Reactions of (3-(DIMETHYLAMINO)-2-AZAPROP-2-EN-1-YLIDENE) Dimethylammonium Chloride (Gold's Reagent) with Carboxylic Acid Derivatives and Grignard Reagents

Summer 1981

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REACTIONS OF [3-(DIMETHYLAMINO)-2-AZAPROP-2-EN-1-YLIDENE] DIMETHYLAMMONIUM CHLORIDE (GOLD'S REAGENT) WITH CARBOXYLIC ACID DERIVATIVES AND GRIGNARD REAGENTS

BY

DALE E. POLK, JR.
B.S., University of Central Florida, 1980

RESEARCH REPORT

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

Summer Quarter 1981
Abstract

An azavinamidium salt, [3-(Dimethylamino)-2-azaprop-2-en-1-ylidene] dimethylammonium chloride was reacted with primary amides, esters containing an \(\alpha\)-methylene group and Grignard reagents. The reaction of this azavinamidium salt with amides and esters produced respectively, acyl amidines and enamino esters. Both of these products were produced in high yields by using relatively mild conditions. Reaction of the salt with Grignard reagents resulted in a novel synthesis of aldehydes. This aldehyde synthesis was shown to be of general utility and to proceed in high yields.
Acknowledgements

This work was supported by grants from the Research Corp., the Agricultural Division of Dow Chemical and the National Science Foundation.
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Glossary of Abbreviations

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<tbody>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>I.R.</td>
<td>Infrared spectrum</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance (proton)</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatograph</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
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<tr>
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<tr>
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<tr>
<td>HOAc</td>
<td>acetic acid</td>
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I. Introduction

A. Iminium Salts.

Organic chemists have given much consideration to the preparation\(^1\) and synthetic use\(^2\) of preformed iminium salts. Iminium salts are of special interest when reacted with nucleophiles which can lead to pyrazoles, oxazoles, pyrimidines, diazepines, quinolines, and quinolizines\(^3\).

The iminium ion \(^{1}\) is the parent from which all other iminium salts are derived\(^4\).

\[
\begin{array}{c}
\text{R}_1^+ \\
\text{C} \\
\text{N} \\
\text{R}_2 \\
\text{R}_4
\end{array}
\quad \leftrightarrow \quad
\begin{array}{c}
\text{R}_1^+ \\
\text{C} \\
\text{N} \\
\text{R}_2 \\
\text{R}_4
\end{array}
\]

\[(\text{I})\]

Vinamidinium salts are closely related to iminium salts and represent vinylogs of amidinium ions\(^5\).
The vinamidinium salts have inherent stability due to the delocalization of charge through the 6 pi electron system. This delocalization of charge gives these systems pseudo aromaticity and their characteristic reaction mode of undergoing substitution instead of addition. The counter anions of the iminium salts usually do not affect the reactivity of the compound. It has been found that changing the counter anion in some salts from chloride to perchlorate will make the salt less hygroscopic and will also decrease the solubility of the salt in some organic solvents and water. The counter anions can be exchanged through acid base type reactions.

All vinamidinium salts exist as one of three geometric isomers. All-cis (U') (2), all trans ('W') (3), and cis-trans ('sickle') (4).

\[
\text{CH}_3\text{N}^{+}\text{CH}_3 \quad \text{CH}_3\text{N}^{+}\text{CH}_3\text{N}^{+}\text{CH}_3
\]

\[
\text{CH}_3\text{N}^{+}\text{CH}_3\text{N}^{+}\text{CH}_3
\]

\[
\text{CH}_3\text{N}^{+}\text{CH}_3
\]
B. Gold's Reagent (Azavinamidinium Salt).

In 1960 Gold reported that the reaction between cyanuric chloride and N,N-dimethylformamide resulted in the quantitative formation of a novel azavinamidinium salt, [3-(dimethylamino)-2-azaprop-2-en-1-ylidene] dimethylammonium chloride (5).

\[
\begin{array}{ccc}
\text{Cl} & \text{Cl} & \text{Cl} \\
\text{N} & \text{N} & \text{N} \\
\text{C} & \text{C} & \text{C} \\
\end{array} + 6\text{(CH}_3\text{)}_2\text{N} - \text{C} - \text{H} \xrightarrow{\Delta} 3 \text{CO}_2 \\
\text{Cl}^\ominus
\]

The following mechanism was proposed for the formation of the iminium salt.
It was subsequently determined by x-ray diffraction that this iminium salt (5) existed in the "W" configuration. This is consistent with $^1$H-NMR Spectrum (CDCl$_3$) since the dimethyl peaks are not equivalent indicating that they are fixed in a plane allowing no free rotation. The equivalency of the "vinylic like" hydrogens indicates molecular symmetry and that the salt exists in the delocalized, deionized state.

