Preparation of 2,5-Diaryl-1,3,4-Oxadiazoles

Spring 1983

Joachim D. Dobe

University of Central Florida

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This report regards the research conducted in the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles as potential insecticides which are closely related to the known insecticide DOWCO 416R, 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole. The following compounds were synthesized: 2-(2,4-dichloro-5-nitrophenyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole, (2-(2,4-dichloro-5-nitrophenyl)-5-phenyl-1,3,4-oxadiazole, 2-(2,4-dichloro-5-aminophenyl)-5-aminophenyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole and 2-(2,4-dichloro-5-aminophenyl)-5-phenyl-1,3,4-oxadiazole.

From the commercially available starting material, 2,4-dichlorobenzoic acid, preparation of the above compounds involved nitration, reduction, esterification, preparation of monoacylhydrazines, preparation of substituted diacylhydrazines and preparation of 2,5-disubstituted-1,3,4-oxadiazoles. All these compounds were characterized via NMR and infrared spectroscopy. In addition, this report includes discussions and recommendations concerning the experimental procedures and conditions for the preparation of these compounds.
PREPARATION OF 2,5-DIARYL-1,3,4-OXADIAZOLE

BY

JOACHIM DAMA DOBE
B.S., Universite D'Abidjan, Ivory Coast, 1979

RESEARCH REPORT

Submitted in partial fulfillment of the requirements for the Master of Science degree in Industrial Chemistry
University of Central Florida
Orlando, Florida

Spring Term
1983
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I wish to thank my beautiful wife Yolande for her patience and moral support, and my family for their continued support throughout my student years. I thank God for protecting, helping, guiding and giving me strength during all my life.
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<th>Definition</th>
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<tbody>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>°C</td>
<td>degrees centigrade</td>
</tr>
<tr>
<td>cc</td>
<td>cubic centimeters</td>
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<td>cm⁻¹</td>
<td>wave numbers</td>
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<td>sodium bicarbonate</td>
</tr>
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</tr>
<tr>
<td>PPA</td>
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</tr>
<tr>
<td>PPM</td>
<td>parts per million (NMR spectrum)</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>Zn</td>
<td>zinc</td>
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I. INTRODUCTION

Insects, which are known vectors in the transmission of many animal and plant diseases, play a destructive role in both our environment and our economy. Insects reportedly cause decreased agricultural production and efficiency in both crop and animal farming. Some insecticides in current use present undesirable aspects such as high human toxicity and long-lived degradation properties in the environment. To improve this situation, researchers are attempting to develop insecticides with more selective biological activity which are less harmful to the environment.

Recently, certain substituted 1,3,4-oxadiazoles such as DOWCO 416R 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole have been reported to be highly successful in controlling manure-breeding insects such as house flies, face flies and horn flies. The objective of this research project was the synthesis of certain 2,5-diaryl-1,3,4-oxadiazoles as potential insecticides. These new compounds are structural derivatives of DOWCO 416R which is currently administered in the feed of warm blooded animals. It passes essentially unchanged through the digestive tract and is eliminated in the feces. For this application, a substance must combine high insecticidal activity with low toxicity and low absorption in the animal.

The derivatives to be synthesized in this phase of the project consisted of 2-(2,4-dichloro-5-nitrophenyl)-5-aryl-1,3,4-oxadiazole and the corresponding 5-amino compound which may potentially
possess better biological properties than DOWCO 416. These compounds will be biologically screened. The general scheme for the synthesis of the above compounds is as follows:

Figure 1. Mechanism for the preparation of 2,5-diaryl-1,3,4-oxadiazoles.
Nitration

Nitration is the most common process for the preparation of aromatic nitro compounds, and a mixture of nitric and sulfuric acid is the usual reagent for effecting nitration.

According to the literature\(^2,3,4\), the concentration of the acids, the nature of the nitrating agents and the temperature are important factors in the nitration reaction. It is known that the active species in nitration is the nitronium ion $\text{NO}_2^+$. Dilute nitric acid is useful for nitrating very reactive aromatic substances, such as phenol, whereas more concentrated nitric acid can be disadvantageous because of its oxidizing properties. Concentrated nitric acid allows nitration to be accomplished at lower temperatures. However, it is constantly being diluted by the water being formed so that the attainment of satisfactory yields requires large amounts of the nitrating agent which limits its usefulness. Alone, nitric acid undergoes appreciable self-dehydration to yield nitronium ions, nitrate ions and water:

$$2 \text{HNO}_3 \rightleftharpoons \text{NO}_2^+ + \text{H}_2\text{O} + \text{NO}_3^- \quad (\text{Eq. 1})$$

To overcome these difficulties, nitration is run in the presence of concentrated sulfuric acid. The presence of sulfuric acid permits another type of ionization:

$$\text{HNO}_3 + \text{H}_2\text{SO}_4 \rightleftharpoons \text{NO}_2^+ + \text{HSO}_4^- + \text{H}_2\text{O} \quad (\text{Eq. 2})$$

This reaction tends to repress the self-dehydration of the nitric acid. Therefore the net concentration of nitronium ions is not
proportional to the concentration of the nitric acid. Also the addition of sufficient sulfuric acid to make the self-ionization of nitric acid relatively unimportant allows the nitronium ions to be produced predominately from the above ionization and the rate to follow a linear law. Nitric acid is completely converted into nitronium ions in concentrated sulfuric acid.

\[ \text{HNO}_3 + 2 \text{H}_2\text{SO}_4 \rightarrow \text{NO}_2^+ + 2 \text{HSO}_4^- + \text{H}_3\text{O}^+ \]  
\hspace{1cm} (Eq. 3)

Solutions of nitric acid in sulfuric acid of various concentrations provide reagents with a wide range of vigor. In fact, the introduction of a solution of nitric acid in sulfuric acid depends on a balance of its acidity, leading to the formation of the nitronium ions, and its basicity, which is considered to catalyze the reaction by aiding in the loss of the proton. The nitration rate increases with the concentration of sulfuric acid to 90% concentration, then decreases for an H\textsubscript{2}SO\textsubscript{4} concentration above 90% (Figure 2). This decrease is related to the diminution of the concentration of bisulphate ions which functions as the base.

