
Fall 1983

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PART I: THE SYNTHESIS OF NEW POTENTIAL INSECTICIDES
PART II: NEW AROMATIC NUCLEOPHILIC SUBSTITUTION
REACTIONS, FLUOROALKOXYLATION AND N,N-DIMETHYLAMINATION

BY

CESAR COLON

B.S., University of Puerto Rico, 1978
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

Fall Term
1983
ABSTRACT

A series of routes are described for the synthesis of new potential insecticides which are symmetrical or asymmetrical similogs of 2,5-Bis(dichlorophenyl)-1,3,4-oxadiazole and its precursor diacyl hydrazine.

Also two new aromatic nucleophilic substitution reactions are discussed. Activated aryl halides are reacted with fluorinated alkoxide anions. In all cases, substitution of the halogen by a fluoroalkoxy group was observed, and activated aryl halides are reacted with HMPA as an N,N-dimethyl aminating agent. In all cases, substitution of the halogen by a dimethyl amino group was observed. The effect of the activating group and the leaving group is described and a possible mechanism is proposed.

All compounds synthesized are characterized and identified by NMR, IR and/or mass spectroscopy.
ACKNOWLEDGEMENTS

First of all, I would like to thank the faculty and staff of the Department of Chemistry for their help and friendliness during my studies at UCF. Special thanks go to Dr. John Idoux and Dr. Guy Mattson as members of my research committee. Most of all, my thanks to Dr. John Gupton III for his encouragement and patience with me during both my undergraduate and graduate studies.

I also thank my family and my wife for their faith and support during my college studies. Finally, and most important, I thank God and the Virgin Mary for being at my side.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>angstroms</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>°C</td>
<td>degrees centigrade</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wave numbers (IR spectrum)</td>
</tr>
<tr>
<td>δ</td>
<td>delta (NMR spectrum)</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
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<td>Δ</td>
<td>heat</td>
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<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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</tr>
<tr>
<td>hr</td>
<td>hours</td>
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<tr>
<td>Hz</td>
<td>Hertz (cycles per second, NMR spectrum)</td>
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<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR spectrum)</td>
</tr>
<tr>
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<tr>
<td>M⁺</td>
<td>molecular ion (mass spectrum)</td>
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<tr>
<td>m/e</td>
<td>mass to charge ratio (mass spectrum)</td>
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<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>------------</td>
</tr>
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<td>min</td>
<td>minutes</td>
</tr>
<tr>
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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>N</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<td>-log [H⁺]</td>
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</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
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<td>THF</td>
<td>tetrahydrofuran</td>
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PART I
SYNTHESIS OF NEW POTENTIAL INSECTICIDES
PART I

I. INTRODUCTION

In the United States approximately 600 species of insects are significant pests that attack people, domestic animals, transmit disease, destroy structures and compete for available supplies of food and fiber. Insects constitute 70% of all animal species, 1% of which are considered significant pests. The estimated total annual loss to agriculture in the United States is 10% of production, with worldwide losses approximately 14%.

For the last two years our research group has been involved in the synthesis and evaluation of similogs of 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole (DOWCO 416) (1),

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{Cl}
\end{array}
\]

(1) DOWCO 416

and its precursor diacylhydrazine (2).

\[
\begin{array}{c}
\text{Cl} \\
\text{C} \text{-NH-NH-C}
\end{array}
\]

(2)
Both (1) and (2) have been disclosed as new insecticides in a 1980 patent issued to Dow Chemical Company. DOWCO 416 was found to be an effective larvacide toward manure-breeding insects such as houseflies, faceflies and hornflies.

Solubility problems made DOWCO 416 commercially unattractive. However, it was found to have significant biological activity to warrant further investigation of similogs of DOWCO 416 which might show similar or enhanced biological activity and possess favorable solubility characteristics (mainly increased lipophilic character).

Besides DOWCO 416, a number of other 2,5-disubstituted -1,3,4-oxadiazoles have also been found by Dow Chemical to be effective for controlling manure-breeding insects and correspond to the following formula:

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

where Ar represents 2-chlorophenyl, 4-fluorophenyl, 4-(trichloromethyl)phenyl, 4-methyl phenyl, 4-cyanophenyl, or 3,5-dichlorophenyl. It was also found that, in general, the oxadiazole and 2,4-dichloro moieties are required in order to observe significant biological activity.

Because of the nature of the compounds which are proposed in this investigation, a series of different synthetic routes
Figure 1. Proposed synthetic scheme for the preparation of DOWCO 416 similogs.
will have to be undertaken in order to prepare the DOWCO 416 similogs. The main synthetic scheme to be employed is depicted in Figure 1. This scheme is similar to those previously reported\textsuperscript{2,3,4}.

Fluorinated alkoxy groups will be introduced into the general synthetic scheme by hydration of a fluorinated alkoxy benzonitrile with base and then by acylating hydrazine hydrate\textsuperscript{5} (Figure 2).

Figure 2. Proposed synthetic scheme for the preparation of trifluoroalkylated hydrazides.
The preparation of the trifluoroalkoxy benzonitrile has been reported by Gupton and coworkers\textsuperscript{34,36}, and will be discussed in greater detail in Part II of this report.

A series of DOWCO 416 similogs will also be prepared from the diacetylhydrazines resulting from the reaction of various monoacylhydrazines with substituted phenylisocyanates (Figure 3).

\[
R^2\text-N=C=O + R^1\text-C\text-NH\text-NH}_2 \xrightarrow{\text{THF}} R^2\text-N\text-C\text-N\text-N\text-C\text-R^1
\]

Figure 3. Proposed synthetic scheme for the preparation of substituted phenyl isocyanate diacetylhydrazines.

The precursor diacetylhydrazine of this series will be of particular interest due to the similarity to the following two insecticides:

DU 19111

and

Demilin
These compounds are suspected to act by blocking the synthesis of chitin\textsuperscript{7}, a structural polysaccharide found in the exoskeletons of insects\textsuperscript{7,8}, and in the walls of fungi\textsuperscript{7,9}. Chitin is absent in mammals, consequently agents which affect chitin metabolism might be selectively toxic to insects and/or fungi.

As mentioned earlier, the 2,4-dichlorophenyl and oxadiazole moieties are thought to be necessary for the activity of the DOWCO 416 similogs. It should be noted that DOWCO 416 is a symmetrical oxadiazole. Considering that the symmetry of the molecule could have some influence on the biological activity, a series of symmetrical oxadiazoles will be synthesized by reacting the corresponding carboxylic acid with hydrazine hydrate and polyphosphoric acid (Figure 4).

$$2 \quad R^2\text{-COH} + \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \xrightarrow{\Delta\text{PPA}} R^2\text{-CON}N\text{-CON}R^2$$

Figure 4. Proposed synthetic scheme for the preparation of symmetrical oxadiazoles.

For the above reasons, and in the interest of achieving low toxicity in mammals and enhanced degradation of insecticides in the environment, this investigator proposes to synthesize and characterize similogs of DOWCO 416 and their precursor diacylhydrazines.
Characterization and identification of all of the compounds synthesized will be achieved through NMR and IR spectroscopy. The diacylhydrazides and oxadiazoles prepared as potential pesticides will be sent to the biochemistry laboratory at the University of Central Florida and to the Agricultural Research Department of Dow Chemical Company for biological studies.
PART II

II. EXPERIMENTAL

A. Preparation of Substituted Methyl Benzoates

\[ \text{X-C-OH} \xrightarrow{\text{NaOH/H}_2\text{O}} \text{ CH}_3\text{I} \xrightarrow{\text{HMPA}} \text{X-C-OCH}_3 + \text{Na}^+\text{I}^- \]

Table I

Experimental data for the preparation of substituted methyl benzoates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4-dichlorophenyl</td>
<td>95&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>3-methylphenyl</td>
<td>97&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>NMR (CDCl<sub>3</sub>) δ 3.86 (s, 3H), 7.23 (d of d, J=8 Hz, J=2 Hz, 1H), 7.41 (d, J=2 Hz, 1H), 7.77 (d, J=8 Hz, 1H); IR (thin film) 3010, 2955, 1735, 1590, 1560, 1475, 1437, 1377, 840 and 770 cm<sup>-1</sup>.

<sup>b</sup>NMR (CDCl<sub>3</sub>) δ 2.32 (s, 3H), 3.85 (s, 3H), 7.21-7.35 (m, 3H), 7.70-8.00 (m, 2H); IR (thin film) 3015, 2945, 1720, 1600, 1585, 1435, 1280, 780, 740 and 690 cm<sup>-1</sup>.
Methyl-2,4-dichlorobenzoate

To a 250 ml Erlenmeyer flask was added 16.0 g (0.084 mol) of 2,4-dichlorobenzoic acid and 100 ml of HMPA. To this mixture was added 6.79 g (0.17 mol) of sodium hydroxide (25% aqueous solution, by weight) while stirring. The resulting mixture was stirred at room temperature for 4 hr, after which 10 ml of water and 47.5 g (0.33 mol) of methyl iodide were added. The flask was then covered with Parafilm and the reaction mixture was stirred at room temperature for 3 days. This mixture was poured into 150 ml of 5% aqueous hydrochloric acid and extracted with ethyl ether (3 x 75 ml). The combined ether extracts were washed with saturated sodium bicarbonate (75 ml) and water (3 x 75 ml). The ether extracts were dried over anhydrous magnesium sulfate. The drying agent was removed and the filtrate was concentrated in vacuo to leave 15.5 g (90% yield) of a brown liquid.