Although Gold reacted (5) with hydrazines $^6$ to produce 1,2,4-triazoles, characterization of the reaction of (5) with other nucleophiles was incomplete. Therefore, it was hoped that the novel reaction of Gold's reagent with other reactants would lead to synthetically useful pathways. The nucleophiles investigated were primary amides, esters containing methylene carbons and Grignard reagents.
II. Experimental

3-[(Dimethylamino)-2-azaprop-2-en-1-ylidene] dimethylammonium Chloride. In a 1 ℓ, one-necked, round-bottomed flask equipped with mechanical stirrer and condenser was added 148 g (0.803 mol) of cyanuric chloride, 200 ml of dioxane and 386 g (5.28 mol) of N,N-dimethylformamide. The mixture was stirred to 80°C for ~75 h at which point a vigorous, exothermic reaction ensued with the evolution of CO₂ gas. The reaction was maintained at 80°C for 3-4 h, at which time gas evolution ceased. The reaction was allowed to cool to room temperature and crystallization of product ensued. The dioxane was removed under vacuum leaving 378 g (96%) of a tan solid; mp: 94-96°C; NMR (CDCl₃) δ 3.22 (s, 3H), 3.40 (s, 3H), and 9.07 (s, 1H); IR (CHCl₃) 3300, 1600, 1410, 1345, 1120 and 1050 cm⁻¹; UV (EtOH): 286 and 242.

N'-benzoyl-N,N-dimethylformamidine (Ia). To a 250 ml, round-bottomed flask equipped with condenser, magnetic stirrer and thermometer was added 1.4 g (0.06 mol) of sodium metal and 100 ml of absolute isopropyl alcohol. After all the sodium had reacted, the solution was allowed to cool to room temperature and 6.1 g (0.05 mol) of benzamide was added and the resulting mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was taken up in chloroform (100 ml) and extracted twice with an aqueous solution of sodium bicarbonate (50 ml portions). The resulting chloroform phase
was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 10.2 g of a dark oil which was crystallized from 10:1 carbon tetrachloride-chloroform to give 8.0 g (91% yield) of a light brown solid; mp 71-73°C; NMR (CDCl₃) δ 3.04 (s,3H), 3.11 (s,3H), 7.41 (m,3H), 8.38 (m, 2H) and 8.55 (s,1H); IR (CHCl₃) 1630 and 1590 cm⁻¹.

N'-(p-Nitrobenzoyl)-N,N-dimethylformamidine* (2a). To a dried, one-necked, 500 ml, round-bottomed flask equipped with condenser, thermometer and magnetic stirrer was added 1.4 g (0.06 mol) of sodium metal and 100 ml of absolute isopropyl alcohol. After all the sodium had reacted, the solution was cooled to room temperature and 8.3 g (0.05 mol) of p-nitrobenzamide was added in one portion. After the solution had stirred for 1 h, 10.6 g (0.065 mol) of Gold's reagent was added and the resulting mixture was refluxed overnight. The reaction mixture was cooled to room temperature and the alcohol was removed in vacuo. The residue was taken up in chloroform (100 ml) and extracted with an aqueous solution of sodium bicarbonate (30 ml). The resulting chloroform phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 13.1 g of a yellow solid. This material was recrystallized from 10:1 carbon tetrachloride-chloroform to give 8.9 g (81%) of a white solid; mp 132-135°C; NMR (CDCl₃) δ 3.20 (s,6H), 8.20 (d,J=10 Hz,2H), 8.34 (d,J=10 Hz,2H) and *prepared by M. Lizzi
N'-nictinoyl-N,N-dimethylformamidine (3a). To a 250 ml round-bottomed flask equipped with condenser, magnetic stirrer and thermometer was added 1.4 g (0.06 mol) of sodium metal and 100 ml of absolute isopropyl alcohol. After all the sodium metal had reacted, the solution was allowed to cool to room temperature and 6.1 g (0.050 mol) of nicotinamide was added. After the solution had stirred for 1 h, 9.8 g (0.060 mol) of Gold's reagent was added and the resulting mixture was refluxed with stirring overnight. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was taken up in chloroform (100 ml) and extracted twice with an aqueous solution of sodium bicarbonate (50 ml portions). The resulting organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 9.4 g of a dark red solid. Recrystallization from 1:1 dioxane-hexane solution afforded 7.9 g (89% yield) of light red crystals; NMR (CDCl$_3$) δ 3.12 (s, 6H), 7.30 (m, 1H), 8.53 (m, 3H), 9.04 (s, 1H); IR (CHCl$_3$) 1650 and 1600 cm$^{-1}$.

