter-ion/solvent system used in generating the anion.

It has been observed that for reactions which take place in solution, complexation of the anion (e.g. by counter-ion, solvent, etc) plays a large role in determing the relative proportions of O- and C-alkylation [68-70]. The greater the amount of free enolate anion present the larger the amount of O-alkylation that will occur. The opposite is also true. It is believed that this is due to the charge distribution in the enolate anion. Specifically, a larger portion of the negative charge will be located on oxygen, a relatvely hard, electronegative atom, as the amount of complexation at the charge center decreases. As a result, the chances that O-alkylation will occur increase. Therefore, by controlling both the type of counter-ion used in anion generation and the nature of the solvent in which the reaction is carried out the relative proportions of O- and C-alkylation can be varied. In general, alkylation at oxygen is favored in instances where polar, aprotic solvents such as HMPA, DMSO, and DMF are used in conjuction with large counterions (i.e. R^4N^+ and K^+) which are more easily dissociated from the anion [67-69].

One method often used to ensure the maximum amount of "directed alkylation" involves carrying out the reaction under heterogeneous conditions. Due to association with metal counter ions in the solid crystalline lattice, a maximum amount of shielding of the oxygen atom in the enolate anion occurs resulting in the maximum amount of C-alkylation [73-76] (eq 18).

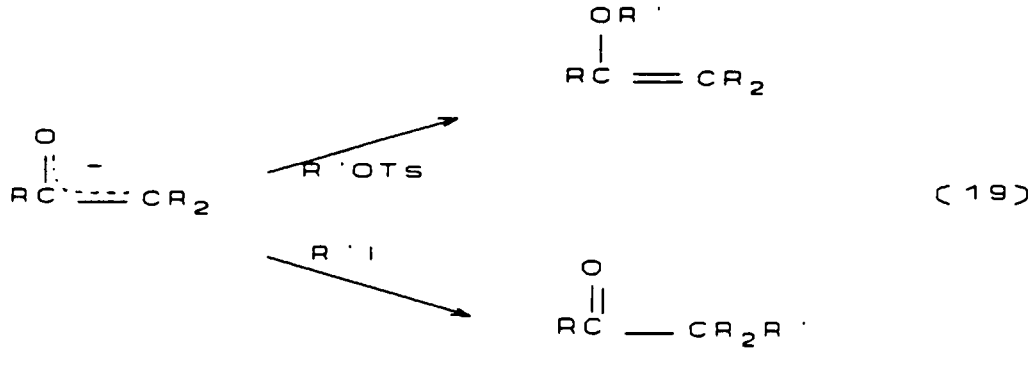


3) Nature of the alkylating agent.

Separate from the conditions under which the enolate anion is generated and/or reacted is the choice of alkylating agent. Numerous examples suggest that the type of reagent employed has a large effect on the ratio of products formed. The type of alkyation which occurs can often be correlated with the leaving group of the alkylating agent. This trend is found to favor C-alkylation in the following approximate order [67, 77-80]:

$$R\text{-}I > R\text{-}Br > R\text{-}Cl > R\text{-}OSO_3R > R\text{-}OSO_2Ar > R_3O^+BF_4^-$$

The rational for these observations is usually based on the principle of hard and soft acids and bases. The small, electronegative oxygen atom is considered a hard base (high charge density, low polarizability) and prefers to coordinate with a hard acid (an alkylating group associated with a hard leaving group, e.g. $^-OSO_3R$, $^-OSO_2Ar$, etc). In contrast, the softer, more polarizable carbon atom will have a greater tendency to coordinate (react) with an alkyl group associated with a soft leaving group (i.e. I, Br, Cl, etc) [81]. This relationship is illustrated by the following example. A comparison of tosylate or sulfate (hard leaving groups) with bromide or iodide (soft leaving groups) revealed that on reaction with enols, the former gave largely O-alkylated products while in the latter case C-alkylation predominated [82-83] (eq 19).



(19)

To summarize, the formation of vinyl ethers via base catalyzed alkylation at oxygen occurs most readily under the following conditions: [68, 69]

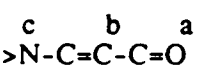
1) Solvents should be non-complexing in order to increase free enolate concentration.

2) Counter-ions should be large in order to encourage anion-cation dissociation.

3) Alkylating agents should contain leaving groups which act as hard bases.

Aside from the generalized O-alkylation scheme described above, other specific methods for the formation of enol ethers have been developed. Several of these are listed below.

One interesting vinyl ether preparation involves the alkylation of enaminoketones with alkyl halides. These reactions take place under a variety of conditions. Enaminoketones have the general structure 7, and unlike simple carbonyl containing compounds possess three sites a, b, and c, at which alkylation can occur.



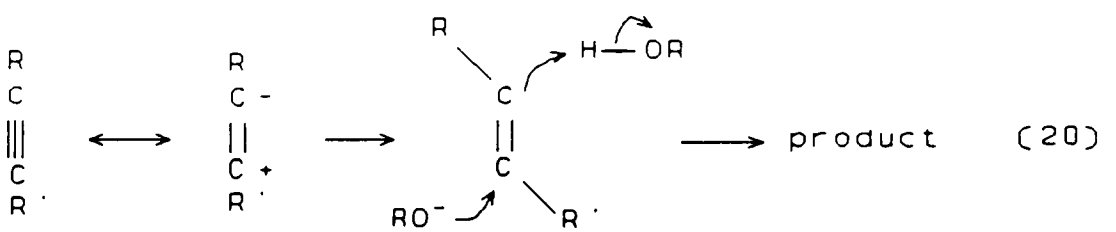
7

Work with these compounds by both Leonard [84] and Meyers [85] agrees with the general observations relating to the alkylation of enolate anions. They found that the structure of the alkylating agent, the nature of the compound to be alkylated, as well as the solvating ability of the reaction medium were all factors in determining the ratio of O- vs. C- alkylation.

For example, cis-enamino ketones in aprotic solvents produced mixtures of C- and O-alkylated products on reaction with alkyl halides. However, protic solvents gave rise to O-alkylated products exclusively [85]. In contrast. trans-enamino ketones were found to be insensitive to solvent effects yielding only O-alkylated products upon reaction with alkyl halides. These examples are of particular interest in that they were carried out in the absence of a basic catalyst allowing more direct observation of nucleophile-solvent interactions.

Another method of vinyl ether formation involves the addition of alcohols to alkynes. The base mediated version of this reaction was first described by Favorskii [86]. The approach is general and applies to a number of alcohols (or other hydroxy containing compounds) and alkynes.

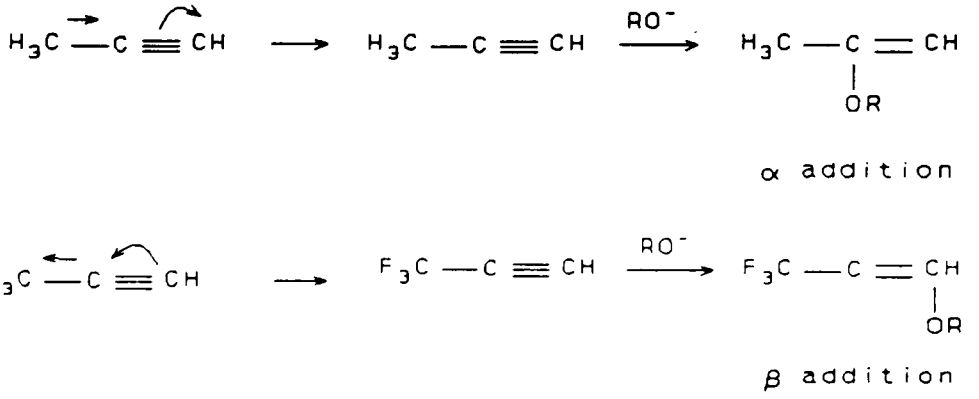
The overall mechanism is believed to involve nucleophilic attack by the alkoxide anion at the most electrophilic site of the triple bond [87,88]. This process is thought to occur in a trans, concerted fashion [61] (eq 20). For unsubstituted acetylenes, the reaction yields the expected alkyl ethenyl ethers.



The conditions under which this reaction takes place vary greatly and are largely dependent on the nature of the nucleophile. In general, more acidic hydroxy compounds require more severe reaction conditions [89]. As a result, while alcohols add smoothly under the influence of mineral bases (i.e. NaOH, KOH, etc.) more acidic compounds such as phenol require stronger organic bases. In addition in these cases, elevated temperatures and pressures are generally required for reaction to occur. Under these conditions, the ethenyl ethers of phenol, cyclohexanol, 2-decanol, and 2-naphthol as well as others have been prepared [90, 91].

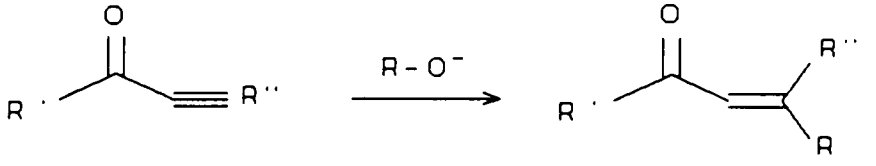
In the case of substituted acetylenes, base-catalyzed reaction occurs, however, the site of addition is dependent on the nature of the substituent. It has been found that electron donating groups adjacent to the triple bond cause it to be polarized in such a way that

addition α to the substituent predominates [92]. In this same position, electron withdrawing groups (e.g. CF_3) cause attack to occur at the β position [92]. This observation is consistent with the influence substituent polarity would have on the electron distribution within the triple bond (eq 21).



(21)

As in the case with acetylene, the reaction with substituted alkynes is a general one involving a variety of alcohols and unsaturated substrates [93-96]. For example, propargyl ketones undergo attack at the β-position to give, β-alkoxy vinyl ketones (eq 22) [97].



(22)

Acid-Catalyzed Preparation

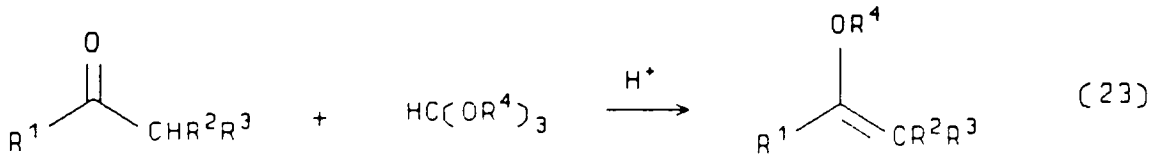
Under the proper conditions, orthoesters can be used to generate various types of enol ethers [98]. In these cases, however, the products are thought to arise from carbonium ion intermediates rather than the O-alkylation of an acid derived enolate ion. Early work in this area was carried out by Claisen [99] who reported that acetyl acetone, ethyl acetoacetate, and diethyl malonate will each react with a mixture of triethylorthoformate and acetic anhydride to yield the corresponding ethoxymethylene derivatives. These are specific examples of the general reaction in which compounds containing activated methylene groups will condense with orthoesters to give alkoxymethylene derivatives. Depending on the nature of the activated methylene compound, this reaction will proceed without catalyst in the presence of Ac_2O or with Ac_2O and $ZnCl_2$. The procedure is very general and numerous examples are known (Scheme 1.3).

$$ZZ'CH_2 + RC(OR')_3 \xrightarrow{Ac_2O} ZZ'C{=}CROR'$$

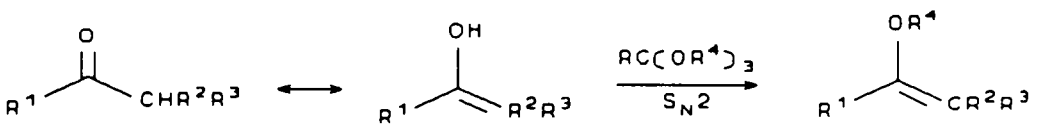
Z	Z'	R	R'	
CN	CN	H, Me, Ar	Et	[100,101]
CN	CO_2Et	H	Et	[102]
CH_3O	CH_3O	H	Et	[103]
N_2O	CO_2Me	H	Et	[104]

Scheme 1.3

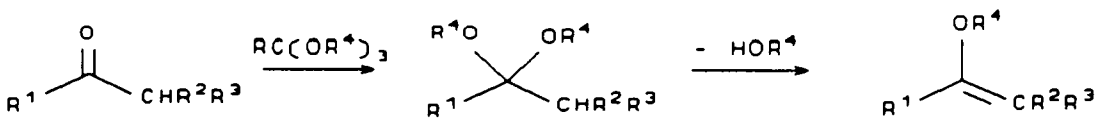
A second procedure for the formation of vinyl ethers from orthoesters involves the reaction of a ketone bearing an α-hydrogen with a trialkylorthoester in the presence of an acid catalyst [105-109] (eq 23). In these cases, the enol ether in theory could form by either O-alkylation of the enol form of the ketone or by elimination of one mole of alcohol from an initially formed ketal (eq 24).



(23)



(24)

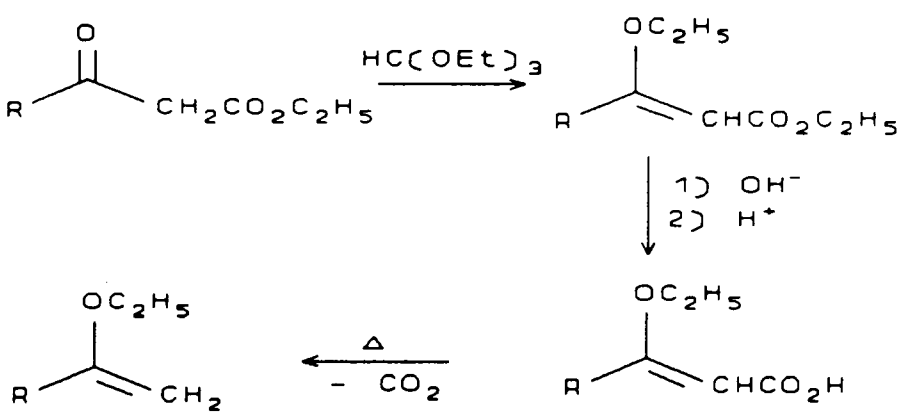


The fact that ketals have been isolated prior to enol ether formation does not preclude their formation by direct alkylation. In fact the only aldehydes which give vinyl ethers under these reaction conditions are those which possess unusually (highly) stable enol forms [86].

In many instances the type of product obtained, vinyl ether or ketal, can be controlled by varying the reaction conditions. For example, low temperature reactions (i.e. room

temperature) followed by neutralization during workup usually result in ketal formation, whereas higher temperature reactions (i.e. reflux) followed by product isolation prior to neutralization generally favors the formation of enol ethers [98].

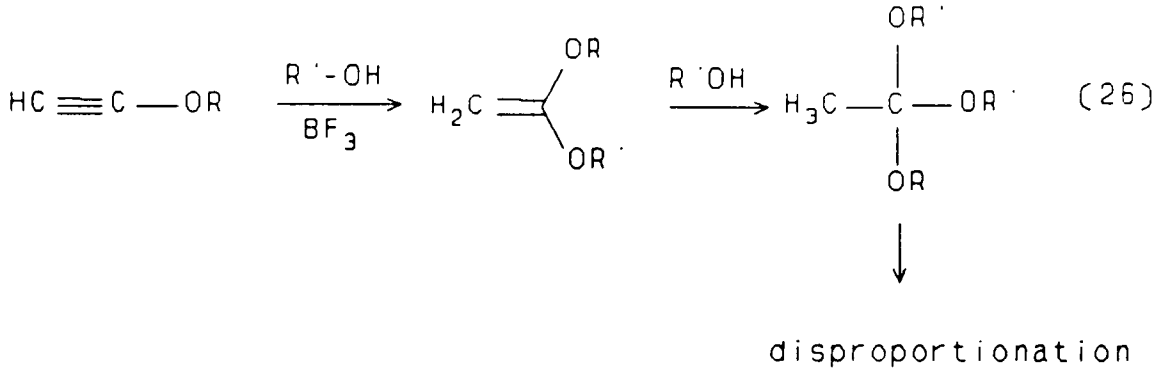
Two indirect routes to preparation of these compounds are also available. Unsaturated ethers of higher molecular weight alcohols can be prepared by heating the ketone with triethylorthoformate and an acid catalyst in a solvent consisting of the appropriate alcohol [110]. In these cases, the initially formed ethyl enol ether undergoes an acid catalyzed exchange reaction with the high molecular weight solvent to give the desired product. In a formal sense, this amounts to a one pot transetherfication process. Also, enol etherfication of β-ketoesters followed by saponification of the ester function and decarboxylation of the alkoxy acid will yield these compounds [111] (eq 25).



(25)

Dialkyl ketones [106], cycloalkanones [106, 102], β-ketoaldehydes [113], β-diketones [114], β-ketoesters [115], and α,β-unsaturated ketones [116] are all examples of compounds which have been converted to enol ethers by reaction with trialkylorthoesters.

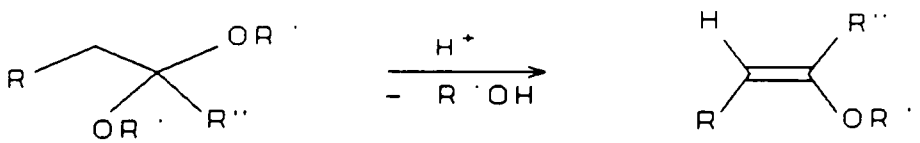
The acid catalyzed addition of alcohols to alkynes to form enol ethers is an example of 1,2-addition of a compound containing an active hydrogen to an unsaturated substrate [117]. However, unless the conditions under which this reaction is carried out are carefully controlled, addition will not stop at the vinyl ether stage, and ketal formation will result [118]. In cases where the triple bond is substituted with an alkoxy group, orthoesters are ultimately produced (eq 26) [119, 120]. However, these compounds often disproportionate under the reaction conditions to give a mixture of ester and ether products. Lewis acids such as BF_3 are often used to catalyze these reactions.



(26)

Several methods used for the acid-catalyzed preparation of enol ethers involve the loss of R-OH from a ketal or acetal. These types of reactions are carried out utilizing a variety of conditions and reagents and involve both general and specific syntheses [61].

Perhaps, the most common of these procedures involves the acid catalyzed elimination of one mole of alcohol from an acetal or ketal possessing an α-hydrogen (eq 27). This method has been used in a number of cases, but is limited in that significant amounts of starting material are often carried through to the product mixture [21]. Several modifications of this technique have been developed which partly overcome this problem. One involves the direct distillation of the crude acetalization reaction mixture prior to neutralization or product



(27)

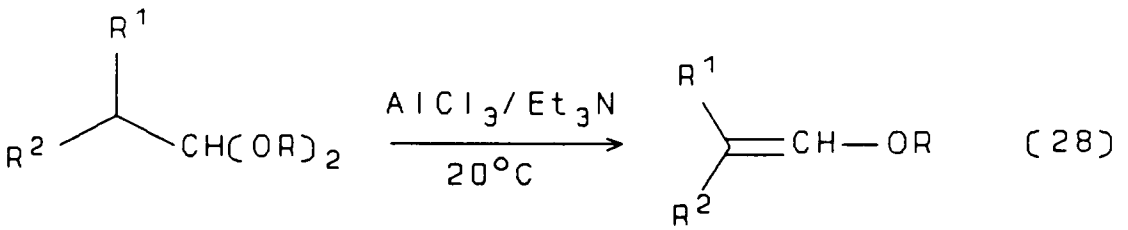
isolation. By this method, the remaining acid catalyst causes decompostion of the acetal or ketal to the vinyl ether [121, 122].

An improvement on this approach which yields the desired enol ether in almost pure form has been developed by Wohl [123]. This technique utilizes an extremely efficient fractionating column which can be set to total reflux after the bulk of the alcohol present in the reaction mixture has been removed. During the period of total reflux, more alcohol gradually accumulates in the top of the column and is taken off slowly until no more is generated. By this method, the conversion of acetal to vinyl ether can be driven to completion.

Another of the acid catalyzed techniques used in the formation of enol ethers from acetals involves the use of sodium or potassium hydrogen sulfate ($NaHSO_4$ or $KHSO_4$) as the acid source [124]. While the mechanism for this elimination reaction is the same as that outlined in equation 25, the procedure is somewhat different. In this case, the acetal or ketal is dripped slowly onto $KHSO_4$ (or its sodium analog) which has been heated under reduced pressure. Under these conditions, R-OH is eliminated to form the desired products which are then trapped and subjected to additional purification procedures.

Lewis acids have been used to effect these same transformations. Barbot and Miginiac [125] carried out low temperature reactions of acetals with both $AlCl_3$ and $MgBr_2$ plus a

tertiary amine to give good yields of the corresponding vinylic ethers. Their work is outlined in equation 28.

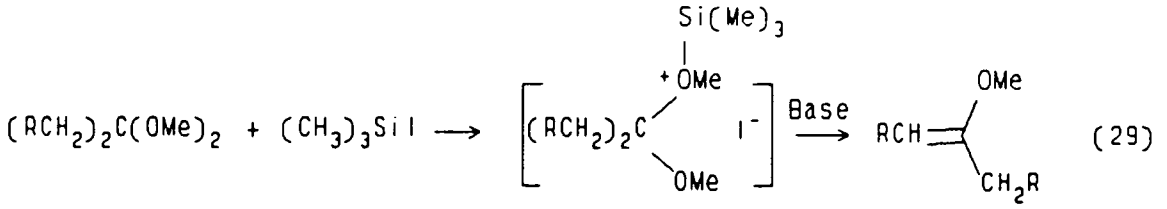


(28)

Addtional Methods of Preparation

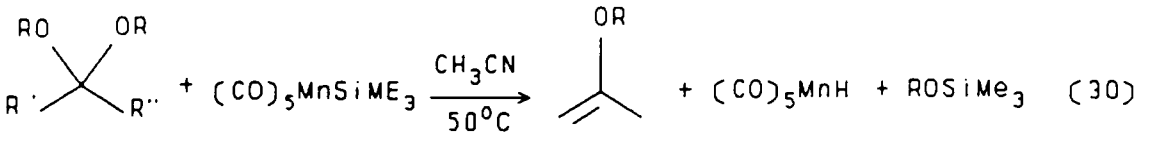
In addition to the procedures already described, several additional enol ether preparations have been recently developed. In many instances, these methods rely on relatively uncommon reagents. In addition, unusual experimental techniques are often required. Several of these approaches are described next.

Muller, et al. report the use of trimethylsilyl iodide (Me_3SiI) to effect a facile preparation of methyl enol ethers from the corresponding acetals [126]. In this case, the silicon reagent (functioning as a Lewis acid) complexes with the ether oxygen allowing siloxy elimination to occur on treatment with weak base (most often hindered amines) (eq 29). This reaction is noted for its mild reaction conditions (i.e., it is usually carried out at R.T. or below in a nearly neutral or weakly basic environment).



(29)

Mansi and Gladysz [127] utilized a silicon containing organo-manganese reagent as part of their vinyl ether synthesis. This transition metal trialkylsilane compound reacts as outlined in equation 30. The advantages associated with this reaction again involve the

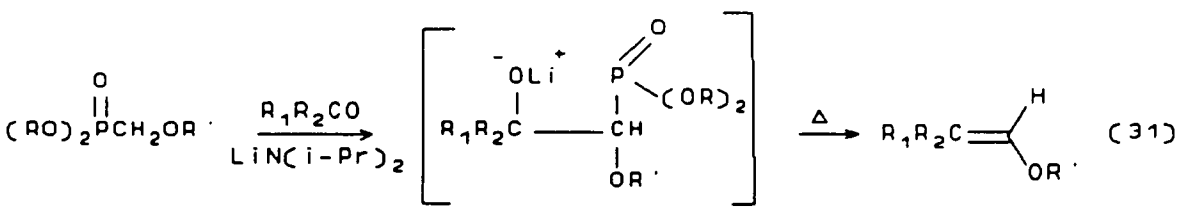


(30)

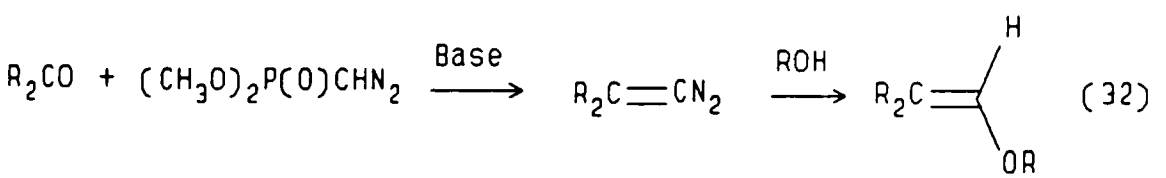
relatively mild conditions employed. Neither an acidic nor basic environment is required and the only by-product is the easily removed, mildly acidic, $(CO)_5MnH$. This same reagent has also been used for the conversion of ketones which possess α-hydrogens to their trimethyl silyl (TMS) enol ethers [128].

Enol ethers can be prepared directly from carbonyl containing compounds by methods which in several respects resemble Wittig-type chemistry. Kluge and Cloudsdale [129] used several different types of alkoxymethyl phosphonate esters to prepare a number of vinyl ethers. The overall reaction, shown in equation 31, involves reaction of the phosphonate reagent with either an aldehyde or ketone to give an intermediate structure which can be converted to the unsaturated ether in either one or two steps. Also, hydrolysis of the product

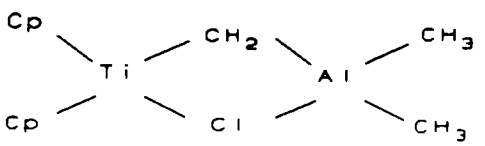
will regenerate the carbonyl function making this sequence a versatile method for the one carbon homologation of aldehydes and ketones [130].



Gilbert et al. [131, 132] took a similar approach to the preparation of vinyl ethers however in this case, the reagent was a diazophosphonate compound. In this base catalyzed procedure, dimethyldiazomethylphosphonate reacts with a ketone to give the dialkyl diazoethane. This compound then reacts with the alcohol present in the reaction mixture to give the aldehydic enol ether of the original ketone (eq 32).

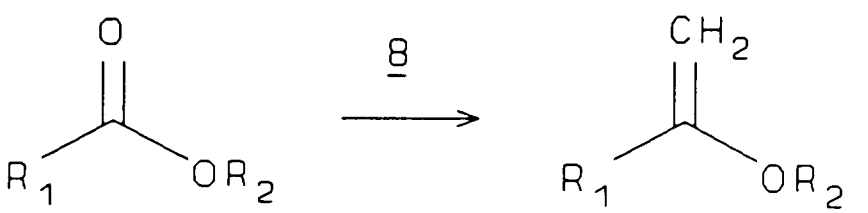


Titanium based chemistry has been used to achieve similar results. In one example, work originally carried out by Tebbe on the homologation of olefins [133] was applied to the carbonyl function of esters in order to prepare methyl enol ethers [134]. This technique involves the use of an electrophilic transition metal ylide, 8, to effect alkylidene transfer to the carbonyl acid derivatives. This reagent reacts with a number of substituted esters to give "methylene" vinyl ether products (eq 33).



8

Cp = cyclopentadiene

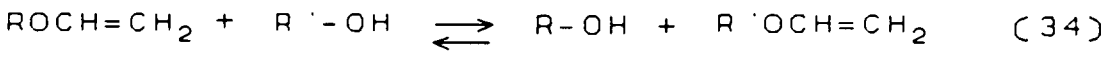


(33)

The major problem experienced with the use of this reagent involves its sensitivity to both oxygen and moisture, however, utilizing the complex as a standard solution in either benzene or toluene circumvents these problems.

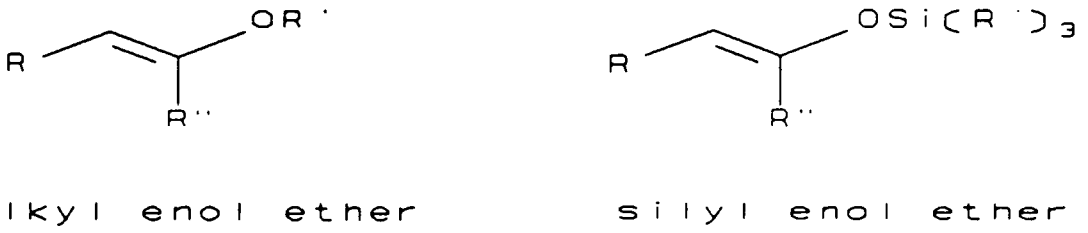
An alternative route to alkyl vinyl ethers involves starting with a readily prepared vinyl ether substrate and allowing this compound to undergo a transetherfication reaction to yield the desired product. Although numerous articles dealing with both the utility and mechanism of this reaction have appeared [135-137] the original work carried out by Watanabe and Conlon [138] remains definitive. In this reaction, vinyl interchange is catalyzed

by homogeneous metal salts (e.g. mercuric salts of weak acids) via a multistep mechanism that is believed to involve acetoxymercuriacetals as intermediates (eq 34).



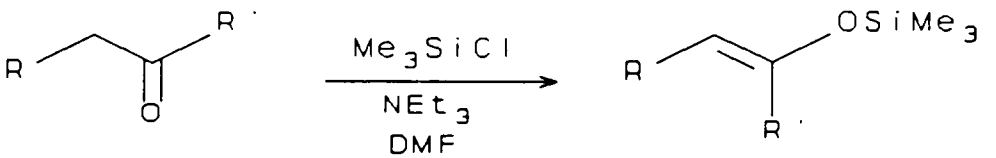
Under these reaction conditions, product yields ranging from poor to excellent have been reported for a variety of enol ethers.

Similar in structure but different in terms of chemical properties to alkyl vinyl ethers are the silyl enol ethers (scheme 1.4). These compounds, which were originally developed to facilitate the stable trapping and storage of enolate anions [139], have recently found a number of additional uses [140, 141].



Scheme 1.4

Trialkyl silyl enol ethers are readily formed by the reaction of a carbonyl containing structure with an alkyl silyl halide under basic conditions [142] (eq 35).



(35)

This reaction is attractive in those cases where exclusive formation of the vinyl ether structure is desired. This is due to the high affinity of silicon for oxygen which results in total (100%) reaction at oxygen. As noted previously, with alkyl vinyl ethers, this is not the case with condition-dependent amounts of both O- and C-alkylated products formed.

Trialkylsilyl enol ethers are relatively stable compounds especially when compared to the metal enolates from which they are derived. However, depending on the types of alkyl groups associated with the silicon center, acidic or basic conditions may be used to regenerate the carbonyl functionality [143].

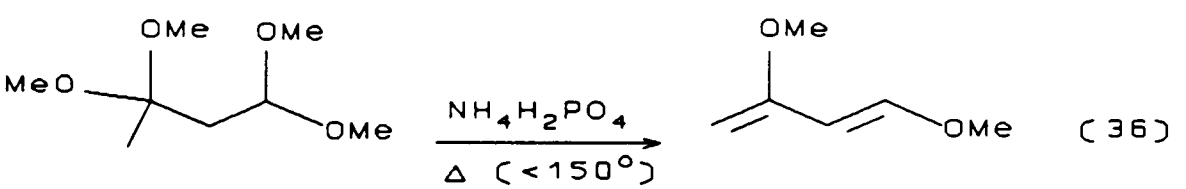
Section 3: Dienol Ethers

Conceptually, 1,3; 1,4; and 2,3 disubstituted dienes are very attractive synthetic targets. The introduction of heteroatom substituents (e.g. alkoxy substituents) to give dienol ethers would enhance the potential synthetic applications of these reagents by allowing increased control of the steric and electronic factors which govern the outcome of certain characteristic reactions (i.e., [4+2] cycloaddition reactions). This enhanced control holds the promise of access to regio- and stereoselective substitution patterns which have previously been unattainable. The use of such dienes in Diels-Alder and related reactions has recently become an area of much activity. This section outlines the methods used to prepare these substituted dienes as well as some of their synthetic applications.

Bis-alkoxy Dienes

Bis-alkoxy dienes (1,3; 1,4; and 2,3 respectively) are in general not readily accessible. As a result, their use as 4 carbon synthons in cycloaddition reactions has been limited. However, in a small number instances, these compouds have been prepared.

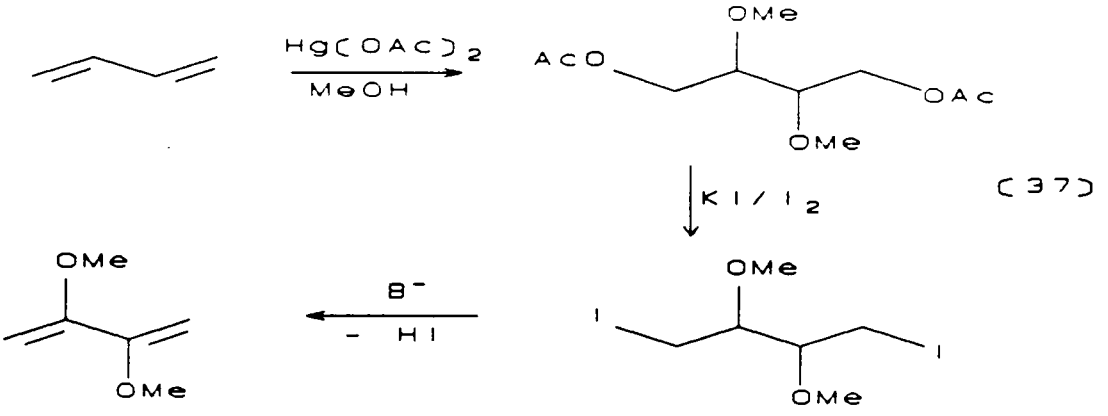
Shavrygina and co-workers [144] reported in 1969 the preparation of both 1,3 and 1,4-dimethoxy butadiene. Their procedure involved the acid catalyzed pyrolysis (cracking) of the appropriate bis-acetal precursors (eq 36).



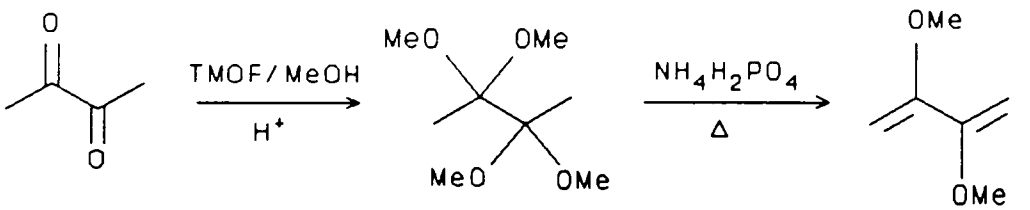
(36)

However, this is one of the few reports in which bis-acetals were successfully converted to dienol ethers under these conditions. Others [140] have attempted to repeat this work with less than satisfactory results.

Johnson et al. [145] reported the preparation of 2,3-substituted bis-alkoxy dienes. This procedure involved the mercuration of 1,3-butadiene using mercuric acetate followed by iodination and base-catalyzed elimination of HI to yield the desired product (eq 37). By changing the reaction solvent, both the methoxy and ethoxy derivatives could be obtained.



A second method by which 2,3-dialkoxy dienes can be generated was developed by McDonald [146]. This technique is similar to that reported by Shavrygina and involves the conversion of biacetyl to its bis-acetal using MeOH and trimethylorthoformate under acidic conditions. This product was then distilled from $NH_4H_2PO_4$ (ammonium dihydrogen phosphate) to give the desired 2,3-dimethoxy diene (eq 38).

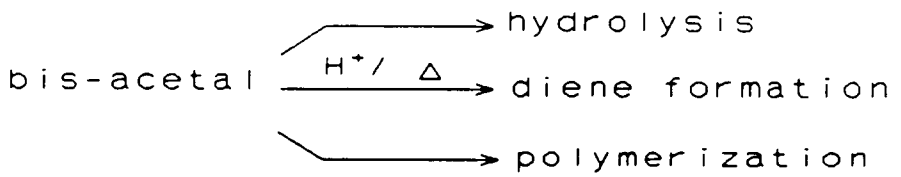


(38)

While it has been shown that these structures do act as dienes in cycloaddition reactions [145], their synthetic potential has been limited due to a general lack of reactivity. This behavior is most likely due to steric or unfavorable conformational effects. As a result, the interest initially shown in these 2,3-disubstituted dienes has decreased to the point where these preparations have found limited application.

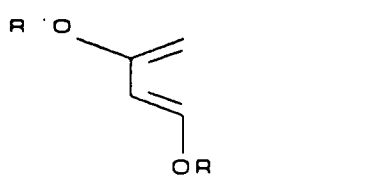
Alkoxytrialkylsiloxy Dienes

The first widespread synthetic use of disubstituted dienes began in 1974 with the work of Danishefsky [140]. Until this time, cylcoaddition reactions had been used extensively, but only a modest number of functionalities had been incorporated into the diene component. The problems encountered by these earlier workers in the preparation of suitable dienes have already been described and in large part relate to the conditions under which these compounds were generated. For example, the acid catalyzed pyrolysis of bis-acetals to generate bis-alkoxy dienes involves an environment which is generally not compatible with the survival of the acid-labile product (eq 39). As outlined, diene formation is just one of a number of possible outcomes for this type of reaction.

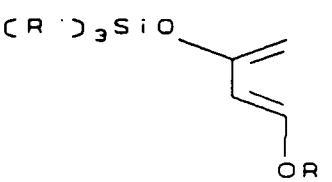


(39)

Danishefsky's approach avoided this problem by substituting a trialkylsiloxy group for one of the alkoxy units in the diene system [140] (scheme 1.5). Preparation of these compounds is outlined in equation 40. This modification gave a stablized disubstituted diene which could be generated under non-reactive (neutral or basic) conditions.

