I. The Use of Polyethers as Phase Transfer Catalysts for the Fluoroalkoxylation of Halogenated Aromatic and Heteroaromatic Systems II. The Grignard Addition and Sodium Cyanoborohydride Reduction of Arylchloropropeniminium Salts

Martin A.M. Moebus
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I. THE USE OF POLYETHERS AS PHASE TRANSFER CATALYSTS FOR THE FLUOROALKOXYLATION OF HALOGENATED AROMATIC AND HETEROAROMATIC SYSTEMS

II. THE GRIGNARD ADDITION AND SODIUM CYANOBOROHYDRIDE REDUCTION OF ARYLCHLOROPROPENIMINIUM SALTS

BY

MARTIN A.M. MOEBUS
B.A., Purdue University at Indianapolis, 1980

RESEARCH REPORT

Submitted in partial fulfillment of the requirements for the Master of Science degree in Industrial Chemistry in the Graduate Studies Program of the College of Arts and Sciences University of Central Florida Orlando, Florida

Spring Term
1985
ABSTRACT

This research addresses two distinct areas of synthetic organic chemistry: the use of phase transfer catalysts for the fluoroalkoxylation of activated haloaromatic and haloheteroaromatic systems, as well as the Grignard addition and sodium cyanoborohydride reduction of aryl chloropropeniminium salts. In Part I of this research, a number of macrocyclic- and linear-polyethers were studied as phase transfer catalysts in the nucleophilic aromatic substitution of haloaromatic systems. The most effective catalyst was determined to be poly(ethylene glycol)-8000 and the reaction conditions were optimized for this catalyst. Subsequently, isomer reactivity, effects of activating groups, effects of leaving groups, and nucleophiles were studied with respect to the selective fluoroalkoxylation of various halogenated aromatic substrates. In Part II, a series of 3-chloro-3-aryl-prop-2-en-yliden-dimethyliminium perchlorates were synthesized, isolated, and subsequently their regio-chemistry was studied with reducing agents and with Grignard reagents. The results indicated that reduction and Grignard addition occurred at the imine (C=N) carbon to form the corresponding N,N-dialkyl allylic amines.
ACKNOWLEDGEMENTS

I would like to thank the faculty and staff of the Department of Chemistry at the University of Central Florida for giving me the opportunity to complete my graduate studies in chemistry. I am particularly thankful and greatly indebted to Dr. John T. Gupton III for his enthusiasm, encouragement, support, and guidance during my graduate research. I am also grateful to Dr. Guy Mattson, Dr. Chris A. Clausen III, and Dr. Graeme Baker for their time and effort as members of my graduate committee. I would also like to thank Dr. Rodger N. Capps and Dr. Robert Y. Ting of the Naval Research Laboratory-USRD for their efforts which enabled me to complete this work.

Finally, I would like to express my deepest appreciation to my parents, my wife, and my daughter for their love and moral support.
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\( \alpha \)  \hspace{1em} \text{alpha}

A  \hspace{1em} \text{Angstrom, } 1 \times 10^{-8} \text{ centimeters}

\( \beta \)  \hspace{1em} \text{beta}

bp  \hspace{1em} \text{boiling point}

15-C-5  \hspace{1em} 15\text{-crown-5}

18-C-6  \hspace{1em} 18\text{-crown-6}

DB  \hspace{1em} \text{dibenzo-}

DCH  \hspace{1em} \text{dicyclohexano-}

\( ^\circ \text{C} \)  \hspace{1em} \text{degrees Centigrade}

CDCl\textsubscript{3}  \hspace{1em} \text{deuterated chloroform}

\text{cm}^{-1}  \hspace{1em} \text{wavenumbers (IR spectrum)}

conver  \hspace{1em} \text{conversion}

\( \delta \)  \hspace{1em} \text{delta (NMR spectrum)}

\( \delta_s \)  \hspace{1em} \text{delta, strong vibrational bend frequency (IR spectrum)}

d  \hspace{1em} \text{doublet (NMR spectrum)}

DMF  \hspace{1em} \text{N,N-dimethylformamide}

DMSO  \hspace{1em} \text{dimethylsulfoxide}

DMSO-d\textsubscript{6}  \hspace{1em} \text{deuterated dimethylsulfoxide}

equiv  \hspace{1em} \text{equivalents}

>  \hspace{1em} \text{greater than}
GLC  gas chromatography
HMPA  hexamethylphosphoramide
Hrs  hours
Hz  Hertz (cycles per second–NMR spectrum)
IR  infrared
i-Pr  2-propyl or isopropyl
J  coupling constant (NMR spectrum)
m  multiplet (NMR spectrum)
M⁺  molecular ion (mass spectrum)
Me  methyl group, CH₃
m/e  mass to charge ratio (mass spectrum)
min  minutes
mL  milliliters
mp  melting point
MPEG  methoxy-polyethylene glycol
M_w  average weight molecular weight
NMR  nuclear magnetic resonance
νₛ  strong vibrational stretch frequency (IR spectrum)
Nuc  nucleophile
PEG  poly(ethylene glycol)
PEG–300  PEG of 300 average molecular weight
PEG’s  polyethylene glycols
PTC  phase transfer catalyst and/or catalysis
PTC’s  phase transfer catalysts
<table>
<thead>
<tr>
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<th>Definition</th>
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<tbody>
<tr>
<td>Rf</td>
<td>fluorinated alkane</td>
</tr>
<tr>
<td>rpm</td>
<td>revolutions per minute</td>
</tr>
<tr>
<td>rxn</td>
<td>reaction</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR spectrum)</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TEBA</td>
<td>triethylbenzylammonium salt</td>
</tr>
<tr>
<td>VHA</td>
<td>Vilsmeir–Haack–Arnold reaction</td>
</tr>
<tr>
<td>v/v</td>
<td>volume/volume</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>w/w</td>
<td>weight/weight</td>
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</table>
PART I

THE USE OF POLYETHERS AS PHASE TRANSFER CATALYSTS FOR THE FLUOROALKOXYLATION OF HALOGENATED AROMATIC AND HETEROAROMATIC SYSTEMS

INTRODUCTION

Prior to the 1930s, organic fluorine chemistry was virtually unknown. Not until after the discovery of freons and after the pressures of World War II did great advances occur in the synthesis of "fluorocarbons". The changes in material properties and reactivities upon the substitution of fluorine or fluorinated groups onto a parent molecule have found many practical applications in today's world. These fluorinated molecules exhibit a wide range of properties: from inert materials, such as Teflon, to biologically active materials, such as the inhalation anesthetic, halothane.\(^1,2,3\)

The enhanced biological effects of fluorine substituted organic molecules find important applications in agriculture and pharmaceutics.\(^2\) Of particular interest to this investigator are the fluoro-aromatic intermediates which incorporate the trifluoroethoxy (\(-\text{OCH}_2\text{CF}_3\)) moiety on the aryl- or heteroaryl-backbone. Examples of such fluoro-
organics are the fluorinated DOWC0–416 and Flecainide Acetate (Figure I).

![Chemical structures]

Figure I. Fluoroethoxylated organic compounds: DOWC0–416 (I) and Flecainide Acetate (II)

DOWC0–416 has shown great promise as an insecticide and toxicological studies have shown that the fluorinated compound is more effective as a larvacide than its non-fluorinated analog.\(^4\) Flecainide acetate, which was developed by Banitt et al., is a potent cardio-antiarrhythmic and is the first fluorinated drug of its kind to be considered for clinical use by the Food and Drug Administration.\(^5,6,7\) If approved, flecainide acetate could replace Lidocaine and Procainamide, which are the currently accepted medications for the treatment of heart attacks.

Its resistance to strong acids and to strong bases, as well as its stability to chemical transformation reactions (reduction of nitro groups, hydrolysis of nitriles,
diazotization of amino groups, and nitration) makes the trifluoroethoxy moiety an important substituent in the chemistry of fluoro-aromatic compounds. For either of the above mentioned compounds, I or II, structure-property correlations indicate that both the number and the position of the trifluoroalkoxy group determine their biological activities. The primary goal of this research is to develop a practical method for the fluoroalkoxylation of activated and unactivated haloaromatic compounds. A comprehensive review of the literature indicates that there are several viable methods for the synthesis of alkoxy aromatics, perfluoroalkoxy aromatics, and fluoroalkoxy aromatics (Figure II).

(a) 
\[
\text{COF}_2 + \text{R} \xrightarrow{\text{HF}, \text{SF}_4} \text{R} \quad \text{OCF}_3
\]

(b) 
\[
\text{R} \xrightarrow{1. \text{NaOH}} \text{R} \quad \text{S} \xrightarrow{2. \text{CSCl}_2} \downarrow \quad \text{OCCl} \quad \xrightarrow{\text{MoF}_6} \text{R} \quad \text{OCF}_3
\]

(c) 
\[
\text{R} \quad \xrightarrow{\text{NaOCH}_3 / \text{HMPA}, 90^\circ C} \text{R} \quad \text{OCH}_3
\]
(d) Sheppard and Aldrich (1963), (b) Mathey and Bensoam (1973), (c) Shaw, Kunnerth, and Swanson (1976), (d) Kornblum (1976), (e) Alperman and Werner (1979), (f) Rico and Wakselman (1981), (g) Rico and Wakselman (1981).

Figure II. Alkoxylation methods in organic synthesis.
Sheppard and Aldrich prepared several aryl- and alkyl-fluoroalkyl ethers by reacting sulfur tetrafluoride with fluoroformates. The fluoroformates utilized in this reaction scheme were prepared by the reaction of phenols or alcohols with carbonyl fluoride at high temperatures and pressures. The final yields ranged from 60 to 80 percent. However, there are several drawbacks to this synthetic method: (1) hydrogen fluoride is a by-product to these reactions and it is easily able to react with other substituents on the parent molecule (phenol or aliphatic alcohol), (2) this reaction scheme does not tolerate temperature excursions above nor below the optimum temperature range of 150-170°C. Friedel-Crafts acylations predominate to form tars if above this range and a marked decrease in yield is also observed at lower temperatures, (3) this reaction requires the use of a "specialized" autoclave which may not always be available in every laboratory and would make this method impractical in industrial scale-up, (4) this method incorporates the use of a very toxic fluorinating agent, SF₄. In an effort to avoid these drawbacks, Mathey and Bensoam developed a two step synthetic scheme which may be performed at atmospheric pressure, at low temperatures, and avoided the use of sulfur tetrafluoride. In their facile reaction scheme, sodium phenoxide was reacted with thionyl chloride.
(Cl–C(S)–Cl) to form the corresponding chlorothioformates in 80 to 90 percent yields. Subsequently, the fluoroalkyl ethers were produced when molybdenum hexafluoride was added to the reaction mixture. However, the incorporation of the thionyl group and the subsequent substitution of the sulfur atom by fluorine constitutes a loss of functionality. This process is, therefore, less appealing for industrial applications where the loss of functional groups means the loss of profits.

In 1976, Shaw and Kornblum et al. developed and reported a method which introduced an alkoxy group directly onto a series of halobenzenes. Using hexamethyl phosphoramide (HMPA) as the reaction solvent, Shaw reacted unactivated halobenzenes with sodium methoxide at 90°C and Kornblum independently investigated the reactions of activated nitrobenzenes with the same nucleophile at 25°C. In both cases, substituted anisoles were isolated in good yields. The simplicity of these methods prompted Gupton, Idoux, and their co-workers to define the scope and the limitations to which fluoroalkoxyations could be applied. Halobenzonitriles, halophenyl sulphones, haloaryl amides, halonitrobenzenes and polyhaloaromatics were studied and the mono- or poly-fluoroalkoxylated products were isolated in high yields. Again, there are several inherent problems to this simple synthetic method:
(1) high temperatures are required to allow the unactivated haloaromatics to react with the nucleophiles, (2) polar or special solvents (i.e., HMPA) must be used in order to convert the unactivated haloaromatics to the respective product, and (3) the cost and the toxicity of the solvent would limit the application of this simple method to laboratory scale operations.

Analogous to the synthesis of fluoroalkyl aryl ethers is the synthesis of aromatic perfluoroethers.21,22,23 Among the more interesting of the known synthetic methods was the incorporation of a perfluoroalkane onto aryl thiolates to form the respective alkyl aryl thioethers. What makes this method so unique is the novel use of a quaternary ammonium salt (TEBA) as a phase transfer catalyst.23 In this way, aryl thiolates could be synthesized and subsequently fluoroalkoxylated in situ. In addition, these investigators used benzene as a solvent which afforded conversions at lower temperatures. Another appealing feature of this synthetic method was that benzene is a much more "inert" solvent than HMPA in the sense that it does not chemically interact with the reactants.18 On the other hand, benzene is hepatotoxic and is also a suspected carcinogen; these drawbacks severely hinder large scale applications of this method in industry.
In 1982, Paradisi et al.\textsuperscript{24} undertook a comprehensive investigation into the feasibility of the direct alkoxylation of 1-chloro-4-nitrobenzene. These studies indicated that the conversion of the substrate to the product $4\text{-NO}_2\text{C}_6\text{H}_4\text{OR}$ was effected by the use of alkali ion complexing agents in the presence of alcohol solvents and aqueous KOH (50%). In their work, these investigators utilized quaternary ammonium salts as well as several macro-polyethers (18-crown-6, Carbowax 20M, MPEG-5000, and Triton X-100) and obtained fairly high yields of the alkyl aryl ether (Figure III). This method is very unique in that it utilizes alcohols as both the reagent and the solvent in the reaction.

![Chemical structure](image)

Figure III. 1-Chloro-4-nitrobenzene in homogeneous 2-propanol and 50% aqueous KOH.

More recently, the use of dicyclohexano-18-crown-6 by Rolla et al.\textsuperscript{25} in the reaction of alkyl thiolates and dichlorobenzenes in aqueous systems, prompted Brunelle to
investigate the phase transfer catalyzed alkyl thiolation of various chloroaromatics. Brunelle discovered a remarkable regioselectivity in his solid-liquid phase transfer catalyzed reactions which had been carried out in toluene.