2-Betadimethylaminomethylene-ethylacetate (1b). To a one-necked, 500 ml, round-bottomed flask equipped with condenser, magnetic stirrer and nitrogen inlet was added 1.4 g (0.06 mol) of sodium metal followed by 100 ml of 100% EtOH. The reaction vessel was allowed to stir until all the sodium had reacted.
After the reaction mixture cooled to room temperature, 4.4 g (0.05 mol) of ethyl acetate was added. After stirring for .5 h, 9.8 g (0.06 mol) of Gold's reagent was added. The reaction vessel was heated to reflux with stirring overnight. After the solvent was removed in vacuo, the remaining residue was taken up in chloroform (100 ml) and extracted with two (75 ml) portions of water. After drying over sodium sulfate, the chloroform was removed in vacuo leaving 8.2 g of a dark brown oily liquid. The liquid was distilled to yield 5.5 g (77% yield) of a light yellow liquid; bp 60-63°C (.8 mm); NMR (CDCl₃) δ 1.31 (t, J=7 Hz, 3H), 2.88 (s, 6H), 4.10 (q, J=7 Hz 2H), 4.51 (d, J=13 Hz 1H, and 7.51 (d, J=13 Hz, 1H); IR (thin film) 1680, 1610 cm⁻¹.

2-Betadimethylaminomethylene-diethylmalonate (2b). To a one-necked, 500 ml, round-bottomed flask equipped with condenser, magnetic stirrer and nitrogen inlet was added 1.4 g (0.06 mol) of sodium metal followed by 100 ml of 100% EtOH. The reaction vessel was allowed to stir until all the sodium had reacted. After the reaction cooled to room temperature, 8.0 g (0.05 mol) of diethyl malonate was added. After stirring for .5 h, 9.8 g of Gold's reagent (0.06 mol) was added. The
reaction vessel was then heated to reflux and stirred overnight. After the solvent was removed in vacuo, the remaining residue was taken up in chloroform (100 ml) and extracted with two (75 ml) portions of water. After drying over anhydrous sodium sulfate, the chloroform was removed in vacuo leaving 8.7 g of a dark brown liquid. The liquid was distilled and the first fraction yielded 1.8 g [bp 50-55°C (.2 mm)] of diethyl malonate; a second fraction yielded 6.2 g (87% yield based on recovered starting material); bp 110-115°C (.2 mm); NMR (CDCl₃) δ 1.22 (t, J=7 Hz, 3H), 3.00 (s, 6H), 4.15 (q, J=7 Hz, 2H) and 7.48 (s, 1H); IR (thin film) 1690, 1615 cm⁻¹.

2-Betadimethylaminomethylene-γ-butyrolactone (3b). To a one-necked, 500 ml, round-bottomed flask equipped with condenser, magnetic stirrer and nitrogen inlet was added 1.4 g (0.06 mol) of sodium metal followed by 100 ml of 100% absolute isopropyl alcohol. The reaction vessel was allowed to stir until all the sodium reacted. After the reaction mixture cooled to room temperature, 4.3 g (0.05 mol) of γ-butyrolactone was added. After stirring for .5 h, 9.8 g of Gold’s reagent (0.06 mol) was added and the reaction mixture was allowed to reflux with stirring overnight. The solvent was removed in vacuo and the remaining residue was taken up in chloroform (100 ml) and extracted with two (75 ml) portions of water.
After drying over sodium sulfate, the chloroform was removed in vacuo leaving 8.2 g of a dark brown liquid. The liquid was distilled to give 6.1 g (86% yield) of a light gold solid\(^9\); bp 120-125°C (.8 mm); mp 93-95°C; NMR (CDCl\(_3\)) \(\delta\) 3.05 (s, 6H), 3.11 (m, J=8 Hz, 2H), 4.22 (t, J=8 Hz, 2H), 7.1 (t, J=5 Hz, 1H); IR (CHCl\(_3\)) 1720, 1625 cm\(^{-1}\).

2-Betadimethylaminomethylene-\(\gamma\)-valerolactone (4b). To a one-necked, 500 ml, round-bottomed flask equipped with condenser, magnetic stirrer and nitrogen inlet was added 1.4 g (0.06 mol) of sodium metal followed by 100 ml of 100% absolute isopropyl alcohol. The reaction vessel was allowed to stir until all the sodium reacted. After the reaction mixture cooled to room temperature, 5.0 g (0.05 mol) of \(\gamma\)-valerolactone was added. After stirring for .5 h, 9.8 g of Gold's reagent (0.06 mol) was added and the reaction mixture was allowed to reflux with stirring overnight. The solvent was removed in vacuo and the remaining residue was taken up in chloroform (100 ml) and extracted with two (75 ml) portions of water. After drying over sodium sulfate, the chloroform was removed in vacuo leaving 8.0 g of a dark brown solid. The solid was recrystallized from 10:1 hexane-chloroform to give 6.4 g (82% yield) of a light gold solid; bp 120-125°C (.8 mm); mp 115-117°C; NMR (CDCl\(_3\)) \(\delta\) 1.41 (d, J=6 Hz, 3H), 2.50 (m, 2H), 3.11 (s, 6H), 4.66 (m, 1H), 7.65 (s, 1H); IR (CHCl\(_3\)) 1725 and 1590 cm\(^{-1}\).
Benzaldehyde (1C). A three-necked, 250 ml, round-bottomed flask was equipped with a condenser, thermometer, magnetic stirrer and addition funnel. The apparatus was flame dried under a flowing nitrogen atmosphere and then allowed to cool to room temperature before the addition of 1.2 g (0.05 mol) of crushed magnesium turnings. A solution of 7.85 g (0.05 mol) of bromobenzene in 100 ml of tetrahydrofuran was added drop-wise to control the exothermic reaction that followed the addition. After the initial reaction ceased, the reaction mixture was heated to reflux and allowed to stir for 2 h to insure complete conversion to the Grignard reagent. After cooling in an ice bath, 8.3 g (0.05 mol) of Gold's reagent was added and allowed to stir at room temperature overnight. The reaction mixture was cooled again and isopropyl alcohol was added to destroy any unreacted Grignard reagent. While the reaction was still below 10°C, 100 ml of 30% by weight HOAc acid was added and the mixture was stirred for 20 min. The contents of the flask were then transferred to a 500 ml separatory funnel and neutralized by a saturated solution of
sodium bicarbonate. The solution was extracted with three (75 ml) portions of chloroform and combined extracts were dried over sodium sulfate. The solvent was removed in vacuo to yield 3.8 g (72% yield) of a clear liquid; bp 88°C (55 mm); NMR (CDCl₃) δ 7.08-7.77 (m, 5H), and 9.83 (s, 1H); IR (CHCl₃) 1705, 1600, 690 cm⁻¹.

