PRECURSORS TO CONFIGURATIONALLY STABLE CHIRAL KETENIMINES

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We hereby recommend that the thesis prepared under our supervision by Joanne Adele Maia

entitled PRECURSORS TO CONFIGURATIONALLY STABLE CHIRAL KETENIMINES

be accepted as fulfilling this part of the requirements for the Degree of Master of Science.

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CHAPTER I

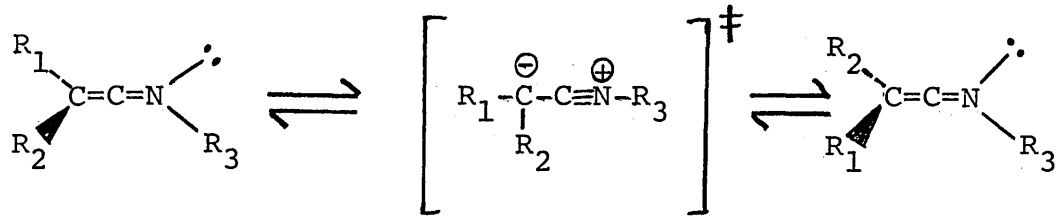
INTRODUCTION

Ketenimines are heterocumulenes characterized by the functional group $\rangle C{=}C{=}N-$. These compounds are isoelectronic with allenes and ketenes. The reactivity and stability of ketenimines vary considerably; some are stable enough to be isolated but readily undergo cycloaddition reactions. Others can only be detected and trapped as reactive intermediates.

The most characteristic reaction of heterocumulenes is thermal cycloaddition to form four membered rings.[1,2] Most of the work in this area has been carried out with the $_{\pi}2 + _{\pi}2$ cycloaddition of ketenes to alkenes. Extensive investigation[2-9] into the mechanism of the cycloaddition reactions has led to the conclusion that the reactions are concerted and that the stereochemistry of the alkene portion is maintained. Since orbital symmetry arguments predict thermally allowed cycloaddition, it has been assumed that the ketene portion reacts in an antarafacial manner. Although considerable indirect evidence[2] supports this assumption, it cannot be tested directly with a ketene since the ketene moiety is not capable of stereoisomerism.

Ketenimines are the nitrogen analogues of ketenes and the ketenimine system is potentially axially asymmetric.

Since the two π bonds are orthogonal, compounds with different substituents attached to the terminal carbon atom are chiral, and two enantiomorphic forms are possible. The ability to observe axial asymmetry, however, depends upon the configurational stability of the ketenimine, which might invert its configuration either by rotation about the carbon-nitrogen double bond or inversion of the nitrogen lone pair.[10] Examination of the literature has revealed that all of the ketenimines synthesized to date have been optically inactive. As a consequence, it has been concluded that the thermal racemization barrier is low enough for rapid interconversion to occur at room temperature. Simons, Kerek, and Ostrogovich[11] using the Hückel molecular orbital method, estimated that this barrier should not be higher than 10 kcal/mol. Lloyd[12] attempted to observe diastereotopic hydrogens in several ketenimines using variable temperature NMR spectroscopy. The protons appeared magnetically equivalent over a temperature range of -60° to 80°C. Jochims and Anet[13,14] used this this method to determine the barriers to racemization of 1a and 1b.



1 3 2

1a and 2a, R_1 = phenyl; R_2 = isopropyl; R_3 = phenyl

1b and 2b, R_1 = methyl; R_2 = isopropyl; R_3 = phenyl

At -113°C the methyl protons of the isopropyl group of compound 1a separate into a pair of doublets with a chemical shift of 4 Hz, corresponding to a free energy of activation for racemization of 9.1 ± 0.2 kcal/mol. The barrier for compound 1b was determined to be 12.2 ± 0.3 kcal/mol. There seems to be a marked substituent effect; replacement of the phenyl group in 1a by methyl in 1b raised the barrier by 3 kcal/mol. The authors postulated a linear polar transition state as the most likely racemization mechanism. This transition state could account for the observed substituent effect. When strongly electronegative groups are bonded to carbon, the linear transition state is energetically favored over the bent geometry and actually becomes the ground state structure. Bullough and Wheatley[15,16] examined the crystal structure of two solid ketenimines bearing

electron withdrawing sulfonyl substituents on carbon. X-ray analysis showed a virtually linear C=C=N-C chain with an unusually short C=N bond having essentially triple bond character. They concluded that the linearity of the chain was brought about by the ability of the electron withdrawing groups to stabilize the linear structure, 3.

Geometrical isomerization due to restricted rotation around a carbon-nitrogen double bond is commonly observed in systems where an electronegative atom such as oxygen, nitrogen, or halogen is bonded to the imino nitrogen.[17-20] This suggests that addition of an electronegative substituent to the imine portion of the ketenimine functional group should stabilize the molecule by raising the thermal inversion barrier. An electronegative atom directly attached to nitrogen should enhance the contribution of resonance structure 1 and 2 by destabilizing structure 3.

The purpose of this research was to investigate synthetic pathways for the preparation of chiral N-alkoxyketenimines. It was expected that ketenimines of this type would be configurationally stable. These compounds would represent the first examples of optically

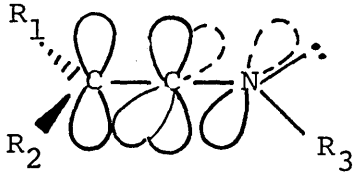
active hetereocumulenes and would serve as useful probes into the stereochemistry of $_{\pi}2 + _{\pi}2$ cycloaddition reactions.

CHAPTER II

History

(A) Structure

Ketenimines are heterocumulenes of general structure 1 and are π-isoelectronic with allenes and ketenes.



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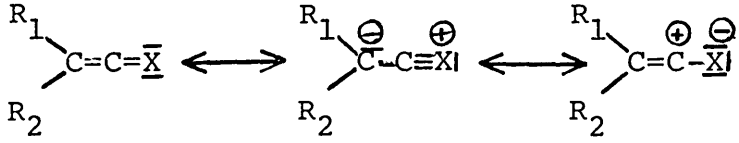
According to valence bond theory, the ground state electron distribution of these systems may be described by resonance structures 4, 5, and 6.



4 5 6

X = CH_2, NR, O

The relative importance of the contributing structures is dictated by the substituents, R_1, R_2, X for the individual cumulenes. Resonance structure 4 emphasizes the nucleophilic properties of the heteroatom

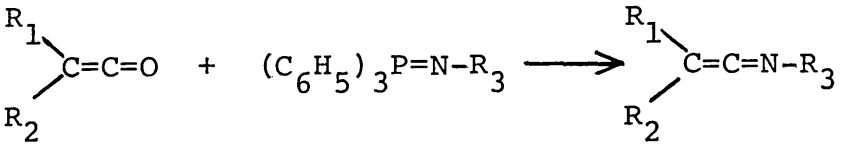
whereas structure 5 emphasizes the nucleophilic properties of the beta carbon atom. Data obtained from ^{13}C-NMR spectra[21,22] reveal that resonance structure 5 contributes more significantly to the ground state structure if the CH_2 group in allene is replaced by an electronegative atom with lone pair electrons. It becomes increasingly important in the order: allene, ketenimine, ketene. This conclusion was substantiated by ^{1}H-NMR experiments conducted by Reilly and Krow[23] which indicated that, although the geometries of cumulenes and heterocumulenes are similar, heteroatom effects cannot be neglected. The authors stated that, "It can be predicted that heteroatoms will effect rotational barriers and bond lengths and energies in cumulenes."

Most ketenimines are colorless or pale yellow oils or low melting solids. They are characterized by their infrared spectra which exhibit distinctive cumulene absorption at 2000 - 2050 cm^{-1} and by their hydrolysis to the corresponding amides. Ketenimines are known with N-alkyl, -aryl, -hydrogen, -phosphorous, -nitroso, and -boron substituents and having N-Sn, N-Si, and N-Ir bonds. Substituents present on carbon have been alkyl, aryl, hydrogen, trifluoromethyl, trimethylsily, ethoxycarbonyl, cyano, sulfonyl, phosphoranylidene, and carbonyl groups.

Stable ketenimines with amino, alkoxy, or thioether substituents directly bonded to either the carbon or nitrogen atoms have not yet been synthesized.

(B) Preparative Methods

The first ketenimines were prepared by Staudinger and Hauser[24] in 1921 by the reaction of various ketenes with a phosphinimine. The resulting products were characterized by hydrolysis with water to give amides. It is interesting to note that those ketenes stabilized by aromatic or electron withdrawing groups yielded the



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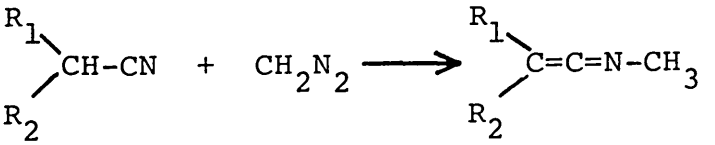
desired ketenimines while ketene, itself, produced a polymeric material (Table I).

Since then a number of other methods have been developed. Dijkstra and Backer[25] have prepared several



ketenimines by the reaction of diazomethane with negatively substituted nitriles.

