
Keith F. Correia
University of Central Florida

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PART I: THE SYNTHESIS OF POTENTIAL AGROCHEMICALS
PART II: THE USE OF GOLD'S REAGENT AS A LYNCH PIN IN
THE FORMATION OF FIVE- AND SIX-MEMBERED HETERO CYCLES

BY

KEITH F. CORREIA
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

Summer Term
1984
ABSTRACT

This research report focuses on two topics: the synthesis of potential agrochemicals and the use of Gold's reagent as a lynch pin to form five- and six-membered heterocycles. A diacyl hydrazide and two oxadiazoles are prepared for use as possible insecticides. Gold's reagent behaves as a one-atom and two-atom lynch pin when reacted with 1,4- and 1,5-dinucleophiles, respectively. Reaction conditions, interpretation of spectral data, and recommendations for further research are provided.
ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. John Gupton for his encouragement and guidance during my graduate research. I would also like to thank the other members of my committee, Dr. Graeme Baker and Dr. Guy Mattson for their insightful comments and suggestions regarding the preparation of this report.

I would like to thank my parents for their continued love and support throughout my undergraduate and graduate studies.

Finally, and most important, I thank God for giving me the strength and desire to succeed.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CDC(_3)</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CH(_3)Cl</td>
<td>chloroform</td>
</tr>
<tr>
<td>cm(^{-1})</td>
<td>reciprocal centimeter (wave number, IR spectrum)</td>
</tr>
<tr>
<td>δ</td>
<td>delta (NMR spectrum)</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>d of d</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>DC(_l)</td>
<td>deuterium chloride</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>D(_2)O</td>
<td>deuterium oxide</td>
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<tr>
<td>DSS</td>
<td>sodium 2,2-dimethyl-2-silapentane-5-sulfonate</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>G.R.</td>
<td>Gold's Reagent</td>
</tr>
<tr>
<td>Δ</td>
<td>heat</td>
</tr>
<tr>
<td>Hg</td>
<td>mercury</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<tr>
<td>H(_2)O(_2)</td>
<td>hydrogen peroxide</td>
</tr>
<tr>
<td>H(_2)</td>
<td>Hertz (cycles per second, NMR spectrum)</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>J</td>
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<tr>
<td>s</td>
<td>singlet</td>
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<tr>
<td>t</td>
<td>triplet</td>
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<tr>
<td>t of t</td>
<td>triplet of triplets</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TLC</td>
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PART I

THE SYNTHESIS OF POTENTIAL AGROCHEMICALS
An important area of agrochemical research is the development of new pesticides. A 1980 patent issued to Dow Chemical Company disclosed several compounds which had been found effective in controlling manure-breeding insects. The compounds were of the general formula

![Chemical Structure](image)

where Ar represents phenyl, 2-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 4-methylphenyl, 4-cyanophenyl, 2,4-dichlorophenyl, or 3,5-dichlorophenyl.

One compound had significant biological activity against such insects as houseflies and hornflies. This was 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole, designated DOWCO 416 (1).
In recent years, research efforts\textsuperscript{2,3,4} have been focused on
the preparation of similogs of DOWCO 416 as well as its diacyl
hydrazide precursor (2) The dichlorophenyl and oxadiazole moieties
together are very biologically active and have been introduced into
many of these compounds.

\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}

(2)

The objective of this research is to synthesize a diacyl hydrazide and its corresponding oxadiazole which incorporate not only
the dichlorophenyl group but also a fluoroalkyl group. The diacyl
hydrazide preparation will primarily be a reaction between a
monoacyl hydrazide and an acid chloride. In order to catalyze
the reaction, 4-dimethylaminopyridine will be added. It should
replace chlorine on the acid chloride, therefore becoming a better
leaving group in the reaction with the monoacyl hydrazide.

The oxadiazole ring closure should be achieved when the diacyl
hydrazide is reacted with polyphosphoric acid.

The biological activity of DOWCO 416 could be attributed,
in part, to the molecule's symmetry. For this reason, this
investigator will attempt the synthesis of a symmetrical oxadiazole
which has a fluoroalkoxy group attached. This compound will be
Figure 1. Sequence of reactions to be followed in the preparation of symmetrical oxadiazoles.
made by following the sequence of synthetic pathways shown in Figure 1.

The preparation of a symmetrical oxadiazole begins with the conversion of a fluoroalkoxylated benzonitrile to the corresponding benzamide. The benzamide is used to make its carboxylic acid. The acid is reacted with hydrazine hydrate and polyphosphoric acid to produce a hydrazide which is converted to an oxadiazole in one step. This method has been employed before and has been proven efficient.\textsuperscript{3,4}

The fluoroalkoxylated benzonitrile mentioned above will be made by a procedure similar to that described by Gupton and co-workers for reacting 2,2,2-trifluoroethanol with chlorobenzonitriles.\textsuperscript{5}

All compounds prepared in this research will be characterized by their NMR and IR spectra. The diacyl hydrazide and the oxadiazoles will be sent to the Agricultural Research Division of Dow Chemical for biological testing.
A. Preparation of N-(Heptafluorobutanoyl)N'-(2,4-dichlorobenzoyl) hydrazine

\[
\begin{align*}
X\!-\!C\!-\!NHNH_2 & + Y\!-\!C\!-\!Cl & \xrightarrow{\text{Et}_3N/\text{CCl}_4} & (\text{CH}_3)_2\!-\!N\!-\!\text{N} \\
\quad & & \quad \\
X\!-\!C\!-\!NHNH\!-\!C\!-\!Y & \\
\end{align*}
\]

\[X = 2,4\text{-dichlorophenyl} \quad Y = \text{heptafluoropropyl}\]

A dry, three-necked, round-bottomed flask was equipped with a thermometer, condenser, and magnetic stirrer and placed under a nitrogen atmosphere. To the flask was added 125 mL of carbon tetrachloride, 5.0 g (0.024 mol) of 2,4-dichlorobenzoylhydrazide, 2.4 g (0.024 mol) of triethylamine and a catalytic amount (20 mg) of 4-dimethylaminopyridine. The reaction vessel was placed in an ice-water bath while a solution of 5.6 g (0.024 mol) heptafluorobutyryl chloride in 30 mL of carbon tetrachloride was added drop-wise through an addition funnel (with drying tube attached). The resulting mixture was stirred overnight at room temperature. The carbon tetrachloride was then removed in vacuo. A white solid was obtained which was vacuum filtered and washed with cold deionized water. The solid was then dried in vacuo (below 0.1 mm Hg) to
give 8.5 g (88.5% yield) of product having a melting point of 137-140°C.