Generally, mononitration proceeds at a low temperature range (0-25°C) and multinitration requires a higher temperature range (>25°C).

Reduction

The amino compounds 2,4-dichloro-5-aminobenzoic acid and methyl 2,4-dichloro-5-aminobenzoate were prepared by reduction of the respective nitro compounds. These compounds were more conveniently obtained by catalytic hydrogenation. Hydrogenations are carried
out readily in a low pressure reactor\textsuperscript{5,6,7,8,9}. The nitro group can also be reduced using zinc\textsuperscript{10} or iron\textsuperscript{9,11} in the presence of acetic acid.

![Figure 2. Rate profiles for nitration in 80-100% sulphuric acid. (Reproduced from Reference 2)](image)

Catalysts\textsuperscript{5,6,7,8,9} used for the reduction of nitro compounds include Raney nickel, palladium on charcoal, and platinum oxide. Platinum oxide is capable of promoting the hydrogenation of nitro groups.
under relatively mild conditions, typically at temperatures below 70°C and hydrogen pressures under 60 psi using ethanol as a solvent. These conditions do not lead to the hydrogenation of esters, carboxylic acids, or most amides. Platinum oxide therefore possesses good selectivity, promoting only the hydrogenation of the nitro group, and a good activity, the reaction going to completion in a short time. The overall rate may be affected by mass transfer resistance of hydrogen because of the rapid reduction of the nitro groups. In liquid-phase catalytic hydrogenations, hydrogen moves from the gas phase through the gas-liquid interface, and from the liquid phase across the liquid-solid interface to the external surface of the catalyst and then into the pore structure of the catalyst. This hydrogen movement to the catalyst is due to concentration gradients which develop when hydrogen is consumed by the catalyzed reaction. The diffusion rate of the hydrogen through the catalyst pores limits the observed reaction rate.

**Ester Formation**

Esters can be formed in a nucleophilic substitution reaction in which the nucleophile is a carboxylate anion. For example, the carboxylate anion is selectively methylated by iodomethane in aqueous solution at room temperature:

\[
\text{Ar-C}^0_0 + \text{CH}_3\text{I} \rightarrow \text{Ar-C-O-CH}_3 + \text{I}^0
\]  

(Eq. 4)

The anions of carboxylic acids are relatively weak nucleophiles toward Sp^3-hybridized carbon.
Esters can also be prepared by other methods. The silver salts of carboxylic acids can also be reacted with methylhalides, the carboxylate anions in alkali can be reacted with an excess of dimethyl sulfate\textsuperscript{12}, or tertiary\textsuperscript{13} or quaternary ammonium salts of the carboxylic acids can be heated to provide esters.

\[
\text{Ar-C}=	ext{O} + \text{CH}_3\text{N} (\text{CH}_3)_3 \rightarrow \text{Ar-C-O-CH}_3 + N(\text{CH}_3)_3 \quad (\text{Eq. 5})
\]

Numerous methods are also available which involve initial electrophilic attack on the carboxylate group, followed by a displacement of the carbonyl carbon atom of the intermediate anhydride\textsuperscript{12,14}.

\[
\text{Ar-C}=	ext{O} + \text{Ar}_1\text{SO}_2\text{Cl} \xrightarrow{\text{Pyridine}} \text{Ar-C-O-SO}_2\text{Ar}_1 + \text{Cl}^- \quad (\text{Eq. 6})
\]

\[
\text{Ar-C-S}_2\text{Ar}_1 + \text{ROH} \xrightarrow{\text{Pyridine}} \text{Ar-C-OR} + \text{Ar}_1\text{SO}_3^- + \text{H}^+ \quad (\text{Eq. 7})
\]

Also these esters can be prepared by reacting the respective carboxylic acids with methyl alcohol\textsuperscript{12,15}. This method has some disadvantages. The reaction rate is quite slow and the equilibrium conversion is limited by the reverse hydrolysis reaction. It can be accelerated by the presence of $H^+$ ions\textsuperscript{15,16,17} which play a catalytic role. This process leads to an equilibrium according to the following equations:

\[
\text{R}_1\text{-OH} + \text{R}_2\text{-CH}=	ext{O} \xrightleftharpoons{H^+} \text{R}_2\text{-CH}=	ext{O} + \text{H}_2\text{O} \quad (\text{Eq. 8})
\]

Temperature affects only the rate of reaction. Factors improving the yield of the ester include the use of an excess of one of the
reactants, and continuous removal of one of the reaction products.

Another advantageous method is to first convert the carboxylic acid to a more reactive functional derivative such as an acyl halide, which is then reacted with the alcohol.

$$\text{R}_1\text{-OH} + \text{R}_2\text{C}=\text{Cl} \rightarrow \text{R}_2\text{C}=\text{O} + \text{HCl}$$  \hspace{1cm} (Eq. 9)

Hydrazide Formation

A hydrazide is an organic compound formed when one or more acyl substituents replaces a hydrogen on the nitrogens of a hydrazine molecule.