B. Preparation of Substituted Hydrazides

\[
\begin{align*}
X-C-O-Y + Z & \xrightarrow{\text{MeOH reflux}} X-C-NH-NH_2 + \text{MeOH} \\
\end{align*}
\]
Table II
Experimental Data for the Preparation of Substituted Hydrazides

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t (hr)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4-dichlorophenyl</td>
<td>methyl</td>
<td>NH₂NH₂·H₂O</td>
<td>72</td>
<td>92ᵃ</td>
</tr>
<tr>
<td>2</td>
<td>2-methylphenyl</td>
<td>methyl</td>
<td>NH₂NH₂</td>
<td>20</td>
<td>80ᵇ</td>
</tr>
<tr>
<td>3</td>
<td>3-methylphenyl</td>
<td>methyl</td>
<td>NH₂NH₂</td>
<td>15</td>
<td>88ᶜ</td>
</tr>
<tr>
<td>4</td>
<td>2-pyridyl</td>
<td>ethyl</td>
<td>NH₂NH₂·H₂O</td>
<td>18</td>
<td>99ᵈ</td>
</tr>
</tbody>
</table>

ᵃNMR (d⁶ DMSO) δ 4.58 (broad s, 2H), 7.50-7.82 (m, 3H), 9.80 (broad s, 1H); IR (nujol mull) 3330, 3280, 3230, 1665, 1640, 1600, 1520, 870, 840 and 655 cm⁻¹.

ᵇNMR (CDCl₃) δ 2.35 (s, 3H), 3.99 (broad s, 2H), 7.11-7.35 (m, 4H); IR (CHCl₃) 3430, 3320, 1660, 1620, 1490, 1465, 1377, 785, 700 and 655 cm⁻¹.

ᶜNo solvent was used in this reaction. NMR (CDCl₃) δ 2.35 (s, 3H), 4.26 (broad s, 2H), 7.23-7.35 (m, 2H), 9.68 (broad s, 1H); IR (CHCl₃) 3440, 3320, 2980, 2915, 1660, 1620, 1580, 1365, 950, 880 and 660 cm⁻¹.

ᵈNo precipitate formed after this reaction was completed. Therefore, 30 ml of THF was added to the flask. This mixture was left overnight and then concentrated in vacuo yielding a solid.
NMR (CDCl$_3$) δ 4.27 (broad s, 2H), 7.22-7.57 (m, 1H), 7.84 (t of d, J=8 Hz, J=2 Hz, 1H), 8.25 (d of d, J=8 Hz, J=2 Hz, 1H), 8.57-8.68 (d of d, J=6 Hz, J=2 Hz, 1H); IR (nujol mull) 3300, 3210, 1675, 1940, 1590, 1575, 1550, 755, 650 and 630 cm$^{-1}$.

2,4-Dichlorobenzhydrazide

A 250 ml, three-necked, round-bottomed flask was equipped with a thermometer, a thermometer adaptor, reflux condenser, 100 ml addition funnel and a stirring bar. To the flask was added 22.5 g (0.45 mol) of hydrazine hydrate and 80 ml of absolute methanol. While stirring the reaction mixture 15.5 g (0.075 mol) of methyl-2,4-dichlorobenzoate was added dropwise from an addition funnel. The resulting mixture was refluxed for 3 days. After cooling to room temperature the methanol was stripped off in vacuo, leaving behind a solid. The solid was filtered, washed with 30 ml each of hexane, water, hexane and dried in vacuo, yielding 14.1 g (92% yield) of a white solid; mp=172-174°C.

C. Preparation of Hydrazides via Substituted Benzamides

\[
\begin{align*}
\text{CH}_3-\text{CH-} & \text{CF}_3 & \overset{10 \text{ NH}_2\text{NH}_2\cdot\text{H}_2\text{O}}{\text{90°C; overnight}} & \overset{\text{O}}{\text{C-}}\text{NH-} & \text{NH}_2 \\
\end{align*}
\]
4-(1,1,1-Trifluoroisopropoxy)benzhydrazide

A 100 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adaptor, reflux condenser and stirring bar. To the flask was added 2.0 g (0.0086 mol) of 4-(1,1,1-trifluoroisopropoxy) benzamide and 4.3 g (0.086 mol) of hydrazine hydrate, while stirring. The resulting mixture was heated overnight at 90°C. The reaction mixture was cooled to room temperature and a solid precipitate formed. The solid was filtered, washed with 10 ml each of hexane and water. Hexane was dried in vacuo yielding 2.23 g (86% yield) of a white solid. NMR (d6 DMSO/CDC13) δ 1.50 (d, J=7 Hz, 3H), 4.11 (broad s, 2H), 4.53-5.13 (hpt, J=7 Hz, 1H), 7.02 (d, J=8 Hz, 2H), 7.91 (d, J=8 Hz, 2H), 7.73-8.04 (m, 2H), 9.61 (broad s, 1H); IR (nujol mull) 3300, 1610, 1575, 1525, 1477, 1330, 1020 and 870 cm⁻¹.

D. Preparation of Aliphatic, Methylphenyl, Pyridyl and 1,1,1-Trifluoroisopropoxy Phenyl Substituted Diacylhydrazines

\[
\begin{align*}
\text{X-C-Cl} & \quad + \quad \text{Y-C-N-NH}_2 \\
\xrightarrow{\text{THF/H}_2\text{O}} & \quad \text{X-C-N-N-C-Y} \\
\text{NaHCO}_3 & \quad + \quad \text{Na}^+ \quad \text{Cl}^-
\end{align*}
\]
### Table III

Experimental Data for the Preparation of Aliphatic, Methylphenyl Pyridyl and 1,1,1-Trifluoroisopropoxy Phenyl Substituted Diacylhydrazines

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>% Yield</th>
<th>mp (°C)</th>
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<tr>
<td>1</td>
<td>propyl</td>
<td>2,4-dichlorophenyl</td>
<td>89(^a)</td>
<td>202-207</td>
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<tr>
<td>2</td>
<td>pentyl</td>
<td>2,4-dichlorophenyl</td>
<td>92(^b)</td>
<td>182-187</td>
</tr>
<tr>
<td>3</td>
<td>tertbutyl</td>
<td>2,4-dichlorophenyl</td>
<td>88(^c)</td>
<td>209-210</td>
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<tr>
<td>4</td>
<td>2,4-dichlorophenyl</td>
<td>2-methylphenyl</td>
<td>71(^d)</td>
<td>222-223</td>
</tr>
<tr>
<td>5</td>
<td>2,4-dichlorophenyl</td>
<td>3-methylphenyl</td>
<td>71(^e)</td>
<td>209-210</td>
</tr>
<tr>
<td>6</td>
<td>2,4-dichlorophenyl</td>
<td>2-pyridyl</td>
<td>92(^f)</td>
<td></td>
</tr>
<tr>
<td>7</td>
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<td>3-pyridyl</td>
<td>75(^g)</td>
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<td>4-pyridyl</td>
<td>81(^h)</td>
<td>229-231</td>
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<tr>
<td>9</td>
<td>2,4-dichlorophenyl</td>
<td>4-(1,1,1-trifluoro-isopropoxy)phenyl</td>
<td>95(^i)</td>
<td>202-204</td>
</tr>
</tbody>
</table>

\(^a\)NMR (\(d^6\) DMSO/\(CDCl_3\)) \(\delta\) 0.93 (t, \(J=8\) Hz, 3H), 1.33-1.92 (m, 2H), 2.22 (t, \(J=6\) Hz, 2H), 7.32-7.63 (m, 3H), 10.04 (broad s, 1H), 10.28 (broad s, 1H); IR (nujol mull) 3240, 3097, 3019, 1655, 1587, 1515, 870, 840, and 800 cm\(^{-1}\).

