A Three Part Research Report: The Synthesis of Potential Insecticides, N-(4-Heteroaryloxybenzoyl)-N'(2,4-Dichlorobenzoyl) Hydrazines: A Reinvestigation of Hexamethylphosphoramide with Ketoximes; Regioselective Fluoralkoxylation and Polyfluoroalkoxylation of Activated Dihalobenzenes and Dihaloheterocycles

1984

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A THREE PART RESEARCH REPORT:
THE SYNTHESIS OF POTENTIAL INSECTICIDES, N-(4-HETEROARYL-OXYBENZOYL)-N’-(2,4-DICHLOROBENZOYL)HYDRAZINES:
A REINVESTIGATION OF HEXAMETHYLPHOSPHORAMIDE WITH KETOXIMES;
REGIOSELECTIVE FLUOROALKOXYLATION AND POLYFLUOROALKOXYLATION
OF ACTIVATED DIHALOBENZENES AND DIHALOHETEROCYCLES

BY

GARY A. DeCRESSENZO
B.S., University of Central Florida, 1982

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
1984
ABSTRACT

This report discusses research in three areas of organic synthesis: The synthesis of potential insecticides; the reinvestigation of the reaction of hexamethylphosphoramide with ketoximes; and the regioselective fluoroalkoxylation and polyfluoroalkoxylation of activated dihalobenzenes and dihaloheterocycles. In Part I, a series of N-(4-heteroaryloxybenzoyl)-N'-(2,3-dichlorobenzoyl)hydrazines are synthesized, and attempts at cyclic dehydration to the corresponding 2,5-disubstituted-1,3,4-oxadiazoles are discussed. In Part II, the synthesis of N,N-dimethyl-N'aryl amidines by the reaction of aryl alkyl and diaryl ketoximes with HMPA is discussed. In Part III, a series of activated dihalobenzenes and dihaloheterocycles are reacted with sodium trifluoroethoxide to study the possibility of regioselective fluoroalkoxylation and polyfluoroalkoxylation of these activated substances.
ACKNOWLEDGEMENTS

I am greatly indebted to Dr. John T. Gupton III for his enthusiastic guidance and patience throughout my graduate and undergraduate research. I am also grateful to Dr. Guy Mattson and Dr. Graeme Baker for their time and input as members of my graduate committee. I would also like to thank Dow Chemical Company for their financial support through research grants which enabled me to further my education and perform this research.

I would like to express my deepest thanks to my family and my fiancee Rişe for their moral support throughout my college career.
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DISCUSSION OF RESULTS

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LIST OF ABBREVIATIONS

Ar  aryl
bp  boiling point
°C  degrees centigrade
cm⁻¹  wave numbers (IR spectrum)
δ   delta (NMR spectrum)
d   doublet
DMF  dimethylformamide
DMSO  dimethylsulfoxide
g  grams
Δ   heat
HMPA  hexamethylphosphoramide
hr  hours
Hz  Hertz (cycles per second, NMR spectrum)
IR  infrared
J   coupling constant (NMR spectrum)
m  multiplet (NMR spectrum)
M⁺  molecular ion (mass spectrum)
m/e  mass/charge ratio (mass spectrum)
MeOH  methanol
ml  milliliters

viii
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tr>
<td>mm</td>
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<tr>
<td>min</td>
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</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
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<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million (NMR spectrum)</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR spectrum)</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR spectrum)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR spectrum)</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
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PART I: THE SYNTHESIS OF POTENTIAL INSECTICIDES, N-(4-HETEROARYLOXYBENZOYL)-N'-(2,4-DICHLOROBENZOYL)HYDRAZINES

INTRODUCTION

Over the past years, considerable attention has been directed towards the synthesis of effective, yet environmentally safe insecticides.

In a collaborative effort between Dow Chemical's Agricultural Products Division and the University of Central Florida, our laboratories have synthesized and screened for biological activity, a series of DOWCO 416 analogs and their precursor diacylhydrazines.¹⁻⁴ These compounds have shown activity in the control of manure breeding insects such as houseflies, faceflies and hornflies. These compounds have the following general structure.⁵

\[
\begin{align*}
\text{Cl} & & \text{Cl} & & \text{Cl} & & \text{Cl} \\
\text{N} & & \text{N} & & \text{Ar} & & \text{Cl} \\
\text{O} & & \text{H} & & \text{H} & & \text{O} \\
\end{align*}
\]

In an attempt to further investigate the activity of these analogs, a series of N-(4-heteroaryloxybenzoyl)-N'-(2,4-dichlorobenzyol)hydrazines have been synthesized and attempts at cyclic dehydration to the corresponding 1,3,4-oxadiazoles are reported.

Initial studies indicate that the mode of action of this class of compounds seems to involve inhibition of chitin synthesis.
in the insects. This form of insecticidal activity allows for selective toxicity towards the insects and does not affect mammalian systems. The proposed synthetic scheme for these compounds is shown in Figure 1.

Figure 1. The Proposed Synthetic Route for the Preparation of N-(4-Heteroaryloxybenzoyl)-N'-(2,4-dichlorobenzoyl)hydrazine and 2,5-disubstituted-1,3,4-oxadiazoles.
It is the intention of this research to develop these aryloxy analogs in an attempt to increase the lipophilicity of these compounds to facilitate ease of formulation.

The following experimental procedure describes the conditions for the synthesis and the spectral properties of these compounds. The heterocyclic groups incorporated into these hydrazines include: 2-chloropyrimidine, 2,5-dichloropyrimidine, 2,3,5,6-tetrachloropyridine, 2,3,5-trichloropyridine and 2,3-dichloro-5-trifluoromethylpyridine.
PART I
EXPERIMENTAL

A. The Synthesis of N-(4-Hydroxybenzoyl)-N'- (2,4-dichlorobenzoyl) hydrazine.

Figure 2. The Synthesis of N-(4-Hydroxybenzoyl)-N'- (2,4-dichlorobenzoyl) hydrazine

A 250 ml three-necked, round-bottomed flask was equipped with a magnetic stirring bar, condenser, thermometer, and 125 ml addition funnel. The flask was charged with 4.29 g (0.050 mol) of sodium bicarbonate, 60 ml water, 90 ml tetrahydrofuran (THF), and 7.60 g (0.050 mol) of 4-hydroxybenzoic acid hydrazide. After dropwise addition of 10.47 g (0.050 mol) of 2,4-dichlorobenzoyl chloride, the reaction mixture was stirred for two hours at room temperature. Removal of THF by rotary evaporation and addition of 100 ml of water yielded 16.00 g of a white solid which was filtered and dried in
vacuo. NMR (d$^6$-DMSO, CDCl$_3$) $\delta$ 6.96 (d, J=8Hz, 2H), 7.46-7.67 (m, 3H), 7.90 (d, J=8Hz, 2H); IR (nujol mull) 3300 (N-H $\tilde{2}^0$ amide stretch), 3200 (broad OH stretch), 1675, 1630 (C=O amide stretch) 865 (2,4-disubstituted aromatic ring), and 810 cm$^{-1}$ (p-disubstituted aromatic ring); mp 230-240°C.

