TRANSITION METAL-FREE CARBONYLATION OF AMINES TO FORMAMIDES

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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To my parents, for everything.
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<tr>
<td>AFA</td>
<td>Acetic formic anhydride</td>
</tr>
<tr>
<td>atm</td>
<td>Atmospheres</td>
</tr>
<tr>
<td>CDI</td>
<td>Carbonyldiimidazole</td>
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<td>CDMT</td>
<td>2-Chloro-4,6-dimethoxy[1,3,5]triazine</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMDTC</td>
<td>Dimethyldithiocarbamate</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>IL</td>
<td>Ionic liquid</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>MTSA</td>
<td>Melamine trisulfonic acid</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave irradiation</td>
</tr>
<tr>
<td>NHC</td>
<td>N-Heterocyclic carbene</td>
</tr>
<tr>
<td>NMM</td>
<td>N-Methylmorpholine</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
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<tr>
<td>Pyr</td>
<td>Pyridine</td>
</tr>
<tr>
<td>SEM</td>
<td>[2-(Trimethylsilyl)ethoxy]methyl</td>
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<tr>
<td>TBD</td>
<td>1,5,7-Triazabicyclo[4.4.0]dec-5-ene</td>
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<tr>
<td>TEMPO</td>
<td>(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl</td>
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<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

TRANSITION METAL-FREE CARBONYLATION OF AMINES TO FORMAMIDES

By

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Chair: Lisa McElwee-White
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Base-mediated carbonylation of amines provides an alternative to current methods of synthesizing formamides, which can involve high temperatures, metal catalysts, or stoichiometric equivalents of formic acid. The conditions for this reaction include potassium carbonate as base, an amine, and methanol as solvent in a vessel charged with CO. Optimization was done for base identity, time, promoter identity, pressure, and base quantity. It was determined that neither a halide promoter nor an oxidant was necessary for this reaction. The optimal conditions for formamide synthesis from amines were amine, 35 atm CO, 3 equiv of K$_2$CO$_3$ as base, methanol as solvent, 7 h, and room temperature.

Isotopic labeling experiments were conducted to determine the source of the formyl hydrogen and the carbonyl moiety, indicating that methanol oxidation is not the source of the carbonyl in the product. The functional group compatibility was examined using para-substituted benzyl amines. Substrates with electron-donating groups produced higher yields than substrates with electron-withdrawing groups. The scope of the reaction was examined using primary and secondary cyclic and acyclic aliphatic...
amines. Control experiments led us to propose a base mediated mechanism, proceeding through methyl formate as an intermediate.
Interest in the preparation of formamide derivatives has been driven by their variety of uses. Formamides serve as intermediates in pharmaceutical syntheses, precursors to fungicides, intermediates in isocyanate, formamidine, and nitrile formation, reagents in functional group conversion, and reagents in the Vilsmeier formylation reaction. Formamides can also be used in allylation and hydrosilation of carbonyl compounds.

**General Formylation**

In order to install the CHO group on a molecule, formylating agents are often used. These include chloral, formic acid, formaldehyde, and formates. One of the earliest of these reports comes from Blicke in 1952. He reported the formylation of amines with chloral (1) (Figure 1-1). This method produced excellent yields with strong organic bases, occurred at low temperature, and the only byproduct was chloroform. Amines that were formylated by this method include primary amines, diamines, cyclic secondary amines, and sterically hindered secondary amines.

![Figure 1-1. Formylation using 1.](image)

Formic acid can be used alone to achieve formylation. This method was reported by Choi and required the use of a Dean-Stark trap (Figure 1-2). The amine and formic acid were dissolved in toluene and the solution was refluxed. The trap was used to collect the water produced by the condensation of the two reactants. By
refluxing, the formamide product was produced in high yields without the need of a
catalyst. This allowed the monitoring of the reaction to take place via thin layer
chromatography, and the absence of a metal catalyst allowed for easier isolation of the
product.

![Chemical structure diagram]

Figure 1-2. Formylation of amines using formic acid.

Another example of N-formylation by formic acid was reported by Hajra.\textsuperscript{12} This
reaction employed solvent-free and catalyst-free conditions. Amine and formic acid
were heated to 80 °C until the reaction reached completion. Reaction time ranged from
25-480 min. This reaction required no specialized glassware. Formamide products
were obtained from substituted aromatic amines as well as primary and secondary alkyl
amines in good to excellent yields. Hydroxyl substituents remained intact after
formylation of the amine. Additionally, no isolable side products were observed. When
a mixture of primary and secondary amines was exposed to the reaction conditions, the
primary amines were selectively formylated.

There are many examples of N-formylation by acetic formic anhydride (AFA), a
mixture of formic acid with acetic anhydride.\textsuperscript{13} One such example was seen by
Krishnamurthy who reported a one-pot procedure for N-monomethylation of primary
amines that proceeds through N-formylation followed by reduction.\textsuperscript{14} Amines were
allowed to react with excess formic acid and acetic anhydride at -20 °C (Figure 1-3).
The reaction reached completion for most amines in less than 15 min and took no
longer than 3 h for any amine. The resultant formamides were isolated in yields
between 97-100%. High yields were achieved for simple alkyl, aromatic, multifunctional, and sterically hindered amines, such as 2.

![Figure 1-3. Formylation of a sterically hindered amine.](image)

Formylation is often used as a means of protecting amino groups in peptide synthesis. du Vigneaud reported a procedure for formylating the $N$-terminus of amino acids in 1932 by the use of formic acid and acetic anhydride. This method was used as a way to resolve $dl$-cystine from inactive cystine. The product $dl$-diformylcystine was able to be readily removed from the product mixture by forming the strychnine salt. However, the yield reported for the $dl$-diformylpeptide was only moderate. This method of formylating amino acids was applied by Yang as a means of protecting the amino group of many individual amino acids. When parent amino acids instead of peptides were exposed to the reaction conditions, the procedure yielded the formamides in yields between 85-90%.

$tert$-Butyl esters of amino acids are unable to be protected by AFA without racemization occurring. Meienhofer reported a modification that allows the formylation of $tert$-butyl amino acid esters with minimal or no racemization. This method combined formic acid with dicyclohexylcarbodiimide (DCC). This mixture was added to solutions of $tert$-butyl amino acid esters. The protected amino acid esters were produced in high yields.
Formic acid in polyethylene glycol has been shown to formylate anilines (Figure 1-4). This reaction can be done at room temperature at relatively moderate reaction times, 4-6 h. The conditions are tolerant of various functional groups such as nitro, halogen, ester, ketone, and alkyl groups. This formylation only takes place under inert atmosphere. Attempts to formylate the oxygen of phenols with these conditions were unsuccessful.

![Figure 1-4. Formylation of aromatic amines using formic acid and polyethylene glycol.](image)

Formylation with formic acid and 2-chloro-4,6-dimethoxy[1.3.5]triazine (CDMT) (3) was reported by Giacomelli. Amines and amino acid esters were formylated in dichloromethane (DCM) at reflux (method A) or under microwave irradiation (method B) (Figure 1-5). Formamides were produced in a one step process. In method A, dry formic acid and the amine were treated with 3 and 4-(dimethylamino)pyridine (DMAP) as a catalyst. N-methylmorpholine (NMM) and DCM were added, and the solution was refluxed. This reaction required 5-20 h to reach completion. However, with the use of microwave irradiation in method B, the reaction produced the formamides in high yields after only 3-6 min. The yields from this reaction were nearly quantitative. Slightly lowered yields were observed when more sterically hindered amines were used. The proposed mechanistic pathway involved the formation of a formate ester intermediate composed of formic acid and 3 which then is attacked by the amine to form the formamide (Figure 1-6). When chiral amino acid esters were used, optical purity was
maintained. This indicated that the chiral center is not involved in the reaction, which is consistent with the proposed pathway.

Figure 1-5. One step preparation of formamides by method A at reflux or method B via microwave irradiation.

In a procedure reported by Yang, melamine trisulfonic acid (MTSA) (4) catalyzed formylation with formic acid in solvent-free conditions (Figure 1-7). The amine, two equiv formic acid, and 3 mol% 4 were stirred at 60 °C until completion of the reaction (40-90 min). Substituted aniline derivatives were examined and all produced excellent
yields of formamides regardless of electron donating or electron withdrawing substituents. Primary and secondary amines also produced formamides in high yields. A proposed mechanism suggests that formic acid is protonated by 4, followed by nucleophilic attack of the amine. Subsequent elimination of water produced the formamide (Figure 1-8).

![Figure 1-7. General reaction of MTSA catalyzed formylation.](image)

Ammonium formate has been shown to formylate both anilines and secondary amines in good to excellent yields (Figure 1-9). Primary amines produced alkyl formate salts instead of the expected products. Benzylamine was an exception, and it successfully produced the formamide in 88% yield. To produce formamides, the amine was dissolved in acetonitrile, ammonium formate was added, and the solution was refluxed between 6-15 h. These conditions are also applicable as protecting groups for chiral molecules. The benzyl ester of L-proline (5) was successfully formylated to 6 in 75% yield without any observed racemization (Figure 1-10). When hydroxyl groups
were present, ammonium formate selectively formylated the nitrogen, leaving the hydroxyl group intact.

\[ \text{N} - 
\begin{array}{c}
R^1 \\
H \\
R^2 \\
\end{array} 
\xrightarrow{\text{HCO}_2\text{NH}_4} 
\begin{array}{c}
R^1 \\
O \\
\text{CHO} \\
R^2 \\
\end{array} 
\]

\[ \text{CH}_3\text{CN}, \text{reflux} \]

R\(^1\), R\(^2\) = alkyl or aryl

Figure 1-9. General formylation by formic acid in ammonium formate.

\[ \begin{array}{c}
\text{N} \\
\text{CO}_2\text{Bn} \\
\text{H} \\
\end{array} 
\xrightarrow{\text{HCO}_2\text{NH}_4} 
\begin{array}{c}
\text{N} \\
\text{CO}_2\text{Bn} \\
\text{CHO} \\
\end{array} 
\]

\[ \text{CH}_3\text{CN}, \text{reflux}, 8 \text{ h} \]

Figure 1-10. Formylation of 5 without racemization of chiral centers.

Swaringen previously reported that amines and triethyl orthoformate produced the corresponding N-ethyl formamides in the presence of sulfuric acid at high temperature.\(^{21}\) Using a similar method, Kaboudin reported simple N-formylation without an alkyl shift onto the nitrogen (Figure 1-11).\(^{22}\) In Kaboudin’s method, formylation of primary amines took place in water with triethyl orthoformate in the absence of base, acid, or catalyst in moderate to good yields. No secondary amines were examined. A number of solvents were examined including ethanol, ethyl acetate, DCM, chloroform, dimethylformamide (DMF), dimethylsulfoxide (DMSO), and water. However, water was chosen as the optimal solvent. Two methods were employed. In method A, the components were refluxed in water, and method B included microwave irradiation at 90 °C. The reaction times associated with method A ranged between 24-48 h. When MW was used reaction times were between 2-3 h.
Deutsch reported formylation of amines by methyl formate and a molecular catalyst (Figure 1-12).\textsuperscript{23} Amidine and guanidine catalysts were examined in the formylation of morpholine and tert-butylamine at room temperature. The best catalyst for this reaction was 1,5,7-triaza[4.4.0]dec-5-ene (TBD) (7).