Monoacylhydrazides are prepared by heating an excess of hydrazine with the corresponding ester.

$$\text{ArCOOCH}_3 + \text{NH}_2\text{NH}_2 \underset{\Delta}{\rightarrow} \text{ArCONHNH}_2 + \text{CH}_3\text{OH}$$ \hspace{1cm} (Eq. 10)

Monoacylhydrazides can also be synthesized by reacting hydrazine with the corresponding aromatic carboxylic acids.

$$\text{ArCOOH} + \text{H}_2\text{NNH}_2 \rightarrow \text{ArCONHNH}_2 + \text{H}_2\text{O}$$ \hspace{1cm} (Eq. 11)

However, as with amines, it is seldom of practical synthetic value owing to the competitive acid-base reaction (Eq. 12).

$$\text{ArCOOH} + \text{NH}_2\text{NH}_2 \leftrightarrow [\text{ArCO}_2]^-[\text{NH}_2\text{NH}_3]^+$$ \hspace{1cm} (Eq. 12)

The unsymmetrical 1,2-diacylhydrazides may be prepared by reacting equal molar amounts of aromatic acyl chloride with the corresponding monoacylhydrazides.

$$\text{Ar}_1\text{CONHNH}_2 + \text{Ar}_2\text{COCl} \underset{\text{THF}}{\rightarrow} \text{Ar}_1\text{CONHNHCOAr}_2$$ \hspace{1cm} (Eq. 13)

Commonly the symmetrical 1,2-diacylhydrazides are prepared in
excellent yields by reaction of acylhalides with hydrazine (Eq. 14). They can also be obtained by the oxidation of the corresponding monoacylhydrazide with iodine (Eq. 15).

\[
\begin{align*}
2 \text{ArCOCl} + \text{H}_2\text{NH}_2 & \rightarrow \text{ArCONHNHCOAr} \quad \text{(Eq. 14)} \\
2 \text{ArCONHNH}_2 + \text{I}_2 & \rightarrow \text{ArCONHNHCOAr} \quad \text{(Eq. 15)}
\end{align*}
\]

Diacylation of a single amino group is possible, although difficult. The product N,N-diacylamines\(^{21}\) (or N-acylamides) are relatively unstable and are powerful acylating agents. Diacylamines are not normally formed from esters.

**Oxadiazole Formation**

2,5-diaryl-1,3,4-oxadiazoles are generally prepared by internal dehydration reactions of the corresponding 1,2-diacylhydrazides in the presence of PPA (Eq. 16).

\[
\begin{align*}
\text{Ar}_1\text{C-NH-NH-C-Ar}_2 & \xrightarrow{\text{PPA}} \text{Ar}_1\text{N} = \text{N} - \text{Ar}_2 + \text{H}_3\text{PO}_4 \quad \text{(Eq. 16)}
\end{align*}
\]

These five-membered ring heterocyclics are easily formed from 1,2-diacylhydrazides. They can also be obtained by using P\(_2\)O\(_5\)\(^{18}\) instead of PPA, or by a universal method involving the reaction of an acylhydrazide with an imido ester or its hydrochloride\(^{22,23,24,25,26,27,28}\) (Eq. 17).

\[
\begin{align*}
\text{ArCONHNH}_2 & \xrightarrow{\text{Ar}_1\text{C(OR)NH}_2\text{HCl}^-} \text{Ar}_1\text{N} = \text{N} - \text{Ar}_1 \quad \text{(Eq. 17)}
\end{align*}
\]
II. EXPERIMENTAL

A. Preparation of 2,4-dichloro-5-nitrobenzoic acid

NOTE: All nitro compounds are poisonous and must be handled carefully. If any nitro compound comes in contact with the skin, remove immediately by washing with ethanol, followed by thorough washing with soap and water.

Into a 500 ml three-neck round bottom flask fitted with a mechanical stirrer, a pressure equalizing addition funnel, and a thermometer, were placed 200 ml of 90% concentrated sulfuric acid. After cooling to 0°C, 95 g (~0.5 mol) of powdered 2,4-dichlorobenzoic acid were added with stirring, followed by the dropwise addition of a cooled mixture of 41.67 ml of 70.6% concentrated nitric acid and 41.67 ml of 90% concentrated sulfuric acid. During the addition of the nitrating acids, which required 45 to 60 min, the temperature of the reaction mixture was kept within a range of 5-15°C.

After the complete addition of the nitrating acids, stirring was continued for 15 to 30 min. The mixture was then poured onto 1300 g of cracked ice and stirred by hand using a glass stirring rod. The crude 2,4-dichloro-5-nitrobenzoic acid separated as a solid and was filtered off by means of suction and washed with water until the pH of the wash filtrate exceeded 2. The crude, wet product was then placed in a beaker and agitated with 200 ml of cold 95% ethyl alcohol in order to remove a small part of the 3-nitro isomer and other impurities. The cooled mixture was then filtered by means of suction,
washed with a 100 ml portion of cold 95% ethyl alcohol and the solid product was dried at 90°C. The yield was 110.45-112.5 g (94-96% of theoretical yield) of a pale yellow product which melted at 160-165°C. After recrystallization from hot 50% ethanol, the product melted at 161-164°C (literature value 161-163°C).