B. The Synthesis of N-(4-Heteroaryloxybenzoyl)-N'-(2,4-dichlorobenzoyl)hydrazines.

![Chemical structures](image)

Figure 3. The Synthesis of N-(4-Heteroaryloxybenzoyl)-N'-(2,4-dichlorobenzoyl)hydrazines.

Table 1. Experimental Data for the Synthesis of N-(4-Heteroaryloxybenzoyl)-N'-(2,4-dichlorobenzoyl)hydrazines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield$^a$ %</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-chloro-2-pyrimidinyl</td>
<td>69$^b$</td>
<td>209-215</td>
</tr>
<tr>
<td>2</td>
<td>2-pyrimidinyl</td>
<td>39$^c$</td>
<td>206-208</td>
</tr>
<tr>
<td>3</td>
<td>3,5-dichloro-2-pyridinyl</td>
<td>42$^d$</td>
<td>218-221</td>
</tr>
<tr>
<td>4</td>
<td>3-chloro-5-trifluoromethyl-2-pyridinyl</td>
<td>98$^e$</td>
<td>225-230</td>
</tr>
<tr>
<td>5</td>
<td>3,5,6-trichloro-2-pyridinyl</td>
<td>97$^f$</td>
<td>272-276</td>
</tr>
</tbody>
</table>

$^a$All yields reported are for crude products.
bSee experimental procedure for spectral data.

cN-(4-(2'-pyrimidinoxy)benzoyl)-N'-(2,4-dichlorobenzoyl)hydrazine

NMR (d<sup>6</sup>-DMSO, CDCl<sub>3</sub>) δ 7.36 (m, 3H), 7.57 (m, 3H), 8.12 (d, J=8Hz, 2H)
8.66 (d, J=8Hz, 2H); IR (nujol mull) 3150, 1650, 1600, 1525, 1450,
1360, 1250, 860, 840 and 780 cm<sup>-1</sup>; mp 206-208°C.

dN-(4-(3',5'-dichloro-2'-pyridinoxy)benzoyl-N'-(2,4-dichlorobenzoyl)hydrazine. NMR (d<sup>6</sup>-DMSO, CDCl<sub>3</sub>) δ 7.28 (d, J=8Hz, 2H),
7.63 (m, 3H), 8.05 (d, J=8Hz, 2H), 8.15 (d, J=8Hz, 1H), 8.27 (d, J=2Hz, 1H); IR (nujol mull) 3200, 1640, 1610, 1580, 1465, 1435,
1390, 870, 830, 790 and 740 cm<sup>-1</sup>; mp 218-221°C.

eN-(4-(3'-chloro-5'-trifluoromethyl-2'-pyridinoxy)
(2,4-dichlorobenzoyl)hydrazine. NMR (d<sup>6</sup>-DMSO, CDCl<sub>3</sub>) δ 7.36 (d, J=8Hz, 2H),
7.60 (m, 3H), 8.11 (d, J=8Hz, 2H), 8.50 (s, broad, 2H); IR (nujol mull) 3200, 1610, 1590, 1465, 1340, 1210, 1140, 1075, 870,
790 and 760 cm<sup>-1</sup>; mp 225-230°C.

fN-(4-(3',5',6'-trichloro-2'-pyridinoxy)benzoyl)-N'-(2,4-dichlorobenzoyl)hydrazine. NMR (d<sup>6</sup>-DMSO, CDCl<sub>3</sub>) δ 7.35 (d, J=8Hz, 2H),
7.70 (m, 3H), 8.13 (d, J=8Hz, 2H), 8.43 (s, 1H); IR (nujol mull) 3180, 1610, 1580, 1470, 1420, 1380, 1210, 1170, 870, 790 and 730
cm<sup>-1</sup>; mp 272-276°C.

The following procedure is typical of the experimental
conditions used.
N-(4-(5′-Chloro-2′-pyrimidinoxy)benzoyl)-N′-(2,4-dichlorobenzoyl) hydrazine

A 250 ml, three-necked, round-bottomed flask was equipped with a magnetic stirring bar, condenser, and thermometer and placed under nitrogen atmosphere. The flask was charged with 0.316 g (0.0060 mol) of a NaH-mineral oil dispersion, 50% by weight, and washed with n-hexane. The hexane was removed by syringe and 100 ml of dry N,N-dimethylformamide was added with stirring. To this mixture was added with stirring, in three portions, 2.00 g (0.00660 mol) of N-(4-hydroxybenzoyl)-N′-(2,4-dichlorobenzoyl)-hydrazine. After the gas evolution had ceased, 0.900 g (0.0060 mol) of 2,5-dichloropyrimidine was added in one portion. The reaction mixture was heated to 100-110°C for sixteen hours. The reaction mixture was cooled to room temperature and poured into 200 ml of cold water, rapidly filtered and washed with an additional 25 ml of cold water. The tan solid product was dried in vacuo on a Kugelrohr apparatus to yield 1.83 g of solid, mp 209-215°C. NMR (d⁶-DMSO, CDCl₃) δ 7.37 (d, J=8Hz, 2H), 7.60 (m, 3H), 8.03 (d, J=8Hz, 2H), 8.75 (s, 2H); IR (nujol mull) 3300 (N-H 2° amide stretch), 1670, 1650 (C=O amide stretch), 1420, 1250 (C-O-C stretch), 865 (2,4-disubstituted aromatic ring) and 810 cm⁻¹ (p-disubstituted aromatic rings).

C. The Synthesis of 2-(4′-Heteroaryloxy)phenyl)-5-(2′,4′-dichlorophenyl)2,3,4-oxadiazoles
Table 2. Experimental Data for the Synthesis of 2-[(4'-Heteroaryl)phenyl]-5-(2',4'-dichlorophenyl)1,3,4-oxadiazoles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-chloro-2-pyrimidinyl</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2-pyrimidinyl</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3,5-dichloro-2-pyridinyl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3-chloro-5-trifluoromethyl-2-pyridinyl</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3,5,6-trichloro-2-pyridinyl</td>
<td></td>
</tr>
</tbody>
</table>

aThe product from this reaction and all other heteroaryloxy diacyl-hydrazines was determined to be 2-(4'-hydroxyphenyl)-5-(2',4'-dichlorophenyl)-1,3,4-oxadiazole. It is apparent from this result that the heteroaryloxy group is not stable to acid and undergoes rapid hydrolysis to the corresponding hydroxy compound. NMR (d₆, DMSO)  δ7.50 (d, J=9Hz, 2H), 7.73-7.84 (m,2H), 8.15 (d, J=9Hz, 2H), 8.18 (d, J=8Hz, 2H); IR(nujol mull) 3300 (broad), 1600, 1390, 850 cm⁻¹; mp, 219-223 C.
The following is typical of the experimental conditions.