p-Methyl-benzaldehyde (2c). A three-necked, 500 ml, round-bottomed flask was equipped with a condenser, thermometer and addition funnel. The apparatus was flame dried under a flowing nitrogen atmosphere before the addition of 5.0 g (.208 mol) of crushed magnesium turnings. A solution of 17.1 g (.01 mol) of p-bromotoluene (Aldrich Chemical Company) in 20 ml of diethyl ether was added dropwise to control the exothermic reaction that followed the addition. After the initial reaction ceased, the reaction mixture was allowed to stir with reflux for 2 h to insure conversion of the alkyl halide to the Grignard reagent. After cooling the reaction mixture in an ice bath, 8.7 g (0.05 mol) of Gold's reagent was added and the mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled again in an ice bath and 5 ml of isopropyl alcohol was added to destroy any unreacted Grignard reagent. While the reaction mixture was still below 10°C, 70 ml of 10% aqueous hydrochloric acid was added and the mixture was stirred for 15 min. Solid sodium bicarbonate was added to neutralize the mixture to a pH of 7
(litmus paper). After separation of the two phases, the aqueous phase was extracted with two (70 ml) portions of diethyl ether and the combined ether extracts were dried over anhydrous sodium sulfate. The diethyl ether was removed in vacuo leaving 14.2 g of a dark brown oil. The material was distilled (Kugelrohr) to yield 8.6 g (89% yield) of a clear yellow liquid; bp 55°C (3 mm), NMR (CDCl₃) δ 2.26 (s,3H), 7.15 (d,J=8 Hz,2H), 7.62 (d,J=8 Hz, 2H) and 9.78 (s,1H); IR (thin film) 1690, 1605 cm⁻¹.

1-Naphthaldehyde (3c). A three-necked, 500 ml, round-bottomed flask was equipped with a condenser, thermometer, magnetic stirrer and addition funnel. The apparatus was flame dried under a flowing nitrogen atmosphere and allowed to cool to room temperature before the addition of 1.7 g (.071 mol) of crushed magnesium turnings. A solution of 10.4 g (.05 mol) of 1-bromonaphthalene (Aldrich Chemical Company) in 100 ml of diethyl ether was added dropwise to control the exothermic reaction that followed the addition. After the initial reaction ceased, the reaction mixture was heated to reflux and allowed to stir for 2 h to insure complete conversion to the Grignard reagent. After cooling the reaction mixture in an ice bath, 8.7 g (.05 mol) of Gold's reagent was added and allowed to stir at room temperature overnight. The reaction mixture was cooled again in an ice bath and 5 ml of isopropyl alcohol was added to destroy any unreacted Grignard
reagent. While the reaction mixture was still below $10^\circ$C, 70 ml of 10% aqueous hydrochloric acid was added and the mixture was stirred for 15 min. Solid sodium bicarbonate was added to neutralize the mixture to a pH of 7 (litmus paper). After separation of the two phases, the aqueous phase was extracted with two (70 ml) portions of diethyl ether and the combined ether extracts were dried over anhydrous sodium sulfate. Removal of the ether in vacuo produced 8.3 g (82% yield) of a yellow liquid$^{12}$; bp $100^\circ$C (1.5 mm); NMR (CDCl$_3$) $\delta$ 7.10-7.90 (m,6H), 8.98-9.28 (m,1H) and 10.12 (s,1H); IR (thin film) 1675 cm$^{-1}$.