\(^b\)NMR (\(d^6\) DMSO/\(d^6\) Unisol) \(\delta\) 0.84 (t, \(J=5\) Hz, 3H), 1.09-1.70 (m, 6H), 2.03-2.34 (t, \(J=6\) Hz, 2H), 7.30-7.80 (m, 3H); IR (nujol mull) 3230, 3093, 3015, 1658, 1587, 1510, 865, 830 and 790 cm\(^{-1}\).
\[ ^c\text{NMR (d}^6\text{DMSO/d}^6\text{Unisol/CDC}_3 \delta 1.28 \text{ (s, 9H)}, 7.27-7.78 \text{ (m, 3H)}, 9.45 \text{ (broad s, 1H)}, 10.06 \text{ (broad s, 1H); IR (nujol mull) 3220, 3035, 1620, 1590, 1510, 865, 835 and 790 cm}^{-1}. \]

\[ ^d\text{NMR (d}^6\text{DMSO/CDC}_3 \delta 2.49 \text{ (s, 3H)}, 7.10-7.66 \text{ (m, 7H); IR (CHCl}_3 \text{), 3380, 3140, 1620, 1584, 1372, 860 and 840 cm}^{-1}. \]

\[ ^e\text{NMR (d}^6\text{DMSO/CDC}_3 \delta 2.36 \text{ (s, 3H)}, 7.22-7.78 \text{ (m, 7H); IR (CHCl}_3 \text{) 3390, 3163, 1626, 1575, 1370, 860 and 830 cm}^{-1}. \]

\[ ^f\text{NMR (d}^6\text{DMSO/CDC}_3 \delta 7.30-7.75 \text{ (m, 4H)}, 7.85-8.27 \text{ (m, 2H), 8.64-8.78 \text{ (m, 1H); IR (nujol mull) 3370, 3215, 1632, 1585, 1495, 860, 820, 790 and 750 cm}^{-1}. \]

\[ ^g\text{NMR (d}^6\text{DMSO/d}^6\text{Unisol) \delta 7.36-7.93 \text{ (m, 4H), 8.18-8.45 \text{ (m, 1H), 8.64-8.93 \text{ (m, 1H), 9.05-9.27 \text{ (m, 1H); IR (nujol mull) 3082, 1590, 1495, 850, 830, 790 and 740 cm}^{-1}. \}

\[ ^h\text{NMR (d}^6\text{DMSO/d}^6\text{Unisol) \delta 7.27-7.69 \text{ (m, 3H)}, 7.75-7.93 \text{ (m, 2H), 8.52-8.82 \text{ (m, 2H); IR (nujol mull) 3105, 1620, 1567, 1507, 870, 840, 790 and 760 cm}^{-1}. \]

\[ ^i\text{NMR (d}^6\text{DMSO/CDC}_3 \delta 1.46 \text{ (d, J=6 Hz, 3H), 4.63-5.17 \text{ (m, 1H), 7.03 \text{ (d, J=8 Hz, 2H), 7.21-7.72 \text{ (m, 3H), 7.79-8.13 \text{ (d, J=8 Hz, 2H); IR (nujol mull) 3240, 1640, 1250, 1175, 1025, 870, 850, 800 and 760 cm}^{-1}. \}

The following was typical of the experimental conditions used in the preparation of aliphatic, methylphenyl, pyridyl, and 1,1,1-trifluoroisopropoxy phenyl substituted diacylhydrazines.
General Procedure

A 250 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adapter, reflux condenser, 100 ml addition funnel, stirring bar and tubing leading from the condenser to a mineral oil bubbler. The flask was charged with the hydrazide (0.015 mol), sodium bicarbonate (0.015 mol) and 50 ml each of THF and water. To the resulting mixture was added the acid chloride (0.015 mol) dropwise, while stirring. The reaction mixture was stirred for 1 hr at room temperature after which 100 ml of water was added to the flask. The flask was placed over an ice-water bath to induce further crystallization. The resulting solid was filtered, washed with cold water and dried in vacuo. The product can be washed in 50 ml of a 10% aqueous hydrochloric acid solution if desired.

E. Preparation of Substituted Diacylhydrazines via Substituted Phenyl Isocyanates

\[
\begin{align*}
X-N=\overset{\text{O}}{\text{C}}=\overset{\text{O}}{\text{C}} & \quad \overset{\text{THF/H}_2\text{O}}{\rightleftharpoons} \quad H \overset{\text{O}}{\text{C}}=\overset{\text{O}}{\text{C}} & \quad X-N=\overset{\text{O}}{\text{C}}=\overset{\text{O}}{\text{C}}
\end{align*}
\]
Table IV
Experimental Data for the Preparation of Substituted Diacylhydrazines via Substituted Phenyl Isocyanates

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>% Yield</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-(trifluoromethyl)phenyl</td>
<td>2,4-dichlorophenyl</td>
<td>83</td>
<td>223-335</td>
</tr>
<tr>
<td>2</td>
<td>3-(trifluoromethyl)phenyl</td>
<td>2,4-dichlorophenyl</td>
<td>85</td>
<td>179-183</td>
</tr>
<tr>
<td>3</td>
<td>4-fluorophenyl</td>
<td>2,4-dichlorophenyl</td>
<td>98</td>
<td>224-226</td>
</tr>
<tr>
<td>4</td>
<td>4-methylphenyl</td>
<td>2,4-dichlorophenyl</td>
<td>94</td>
<td>229-231</td>
</tr>
</tbody>
</table>

\[ a \text{NMR (d}^6 \text{DMSO/CDCl}_3) \delta 6.96-7.59 \text{ (m, 6H), 7.98 (m, 2H), 9.11 (s, 1H), 10.32 (s, 1H); IR (nujol mull) 3350, 3240, 3290, 1620, 1550, 1330, 1120 and 760 cm}^{-1}. \]

\[ b \text{NMR (d}^6 \text{DMSO/CDCl}_3) \delta 7.27-7.85 \text{ (m, 6H), 8.14 (s, 1H), 8.62 (s, 1H), 9.31 (s, 1H), 10.46 (s, 1H); IR (nujol mull) 3370, 3220, 3138, 3040, 1655, 1580, 1340, 1240, 1180, 1130, 880, 830, 800 and 700 cm}^{-1}. \]

\[ c \text{NMR (d}^6 \text{DMSO/CDCl}_3) \delta 6.79-7.25 \text{ (t, J=10 Hz, 2H), 7.30-7.76 (m, 5H), 8.08-8.38 (m, 1H), 8.88 (s, 1H), 10.30 (s, 1H); IR (nujol mull) 3360, 3250, 3190, 3040, 1620, 1560, 1220, 870, 840 and 810 cm}^{-1}. \]

\[ d \text{NMR (d}^6 \text{DMSO) \delta 2.36 (s, 3H), 3.52 (s, 1H), 7.20 (d, J=8 Hz, 2H), 7.45 (d, J=8 Hz, 2H), 7.70-7.90 (m, 3H), 8.48 (broad s, 1H), 8.88 (broad s, 1H); IR (nujol mull) 3340, 3040, 1600, 1550, 1240, 870, 840 and 800 cm}^{-1}. \]
N-(4-Fluorophenylaminoformyl)-N-’-(2,4-Dichlorobenzoyl)hydrazine

A 250 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adaptor, reflux condenser, 100 ml addition funnel, stirring bar and tubing leading from the condenser to a mineral oil bubbler. The flask was charged with 3.1 g (0.015 mol) of 2,4-dichlorobenzhydrazide, 60 ml of THF and 10 ml of water. To the resulting mixture was added 2.1 g (0.015 mol) of p-fluorophenyl isocyanate dropwise, while stirring. The reaction mixture was stirred overnight at room temperature after which it was concentrated in vacuo. The resulting solid was filtered, washed with water and dried in vacuo, yielding 5.0 g (98% yield) of a white solid.

F. Preparation of Unsymmetrical 2,5-Disubstituted-1,3,4-Oxadiazoles via Polyphosphoric Acid

\[
\begin{align*}
\text{or} & \\
\text{or} & \\
Y &= 2,4\text{-dichlorophenyl}
\end{align*}
\]
Table V

Experimental Data for the Preparation of Unsymmetrical 2,5-Disubstituted-1,3,4-Oxadiazoles via Polyphosphoric Acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>% Yield</th>
<th>mp (°C)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>propyl</td>
<td>89&lt;sub&gt;a&lt;/sub&gt;</td>
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<td>50-52</td>
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<td>2</td>
<td>pentyl</td>
<td>92&lt;sub&gt;b&lt;/sub&gt;</td>
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<td>42-44</td>
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<tr>
<td>3</td>
<td>tertbutyl</td>
<td>90&lt;sub&gt;c&lt;/sub&gt;</td>
<td></td>
<td>78-80</td>
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<td>4</td>
<td>2-methylphenyl</td>
<td>93&lt;sub&gt;d&lt;/sub&gt;</td>
<td></td>
<td>132-35</td>
</tr>
<tr>
<td>5</td>
<td>3-methylphenyl</td>
<td>98&lt;sub&gt;e&lt;/sub&gt;</td>
<td></td>
<td>102-105</td>
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<tr>
<td>6</td>
<td>3-pyridyl</td>
<td>89&lt;sub&gt;f&lt;/sub&gt;</td>
<td></td>
<td>149-154</td>
</tr>
<tr>
<td>7</td>
<td>4-pyridyl</td>
<td>75&lt;sub&gt;g&lt;/sub&gt;</td>
<td></td>
<td>259-264</td>
</tr>
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<td>8</td>
<td>4-methylphenyl</td>
<td>99&lt;sub&gt;h&lt;/sub&gt;</td>
<td></td>
<td>207-210</td>
</tr>
</tbody>
</table>

<sup>a</sup>NMR (d<sup>6</sup> Unisol/CDC<sub>3</sub>) δ 1.08 (t, J=6 Hz, 3H), 1.58-2.20 (hex, J=6 Hz, 2H), 2.93 (t, J=6 Hz, 3H), 7.36-7.68 (m, 2H), 7.97 (d, J=8 Hz, 2H); IR (nujol mull) 3075, 1592, 1576, 1470, 1020, 960, 865, 815 and 740 cm<sup>-1</sup>.