The hydrazide was subjected to thin-layer chromatography on Silica Gel 7GF using chloroform/methanol as the eluent (Rf value between 0.5 and 0.8). Summation of all evidence showed the product to be 95% pure. IR (Nujol): 3280, 3180, 1730, 1660, 1590, 1520, 1470, 1375, 1355, 1295, 1225, 1185, 1165, 1140, 1125, 1105, 1075, 1045, 950, 910, 875, 855, 830, 770, 760, 730 and 710 cm⁻¹. NMR (CDCl₃),(d₆-DMSO): broad multiplet in aromatic region, δ 7.20-7.70; mass spectrum m/e 177, 197, 227, 255.

B. Preparation of 2-(2,4-Dichlorophenyl)-5-(heptafluorobutanoyl)-1,3,4-oxadiazole

\[
\begin{align*}
X - C - N\text{HNNH}_2 - C - Y & \quad \text{PPA} \quad 130°C \quad 5 \text{ Hrs} \\
\end{align*}
\]

\[X = 2,4\text{-dichlorophenyl} \quad Y = \text{heptafluoropropyl}\]

Polyphosphoric acid (12.0 g) was weighed directly into a dry, three-necked, round-bottomed flask (400 g of PPA are used for every 0.2 mol of diacyl hydrazide). The flask was then equipped with a thermometer, a condenser with drying tube, and a magnetic stirrer. The acid was heated to 50°C to reduce its viscosity. Then 2.4 g (0.006 mol) of N-(heptafluorobutanoyl)-N'-(2,4-dichlorobenzoyl)-hydrazine were added. The mixture was heated with stirring for five hours at 130°C. The flask was then cooled below 100°C.
and 45 mL of water were added (150 mL of water are added for every 40 g of PPA used). The mixture was then stirred for several minutes, allowing a precipitate to form. The contents of the flask were poured into a beaker which was cooled in an ice-water bath. The solid was vacuum filtered, washed with cold water, and dried in vacuo to yield 1.7 g (73.9% yield) of product having a melting point of 55-57°C.

The product was subjected to thin-layer chromatography on Silica Gel 7GF using chloroform/methanol as the eluent. It was found to be at least 95% pure by the analytical methods used ($R_f$ value between 0.6 and 0.8). IR (Nujol): 1595, 1555, 1455, 1410, 1370, 1350, 1270, 1220, 1195, 1165, 1145, 1120, 1105, 1080, 1045, 1005, 980, 960, 920, 875, 825, and 745 cm$^{-1}$. NMR (CDCl$_3$, d$_6$-DMSO): $\delta$ 7.52-7.75 (m, 2H), 8.11 (d, J=8Hz, 1H).

C. Preparation of 4-(2',2',3',3'-Tetrafluoropropoxy)-benzonitrile

\[
\text{NaH} + \text{CF}_2\text{HCF}_2\text{CH}_2\text{OH} \quad + \quad \text{NC-} \quad \begin{array}{c}
\text{Cl} \\
\text{HMPA} \quad 200^\circ\text{C} \\
\text{6 Hrs} \\
\text{NC-} \quad \text{OCH}_2\text{CF}_2\text{CF}_2\text{H}
\end{array}
\]

A dry, three-necked, round-bottomed flask having a thermometer, condenser, and a magnetic stirrer was placed under a nitrogen
atmosphere. To the flask was charged 2.8 g (0.06 mol) of a 50:50 dispersion of sodium hydride in mineral oil. The sodium hydride was washed with 15-20 mL of hexane. The reaction vessel was kept in an ice-water bath to reduce foaming during the addition of 70 mL dry HMPA and 13.2 g (0.1 mol) of 2,2,3,3-tetrafluoropropanol. This was followed by the addition of 6.9 g (0.05 mol) of 4-chlorobenzonitrile. The reaction mixture was heated with stirring at 200°C for six hours. It was then cooled to room temperature, poured into 150 mL of water, and extracted with three 70 mL portions of ether. The combined ether extracts were washed with three 50 mL portions of water. The resultant ether phase was dried over anhydrous sodium sulfate for an hour. The solution was filtered, and the ether was removed in vacuo. The crude product was recrystallized from a 50:50 mixture of water and 95% ethanol to give 7.3 g (62% yield) of nitrile having a melting point of 78-83°C.

IR (Nujol): 2240, 1610, 1585, 1510, 1465, 1380, 1320, 1310, 1290, 1270, 1230, 1210, 1180, 1105, 1070, 955, 945, 845, 840, 820, 730, and 685 cm⁻¹. NMR (CDC₁₃): δ 4.41 (t, J=10Hz, 2H), 6.03 (t of t, J=4Hz, J=54Hz, 1H), 6.99 (d, J=8Hz, 2H), 7.64 (d, J=8Hz, 2H).
D. Preparation of 4-(2'-2',3',3'-Tetrafluoropropoxy)-benzamide

\[ \text{R-CN} + 6\text{N NaOH} \]

\[
\text{reflux}\quad \text{overnight}\quad \text{95\% EtOH}\quad \text{30\% H}_2\text{O}_2
\]

\[ \text{R-C-NH}_2 \]

\[ \text{R=} \quad \text{OCH}_2\text{CF}_2\text{CF}_2\text{H} \]

Into a dry, three-necked, round-bottomed flask equipped with a thermometer, condenser, drying tube, and magnetic stirrer was placed 2.0 g (0.009 mol) of 4-(2',2',3',3'-tetrafluoropropoxy)benzonitrile. This was followed by the addition of 1.0 mL of 6N NaOH, 4.6 mL of 95% ethanol, and 0.51 g (0.05 mol) of 30% H\text{2}O\text{2}. An ice-water bath was kept handy in the event the reaction between sodium hydroxide and hydrogen peroxide became too vigorous. The reaction mixture was refluxed with stirring overnight. The mixture was then cooled to room temperature and its pH was checked to be sure it was neutral. The ethanol was removed in vacuo. A solid remained which was collected by vacuum filtration and washed with water. The dry product had a mass of 1.5 g (68% yield) and a melting point of 123-129°C.
IR (Nujol): 3370, 3200, 1640, 1520, 1460, 1430, 1405, 1315, 1260, 1205, 1185, 1130, 1070, 955, 850, 800, 755, 680, 670, 650, and 630 cm\(^{-1}\). NMR (CDCl\(_3\), d\(_6\)-DMSO): \(\delta\) 3.03 (s, 2H), 4.44 (t, J=10Hz, 2H), 6.20 (t of t, J=4Hz, J=54Hz, 1H), 6.98 (d, J=8Hz, 2H), 7.93 (d, J=8Hz, 2H).