![Figure IV. The phase transfer catalyzed reaction of PCB with alkyl thiolates.](image)

Di-, tri-, and tetra-haloaromatics were studied and a number of phase transfer catalysts were evaluated by Brunelle. Among the many catalytic agents utilized, crown ethers and poly(ethylene glycols) were determined to be highly effective agents. In addition, Brunelle concluded that strong bases like KH or t-BuOK were not necessary to form the thiolate; instead, pulverized solid KOH could be directly charged into the reaction vessel. This method, therefore, forms an in situ synthesis of potassium-alkyl thiolate in the presence of a phase transfer catalyst. A practical application of Brunelle’s work utilizes a
poly(ethylene glycol) as a phase transfer catalyst in a patented process of reducing PCB levels in transformer fluids. 27

The applications of phase transfer catalysts to industrial organic syntheses are rapidly growing in number. 28 Therefore, we decided to examine the feasibility of phase transfer catalyst mediated fluoroalkoxylation of activated haloaryl and halo-heteroaryl substrates with fluorinated alcohols in the presence of a base. Coury has studied quaternary ammonium and quaternary phosphonium salts and has evaluated their effectiveness as PTC’s with the same systems. 29 In this work, macrocyclic ethers and linear polyethers will be evaluated as phase transfer catalysts. The effects of temperature, solvent, and the type of base (NaH, NaOH(aq), NaOH(s)) on the catalytic activity of a series of phase transfer catalysts will be studied. In addition, the effect of different activating groups will be studied with respect to the type of reaction conditions and, also, with respect to the extent of activation in the ortho-, meta-, and para-positions. Thirdly, the effect of leaving group type and the effect of nucleophiles on the PTC mediated nucleophilic aromatic substitution of an activated halo-aryl system will be evaluated. And, lastly, a regioselectivity study on various poly-haloaromatic systems will be conducted under
phase transfer catalyzed conditions. In this study, the substrates chosen are those that are expected to yield products which are identical to those which had been previously reported by Gupton and Idoux.\textsuperscript{13-20} The purity of the reaction mixture will be determined by GLC and new compounds will be characterized by NMR, IR, and mass spectrometry.
PART I
EXPERIMENTAL

A. Feasibility Study

\[
\begin{align*}
\text{NO}_2\text{Cl} + \text{HOCH}_2\text{CF}_3 + \text{NaH} &\xrightarrow{18\text{-C-}6} \text{C}_6\text{H}_6 \quad 78 \degree\text{C} \\
\text{NO}_2\text{OCH}_2\text{CF}_3 + \text{NaCl} + \text{H}_2 
\end{align*}
\]

Table 1.

The 18-crown-6 catalyzed reactions of Na-OCH$_2$CF$_3$ with 4-chloronitrobenzene in benzene as a solvent.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. ($^\circ$C)</th>
<th>PTC$^b$ conc. (mole %)</th>
<th>Rxn. $^c$ Time (Hrs)</th>
<th>Conver. $^d$ by GLC (%)</th>
<th>Crude$^e$ Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>0.0</td>
<td>48</td>
<td>0.0</td>
<td>00.0$^f$</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>21.0</td>
<td>24</td>
<td>0.0</td>
<td>00.0$^f$</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>0.0</td>
<td>24</td>
<td>0.0</td>
<td>00.0$^f$</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>21.0</td>
<td>23</td>
<td>95.0</td>
<td>59.7</td>
</tr>
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</table>
a. All entries utilize 1.1 equivalents of NaH as base and 1.5 equivalents of $R_f$-OH relative to the amount of substrate charged.

b. The mole percent value is relative to the amount of substrate charged.

c. The reaction time was determined by means of an automatic, 17-jeweled, Benrus chronometer.

d. The conversions for all entries were determined by GLC. Samples were taken directly from the reaction vessel and injected into the instrument by means of a micro syringe. Conversions are based on known response factors for the pure starting material as well as for the pure product. The GLC conditions utilized are identical to those used by Coury.29

e. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

f. GLC and NMR analyses indicated less than 5% conversion of substrate to product.
Table 2

The 18-crown-6 catalyzed reactions of Na-OCH₂CF₃ with 4-chloronitrobenzene in toluene as a solvent.¹

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>PTCconc. (mole %)</th>
<th>Rxn. Time (Hrs)</th>
<th>Conver. by GLC (%)</th>
<th>Crude Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>0.0</td>
<td>21</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>25.0</td>
<td>24</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>0.0</td>
<td>21</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>111</td>
<td>25.0</td>
<td>24</td>
<td>58.0</td>
<td>71.3</td>
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<td>5</td>
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<td>10.0</td>
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<td>57.4</td>
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<tr>
<td>7</td>
<td>111</td>
<td>25.0</td>
<td>23</td>
<td>64.0</td>
<td>50.9</td>
</tr>
<tr>
<td>8</td>
<td>111</td>
<td>40.0</td>
<td>22</td>
<td>62.2</td>
<td>75.0</td>
</tr>
</tbody>
</table>

¹ Entries 1, 2, 3, and 4 were charged with 1.1 equivalents of NaH and entries 5, 6, 7, and 8 were charged with 1.1 equivalents of solid NaOH. All entries were charged with 1.5 equivalents of HO-CH₂CF₃. The number of equivalents charged refers to the amounts of reactants added relative to the amount of substrate charged.
b. The mole percent value is relative to the amount of substrate charged.

c. The reaction time was determined by means of an automatic, 17-jeweled, Benrus chronometer.

d. The conversions for all entries were determined by GLC. Samples were taken directly from the reaction vessel and injected into the instrument by means of a micro syringe. Conversions are based on known response factors for the pure starting material as well as for the pure product. The GLC conditions utilized are identical to those used by Coury.²⁹

e. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

f. GLC and NMR analyses indicated less than 5% conversion of substrate to product.

g. This reaction vessel was charged with 1.1 equivalents of NaOH as a 50% aqueous solution by weight.

The following reaction procedure is typical of the experimental conditions in the phase transfer catalyzed fluoroalkoxylation which were mediated by 18-crown-6 in benzene or toluene as solvents.
4-(2,2,2-Trifluoroethoxy)nitrobenzene

A 250 mL, round-bottomed, three-necked flask was equipped with a condenser, a thermometer, and a magnetic stirrer. Into the flask were placed 0.559 grams (0.0140 mole) of powdered sodium hydroxide, 1.905 grams (0.0190 mole) of 2,2,2-trifluoroethanol and 100 mL of toluene. The mixture was stirred and 1.423 grams (0.00058 mole) of 18-crown-6 was added, followed by the addition of 2.00 grams of 4-chloronitrobenzene. The resulting mixture was allowed to reflux for 24 hours and was subsequently cooled to room temperature. The crude mixture was extracted with cold water (3 times 50 mL) and with brine (2 times 25 mL) and then dried over anhydrous magnesium sulfate. The organic phase was concentrated in vacuo and the resulting solid was weighed to obtain a crude yield.
Table 3

The 18-crown-6 catalyzed reactions of Na–OCH$_2$CF$_3$ with 4-chloronitrobenzene in different solvents.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Solvent$^b$</th>
<th>PTC$_c$ conc. (mole%)</th>
<th>Rxn. Time (Hrs)</th>
<th>Conver.$^e$ by GLC (%)</th>
<th>Crude Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>101</td>
<td>A</td>
<td>0.0</td>
<td>26</td>
<td>0.0</td>
<td>0.0g</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>A</td>
<td>25.0</td>
<td>22</td>
<td>58.7</td>
<td>46.9</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>A</td>
<td>25.0</td>
<td>22</td>
<td>62.2</td>
<td>48.5</td>
</tr>
<tr>
<td>4</td>
<td>154</td>
<td>B</td>
<td>0.0</td>
<td>22</td>
<td>74.3</td>
<td>53.8</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>C</td>
<td>21.0</td>
<td>23</td>
<td>95.0</td>
<td>59.7</td>
</tr>
<tr>
<td>6</td>
<td>111</td>
<td>D</td>
<td>25.0</td>
<td>23</td>
<td>64.0</td>
<td>50.9</td>
</tr>
<tr>
<td>7</td>
<td>111</td>
<td>D</td>
<td>40.0</td>
<td>22</td>
<td>62.2</td>
<td>75.0</td>
</tr>
</tbody>
</table>

$a.$ Entries 1, 2, and 5 were charged with 1.1 equivalents of NaH and entries 3, 4, 6, and 7 were charged with 1.1 equivalents of solid NaOH but all entries were charged with 1.5 equiv. of HO–CH$_2$CF$_3$. The equivalent amounts refer to the amounts of reagents added relative to the amount of substrate.

$b.$ SOLVENTS: (A)1,4-dioxane, (B)diglyme, (C)benzene, (D)toluene.
c. The mole percent value is relative to the amount of substrate charged.

d. The reaction time was determined by means of an automatic, 17-jeweled, Benrus chronometer.

e. The conversions for all entries were determined by GLC. Samples were taken directly from the reaction vessel and injected into the instrument by means of a micro syringe. Conversions are based on known response factors for the pure starting material as well as for the pure product. The GLC conditions utilized are identical to those used by Coury. 29

f. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

g. GLC and NMR analyses indicated less than 5% conversion of substrate to product.
Table 4

The effect of different catalysts on the reaction between Na-OCH₂CF₃ and 4-chloronitrobenzene in toluene.ᵃ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base b conc. (equiv)</th>
<th>R₂-OH c conc. (equiv)</th>
<th>Phase Transfer Catalyst</th>
<th>Conver. d by GLC (%)</th>
<th>Crude e Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.5</td>
<td>15-Crown-5</td>
<td>60.3</td>
<td>66.4</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>1.5</td>
<td>18-Crown-6</td>
<td>62.2</td>
<td>75.0</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>1.5</td>
<td>DB-18-C-6</td>
<td>57.0</td>
<td>73.5</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>1.5</td>
<td>DIGLYME</td>
<td>59.6</td>
<td>9.5</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>1.5</td>
<td>1,4-DIOXANE</td>
<td>0.0</td>
<td>0.0ᶠ,g</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>1.5</td>
<td>HMPA</td>
<td>0.0</td>
<td>0.0ᵍ</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>1.5</td>
<td>PEG-300</td>
<td>12.7</td>
<td>55.8</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>1.5</td>
<td>PEG-600</td>
<td>36.7</td>
<td>44.1</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>1.5</td>
<td>PEG-1000</td>
<td>40.4</td>
<td>54.4</td>
</tr>
<tr>
<td>10</td>
<td>1.1</td>
<td>1.5</td>
<td>PEG-1500</td>
<td>49.6</td>
<td>43.4</td>
</tr>
<tr>
<td>11</td>
<td>1.1</td>
<td>1.5</td>
<td>PEG-3400</td>
<td>61.0</td>
<td>35.6</td>
</tr>
<tr>
<td>12</td>
<td>1.1</td>
<td>1.5</td>
<td>PEG-8000</td>
<td>75.7</td>
<td>51.5</td>
</tr>
<tr>
<td>13</td>
<td>1.1</td>
<td>1.5</td>
<td>PEG-14000</td>
<td>62.6</td>
<td>47.2</td>
</tr>
</tbody>
</table>

ᵃ All entries were charged with 40 mole percent of the catalytic agent listed. All reactions were
allowed to heat at reflux for 22 hours prior to work-up procedures.

b. Unless otherwise indicated, solid NaOH powder was charged into the reactor and the equivalents indicated are relative to the amount of substrate charged.

c. All entries incorporate amounts of HO-CH₂CF₃ relative to the amount of substrate charged.

d. The conversions for all entries were determined by GLC. Samples were taken directly from the reaction vessel and injected into the instrument by means of a micro syringe. Conversions are based on known response factors for the pure starting material as well as for the pure product. The GLC conditions utilized are identical to those used by Coury.²⁹

e. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

f. NaH was utilized as the base in this reaction.

g. GLC and NMR analyses indicated less than 5% conversion of substrate to product.

The following reaction procedure is typical of the experimental conditions in the phase transfer catalyzed fluoroalkoxylation which were assisted by PEG-8000.
4-(2,2,2-Trifluoroethoxy)nitrobenzene

A 250 mL, round-bottomed, three-necked flask was equipped with a condenser, a thermometer, and a magnetic stirrer. Into the flask were placed 0.88 grams (0.022 mole) of powdered sodium hydroxide, 2.54 grams (0.0254 mole) of 2,2,2-trifluoroethanol and 100 mL of toluene. The mixture was stirred and 5.08 grams (0.000635 mole) of poly(ethylene glycol)-8000 was added, followed by the addition of 2.00 grams of 4-chloronitrobenzene. The resulting mixture was allowed to reflux for 24 hours and was subsequently cooled to room temperature. The crude mixture was extracted with cold water (2 times 500 mL) and with brine (1 times 100 mL) and then dried over anhydrous magnesium sulfate. The organic phase was concentrated in vacuo and the resulting solid was weighed to obtain a crude yield.
### B. Maximization Study

Table 5

Reactions of Na-OCH$_2$CF$_3$ with 4-chloronitrobenzene at reflux catalyzed by PEG-8000 with toluene as solvent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base$^a$ conc. (equiv)</th>
<th>$R_f$-OH$^b$ conc. (equiv)</th>
<th>PEG-8000$^c$ conc. (mole %)</th>
<th>Rxn. Time (Hrs)</th>
<th>Conver. by GLC ( % )</th>
<th>Crude Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.5</td>
<td>60</td>
<td>22</td>
<td>78.0</td>
<td>40.7</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>1.5</td>
<td>40</td>
<td>22</td>
<td>75.7</td>
<td>51.7</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>1.5</td>
<td>20</td>
<td>22</td>
<td>51.9</td>
<td>60.4</td>
</tr>
<tr>
<td>4</td>
<td>1.7</td>
<td>2.0</td>
<td>40</td>
<td>50</td>
<td>44.2</td>
<td>83.3$^f$</td>
</tr>
<tr>
<td>5</td>
<td>1.7</td>
<td>2.0</td>
<td>30</td>
<td>50</td>
<td>97.1</td>
<td>43.8</td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
<td>2.0</td>
<td>20</td>
<td>56</td>
<td>91.7</td>
<td>62.0</td>
</tr>
<tr>
<td>7</td>
<td>1.7</td>
<td>2.0</td>
<td>10</td>
<td>56</td>
<td>96.9</td>
<td>59.3</td>
</tr>
<tr>
<td>8</td>
<td>1.7</td>
<td>2.0</td>
<td>5</td>
<td>52</td>
<td>72.5</td>
<td>76.5$^g$</td>
</tr>
<tr>
<td>9</td>
<td>1.7</td>
<td>2.0</td>
<td>5</td>
<td>32</td>
<td>97.3</td>
<td>78.3$^h$</td>
</tr>
<tr>
<td>10</td>
<td>1.7</td>
<td>2.0</td>
<td>5</td>
<td>32</td>
<td>100.0</td>
<td>61.0$^i$</td>
</tr>
<tr>
<td>11</td>
<td>1.7</td>
<td>2.0</td>
<td>5</td>
<td>24</td>
<td>100.0</td>
<td>71.3$^j$</td>
</tr>
</tbody>
</table>

a. Unless otherwise indicated, solid NaOH powder was charged into the reactor and the equivalents indicated are relative to the amount of substrate charged.
b. All entries incorporate amounts of HO-CH₂CF₃ relative to the amount of substrate charged.

c. The mole percent value is relative to the amount of substrate charged.

d. The conversions for all entries were determined by GLC. Samples were taken directly from the reaction vessel and injected into the instrument by means of a micro syringe. Conversions are based on known response factors for the pure starting material as well as for the pure product. The GLC conditions utilized are identical to those used by Coury.²⁹

e. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

f. This reaction vessel was charged with 1.1 equivalents of NaOH as a 50% aqueous solution by weight.

g. This reaction was allowed to run at a mean temperature of 70°C.

h. A time study was performed on this reaction. Samples were taken in 15 minute intervals relative to the time that the substrate was charged into the reaction vessel.

i. This reaction utilized NaH as a base.
j. Water was azeotropically removed from this reaction mixture by adapting a Dean-Stark trap onto the reaction vessel.