**TABLE 1**

<table>
<thead>
<tr>
<th>Compound</th>
<th>M.P.</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-dichloro-5-nitrobenzoic acid</td>
<td>161-164°C</td>
<td>94-96</td>
</tr>
</tbody>
</table>

**NMR-IR Data**

**NMR:** \( (\text{CDCl}_3) \delta 12.65 (m, 1\text{H}); 7.75 \text{ and } 8.55 (m, 2\text{H}) \)

**IR:** (mineral oil) cm\(^{-1}\) 3120, 1725-1700 (broad), 1550 and 1309.

**B. Preparation of Amino Compounds**

**Method A\textsuperscript{10}: 2,4-dichloro-5-aminobenzoic acid**

A sample of 41.43 g (0.1756 mol) of 2,4-dichloro-5-nitrobenzoic acid was dissolved in 123 ml of water containing 9.60 g of sodium carbonate. The solution was then acidified with 17.6 ml of 40% acetic acid and heated until the precipitate dissolved completely. The solution obtained was added over a period of 2 hr by means of a dropping funnel to a boiling suspension of 175.56 g. of zinc dust in 445 ml of 0.63% acetic acid. The reaction proceeded with strong frothing of the solution so that vigorous stirring was necessary during the addition to avoid mechanical losses. At the end of the reaction, the solution was cooled and a solution of 9.6 g of sodium carbonate
in 35.1 ml of water was added while stirring. The reaction mixture was filtered to remove the zinc dust, and the filtrate adjusted to pH 5 with 10% hydrochloric acid, liberating a voluminous white precipitate, which was collected by vacuum filtration and dried in a dessicator. A yield of 25.16 g (~65.6% of theoretical yield) of 2,4-dichloro-5-aminobenzoic acid was obtained. After recrystallizing from hot 50% ethanol, the substance had a mp of 196-199°C. The literature reported 90% yield\textsuperscript{10}, but even though the highest speed of the mechanical stirrer was used, lower yields were obtained.

The solution containing the 2,4-dichloro-5-nitrobenzoic acid crystallized on cooling in the dropping funnel in several runs, so the solution was added to the boiling zinc solution over a period of 35-60 min, and the reaction was kept running for 2 more hr.

Method B\textsuperscript{11}: 2,4-dichloro-5-aminobenzoic acid

In a 500 ml three-neck round bottom flask were placed 58 g of iron powder, 300 ml water, 5 ml glacial acetic acid, and 50 ml of 2-propanol. Over the course of 90 min, while stirring and refluxing, 47 g (0.2 mol) of 2,4-dichloro-5-nitrobenzoic acid was gradually added. Refluxing and stirring were continued for 3 hr before adjusting the pH to 10 with a 10% sodium hydroxide solution. The hot solution was filtered and the cake was digested with additional alkaline solution. The combined filtrates were concentrated under reduced pressure to a volume of about 500 ml. The filtrates were put in a suction filtration Erlenmeyer flask which was sealed with a rubber stopper. The Erlenmeyer flask was then heated to 80°C by means of a hot water
bath in order to remove all the water present in the solution. After cooling, the solution was brought to a pH of 6.5-7.0 with hydrochloric acid. After chilling, the resultant semi-solid mass was filtered by suction and recrystallized from hot 50% ethanol. The yield of dry product was 13.54 g (33% of theoretical yield). The mp of this material was 196-200°C.

Method C: 2,4-dichloro-5-aminobenzoic acid

A low pressure Parr hydrogenator was charged with a solution of 10 g (0.042 mol) of 2,4-dichloro-5-nitrobenzoic acid, 2 mg of platinum oxide and 25 ml of 95% ethyl alcohol. After shaking for 1 hr, the solution was filtered to remove the catalyst and the filtrate was cooled in an ice bath to allow the product to crystallize. About a 7 psi drop in H₂ pressure per 1.0 mol of H₂ absorbed was generally observed in the apparatus. A yield of 7.1 g of crude 2,4-dichloro-5-aminobenzoic acid (81.32% of theoretical yield) was obtained. When 100 ml of 95% ethanol was used the yield was 61% of theoretical amount. After recrystallization from hot 50% ethyl alcohol, 6.99 g of product was obtained and the mp was 196-200°C. Literature value 198-199°C¹¹, 196-197°C¹⁰.

<table>
<thead>
<tr>
<th>Method</th>
<th>Compound</th>
<th>M.P.</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2,4-dichloro-5-aminobenzoic acid</td>
<td>196-199</td>
<td>65.6</td>
</tr>
<tr>
<td>B</td>
<td>2,4-dichloro-5-aminobenzoic acid</td>
<td>196-200</td>
<td>33</td>
</tr>
<tr>
<td>C</td>
<td>2,4-dichloro-5-aminobenzoic acid</td>
<td>196-200</td>
<td>81.32</td>
</tr>
</tbody>
</table>

NMR: (d₆-DMSO/CDCl₃)s 7.38 and 7.28 (s,2H)

IR: (mineral oil) cm⁻¹ 3480 and 3400, 1700, 1300, 780.
C. Preparation of Methyl 2,4-dichloro-5-nitrobenzoate

\[
\begin{align*}
\text{Ar-C-OH} & \xrightarrow{\text{NaOH/H}_2\text{OCH}_3\text{I}} \text{HMPA} \\
\text{Ar-C-OCH}_3 & + \text{Na}^+ \text{I}^-
\end{align*}
\]

Into a 250 ml Erlenmeyer flask with a magnetic stirring bar were placed 23.6 g (0.10 mol) of powdered 2,4-dichloro-5-nitrobenzoic acid and 60 ml of HMPA. The solution was stirred until complete dissolution. With continued stirring, 13.2 ml of a 25% solution of sodium hydroxide (0.11 mol) were added. This solution was then stirred for 2 hr at room temperature. Then 10 ml water and 28.4 g (0.20 mol) of methyl iodide (100% excess) were added. The water was added to dissolve the sodium salt that had precipitated. Stirring was continued at room temperature for 3 hr. The reaction mixture was then poured into a 500 ml separatory funnel containing 100 ml of 5% hydrochloric acid solution. This aqueous system was extracted with three 75 ml portions of purified diethyl ether. The combined ether extracts were washed with 60 ml of saturated sodium bicarbonate and then with three 75 ml portions of water. The extract was dried over anhydrous magnesium sulfate overnight. After filtration, the ether was removed under vacuum. The 23 g of residue (92% of theoretical yield) crystallized readily with a mp of 52-57°C. Recrystallization from hot 50% ethanol leads to a high purity compound.