$2-(4'-\text{Chloro}-2'-\text{pyrimidinoxy})\text{phenyl}-5-(2',4'-\text{dichlorophenyl})\overline{1,3,4}$-oxadiazole

A 100 ml three-necked, round-bottomed flask was equipped with a magnetic stirring bar, thermometer and condenser, and charged with 20 ml of phosphorus oxychloride. To the flask was added with stirring 1.00 g of N-(4-(5'-chloro-2'-pyrimidinoxy)benzoyl-N'-(2,4-dichlorobenzoyl)hydrazine in one portion. The reaction mixture was heated to 100°C for 20 hours, cooled to room temperature, and poured slowly into 200 ml of ice/water and rapidly filtered to yield a white solid which was dried on a Kugelrohr apparatus.
PART I

DISCUSSION OF RESULTS

As seen in Table 1, a series of N-(4-heteroaryloxybenzoyl)-N'-
(2,4-dichlorobenzoyl)hydrazines have been synthesized in good yields. These compounds have been characterized by NMR and IR spectroscopy and melting points have been tabulated.

The starting N-(4-hydroxybenzoyl)-N'- (2,4-dichlorobenzoyl)-
hydrazine was prepared in excellent yield by the acylation of 4-
hydroxybenzoic acid hydrazide with 2,4-dichlorobenzoyl chloride. Inspection of the IR spectra of this product shows the absence of the $^1\text{amide}$ stretch at 3320 cm$^{-1}$. However, the $^2\text{amide}$ stretch which occurs at 3360-3340 cm$^{-1}$ is still present. The conversion of the hydrazide to the diacylhydrazine also results in a shift of the carbonyl amide stretch to lower wavenumbers by approximately 50 cm$^{-1}$. The most definitive spectral changes occur in the NMR, where the broad NH$_2$ singlet between 3.80-4.75 ppm is no longer present in the diacylhydrazine. Also evident in the NMR spectra is the presence of additional aromatic hydrogens due to the incorporation of the 2,4-dichlorobenzoyl moiety.

The reaction of N-(4-hydroxybenzoyl)-N'- (2,4-dichlorobenzoyl)-
hydrazine with haloheterocycles through a nucleophilic substitution of the phenoxide generated in situ from the reaction of the hydroxy-
benzoic acid hydrazide with NaH, produced the heteroaryloxybenzoyl hydrazines as verified by the following structural assignments. The OH stretching vibration in the IR spectra at 3500-3200 cm⁻¹ is absent and there is an additional absorption at 1250 cm⁻¹ which is due to the asymmetric stretching of the C-O-C ether bond. In the NMR spectra there are additional absorptions in the aromatic region due to the aromatic H's of the heteroaryl moiety and a downfield shift of the aromatic H's ortho to the aryloxy group from 6.96 to 7.37 ppm.

As seen in Table 2, the cyclic dehydration of the diacyl-hydrazines to their corresponding 2,5-disubstituted -1,3,4-oxadiazoles was unsuccessful using the standard conditions.¹-³ The product of these reactions was the 2-[4'-hydroxyphenyl]-5-(2',4'-dichlorophenyl)-1,3,4-oxadiazole, which indicates that the heteroaryloxy moiety is not stable to acid and undergoes rapid hydrolysis. Attempts have been made to react this hydroxyphenyl oxadiazole under the conditions of the heteroaryloxybenzoyl hydrazine synthesis, however the proper heteroaryloxyphenyl oxadiazoles were never isolated. The lack of reactivity of these phenoxides generated from the byproduct hydroxyoxadiazole (Table 2, note a) has not been explained to date.
Suggestions for further investigation of these oxadiazoles include:

1. In attempts to synthesize the heteroarylphenyl oxadiazoles, the use of hexamethylphosphoramide (HMPA) as a solvent may be helpful since it has been reported that HMPA lowers the energy of activation of some aromatic nucleophilic substitution reactions and also increases the rate of these reactions up to 100-fold as compared to DMF as the solvent.

2. Another alteration would include the evaluation of other dehydrating agents to affect the cyclic dehydration of the diacylhydrazides.
PART II: A REINVESTIGATION OF THE REACTION OF HEXAMETHYLPHOSPHORAMIDE WITH KETOXIMES

INTRODUCTION

The use of hexamethylphosphoramide as a highly polar, aprotic solvent has been known for years. However, the use of HMPA as a reactant has only recently been investigated.\textsuperscript{7-10} The reaction of HMPA with activated halobenzenes has been reported to effect N,N-dimethylation by a nucleophilic substitution mechanism.\textsuperscript{7}

It is the intent of this research to investigate the reaction of HMPA with a variety of aryl alkyl and diaryl ketoximes. Monson and coworkers have reported\textsuperscript{11} reacting several aryl alkyl ketoximes with HMPA at 220-240°C for 10 minutes to produce the corresponding amides by a Beckmann type rearrangement.

\[
\begin{align*}
R^1 & = \text{aryl} & R^2 & = \text{alkyl} \\
\text{N} & \text{H} & \text{O} \\
\text{R}^1 & \text{N} & \text{C} & \text{R}^2 \\
220^\circ & \text{C} & 10 \text{ min} & \text{HMPA} \\
\end{align*}
\]

50-90\% yield

It was later reported in an independent project by Pedersen and coworkers\textsuperscript{12} that the reaction of HMPA with ketoximes produced mainly starting ketoxime, and small amounts of amide and amidine. He later reported\textsuperscript{13} that benzephenone oxime reacted with HMPA in the presence of polyphosphoric acid to produce the corresponding N,N-dimethyl-N-phenyl benzamide in good yields.
Due to the ambiguity of these results, it is the intent of this report to reinvestigate and clarify the nature of this important transformation. The results of this study are shown in Table 1.
PART II

EXPERIMENTAL

The Synthesis of N,N-dimethyl-N'-arylamidines

\[
\begin{align*}
\text{RCN} & \xrightarrow{\text{HMPA}} \xrightarrow{\Delta} \text{(CH}_3\text{)}_2\text{NCR}^2 \\
R^1 & \quad R^2
\end{align*}
\]