![Reaction of amine with triethyl orthoformate in water.]

Figure 1-11. Reaction of amine with triethyl orthoformate in water.

Formic acid and a catalytic amount of sodium formate have been reported to produce formamides from amines at room temperature in solvent-free conditions.\textsuperscript{24} Functionalized anilines, primary amines, cyclic secondary amines, and sterically hindered secondary amines all produced good to excellent yields of formamides. Reactions reached completion between 0.33-8 h. When either phenol or benzyl alcohol was exposed to the reaction conditions, no O-formylated products were formed. Additionally, when hydroxyl groups were present on the amines, they remained intact when the products were formed. The sodium formate used in the reaction could be isolated from the reaction mixtures and reused up to four times without a loss of activity.

![Formylation of amines by methyl formate and catalyst.]

Figure 1-12. Formylation of amines by methyl formate and catalyst.

\textit{N}-formylation of anilines and simple primary amines in solvent-free conditions by the use of formic acid with a reusable resin was reported by Pasha.\textsuperscript{25} Amberlite IR-
120[H⁺], a heterogeneous catalyst, was aided by microwave irradiation to formylate amines in excellent yields. Amberlite IR-120 and the amine were combined and formic acid was added. The substrates were exposed to microwave irradiation for 20 s intervals until all starting material was consumed. All conversions were complete between 60-120 s regardless of amine or substituents. A control was done in which the amine and formic acid were combined and irradiated without Amberlite IR-120. No formamide product was produced after 180 s. Once the catalyst was added to this trial, the product formed in 60 s. At the end of each reaction the resin was easily reisolated. Further study showed that after thorough washing with ethyl acetate and drying, the resin was reusable up to five times without a loss in activity. The proposed mechanistic pathway involved coordination to the resin through hydrogen bonds (Figure 1-13). The amine and formic acid coordinated to the resin, attack occurred at the carbonyl by the amine, and through a rearrangement the formamide was produced leaving water coordinated to the resin.

Figure 1-13. Amberlite IR-120 catalyzed formylation. Figure adapted from reference 25.

Jang reports N-formylation in solvent-free conditions with molecular iodine (I₂) as a catalyst.²⁶ After optimization studies done on aniline, it was determined that aniline, 5
mol% I₂, and two equiv of formic acid produced formanilide in excellent yield after 2 h at 70 °C. Several factors caused the yield to decrease including higher reaction temperature, less formic acid, and use of acetonitrile as solvent. After optimization was completed, several aniline derivatives as well as primary and secondary amines were subjected to the reaction conditions and produced formamides in good to excellent yields. Reaction times were adjusted to ensure completion. All trials were between 2-8 h. The role of I₂ was then examined. As it is known that I₂ reacts with formic acid to produce HI,²⁷ it was assumed that HI was the active catalytic species, generated in situ. Protonated formic acid is attacked by the amine, followed by proton transfer to provide 8, and finally through elimination of water and a proton, the formamide is formed (Figure 1-14).

\[
\text{I}_2 + \text{HCO}_2\text{H} \rightarrow \text{HI} + \text{CO}_2
\]

Figure 1-14. Mechanism of I₂ catalyzed formylation.

Complex molecular catalysts may also be used for N-formylation. Hu reported the use of thiamine hydrochloride (9) as a catalyst to produce formamides from amine and formic acid in solvent-free conditions (Figure 1-15).²⁸ This method was successfully applied to aromatic and aliphatic amines. Yields ranged from 88-96%. When other carboxylic acids were used in place of formic acid, the corresponding amides were produced using this catalytic method. While the mechanistic pathway is not known, a
proposed mechanism suggests that the catalyst activates formic acid through hydrogen bonding, after nucleophilic attack of the amine at the carbonyl of formic acid, and the formamides were produced through the elimination of water (Figure 1-16).

![Chemical structure](image)

Figure 1-15. Solvent-free formylation catalyzed by 9.

![Mechanistic pathway](image)

Figure 1-16. Proposed mechanistic pathway of formamide production with 9.

Other solvent-free, acid catalyzed methods have been reported. Hajela reported silica supported perchloric acid (HClO₄-SiO₂) catalyzed N-formylation of aromatic and cyclic secondary amines (Figure 1-17).²⁹ When substrates with hydroxyl groups were
exposed to this reaction, formylation occurred selectively at the amino position. Other silica supported acids including sulfuric (H$_2$SO$_4$), fluoroboric (HBF$_4$), and trifluoroacetic (TFA) acids were examined but all produced lower yields of products. The catalyst was easily removed at the completion of the reaction and after washing and drying, could be used up to three times without a loss in activity.

![Chemical Equation]

Figure 1-17. Silica supported acid catalyzed $N$-formylation.

Ionic liquids (IL) have recently been reported to catalyze formylation. IL are attractive because of their stability, ease of removal, and easy synthesis. Baghbanian reports that amine, formic acid, and TBD based ionic liquids produced formamides from aromatic, alkyl, and heteroaromatic amines as well as amino alcohols in good to excellent yields. Three related ionic liquids were examined (10, 11, and 12) with 10 being the preferred IL (Figure 1-18). In optimization studies, 5 mol% 10, 1.3 equiv formic acid, and 10 min were chosen as the reaction conditions (Figure 1-19). This is a solvent-free method and when solvent was used yields decreased. The IL was easily separated from the product and reused up to six times without a loss in activity. A proposed mechanism indicated that the reaction was mediated through hydrogen bonding with the catalyst (Figure 1-20).
Figure 1-18. TBD based IL examined for catalytic activity towards N-formylation.

\[ \text{R}^1 \text{NH} + \text{HCOOH} \xrightarrow{10, 5 \text{ mol}\%} \text{R}^1 \text{NCOH} \]

\( \text{R}^1 = \text{aryl, alkyl} \)
\( \text{R}^2 = \text{aryl, alkyl, H} \)

Figure 1-19. Optimized conditions for IL catalyzed formylation.

Figure 1-20. Mechanistic pathway for formamide production.
Another example of IL catalyzed formylation was reported by Lee.\textsuperscript{31} In this case CO was used as the carbonyl source without formic acid. Amine, IL and 40 atm CO produced formamides from primary and secondary amines in moderate to excellent yields. A selection of IL and a selection of counterions were examined. Optimization studies were performed and 1-butyl-3-methylimidazolium carbonate (13) was chosen as the best IL to catalyze \textit{N}-formylation. Other optimized conditions include 40 atm CO, methanol solvent, 140 °C, and 1 mol% 13 (Figure 1-21). No urea products were observed in the reaction mixtures. Recyclability of 13 was examined. The catalyst could be used for five trials with no loss in selectivity and only a 20% reduction in activity.

\[
\begin{align*}
  \text{R}_2\text{NH} & \quad 1 \text{ mol}\% \\
  & \xrightarrow{	ext{40 atm CO, CH}_3\text{OH, 140 °C, 4 h}} \\
  & \quad \text{13} \\
  & \quad \text{R}_2\text{N}═\text{CHO}
\end{align*}
\]

Figure 1-21. Formylation of amines using CO catalyzed by 13.

A method has emerged recently that uses the Reimer-Tiemann (R-T) reaction to produce formamides from secondary amines (Figure 1-22).\textsuperscript{32} Alkyl, cyclic, and \textit{N}-methylaniline derivatives all produced formamides in good to excellent yields. The best yields were obtained with cyclic amines. Reduced yields were seen for open chain aliphatic amines, suggesting that steric bulk may have been an issue. A mechanistic pathway consistent with the Reimer-Tiemann reaction was proposed (Figure 1-23). First, chloroform reacted with sodium ethoxide to form the chloroform carbanion (14). The carbanion was readily converted into dichlorocarbene (15). Then 15 reacted with the amine and through the R-T reaction produced the formamide product.
Group 3 metals have also been reported to catalyze formylation of amines. Jang reported solvent-free conditions in which amine, formic acid, and 10 mol% indium at 70 °C produced formamide in moderate to excellent yields (Figure 1-24). Without indium, these conditions did not produce as high a yield. The reaction times vary between 1-24 h depending on the electronics and steric's of the amine. Aniline derivatives, primary amines, secondary amines, and amino alcohols were all successfully formylated in these solvent-free conditions. These conditions were then applied to protect the amino
group of methyl and benzyl α-amino acid esters. The formylation proceeded successfully in good yields. Additionally, no racemization was observed.

\[
\text{R–NH}_2 + \text{HOOC} \xrightarrow{\text{In, 10 mol\%}} \text{R–NCO} \quad \text{70 °C, 1.5-24 h}
\]

Figure 1-24. Indium catalyzed formylation of amines.

**Transition Metal Catalyzed Formylation**

In addition to simple formylating agents, transition metals have been used to formylate amines using stoichiometric amounts of formic acid or another formylating agent. Transition metal catalysts have also been used to formylate amines using CO as the carbonyl source.\(^{34-42}\) When CO is used as the carbonyl source, formamide products are much less commonly obtained than ureas.\(^{43-45}\)

A variety of transition metal Lewis acids have been reported to \(N\)-formylate amines. ZnO was reported by Hosseini-Sarvari as a Lewis acid catalyst for the solvent-free formylation of amines with formic acid.\(^{46}\) Optimal conditions of this reaction are 3 equiv of formic acid, 50 mol\% catalyst, 70 °C, and 10-720 min (Figure 1-25). Aromatic, primary and secondary amines were formylated in good to excellent yields. The progress of the reaction was monitored by TLC, and longer reaction times were necessary for aromatic amines containing electron withdrawing groups as well as for secondary amines. Decreased yield was not observed when the reaction was scaled up from 1 mmol amine to 100 mmol amine. O-formylation of alcohols was not observed. Amines containing hydroxyl groups were selectively formylated at the amino group. When a mixture of primary and secondary amines was subjected to the reaction conditions, primary amines were selectively formylated. ZnO was easily filtered out of
the reaction mixture at the completion of the reaction. The catalyst was washed with DCM and could be successfully recycled up to three times.

$$\begin{align*}
\text{R}^1_\text{NH} + \text{HO}-\text{O} &\xrightarrow{\text{ZnO, 50 mol%}} \text{R}^1_\text{N}-\text{O} \\
\text{R}^2_\text{H} &\xrightarrow{\text{solvent-free, 70 °C}} \text{R}^2_\text{H}
\end{align*}$$

Figure 1-25. ZnO catalyzed formylation of amines with formic acid.

Similar, Lewis acid (LA) catalyzed, solvent-free conditions for formylation were reported by Rao.\textsuperscript{47} A Lewis acid catalyst and formic acid were used and produced high yields of the desired formamide products (Figure 1-26). Lewis acids such as FeCl\textsubscript{3}, AlCl\textsubscript{3}, and NiCl\textsubscript{2} worked well, but ZnCl\textsubscript{2} produced the best results. The optimum conditions are 10 mol\% catalyst, 3 equiv of formic acid, 70 °C, and 10-900 min. The reaction was monitored by TLC and required longer reaction times for electron poor aromatic amines as well as secondary amines.