Use of this procedure for the preparation of the corresponding amino ester by the treatment of 2,4-dichloro-5-aminobenzoic acid with methyl iodide yielded a mixture of the desired compound with the N-methylamino derivative in approximately 3 to 1 ratio. The 5-amino
methyl ester was therefore prepared by the hydrogenation of the 5-nitro methyl ester.

Methyl 2,4-dichloro-5-aminobenzoate was also prepared by hydrogenation of methyl 2,4-dichloro-5-nitrobenzoate. The yield was 89% of theoretical yield.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M.P.</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Methyl 2,4-dichloro-5-nitrobenzoate</td>
<td>52-57</td>
<td>92</td>
</tr>
<tr>
<td>2. Methyl 2,4-dichloro-5-aminobenzoate</td>
<td>95-99</td>
<td>89</td>
</tr>
</tbody>
</table>

**Compound 1**

NMR-IR Data

NMR: (C\(_6\)Cl\(_3\)) 6 4.0 (m,3H), 7.7 and 8.5 (5,2H).

IR: (mineral oil) cm\(^{-1}\) 1715, 1550 and 1349, 1091, 785.

**Compound 2**

NMR: (\(d_6\)DMSO/C\(_6\)Cl\(_3\)) 6 3.8 (m,3H) 4.6-4.81 (broad, 2H)

IR: (mineral oil) cm\(^{-1}\) 3478 and 3378, 1715, 1631, 1300, 1102.

D. Preparation of Hydrazides

1. Preparation of monoacylhydrazines

\[ \text{Ar}-\text{C-O-CH}_3 + \text{H}_2\text{N-NH}_2 \xrightarrow{\text{MeOH}} \text{Ar}-\text{C-NH-NH}_2 + \text{CH}_3\text{OH} \]

N-(2,4-dichloro-5-nitrobenzoyl)hydrazine

Into a 500 ml three-neck round bottom flask, fitted with a mechanical stirrer, a condenser, thermometer and a drying tube containing anhydrous calcium sulfate were directly weighed 14.4 g (0.288 mol) of hydrazine monohydrate in a fume hood. Then 125 ml of methanol were added. While stirring the solution at room temperature, 12 g (0.048 mol) of powdered methyl 2,4-dichloro-5-nitrobenzoate were added.
gradually. Stirring was continued at room temperature for 2-4 hr. Then the reaction was refluxed with stirring overnight. After cooling the flask, the methanol was removed using a rotary evaporator. The solid residue was removed from the flask with hexane, filtered, washed with 30-40 ml of hexane, then with water until an amber color was obtained. The product was then washed with 30 ml of hexane. The product, 2,4-dichloro-5-nitrobenzoylhydrazine, was found to be soluble in 5% hydrochloric acid. The product was dried at a pressure of 3.0 mm Hg yielding 10.98 g (91.5% yield of an amber solid.

N-(2,4-dichloro-5-aminobenzoyl) hydrazine

This compound was prepared in a manner similar to that described above by the reaction of 2.39 g of methyl 2,4-dichloro-5-aminobenzoate, 3.27 g of hydrazine monohydrate in 50 ml of methanol. The yield of dry product was 1.99 g (83% of theoretical yield).

---

<table>
<thead>
<tr>
<th>Aryl Group</th>
<th>Color</th>
<th>M.P.</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2,4-dichloro-5-nitrophenyl</td>
<td>amber</td>
<td>224-226</td>
<td>91.5</td>
</tr>
<tr>
<td>2. 2,4-dichloro-5-aminophenyl</td>
<td>white</td>
<td>192-193</td>
<td>83</td>
</tr>
</tbody>
</table>

NMR-IR Data

1. NMR: \((d_6\text{DMSO/Cl}_3)\)
   - 3.74 (S,2H), 6.97 (S,1H), 8.43 and 8.62 (S,2H).
   - IR: (mineral oil) cm\(^{-1}\)
     - 3400-3300 and 3300-3250 (broad), 1670, 1640, 1551 and 1360, 780.

2. NMR: \((d_6\text{DMSO/Cl}_3)\)
   - 9.35 (broad), (S,1H), 7.15 and 6.85 (m,2H), 528 (broad), (S,2H).
   - IR: (mineral oil) cm\(^{-1}\)
     - 3469 and 3360, 3325 and 3290 (broad), 1651, 1620, 1600, 1331, 785.
2. Preparation of substituted 1,2-diarylhydrazides

N-(2,4-dichloro-5-nitrobenzoyl)-N'-(2,4-dichlorobenzoyl) hydrazine

Into a 500 ml one-neck round bottom flask fitted with a magnetic stirring bar, a condenser and a 100 ml addition funnel were added 12.50 g (0.05 mole) of 2,4-dichloro-5-nitrobenzoylhydrazide, 4.2 g (0.50 mol) of sodium bicarbonate, 120 ml of THF and 120 ml of water. (The relative amounts of water and THF are dependent upon the solubility of the solids in this binary system). The mixture was stirred until the solids were completely dissolved. With continued stirring, 10.5 g (0.050 mol) of 2,4-dichlorobenzoyl chloride were added dropwise to the flask at room temperature. Stirring was continued overnight at room temperature. Two phases were observed. The THF and water were removed using a rotary evaporator. Some cracked ice was added to the flask in order to facilitate removal of the product on the wall of the flask. The product was poured into approximately 100 ml of ice water, and stirred until all of the ice melted in order to induce further crystallization. The resulting golden-yellow solid was filtered, washed with 100 ml cold water, then 30 ml of 5% HCl solution in order to remove the unreacted monoacylhydrazine and then washed with water until the pH of the wash liquid reached 7. After drying under vacuum the yield of N-(2,4-dichloro-5-nitrobenzoyl)-N'-(2,4-dichlorobenzoyl) hydrazine was 19.5 g (92.2% of theoretical yield).