Table 3. Experimental Data for the Reaction of HMPA with Ketoximes

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
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<th>Temp (°C)</th>
<th>% Yield(^a)</th>
<th>bp or mp (°C)</th>
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<td>phenyl</td>
<td>methyl</td>
<td>2</td>
<td>225</td>
<td>46 (64)(^b)</td>
<td>72/0.2 mm</td>
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<tr>
<td>2</td>
<td>phenyl</td>
<td>methyl</td>
<td>0.2</td>
<td>230</td>
<td>0(^d)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>phenyl</td>
<td>methyl</td>
<td>1</td>
<td>130</td>
<td>(50)(^e)</td>
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<tr>
<td>4</td>
<td>phenyl</td>
<td>methyl</td>
<td>3</td>
<td>225</td>
<td>(39) (73)(^f)</td>
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<tr>
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<td>methyl</td>
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<td>235</td>
<td>54(^g)</td>
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<tr>
<td>6</td>
<td>4-bromo-phenyl</td>
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<td>52 (83)(^h)</td>
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<td>4-methoxy-phenyl</td>
<td>methyl</td>
<td>1</td>
<td>235</td>
<td>30(^i)</td>
<td>73</td>
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<tr>
<td>8</td>
<td>phenyl</td>
<td>phenyl</td>
<td>4</td>
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<td>26 (62)(^j)</td>
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<td>methyl</td>
<td>4</td>
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<tr>
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<td>ethyl</td>
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<td>230</td>
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</tbody>
</table>

\(^a\) Yields based on HMPA, \(^b\) bp at 1 atm, \(^c\) bp at 0.1 atm, \(^d\) bp at 0.2 atm, \(^e\) bp at 0.3 atm, \(^f\) bp at 0.5 atm, \(^g\) bp at 1 atm, \(^h\) bp at 0.2 atm, \(^i\) bp at 0.3 atm, \(^j\) bp at 0.5 atm, \(^k\) bp at 1 atm, \(^l\) bp at 0.2 atm, \(^m\) bp at 0.3 atm.
Table 3 -continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Time (hr)</th>
<th>Temp ($^{\circ}C$)</th>
<th>% Yield$^a$</th>
<th>bp or mp ($^{\circ}C$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>n-hexyl</td>
<td>methyl</td>
<td>2</td>
<td>230</td>
<td>$0^n$</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>n-propyl</td>
<td>methyl</td>
<td>4</td>
<td>220</td>
<td>$0^o$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$The yields in parentheses are crude yields. The yields not in parentheses are distilled or recrystallized yields. All trials which gave positive results were subjected to thin layer chromatography on Silica Gel 7GF with chloroform as the eluant. Under these conditions the purified products were found to be greater than 90% pure ($R_f$ values between 0.2 and 0.8).

$^b$N,N-dimethyl-N'-phenylacetamidine; NMR (CDCl$_3$) $\delta$ 1.80 (s, 3H), 2.98 (s, 6H) and 6.62-7.44 (m, 5H); IR (thin film) 1620, 1600, 1400, 1300, 1200, 1010, 790, 730 and 700 cm$^{-1}$; mass spectrum m/e 162 (M$^+$).

$^c$The crude product was analyzed by NMR, IR and TLC and was found to contain a mixture of N,N-dimethyl-N'-phenylacetamidine and acetonilide based on comparison with authentic samples.

$^d$This reaction was a repeat of Entry 1 with the exception that 3 ml of H$_2$O were added to the reaction mixture. The reflux temperature never exceeded 130°C and only the starting oxime was isolated.

$^e$This reaction was a repeat of an experiment reported by Pedersen$^7$ in which benzophenone oxime (0.05 mol) was treated with HMPA (0.1 mol) and polyphosphoric acid (0.025 mol).
fN,N-dimethyl-N′-4-methyl-phenylacetamidine; NMR (CDCl₃) δ 1.83 (s, 3H), 2.28 (s, 3H), 3.00 (s, 6H), 6.65 (d, J=8Hz, 2H) and 7.10 (d, J=8Hz, 2H); IR (thin film) 1610, 1390, 1300, 1190, 1000, 850, 840 and 750 cm⁻¹; mass spectrum m/e 176 (M⁺).

gN,N-dimethyl-N′-4-bromo-phenylacetamidine; NMR (CDCl₃) δ 1.82 (s, 3H), 3.00 (s, 6H), 6.61 (d, J=8Hz, 2H) and 7.43 (d, J=8Hz, 2H); IR (thin film) 1630, 1600, 1490, 1400, 1300, 1200, 1080, 1030, 1000, 840 and 760 cm⁻¹; mass spectrum m/e 242, 240 (M⁺).

hN,N-dimethyl-N′-4-methoxy-phenylacetamidine; NMR (CDCl₃) δ 1.82 (s, 3H), 3.02 (s, 6H), 3.78 (s, 3H), 6.66 (d, J=8Hz, 2H) and 6.90 (d, J=8Hz, 2H); IR (thin film) 1610, 1530, 1400, 1230, 1020, 850 and 750 cm⁻¹; mass spectrum m/e 192 (M⁺).

iN,N-dimethyl-N′-phenylbenzamidine; NMR (CDCl₃) δ 2.95 (s, 6H) and 6.50-7.12 (m, 10H); IR (nujol) 1580, 1380, 1080, 780, 710 and 695 cm⁻¹; mass spectrum m/e (M⁺).

jN,N-dimethyl-N′-4-methyl-phenylpropionamidine; NMR (CDCl₃) δ 1.02 (t, J=8Hz, 3H), 2.31 (q, J=8Hz, 2H), 2.31 (s, 3H), 3.03 (s, 6H), 6.64 (d, J=8Hz, 2H) and 7.08 (d, J=8Hz, 2H); IR (thin film) 1610, 1390, 1290, 1190, 1050 and 840 cm⁻¹; mass spectrum m/e 190 (M⁺).

kN,N-dimethyl-N′-4-methoxy-phenylpropionamidine; NMR (CDCl₃) δ 1.00 (t, J=8Hz, 3H), 2.20 (q, J=8Hz, 2H), 2.99 (s, 6H), 3.73 (s, 3H), 6.63 (d, J=8Hz, 2H) and 6.83 (d, J=8Hz, 2H); IR (thin film) 1610 1510, 1400, 1240, 1190, 1000, 840 and 760 cm⁻¹; mass spectrum m/e 206 (M⁺).
Only starting material was isolated in this reaction.

In this reaction the oxime (0.016 mol), HMPA (10 ml) and polyphosphoric acid (0.0075 mol) were heated at 230°C for 2 hr and only the starting oxime was obtained.