Phenylacetaldehyde (4c). A three-necked, 500 ml, round-bottomed flask was equipped with a condenser, thermometer, magnetic stirrer and rubber septum. The apparatus was flame dried under a flowing nitrogen atmosphere. To the flask was added 8.3 g (0.050 mol) of Gold's reagent and 100 ml of dry tetrahydrofuran. The mixture was cooled in an ice bath before 50 ml (0.055 mol) of a 1.1 M benzylmagnesium chloride in tetrahydrofuran solution (Alfa Ventron Corp.) was added via syringe. The resulting mixture was refluxed with stirring overnight. The reaction was cooled in an ice bath before the addition of 5 ml of isopropyl alcohol and 70 ml of 10% aqueous hydrochloric acid. After stirring for 20 min, the mixture was neutralized to a pH of 7 (litmus paper) with solid sodium bicarbonate. After saturating the solution with sodium chloride, the
mixture was extracted with chloroform (3 x 80 ml) and the combined extracts were dried over anhydrous magnesium sulfate and concentrated to give 6.2 g of a dark brown oil; bp 50°C (.9 mm); NMR (CDCl₃) δ 3.42 (d, J=2 Hz, 2H), 6.89-7.35 (m, 5H) and 9.52 (t, J=2 Hz, 1H); IR (thin film) 1725 and 1610 cm⁻¹.

Cyclohexanecarboxaldehyde (5c). A three-necked, 500 ml, round-bottomed flask was equipped with a condenser, thermometer, magnetic stirrer and a rubber septum. The apparatus was flame dried under a nitrogen atmosphere and allowed to cool to room temperature. To the flask was added 8.3 g (0.05 mol) of Gold's reagent and 100 ml of dry tetrahydrofuran. The mixture was cooled in an ice bath before the addition of 30 ml (0.06 mol) of a 2.0 M solution of cyclohexylmagnesium chloride in tetrahydrofuran (Alfa Ventron Corp.) was added via syringe. The resulting mixture was refluxed with stirring overnight. The reaction was cooled in an ice bath before the addition of 5 ml of isopropyl alcohol and 70 ml of 10% aqueous hydrochloric acid. After stirring for 15 min, the reaction mixture was neutralized to a pH of 7 (litmus paper) with solid sodium bicarbonate. After saturating the solution with sodium chloride, the mixture was extracted with chloroform (3 x 80 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated to give 4.3 g of a brown oil. This material was distilled (Kugelrohr)
to yield 3.1 g (55% yield) of a clear liquid\textsuperscript{14}, bp 60°C (50 mm); NMR (CDCl\textsubscript{3}) \( \delta \) 82-2.45 (m, 11J) and 9.52 (d, J=0.5 Hz, 1H); IR (thin film) 1730 cm\textsuperscript{-1}.

\textbf{Heptanal (6c).} A three-necked, 500 ml, round-bottomed flask was equipped with a condenser, thermometer, magnetic stirrer and a rubber septum. The apparatus was flame dried under a nitrogen atmosphere and allowed to cool to room temperature. To the flask was added 8.3 g (.05 mol) of Gold’s reagent and 100 ml of dry tetrahydrofuran. The mixture was cooled in an ice water bath before 22 ml (.055 mol) of a 2.5 M solution of n-hexylmagnesium bromide in tetrahydrofuran (Alfa Ventron Corp.) was added dropwise via syringe. The resulting mixture was refluxed for several hours and stirred overnight at room temperature. The reaction was cooled in an ice water bath before 5 ml of isopropyl alcohol and 70 ml of 10\% aqueous hydrochloric acid was added. After stirring for 15 min, the mixture was neutralized to a pH of 7 (litmus paper) with solid sodium bicarbonate. After saturating the solution with sodium chloride, the solution was extracted with chloroform (3 x 80 ml). The combined chloroform extracts were dried over anhydrous sodium sulfate and concentrated to give 8.8 g of a brown oil\textsuperscript{15}. This material was distilled (Kugelrohr) to yield 4.2 g of a yellow oil; bp 52°C (48 mm); NMR (CDCl\textsubscript{3}) \( \delta \) 80 (t, J=4 Hz, 3H), 1.00-1.83 (m, 8H), 2.17-2.53 (m, 2H) and 9.66 (t, J=2 Hz, 1H); IR (thin film) 1730 cm\textsuperscript{-1}. 
Nonanal (7c). A three-necked, 500 ml, round-bottomed flask was equipped with a condenser, thermometer, magnetic stirrer and a rubber septum. The apparatus was flame dried under a nitrogen atmosphere and allowed to cool to room temperature. To the flask was added 8.3 g (.05 mol) of Gold's reagent and 100 ml of dry tetrahydrofuran. The mixture was cooled in an ice water bath before 34 ml (.055 mol) of a 1.6 M solution of n-octylmagnesium bromide in tetrahydrofuran (Alfa Ventron Corp.) was added dropwise via syringe. The resulting mixture was refluxed for several hours and stirred overnight at room temperature. The reaction was cooled in an ice water bath before 5 ml of isopropyl alcohol and 70 ml of 10% aqueous hydrochloric acid was added. After stirring for 15 min, the mixture was neutralized to a pH of 7 (litmus paper) with solid sodium bicarbonate. After saturating the solution with sodium chloride, the solution was extracted with chloroform (3 x 80 ml). The combined chloroform extracts were dried over anhydrous sodium sulfate and concentrated to give 9.0 g of a brown oil. This material was distilled (Kugelrohr) to yield 5.6 g (79% yield) of a yellow oil; bp 32°C (.9 mm); NMR (CDCl₃) δ .75 (t, J=5 Hz, 3H), .90-1.66 (m, 12H), 2.10-2.45 (m, 2H) and 9.62 (t, J=2 Hz, 1H): IR (thin film) 1725 cm⁻¹.
III. Results and Discussion.