<sup>b</sup>NMR (d<sup>6</sup> Unisol/CDC<sub>3</sub>) δ 0.74-1.12 (t, J=6 Hz, 3H), 1.20-2.16 (m, 6H), 2.97 (t, J=6 Hz, 2H), 7.34-7.70 (m, 2H), 8.04 (d, J=8 Hz, 1H); IR (nujol mull) 3065, 1592, 1574, 1470, 1020, 960, 865, 850, 815 and 740 cm<sup>-1</sup>.

<sup>c</sup>NMR (CDC<sub>3</sub>) δ 1.77 (s, 9H), 7.61-7.94 (m, 2H), 8.15 (d, J=3 Hz, 1H); IR (nujol mull) 1597, 1572, 1470, 1020, 964, 865, 825, 760 and 740 cm<sup>-1</sup>. 
\[d^{1}NMR\ (d^6\ \text{Unisol})\delta\ 2.78\ (s,\ 3H),\ 7.27-7.62\ (m,\ 5H),\ 8.10\ (d,\ J=8\ Hz,\ 2H);\ \text{IR}\ (CHCl_3)\ 2980,\ 1590,\ 1450,\ 1032,\ 965\ \text{and}\ 870\ cm^{-1}.

\[e^{1}NMR\ (CDCl_3)\delta\ 2.42\ (s,\ 3H),\ 7.24-7.55\ (m,\ 4H),\ 7.81-8.11\ (m,\ 3H);\ \text{IR}\ (CHCl_3)\ 2980,\ 2910,\ 1588,\ 1450,\ 1035,\ 965\ \text{and}\ 870\ cm^{-1}.

\[f^{1}NMR\ (d^6\ \text{TFA})\delta\ 7.50\ (d\ of\ d,\ J=8\ Hz,\ J=2\ Hz,\ 1H),\ 7.60\ (d,\ J=2\ Hz,\ 1H),\ 8.10\ (d,\ J=8\ Hz,\ 1H),\ 8.27-8.65\ (m,\ 1H),\ 9.02-10.00\ (m,\ 3H);\ \text{IR}\ (\text{nujol\ mull})\ 3057,\ 1600,\ 1540\ \text{and}\ 1450\ cm^{-1}.

\[g^{1}NMR\ (\text{TFA})\delta\ 7.55\ (\text{broad}\ d,\ J=8\ Hz,\ 1H),\ 7.72\ (\text{broad}\ s,\ 1H),\ 8.09\ (d,\ J=8\ Hz,\ 1H),\ 8.90-9.28\ (m,\ 4H);\ \text{IR}\ (\text{nujol\ mull})\ 3090,\ 1590,\ 1450,\ 1045,\ 870,\ 750\ \text{and}\ 700\ cm^{-1}.

\[h^{1}NMR\ (d^6\ \text{Unisol})\delta\ 2.36\ (s,\ 3H),\ 7.20\ (d,\ J=8\ Hz,\ 2H),\ 7.30-7.80\ (m,\ 4H),\ 8.00\ (d,\ J=8\ Hz,\ 1H);\ \text{IR}\ (\text{nujol\ mull})\ 1675,\ 1590,\ 1470,\ 1275,\ 1030\ \text{and}\ 870\ cm^{-1}.

2-(3-Pyridyl)-5-(2,4-Dichlorophenyl)-1,3,4-Oxadiazole

A 250 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adapter, reflux condenser and stirring bar. The flask was charged with 24.8 g of PPA (400 g of PPA was used for every 0.2 mol of hydrazide utilized in the reaction) and heated. Between 50-60°C, the viscosity of the PPA decreased enough to allow stirring, at which time 4.0 g (0.013 mol) of N-(3-pyridyl)-N'-(2,4-dichlorophenyl) hydrazine was added to the flask. The resulting mixture was heated to 125-130°C for five hr and after cooling to
approximately 100°C, 93 ml of water (1.5 liter of water was added for every 400 g of PPA utilized in the reaction) was added to the flask. A precipitate formed while cooling to room temperature, after which the reaction mixture was poured into a beaker and cooled in an ice-water bath. The resulting solid was filtered, washed with cold water and dried in vacuo, yielding 3.4 g (89% yield) of a gray solid.

G. Preparation of Unsymmetrical 2,5-Disubstituted-1,3,4-Oxadiazoles via Phosphorus Oxychloride

\[
\begin{array}{c}
\text{or} \\
\text{Reflux 3 hr}
\end{array}
\]

\[\text{POCl}_3\]

\[
Y=2,4\text{-dichlorophenyl}
\]
Table VI
Experimental Data for the Preparation of Unsymmetrical 2,5-Disubstituted-1,3,4-Oxadiazoles via Phosphorus Oxychloride

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>% Yield</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-pyridyl</td>
<td>72a</td>
<td></td>
<td>232-235</td>
</tr>
<tr>
<td>2</td>
<td>2-(trifluoromethyl)phenyl</td>
<td>91b</td>
<td></td>
<td>167-170</td>
</tr>
<tr>
<td>3</td>
<td>3-(trifluoromethyl)phenyl</td>
<td>83c</td>
<td></td>
<td>186-189</td>
</tr>
<tr>
<td>4</td>
<td>4-fluorophenyl</td>
<td>99d</td>
<td></td>
<td>117-122</td>
</tr>
<tr>
<td>5</td>
<td>4-(1,1,1-trifluoroisopropoxy)phenyl</td>
<td>90e</td>
<td></td>
<td>114-115</td>
</tr>
</tbody>
</table>

aNMR (d^6 DMSO) δ 7.37-7.96 (m, 4H), 8.08-8.49, (m, 2H), 8.59-9.03 (m, 2H); IR (nujol mull) 3030, 1590, 1450, 1020 and 970 cm\(^{-1}\).

bNMR (d^6 DMSO) δ 7.37-8.01 (m, 7H); IR (nujol mull) 3440, 1610, 1560, 1545, 1470, 1330, 1260, 1180, 1115, 1020, 870 and 760 cm\(^{-1}\).

cNMR (d^6 DMSO/CDC\(_3\)) δ 7.34-7.81 (m, 5H), 7.9308.31 (m, 2H); IR (nujol mull) 1680, 1610, 1470, 1340, 1195, 1170, 1130, 1035, 880, 870, 800 and 700 cm\(^{-1}\).

dNMR (d^6 DMSO/CDC\(_3\)) δ 7.00 (t, J=8 Hz, 2H), 7.40-7.85, (m, 4H), 7.98 (d, J=8 Hz, 1H); IR (nujol mull) 1690, 1610, 1510, 1470, 1230, 1030, 865 and 835 cm\(^{-1}\).

eNMR (d^6 DMSO)/CDC\(_3\)) δ 1.51 (d, J=6 Hz, 3H), 5.30 (hept, J= 6 Hz, 1H); 7.31 (d, J=8 Hz, 2H), 7.55 (d of d, J=8 Hz, J=2 Hz, 1H), 7.70
(d, J=2 Hz, 1H), 8.10 (d, J=8 Hz, 2H), 8.20 (d, J=8 Hz, 1H); IR (nujol mull) 1610, 1500, 1450, 1290, 1250, 1170, 1025, 970, 870, 850, 745 and 700 cm\(^{-1}\).

2-[4-(1,1,1-Trifluoroisoproxy)Phenyl]-5-(2,4-dichlorophenyl)-1,3,4-Oxadiazole

A 100 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adapter, reflux condenser and stirring bar. The flask was charged with 1.5 g (0.004 mol) of N-[4-(1,1,1-trifluoroisoproxy)benzoyl]-N-(2,4-dichlorobenzoyl)hydrazine and 15 ml of POCl\(_3\) while stirring. The resulting mixture was refluxed for 3 hr after which it was cooled to room temperature and poured slowly into 100 ml of ice, while stirring. This mixture was stirred for several minutes, allowing formation of a precipitate. The solid was filtered, washed with cold water and dried in vacuo, yielding 1.39 g (90% yield) of a tan colored solid.

H. Preparation of Symmetrical 2,5-Disubstituted-1,3,4-Oxadiazoles

\[
\begin{align*}
X-\text{C-OH} + 5\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} & \xrightarrow{\text{PPA} \at 130^\circ\text{C} \at 3\text{ hr}} X-\text{N=O=N} \quad + \text{H}_3\text{PO}_4 \\
\end{align*}
\]
Table VII

Experimental Data for the Preparation of Symmetrical 2,5-Disubstituted-1,3,4-Oxadiazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>% Yield</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-(2,2,2-trifluoroethoxy)phenyl</td>
<td>46\textsuperscript{a}</td>
<td>143-144</td>
</tr>
<tr>
<td>2</td>
<td>4-(2,2,2-trifluoroethoxy)phenyl</td>
<td>64\textsuperscript{b}</td>
<td>207-210</td>
</tr>
</tbody>
</table>

\textsuperscript{a}NMR (d\textsuperscript{6} DMSO/CDCl\textsubscript{3}) \(\delta\) 4.80 (q, J=8 Hz, 4H) 7.16-8.15 (m, 8H); IR (nujol mull) 1590, 1460, 1290, 1170, 1150, 790 and 680 cm\textsuperscript{-1}.