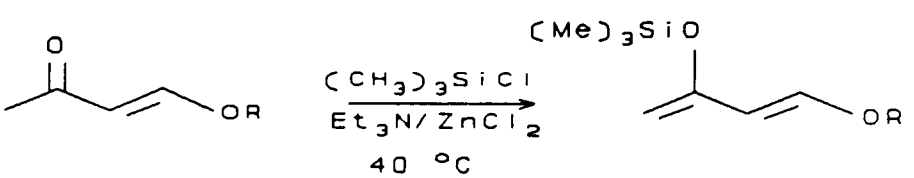


bis-alkoxy diene



alkoxytrialkylsilloxy diene

Scheme 1.5

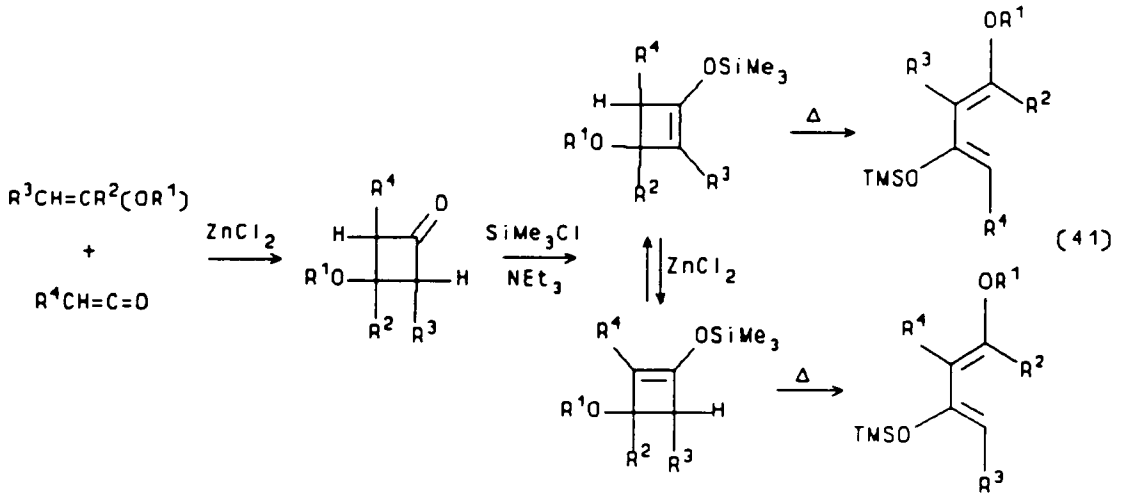


(40)

The 1,3 substitution pattern of these dienes makes them attractive in several respects. Most important, is the observation that these compounds undergo regioselective cycloaddition reactions to yield a single regioisomer [147]. This means that these reactions give rise to a predictable product composition which reduces or eliminates the problems associated with separation of isomeric mixtures.

A second point relates to the reactivity of these dienes. The oxygen atom in the 1 and 3 positions provides a resonance stablized electron rich diene system via resonance effects. This makes these structures very reactive dienophiles and allows their addition to even unreactive olefins [147].

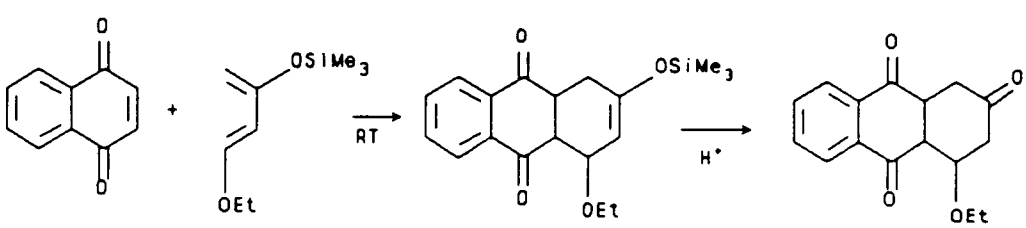
Additional approaches to the synthesis of 1-alkoxy-3-trialkyl siloxy dienes have been developed. Aben and Scheeren [148] investigated the acid catalyzed addition of ketenes to 1-alkoxyalkenes to yield alkoxycyclobutanones which following trialkysilation under basic conditions give trans-3-alkoxy-1-trialkyl siloxy cyclobutenes. These compounds undergo electrocyclic ring opening at less than 100°C to give the desired disubstituted products (eq 41).



This method of preparation is more versatile than that developed by Danishefsky in that it allows for the incorporation of a large and controlled number of substituents into the final product.

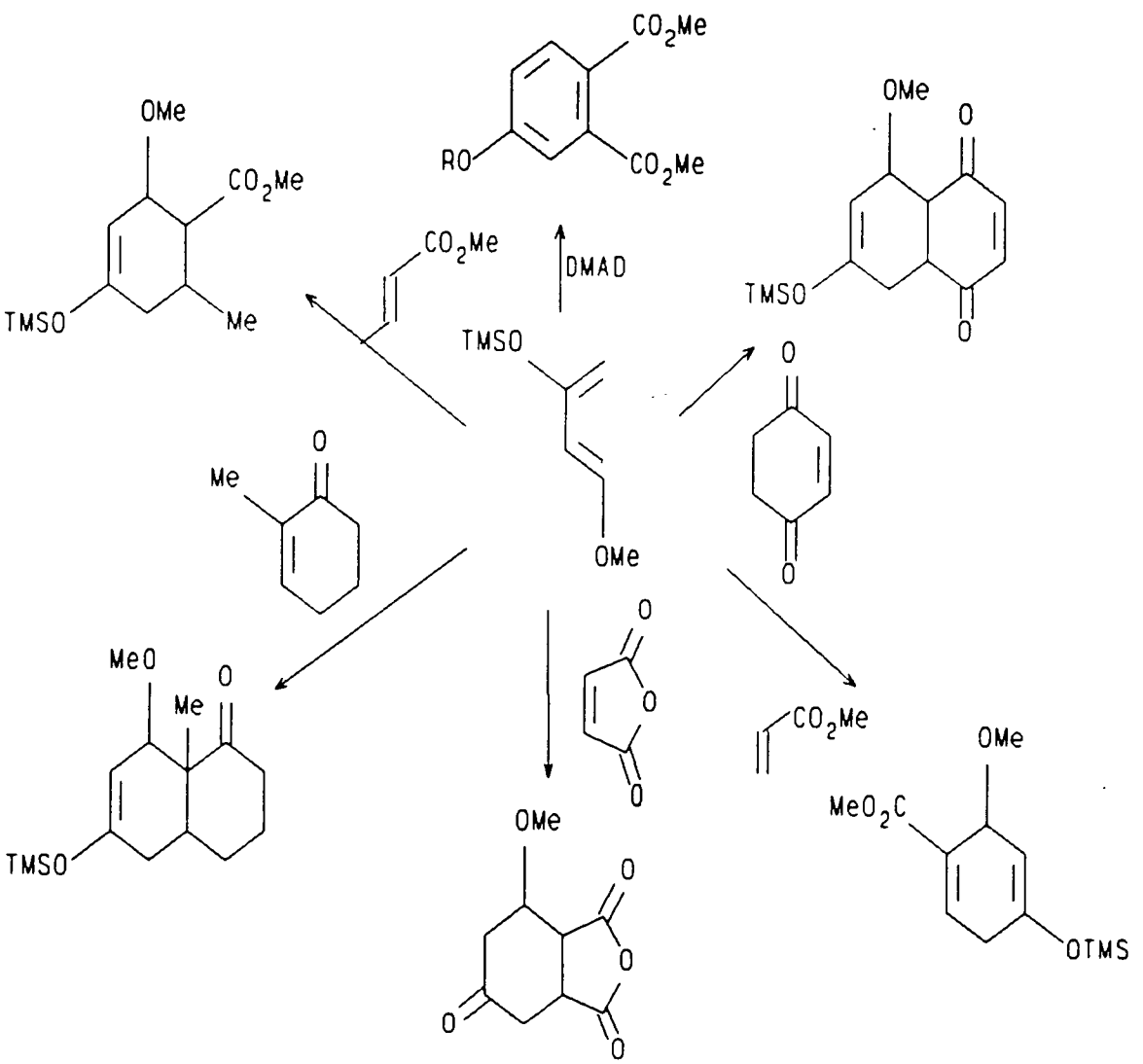
A number of synthetic targets, both naturally and non-naturally occuring, have been prepared using 1-alkoxy-3-trialkyl siloxy dienes in both their original (e.g. Danishefsky's diene) and modified forms.

Aben and co-workers have utilized these highly reactive dienes in reactions with quinones to give functionalized, linearly fused tricyclic systems [148] (eq 42). These structures are attractive in that they offer entry into the anthracyclinone system including adriamycinone and its analogs [149].

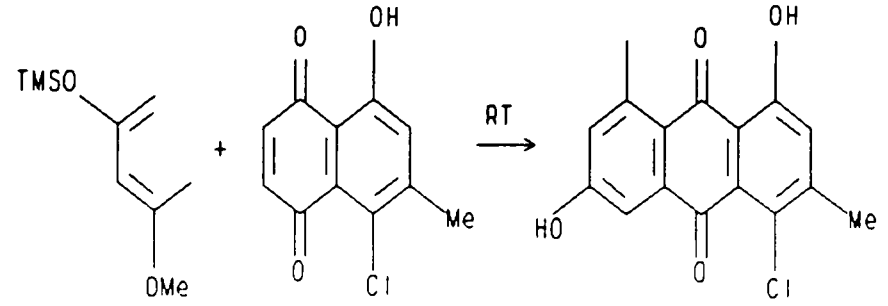


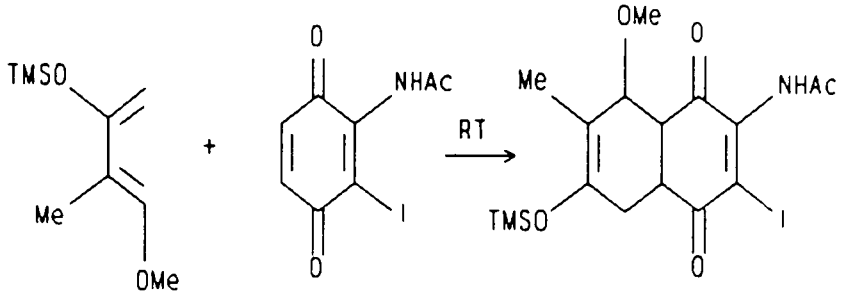
(42)

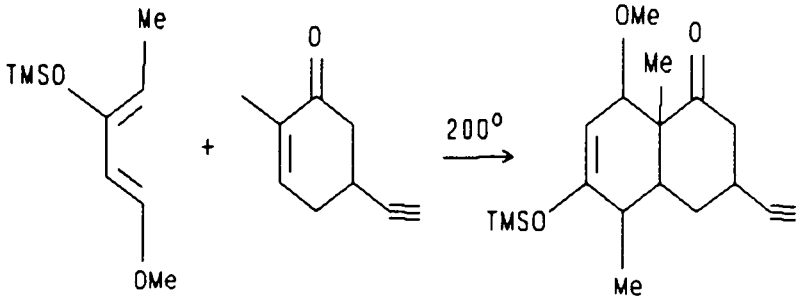
Danishefsky has made extensive use of his diene in preparing a number of synthetic targets [150]. Several of these are outlined in scheme 1.6. Synthetic applications by other workers are presented in scheme 1.7 [151-153].


CO2Me
RO
CO2Me
OMe
CO2Me
TMSO
Me
CO2Me
DMAD
TMSO
OMe
O
TMSO
O
O
Me
O
OMe
MeO
Me
O
TMSO
O
O
O
OMe
O
O
O
CO2Me
OMe
MeO2C
OTMS

Scheme 1.6


TMSO
OMe
+
O
OH
Me
O
Cl
RT
HO
[151]

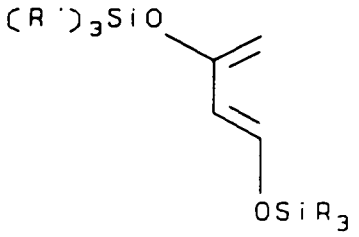

TMSO
Me
OMe
+
O
NHAc
I
RT
OMe
TMSO
[152]


Me
TMSO
OMe
+
O
200°
OMe
Me
TMSO
[153]

Scheme 1.7

Bis-trialkylsiloxy Dienes

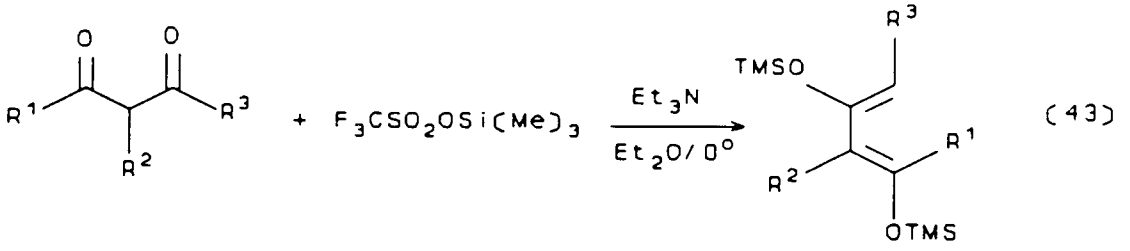
An extension of the outlined methodology involves the use of bis-alkylsiloxy substituted dienes. In these cases, both alkoxy substituents have been replaced by their trialkylsilane analogs (Scheme 1.8).



bis-alkylsiloxy diene

Scheme 1.8

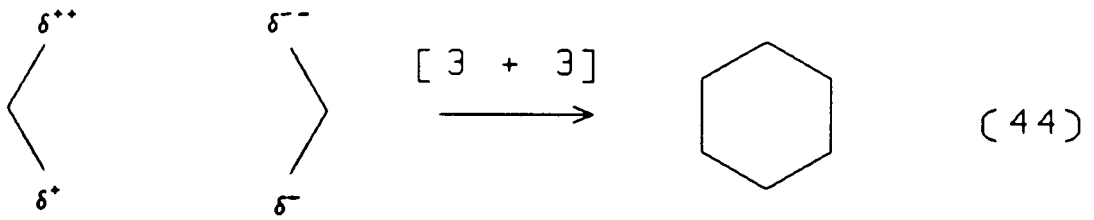
One method for the preparation of these compounds has been developed by Krageloh and Simchen [154] and is shown in equation 43.



(43)

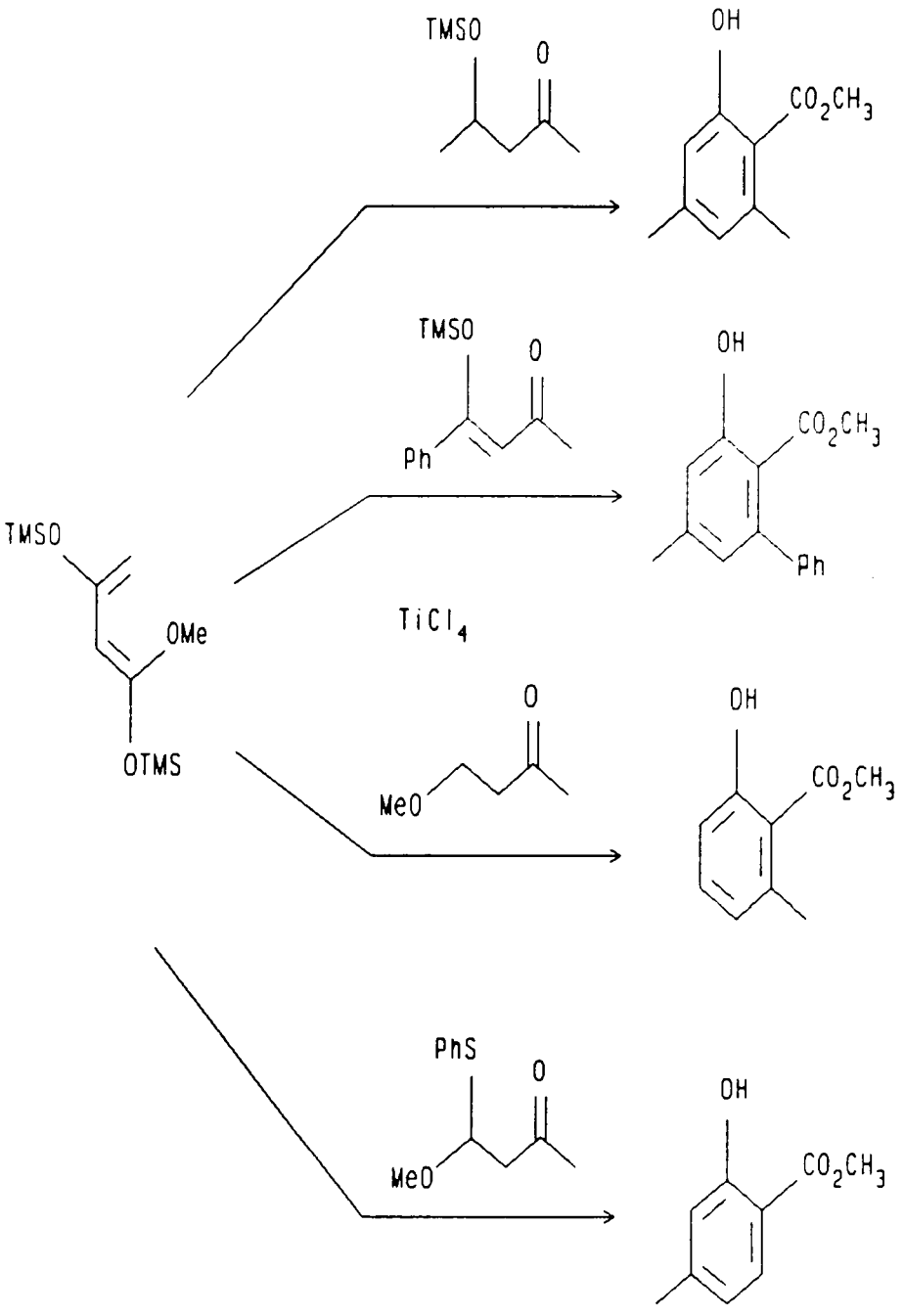
These types of dienes have found application in the field of synthetic organic chemistry most notably in the work of Chan and Brownbridge [155]. Their approach involves the condensation of two three carbon units (a [3+3] cycloaddition reaction) in the construction of six membered rings. The regiochemistry of this reaction is controlled by the differential reactivities of the several condensation sites. The basic concept is outlined in equation 44.

The double charged positions represent the more nucelophilic and electrophilic sites, respectively.



(44)

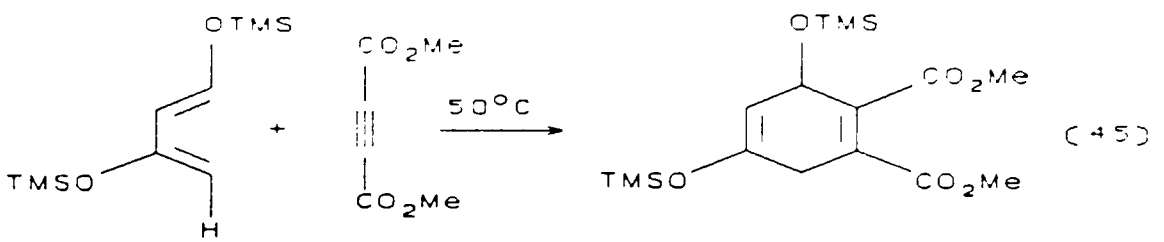
The feasibility of this approach in the preparation of cyclized products was established by the synthesis of several substituted methyl salicylates. This work involved the reaction of 1,3-bis(trimethylsiloxy)-1-methoxy butadiene with several different β-dicarbonyl equivalents in the presence of $TiCl_4$ (scheme 1.9). In each of these cases, the dienol ether serves as the source of nucleophilic reaction sites while the β-dicarbonyl equivalent serves as the electrophilic source.


TMSO
O
OH
CO_2CH_3
TMSO
O
Ph
OH
CO_2CH_3
Ph
TMSO
OMe
OTMS
$TiCl_4$
O
MeO
OH
CO_2CH_3
PhS
O
MeO
OH
CO_2CH_3

Scheme 1.9

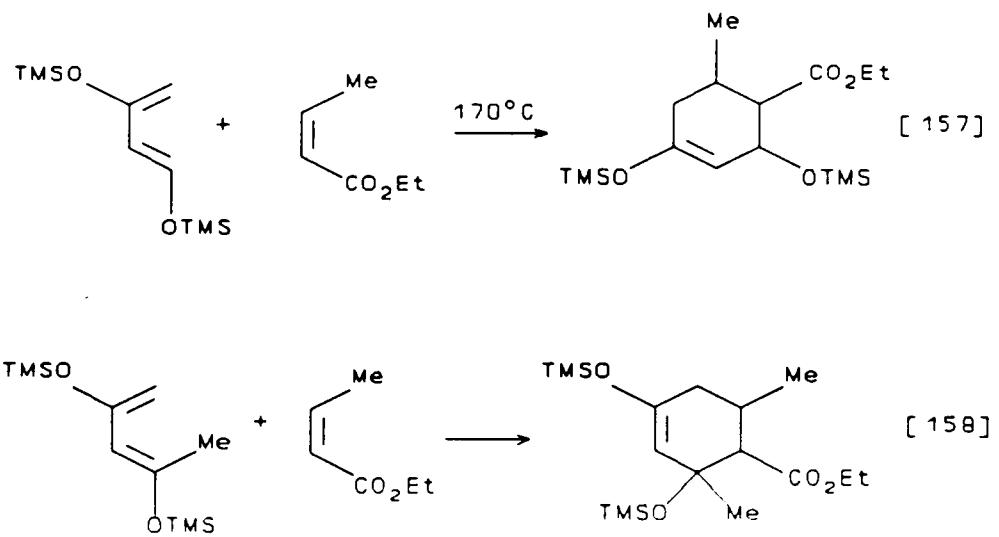
Work utilizing similar starting materials (i.e., 1,3-bis(trialkylsiloxy)dienes), but different methodology ([4+2] cycloadditon) has been carried out by several Japanese investigators.

Yamamoto [156] made use of Chan's original reagent (1,3-bis(trimethylsiloxy)-1,3-butadiene) in his synthesis of several dimethyl hydroxy substituted phthalates. In these reactions the substituted diene reacted with dimethylacetylenedicarboxylate (DMAD) under Diels-Alder conditions to give the cyclized product (eq 45).



(45)

Ibuka [157, 158] took a similar approach in his syntheses of dl-pumilitoxin C and (±)-α-vetrispirene. In each case the key step involved the [4+2] cyclization of a 1,3-bis(alkylsiloxy) substituted diene with the properly functionalized dieneophile to give the desired intermediate (Scheme 1.10).


TMSO
OTMS
Me
CO2Et
170°C
Me
CO2Et
TMSO
OTMS
[157]
(46)
TMSO
Me
OTMS
Me
CO2Et
TMSO
Me
Me
CO2Et
TMSO
Me
[158]

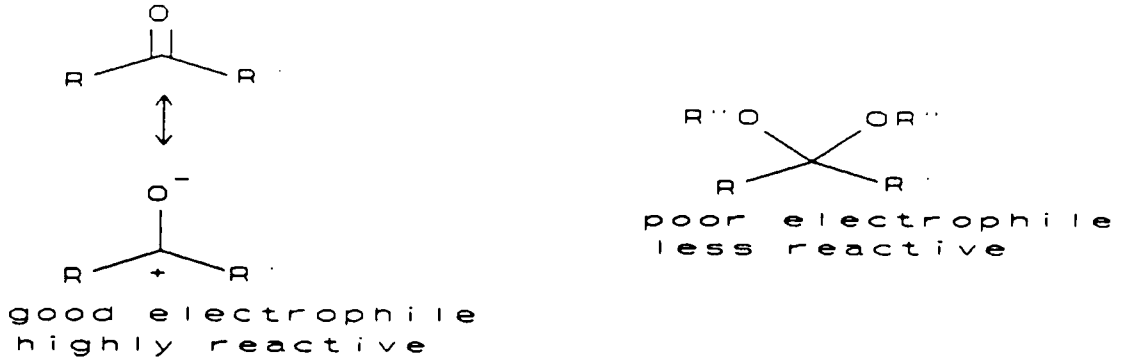
Scheme 1.10

Chapter 2

Bis(trifluoroethyl) Ketals

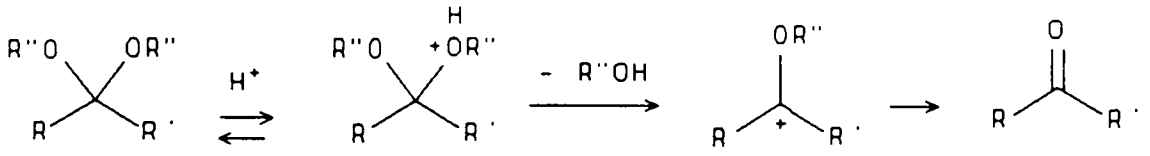
Introduction

As functional groups, ketals and acetals have found wide application in many areas of synthetic organic chemistry [159, 160]. While their use as synthons in a variety of instances is well documented, the major application of these structures relates to their use as protecting groups for the carbonyl function [11, 12]. The conversion of the carbon-oxygen double bond into the diether linkage decreases the electrophilicity of this center which in turn greatly reduces its reactivity (scheme 2.1).



Scheme 2.1

The major drawback to the use of ketals and acetals in this capacity is their behavior towards acidic medium. In general, these compounds are acid sensitive and in such an environment rapidly hydrolyze, to regenerate the original carbonyl containing structure. In fact, these are the conditions under which the ketal protecting group is most often removed. The general hydrolytic mechanism is the reverse of acid catalyzed ketal formation and is outlined below (Scheme 2.2). The acid labile nature of these structures is not limited to protic acids. There are numerous examples of ketal hydrolysis which make use of Lewis acids (e.g. BF_3, BCl_3, $AlCl_3$, etc.) as well as other types of base (oxygen) complexing reagents as catalysts.



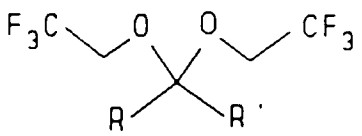
Scheme 2.2

As a result of their inherent sensitivity, compounds other than ketals have been employed as carbonyl protecting groups under acid conditions. It is often found, however, that these structures are less than ideal for many applications. Problems relating to both introduction and removal of these protecting groups have been encountered [161].

During a study involving Lanthanide Shift Reagents (LSR's) and the mechanism of their complexation with various organic substrates, the need arose for a specific type of carbonyl protecting group. This protecting group needed to be acid stable (LSR's are Lewis acids) and non-complexing with the shift reagent. This chapter deals with our efforts to develop a protecting group which met these requirements.

Preparation and Applications

Although no carbonyl protecting groups combining the desired characteristics were available, results from past work in our laboratory along with evidence gathered from literature sources gave us reason to believe that bis(trifluoroethyl) ketals might serve this purpose. The general structure for these compounds is shown in Scheme 2.3.



R, R' = alkyl, aryl

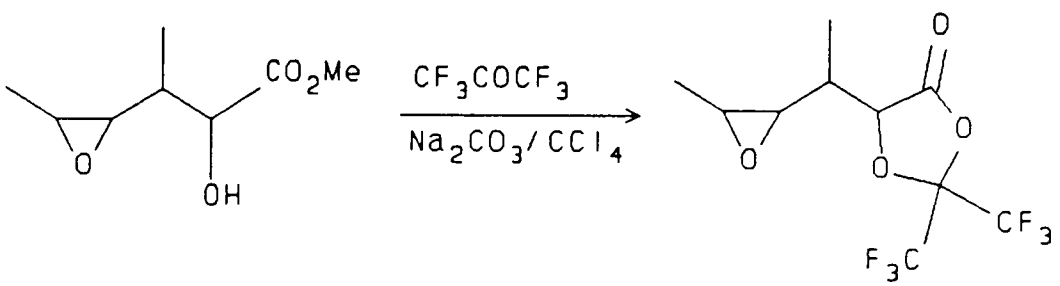
Scheme 2.3

Theoretically, we would predict that these compounds would be more stable to acid conditions than their non-halogenated counterparts. This stablization is directly related to the electronic structure of the ketal and its hydrolytic intermediates and can be attributed primarily to two reinforcing trends. As outlined above, the first step in ketal hydrolysis involves complexation at oxygen by an acid catalyst. In the general sense, this is an acid-base reaction with oxygen serving as the base. In this case, however, we would expect the highly electronegative flourine atoms to inductively displace electron density from the vicinity of the oxygen atoms making complexation at those sites less likely. We would expect this effect to result in a decrease in the rate of acid catalyzed hydrolysis. Also, in those instances where complexation did occur, the loss of CF_3CH_2OH (the second and generally the rate determining step in acid catalyzed hydrolysis) would also be disfavored due to destablization of the carbonium ion intermediate by the remaining trifluoroethoxy group.

Results from the literature would seem to support this hypothesis. For example, in his study of the acid catalyzed cycloaddition reaction of β-dicarbonyl compounds in the presence of 2,2,2-trifluorodiazoethane (TFD), Roy isolated several structures in which the bis(trifluoroethyl) ketal functionality had been incorporated [1]. During the course of his studies, he found that these structures were unusually stable to acid catalyzed hydrolysis. Isidor and Carlson observed analogous behavior in their work with bis(trichloroethyl) ketals

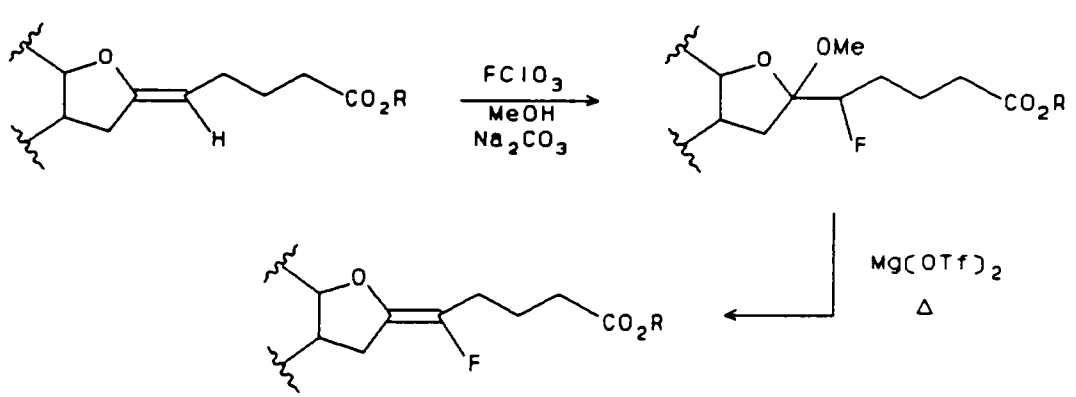
[162].

Other reports of the effect strong electron-withdrawing groups have on the reactivity of ketal and ketal like structures agree with these results. Bartlett [163] made use of the electron withdrawing ability of the trifluoromethyl group in his synthesis of (±)-Tirandamycin A. In this case hexafluoroacetone was used to prepare a ketal lactone in which the -CF_3's electron withdrawing properties deactivated the lactone carbonyl towards internal nucleophilic attack (eq 47). Swenton [164] utilized fluorine's electron withdrawing abilities



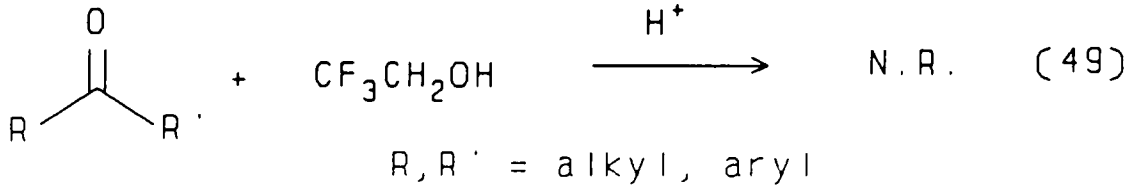
(47)

in his studies of the platelet aggregation inhibitor Prostacyclin. In this instance, substitution of a fluorine atom for a hydrogen atom to form the 5-fluoro derivative inhibited the hydration of the enol ether moiety (eq 48).



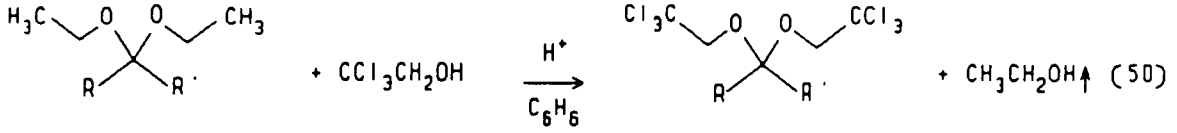
(48)

Although numerous methods have been developed for the preparation of acetals and ketals, a general procedure for the preparation of bis(trifluoroethyl) (TFE) ketals has not been reported. The direct acid catalyzed preparation of these compounds from the corresponding ketone and alcohol (2,2,2-trifluorethanol) was found to be ineffective (eq 49).



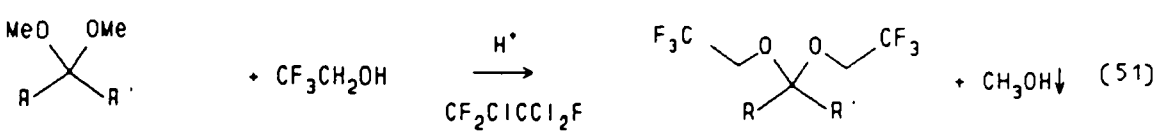
This is in agreement with other work and presumably is due to the poor nucleophilic character of 2,2,2-trifluoroethanol which can be attributed to the powerful electron withdrawing effect of the β-fluorine atoms [165, 166]. Due to the failure of this direct approach, alternate methods were examined.

Isidor and Carlson reported the preparation of both mono- and bis(trichloroethyl) ketals by an acid catalyzed alcohol exchange reaction [162]. This method involved reacting 2,2,2-trichloroethanol (TCE) with the appropriate methyl or ethyl ketal under acid conditions. The reaction was driven to completion by removal of the unwanted alcohol as an azeotrope with benzene (eq 50).



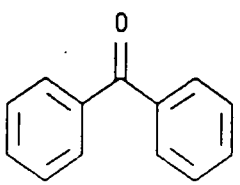
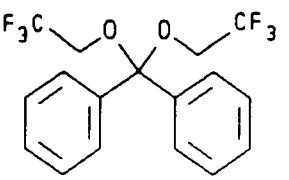
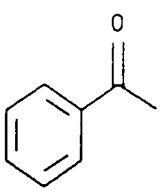
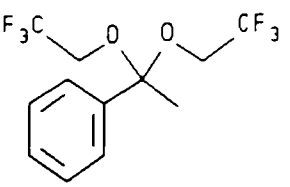
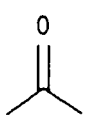
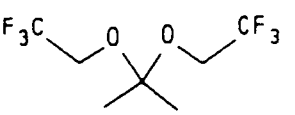
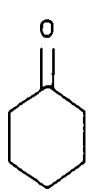
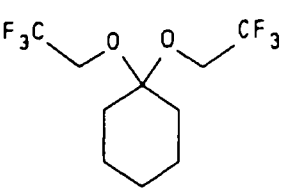
Our initial attempts to apply this methodology to the formation of TFE ketals were less than successful. The major difficulty was the selective removal of the undesired alcohol (e.g. methanol or ethanol) in the presence of CF_3CH_2OH under equilibrium conditions. As previously stated, this was accomplished by Isidor and Carlson through azeotropic distillation (i.e. methanol/benzene). However, the boiling point similarities of 2,2,2-trifluoroethanol and the corresponding azeotropic mixture prevented the use of this approach in the trifluoroethyl case. Due to our inability to drive the reaction to completion, the product mixture always contained a substantial proportion of the undesired unsymmetrical ketal (mono-substitution product). These compounds proved difficult to separate from the bis-ketals and made this particular approach less than satisfactory.

A different methodology to remove the undesired alcohol (methanol) and make the exhange reaction practical in the preparation of bis(trifluoroethyl) ketals was eventually developed. This involved using 1,1,2-trifluorotrichloroethane (Freon 112), which forms a ternary azeotrope with methanol and trifluoroethanol as the reaction solvent. Using a Soxhlet extractor, this azeotropic distillate was condensed and passed through a bed of freshly activated 4Å molecular sieves prior to its return to the reaction mixture. This process selectively removed the MeOH from the reaction system while allowing the CF_3CH_2OH to remain. This, in turn, forced the reaction to completion. Using this methodology (eq 51), the model compounds listed in Table 2.1 were converted to their bis-(trifluoroethyl) derivatives via the intermediate methyl ketals.



(51)

Table 2.1

Starting Ketone	TFE KETAL	Yield[1]
		82 %
		83 %
		63 %
		73 %

1) isolated yields

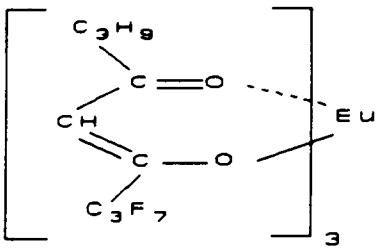
As indicated, this alcohol exchange reaction provides a convenient and high yielding method for the preparation of bis(trifluoroethyl) ketals. These products were generally quite clean and could be separated from any hydrolytic byproducts by either chromatography or distillation. The 270 MHz ^1H NMR spectra of the TFE ketal of acetophenone is illustrated in Figure 2.1.