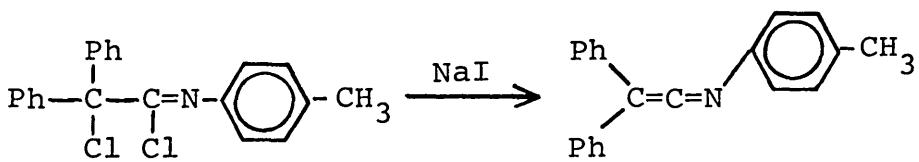
TABLE I

KETENIMINES PREPARED FROM KETENES[24]

Compound Number	R_1	R_2	R_3	Physical Properties
7a	Ph	Ph	Ph	yellow, crystalline
7b	Ph	Ph	CH_3	yellow, liquid
7c	$COOC_2H_5$	$COOC_2H_5$	Ph	colorless, crystalline
7d	CH_3	CH_3	Ph	green, oil
7e	H	H	Ph	colorless, polymerizes
7f	H	H	C_2H_5	polymer only

A number of workers[26-28] have used photolysis to prepare ketenimines. Some of these compounds have been isolated. Others, identified by their 2000-2050 cm^{-1} absorption band in the crude protolyzate, are assumed intermediates.[29]

More general and convenient methods for the synthesis of ketenimines involve simple elimination reactions. In 1953 Stevens and French[30] found that α-chloroimidoyl halides can be dehalogenated with sodium iodide in acetone. They prepared diphenylketen-p-tolylimine (8) in 83.5% yield and found that the reactions of this compound with water, alcohol and chlorine were analogous to the



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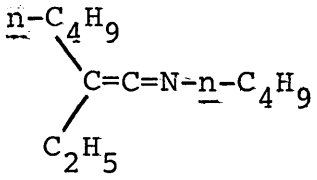
reactions of ketenes with these reagents. Although the dehalogenation method fails to produce ketenimines with dialkyl substitution on carbon, the synthesis is successful for preparing diaryl ketenimines.

Alkyl substituted ketenimines as well as aryl substituted ketenimines can be prepared by the dehydrohalogenation of imidoyl chlorides bearing a single alpha hydrogen.[31] Dehydrohalogenation is accomplished by the

reaction of triethylamine in refluxing benzene. Compound 9 which was formed in 57% yield was the first all aliphatic



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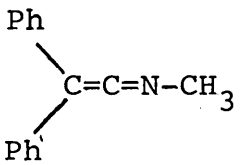
ketenimine to be reported.

Diphenylketene-N-methylimine (10) was prepared in 42% yield by the dechlorination method while dehydrochlorination gave only a 2.4% yield of the ketenimine.



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The low yield was attributed to the formation of a dimeric product in 60% yield. The catalytic effect of organic amine hydrochlorides on the dimerization of ketenes is well known,[32] and the formation of a large amount of dimer in this reaction is probably due to a similar catalytic effect. Stevens and French,[31] in a comparison of the dechlorination and dehydrochlorination methods, reported, "For the preparation of large amounts

of ketenimines, the dehydrochlorination method appears to be the method of choice. However, for those ketenimines which are easily dimerized, the dehalogenation of the α-chloroimino chlorides appears to be the better method."

In 1964 Stevens and Singhal[32] reported a new synthesis for the preparation of triarylketenimines. They used phosphorous pentoxide in the presence of alumina or Florisil and a tertiary amine to dehydrate secondary amides to the corresponding ketenimines. Good yields were obtained for the preparation of ketenimines bearing three aromatic groups. This method was also successful for preparing diarylketene-N-alkylimines although in lower yield than by either of Stevens' other methods.

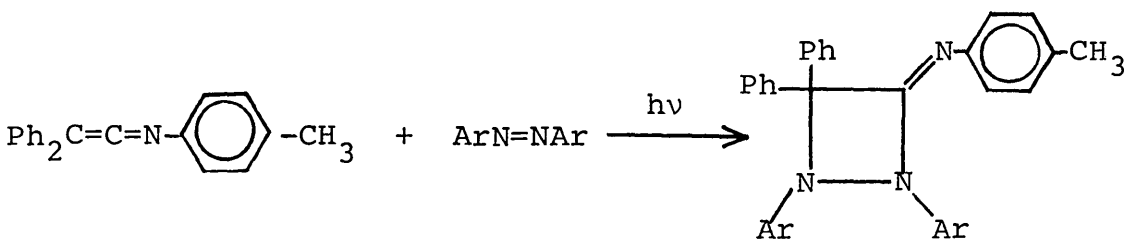
(C) Reactivity

Since ketenimines are isoelectronic with allenes and ketenes, their chemical behavior parallels the reactions of these compounds. In recent years ketenimines have attracted interest as dehydrating agents for peptide synthesis[33,34] and have been implicated in chemical evolution studies to explain prebiological protein formation.[35]

As formal dehydration products of amides, ketenimines readily add water to regenerate the amide. The hetero-cumulene linkage reacts with electrophiles, such as

halogens and hydrogen halides, to form addition products. Nucleophilic addition to the central carbon atom also gives addition products.[36] Some reactions of triphenylketenimine are shown in Table II.

Photochemical cycloaddition also occurs across the C=C of ketenimines. A number of four membered heterocycles

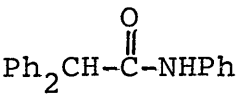
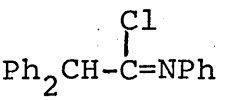
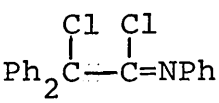
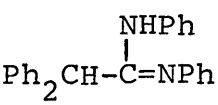
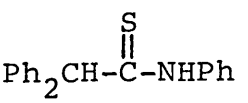
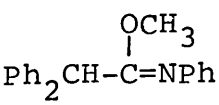
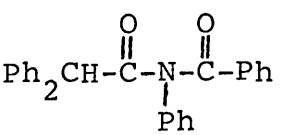
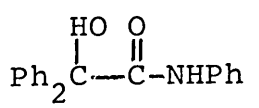
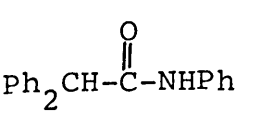


have been synthesized by the photochemically allowed $_{\pi}2_{s} + _{\pi}2_{s}$ process.[38,39]

In theory ketenimines play an antarafacial role as the $_{\pi}2_{a}$ component in concerted thermally allowed $[_{\pi}2_{s} + _{\pi}2_{a}]$ cycloadditions. This theory, however, has yet to be proved conclusively since no configurationally stable ketenimines are now known. Thermal cycloaddition occurs across the C=C of ketenimines with ketones[40] and nitroso compounds.[41] Other thermal cycloadditions have been reported. No information is available in the literature to indicate whether any of the thermal cycloadditions are concerted or nonconcerted processes.

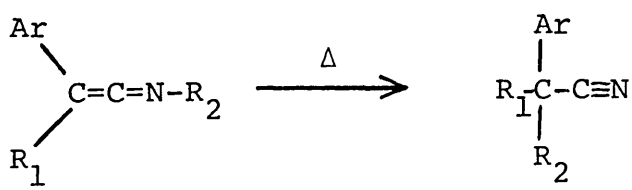
TABLE II

SOME REACTIONS OF TRIPHENYLKETENIMINE[37]

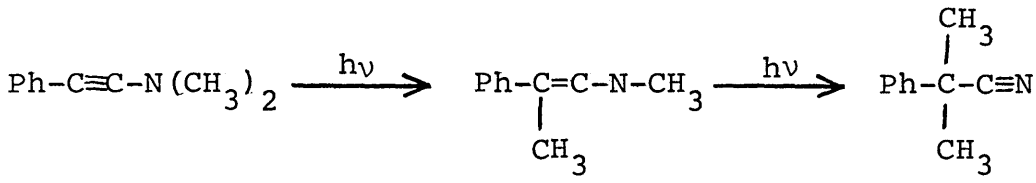
Reagent	Product
H_2O/H^+	
HCl	
Cl_2	
$PhNH_2$	
H_2S	
CH_3OH/CH_3O^-	
PhCOOH	
O_2	$Ph_2C{=}O + Ph{-}N{=}C{=}O$
$H_2O/HCl/DMSO$	
$(C_2H_5)_2O/HCl/DMSO$	

Little is known about the mechanism of ketenimine reactions. This partly arises from the difficulty of preparing and handling such reactive species which undergo chemical reactions so readily and under a wide variety of conditions. Staudinger,[24] Stevens,[31] and Barker[42] have reported that ketenimines and in some cases ketenimine precursors yield polymeric and dimeric materials when heated. No structures were proposed for the polymeric materials but Barker has identified some of the dimeric and trimeric products.

Thermal and photolytic rearrangement of ketenimines to nitriles may occur[22,23] by a 1,3 shift.[29,43,44] This rearrangement can be fast when the group attached to



nitrogen, R_2, is benzylic and the terminal carbon has at least one aryl group attached to it. A 90% yield of nitrile was produced by heating diphenylketen-N-benzylimine at 60°C in CCl_4.[44] Ketenimine 11 is an assumed



11 12

intermediate in the formation of α-phenylisobutyronitrile (12) from the photolysis of N,N-dimethylphenylacetylene.[29]

CHAPTER III

Results and Discussion

The purpose of this work was to investigate a method for the preparation of chiral N-alkoxyketenimines. The two most general and convenient methods of synthesizing ketenimines are dehydrochlorination of imino chlorides[31] and dechlorination of α-chloroimino chlorides.[30] A number of N-alkoxyimidoyl chlorides (hydroximoyl chlorides) have been made in this laboratory and their syntheses have been well documented by Johnson and coworkers.[17,18,45,46] These methods served as the basis for both the syntheses of hydroximoyl halides and the syntheses of α-halohydroximoyl halides.

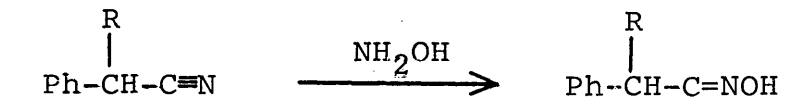
A. Preparation of Hydroximoyl Halides

1. Preparation of O-Methylphenylacetohydroximoyl Halides.

Preparations of O-methylphenylacetohydroximoyl halides were carried out according to Scheme I.