\textsuperscript{b}NMR (d\textsuperscript{6} DMSO/CDCl\textsubscript{3}) \(\delta\) 4.85 (q, J=8 Hz, 4H) 7.30 (d, J=9 Hz, 4H), 8.14 (d, J=9 Hz, 4H); IR (nujol mull) 1615, 1490, 1450, 1290, 1250, 1170, 1015, 970 and 845 cm\textsuperscript{-1}.

2,5-Bis[4-(2,2,2-Trifluoroethoxy)phenyl]-1,3,4-Oxadiazole

A 100 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adapter, reflux condenser and stirring bar. The flask was charged with 9.0 g of PPA (400 g of PPA was added for 0.2 mol of hydrazine hydrate utilized in the reaction) and heated. Between 50-60°C the viscosity of the PPA decreased enough to allow stirring, at which time 0.22 g (0.0045 mol) of hydrazine hydrate was added dropwise. To the mixture was added 2.0 g (0.009 mol) of p-trifluoroethoxybenzoic acid in one portion. The resulting mixture was then heated to 125-130°C for 5 hr. The mixture was then cooled to approximately 100°C and 33.7 ml of water (1.5 liters
of water was added to the flask for every 400 g of PPA utilized in
the reaction) was added to the flask. A precipitate formed while
cooling to room temperature, after which the reaction mixture was
poured into a beaker and cooled in an ice-water bath. The result-
ing solid was filtered, washed with cold water and dried in vacuo,
yielding 2.4 g (64% yield).

I. Preparation of 2,2,2-Trifluoroethoxy Substituted Benzoic Acids

\[
\begin{array}{ccc}
X-C-NH_2 & \xrightarrow{10\% HCl \text{ reflux} \ 24 \text{ hr}} & X-C-OH + NH_4^+Cl^- \\
\end{array}
\]

Table VIII

Experimental Data for the Preparation of 2,2,2-Trifluoroethoxy
Benzoic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>% Yield</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-(2,2,2-trifluoroethoxy)phenyl</td>
<td>95\textsuperscript{a}</td>
<td>108-109</td>
</tr>
<tr>
<td>2</td>
<td>4-(2,2,2-trifluoroethoxy)phenyl</td>
<td>88\textsuperscript{b}</td>
<td>201-203</td>
</tr>
</tbody>
</table>

\textsuperscript{a}NMR (CDCl\textsubscript{3}) \delta 3.76 (q, J=8 Hz, 2H), 7.02-7.43 (m, 2H), 7.48-
7.79 (m, 2H); IR (nujol mull) 1700, 1590, 1250, 1170, 1070, 970,
855, 755 and 680 cm\textsuperscript{-1}.

\textsuperscript{b}NMR (d\textsuperscript{6} DMSO/CDCl\textsubscript{3}) \delta 4.50 (q, J=8 Hz, 2H), 7.00 (d, J=8 Hz,
2H), 8.00 (d, J=8 Hz, 2H); IR (nujol mull) 3425, 1700, 1600, 1510, 1285,
1250, 1170, 1070, 970 and 850 cm\textsuperscript{-1}.
3-(2,2,2-Trifluoroethoxy) Benzoic Acid

A 250 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adapter, reflux condenser and stirring bar. To the flask was added 3.5 g (0.016 mol) of 3-(2,2,2-trifluoroethoxy) benzamide and 100 ml of a 10% aqueous hydrochloric acid solution. The resulting mixture was refluxed overnight and after cooling to room temperature, 100 ml of water was added. The mixture was stirred for 30 min during which time a solid precipitated out. The resulting solid was filtered, washed with water and dried in vacuo, yielding 3.35 g (95% yield) of a white solid.

J. Preparation of Trifluoroalkoxy Substituted Benzamides

\[ X - \text{C} = \text{N} + 2\text{H}_2\text{O}_2 + 6\text{N NaOH} \xrightarrow{\text{EtOH \ reflux \ 4-5 \ hr}} X - \text{C} - \text{NH}_2 \]

Table IX
Experimental Data for the Preparation of Trifluoroalkoxy Substituted Benzamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-(2,2,2-trifluoroethoxy)phenyl</td>
<td>75\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>4-(2,2,2-trifluoroethoxy)phenyl</td>
<td>95\textsuperscript{b}</td>
</tr>
<tr>
<td>3</td>
<td>4-(1,1,1-trifluoroisopropoxy)phenyl</td>
<td>80\textsuperscript{c}</td>
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\( ^a_{\text{NMR}} \) (d\(^6\) DMSO/CDC\(_3\)) \( \delta \) 4.55 (q, J=8 Hz, 2H), 6.78-8.06 (m, 6H); IR (nujol mull) 3390, 3200, 1650, 1575, 1285, 1250, 1170, 1070, 970, 780 and 680 cm\(^{-1}\).

\( ^b_{\text{NMR}} \) (d\(^6\) DMSO/CDC\(_3\)) \( \delta \) 4.64 (q, J=8 Hz, 2H), 7.00 (broad pk, 1H), 7.10 (d, J=8 Hz, 2H), 7.80 (broad pk, 1H), 8.04 (d, J=8 Hz, 2H); IR (nujol mull) 3400, 3300, 1650, 1620, 1580, 1520, 1285, 1250, 1170, 1070, 980 and 850 cm\(^{-1}\).

\( ^c_{\text{NMR}} \) (d\(^6\) DMSO/CDC\(_3\)) \( \delta \) 1.49 (d, J=6 Hz, 3H), 4.85 (hept, J=6 Hz, 1H), 6.90 (d, J=8 Hz, 2H), 7.00 (broad pk, 2H), 7.79-8.06 (d, J=8 Hz, 2H); IR (nujol mull) 3370, 3195, 1670, 1575, 1570, 1290, 1250, 1175, 1030 and 850 cm\(^{-1}\).

4-(2,2,2-Trifluoroethoxy)benzamide

A 100 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adapter, reflux condenser and stirring bar. To the flask was added 7.5 ml of ethanol (400 ml of ethanol was added for every 0.75 ml of nitrile utilized in the reaction), 0.44 g (.024 mol) of hydrogen peroxide (30% solution, and 2.1 g (0.012 mol) of 4-(2,2,2-trifluoroethoxy)benzonitrile while stirring. The resulting mixture was cooled to 10\(^{\circ}\)C, after which 0.5 ml of 6N sodium hydroxide (30 ml of 6N sodium hydroxide was added for every 0.75 mol of nitrile utilized in the reaction) was added dropwise. The reaction mixture was refluxed for 4 hr and after cooling to room temperature, the mixture was neutralized with a 10% aqueous hydrochloric acid solution. The solvent was stripped off in vacuo and the remaining
solid was filtered, washed with 30 ml of water and dried in vacuo, yielding 2.91 g (95% yield) of a white solid; mp=169-171°C.
PART I

III. DISCUSSION OF RESULTS

A series of synthetic routes (Figures 1, 2 and 3) have been taken for the preparation of diacylhydrazines (Tables III and IV) and 2,5-disubstituted-1,3,4-oxadiazoles as potential insecticides. All key components in the different synthetic routes have been characterized from their NMR and IR spectra.\(^{10,11,12}\)

Preparation of methyl benzoates (Table I) began with the corresponding carboxylic acid.\(^{13}\) The NMR of the methyl benzoate is characterized by the appearance of a singlet around 3.85 ppm, which integrates for the three hydrogens of the \(-O-CH_3\) group. The IR spectra revealed a strong carbonyl absorption in the 1720-1735 cm\(^{-1}\) range.

The first step in the preparation of trifluoroalkoxy benzonitrile to the corresponding amide (Table IX). The IR spectra gave the most information, with the appearance of the \(N-H\) \(^1\) amide stretch in the 3370-3400 cm\(^{-1}\) range and the amide carbonyl stretch in the 1620-1670 cm\(^{-1}\) range. Also, the disappearance of the nitrile group absorption from the 2200-2230 cm\(^{-1}\) region of the IR spectra (see Table X) was indicative of total conversion to the desired products.

All the compounds containing a 2,2,2-trifluoroethoxy group (Tables IX, X and XI) consistently revealed in their NMR spectra...
a quartet (J=8 Hz) in the 3.76-4.85 ppm range, which integrated for
the two hydrogens in the -O-CH₂-CF₃ group. The NMR of the compounds
containing the 1,1,1-trifluoroisopropoxy group revealed a heptet
(Part I-C and Table III-entry 3) in which the 4.5-5.2 ppm
range integrated for the hydrogen on carbon number two of the 1,1,1-
trifluoroisopropoxy group. The IR spectra of the compounds with a
difluoroalkoxy group consistently reveal an absorption band at
1250 cm⁻¹, which corresponds to the aryl alkyl ether (C-O-C)
asymmetrical stretch. The C-O-C symmetrical stretch was found to
vary from about 1025 cm⁻¹ for the 1,1,1-trifluoroisopropoxy ester
linkage to approximately 1070 cm⁻¹ for the 2,2,2-trifluoroethoxy
ester linkage.

As expected, in going from an ester (Table II) or an amide
(Part I-C) to the corresponding hydrazide and then to the
diacylhydrazines, the carbonyl absorption bands in the IR spectra
move to lower frequencies because of the increase in single bond
character, due mainly to the increase in conjugation.