The ready availability of TFE ketals provided the opportunity to explore their potential applications. As previously indicated, we believed that the highly electronegative flourine atoms would cause these compounds to behave differently from their non-halogenated analogs with respect to their reactivity towards electrophilic complexing reagents. Accordingly, several experiments were proposed to examine this behavior . These experiments are described below.

Lanthanide Shift Reagent Study

Since the incentive to prepare TFE ketals involved their use as a non-reactive/non-complexing carbonyl protecting group, it was this area we examined first. The experiment was designed as follows.

Three sets of compounds were examined in an effort to determine the magnitude of their interaction with the lanthanide shift reagent $Eu(fod)_3$ (Scheme 2.4). These compounds are listed in Table 2.2.



Scheme 2.4

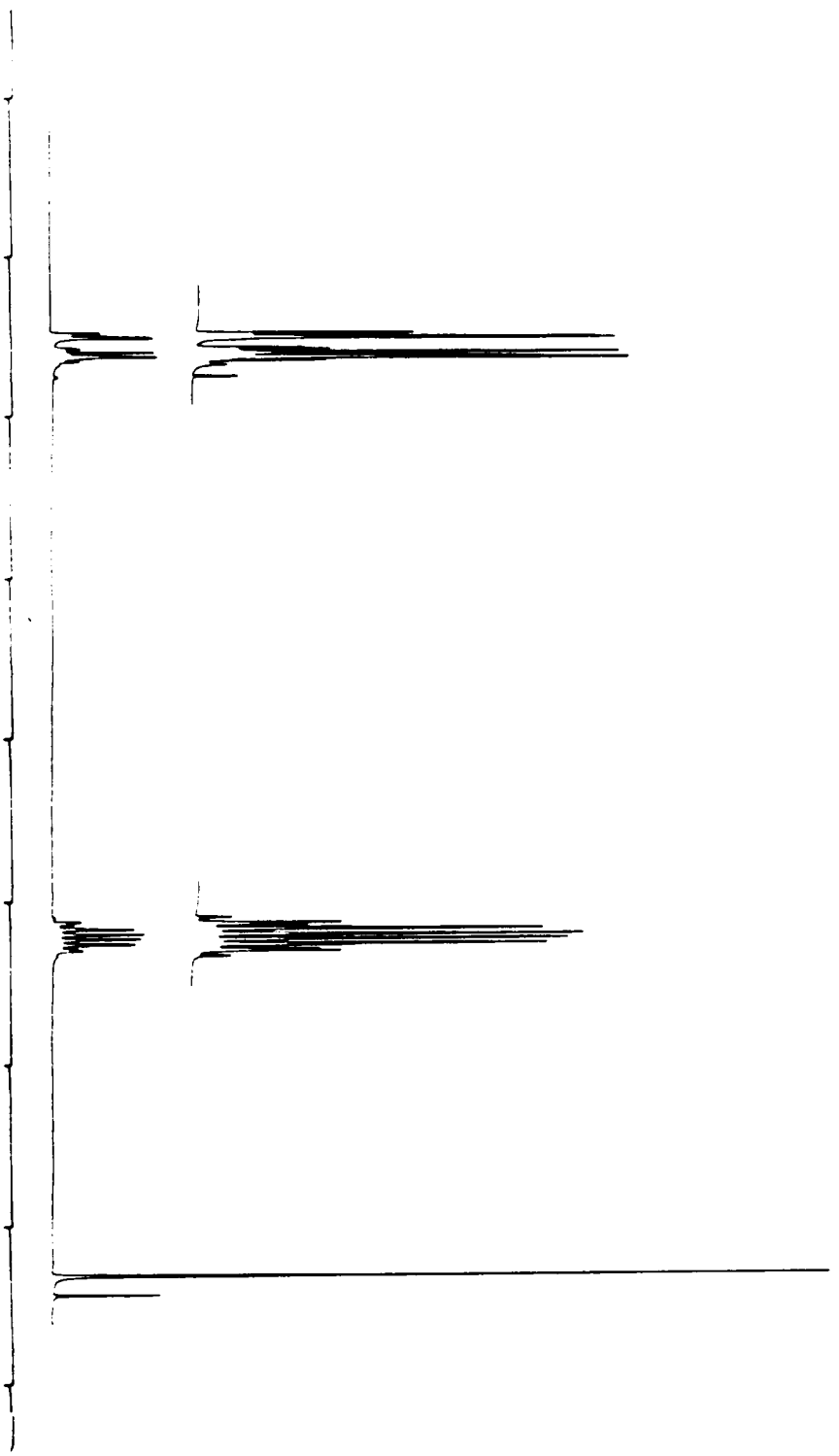
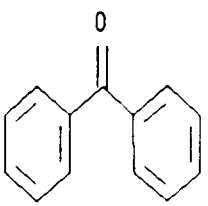
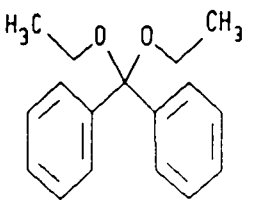
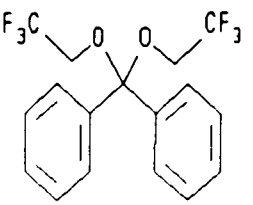
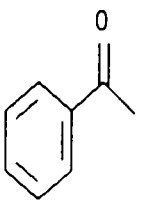
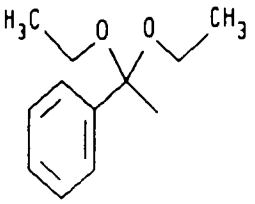
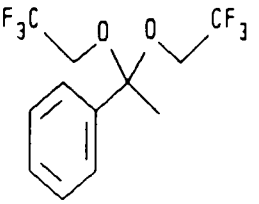
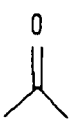
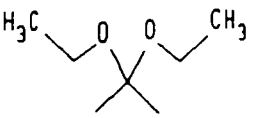
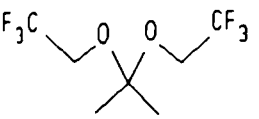
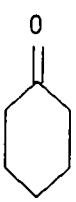
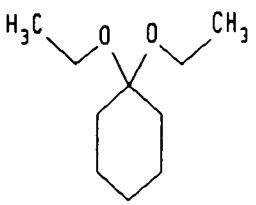
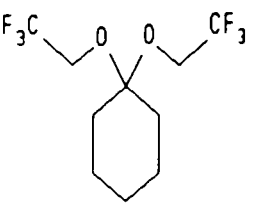


Figure 2.1 270 MHz ^{1}H NMR spectra of the TFE ketal of acetophenone.

Table 2.2

Model Compounds for LSR Study

Ketone	Ethyl Ketal	TFE Ketal
		
		
		
		

The carbonyl containing structures served as a control group as their behavior towards LSR's is well documented. The ethyl ketal derivatives of these compounds were included in this study for two reasons. First, they are identical to the TFE derivatives in every respect with the exception of the halogen substituents. As such, this would allow for at least a qualitative estimate of the effect the electronegative fluorines electron withdrawl had on the basicity of the oxygen sites. Second, the behavior of ketal derivatives in general towards LSR's had not been rigorously investigated, therefore, the possibility existed that the ethyl ketal might serve our purposes as a protecting group thereby saving the additional effort involved in the preparation of the TFE derivatives.

The experiment consisted of adding incremental amounts of $Eu(fod)_3$ to a $CDCl_3$ solution of each of the compounds listed in Table 2.2 and then observing the ^1H NMR of each solution paying particular attention to the chemical shifts of those protons nearest the sites of possible LSR complexation. The position of these shifts, relative to the chemical shifts of the compounds in the absence of shift reagent, indicates the magnitude of the interaction between the shift reagent and the compound. Figures 2.2 - 2.5 and Tables 2.3 - 2.6 illustrate the results of this study.

Figure 2.2 gives the ^1H NMR lanthanide induced shift (LIS) for the methyl protons of acetone, 2,2-diethyoxypropane, and 2,2-bis(trifluorethoxy)propane as a function of moles of added $Eu(fod)_3$. The strong nucleophilic character of the carbonyl oxygen toward LSR complexation is well established and the observed LIS's for acetone were expected. Smaller but still significant ^1H LIS's were also observed for the methyl protons of 2,2-diethoxypropane. In sharp contrast, ^1H NMR LIS's for the 2,2-bis(trifluoroethoxy) derivative were not observed even at very high LSR/substrate ratios.

Figure 2.3 presents similar ^1H NMR LIS data for acetophenone and its ketal derivatives. Once again chemical shifts for the methyl protons of the ethoxy and

trifluoroethoxy ketals as well as the parent carbonyl compound are plotted as a function of added shift reagent. As in the previous case, both the ketone and its ethoxy derviative show evidence of LSR complexation based on their ^{1}H NMR chemical shifts. However, once again, no significant LIS's were observed (less than 0.01 ppm) for the bis(trifluoroethyl) derivative.

When the methylene protons adjacent to the ketal oxygen were monitored, the results were similar to those previously observed. In figure 2.4, we can see by the magnitude of the LIS, that complexation occurs at the ketal oxygen of 2,2-diethoxycyclohexane while it is completely absent in the 2,2-bis(trifluoro)ethoxy derivative. A similar example with identical results is presented in figure 2.5.

These ^{1}H NMR LIS results clearly support our initial hypothesis regarding the effect strong electron withdrawing groups have on the behavior of ketals toward LSR complexation. These results suggest that bis(trifluoroethyl) ketals could be effectively used as protecting groups in Lanthanide shift studies possibly providing a new approach to LIS studies of polyfunctional molecules.

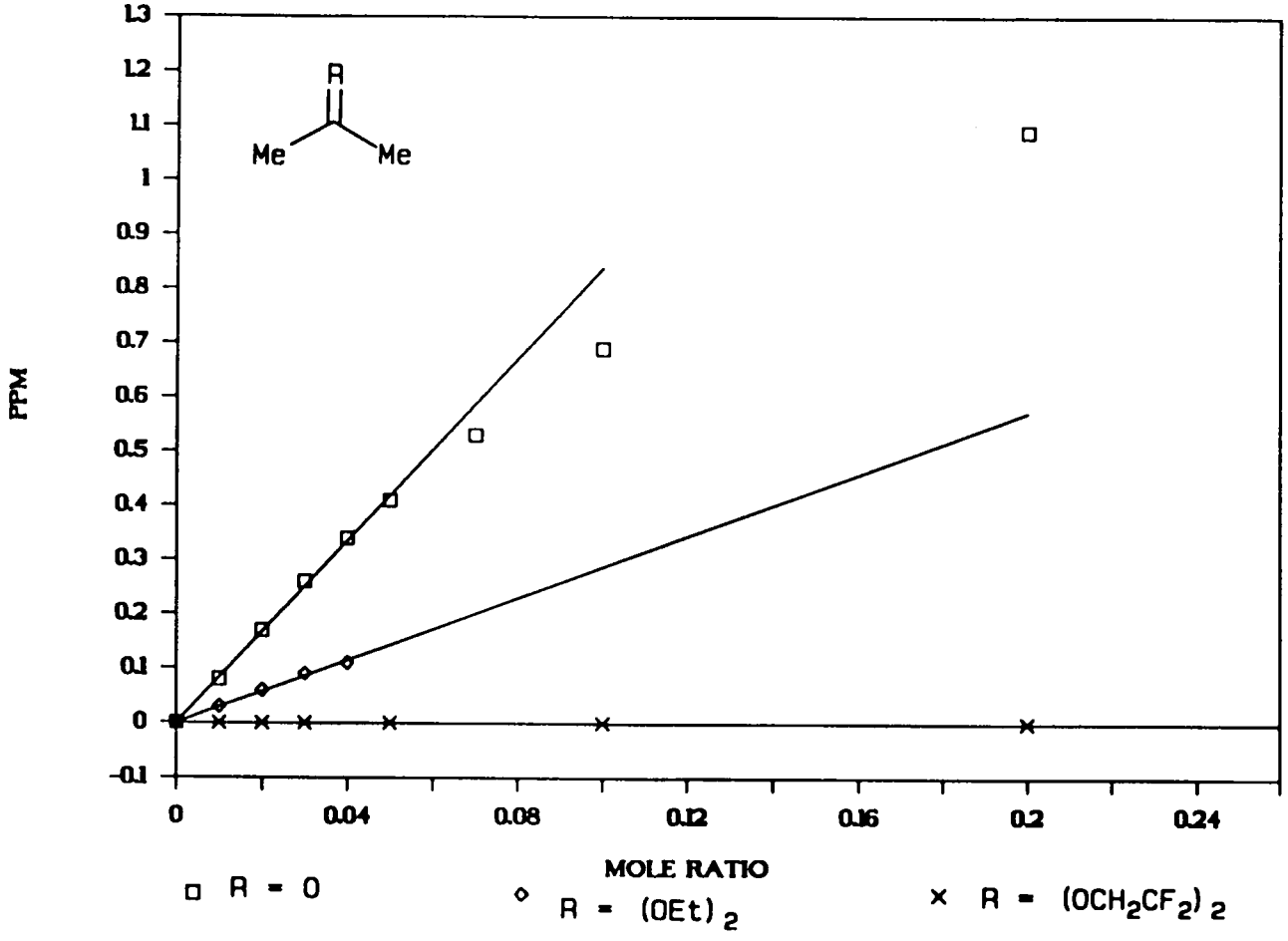


Figure 2.2. Chemical shifts for the α methyl protons of acetone and its diethyl and trifluoro ketal analogs as a function of added $Eu(fod)_3$

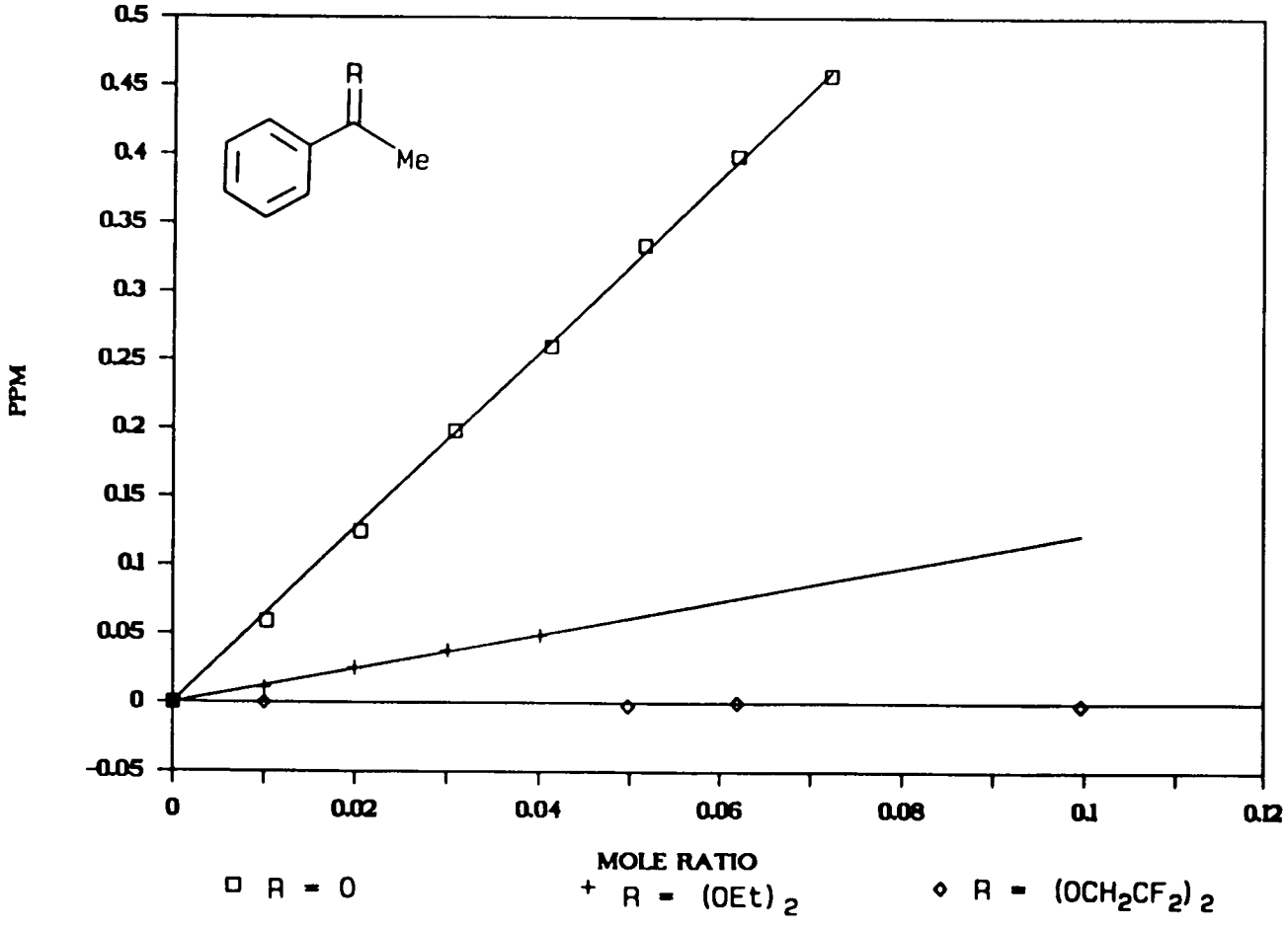


Figure 2.3. Chemical shifts for the α methyl protons of acetophenone and its diethyl and trifluoro ketal analogs as a function of added $Eu(fod)_3$

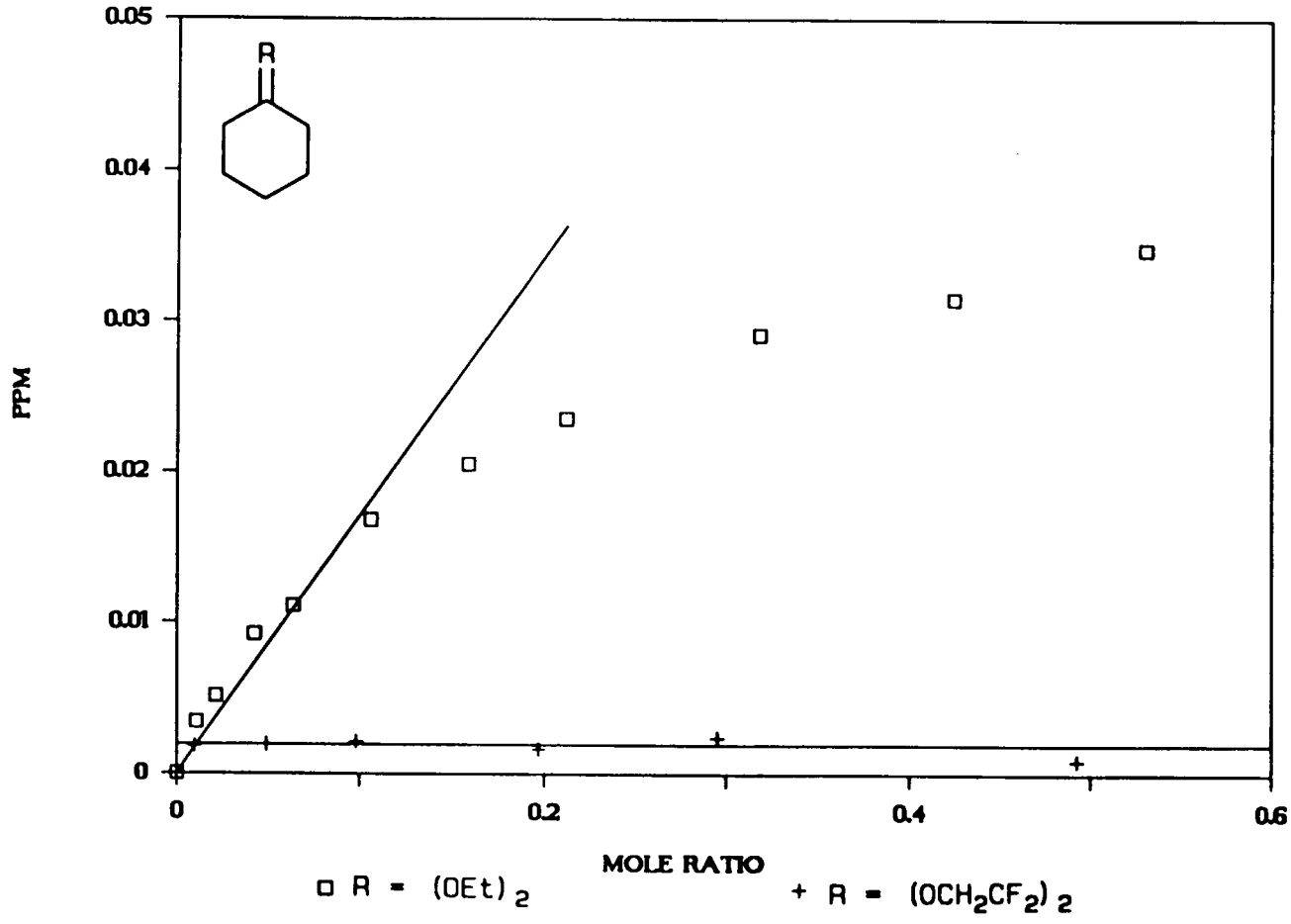


Figure 2.4. Chemical shifts for the ketal methylene protons of the diethyl and trifluoroethyl ketal derivatives of cyclohexanone as a function of added $Eu(fod)_3$

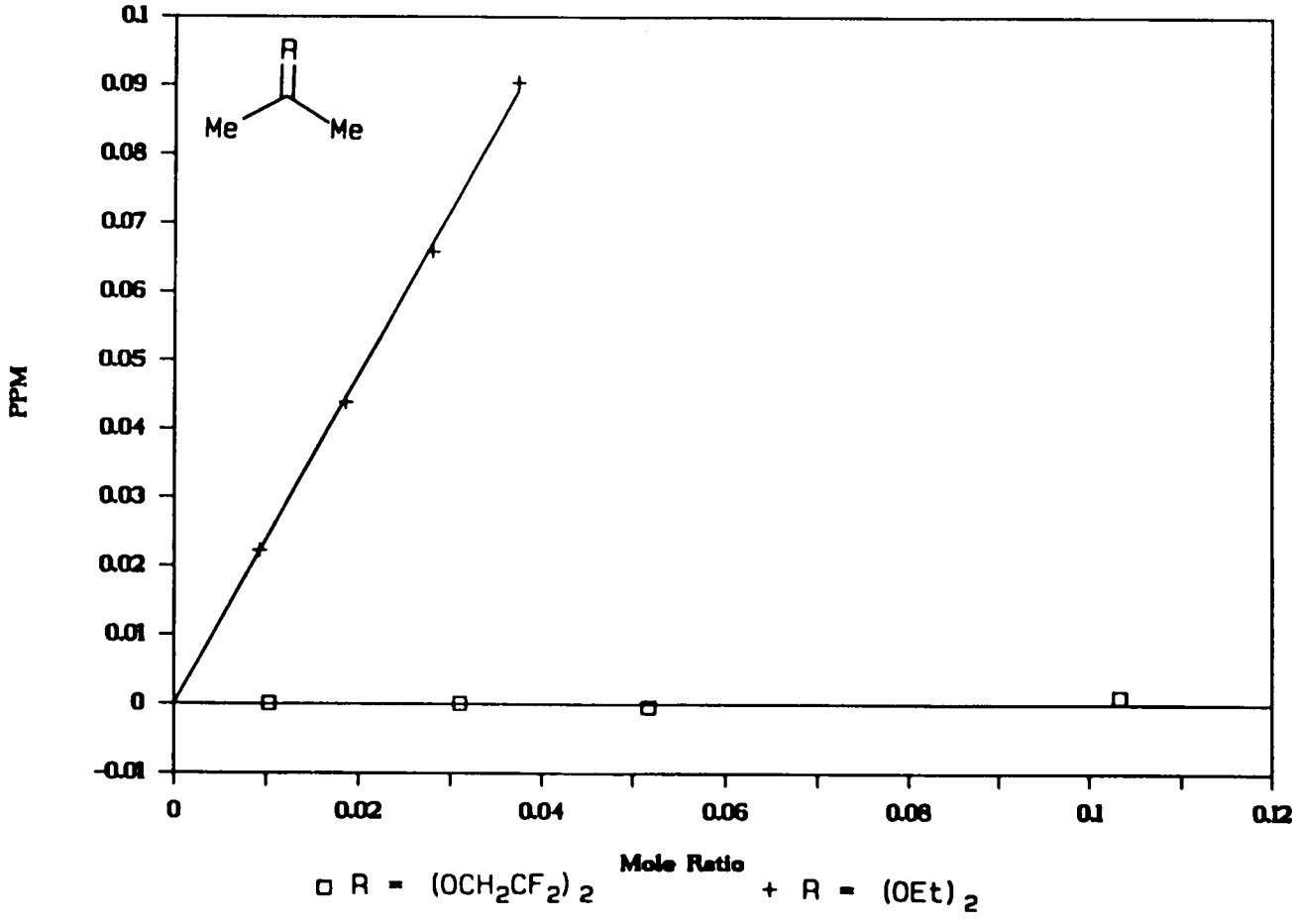


Figure 2.5. **Chemical shifts for the ketal methylene protons of the diethyl and trifluoroethyl ketal derivatives of acetone as a function of added $Eu(fod)_3$**

Table 2.3. **Changes in chemical shift (Δ ppm) as a function of added $Eu(fod)_3$ for the α methyl protons of acetone and its ketal analogs.**

Molar Ratio $Eu(fod)_3$/[S]	Acetone Δ ppm	Ethyl Ketal Δ ppm	Trifluoro-ethyl Ketal Δppm
0.00	0.00	0.00	0.00
0.01	0.08	0.03	0.00
0.02	0.17	0.06	
0.03	0.26	0.09	0.00
0.04	0.34	0.11	
0.05	0.41		0.00
0.07	0.53		
0.10	0.69		0.00
0.20	1.09		0.00
0.50			0.00

Table 2.4. **Changes in chemical shift (Δ ppm) as a function of added $Eu(fod)_3$ for the α methyl protons for acetophenone and its ketal analogs.**

Molar Ratio $Eu(fod)_3$/[S]	Aceto-phenone Δ ppm	Ethyl Ketal Δ ppm	Trifluoro-ethyl Ketal Δ ppm
0.00	0.00	0.00	- 0.0002
0.01		0.0107	- 0.0004
0.0103	0.059		
0.02		0.0252	
0.0206	0.125		
0.0301		0.378	
0.0309	0.198		
0.0401		0.0487	
0.0413	0.26		
0.0498			- 0.0023
0.0516	0.334		
0.0619	0.399		
0.0722	0.458		
0.0996			- 0.0019
0.2987			- 0.0011

Table 2.5. **Changes in chemical shift (Δ ppm) as a function of added Eu(fod)$_3$ for the ketal methylene protons of cyclohexanone ethyl ketal and trifluoroethyl ketal.**

Molar Ratio Eu(fod)$_3$/[S]	Ethyl Ketal Δ ppm	Trifluoro-ethyl Ketal Δppm
0.00	0.00	0.00
0.0098		0.0018
0.0106	0.0034	
0.0212	0.0051	
0.0424	0.0092	
0.0492		0.0019
0.0636	0.0111	
0.984		0.0021
0.1061	0.0168	
0.1591	0.0205	
0.1969		0.0016
0.2121	0.0235	
0.2953		0.0024
0.3183	0.0291	
0.4243	0.315	
0.4922		0.0009
0.5304	0.0348	
0.689		0.0022
0.9844		0.0028

Table 2.6. **Changes in chemical shift (Δ ppm) as a function of added $Eu(fod)_3$ for the ketal methylene protons for the ethyl ketal and trifluoroethyl ketal of acetone.**

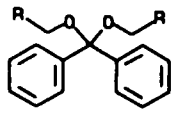
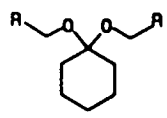
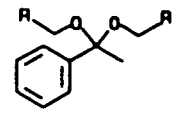
Molar Ratio $Eu(fod)_3$/[S]	Ethyl Ketal Δ ppm	Trifluoro-ethyl Ketal Δ ppm
0.00	0.00	0.00
0.0093	0.0223	
0.0103		0.0001
0.0186	0.0439	
0.028	0.0659	
0.031		0.0001
0.0373	0.0905	
0.0517		- 0.0004
0.1033		0.0010
0.155		- 0.0006
0.2067		0.00
0.31		- 0.0002
0.4134		0.0016
0.5167		0.0016

Acid Catalyzed Hydrolysis Study

The results from the LSR study were conclusive and indicated that the electronegative β-fluorine atoms did deactivate the ketal oxygens towards complexation with weak Lewis acids. Encouraged by these results, we decided to determine the overall potential of bis(trifluoroethyl) ketals as acid stable carbonyl protecting groups. To accomplish this, a study of the reactivity of TFE ketals toward acid catalyzed hydrolysis was carried out. This study is outlined below.

As in the LSR experiments, the same four model compounds were used. However, due to the nature of the experiment (i.e., ketal stability under acid conditions) only the ethoxy and TFE derivatives were examined. The study was designed to determine the relative stabilities of the various structures to specific acid conditions, and was accomplished by monitoring the percent of ketal hydrolysis as a function of time. Once again, ethoxy ketals were chosen for comparison because they differ only from their TFE analogs only in the nature of the β substituent (i.e., 3 hydrogens vs. 3 fluorines). In this way, any differences observed in hydrolysis rates between the two types of ketals could be directly attributed to the effect of the electron withdrawing group. Due to significant ^{1}H NMR chemical shift differences in the spectra of the starting ketals and the hydrolysis products, the reactions were readily monitored by ^{1}H NMR. Quantitative rate information was determined using the ^{1}H NMR integration area for the corresponding signals. At all times, an excess of acid was present in the reaction mixture. Experimental results are summarized in Table 2.7.

Table 2.7. Comparison Rate Data for the Acid Catalyzed Hydrolysis of Ethyl and TFE Ketals


R =	CH_3	CF_3	CH_3	CF_3	CH_3	CF_3	CH_3	CF_3
Solvent	CD_3CN	CD_3CN	DMSO	DMSO	CD_3CN	CD_3CN	DMSO	DMSO
Time Monitored Hydrolysis ( ) - 8 X 10^{-4} N DCl[1]	2.27 X 10^2 s (100)	7.47 X 10^4 s (0)	1.72 X 10^3 s (85)		< 7.3 X 10^1 s (100)	3.63 X 10^3 s (95)	1.91 X 10^2 s (100)	
Time Monitored Hydrolysis ( ) - 1 X 10^{-2} N DCl[2]	2.27 X 10^2 s (100)	6.63 X 10^4 s (75)		4.32 X 10^5 s (0)		< 3.12 X 10^2 s (100)		8.64 X 10^4 s (20)

1) 5 ml of 0.001N DCl/D_2O was added to 1 ml of ketal solution this gave an effective acid concentration of 0.0008N

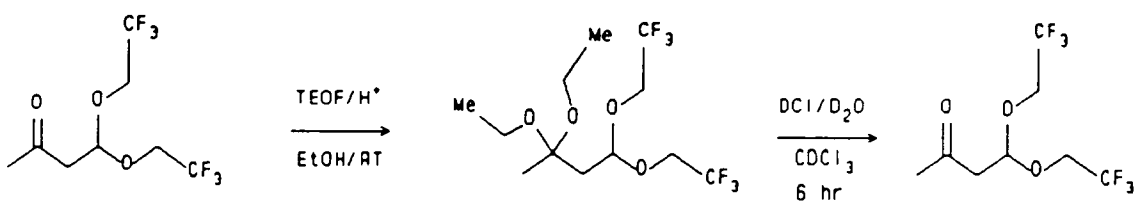
2) 1 ml of 0.02N DCl/D_2O was added to 1 ml of ketal solution this gave an effective acid concentration of 0.01N

The magnitude of the difference in the observed rates of hydrolysis for the two types of ketals is consistent with the information obtained in the LSR study. In each case, the ethyl ketals undergo complete hydrolysis many times faster than their TFE analogs. The general trend can be illustrated by examining the reaction rates of the two acetophenone derivatives. At an effective acid concentration of 0.0008 N DCl/CD_3CN, the times required for the hydrolysis of the TFE and diethyl ketals were ~45 min. and <2.0 min., respectively. In fact, the rate of hydrolysis in the later case may have been much less than 2.0 min., however, due to limitations in the experimental technique 2.0 min. is the minimum time lapse before analysis can begin.

The cyclohexyl case is also illustrative of the effect substitution of fluorine for hydrogen has on the reactivity of these compounds. In this instance, under the two sets of experimental conditions outlined, no hydrolysis of the TFE ketal takes place. In fact the acid concentration was raised to 0.01N DCl/CD_3CN before appreciable hydrolysis rates for the trifluoro substituted derivative were observed. In contrast, the ethyl analog reacts readily under the most mild acid conditions.

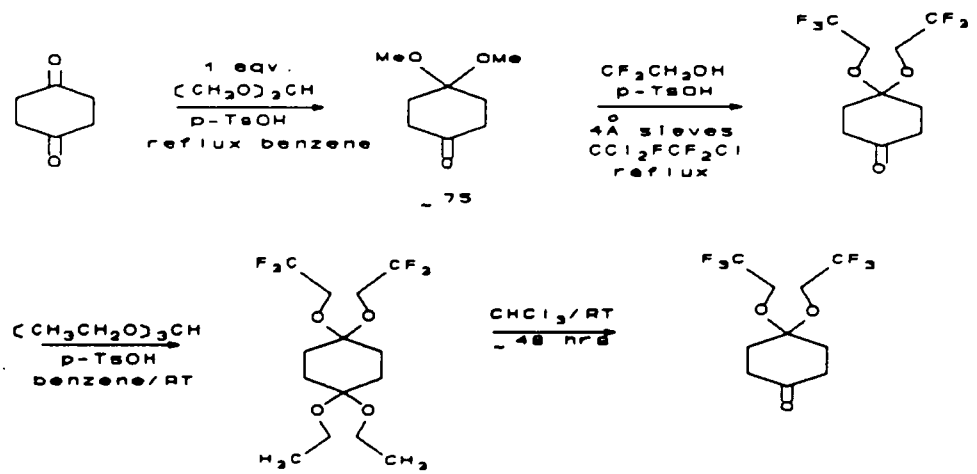
Protecting Group Study

The results from the hydrolysis study suggested a number of potential applications for TFE ketals. Of these, perhaps the most promising, involves the formation and/or removal of these functions in the presence of other types of ketal functionalities. This is made possible both by their method of preparation and their stable behavior towards acid environments. Appropriate use of these two properties could allow for the selective protection and/or deprotection of various sites within a structure possessing several carbonyl or potential carbonyl moieites. Toward this end, we have studied the selective introduction and removal of an ethyl ketal in the presence of the TFE functionality. Examples are outlined in schemes 2.5 and 2.6.



Scheme 2.5

In the first example, the β-keto trifluoroethylacetal was prepared from its methoxy analog under the previously described exchange conditions. The carbonyl functionality of this compound was next functionalized to its ethoxy derivative by reaction with triethylorthoformate (TEOF) and p-TsOH (catalytic) at room temperature to give the bis-acetal. The alkyl ketal was then removed quantitatively in the presence of the TFE moiety (selective deprotection) using a mineral acid catalyst.



Scheme 2.6

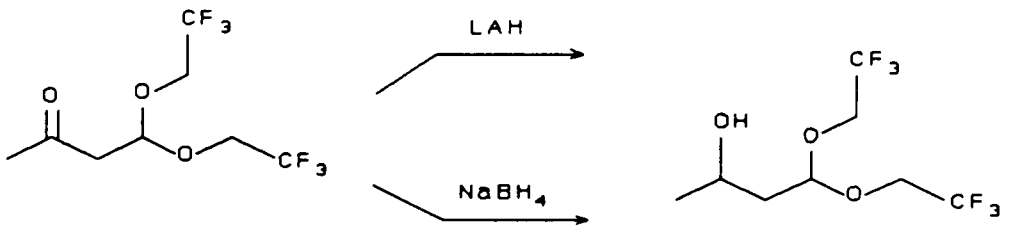
The reaction outlined in scheme 2.6 was carried out in order to determine the relative reactivities of the two types of ketals toward acid catalyzed hydrolysis in cases where they were prepared from structually identical precursors. In this experiment, the dione was converted to the monoketal by reaction with one equivalent of trimethylorthoformate (TMOF). Again exchange conditions were used to transform this compound into the trifluoroethyl mono-ketal. The ethyl functionality was introduced at the remaining carbonyl site under the conditions outlined to give the unsymmetrical bis-ketal. This structure was then converted back to its TFE mono-ketal precursor by acid catalyzed hydrolysis.

It should be emphasized that in both cases, the ethyl ketal functionality was introduced without loss or exchange of the trifluoroethoxy groups. This was also true for the deprotection step.

If TFE ketals are to find use as protecting groups, we felt it necessary to investigate their behavior towards reducing conditions as well as develop preparative conditions for their removal. Details relating to work in both of these areas are given below.