N-(2,4-dichloro-5-nitrobenzoyl)-N' benzoyl hydrazine

This compound was prepared in a manner similar to that described above, by the reaction of 0.9125 g of N-2,4-dichloro-5-nitrobenzoyl hydrazine, 0.3066 g of sodium bicarbonate, and 0.5086 g of benzoyl
### TABLE V

Experimental Data for the Preparation of Diacylhydrazines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar₁</th>
<th>Ar₂</th>
<th>Color</th>
<th>M.P. (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4-dichloro-5-nitrophenyl</td>
<td>2,4-dichlorophenyl</td>
<td>golden-yellow</td>
<td>276 (dec)</td>
<td>97.0</td>
</tr>
<tr>
<td>2</td>
<td>2,4-dichloro-5-nitrophenyl</td>
<td>phenyl</td>
<td>golden-yellow</td>
<td>251-256 (dec)</td>
<td>98.3</td>
</tr>
<tr>
<td>3</td>
<td>2,4-dichloro-5-aminophenyl</td>
<td>2,4-dichlorophenyl</td>
<td>white</td>
<td>243-247</td>
<td>99.4</td>
</tr>
<tr>
<td>4</td>
<td>2,4-dichloro-5-aminophenyl</td>
<td>phenyl</td>
<td>white</td>
<td>204-210</td>
<td>99.8</td>
</tr>
</tbody>
</table>

### NMR/IR DATA

Entry 1  
N-(2,4-dichloro-5-nitrobenzoyl)-N-(2,4-dichlorobenzoyl)hydrazine  
IR (mineral oil) cm⁻¹ 3379, 3199 (broad), 1670, 1620, 1465 and 790.  
NMR (DMSO-CDCl₃) 3.91 (m,2H), 6.5-8.65 (broad, 3H), 9.58, and 9.67 (s,2H).

Entry 2  
NMR (DMSO-CDCl₃) 3.98 (m,2H), 6.68-8.4 (broad m,5H), 9.59 and 9.7 (s,2H)  
IR (mineral oil) cm⁻¹ 3390-3140 (broad), 1670, 1625, 1465 and 790.

Entry 3  
NMR (DMSO-CDCl₃) 3.4 (m,2H), 5.55 (s,2H), 7.15-7.8 (s,3H) and 8.19 (s,2H).  
IR (mineral oil) cm⁻¹ 3491 and 3385, 3240 (broad), 1666, 1600, 1470, 790.

Entry 4  
NMR (DMSO-CDCl₃) 3.76 (broad m,2H), 6.8-7.85 (broad s,5H), 9.5 and 9.9 (s,2H)  
IR (mineral oil) cm⁻¹ 3491 and 3385, 3240 (broad), 1666, 1610, 1470, 790.
chloride in 60 ml of THF and 60 ml of water. The yield of the dry product was 1.2701 g (98.3% of theoretical yield).

\[
\text{N-}(2,4\text{-dichloro-5-aminobenzoyl})-\text{N-}(2,4\text{-dichlorobenzoyl}) \text{ hydrazine}
\]

This compound was prepared in a manner similar to that described above, by the reaction of 1.1640 g of N-2,4-dichloro-5-aminobenzoylhydrazine, 0.4444 g of sodium bicarbonate, and 0.7437 g of benzoyl chloride in the presence of 60 ml of THF and 60 ml of water. The yield of dry product was 1.71 g (99.75% of theoretical yield).

3. Preparation of 2,5-disubstituted-1,3,4-oxadiazoles

\[
\begin{align*}
\text{Ar}^- \text{C-} & \text{NH-NH-} \text{Ar}_2 \; \xrightarrow{\text{PPA}} \; \text{Ar}_1^- \text{N-} \text{N}^- \text{Ar}_2 + \text{H}_3\text{PO}_4
\end{align*}
\]

2-(2,4-dichloro-5-nitrophenyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole

The equipment consisted of a 250 ml three-neck round bottom flask fitted with a Friedrich condenser, thermometer and a mechanical stirrer. In this reaction, 200 g of PPA was used for every 0.1 mol of diacylhydrazine. To the flask was added 56 g of PPA which was weighed directly into the flask in a fume hood. The flask was heated to about 50°C in order to decrease the viscosity of the PPA at which time 11.8 g (0.028 mol) of N-[2,4-dichloro-5-nitrobenzoyl]-N- (2,4-dichlorobenzoyl) hydrazine was added in one portion. The reaction mixture was heated with stirring for 5 hr at 130°C. The flask and contents were cooled to below 100°C and 210 ml of water was added to the flask (300 ml water is added to the flask for every 80 g of PPA utilized in the reaction). This mixture was stirred for 45-50 min and a precipitate formed. The contents of the flask were poured into a beaker containing about 300 g
of cracked ice. This was then stirred until the ice was completely melted. The cooled solution was then filtered. The solid product was washed with 500 ml cold water, vacuum filtered thoroughly and dried at 0.7 mm Hg. The yield of dry product was 10 g (88% of theoretical yield).