This catalyst, ZnCl\textsubscript{2}, is inexpensive, environmentally friendly, and tolerated a variety of functional groups such as nitro, halogen, ester, ketone, and alkyl. The proposed reaction mechanism is similar to other acid catalyzed reactions of formic acid and amine. Interestingly, Rao’s report came three years after Hosseini’s report of ZnO catalyzed formylation and yet Rao did not cite the previous work and incorrectly claimed that their conditions were the first report of Lewis-acid catalyzed $N$-formylation of amines with formic acid.

$$\begin{align*}
\text{R}^1_\text{NH} + \text{HO}-\text{O} &\xrightarrow{\text{ZnCl}_2, 10 \text{ mol\%}} \text{R}^1_\text{N}-\text{O} \\
\text{R}^2_\text{H} &\xrightarrow{\text{solvent-free, 70 °C}} \text{R}^2_\text{H}
\end{align*}$$

Figure 1-26. Solvent-free formylation of amines using ZnCl\textsubscript{2} catalyst.
Heydari reports a catalyst for the formylation of amines with formic acid.\textsuperscript{48} Sulfonic acid supported on hydroxyapatite (HAp)-encapsulated-\(\gamma\)-Fe\(_2\)O\(_3\) nanocrystallites catalyze formylation of aromatic, primary, and secondary amines (Figure 1-27). No O-formylation occurred on amines containing hydroxyl groups. Optimum conditions are amine, 1.2 equiv of formic acid, 0.9 mol\% \(\text{SO}_3\)H (\(\gamma\)-Fe\(_2\)O\(_3\)@ HAp-\(\text{SO}_3\)H), and room temperature. The reaction was monitored by TLC and required 15-60 min to reach completion. This is a magnetic, solid-state catalyst with no air/moisture sensitivity. The catalyst was easily removed from the reaction mixtures by attaching an external magnet to the vessel and decanting the reaction solutions. After washing and drying the catalyst could be reused for four consecutive trials without a loss in activity. In order to ascertain whether acid was detaching from the particles and catalyzing the reaction homogenously, the reaction was performed for 10 min, the catalyst was removed by an external magnet, and the reaction was allowed to continue for 3 h. At the end of this time, no significant amount of product had formed.

![Figure 1-27. Formylation of amines by formic acid](image)

**Figure 1-27.** Formylation of amines by formic acid

Formylation of amines with formic acid and TiO\(_2\)-P25 or sulfated titania was reported by Swaminathan.\textsuperscript{49} This was an extension of their research on semiconductor photocatalysts. They found that at room temperature either TiO\(_2\)-P25 or TiO\(_2\)-SO\(_4^{2-}\) catalyzed formylation of amines with formic acid in short reaction times (Figure 1-28). This method was applied to substituted aromatic amines as well as primary and
secondary aliphatic amines. In all cases studied, TiO$_2$-SO$_4^{2-}$ produced better yields, ranging from moderate to excellent. In recyclability tests, TiO$_2$-SO$_4^{2-}$ could be reused up to five times without a loss in activity, while TiO$_2$-P25 suffered a 50% drop in activity during the second trial. A proposed mechanism suggests that the reaction is similar to other acid catalyzed formylations (Figure 1-29). The catalyst is a Lewis acid and coordinates formic acid in order to facilitate nucleophilic attack of the amine on the carbonyl. Then through loss of water and rearrangement, the formamide product is produced. This was the first example of a semiconductor oxide heterogeneous catalyst employed in N-formylation at room temperature.

\[ \text{HCO}_2\text{H, CH}_3\text{CN} \xrightarrow{\text{TiO}_2\text{-P25 (or) TiO}_2\text{-SO}_4^{2-}} \text{rt, 30-45 min} \]

Figure 1-28. Amine formylation from formic acid catalyzed by TiO$_2$-P25 or TiO$_2$-SO$_4^{2-}$.

\[ \text{HCHO} + \text{Acidic sites of TiO}_2\text{-P25} \xrightarrow{+\text{H}^+} \text{NHCH}_2\text{OH} \xrightarrow{-\text{H}_2\text{O}} \]

Figure 1-29. Mechanism of TiO$_2$-P25 catalyzed formylation.
Another easily removed and recycled transition metal catalyst was reported by Akamanchi.\textsuperscript{50} Sulfated tungstate (15) catalyzed the reaction of amines with formic acid to produce formamidoximes in solvent-free conditions (Figure 1-30). The optimized conditions are 10 mol\% 15, 70 °C, 1.2 equiv of formic acid, and 10-45 min. The catalyst was easily isolated after the reaction and could be reused up to four times without experiencing any loss of activity.

A broad scope was examined including primary, secondary, aromatic, heteroaromatic, and alkyl amines as well as α-amino acids. Yields ranged from 85-99%. Studies were done to understand the interaction between the catalyst and the reagents. They indicated that formic acid was adsorbed onto the catalyst, but amine was not adsorbed. This suggests a mechanism in which the catalyst activates the formic acid followed by nucleophilic attack, similar to other acid catalyzed formylations.

![Figure 1-30. N-formylation of amines with formic acid and sulfated tungstate catalyst.](image)

More recently Hong reported another Lewis acid, a fluorous silica gel supported hafnium (IV)bis(perfluoroocatanesulfonyl)imide complex (FSG-$\text{Hf[N(SO}_2\text{C}_8\text{F}_{17}]}_2\text{H})$, that formylated amines in aqueous formic acid (Figure 1-31).\textsuperscript{51} Optimum conditions were 1 mol\% catalyst, 70 °C, and 3 equiv of formic acid. The catalyst could be reused for up to three cycles without loss of activity.
Aromatic amines produced the desired formamides in high yields regardless of substituent. However, when electron withdrawing groups were present, longer reaction times were necessary. Aliphatic \( n \)-butylamine and secondary diphenylamine produced good yields. Hong proposed that the catalyst and the higher loading of formic acid provided electronic assistance to the reacting formic acid carbonyl, which allowed for more facile nucleophilic attack by the amine (Figure 1-32).

\[
R^1 \text{NH} + HOC(\text{aq}) \xrightarrow{\text{FSG-Hf[N(SO}_2\text{C}_8\text{F}_{17}]_4, 1 \text{ mol}\%}} R^1 \text{C}(\text{NH})_2
\]

\( R^1 = \text{aryl, alkyl} \)
\( R^2 = \text{aryl, H} \)

Figure 1-31. \( N \)-formylation catalyzed by FSG-Hf[N(SO\(_2\)C\(_8\)F\(_{17}\)]\(_2\)]\(_4\).

Figure 1-32. Electronic assistance for nucleophilic attack of amine on formic acid.

Williams reported \( N \)-formylation of amines with paraformaldehyde by an iridium catalyst.\(^{52}\) Optimal conditions of this reaction were amine, paraformaldehyde (3 equiv of the monomer), 1 mol\% \([\text{Cp}^*\text{IrI}_2]_2\) as catalyst, water as solvent, reflux, and 5-10 h (Figure 1-33). Primary amines produced the expected formamides in high yields. Secondary amines produced the expected formamides in moderate to excellent yields. When an
An enantiomERICALLY pure amine was reacted, the formamide product retained most but not all of its enantiomeric purity. Primary anilines did not afford product under these conditions. The acyclic secondary aniline examined produced the formamide in only 46% yield, but indoline, a cyclic secondary aniline, produced the formamide in 91% yield.

A similar mechanism was proposed by Friend when gold is used with oxygen (Figure 1-34). One important distinction between these two mechanisms is that gold requires ozone (O₃) to introduce adsorbed oxygen, while silver can employ oxygen (O₂).

These are examples in which the catalyst interacts with the amine directly during reaction with a formylating agent.

\[
\begin{align*}
\text{R}^1\text{NH} & \quad \text{paraformaldehyde} \\
& \quad (3 \text{ equiv of monomer}) \\
\quad & \quad \text{[Cp*Irl₂]₂ (1 mol\%)} \\
& \quad \text{H₂O, reflux, 5-10 h}
\end{align*}
\]

Figure 1-33. Iridium catalyzed formylation of amines with paraformaldehyde.

Formylation of dimethyl amine with formaldehyde was studied collaboratively by Madix and Friend on silver and gold surfaces. Oxygen assisted formylation of dimethylamine on metallic silver surfaces was reported by Madix.

The proposed mechanistic pathway involves molecular oxygen dissociating on the silver surface, coordination and deprotonation of the amine occurs, formaldehyde is introduced and attacked at the carbonyl, and finally β-hydride elimination occurs to produce the formamide (Figure 1-34).
Gold nanoparticles were reported by Sakurai to catalyze the formylation of amines with methanol or formaldehyde.\textsuperscript{55} Gold nanoclusters stabilized by poly(N-vinyl-2-pyrrolidione) (Au:PVP) acted as the catalyst in aerobic oxidation conditions. Optimum conditions for this reaction when methanol was used as the formyl source were 10 atom\% catalyst, 200 mol\% LiOH as base, 1:2 methanol:water solvent, 80 °C (reflux), and 8 h (Figure 1-35). When these conditions were applied to \textit{N}-methylaniline, two products were formed: 94\% yield of \textit{N}-methylanilide \textit{16} and 5\% yield of anilide \textit{17}. Methanol oxidation leads to formaldehyde, formic acid, methyl formate, and carbon dioxide. In order to ascertain which intermediate was reacting with the amine, formylative agents were used in place of methanol. The solvent system used was ethanol:water, the reaction time was reduced to 1 h, and the temperature was reduced...
to 50 °C. Without methanol or a formylating agent no reaction occurred. When formaldehyde was used in place of methanol as a 37% solution, 16 was formed in 81% yield. When either methyl formate or formic acid was used in place of methanol, no reaction occurred. Optimum conditions for this reaction when formaldehyde was used as the formyl source were 1.5 equiv of formaldehyde, 1 atom% catalyst, 100 mol% NaOH as base, 1:2 ethanol:water solvent, 27 °C, and 9 h. A wide selection of amines was subjected to these new conditions. Yields were best for aromatic amines. Sterically hindered and electron poor aromatic species produced little to no product. Aromatic, primary, and secondary alkyl amines produced high yields of formamides.

Figure 1-35. N-formylation of amines with methanol by nanogold particles.

Glorius reported N-formylation of amines by methanol activation catalyzed by a ruthenium N-heterocyclic carbene complex (18) (Figure 1-36).56 This complex was also reported to catalyze amide synthesis. The optimized conditions for the amide synthesis were initially applied to the activation of methanol. These conditions were 1 mol% 18, 1.5 equiv of alcohol, toluene solvent, inert atmosphere, at reflux, and 24 h. When these conditions produced only trace amount of the formamide, the amount of methanol was increased to 3.3 equiv. Attempted optimizations of equiv of reactants, concentration, solvent identity, and temperature did not increase the yield. When the reaction was run in a sealed container, the yield was lower and a build-up of gas was observed. This was presumed to be hydrogen gas and thus the introduction of a sacrificial hydrogen
acceptor was added to shift the equilibrium towards product. Styrene was chosen as this acceptor, and with this additive 96% conversion of starting material to formamide was observed.

Figure 1-36. Ru-NHC catalyzed methanol activation and formylation of amines. A) Catalyst 18. B) Optimum conditions.