Phenylacetamidoxime (14a) was prepared using the methods of Knudsen[47] by reacting phenylacetonitrile with hydroxylamine. The crude product, obtained in good yield, could not be recrystallized easily because it oiled out in the solvent. It was, however, pure enough (m.p. 64.5-

SCHEME I

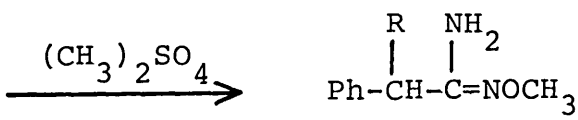


13a, R=H

13b, R=OCH_3

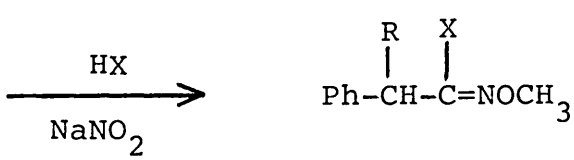
14a, R=H

14b, R=OCH_3



15a, R=H

15b, R=OCH_3



16a, R=H; X=Cl

16b, R=H; X=Br

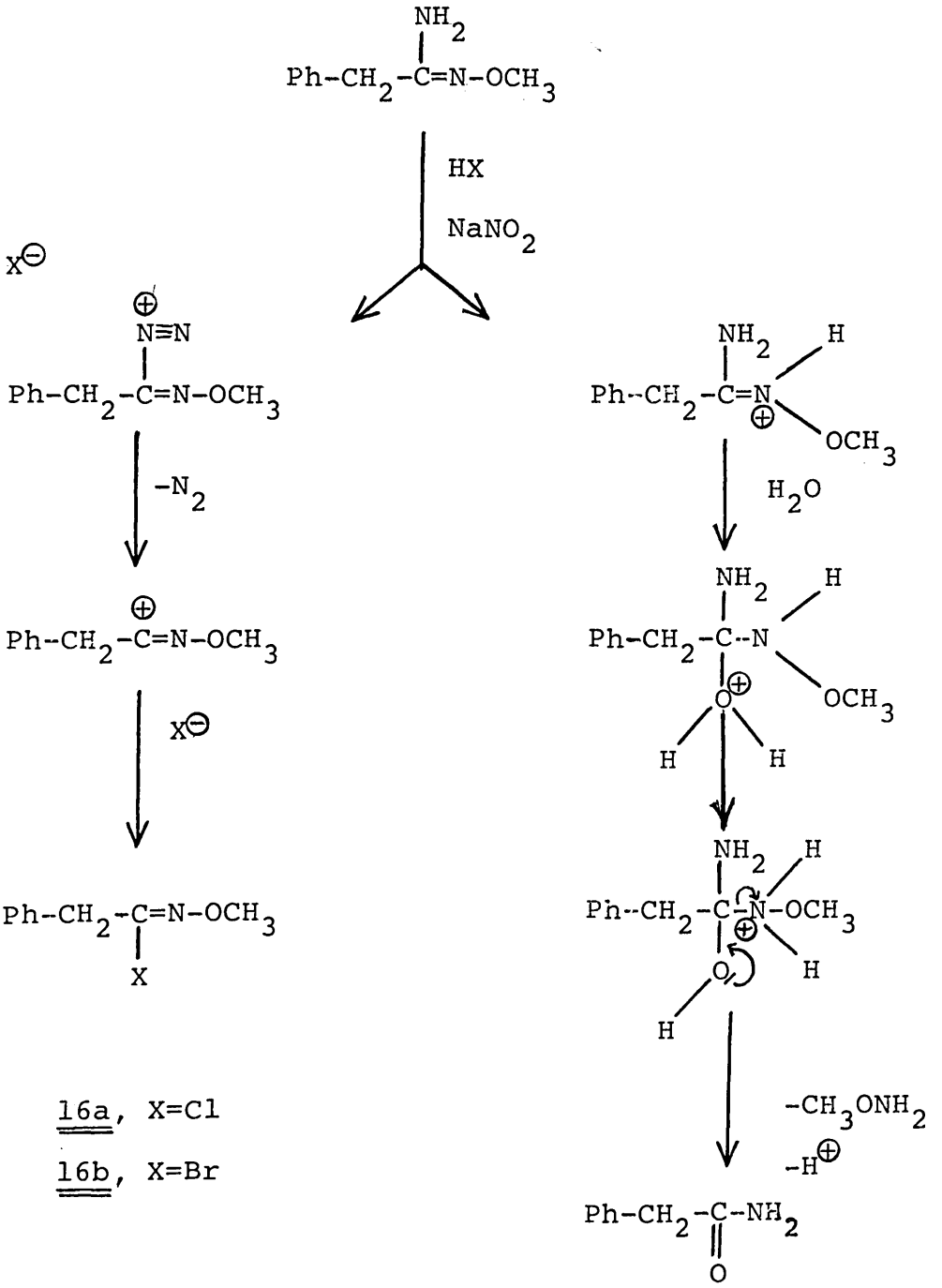
16c, R=OCH_3; X=Cl

68.0°C [lit[47] m.p. 67°C]) to obtain good supporting spectral data.

O-Methylphenylacetamidoxime (15a) was synthesized by generating the sodium salt of the amidoxime in situ and alkylating with dimethyl sulfate. The yield, 47.9%, was based on the weight of crude amidoxime. It was necessary to use equimolar amounts of dimethyl sulfate and amidoxime since alkylation of the amide functional group can occur as well as alkylation of the oxime moiety. The product was easily recrystallized from hexane-ether to give a very pure crystalline compound (m.p. 64.5-65.0°C).

O-Methylphenylacetohydroximoyl chloride (16a) was prepared by the method of Johnson and Cornell.[46] Treatment of the methylated amidoxime with hydrochloric acid in the presence of nitrous acid gave a good yield of the hydroximoyl chloride, a distillable oil with a distinctive odor. This method was also used to synthesize O-methylphenylacetohydroximoyl bromie (16b) but in lower yield. The mechanism for these reactions is shown in Scheme II. During the preparation of 16a and 16b phenylacetamide (17) is produced as a side product, presumably by way of acid catalyzed hydrolysis of the starting material.

SCHEME II



16a, X=Cl

16b, X=Br

17

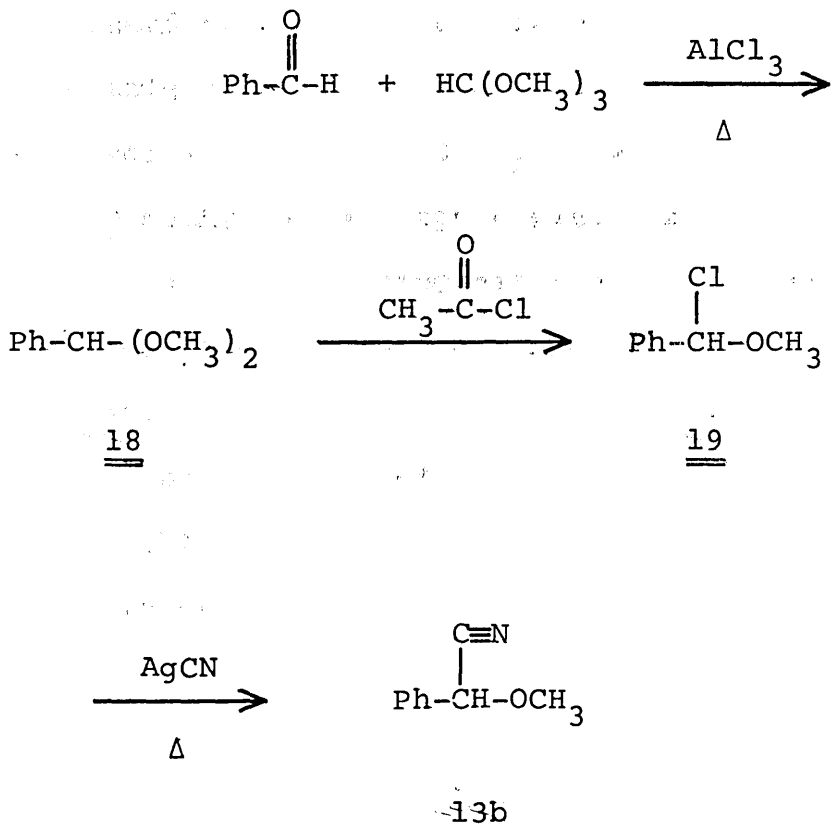
2. Preparation of O-Methyl-α-methoxyphenylacetohydroximoyl Chloride (16c)

α-Methoxyphenylacetonitrile (13b) was shown to be a by product of the reaction of O-methylphenylacetohydroximoyl chloride with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (see section C1). The structure was proved conclusively by an independent synthesis using the method of Bailey[48] as modified by Padwa.[49] Since compound 13b could easily be synthesized in a pure form and in high yield it became the starting material for the synthesis of a hydroximoyl chloride with an electron withdrawing substituent in the alpha position, compound 16c.

α-Methoxyphenylacetamidoxomie (14b) was prepared from α-methoxyphenylacetonitrile (13b) as described previously. This methoxy substituted amidoxime has a much higher melting point than the unsubstituted compound (13a) and is less soluble in the refluxing solvent. Most of the precipitate which formed during the reaction was found to be product. It was easily recrystallized from benzene.

Methylation was accomplished by generating the sodium salt of α-methoxyphenylacetamidoxime in situ and adding dimethyl sulfate. The crude O-methyl-α-methoxyphenylacetomidoxime (15b) could not be recrystallized.