2-(2,4-dichloro-5-nitrophenyl)-5-phenyl-1,3,4-oxadiazole

This compound was prepared in a manner similar to that described above, by the reaction of 1.0464 g of N-(2,4-dichloro-5-nitrobenzoyl)-N'-benzoylhydrazine, 5.9118 g of PPA and 22.17 ml of water. The yield of dried product was 0.8642 g (87.02% of theoretical yield).

2-(2,4-dichloro-5-aminophenyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole

This compound was prepared in a manner similar to that described above, by the reaction of 2.0219 g of N-(2,4-dichloro-5-aminobenzoyl)-N-(2,4-dichlorobenzoyl)hydrazine, 10.2985 g of PPA and 38.6 ml of water. The yield of dried product was 1.915 g (99.25% of theoretical yield).

2-(2,4-dichloro-5-aminophenyl)-5-phenyl-1,3,4-oxadiazole

This compound was prepared in a manner similar to that described above, by the reaction of 1.2820 g of N-(2,4-dichloro-5-aminobenzoyl)-N'-benzoyl hydrazine, 7.9135 g of PPA and 29.68 ml of water. The yield of dried product was 1.2 g (99.11% of theoretical yield).
TABLE VI
Experimental Data for the Preparation of Oxadiazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>$Ar_1$</th>
<th>$Ar_2$</th>
<th>M.P. ($^\circ$C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4-dichloro-5-nitrophenyl</td>
<td>2,4-dichlorophenyl</td>
<td>201-202 (dec)</td>
<td>88.18</td>
</tr>
<tr>
<td>2</td>
<td>2,4-dichloro-5-nitrophenyl</td>
<td>phenyl</td>
<td>198-200 (dec)</td>
<td>87.02</td>
</tr>
<tr>
<td>3</td>
<td>2,4-dichloro-5-aminophenyl</td>
<td>2,4-dichlorophenyl</td>
<td>222-225</td>
<td>99.25</td>
</tr>
<tr>
<td>4</td>
<td>2,4-dichloro-5-aminophenyl</td>
<td>phenyl</td>
<td>200-203</td>
<td>99.11</td>
</tr>
</tbody>
</table>

NMR-IR DATA

<table>
<thead>
<tr>
<th>Entry</th>
<th>NMR ($d^6$-DMSO/$C_CCl_3$)</th>
<th>IR (mineral oil) cm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.20-7.80 (m, 3H) and 7.90-8.20 (m, 2H)</td>
<td>1630, 1600 and 1385, 1040, 975.</td>
</tr>
<tr>
<td>2</td>
<td>7.25-8.20 (broad s, 5H), 8.90 and 9.65 (s, 2H)</td>
<td>1630, 1040, 1535 and 1385.</td>
</tr>
<tr>
<td>3</td>
<td>7.19-7.49 (m, 3H), 7.79-7.93 (s, 2H) and 3.98 (m, 2H)</td>
<td>3480 and 3350, 1635, 1595, 1100, 1040 and 975.</td>
</tr>
<tr>
<td>4</td>
<td>7.60-7.90 (broad m, 5H), 8.10-8.35 (s, 2H)</td>
<td>3460 and 3350, 1630, 1595, 1100, 1040 and 970.</td>
</tr>
</tbody>
</table>
III. DISCUSSION OF RESULTS

Four new 2,5-disubstituted-1,3,4-oxadiazoles were synthesized in good to excellent yields. The final products and the intermediates were characterized by IR and NMR spectra. The products were purified by recrystallization.

In order to synthesize 2,5-disubstituted-1,3,4-oxadiazoles, the carboxylic acid was first nitrated then esterified. Some of the nitro methyl ester was hydrogenated to the amine. The methyl esters were then converted to monoacylhydrazines which were converted to diacylhydrazines. The diacylhydrazines were then ring closed to form the oxadiazoles.

2,4-dichloro-5-nitrobenzoic acid was synthesized by means of mixed acids (HNO₃-H₂SO₄) and obtained in high yield. Its infrared spectra shows a strong carbonyl acid stretch at 1725-1700 cm⁻¹, the carboxylic O-H stretch at 3120 cm⁻¹, a N=O (nitro) stretch at 1550 and 1309 cm⁻¹, while its NMR spectra reveal a singlet for the carboxylic hydrogen at 12 ppm and two separated singlets for the "ortho" and "meta" phenylic hydrogen at 8.5 and 7.7 ppm. This confirms that the hydrogen in position 5 in the aromatic ring has been substituted and that there was a mononitration.