E. Preparation of 4-(2',2',3',3'-Tetrafluoropropoxy)-benzoic Acid

\[
\begin{align*}
R-C-NH_2 + 10\% \text{ HCl} & \xrightarrow{\text{reflux \ overnight}} R-C-OH \\
R &= \text{OCH}_2\text{CF}_2\text{CF}_2\text{H}
\end{align*}
\]

A dry, three-necked, round-bottomed flask was equipped with a thermometer, magnetic stirrer, and a condenser with a drying tube. To the flask was added 1.0 g (0.004 mol) of 4-(2',2',3',3'-tetrafluoropropoxy)-benzamide and 60 mL of 10% hydrochloric acid. The reaction mixture was refluxed with stirring overnight. The mixture was cooled to room temperature and 70 mL of water were added. It was stirred for 15 minutes, at which time a precipitate formed. The solid was collected by vacuum filtration and washed with cold water. The solid was dried in vacuo (below 0.2 mm Hg) to give 0.8 g (80% yield) of the carboxylic acid. It had a melting point of 185-188°C.
IR (Nujol): 1680, 1605, 1585, 1515, 1460, 1435, 1380, 1295, 1260, 1200, 1175, 1100, 1070, 945, 855, 835, 770, and 695 cm⁻¹.

NMR (CDCl₃, d₆-DMSO): δ 4.40 (t, J=10Hz, 2H), 6.24 (t of t, J=4Hz, J=54Hz, 1H), 6.89 (d, J=8Hz, 2H), 7.88 (d, J=8Hz, 2H).

F. Preparation of 2,5-Bis-[4-(2',2',3',3'-tetrafluoropropoxy)-phenyl]-1,3,4-oxadiazole

\[
2R-\text{C-OH} + \text{NH}_2\text{NH}_2\text{H}_2\text{O} + \text{PPA} \xrightarrow{130^\circ C \atop 5 \text{ Hrs}}
\]

\[
R = \begin{array}{c}
\text{OCH}_2\text{CF}_2\text{CF}_2\text{H}
\end{array}
\]

Polyphosphoric acid (6.0 g) was weighed into a dry, three-necked, round-bottomed flask (based on the relationship, 400 g of PPA are used for every 10 g of hydrazine hydrate). The flask was then equipped with a thermometer, magnetic stirrer, and a condenser with a drying tube. The acid was heated to 40°C and 0.15 g (0.003 mol) of hydrazine hydrate were added. At 90°C, 1.6 g (0.006 mol) of 4-(2',2',3',3'-tetrafluoropropoxy)-benzoic acid were added. The mixture was heated with stirring at 130°C for five hours. It was then cooled to 90°C and 22.5 mL of water were added (using a basis of 1500 mL of water for every 400 g of PPA). The mixture was stirred and allowed to cool to room temperature.
A precipitate formed which was collected by vacuum filtration and washed with water. The solid was dried in vacuo (below 0.2 mm Hg) to give 1.5 g (51.7% yield) of oxadiazole having a melting point of 168-170°C.

IR (Nujol): 1610, 1455, 1420, 1375, 1300, 1260, 1240, 1195, 1175, 1100, 1030, 955, 855, 835, 750, 740, and 700 cm$^{-1}$. NMR (CDCl$_3$, d$_6$-Acetone): $\delta$ 4.27 (t, $J=10$ Hz, 2H), 6.04 (t of t, $J=4$ Hz, $J=54$ Hz, 1H), 6.88 (d, $J=8$ Hz, 2H), 7.80, (d, $J=8$ Hz, 2H).
DISCUSSION OF RESULTS

The preceding synthetic methods have been used to prepare compounds for application as potential insecticides. These compounds were a diacyl hydrazide and two 2,5-disubstituted-1,3,4-oxadiazoles. All products made by the different synthesis schemes have been characterized and identified by NMR, IR, and, in the case of the diacyl hydrazide, mass spectroscopy.

Mass spectroscopy proved to be the most useful tool in identifying N-(heptafluorobutanoyl)-N'-(2,4-dichlorobenzoyl)hydrazine. Due to its large molecular weight, the compound did not show a molecular ion in its mass spectrum. It did, however, register the four distinct fragments shown below which were indicative of the hydrazide's structure.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \\
\text{m/e} = 177
\end{align*}
\]

\[
\begin{align*}
\text{O} & \\
\text{C} & \quad \text{CF}_2\text{CF}_2\text{CF}_3 \\
\text{m/e} = 197
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{NH} \quad \text{N} \\
\text{O} & \quad \text{C} & \quad \text{CF}_2\text{CF}_2\text{CF}_3 \\
\text{m/e} = 227
\end{align*}
\]

\[
\begin{align*}
\text{O} & \\
\text{C} & \quad \text{N} \quad \text{N} \quad \text{H} \\
\text{CF}_2\text{CF}_2\text{CF}_3 & \\
\text{m/e} = 255
\end{align*}
\]
The preparation of the symmetrical oxadiazole began with the fluoroalkoxylation of a chlorobenzonitrile. All subsequent compounds containing the tetrafluoropropoxy group (-OCH$_2$CF$_2$CF$_2$H) showed two unique patterns in their NMR spectra. First, a triplet appeared in the 4.2-4.4 ppm region as a result of the two hydrogens at the C-1' position. The second pattern was a triplet of triplets at 6.0-6.25 ppm due to the splitting of the hydrogen at the C-3' position.