SCHEME III



18 19

13b

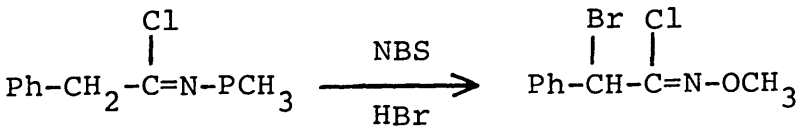
It was purified by washing the ether extract with sodium hydroxide to remove any unreacted starting material. Addition of more than equimolar amounts of dimethyl sulfate caused methylation of the amino group as well as the oxime moiety.

The hydroximoyl chloride (16c) was prepared from the crude O-methyl-α-methoxyphenylacetamidoxime using hydrochloric acid and sodium nitrite by nitrosative deamination in the presence of chloride ion.

B. Preparation of α-Bromo-hydroximoyl Halides

1. Preparation of O-Methyl-α-bromo-phenylaceto-hydroximoyl Chloride (20)

The acid catalyzed reaction of acyl halides with free bromine via the Hell-Volhard-Zelinsky procedure gives alpha-brominated products exclusively.[50,51] Harpp, et al.[52] have found that N-bromosuccinimide (NBS) also alpha-brominates a number of acyl chlorides in good yield. In this study the procedure of Harpp was used to synthesize compound 20. Washing the crude product with sodium



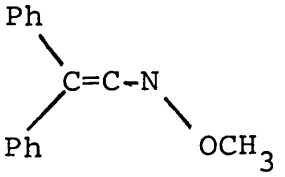
16 20

sulfite proved to be necessary since distillation of the unwashed material released a noticeable and very irritating amount of free bromine into the room. Only alpha-bromination was observed.

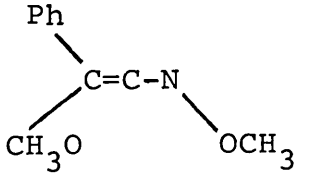
2. Attempted Bromination of O-Methyl-α-methoxyphenylacetohydroximoyl Chloride (16c)

The reaction of the hydroximoyl chloride (16c) with N-bromosuccinimide and a catalytic amount of hydrobromic acid did not give the expected alpha brominated product (21). O-Methyl-α-ketophenylacetohydroximoyl chloride (22) was formed in quantitative yield. A proposed mechanism for this reaction is shown in Scheme IV.

C. Dehydrochlorination Reactions



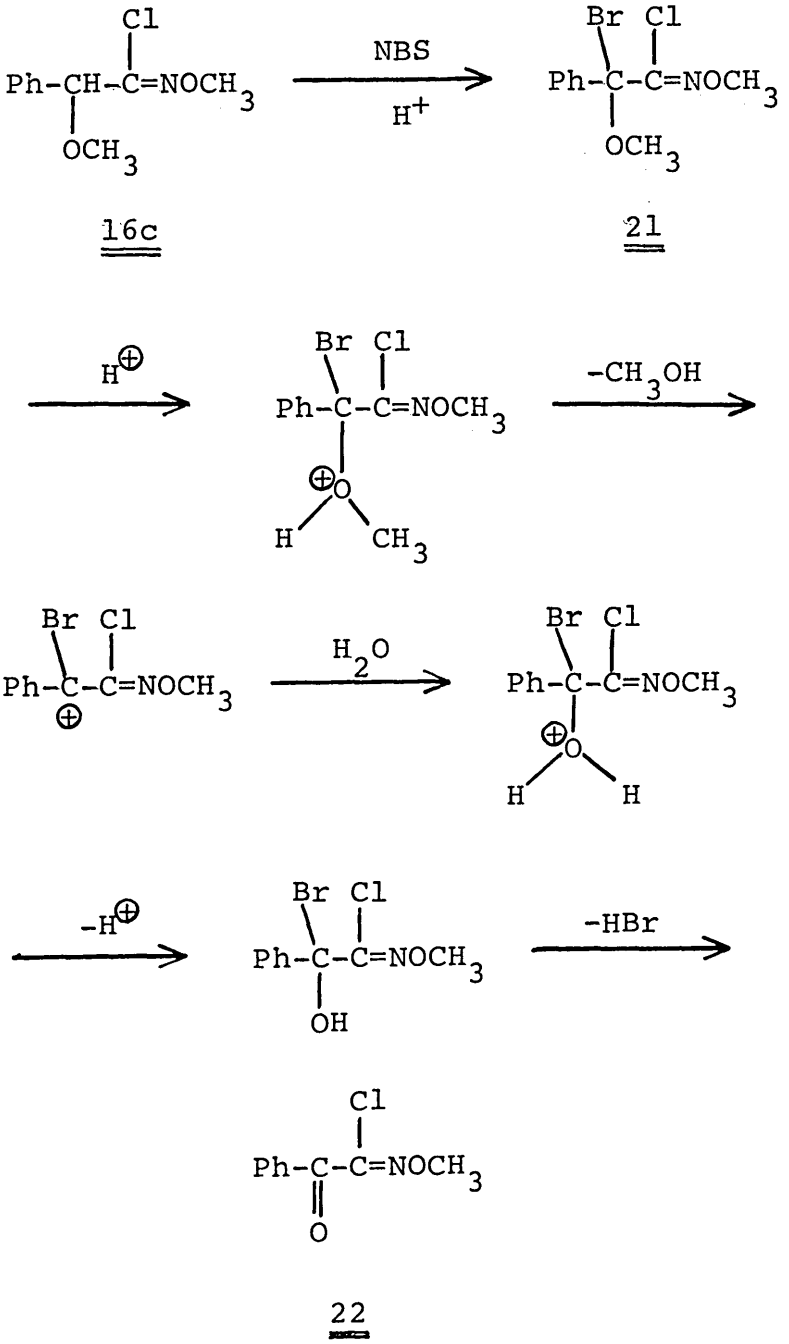
23



24

Synthesis of N-methoxy-phenylketenimine (23) and N-methoxyphenylmethoxyketenimine (24) from the corresponding hydroximoyl chlorides was attempted using the method of Stevens and French.[31] No reaction was observed when triethylamine was used as the base. 1,5-Diazabicyclo[5.4.0]undec-5-ene was chosen since it

SCHEME IV

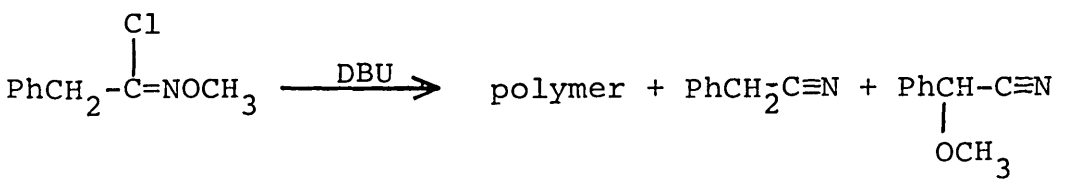


16c 21 22

is a strong organic base and soluble in benzene. It has also been shown to be more effective than triethylamine in synthesizing some ketenimines[53] by accelerating the beta elimination of less acidic protons.

1. Reaction of O-Methylphenylacetohydroximoyl Chloride with DBU

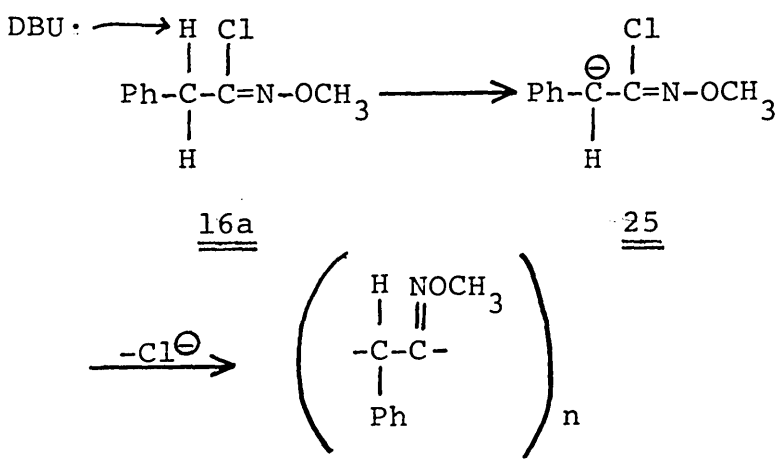
The addition of DBU to the hydroximoyl chlorides was carried out under a variety of conditions, i.e., in cold, at room temperature, under reflux, and under an inert atmosphere. The same end results were observed for the reaction of 16a with DBU under all conditions. A white precipitate, which proved to be the hydrochloride salt of DBU, formed and heat was evolved. The major product was a viscous, red-black, polymeric material. Two side products, phenylacetonitrile (13a) and α-methoxyphenylacetonitrile (13b) were isolated and identified by comparision of NMR and IR spectra to the spectra of authentic samples.