This reaction was a repeat of Entry 12 except that the reaction was carried out in a Paar pressure vessel.

Entries 11 through 14 were provided by R. Leonard.

The following procedure is typical of the experimental conditions used in the conversion of the ketoximes to the corresponding N,N-dimethylamidines.

N,N-dimethyl-N'-phenylacetamidine

A round-bottomed flask was equipped with a magnetic stirrer, and condenser and placed under a nitrogen atmosphere. HMPA (50 ml) was placed in the flask and acetophenone ketoxime (6.0 g, 0.044 mol) was added in one portion. The mixture was heated at 225°C for 2 hr and cooled to room temperature. The resulting dark brown mixture was poured into 100 ml of water and extracted with ether (3 x 50 ml). The combined ether extracts were extracted with water (2 x 50 ml), dried with anhydrous magnesium sulfate, filtered and concentrated to give 4.6 g (64% crude yield) of a dark brown oil. This material was distilled (72-78°C/0.2 mm) to give 3.3 g (46% yield) of a yellow oil. Spectral data and other physical properties are shown in Table 3.
PART II
DISCUSSION

The first example studied was acetophenone oxime (Table 3, entry 1) which was heated in HMPA at 220-240°C for 2 hr, and yielded N,N-dimethyl-N'-phenylacetamidine in 46% distilled yield. This compound was also prepared by an independent route using aceticanilide as the starting material. The products of both reactions were identical by TLC and spectral analysis.

We subsequently repeated Manson's conditions (HMPA, 10 min, 220°C) for acetophenone oxime (Table 3, entry 2) and found the crude product to contain a mixture of aceticanilide and N,N-dimethyl-N'-phenyl-acetamidine. The confirmation of this product was done using NMR, IR and TLC of authentic samples.

In order to determine why Pedersen isolated mainly starting material from the reaction of HMPA with acetophenone oxime, the reaction was repeated except for the addition of 3 ml of water added to the reaction mixture before heating (Table 3, entry 3). The added water lowered the reflux temperature to 130°C and only starting material was isolated. We therefore have determined from this experiment that a volatile contaminant such as water present in the reaction mixture, or a reaction temperature less than 220°C may inhibit the reaction. We have also repeated Pedersen's conditions with polyphosphoric acid and HMPA with
acetophenone oxime (Table 3, entry 4) and a 50% crude yield of N,N-dimethyl-N'-phenyl acetamidine was obtained.

As seen by the remaining entries in Table 3, a number of aryl alkyl and diaryl ketoximes have been reacted with HMPA in the absence of any acid catalysis, and the yields of corresponding N,N-dimethyl amidines ranged for 30-50% upon distillation. The yields of crude products were between 60-80%. Several trials were attempted on dialkyl ketoximes (Table 3, entries 11-14) with and without acid catalysis. In all cases no amidine product was observed. We have no explanation for this lack of reactivity at this time.

Based upon our work, and that of Monson and Pedersen, the following mechanism for the reaction of aryl alkyl ketoximes with HMPA has been proposed. (See Figure 4.)
Figure 4. Proposed Mechanism for the Reaction of Aryl Alkyl Ketoximes with HMPA.
PART II

CONCLUSION

The use of hexamethylphosphoramide as a reactant is of increasing interest, as is its use as an excellent aprotic solvent. As seen in this research, it has become quite evident that aryl alkyl ketoximes can be converted to their corresponding N,N-dimethyl-N'-aryl amidines without the use of acid catalysis. Since acidic media is not necessary, the reaction appears to be suitable for acid labile groups under the conditions of this experiment.
PART II

RECOMMENDATIONS

It has been shown by the above research that N,N-dimethyl-N'-aryl amidines are easily accessible. Therefore it would be of interest to study the possible transformations of these amidine products. It would also be of great interest to study possible reactions of dialkyl analogs of HMPA with ketoximes in attempts to synthesize various N,N-dialkyl-N'-aryl amidines. A study to determine why the dialkyl ketoximes did not undergo the transformation reported in this paper could prove quite useful.
PART III: REGIOSELECTIVE FLUOROALKOXYLATION AND POLYFLUOROALKOXYLATION OF ACTIVATED DIHALOBENZENES AND DIHALOHETEROCYCLES

INTRODUCTION

The introduction of fluorine functionalities into organic compounds has become a major interest due to abundant applications as polymers, blood substitutes, and agricultural and pharmaceutical products. The majority of the synthetic routes for the formation of fluoroalkoxy compounds has involved the reaction of nucleophilic phenoxide intermediates with haloalkyl fluorides, fluoroalkenes, and fluoroalkylsulfonates. Our laboratories have developed a convenient means of introducing fluoroalkoxy groups into aromatic systems by a direct nucleophilic substitution of activated halobenzenes with a variety of fluoroalkoxides. It is the intent of this study to determine whether polyfluoroalkoxylation of dihalobenzenes is possible, and if regioselective fluoroalkoxylation can be achieved on dihalobenzenes with the same halogens or with different halogens. It is also the intent of this study to determine whether these transformations can be accomplished on dihaloheterocycles (see Table 5).

The following table delineates our study of the regioselective monofluoroalkoxylation and polyfluoroalkoxylation of activated dihalobenzenes.
PART III
EXPERIMENTAL

A. Regioselective Fluoroalkoxylation and Polyfluoroalkoxylation of Activated Dihalobenzenes and Dihaloheterocycles

![Chemical Structures]