The following reaction procedure is typical of the experimental conditions in the phase transfer catalyzed fluoroalkoxylation studies of the maximization studies.

4-(2,2,2-Trifluoroethoxy)nitrobenzene

A 250 mL, round-bottomed, three-necked flask was equipped with a condenser, a thermometer, a Dean-Stark trap, a magnetic stirrer, and was placed under a nitrogen atmosphere. Into the flask were placed 0.88 grams (0.022 mole) of powdered sodium hydroxide, 2.54 grams (0.0254 mole) of 2,2,2-trifluoroethanol and 100 mL of toluene. The mixture was stirred and 5.08 grams (0.000635 mole) of poly(ethylene glycol)-8000 was added, followed by the addition of 2.00 grams of 4-chloronitrobenzene. The resulting mixture was allowed to reflux for 24 hours and was subsequently cooled to room temperature. The crude mixture was extracted with warm water (2 times 500 mL) and with brine (1 times 100 mL) and then dried over anhydrous magnesium sulfate. The organic phase was concentrated in vacuo to give 2.0 grams of a semisolid which was distilled under vacuum (Kugelrohr, 70-73°C at 0.3 mm Hg) to yield 1.14 grams (41%) of a pale-yellow solid which had physical properties (IR, NMR, and GLC retention times) identical to the known compound.
C. Leaving Group Study

![Chemical Reaction](image)

Table 6.

The effect of the leaving group on the reactivity of various ortho-substituted nitrobenzenes with Na-OCH$_2$CF$_3$ in toluene.$^{a,b}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Base$^c$ conc. (equiv)</th>
<th>$R_f$-OH$^d$ conc. (equiv)</th>
<th>Rxn.$^e$ Time (min)</th>
<th>Conversion$^f$ by GLC ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO$_2$</td>
<td>1.2</td>
<td>2.0</td>
<td>15</td>
<td>80.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>120</td>
<td>100.0</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>1.2</td>
<td>2.0</td>
<td>15</td>
<td>71.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>120</td>
<td>100.0</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>1.2</td>
<td>2.0</td>
<td>15</td>
<td>63.8</td>
</tr>
<tr>
<td></td>
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<td>&quot;</td>
<td>120</td>
<td>99.5</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
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<td>2.0</td>
<td>15</td>
<td>20.6</td>
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<td>&quot;</td>
<td>&quot;</td>
<td>120</td>
<td>68.1</td>
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<tr>
<td>5</td>
<td>I</td>
<td>1.2</td>
<td>2.0</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>120</td>
<td>11.3</td>
</tr>
</tbody>
</table>
a. All entries were catalyzed by 5 mole % PEG-8000 and water was azeotropically removed from the reaction mixture by means of a Dean-Stark trap. All entries were stirred at a rate of 850 rpm as determined by a commercially available strobe light.

b. The reaction conditions implemented in this study are identical to those reported by Coury.29

c. Unless otherwise indicated, solid NaOH powder was charged into the reactor and the equivalents indicated are relative to the amount of substrate charged.

d. All entries incorporate amounts of HO-\(\text{CH}_2\text{CF}_3\) relative to the amount of substrate charged.

e. The reaction time was determined by means of an automatic, 17-jeweled, Benrus chronometer.

f. The conversions for all entries were determined by GLC. Samples were taken directly from the reaction vessel and injected into the instrument by means of a micro syringe. Conversions are based on known response factors for the pure starting material as well as for the pure product. The GLC conditions utilized are identical to those used by Coury.29
Table 7

The position of the chlorine atom on the ring and its effect on the reactivity of chloronitrobenzene isomers with Na-OCH₂CF₃ in toluene.ᵃᵇ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Baseconc. (equiv)</th>
<th>Rₓ-OHconc. (equiv)</th>
<th>Rxn. Time (min)</th>
<th>Conversion by GLC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Cl</td>
<td>1.2</td>
<td>2.0</td>
<td>15</td>
<td>63.8</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>120</td>
<td>99.5</td>
</tr>
<tr>
<td>2</td>
<td>3-Cl</td>
<td>1.2</td>
<td>2.0</td>
<td>15</td>
<td>0.0</td>
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<td></td>
<td>&quot;</td>
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<td>&quot;</td>
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<td>3</td>
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<td>&quot;</td>
<td>120</td>
<td>50.2</td>
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<tr>
<td>4</td>
<td>4-Cl</td>
<td>1.2</td>
<td>2.0</td>
<td>15</td>
<td>3.0ᵍ</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>120</td>
<td>52.5</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>2400</td>
<td>99.0</td>
</tr>
</tbody>
</table>

ᵃ. All entries were catalyzed by 5 mole % PEG-8000 and water was azeotropically removed from the reaction mixture by means of a Dean-Stark trap. All entries were stirred at a rate of 850 rpm as determined by a commercially available strobe light.
b. The reaction conditions implemented in this study are identical to those reported by Coury. 29

c. Unless otherwise indicated, solid NaOH powder was charged into the reactor and the equivalents indicated are relative to the amount of substrate charged.

d. All entries incorporate amounts of HO-CH₂CF₃ relative to the amount of substrate charged.

e. The reaction time was determined by means of an automatic, 17-jeweled, Benrus chronometer.

f. The conversions for all entries were determined by GLC. Samples were taken directly from the reaction vessel and injected into the instrument by means of a micro syringe. Conversions are based on known response factors for the pure starting material as well as for the pure product. The GLC conditions utilized are identical to those used by Coury. 29

g. This reaction was conducted without the azeotropic removal of water.

The following reaction procedure is typical of the experimental conditions in the phase transfer catalyzed fluoroalkoxylations of the leaving group and isomer reactivity studies.
4-(2,2,2-Trifluoroethoxy)nitrobenzene

A 250 mL, round-bottomed, three-necked flask was equipped with a condenser, a thermometer, a Dean-Stark trap, magnetic stirrer, and was placed under a nitrogen atmosphere. Into the flask were placed 1.22 grams (0.030 mole) of powdered sodium hydroxide, 5.00 grams (0.0250 mole) of 2,2,2-trifluoroethanol and 75 mL of toluene. The mixture was stirred and 10.00 grams (0.00125 mole) of poly(ethylene glycol)-8000 was added, followed by the addition of 3.53 grams (0.0250 mole) of 2-fluoro-nitrobenzene. While the heating mantle was warming the above mixture to reflux, 1.0 mL aliquots were removed by means of a graduated syringe at 15 minute intervals. These samples were diluted with acetone to 3.0 mL and of this solution, a 1.0 µL volume was injected into a Shimadzu Gas Chromatograph which contained a 3% SP 2401 solid support column at 180°C. The percent conversion was determined. The resulting data were then plotted with the aid of an Apple computer, which was interfaced with a Hewlett-Packard 7479A plotter. Data were only collected for a 2 hour period, which started immediately after the substrate was charged into the reaction vessel. The results obtained during the leaving group study are presented in Figure V as a plot of percent conversion vs. time.
The lines A through G represent the best fitted curves for substituted nitrobenzenes where: A = ortho-nitro, B = ortho-fluoro, C = ortho-chloro, D = ortho-bromo, E = ortho-iodo, F = para-chloro, and G = meta-chloro.

Figure V. A plot of the leaving group reactivities for various substituted nitrobenzenes as determined by percent conversion in time.
D. Activating Group Study

\[
\begin{array}{c}
\text{X} + \text{NaOH}_\text{s} \xrightarrow{\text{PEG-8000, C}_6\text{H}_5\text{CH}_3, 111^\circ\text{C}} \text{HOCH}_2\text{C}_2 \xrightarrow{\text{H}_2\text{O} + \text{Na}} \text{X} + \text{OCH}_2\text{CF}_3
\end{array}
\]

Table 8

The PEG-8000 catalyzed fluoroalkoxylation of various non-heterocyclic activated substrates in toluene.\(^a\,b\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Base(^c) conc. (equiv)</th>
<th>(R_f)-OH(^d) conc. (equiv)</th>
<th>Rxn.(^e) Time (Hrs)</th>
<th>Crude(^f) Yield (%)</th>
<th>Purified(^g) Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CN</td>
<td>2-CL</td>
<td>6.8</td>
<td>8.0</td>
<td>48</td>
<td>76.4</td>
<td>59.5</td>
</tr>
<tr>
<td>2</td>
<td>CN</td>
<td>4-Cl</td>
<td>6.8</td>
<td>8.0</td>
<td>48</td>
<td>55.0</td>
<td>34.8</td>
</tr>
<tr>
<td>3</td>
<td>NO(_2)</td>
<td>2-Cl</td>
<td>1.2</td>
<td>2.0</td>
<td>2</td>
<td>62.0</td>
<td>h</td>
</tr>
<tr>
<td>4</td>
<td>NO(_2)</td>
<td>4-Cl</td>
<td>1.7</td>
<td>2.0</td>
<td>24</td>
<td>71.3</td>
<td>41.0</td>
</tr>
<tr>
<td>5</td>
<td>NO(_2)</td>
<td>2-NO(_2)</td>
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<td>2.0</td>
<td>2</td>
<td>85.7</td>
<td>81.5</td>
</tr>
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<td>3-NO(_2)</td>
<td>5.1</td>
<td>6.0</td>
<td>48</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4ClPhSO(_2)</td>
<td>4-Cl</td>
<td>1.7</td>
<td>2.0</td>
<td>24</td>
<td>84.5</td>
<td>50.5(^i)</td>
</tr>
</tbody>
</table>

\(^a\) All entries were catalyzed by 5 mole % PEG-8000 and water was azeotropically removed from the reaction mixture by means of a Dean–Stark trap.
b. The spectral properties and the physical constants of these products matched those of known samples (see Gupton et al. 13-18)

c. Unless otherwise indicated, solid NaOH powder was charged into the reactor and the equivalents indicated are relative to the amount of substrate charged.

d. All entries incorporate amounts of Ho-CH₂CF₃ relative to the amount of substrate charged.

e. The reaction time was determined by means of an automatic, 17-jeweled, Benrus chronometer.

f. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

g. Unless otherwise stated, the purified yields refer to the yield obtained after Kugelrohr distillation.

h. This entry is the crude product obtained from the leaving group study.

i. This reaction product was purified by recrystallization in isopropyl alcohol.
E. Regioselectivity Study

**TABLE 9.**

The polysubstitution and regioselective monosubstitution of activated dihaloarenes in toluene.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(^b)</th>
<th>Yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>88.3 (49.3)(^d)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>61.2 (30.0)(^e)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>53.2 (29.7)(^d)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>95.6 (57.7)(^f)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>89.9 (80.9)(^g)</td>
</tr>
</tbody>
</table>
a. Water was azeotropically removed from the reaction mixture by means of a Dean-Stark trap.

b. The spectral properties and the physical constants of these products matched those of known samples (see Gupton et al. 13-18).

c. Percent yields refer to the crude product yields followed by their purified yields in parentheses. Calculations are based on the theoretical conversion of starting material to product.

d. Standard reaction conditions resulted in a mixture of starting material and monosubstituted product after 24 hours. It was necessary to increase the base equivalents to 3.4 equiv. NaOH$_{\text{(s)}}$ and also increase the HO-CH$_2$CF$_3$ equivalents to 4.0. Prolonging the reaction time at reflux for 96 hours but maintaining the PTC concentration at 5 mole % resulted in 100% conversion as determined by GLC.

e. Standard reaction conditions resulted in a mixture of starting material and the monosubstituted product after 24 hours. It was necessary to increase the base equivalents to 3.4 equiv. NaOH$_{\text{(s)}}$ and also increase the HO-CH$_2$CF$_3$ equivalents to 4.0. Maintaining the reaction at reflux for 24 hours and keeping the PTC concentration at 5 mole % resulted in 98% conversion as determined by GLC.
f. In order to insure that the reaction proceeded with mono-substitution, it was necessary to decrease the base equivalents to 1.1 equiv. NaOH(s), but maintain the HO-CH₂CF₃ and PTC levels at standard conditions. After a reaction time of 48 hours, the reaction had gone to 100% conversion as determined by GLC.

g. Standard reaction conditions resulted in a mixture of starting material and the monosubstituted product after 24 hours. It was necessary to increase the base equivalents to 3.4 equiv. NaOH(s) and also increase the HO-CH₂CF₃ equivalents to 4.0. Maintaining the reaction at reflux for 48 hours and keeping the PTC concentration at 5 mole % resulted in 100% conversion as determined by GLC.
F. Fluoroalkoxylation of Heterocyclic Systems

Table 10

The regioselective monosubstitution and disubstitution of halo-heterocyclic compounds in toluene.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product\textsuperscript{b}</th>
<th>Yield (%)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>100.0\textsuperscript{d}(73.9)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>89.3\textsuperscript{d}(64.9)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>95.3\textsuperscript{e}(89.1)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>66.0\textsuperscript{f}(51.4)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Substrate 5" /></td>
<td><img src="image10.png" alt="Product 5" /></td>
<td>77.8\textsuperscript{g}</td>
</tr>
</tbody>
</table>
a. Water was azeotropically removed from the reaction mixture by means of a Dean-Stark trap.