In going from an amide to a carboxylic acid (Table VIII), the
carbonyl group absorption band shifts to higher frequency due to
an increase in the double bond character of the carbonyl group.

The IR spectra of the hydrazides (Table II) are characterized
by absorption bands at 3420 and 3440 cm⁻¹ for the N-H 1° amine
stretch, 3320-3330 cm⁻¹ for the N-H 2° amide stretch, 1660-1675
1620 cm\(^{-1}\) for the carbonyl amide stretch and 1620 the the N–H \(^1\) amine bend. The NMR spectra of the hydrazides typically shows a broad singlet in the 4.0-4.6 ppm range, which integrates for the two hydrogens of the N–H group.

The diacylhydrazines lack the broad singlet in the NMR spectra and the N–H \(^1\) amine stretch in the IR spectra, which appear in the corresponding spectra of the hydrazides. The IR spectra of the diacylhydrazides typically reveal an absorption in the 3340-3390 cm\(^{-1}\) range due to the N–H \(^2\) amide stretch and the carbonyl amide stretch in the 1655-1620 cm\(^{-1}\) range.

Thus, as can be seen, the IR spectra is most informative in the characterization of the hydrazides and diacylhydrazines. This is also true for the 2,5-disubstituted-1,3,4-oxadiazoles (Tables V-VII). The N–H \(^2\) stretch and carbonyl stretch are absent. The absorption bands at 960-970 cm\(^{-1}\) and 1020-1035 cm\(^{-1}\) are due to the C–O group and 1610-1590 cm\(^{-1}\) are due to the C=N valence vibration.

The spectral data obtained are consistent with previous reports on the preparation of DOWCO 416 similogs, and analogous compounds of the hydrazides and the 2,5-disubstituted-1,3,4-oxadiazoles.
PART I

CONCLUSIONS

A total of twenty-eight potential insecticides were synthesized, by various routes, in good to excellent yields. These compounds are of the following general formulas:

\[
\begin{align*}
\text{(6)} & : \quad \text{R-C-N-N-C-Y} \\
\text{(7)} & : \quad \text{R-C-N-N-C-N-Z} \\
\text{(8)} & : \quad \text{R-C-N-N-C-Y} \\
\text{(9)} & : \quad \text{R-C-N-N-C-N-Z} \\
\text{(10)} & : \quad \text{X-C-N-N-C-X}
\end{align*}
\]
wherein:

R represents 2,4-dichlorophenyl;

Y represents propyl, pentyl, tert-butyl, 2-methylphenyl, 3-methylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl or 4-(1,1,1-trifluoroisopropoxy)phenyl;

Z represents 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-fluorophenyl or 4-methylphenyl;

X represents 3-(2,2,2-trifluoroethoxy)phenyl or 4-(2,2,2-trifluoroethoxy)phenyl.

All compounds have been characterized by NMR and IR spectroscopy and have been forwarded to the biochemistry laboratory at the University of Central Florida Department of Chemistry, and to the Agricultural Research Department of Dow Chemical Company for biological studies.
This investigation involved but a small group of compounds which have the potential of aiding humanity in the fight against pests. Thus the search for pesticides with enhanced activity and selectivity must continue.

The various methods described in this investigation have made it feasible to extend the gamut of potential insecticides, including the synthesis of the following:

1. Structural isomers of compounds (7), (9) and (10) where:
   - $Z=4$-trifluoromethyl phenyl, 2-fluorophenyl, 3-fluorophenyl, or 3-methylphenyl;
   - $X=2$-(2,2,2-trifluoroethoxy)phenyl.

2. Other similogs of compounds (6), (7), (8), (9) and (10) where:
   - $Y=$ longer aliphatic chains branched or unbranched, substituted pyridyl groups, mono and disubstituted trifluorophenyl or trifluoro alkoxy substituted heteroaryl;
   - $Z=$ a variety of substituted phenyl compounds, depending on the phenylisocyanate derivatives which are commercially available;
X=mono and disubstituted trifluoroalkoxy phenyl or trifluoroalkoxy hereroaryl.

Water solubility problems have been encountered during biological testing of the compounds which have been synthesized. Therefore, further investigation as to the attachment of groups which can enhance hydrogen bonding such as:

\[
\begin{align*}
-C-R, & \quad -C-OR, \quad -C-O-C-R, \quad -C-NH_2, \quad -C-NR_2, \quad -NR_2, \quad -R-OH, \quad -O-R \\
\end{align*}
\]

to similogs of DOWCO 416 and its precursor diacylhydrazine is recommended.
PART II

NEW AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS: TRIFLUOROALKOXYLATION AND N,N-DIMETHYLAMINATION
PART II

I. INTRODUCTION

The development of fluorinated organic materials has been closely related to their practical applications since the early 1930's when large scale producers became interested in fluorine chemistry, after the discovery of fluorinated refrigerants commonly called "freons". From then on, fluorine derivatives have had a variety of important applications as polymers, propellants, blood substitutes, pharmaceuticals and pesticides.

In the case of fluoroalkoxy aromatics, the majority of the previously reported synthetic routes involve the reaction of an electrophilic haloalkyl fluoride, fluoroalkene, or a fluoroalkyl sulfonate with a nucleophilic phenol derivative.

Shaw and Kornblum offer more simplistic and convenient methods than those mentioned above, by the direct introduction of the corresponding alkoxy groups to unactivated and activated halo-benzenes. Shaw and co-workers reported that unactivated halo-benzenes react by a bimolecular displacement mechanism (SnAr) with sodium methoxide in HMPA at 90°C to produce good yields of methyl phenyl ethers (Figure 5-a).

Kornblum and co-workers also reported that activated nitro-benzenes will readily undergo nucleophilic displacement of the nitro group by reacting sodium methoxide in HMPA at 25°C to produce good yields of the corresponding methoxy nitrobenzene (Figure 5-b).
Figure 5. Previous reports on methoxylaton of a) unactivated halobenzenes and b) activated dinitrobenzenes.

From these observations, it is proposed to investigate the reaction of sodium 2,2,2-trifluoroethoxide with unactivated and activated halobenzenes in HMPA to produce 2,2,2-trifluoroethoxy benzenes (Figure 6).

Figure 6. Proposed synthetic scheme for the trifluoroethoxylation of unactivated and activated chlorobenzenes.
In addition to the investigation proposed above, the use of HMPA to effect N,N-dimethylation of an aromatic substrate via aromatic nucleophilic substitution will also be investigated.

Figure 7. Previous reactions done with HMPA as a N,N-dimethyl-aminating agent: a) acids to amides\textsuperscript{26}, b) uracils to aminopyrimidines\textsuperscript{22} and c) activated nitrobenzenes to anilines\textsuperscript{28-30}. 
The use of HMPA as an agent for the introduction of a dimethylamino group has captured the interest of several researchers\textsuperscript{26-30}. For example, HMPA has been used for the conversion of acids to amides (Figure 7-a)\textsuperscript{26}, uracils to aminopyrimidines (Figure 7-b) and substituted cyano- and nitrobenzenes\textsuperscript{27} to the corresponding N,N-dimethylanilines (Figure 7-c)\textsuperscript{28-30}. The synthetic usefulness of these reports leads to an interest in further investigations of HMPA as a N,N-dimethylaminating agent. Therefore it is proposed to react HMPA with activated chlorobenzenes to produce the corresponding N,N-dimethylaniline (Figure 8).

![Figure 8](image)

Figure 8. Proposed synthetic scheme for the preparation of N,N-dimethylanilines.

Thus, in this section, two applications of nucleophilic aromatic substitution on activated aryl halides will be investigated by 1) trifluoroalkoxylation with HMPA as solvent and 2) N,N-dimethylamination in which HMPA is one of the reacting species. Characterization of all products will be done by NMR, IR and mass spectrometry.
II. Experimental

A. Preparation of 2,2,2-Trifluoroethoxy Benzonitriles

![Chemical structure](image)

Table X

Experimental Data for the Preparation of 2,2,2-Trifluoroethoxybenzonitriles

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
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<th>Z</th>
<th>% Yield(^a)</th>
<th>mp (°C)(^h)</th>
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<td>CN</td>
<td>79(57)(^c)</td>
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<td>CN</td>
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<td>6-CH(_3)</td>
<td>CN</td>
<td>97(^e)</td>
<td>88-92</td>
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<tr>
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<td>5-NO(_2)</td>
<td>CN</td>
<td>98(^f)</td>
<td>94-96</td>
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<tr>
<td>6</td>
<td>2-Cl</td>
<td>H</td>
<td>Cl</td>
<td>Trace(^g)</td>
<td>-----</td>
</tr>
</tbody>
</table>

\(^a\)The yields in parentheses refer to recrystallized products. The yields not in parentheses are crude yields. No attempt has been made to optimize the reaction conditions or the recrystallization step.