Table 4. Reactions of NaOCH₂CF₃ with Activated Dihalobenzenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Ratio to Substrate</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CN</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>3/1</td>
<td>150°</td>
<td>HMPA</td>
<td>3</td>
<td>85b</td>
</tr>
<tr>
<td>2</td>
<td>NO₂</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>2.2/1</td>
<td>153°</td>
<td>DMF</td>
<td>3</td>
<td>63c</td>
</tr>
<tr>
<td>3</td>
<td>NO₂</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>1.1/1</td>
<td>153°</td>
<td>DMF</td>
<td>2</td>
<td>45d</td>
</tr>
<tr>
<td>4</td>
<td>CN</td>
<td>2-Cl</td>
<td>6-Cl</td>
<td>2/1</td>
<td>153°</td>
<td>DMF</td>
<td>3</td>
<td>54e</td>
</tr>
<tr>
<td>5</td>
<td>CN</td>
<td>2-Cl</td>
<td>6-Cl</td>
<td>1.1/1</td>
<td>153°</td>
<td>DMF</td>
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<td>97f</td>
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<td>90°</td>
<td>DMF</td>
<td>2</td>
<td>77g</td>
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<tr>
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<td>NO₂</td>
<td>4-Cl</td>
<td>3-Cl</td>
<td>1.1/1</td>
<td>153°</td>
<td>DMF</td>
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<td>58h</td>
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<td>4-Cl</td>
<td>3-Cl</td>
<td>2.2/1</td>
<td>153°</td>
<td>DMF</td>
<td>2</td>
<td>65i</td>
</tr>
<tr>
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<td>3-Cl</td>
<td>1.1/1</td>
<td>150°</td>
<td>HMPA</td>
<td>2</td>
<td>63j</td>
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<tr>
<td>10</td>
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<td>3-Cl</td>
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<td>2</td>
<td>56k</td>
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<td>2-Cl</td>
<td>3-Cl</td>
<td>3.5/1</td>
<td>153°</td>
<td>DMF</td>
<td>3</td>
<td>31l</td>
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Table 4 - continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Ratio NaOCH$_2$CF$_3$ to substrate (temp. °C)</th>
<th>Solvent</th>
<th>Product (%)</th>
<th>Yield$^a$</th>
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<tr>
<td>12</td>
<td>NO$_2$</td>
<td>2-Cl</td>
<td>5-Cl</td>
<td>1.1/1 25°</td>
<td>DMF</td>
<td>2</td>
<td>52$^m$</td>
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<tr>
<td>13</td>
<td>NO$_2$</td>
<td>2-Cl</td>
<td>5-Cl</td>
<td>2.2/1 150°</td>
<td>HMPA</td>
<td>--</td>
<td>--n</td>
</tr>
<tr>
<td>14</td>
<td>CN</td>
<td>3-Cl</td>
<td>5-Cl</td>
<td>1.1/1 150°</td>
<td>HMPA</td>
<td>2</td>
<td>46$^o$</td>
</tr>
<tr>
<td>15</td>
<td>CN</td>
<td>3-Cl</td>
<td>5-Cl</td>
<td>2.2/1 150°</td>
<td>HMPA</td>
<td>2</td>
<td>28$^p$</td>
</tr>
</tbody>
</table>

$^a$The yields reported refer to distilled or recrystallized products. All trials were subjected to thin layer chromatography on silica gel 7GF with chloroform, or chloroform/ethyl acetate elutants. Under these conditions, the purified products were found to be greater than 90% pure. ($R_f$ values 0.2-0.8).

$^b$2,4-Di-2',2',2'-trifluoroethoxybenzonitrile; mp 109-110°C (recrystallized from iPrOH/H$_2$O); NMR (CDCL$_3$/Me$_2$SO-d$_6$) $\delta$ 4.70 (q, J=8Hz, 2H), 4.78 (q, J=8Hz, 2H), 6.83 (d of d, J=8Hz, J=2Hz, 1H), 7.04 (d, J=8Hz, 1H), and 7.64 (d, J=8Hz, 1H); IR (nujol) 2240, 1620, 1285, 1180, 1070, 860, 845, 830 and 750 cm$^{-1}$; mass spectrum m/e 299 (M$^+$).

$^c$2,4-Di-2',2',2'-trifluoroethoxynitrobenzene; mp 110-113°C (recrystallized from iPrOH/H$_2$O); NMR (CDCL$_3$/acetone-d$_6$) $\delta$ 4.70 (q, J=8Hz, 2H), 4.74 (q, J=8Hz, 2H), 6.88 (d of d, J=8Hz, J=2Hz, 1H), 7.03 (d, J=2Hz, 1H) and 8.06 (d, J=8Hz, 1H); IR (nujol) 1620, 1520, 1365, 1280, 1185, 970, 860, 840, 815 and 750 cm$^{-1}$; mass spectrum m/e 319 (M$^+$).

$^d$4-Chloro-2-2',2',2'-trifluoroethoxybenzonitrile; bp 68-72°C 0.3 mmHg, NMR spectra indicate a mixture of monofluoroethoxy-chloro-
nitrobenzenes; inspection of the integration shows approximately 70% ortho product and 30% 4-2′,2′,2′-trifluoroethoxy-2-chloronitrobenzene para product. NMR (CDCl₃) δ 4.58 (m, 2H), 7.10-7.40 (m, 2H), 7.98 (m, 1H); IR (solution cells, CHCl₃) 1650, 1580, 1530, 1485, 1350, 1295, 1250, 1175, 1080, 975, 920 and 840 cm⁻¹.

e2,6-Di-2′,2′,2′-trifluoroethoxybenzonitrile; mp 86-90°C (recrystallized from iPrOH/H₂O); NMR (CDCl₃) δ 4.53 (q, J=8Hz, 4H), 6.88 (d, J=8Hz, 2H) and 7.63 (t, J=8Hz, 1H); IR (CHCl₃) 2240, 1600, 1590, 1290, 1260, 1240, 1170, 1130, 715 and 685 cm⁻¹; mass spectrum m/e 299 (M⁺).

fThe product isolated by this reaction was of higher purity, by thin layer chromatography, and had the same Rₚ value as entry 6. The spectral data was identical to entry 6, however the yield was much higher and the melting point was 92-93°C.

g2-Chloro-6-2′,2′,2′-trifluoroethoxybenzonitrile; mp 110-113°C, (recrystallized from iPrOH/H₂O); NMR (CDCl₃) δ 4.35 (d, J=8Hz, 2H), 6.96 (d of d, J=0.5Hz, J=8Hz, 1H), 7.19 (d of d, J=0.5Hz, J=8Hz, 1H), 7.55 (t, J=8Hz, 1H); IR (nujol mull) 2235, 1590, 1580, 1470, 1270, 1170, 1075, 970, 900, 860, 780 and 710 cm⁻¹; mass spectrum m/e 237 (M⁺).

h3-Chloro-4-2′,2′,2′-trifluoroethoxynitrobenzene; bp 77-78°C (0.4 mm); mp 48-49°C; NMR (CDCl₃) δ 4.58 (q, J=8Hz, 2H), 7.10 (d, J=8Hz, 1H), 8.30 (d of d, J=8Hz, J=2Hz, 1H) and 8.40 (d, J=2Hz, 1H); IR (CCl₄) 1590, 1525, 1490, 1345, 1290, 1250, 1170, 1075, 970, 900 and 860 cm⁻¹; mass spectrum m/e 257, 255 (M⁺).
i3-Chloro-4-2,2',2'-tribluoroethoxynitrobenzene; inspection by NMR shows this product is identical to entry 7. This result shows that only monofluoroalkoxylation can be attained under these conditions.