The fluoroalkoxylated nitrile's IR spectrum showed a characteristic peak at 2240 cm$^{-1}$ due to the C≡N absorption.

The NMR spectrum of the amide prepared from this nitrile had a singlet at 3.03 ppm corresponding to the two hydrogens attached to the nitrogen. The IR spectrum revealed peaks at 3370 and 3200 cm$^{-1}$ due to $\text{NH}_2$ stretching. Carbonyl absorption appeared at 1640 cm$^{-1}$. Bending of the N–H bond caused the peak seen at 1585 cm$^{-1}$.

Infrared analysis of the carboxylic acid used to make the symmetrical oxadiazole showed a carbonyl peak at 1680 cm$^{-1}$. Absorption bands at 1380 and 1200 cm$^{-1}$ were a result of O–H bending and C–O stretching, respectively.

The IR spectra of both 2,5-disubstituted-1,3,4-oxadiazoles were most helpful in their identification. Absorption due to the C–O bond occurred at 950-960 cm$^{-1}$ and 1030-1050 cm$^{-1}$. Vibrations resulting from the C≡N bond appeared at 1610-1595 cm$^{-1}$. The spectral data for these products agrees with that reported previously for analogous compounds of 2,5-disubstituted-1,3,4-oxadiazoles.$^8$,$^9$
CONCLUSIONS

Three compounds were synthesized by the methods described for use as potential insecticides. They are N-(heptafluorobutanoyl)-N'-(2,4-dichlorobenzoyl)hydrazine, its corresponding 1,3,4-oxadiazole, and 2,5-bis-[4-(2',2',3',3'-tetrafluoropropoxy)phenyl]-1,3,4-oxadiazole. The oxadiazoles were characterized by NMR and IR spectroscopy. The diacyl hydrazide was best identified by its mass spectrum. These compounds were sent to the Agricultural Research Division of Dow Chemical for biological testing.
RECOMMENDATIONS

The following are suggestions to aid in future pesticide research:

1. This investigator achieved only minimal success in preparing batches of 4-(2',2',3',3'-tetrafluoro-propoxy)benzonitrile by procedures described in this report. Conditions for this reaction should be modified and/or new solvents for recrystallization should be evaluated.

2. Unsymmetrical oxadiazoles could be made starting with the nitrile mentioned above. This could be accomplished by using previously reported methods with slight modifications, if necessary.
PART II

THE USE OF GOLD'S REAGENT AS A LYNCH PIN IN THE FORMATION OF FIVE- AND SIX-MEMBERED HETEROCYCLES
INTRODUCTION

The preparation of the compound [3-(dimethylamino)-2-azaprop-2-en-1-ylidene] dimethylammonium chloride was first detailed by Gold in 1960. The synthetic utility and versatility of this azavinamidinium salt, referred to as "Gold's reagent" (3), have been explored in recent years.

\[
\text{Cl}^+\text{(CH}_3\text{)}_2\text{N}^-\text{C}\equiv\text{N}^-\text{N(CH}_3\text{)}_2
\]

(3)

Gupton and coworkers have investigated the reaction of Gold's reagent with various mononucleophilic species. It is an effective \(\beta\)-dimethylamino methylenating agent in the conversion of primary aryl amines to N,N-dimethylamidines, aryl methyl ketones to N,N-dimethylenamino ketones, and arylamides to N'-acyl-N,N-dimethylformamidines\(^\text{11}\) (Figure 2). Reactions with unsymmetrical enolate anions have also yielded the corresponding enamino ketones\(^\text{12}\) (Figure 3). Gold's reagent has been reacted with esters and nitroarenes to form enaminoesters and nitroenamines, respectively\(^\text{13}\) (Figure 4).
Figure 2. Examples of Gold's reagent's use as a β-dimethylamino methylenating agent.
Reactions between Gold's reagent and Grignard reagents have been studied (Figure 5). Gold's reagent is a very good formylating agent for organomagnesium species. It has been reacted with organomagnesium species followed by borane addition to produce alkyl and aryl N,N-dimethylamines.

![Figure 3. The reaction of Gold's reagent with unsymmetrical enolate anions.](image)

![Figure 4. The reactions of Gold's reagent with esters and nitroarenes.](image)
Figure 5. The reactions of Gold's reagent with Grignard reagents.

Reactions between Gold's reagent and dinucleophilic compounds have not been fully investigated. Gold has reacted amidines with his azavinamidinium salt to produce 2-monosubstituted and 2,4-disubstituted-1,3,5-triazines. Gold has also synthesized 1,2,4-triazoles by reacting hydrazines with Gold's reagent. Jutz and coworkers have reacted Gold's reagent with 2-cyanomethyl pyrrole to form a 5-azaindole.

The two preceding reports show how Gold's reagent reacts with 1,2- and 1,3-dinucleophiles. They are also examples of how Gold's reagent can function as a three-atom lynch pin (−CH=N−CH=) (Figure 6), i.e., it donates three atoms to link two nucleophilic groups thus forming new cyclic systems.

The purpose of this research is to determine how Gold's reagent will react with 1,4- and 1,5-dinucleophiles. The 1,4-dinucleophiles that will be studied are o-aminophenols and o-phenylenediamines. The 1,5-dinucleophiles are o-aminobenzoic acids, anthranilamide, and o-hydroxyacetophenone. This investigator will attempt to react these compounds with Gold's reagent and observe whether the
Figure 6. Reactions of Gold's reagent with 1,2- and 1,3-dinucleophiles.
Figure 7. Equations illustrating how Gold's reagent might act as a one-atom (a) or two-atom (b) lynch pin. The designated (*) atoms are those donated by Gold's reagent. Nucleophilic groups are represented by Z and $Z_1$. 
azavinamidinium salt acts as a three-atom lynch pin or if it functions in another capacity—possibly as a one- or two-atom lynch pin (See Figure 7).

All the compounds which will be examined in this research have been used previously to form products which could just as readily have been prepared through lynch pin transformations. Ortho-aminophenols have been reacted with nitriles and carboxylic acid derivatives to make benzoxazoles. Excellent yields of benzimidazole are obtained when o-phenylenediamine is heated with formic acid at 100°C for two hours. Chromone is the result of a spontaneous reaction between o-hydroxyacetophenone and N,N-dimethylformamide dimethyl acetal (Figure 8). These products are all examples of what a one-atom lynch pin transformation could accomplish. A proposed mechanism for such a synthetic pathway is given in Figure 9. The mechanism involves a nucleophilic attack on Gold's reagent and cyclization of the resulting intermediate with a loss of dimethyl amine.