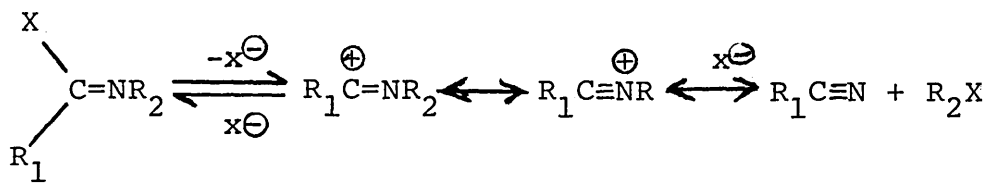
16a 13a 13b

76% 15% 7%

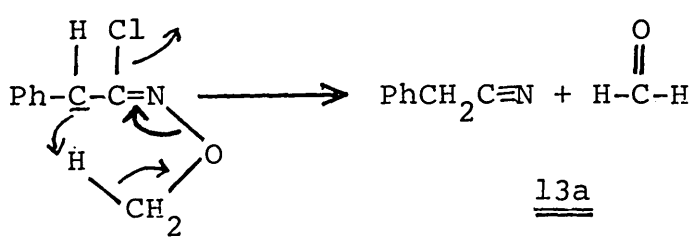
Staudinger[24] and Stevens[31] have reported that ketenimines and ketenimine precursors, when heated, yield polymeric materials. It is also known that imidoyl halides having one or more hydrogens on the alpha-carbon atom undergo self-condensation.[54] To determine if the polymeric material was being produced by way of a ketenimine or if it was due to self-condensation of the hydroximoyl chloride, a number of trapping agents (styrene, tetrachloroethylene, ethyl vinyl ether) were added to the reaction mixture. These compounds are known to "trap" ketenes by reacting with them to form four-membered cyclic addition products. In every case, no new compounds were detected and the product distribution was the same as when the reaction was run without the trapping agent. This suggests that polymerization occurs by self-condensation of the hydroximoyl chloride, possibly through an intermediate carbanion (25).



Imidoyl halides are known to undergo pyrolytic degradation to nitriles[54] by way of nitrilium ion intermediates. Johnson and Cornell[54] have found that

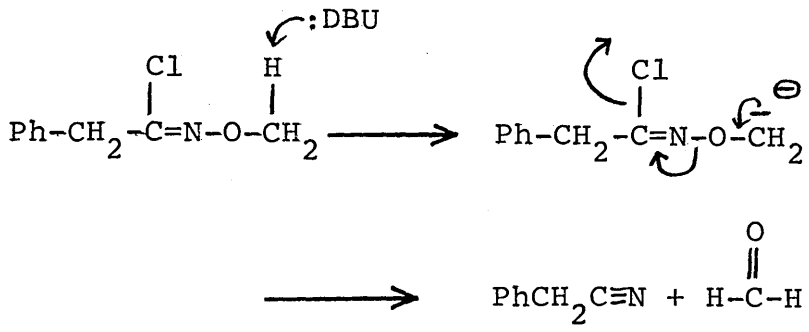


temperatures greater than 80°C are necessary to form nitrilium ions from O-methylbenzohydroximoyl halides. Since the formation of 13a took place even when the temperature of the reaction mixture was kept below 10°C, such a mechanism seems unlikely, especially in the presence of a strong base. Two alternate mechanisms are proposed. An intramolecular elimination of an



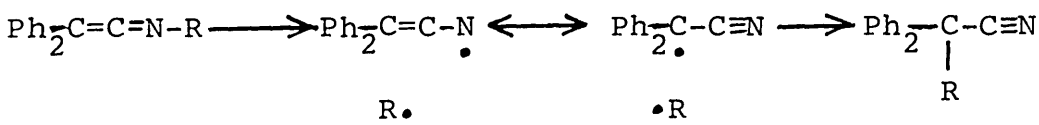
13a

alpha carbanion through a six membered ring transition state could produce phenylacetonitrile (13a).



Alternatively, attack by DBU at a methoxy proton could also account for the formation of phenylacetonitrile.

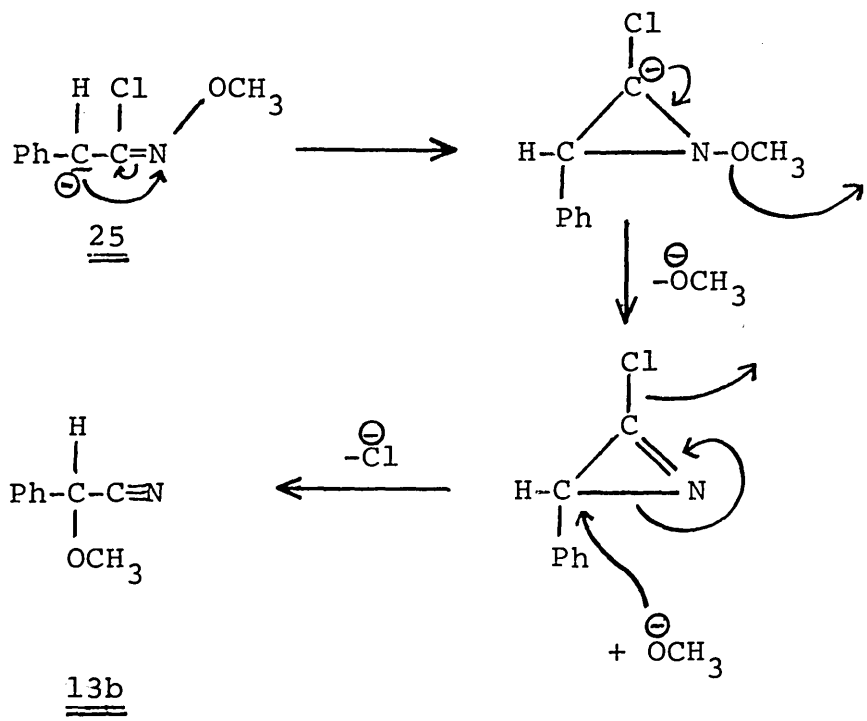
Nitriles formed by 1,3 rearrangement of ketenimines have been observed in both photochemical[55,56] and thermal reactions.[57] Singer and Lee[44] have measured the rate of rearrangement of a number of N-(arylmethyl)-ketenimines to nitriles. The reaction proceeds at moderate temperatures (25-65°C) in quantitative yield. The mechanism was proposed to be homolytic cleavage to a caged radical pair followed by rearrangement to the



nitrile. The formation of 13b by this mechanism seems unlikely because the first order rate constants of rearrangement of the ketenimines were found to be from

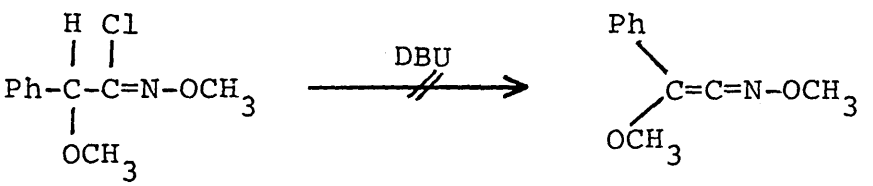
10^{-4} to $10^{-5}s^{-1}$. This rate is slow when compared to what would be expected for the reaction of a trapping agent with a reactive ketenimine. It was shown that addition of trapping agents to the reaction mixture had no effect and, therefore, it is suggested that no ketenimines are formed in these reactions.

An alternative mechanism by way of the carbanion, 25, could account for the formation of 13b:



2. Reaction of O-Methyl-α-methoxyphenylacetohydroximoyl Chloride with DBU

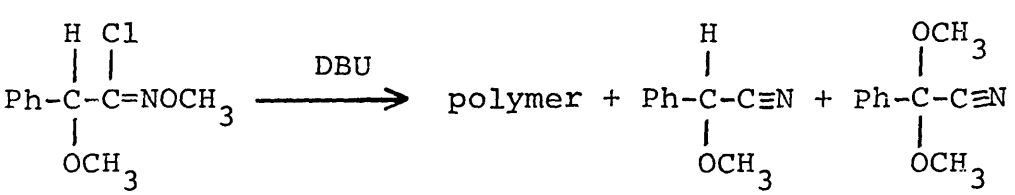
It was expected that dehydrochlorination of O-methyl-α-methoxyphenylacetohydroximoyl chloride (16c) would produce a ketenimine since Stevens and French[31] found that dehydrochlorination of imidoyl chlorides to ketenimines works best when the alpha carbon bears a



16c 24

single hydrogen atom. It was also expected that the electron withdrawing group on the carbon end of the ketene moiety would stabilize the cumulated π bond system.

The same experimental results were observed as the reaction of O-methylphenylacetohydroximoyl chloride with DBU. The red-black polymeric substance, however, was water soluble. No attempt was made to identify the



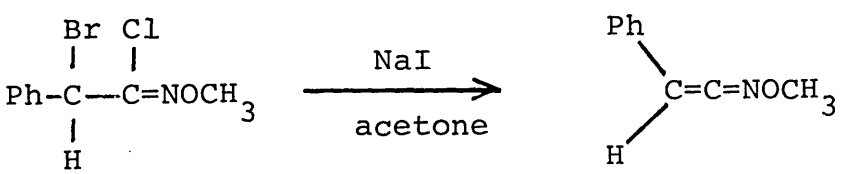
23 13b 26

polymer. One of the benzene soluble side products was identified as α-methoxyphenylacetonitrile (13b) by comparison of the NMR and IR spectra to the spectra of an authentic sample. The other benzene soluble side product was tentatively identified as α,α-dimethoxyphenylacetonitrile (26) based on its NMR spectra.

Since it appeared that the same results could be expected from the dehydrochlorination of both hydroximoyl chlorides and no ketenimines were produced, this synthetic approach was abandoned.