The reduction of the nitro carboxylic acid and methyl ester went readily, yielding the desired amines. The infrared spectra of 2,4-dichloro-5-aminobenzoic acid reveals two stretches at 3500 cm⁻¹ and 3400 cm⁻¹ for the N-H (primary amine), a strong carbonyl acid stretch
at 1700 cm$^{-1}$, and a C–N (amine) stretch at 1300 cm$^{-1}$. Its NMR spectra shows two closed singlets for the two isolated aromatic hydrogens at 7.38 and 7.28 ppm due to the C–N–H vibration. The NMR spectra of methyl 2,4-dichloro-5-nitrobenzoate shows two separated singlets for the two aromatic hydrogens at 8.5 and 7.7 ppm, a singlet at 4.0 ppm for the three methyl hydrogens, while its infrared spectra shows a carbonyl stretch at 1715 cm$^{-1}$ due to the conjugation in the aromatic ring which has moved the absorption of the carbonyl to a higher frequency. The NMR spectra of methyl 2,4-dichloro-5-aminobenzoate shows two closed singlets (overlapping) at 7.21 and 7.30 ppm for the two aromatic hydrogens, as in 2,4-dichloro-5-aminobenzoic acid, a broad singlet at 4.6-4.8 ppm for the two amine hydrogens and a singlet at 3.8 ppm for the three methyl hydrogens. These spectra were indicative of the respective esters. The conversion of the esters into the hydrazides shows a reduced carbonyl amide stretching frequency which has moved to the right at about 1670 cm$^{-1}$. The monoacylhydrazines show in their infrared spectra a peak at 3100-3300 cm$^{-1}$ for the first amine stretch (N–H) and a peak at 3300-3290 cm$^{-1}$ for an N–H$^0$ amide, and a peak of 1620 cm$^{-1}$ for the N–H bending (1$^0$ amine). In their NMR spectra, it is seen that the amide (N--$^1$H) hydrogen shows up at 6.97 ppm, while the two amine N–H (–N–NH$_2$) hydrogens show at 3.74 ppm for the nitro compound. These data were in agreement with those given in various sources$^{29,30,31,32}$. According to Smith$^{29}$ the spectra of hydrazides, as in amides, show two bands in the "carbonyl region" at 1620 cm$^{-1}$ and 1630-1670 cm$^{-1}$. These absorptions are also cited by Jensen$^{30}$, Prevorsek$^{31}$ and others. According to Zabicky$^{32}$ the
crystalline hydrazides reveal three amide absorptions; 1625-1670 cm\(^{-1}\) (carbonyl), 1530-1570 cm\(^{-1}\) (C-N-H vibration) and 1200-1305 cm\(^{-1}\). \(\text{NH}_2\) deformation causes the weak band at 1610-1620 and accounts for the fact that hydrazide dissolved in chloroform will cause a shifted carbonyl stretch (1645-1690 cm\(^{-1}\)) and C-N-H (1500 cm\(^{-1}\)). For a dilute solution the N-H stretch band (\(\text{NH}_2\) amine) shows at about 3450 cm\(^{-1}\) and with the increase of concentration of the solution, a band gradually shows at 3340 cm\(^{-1}\). The intermolecular hydrogen bonds formation in concentrated solutions\(^{32}\) probably causes this absorption. As observed experimentally, hydrazides usually display a broad singlet (3.7-4.75) for the two hydrogens (-NH\(_2\)) in the NMR spectra. This singlet may be displaced to the left due to the C-N-H vibration of the amine group present on the phenyl radical. Diacylhydrazines usually show in the infrared spectra a broad N-H \(\text{NH}_2\) amide stretch at 3290-3370 cm\(^{-1}\) (this can be displaced by other groups such as \(-\text{NH}_2\) on the aromatic ring due to C-N-H vibration) and a carbonyl amide stretch at about 1620 cm\(^{-1}\) which is approximately 50 cm\(^{-1}\) lower than that of hydrazides. As seen experimentally, there is the absence of the 2H singlet for \(\text{NH}_2\) in the NMR spectrum, and the two amide hydrogens \(-\text{NH-NH-C-}\) show at about 3.98 ppm.

It is seen that the 2,5-disubstituted-1,3,4-oxadiazoles show in their NMR and infrared spectrum the absence of the \(-\text{N-H}\) bond in their respective regions (at about 4 ppm for the NMR and in the region of 3100-3380 cm\(^{-1}\) for the IR). The IR spectra also reveals a band at 1630 cm\(^{-1}\) for the C=N valence vibration, and two bands at 975 and
1040 cm\(^{-1}\) for the C-O bond. This indicates that the N-H amide bonds are no longer present, and there was formation of five-membered rings with three hetero atoms including double bonds N=C formation. These experimental data were verified by various literature sources. According to Katritsky and Boulton\(^{22}\), the C-O bond shows at 970 cm\(^{-1}\) while the C=N valence vibration shows at 1560-1640 cm\(^{-1}\). These data were also confirmed by others\(^{34,35}\). Sauer et al.\(^{33}\) relate infrared data for highly conjugated systems involving two or more 1,3,4-oxadiazole rings; two peaks at about 1440 cm\(^{-1}\) and 1570 cm\(^{-1}\) were observed. Generally, in 2,5-disubstituted-1,3,4-oxadiazoles there is an absence of N-H bonds in NMR and IR and the C=N stretch is at about 1590 cm\(^{-1}\).

The spectra of the oxadiazoles and the intermediates are consistent with their structural features.
IV. CONCLUSIONS

In the investigation of potential insecticides with improved biological activity, six classes of compounds were synthesized in good to excellent yields. These compounds include 2,4-dichloro-5-nitrobenzoic diacylhydrazines and 2,5-disubstituted-1,3,4-oxadiazoles. These compounds were characterized by using NMR and infrared spectroscopy.
V. RECOMMENDATIONS

To aid in future research, the following suggestions are offered:

1. For the mononitration of 2,4-dichlorobenzoic acid, one should strictly control the temperature, since a high temperature will favor dinitration and a lower temperature (>10°C) will decrease the yield.

2. In the catalytic hydrogenation of the nitro compounds, one should use the minimum amount of solvent which dissolves the reactant in order to maximize the yield.

3. Methyl 2,4-dichloro-5-aminobenzoate cannot be prepared using iodomethane since a mixture of two products results. This compound can be obtained by catalytic hydrogenation of methyl 2,4-dichloro-5-nitrobenzoate using platinum oxide.

4. The preparation of diacylhydrazines requires equal molar amounts of reactants. These reactions go well at room temperature, therefore it is not necessary to heat the mixture. One should extend the reaction time to possibly improve the yield.

5. In the preparation of 2,5-disubstituted-1,3,4-oxadiazoles, the reactant ratio is very important. The yield decreases as the amount of PPA is increased. Therefore one should run the reaction at a ratio of 400 g of PPA per every 0.2 mole of diacylhydrazine.
REFERENCES