\(^b\)\(^{\text{NMR (CDCl}}_3\)) \(\delta 4.53 (q, J = 8 \text{ Hz, 2H})\) and 6.87-7.83 (m, 4H); \(\text{IR (CHCl}}_3\) 3080, 2230, 1600, 1580, 1490, 1450, 1250, 1165, 1110, and 1060 cm\(^{-1}\); mass spectrum m/e 201 (M\(^+\)).
\( \text{C} \) NMR (\( \text{CDCl}_3 \)) \( \delta \) 4.42 (q, \( J = 8 \) Hz, 2H) and 7.00-7.68 (m, 4H); IR (\( \text{CHCl}_3 \)) 3080, 2230, 1590, 1580, 1480, 1430, 1285, 1250, 1165, 1070 and 970 cm\(^{-1}\); mass spectrum m/e 201 (\( M^+ \)).

\( \text{d} \) NMR (\( \text{CDCl}_3 \)) \( \delta \) 4.50 (q, \( J = 8 \) Hz, 2H), 7.08 (d, \( J = 8 \) Hz, 2H) and 7.70 (d, \( J = 8 \) Hz, 2H); IR (\( \text{CHCl}_3 \)) 3080, 2220, 1600, 1500, 1280, 1240, 1170, 1070, 970 and 830 cm\(^{-1}\); mass spectrum m/e 201 (\( M^+ \)).

\( \text{e} \) During the workup, upon addition of 100 ml 5\% HCl, this product crystallized out immediately. The product was placed in an ice bath to enhance crystallization, filtered and washed with water until the pH of the was water was pH = 7. The solid was then dried under vacuum. \( \text{e} \) NMR (\( \text{CDCl}_3 \)) \( \delta \) 2.50 (s, 3H), 4.48 (q, \( J = 8 \) Hz, 2H), 6.90 (m, 2H) and 7.47 (t, \( J = 8 \) Hz, 1H); IR (\( \text{CHCl}_3 \)) 3080, 2220, 1600, 1580, 1470, 1450, 1285, 1245, 1165, and 1110 cm\(^{-1}\); mass spectrum m/e 215 (\( M^+ \)).

\( \text{f} \) NMR (\( \text{CDCl}_3 \)) \( \delta \) 4.91 (q, \( J = 8 \) Hz, 2H), 7.58 (d, \( J = 10 \) Hz, 1H) and 8.20-8.78 (m, 2H); IR (\( \text{CHCl}_3 \)) 3080, 2220, 1610, 1585, 1535, 1490, 1350, 1300, 1255, 1210, 1165, 1085, 1050, 970, 960, 910 and 820 cm\(^{-1}\); mass spectrum m/e 246 (\( M^+ \)).

\( \text{g} \) Determined by NMR analysis of the crude reaction mixture.

\( \text{h} \) The melting points are uncorrected.

The following procedure is typical of the experimental conditions used for the reaction of chlorobenzonitriles with sodium 2,2,2-trifluoroethoxide in HMPA.
Para-Nitro-N,N-Dimethylaniline

Para-chloronitrobenzene (3.94 g, 0.025 mol) was placed in a three necked flask which had been fitted with a condenser, thermometer and magnetic stirrer, and was placed under a nitrogen atmosphere. HMPA (25 ml) was added and the resulting solution was heated at 150°C for 24 hr. The mixture was cooled to room temperature and poured into 100 ml of water. This mixture was extracted with ether (3 x 75 ml) and the combined ether extracts were washed with water (2 x 100 ml) and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated in vacuo to leave a yellow solid (3.50 g, 84% yield). This material can be further purified, if desired, by dissolving the solid in ether (50 ml) and extracting the ether with 18% (w/w/) aqueous hydrochloric acid (3 x 30 ml). The hydrochloric acid phase is separated and the pH is adjusted to 11 by addition of 10% aqueous sodium hydroxide with cooling. The resulting solid is isolated by filtration and dried in vacuo.
B. Preparation of Cyano and Nitro N,N-Dimethylanilines by Reaction with HMPA

![Chemical structure]

Table XI
Experimental Data for the Preparation of Cyano and Nitro, N,N-Dimethylanilines by Reaction with HMPA

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Reaction Temp. (°C)</th>
<th>Time (hr)</th>
<th>% Yielda</th>
<th>bp or mp (°C)</th>
</tr>
</thead>
<tbody>
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<td>3-CN</td>
<td>150</td>
<td>24</td>
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<td>110-111</td>
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<tr>
<td>2</td>
<td>NO₂</td>
<td>2-Cl</td>
<td>H</td>
<td>150</td>
<td>20</td>
<td>68(44)c</td>
<td>68-92/.08 mm</td>
</tr>
<tr>
<td>3</td>
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<td>15d</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>NO₂</td>
<td>4-Cl</td>
<td>H</td>
<td>150</td>
<td>24</td>
<td>84e</td>
<td>168-170</td>
</tr>
<tr>
<td>5</td>
<td>NO₂</td>
<td>2-Cl</td>
<td>5-CH₃</td>
<td>200</td>
<td>48</td>
<td>62(59)f</td>
<td>85-88/.08 mm</td>
</tr>
<tr>
<td>6</td>
<td>CN</td>
<td>2-Cl</td>
<td>H</td>
<td>200</td>
<td>48</td>
<td>64(59)g</td>
<td>58-65/.06 mm</td>
</tr>
<tr>
<td>7</td>
<td>CN</td>
<td>3-Cl</td>
<td>H</td>
<td>180</td>
<td>48</td>
<td>Traceh</td>
<td>---</td>
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<tr>
<td>8</td>
<td>CN</td>
<td>4-Cl</td>
<td>H</td>
<td>200</td>
<td>48</td>
<td>84(66)i</td>
<td>80-81</td>
</tr>
</tbody>
</table>

aThe yields in parentheses refer to recrystallized or distilled products. The yields not in parentheses are crude yields. No attempt has been made to optimize the reactions conditions.
$^{b}$NMR (CDCl$_3$) δ 3.37 (s, 6H), 6.80 (d, J = 10 Hz, 1H), 8.17 (d of d, J = 10 Hz, J = 2 Hz, 1H), and 8.40 (d, J = 2 Hz, 1H); IR (CHCl$_3$) 2880, 2800, 2200, 1600, 1500, 1330, 910 and 810 cm$^{-1}$; mass spectrum m/e 191 (M$^+$).

$^{c}$NMR (CDCl$_3$) δ 2.72 (s, 6H) and 6.60-7.87 (m, 4H); IR (thin film) 2880, 2770, 1600, 1500, 1340, 1290, 1155, 1040 and 740 cm$^{-1}$; mass spectrum m/e 166 (M$^+$).

$^{d}$Determined by NMR analysis of the crude mixture.

$^{e}$NMR (CDCl$_3$) δ 3.10 (s, 6H), 6.60 (d, J = 10 Hz, 2H) and 8.15 (d, J = 10 Hz, 2H); IR (CHCl$_3$) 1590, 1510, 1480, 1320 and 1110 cm$^{-1}$; mass spectrum m/e 166 (M$^+$).

$^{f}$NMR (CDCl$_3$) δ 2.28 (s, 3H), 2.80 (s, 6H), 6.92 (d, J = 8 Hz, 1H), 7.22 (d of d, J = 8 Hz, J = 2 Hz, 1H) and 7.55 (d, J = 2 Hz, 1H); IR (thin film) 1620, 1520, 1340, 1280, 910 and 790 cm$^{-1}$.

$^{g}$NMR (CDCl$_3$) δ 2.90 (s, 6H), 6.68-6.93 (m, 2H) and 7.20-7.56 (m, 2H); IR (thin film) 2840, 2800, 2200, 1590, 1280, 1160, 1040 and 750 cm$^{-1}$; mass spectrum m/e 146 (M$^+$).

$^{h}$Determined by NMR analysis of the crude reaction mixture.

$^{i}$NMR (CDCl$_3$) δ 3.07 (s, 6H), 6.65 (d, J = 8 Hz, 2H) and 7.46 (d, J = 8 Hz, 2H); IR (CHCl$_3$) 2860, 2810, 2200, 1600, 1360, 1060, 1000 and 810 cm$^{-1}$; mass spectrum m/e 146 (M$^+$).

The following procedure is typical of the experimental conditions used for the reaction of chlorobenzonitriles and chloronitrobenzenes with HMPA.
Ortho-2,2,2-Trifluoroethoxybenzonitrile

A 250 ml, three-necked, round-bottomed flask was equipped with a thermometer, thermometer adapter, reflux condenser, stirring bar and a nitrogen inlet. The flask (maintained under nitrogen atmosphere) was charged with 2.6 g (0.055 mol) of sodium hydride (50% by weight mineral oil). Twenty ml of hexane was added to remove the mineral oil from the sodium hydride. This mixture was stirred for 10-15 min after which the sodium hydride was permitted to settle out and the hexane-mineral oil solution was removed. To the remaining sodium hydride was added 50 ml of HMPA (dried over 4Å molecular sieves) and 10.0 g (0.10 mol) of 2,2,2-trifluoroethanol. The reaction became exothermic and an ice bath was used to help dissipate the heat. The resulting solution was stirred at room temperature allowing hydrogen gas to evolve (this was detected by using a mineral oil bubbler). After 20 min, 6.9 g (0.05 mol) of 2-chlorobenzonitrile was added in one portion. The resulting mixture was heated at 90-150° overnight and after cooling to room temperature was poured into 100 ml of 5% aqueous hydrochloric acid. The mixture was extracted with ether (3x70 ml) and the combined ether extracts were washed with additional aqueous hydrochloric acid (2x50 ml). After drying the ether phase over anhydrous magnesium sulfate and concentrating it in vacuo, the ortho-2,2,2-trifluoroethoxybenzonitrile was obtained as a tan solid (95% crude yield). The product can be recrystallized from 4:1 water/isopropanol mixture if desired.
PART II

III. DISCUSSION OF RESULTS

A series of 2,2,2-trifluoroethoxy benzonitriles (Table X) and N,N-dimethylamino substituted benzonitriles and nitrobenzenes (Table XI) have been synthesized in good to excellent yields.