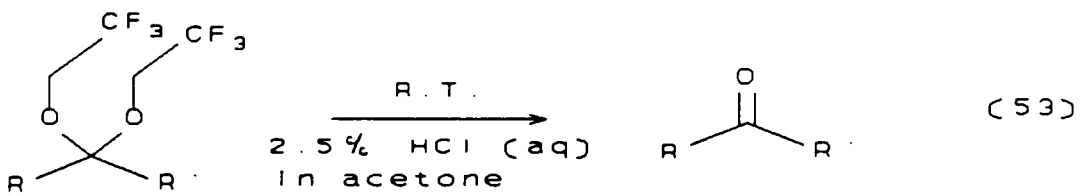
Equation 52 outlines the behavior of 4,4-bis(trifluoroethoxy)-2-butanone on treatment with $NaBH_4$ and $LiAlH_4$ respectively. In each instance, the protecting group

exhibited stability toward the reductive environment while the carbonyl functionality underwent clean reduction to the corresponding hydroxy group. This was not unexpected and is indicative of the general behavior exhibited by these compounds towards strong bases.



(52)

In order to remove these structures and regenerate the original carbonyl function, the hydrolytic conditions utilized by Nakanishi in his synthesis of the drimane sesquiterpene, Warburganal, were applied [167]. The reaction conditions are outlined in equation 53 while the experimental results are compliled in Table 2.8. In this case, the rate of hydrolysis of

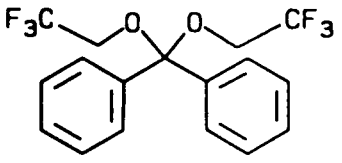
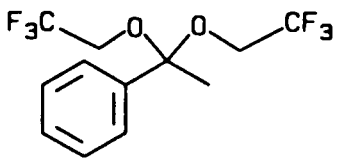
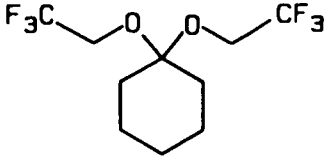
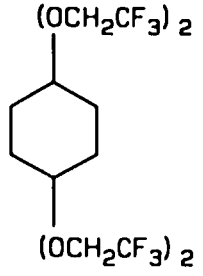


(53)

only the TFE ketals was examined.

As the results indicate, these conditions do allow for the quantitative removal of the TFE moiety. Rate differences observed between the various compounds can be explained on the basis of structual and/or electronic effects. In no instance was the time required for hydrolysis of unusual length. When used as a specific deprotection procedure, this general method can be adapted to the particular system under consideration in order to optimize results.

Table 2.8. Time Required for Hydrolysis of TFE Ketals using Nakanishi's Conditions[1]

Compound				
Time Monitored Hydrolysis ( )	8 hours (~ 60 %)	1 hour (100 %)	4 hours (100 %)	4 hours (100 %)

1) These hydrolysis reactions were carried out in 2.5 (aq) HCl in acetone at room temperature.

Summary

Our investigation of TFE ketals began with one specific goal : the development of these compounds as non-invasive LSR stable carbonyl protecting groups. However, as the properties exhibited by these structures became better realized, their applications : both potential and actual : rapidly increased. We have been able to show that TFE ketals are well suited to our original purpose. They neither react nor complex with LSR's therby increasing the number and types of applications involving shift reagents. In addition, it was found that TFE ketals also exhibited remarkable stability (relative to other types of ketals) towards acid catalyzed hydrolysis. This observation gave rise to the second and potentially most widespread application for these structures : acid stable carbonyl protecting groups. For example, we have shown that TFE ketals could be used to protect a carbonyl function in a compound which during subsequent reactions would be subject to acid conditions. The ability of these structures to withstand other types of harsh reaction conditions adds to their attractiveness. A second application we have addressed, also making use of the relative acid stabilities, involves selective protection and/or manipulation of carbonyl functions within a stucture possessing multiple carbonyl groups. Toward this end, we have developed the methodology for the selective introduction and removal of alkyl ketals in the presence of the TFE structure.

Although not exhausive, these applications illustrate the potential TFE ketals possess as organic functional groups. Now that the questions associated with both preparation and behavior have been addressed, these compounds should find wide use by organic chemists.

Experimental

Equipment. NMR data was obtained using either a Bruker WP-270 Spectrometer (^{1}H NMR 270 MHz/ ^{13}C NMR 67.5 MHz), a Bruker WP-200 Spectrometer (^{1}H NMR 200 MHz/ ^{13}C NMR 50 MHz), or a Bruker NR 80 Spectrometer (^{1}H NMR 80 MHz/ ^{13}C NMR 20 MHz). Samples were dissolved in either $CDCl_3$, deutero DMSO, or deutero acetonitrile. Chemical shifts are referenced to either TMS or residual solvent ^{1}H resonances. Solvents were dried as follows. Benzene, xylene, ethyl ether, and THF were distilled immediately prior to use from sodium metal. 1,1,2-trichlorotrifluoroethane (freon 112) was dried by passage through a short column of freshly activated neutral alumina. Methylene chloride was dried by distillation from P_2O_5. Elemental combustion analysis was carried out by Galbraith Laboratories Inc. Starting materials and reagents were obtained from commercial sources.

Attempted ketalization of benzophenone with CF_3CH_2OH under acidic conditions. Benzophenone (9.10 g, 0.05 moles) was placed into a 250 mL round bottomed flask. To this was added 2,2,2-trifluoroethanol (75.5 g, 0.76 moles) and p-toluenesulfonic acid monohydrate (0.20 g, 1.1 mmoles). On dissolution of the solid, the mixture turned a clear yellow color. The flask was fitted with a Soxhlet extractor and the cup was filled with ~ 70 g of freshly activated 3 Å molecular sieves. The mixture was brought to reflux. After ~ 18 hours, the molecular sieves were replaced with a freshly activated charge. Heating was continued for an additional 18 hours. During the course of the reaction, the solution remained a clear yellow color. After cooling, the product mixture was taken up in a quantity of methylene chloride. The organic layer was washed twice with 50 mL of 5% (aq) $NaHCO_3$, twice with 50 mL of H_2O, then dried over K_2CO_3. Evaporation of the solvent yielded a quantity of a yellow oil. ^{1}H NMR analysis indicated that this product was unreacted starting material. No ketal formation had occurred.

Preparation of Dimethyl and Diethyl Ketals

Preparation of Benzophenone Dimethyl Ketal. Benzophenone (50.0 g, 0.274 moles) was placed into solution in 140 mL of anhydrous methanol. To this was added trimethylorthoformate (48.7 g, 0.459 moles) and p-toluenesulfonic acid monohydrate (0.2 g, 1.05 mmoles). The reaction flask was fitted with a water cooled reflux condenser and a calcium sulfate drying tube. The solution was brought to reflux. After approximately 72 hours, heating was discontinued. After cooling, the product mixture was poured into a beaker where it solidified. This material was filtered to remove any residual liquid and the solids were washed several times with cold methanol. The desired product was separated from the unreacted starting material by recrystallization of the crude product mixture from ice-cold methanol (2 g product mixture/1 mL methanol). The pure ketal was recrystallized a final time from absolute ethanol. M.P. 106-108 °C uncorrected. The compound afforded the following spectroscopic data: ^{1}H NMR δ 7.50 (d, 4H, J = 8 Hz), 7.32 - 7.20 (br. m, 6 H), 3.13 (s, 6 H), ^{13}C NMR δ 142.41 (s), 127.94 (s), 127.40 (s), 126.91 (s), 102.86 (s), 49.26 (s).

Preparation of Benzophenone Diethyl Ketal. Benzophenone (27.3 g, 0.150 moles) was placed into solution in 60 mL absolute ethanol. To this was added triethylorthoformate (30.5 g, 0.206 moles) and p-toluenesulfonic acid monohydrate (0.2 g, 1.05 mmoles). The reaction flask was fitted with a water cooled reflux condenser and a calcium sulfate drying tube. The solution was brought to reflux. After approximately 30 hours, heating was discontinued. Sodium ethoxide was added to the cooled product mixture to neutralize any residual acid. Low boiling components were removed from the product mixture by rotary evaporation. Following this step, the remaining material was taken up in CH_2Cl_2 and water soluble by-products were removed by washing several times with H_2O. The organic layer was dried over K_2CO_3 and any residual low boiling components were removed in VACUO. The desired compound, benzophenone diethyl ketal, was separated from the product mixture by

chromatography on freshly activated neutral alumina (EM Reagents, activity I) using 100% hexane as the eluent. The compound afforded the following spectroscopic data: ^{1}H NMR δ 7.53 (d, 4H, J = 6 Hz), 7.29 - 7.18 (br. m, 6H), 3.32 (q, 4H, J = 7 Hz), 1.21 (t, 6H, J = 7 Hz). ^{13}C NMR δ 143.41 (s), 127,86 (s), 127,24 (s), 126.85 (s), 102.16 (s), 57.08 (s), 15.12 (s).

Preparation of Cyclohexanone Dimethyl Ketal. Cyclohexanone (98.2 g, 1.0 moles) was placed into solution in 160 mL of anhydrous methanol. To this was added trimethylorthoformate (132.8 g, 1.25 moles) and p-toluenesulfonic acid monohydrate (0.95 g, 4.99 mmoles). The reaction flask was fitted with a water cooled reflux condenser and a calcium sulfate drying tube. The solution was brought to reflux. After approximately 13 hours heating was discontinued. The product mixture was neutralized with sodium methoxide and residual solids were removed by filtration. The product mixture was dried over $MgSO_4$ and low boiling components (b.p. $\leq$ 70 °C) were removed by fractional distillation. The remaining product was taken up in CH_2Cl_2 and washed twice with 25 mL portions of H_2O to remove any water soluble by-products. The organic was dried over $MgSO_4$ and volatiles were removed in VACUO. The desired ketal product was isolated in its pure form by vacuum distillation. B.P. 86-88 °C @ 50 mm Hg. The compound afforded the following spectroscopic data: ^{1}H NMR δ 3.09 (s, 6H), 1.55 - 1.29 (br. m, 10H). ^{13}C NMR δ 99.86 (s), 47.16 (s), 32.70 (s), 25.59 (s), 22.77 (s).

Preparation of Cyclohexanone Diethyl Ketal. Cyclohexanone (24.5 g, 0.25 moles) was placed into solution in 60 mL of absolute ethanol. To this was added triethylorthoformate (44.5 g, 0.30 moels) and p-toluenesulfonic acid monohydrate (0.25 g, 1.31 mmoles). The reaction flask was fitted with a water reflux cooled condenser and a calcium sulfate drying tube. The solution was brought to reflux. After approximately 9 hours heating was discontinued. Sodium ethoxide was added to the cooled product mixture to neutralize any residual acid. Solids were removed by filtration and the product mixture was washed twice with 25 mL portions of H_2O to remove any water soluble by-products. The

organic layer was dried over K_2CO_3 and volatiles were removed in VACUO. The desired ketal product was isolated by distillation. The first step of this process involved distillation at atmospheric pressure to remove any residual ethanol. The second step was a distillation at reduced pressure to yield the pure product. B.P 74-75 °C @ 16 mm Hg. The compound afforded the following spectroscopic data: ^{1}H NMR δ 3.43 (q, 4H, J = 7 Hz), 1.64 - 1.28 (br. m, 10 H), 1.14 (t, 6H, J = 7 Hz). ^{13}C NMR δ 100.37 (s), 55.20 (s), 34.32 (s), 26.13 (s), 23.48 (s), 15.98 (s).

Preparation of Acetophenone Dimethyl Ketal. Acetophenone (16.2 g, 0.135 moles) was placed into solution in 24 mL of anhydrous methanol. To this was added trimethylorthoformate (22.2 g, 0.210 moles) and concentrated HCl (6 drops). The reaction flask was fitted with a water cooled reflux condenser and a calcium sulfate drying tube. The solution was brought to reflux. After approximately 72 hours heating was discontinued. After cooling the product mixture was made basic using sodium methoxide. The solids were removed by filtration and MeOH was removed by rotary evaporation. The desired ketal product was isolated by distillation of the product mixture at reduced pressure. B.P. 96-98 °C @ 18 mm Hg. The compound afforded the following spectroscopic data: ^{1}H NMR δ 7.48 (d, 2H, J = 7 Hz), 7.33 - 7.28 (br. m, 3H), 3.17 (s, 6H), 1.52 (s, 3H). ^{13}C NMR δ 142.79 (s), 127.80 (s), 127.26 (s), 126.07 (s), 101.39 (s), 48.55 (s), 25.82 (s).

Preparation of Acetophenone Diethyl Ketal. Acetophenone (18.0 g, 0.15 moles) was placed into solution in 60 mL of absolute ethanol. To this was added triethylorthoformate (31.5 g, 0.213 moles) and p-toluenesulfonic acid monohydrate (0.2 g, 1.05 momoles). The reaction flask was fitted with a water cooled reflux condenser and a calcium sulfate drying tube. The solution was brought to reflux. After approximately 28 hours heating was discontinued. Sodium ethoxide was added to the cooled product mixture to neutralize any residual acid. Solids were removed by filtration and ethanol was removed in VACUO. The desired ketal product was isolated from the product mixture by distillation at reduced

pressure. B.P. 100-101 °C @ 16 mm Hg. The compound afforded the following spectroscopic data: ^{1}H NMR δ 7.53 (d, 2H, J = 8 Hz), 7.37 - 7.26 (br. m, 3H), 3.52 - 3.32 (br. m, 4H), 1.56 (s, 3H), 1.22 (t, 6H, J = 7 Hz). ^{13}C NMR δ 143.81 (s), 127.80 (s), 127.19 (s), 126.06 (s), 101.07 (s), 56.46 (s), 26.00 (s), 15.20 (s).

Acetone dimethyl ketal was obtained commercially from Aldrich Chemical Company. The compound afforded the following spectroscopic data: ^{1}H NMR δ 3.18 (s, 6H), 1.32 (s, 6H). ^{13}C NMR δ 99.60 (s), 47.89 (s), 23.62 (s).

Preparation of acetone diethyl ketal. Acetone (14.5 g, 0.25 moles) was placed into soltuion in 60 mL of absolute ethanol. To this was added triethylorthoformate (44.5 g, 0.30 moles) and p-toluenesulfonic acid monohydrate (0.2 g, 1.05 mmoles). The reaction flask was fitted with a water cooled reflux condenser and a calcium sulfate drying tube. The solution was brought to reflux. After approximately 15 hours heating was discontinued. Sodium ethoxide was added to the cooled product mixture to neutralize any residual acid. Solid impurites were removed by filtration. The desired ketal product was isolated by distillation at reduced pressure. B.P. 44-45 °C 60 mm Hg. The compound afforded the following spectroscopic data: ^{1}H NMR δ 3.45 (q, 4H, J = 7.1 Hz), 1.33 (s, 6H), 1.14 (t, 6H, J = 7.1 Hz). ^{13}C NMR δ 99.58 (s), 55.83 (s), 24.97 (s), 15.51 (s).

Preparation of Trifluoroethyl Ketals

Preparation of Benzophenone-2,2,2-bis(trifluoroethyl) Ketal. Benzophenone dimethyl ketal (1.0 g, 4.39 mmoles) was added to a 100 mL, 3 necked, round bottomed flask containing approximately 60 mL of CF_2ClCCl_2F (freon 112) which was dried just prior to use. The reaction flask was fitted with a Soxhlet extractor which contained ~ 70 g of freshly activated 4Å molecular sieves. A water cooled reflux condenser and an ice/H_2O cooled condenser were place in series with the Soxhlet. The reaction was carried out under an N_2 atmosphere. The reaction mixture was brought to reflux. After a short period of time, the

cup of the Soxhlet filled with liquid and material began returning to the reaction flask. At this time, 2,2,2-trifluoroethanol (13.8 g, 0.137 moles) was added rapidly to the reaction mixture. Immediately following this, p-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmoles) was also added. Aliquots were removed periodically and analyzed by ^{1}H NMR. The reaction was allowed to proceed until this analysis indicated that the entire amount of benzophenone dimethyl ketal had been converted to either its trifluoroethyl analog or the starting ketone. The reaction time averaged between 12 and 24 hours. The product mixture was treated as follows. After cooling, the solution was taken up in approximately 50 mL of CH_2Cl_2. It was washed twice with 25 mL portions of 5% (aq.) NaOH followed by two washings with 25 mL portions of H_2O. The organic layer was dried over K_2CO_3 and volatiles were removed in VACUO, to leave a crude product mixture consisting of the trifluoroethyl ketal and its parent ketone. Separation of the ketal product from the undesired carbonyl compound was accomplished by chromatography on freshly activated neutral alumina (EM Reagents Neutral Alumina Oxide 90 Active) using 95:5, hexane:CH_2Cl_2 as the eluting solvent. The compound afforded the following spectroscopic data: ^{1}H NMR δ 7.50 (d, 4H, J = 8 Hz), 7.38 - 7.29 (br. m, 6H), 3.67 (q, 4H, J = 8.6 Hz). ^{13}C NMR δ 139.59 (s), 128.84 (s), 128.65 (s), 124.23 (q, $^1J_{CF}$ = 276 Hz), 103.72 (s), 60.60 (q, $^2J_{CF}$ = 37 Hz). Elemental analysis: Theory 56.04 % C, 3.87 % H. Found 56.01 % C, 4.05 % H.

Preparation of Cyclohexanone-2,2,2-bis(trifluoroethyl) Ketal. Cyclohexanone dimethyl ketal (1.0 g, 6.94 mmoles) was added to a 100 mL, 3 necked, round bottomed flask containing approximately 75 mL of CF_2ClCCl_2F (freon 112) which was dried just prior to use. The reaction flask was fitted with a Soxhlet extractor which contained ~ 70 g of freshly activated 4Å molecular sieves. A water cooled reflux condenser and an ice/H_2O cooled condenser were place in series with the Soxhlet. The reaction was carried out under an N_2 atmosphere. The reaction mixture was brought to reflux. After a short period of time, the cup of the Soxhlet filled with liquid and material began returning to the reaction flask. At

this time, 2,2,2-trifluoroethanol (7.4 g, 0.074 moles) was added rapidly to the reaction mixture. Immediately following this, p-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmoles) was also added. Aliquots were removed periodically and analyzed by ^1H NMR. The reaction was allowed to proceed until this analysis indicated that the entire amount of cyclohexanone dimethyl ketal had been converted to either its trifluoroethyl analog or the starting ketone. The reaction time averaged between 12 and 24 hours. The product mixture was treated as follows. After cooling, the solution was taken up in approximately 50 mL of CH_2Cl_2. It was washed twice with 25 mL portions of 5% (aq.) NaOH followed by two washings with 25 mL portions of H_2O. The organic layer was dried over K_2CO_3 and volatiles were removed in VACUO, to leave a crude product mixture consisting of the trifluoroethyl ketal and its parent ketone. Separation of the ketal product from the undesired carbonyl compound was accomplished by chromatography on freshly activated neutral alumina (EM Reagents Neutral Alumina Oxide 90 Active) using 100% hexane as the eluting solvent. The compound afforded the following spectroscopic data: ^1H NMR δ 3.81 (q, 4H, J = 8.7 Hz), 1.68 - 1.40 (br. m, 10H). ^{13}C NMR δ 124.67 (q, $^1J_{CF}$ = 276 Hz), 102.48 (s), 59.22 (q, $^2J_{CF}$ = 35 Hz), 33.56 (s), 25.44 (s), 23.01 (s). Elemental analysis: Theory 42.86 % C, 5.05 % H, actual 42.44 % C, 4.92 % H.

Preparation of Acetophenone-2,2,2-bis(trifluoroethyl) Ketal. Acetophenone dimethyl ketal (0.97 g, 5.83 mmoles) was added to a 100 mL, 3 necked, round bottomed flask containing approximately 75 mL of CF_2ClCCl_2F (freon 112) which was dried just prior to use. The reaction flask was fitted with a Soxhlet extractor which contained ~ 70 g of freshly activated 4Å molecular sieves. A water cooled reflux condenser and an ice/H_2O cooled condenser were place in series with the Soxhlet. The reaction was carried out under an N_2 atmosphere. The reaction mixture was brought to reflux. After a short period of time, the cup of the Soxhlet filled with liquid and material began returning to the reaction flask. At this time, 2,2,2-trifluoroethanol (11.0 g, 0.110 moles) was added rapidly to the reaction

mixture. Immediately following this, p-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmoles) was also added. Aliquots were removed periodically and analyzed by ^1H NMR. The reaction was allowed to proceed until this analysis indicated that the entire amount of acetophenone dimethyl ketal had been converted to either its trifluoroethyl analog or the starting ketone. The reaction time averaged between 12 and 24 hours. The product mixture was treated as follows. After cooling, the solution was taken up in approximately 50 mL of CH_2Cl_2. It was washed twice with 25 mL portions of 5% (aq.) NaOH followed by two washings with 25 mL portions of H_2O. The organic layer was dried over K_2CO_3 and volatiles were removed in VACUO, to leave a crude product mixture consisting of the trifluoroethyl ketal and its parent ketone. Separation of the ketal product from the undesired carbonyl compound was accomplished by chromatography on freshly activated neutral alumina (EM Reagents Neutral Alumina Oxide 90 active) using 100% hexane as the eluting solvent. The compound afforded the following spectroscopic data: ^1H NMR δ 7.51 (d, 2H, J = 6 Hz), 7.39 - 7.24 (br. m, 3H), 3.86 - 3.72 (br. m, 4H), 1.66 (s, 3H). ^{13}C NMR δ 139.90 (s), 128.80 (s), 128.65 (s), 126.07 (s), 124.19 (q, $^1J_{CF}$ = 276 Hz), 103.02 (s), 59.69 (q, $^2J_{CF}$ = 37 Hz), 26.30 (s). Elemental analysis: Theory 47.68 % C, 4.01 % H, Found 47.64 %, 4.09 % H.

Preparation of acetone-2,2,2-bis(trifluoroethyl) ketal. Acetone dimethyl ketal (1.0 g, 0.62 mmoles) was added to a 100 mL, 3 necked, round bottomed flask containing approximately 75 mL of CF_2ClCCl_2F (freon 112) which was dried just prior to use. The reaction flask was fitted with a Soxhlet extractor which contained ~ 70 g of freshly activated 4Å molecular sieves. A water cooled reflux condenser and an ice/H_2O cooled condenser were place in series with the Soxhlet. The reaction was carried out under an N_2 atmosphere. The reaction mixture was brought to reflux. After a short period of time, the cup of the Soxhlet filled with liquid and material began returning to the reaction flask. At this time, 2,2,2-trifluoroethanol (6.9 g, 0.069 moles) was added rapidly to the reaction mixture. Immediately following this, p-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmoles) was also added.

Aliquots were removed periodically and analyzed by ^1H NMR. The reaction was allowed to proceed until this analysis indicated that the entire amount of acetone dimethyl ketal had been converted to either its trifluoroethyl analog or the starting ketone. The reaction time averaged between 12 and 24 hours. The product mixture was treated as follows. After cooling, the solution was taken up in approximately 50 mL of CH_2Cl_2. It was washed twice with 25 mL portions of 5% (aq.) NaOH followed by two washings with 25 mL portions of H_2O. The organic layer was dried over K_2CO_3 and volatiles were removed in VACUO, to leave a crude product mixture consisting of the trifluoroethyl ketal and the parent ketone. Separation of the ketal product from the undesired carbonyl component was accomplished by distillation at atmospheric pressure. B.P. 109-110 °C. The compound afforded the following spectroscopic data: ^1H NMR δ 3.82 (q, 4H, J = 8.6 Hz), 1.43 (s, 6H). ^{13}C NMR δ 124.15 (q, $^1J_{CF}$ = 277 Hz), 101.93 (s), 59.70 (q, $^2J_{CF}$ = 34 Hz), 24.14 (s). Elemental analysis: Theory 35.00 % C, 4.21 % H, Found 35.08 % C, 4.46 % H.

Lanthanide Shift Reagent Study of Ethyl and Trifluoroethyl Ketals

Sample Preparation. The ketones used in this study were all available from commercial sources. Purification, if required, was carried out by standard procedures. The ethyl and TFE ketals were prepared as described previously in this chapter. Spectroscopic data for these compounds is reported vide supra. Stock solutions for each of the compounds studied as well as $Eu(fod)_3$ were prepared using $CDCl_3$ as the solvent. The concentration of each solution is reported in table 2.9.

$Eu(fod)_3$ Studies. The experiment was conducted as follows. 0.4 mL of the stock solution of a given compound was placed into a 5.0 mm NMR tube. The ^1H NMR of this solution was recorded. To this solution were added incremental amounts of the $Eu(fod)_3$ stock solution (0.01 mL or multiples thereof). After each addition the ^1H NMR of the sample solution was recorded. Information gathered in this manner was used to determine the extent of complexation the various types of compounds undergo with $Eu(fod)_3$. The individual experiments are grouped according to structure and are outlined below.

$Eu(fod)_3$ Studies of Acetone and its Ethyl and TFE Analogs. $Eu(fod)_3$ was added incrementally to the stock solution of acetone and its ketal analogs. Table 2.3 lists the chemical shifts of the α-methyl protons of each of these compounds as a function of added shift reagent.

$Eu(fod)_3$ Studies of Acetophenone and its Ethyl and TFE Analogs. $Eu(fod)_3$ was added incrementally to the stock solution of acetophenone and its ketal analogs. Table 2.4 reports the chemical shifts for the α-methyl protons of each of these compounds as a function of added shift reagent.

$Eu(fod)_3$ Studies of the Ethyl and TFE Ketals of Cyclohexanone. $Eu(fod)_3$ was added incrementally to the stock solutions of the ethyl and TFE ketals of cyclohexanone. Table 2.5 lists the chemical shifts for the ketal methylene protons of each of these compounds as a

function of added shift reagents.

$Eu(fod)_3$ Studies of the Ethyl and TFE Ketals of Acetone. $Eu(fod)_3$ was added incrementally to stock solutions of the ethyl and TFE ketals of acetone. Table 2.6 reports the chemical shifts for the ketal methylene protons of each of these compounds as a function of added shift reagents.

Table 2.9. **Concentrations of the Stock Solutions Used in the Lanthanide Shift Reagent Study.**

Compound	Solvent	Concentration
$Eu(fod)_3$	CD_3Cl	6.0×10^{-3} M
Benzophenone	CD_3Cl	1.49×10^{-2} M
Benzophenone diethyl ketal	CD_3Cl	1.50×10^{-2} M
Benzophenone bis(trifluoroethyl) ketal	CD_3Cl	1.50×10^{-2} M
Acetophenone	CD_3Cl	1.46×10^{-2} M
Acetonphenone diethyl ketal	CD_3Cl	1.47×10^{-2} M
Acetophenone bis(trifluoroethyl) ketal	CD_3Cl	1.51×10^{-2} M
Cyclohexanone	CD_3Cl	1.55×10^{-2} M
Cyclohexanone diethyl ketal	CD_3Cl	1.42×10^{-2} M
Cyclohexanone bis(trifluoroethyl) ketal	CD_3Cl	1.53×10^{-2} M
Acetone	CD_3Cl	1.5×10^{-2} M
Acetone diethyl ketal	CD_3Cl	1.61×10^{-2} M
Acetone bis(trifluoroethyl) ketal	CD_3Cl	1.45×10^{-2} M

Ketal Hydrolysis: Comparative Study

Sample Preparation. The ethyl and trifluoroethyl ketals used in this study were prepared according to the procedures outlined earlier in this chapter. The ketones used for comparative purposes were obtained from commercial sources. The experiments described in this section were conducted using either CD_3CN or d_6-DMSO as solvent and spectroscopic data obtained for each compound in the appropriate solvent is listed in Appendix II. Stock solutions of each ketone and its ketal derivatives were prepared using either CD_3CN or d_6-DMSO as solvent and information relating to their concentrations can be found in Table 2.10. The acid catalyst, DCl (obtained as a 37% w/w solution in D_2O), was also prepared as a stock solution in CD_3CN and d_6-DMSO.

Hydrolysis Study. The general experiment was conducted as follows. The percent of ketal hydrolysis as a function of time was determined at two different acid concentrations. In the first set of experiments, each of the 4 pairs of ethyl and TFE ketals were added to a solution which was approximately 0.0008 N in acid, The percent hydrolysis at a given time was determined using ^1H NMR (for a discussion of this technique see pg.). The actual experiment involved adding 1.0 mL of a 0.001 N DCl stock solution to 5.0 mL of the ketal stock solution, swirling for 15 seconds, and placing a 1.0 mL aliquot of this mixture into a 5 mm NMR tube for analysis. The elapsed time to a given measurement was calculated from the moment 1/2 the acid catalyst had been added to the ketal solution. The operations involved in preparing the sample for NMR analysis account for the delay prior to data collection. The method of analysis also accounts for the use of deuterated reagents in the experiments. The second set of experiments were conducted in an identical fashion except that the solution was approximately 0.01N in acid. This was accomplished by adding 1.0 mL of a 0.02 N DCl stock solution to 1.0 mL of the ketal stock solution. In each case, an excess of acid was present.

Hydrolysis of benzophenone diethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in CD_3CN was added to 5.0 mL of a 4.1 X 10^{-3} M solution of benzophenone diethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of benzophenone trifluoroethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in CD_3CN was added to 5.0 mL of a 2.7 X 10^{-3} M solution of benzophenone trifluoroethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of acetophenone diethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in CD_3CN was added to 5.0 mL of a 7.5 X 10^{-3} M solution of acetophenone diethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of acetophenone trifluoroethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in CD_3CN was added to 5.0 mL of a 2.5 X 10^{-3} M solution of acetophenone trifluoroethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of cyclohexanone diethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in d_6-DMSO was added to 5.0 mL of a 4.4 X 10^{-3} M solution of cyclohexanone diethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The

percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of cyclohexanone trifluoroethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in d_6-DMSO was added to 5.0 mL of a 4.0 X 10^{-3} M solution of cyclohexanone trifluoroethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of acetone diethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in d_6-DMSO was added to 5.0 mL of a 7.2 X 10^{-3} M solution of acetone diethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of acetone trifluoroethyl ketal at 0.0008 N acid concentration. 1.0 mL of a 1.0 X 10^{-3} N solution of DCl in d_6-DMSO added to 5.0 mL of a 3.8 X 10^{-3} M solution of acetone trifluoroethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of benzophenone diethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in CD_3CN was added to 1.0 mL of a 4.1 X 10^{-3} M solution of benzophenone diethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of benzophenone trifluoroethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in CD_3CN was added to 1.0 mL of a 2.7 X 10^{-3} M solution of benzophenone trifluoroethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL

aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of acetophenone diethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in CD_3CN was added to 1.0 mL of a 7.5 X 10^{-3} M solution of acetophenone diethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of acetophenone trifluoroethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in CD_3CN was added to 1.0 mL of a 2.5 X 10^{-3} M solution of acetophenone trifluoroethyl ketal in CD_3CN. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of cyclohexanone diethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in d_6-DMSO was added to 1.0 mL of a 4.4 X 10^{-3} M solution of cyclohexanone diethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of cyclohexanone trifluoroethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in d_6-DMSO was added to 1.0 mL of a 4.0 X 10^{-3} M solution of cyclohexanone trifluoroethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7

Hydrolysis of acetone diethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in d_6-DMSO was added to 1.0 mL of a 7.2 X 10^{-3} M solution of acetone diethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Hydrolysis of acetone trifluoroethyl ketal at 0.01 N acid concentration. 1.0 mL of a 2.0 X 10^{-2} N solution of DCl in d_6-DMSO was added to 1.0 mL of a 3.8 X 10^{-3} M solution of acetone trifluoroethyl ketal in d_6-DMSO. After swirling 15 seconds a 1.0 mL aliquot of this mixture was placed in a 5 mm NMR tube and spectroscopic analysis was carried out. The percent of ketal hydrolysis as a function of time for this compound is recorded in table 2.7.

Table 2.10. Concentrations of the Stock Solutions Used in the Ketal Hydrolysis Study.

Compound	Solvent	Concentration
DCl (37% by weight in D_2O)	CD_3CN	1.98×10^{-2} M
DCl (37% by weight in D_2O)	CD_3CN	9.9×10^{-4} M
Benzophenone bis(trifluoroethyl) ketal	CD_3CN	2.7×10^{-3} M
Benzophenone diethyl ketal	CD_3CN	4.1×10^{-3} M
Acetophenone bis(trifluoroethyl) ketal	CD_3CN	2.5×10^{-3} M
Acetophenone diethyl ketal	CD_3CN	7.5×10^{-3} M
DCl (37% by weight in D_2O)	d_6-DMSO	2.0×10^{-2} M
DCl (37% by weight in D_2O)	d_6-DMSO	1.0×10^{-3} M
Cyclohexanone bis(trifluoroethyl) ketal	d_6-DMSO	4.0×10^{-3} M
Cyclohexanone diethyl ketal	d_6-DMSO	4.4×10^{-3} M
Acetone bis(trifluoroethyl) ketal	d_6-DMSO	3.8×10^{-3} M
Acetone diethyl ketal	d_6-DMSO	7.2×10^{-3} M

Ketal Hydrolysis: Preparative Study

Sample Preparation. The trifluoroethyl ketals of benzophenone, acetophenone, and cyclohexanone used in this study were prepared according to the procedures outlined earlier in this chapter. The bis(trifluoroethyl) ketal of 1,4-cyclohexanedione was formed as a by-product during the preparation of the mono-trifluoroethoxy ketal of this compound. Conditions relating to its formation and isolation can be found in the section which describes the use of TFE ketals as a protecting group.

Hydrolysis Study. The general experiment was conducted as follows. Each of the compounds under study was weighed into a 10 mL , one necked round bottom flask. To the flask was added 4.0 mL of a solution consisting of 3.4 mL of reagent grade HCl (37% (aq)) in 46.6 mL of spectral grade acetone (this gives a solution which is 2.5% HCl (aq) in acetone). These mixtures were allowed to stir at room temperature with 1.0 mL aliquots being removed periodically for analysis by ^{1}H NMR. For the 3 monoketals utilized in this study, the percent of hydrolysis at any time, t_i, was determined by the methods outlined in the previous section. The rate of hydrolysis for the bis(trifluoroethyl) ketal of 1,4-cyclohexanedione was determined by following the chemical shift changes in the protons at the 2, 3, 5, and 6 positions on the ring. Prior to analysis, aliquots were quenched with a 5% (aq) $NaHCO_3$ solution.

Hydrolysis of benzophenone trifloroethyl ketal using 2.5% HCl (aq) in acetone. Benzophenone trifluoroethyl ketal (0.103 g, 0.28 mmoles) was weighed into a 10 mL, round bottomed flask. 4.0 mL of 2.5% HCl (aq) in acetone was added and the resulting mixture was allowed to stir at room temperature. Periodically, 1.0 mL aliquots were removed, neutralized with 5% (aq) $NaHCO_3$, and analyzed by ^{1}H NMR. The results of this anlysis are given in Table 2.8.

Hydrolysis of acetophenone trifluoroethyl ketal using 2.5% HCl (aq) in acetone. Acetophenone trifluoroethyl ketal (0.100 g, 0.33 mmoles) was weighed into a 10 mL, round

bottomed flask. 4.0 mL of 2.5% HCl (aq) in acetone was added and the resulting mixture was allowed to stir at room temperature. Periodically, 1.0 mL aliquots were removed, neutralized with 5% (aq) $NaHCO_3$, and analyzed by ^1H NMR. The results of this anlysis are given in Table 2.8.

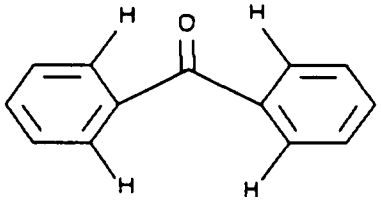
Hydrolysis of cyclohexanone trifluoroethyl ketal using 2.5% HCl (aq) in acetone. Cyclohexanone trifluoroethyl ketal (0.096 g, 0.34 mmoles) was weighed into a 10 mL, round bottomed flask. 4.0 mL of 2.5% HCl (aq) in acetone was added and the resulting mixture was allowed to stir at room temperature. Periodically, 1.0 mL aliquots were removed, neutralized with 5% (aq) $NaHCO_3$, and analyzed by ^1H NMR. The results of this anlysis are given in Table 2.8.

Hydrolysis of 1,4-cyclohexanedione bis(trifluoroethyl) ketal using 2.5% HCl (aq) in acetone. 1,4-cyclohexanedione bis(trifluoroethyl) ketal (0.095 g, 0.20 mmoles) was weighed into a 10 mL, round bottomed flask. 4.0 mL of 2.5% HCl (aq) in acetone was added and the resulting mixture was allowed to stir at room temperature. Periodically, 1.0 mL aliquots were removed, neutralized with 5% (aq) $NaHCO_3$, and analyzed by ^1H NMR. The results of this anlysis are given in Table 2.8.

Determination of Percent Hydrolysis by ^{1}H NMR

The rates of hydrolysis for the ethyl and trifluoroethyl ketals examined in this series of experiments were determined using ^{1}H NMR. Although the proton resonances monitored during the course of a given reaction were dictated by the general structure of the compound involved, the methods used for analogous structures were identical. For example, in determining the relative rates of hydrolysis for the ethyl and TFE ketals of acetophenone, the same peak (or sets of peaks) were used to provide analytical data on both starting materials and products (ketals and ketones). Outlined below are the procedures used to accomplish this for each of the four cases.