The scope was examined using primary, secondary, tertiary, and benzyl amines. Overall yields ranged from 27-99%. The lowest yields corresponded to bulkier substrates and electron poor benzyl amines. Aromatic amines did not react. When optically pure phenylethylamine was reacted, the reaction produced a 77% yield and no loss of enantiomeric purity was observed. During the examination of the reaction scope the catalyst 18 was formed in situ from the pre-catalyst Ru(cod)(2-methylallyl)₂, the HCl salt of the NHC ligand, and base (Figure 1-36). To ensure this reaction was not base catalyzed, the catalyst was prepared and isolated before the reaction and then introduced with the NHC ligands attached. The yield of the reaction did not decrease. When excess base was introduced the reaction yield decreased. The NHC used was ICy. The identity of the NHC was examined but other NHCs achieved lowered conversion of starting material. The pre-catalyst without NHC ligands did not catalyze the reaction. Through examination of the reaction with NMR studies, a possible mechanism was proposed (Figure 1-37). First, methanol is deprotonated and
coordinates to Ru as methoxide. β-Hydride elimination occurs and produces coordinated formaldehyde. The carbonyl of formaldehyde undergoes nucleophilic attack by the amine, then hydrogen (H₂) is lost as the amine is deprotonated. A second β-hydride elimination occurs to form the formamide product. The formamide product may be exchanged with methanol and a second H₂ is liberated as the original methoxide complex is formed, beginning the catalytic cycle again.

![Mechanism for Ru-catalyzed methanol dehydrogenation followed by cross-coupling with amine to produce the formamide.](image)

Reddy reported formylation of primary and secondary amines by the catalytic oxidation of methanol in solution by copper salts. This transformation was achieved in the presence of hydrogen peroxide (H₂O₂) and basic copper hydroxyl salts (Figure 1-37).
Optimized conditions for the formylation of amines were amine, 30 mol% CuCl$_2$•H$_2$O, methanol solvent, 3.4 equiv of 6.0% w/w H$_2$O$_2$, room temperature, and 45-90 min. All amines were selectively converted to formamides. Primary and secondary amines were formylated in 63-80% yields. The mode of H$_2$O$_2$ addition was very important to the reaction. When slow addition of H$_2$O$_2$ occurred, formylated product was instantly formed. When the same amount of H$_2$O$_2$ was added as two equal portions, reaction times were longer and more H$_2$O$_2$ was necessary as decomposition of the peroxide was observed.

![Chemical structure](image)

Figure 1-38. N-formylation of amines with formaldehyde by nanogold particles.

Saegusa reported formylation of amines by copper complexes and carbon monoxide.$^{58}$ Various metal complexes were examined. The most active of these complexes was CuCl. This reaction selectively formed formamides with only trace amounts of urea observed. This reaction was found to be accelerated in water. This was attributed to the fact that the CuCl-CO complex is favored in water solvent. Aliphatic amines were subjected to this reaction and secondary amines proved more facile to formylation than primary amines. Aromatic amines did not react with CuCl catalyst but they were formylated when chloroauric acid (HAuCl$_4$•H$_2$O) was used as catalyst.

Remple reported a ruthenium catalyst that produced formamides from cyclic secondary amines using only 1 atm of carbon monoxide gas at 75 °C (Figure 1-39).$^{36}$ The mild conditions in this reaction required long reaction times (20-200 h) to ensure
completion. These conditions were unsuccessful formylating primary or acyclic secondary amines.

![Diagram of Ruthenium catalyzed carbonylation of amines]

Figure 1-39. Ruthenium catalyzed carbonylation of amines.

Watanabe reported triruthenium dodecacarbonyl (Ru\(_3\)(CO)\(_{12}\)) catalyzed formylation of amines using CO as the carbonyl source.\(^{59}\) Different ruthenium and rhodium catalysts were examined. The rhodium based catalysts produced significant amounts of urea. The best catalytic activity toward formamide production was shown by Ru\(_3\)(CO)\(_{12}\). Optimum conditions were 0.17 mol% catalyst, 40 atm CO, benzene as solvent, 120-180 °C, and 6 h. Primary aliphatic amines successfully produced formamide products in these conditions. Carbonylation of piperidine produced the formamide in only moderate yield due to formation of urea. This catalyst worked best for basic primary amines.

Jenner reported that ruthenium compounds catalyzed primary and secondary amines with CO as the carbonyl source.\(^ {34}\) Ruthenium trichloride trihydrate (RuCl\(_3\)•3H\(_2\)O) showed the highest activity and selectivity towards the formation of formamides from primary amines. Two other catalysts were tested, Co(OAc)\(_2\)•4H\(_2\)O and RhCl\(_3\)•3H\(_2\)O. The cobalt catalyst showed low conversion, and the rhodium catalyst showed high activity but low selectivity towards the formamide product. Only primary amines with an α-hydrogen were carbonylated. This may be indicative the pathway of formamide formation, or it could be a steric issue. Cyclic secondary amines were carbonylated to the corresponding formamides. However a competing reaction was the
transalkylation which forms a trialkyl amine and a primary amine from two equiv of secondary amine. The newly formed primary amine was also carbonylated to the formamide product. Cobalt-ruthenium catalysts improved the selectivity for formylation of dialkylformamides from secondary amines. Adjustments of temperature and/or pressure increased the selectivity of reaction toward formamide products. The primary formamide and urea products were byproducts of these reactions.

In related work, Jenner reported the effect of solvent on carbonylation of amines with RuCl$_3$$\cdot$3H$_2$O.$^{35}$ Solvents with varying dielectric constants were examined. No correlation between the yield of formamide and dielectric constant was found. Methanol was the best solvent for ruthenium catalyzed carbonylation. In water, depending upon the amine identity, either more urea was formed or the conversion of amine was sharply decreased. The previously examined cobalt-ruthenium catalyst produced selectivity for formamide in methanol similar to that of the ruthenium catalyst with no significant improvement. Higher pressure, 750 atm, and high temperature, 180 °C, suppressed the urea formation and increased formamide selectivity. The best conversion and selectivity were observed when excess methanol was present, which indicated that the alcohol was stoichiometrically involved in the reaction. The proposed reaction pathway for this reaction was initial formation of methyl formate from methanol and CO, followed by attack from the dialkylamine forming the formamide and regenerating methanol. This reaction was successfully applied to dialkylamines and aromatic amines. However, aromatic amines still show lower conversion and selectivity than alkylamines. Sterically hindered amines such as tert-butylamine, which was unreactive without methanol,
underwent selective formylation in the presence of ruthenium catalyst and methanol solvent.

McElwee-White reported a tungsten catalyst (19) that produced formamides (Figure 1-40). This catalyst selectively formed formamides from secondary amines and ureas from primary amines. This method will be discussed in Chapter 2.

![Figure 1-40. Tungsten dimer catalyst.](image)

**Conclusions**

There are many methods of formylating amines. Formylating agents, such as formic acid, alkyl formates, formaldehyde, and paraformaldehyde, can produce formamides with the aid of molecular and transition metal catalysts in a variety of conditions. Many types of amines can be formylated in excellent yields: primary, acyclic secondary, cyclic secondary, and aromatic amines as well as amino acids. Enantiomeric purity can be maintained during formylation. Catalysts can also perform N-formylation with CO as the carbonyl source with molecular or transition metal catalysts. Disadvantages of these methods include the requirement of stoichiometric amounts of formylating agents, expensive or complex catalysts, high temperatures, and high CO pressures.
CHAPTER 2
CARBONYLATION USING TUNGSTEN CATALYSTS

Industrial scale carbonylation generally uses phosgene or one of its derivatives as a carbonyl source (Figure 2-1). These are unattractive options due to the toxicity of phosgene and atom economy of the derivatives. The McElwee-White research group has been studying carbonylation as an alternative to phosgene for many years. A variety of conditions have been used to produce products such as ureas, formamides, hydantoin, and dihydrouracils. These moieties have been formed most commonly using carbon monoxide gas with W(CO)₆ as catalyst, oxidant, and base. In the most recent method, the transition metal catalyst has been eliminated completely creating a greener method for synthesis of carbonyl compounds.

![Figure 2-1. Phosgene and examples of derivatives. A) Phosgene. B) DMDTC. C) CDI.](image)

**Initial Urea Formation**

The W(CO)₆ catalyzed carbonylation began when a dimer tungsten complex (19) was found to produce formamides and ureas from secondary and primary amines respectively (Figure 2-2). Using this method, secondary amines selectively form formamides (20) in yields ranging from 8-61% and primary amines selectively form ureas (21) in yields ranging from 56-105% with no added carbon monoxide gas (yields calculated per equiv of tungsten).
When the tungsten dimer is used without any added carbon monoxide gas, turnover numbers (TON) of up to 12 per dimer can be achieved forming the carbonylated products. When 100 atm of carbon monoxide gas was added to the reaction, TON were able to reach 25 per dimer. Carbonylation of amines by the tungsten dimer with iodine (I$_2$) added as an oxidant suggested that other tungsten carbonyl complexes may also afford these transformations. The inexpensive and readily available metal complex W(CO)$_6$ was chosen as a precatalyst. This complex afforded no product without I$_2$ present. But when the precatalyst (W(CO)$_6$), oxidant (I$_2$) and base (K$_2$CO$_3$) were present with 100 atm of added carbon monoxide gas, the process yielded 39 TON per tungsten (Figure 2-3).

Figure 2-3. Carbonylation of primary amines to ureas using W(CO)$_6$/I$_2$. 

**Urea Formation Using W(CO)$_6$ Catalyst**

When the tungsten dimer is used without any added carbon monoxide gas, turnover numbers (TON) of up to 12 per dimer can be achieved forming the carbonylated products. When 100 atm of carbon monoxide gas was added to the reaction, TON were able to reach 25 per dimer. Carbonylation of amines by the tungsten dimer with iodine (I$_2$) added as an oxidant suggested that other tungsten carbonyl complexes may also afford these transformations. The inexpensive and readily available metal complex W(CO)$_6$ was chosen as a precatalyst. This complex afforded no product without I$_2$ present. But when the precatalyst (W(CO)$_6$), oxidant (I$_2$) and base (K$_2$CO$_3$) were present with 100 atm of added carbon monoxide gas, the process yielded 39 TON per tungsten (Figure 2-3).
As carbonylation of primary amines by W(CO)$_6$ was probed further, many variables such as catalyst, temperature, pressure, equiv of base, and solvent were optimized. Similar group 6 metal catalysts, Mo(CO)$_6$ and Cr(CO)$_6$, were examined for efficiency. Both metal complexes produced lower yields than tungsten carbonyl which was surprising as third row metals are usually less effective catalysts. Optimized conditions include a higher temperature (90 °C), 80 atm CO pressure, and 1.5 equiv of base (K$_2$CO$_3$). Many solvents – polar and non-polar, halogenated and non-halogenated, organic and aqueous – were examined. DCM was the best single solvent for forming N,N'-disubstituted ureas. In some cases a biphasic solvent system increased yields. For primary amines such as $n$-propylamine, $n$-butylamine, or $i$-propylamine, the yields were highest in DCM. For the wide range of benzylamines examined, the DCM:water biphasic solvent system increased nearly all of the yields of ureas. During the reaction each equiv of urea produced also formed two equiv of the amine hydroiodide as the amines forming urea were deprotonated. These amine salts have lowered solubility in DCM so the addition of water allows them to be deprotonated by the base in aqueous solution. The amines can then reenter the organic layer and participate in urea formation.