D. Attempted Dehalogenation of O-Methyl-α-bromophenylacetohydroximoyl Chloride (20)

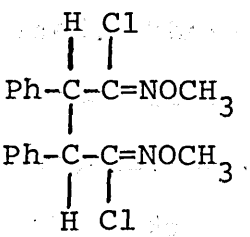
The synthesis of N-methoxy-phenylketenimine (23) by the dehalogenation of 20 was attempted using the method of Stevens and French.[30] The reaction was followed by



20 23

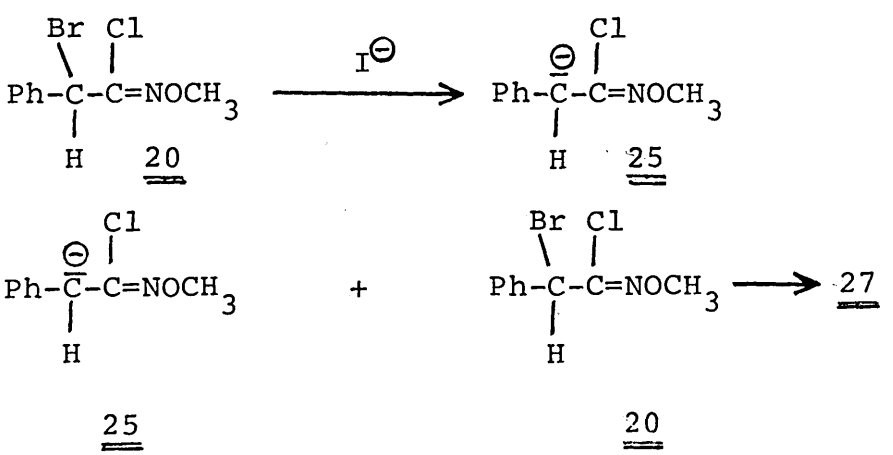
periodically removing aliquots from the refluxing mixture and checking the infrared spectrum for the ketenimine absorption band. No absorption at 1900 to 2200 cm^{-1} was noted. A quantitative yield of a high

melting solid was produced. This was identified by elemental analysis and NMR, IR and mass spectra as O,Ó-dimethyl-α,ά-diphenylsuccinobis (hydroximoyl chloride), 27.



27

The formation of 27 can be explained by the generation of a carbanion (25) followed by rapid attack of the carbanion on 20. This reaction is analogous to the reaction of alpha halo-acyl compounds which readily

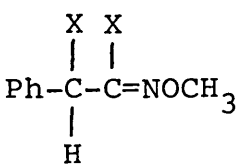


undergo nucleophilic substitution by an S_N2 mechanism.[58] In the case of the carbanion (25), the nucleophilic

substitution occurs on a second molecule of 20.

E. Conclusions

Although the attempted syntheses of N-methoxyketenimines were unsuccessful, a number of new and interesting compounds were synthesized. These compounds, with small modifications may yield the desired products. It is suggested that the dehalogenation of O-methyl-α-bromophenylacetohydroximoyl chloride (20) with sodium iodide failed because of the difference in reactivity of the two halides. It is possible to synthesize both the dibromo and dichloro hydroximoyl halides (28) by established



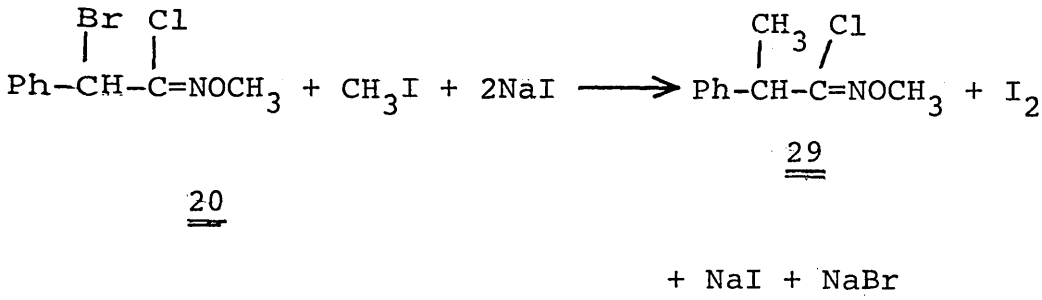
X = Br, Cl

28

routes. Perhaps one or both of these compounds will yield ketenimines when treated with sodium iodide in acetone.

Evidence[59] shows that ketene synthesis is not favored when there is a hydrogen atom on the distal carbon of the ketene moiety. This may also be true for ketenimines. It is possible that the intermediate carbanion (25) found in the reaction of 20 with sodium

iodide could be trapped with alkylating agents such as methyl iodide. Compound 29 might be dehydrochlorinated

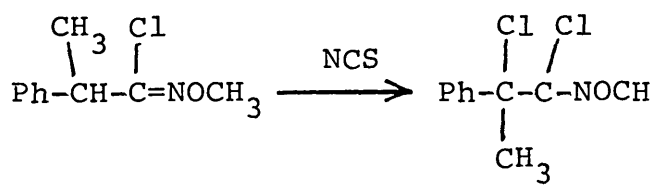


20

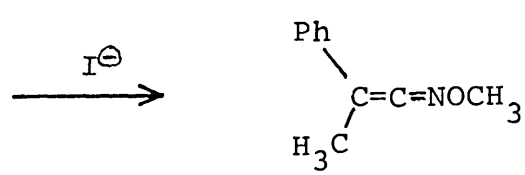
29

+ NaI + NaBr

to a ketenimine. Stevens and French[31] found that compounds with only one hydrogen atom on the alpha carbon form ketenimines when treated with triethylamine. If this approach fails, compound 29 could be alpha-chlorinated with N-chlorosuccinimide (NCS) for form 30 which then could be dechlorinated with sodium iodide to N-methoxy-phenylmethylketenimine (31).



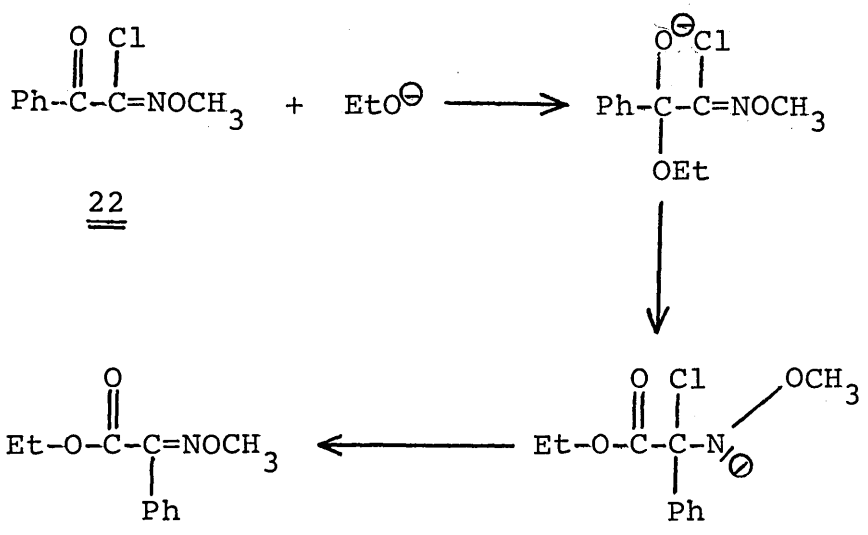
29 30



31

It is further suggested that O-methyl-α-ketophenylacetohydroximoyl chloride (22) could be used as a probe for investigating the stereochemistry of benzylic acid type rearrangement as shown in Scheme V.

SCHEME V


O Cl
Ph-C-C=NOCH3
+
EtO⊖
O⊖ Cl
Ph-C-C=NOCH3
OEt
22
O
Et-O-C-C=NOCH3
Ph
O Cl
OCH3
Et-O-C-C-N⊘
Ph

CHAPTER IV

Experimental

(A) Preparation of Compounds

Most reactions were carried out with technical grade chemicals. The nuclear magnetic resonance spectra were recorded in deuterated solvents at ambient temperatures on a Varian Model A-60A NMR spectrometer or a Varian EM-390 NMR spectrometer. The chemical shifts are expressed in δ relative to a tetramethylsilane internal standard. Infrared spectra were obtained either neat (liquids) or as Nujol mulls (solids) between sodium chloride plates with a Pye-Unicam SP1100 spectrophotometer. Mass spectra were recorded at 70eV ionizing potential on a CEC 21-104 mass spectrometer. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Product analyses and distributions were performed on a Varian Aerograph Model 90-P Gas Liquid Chromatograph (GLC) using a 18' x 3/8" column packed with 25% SE-30 silicon rubber on Chromosorb W (45/60 mesh). Elemental analyses of compounds were done by Atlantic Microlabs, Inc., Atlanta, Georgia.

(1) Preparation of Phenylacetamidoxime (14a)

A solution of hydroxylamine hydrochloride (47.0 g, 0.676 mol) in methanol (500 ml) was prepared and placed

in an ice bath. A solution of sodium carbonate (70.0 g, 0.660 mol) in water (300 ml) was slowly added with stirring. After stirring for one hour, the solution was filtered. The filtrate was put into a round bottom flask and returned to the ice bath. Phenylacetonitrile (75.0 g, 0.640 mol) was slowly added with stirring. The mixture was refluxed at 76°C for 18-48 hours, cooled to room temperature and filtered. The filtrate was rotary evaporated to remove the methanol and then extracted with ether (2 x 100 ml). The ether extract was dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation yielding an oil (73.1 g, 73.6%) which slowly crystallized when allowed to stand in an evaporating dish. The crude product (14a) melted at 64.5-68.0°C (lit[47] m.p. 67°C) and could not be recrystallized. IR (Nujol) 3495 and 3380 ($N-H_2$), 1665 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.38 (s, 2, CH_2), 4.38-4.75 (br s, 2, NH_2), 7.25 (s, 5, aromatic).