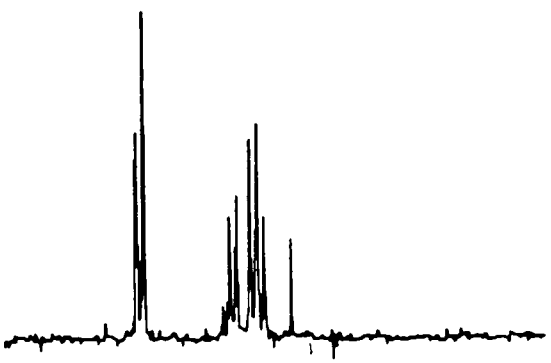
Determination percent hydrolysis for the diethyl and trifluoroethyl ketals of benzophenone. For these compounds, the percent hydrolysis at any time, t_i, was determined as follows. The parent carbonyl structure for these compounds, benzophenone, exhibits 3 separate sets of peaks in the aromatic region (7 - 8 ppm) of its ^{1}H NMR spectra. The set of peaks farthest down field correspond to the 4 protons attached to sites adjacent to the carbonyl function (Scheme 2.7).



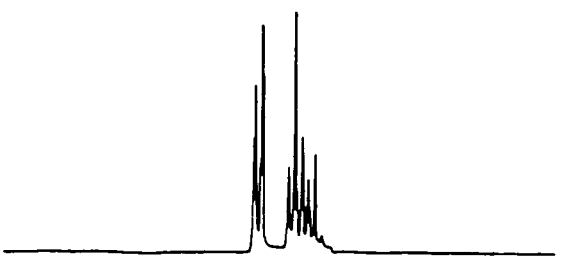
The 4 protons associated with the downfield resonances

Scheme 2.7

The 6 remaining aromatic protons correspond to the upfield peaks. On derivatization to the ketal structure (ethyl or trifluoroethyl), the signal from the 4 downfield protons merges with that of the 6 upfield protons to give a broad multiplet corresponding to all aromatic protons (10) in the respective compounds (Scheme 2.8).



^{1}H Aromatic Region: Ketone



^{1}H Aromatic Region: Ketal

Scheme 2.8

The percent hydrolysis in this system was determined as follows:

1) integrated values for those peaks corresponding to the ortho-protons of the hydrolysis product (the carbonyl containing compound) are determined.

2) This value is multiplied by 2.5 and subtracted from the integration value determined for all other aromatic protons in the hydrolysis mixture.

3) This first value is then divided by the sum of itself and the value obtained by the subtraction performed above. This result corresponds to the amount of hydrolysis product (relative to starting ketal) which is present in the mixture at the time of ^{1}H NMR analysis.

Determination of percent hydrolysis for the diethyl and trifluoroethyl ketals of acetophenone. For these compounds the percent hydrolysis at any time, t_i, was determined in a manner identical to that used in the benzophenone case.

Determination of percent hydrolysis for the diethyl and trifluoroethyl ketals of acetone. For these compounds, the percent hydrolysis at any time, t_i, was determined as follows. The ^1H NMR signal for the methyl groups α to either the carbonyl center or the ketal center have characteristic and separate chemical shifts. The percent of hydrolysis product present in the mixture of starting ketal and product ketone can be determined by dividing the integration value obtained for the peak corresponding to the carbonyl α methyl protons by the sum of this same value and the integration value obtained for the peak corresponding to the ketal (either ethyl or TFE) α methyl protons.

Determination of percent hydrolysis for the diethyl and trifluoroethyl ketal of cyclohexanone. For these compounds, the percent hydrolysis at any time, t_i, was determined as follows. The ^1H chemical shifts for cyclohexanone fall in two regions. One set of signals, corresponding to the 4 protons α to the carbonyl function, are found as a multiplet at ~ 2.3 ppm relative to TMS. The second set, also in the form of a broad multiplet, and corresponding to the remaining 6 ring protons, lie in the region 1.7 to 2.0 ppm. As with the previous cases, on derivatization to the ketal structure, the downfield signals shift upfield and merge with the second set of resonances. The percent hydrolysis in this system was determined as follows:

1) integrated values for those peaks corresponding to the α carbonyl protons of the hydrolysis product (ketone) were determined.
2) this value is multiplied by 2.5 and subtracted from the integrated value determined for all other ^1H resonance in the hydrolysis mixture.
3) This first value is then divided by the sum of itself and the value obtained by the subtraction performed above. This result corresponds to the amount of hydrolysis product (relative to starting ketal) which is present in the mixture at the time of ^1H NMR analysis.

Study of Bis(trifluoroethoxy) Ketals as Protecting Groups

Preparation of 4,4-bis(trifluoroethoxy)-2-butanone. 4,4-dimethoxy-2-butanone (30.0 g, 0.23 moles), CF_3CH_2OH (82.4 g, 0.83 moles) and CCl_2FCF_2Cl ~ 300 mL (dried just prior to use), were mixed together in a 500 mL, 3 necked, round bottomed flask. This flask was fitted with a N_2 inlet and a Soxhlet extraction apparatus, which had been filled with ~ 100 g of freshly activated 4 Å molecular sieves. P-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmoles) was added and the reaction mixture was brought to reflux. After ~ 72 hours, heat was removed and the solution (which had turned a dark blue color) was allowed to cool to room temperature. This product mixture was taken up in a quantity of CH_2Cl_2 and washed several times with 5% (aq) NaOH to removed any residual acid. The organic layer was then washed several times with H_2O and dried over K_2CO_3. Volatiles were removed in VACUO to leave a brown colored oil. This material was distilled at reduced pressure to yield the desired product. This material was a clear liquid. B.P. 62 - 63 °C @ 4 mm Hg. The compound afforded the following spectroscopic data: ^1H NMR δ 5.19 (t, 1H, J = 6 Hz), 3.93 (q, 4H, J = 8 Hz), 2.83 (d, 2H, J = 6 Hz), 2.18 (s, 3H). Elemental Analysis: Theory 35.83% C, 3.76% H. Found 35.81% C, 3.32 % H.

Preparation of 2,2-diethoxy-4,4-bis(trifluoroethoxy)-butane. To 4,4-bis(trifluoroethoxy)-2-butanone (0.27 g, 1.0 mmoles) was added 10 mL of absolute ethanol. This mixture was placed into a 25 mL, 1 necked round bottomed flask. To this was added triethylorthoformate (1.49 g, 10.1 mmoles) and a catalytic amount of p-toluenesulfonic acid monohydrate. The reaction mixture was allowed to stir at room temperature for ~ 6 hours. During this period, the solution went from clear to a deep yellow color. The product mixture was taken up in a quantity of CH_2Cl_2 and washed twice with 5% (aq) $NaHCO_3$ to remove any residual acid. The organic layer was then washed twice with water and dried over K_2CO_3. Volatiles were removed in VACUO to yield a crude product which by ^1H NMR analysis corresponded to the desired bis-ketal. This compound afforded the following spectroscopic

data: ^{1}H NMR δ 4.95 (t, 1H, J = 6 Hz), 3.90 (q, 4H, J = 9 Hz), 3.45 (q, 4H, J = 7 Hz), 2.03 (d, 2H, J = 6 Hz), 1.57 (s, 3H), 1.16 (t, 6H, J = 7 Hz).

Preparation of 4,4-dimethoxycyclcohexanone. To 1,4-cyclcohexanedione (2.13 g, 19.0 mmoles) was added trimethylorthoformate (2.02 g, 19.1 mmoles) , 26 mL dry benzene, and a catalytic amount of p-toluenesulfonic acid. This mixture was placed into a 50 mL, 1 necked round bottomed flask which had been fitted with a water cooled reflux condenser and a $CaCl_2$ drying tube. The reaction mixture was brought to reflux. After 12 hours heat was removed, and the product mixture was allowed to cool to room temperature. The crude material was taken up in a quantity of CH_2Cl_2 and washed twice with 5% (aq) $NaHCO_3$ to remove any residual acid. The organic layer was washed twice with H_2O and dried over K_2CO_3. Following removal of solvent, a yellow oil remained. ^{1}H NMR analysis indicated that this product consisted of a 75 : 25 mixture of mono to bis methoxy cyclohexyl ketal. These compounds afforded the following spectroscopic data: 4,4-dimethoxycyclohexanone ^{1}H NMR δ 3.22 (s, 6H), 2.33 (t, 4H, J = 7 Hz), 1.97 (t, 4H, J = 7 Hz). 1,1,4,4-Tetramethoxycyclohexane ^{1}H NMR δ 3.12 (s, 12H), 1.66 (s, 8H).

Preparation of 4,4-bis(trifluoroethoxy)-cyclohexanone. The crude mixture of mono and bis methoxycyclohexyl ketals (0.90 g) was added to a 3 necked, 100 mL round bottomed flask containing CF_3CH_2OH (15.1 g, 0.15 moles) and CCl_2FCF_2Cl 60.0 mL. The flask was fitted with a nitrogen inlet and Soxhlet extraction apparatus containing ~ 70 g of freshly acitvated 4 Å molecular sieves. The reaction was allowed to reflux for 18 hours. At the end of this time, the product mixture was taken up in a quantity of CH_2Cl_2 and washed twice with 5% (aq) NaOH to removed any residual acid. The organic layer was washed twice with water and dried over K_2CO_3. Volatiles were removed <u>in VACUO</u> to yield a quantity of semi-solid material. Analysis of this material by ^{1}H NMR showed it to be a mixture of the mono and bis trifluoroethoxy ketals of the starting dione. These compounds were separated by chromatography on silica gel. The bis(trifluoroethyl) ketal was eluted using 75% CH_2Cl_2/25%

hexane. The mono trifluoroethoxy ketal was eluted using acetone. The compounds afforded the following spectroscopic data: 4,4-bis(trifluoroethoxy)cyclohexanone ^{1}H NMR δ 3.92 (q, 4H, J = 8 Hz), 2.58 (t, 4H, J = 7 Hz), 2.12 (t, 4H, J = 7 Hz). 1,1,4,4-Tetra(trifluoroethoxy)cyclohexane ^{1}H NMR δ 3.84 (q, 8H, J = 8 Hz), 1.84 (s, 8H).

Preparation of 1,1-diethoxy-4,4-bis(trifluoroethoxy) cylcohexane. To a 25 mL, 1 necked round bottomed flask containing 4,4-bis(trifluoroethoxy) cyclohexanone (0.51 g, 1.7 mmoles), was added triethylorthoformate (0.30 g, 2.1 mmoles), benzene (~ 10 mL) and a catalytic amount of p-toluenesulfonic acid. The reaction mixture was allowed to stir at room temperature for 2 hours. At the end of this time, the product mixture was taken up in CH_2Cl_2 and washed once with 5% (aq) $NaHCO_3$ to remove any residual acid. The organic layer was washed twice with water and dried over K_2CO_3. Volatiles were removed in VACUO. ^{1}H NMR analysis determined that this product was predominately the desired bis-ketal. Purification was accomplished by chromatography on silica gel using CH_2Cl_2 as the eluent. This compound afforded the following spectroscopic data: ^{1}H NMR δ 3.82 (q, 4H, J = 8Hz), 3.43 (q, 4H, J = 7 Hz), 1.76 (s, 4H), 1.54 (s, 4H), 1.18 (t, 6H, J = 7 Hz). ^{13}C NMR δ 124.22 (q, $^1J_{CF}$ = 276 Hz), 100.79 (s), 99.21 (s), 59.22 (q, $^2J_{CF}$ = 37 Hz), 55.53 (s), 36.32 (s), 29.47 (s), 15.26 (s).

Reaction of 2,2-diethoxy-4,4-bis(trifluoroethoxy)-butane under acidic conditions. The crude bis-acetal was taken up in a small quantity of CD_3Cl. This mixture was placed into a 5 mm NMR tube. The ^{1}H spectra of this material corresponded to the bis-ketal structure. A small amount of a 0.2 N DCl/D_2O solution was added to this mixture and shaken. Following separation of the layers (~ 30 minutes) the ^{1}H spectra was again recorded. The spectra indicated that the ethyl ketal function had been quantitatively hydrolyzed while the TFE functionalities remained intact.

Reaction of 1,1-diethoxy-4,4-bis(trifluoroethoxy)-cyclohexane under acidic conditions. The purified bis-ketal was taken up in a small amount of CD_3Cl. This solution

was placed in 5 mm NMR tube and monitored by ^1H NMR analysis over a period of several hours. The ethyl ketal functionality in this structure is quite labile and begins to hydrolyze due to the acidic nature of $CDCl_3$. After ~ 30 hours at room temperature, > 50% of the ethyl ketal had hydrolyzed. By comparison, the trifluoroethoxy functionality is completely stable to these conditions. On treatment with a small amount of dilute DCl/D_2O solution, the remaining ethoxy groups are hydrolyzed in < 5 minutes while the TFE moiety is uneffected.

Reaction of 4,4-bis(trifluoroethoxy)-2-butanone with $NaBH_4$. To 4,4-bis(trifluoroethoxy)-2-butanone (0.278 g, 1.04 mmoles) was added ~ 30 drops of dry THF. Sodium borohydride (0.021 g, 0.56 mmoles) was placed in solution in 3.5 mL of dry THF and added dropwise to the ketal solution which had been cooled to 0 °C. This reaction mixture was allowed to warm to room temperature with stirring. Following extraction of the organic components into CH_2Cl_2 and several washes with water, the organic layer was separated and dried over K_2CO_3. Removal of volatiles in VACUO yielded a quantity of a colorless liquid which by spectral analysis appeared to be the reduction product, 4,4-bis(trifluoroethyoxy)-2-butanol. This compound afforded the following spectroscopic data: ^1H NMR δ 5.00 (t, 1H, J = 7 Hz), 3.92 (q, 4H, J = 8 Hz), 3.75 - 3.68 (m, 1H), 1.79 (dd, 2H, $J_1 = J_2 = 7$ Hz), 1.22, (d, 3H, J = 7 Hz).

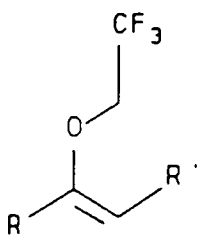
Reaction of 4,4-bis(trifluoroethoxy)-2-butanone with $LiAlH_4$. To 4,4-bis(trifluoroethoxy)-2-butanone (0.200g, 0.75 mmoles) was added dry THF. Lithium aluminum hydride (0.029 g, 0.77 mmoles) was placed into solution in dry THE (1 : 10, $LiAlH_4$: THF) and added slowly with cooling to the ketal solution. This mixture was allowed to stir for ~ 1 hour. At the end of this time, 28 μL H_2O, 56 μL 5% (aq) NaOH, and 28 μL H_2O were added to the reaction mixture in that order. This mixture was filtered through a bed of sand and the filtrate was extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over K_2CO_3. Following removal of volatiles in VACUO, a quantity of colorless liquid remained which by spectral analysis appeared to be the reduction product 4,4-

bis(trifluoroethoxy)2-butanol. The compound afforded the following spectroscopic data: ^1H NMR δ 5.00 (t, 1H, J = 7 Hz), 3.92 (q, 4H, J = 8 Hz), 3.75 - 3.68 (m, 1H), 1.79 (dd, 2H, $J_1 = J_2 = 7$ Hz), 1.22, (d, 3H, J = 7 Hz).

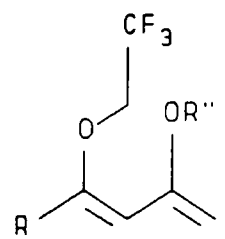
Chapter 3

Introduction

As a continuation of the work presented in chapter 2, an investigation of other types of trifluoroethoxy derivatives of carbonyl containing compounds was undertaken. Specifically, the trifluoroethoxy substituted (TFE) enol and dienol ethers shown in Scheme 3.1 were targeted for study.



TFE Enol Ether



TFE Dienol Ether

Scheme 3.1

For our purposes R = H, propyl, or phenyl; R' = acyl, and R" = $Si(R)_3$.

There were two reasons we chose to study these types of structures. The first relates to the work carrried out by Roy and Dorn in which these types of compounds were proposed as possible reaction intermediates in a novel acid catalyzed cycloaddition reaction [1]. The independent synthesis of these structures would help test the validity of this proposal. The second reason relates to the interesting behavior exhibited by trifluoroethoxy substituted compounds. Our work with TFE ketals gave us reason to believe that similarly substituted ene's and diene's might also exhibit unusual and interesting behavior within the context of their characteristic reactions.

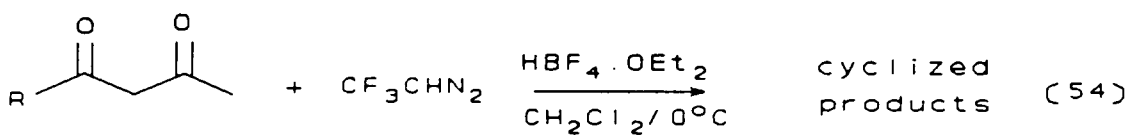
This chapter deals with the preparation of a number of TFE substituted enol and dienol ethers. Successful as well as unsuccessful approaches to the formation of these

compounds are detailed. Synthetic applications and relative reactivities of these compounds are discussed in chapter 4.

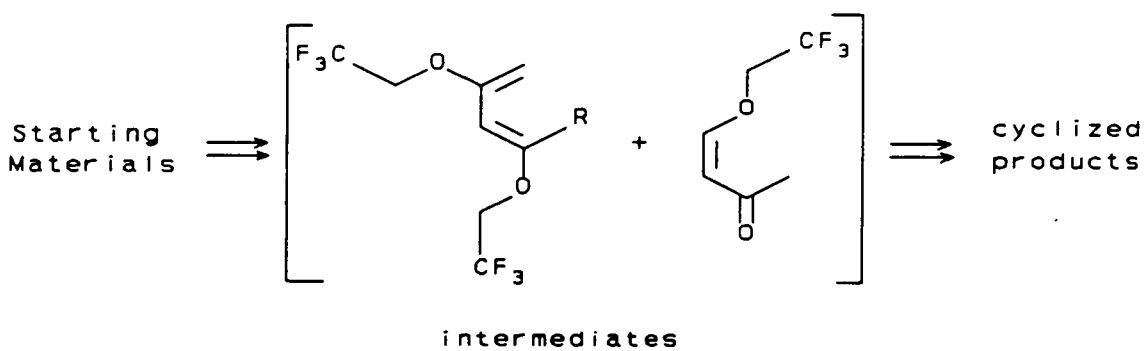
Trifluoroethoxy-β-Keto Enol Ethers

Several different approaches were investigated in our attempts to develop a general method for the synthesis of TFE enol ethers. A number of promising but unsuccessful routes to these compounds were explored before positive results were obtained.

Our first attempts to prepare the target compounds involved modification of the procedure originally developed by Roy [1]. He found that the reaction of 2,2,2-trifluorodiazoethane (TFD) with β-diketones in the presence of $HBF_4{\cdot}OEt_2$ gave rise to a number of cyclized condensation products (eq 54).



He proposed that this process proceeded by a type of [4+2] cycloaddition reaction which involved TFE enol and dienol ethers as key reaction intermediates (Scheme 3.2).



Scheme 3.2

Thus, there was reason to believe that by varying component stoichiometry and/or reaction conditions, any TFE enol ether intermediates which did form could be isolated prior to subsequent reaction (cyclization). If successful, this procedure would constitute a general approach to the compounds of interest.

Our efforts in this direction proceeded along two lines. The first involved the use of a limiting reagent - in this case CF_3CHN_2 - to control the extent of reaction. In theory, this approach is feasible. If TFE enol and dienol ethers are intermediates in the cycloaddtion reaction, their formation must result from the reaction of the β-dicarbonyl compounds with TFD. The reaction stoichiometry would indicate that at least 3 equivalents of TFD are required for the formation of 1 equivalent of product. If less than this minimum amount of the diazo compound were present, quantities of the intermediate structures would form but remain unreacted. If these compounds were of sufficient stability, they could be isolated from the product mixture.

In our case, this approach proved unsuccessful. By varying the stoichiometry of the reaction mixture, we succeeded only in changing the overall proportion of cyclized component relative to starting material found in the product mixture. We found no direct evidence to indicate the formation or presence of TFE enol and/or dienol ethers at any time in the reaction sequence.

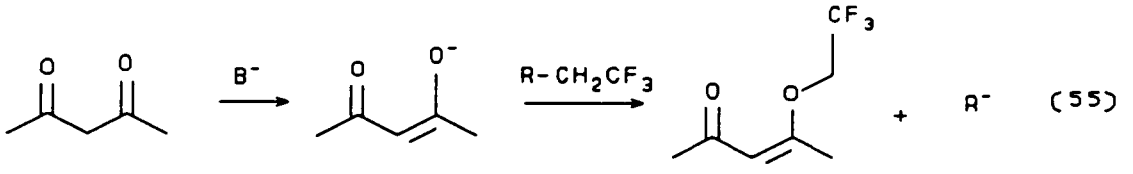
The second effort to isolate TFE containing intermediates from the cyclization reaction mixture was a variation on the method just described. However, rather than attempting to control the course of the reaction through its stoichiometry, this procedure involved manipulating the temperature at which the reaction was allowed to occur.

Roy found that the cyclization reaction took place at 0°C. We felt that at some lower temperature, enol ether formation might occur without subsequent cyclization. It was reasoned that by carefully observing the reaction mixture as a function of temperature (e.g. checking for color change and evolution of nitrogen) the point at which intermediate formation occurred could be determined. This would in turn allow for the isolation of these compounds. As in the first case, this approach also failed. Although there were numerous indications that reaction was taking place, the material isolated following neutralization of the reaction mixture with Et_3N corresponded to mixtures of starting material and cyclized

product. Once again, none of the proposed intermediates were observed.

Although these results were discouraging, they were taken neither as positive nor negative evidence regarding the intermediacy of trifluoroethoxy enol and dienol ethers in the cyclization process or the relative stabilities of these compounds. There were several explanations as to why these approaches had not yielded the desired results. These include, but are not limited to, the reactivities of the intermediate structures relative to their rate of formation, the stability of the intermediates relative to the conditions of their formation, and the overall stabilities of the various reaction products relative to their intermediates.

A second proposed route to the formation of TFE enol ethers again involved 1,3-dicarbonyl compounds as starting materials. However, in this case, it was base catalyzed chemistry involving alkylation at oxygen that we hoped would yield the target compounds (eq 55).

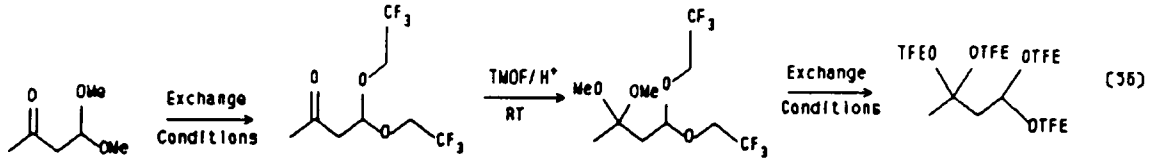


(55)

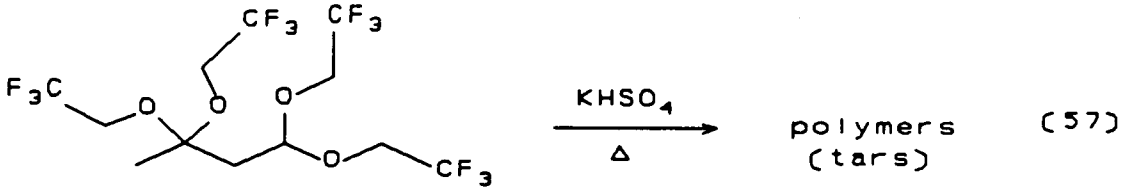
This scheme involved initial formation of the enolate anion from the acidic β-diketone followed by reaction with an appropriate CF_3CH_2- containing alkylating agent. In theory and by analogy [67], this sequence should have proceeded smoothly, however, once again the results were less than hoped for. Several reasons for the failure of this particular approach are possible. The most obvious involves other competing reactions, in particular, base catalyzed condensation of the initially formed enolate anion with the second carbonyl function of the starting compound. Both NMR and MS data on product mixtures isolated from these reactions seemed to bear this out as they indicated the presence of only high

molecular weight components and none of the desired product. Another possiblity is that the strongly electron withdrawing CF_3CH_2- group polarized the alkylating agent (p-$TsOCH_2CF_3$) in such a manner that attack by the oxyanion to give the O-alkylated product proved unfavorable.

A third approach, which again proved unsuccessful, involved the acid catalyzed cracking of mono and bis trifluoroethoxy ketals. These compounds were prepared by the acid catalyzed exchange reaction described in chapter 2 (eq 56). However, pyrolysis of these

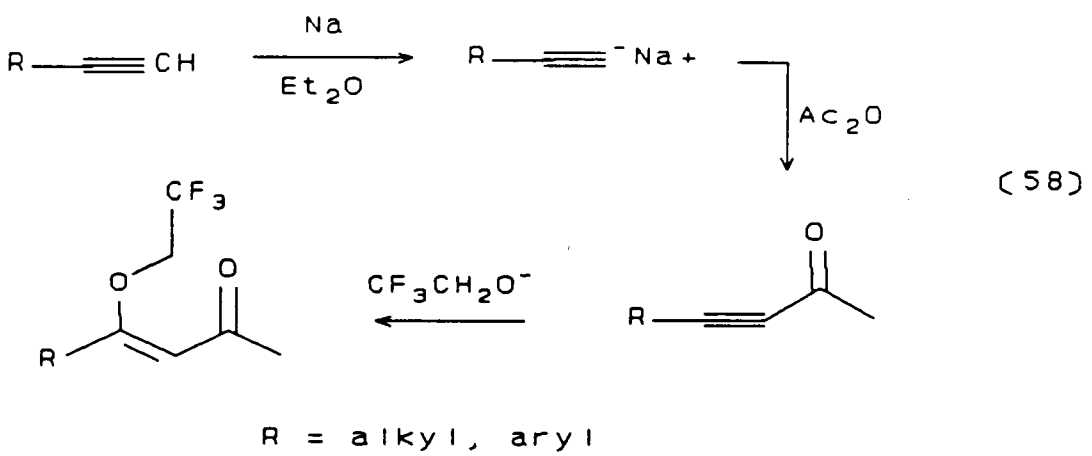


compounds under the conditions outlined gave rise to only high molecular weight, polymeric type materials (tars) rather than the desired enol and dienol ethers (eq 57). In this case, the



lack of success can most likely be attributed to the lability and/or reactivity of any vinyl ether type moieties which did form under these reaction conditions.

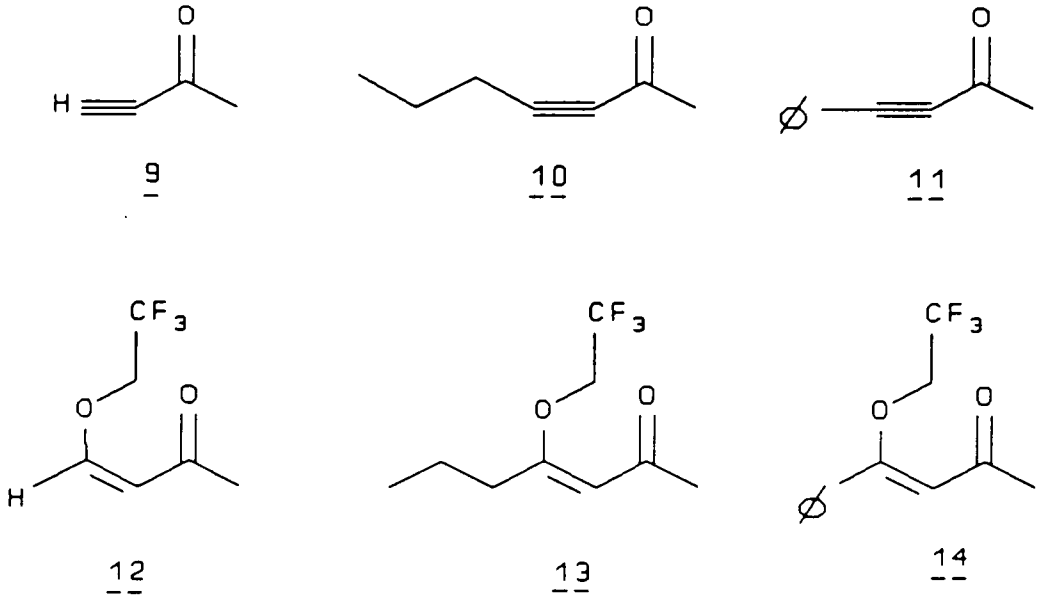
After these failures, a general methodology for the preparation of TFE-β-keto enol ethers was finally developed. However, unlike the schemes previously outlined, this route utilized propargyl ketones (α, β-alkynyl ketones) rather than 1,3-dicarbonyl compounds as precursors to the target compounds. The overall reaction is outlined in equation 58.



(58)

R = alkyl, aryl

In this sequence, a terminal alkyne (R = H, alkyl, aryl) reacts with sodium metal to form the alkynl anion. This salt is then condensed with acetic anhydride to form the substituted propargyl ketone. The final step involves attack of the base generated trifluoroethoxy anion at the β position of the triple bond to give the desired product. In these cases, R is limited only by the type of terminal acetylene available. Using this methodology, the phenyl, propyl, and hydrogen substituted trifluoroethoxy-β-keto enol ethers 12 - 14 were prepared from the alkynl precursors 9 - 11 (Scheme 3.3).

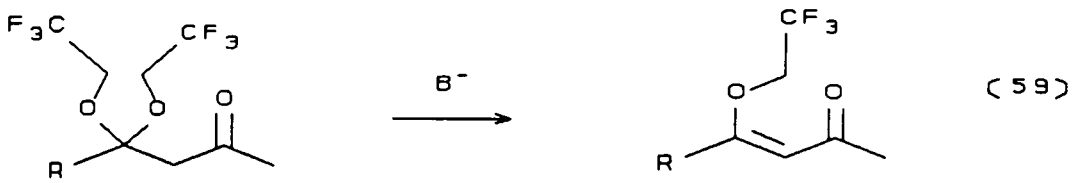


Scheme 3.3

It is interesting to note that in the case of the proton and propyl substituted adducts, only the trans regioisomer formed, however, in the phenyl substituted example, both cis and trans isomers formed in an appoximately 60 : 40 ratio respectively.

In the case of compound 12 (hydrogen substituted) an additional preparation was developed. In a formal sense, this method involves the use of β-dicarbonyl (or β-dicarbonyl equivalent) starting compounds. This procedure utilized a hindered base (K^+ $OtBu^-$) to catalyze the elimination of one mole of CF_3CH_2OH from the β-keto-trifluoroethyl acetal to yield the enol ether derivative (eq 59).

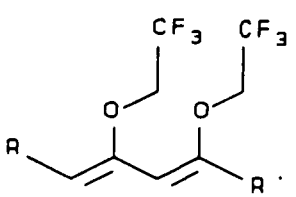
The major drawback to this approach involved the preparation of the appropriate starting ketals. However, in the case R = H, this was not a problem since the enol ether precursor was readily prepared from 4,4-dimethoxy-2-butanone as described in chapter 2.



(59)

1-Trifluoroethoxy-3-Trialkylsiloxy Dienol Ethers

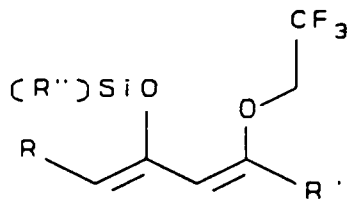
As detailed in Chapter 1, methods for the preparation of 1,3-bis(alkoxy) substituted dienes are not well developed, with those that have been perfected being quite specific and limited in application. For this reason, the preparation of 1,3-bis(trifluoroethoxy) substituted dienes (Scheme 3.4) was not pursued.



1,3-bis(trifluoroethoxy) diene

Scheme 3.4

However, an alternative method which allowed ready entry into the trifluoroethoxy substituted dienol ethers did exist. This approach involved applying methodology developed by Danishefsky [140] and used in the synthesis of his widely utilized diene (1-methoxy-3-trimethylsiloxy-1,3-butadiene) to the trifluoroethyl-β-keto enol ethers whose preparation was outlined in the preceeding section. This work resulted in the preparation of a series of dienol ethers which contained trifluoroethyl substituents in the 1 position and trialkylsilyl substituents in the 3 position (Scheme 3.5).

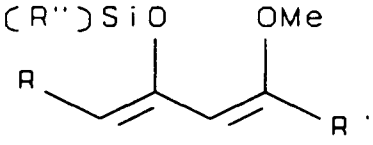


R, R' = alkyl, aryl

R'' = $(Me)_3$, $(Me)_2$t-Bu

Scheme 3.5

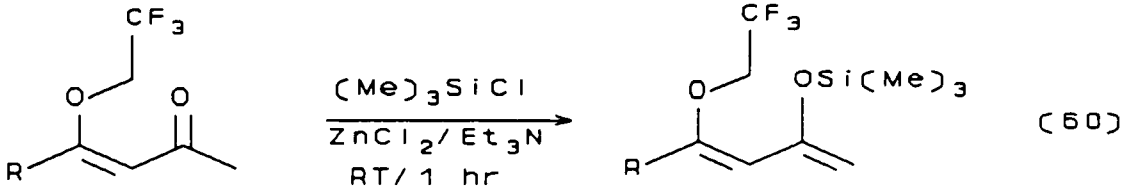
Although these structures differ from the compounds originally targeted for preparation (1,3-bis(trifluoroethyl) dienol ethers), we reasoned that a study of their behavior would still provide valuable insight into the effect the trifluoroethoxy group has on the reactivities of structures into which it had been incorporated. In addition, a large body of information concerning the methoxy analog (Scheme 3.6) had been collected and we felt that comparison of the behavior of this compound, whose electronic and steric requirements are well understood, with the trifluoroethoxy substituted structure would be very informative.



methoxy analog

Scheme 3.6

The procedure for the preparation of 1-alkoxy-3-trimethylsiloxy dienes from 3-keto-1-alkyl enol ethers as developed by Danishefsky is outlined belowed (eq 60).

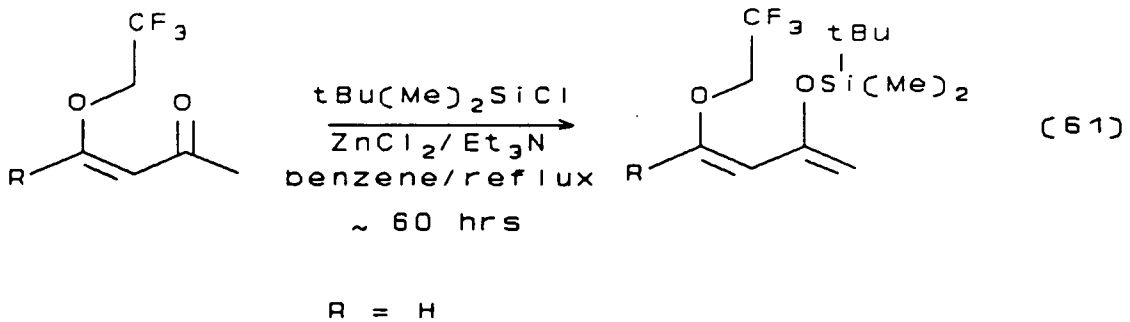


(60)

R = H, alkyl, aryl

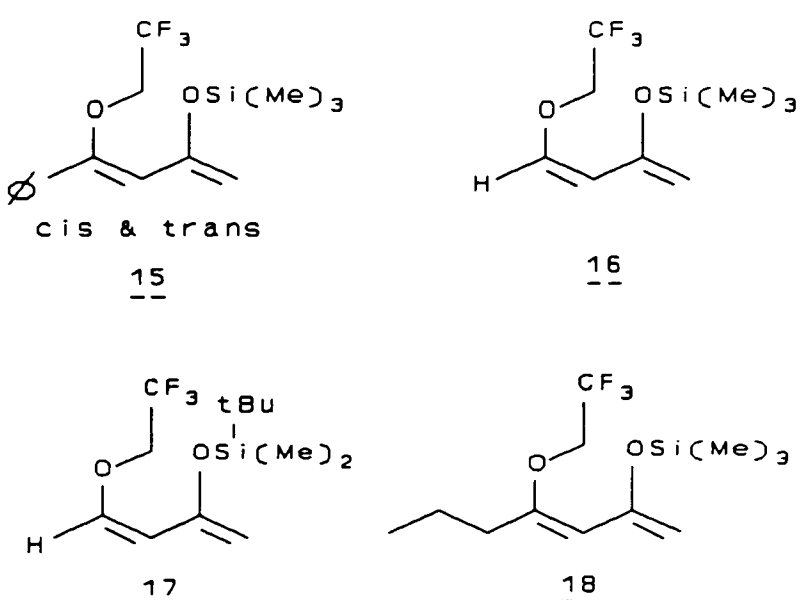
This reaction takes place readily under very mild conditions and in high yield. In part this is due to the high affinity of silicon for oxygen. It is the formation of the silicon-oxygen bond which is the driving force behind this reaction. The high affinity of these two atoms for one another is also the reason the silation occurs exclusively at oxygen.

As an extension of this methodology, t-butyldimethylsilyl chloride ($ClSiMe_2t$-Bu) was substituted for trimethylsilyl chloride ($ClSiMe_3$). This reaction is shown in equation 61.