During the examination of substituted benzylamines, it was found that a wide range of substituents will tolerate these carbonylation conditions. This includes halogen containing compounds, ether and thioether compounds, and amines with unprotected alcohols. Ureas are also formed in the presence of carboxylic acids, esters, cyano, and nitro groups.
These newly optimized conditions were then applied to secondary amines. In the previous reactions of secondary amines, formamide products were selectively formed. However, using these newly optimized conditions only trace amounts of formamides were observed and the major products were tetrasubstituted ureas (22) (Figure 2-4). Yields were low to moderate. This was attributed to the inability of any of the bases examined to deprotonate the amine salt (23) that is formed as 22 forms. As one urea molecule is formed, four equiv of amine are consumed, two become part of 22 and two act as a sacrificial base to deprotonate each of the amines that react (Figure 2-5). This method is still an attractive, alternative method for the formation of tetrasubstituted ureas from secondary amines.

\[
\text{RR'}\text{NH} + \text{W(CO)}_6, \text{I}_2 \xrightarrow{\text{CO, K}_2\text{CO}_3, \text{CH}_2\text{Cl}_2} \text{R'}\text{N} - \text{N}\text{R'}
\]

![Figure 2-4. Formation of 22 from secondary amines.](image)

\[
4 \text{R}_2\text{NH} + \text{I}_2 + \text{CO} \xrightarrow{\text{catalyst}} \text{R}_2\text{N} - \text{NR}_2 + 2 [\text{R}_2\text{NH}_2]^+ \text{I}^-
\]

![Figure 2-5. Consumption of four equiv of amine to produce one equiv of urea.](image)

**Cyclic Ureas**

The next amines of interest were \(\alpha,\omega\)-diamines. These molecules were studied for their ability to be converted into cyclic ureas. This was the first example of transition metal catalysis using carbon monoxide to form cyclic ureas (24) from both primary and secondary \(\alpha,\omega\)-diamines (Figure 2-6). Primary diamines formed 24 in yields ranging from 38-51% and secondary diamines formed 24 in yields ranging from
10-52% (yields calculated per equiv of amine). In both cases high dilution conditions were necessary to prevent oligomers from forming. Formamides were not observed in either diamine case.

\[
\text{RHN} \quad \text{NHR} \quad \xrightarrow{\text{W(CO)}_6, I_2} \quad \text{R} \quad \text{N} \quad \text{N} \quad \text{R} \\
\text{CO, K}_2\text{CO}_3 \quad \text{CH}_2\text{Cl}_2
\]

Figure 2-6. Carbonylation of primary (R=H) and secondary (R=Me, Et, 'Pr, Bn) \(\alpha,\omega\)-diamines to form \text{22}.

This process was then optimized to produce better yields.\(^{67}\) The pressure was reduced from 100 atm to 80 atm, and in some cases the temperature was raised from 25 °C to 90 °C. In addition, the amount of \text{W(CO)}_6 was increased from 1 mol% to 4 mol% for primary amines and from 0.7 mol% to 4 mol% for secondary amines, and a number of secondary amines used a biphasic DCM:water solvent system. Yields for primary amines were increased to 33-80%. Secondary amine yields did not see an overall improvement and remained between 10-52%. The best results were achieved when the \(N\)-alkyl substituent is a methyl group. During the reaction of secondary diamines, the tetrahydropyrimidine derivatives (such as \text{25}) were also observed (Figure 2-7). Control experiments showed that the tetrahydropyrimidine derivative also forms without the presence of the catalyst or CO. This side product may be responsible for the lowered yields observed.

\[
\text{PhH}_2\text{CHN} \quad \xrightarrow{\text{W(CO)}_6, I_2} \quad \text{Bn} \quad \text{N} \quad \text{N} \quad \text{Bn} \\
\text{CO, K}_2\text{CO}_3 \quad \text{CH}_2\text{Cl}_2
\]

\[
\text{PhH}_2\text{CHN} \quad \text{NHCH}_2\text{Ph} \quad \xrightarrow{\text{W(CO)}_6, I_2} \quad \text{Bn} \quad \text{N} \quad \text{N} \quad \text{Bn} \quad + \quad \text{Ph} \quad \text{N} \quad \text{Bn}
\]

Figure 2-7. Carbonylation of \text{26} to form cyclic urea \text{27} and tetrahydropyrimidine \text{25}. 
Complex Targets

To illustrate the utility of this new method, these conditions were applied towards the formation of complex target molecules. The core structures of DMP 323 (28) and DMP 450 (29), two HIV protease inhibitors, contain a tetrasubstituted urea moiety (Figure 2-8). The previously reported method of installing the urea moiety involved using phosgene or a phosgene derivative. The yields of urea formed by W(CO)$_6$/CO are comparable to those obtained by using CDI. In both methods the yields vary substantially with the identity of the protecting group used (Figure 2-9).

![Figure 2-8. Functionalized diamines. A) DMP 323 (28). B) DMP 450 (29).](image)

![Figure 2-9. Carbonylation of diamines with protected alcohols to form 30, the core structure of 28 and 29. A) Catalytic carbonylation. B) Carbonylation via the phosgene derivative CDI.](image)
Additional substrates were tested using this methodology (Figure 2-10). The reaction conditions were optimized by increasing the temperature to 80 °C and using dichloroethane (DCE) as the solvent. The urea (30) was formed under these conditions and in some cases the alcohols did not require protecting groups.

![Chemical structure](image)

Figure 2-10. Diamine substrates forming 30 by catalytic carbonylation.

Another extension of this methodology includes the application to forming biotin (Vitamin H) derivatives. The attempts to synthesize biotin (31) were unsuccessful but may be due to the low solubility of the diamine substrate (Figure 2-11). The precursor to the methyl ester of biotin was soluble in organic solvents and when carbonylated yielded the derivative (32) in 84% yield.

![Molecular structures](image)

Figure 2-11. Complex targets. A) Biotin (31). B) Methyl ester derivative of Biotin (32).

Other derivatives of biotin (33) were also examined (Figure 2-12). Yields produced using W(CO)$_6$ and CO were comparable to those obtained when using CDI. Yields were moderate to good with a large dependence upon the solubility of the
diamine and urea in DCM. This method provides an alternative to phosgene or phosgene derivatives in the preparation of 32 and 33.

![Reaction scheme](image)

Figure 2-12. Preparation of biotin derivatives (X=O, N-Boc, CH₂CH₃; R¹=H, CH₃; R²=H, CH₃, (CH₂)₄CH₃).

**Ureas from Amino Alcohols**

Amino alcohols were studied using the tungsten catalyst to examine the selectivity between forming ureas or carbamates. Examples of 1,2-, 1,3-, 1,4-, and 1,5-amino alcohols with various substitutions were examined. In the W(CO)₆ catalyzed conditions the acyclic urea (34) was selectively formed over the cyclic carbamate (35) in all cases, and the acyclic carbamate (36) was not observed (Figure 2-13). These conditions do not require the use of a protecting group on the alcohol. These results were compared to carbonylation from DMDTC and CDI, phosgene derivatives. The phosgene derivatives show varied selectivity between 34 and 35 formation making the tungsten catalyst an attractive option for urea formation.

![Reaction scheme](image)

Figure 2-13. Selective carbonylation of amino alcohols to 34.
Hydantoins

The next class of molecules examined was hydantoins. These molecules contain a cyclic urea moiety. The effectiveness of the W(CO)$_6$ catalytic conditions to install this carbonyl was examined using α-amino amides (Figure 2-14). Hydantoins (37) were formed in these conditions with yields ranging from 11-75%. The conditions needed to be modified to produce a high yield, but this synthesis was successfully applied to the pharmaceutical phenytoin (38), a commonly prescribed anticonvulsive (Figure 2-14).

![Chemical structures of hydantoins](image)

Figure 2-14. Formation of hydantoins (37). A) General hydantoin reaction. B) Phenytoin (38).

Dihydrouracils

Another class of molecules that can be synthesized in these conditions is dihydrouracils. These molecules are of interest for their biological activity. By employing the conditions used to form hydantoins, the dihydrouracil (39) was produced in 88% yield (Figure 2-15). When substitution was introduced at the β-position, symmetrical ureas (40) were formed and no cyclic product was present (Figure 2-16). Alternatively, with an α-methyl substituted amino amide, 39 was formed in <10% yield. For all other substitutions, only DBU salts were formed at the completion of the reaction. Other conditions may need to be employed to make this an attractive synthesis of 39.
Figure 2-15. Formation of dihydrouracils from unsubstituted amino amides.

\[
\begin{align*}
\text{H}_2\text{N} & \hspace{1cm} \alpha \hspace{1cm} \text{O} \\
\text{Ph} & \hspace{1cm} \beta \\
\end{align*}
\]

\[
\begin{array}{c}
\text{W(CO)}_6, \text{I}_2 \\
\text{CO, DBU} \\
\text{DCE}
\end{array}
\]

\[
\begin{align*}
\text{O} & \hspace{1cm} \alpha \\
\text{Ph} & \hspace{1cm} \beta \\
\end{align*}
\]

Figure 2-16. Formation of 40 instead of 39 when β-substituted amino amides were carbonylated.

**N,N'-Diarylureas**

In previous works aniline, an aryl amine, was unable to produce urea when K$_2$CO$_3$ was used as the base.$^{64}$ When other bases were screened it was found that while DBU and pyridine only produced the urea in trace amounts, the use of DMAP increased the yield to 81% (Figure 2-17).$^{75}$ The optimal conditions for urea formation from aromatic amines were 40 °C, 80 atm CO, 1 equiv I$_2$, 2 equiv DMAP, 8 h, and DCM as solvent. A large number of $p$-substituted aryl amines were subjected to these optimized conditions to form symmetrical N,N'-diarylureas, such as 41. Yields ranged from moderate to good for functional groups such as halogens, ethers, thioethers, nitro, cyano, and esters. Vinyl, hydroxyalkyl, and carboxylic acid substituted arylamines produced no product.

\[
\begin{align*}
\text{NH}_2 \\
\text{Ph} \\
\end{align*}
\]

\[
\begin{array}{c}
\text{W(CO)}_6, \text{I}_2 \\
\text{CO, DMAP, CH}_2\text{Cl}_2
\end{array}
\]

Figure 2-17. Carbonylation of aniline to N,N'-diphenylurea (41).
Unsymmetrical ureas were then examined under these conditions. In some cases the unsymmetrical urea was the primary product and in others the symmetric ureas dominated. By altering the ratios of the aryl amines, it was possible to force more unsymmetrical urea to form.

The reaction mechanism was probed with $N$-methylaniline. It was previously thought that an isocyanate may form from the amine and CO which is then attacked by a second amine to form ureas. If this is the only pathway, a $N$-substituted arylamine should not form any urea. Using these conditions, it was found that no urea formed from the $N$-methylaniline alone. However, when aniline was combined with excess $N$-methylaniline, the trisubstituted urea was the major product with only trace diphenylurea observed. Other aniline derivatives were examined with $N$-methylaniline and all produced trisubstituted arylureas. These results are consistent with an isocyanate intermediate.