b. The spectral properties and the physical constants of these products matched those of known samples (see Gupton et al. 13-18)

c. Percent yields refer to the crude product yields followed by their purified yields in parenthesis. Calculations are based on the theoretical conversion of starting material to product.

d. Substitution occurred at standard conditions: 1.7 equiv. NaOH solid and 2.0 equiv. HO-CH₂CF₃ at reflux in toluene for 24 hours. Determination of extent of reaction was done by GLC.

e. Standard reaction conditions resulted in a mixture of mono- and di-substituted products after 24 hours. It was necessary to reduce the base equivalents to 1.1 equiv. NaOH(s) and prolong the reaction time at a temperature of 60°C for 168 hours to effect no better than 97.2% conversion as determined by GLC.

f. Standard reaction conditions resulted in a mixture of mono- and di-substituted products after 24 hours. It was necessary to increase the base equivalents to 5.1 equiv. NaOH(s) and also increase the HO-CH₂CF₃ equivalents to 6.0. Prolonging the
reaction time at reflux for 72 hours but maintaining the PTC concentration at 5 mole % resulted in 100% conversion as determined by GLC.

g. Within 24 hours, standard reaction conditions resulted in 100% conversion as determined by GLC. However, the product was inseparable from toluene and was distilled upon rotoevaporation during the workup procedure.
G. Nucleophile Study

\[
\text{NO}_2^– \text{NO}_2^– \xrightarrow{\text{NaOH}_s / \text{HO} \text{CH}_2(\text{CF}_2)_x \text{CF}_3} \xrightarrow{\text{PEG-8000, C}_6\text{H}_5\text{CH}_3} \text{111°C} \quad \text{OCH}_2(\text{CF}_2)_x \text{CF}_3
\]

Table 11

The effect of nucleophiles on the PEG-8000 catalyzed fluoroalkoxylation of 1,2-Dinitrobenzene.\(^a, b\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Yield (%)(^c,d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-O-CH(_2)CF(_3)</td>
<td>85.7 (81.5)</td>
</tr>
<tr>
<td>2</td>
<td>-O-CH(_2)CF(_2)CF(_3)</td>
<td>98.8 (78.0)(^e)</td>
</tr>
<tr>
<td>3</td>
<td>-O-CH(_2)CF(_2)CF(_2)CF(_3)</td>
<td>87.4 (78.4)(^f)</td>
</tr>
</tbody>
</table>

\(^a\) Water was azeotropically removed from the reaction mixture by means of a Dean-Stark trap.

\(^b\) The spectral properties and the physical constants of these products matched those of known samples (see Gupton et al.\(^13-18\)).

\(^c\) Percent yields refer to the crude product yields followed by their purified yields in parentheses.
Calculations are based on the theoretical conversion of starting material to product.

d. Substitution occurred at standard conditions: 1.7 equiv. NaOH solid and 2.0 equiv. HO-CH₂CF₃ at reflux in toluene for two hours. Determination of extent of reaction was done by GLC.

e. 2-(3,3,3,2,2-Pentafluoropropoxy)nitrobenzene: b.p. 71.5 °C (0.1 mm Hg); NMR(CDCl₃) δ 4.62 (t, J=14 Hz, 2H), 7.25 (m, 2H), 7.65 (d of t, J=8 Hz, J=2 Hz, 1H), 7.95 (d of d, J=8 Hz, J=2 Hz, 1H); IR(neat) 3080, 2940, 2880, 1608, 1530, 1355, 1200, 1060, 872, 745 cm⁻¹; mass spectrum m/e 271 (M⁺).

f. For spectral properties and physical constants, see research report by Coury. 29
PART I

DISCUSSION OF RESULTS

In light of the fact that phase transfer catalysis is a relatively new field in the realm of organic chemistry, this investigator feels that prior to discussing the experimental results, a brief introduction should be presented on the properties and mode of action of phase transfer catalysts.

Much like their inorganic counterparts, phase transfer catalysts may be defined as agents which lower the activation energy of a reaction pathway and their structures are not incorporated into the final product. Unlike their inorganic counterparts, however, phase transfer catalysts are organic molecules which exhibit the unusual property of being soluble in both polar and non-polar solvents. There are a large number of molecules which may function as phase transfer catalysts but quaternary ammonium salts and crown ethers are among the most frequently used catalysts in organic syntheses. The crowns are particularly interesting substances because of their unusual structure. They are defined as macrocyclic
ethers and may be described as a large polyether molecule whose oxygen atoms are directed toward the center of a donut; where the substance of the donut is the hydrocarbon backbone (-CH₂CH₂-) of the macrocyclic polyether.

A literature search reveals that there are many different synthetic reactions which incorporate the use of crown ethers to drive a reaction between two immiscible phases. Due to Pedersen’s systematic study in 1967, it is now known that crown ethers form complexes with metal salts and solubilize them into non-polar solvents. The nature of the interaction between the salt’s metal atom and the crown ether appears to be an ion-dipole interaction; expressly between the cation and the negatively charged oxygen atoms of the polydentate ring. The stability of this "metal-crown" complex is dependent upon several factors.

1. The relative size of the cation and the pore diameter of the polydentate ring.
2. The number of oxygen atoms comprising the polydentate ring.
3. The ionic charge density on the cation.
4. The symmetry of substituent groups about the polydentate ring.
5. The tendency of the cation to associate with the organic phase or with the aqueous phase.
6. The tendency of the leaving group (electrophile) and/or the tendency of the nucleophile to solubilize in the organic (non-polar) solvent.

The mechanism by which crown ethers catalyze the reactions in this investigation is a second order, aromatic, nucleophilic substitution in which the first step is the rate determining step. However, unlike other substitution reactions, cation complexation must be incorporated into the mechanistic scheme (Figure VI).

\[
\text{CROWN-M}^+\text{Nuc}^- + \text{R-X} \rightarrow \text{R-Nuc} + \text{CROWN M}^+\text{X}^- \\
\text{organic phase} \\
\text{CROWN M}^+\text{Nuc}^- \ldots \ldots \text{interphase} \ldots \ldots \ldots \ldots \text{CROWN M}^+\text{X}^- \ldots \ldots \\
\text{solid phase} \\
\text{CROWN} + \text{M-Nuc}^- \rightleftharpoons \text{M}^+\text{X}^- + \text{CROWN}
\]

Figure VI. A mechanistic scheme of PTC systems utilizing crowns as catalysts.

The above scheme is a modified version of those found in Starks and in Weber and \(M^+\) represents a metal cation which may be a member of the elements in groups IA, IB, IIB (and a few may be from groups IIIA, IIIB, IVB) of the periodic table.\(^{33,36,37}\) As can be seen, the effectiveness of a
crown ether in catalyzing a reaction between two immiscible reactants is primarily dependent upon the ability of the crown to incorporate the metal cation into its pore. In the presence of water, however, the effective diameter of the cation is increased by hydration and thus the catalytic activity of most crown ethers is drastically reduced. \(^{34,38}\) Consequently, most phase transfer catalyzed systems which incorporate crowns are performed under solid-liquid conditions. These reaction conditions utilize toluene or benzene as non-polar solvents to dissolve the substrates.

During the course of our investigation, seven studies were performed in order to determine the effectiveness of polyethers in catalyzing the fluoroalkoxylation of activated haloaryl and haloheteroaryl systems:

1. Feasibility Study
2. Maximization Study
3. Leaving Group Study
4. Activating Group Study
5. Regioselectivity Study
6. Heterocyclic Systems Study
7. Nucleophile Study

In each of these studies, nucleophilic substitution occurred at the halogenated position on the aromatic ring system and the results closely paralleled those by Gupton et al. \(^{13-20}\) and Coury. \(^{29}\)
In the feasibility study on phase transfer catalyzed fluoroalkoxylation, 4-chloronitrobenzene served as our standard substrate and several factors were considered with respect to the extent of conversion: the influence of solvents, reaction temperature, base concentration, catalyst concentration and pore size. Tables 1, 2, 3, and 4 summarize the results of the feasibility study. The literature indicates that there are four crown ethers that are widely used in phase transfer catalyzed systems: 15-crown-5, 18-crown-6, dibenzo-18-crown-6, and dicyclohexano-18-crown-6 (see Figure VII).

Figure VII. Four commonly used crown ethers in PTC.
These molecules complex strongly with metal cations having ionic diameters which approximately equal the size of their pores. Most often, either a sodium salt or a potassium salt is used during PTC work. The sodium cation and the potassium cation have an ionic diameter of 1.94Å and 2.66Å respectively. The 18-membered crowns, having a pore diameter of 2.6 to 3.2Å are, therefore, best suited as phase transfer catalytic agents in reactions involving sodium or potassium salts. In addition, it has been suggested by various investigators that the catalytic activity of a PTC varies between solvent systems, but that 18-crown-6 seemed to be more efficacious in nucleophilic substitution reactions. In this investigation, a nested experimental design was used to study three variables simultaneously: the effects of base, solvent, and reaction temperature on substrate substitution. It was observed that at room temperature, no detectable conversion had occurred in either benzene (Table 1) or the toluene (Table 2) reaction vessels. However, the conversions increased upon reflux, but distinctly different results are observed in the two systems. The results indicate that a 63.8 percent greater conversion is obtained in the reaction vessel which utilized benzene (Table 1, entry 4) over the reaction vessel which utilized toluene (Table 2, entry 4). Furthermore, similar conversions were observed when NaOH
was used instead of NaH (Table 2, entries 4 and 7). The conclusions that may be inferred are two fold: (1) the activity of 18-C-6 is greater in benzene than in toluene, and (2) the selectivity of the catalyst is unaffected when solid sodium hydroxide is used as opposed to sodium hydride. One may explain the activity of 18-C-6 in terms of selective solubilities of the crown and its complexes. If the CROWN-Na\(^+\)X\(^-\) complex were more soluble in toluene than in benzene, the ability of the crown to exchange the electrophile with the nucleophile would necessarily decrease. This decrease in the rate of "ion exchange" would be observed as a decrease in conversion. The selectivity of the crown for the sodium ion remains unaffected throughout the study. However, since a 60 percent dispersion of NaH in oil requires a careful and thorough washing in hexane under nitrogen, the number of operations for the reaction procedure is reduced when NaOH is used.

Included in Table 2 (entries 5, 7, and 8) is a study concerning the effect of catalyst concentration on the extent of conversion. As may be observed, a 48.9 percent increase in conversion occurs when the reaction mixture in toluene is charged with 25 mole percent of the catalyst as opposed to 10 mole percent catalyst. However, when the catalyst concentration was increased to 40 mole percent, no
significant change occurred in terms of conversion with respect to the results obtained in Table 2, entry 7. On the basis of these results, it was decided that an 18-C-6 concentration of 40 mole percent would insure a maximum conversion in the fluoroalkoxylation of the substrate: 4-chloronitrobenzene. However, it was felt necessary to investigate other solvent systems which might be incorporated as alternatives to either toluene or benzene. Table 3 of this experimental section (i.e., Feasibility Study) pertains to reflux conditions where 1,4-dioxane (entries 1-3) and diglyme (entry 4) were compared to the results obtained in benzene (entry 5) and to those in toluene (entries 6 and 7). A nested experimental design investigated two variables: the effect of catalyst concentration in 1,4-dioxane and in toluene. The results indicated no significant difference in terms of conversion and it may be inferred that the activity of 18-C-6 in dioxane was the same as its activity in toluene. On the other hand, diglyme gave intermediate results. Several references have been made with respect to the use of glymes as catalytic agents.24,40,43 It was thought to be appropriate to run a reaction in diglyme, but in the absence of 18-C-6. The results were surprising. The conversion obtained for this experiment (Table 3, entry 4) was 22.0 percent lower with respect to that in benzene and
48.4 percent higher with respect to that in toluene. It seemed most unusual that a linear, short-chain polyether was able to catalyze the fluoroalkoxylation of the substrate. However, when the number of ether linkages (-CH₂OCH₂⁻) are considered, it becomes evident that the diglyme molecule has the essential groups to comprise half of the functional groups that are found in 18-C-6. It may then be imagined that two diglyme molecules are required to sequester the sodium cation of the Na⁺OCH₂CF₃ and Na⁺Cl⁻ complexes during the progress of the reaction (Figure VIII).

Figure VIII. The orientation of diglyme about the sodium cation.