(61)

As indicated by the different conditions required for the formation of the two types of dienes, the t-butyldimethylsilyl substituent is more difficult to introduce. This is most likely a steric effect related to the size of the t-butyl group. Scheme 3.7 lists the dienol ethers prepared by this procedure.



Scheme 3.7

Experimental

Preparation of 3-heptyn-2-one (10) [168]. Sodium metal (10.65 g, 0.463 moles) was cut into small pieces and placed into a 250 mL, 3 necked, round bottomed flask which contained ~ 100 mL of dry ethyl ether. The flask was fitted with a dropping funnel, a water cooled reflux condenser in series with a ice/H_2O condenser, and a nitrogen inlet. 1-Pentyne (25.0 g, 0.368 moles) was added dropwise with stirring to the mixture of sodium in ether. The addition took ~ 20 minutes. At the end of this addition period, the reaction mixture had gone from clear to an opaque, yellow color. After stirring for ~ 8 hours, the mixture of sodium, 1-pentyne and ether had become quite thick. Additional ether was added to remedy this. After 20 total hours of stirring, the solution had taken on a floculent appearence and was cream colored. Particles of solid sodium metal were no longer present. It was determined that formation of the metal-alkyne adduct had reached completion. Freshly distilled acetic anhydride (50.0 g, 0.490 moles) was added to ~ 100 mL dry ethyl ether. This mixture was placed into a 500 mL round bottomed flask and cooled to 0°C in an ice/H_2O bath. Using a large bore, double tipped needle the solution of sodium alkyne in ether was transferred with stirring into the solution of acetic anhydride and ether. A small amount of additional dry ethyl ether were used to aid in this transfer. Following completion of this process, the reaction mixture was allowed to warm to room temperature and stir for 24 hours. At that time, ~ 100 mL of 3 N HCl (aq) was added and the mixture was allowed to stir an additional 80 hours. At this point, stirring was stopped and the mixture separated into 2 layers. The organic layer was isolated and washed several times with water followed by a final wash with 5% (aq) $NaHCO_3$. This layer was dried over K_2CO_3 and most of the residual ether was removed by rotary evaporation. The remaining material was distilled at reduced pressure to give the desired 3-heptyn-2-one (11.8 g, 0.102 moles, 27.6% yield). B.P. 59 - 60 °C @ 15 mm Hg. The compound afforded the following spectroscopic data: ^{1}H NMR δ 2.20 (t, 2H, J = 7 Hz), 2.17 (s, 3H), 1.36 (sext, 2H, J = 7 Hz), 0.90 (t, 3H, J = 7 Hz), ^{13}C NMR δ 184.13

(s), 93.33 (s), 80.30 (s), 32.31 (s), 20.98 (s), 20.51 (s), 13.01 (s).

Preparation of 4-phenyl-3-butyn-2-one (11) [168]. Sodium metal (5.3 g, 0.230 moles) was cut into small pieces and placed into a 250 mL, 3 necked round bottomed flask which contained ~ 100 mL of dry ethyl ether. The flask was fitted with a dropping funnel, a water cooled reflux condenser in series with an ice/H_2O condenser, and a nitrogen inlet. Phenyl acetylene (20.0 g, 0.198 moles) was added dropwise with stirring to the mixture of sodium in ether. The mixture warmed slightly during the addition which took ~ 10 minutes. During this process, the solution went from clear to a light brown color. The reaction mixture was allowed to stir with periodic addition of dry ether until solid sodium was no longer present. This took ~ 10 hours. Freshly distilled acetic anhydride (excess) was placed along with 100 mL dry ethyl ether into a 500 mL round bottomed flask. The flask was fitted with a water cooled reflux condenser and a nitrogen inlet. Using a double tipped needle the solution of sodium phenyl acetylide in ether was transferred into the mixture of ice cold acetic anhydride/ethyl ether. During this transfer process, a white vapor was evolved and heat was generated. Following this addition, the reaction mixture was allowed to warm to room temperature and stir for 12 hours. At the end of that time, the mixture was cooled to 0°C in an ice/H_2O bath and ~ 100 mL of 3 N HCl(aq) was added. This caused the yellow solution to turn a reddish-brown color. The reaction mixture was left to stir at room temperature for an additional 48 hours. At this point, the organic layer was separated from the aqueous layer and washed several times with water followed by a final wash with 5% (aq) $NaHCO_3$. After drying over K_2CO_3, residual ether was removed by rotary evaporation. The remaining material was distilled at reduced pressure to yield the desired 4-phenyl-3-butyn-2-one (15.24 g, 0.106 moles, 53.4% yield). B.P. 111 - 113 °C @ 10 mm Hg. The compound afforded the following spectroscopic data: ^1H NMR δ 7.53 (m, 2H), 7.42 - 7.31 (br. m, 3H), 2.40 (s, 3H), ^{13}C NMR δ 183.66 (s), 132.56 (s), 130.37 (s), 128.26 (s), 119.59 (s), 89.74 (s), 88.02 (s), 32.23 (s).

Preparation of 3-butyn-2-one (9) [169]. Chromium (VI) oxide (CrO_3) (50.0 g, 0.500 moles) was mixed with 130 mL water and 45 mL conc. sulfuric acid (H_2SO_4) to form a solution. This solution was added dropwise with stirring to a mixture of 3-butyne-2-ol (50.0g, 0.714 moles) in ~ 110 mL of water over a period of 10 hours. The reaction was carried out at room temperature under a nitrogen atmosphere. Following this addition the mixture was allowed to stir at room temperature for an additional 24 hours. Workup involved extraction of the product mixture 3 times to a total of 600 mL with ethyl ether, washing this organic layer several times with water, followed by drying over $MgSO_4$. Fractional distillation of this organic layer through a vigeraux column yielded the desired 3-butyn-2-one (5.0 g, 0.074 moles, 10.2% yield). B.P. 108 - 110 °C @ atmsopheric pressure. The compound afforded the following spectroscopic data: ^1H NMR δ 3.21 (s, 1H), 2.31 (s, 3H). ^{13}C NMR δ 184.84 (s), 78.79 (s), 65.48 (s), 32.31 (s).

Preparation of (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13). Sodium metal (1.25 g, 54.3 mmoles) was cut into small pieces and added with stirring to 2,2,2-trifluoroethanol (54.9 g, 0.549 moles). This process was carried out under a nitrogen atmosphere in a 2 necked round bottomed flask fitted with a water cooled reflux condenser. The sodium metal reacted rapidly with the alcohol evolving enough heat to cause the mixture to reflux. Following dissolution of the entire amount of metal the reaction mixture was allowed to cool to room temperature. Next, 3-heptyn-2-one (10) (6.0 g, 54.4 mmoles) was added dropwise to this solution of sodium trifluoroethoxide over a period of ~ 10 minutes. As this process took place, the clear solution began to take on a yellow coloration. The reaction mixture was refluxed 12 hours. At the end of this time the product mixture was cooled to room temperature, and taken up in a quantity of methylene chloride. This organic layer was washed with several portions of water (until no longer basic) and dried over $MgSO_4$. The volatiles were removed in VACUO leaving a yellow oil. This material was distilled at reduced pressure to yield (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (9.21.g,

0.044 moles, 80.3% yield). B.P. 90 - 92 °C @ 15 mm Hg. The compound afforded the following spectroscopic data: ^{1}H NMR δ 5.35 (s, 1H), 4.09 (q, 2H, J = 8 Hz), 2.71 (t, 2H, J = 7.5 Hz), 0.90 (t, 3H, J = 7.5 Hz). ^{13}C NMR δ 195.60 (s), 172.95 (s), 122.71 (q, $^1J_{CF}$ = 276 Hz), 100.36 (s), 64.54 (q, $^2J_{CF}$ = 36.8 Hz), 33.17 (s), 31.52 (s), 20.20 (s), 13.10 (s). Elemental analysis: Theory 51.43% C, 6.23% H. Found 51.13% C. 6.33% H.

Preparation of (Z)-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12): Method A. Sodium metal (1.80 g, 78.3 mmoles) was cut into small pieces and added with stirring to 2,2,2-trifluoroethanol (34.3 g, 0.343 moles). This process was carried out under a nitrogen atmosphere in a 2 necked round bottomed flask fitted with a water cooled reflux condenser. The sodium metal reacted rapidly with the alcohol evolving enough heat to cause the mixture to reflux. Periodic cooling of this solution in an ice/H_2O bath was used in order to prevent the loss of CF_3CH_2OH. Following dissolution of the entire amount of metal, the reaction mixture was allowed to cool to room temperature. At this point, 3-butyn-2-one (9) (4.79 g, 70.4 mmmoles) was added dropwise. This process took ~ 45 minutes during which time the reaction mixture went from clear to a reddish-brown color and evolved a white vapor. The solution was allowed to stir 14 hours at room temperature. Workup involved taking the product mixture up in a quantity of methylene chloride, washing with water until no longer basic, then drying over $MgSO_4$. Volatiles were removed in VACUO to give a crude product. This material was distilled at reduced pressure from potassium t-butoxide to yield (Z)-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (9.05 g, 53.9 mmoles, 76.5% yield). B.P 70 - 72 °C @ 10 mm Hg. This compound afforded the following spectroscopic data: ^{1}H NMR δ 7.41 (d, 1H, J = 13 Hz), 5.66 (d, 1H, J = 13 Hz), 4.18 (q, 2H, J = 8 Hz), 2.16 (s, 3H). ^{13}C NMR δ 196.25 (s), 160.07 (s), 125.54 (q, $^1J_{CF}$ = 278 Hz), 109.04 (s), 67.52 (q, $^2J_{CF}$ = 36 Hz), 27.64 (s). Elemental analysis: Theory 42.87% C, 4.20% H. Found 40.45% C, 4.24% H.

Method B. To a 25 mL round bottomed flask was added 4,4-bis(2,2,2-trifluoroethoxy)-2-butanone (14.20 g, 53.0 mmoles) and potassium t-butoxide (1.0 g, 8.93

mmoles). The flask was fitted with a short path distillation apparatus. The system presssure was reduced to 10 mm Hg and heat was applied. Distillation yielded the desired product in 97.9% yield. B.P. 71 - 73 °C @ 10 mm Hg.

Preparation of (E) and (Z)-(2,2,2-trifluoroethoxy)-4-phenyl-3-buten-2-one (14). Sodium metal (1.73 g, 75.2 mmoles) was cut into small pieces and added with stirring to 2,2,2-trifluoroethanol (41.2 g, 0.412 moles) which had been cooled to 0°C in a 100 mL, 2 necked round bottomed flask under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and after several hours, the sodium metal had completely dissolved. 4-phenyl-3-butyn-2-one (11) (7.2 g, 50.0 mmoles) was mixed with 20.0 mL CF_3CH_2OH and added dropwise to this solution over a period of ~ 35 minutes. Following this addition heat was applied and the reaction mixture was allowed to reflux for 12 hours. At the end of this time, the solution had turned a yellow-orange color. Heat was removed and after cooling to room temperature, the product mixture was taken up in a quantity of CH_2Cl_2, and washed with water until no longer basic. The organic layer was dried over $MgSO_4$ and the solvent was removed in VACUO to leave an amber colored oil. This material was distilled from potassium t-butoxide (1.0 g, 8.93 mmoles) to yield (E) and (Z)-(2,2,2-trifluoroethoxy)-4-phenyl-3-buten-2-one (9.6 g, 39.5 mmoles, 79% yield). (E) : (Z) ratio ~ 40 : 60. B.P. 108 - 110 °C @ 3 mm Hg. The compounds afforded the following spectroscopic data: (Z) isomer ^{1}H NMR δ 7.57 - 7.53 (b, 2H), 7.51 - 7.38 (b, 3H), 5.86 (s, 1H), 4.33 (q, 2H, J = 8 Hz), 2.40 (s, 3H). ^{13}C NMR δ 196.23 (s), 163.96 (s), 133.34 (s), 130.92 (s), 128.81 (s), 127 (s), 123.16 (q, $^1J_{CF}$ = 266 Hz), 110.93 (s), 68.60 (q, $^2J_{CF}$ = 36.Hz), 31.13 (s). (E) isomer ^{1}H NMR δ 7.57 - 7.53 (b, 2H), 7.51 - 7.38 (b, 3H), 5.61 (s, 1H), 4.27 (q, 2H, J = 8 Hz), 1.93 (s, 3H). ^{13}C NMR δ 129.12 (s), 128.10 (s), 122.89 (q, $^1J_{CF}$ = 266 Hz), 105.68 (s), 65.26 (q, $^2J_{CF}$ = 36 Hz), 30.51 (s). Elemental analysis: Theory 59.02% C, 4.54% H,. Found 58.75% C, 4.61% H.

Preparation of 1-(2,2,2-trifluoroethoxy)-3-trimethylsiloxy-1,3-butadiene (16). Triethylamine (4.0 g, 41.7 mmoles) and anhydrous zinc chloride (0.13 g, 0.95 mmoles) were added to a 25 mL, 2 necked round bottomed flask fitted with a water cooled reflux condenser and under a nitrogen atmosphere. These compounds were stirred together at room temperature until the $ZnCl_2$ had formed a suspension in the Et_3N. This mixture was then cooled to 0°C in an ice/H_2O bath and (E)-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) (2.0 g, 11.9 mmoles) in benzene (7.0 g, 89.7 mmoles) was rapidly introduced through a rubber septum using a syringe. At this point, the reaction mixture went from an off-white colored suspension to a bright yellow solution. This procedure was followed by the addition of trimethylsilyl chloride (2.90 g , 26.7 mmoles) which was also introduced by syringe. This addition caused the reaction mixture to turn a deep red color. After stirring for 1.5 hours at 40 °C, the product mixture was cooled to room temperature and a quantity of CH_2Cl_2 was added. This organic layer was washed several times with water and dried over K_2CO_3. Volatiles were removed in VACUO to leave a reddish-brown oil which by its odor contained traces of Et_3N. The product diene (1.94 g, 8.1 mmoles, 67.9% yield) was recovered by distillation at reduced pressure. B.P. 73 - 75 °C @ 11 mm Hg. The compound afforded the following spectroscopic data: ^1H NMR δ 6.61 (d, 1H, J = 12 Hz), 5.38 (d, 1H, J = 12 Hz), 4.05 (s, 2 H), 3.95 (q, 2H, J = 8 Hz), 0.12 (s, 9H). ^{13}C NMR δ 152.87 (s), 147.95 (s), 128.34 (s), 123.26 (q, $^1J_{CF}$ = 276 Hz), 107.24 (s), 92.94 (s), 67.28 (q, $^2J_{CF}$ = 37 Hz), - 0.12. Elemental analysis: Theory 44.99% C, 6.29% H. Found 40.63% C, 5.39% H.

Preparation of 4-(2,2,2-trifluoroethoxy)-2-(trimethylsiloxy)-1,3-heptadiene (18). A 50 mL , 2 necked, round bottomed flask was fitted with magnetic stirring bar, a nitrogen inlet, and a water cooled reflux condenser. The flask was purged with N_2. Triethylamine (15.3 g, 0.150 moles) and anhydrous zinc chloride (0.35 g, 2.57 mmoles) were added. This mixture was stirred at room temperature for ~ 2 hours (long enough for the $ZnCl_2$ to form a suspension in the amine). (E)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13) (3.15 g, 15.0

mmoles) was taken up in 10.0 mL dry benzene. This solution was added by syringe to the stirring suspension. Following addition, the reaction mixture went from an opague white to a yellow/green color. After several more minutes, trimethylsilyl chloride (8.14 g, 75.0 mmoles) was added using a syringe. This caused the solution to immediately turn a pinkish/red color. The reaction was allowed to stir for 11 hours at room temperature. At the end of this time the product mixture was taken up a quantity of CH_2Cl_2, washed several times with water and dried over K_2CO_3. Volatiles were removed in VACUO to leave an amber colored liquid. The desired compound (3.40 g, 12.0 mmoles, 80.3% yield) was recovered by distillation at reduced pressure. B.P. 90 - 92 °C @ 9 mm Hg. The compound afforded the following spectroscopic data. ^{1}H NMR δ 4.92 (s, 1H), 4.14 (d, 2H, J = 5 Hz), 3.99 (q, 2H, J = 7 Hz), 2.48 (t, 2H, J = 7 Hz), 1.54 (sextet, 2H, J = 8 Hz), 0.90 (t, 3H, J = 7 Hz), 0.23 (s, 9H). ^{13}C NMR δ 159.33 (s), 153.81 (s), 123.41 (q, $^1J_{CF}$ = 276 Hz), 100.35 (s), 93.17 (s), 64.62 (q, $^2J_{CF}$ = 37 Hz), 32.93 (s), 20.97 (s), 13.63 (s), - 0.06 (s). Elemental analysis: Theory 51.04% C, 7.50% H. Found 50.55% C, 7.31% H.

Preparation of (E) and (Z)-1-phenyl-1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (15). Triethylamine (3.0 g, 29.4 mmoles) and anhydrous zinc chloride (0.10 g, 0.7 mmoles) were added to a 2 necked, 25 ml, round bottomed flask which had been fitted with a water cooled reflux condenser, a magnetic stirring bar, and a nitrogen inlet. These compounds were stirred together at room temperature until the $ZnCl_2$ had formed a suspension in the amine (~ 25 minutes). A mixture of (E) and (Z)-4-(2,2,2-trifluoroethoxy)-4-phenyl-3-buten-2-one (14) (2.44 g, 10.0 mmoles) was placed into solution in 6.0 g dry benzene. This mixture was rapidly introduced to the stirred suspension through a rubber septum using a syringe. Next, trimethylsilyl chloride (2.50 g, 23.0 mmoles) was rapidly introduced in this same manner. At this point, the solution underwent a gradual color change from white to light red. The temperature of the reaction mixture was raised to ~ 45 °C and allowed to remain there for 18 hours. At the end of this time, heat was removed and the

product was taken up in a quantity of CH_2Cl_2. This organic layer was washed several times with H_2O then dried over K_2CO_3. Volatiles were removed in VACUO to leave a brown liquid. This material was distilled at reduced pressure to yield the desired product. B.P. 98 - 100 °C @ 2 mm Hg. This mixture afforded the following spectroscopic data: (Z) isomer ^1H NMR δ 7.56 - 7.28 (br m, 5H), 5.69 (s, 1H), 4.79 (br s, 1H), 4.21 (br s, 1H), 4.13 (q, 2H, J = 8 Hz), 0.18 (s, 9H). (E) isomer ^1H NMR δ 7.56 - 7.28 (br m, 5H), 5.46 (s,1H), 4.50 (br s, 1H), 4.16 (br s, 1H), 4.09 (q, 2H, J = 8 Hz), -0.17 (s, 9H). Mixture of (Z) and (E) ^{13}C NMR δ 155.76 (s), 153.97 (s), 152.87 (s), 152.01 (s), 135.06 (s), 134.90 (s), 129.67 (s), 129.04 (s), 128.89 (s), 128.65 (s), 127.56 (s), 126.39 (s), 123.57 (q, $^1J_{CF}$ = 276 Hz), 123.41 (q, $^1J_{CF}$ = 276 Hz), 111.77 (s), 105.29 (s), 97.87 (s), 95.05 (s), 67.62 (q, $^2J_{CF}$ = 32 Hz), 65.59 (q, $^2J_{CF}$ = 32 Hz), - 0.12 (s), - 0. 59 (s).

Preparation of 1-(2,2,2-trifluoroethoxy)-3-(t-butyldimethylsiloxy)-1,3-butadiene (17). Triethylamine (5.4 g, 53.8 mmoles) and anhydrous zinc chloride (0.17 g, 1.2 mmoles) were placed into a 25 mL, 2 necked round bottomed flask, which had been fitted with a magnetic stir bar, a water cooled reflux condenser, and a nitrogen inlet. The mixture was allowed to stir until the $ZnCl_2$ had formed a suspension in the amine (~ 30 minutes). 4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) (2.12 g, 12.6 mmoles) was dissolved in 5.0 mL of dry benzene. This mixture was transferred rapidly to the reaction flask using a syringe. Following this addition, the reaction mixture went from opaque white to an orange/red color. T-butyldimethylsilyl chloride (4.5 g, 29.9 mmoles) was dissolved in 5.0 mL dry benzene and introduced to the reaction flask by syringe (an additional 3.0 mL of benzene was used to aid in this transfer). At this point, heat was applied and the reaction mixture was allowed to reflux. After a total reaction time of ~ 52 hours, heating was discontinued and the product mixture was washed several times with 5% $NaHCO_3$ (in order to hydrolyze any remaining alkyl silyl chloride and neutralize the HCl this process liberates) followed by a wash with H_2O. The organic layer was separated and dried over K_2CO_3. Volatiles were removed in

VACUO to yield a quantity of an amber colored liquid. The material was distilled at reduced pressure to give the desired product. This compound afforded the following spectroscopic data: ^{1}H NMR δ 6.76 (d, 1H, J = 12 Hz), 5.46 (d, 1H, J = 12 Hz), 4.12 (br, s, 2H), 4.05 (q, 2H, J = 8 Hz), 0.94 (s, 9H), 0.17 (s, 6H). ^{13}C NMR δ 153.08 (s), 147.87 (s), 129.36 (s), 123.21 (q, $^{1}J_{CF}$ = 280 Hz), 107.46 (s), 92.79 (s), 67.30 (q, $^{2}J_{CF}$ = 32 Hz), - 0.11 (s), - 4.24 (s), - 4.72 (s).

Chapter 4

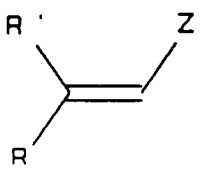
Introduction

The material presented in this chapter deals with our investigation into the effect incorporation of the trifluoroethoxy group has on the reactivity of several types of organic substrates. Specifically, this work involved the study of trifluoroethoxy substituted enol and dienol ethers (whose preparation was outlined in chapter 3) with respect to several types of reactions. In order to accomplish this, a number of experiments were carried out. Where possible, these experiments were chosen so that comparisons could be made between this work and work previously carried out. In this way, known behavior could be used to explain observations made with regard to the systems under study. An example of this can be seen in the work involving reactions of 1,3-disubstituted dienes. Several experiments reported here are identical to a number of experiments carried out by Danishefsky in his study of these compounds [150]. However, in our systems, the methoxy function has been replaced by a trifluoroethoxy function. By making this change in the structure and then repeating the known work, the effect of the CF_3CH_2O- group on substrate behavior can be more readily determined.

This chapter is divided into two main sections. The first outlines work carried out involving several acyl substituted trifluoroethoxy enol ethers. Included are examples of their use as reactants in both conjugate addition and cycloaddition reactions. The second section deals mainly with the behavior of several 1-trifluoroethoxy-3-trialkylsiloxy-1,3-butadienes. Most of this work involved observations regarding the reactivities of these structures with respect to their utility as 4 carbon synthons in cycloaddition reactions. Some of the information generated by the experiments outlined in this latter section gives additional insight into the work originally carried out by Roy et al [1].

Reactions of Trifluoroethoxy Substituted Enol Ethers

Substituted olefins have been used extensively in organic synthesis. They undergo several types of carbon-carbon bond forming reactions including ene reactions [170], conjugate addition reactions [171], [2+2] cycloaddition reactions [172] and Diels-Alder reactions [173]. Among substituted alkenes, one type which has found wide application are those substituted with an electron withdrawing group in the β-position. In general, their structure conforms to 19 where Z = CN, NO_2, C=O, CF_3, etc (Scheme 4.1).



19

Z = CN, NO_2, C=O, CF_3

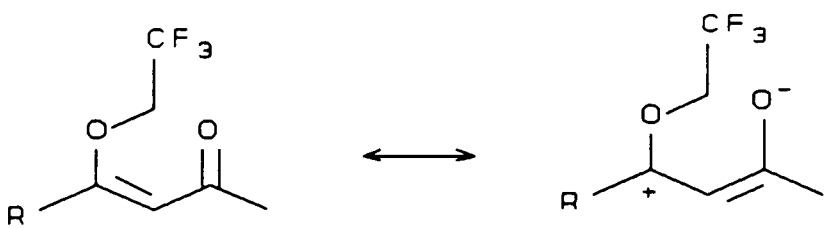
Scheme 4.1

These electron deficient olefins are particularly reactive with respect to conjugate addition and cycloaddition reactions [171, 172].

A general method for the preparation of acyl substituted trifluoroethoxy enol ethers was described in chapter 3. In terms of structure, these compounds closely resemble the β-substituted alkenes described above. However, these olefins are also directly substituted with a CF_3CH_2O group making them vinyl ethers as well.

In theory, one would expect these types of compounds to be particularly reactive in situations where electron poor olefinic substrates are required. For example, it is known that electron deficiency tends to increase the affinity of alkenes towards dienes in Diels-Alder reactions. Therefore, these compounds might behave as highly reactive dienophiles. Also, one would expect the trifluoroethoxy group at the β-position of the α,β-unsaturated

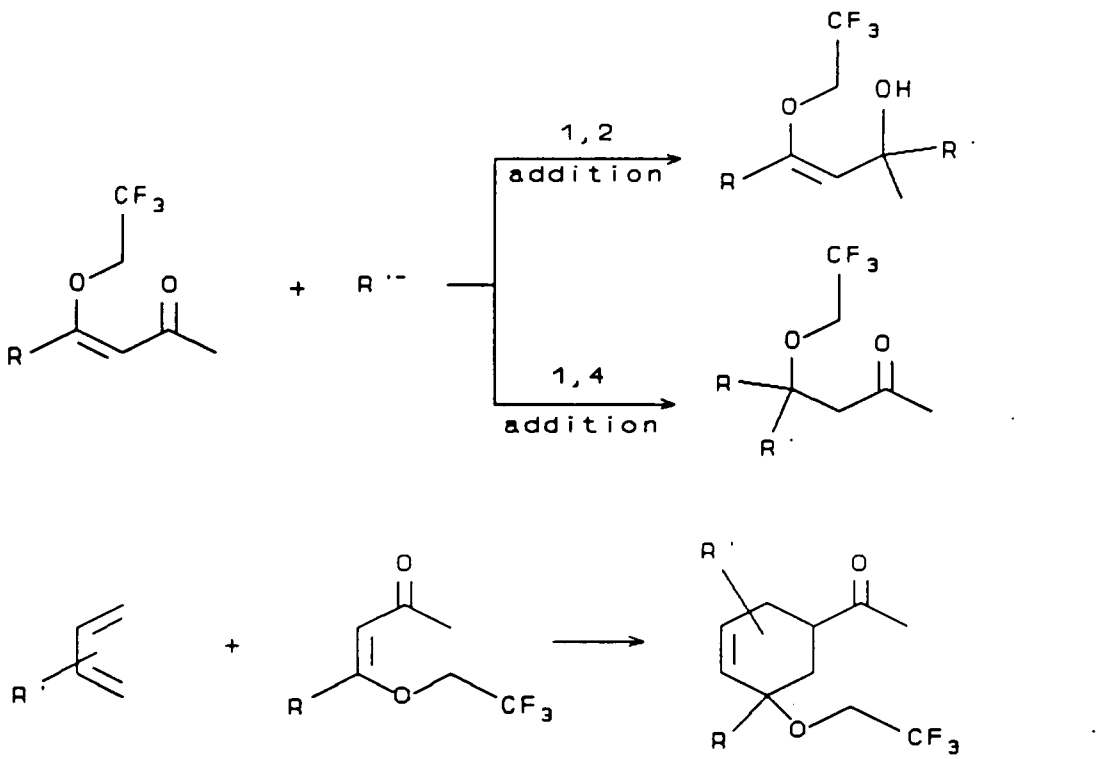
system to enhance the electrophilicity of that center making these compounds excellent substrates for nucleophilic attack (Scheme 4.2).



Scheme 4.2

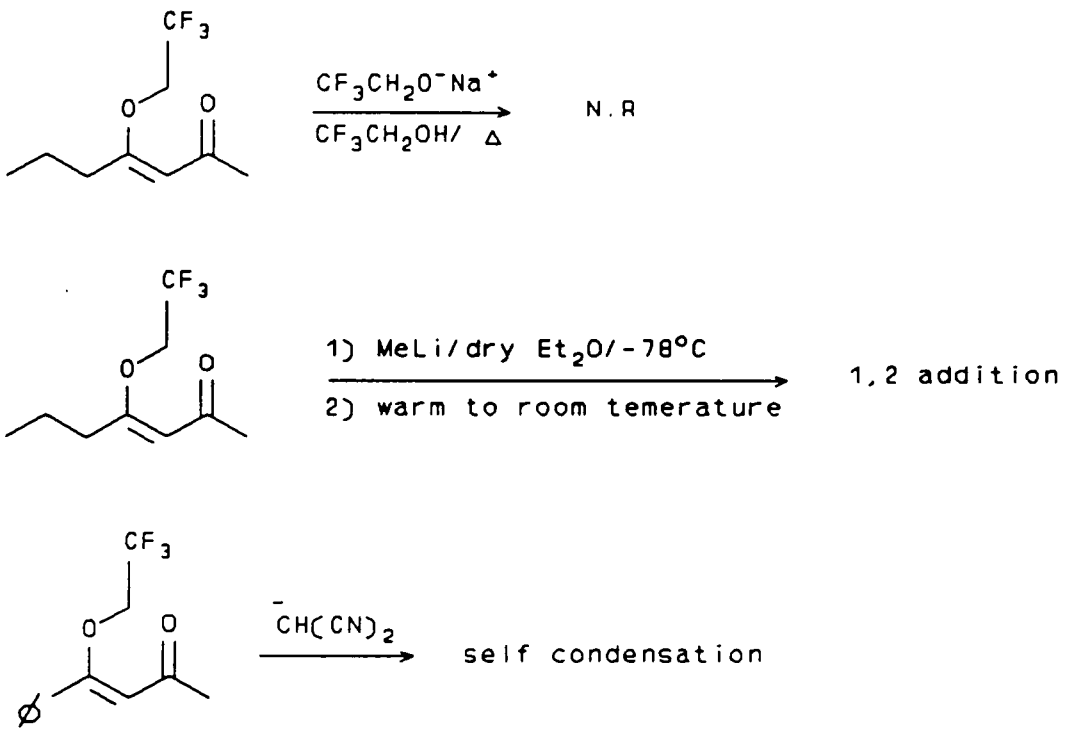
Accordingly, an investigation into the reactivity of acyl substituted trifluoroethoxy enol ethers with respect to these types of reactions was initiated. Our observations with respect to their behavior are recorded below.

Scheme 4.3 outlines the general types of reactions one might expect trifluoroethoxy substituted olefins to undergo. In the first case the unsaturated system is acting as a substrate for attack by the nucleophile R:⁻. In this example, products arising from both 1,2 and 1,4 addition can result. In the second case, the olefin acts as a dienophile in a generalized cycloaddition reaction. The ability of these structures to function as substrates for nucleophilic attack will be discussed first.



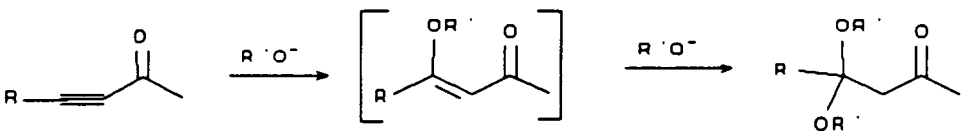
Scheme 4.3

The series of reactions shown in Scheme 4.4 were carried out. In each of these examples, the trifluoroethoxy substituted olefin is allowed to react with a nucleophile, and although these reactions were similar in that respect, the results from the various experiments were quite different.



Scheme 4.4

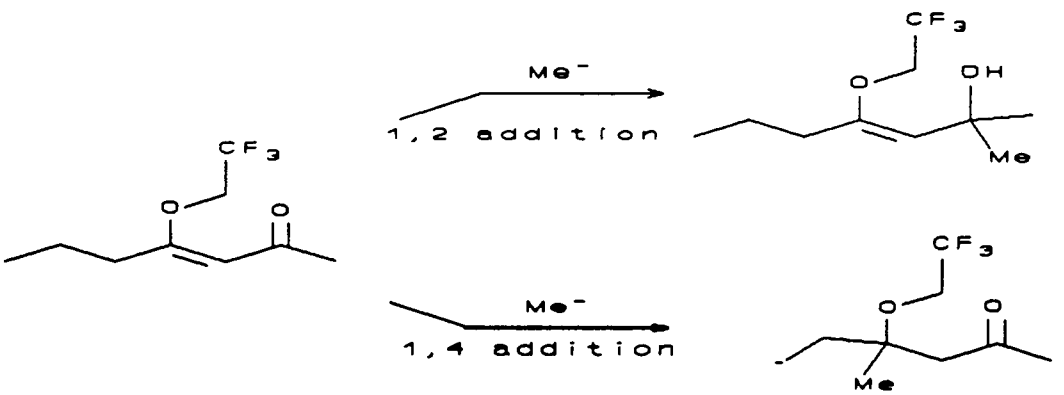
In the first example, reaction of the propyl substituted TFE enol ether with the trifluoroethoxy anion provided only unreacted starting material from the product mixture. This result, which indicated that attack at the β-position of the unsaturated system had not occurred, was somewhat surprising in that this reaction corresponds to the second step of the known procedure by which ketals are formed from alkynl ketones (eq 62). However, even under vigorous reaction conditions, the addition of a second mole of trifluoroethanol to this system did not occur.



(62)

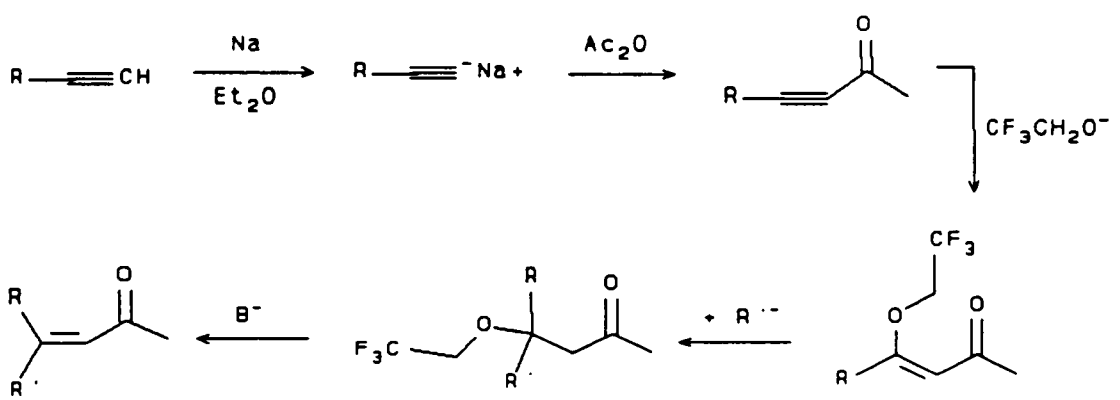
There are several possible reasons for this general lack of reactivity. The first and most obvious relates to the nucleophilicity of the trifluoroethoxy anion. The strong electron withdrawing tendencies of the β-fluorines tend to stabilize the anionic form of this alcohol, thereby lessening its nucleophilic character. It is interesting to note that the reactions generalized in equation 62 all use non-halogenated alcohols, which are more basic than their trifluoroethyl analog by several orders of magnitude. The second reason for the lack of reactivity in this case could well be due to the steric environment associated with the β-position. It is possible that this disubstituted position is too crowded to allow entry of the $CF_3CH_2O^-$ group.

The second reaction outlined in Scheme 4.4 was designed to compensate for the two problems described above. In this case, the small, highly nucleophilic reagent, methyl lithium, was reacted with the same substrate used in the first example. The results of this experiment were somewhat more satisfying in that spectral analysis of the product mixture indicated that reaction had indeed occurred. However, as outlined in Scheme 4.3, there were two possible sites at which a nucleophile might add to a substrate of this structure. Products corresponding to these two modes of attack are shown in Scheme 4.5.



Scheme 4.5

Due to the characteristic resonances associated with each of these compounds, ^{1}H and ^{13}C NMR data were used to determine that the product formed during this reaction was the carbinol, resulting from 1,2-addition of Me^- across the carbon-oxygen double bond. As in the first example, this result was somewhat disappointing, as we had hoped to make use of these types of compounds as intermediates in a reaction scheme that would allow for the synthesis of selectively substituted α,β-unsaturated ketones (Scheme 4.6).

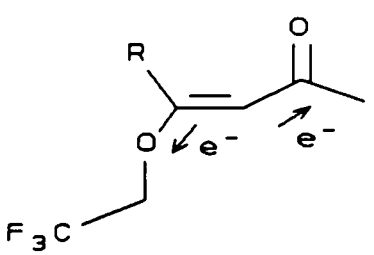


Scheme 4.6

However, the propensity for carbanions to react at the two rather than the four position of these olefinic structures rendered this approach unworkable.

The last example outlined in Scheme 4.4 involved reaction of the phenyl substituted trifluoroethoxy enol ether with the anion of malononitrile. We were interested in determining what effect, if any, the use of a fairly "soft" carbon nucleophile would have on the reactivity of these systems. Although reaction did occur in this case, product composition could not be conclusively determined. However, spectral analysis did indicate the presence of high molecular weight components in the product mixture which most likely resulted from self condensation of the starting material. This idea seems plausible when one considers that the anionic form of malononitrile was generated by reaction with the hindered base potassium t-butoxide. It is possible that this base could also catalyze condensation reactions between the carbonyl functions present in the olefinic substrates.