(2) Synthesis of O-Methylphenylacetamidoxime (15a)

Phenylacetamidoxime (77.4 g, 0.516 mol) was dissolved in 0.7 N sodium hydroxide solution (918 ml, 0.640 mol) and cooled in an ice bath. Dimethyl sulfate (60 ml, 0.633 mol) was slowly added with stirring. The solution was kept below 10°C and stirred for 6 hours. The solution was extracted with ether (2 x 100 ml). The combined ether

extracts were dried over anhydrous magnesium sulfate. The ether was removed by rotary evaporation and the residue was recrystallized from hexane-ether to yield white crystals (40.5 g, 47.9%) m.p. 64.5-65.0°C; IR (Nujol) 3475 and 3380 (N-H_2), 1660 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.43 (s, 2, $C\underline{H}_2$), 3.81 (s, 3, $OC\underline{H}_3$), 4.18-4.82 (br s, 2, $N\underline{H}_2$), 7.32 (s, 5, aromatic).

Analysis calculated for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.87; H, 7.41; N, 17.03.

(3) Synthesis of O-Methylphenylacetohydroximoyl Chloride (16a)

O-Methylphenylacetamidoxime (12.0 g, 0.073 mol) was dissolved in a solution of hydrochloric acid (16 ml, 0.197 mol) in water (40 ml) and cooled in an ice bath. A solution of sodium nitrite (8.28 g, 0.120 mol) in water (40 ml) was slowly added and the solution was stirred for 4 hours. The mixture was extracted with ether (3 x 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and rotary evaporated to yield a yellow oil (7.30 g, 54.4%). Fractional distillation in vacuo yielded a light yellow oil (5.41 g, 40.3%) b.p. 50-52°C/0.1 torr; IR (neat) 1620 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.76 (s, 2, $C\underline{H}_2$), 3.94 (s, 3, $OC\underline{H}_3$), 7.31 (s, 5, aromatic); mass spectrum, m/z (rel intensity) 183(M^+, 12.9), 148(10.2), 117(21.8), 116(87.5) 91(100.).

Analysis calculated for $C_9H_{10}NOCl$: C, 58.87; H, 5.49; N, 7.63; Cl, 19.31. Found: C, 59.04; H, 5.59; N, 7.70; Cl, 19.19.

(4) Synthesis of O-Methylphenylacetohydroximoyl Bromide (16b)

O-Methylphenylacetamidoxime (6.77 g, 0.041 mol) was dissolved in a solution of hydrobromic acid (10 ml, 0.090 mol) in water (50 ml) and cooled in an ice bath. A solution of sodium nitrite (4.28 g, 0.062 mol) in water (50 ml) was slowly added after which time the solution was stirred for 2 hours. The mixture was extracted with ether (2 x 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and rotary evaporated to yield a yellow oil. Fractional distillation in vacuo yielded a light yellow oil (1.86 g, 19.8%) b.p. 100-101°C/1.8 torr; IR (neat) 1620 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.86 (s, 2, $C\underline{H}_2$); 3.98 (s, 3, $OC\underline{H}_3$), 7.28 (s, 5, aromatic).

Analysis calculated for $C_9H_{10}NOBr$: C, 47.39; H, 4.42; N, 6.14; Br, 35.03. Found: C, 47.51; H, 4.45; N, 6.15; Br, 34.89.

(5) Synthesis of O-Methyl-α-bromophenylacetohydroximoyl Chloride (20)

O-Methylphenylacetohydroximoyl chloride (8.19 g, 0.044 mol) and N-bromosuccinimide (9.50 g, 0.053 mol) were put

into a round bottom flask with carbon tetrachloride (200 ml). Seven drops of hydrobromic acid (48%) were added and the flask was fitted with a reflux condensor protected with a calcium chloride drying tube. The mixture was refluxed for 18-20 hours, cooled to room temperature, and rotary evaporated until only a small amount of liquid was left. The residue was washed out of the flask into a filter funnel with carbon tetrachloride (4 x 50 ml). The filtrate was washed with 0.1 N sodium sulfite (2 x 50 ml) to remove bromine and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a yellow oil (11.76 g, 102%). Distillation in vacuo yielded a colorless oil (8.02 g, 69.6%) b.p. 110-116°C/1.5-1.8 torr; IR (neat) 1595 (C=N) cm^{-1}; NMR (CCl_4) δ 3.92 (s, 3, $OC\underline{H}_3$), 5.90 (s, 1, $C\underline{H}$), 7.28-7.33 (m, 3, aromatic), 7.52-7.68 (m, 2, aromatic); mass spectrum, m/z (rel intensity) 184(26.4), 182(80.5) 153(17.2), 151(51.7), 116(100.).

Analysis calculated for $C_9H_9NOClBr$: C, 41.17; H, 3.45; N, 5.34; Cl, 13.50; Br, 30.44. Found: C, 41.32; H, 3.50; N, 5.31; Cl, 13.47; Br, 30.36.

(6) Preparation of Benzaldehyde Dimethyl Acetal (18)

Compound 18 was prepared according to the method of Bailey.[48]

A mixture of benzaldehyde (106 g, 1.00 mol), trimethylorthorformate (161 g, 1.52 mol), methanol (102 g, 3.20 mol) and finely powdered aluminum chloride (2 g) was refluxed for 30 minutes. The excess solvent was removed by rotary evaporation and the remaining material was distilled in vacuo to yield a colorless oil (138 g, 90.8%) b.p. 108-110°C/30 torr (lit[60] b.p. 207°C); NMR (CCl_4) δ 3.22 (s, 6, OCH_3), 5.37 (s, 1, CH), 7.24-7.58 (m, 5, aromatic).

(7) Preparation of α-Chlorobenzyl Methyl Ether (19)

Compound 19 was prepared according to the method of Bailey.[48]

A mixture of benzaldehyde dimethyl acetal (51.0 g, 0.336 mol) and acetyl chloride (160 ml, 2.25 mol) was placed in a round bottom flask equipped with a reflux condensor protected by a calcium chloride drying tube and allowed to stir at room temperature for 18 hours. The excess acetyl chloride and the methyl acetate formed during the reaction were removed by rotary evaporation at 30°C to yield a yellow liquid (52.1 g, 99.2%); NMR (CCl_4) δ 3.56 (s, 3, OCH_3), 6.37 (s, 1, CH), 7.22-7.56 (m, 5, aromatic).

(8) Preparation of α-Methoxyphenylacetonitrile (13b)

Compound 13b was prepared according to the method of Padwa.[49]

α-Chloro benzyl methyl ether (86.0 g, 0.550 mol) was dissolved in anhydrous ether (700 ml) and placed in a round bottom flask equipped with a reflux condensor protected with a calcium chloride drying tube. Silver cyanide (73.6 g, 0.550 mol) was added and the mixture was refluxed for 5 hours and then stirred at room temperature for approximately 84 hours. After filtrating, the filtrate was rotary evaporated to yield a yellow oil (70.4 g, 87.1%). Fractional distillation in vacuo yielded a colorless oil (64.6 g, 79.9%) b.p. 73-77°C/0.5 torr; IR (neat), 1500, 1465, 1205, 1105 cm^{-1}; NMR ($CDCl_3$) δ 3.45 (s, 3, $OC\underline{H}_3$), 5.16 (s, 1, C$\underline{H}$), 7.38 (s, 5, aromatic); mass spectrum, m/z (rel intensity) 147(M^+, 30.8), 121(5.7), 116(100.), 91(10.0).

Analysis calculated for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.58; H, 6.22; N, 9.44.

(9) Preparation of α-Methoxyphenylacetamidoxime (14b)

A solution of hydroxylamine hydrochloride (32.7 g, 0.471 mol) in methanol (350 ml) was prepared and cooled in an ice bath. A solution of sodium carbonate (48.8 g, 0.460 mol) in water (210 ml) was slowly added. The mixture was stirred for 1 hour and filtered. The filtrate

was placed in a round bottom flask and α-methoxyphenylacetonitrile (64.6 g, 0.439 mol) was added slowly. The mixture was refluxed for 24 hours, cooled to room temperature and rotary evaporated to remove the methanol. The solid was filtered and recrystallized from benzene to yield white crystals (57.8 g, 89.6%) m.p. 128.5-129.5°C; IR (Nujol) 3500 and 3380 (N-H_2) 1680 (C=N) cm^{-1}; NMR (d_6-DMSO) δ 3.38 (s, 3, OCH_3), 4.37 (s, 1, CH), 5.33 (s, 2, NH_2), 7.30-7.61 (m, 5, aromatic), 9.50 (s, 1, OH); NMR ($CDCl_3$) δ 3.50 (s, 3, OCH_3), 4.60-4.80 (br s, 2, NH_2), 4.75 (s, 1, CH), 7.33-7.58 (m, 5, aromatic), 7.70-8.40 (br, s, 1, OH).

Analysis calculated for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.03; H, 6.75; N, 15.50.

(10) Preparation of O-Methyl-α-methoxyphenylacetamidoxime (15b)

α-Methoxyphenylacetamidoxime (8.21 g, 0.046 mol) was suspended in 0.7 N sodium hydroxide (115 ml, 0.081 mol) and water (500 ml). The suspension was heated with stirring until the solid dissolved. Dimethylsulfate (4.7 g, 0.50 mol) was slowly added. Heating was discontinued and the mixture was stirred at room temperature for 4 hours. After storage in the refrigerator for 8 hours, the mixture was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate. Removal of the solvent by rotary

evaporation produced a colorless oil which crystallized on standing. The white crystals (6.00 g, 52.0%) melted at 73.0-76.0°C and could not be recrystallized. IR (Nujol) 3480 and 3320 (N-H_2), 1650 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.41 (s, 3, $COCH_3$), 3.80 (s, 3, $NOCH_3$), 4.30-4.71 (br s, 2, NH_2), 4.68 (s, 1, CH), 7.26-7.54 (m, 5, aromatic).

Analysis calculated for $C_{10}H_{14}N_2O_2$: C, 54.70; H, 4.08; N, 7.09; Cl, 17.44. Found: C, 54.77; H, 4.09; N, 7.07; Cl, 17.89.