![Figure 8. Synthesis of chromone using o-hydroxyacetophenone.](image)
Figure 9. The proposed mechanism for a one-atom lynch pin transformation with Gold's reagent.
Ortho-aminobenzoic acids have been used in the synthesis of 3H-quinazolin-4-ones (4-hydroxyquinazolines). A common preparation method involves reacting an acylantranil, made from an acetylated analog of anthranilic acid, with a primary amine at 200°C (Figure 10).

Recently Ganjian and Lalezari have reported on a procedure for making substituted 3H-quinazolin-4-ones under mild conditions. Anthranilic acid is condensed with either ethyl phenyliminoacetate or p-methyl-phenyliminofonnate in methanol at room temperature for 1-4 hours (Figure 11).

The synthesis of 3H-quinazolin-4-ones could also be achieved through a two-atom lynch pin transformation.

Figure 10. A common method for the preparation of 3H-quinazolin-4-ones.
Two possible mechanisms for this type of reaction can be seen in Figures 12 and 13. The first mechanism concerns the formation of an eight-membered intermediate which closes to a 6-4 fused system. This system undergoes a retrograde 2+2 cyclo addition to yield the desired product. The second mechanism has an intermediate formed through a one-atom lynch pin transformation. This intermediate is attacked by an amidine by-product which opens the ring system. This leads to a 2+2 cyclo addition that forms a 6-4 fused system. This system experiences a loss of DMF to give the quinazolinone. This two-atom lynch pin reaction could occur with either o-aminobenzoic acid or anthranilamide.

Figure 11. Synthesis of substituted 3H-quinazolin-4-ones at room temperature.

This investigator hopes to provide evidence of how Gold's reagent reacts with these 1,4- and 1,5-dinucleophiles. All products will be analyzed by NMR, IR, and mass spectroscopy.
Figure 12. The first of two proposed mechanisms for a two-atom lynch pin transformation with Gold's reagent.
Figure 13. The second of two proposed mechanisms for a two-atom lynch pin transformation with Gold’s reagent.
A. Preparation of Benzoxazoles

\[
\text{Dioxane} \xrightarrow{\text{reflux overnight}} \text{NaOAc/HOAc} \xrightarrow{\text{reflux 3 hrs}}
\]

Table 1
Experimental Data for the Preparation of Benzoxazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>% Yield(^a)</th>
<th>b.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>58(^b)</td>
<td>36-40 (0.1 mm Hg)(^{22})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(lit. 45 at 4 mm Hg)</td>
</tr>
<tr>
<td>2</td>
<td>4-CH(_3)</td>
<td>53(^c)</td>
<td>45-50 (0.05 mm Hg)</td>
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<tr>
<td>3</td>
<td>5-CH(_3)</td>
<td>39(^d)</td>
<td>44-46 (0.1 mm Hg)</td>
</tr>
</tbody>
</table>

\(^a\)All yields refer to distilled compounds. All compounds were subjected to thin-layer chromatography on Silica Gel 7GF with chloroform/methanol as the eluent (R\(_f\) values between 0.4 and 0.8). The evidence of all analytical methods used showed the products to be better than 95% pure.
**Benzoxazole**

A dry, three-necked, round-bottomed flask was equipped with a condenser, thermometer, and magnetic stirrer and placed under a nitrogen atmosphere. Into the flask was added 100 mL of dry dioxane followed by 5.5 g (0.050 mol) of o-aminophenol and 9.9 g (0.061 mol) of Gold's reagent. The mixture was refluxed overnight with stirring. It was then cooled to room temperature and 4.1 g (0.05 mol) of anhydrous sodium acetate were added along with 2 mL of glacial acetic acid. The mixture was refluxed for 3 hours. It was cooled to room temperature and the solvent removed in vacuo. The residue was
taken up in 100 mL of chloroform and extracted with three 50 mL portions of saturated sodium bicarbonate. The resulting chloroform phase was dried over anhydrous sodium sulfate for approximately one hour. The solution was filtered and concentrated in vacuo. NMR analysis of the crude product revealed the presence of DMF and dioxane. To remove DMF, the crude product was taken up in 50 mL of diethyl ether and washed with three 20 mL portions of water. The combined ether extracts were dried for an hour over anhydrous sodium sulfate. The solution was filtered and the diethyl ether removed in vacuo. Final purification of the compound was accomplished by distilling it with a Kugelrohr apparatus attached to a vacuum pump. This yielded 3.5 g (58%) of a liquid product. The liquid was collected at 36-40°C and 0.1 mm Hg.

B. Preparation of Benzimidazoles

\[
\begin{align*}
\text{X} & \quad \text{NH}_2 \\
\text{NH}_2 & \quad \text{G.R.} \\
\text{Dioxane} & \quad \text{reflux overnight} \\
\text{NaOAc/} & \quad \text{HOAc} \\
\text{reflux 3 hrs} &
\end{align*}
\]
### Table II

#### Experimental Data for the Preparation of Benzimidazoles

<table>
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<tr>
<th>Entry</th>
<th>X</th>
<th>% Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>m.p. (°C)</th>
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<td>63&lt;sup&gt;b&lt;/sup&gt;</td>
<td>164-171</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(lit. 170.5)&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>4,5-Dimethyl</td>
<td>83&lt;sup&gt;c&lt;/sup&gt;</td>
<td>198-202</td>
</tr>
<tr>
<td>3</td>
<td>4-CH₃</td>
<td>74&lt;sup&gt;d&lt;/sup&gt;</td>
<td>114-117</td>
</tr>
</tbody>
</table>

<sup>a</sup> All yields refer to crude products with the exception of entry 3. This product had to be distilled (b.p.=120-128°C at 0.05 mm Hg). A viscous yellow liquid was obtained and crystallization was induced. All compounds were analyzed by thin-layer chromatography on Silica Gel 7GF using chloroform/methanol as the eluent (R_f values between 0.2 and 0.8). All analytical results showed the products to be better than 95% pure.