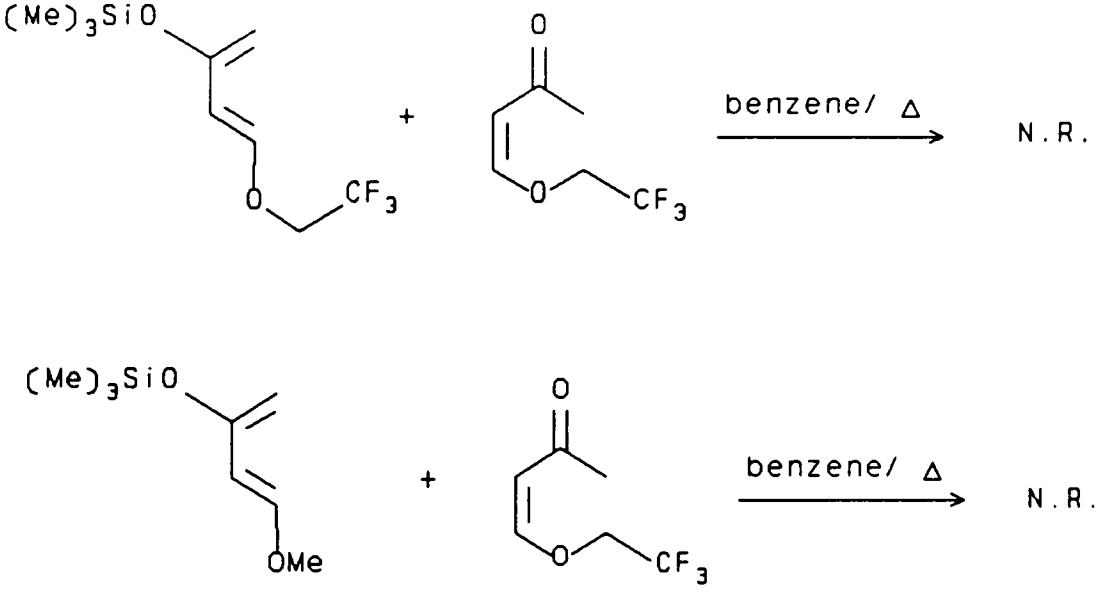
We next turned our attention to investigation of the use of acyl substituted trifluoroethoxy substituted enol ethers as 2 carbon synthons in [4+2] cycloaddition reactions. As stated earlier, the electronic demands associated with this type of reaction would seem to make these compounds ideal substrates (Scheme 4.7).



Scheme 4.7

Much of the work carried out relative to these compounds involved the use of trifluoroethoxy substituted dienes as the 4 carbon component in reaction schemes that utilized Lewis acid catalysts. However, these experiments will be covered in the section pertaining to the reactivity of the substituted dienes. The remainder of this section will deal only with those experiments which examined the reactivity of these compounds as dienophiles in the absence of acid catalysts.

The reactions carried out in this part of the study are shown in Scheme 4.8.



Scheme 4.8

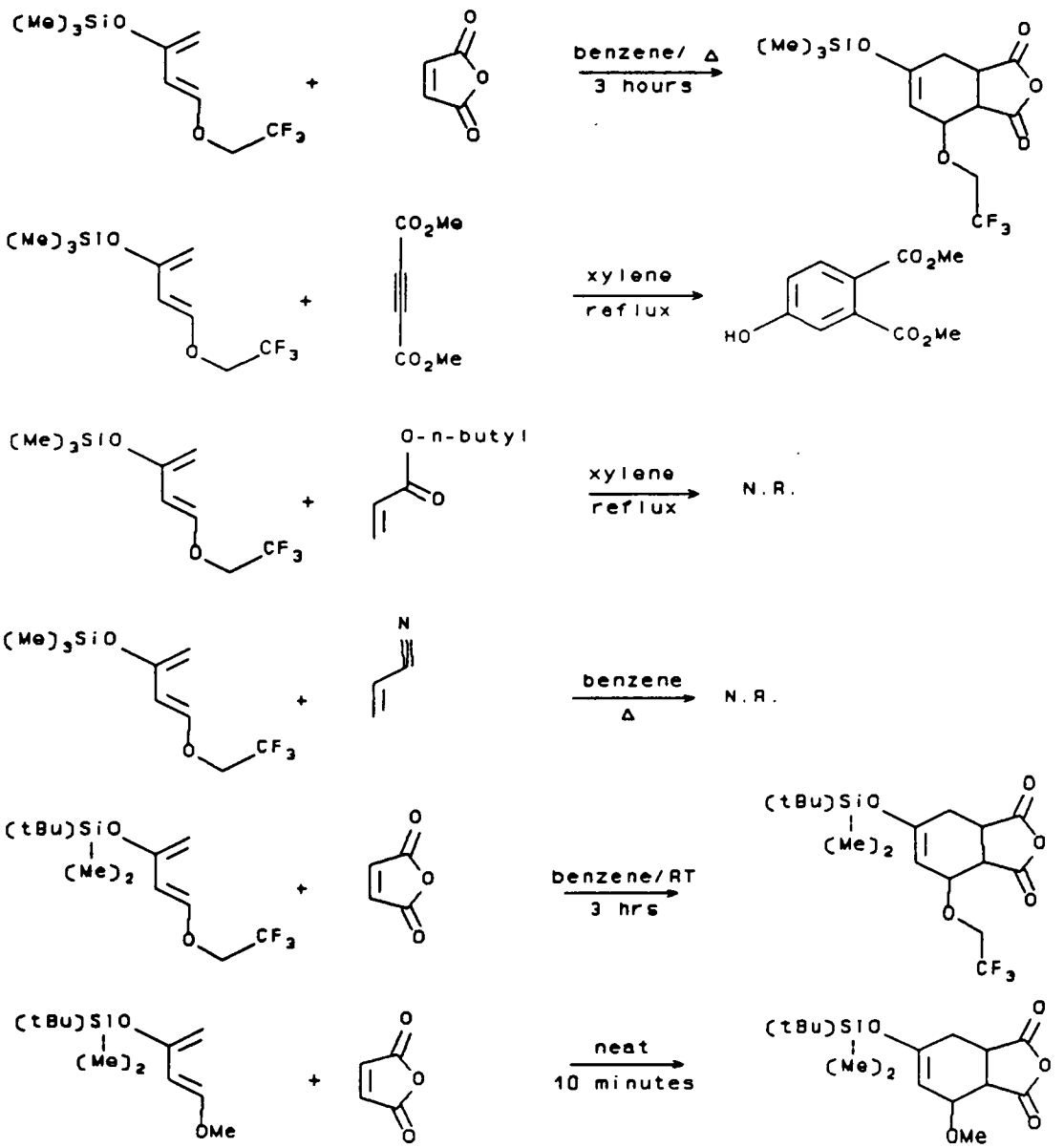
Although the number of different reactions carried out was small, they were designed in such a way that a considerable amount of information relating to the reactivity of the olefinic component could be obtained.

In the first example, the acyl substituted trifluoroethoxy enol ether is combined with its trimethylsiloxy derivative in refluxing benzene. Periodic examination of the reaction mixture by ^{1}H NMR revealed the presence of only unreacted starting materials. Even after refluxing for 24 hours, no evidence for the formation of cycloaddition products was obtained. The reason for the absence of adduct formation under these conditions is most likely due to a lack of reactivity on the part of one of the components in the mixture. However, as the reactivities of neither of these structures is well established, it is difficult to draw conclusions. The second experiment outlined in this scheme was carried out in order to clarify this situation. In this case, the methoxy substituted diene (whose behavior under these conditions is well characterized) was combined with the trifluoroethoxy substituted olefin. As before, the reaction was carried out in refluxing benzene and product formation was monitored by ^{1}H NMR. The results obtained from this experiment were identical to those observed in the first example. After 24 hours, the only materials present in the reaction mixture corresponded to unreacted starting materials. The results of these two experiments taken together tend to indicate that at least under these reaction conditions, it is a lack of reactivity on the part of the dienophile which is responsible for the lack of adduct formation.

Reactions of Trifluoroethoxy Substituted Dienol Ethers

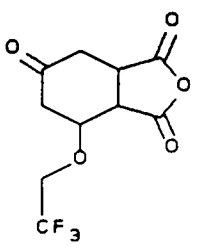
This section deals exclusively with the reactivity of 1-trifluoroethoxy-3-trialkylsiloxy-1,3-dienes as 4 carbon synthons in cycloaddition reactions. It is divided into two parts. The first deals with reactions involving these compounds in which no catalysts were not employed. The second part details the behavior of these structures under conditions which did make use of catalysts (Lewis acids).

The reactions shown in Scheme 4.9 were carried out in order to investigate the behavior of the trifluorethoxy substituted dienes under Diels-Alder conditions. As one can see, a number of different dienophiles as well as reaction conditions were utilized.

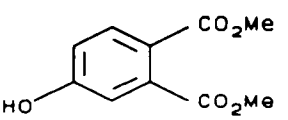


Scheme 4.9

The first two reactions outlined in this scheme are analogous to work performed by Danishefsky [150]. However, as observed earlier, his diene contained a methoxy rather than a trifluoroethoxy substituent at the one position. By comparing the behavior of the TFE substituted diene with that of its methoxy analog, we were able to determine the effect the halogenated substituent had on the reactivity of the diene system. These first two examples yielded the expected adducts following hydrolytic workup (Scheme 4.10).



maleic anhydride adduct



dimethyl acetylene dicarboxylate adduct

Scheme 4.10

In all respects, these structures are strictly analogous to the products observed by Danishefsky in his work. The only observed differences between these two sets of reactions involved how rapidly they occurred. In both cases, the trifluoroethoxy substituted dienes required either a longer period of time or more vigorous conditions for reaction to occur. However, this result was not unexpected. It has been established that electron rich dienes exhibit enhanced reactivity in these types of reactions [173]. Since the trifluoroethoxy group is electron withdrawing in an inductive sense, this decreased reactivity relative to the methoxy substituted diene is reasonable.

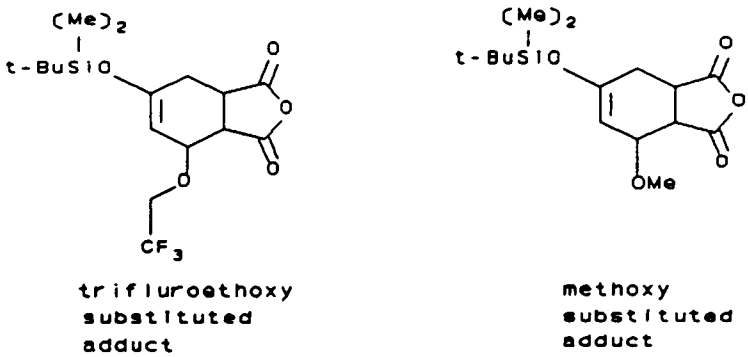
Examples 3 and 4 from Scheme 4.9 illustrate this general lack of reactivity quite well. In example 3, heating the TFE substituted diene with n-butylacrylate (which is less reactive than the first two dienophiles examined) in xylene for ~ 18 hours produced only a trace of the cycloadduct. This is in contrast to the methoxy analog which under similar conditions,

reportedly gave a good yield of cyclized product [150]. Similar results were observed for the reaction with acrylonitrile.

The last two examples in Scheme 4.9 were used to determine what effect increasing the size of the trialkylsiloxy derivative would have on diene reactivity. Results from these experiments were quite interesting. It seems that substitution of the t-butyldimethylsilyl group for the trimethylsilyl group does not decrease the reactivity of these dienes, in fact it may increase it. This observation can be rationalized on the basis of the conformational requirements associated with these types of reactions. In most cases, in order for cycloaddition to occur, the diene must assume the cisoid conformation (Scheme 4.11) [174].

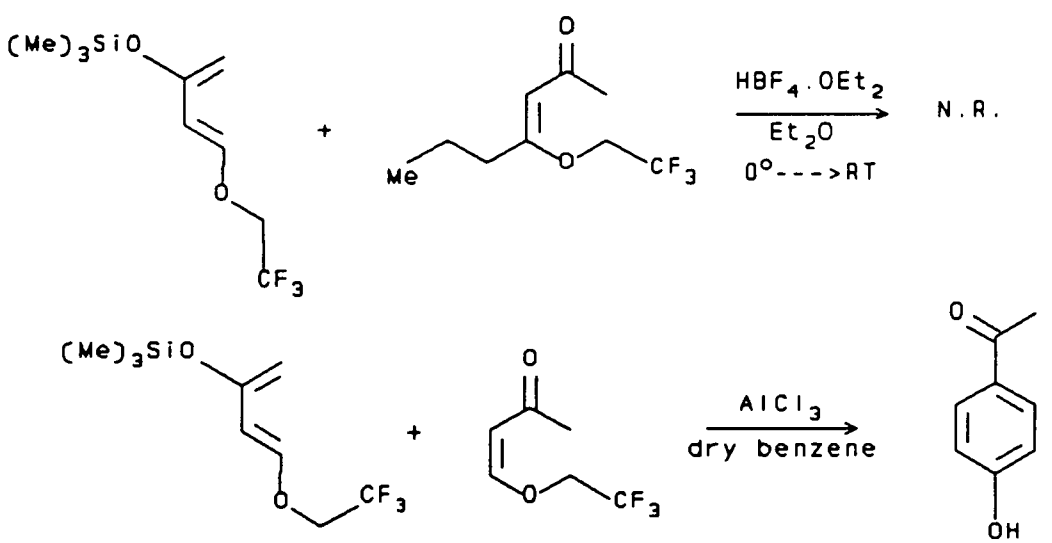
Scheme 4.11

Careful consideration of the effect that bulky groups in the 3 position of the diene would have on conformation seem to indicate that such groups might actually encourage these structures to assume the cisoid form. This behavior is probably due to unfavorable interactions between substituents in the 1 and 3 position in the transoid conformation. The products from these two reaction are shown in Scheme 4.12.



Scheme 4.12

The series of reactions outlined in Scheme 4.13 were carried out in order to determine the effect Lewis acid catalysts would have on the reactivity of the trifluoroethoxy substituted dienes.

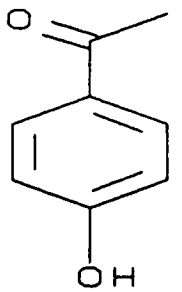


Scheme 4.13

In these examples, TFE substituted compounds were used for both the 2 and 4 carbon components. The reason for this relates to Roy's work [1]. As described in the Introductory Section, it was proposed that intermediates formed in the Lewis acid catalyzed, condensation reaction of β-dicarbonyl compounds might corresponded in structure to trifluoroethoxy substituted enol and dienol ethers. Although the diene units used in these reactions differ in their substitution at the 3 position from the intermediates proposed by Roy, we reasoned that the structures were sufficiently similar that some added insight into this earlier work might be gained through these reactions.

The first example outlined in Scheme 4.13 is illustrative with regard the reactivity of the alkylsiloxy group. This reaction was carried out several times and in each case, the results were the same. After treatment of a solution of the ene and diene with $HBF_4{\cdot}OEt_2$, the only material recovered from the reaction mixture corresponded to the enol ether component of the starting material. None of the original diene was present. Since there were no indications that cyclization reactions were occurring, another explanation for the disappearence of the diene was needed. We eventually determined that trace amounts of fluoride anion present in the acid catalyst were causing rapid hydrolysis of the diene component to the exclusion of any other reactions. The high affinity of fluorine for silicon is well known and solutions of fluoride anion (in the form of $NH_4^+BF_4^-$) are often used in schemes designed to remove alkylsiloxy protecting groups [175].

The second example outlined in Scheme 4.13 was designed in an effort to overcome this problem. As a result, $AlCl_3$ rather than $HBF_4{\cdot}OEt_2$ was utilized as the acid component. The results from this experiment were encouraging. Although some hydrolytic by-products did form during the reaction, also formed were quantities of a cyclized product whose structure was shown by ^1H and ^{13}C NMR to correspond to that give in Scheme 4.14.



Scheme 4.14

The most promising aspect of this last reaction is that it provided the first direct evidence that acyl substituted trifluoroethoxy enol ethers would participate in cycloaddition reactions. This is in contrast to earlier observations regarding the lack of reactivity in these systems. Also, the regiochemistry of the addition product corresponds to that observed by Roy in his work with similar systems. This tells us that although the structures proposed as reaction intermediates in the earlier work may not be entirely correct, there is reason to believe that they are closely related to the actual structures involved.

Summary

Our work involving trifluoroethoxy substituted compounds gave rise to a number of interesting results. Some of these were expected, others were not. Perhaps most surprising was the overall lack of reactivity exhibited by the acyl substituted trifluoroethyl enol ethers. While it was not too surprising that these structures showed little tendency to react with nucleophiles (considering the steric factors associated with the 4 position), we had fully expected these compounds to be reactive dienophiles. However, it is possible that in this respect, steric factors also played a role.

The behavior of the trifluoroethoxy dienes was in general what we had expected. Electron withdrawing groups are known to deactivate dienes with respect to cycloaddition. The comparison drawn between these compounds and their methoxy analogs helped to

illustrate this point.

The most interesting result of this work, undoubtedly, involves the products obtained from the Lewis acid catalyzed reactions of the TFE substituted enes and dienes. The fact that cyclization occurs under these conditions to give products very similar to those observed by Roy lends support to his proposal concerning the mechanistic aspects of his work.

Experimental

Reaction of (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13) with sodium trifluroethoxide. 2,2,2-trifluoroethanol (13.7 g, 0.137 moles) was added to a single necked, round bottomed flask which had been fitted with a water cooled reflux condenser and a magnetic stir bar. This material was cooled to 0°C in an ice/H_2O bath. Metallic sodium (0.25 g, 10.0 mmoles) was cut into small pieces and added slowly with stirring to the cooled alcohol solution. After several minutes, the metal had completely dissolved. To this mixture, (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13) (0.42 g, 2.0 mmoles) was added dropwise with stirring. Following this addition, the ice/H_2O bath was removed and heat was applied. The system was allowed to reflux for ~ 24 hours. Periodically, aliquots were removed and analyzed by ^1H NMR. At no time during this time were compounds other than the starting materials observed.

Reaction of (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13) with methyl lithium. A solution of (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13) (0.104 g, 0.50 mmoles) in 5 mL of anhydrous ethyl ether was placed into a 2 necked, 10 mL round bottomed flask fitted with a nitrogen inlet, water cooled reflux condenser, and magnetic stir bar. This mixture was cooled to -78 °C in a dry ice/acetone bath. Methyl lithium (0.4 mL of a 1.4 M solution in diethyl ether) was added dropwise to this solution over a period of ~ 5 minutes. After 1.5 hours, an aliquot was removed from the reaction mixture (which had gone from colorless to yellow during this period) and analyzed by ^1H NMR. This spectra indicated that reaction had occurred. The reaction mixture was allowed to warm to room temperature and left to stir overnight. During this time, most of the ether evaporated leaving a brown residue which gave a yellow solution when taken up in CH_2Cl_2. This solution was washed once with water to remove any unreacted base and then dried over K_2CO_3. Following removal of volatiles, the product mixture was analyzed by ^1H and ^{13}C NMR. The analysis

determined that this product was the result of 1,2 addition of methyl anion across the carbon-oxygen double bond to give (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-methyl-2-ol. This compound afforded the following spectroscopic data: ^{1}H NMR δ 4.53 (s, 1H), 3.89 (q, 2H, J = 8 Hz), 2.42 (t, 2H, J = 7 Hz), 1.52 (sextet, 2H, J = 7 Hz), 1.36 (s, 6H), 0.89 (t, 3H, J = 7 Hz). ^{13}C NMR δ 158.06 (s), 122.71 (q, $^1J_{CF}$ = 276 Hz), 108.33 (s), 100.56 (s), 69.72 (s), 64.44 (q, $^2J_{CF}$ = 36 Hz), 32.50 (s), 31.94 (s), 20.55 (s), 13.88 (s).

Reaction of (E) and (Z)-4-(2,2,2-trifluoroethoxy)-4-phenyl-3-buten-2-one (14) with malononitrile in the presence of potassium t-butoxide. Potassium t-butoxide (0.56 g, 5.0 mmoles) was placed into solution in t-butanol (15.0 g, 0.20 moles). This mixture was transferred to a two necked, 25 mL, round bottomed flask fitted with a water cooled reflux condenser, $CaCl_2$ drying tube, and magnetic stir bar. Malononitrile (0.132 g, 2.0 mmoles) was taken up in a small amount of t-butanol and added at room temperature with stirring to the reaction mixture. After ~ 30 minutes, a mixture of (E) and (Z)-4-(2,2,2-trifluoroethoxy)-4-phenyl-3-buten-2-one (14) (0.14 g, 0.57 mmoles) was added to the reaction flask. Almost immediately, a color change took place with the solution going from a white to an orange color. After an additional 12 hours at room temperature, the reaction mixture was extracted into CH_2Cl_2 and washed several times with H_2O. The organic layer was separated, dried over K_2CO_3, and volatiles were removed in VACUO to leave a pink colored residue. Thin layer chromatography of this product mixture (neutral alumina, 75 : 25, CH_2Cl_2 : hexane) indicated that at least 3 components were present. Analytical quantities of these compounds were isolated by column chromatography, and were analyzed using ^{1}H and ^{13}C NMR. This analysis indicated that compounds resulting from the simple addition of malononitrile to the unsaturated system were not formed.

Reaction of (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13) with 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16). A solution of (Z)-4-(2,2,2-trifluoroethoxy)-3-hepten-2-one (13) (0.174 g, 1.0 mmoles) in 5 mL dry benzene was placed

into a 2 necked, 25 mL, round bottomed flask which had been fitted with a water cooled reflux condenser, a nitrogen inlet and a magnetic stir bar. 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.236 g, 0.98 mmoles) was placed into solution in 10.0 mL of dry benzene and added dropwise with stirring to the reaction vessel. Heat was applied and the reaction was brought to reflux. After 24 hours, heating was discontinued and the reaction mixture was taken up in a quantity of CH_2Cl_2. Solvents were removed in VACUO. ^1H NMR analysis determined that this product mixture contained only unreacted starting materials.

Reaction of (Z)-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) with 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16). To a 5 mL, one necked round bottomed flask which had been fitted with a mangetic stir bar, water cooled reflux condenser, and $CaCl_2$ drying tube were added (Z)-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) (0.110 g, 0.65 mmoles), 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.172 g, 1.00 mmoles), and 5 mL of benzene. Heat was applied, and aliquots were removed periodically and analyzed by ^1H NMR. The only compounds isolated from this reaction mixture corresponded in structure to the starting materials.

Reaction of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) with maleic anhydride. A solution of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.45 g, 1.9 mmoles) in 5.0 mL dry benzene was placed into a 10 mL, one necked, round bottomed flask which had been fitted with a water cooled reflux condenser and a magnetic stir bar. Maleic anhydride (0.11 g, 1.12 mmoles), which had been purified immediately prior to use by sublimation, was added to the reaction vessel. Heat was applied and the reaction temperature was maintained at ~ 85 °C for 3 hours. After cooling, the reaction mixture was poured into 30 mL of 4 : 1 THF : 0.12 N HCl. After stirring ~ 15 minutes, this solution was extracted with $CHCl_3$. The organic layer was washed 2 times with water and dried over $MgSO_4$. The volatiles were removed in VACUO leaving a light brown oil. ^1H and ^{13}C NMR

analysis indicated that this material was the cycloaddition product. The product afforded the following spectroscopic data: ^{1}H NMR δ 5.09 (dd, 1H, J_1 = 7 Hz, J_2 = 3 Hz), 4.59 (dd, 1H, J_1 = 7 Hz, J_2 = 5 Hz), 3.72 (q, 2H, J = 9Hz), 3.49 -3.40 (m, 1 H), 3.19 (dd, 1H, J_1 = 9 Hz, J_2 = 4 Hz), 2.78 (ddd, 1H, J_1 = 18 Hz, J_2 = 6 Hz, J_3 = 2 Hz), 2.45 (dd, 1H, J_1 = 18 Hz, J_2 = 5 Hz), 1.23 (s, 9H). ^{13}C NMR δ 172.95 (s), 169.99 (s), 157.64 (s), 123.53 (q, $^1J_{CF}$ = 276 Hz), 98.26 (s), 72.53 (s), 65.05 (q, $^2J_{CF}$ = 36 Hz), 45.98 (s), 37.08 (s), 26.45 (s), -0.04 (s).

Reaction of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) with dimethylacetylenedicarboxylate (DMAD). A mixture of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.320 g, 1.37 mmoles) and dimethylacetylenedicarboxylate (0.145 g, 1.02 mmoles) was placed in a 10 mL, 1 necked round bottomed flask which had been fitted with a water cooled reflux condenser, a magnetic stir bar, and $CaCl_2$ drying tube. Approximately 2.0 mL of dry xylene was added to the mixture. Heat was applied and the solution was allowed to reflux for 2 hours. After cooling, a quantity of CH_2Cl_2 was added and the mixture was washed twice with 5% $NaHCO_3$ (aq) and once with H_2O. The organic layer was separated and dried over $MgSO_4$. Volatiles were removed in VACUO to leave a quantity of yellow liquid. ^{1}H NMR analysis of this material determined that it was the expected cycloadduct. This compound afforded the following spectroscopic data: ^{1}H NMR δ 7.72 (d, 1H, J = 8 Hz), 6.97 (d, 1H, J = 1 Hz), 6.90 (dd, 1H, J_1 = 8 Hz, J_2 = 1 Hz), 3.88 (s, 3H), 3.83 (s, 3H).

Reaction of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) with n-butyl acrylate. A mixture of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.316 g, 1.35 mmoles) and n-butyl acrylate (0.131 g, 1.02 mmoles) was placed in a 10 mL, one necked round bottomed flask which had been fitted with a water cooled reflux condenser, a magnetic stir bar, and $CaCl_2$ drying tube. Approximately 2.0 ml of dry xylene was added to this mixture. Heat was applied and the reaction was allowed to reflux for 6.0 hours. At this time, an aliquot was removed and analyzed by ^{1}H NMR. This analysis

indicated that only unreacted starting materials were present in the reaction mixture.

Reaction of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) with acrylonitrile. A mixture of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.234 g, 1.0 mmoles) and acrylonitrile (0.132 g, 2.5 mmoles) was placed in a 10 mL, one necked round bottomed flask which had been fitted with a water cooled reflux condenser, a magnetic stir bar, and $CaCl_2$ drying tube. Approximately 5.0 mL of dry benzene was added to this mixture. Heat was applied, and the reaction mixture was allowed to reflux for 18 hours. At the end of this time, heating was discontinued and an aliquot was removed and analyzed by ^1H NMR. This analysis indicated that no reaction had occurred and that the only components present were unreacted starting materials.

Reaction of 3-(t-butyldimethylsiloxy)-1-(2,2,2-trifluoroethoxy)-1,3-butadiene (17) with maleic anhydride. A mixture of 3-(t-butyldimethylsiloxy)-1-(2,2,2-trifluoroethoxy)-1,3-butadiene (17) (0.142 g, 0.50 mmoles) and maleic anhydride (0.50 g, 0.510 mmoles), which had been purified immediately prior to use by sublimation, was placed in a 10 mL, one necked round bottomed flask which had been fitted with a water cooled reflux condenser, a magnetic stir bar, and a $CaCl_2$ drying tube. To this mixture was added ~ 5 mL dry benzene. After stirring 6 hours at room temperature, the volatiles were removed in VACUO, and the residual material was analyzed by ^1H NMR. This analysis indicated that cycloadduct formation had occurred. The product yielded the following spectroscopic data: ^1H NMR δ 5.10 (dd, 1H, $J_1 = 7$ Hz, $J_2 = 3$ Hz), 4.59 (dd, 1H, $J_1 = 7$ Hz, $J_2 = 4$ Hz), 3.73 (q, 2H, $J = 7$ Hz), 3.52 - 3.42 (m, 1H), 3.20 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 4$ Hz), 2.79 (ddd, 1H, J_1 18 Hz, $J_2 = 6$ Hz, $J_3 = 3$ Hz), 2.45 (dd, 1H, $J_1 = 18$ Hz, J_2 8Hz), 0.94 (s, 9H), 0.18(s, 6H).

Reaction of 3-(t-butyldimethylsiloxy)-1-methoxy-1,3-butadiene with maleic anhydride. A mixture of 3-(t-butyldimethylsiloxy)-1-methoxy-1,3-butadiene (0.104 g, 0.49 mmoles) and maleic anhydride (0.049 g, 0.50 mmoles), purified immediately prior to use by sublimation, were placed in a 5 mL single necked round bottomed flask which had been fitted

with a $CaCl_2$ drying tube and a magnetic stir bar. On mixing, an exothermic reaction took place. After ~ 10 minutes, a sample of this material was removed and analyzed by ^1H NMR. This analysis indicated that adduct formation had taken place to yield the expected product. This compound afforded the following spectroscopic data: ^1H NMR δ 5.14 (dd, 1H, J_1 = 7 hz, J_2 = 3 Hz), 4.28 (dd, 1H, J_1= 7 Hz, J_2 = 4 Hz), 3.46 - 3.36 (m, 1H), 3.19 (s, 3 H), 3.13 (dd, 1H, J_1 = 8 Hz, J_2 = 4 Hz), 2.76 (ddd, 1H, J_1 = 18 Hz, J_2 6 Hz, J_3 = 3 Hz), 2.39 (dd, 1H, J_1 = 18 Hz, J_2 = 8 Hz, 0.96 (s, 9H), 0.21 (s, 6H).

Reaction of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) with (Z)-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) in the presence of HBF_4·OEt_2. A solution of (Z)-4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) (0.234 g, 1.0 mmoles) in ~ 20 mL dry ethyl ether was added to a 50 mL, 2 necked round bottomed flask that had been fitted with a water cooled reflux condenser, a magnetic stir bar, a nitrogen inlet, and a dropping funnel. HBF_4·OEt_2 (0.1 mL, 85% solution in ethyl ether) was added rapidly to this solution. A quantity of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.210 g, 1.0 mmoles) was taken up in 10 mL dry ethyl ether and added dropwise over a period of ~ 1 hour to the reaction mixture. As this process occurred, the solution went from clear to a yellow color, which gradually darkened as addition proceeded. The mixture was allowed to stir at room temperature for ~ 1 hour at which time an aliquot was removed and analyzed using ^1H NMR. This analysis revealed that only the substituted enol ethers remained in the reaction flask. Neither diene nor cycloadduct were observed.

Reaction of 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) with 4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) in the presence of $AlCl_3$. A 50 mL, 3 necked round bottomed flask was fitted with a water cooled reflux condenser, a nitrogen inlet, and a magnetic stir bar. To this was added anhydrous $AlCl_3$ (0.015 g, 0.11 mmoles) and 25 mL dry benzene. This mixture was allowed to stir for ~ 1 hour until the Lewis acid had formed a suspension in the benzene. A quantity of 4-(2,2,2-trifluoroethoxy)-3-buten-2-one (12) (

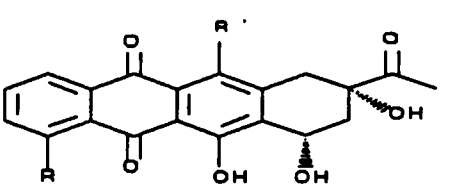
0.210 g, 1.00 mmoles) was taken up in 10 mL of dry benzene and added dropwise to the reaction flask over a period of ~ 45 minutes. As this addition progressed, the mixture went from a suspension to a bronze colored solution (the solid $AlCl_3$ dissolved). 1-(2,2,2-trifluoroethoxy)-3-(trimethylsiloxy)-1,3-butadiene (16) (0.230 g, 0.98 mmoles) was taken up in 10 mL of dry benzene and added dropwise with stirring over a period of ~ 25 minutes to the reaction flask. During this procedure, the bronze colored solution turned bright yellow and then proceeded to darken until it was a reddish-brown color. The mixture was allowed to stir at room temperature for ~ 18 hours. At the end of this time, a quantity of CH_2Cl_2 was added, and the organic layer was washed several times with 5% (aq) $NaHCO_3$ to remove residual acid. Following two washes with water, the organic layer was dried over $MgSO_4$ and volatiles were removed in VACUO to yield a quantity of a brown liquid. Chromatography of this product (silica gel, 10% : 90% acetone : CH_2Cl_2) revealed 3 separate components. Of these, one corresponded to the enol ether starting material and one was identified by ^1H and ^{13}C NMR as being the cycloaddition adduct, p-hydroxy acetophenone. This adduct, which accounted for ~ 20 % of the product mixture, yielded the following spectroscopic data: ^1H NMR δ 7.91 (d, 2H, J = 8 Hz), 6.91 (d, 2H, J = 8 Hz), 2.57 (s, 3H). ^{13}C NMR δ 197.40 (s), 160.56 (s), 131.00 (s), 130.28 (s), 115.37 (s), 26.21 (s).

Appendix I

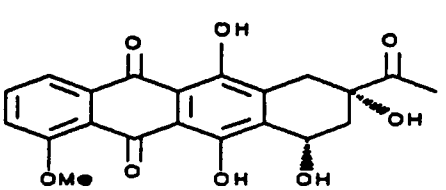
Preparation of Naphthyl Substituted β-Diketones

During the course of our investigation into the behavior of trifluoroethoxy substituted compounds, several studies were undertaken in order to examine the synthetic potential of these compounds. Chapter 4 describes a number of experiments directly related to this goal. However, these were not the only attempts made to utilize these types of compounds in terms of synthetic applications. During the early phase of this research, a number of schemes were proposed which utilized the cyclization reaction of β-dicarbonyl compounds in the presence of TFD and $HBF_4{\cdot}OEt_2$ as the key step. The methodology employed in these schemes included variations on the work carried out by Roy and involved mixed condensation (condensation of two dissimilar β-dicarbonyl units) as well as self condensation reactions.

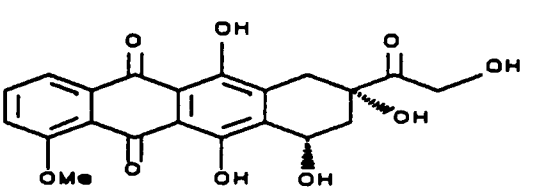
The most promising of these proposals targeted the preparation of a number of compounds in the anthracyclinone system. The general structure for these compounds as well as specific structures for certain members of this group are shown in Scheme I.1.



general structure



Daunomycinone

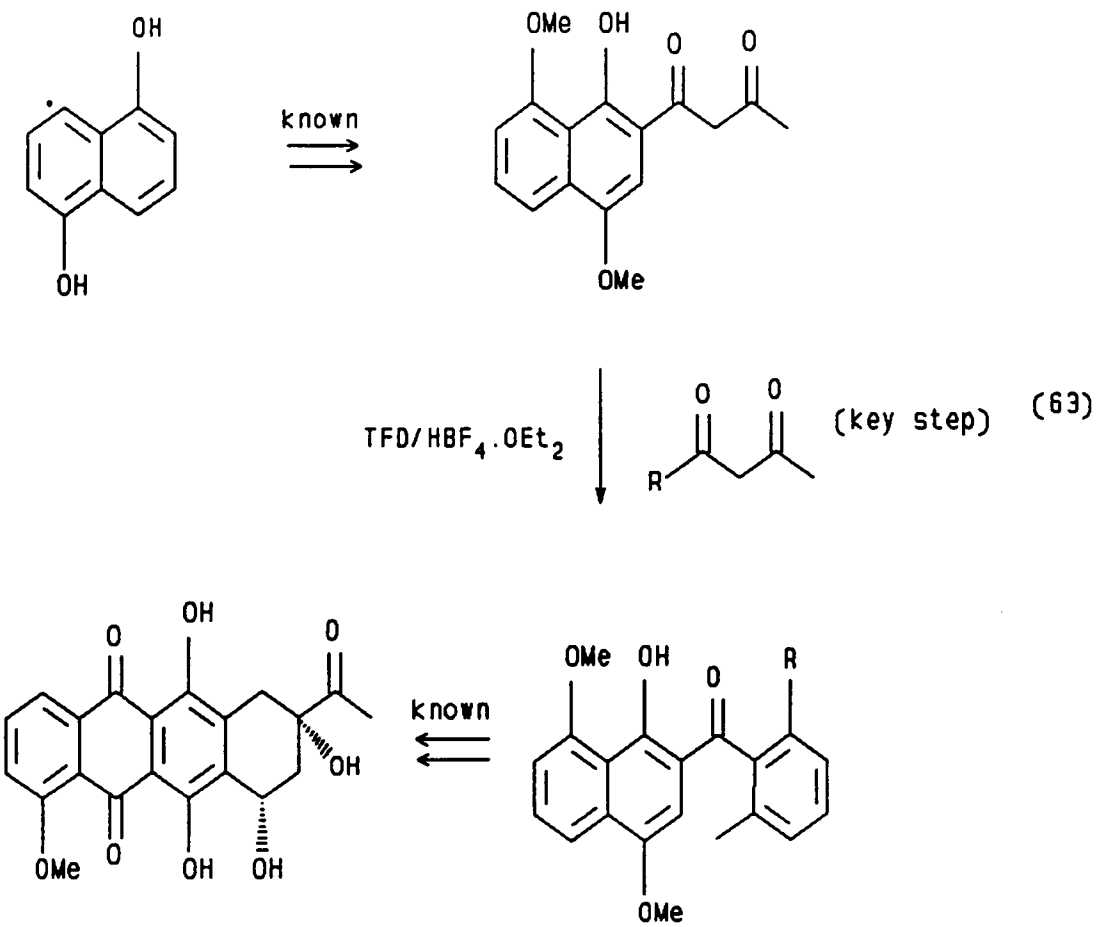


Adriamycinone

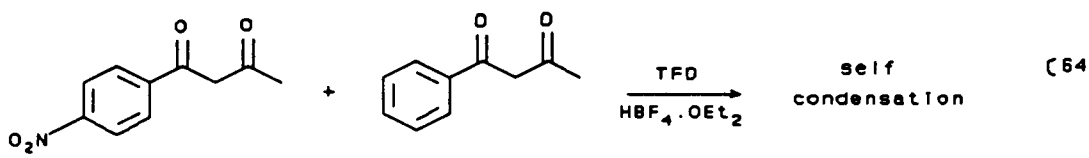
Scheme I.1

Due to their antitumor/anticancer activity these compounds have recently become the focus of much interest including numerous attempts at their synthetic preparation [176].