**Metal-Free Carbynylation**

During control experiments done on the $W$(CO)$_6$ catalyzed method, it was discovered that without the metal catalyst, a NaIO$_4$/NaI oxidant and promoter system would cause the transformation of 4-methoxybenzylamine (42) to 1,3-bis(4-methoxybenzyl)urea (43) in high yields (72-96%).$^{61}$ Initially, the formamide product (44) was also observed in the product mixture (Figure 2-18).

However, when the promoter identity was changed from I$_2$ to NaI, only the 43 was observed, optimizing away from 44. In order to increase yields, the solvent system was changed to a biphasic DCM:water system and the base was changed to DMAP from potassium carbonate (Figure 2-19). These optimized conditions were applied to a variety of substituted benzyl amines.
Figure 2-18. Oxidative carbonylation of 42 forming 43 and 44.

Figure 2-19. Optimized conditions for urea synthesis using NaIO$_4$ and NaI.

Conclusions

Tungsten hexacarbonyl is a very useful catalyst for carbonylating amines. Formamides, N,N'-di- and N,N,N',N'-tetra-substituted ureas, cyclic ureas, hydantoin, dihydouracils, and N,N'-diarylureas have all been successfully formed using W(CO)$_6$ in a variety of conditions. The core structures of complex target molecules like biotin and DMP 450 were also successfully produced with this catalyst. This work was further developed when metal-free conditions were found that formed ureas from oxidative carbonylation of primary amines.
CHAPTER 3
TRANSITION METAL-FREE CARBONYLATION OF AMINES TO FORMAMIDES

In conjunction with previous work carbonylating amines to ureas in the absence of a transition metal catalyst, which used NaIO₄ as an oxidant and NaI as a promoter, the effect of solvent was examined. Using similar conditions, it was found that amines could be converted to formamides in methanol solvent without formation of urea.

During our studies of NaIO₄-induced carbonylation of amines to ureas, formamide derivatives were also observed as byproducts. In the course of our optimization studies, the reaction was carried out in methanol instead of the standard biphasic DCM:water solvent mixture. In methanol, only 44 was produced from the carbonylation of 42, without 43 detected in the reaction mixtures (Figure 3-1). These new conditions were then examined to maximize the yield of the formamide.

Figure 3-1. Initial use of methanol solvent to form 44 from 42.

Early Optimization

The initial observation of formamides in the product mixtures involved DMAP as the base in the reaction because it was the preferred base in the urea synthesis. However, incomplete separation of product and base during flash chromatography of the reaction mixtures containing DMAP led to low yields of formamides. Other bases were examined to determine their efficacy for formamide synthesis. The bases studied were DBU, potassium carbonate and pyridine. All three resulted in formation of the formamide product (Table 3-1). The highest yields were obtained from DBU and
K₂CO₃, with K₂CO₃ preferred due to its much lower cost and ease of removal during aqueous workup.

**Table 3-1. Selection of base for conversion of 42 to 44.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMAP</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>Pyr</td>
<td>31</td>
</tr>
</tbody>
</table>

*Conditions: 4.0 mmol amine, 4.0 mmol NaI, 6.4 mmol NaIO₄, 16 mmol K₂CO₃, 45 atm CO, 60 mL CH₃OH, 24 h, 90 °C. *Product observed spectroscopically.

Preliminary optimization experiments addressed reaction time (Table 3-2). After 8 h, the reaction yields stabilized, indicating that the product does not decompose under the reaction conditions. This is different than the urea reactions where longer reaction times led to decreased yields and decomposed products. The last preliminary optimization was temperature. When 44 was first observed, the temperature of the reaction was 90 °C. The temperature was increased from that of the optimized temperature for urea synthesis under similar conditions (25 °C) due to the lack of solubility of the oxidant and base in methanol. However, when the reaction was run at room temperature in attempts to utilize a multi-chamber vessel for small scale reactions, the yield did not decrease. Future experiments were run without heating.

**Table 3-2. Reaction time for conversion of 42 to 44.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>75</td>
</tr>
</tbody>
</table>

*Conditions: 4.0 mmol amine, 4.0 mmol NaI, 6.4 mmol NaIO₄, 16 mmol K₂CO₃, 45 atm CO, 60 mL CH₃OH, 90 °C.*
Control Experiments

After a suitable base was selected and an initial time study was completed, various control experiments were conducted. A concern of these conditions is the possibility that the formyl group in the products could be derived from the oxidation of methanol by periodate, not from the carbon monoxide. Control experiments with methanol oxidation products but without carbon monoxide were run to investigate the origin of the carbonyl group during formylation of 42. When either formic acid or 37% w/w formaldehyde/water was used as the solvent with no addition of carbon monoxide, no 44 was detected by IR or $^1$H NMR analysis. The reaction was also run using ethanol as a solvent instead of methanol. If alcohol oxidation to the aldehyde were occurring and reacting with the amine, we would expect the amide product to form. However, 44 was produced in a 40% yield.

Isotopic Labeling Experiments

Another method to examine possible methanol incorporation is to label the methanol. An isotopic labeling experiment in which the methanol solvent was 50% $^{13}$CH$_3$OH produced 44 with $^{13}$C in only natural abundance as determined by mass spectrometry (Figure 3-2). This result confirms that the source of the carbonyl is carbon monoxide and not the methanol solvent.

Although the $^{13}$C labeling experiments establish that the formyl carbonyl is not derived from methanol, the formyl hydrogen could be incorporated from the methyl group by H-abstraction or from the hydroxyl group by proton transfer (Figure 3-3). The carbonylation reaction of 42 was run in CD$_3$OH, to look for incorporation of deuterium label at the formyl position of 44 as a result of radical abstraction from the labeled methyl group. However, the IR spectra of the products obtained in CH$_3$OH and CD$_3$OH
were identical as were the integrations of the formyl hydrogen peak in the $^1$H NMR spectra.

![Chemical structure](image)

Figure 3-2. Possible outcomes for incorporation of $^{13}$C from labeled methanol.

![Chemical structure](image)

Figure 3-3. Incorporation of deuterium from deuterated methanol.

In contrast, running the experiment in CH$_3$OD resulted in incorporation of deuterium, as evidenced by a shift of νCO in the IR spectrum from 1642 cm$^{-1}$ in 44 to 1624 cm$^{-1}$ in 44-d. Presence of the label was confirmed by a decreased relative integration value of the formamide proton at 8.1 ppm in the $^1$H NMR spectrum of 44-d to 0.1 H from its original value of 1.0 H in the spectrum of 44. The $^2$H NMR spectrum of 44-d shows a formyl deuterium peak at 8.1 ppm, the same chemical shift as the
hydrogen in the $^1$H NMR. The mass spectrum of formamide 44-d also confirms the presence of the deuterium label. These labeling experiments identify the methanol hydroxyl proton as the source of the formyl hydrogen.

**A New Perspective**

Periodate is known to generate radical species. Thus, based upon bond energies and resonance stabilization, if the reaction proceeded by a radical mechanism, it was expected that the hydrogen incorporating into the formamide product would be the results of a hydrogen abstraction from the methyl portion of the solvent, not from the proton attached to the oxygen. The reaction was run with TEMPO, a known radical trap (1:1 NaIO$_4$:TEMPO) in order to ascertain the presence of a long lived radical species. The yield of this reaction was 79%, not the decreased yield expected of a radical pathway. Additionally, no amine adduct was observed. This result, coupled with the result of the deuterium labeling study, led us to believe that the reaction was not going through a radical pathway. Thus, a further examination of the role of periodate and of the reaction mechanism began.

New control experiments addressed the necessity of each piece of the reaction. An examination of the promoter identity was done (Table 3-3)$^1$. Various iodide salts with different counterions were examined. The yields were not affected by the counterion identity. However, when the yield of the reaction did not change with the removal of the promoter, it was determined that the promoter was not necessary. In further experiments NaI was left out of the reaction conditions.

---

$^1$ Promoter study performed by Lilli Carpo.
Table 3-3. Examination of promoter identity for the conversion of 42 to 44.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Promoter</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaI</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>(NBu₄)I</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>KI</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>I₂</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>70</td>
</tr>
</tbody>
</table>

Conditions: 3.0 mmol amine, 3.0 mmol promoter, 4.8 mmol NaIO₄, 12 mmol K₂CO₃, 45 atm CO, 45 mL CH₃OH, 24 h, 90 °C.

When NaIO₄ was present but the base was removed, no product formed. When the base and NaIO₄ were both removed, no product formed. When NaIO₄ was removed but the base was still present the reaction achieved the same yields as previously observed. Thus unlike urea formation, this carbonylation is not oxidative but possibly base mediated. The reaction was run without any base and no product formed. The reaction was run in water instead of methanol with base and NaIO₄ and while the product was observed by TLC, the yield was too small to isolate, <1%. This is a drastic difference than the 78% yield that is obtained when methanol is the solvent. When the reaction was run in water with base but no NaIO₄ the product was not observed at all.

Conclusions

Carbonylation of amines in methanol selectively produces formamides. Potassium carbonate was chosen as the optimal base for this conversion. Sodium iodide and NaIO₄ were discovered to be unnecessary. The only necessary components in this reaction are amine, base, carbon monoxide, and methanol. Further optimizations were performed on this reaction without NaIO₄ present.
CHAPTER 4
BASE MEDIATED CARBONYLATION

Optimization

Optimization studies were conducted on 4-methoxybenzylamine beginning with the most recent conditions sans oxidant. These conditions consisted of 1 equiv (0.004 mol) amine, 4 equiv K$_2$CO$_3$, 60 mL methanol, 24 h, 25 °C, and 45 atm carbon monoxide. Conditions were then optimized for time (Table 4-1), base quantity (Table 4-2), and pressure (Table 4-3 and Table 4-4).

Table 4-1. Time optimization for the conversion of 42 to 44.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>81</td>
</tr>
</tbody>
</table>

Conditions: 4 mmol amine, 16 mmol K$_2$CO$_3$, 45 atm CO, 60 mL CH$_3$OH, 25 °C.

Table 4-2. Base quantity optimization for the conversion of 42 to 44.

<table>
<thead>
<tr>
<th>Entry</th>
<th>K$_2$CO$_3$ (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>78</td>
</tr>
</tbody>
</table>

Conditions: 4 mmol amine, 45 atm CO, 60 mL CH$_3$OH, 8 h, 25 °C.

Table 4-3. Pressure optimization for 7 h reaction time for the conversion of 42 to 44.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure CO (atm)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>78</td>
</tr>
</tbody>
</table>

Conditions: 4 mmol amine, 12 mmol K$_2$CO$_3$, 60 mL CH$_3$OH, 7 h, 25 °C.