<sup>b</sup>Benzimidazole; IR (Nujol): 3300, 3100, 1625, 1590, 1485, 1460, 1410, 1370, 1350, 1305, 1275, 1250, 1205, 1160, 1135, 1115, 1005, 960, 935, 890, 850, 770, 750, 635, 630 and 620 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>, d<sub>6</sub>-DMSO): δ 7.13 (d of d, J=2Hz, J=6Hz, 2H), 7.58 (d of d, J=2Hz, J=6Hz, 2H), 8.04 (s, 1H); mass spectrum m/e 118 (M+).

<sup>c</sup>5,6-Dimethylbenzimidazole; IR (Nujol): 1470, 1410, 1375, 1335, 1305, 1265, 1240, 1160, 1085, 1025, 1000, 955, 865, 845, and 800 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>, d<sub>6</sub>-DMSO): δ 2.34 (s, 6H), 7.40 (s, 2H), 7.97 (s, 1H); mass spectrum m/e 146 (M+).
$^d_5$-Methylbenzimidazole; IR (Nujol): 1625, 1585, 1460, 1420, 1375, 1340, 1295, 1280, 1250, 1205, 1165, 1125, 1035, 1005, 955, 880, 875, 865, 810, 800, 745, and 635 cm$^{-1}$. NMR (CDCl$_3$): $\delta$ 2.67 (s, 3H), 7.33 (d, J=8Hz, 1H), 7.67-8.02 (m, 2H), 8.45 (s, 1H); mass spectrum m/e 132 (M+).

**Benzimidazole**

A dry, three-necked, round-bottomed flask with condenser, thermometer and magnetic stirrer was placed under a nitrogen atmosphere. Into the flask was placed 100 mL of dry dioxane followed by the addition of 5.4 g (0.05 mol) of o-phenylenediamine and 9.9 g (0.061 mol) of Gold's reagent. The mixture was refluxed with stirring overnight. It was then cooled to room temperature. This was followed by the addition of 4.1 g (0.05 mol) of anhydrous sodium acetate and 2 mL of glacial acetic acid. The reaction mixture was refluxed for three hours and cooled to room temperature. Solvent was removed in vacuo and the residue was taken up in 100 mL of chloroform. It was extracted with three 50 mL portions of saturated sodium bicarbonate. The resulting chloroform phase was dried over anhydrous sodium sulfate for approximately 45 minutes. The solution was then filtered and concentrated in vacuo. A solid product remained which was collected by vacuum filtration. The yield of this reaction was 3.7 g (63%).
C. Preparation of 4-Hydroxyquinazoline from Anthranilamide

\[
\begin{align*}
\text{C. Preparation of 4-Hydroxyquinazoline from Anthranilamide} \\
\begin{align*}
\text{Anthranilamide} & \quad \text{Dioxane} & \quad \text{reflux overnight} \\
\text{G.R.} & \quad \text{NaOAc/HOAc} & \quad \text{reflux 3 hrs}
\end{align*}
\end{align*}
\]

A dry, three-necked, round-bottomed flask equipped with a condenser, thermometer and magnetic stirrer was placed under a nitrogen atmosphere. Into the flask was placed 100 mL of dry dioxane followed by 6.8 g (0.05 mol) of anthranilamide and 9.9 g (0.061 mol) of Gold's reagent. The mixture was refluxed with stirring overnight. It was subsequently cooled to room temperature. Next was added 4.1 g (0.05 mol) of anhydrous sodium acetate and 2 mL of glacial acetic acid. This mixture was refluxed for three hours, then cooled to room temperature. The dioxane was removed in vacuo leaving a solid residue. The solid was collected by vacuum filtration and washed with a minimum of deionized water. The solid was dried in vacuo (below 0.1 mm Hg). The product yield was 4.9 g (67%). The solid's melting point was 220-225°C (lit. 216-218°C). 22
IR (Nujol): 3220, 3160, 1705, 1670, 1615, 1470, 1410, 1395, 1380, 1335, 1325, 1310, 1260, 1250, 1235, 1175, 1155, 1130, 925, 915, 825, 810, 805, 780, 765, 695 and 685 cm\(^{-1}\). NMR (DCl, D\(_2\)O, DSS): \(\delta 7.64-8.42\) (m, 4H), 9.36 (s, 1H).

D. Preparation of 4-Hydroxyquinazolines from Ortho-Aminobenzoic Acids

\[
\text{X} - \text{COOH} + \text{G.R.} \xrightarrow{\text{NaH, Dioxane}} \xrightarrow{\text{reflux overnight}} \xrightarrow{\text{MeOH/HOAc}} \text{reflux 3 hrs}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(X)</th>
<th>% Yield(^a)</th>
<th>m.p. ((^\circ)C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>48(^b)</td>
<td>221-222 (lit. 216-218)(^22)</td>
</tr>
<tr>
<td>2</td>
<td>3-CH(_3)</td>
<td>63(^c)</td>
<td>264-267</td>
</tr>
<tr>
<td>3</td>
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<td>51(^d)</td>
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</tr>
<tr>
<td>4</td>
<td>5-CH(_3)</td>
<td>32(^e)</td>
<td>245-250</td>
</tr>
<tr>
<td>5</td>
<td>6-CH(_3)</td>
<td>58(^f)</td>
<td>225-227</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>5-Cl</td>
<td>49(^h)</td>
<td>265-269</td>
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</table>
All yields refer to crude products except for entry 7 which was recrystallized from a 50:50 mixture of methanol and water. All compounds were subjected to thin-layer chromatography on Silica Gel 7GF with either ethyl acetate or chloroform/ethyl acetate as the eluent ($R_f$ values between 0.2 and 0.8). Summation of the evidence showed the products to be greater than 95% pure.

b4-Hydroxyquinazoline; IR (Nujol): 3110, 1695, 1660, 1375, 1250, 1230, 1170, 1110, 920, 910, 830, 800, and 770 cm$^{-1}$. NMR (DCl, D$_2$O, DSS): $\delta$ 7.91-8.61 (m, 4H), 9.46 (s, 1H); mass spectrum m/e 146 (M+).