The results obtained in the diglyme experiment initiated a study into the fluoroalkoxylation of 4-chloronitrobenzene as mediated by linear polyethers in toluene and the results were compared to similar experiments, which were mediated by the macrocyclic polyethers (Table 4). Toluene was chosen as the solvent due to its reduced toxicity (as
compared to that of benzene) and, more importantly, due to its ability to form an azeotrope with water. This is an important property that lends itself quite nicely to industrial applications. A group of crowns were run as standards for comparison purposes (Table 4, entries 1-3). It may be observed that a statistically insignificant difference in conversion occurs when 15-C-5 is used as opposed to 18-C-6 and that a a 9.2 percent decrease in conversion is observed when DB-18-C-6 is used instead of 18-C-6. A decrease in pore size (Table 4, entry 1) with respect to that of 18-C-6 has very little effect on the catalytic activity of the 15-membered crown. This result may be due to the use of anhydrous, powdered sodium hydroxide which would insure the absence of hydrated sodium cations. The slight decrease in catalytic activity observed in the DB-18-C-6 mediated reaction may be explained by the fact that this PTC is much more soluble in the solvent and is less capable of extracting and sequestering the metal cation. 31,35

Gupton et al. used HMPA successfully as a solvent in the fluoroalkoxylation of 4-chloronitrobenzene. 13 In this investigation, the effect of catalytic amounts of HMPA on the extent of conversion was poor (Table 4, entry 6). That is to say, HMPA did not catalyze the fluoroalkoxylation of the substrate to any significant extent when it was present
in catalytic amounts (in toluene). 1,4-Dioxane gave similar results when it was present in catalytic amounts (Table 4, entry 5). However, when diglyme was used in catalytic amounts (Table 4, entry 4), only a 24.7 percent decrease in conversion was observed relative to that obtained in Table 3, entry 3. On the other hand, there was no significant difference in conversions between the use of diglyme and the use of 18-C-6 in catalytic amounts; although, 18-C-6 was more effective on a crude yield basis. In all, it was felt that linear polyethers ought to be considered as potential phase transfer catalytic agents for nucleophilic aromatic substitution reactions. Since the introduction of PEG’s by Lehmkuhl et al. in 1977, polyethylene glycols have received much attention due to their effectiveness as catalytic agents in a variety of organic reactions. Unlike the quaternary salts, PEG’s are very stable to attack by base and are especially important in base catalyzed reactions. Several investigators have studied the use of PEG-400 as a catalytic agent in various synthetic methods. In this research, an investigation was launched on the effect of average polymer chain-length with respect to the fluoroalkoxylation of the 4-chloronitrobenzene molecule. The results are listed in Table 4 (entries 7-13) and are schematically represented below (Figure IX).
Figure IX. The effect of PEG chain length on the extent of conversion in the fluoroalkoxylation of 4-chloro-nitrobenzene.
It is important to note that in each reaction, 40 mole percent of a particular molecular weight PEG was charged into the reaction vessel. The series of PEG's in this study encompass a wide range of molecular weights, $M_w$, from 300 to 14000. As may be observed, there is a gradual rise in conversion (from 12.7 to 75.7 percent) as the average molecular weight increases. One would normally expect an asymptotic relationship between the extent of conversion and the number of oxyethylene groups ($\text{OCH}_2\text{CH}_2$). However, this study indicates that a peak conversion occurs upon the use of PEG-8000 to catalyze the reaction and that a parabolic relationship is more likely to occur. It has been postulated that this decrease in conversion is due to three possible factors.41

(1) As the molecular weight of the PEG increases, the number of oxyethylene groups also increases; which, in turn, increases the number of binding sites available for the formation of the PEG-$\text{Na}^+\text{Nuc}^-$ complex. In addition to an increased capacity for "complex" formation is the increased ability for the polymer to twist and bend to form a third phase in the reaction mixture (i.e., the PEG phase) in which the complex may be soluble. Thus, when the PEG backbone exceeds the length of PEG-8000 (i.e., 170 oxyethylene units), the activity of the polymer decreases.
(2) As the molecular weight of the polymer increases, the catalyst is more effective in separating the salt \((\text{NaOCH}_2\text{CF}_3)\) into the cation and its counter ion. This would increase the nucleophilicity of the fluoroalkoxy group. However, when the average molecular weight of the PEG increases above 8000, the large molecule may be lipophilic enough to retain the nucleophile in a PEG matrix. Hence, a large molecular weight would decrease the extent of conversion for the reaction by not allowing the nucleophile to be readily available to the halogenated substrate.

(3) The terminal hydroxy groups on the polymer are important functional groups since they aid in the catalytic process. As the molecular weight of the PEG increases past 8000, the contribution of the alpha-hydroxy termini in complexing with the salt decreases proportionally.

In addition to the "solid-liquid" conditions mentioned above, "liquid-liquid" phase transfer catalyzed reactions in a 50 percent aqueous NaOH solution were also conducted (Table 2, entry 6; Table 5, entry 4). The results of these studies were surprising. The reaction which was mediated by 18-C-6 resulted in no detectable conversion; a 100 percent decrease in conversion with respect to a similar "solid-liquid" reaction (Table 2, entry 8). On the other hand, a PEG-8000 catalyzed reaction under "liquid-liquid" conditions resulted in a 41.6 percent decrease in
conversion with respect to that in the "solid-liquid" conditions (Table 5, entry 2). Although not reported, DB-18-C-6 was also subjected to "liquid-liquid" conditions and resulted in a 3.5 percent conversion. These results are surprising in the sense that the conversions for the crowns were so low; the literature, however, seems to indicate the opposite results for the 18-membered crowns. With respect to the PEG-8000 mediated reaction, the decrease in the extent of conversion was expected. Since the polyether has a large number of functional groups available for sequestering the sodium cation, and since it is able to conform to the size of a hydrated cation, the PEG-8000 mediated reaction was expected to have a conversion in the order of 30 to 50 percent. It may be postulated that a "water in oil" type of emulsion had occurred which resulted in a decreased reaction rate (i.e., micellar reaction kinetics). Under these conditions, the fluorinated alcohol may be sequestered in small water vessicles and the sodium cation would be sequestered in the PEG matrix. Hence, the likelihood of forming the PEG-8000-Na\(^{+}\)-OCH\(_2\)CF\(_3\) complex would be diminished considerably.

Since the catalyst (PEG-8000) was determined to be more effective under "solid-liquid" reaction conditions, a maximization study was conducted under anhydrous conditions which incorporated solid, anhydrous sodium hydroxide powder
in dry toluene. The maximization study in this investigation was conducted in order to determine the optimum reaction conditions for the PEG-8000 mediated systems. The ratio of base to fluorinated alcohol and the catalyst concentration were altered. The goal of this phase of the research was to optimize both the yield and the extent of conversion. Entries 1-3 of Table 5 indicate that as the PEG concentration decreased from 60 to 20 mole percent, there was a corresponding decrease in conversion. When the concentration of NaOH and R_f-OH were increased by 0.5 equivalents with respect to the moles of substrate (Table 5, entries 4-11), a 43.4 percent increase is observed in the extent of conversion with a concurrent 2 fold increase in reaction time (entry 6 compared with entry 3). However, the use of 5 mole percent PEG-8000 resulted in the highest extent of conversion and the greatest amount of crude product (Table 5, entry 9) when excess NaOH and R_f-OH are charged into the reaction vessel. When NaH (entry 10) was substituted for NaOH (entry 9), the reaction was driven to 100 percent conversion. This indicated that the presence of water, which formed during the reaction between NaOH and the alcohol, allowed for the formation of a "liquid-liquid" reaction condition and slightly decreased the extent of conversion. However, the use of NaH severely limits the utility of this reaction if it were to be
considered for industrial application. Having chosen toluene as the solvent system in these studies enabled the azeotropic removal of water from the reaction mixture. Either Soxhlet extractors or Dean–Stark traps may be used towards this goal. A Dean–Stark trap was implemented on a sodium hydroxide/PEG-8000 catalyzed reaction (Table 5, entry 11) and, as expected, the extent of conversion increased to 100 percent and the crude yield closely matched that of an earlier study (entry 9). The effect of temperature on the extent of conversion in the NaOH/5 mole percent PEG systems was also studied (Table 5, entry 8). The result indicated that respectable yields and conversions could be achieved only after prolonged reaction times.

Another facet in the maximization of reaction conditions was the development of a separation scheme. It is well known that PEG's are high boiling solids that exhibit a characteristic "cloud point" when dissolved in a solvent at a particular temperature. PEG's are frequently used as surfactants and emulsifiers for a variety of commercial applications. Herein lay the difficulty in the separation of the catalyst from the product. In earlier studies of this research, the NMR spectra of the crude products indicated the presence of a broad singlet in the 3.5 to 3.9 δ region; attributed to the -CH₂-O-
functional group in the molecule. After several separation schemes had been tried (freezing point depression, solid-liquid chromatography, salting out, aqueous extraction, and distillation), it was determined that aqueous extraction (using warm water, 30-35°C) followed by distillation (under reduced pressure) was most efficacious.

In the leaving-group study on the PEG-8000 mediated fluoroalkoxylation of various nitrobenzenes, the leaving tendency of substituent groups was correlated in terms of the conversion extent/time. Figures X and XI schematically represent the results obtained during a time study in which the stirring rate was identical for each of the reaction vessels and where the same heating mantle was used. Figure X indicates that ortho activation by the nitro group permits the reaction to proceed much faster than for the para-substituted substrate.
The lines in the plot represent the best fitted curves for the leaving group reactivities of the ortho-, para-, and meta-chloronitrobenzenes.

Figure X. The PEG-8000 mediated fluoroalkoxylation of the Chloronitrobenzene isomers.
The meta-substituted substrate is not activated at the meta position by the nitro group and, thus, the fluoroalkoxylation does not proceed at all. The following order of leaving-group reactivities summarizes the results obtained on the chloronitrobenzene isomers:

\[ o-\text{Cl} > p-\text{Cl} >> m-\text{Cl} \]

In a typical two-step $S_N$Ar mechanism in which the first step is rate limiting, the following order in leaving-group reactivity is observed: \[ o-\text{NO}_2 > o-\text{F}, o-\text{Cl} > o-\text{Br} > o-\text{I}. \]

Figure XI illustrates the results on the leaving-group reactivity of various ortho-substituted nitrobenzenes in toluene as catalyzed under NaOH/PEG-8000 conditions.
The lines A through E represent the best fitted curves for the leaving group reactivities of various ortho-substituted nitrobenzenes where A = nitro, B = fluoro, C = chloro, D = bromo, and E = iodo.

Figure XI. The PEG-8000 mediated fluoroalkoxylation of various ortho-substituted nitrobenzenes.
When conversions are compared for the halogenated nitrobenzenes, a trend is immediately apparent. The leaving group reactivity drastically decreases as the halogen electronegativity decreases. It has been proposed that the larger the halogen anion, the greater its lipophilic character. When toluene is used as a solvent, the order of halogen anion lipophilicity is as follows: $I^- \gg Br^- > Cl^- > F^-$. Therefore, it is postulated that PTC mediated reactions are subject to "poisoning" when large diameter halogen atoms are the leaving groups on a substrate. At the initial stages of a PTC mediated reaction, the catalyst complexes with the sodium fluoroalkoxide salt and transfers the nucleophile into the non-polar medium. Subsequently, the catalyst complexes with the halogen anion and proceeds to exchange it with another nucleophile. However, as the number of such exchanges increases, the concentration of the lipophilic halogen anion also increases in the non-polar medium. This concentration of halogen anions may reach saturation in the toluene layer which subsequently leads to catalyst poisoning.

The results of the activating group study closely paralleled the results reported by Gupton et al. where HMPA and DMF were used as solvents in the reaction conditions. However, it is important to note that for the
nitrile substrates (Table 8, entries 1 and 2), the reaction conditions were required to be more rigorous than the standard reaction conditions. An increase in catalyst concentration and an increase in the NaOH/Rf-OH ratio was necessary to effect a complete conversion of the substrate to the corresponding fluoroalkoxylated product. These reactions may be somewhat different from the PEG-8000 catalyzed reactions since the same substrates did not follow this pattern in the study by Coury.29,54

Tables 9 and 10 summarize the results of the regioselective fluoroalkoxylation study on various aryl and heteroaryl substrates. As expected, polysubstitution in these investigations followed the order of leaving-group reactivities. Polysubstitution was achieved at both activated halogens on 2,6-dichloronitrobenzene (Table 9, entry 5). Only monosubstituted products were isolated for each of the following substrates: 2,3-dichloronitrobenzene, 3,4-dichloronitrobenzene, and 2,5-dichloronitrobenzene. Each of these substrates incorporate a chlorine atom meta to the nitro group; a position that has been shown to be deactivated to nucleophilic substitution reactions. As expected, monosubstitution also occurred on the 2-chloro-6-fluoronitrobenzene substrate; where, fluoroalkoxylation predominantly occurred at the fluorine substituted position on the aromatic ring. In the case of the heterocyclic
substrates, monosubstitution occurred as expected on the halogenated positions of 2-chlorolepidine and 3-chloro-2,5-dimethylpyrazine. Monosubstitution was also easily achieved on the 4-chloro-position of quinoline while the 7-chloro-position was left unsubstituted (Table 10, entry 2). However, in the case of 3,6-dichloropyrazidine monosubstitution occurred under mild conditions. All reactions in this study closely followed the results reported by Gupton et al. In general, the heterocyclic substrates exhibited faster and cleaner substitution products than did the nitrobenzene substrates.

For the most part, 2,2,2-trifluoroethanol was utilized as the nucleophile in this investigation. This fluorinated alcohol was chosen due to the fact that it simplified the NMR spectrum considerably and also because it was readily available. In addition, it was known that the nucleophilicity of the fluoroalkoxy moiety was inversely proportional to the number of fluorine atoms along the alky1 chain. In the nucleophile study, three fluorinated alcohols were compared in terms of the extent of conversion and in terms of the rate of conversion. The experimental results obtained during this study indicate that there is no difference in the selectivity between reactions when PEG-8000 is used in catalytic amounts. The substrate (1,2-dinitrobenzene) was substituted by the nucleophile to form
the corresponding aryl-fluoroalkyl ether. Each of the
three nucleophiles effected 100 percent conversion of the
substrate within a 2 hour interval. The heptafluoro-
butoxynitrobenzene product was carefully characterized by
Coury. In this investigation, the
pentafluoropropoxynitrobenzene product was characterized by
GLC, NMR, IR, and Mass Spectrometry.

The NMR spectrum of 1-(2,2,3,3,3-pentafluoropropoxy)
nitrobenzene was very similar to that of the
heptafluorobutoxynitrobenzene homolog.

![Chemical Structure]

$H_a$ could be found furthest downfield as a doublet centered
at $\delta$ 7.95. $H_c$ is found further upfield as a doublet of
triplets (ortho-ortho-meta coupled) centered at $\delta$ 7.65. Both $H_b$ and $H_d$ could be found as a multiplet centered at $\delta$
7.25. Ortho coupling constants were on the order of 6 Hz
while the meta coupling constants were in the order of 2 Hz.
Due to the adjacent fluorine atoms, the methylene hydrogens
on the propoxy group were observed as a broad triplet
centered at $\delta$ 4.62 with a coupling constant of 14 Hz.
The IR spectrum of 2-(2',2',3',3',3'-pentafluoropropoxy)nitrobenzene exhibited the characteristic bands of fluoroalkoxyalted nitrobenzenes. A strong asymmetric O-N-O stretch was observed at 1530 cm\(^{-1}\) and a strong O-N-O stretch was also visible at 1355 cm\(^{-1}\). The alkyl aryl ether symmetrical stretch was observed at 1055 cm\(^{-1}\) and its asymmetrical band was found at 1230 cm\(^{-1}\). In addition, the broadened absorption that is so characteristic of C-F molecules was observed between 1400-1500 cm\(^{-1}\).\(^{55}\)

The results indicated that each of the fluoroalkoxylation studies closely followed those of Gupton et al. and Coury.\(^{29}\) However, there were a few differences in the net results. The activating group study indicated that the cyano group was not very activating under phase transfer catalysis in toluene. The effects are clearly evident in the need for greater equivalents of reagents and catalyst over the standard reaction conditions. As opposed to HMPA or DMF reaction conditions, phase transfer catalyzed conditions under a PEG-8000/toluene system afforded increased selectivity in terms of the fluoroalkoxylation of heterocycles. In the case of the o-, m-, and p-substitution study, this investigation indicated that the meta halogenated position of halonitrobenzenes is not capable of undergoing nucleophilic aromatic substitutions. This was not observed when similar
reactions were performed in HMPA or DMF. This study, therefore, indicates that the regioselective substitution of activated haloaryl and haloheteroaryl systems is easily effected in a PEG-8000/toluene system. These phase transfer catalyzed reaction conditions resulted in good yields and good selectivity. However, the use of PEG-8000 as a catalyst requires extensive aqueous extractions in order to separate it from the product of interest.