The scheme originally proposed for the general synthesis of these tetracyclic structures is outlined in equation 63. As seen here, the key step in this reaction sequence involves the acid catalyzed condensation of the naphthyl substituted β-diketone with its substituted analog. This approach was attractive in that it held the potential for significantly reducing the number of steps previously required to reach this point [176].



Although the reasoning used to develop the approach outlined above was sound, this line of research was eventually abandoned. The main reason for this action was our inability to perfect the mixed condensation technique. Using the model system outlined in equation 64, we had hoped to form products which incorporated 1 molecule of each of the β-dicarbonyl subunits. However, the only materials isolated from these reaction mixtures corresponded to either self condensation products or unreacted starting materials. Due to this

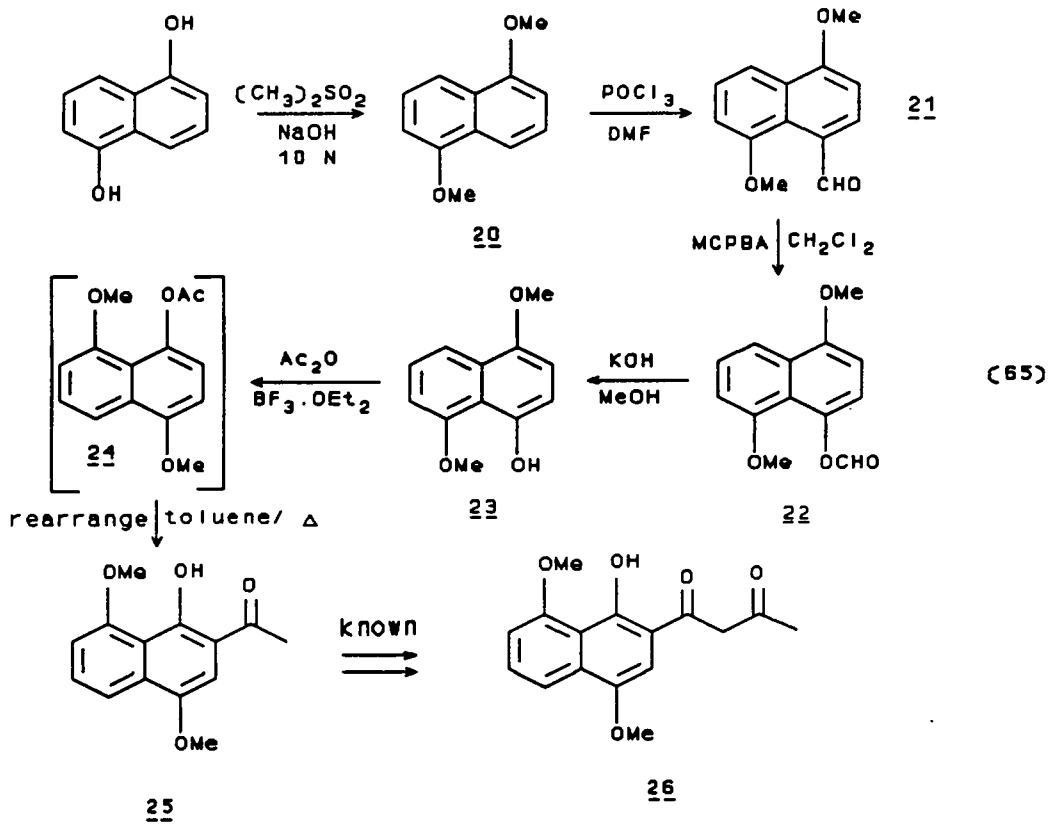


(64)

absence of positive results, synthetic applications involving mixed condensation reactions were set aside until a better understanding of the reactivities and reaction requirements of the compounds being utilized had been gained.

One positive aspect to this line of research did develop. It was determined rather early on that if these mixed condensation reactions were going to find wide synthetic utility, a general method for the synthesis of aryl substituted β-diketones was needed. Our successful development of such a method is outlined below.

A key intermediate in the proposed synthesis of the tetracyclic structure outlined in equation 63 is the naphthyl substituted β-dicarbonyl structure. However, compounds of this general form are not commercially available, therefore, they must be prepared. One such preparation is described below (eq 65) [177, 178].



In this series of reactions, the starting material, 1,5-dihydroxynaphthalene, is methylated at both hydroxyl positions using dimethylsulfate in 10 N (aq) NaOH. Carbonylation of this product at the four position ($POCl_3$, DMF) followed by oxidation with MCPBA gave the naphthyl formate (22). Ester hydrolysis yielded structure (23) which was treated with $Ac_2O/BF_3{\cdot}OEt_2$ to form the naphthyl acetate (24). This material (not isolated) was then heated in toluene causing a thermal rearrangement to occur which gave rise to the substituted aryl ketone (25). Several procedures are available for converting this structure into the naphthyl substituted β-diketone (26).

Experimental

Preparation of 1,5-dimethoxy naphthalene (20). 1,4-dihydroxy naphthalene (200.0 g, 1.25 moles) was placed into a 3 necked, 3 liter, round bottomed flask fitted with a dropping funnel, magnetic stirring bar, and a water cooled reflux condenser. To this material was added ~ 220 mL of 10 N NaOH and ~ 440 mL of distilled H_2O. Dimethyl sulfate (213.3 g, 1.69 moles) was added dropwise with stirring to this reaction mixture over a period of 2 hours. During the course of this addition, the solution became quite thick. Following addition, the reaction was allowed to stand for 30 minutes with agitation at 5 minutes intervals. At the end of this time, 200 mL of 10 N NaOH and 220 mL of distilled H_2O were addded and the solution was allowed to stir an additional hour. The product mixture was then cooled to 0 °C in an ice/H_2O bath and filtered to yield a quantity of the crude methylated product. This material was dried overnight at ~ 100 °C. The product, which was further purified by recrystallization, consisted of a dark brown colored solid. ^1H NMR data indicated formation of the desired product.

Preparation of 4,8-dimethoxy-1-naphthalene carboxaldehyde (21). 1,5-diemthoxy naphthalene (37.0 g, 0.197 moles) was placed into a 3 necked, 3 liter, round bottomed flask which was fitted with a water cooled reflux condenser and a mechanical stirring unit. To this material was added 40 mL of toluene and dimethylformamide (26.4 mL, 0.362 moles). This reaction mixture was then cooled to 0 °C in an ice/H_2O bath and allowed to stir until it formed a slurry. Phosphorous oxychloride (41.1 g, 0.268 moles) was added dropwise to this mixture over a period of ~ 3 minutes. During this time, the brown colored solution gave off a white vapor which rapidly dissipated. Stirring at 0 °C was continued for an additional 30 minutes. At the end of this time, heat was applied and the reaction was allowed to reflux for ~ 2 hours. At the end of this time, the hot solution was poured with stirring over a mixture of 600 mL 10% NaOH (aq) and 200 g of ice. This procedure gave rise to a brown solution

which contained a large amount of an insoluble greenish colored material. This mixture was filtered and the aqueous filtrate was extracted 6 times to a total of 600 mL with benzene. The solid material was also washed with benzene. These organic fractions were combined and washed 3 times to a total of 300 mL with 5% HCl (aq), 2 times to a total of 300 mL with distilled water,and 1 time with 150 mL brine. The organic layer was then dried over $MgSO_4$ and the solvent was removed in VACUO to yield ~ 13.6 g of a brown colored solid. ^1H NMR data indicated formation of the desired product.

Preparation of 4,8-dimethoxy-1-naphthyl formate (22). 4,8-dimethoxy-1-naphthalene carboxaldehyde (6.48 g, 0.030 moles) was taken up in 325 mL CH_2Cl_2. To this solution was added m-chloroperoxybenzoic acid (MCPBA) (12.2 g, 0.071 moles), and the resulting mixture was allowed to stir for 2.5 hours. At this point, ~ 100 mL of 10% (aq) $Na_2S_2O_3$ was added and stirring was continued for an additional 30 minutes. At the end of this time, this material was poured into an additional 250 mL of 10% (aq) $Na_2S_2O_3$ and shaken vigorously. The phases were separated, and the aqueous phase was extracted twice with methylene chloride to a total of 200 mL. The organic portions were combined, dried over $MgSO_4$, and the solvent was removed in VACUO to yield the crude formate. This material was used without further purification.

Preparation of 4,8-dimethoxy-1-naphthol (23). The crude formate was dissolved in 200 mL 1 : 1, THF : CH_3OH. This solution was cooled to 0 °C in an ice/H_2O bath, and KOH (4.25 g, 0.08 moles) in 40 mL of ice cold MeOH was added. Immediately, the brown colored solution turned black. After 15 minutes, enough 5% (aq) HCl was added to the reaction mixture to cause the pH to drop to ~ 1. This acidic solution was then poured into 1000 mL of H_2O. This system was extracted 3 times with CH_2Cl_2 to a total of ~ 450 mL. The organic phases were combined, washed twice to a total of 400 mL with H_2O and once with 200 mL brine. The organic layer was dried over $MgSO_4$, and the solvent was removed in VACUO to yield the crude naphthol. Filtration of this material through silica gel gave the

crystalline product. ^1H NMR data indicated formation of the desired product.

Preparation of 1-hydroxy-4,8-dimethoxy-2-acetonaphthone (25). 4,8-dimethoxy-1-naphthol (1.0 g, 4.9 mmoles) was taken up in 10 mL toluene. Acetic anhydride (0.54 g, 5.3 mmoles) and BF_3OEt_2 (0.1 mL) were rapidly added to this solution. Heat was applied, and the mixture was allowed to reflux for ~ 5 minutes. After cooling, a quantity of CH_2Cl_2 was added and the organic phase was washed with H_2O then dried over $MgSO_4$. Removal of solvent in VACUO left a crude product which by ^1H and ^{13}C NMR analysis proved to be the rearrangement product (25). This compound afforded the following spectrscopic data: ^1H NMR δ 13.53 (br. s, 1H), 7.83 (dd, 1H, J_1 = 8 hz, J_2 = 1 Hz), 7.55 (t, 1H, J = 8 Hz), 6.99 (s, 1H), 6.96 (br. d, 1H, J = 8 Hz), 4.96 (s, 3H), 3.97 (s, 3 H), 2.71 (s, 3H). ^{13}C NMR δ 201.91 (s), 159.20(s), 147.00 (s), 129.88 (s), 114.91 (s), 107.38 (s), 103.01 (s), 56.43 (s), 55.90 (s), 28.68 (s).

Appendix II

^{1}H NMR Data For Compounds Used in the Ketal Hydrolysis Study

Benzophenone. ^{1}H NMR (CD_3CN) δ 7.81 - 7.72 (m, 4H), 7.69 - 7.60 (m, 2H), 7.58 - 7.5 (m, 4H).

Benzophenone diethyl ketal. ^{1}H NMR (CD_3CN) δ 7.50 (d, 4H, J = 6 Hz), 7.38 - 7.19 (m, 6H), 3.30 (q, 4H, J = 7 Hz), 1.20 (t, 6H, J = 7 Hz).

Benzophenone bis(trifluoroethyl) ketal. ^{1}H NMR (CD_3CN) δ 7.51 (d, 4H, J = 6 Hz), 7.46 - 7.34 (m, 6H), 3.79 (q, 4H, J = 8.8 Hz).

Acetophenone. ^{1}H NMR (CD_3CN) δ 7.98 (d, 2H, J = 6 Hz), 7.66 - 7.58 (m, 1H), 7.53 - 7.47 (m, 2H), 2.58 (s, 3H).

Acetophenone diethyl ketal. ^{1}H NMR (CD_3CN) δ 7.51 (d, 2H, J = 6 Hz), 7.41 - 7.28 (m, 3H), 3.54 - 3.23 (m, 4H), 1.48 (s, 3H), 1.16 (t, 6H, J = 7 Hz).

Acetophenone bis(trifluoroethyl) ketal. ^{1}H NMR (CD_3CN) δ 7.62 (dd, 2H, J_1 = 6 Hz, J_2 = 1 Hz), 7.60 - 7.50 (m, 3H), 4.11 - 3.88 (m, 4H), 2.25 (s, 3H).

Cyclohexanone. ^{1}H NMR (CD_3CN) δ 2.28 (t, 4H, J = 7 Hz), 1.87 - 1.76 (broad, 4H), 1.75 - 1.65 (broad, 2H).

Cyclohexanone diethyl ketal. ^{1}H NMR (CD_3CN) δ 3.41 (q, 4H, J = 7 Hz), 1.62 - 1.54 (broad, 4H), 1.61 - 1.32 (broad, 6H), 1.09 (t, 6H, J = 7 Hz).

Cyclohexanone bis(trifluoroethyl) ketal. ^{1}H NMR (CD_3CN) δ 3.93 (q, 4H, J = 9.0 Hz), 1.76 -1.68 (broad, 4H), 1.59 - 1.34 (broad, 6H).

Acetone. ^{1}H NMR (CD_3CN) δ 2.09 (s).

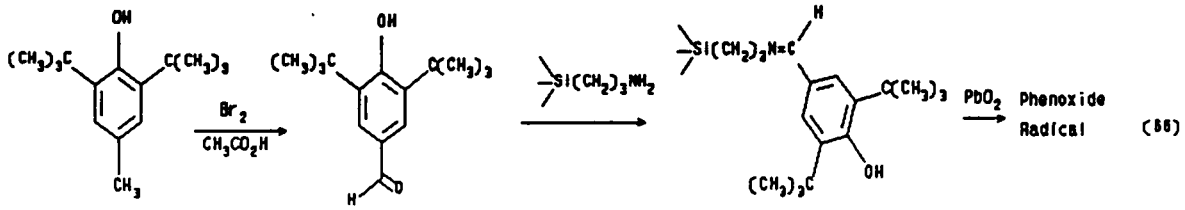
Acetone diethyl ketal. ^{1}H NMR (CD_3CN) δ 3.42 (q, 4 H, J = 7 Hz), 1.27 (s, 6H), 1.09 (t, 6H, J = 7 Hz).

Acetone bis(trifluoroethyl) ketal. ^{1}H NMR (CD_3CN) δ 3.95 (q, 4H, J = 9.0 Hz), 1.41 (s, 6H).

Appendix III

Preparation of An Immobilized Phenoxide Free Radical For Use in SLIT ^{1}H DNP Experiments [179]

The immobilized phenoxide free radical (27) was prepared as outlined in equation 66.



(66)

27 28

This three step procedure utilized 2,6-di-*tert*-butyl-4-methylphenol as starting material. Oxidation of this compound with bromine in acetic acid gave rise to the substituted benzaldehyde which was then condensed with the amine capped silica gel to give the immobilized phenoxide precursor. The free radical was generated from this material by reaction with lead oxide.

Experimental

Preparation of 3,5-di-tert-butyl-4-hydroxybenzaldehyde (27) [180]. To a mixture of 800 mL of glacial acetic acid and 200 mL water was added 2,6-di-*tert*-butyl-4-methylphenol (80 g, 0.363 moles). This solution was placed into a 3 L, 3 necked round bottomed flask which had been fitted with a mechanical stirrer, a water cooled reflux condenser, and a dropping funnel. Bromine (37 mL) was added slowly to the reaction mixture over a period of 2 hours. Following this addition, the mixture was stirred for an additional hour. At the end of this time 500 mL of ice water was added and the cloudy suspension was stored in the deep freeze for 48 hours. The cooled mixture was filtered and the recovered product (a pale yellow solid) was washed with a small amount of 1:1 glacial acetic acid : water then dried under vacuum. The product was purified by recrystallization from hexane. M.P. 187 - 188°C. This compound afforded the following spectroscopic data: ^{1}H NMR δ 9.85 (s, 1H), 7.73 (s, 2H), 5.86 (s, 1H), 1.48 (s, 18H).

Preparation of Immobilized Phenoxide Free Radical Precursor (28). To a 100 mL, 3 neck, round bottomed flask was added 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (1.0 g, 4.27 mmoles)) and 0.5 g of amino capped silica gel (Baker). The flask was equipped with a magnetic stirring bar and a Soxhlet extractor containing approximately 75 g of freshly activated 3Å molecular sieves. About 75 mL of anhydrous benzene was added, and the mixture was refluxed for 3 days. The derivatized silica gel was filtered and washed several times with hot benzene and dried under vacuum.

References

1) J.T. Roy, Ph.D. Thesis 1984 Virginia Polytechnic Institute and State University.

2) M.E. Evans, *Carbohydr. Res.* 21, 473 (1972).

3) P.A. Gent, *J. Chem. Soc. Perkin Trans. 1*, 1973, 1858.

4) D. Horton, W. Weckerle, *Carbohydr. Res.* 44, 227 (1975).

5) D.M. Clode, *Chem. Rev.* 79, 491 (1979).

6) P.P. Singh et al., *Tetrahedron Lett.* 1977, 439.

7) J.J. Brown, R.H. Lenhard, S. Berstein, *J. Am. Chem. Soc.* 86, 2183 (1964).

8) J.R. Bull et al., *J. Chem. Res. (5)*, 1979, 224.

9) N. Yamazaki, *J. Chem. Soc. Chem. Commun.* 1979, 807.

10) N. Yamazaki, *J. Org. Chem.* 44, 1720 (1979).

11) T.W. Greene, "Protective Groups in Organic Chemistry", Ch. 4 pp 114 - 129, John Wiley & Sons, New York, 1981.

12) F.A.J. Meskens, *Synthesis*, 13, 501 (1981).

13) J. March, "Advanced Organic Chemistry", 3rd ed., pp 789-791, Wiley-Interscience, New York, 1985.

14) S.R. Sandler, W. Karo, "Organic Functional Group Preparations Vol. 3", pp 12-13, Academeic Press, Inc., New York, 1972.

15) H. Zinke-Allmang, W. Scheimeier, **German Patent** (DOS) 2636278, BASF AG (1978); C.A. 88, 169599 (1978).

16) G. Schill et al., *Chem. Ber.* 112, 3603 (1979).

17) K. Blumberg, A. Fucello, T. Vanes, *Carbohydr. Res.* 70, 217 (1979).

18) D.P. Roelofsen, H. van Bekkum, *Synthesis*, 4, 419 (1972).

19) A.R. Pinder, H.Smith, *J. Chem. Soc.* 1954, 113.

20) R.C. Elderfield, F.W. Short, in *Heterocyclic Compounds*, vol. 3, John Wiley & Sons, New York, London, 1957, p. 52.

21) H. Meerwein, In Houben-Weyl, *Methodem der Organischen Chemie*, 4th Edn., E. Muller, Ed., vol. VI/3, Georg Thieme Verlag, Stuttgart, 1965.

22) S. Patai, Ed., "The Chemistry of the Ether Linkage", John Wiley & Sons, New York, London, 1967, chapter 7.

23) J.P. Ward, in *Methodicum Chimicum*, F. Korte, Ed., vol. 5, Georg Thieme Verlag, Stuttgart, 1975, pp. 511-524.

24) V.I. Stenberg, D.A. Kubik, *J. Org. Chem.* **39**, 2815 (1974).

25) J. Toulec, M. Alaya, *Tetrahedron lett.* **1978**, 5207.

26) J.D. Roberts and M.C. Caserio, "Basic Principles of Organic Chemistry", p. 447, Benjamin, New York, 1964.

27) D.L. Saitman et al., *J. Org. Chem.* **44**, 2838 (1979).

28) E.C. Blossey, L.M. Turner, D.C. Neckers, *J. Org. Chem.* **40**, 959 (1975).

29) T.S. Daris et al., *J. Org. Chem.* **40**, 1478 (1975).

30) W. Reusch et al., *J. Org. Chem.* **44**, 3666 (1979).

31) N.B. Lorette, W.L. Howard, *J. Org. Chem.* **25**, 521 (1960).

32) A. Kankaanpera et al., *J. Am. Chem. Soc.* **95**, 3618 (1973).

33) C. Piantadosi et al., *J. Org. Chem.* **28**, 242 (1963).

34) K. Moedritzer, J.R. Van Wazer, *J. Org. Chem.* **30**, 3925 (1965).

35) G. Bauduin, Y. Pietrasanta, *Tetrahedron*, **29**, 4225 (1973).

36) G. Bauduin, Y. Pietrasanta, B. Pucci, *Tetrahedron*, **33**, 3105 (1977).

37) G. Bauduin, Y. Pietrasanta, B. Pucci, *Tetrahedron Lett.* **1975**, 2889.

38) D.H.R. Barton, C.C. Dawes, P.D. Magnus, *J. Chem. Soc. Chem. Commun.* **1977**, 432.

39) W.L. Howard, N.B. Lorette, *J. Org. Chem.* **25**, 525 (1960).

40) W.L. Howard, N.B. Lorette, **U.S. Patent** 3024284, Dow Chemical Co. (1962); **C.A. 57**, 8441 (1962).

41) J.A. Marshall, G.A. Flynn, *Synth. Commun.* **9**, 123 (1979).

42) G.L. Larson, A. Hernandez, *J. Org. Chem.* **38**, 3935 (1973).

43) J.L. Luche, A.L. Gemal, *J. Chem. Soc. Chem. Commun.* **1978**, 976.

44) A.L. Gemal, J.L. Luche, *J. Org. Chem.* **44**, 4187 (1979).

45) E. Schmitz, *Chem. Ber.* **91**, 410 (1958).

46) R.B. Loftfield, L. Schaad, *J. Am. Chem. Soc.* **76**, 35 (1954).

47) C.L. Stevens, E. Farkes, B. Gillis, *J. Am. Chem. Soc.* **76**, 2695 (1954).

48) C.L. Steven, B.T. Gillis, *J. Am. Chem. Soc.* **79**, 3448 (1957).

49) S. Searles, R. Liepins, H.M. Kash, *J. Org. Chem.* **26**, 36 (1961).

50) H.E. Simmons, D.W. Wiley, *J. Am. Chem. Soc.* **82**, 2288 (1960).

51) S. Antus, F. Boross, M. Nogradi, *J. Chem. Soc. Chem. Commun.* **1977**, 333.

52) S. Antus, F. Boross, M. Nogradi, *Justus Liebigs Ann. Chem.* **1978**, 107.

53) H. Bredereck, F. Effenberger, G. Simchen, *Angew. Chem.* **73**, 493 (1961).

54) W. Voelter, C. Djerassi, *Chem. Ber.* **101**, 1154 (1968).

55) **British Patent** 1309156, Atlas Chemical Industries Inc. (1969; **C.A. 79**, 19051 (1973).

56) D.Y. Waddan, **British Patent** 1046608, Shell International Research Maatschappij NV (1965); **C.A. 66**, 18714 (1967).

57) R.V. Hoffmann, *Tetrahedron Lett.* **1974**, 2415.

58) M.K.M. Dirania, J. Hill, *J. Chem. Soc. [C].* **1971**, 1213.

59) M.K.M. Dirania, H.W. Imseeh, *Chem. Ind. (London)*, **1976**, 788.

60) J. March, "Advanced Organic Chemistry", 3rd. ed., Wiley-Interscience, New York, 1985, p 790.

61) M.F. Shostakovskii et al., *Russian Chemical Reviews*, **37**. 907 (1968).

62) G. Wash et al., *J. Am. Chem. Soc.* **63**, 2975 (1941).

63) H. Rinderknecht, *J. Am. Chem. Soc.* **73**, 5770 (1951).

64) N.J. Leonard, J.A. Adamcik, *J. Am. Chem. Soc.* **81**, 595 (1959).

65) H.D. Zook et al., *J. Org. Chem.* **33**, 2222 (1968).

66) A.I. Meyers, A.H. Reine, R. Gault, *J. Org. Chem.* **34**, 698 (1969).

67) W.J. LeNoble, H.F. Morris, *J. Org. Chem.* **34**, 1969 (1969).

68) W.J. Lenoble, *Synthesis*, **2**, 1 (1970).

69) S. Huning, *Angew. Chem., Intern. Ed. Engl.* **3**, 548 (1964).

70) R. Gompper, *Angew. Chem., Intern. Ed. Engl.* **3**, 560 (1964).

71) P. Sykes, "A Gudidebook to Mechanism in Organic Chemistry", 5th Edn., Longeman Inc, New York, 1981 pp 36-43.

72) H.O. House, "Modern Synthetic Reactions", 2nd Edn., Benjamin/ Cumming/ Menlo Park, CA., 1972 p 523.

73) D.Y. Curtin, R.J. Crawford, M. Wilhelm, *J. Am. Chem. Soc.* **80**, 1391 (1958).

74) D.Y. Curtin, D.H. Dybvig, *J. Am. Chem. Soc.* **84**, 225 (1962).

75) N. Kornblum, A. Lurie, *J. Am. Chem. Soc.* **81**, 2705 (1959).

76) E.C. Taylor et al., *J. Am. Chem. Soc.* **90**, 2421 (1968).

77) N. Kornblum, R.A. Brown, *J. Am. Chem. Soc.* **86**, 2681 (1964).

78) G. Brieger, W.M. Pelletier, *Tetrahedron Letters*, **1965**, 3555.

79) F.H. Bottom, F.J. McQuillin, *Tetrahedron Letters*, **1967**, 1975.

80) A.L Kurz et al., *Tetrahedron Letters*, **1968**, 3679.

81) R.G. Pearson, J. Songstad, *J. Am. Chem. Soc.* **89**, 1828 (1967).

82) W.S. Johnson et al., *J. Am. Chem. Soc.* **84**, 2181 (1962).

83) D. Caine, *J. Org. Chem.* **29**, 1868 (1964).

84) N.J. Leonard, J.A. Adamcik, *J. Am. Chem. Soc.* **81**, 595 (1959).

85) A.I. Meyers, A.H. Reine, R. Gault, *J. Org. Chem.* **34**, 698 (1969).

86) A.F. Favorskii, M.F. Shostakovskii, *Zhur. Obshch. Khim.*, **113**, 1 (1943).

87) S.I. Miller, *J. Am. Chem. Soc.* **78**, 6091 (1956).

88) S.I. Miller, G. Shkapenko, *J. Am. Chem. Soc.* **77**, 5038 (1955).

89) J.W. Copenhaver, M.H. Bigelow, "Acetylene and Carbon Monoxide Chemistry", 1949, p. 305.

90) M.F. Shostakovskii, et al., *Izv, Akad. Nauk. Sssr, Otd. Khim. Nauk.*, **1952**, 484.

91) M.F. Shostakovskii, et al., *Izv, Akad. Nauk. Sssr, Otd. Khim. Nauk.*, **1957**, 339.

92) M.F. Shostakovskii, et al., *Russian Chemical Reviews*, **33**, 65 (1964).

93) A.L. Henne, M. Nager, *J. Am. Chem. Soc.* **74**, 650 (1952).

94) S.J. Cristol, et al., *J. Am. Chem. Soc.* **76**, 4558 (1954).

95) L. Claisen, *Chem. Ber.* **36**, 3664 (1903).

96) L.N. Owen, *J. Chem. Soc.* **1945**, 385.

97) K. Bowden, E.A. Braude, E.R. Jones, *J. Chem. Soc.* **1946**, 945.

98) R.H. DeWolfe, "Carboxylic Ortho Acid Derivatives: Preparation and Synthetic Applications", pp 149-152, Academic Press Inc., New York, 1970.

99) L. Claisen, *Chem. Ber.* **26**, 2729 (1893).

100) L. Brooker. A.L. Sklar, H. Cressman, *J. Am. Chem. Soc.* **67**, 1875 (1945).

101) E.C. Taylor, E.E. Garcia, *J. Org. Chem.* **29**, 2116 (1964).

102) C.C. Price, N.J. Leonard, H.F. Herbrandson, *J. Am. Chem. Soc.* **68**, 1252 (1946).

103) L. Nicholl, P.J. Tarsio, H. Blohm, **U.S. Patent** 2,824,121 (1948); *Chem. Abstr.* **52**, 11809 (1958).

104) M.J. Kamlet, *J. Org. Chem.* **24**, 714 (1959).

105) R.J. Crawford, R. Raap, *Can. J. Chem.* **43**, 356 (1965).

106) H.O. House, V. Kramar, *J. Org. Chem.* **28**, 3362 (1963).

107) A. Michael, *J. Am. Chem. Soc.* **57**, 159 (1935).

108) K. Morita, M. Nishimura, Z. Suzuki, *J. Org. Chem.* **30**, 533 (1965).

109) K. Morita, G. Slomp, E.V. Jensen, *J. Am. Chem. Soc.* **84**, 3779 (1962).

110) C.A. Mackenzie, J.H. Stocker, *J. Org. Chem.* **20**, 1695 (1955).

111) L. Claisen, *Chem. Ber.* **29**, 1005 (1896).

112) G.E. Lienhard, T.C. Wang, *J. Am. Chem. Soc.* **91**, 1146 (1968).

113) E.E. Royais, K.C. Brannock, *J. Am. Chem. Soc.* **75**, 2050 (1953).

114) E.G. Meek, J.H. Turnbull, W. Wilson, *J. Chem. Soc.* **1953**, 811.

115) M.A. Dolliver et al., *J. Am. Chem. Soc.* **60**, 440 (1938).

116) R.J. Crawford, R. Raap, *Can. J. Chem.* **43**, 356 (1965).

117) J. March, "Advanced Organic Chemistry", 3rd. ed., pp 684-685, Wiley-Interscience, New York, 1985.

118) D.B. Killian, G.F. Hennion, J.A. Nieuwland, *J. Am. Chem. Soc.* **58**, 80,892 (1936).

119) H.C. Volger, J.F. Arens, *Rec. Trav. Chim.* 77, 1170 (1958).

120) T.L. Jacobs, R. Cramer, J.E. Hanson, *J. Am. Chem. Soc.* 64, 223 (1942).

121) D.G. Lindsay, C.B. Reese, *Tetrahedron*, **21**, 1673 (1965).

122) R.C. Cookson, P. Singh, *J. Chem. Soc. [C]*, **1971**, 1477.

123) R.A. Wohl, *Synthesis*, **6**, 38, (1974).

124) L.J. Dolby, *Organic Prep. and Procd.* **1**, 229 (1969).

125) F. Barbot, P. Miginiac, *Helv. Chim. Acta.* **62**, 1451 (1979).

126) R.D. Miller, D.R. McKean, *Tetrahedron Letters*, **23**, 323 (1982).

127) M. Marsi, J.A. Gladysz, *Organometallics*, **1**, 1467

128) D Johnson, J.A. Gladysz, *J. Am. Chem. Soc.* **101**, 6433 (1979).

129) A.F. Kluge, I.S. Cloudsdale, *J. Org. Chem.* **44**, 4847 (1979).

130) A.F. Kluge, *Tetrahedron Letters*, **1978**, 3629.

131) J.C. Gilbert, U. Weerasooriya, *Tetrahedron Letters*, **21**, 2041 (1980).

132) J.C. Gilbert et al., *Tetrahedron Letters*, **21**, 5003, (1980).

133) F.N. Tebbe, G.W. Parshall, G.S. Reddy, *J. Am. Chem. Soc.* **100**, 3612 (1978).

134) S.H. Pine, R. Zahler, D. Evans, R. Grubbs, *J. Am. Chem. Soc.* **102**, 3270 (1980).

135) G.A. Gareev, *Zh. Org. Khim.* **18**, 36 (1982).

136) G. Slinckx, G. Smets, *Tetrahedron*, **22**, 3163 (1966).

137) D.M. Jones, N.F. Wood, *J. Chem. Soc.* **1965**, 1560.

138) W.H. Watanabe, L.E. Conlon, *J. Am. Chem. Soc.* **79**, 2828 (1957).

139) G. Stork, *Chem. Eng. News*, **45**, 138 (Feb. 20, 1967).

140) S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc.* **96**, 7807 (1974).

141) T.W. Greene, "Protective Groups in Organic Chemistry", Ch. 2 pp 40-43, John Wiley & Sons, New York, 1981.

142) H.O. House, L. Cauba, M. Gall, H. Olmstead, *J. Org. Chem.* **34**, 2324 (1968).

143) G. Stork, P.F. Hudrlik, *J. Am. Chem. Soc.* **90**, 4462 (1968).

144) O.A. Shavrygina, S.M. Makin, *Khim.-Farm. Zh.* **3**, 17 (1969).

145) J.R. Johnson, W.H. Jobling, G.W. Bodamer, *J. Am. Chem. Soc.* **63**, 131 (1941).

146) E. McDonald, A. Suksamrarn, R.D. Wylie, *J. Chem. Soc. Perkin I*, **1979**, 1893.

147) S. Danishefsky, T. Kitahara, *J. Org. Chem.* **40**, 538 (1975).

148) R.W. Aben, H.W. Scheeren, *J. Chem. Soc. Perkin I*, **1979**, 3132.

149) F. Farina, P. Prados, *Tetrahedron Letters*, **1979**, 477.

150) S. Danishefsky, T. Kitahara, C.F. Yan, J. Morris, *J. Am. Che. Soc.* **101**, 6996 (1979).

151) G. Roberge, P. Brassard, *J. Chem. Soc. Perkin I*, **1978**, 1041.

152) A. Kozikowski, K. Sugiyama, J. Springer, *Tetrahedron Letters*, **21**, 3257 (1980).

153) T. Harayama, H. Cho, Y. Inubushi, *Tetrahedron Letters*, **18**. 3273 (1977).

154) K. Krageloh, G. Simchen, *Synthesis*, **13**, 30 (1981).

155) T.H. Chan, P. Brownbridge, *J. Am. Chem. Soc.* **102**, 3534 (1980).

156) K. Yamamoto, S. Suzuki, J. Tsuii, *Chem. Letters*, **1978**, 649.

157) T. Ibuka, Y. Mori, Y. Inubushi, *Tetrahedron Letters*, **17**, 3169 (1976).

158) T. Ibuka, K. Hayashi, H. Minakaaata, Y. Inubushi, *Tetrahedron Letters*, **20**, 159 (1979).

159) M.I. Page, *Org. React. Mech.* **1981-1982**, 1.

160) A.J. Kirby, *Acc. Chem. Res.* **17**, 305 (1984).

161) T.W. Greene, "Protective Groups in Organic Chemistry", Ch. 4 pp 142 - 147, John Wiley & Sons, New York, 1981.

162) J.L. Isidor, R.M. Carlson, *J. Org. Chem.* **38**, 554 (1973).

163) P.A. Bartlett, *J. Am. Chem. Soc.* **108**, 5559 (1986).

164) L.J. Swenton, *J. Org. Chem.* **52**, 978 (1987).

165) K.L. Koller, H.C. Dorn, *Anal. Chem.* **54**, 529 (1982).

166) R.C. Bergstrom, et al., *J. Am. Chem. Soc.* **98**, 3301 (1976).

167) K. Nakanishi, et al., *J. Am. Chem. Soc.* **101**, 4398 (1979).

168) D. Nightinggale, F. Wadsworth, *J. Am. Chem. Soc.* **67**, 416 (1945).

169) K. Bowden, et al., *J. Chem. Soc.* **1946**, 39.

170) H.M.R. Hoffman, *Angew. Chem. Int. Ed. Engl.* **8**, 556 (1969).

171) H.O. House, "Modern Synthetic Reactions", 2nd ed., pp 595 - 623, W.A. Benjamin, New York, 1972.

172) D.N. Reinhoudt, *Adv. Heterocy. Chem.* **21**, 253 (1971).

173) G. Brieger, and J.N. Bennet, *Chem. Rev.* **80**, 63.

174) J. March, "Advanced Organic Chemistry", 3rd ed., pp 745 - 747, Wiley-Interscience, New York, 1985.

175) T.W. Greene, "Protective Groups in Organic Chemistry", Ch. 2 p 43, John Wiley & Sons, New York, 1981.

176) T.R. Kelly Ed., "Recent Aspects of Anthracyclinone Chemistry", Tetrahedron Symposia-In-Print Series Number 17, Pergamon Press, New York, 1984.

177) C.A. Naylor, and J.H. Gardener, *J. Am. Chem. Soc.* **53**, 4109 (1931).

178) R.L. Hannan, et al., *J. Org. Chem.* **44**, 2153 (1979).

179) R. Gitti, et al., *J. Am. Chem. Soc.* **110**, 2294 (1988).

180) L.A. Cohen, *J. Org. Chem.* **22**, 1333 (1957).

The vita has been removed from the scanned document