(11) Synthesis of O-Methyl-α-methoxyphenylaceto-hydroximoyl Chloride (16c)

O-Methyl-α-methoxyphenylacetamidoxime (6.00 g, 0.031 mol) was dissolved in a solution of hydrochloric acid (7.0 ml, 0.086 mol) in water (150 ml) and cooled in an ice bath. A solution of sodium nitrite (3.45 g, 0.050 mol) in water (50 ml) was added slowly. The mixture was stirred for 4 hours and then extracted with ether (2 x 50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and rotary evaporated to yield a yellow oil. Distillation in vacuo yielded a light yellow oil (2.00 g, 30.2%) b.p. 89-91°C/0.4 torr; IR (neat) 1600 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.45 (s, 3, $COCH_3$), 4.00 (s, 3, $NOCH_3$), 5.10 (s, 1, CH), 7.33-7.61 (m, 5, aromatic).

Analysis calculated for $C_{10}H_{12}NClO_2$: C, 56.21; H, 5.66;

N, 6.56; Cl, 16.59. Found: C, 56.35; H, 5.72; N, 6.50; Cl, 16.44.

(12) Attempted Bromination of O-Methyl-α-methoxyphenylacetohydroximoyl Chloride (16c)

O-Methyl-α-methoxyphenylacetohydroximoyl chloride (2.00 g, 0.009 mol) and N-bromosuccinimide (2.10 g, 0.012 mol) were placed in a round bottom flask with carbon tetrachloride (50 ml). Seven drops of hydrobromic acid (48%) were added and the flask was fitted with a reflux condensor protected by a calcium chloride drying tube. The mixture was refluxed for 24 hours, cooled to room temperature, condensed to a small volume, and filtered. The solid material was washed with carbon tetrachloride (4 x 50 ml), dried over anhydrous magnesium sulfate and rotary evaporated to yield a light yellow oil (1.72 g). The product distribution was determined by GLC analysis. The oil contained 30% of the hydroximoyl chloride (16c) and 70% O-methyl-α-ketophenylacetohydroximoyl chloride (22). The analytical sample of compound (22) was obtained as a colorless oil by microdistillation of the GLC effluent; IR (neat) 1680 (C=O), 1600 (C=N) cm^{-1}; NMR (CCl_4) δ 4.17 (s, 3, OCH_3), 7.30-7.62 (m, 3, aromatic), 7.92-8.14 (m, 2, aromatic); mass spectrum, m/z (rel intensity) 197(M^+, 5.97), 131(6.06), 105(100).

Analysis calculated for $C_9H_8NO_2Cl$: C, 54.70; H, 4.08; N, 7.09; Cl, 17.94. Found: C, 54.77; H, 4.09; N, 7.07; Cl, 17.89.

B. Dehydrochlorination Reactions

(1) Reaction of O-Methylphenylacetohydroximoyl Chloride (16a) with Triethylamine

Freshly distilled triethylamine (4.0 ml, 0.029 mol) was dissolved in dry benzene. A solution of O-methylphenylacetohydroximoyl chloride (1.32 g, 0.007 mol) in dry benzene (25 ml) was added. A reflux condensor protected with a calcium chloride drying tube was added and the mixture refluxed for 46 hours. The excess triethylamine was removed by adding water and bubbling carbon dioxide gas through the two layers. The benzene layer was separated, dried over anhydrous magnesium sulfate, and rotary evaporated to yield a yellow oil (1.21 g). Analysis by NMR and GLC showed only the presence of unreacted hydroximoyl chloride.

(2) Reaction of O-Methylphenylacetohydroximoyl Chloride (16a) with 1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU)

O-Methylphenylacetohydroximoyl chloride (3.00 g, 0.016 mol) dissolved in dry benzene (25 ml) was placed in a round bottom flask. The flask was fitted with a reflux condensor protected by a calcium chloride drying

tube. DBU (5.0 ml, 0.032 mol) was added slowly. The mixture turned yellow, a white precipitate formed, and heat was evolved. The mixture was stirred at room temperature for 18 hours during which time it became red-black in color. The excess DBU was removed by adding water and bubbling carbon dioxide gas through both layers. The benzene layer was separated, dried over anhydrous magnesium sulfate and rotary evaporated to yield a viscous red-black material (2.55 g). Distillation in vacuo yielded 0.62 g of a colorless oil, b.p. 53-56°C/1.2 torr. Analysis of the oil by GLC showed the product distribution to be 11% unreacted hydroximoyl chloride, 61% benzyl cyanide and 27% α-methoxyphenylacetonitrile. Good spectral data of the red-black material could not be obtained because it charred on distillation. Elemental analysis of the crude material supports the evidence that it is a polymer of formula $(C_9H_9NO)_n$.

Analysis calculated for $(C_9H_9NO)_n$: C, 73.45; H, 6.16; N, 9.52. Found: C, 76.08; H, 6.42; N, 8.07.

(3) Reaction of O-Methyl-α-methoxyphenylacetohydroximoyl Chloride (16c) with DBU

O-Methyl-α-methoxyphenylacetohydroximoyl chloride (0.80 g, 3.75 mmol) was dissolved in dry benzene and placed in a round bottom flask. The flask was fitted with

a reflux condensor protected by a calcium chloride drying tube. DBU (1.15 ml, 7.70 mmol) was slowly added and the mixture refluxed for 72 hours. The mixture turned red-black in color. The excess DBU was removed by adding water and bubbling carbon dioxide gas through the layers. The benzene layer was separated, dried over anhydrous magnesium sulfate and rotary evaporated to yield a small amount of light purple oil. Analysis by GLC showed the product distribution to be 78% unreacted hydroximoyl chloride, 20% α-methoxyphenylacetonitrile, and a small amount of two other compounds. The more abundant of these compounds, assigned structure 26, tested Beilstein negative; NMR (CCl_4) δ 3.40 (s, 6, OCH_3), 7.42-7.53 (m, 3, aromatic), 7.58-7.66 (m, 2, aromatic). Not enough of the second compound could be collected for identification.

(C) Dehalogenation of O-Methyl-α-bromophenylaceto-hydroximoyl Chloride (21)

O-Methyl-α-bromophenylacetohydroximoyl chloride (4.00 g, 0.015 mol), dry acetone (130 ml), and sodium iodide (20.70 g, 0.138 mol) were placed in a round bottom flask. The flask was fitted with a reflux condensor protected by a calcium chloride drying tube. The mixture was refluxed for 2 hours, cooled to room temperature, and evaporated. The residue was suspended

in hot water (100°C), filtered, washed with additional hot water (500 ml), and washed with 0.1 M sodium sulfite (300 ml). The remaining solid was dissolved in hot hexane (300 ml) and filtered. The filtrate was washed with 0.1 M sodium sulfite (2 x 100 ml), dried over anhydrous magnesium sulfate, and rotary evaporated to yield 2.16 g of yellow-brown solid.

The crude sample was divided into equal parts and two methods of purification were used. (1) The impure material was recrystallized by dissolving in boiling hexane and rapid cooling in an ice bath to produce white-yellow crystals (43% recovery) which melted at 118-156°C. (2) The impure material (0.4 g) was dissolved in a minimal amount of boiling hexane and applied to a silica gel column (Macherey, Nageld Co., 0.1-0.2 mm, 2.5 x 46 cm) and eluted with 20% benzene/hexane until a wide yellow band separated from the brown material at the top oc the column. The eluting solvent was changed to 50% benzene/hexane to increase the band movement. When the yellow band was half way down the column, the top of the column (~6cm) was allowed to run dry and scraped out of the column to remove the brown material. The column was stripped by eluting with benzene. The eluants were rotary evaporated to produce a bright yellow solid. The

solid was washed with room temperature hexane until no more yellow could be seen to yield 0.22 g white powder (55% recovery) which melted at 142-170°C. The analytical sample of 27 was obtained by repeated recrystallization from hot hexane of either of the two partially purified samples to produce white crystals; m.p. 179.0-179.5°C; IR (Nujol) 1615 (C=N) cm^{-1}; NMR (CCl_4) δ 3.72 (s, 3, OCH_3), 4.68 (s, 1, CH), 7.26-7.53 (m, 5, aromatic); mass spectrum, m/z (rel intensity) 364(M^+, 0.17), 329(4.75), 184(32.4), 182(100.), 151(44.6), 116(33.1).

Analysis calculated for $C_{18}H_{18}N_2O_2Cl$: C, 59.19; H, 4.97; N, 7.67; Cl, 19.41. Found: C, 59.49; H, 5.16; N, 7.68; Cl, 19.20.

(D) Trapping Experiments

O-Methylphenylacetohydroximoyl chloride (3.10 g, 17 mmol) was dissolved in 50 ml dry benzene. The freshly distilled trapping agent (52 mmole of styrene, ethylvinyl-ether, or tetrachloroethylene) was added and the mixture placed under an atmosphere of nitrogen gas. DBU (5 ml, 33 mmol) was slowly added with stirring. The mixture turned yellow and a white precipitate formed. After 2 hours, the excess DBU was removed by bubbling carbon dioxide gas through the mixture and washing with water. The benzene layer was dried over anhydrous magnesium

sulfate and evaporated to give a yellow oil. The oil was separated on a silica gel column (20 x 2 cm). Two fractions were obtained by eluting with benzene followed by acetone. Both fractions were rotary evaporated. NMR and GLC of the benzene fraction showed it to be a mixture of benzyl cyanide, starting material, and α-methoxyphenylacetonitrile. The acetone fraction was a yellow very viscous oil. NMR showed one very broad peak, δ 7.0-7.7. It appeared to be a polymer. All trapping agents gave the same results.

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