The advantages to the use of PEG-8000 as a phase transfer catalyst are:

(1) it allows for the use of a cheaper, more industrially applicable, and less toxic solvent,
(2) it allows for the use of a more readily available, and more convenient base,
(3) it allows for the use of a less expensive catalyst that is also very stable to base and to prolonged heating,
(4) it allows for reactions to proceed under milder conditions and results in increased reaction selectivity,
(5) it allows for high conversions of reactants to products and high yields of the substituted product.
PART I

CONCLUSIONS

The fluoroalkoxylation of activated haloaryl and haloheteroaryl substrates has been successful under "solid-solid" phase transfer catalytic conditions in which toluene was the solvent. Of the macrocyclic and linear polyethers studied, poly(ethylene glycol)-8000 was most effective in promoting the in situ synthesis of sodium fluoroalkoxides for the subsequent phase transfer catalyzed substitution onto halogenated systems.

The stability of the catalyst and the use of inexpensive starting materials, less toxic solvents, mild reaction conditions, and greater selectivity makes this synthetic method very useful for fluoroalkoxylation of haloaromatic systems.
PART I

RECOMMENDATIONS

The following are suggestions for future research in the area of PEG assisted aromatic nucleophilic fluoroalkoxylation:

(1) All work performed in this investigation is relative to activated benzene systems. While some data has been compiled on non-activated systems, the effectiveness of PEG mediated phase transfer catalyzed fluoroalkoxylation of such systems should be studied further.

(2) The use of aqueous extraction in the purification of the isolated products was very tedious and created much waste. It is proposed that PEG’s of various molecular weights be made into solid-supported catalysts so as to eliminate the need for an aqueous work-up. Dihalosilanes would be very useful in affixing the linear polyether onto a silica matrix.
PART II

THE GRIGNARD ADDITION AND SODIUM CYANOBOROHYDRIDE REDUCTION OF ARYLCYANOPROPENIMINIUM SALTS

INTRODUCTION

The imine or azomethine functional group (N=C) is incorporated in the parent molecules of a wide variety of natural products and it is a very important group in the realm of synthetic organic chemistry.\(^{56,57}\)

Since the 1960s, many review articles have been written concerning various aspects of synthetic azomethine chemistry.\(^{57-60}\) Of particular interest to investigators is the chemistry of imines (R'R"C=N-H) and iminium salts (R'R"C=NR\(_2^+X^-\)). Iminium intermediates are normally formed in situ during the Mannich, Gatterman, and Hoesch synthetic methods.\(^{61,62}\) The resulting iminium salts are not isolated, but are converted to the corresponding aldehydes and ketones upon hydrolytic work-up. The interest in imines has intensified due to the investigations concerning a simple iminium salt: the Eschenmoser reagent (Figure XII).
There are many methods by which this simple iminium salt may be synthesized, and its chemical properties are determined by the two resonance forms in which it exists (Figure XIII).

\[ \begin{align*}
\text{H}_3\text{C} & \quad \text{N} \quad \text{= C} \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{C} \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{C} \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{C} \quad \text{H}
\end{align*} \]

Figure XIII. The two resonance forms of the iminium ion.

The reactions of simple iminium salts with Grignard and lithium reagents has been described by Poulter et al.\textsuperscript{63} The products of these reactions are dialkylaminoalkanes, which may be converted to alkenes by oxidation. Vinamidinium salts are the vinylogous counterparts of the Eschenmoser reagent and their chemistry has been studied by several investigators.\textsuperscript{29,64-67} In each case, the
corresponding dialkylaminoalkene was produced. Similarly, the reduction of iminium salts has received great attention due to the potential synthetic applications. In 1981, Sundberg et al. reported that thioenaminones could be selectively methylated and subsequently reduced in the presence of a borohydride to yield the corresponding dialkylamino-vinyl sulfides. This prompted Gupton et al. to conduct a study on the reduction of arylvinamidinium perchlorates with sodium borohydride and sodium cyanoborohydride to form the corresponding N,N-dimethylallylic amines.

The vinamidine system is particularly interesting. This system may be referred to as a "push-pull" alkene where an electron donor is attached to one end of the alkene and an electron withdrawing group is attached onto the other end of the alkene system (Figure XIV).

![Figure XIV. A simple vinamidinium system and two of its resonance forms.](image)

An enhanced stability is achieved relative to other carbocations in the formation of a more stable resonance...
structure by the delocalization of electrons from the donor group. Similarly, the vinamidinium salt exists as a charged species and is accompanied by a counter ion which is derived from an acid chloride, i.e., POCl\textsubscript{3}, COCl\textsubscript{2}, SOCl\textsubscript{2}, or (COCl)\textsubscript{2} (Figure XV).

![Figure XV. A symmetrical vinamidinium salt.](image)

These salts exhibit an enhanced stability by the delocalization of their six pi electrons. Since the two alpha (α) carbons of the symmetrical vinamidine system are electrophilic, and the beta (β) carbon is nucleophilic; the salt will undergo substitution reactions with both electrophiles and nucleophiles to form sigma complexes.\textsuperscript{62,73-76}

The investigations by Gupton et al. involved the chemistry of the 2-arylvinamidinium salt: 3-dimethylamino-2-phenyl-prop-2-en-1-yliden-dimethyliminium perchlorate (see Figure XV above).\textsuperscript{66,67,72} Since this substrate is
symmetrical about the $\beta$ carbon, two equivalent electrophilic sites are available for nucleophilic attack. In the presence of a mild reducing agent, this substrate yields the corresponding N,N-dimethyl-2-aryl allylic amine or the N,N-dimethyl-2-aryl-3-cyanoenamine depending on the borohydride used in the reduction procedure. In the presence of organometallic reagents, the 2-arylvinamidinium salt formed the 3-alkyl-2-aryl acroleins after acid workup. In their continuing interests, Gupton and Coury wished to investigate the chemistry of an asymmetrical arylvinamidinium salt. The molecular system chosen for their studies was the 3-dimethylamino-3-phenyl-prop-2-en-1 yliden-dimethyliminium perchlorate (III), a derivative of its chloropropeniminium salt (IV).

Figure XVI. A chloropropeniminium salt (IV) and its vinamidine (III) derivative.

Addition of Grignard reagents primarily yield the 1,2-addition products and formed the $\alpha,\beta$-unsaturated ketones upon subsequent acid workup.
Figure XVII. 1,2-addition and 1,4-addition of vinamidine systems.

In light of these results, a study was conducted to determine the effect of the highly electronegative chloro substituent on the regiochemistry of an unsymmetrical chloropropeniminium salt. We proposed to investigate the reaction of Grignard reagents and reducing agents with the 3-chloro-3-aryl-prop-2-en-1-yliden-dimethyliminium perchlorate (III). This substrate has been synthesized by the facile Vilsmeier-Haack-Arnold method. In the presence of sufficient acid, the proper VHA intermediate is produced (Figure XVIII) which subsequently reacts with the enol tautomer of an acetophenone (Figure XIX).

Figure XVIII. The formation of the VHA reagent.
Figure XIX. The proposed mechanism in the synthesis of the chloropropenimininium salt by the VHA intermediate.
The unsymmetrical chloropropeniminium system described above also offers two non-equivalent electrophilic sites for nucleophilic attack and should produce the 1,2 addition product and/or the 1,4 addition product (see Figure XVII above). Various alkyl and aryl Grignard reagents will be utilized in determining the electrophilic site that is most susceptible to nucleophilic attack on the chloropropeniminium system. To accomplish this goal, (1) we propose to synthesize a series of 3-chloro-3-aryl-propheniminium salts in a method patterned after that described by Liebscher\textsuperscript{74} and also by Coury\textsuperscript{29}, (2) after purification of the above chloropropeniminium salts, we propose to subject the various salts to sodium borohydride and sodium cyanoborohydride reduction in a method that roughly parallels that of Gupton, Andrew, and Lizzi\textsuperscript{72}, (3) we propose to investigate the chemistry of selected 3-chloropropeniminium salts with a series of alkyl and aryl Grignard reagents in a method that is similar to that described by Gupton et al.\textsuperscript{66,67} and that of Coury.\textsuperscript{29}
PART II

EXPERIMENTAL

A. The Synthesis of Arylchloropropeniminium Salts

![Reaction Scheme]

1. POCl₃, DMF, 65°C
2. MeOH, HClO₄, 0°C

Table 12.

The synthesis of a series of arylchloropropeniminium salts by means of the Vilsmeir-Haack-Arnold reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Reaction Time</th>
<th>Crude Yield (%)</th>
<th>Purified Yield (%)</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>7</td>
<td>47.3</td>
<td>42.1</td>
<td>177-178</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>7</td>
<td>34.7</td>
<td>27.1</td>
<td>122-124</td>
</tr>
<tr>
<td>3</td>
<td>CH₃</td>
<td>7</td>
<td>72.8</td>
<td>59.3</td>
<td>198-199</td>
</tr>
<tr>
<td>4</td>
<td>OCH₃</td>
<td>7</td>
<td>68.6</td>
<td>65.8</td>
<td>187-188</td>
</tr>
<tr>
<td>5</td>
<td>3-NO₂</td>
<td>7</td>
<td>58.9</td>
<td>47.4</td>
<td>180-181</td>
</tr>
<tr>
<td>6</td>
<td>4-NO₂</td>
<td>7</td>
<td>72.4</td>
<td>63.1</td>
<td>228-229</td>
</tr>
</tbody>
</table>

78
a. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

b. The purified yield refers to the yield obtained after recrystallization of the crude product and after thorough drying of the crystalline material.

c. The melting points reported are uncorrected.

d. 3-Chloro-3(phenyl)-prop-2-en-1-yliden-dimethyl iminium perchlorate: mp 177-178°C (recrystallized from methanol/ethyl ether); NMR(DMSO-d$_6$) δ 3.75 (s,3H), 3.85 (s,3H), 7.57-7.78 (m,4H), 8.08-8.18 (m,2H), 9.03 (d,J=10 Hz,1H); IR(nujol) 1640, 1565, 1220, 1080, 835, 775, 682, 625 cm$^{-1}$

e. 3-Chloro-3(4-fluorophenyl)-prop-2-en-1-yliden-dimethyliminium perchlorate: mp 122-124°C (recrystallized from methanol/ethyl ether); NMR(DMSO-d$_6$) δ 3.75 (s,3H), 3.85 (s,3H), 7.32-7.78 (m,3H), 8.22 (d of d,J=6 Hz,J=2 Hz,2H), 9.03 (d,J=10 Hz,1H); IR(nujol) 1645, 1565, 1415, 1404, 1280, 1245, 1220, 1080(broad), 842, 692, 622 cm$^{-1}$.

f. 3-Chloro-3(4-methylphenyl)-prop-2-en-1-yliden-dimethyliminium perchlorate: mp 198-199°C (recrystallized from methanol/ethyl ether); NMR(DMSO-d$_6$) δ 2.48 (s,3H), 3.75 (s,3H), 3.85 (s,3H), 7.45 (d,J=8 Hz,2H), 7.78 (d,J=10 Hz,1H),
8.13 (d, J=8 Hz, 2H), 9.11 (d, J=10 Hz, 1H); IR (nujol) 1632, 1565, 1225, 1190, 1082, 830, 818, 622 cm$^{-1}$.

g. 3-Chloro-3(4-methoxyphenyl)-prop-2-en-1-yliden dimethyliminium perchlorate: mp 187-188$^\circ$C (recrystallized from methanol/ethyl ether);
NMR (DMSO-d$_6$) $\delta$ 3.82 (s, 3H), 3.95 (s, 3H), 4.07 (s, 3H), 7.40 (d, J=8 Hz, 2H), 7.85 (d, J=10 Hz, 1H), 8.42 (d, J=10 Hz, 2H), 9.28 (d, J=10 Hz, 1H);
IR (nujol) 1643, 1598, 1555, 1502, 1402, 1272, 1255, 1228, 1170, 1080, 1022, 830, 623 cm$^{-1}$.

h. 3-Chloro-3(3-nitrophenyl)-prop-2-en-1-yliden dimethyliminium perchlorate: mp 180-181$^\circ$C (recrystallized from methanol/ethyl ether);
NMR (DMSO-d$_6$) $\delta$ 3.80 (s, 3H), 3.90 (s, 3H), 7.80-8.10 (m, 2H), 8.50 (d of t, J=8 Hz, J=1 Hz, 2H), 8.85 (s, 1H), 9.15 (d, J=10 Hz, 1H); IR (nujol) 3080, 1652, 1588, 1535, 1355, 1240, 1220, 1190, 1080, 740, 625 cm$^{-1}$.

i. 3-Chloro-3(4-nitophenyl)-prop-2-en-1-yliden dimethyliminium perchlorate: mp 28-229$^\circ$C (recrystallized from methanol/ethyl ether);
NMR (DMSO-d$_6$) $\delta$ 3.78 (s, 3H), 3.87 (s, 3H), 7.90 (d, J=10 Hz, 1H), 8.43 (s, 4H), 9.13 (d, J=10 Hz, 1H);
IR (nujol) 3100, 3070, 1665, 1588, 1518, 1352, 1242, 1215, 1190, 1080, 852, 838, 752, 625 cm$^{-1}$.
The following reaction procedure is typical of the experimental conditions employed in the synthetic phase of the investigation.