c8-Methyl-4-hydroxyquinazoline; IR (Nujol): 3190, 1690, 1610, 1570, 1375, 1330, 1290, 1240, 1150, 1080, 1000, 935, 860, 805, 765 and 720 cm$^{-1}$. NMR (DCl, D$_2$O, DSS): $\delta$ 2.32 (s, 3H), 7.28-7.92 (m, 3H), 9.00 (s, 1H); mass spectrum m/e 160 (M+).

d6-Methyl-4-hydroxyquinazoline; IR (Nujol): 3125, 1690, 1660, 1620, 1610, 1380, 1250, 1165, 930, 900, and 830 cm$^{-1}$. NMR (DCl, D$_2$O, DSS): $\delta$ 2.48 (s, 3H), 7.53-790 (m, 2H), 7.98 (d, $J=2$ Hz, 1H), 9.25 (s, 1H); mass spectrum m/e 160 (M+).

e6-Methyl-4-hydroxyquinazoline; this compound exhibited the same NMR and IR spectra as entry 3. The reaction was carried out identical to that for entry 3 with the exception that no sodium hydride, methanol, or acetic acid were used.

f5-Methyl-4-hydroxyquinazoline; IR (Nujol): 1680, 1660, 1625, 1600, 1380, 1300, 1295, 1260, 1045, 965, 860, 815, 790, and 770 cm$^{-1}$. NMR (CDCl$_3$, d$_6$-DMSO): $\delta$ 2.70 (s, 3H), 7.13-7.81 (m, 3H), 8.02 (s, 1H);
mass spectrum m/e 160 (M+).

9-Chloro-4-hydroxyquinazoline; the crude product had to be washed with 50 mL of saturated sodium bicarbonate for 30 minutes to remove acidic impurities. IR (Nujol): 3160, 1685, 1665, 1610, 1375, 1235, 1225, 1085, 1065, 915, 875, and 780 cm⁻¹. NMR (CDCl₃, d₆-DMSO): δ 7.50 (d of d, J=8Hz, J=2Hz, 1H), 7.73 (d, J=2Hz, 1H), 8.18 (s, 1H), 8.20 (d, J=8Hz, 1H); mass spectrum m/e 182, 180 (M+).

6-Chloro-4-hydroxyquinazoline; IR (Nujol): 1690, 1605, 1375, 1320, 1270, 1235, 1175, 1130, 1090, 1060, 925, 895, 850, and 830 cm⁻¹. NMR (d-TFA): δ 7.43-7.78 (m, 2H), 8.10 (d, J=2Hz, 1H), 9.00 (s, 1H); mass spectrum m/e 182, 180 (M+).

6-Methyl-4-hydroxyquinazoline

A dry, three-necked, round-bottomed flask equipped with a thermometer, condenser, and magnetic stirrer was placed under a nitrogen atmosphere. Into the flask was placed 2.6 g (0.053 mol) of a 50% sodium hydride-mineral oil dispersion. The sodium hydride was washed with 10 mL of hexane. The 100 mL of dry dioxane was added. To minimize gas evolution, the reaction vessel was cooled in an ice-water bath during the addition of 7.6 g (0.05 mol) of 2-amino-5-methylbenzoic acid and 9.9 g (0.061 mol) of Gold's reagent. The reaction mixture was refluxed overnight with stirring. It was then cooled to room temperature and 3 mL of methanol followed by 10 mL of glacial acetic acid were added. This mixture was refluxed for three hours, then cooled to room temperature. The solvent was
removed in vacuo. To the resultant solid was added approximately 60 mL of ice-water. The pH of the mixture was adjusted to 6-7 as needed with dilute NaOH. The mixture was filtered and the tan solid collected was dried in vacuo (below 0.1 mm Hg). The product yield was 51% and the melting point was 263-265°C.

This reaction was repeated without using sodium hydride, methanol, and acetic acid. The product yield was 32%. The solid obtained had a lower melting point (245-250°C) than that of the previous reaction. Spectral and chromatographic (TLC) properties of the two solids were identical.

E. Preparation of Chromone from Ortho-Hydroxyacetophenone

A dry, three-necked, round-bottomed flask was equipped with a condenser, thermometer, magnetic stirrer and placed under a nitrogen atmosphere. Into the flask were placed 75 mL of dry THF and 12.4 g (0.122 mol) of diisopropylamine. The temperature of the
mixture was lowered to 0°C by placing the reaction vessel in an ice-water bath. Next, 70.0 mL (0.112 mol) of n-butyl lithium were added by syringe through a rubber septum in one neck of the flask (addition of NaCl to the ice bath prevented any large temperature changes). The reaction mixture was stirred for 30 minutes at 0°C in order to form lithium diisopropyl amide. Then a solution of 5.0 g (0.037 mol) o-hydroxyacetophenone in 10 mL of dry THF was added and the mixture was left to stir for one hour. After this time, 6.7 g (0.041 mol) of Gold's reagent were added and the mixture was stirred in the ice bath an additional 30 minutes. The ice bath was then removed and the mixture was stirred overnight at room temperature. To the reaction mixture was added 5 mL of methanol and 20 mL of glacial acetic acid. The reaction temperature immediately rose to 45°C. The mixture was then refluxed for 3.5 hours. Next, it was cooled to room temperature and the solvent was removed in vacuo. The residue was partitioned between 75 mL of water and 75 mL of chloroform. The aqueous phase was extracted with two additional portions of chloroform (70 mL each). The combined chloroform extracts were washed with two 40 mL portions of saturated sodium bicarbonate. The resulting chloroform phase was dried over anhydrous sodium sulfate for at least 45 minutes. The drying agent was filtered off and the chloroform was removed in vacuo.

The NMR spectrum of the crude material showed the desired chromone and its uncyclized precursor. The crude product was
taken up in 40 mL of acetic acid and refluxed overnight. It was then cooled to room temperature and the acetic acid was removed in vacuo. The residue was taken up in 50 mL of water and extracted with three 50 mL portions of chloroform. The combined chloroform extracts were washed with two 20 mL portions of saturated sodium bicarbonate. They were dried over anhydrous sodium sulfate. The drying agent was filtered off and the chloroform was removed in vacuo. The product was purified by short-path distillation. Four fractions were collected over a temperature range of 70-78°C at pressures of 0.5-0.05 mm Hg. The pot residue was further distilled using a Kugelrohr apparatus with a vacuum pump. A solid was collected at 80°C and 0.5 mm Hg. All distillation products were subjected to TLC analysis which revealed starting material present in the first two fractions. The other fractions, including that distilled with the Kugelrohr, were pure chromone. The combined pure product had a mass of 1.7 g (31.4% yield) and melted at 54-60°C (lit. 59°C).