A. Reaction of Carboxylic Acid Derivatives with Gold's Reagent

When Gold's reagent was reacted with primary amides, acyl amidines were produced (see Table A).

\[
\text{RCNH}_2 + 5 \xrightarrow{\sim} \text{RCN} + \text{HN-N-CH}_3 + \text{HN-N-CH}_3
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-C-NH₂</th>
<th>% Yield</th>
</tr>
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<td>91</td>
</tr>
<tr>
<td>2.a</td>
<td><img src="image2.png" alt="Image" /></td>
<td>81</td>
</tr>
<tr>
<td>3.a</td>
<td><img src="image3.png" alt="Image" /></td>
<td>89</td>
</tr>
</tbody>
</table>
When Gold's reagent was reacted with esters containing an \(\alpha\)-methylene group, enamino esters were produced (see Table B).

\[
\begin{align*}
R^1-\text{CH}_2-\text{C}=\text{O}-R^2 + \text{G} & \rightarrow R^1-\text{C}=\text{N}(\text{CH}_3)_2 + \\
& \text{H}^\prime-\text{N}(\text{CH}_3)_2
\end{align*}
\]

Table B

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1-\text{CH}_2-\text{C}=\text{O}-R^2)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.b</td>
<td>(\text{CH}_3-\text{C}=\text{O}-\text{CH}_2-\text{CH}_3)</td>
<td>68</td>
</tr>
<tr>
<td>2.b</td>
<td>(\text{CH}_3-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}=\text{O}-\text{CH}_2-\text{CH}_3)</td>
<td>89*</td>
</tr>
<tr>
<td>3.b</td>
<td>(\text{O})</td>
<td>86</td>
</tr>
<tr>
<td>4.b</td>
<td>(\text{O}) (\text{CH}_3)</td>
<td>82</td>
</tr>
</tbody>
</table>

*yield based on recovered starting material

To demonstrate the significance of this work, it is necessary to review and compare this route to the existing means of producing acyl amidines and enamino esters. Of the existing
methods, the use of formamide acetals is preferred. \(N'\)-Acyl-\(N, N\)-dimethylamidines can be prepared by the reaction of primary amides with \(N, N\)-dimethylalkanamide dimethyl acetals (6).

\[
\begin{align*}
R-\text{C-NH}_2 + H-\text{C-NCH}_3 & \xrightarrow{\Delta} R-C-N\text{-CH}_3 \\
\text{CH}_3 & \quad + 2\text{CH}_3\text{OH}
\end{align*}
\]

Another formamide acetal, Bis-dimethylamino-t-butoxy methane (7) can also be used to produce enamino esters by reaction with esters.

\[
\begin{align*}
\text{R^1-CH}_2\text{-C=O-R^2} + \text{N(CH}_3\text{)_2-C-C(OCH}_3\text{)_3} & \xrightarrow{} \text{R^1-C=O-R^2} \\
\text{N(CH}_3\text{)_2} & \quad \text{CH}_3 \quad \text{CH}_3
\end{align*}
\]

For the production of acyl amidines and enamino esters, Gold's reagent and formamide acetals (6 or 7) form products in the same yield range. Gold's reagent, however, offers some distinct advantages over the use of bis-aminoalkoxy methanes and orthamides. Gold's reagent is easily prepared from inexpensive, readily available raw materials which are relatively non-toxic. Also, though it is hygroscopic, Gold's reagent has long term stability and can be stored (dessicated) almost indefinitely, unlike some orthoamides. In contrast to the orthamide route to the enamino esters, where reactions are
done at high pressures (60 atm) and temperatures (above 150°C), Gold's reagent is reacted with all carboxylic acid derivatives under relatively mild conditions.

Reaction of Gold's Reagent with Amides. The synthesis of acyl amidines through the reaction of unsubstituted amides with Gold's reagent involves three steps; the formation of amide anion, the nucleophilic attack of the anion on the electron deficient carbon of the iminium salt, and finally the elimination of N,N-dimethylformamide.

The formation of the amide nucleophile can be accomplished by the reaction of the amide with a sodium alkoxide/alcohol mixture. Sodium isoproxide/isopropanol is recommended because of its higher boiling point. Triethylamine can also be used as a solvent, with the advantage of effecting reaction at room temperature.