3-Chloro-3(3-nitrophenyl)-prop-2-en-1-yliden-dimethylimminium perchlorate

To a dry 250 mL, three-necked, round-bottomed flask immersed in a saline ice bath and equipped with a thermometer, a condenser, a magnetic stirrer, rubber septum, and placed under a nitrogen atmosphere were added 34.07 grams (0.22 mole) of phosphorous oxychloride and 29.54 grams (0.4 mole) of dimethylformamide. The mixture was allowed to stir at 0°C for 15 minutes, removed from the ice-water bath, and then allowed to stir at room temperature for one hour. Subsequently, 17.38 grams (0.1 mole) of 3-nitroacetophenone was added to the reaction mixture as a single step. However, the reaction temperature was not allowed to exceed 75°C and was controlled by the use of a cold-water bath until the exothermic reaction subsided (approximately 90 minutes). Subsequently, the cold-water bath was removed and a heating mantle was applied to maintain the reaction temperature at 75°C. After 3.5 hours, the reaction mixture was poured into a 1000 mL beaker containing 500 mL of ice-cold anhydrous methanol and 25 mL of 70 percent (w/w) aqueous perchloric acid. The resulting solution was vigorously
agitated and cooled to 0°C. Crystallization was induced by scratching the walls of the beaker with a glass stirring rod. The light-yellow crystals were then collected by vacuum filtration and air dried to give 19.96 grams (58.87 percent yield) of the perchlorate salt (mp 162-165°C). The crude product was recrystallized in a solution of anhydrous methanol in ether (50:50 v/v) to afford 16.05 grams (47.35 percent yield) of a bone-white crystalline material (mp 180-181°C).
B. The Reduction of Arylchloropropeniminium Salts

![Chemical Structure](image)

Table 13.

The reduction of arylchloropropeniminium salts with sodium borohydride and sodium cyanoborohydride.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Reducing Agent</th>
<th>Reaction Time (Hrs)</th>
<th>Crude Yield (%)</th>
<th>Purified Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>NaBH₄</td>
<td>18</td>
<td>100.0</td>
<td>64.3</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>NaBH₃CN</td>
<td>18</td>
<td>98.9</td>
<td>71.9</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>NaBH₃CN</td>
<td>18</td>
<td>100.0</td>
<td>65.4</td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>NaBH₃CN</td>
<td>18</td>
<td>100.0</td>
<td>67.2</td>
</tr>
<tr>
<td>5</td>
<td>OCH₃</td>
<td>NaBH₃CN</td>
<td>18</td>
<td>100.0</td>
<td>63.8</td>
</tr>
<tr>
<td>6</td>
<td>3-NO₂</td>
<td>NaBH₃CN</td>
<td>4</td>
<td>100.0</td>
<td>69.7</td>
</tr>
<tr>
<td>7</td>
<td>4-NO₂</td>
<td>NaBH₃CN</td>
<td>4</td>
<td>100.0</td>
<td>12.1</td>
</tr>
</tbody>
</table>
a. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

b. The purified yield refers to the yield obtained after distillation of the crude, liquid product.

c. This entry utilizes sodium borohydride as a reducing agent. The reduction, however, proceeded much more quickly with the cyanoborohydride.

d. E-1-Chloro-3-N,N-dimethylamino-1-phenyl-1-propene: bp 73.5°C (0.5 mmHg); NMR($\text{CDCl}_3$) $\delta$ 2.26 (s,6H), 3.25 (d,$J=6$ Hz,2H), 6.23 (t,$J=6$ Hz,1H), 7.13-7.38 (m,3H), 7.43-7.71 (m,2H); IR(neat) 3045, 2965, 2935, 2850, 2810, 2760, 1485, 1440, 1355, 1250, 1030, 755, 690 cm$^{-1}$; mass spectrum m/e 197, 195 ($M^+$).

e. E-1-Chloro-3-N,N-dimethylamino-1-(4-fluorophenyl)-1-propene: bp 64.0°C (0.2 mmHg); NMR($\text{CDCl}_3$) $\delta$ 2.35 (s,6H), 3.29 (d,$J=6$ Hz,2H), 6.22 (t,$J=6$ Hz,1H) 7.04 (t,$J=8$ Hz,2H), 7.60 (d of d,$J=6$ Hz,$J=10$ Hz, 2H); IR(neat) 2965, 2935, 2850, 2815, 1595, 1502, 1450, 1230, 1158, 1025, 837, 800 cm$^{-1}$; mass spectrum m/e 215, 213 ($M^+$).

f. E-1-Chloro-3-N,N-dimethylamino-1-(4-methylphenyl)-1-propene: bp 75.0°C (0.2 mmHg); NMR($\text{CDCl}_3$) $\delta$ 2.28 (s,9H), 3.25 (d,$J=6$ Hz,2H), 6.19 (t,$J=6$ Hz, 1H),
7.07 (d, J=8 Hz), 2H), 7.45 (d, J=8 Hz), 2H); IR(neat) 3020, 2965, 2935, 2850, 2810, 2765, 1502, 1450, 1357, 1025, 820, 802 cm⁻¹; mass spectrum m/e 211, 209 (M⁺).

g. E-1-Chloro-3-N,N-dimethylamino-1(4-methoxyphenyl)-1-propene: bp 93.5°C (0.2 mm Hg); NMR(CDC1₃) δ 2.28 (s, 6H), 3.22 (d, J=6 Hz), 3.72 (s, 3H), 6.10 (t, J=6 Hz, 1H), 6.78 (d, J=10 Hz), 2H), 7.32 (d, J=10 Hz), 2H); IR(neat) 2930, 2810, 2765, 1602, 1505, 1450, 1295, 1250, 1175, 1032, 830, 625 cm⁻¹; mass spectrum m/e 227, 225 (M⁺).

h. E-1-Chloro-3-N,N-dimethylamino-1-(3-nitrophenyl)-1-propene: bp 111.5°C (0.3 mm Hg); NMR(CDC1₃) δ 2.37 (s, 6H), 3.35 (d, J=6 Hz), 2H), 6.57 (t, J=6 Hz, 1H), 7.67 (t, J=8 Hz, 1H), 8.02 (d, J=8 Hz, 1H), 8.23 (d, J=8 Hz), 1H), 8.37 (s, 1H); IR(neat) 3080, 2970, 2940, 2855, 2815, 2770, 1530, 1452, 1350, 1100, 1030, 805, 740, 705 cm⁻¹; mass spectrum m/e 242, 240 (M⁺).

i. E-1-Chloro-3-N,N-dimethylamino-1-(4-nitrophenyl)-1-propene: bp 113.0°C (0.3 mm Hg); NMR(CDC1₃) δ 2.43 (s, 6H), 3.67 (d, J=6 Hz), 2H), 6.65 (t, J=6 Hz, 1H), 7.80 (d, J=10 Hz), 2H), 8.24 (d, J=10 Hz, 2H); IR(neat) 3100, 3070, 2970, 2940, 2850, 2815, 2770, 1598, 1520, 1455, 1345, 1110, 1030, 857, 752, 705,
690 cm⁻¹; no mass spectrum available since the material formed a tar upon distillation.

The following reaction procedure is typical of the experimental conditions employed in the sodium cyanoborohydride reduction phase of the investigation.

3-Chloro-3-N,N-dimethylamino-1-(3-nitrophenyl)-1-propene

To a dry 250 mL, three-necked, round-bottomed flask immersed in an ice-water bath were added 1.70 grams (0.005 mole) of 3-chloro-3(3’nitrophenyl)-prop-2-en-1-ylidenedimethylaminium perchlorate, 0.66 gram (0.01 mole) sodium cyanoborohydride, and 100 mL of anhydrous methanol. The mixture was stirred for four hours at ice-water temperature (4°C). The solution was concentrated in vacuo to obtain a viscous, oily residue. To this residue were then added 50 mL of a 10 percent (v/v) ammonium hydroxide solution with continuous agitation. After ten minutes, 50 mL of chloroform were added and the resulting mixture was allowed to stir for an additional 15 minutes. Subsequently, the mixture was transferred to a 250 mL separatory funnel. The organic layer was separated and the aqueous layer was extracted with chloroform (2 X 25 mL). The combined organic volumes were transferred to a 250 mL separatory funnel, thoroughly washed with distilled water (3 X 50 mL), and then dried over anhydrous magnesium
sulfate. The organic phase was concentrated in vacuo to give 1.23 grams of a viscous, amber liquid which was distilled (Kugelrohr, 111.5 at 0.3 mm Hg) to yield 1.01 grams (69.7 percent yield) of a viscous, pale-yellow liquid which had physical properties (NMR, IR, and GLC retention times) characteristic of allylic amines.
C. The Alkylation of Arylchloropropeniminium Salts

\[
\begin{align*}
\text{ClO}_4^- & \quad \text{Cl} \\
 & \quad \text{N} \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{R-Mg-Y / THF} & \quad 27^\circ \text{C} \\
\text{Y} = \text{Br, Cl} \\
\end{align*}
\]

Table 14.

The alkylation of arylchloropropeniminium salts by the use of Grignard reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>Reaction Time (Hrs)</th>
<th>Crude\textsuperscript{a} Yield (%)</th>
<th>Purified\textsuperscript{b} Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>CH\textsubscript{3}</td>
<td>48</td>
<td>76.0</td>
<td>62.9</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CH\textsubscript{2}CH\textsubscript{3}</td>
<td>48</td>
<td>91.1</td>
<td>85.3</td>
</tr>
<tr>
<td>3</td>
<td>OCH\textsubscript{3}</td>
<td>CH\textsubscript{3}</td>
<td>48</td>
<td>77.7</td>
<td>17.4</td>
</tr>
<tr>
<td>4</td>
<td>OCH\textsubscript{3}</td>
<td>CH\textsubscript{2}CH\textsubscript{3}</td>
<td>48</td>
<td>99.8</td>
<td>87.6</td>
</tr>
<tr>
<td>5</td>
<td>OCH\textsubscript{3}</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>48</td>
<td>91.4</td>
<td>68.9</td>
</tr>
<tr>
<td>6</td>
<td>OCH\textsubscript{3}</td>
<td>CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}</td>
<td>48</td>
<td>157.8</td>
<td>49.7</td>
</tr>
</tbody>
</table>
a. The percent crude yield refers to the crude product yield based on the theoretical conversion of starting material to product.

b. The purified yield refers to the yield obtained after distillation of the crude, liquid product.

c. E-1-Chloro-3-N,N-dimethylamino-1-phenyl-1-butene:
   bp 71.0°C (0.3 mm Hg); NMR(CDCl₃) δ 1.35 (d, J=7 Hz, 3H), 2.32 (s, 6H), 3.33-3.83 (m, 1H), 6.21 (d, J=9 Hz, 1H), 7.23-7.48 (m, 3H), 7.51-7.78 (m, 2H); IR(neat) 3050, 3020, 2965, 2930, 2855, 2810, 1630, 1590, 1490, 1370, 1330, 1225, 1155, 1130, 1095, 1085, 1040, 980, 910, 888, 860, 760, 695, 675, 610 cm⁻¹; mass spectrum m/e 211, 209 (M⁺).

d. E-1-Chloro-3-N,N-dimethylamino-1-phenyl-1-pentene:
   bp 74.5°C (0.3 mm Hg); NMR(CDCl₃) δ 0.95 (t, J=7 Hz, 3H), 1.33-2.00 (m, 2H), 2.33 (s, 6H), 3.35-3.77 (m, 1H), 6.13 (d, J=9 Hz, 1H), 7.25-7.50 (m, 3H), 7.54-7.79 (m, 2H); IR(neat) 3050, 3020, 2960, 2925, 2880, 2815, 2770, 1625, 1490, 1445, 1345, 1240, 1225, 1155, 1100, 1075, 1060, 1040, 1015, 990, 895, 855, 760, 695, 675, 610 cm⁻¹; mass spectrum m/e 225, 223 (M⁺).

e. E-1-Chloro-3-N,N-dimethylamino-1-(4-methoxyphenyl)-1-butene: bp 99.0°C (0.3 mm Hg); NMR(CDCl₃) δ 1.23 (d, J=7 Hz, 3H), 2.33 (s, 6H), 3.33-3.67 (m, 1H),
3.80 (s,3H), 6.05 (d,J=9 Hz,1H), 6.87 (d,J=9 Hz,2H), 7.54 (d,J=9 Hz,2H); IR(neat) 2965, 2930, 2855, 2830, 2815, 2770, 1605, 1510, 450, 1298, 1255, 1178, 1035, 888, 830, 789, 665, 630 cm⁻¹; mass spectrum m/e 241, 239 (M⁺).

f. E-1-Chloro-3-N,N-dimethylamino-1(4-methoxyphenyl)-1-pentene: bp 106.5°C (0.3 mm Hg); NMR(CDCl₃) δ 0.98 (t,J=9 Hz,3H), 1.33-1.98 (m,2H), 2.40 (s,6H), 3.33-3.83 (m,1H), 3.88 (s,3H), 6.15 (d,J=9 Hz,1H), 7.03 (d,J=9 Hz,2H), 7.74 (d,J=9 Hz,2H); IR(neat) 2955, 2930, 2860, 2830, 2810, 2770, 1605, 1575, 1505, 1455, 1350, 1295, 1252, 1178, 1112, 1035, 1015, 990, 895, 830, 665, 630 cm⁻¹; mass spectrum m/e 255, 253 (M⁺).

g. E-1-Chloro-3-N,N-dimethylamino-1(4-methoxyphenyl)-3-phenyl-1-propene: bp 135.0°C (0.3 mm Hg); NMR(CDCl₃) δ 2.33 (s,6H), 3.80 (s,3H), 4.48 (d,J=9 Hz,1H), 6.40 (d,J=9 Hz,1H), 6.99 (d,J=9 Hz,2H), 7.35-7.90 (m,6H); IR(neat) 3055, 3020, 2970, 2940, 2895, 2855, 2830, 2810, 2765, 1605, 1510, 1452, 1415, 1295, 1255, 1230, 1178, 1150, 1115, 1100, 1085, 1070, 1035, 1018, 920, 908, 835, 780, 760, 740, 701, 670, 625 cm⁻¹; mass spectrum m/e 303, 301 (M⁺).
h. E-1-Chloro-3-N,N-dimethylamino-1(4-methoxyphenyl)-4-phenyl-1-butene: bp 154.5°C (0.3 mm Hg);
NMR(CDC13) δ 2.32 (s,6H), 2.54-3.27 (m,2H), 3.68 (s,3H), 3.77-4.16 (m,1H), 6.00 (d,J=10 Hz,1H),
6.83 (d,J=9 Hz,2H), 7.45 (s,broad,5H), 7.66 (d,J=9 Hz,2H); IR(neat) 3055, 3020, 2930, 2850, 2830,
2810, 2770, 1605, 1575, 1508, 1452, 1295, 1255, 1178, 1112, 1085, 1032, 900, 885, 830, 745, 700,
665, 630 cm⁻¹.