The TLC analysis was performed on Silica Gel 7GF using chloroform/methanol as the eluent (Rf values between 0.2 and 0.8). Analytical evidence showed the product to be 95% pure. IR (CHCl₃): 1670, 1635,1620,1585,1480,1420,1365,1340,1270,1260,1210,1145,1055,1030, 880, 850, 820, 695 and 680 cm⁻¹. NMR (CDCl₃): δ 6.41 (d, J=6Hz, 1H), 7.33-7.78 (m, 3H), 8.00 (d, J=6Hz, 1H), 8.34 (d of d, J=8Hz, J=1Hz, 1H).
DISCUSSION OF RESULTS

Gold's reagent acted as either a one-atom or two-atom lynchpin in the synthesis of benzoxazoles, benzimidazoles, chromone, and 4-hydroxyquinazolines. All compounds were identified by spectral analysis.

The benzoxazoles and benzimidazoles were analyzed by IR, NMR, and mass spectroscopy. The IR spectra of the benzoxazoles showed C-C and C-N stretching vibrations at 1330-1525 cm$^{-1}$. The C-H stretching vibrations appeared at 3100-3120 cm$^{-1}$. Absorption due to the heterocyclic ring system was seen at 1600-1615 cm$^{-1}$. The NMR spectrum of each benzoxazole showed a singlet at 8.0 ppm indicative of the hydrogen at the C-2 position.

Absorption bands in the benzimidazoles' IR spectra appeared at 770-880 cm$^{-1}$ for the imidazole ring. The aromatic C-C and C-N stretching frequencies were at 1460-1625 cm$^{-1}$. The NMR spectra of the benzimidazoles showed a singlet at either 8.0 or 8.45 ppm for the hydrogen at the C-2 position.

Preparation of the 4-hydroxyquinazolines began with the corresponding o-aminobenzoic acids (or anthranilamide for the unsubstituted hydroxyquinazoline). Spectral analysis of these compounds revealed them to be 3H-quinazolin-4-ones, the tautomeric form of 4-hydroxyquinazolines. The IR spectra of these compounds were very useful in their identification since 3H-quinazolin-4-ones show two
or three strong absorption bands at the "double bond" region, 1700-1500 cm\(^{-1}\).\(^{25,26}\) This was true of the compounds described in this report. Two or three peaks appeared at 1600-1700 cm\(^{-1}\). The NMR spectrum of the unsubstituted 4-quinazolinone, when run in a DCl-D\(_2\)O mixture, showed a strong shift of one of the aromatic hydrogens. It appeared as a singlet in the 9.0-9.5 ppm range due to its proximity to a deuterated nitrogen (as seen below). This phenomenon was observed in many of the other examples studied. Mass spectra of the compounds showed molecular ions characteristic of their structure.

Chromone was identified by its IR and NMR spectra. Its IR spectrum showed a very strong carbonyl absorption at 1670 cm\(^{-1}\). The NMR spectrum revealed a doublet at 6.41 ppm for the hydrogen at the C-3 position and another doublet at 8.00 ppm for the hydrogen at the C-2 position. This spectral data is in good agreement with literature values reported for chromone.\(^{27}\)
CONCLUSIONS

Gold's reagent has been successfully used in the synthesis of substituted and unsubstituted benzoxazoles, benzimidazoles, and 3H-quinazolin-4-ones. It has also been effective in the preparation of chromone. All compounds were characterized by NMR and IR spectroscopy. Most of the compounds were also identified by mass spectroscopy.

The results of this research offer proof that Gold's reagent can function as a one-atom lynch pin for 1,4-dinucleophiles. Depending on the reaction conditions, Gold's reagent behaves as either a one-atom or two-atom lynch pin for 1,5-dinucleophiles.
RECOMMENDATIONS

The following are recommendations for further research into
Gold's reagent's lynch pin transformations.

1) The action of Gold's reagent with 1,4- and 1,5-dinucleo-
philes should be studied in greater detail. The compounds
shown below are suggested as possibilities for future
research.

\[ \text{Compounds:} \]

- \( \text{\( \text{O} \)} \text{\( \text{NH}_2 \)} \text{\( \text{OH} \)} \)
- \( \text{\( \text{O} \)} \text{\( \text{CH}_3 \)} \text{\( \text{NH}_2 \)} \)
- \( \text{\( \text{O} \)} \text{\( \text{CH}_3 \)} \text{\( \text{CH}_3 \)} \)
- \( \text{\( \text{O} \)} \text{\( \text{NH}_2 \)} \text{\( \text{NHR} \)} \)
- \( \text{\( \text{O} \)} \text{\( \text{OH} \)} \text{\( \text{OH} \)} \)
- \( \text{\( \text{O} \)} \text{\( \text{NH}_2 \)} \text{\( \text{SH} \)} \)
Unsuccessful attempts have been made by this investigator with salicylamide, o-aminoacetophenone and salicylic acid. Conditions different from those described in this report should be studied (e.g., greater stoichiometric amount of Gold's reagent, different solvent, etc.).

2) Reactions in which the lynch pin transformation results in a substituted cyclic system should be investigated. An example is shown below.

![Chemical Structure](image)

3) Synthesis of 3H-quinazolin-4-one from anthranilamide gives a higher yield than synthesis of the same product from anthranilic acid. Preparation of substituted 3H-quinazolin-4-ones (see Experimental, Part D) from the corresponding ortho-aminobenzamides should be considered to determine if higher yields of these compounds can be obtained. The findings of such a study could be significant if one or both of these procedures were considered for industrial scale-up.

4) The reaction conditions for the chromone preparation need to be modified in order to make the synthesis more convenient. After the 20 mL addition of acetic acid, the reaction mixture
could be refluxed overnight instead of just 3.5 hours to eliminate the uncyclized precursor. Another change would be to remove the solvent after the methanol addition and reflux the crude material in acetic acid overnight.
REFERENCES