It is necessary that anhydrous conditions should be maintained throughout the reaction and it is desirable that a flowing nitrogen atmosphere be used.

The nucleophilic attack by the amide on the 1 or 3 carbon of the iminium ion probably forms an intermediate which cannot be isolated. It is apparent from the triethylamine trials that the kinetics and thermodynamics of this formation are favorable even at room temperature.

The elimination as proposed by Gupton involves a transition state with a nitrogen of the reaction intermediate
(Scheme I) supplying its unshared pair of electrons for the proton removal.

\[
\begin{align*}
R-C-NH_2 & \xrightarrow{\text{NaOCH(CH}_3\text{)}_2, \text{HOCH(CH}_3\text{)}_2} R-C-NH \\
R-C-NH & + \overset{\text{CH}_3}{\overset{\text{N}}{\overset{\text{N} \text{CH}_3}{\text{CH}_3}}} & \rightarrow \overset{\text{H}}{\overset{(\text{CH}_3)_2N}{\overset{\text{N} \text{CH}_3}{\text{CH}_3}}} \\
\overset{\text{H}}{\overset{(\text{CH}_3)_2N}{\overset{\text{N} \text{CH}_3}{\text{CH}_3}}} & \rightarrow R-C-N & + \overset{\text{H}}{\overset{(\text{CH}_3)_2N}{\overset{\text{N} \text{CH}_3}{\text{CH}_3}}}
\end{align*}
\]

Scheme I

One of the advantages of this synthetic route to acylamidines is that the reaction is usually clean (crude product 80% acyl amide by (TLC)) and the workup of the reaction mixture is straightforward.

The reaction mixture is taken up in chloroform and extracted with saturated sodium carbonate solution. The aqueous phase must be kept alkaline because the acyl amide will hydrolyze in acidic medium back to the starting amide. After
drying, the chloroform is evaporated leaving a mixture which is usually 90% pure (NMR).

**Reaction of Gold's Reagent with Esters.** Like the acylamidines, the enamino ester synthesis begins with the formation of the nucleophile and ends with the elimination of N,N-dimethylformamidine. The alkoxide system which is compatible with the ester is used, because of possible transesterification. The reaction site of the ester is alpha to the carbonyl group and the elimination of N,N-dimethylformamidine, workup of the reaction, and reaction yields are all comparable with that of the primary amides.

**B. Reaction of Gold's Reagent with Grignard Reagents.**

Grignard nucleophiles were reacted with Gold's reagent and the resulting intermediates hydrolyzed to one carbon elongated aldehydes.

\[
R{-}\text{Mg}{-}X + 5 \xrightarrow{\text{THF or Et}_2\text{O}} \xrightarrow{10\% \text{ HCl in H}_2\text{O}} \xrightarrow{\text{O}} R{-}C{-}H
\]
Aldehydes, because of their versatile chemical properties, rank as one of the most important functional groups. Although there has been considerable research done on the synthesis of aldehydes by carbon-carbon coupling reactions\textsuperscript{9}, extensive work has not been done on the formylating of Grignard nucleophiles in a one step process.

The most efficient method of formylation to date has been reported by Myers. He investigated formylating Grignard reagents with N-formyl-N-methyl-2-amino pyridine\textsuperscript{19}.

\[
R\text{-}\text{Mg-X} + \text{2-aminopyridine} \xrightarrow{1. \text{THF}} \text{2-[(N-formyl)]-aminopyridine} \xrightarrow{2. \text{H}_2\text{O}} R\text{-}C\text{-H} + \text{N-methylaminopyridine}
\]

To prepare (7), 2-aminopyridine is added to phenol formate to give 2-(N-formyl)-aminopyridine. This formamide is then methylated to give the final product (7). The overall yield for the two step process is 80%.

Although the yield of aldehyde and the reaction utility for both Myer's reagent and Gold's reagent are similar, Myer's reagent is more expensive and usually requires the recovery of 2-N-methylaminopyridine by-product.

Myers has also reported the use of 2-oxazolines to formylate Grignard reagents\textsuperscript{20}. 
Again, the aldehyde yields for this method are comparable to the use of Gold's reagent. However, this method fails for aliphatic Grignard reagents.

**Aldehyde Preparation.** The aldehyde synthesis through the Grignard-iminium salt pathway involves three steps; the conversion of the alkyl halide to the Grignard reagent; attack of the resulting nucleophile on the 1 or 3 carbon of the iminium salt to form the uncharged intermediate; and finally an acid/water hydrolysis to the one carbon elongated aldehyde.