The following reaction procedure is typical of the experimental conditions in the Grignard addition phase of the investigation.

E-1-Chloro-3-N,N-dimethylamino-1(4-methoxyphenyl)-1-pentene

To a dry 250 mL, three-necked, round-bottomed flask immersed in a saline ice bath and equipped with a thermometer, a condenser, a magnetic stirrer, rubber septum, and placed under a nitrogen atmosphere were added 1.62 grams (0.005 mole) of 3-chloro-3(4-methoxyphenyl)-prop-2-en-1-yliden-dimethyliminium perchlorate and 100 mL of anhydrous, distilled THF. The mixture was stirred until cool (10°C) and 5.0 mL of a 2.00M CH₃CH₂-MgBr/THF suspension (0.1 mole) was injected through the rubber septum by means of a 10.0 mL graduated syringe. The mixture was stirred for two hours at ice-water temperature. The ice water bath was removed and the reaction mixture was
allowed to react at room temperature for 46 hours. Subsequently, 20.0 mL of anhydrous methanol were added dropwise to quench the excess Grignard reagent and the resulting mixture was allowed to stir for one hour. The solution was concentrated in vacuo to obtain a viscous, oily, red-colored residue. To this residue were added 50 mL of chloroform and 100 mL of water. This mixture was agitated continuously for 15 minutes. Subsequently, the mixture was transferred to a 250 mL separatory funnel. The organic layer was decanted and then dried over anhydrous magnesium sulfate. The aqueous layer was extracted with a second 50 mL portion of chloroform, allowed to separate, decanted, and combined with the first extraction. The organic phase was concentrated in vacuo to give 1.27 grams of a viscous, amber liquid which was distilled (Kugelrohr, 106.5°C at 0.3 mm Hg) to yield 1.02 grams of a viscous, pale-yellow liquid which had physical properties (NMR and IR) characteristics of allylic amines. GLC was used to determine the purity of the distilled product.
PART II

DISCUSSION OF RESULTS

A study of chloropropeniminium salt chemistry was conducted in three phases: synthesis, borohydride reduction and Grignard addition. In the first phase of this investigation, 3-chloro-3-aryl-propeniminium salts were synthesized by the reaction of the VHA intermediate, which is formed in situ, with an acetophenone derivative to form the corresponding enaminoketone. Excess of the acid chloride (POCl₃) insures the formation of the 3-chloro-3-arylpropeniminium•OPOCl₂ salt. This complex however, is very soluble in DMF. The addition of perchloric acid (HClO₄) permits the formation of HOPOCl₂ and facilitates the isolation of the arylchloropropeniminium perchlorate. This salt is formed in a methanol/DMF solvent system and the crystals are easily separated from the mother liquor by vacuum filtration. The isolation and purification of the salt were necessary in order to ascertain its physical and chemical properties in the absence of possible contaminating by-products. All of the salts isolated and reported in Table 12 had several, similar characteristics:
(1) a needle-like appearance

(2) a brilliant yellow color

(3) a high melting point

(4) a tendency to dissolve in acetone, DMSO, and water and (5) were isolated in high yields (approximately 50-70 percent). These salts were characterized by means of NMR and IR spectral data.

In order to substantiate the synthesis of these substances, it was necessary to visualize the imine characteristic bands: the N,N-dimethyl functional group, C-Cl, and the C=C unsaturation. The nujol peaks, however, masked the $\nu_3\text{CH}_3$ and $\delta_3\text{CH}_2$ bands (2820-2760 cm$^{-1}$ and 1440-1390 cm$^{-1}$ respectively). On the other hand, the characteristic C=N functional group could be visualised in the range of 1675-1620 cm$^{-1}$; as was the C-Cl stretch band at 800-600 cm$^{-1}$.

NMR analysis reveals several characteristic peaks for the isolated salts.
The spectra for the six compounds listed in Table 12 showed a characteristic pair of singlets for $H_d$ centered at $\delta 3.8$ and $\delta 3.9$. The appearance of two separate absorptions for the two $N$-$CH_3$ groups indicated that the electronic environment about each methyl group is different. Absorptions for the allylic hydrogens, $H_a$, were centered at $\delta 9.1$ and appeared as a doublet with a coupling constant of 10 Hz. The vinyl hydrogen absorptions, $H_v$, varied in spectral position depending on the substituent group on the aromatic ring at position C$_3$ of the imine. $H_v$ for entries 3, 4, 5, and 6 is centered at approximately $\delta 7.8$. The same hydrogen, however, cannot be easily visualized for entries 1 and 2 because they are obscured by a multiplet in entry 1 and by a quartet in entry 2. In the aromatic region of the NMR spectrum, characteristic splitting patterns are observed for each of the substituted phenyl groups. The $H_b$ hydrogens were located in the region downfield from the $H_c$ hydrogens in all cases except for entry 2. This may be explained by the inductive and electronic effects of the fluorine substituent.
The meta-nitro phenyl-substituted chloropropeniminium salt exhibits an \( H_v \) hydrogen and an \( H_g \) hydrogen that are practically identical in chemical shift. The \( H_e \) and \( H_f \) hydrogens, in like fashion, appear at \( \delta 8.50 \) as a doublet and, the characteristic \( H_b \) hydrogen for this molecule has a spin-spin coupled triplet that appears at \( \delta 8.85 \). The orientation of groups about the \( C=\)C unsaturated carbons has been proposed by Liebscher, whose work indicates that the "E" isomer is favored for the imine backbone: \( C=\)C-\( C=N \). It is important to note that the NMR samples of these iminium salts were prepared with deuterated DMSO. It was observed that these chloropropenimininium perchlorates slowly reacted with the deuterated solvent. A broad singlet was observed to intensify with time. This singlet was observed in the aliphatic region of the NMR spectrum; centered at \( \delta 2.5 \) with a corresponding decrease in the intensity of the allylic hydrogen peak. It is known that DMSO readily reacts with alkyl halides (see below).
In order to more fully characterize the regiochemistry of the C=C-C=N backbone, reductions and Grignard additions were carried out on the purified salts. The reduction products in this portion of the investigation were isolated in exceptional purity (i.e., no boron-nitrogen complexes were formed) and they exhibited characteristic peaks in the IR spectrum. The N-C bands for the $\nu_\text{s} \text{CH}_3$ and $\delta_\text{s} \text{CH}_3$ were easily observed for these compounds as were the $\nu_\text{s} \text{CH}_2$ and $\delta_\text{s} \text{CH}_2$ bands. The absence of the C=N stretch frequency at 1675-1620 cm$^{-1}$ clearly identified the isolated products as tertiary amines. The NMR spectra for the reduction products also had several characteristic spectral patterns.

For all entries in Table 13, the N,N-dimethyl hydrogens ($H_d$) appeared as a singlet at $\delta$ 2.3 and integrated for six hydrogens. Similarly, all entries exhibited an $H_a$ hydrogen in the region of $\delta$ 3.3 as a doublet which integrated for two hydrogens. $H_v$ appeared in the $\delta$ 6.2 region as a triplet for all entries. This triplet integrated for two hydrogens in each of the isolated products. In the
aromatic region of the spectrum, the previously observed splitting patterns for the salts were closely followed by the reduction products. From these results, it may be inferred that a 1,2 addition predominates in the sodium borohydride and cyanoborohydride reduction of the chloropropeniminium salts to form the corresponding allylic dialkylamines.

To conclusively determine the predominant site of nucleophilic attack, selected salts were purified and reacted with Grignard reagents. The criterion for salt selection in this study were: (1) availability of the perchlorate salt and (2) simplicity of the NMR spectral pattern to facilitate the characterization of the alkylated products. Both alkyl and aryl Grignard reagents were allowed to react with the salt in separate reaction vessels for a period of 48 hours, at room temperature. Completion of the reaction was correlated with a decrease in the turbidity of the reaction mixture. The products were easily isolated and characterized. Table 14 summarizes the results of this investigation and indicates that the alkylated and arylated products may be isolated in high yields. The presence of an impurity for entry 6 resulted in an abnormally high crude yield (157 percent). It is believed that this impurity is 1,2-diphenylethane, a common contaminant in commercially available benzyl-Grignard
reagents. IR spectral patterns indicated the absence of the imine C=N functional group and also indicated the presence of the N,N-dimethyl group in the characteristic regions described above. NMR analysis reveals several characteristic peaks for the Grignard addition products.

All six entries of Table 14 exhibit the characteristic $H_d$ hydrogen as a singlet at $\delta$ 2.3 for the N,N-dimethyl group. For entries 3 to 6, the $-OCH_3$ peak was easily observed as a singlet at $\delta$ 3.8. $H_v$ for all entries characteristically appeared as a doublet in the aromatic region at $\delta$ 6.1. $H_b$ and $H_c$ appeared as doublets in their expected positions. The spectral pattern for $H_a$, however, varied with the R group which was attached to the allylic carbon. $H_a$ appeared as a weak multiplet centered at $\delta$ 3.5 except for entry 5 where a doublet occurs further downfield at $\delta$ 4.5. Each of these peaks integrated for one hydrogen. Grignard addition was further substantiated by the appearance of the expected spectral and splitting patterns of each substituent group, R. Entries 1 and 3 indicated the
presence of a methyl group at δ 1.3 as a doublet integrating for three hydrogens. Entries 2 and 4 gave the characteristic patterns expected for an ethyl group: (1) a triplet at δ 0.98 integrating for three hydrogens and (2) a multiplet at δ 1.7 integrating for two hydrogens. However, the data for entries 5 and 6 was more difficult to interpret because of the presence of an additional phenyl group. The hydrogen positioned ortho to the site of alkylation appeared in the same region as did H_b in the 4’methoxyphenyl-substituted chloropropeniminium salt (Table 14, entry 3). The other three hydrogens of this aromatic substituent appeared as a doublet centered at δ 7.0. In changing the R group from a phenyl to a benzyl substituent (addition of a methylene group) simplified the spectrum considerably. The aromatic hydrogens of the benzyl substituent were easily observed as a broad singlet at δ 7.45 integrating for five hydrogens. This broad singlet was flanked by the characteristic H_b and H_c doublets that are associated with the 4’methoxyphenyl substituent. The benzyl CH_2 group was also easily identified as a doublet of doublets centered at δ 2.4. These data indicated that Grignard addition had occurred to form a chiral center at C_1 had resulted in the formation of an allylic dialkylamine.
PART II

CONCLUSIONS

The facile VHA method of synthesizing 3-chloro-3-aryl propeniminium perchlorate salts afforded high yields of crystalline materials, which enabled the physical and chemical characterization of the vinylogous iminium systems. The sodium borohydride and cyanoborohydride reductions were conducted in alcoholic media and the crude reduction products were essentially analytically pure and were completely free of boron-nitrogen complexes. Similarly, the Grignard addition products were isolated in analytically pure yields with little difficulty. These investigations indicate that these reactions predominantly undergo addition at the methine carbon to form the corresponding tertiary amines. These results parallel those by Coury\textsuperscript{29}, who studied the asymmetrical vinamidinium analog of these perchlorate salts. Therefore, the effect of the chlorine substituent on regiochemistry of these vinylogous iminium perchlorates is similar to the effect of the NH\textsubscript{2} substituent on the chemistry of the analogous vinamidine system.
PART II

RECOMMENDATIONS

The following are suggestions for future research in the area of unsymmetrical, vinylogous, aryl-haloiminium salts.

(1) Hickmott has reviewed the chemistry of a wide number of conjugated imines. However, investigations have not been conducted on conjugated imine systems where one or more than one of the unsaturated carbons are halogenated. It would be interesting to study the effect of conjugation and the effect of the number of halogen substituents on the regiochemistry of the vinylogous iminium salt.

(2) Liebscher reports the syntheses of a number of aryl chloropropeniminium salts but did not report the synthesis of aryl bromopropeniminium salts. It would be interesting to study the stereochemistry of these vinylogous imines in the presence of Grignard reagents, reducing agents, and other nucleophiles.

(3) In this investigation, the oxidation of the iminium salts was observed in the presence of DMSO-d$_6$ but the products were not isolated nor characterized. As a follow-
up, it would be suggested to determine the exact product or products formed during this reaction.

(4) It is recommended that the crystalline solids be purified for all investigations. It was found that recrystallization in a 50/50 (v/v) of anhydrous methanol in ethyl ether was most efficacious. Distillation of these materials may be effected easily, however, this technique severely decreases the yields.
INSTRUMENTATION AND EQUIPMENT

Proton NMR spectra were obtained from samples which were dissolved in CDCl₃ or in DMSO-d₆. Tetramethysilane was used as an internal standard at 60 MHz and spectra were recorded with a Varian EM-360A nuclear magnetic resonance spectrometer.

Infrared spectra were recorded with a Perkin-Elmer 1420 ratio recording infrared spectrometer. Samples were applied as thin films on salt plates and they were prepared as nujol mulls or as neat films.

Mass spectra were obtained from purified materials and recorded on photosensitive films by a Hitachi Perkin-Elmer RMU-6E mass spectrometer.

Melting points were determined on purified materials with a Fisher-Johns melting point apparatus and were reported as uncorrected temperatures.

Gas chromatographic assays were conducted on both crude and purified materials. GLC traces were obtained from a Shimadzu GC-7A gas chromatograph which was interfaced with a Shimadzu C-R1B Chromatopac recorder. The gas chromatographic columns used in this research were of two types: 3% SB2401 (100/120 Supelcoport; R-01862 SUPELCO)
and 10% SP2100 (10 feet x 0.125 inch column; 20% SP2100, 1% Carbowax, 160/120 Supelcoport H08684). The SB2401 column was most frequently used and its operating temperatures were in the range of 160–200°C.

Solvents were removed in vacuo with the aid of a Rinco Rotovapor rotary evaporator and a thermostatically controlled hot water bath.

Distillation of substances were performed under high vacuum (0.2–0.5 mmHg). A Welch DUO-SEAL 1402 vacuum pump was used in conjunction with a Neslab CC-60 CRYCOOL immersion cooler. Boiling points were reported at the operating pressure.

Reaction mixtures were stirred with the aid of a Curtin MAGNESTIR S8290 (50/60 Hz, 115 volt). The stirring rate for the leaving group studies of Part I were determined by the use of a General Radio STROBTAC (Type 1538-A) strobe light.


36. A modified version of the mechanism described in 31 and 32.