j3-Chloro-4-2',2',2'-trifluoroethoxybenzonitrile; mp 74-75°C (recrystallized from MeOH/H₂O); NMR (CDCl₃) δ 4.52 (q, J=8Hz, 2H), 7.08 (d, J=8Hz, 2H) and 7.48-7.90 (m, 2H); IR (nujol) 2230, 1595, 1495, 1310, 1295, 1255, 1180, 1085, 975, 900, 860 and 810 cm⁻¹; mass spectrum m/e 237 (M⁺).

k3-Chloro-2-2',2',2'-trifluoroethoxynitrobenzene; bp 60-62°C, 0.2 mm Hg; NMR (CDCl₃) δ 4.55 (q, J=8Hz, 2H), 7.18 (t, J=8Hz, 1H), 7.52-7.90 (m, 2H); IR (neat) 1595, 1530, 1460, 1360, 1290, 1250, 1160, 1080, 1040, 965, 870, 810, 760, 740 and 680 cm⁻¹.

l2,3-Di-(2',2',2'-trifluoroethoxynitrobenzene; bp 60°C, 0.1 mm Hg, NMR (CDCl₃) δ 4.40 (q, J=8Hz, 4H), 6.80-7.30 (m, 3H); IR (neat) 1585, 1480, 1450, 1285, 1260, 1230, 1165, 1080, 995, 965, 770 and 735 cm⁻¹.

m5-Chloro-2-2',2',2'-trifluoroethoxynitrobenzene; bp 60-65°C, 0.3 mm Hg NMR (CDCl₃) δ 4.52 (q, J=8Hz), 7.20 (d, J=8Hz, 1H), 7.63 (d of d, J=2Hz, J=8Hz, 1H), 7.98 (d, J=2Hz, 1H); IR (CDCl₃ solution cells), 1610, 1535, 1490, 1350, 1290, 1260, 1170, 890 and 810 cm⁻¹.

nThe polytrifluoroethoxylation of 2,5-dichloronitrobenzene was attempted at 150°C using HMPA and DMF as solvents. In both cases the crude products and distilled products were not pure enough to determine their structure. No explanation for this is known at this time.
3-Chloro-5-2',2',2'-trifluoroethoxybenzonitrile; bp 62-65°C, 0.2 mmHg, NMR (CDCl₃) δ 4.52 (q, J=8Hz, 2H), 7.20-7.60 (m, 3H); IR (nujol mull) 3080, 2250, 1740, 1590, 1450, 1430, 1320, 1290, 1260, 1165, 1100, 1080, 970, 860, 810, 745, 695 and 670 cm⁻¹.

The polytrifluoroethoxylation of 3,5-dichlorobenzonitrile was attempted and upon distillation the only product isolated was the monofluoroalkoxylated product which was identical by NMR and TLC to entry 14.

The following procedure is typical of the experimental conditions used for the preparation of monofluoroalkoxylated and polyfluoroalkoxylated benzenes.

3-Chloro-4-2',2',2'-trifluoroethoxy nitrobenzene

A dry, three-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser, thermometer, and rubber septum, and was placed under a nitrogen atmosphere. Into the flask was placed 1.37 g (0.0286 mol) of a 50% by weight NaH-mineral oil mixture which was subsequently washed with hexane. To the sodium hydride was added 125 ml of DMF (dried over 4Å molecular sieves) and 2.86 g (0.0286 mol) of 2,2,2-trifluoroethanol, respectively. The mixture was allowed to stir for 20 minutes and 5.00 g (0.0260 mol) of 3,4-dichloronitrobenzene was added in one portion. The resulting mixture was heated at reflux (150°C) for 18 hours, cooled to room temperature and the solvent was removed in vacuo by Kugelrohr distillation. The residue was carefully diluted with 100 ml of ice water, extracted with ether
and dried over anhydrous magnesium sulfate. After removing the drying agent, the organic phase was concentrated in vacuo to yield 5.30 g of a dark liquid. This material was Kugelrohr distilled to give 3.25 g (58%) of a solid (bp 77-78°C at 0.4 mm Hg and a mp of 48-49°C). For spectral data and physical properties see Table 4 footnotes.

This procedure is for a monofluoroalkoxylation. See Table 4 for alterations in solvent, temperature, reactant ratios and products for polyfluoroalkoxylations.

In order to determine the structural assignments without ambiguity for the monofluoroalkoxylated halobenzonitriles and nitrobenzenes, the following catalytic hydrogenolysis reactions have been carried out. 19

\[
\begin{align*}
\begin{array}{c}
\text{C}_6\text{H}_5\text{Cl} & \text{OCH}_2\text{CF}_3 \\
9p & \text{X}=\text{CN}
\end{array} \\
\begin{array}{c}
\text{C}_6\text{H}_4\text{Me} & \text{OCH}_2\text{CF}_3 \\
7p & \text{X}=\text{NO}_2
\end{array}
\end{align*}
\]

\[
\text{H}_2/\text{Pd on C} \\
\text{MeOH} \\
\text{NaOAc}
\]

\[
\begin{align*}
\begin{array}{c}
\text{C}_6\text{H}_5\text{H} & \text{OCH}_2\text{CF}_3 \\
9a & \text{Y}=\text{CN}
\end{array} \\
\begin{array}{c}
\text{C}_6\text{H}_4\text{Me} & \text{OCH}_2\text{CF}_3 \\
7b & \text{Y}=\text{NH}_2
\end{array}
\end{align*}
\]

Compound 9a had previously been prepared 18,20 by the reaction of 4-chlorobenzonitrile with sodium trifluoroethoxide. Compound 9a which was obtained by the catalytic hydrogenolysis of the product on entry 9 in Table 4, had identical spectral properties.
Although compound 7b had not been prepared previously, 4-2',2',2'-trifluoroethoxynitrobenzene had been prepared and was reduced with H2/Pd on carbon in methanol to give a compound which was identical to 7b by NMR and TLC behavior. These catalytic hydrogenolysis reactions substantiate the regiochemical assignments of the 3-chloro-4-trifluoroethoxy products.