The first and most critical step in terms of yield and purification of product is the preparation of the Grignard nucleophile. As in all organometallic synthesis, care must be taken in the handling and use of reactants. Completely anhydrous conditions are required. The solvents, either diethyl ether or tetrahydrofuran, should be refluxed over metallic sodium for at least 24 hours before use. It is recommended that the alkyl halide be distilled or dried over molecular sives (4A) for 48 hours. Flame drying of the reaction apparatus under an inert atmosphere is also required if humid conditions exist.
If the alkyl halide is not completely converted to the Grignard reagent, separation of the aldehyde from the starting halide is difficult due to their close boiling points. This problem is particularly acute in the case of the alkyl bromides where the boiling points are usually within 5°C of each other. Any Grignard reagent that does not react with the iminium salt to form the intermediate will be protonated upon workup. These dehalogenated products have boiling points well below the corresponding aldehydes.

The second step, the formation of the intermediate (8), occurs readily at room temperature. The intermediate was not isolated but previous work by Gupton indicates attack by the nucleophile is on the electron deficient 1 or 3 carbon.

\[
R-Mg-X + 5 \quad \begin{array}{c}
\text{(CH}_3\text{)}_2\text{N} \\
\text{N(CH}_3\text{)}_2
\end{array} \quad \text{H} \quad \text{H} \quad + \quad \text{MgXCl}
\]

The elimination of N,N-dimethylformamidine, which occurs in the carboxylic acid derivatives is not observed because the \(\alpha\)-hydrogens are not sufficiently acidic.

The hydrolysis of the intermediate occurs under mildly acidic conditions (at temperatures below 10°C in dilute hydrochloric or acetic acid). These mild conditions for the hydrolysis are desirable because stronger acidic conditions and higher temperatures could result in side reactions of the
aldehyde group or other functional groups contained in the product molecule. A proposed mechanism for the hydrolysis of the intermediate is as follows:

Another advantage of this synthetic route is the simple but effective workup of the reaction mixture. Chromatographs of the crude reaction mixture indicate the products to be >90% pure.
IV. Conclusions

The data gained from this investigation of Gold's reagent indicates that this iminium salt has potential in both industrial and laboratory use. It is ideally suitable from an industrial-economic view because it is produced from readily available and inexpensive raw materials. Since the reaction conditions are mild for its preparation, Gold's reagent can be produced in the laboratory without any special equipment or experience.

Of the industrial advantages of Gold's reagent, perhaps out-weighing its low cost, is its one-step production. This procedure is quick (3-4 hours), clean, and proceeds in high reproducible yields. This procedure eliminates any need for a purification of the iminium salt. Although more complete investigative work must be done, one can perceive these characteristics and the reactions studied as pointing to Gold's reagent as a viable industrial and laboratory intermediate.
V. Recommendations

I. Before any industrial applications of these reactions are possible, complete optimization and characterization of reactions is needed, i.e., it may be possible for the reactions with the carboxylic acid derivatives to proceed to completion with only a half-equivalent of Gold's reagent. That is, if the eliminated N,N-dimethyl formamidine will react with the amides or esters.

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} - \text{C} = \text{N} - \text{H} & \quad + & \quad \text{R} - \text{C} - \text{X} \quad \text{H} & \quad \rightarrow & \quad \text{R} - \text{C} - \text{X} \\
\text{CH}_3 & \quad \text{H} & & \quad \text{H} & & \quad \text{H} & & \quad \text{N} - \text{C} = \text{N} - \text{CH}_3 \\
\text{N} - \text{C} = \text{N} - \text{CH}_3 & & \quad + & \quad \text{NH}_3
\end{align*}
\]

II. The reaction of acyl amidines with Grignard and lithium nucleophiles should be completely characterized. Preliminary work on the reaction indicates a novel synthesis of monosubstituted amides.

\[
\begin{align*}
\text{R} - \text{C} - \text{N} & \quad \text{H} & \quad \text{N} - \text{CH}_3 & \quad + & \quad \text{R}^{\ominus} & \quad \rightarrow & \quad \text{R} - \text{C} - \text{N}^{\ominus} \\
\text{H} & & \quad \text{N} - \text{CH}_3 & & \quad \text{R}^{\ominus} & & \quad \text{CH}_3
\end{align*}
\]
III. The reaction of thionyl compounds with Gold's reagent should be completely characterized. Thionyl reagents may react like derivatives of carboxylic acids to form amidines:

\[
14 + R^2I \rightarrow R-C-NR^2
\]

\[
\xrightarrow{H^+} \rightarrow R-C-NRH
\]

\[
\xrightarrow{H_2O} \rightarrow R-C-NR^2
\]

Alternatively, thionyl reagents may react like amidines and cyclize:

\[
\xrightarrow{5} + R-C-NH_2 \rightarrow \text{[Cyclization Product]}
\]

\[
\xrightarrow{HN(CH_3)_2}
\]
Instrumentation and Equipment

The following instruments were used in this research:

1. Fischer-Johns melting point apparatus
2. Perkin-Elmer 457 Grating Infrared Spectrometer
3. Varian EM360A Nuclear Magnetic Resonance Spectrometer
4. Perkin-Elmer 900 Gas Chromatograph
References


11. Ibid., p. 901.

12. Ibid., p. 684.

13. Ibid., p. 749.


15. Ibid., p. 509.

16. Ibid., p. 716.