Table 4-4. Pressure optimization for 24 h reaction time for the conversion of 42 to 44.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure CO (atm)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>84</td>
</tr>
</tbody>
</table>

Conditions: 4 mmol amine, 8 mmol K$_2$CO$_3$, 60 mL CH$_3$OH, 24 h, 25 °C.
It was difficult to decide on a set of optimized conditions because there is a delicate balance between reaction time, equiv of base, and pressure. The reaction reached completion in 7 h when 45 atm of CO and four equiv of K$_2$CO$_3$ were used. At 8 h reaction time, only 3 equiv of base were needed to get the standard yield of product. Using 3 equiv of base at 7 h, we see that the pressure can be reduced to 35 atm. However, if lower pressure is desired, the reaction can be extended to 24 h and use only 25 atm CO with 2 equiv of base to achieve the same yield. This reaction is able to reach achieve similar yields when higher pressures or higher concentration of base are used.

It is also important to note that there is a significant dependence upon the stirring of the reaction. Yields dropped 10-20% in different sets of conditions when a smaller stir plate was used for the reaction. This problem was identified and all reactions were done on large, stronger stir plates that resulted in more vigorous stirring.

**Substituent Effects**

The optimization reactions were all conducted using 42 as starting material. We next wanted to examine the effect of the *para* substituent on the benzylamines as well as the functional group tolerance of this method. A selection of benzyl amines with different functional groups at the *para* position were tested (Table 4-5).

The amines are organized according to their Hammett $\sigma_{para}$ values. This value is effectively a measure of the donating or withdrawing effect of the substituent when it is on the *para* position of the benzene ring. These values take into account both inductive effects of the substituent as well as resonance effects. Negative values indicate a substituent is overall electron donating and positive values indicate that the substituent is overall electron withdrawing.
Table 4-5. Carbonylation of 4-substituted benzylamines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>( \sigma_{\text{para}} )</th>
<th>Product</th>
<th>Yield(^d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>42</td>
<td>-0.27</td>
<td>44</td>
<td>78</td>
</tr>
<tr>
<td>2(^b)</td>
<td>45</td>
<td>-0.17</td>
<td>46</td>
<td>61</td>
</tr>
<tr>
<td>3(^c)</td>
<td>47</td>
<td>-0.02</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td>4(^b)</td>
<td>49</td>
<td>0</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>5(^b)</td>
<td>51</td>
<td>0.06</td>
<td>52</td>
<td>67</td>
</tr>
<tr>
<td>6(^c)</td>
<td>53</td>
<td>0.18</td>
<td>54</td>
<td>33(^a)</td>
</tr>
<tr>
<td>7(^b)</td>
<td>55</td>
<td>0.23</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>8(^b)</td>
<td>57</td>
<td>0.23</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>9(^c)</td>
<td>59</td>
<td>n/a ((\text{CO}_2\text{Et} = 0.40))</td>
<td>60</td>
<td>27(^a)</td>
</tr>
<tr>
<td>10(^b)</td>
<td>61</td>
<td>0.45</td>
<td>62</td>
<td>25</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield per equiv of amine. \(^b\)Conditions: 4 mmol amine, 12 mmol K\(_2\)CO\(_3\), 35 atm CO, 60 mL CH\(_3\)OH, 7 h, 25 °C. \(^c\)Conditions: 2 mmol amine, 6 mmol K\(_2\)CO\(_3\), 35 atm CO, 30 mL CH\(_3\)OH, 7 h, 25 °C. \(^d\)One extra equiv of base was added because the amine was an HCl salt.
Table 4-5. Continued.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>( \sigma_{para} )</th>
<th>Product</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11(^c)</td>
<td><img src="image1.png" alt="Amine 63" /></td>
<td>0.54</td>
<td><img src="image2.png" alt="Product 64" /></td>
<td>23</td>
</tr>
<tr>
<td>12(^b)</td>
<td><img src="image3.png" alt="Amine 65" /></td>
<td>0.66</td>
<td><img src="image4.png" alt="Product 66" /></td>
<td>17(^d)</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield per equiv of amine. \(^b\)Conditions: 4 mmol amine, 12 mmol \( \text{K}_2\text{CO}_3 \), 35 atm CO, 60 mL CH\(_3\)OH, 7 h, 25 °C. \(^c\)Conditions: 2 mmol amine, 6 mmol \( \text{K}_2\text{CO}_3 \), 35 atm CO, 30 mL CH\(_3\)OH, 7 h, 25 °C. \(^d\)One extra equiv of base was added because the amine was an HCl salt.

The yields of the formamides produced by their corresponding amines follow a trend that better electron donating groups on the ring produce higher yields. This is consistent with nucleophilic attack of the amine on the carbonyl species present. The yields of formamides produced by the electron poor species are rather low. For comparison purposes, the conditions used in this study were optimized using an electron rich species and were not changed. Using the same conditions facilitates seeing the trend based upon electron density.

A previous examination of substrate scope was done before \( \text{NaIO}_4 \) was eliminated from the reaction conditions (Table 4-6). These previous conditions employed higher pressure and more equiv of base. Yields of many of these substituted formamides are higher but that is believed to be a result of the higher pressure and additional base.
Table 4-6. Carbonylation of 4-substituted benzylamines with NaIO₄ present.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Yield⁺ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵇ</td>
<td>42</td>
<td>44</td>
<td>80</td>
</tr>
<tr>
<td>2ᶜ</td>
<td>47</td>
<td>48</td>
<td>68</td>
</tr>
<tr>
<td>3ᵈ</td>
<td>49</td>
<td>50</td>
<td>61</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>51</td>
<td>52</td>
<td>79</td>
</tr>
<tr>
<td>5ᵉ</td>
<td>53</td>
<td>54</td>
<td>36ᶠ</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>55</td>
<td>56</td>
<td>86</td>
</tr>
<tr>
<td>7ᵇ</td>
<td>57</td>
<td>58</td>
<td>92</td>
</tr>
<tr>
<td>8ᵇ</td>
<td>67</td>
<td>68</td>
<td>7⁷</td>
</tr>
</tbody>
</table>

⁺Isolated yield per equiv of amine. ᵇConditions: 4.0 mmol amine, 6.4 mmol NaIO₄, 16 mmol K₂CO₃, 60 mL CH₃OH, 25 °C. ᶜConditions: 2.5 mmol amine, 4.0 mmol NaIO₄, 9.9 mmol K₂CO₃, 40 mL CH₃OH, 8 h, 25 °C. ᵈConditions: 4.0 mmol amine, 4.0 mmol NaI, 6.4 mmol NaIO₄, 16 mmol K₂CO₃, 60 mL CH₃OH, 90 °C. ᵉConditions: 1.5 mmol amine, 1.5 mmol NaI, 2.4 mmol NaIO₄, 6.0 mmol K₂CO₃, 20 mL CH₃OH, 90 °C. ᶠOne extra equiv of base was added because the amine was an HCl salt.

Other Amines

A variety of other amines was also subjected to these reaction conditions (Table 4-7, Table 4-8). The conditions optimized for 42 at 24 h reaction time were used for primary amines (Table 4-7) and the conditions optimized at 7 h reaction time were used for the cyclic secondary amines (Table 4-8). It was unknown how acyclic secondary
amines would react, so longer reaction times were employed. Previous work had shown that cyclic secondary amines produced good results in short reaction times.

Table 4-7. Carbonylation of primary amines to formamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>69</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>2(^b)</td>
<td>71</td>
<td>72</td>
<td>37</td>
</tr>
<tr>
<td>3(^b)</td>
<td>73</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>4(^c)</td>
<td>75</td>
<td>76</td>
<td>61</td>
</tr>
<tr>
<td>5(^b)</td>
<td>77</td>
<td>78</td>
<td>Trace</td>
</tr>
<tr>
<td>6(^c)</td>
<td>79</td>
<td>80</td>
<td>71</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield based on equiv of amine. \(^b\)Conditions: 1 mmol amine, 4 mmol K\(_2\)CO\(_3\), 25 atm CO, 15 mL CH\(_3\)OH, 24 h, 25 °C. \(^c\)Conditions: 2 mmol amine, 4 mmol K\(_2\)CO\(_3\), 25 atm CO, 15 mL CH\(_3\)OH, 24 h, 25 °C.

Table 4-8. Carbonylation of secondary amines to formamides.

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Amine</th>
<th>Product</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>82</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>84</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>86</td>
<td>66</td>
</tr>
</tbody>
</table>

\(^a\)Conditions: 4 mmol amine, 12 mmol K\(_2\)CO\(_3\), 35 atm CO, 7 h, 25 °C. \(^b\)Isolated yield based on equiv of amine.

\(n\)-Butylamine, \(i\)-butylamine, and cyclohexylamine were formylated in good yield but amines with shorter alkyl groups exhibit lower yields. This may be attributed to the solubility of the formamides in water which inhibits their isolation during the reaction.
workup. Cyclic secondary amines produced the formamides in moderate to good yields.

**Proposed Mechanism**

A possible reaction mechanism involves base mediated carbonylation through a methyl formate intermediate (Figure 4-1). This mechanism is consistent with our experimental data. There is literature precedent for the formation of methyl formate when base, methanol, and carbon monoxide are mixed at high pressures. Jogunola reported the formation of methyl formate when potassium methoxide was combined with carbon monoxide followed by proton transfer from methanol, thereby regenerating methoxide.

![Figure 4-1. Proposed mechanism for the base mediated pathway to formamides.](image-url)
Similar to our experimental results, Jogunola reported a relationship between stirring rate and methyl formate concentration. The faster stirring speeds produced a marked increase in methyl formate concentration due to the increased mass transfer area of the gas bubbles, which led to increased gas absorption. We saw a strong relationship between yield and stirring. Smaller stir plates did not produce yields as high as when the reaction was performed on a larger, more vigorous stir plate.

Methyl formate, amine 42, and K$_2$CO$_3$, and were stirred at room temperature until starting material was no longer observed via TLC$^2$. This yielded 44 in quantitative yield. This control was repeated with the addition of NaIO$_4$ to determine whether the pathway would proceed with periodate present. The product 44 was produced again in quantitative yield. These results are consistent with the reaction occurring via formation of methyl formate from methanol and CO, followed by nucleophilic displacement of methanol by the amine.

**Conclusions**

Two sets of optimized conditions were identified. For a shorter reaction time of 7 h, 35 atm CO and 3 equiv of base are necessary. When the reaction is run for 24 h, 25 atm CO and 2 equiv of base are sufficient. Product formation is sensitive to stirring. Substituted benzylamines are formylated in moderate to good yields. Primary and secondary amines were formylated in a range of yields depending upon the structure of the amine. We propose a base mediated mechanistic pathway leading through methyl formate as an intermediate.

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$^2$ Methyl formate control experiments performed by Jennifer Johns.
CHAPTER 5
EXPERIMENTAL SECTION

General Methods

Starting materials and reagents were purchased from Sigma-Aldrich or Acros Organics and used without further purification unless specified. 4-Methoxybenzylamine was purified by distillation under reduced pressure. Carbon monoxide was purchased from Airgas. $^1$H and $^{13}$C NMR spectra were obtained on Varian Gemini 300, VXR 300, and Mercury 300 MHz spectrometers. $^2$H NMR spectra were obtained on an Inova 500 MHz spectrometer. Infrared spectra were measured on a Perkin-Elmer 1600 FTIR either as pure solid or as neat oil. Elemental analysis was performed at the University of Florida. High-resolution mass spectrometry (HRMS) was performed by the University of Florida analytical service.