B. Reactions of NaOCH2CF3 with Dihaloheterocycles

\[
\text{X} - \text{R} - \text{X} \xrightarrow{\text{NaOCH}_2\text{CF}_3} \text{X} - \text{R} - \text{OCH}_2\text{CF}_3 \quad \text{or} \quad \text{R} - (\text{OCH}_2\text{CF}_3)_2
\]

R=pyrimidine, pyridazine
X=Cl

Table 5. Reactions of NaOCH2CF3 with Dihaloheterocycles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ratio NaOCH2CF3</th>
<th>Temp (°C)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,6-dichloropyridazine</td>
<td>1.1/1a</td>
<td>-5</td>
<td>2-(2',2',2'-trifluoroethoxy)-6-pyridazine</td>
</tr>
<tr>
<td>2</td>
<td>2,6-dichloropyridazine</td>
<td>2.2/1b</td>
<td>153</td>
<td>2,6-bis(2',2',2'-trifluoroethoxy) pyridazine</td>
</tr>
<tr>
<td>3</td>
<td>2,4-dichloropyrimidine</td>
<td>2.2/1c</td>
<td>-5</td>
<td>2,4-bis(2',2',2'-trifluoroethoxy) pyrimidine</td>
</tr>
</tbody>
</table>

aSee experimental procedure for spectral data.
b2,6-Bis(2',2',2'-trifluoroethoxy)pyridazine; mp 78-83 C, yield 57.1%; NMR (d6-DMSO, CDCl3) δ 4.92 (q, J=8Hz, 2H), 7.16 (s, 2H); IR (nujol
C₂₅,₄-Bis(2,₂,₂-trifluoroethoxy)pyrimidine; bp 58°C, 0.3 mm Hg, yield 54%. NMR (CDCl₃) δ 4.82 (q, J=8Hz, 4H), 6.61 (d, J=6Hz, 1H), 8.38 (d, J=6Hz, 1H); IR (neat), 2960, 1590, 1470, 1450, 1420, 1350, 1270, 1170, 1110, 1060, 990, 960, 850, 790 and 670 cm⁻¹.

The following procedure is typical of the experimental conditions used for the preparation of monofluoroalkoxylated and polyfluoroalkoxylated heterocycles.

2-(2',2',2'-Trifluoroethoxy)-6-chloropyridazine

A dry, three-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser and thermometer, and charged with 0.886 g (0.0184 mol) NaH-mineral oil, 50% by weight solid dispersion. The mineral oil was removed by washing with hexane which was removed by syringe. To the washed NaH was added 50 ml of dry N,N-dimethylformamide. After 20 minutes of stirring, 1.84 g (0.0184 mol) of 2,2,2-trifluoroethanol was added dropwise and the mixture was allowed to stir until gas evolution had ceased. The mixture was then cooled in a saturated NaCl ice bath to -5°C. To this mixture was added in one portion 2.50 g (0.0168 mol) 2,6-dichloropyridazine and the resulting mixture was stirred at -5°C for 2 hours. The mixture was allowed to warm to room temperature and the DMF was distilled on the Kugelrohr apparatus. The residue was taken up in 100 ml of water and extracted with diethyl ether (3 x 60 ml). The combined extracts were washed with water (2 x 25 ml). The ether
phase was dried over MgSO₄ and filtered. The ether was removed in vacuo on the rotary evaporator to yield 3.04 g of a yellow liquid which was distilled at 62-65°C and 0.3 mmHg to yield 2.2 g (62%) product. NMR δ 4.96 (q, J=8Hz, 2H), 7.16 (d, J=8Hz, 1H), 7.60 (d, J=8Hz, 1H); IR (nujol mull) 3030, 1580, 1420, 1250, 1150, 1050, 960, 860, 840 and 720 cm⁻¹.
PART III

DISCUSSION OF RESULTS

As shown in Table 4 (entries 1, 2, 4 and 11) monoactivated (CN or NO₂) 2,3, 2,4, and 2,6-dichlorobenzenes undergo smooth polyfluoroalkoxylation to their corresponding difluoroalkoxylated products. The 3,4-dichloronitrobenzene polyfluoroalkoxylation attempt only yielded the monosubstituted product, with substitution occurring at the 4-Cl position, para to the activating group (entry 8). The 3,5-dichlorobenzonitrile polysubstitution attempt yielded only the monosubstituted product (entry 15). The 2,5-dichloronitrobenzene attempt (entry 13) yielded upon distillation a mixture of products with the polysubstitution product present to an extent of 50%, as determined by gas chromatographic analysis of the distilled material.

In entries 5, 7, 9, 10, 12 and 14, clean regioselective monofluoroalkoxylation of the monoactivated (CN or NO₂) 2,6, 3,4, 2,3, 2,5, and 3,5-dichlorobenzenes was accomplished under the specified experimental alterations (see Table 4 for temperature, solvent and molar ratios of reactants). The 2,4-dichloronitrobenzene monofluoroalkoxylation attempt (entry 3) yielded a mixture of 2-fluoroalkoxylated and 4-fluoroalkoxylated products in a 70 to 30% ratio, respectively. When two different halogens are present such as 2-chloro-6-fluorobenzonitrile, substitution occurs at the fluorine position (entry 6). This entry confirms our assumptions that the mechanism
for this substitution reaction is an SnAr mechanism. Fluoro is generally the poorest leaving group of the halogens when the second step of the SnAr mechanism is rate determining, or if the reaction follows the benzyne mechanism. Since the fluoro group is the leaving group, the first step is rate determining.

As shown in Table 5 (entries 2 and 3) dichloropyridazines and dichloropyrimidines may be polyfluoroalkoxylated if the halogens are ortho to the nitrogen. In the case of 2,4-dichloropyrimidine, it is necessary to keep the reaction temperature at a minimum to avoid dimethylaminated byproducts which may form from reaction with the solvent DMF. Ortho chloro heteroaromatics seem to be highly activated towards nucleophilic substitution with trifluoroethoxide as seen by the -5°C reaction temperature.

Table 5, entry 1 indicates that monofluoroalkoxylation of dihalopyridazines can be accomplished if the positions of possible substitution are equivalent. Monofluoroalkoxylation of 2,4-dichloropyrimidine attempts produced a mixture of both monofluoroalkoxylated and polyfluoroalkoxylated products even at -5°C reaction temperatures. Selectivity in this case seems unlikely.
PART III
CONCLUSIONS

In conclusion, it has been shown that the fluoroalkoxylation of activated dihalobenzenes and dihaloheteroaromatics with sodium trifluoroethoxide in a polar aprotic solvent can be regioselective in most instances. Polyfluoroalkoxylation can also be performed in many instances. This research has advanced the understanding of the scope of these trifluoroethoxylations and has opened new possibilities for the incorporation of fluorine into organic compounds.
PART III
RECOMMENDATIONS

Further research in the area of fluoroalkoxylation is now under investigation by Dr. Gupton and coworkers. Some of the areas being investigated include the incorporation of various fluoroalkoxide intermediates into aromatic and haloaromatic systems. It would also be of interest to determine the largest possible number of fluoroalkoxy groups that can be substituted into an aromatic substrate. Since HMPA is a relatively expensive solvent for large scale reactions of this type, the evaluation of alternative solvents would also be of considerable interest.
REFERENCES