All products were characterized by NMR, IR\textsuperscript{10-12} and mass spectroscopy. NMR spectra were found to be the most informative. For the trifluoroethoxylated compounds (Table X) the NMR spectra consistently revealed a quartet at approximately 4.5 ppm (J=8 Hz) which integrated for the two hydrogens on the 2,2,2-trifluoroethoxy group. The NMR spectra of the N,N-dimethylaminated compounds (Table XI) revealed a singlet in the range of 2.28-3.37 ppm, which integrated for the six hydrogens on the N,N-dimethylamino group. Compounds containing a methyl group on the aromatic ring (Table X, entry 4 and Table XI, entry 5) revealed singlets at 2.5 and 2.28 ppm respectively which integrated for the three hydrogens on the methyl group.

The aromatic hydrogens for both trifluoroethoxylated and N,N-dimethylaminated compounds appear in the 6.6-8.8 ppm range of the NMR spectra and are consistent with the respective substitution pattern and substituent effects.

The IR spectra of the benzonitrile compounds (Table X, entries 1-5 and Table XI, entries 1, 6) consistently revealed absorption
bands in the 2200 to 2230 cm\(^{-1}\) range corresponding to the conjugated C\(\equiv\)N stretch. The IR spectra of compounds containing the N–O group (Table X, entry 5 and Table XI, entries 1, 2, 4 and 5) reveal two strong absorption bands. One in the 1500 to 1535 cm\(^{-1}\) range is due to the symmetric N–O stretch. Absorption bands in the 1050 to 1070 cm\(^{-1}\) range of the trifluoroethoxylated products are due to the aryl alkyl ether C–O–C symmetrical stretch. The C–O–C asymmetrical stretch absorption bands are seen in the 1245 to 1255 cm\(^{-1}\) range. The C–F absorption band is seen at 1165 or 1170 cm\(^{-1}\) (Table X, entries 1-5). Based on Shaw's\(^{24}\) work of methoxylation of unactivated halobenzenes, it was initially attempted to react sodium 2,2,2-trifluoroethoxide with ortho-dichlorobenzene at 90, 150 or 200\(^\circ\)C, but only minimal amounts of the desired product were obtained. This was not totally unexpected since 2,2,2-trifluoroethanol is a relatively poor nucleophile (pK\(_{a}\) of 2,2,2-trifluoroethanol is reported to be 12.4 relative to a value of 15.9 for ethanol\(^{31}\)). However, when the halobenzene contained an activating nitrile group and was then reacted with the 2,2,2-trifluoroethoxide ion at 90-150\(^\circ\)C in HMPA excellent yields of the corresponding fluoroalkoxy benzene were obtained. As expected, the cyano group was found to be very effective in activating the benzene ring toward reaction with the trifluoroethoxide ion, including substrates in which the activating group is substituted meta to the leaving group (Table X, entry 2) as well as ones that also contain an electron-releasing group (Table X, entry 4). When two activating
groups are present (Table X, entry 5) the reaction will occur at less than 100°C.

In reference to the N,N-dimethylamination with HMPA, it was found that the nitro and cyano groups are very effective in activating the benzene ring. Ortho or Para (Table XI, entries 1, 2, 4-6 and 8) substitution appears to be necessary to make such transformations synthetically useful. The meta isomers (Table XI, entries 3 and 7) produce some product, but their reaction with HMPA probably does not constitute a useful synthetic procedure. Electron-releasing groups appear to deactivate this reaction as exemplified by the higher reaction temperature and longer reaction time required for the conversion of 1-chloro-4-methyl-2-nitrobenzene (Table XI, entry 5) to 2-nitro-4-methyl-N,N-dimethylaniline.

Due to the nature and positional requirements of the activating and deactivating groups, the relative reactivity of the leaving groups and the fact that there was no indication of formation of regioisomeric substitution products, an SnAr mechanism\textsuperscript{32} is implicated (Figure 9).

This particular mechanism is based on an analogy between HMPA and the trisaminomethanes which react under most circumstances by first ionizing into a cationic and anionic form (Figure 10). Thus, there is a possibility that HMPA may have some ionic character at elevated temperatures.
Figure 9. Proposed SnAr mechanism of HMPA on activated chlorobenzenes.
Figure 10. Ionization of trisaminomethanes

The results of these two nucleophilic aromatic substitutions have been reported\textsuperscript{34,35}. In an effort to define the scope and limitations of the direct aromatic nucleophilic fluoroalkoxylation reaction, our research group has recently reported\textsuperscript{36} the effect of solvent, time, temperature, the activating group, the leaving group, and nucleophile on this reaction with activated aryl and heteroaryl halides. Also, the HMPA reaction studies have been extended to activated heteroaryl halides. The effect of the activating group and the leaving group is described\textsuperscript{37} and further evidence of a possible SnAr mechanism is given.
PART II

IV. CONCLUSIONS

Two new applications of nucleophilic aromatic substitution have been achieved:

1. Sodium 2,2,2-trifluoroethoxide has been found to react with cyano-substituted chlorobenzene in HMPA at temperatures of 90-150°C, to give the corresponding 2,2,2-trifluoroethoxy benzonitrile (Table X) in good to excellent yields. This new method for the incorporation of the 2,2,2-trifluoroethoxy group onto an aromatic ring is particularly attractive due to the convenient reaction conditions, the simplicity of the isolation step, the purity of the product obtained and the ready availability and moderate cost of 2,2,2-trifluoroethanol.

2. A new synthetic method which is clean, simple and efficient has been found by reacting HMPA with cyano and/or nitro-substituted chlorobenzenes at temperatures of 150-200°C to give the corresponding N,N-dimethylaniline in good yields.
PART II

V. RECOMMENDATIONS

The following are suggestions for future research.

In reference to the trifluoroalkoxylation of activated halo­benzenes in HMPA:

1. DMF, 1-methyl-2-pyrrolidone and DMSO have also been found as solvents to direct trifluoroalkoxylation. Further research can be conducted using other dipolar, aprotic solvents that provide the necessary polarity and temperature control to promote the reaction.

2. Electron-withdrawing groups such as: \(-N(CH_3)_3^+\), \(-SO_3H\), \(-COOH\), \(-CHO\) or \(-COR\) are known to activate the halogen ortho or para to them. Therefore compounds containing these substrates can potentially effect the trifluoroalkoxylation.

3. Trifluoroethoxylation of halogenated heterocyclic compounds can also be investigated. Further investigation is encouraged due to the fact that the reaction has been found to occur on chlorinated nitrogen containing heterocyclic compounds.

In reference to the N,N-dimethylamination of cyano- and nitro-substituted chlorobenzenes:
1. An excellent study has been reported by Gupton, Idoux and co-workers using HMPA for N,N-dimethylamination of activated aryl and heteroaryl compounds. Further investigation is recommended as an expansion of this report, such as:
   a) Fluorine on activated aryl and heteroaryl compounds.
   b) The use of other activating substrates on the ring such as \(-\text{N} (\text{CH}_3)_3^+\) and \(-\text{SO}_3\text{H}\).
   c) The results of these recommended investigations should also provide further evidence for the proposed SnAr mechanism and ionic character of HMPA at elevated temperatures.

2. When conducting reactions in HMPA at elevated temperatures (150-200°C), one should be aware of potential reactions with the solvent. Temperatures exceeding 200°C for an extended length of time, in the case of N,N-dimethylamination, tend to form emulsions which are very difficult to work up.

3. HMPA should be handled with the precautions appropriate for a potential carcinogen. Although there is no data on the toxic effects of HMPA in humans, preliminary results of an inhalation toxicity of HMPA released by DuPont showed the development of nasal tumors in rats exposed to 400 and 4000 ppb of HMPA daily after 8 months.
INSTRUMENTATION AND EQUIPMENT

Infrared spectra were recorded on a Perkin-Elmer Model 457 infrared spectrometer or on a Nicolet MX-S FT-IR spectrometer. Samples were run as thin films, nujol mulls or CHCl₃ solutions. NMR spectra were obtained in CDCl₃, Me₂, So-d₆, TRA or TFA-d₆ solutions [(CH₃)₄Si as internal standard] at 60 MHz with a Varian EM-360A spectrometer. Removal of solvents in vacuo was performed using a Rinco Rotovapor rotary evaporator. All boiling points and melting points are uncorrected, and melting points were recorded on a Fisher-Johns melting point apparatus. All starting materials used were purchased from either Aldrich Chemical Co., Milwaukee, WI, or PCR Research Chemicals, Inc., Gainesville, FL.