General Procedure for Carbonylation of Amines to Formamides

Procedure A

\[ \text{N-(4-Methoxybenzyl)formamide (44).} \]

To a 300 mL glass liner for a Parr high-pressure vessel were added methanol (60 mL), NaI (0.600 g, 4.00 mmol), NaIO$_4$ (1.37 g, 6.40 mmol), potassium carbonate (2.21 g, 16.0 mmol) and amine 42 (0.631 g, 4.06 mmol). The liner was placed in the vessel and methanol was added to the space between the liner and vessel. The vessel was then closed, charged to 45 atm with carbon monoxide, heated to 90 °C and stirred for 24 h. At the completion of the reaction the solution was placed in a separatory funnel. Saturated sodium sulfite was added to the solution and mixed thoroughly. Water was added to dissolve the solid salt
present and the mixture was extracted with DCM (3 x 25 mL). The organic layers were combined and the solvent was removed via rotary evaporation leaving an off white solid residue. The solid was purified via column chromatography using silica gel and ethyl acetate/hexanes as the eluent (50:50 ethyl acetate: hexanes shifted to pure ethyl acetate) to provide 44 as a white solid (0.604 g, 80% yield). The compound was identified by comparison with literature data.\textsuperscript{78} \textsuperscript{1}H NMR (DMSO-\textit{d}_6): \(\delta\) 8.43 (br s, 1 H), 8.10 (s, 1 H), 7.19 (d, \(J = 8.5\) Hz, 2 H), 6.88 (d, \(J = 8.5\) Hz, 2 H), 4.23 (d, \(J = 6.0\) Hz, 2 H), 3.73 (s, 3 H); \textsuperscript{13}C NMR (DMSO-\textit{d}_6): \(\delta\) 160.9, 158.2, 130.9, 128.7, 113.7, 55.1, 40.2; IR (solid) 1641 cm\(^{-1}\); HRMS (ESI): Calcd for C\(_9\)H\(_{11}\)NO\(_2\) [M+Na\(^{+}\)] 188.0682, found 188.0690.

**Procedure B**

\[
\begin{align*}
\text{N-(Benzyl)formamide (50).} & \quad \text{To a 300 mL glass liner for a Parr high-pressure vessel were added methanol (60 mL), potassium carbonate (1.66 g, 12.0 mmol), and amine 49 (0.429 g, 4.00 mmol). The liner was placed in the vessel. The vessel was then closed, charged to 35 atm with carbon monoxide, and stirred for 7 h. At the completion of the reaction the solution was placed in a separatory funnel. Water was added to dissolve any solid base and to achieve separation between methanol and DCM. The mixture was extracted with DCM (3 x 25 mL). The organic layers were combined and the solvent was removed via rotary evaporation leaving an off white solid residue. The solid was purified via column chromatography using silica gel and ethyl acetate/hexanes as the eluent (50:50 ethyl acetate: hexanes shifted to pure ethyl}
\end{align*}
\]
acetate) to provide 50 as a white solid (0.268 g, 49% yield). The compound was identified by comparison with literature data.\textsuperscript{48} \textsuperscript{1}H NMR (DMSO-\textit{d}_6): \delta 8.51 (br s, 1 H), 8.14 (s, 1 H), 7.42 - 7.13 (m, 5 H), 4.30 (d, \textit{J} = 6.1 Hz, 2 H); IR (solid) 1638 cm\textsuperscript{-1}.

**Procedure C**

![N-Formylpiperidine](image)

\textit{N-Formylpiperidine (84)}. To a 300 mL glass liner for a Parr high-pressure vessel were added methanol (60 mL), potassium carbonate (1.66 g, 12.0 mmol) and amine 83 (0.325 g, 3.82 mmol). The liner was placed in the vessel. The vessel was then closed, charged to 35 atm with carbon monoxide, and stirred for 7 h. At the completion of the reaction the solution was placed in a separatory funnel. Water was added to dissolve any solid base and to achieve separation between methanol and chloroform. The mixture was extracted with chloroform (3 x 25 mL). The organic layers were combined and the solvent was removed via rotary evaporation leaving a slightly yellow oil residue. The oil was purified via column chromatography using silica gel and CHCl\textsubscript{3}/CH\textsubscript{3}OH as the eluent (CHCl\textsubscript{3} shifted to 100:5 CHCl\textsubscript{3}/CH\textsubscript{3}OH) to provide 84 as a colorless oil (0.335 g, 78% yield). The compound was identified by comparison with literature data.\textsuperscript{32}
Procedure D

N-Butylformamide (74). To a 25 mL glass vial for a multi-chamber Parr high-pressure vessel were added methanol (15 mL), potassium carbonate (0.553 g, 4.00 mmol) and amine 73 (0.0788 g, 1.08 mmol). The liner was placed in the vessel. The vessel was then closed, charged to 25 atm with carbon monoxide, and stirred for 24 h. At the completion of the reaction the solution was acidified with 3.0 M HCl to approximately pH 2 and placed in a separatory funnel. Water was added to achieve separation between methanol and DCM. The mixture was extracted with DCM (3 x 10 mL). The organic layers were combined and the solvent was removed via rotary evaporation to afford 74 as a colorless oil (0.0828 g, 77% yield). The compound was identified by comparison with literature data.\(^\text{79}\)

Carbonylation Products

N-(Methoxybenzyl)formamide-d, \(p\)-CH\(_3\)OC\(_6\)H\(_4\)CH\(_2\)NHCD\(_6\) (44-d)

Procedure A was used at 25 °C with amine 42 (0.285 g, 2.077 mmol), NaIO\(_4\) (0.6845 g, 3.200 mmol), potassium carbonate (1.11 g, 8.00 mmol) and 20 mL CH\(_3\)OD. The product was identified by comparison with literature data.\(^\text{78}\) \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 8.10 (s, 0.1 H), 7.19 (d, \(J = 8.5\) Hz, 2 H), 6.88 (d, \(J = 8.5\) Hz, 2 H), 4.23 (d, \(J = 6.0\) Hz, 2 H), 3.73 (s, 3 H); \(^2\)H NMR (DMSO-\(d_6\)) 8.10 (s); IR (solid) 2186, 2171, 1623 cm\(^{-1}\); HRMS (DART): Calcd for C\(_9\)H\(_{16}\)DNO\(_2\) [M+H]\(^+\) 167.0925, found 167.0928.
**N-(4-Nitrobenzyl)formamide (68).**

Procedure A was used with the HCl salt of amine 67 (0.755 g, 4.01 mmol). The procedure was altered to include an additional purification via column chromatography using silica gel and 7:3 ethyl acetate: DCM. The product was afforded in a 7% yield and was identified by comparison to literature data.

**N-(4-Methylbenzyl)formamide (46).**

Procedure B was used with amine 45 (0.483 g, 3.99 mmol) and afforded the product in a 61% yield. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.46 (br s, 1 H), 8.12 (s, 1 H), 7.22 - 7.02 (m, 4 H), 4.25 (d, $J = 6.0$ Hz, 2 H), 2.27 (s, 3 H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 160.9, 142.2, 135.9, 128.8, 127.3, 40.5, 20.7; IR (solid) 1650 cm$^{-1}$; HRMS (ESI): Calcd for C$_9$H$_{12}$NO [M+H]$^+$ 150.0913, found 150.0915; Anal. Calcd for C$_9$H$_{11}$NO: C, 72.46; H, 7.43; N, 9.39; found: C, 72.64; H, 7.62; N, 9.31.

**N-(4-Vinylbenzyl)formamide (48).**

Procedure B was altered to use methanol (30 mL), potassium carbonate (0.829 g, 6.00 mmol), and amine 47 (0.263 g, 1.97 mmol) to afford the product in a 71% yield. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.51 (br. s., 1 H), 8.14 (s, 1 H), 7.43 (d, $J = 7.9$ Hz, 2 H), 7.21 (d,
$J = 7.9 \text{ Hz, } 2 \text{ H}$, 6.71 (dd, $J = 10.8, 17.7 \text{ Hz, } 1 \text{ H}$), 5.80 (d, $J = 17.7 \text{ Hz, } 1 \text{ H}$), 5.23 (d, $J = 10.8 \text{ Hz, } 1 \text{ H}$), 4.29 (d, $J = 5.8 \text{ Hz, } 2 \text{ H}$); $^{13}$C NMR (DMSO-$d_6$): δ 160.7, 138.4, 136.0, 135.5, 127.2, 125.8, 113.7, 40.2; IR (solid) 1651 cm$^{-1}$; HRMS (ESI): Calcd for $C_{10}H_{12}NO$ [M+H]$^+$ 162.0913, found 162.0913; Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.40; H, 7.31; N, 8.35.

![Image](image-url)

$N$-(4-Fluorobenzyl)formamide (52).

Procedure B was used with amine 51 (0.501 g, 4.00 mmol) and afforded the product in a 67% yield. The solid was identified by comparison with literature data.²¹

![Image](image-url)

$N$-(4-Iodobenzyl)formamide (54).

Procedure B was altered to use methanol (30 mL), potassium carbonate (1.11 g, 8.03 mmol) and the HCl salt of amine 53 (0.538 g, 1.82 mmol) to afford the product in a 33% yield. $^1$H NMR (DMSO-$d_6$): δ 8.52 (br s, 1 H), 8.12 (s, 1 H), 7.68 (d, $J = 8.3 \text{ Hz, } 2 \text{ H}$), 7.07 (d, $J = 8.2 \text{ Hz, } 2 \text{ H}$), 4.24 (d, $J = 6.3 \text{ Hz, } 2 \text{ H}$); $^{13}$C NMR (CDCl$_3$): δ 160.9, 137.8, 137.2, 129.6, 93.1, 41.6; IR (solid) 1648 cm$^{-1}$; HRMS (APCI): Calcd for $C_8H_8INO$ [M+H]$^+$ 261.9723, found 261.9723; Anal. Calcd for $C_8H_8INO$: C, 36.81; H, 3.09; N, 5.37; found: C, 37.06; H, 3.03; N, 5.13.
\textit{N-(4-Bromobenzyl)formamide (56)}.  

Procedure B was used with amine 55 (0.753 g, 4.05 mmol) and afforded the product in a 48\% yield. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.54 (br s, 1 H), 8.15 (s, 1 H), 7.51 (d, $J$ = 8.0 Hz, 2 H), 7.22 (d, $J$ = 8.0 Hz, 2 H), 4.27 (d, $J$ = 6.0 Hz, 2 H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 161.1, 138.5, 131.2, 129.5, 119.9, 40.1; IR (solid) 1647 cm$^{-1}$; HRMS (APCI): Calcd for C$_8$H$_9$BrNO [$M+H]^+$ 213.9862, found 213.9867; Anal. Calcd for C$_8$H$_8$BrNO: C, 44.89, H, 3.77; N, 6.54; found: C, 44.87; H, 3.77; N, 6.54.

\textit{N-(4-Chlorobenzyl)formamide (58)}.  

Procedure B was used with amine 57 (0.566 g, 3.99 mmol) and afforded the product in a 47\% yield. The solid was identified by comparison with literature data.$^{81}$

\textit{Methyl 4-(formamidomethyl)benzoate (60)}.  

Procedure B was altered to use methanol (30 mL), potassium carbonate (1.11 g, 8.03 mmol) and the HCl salt of amine 59 (0.396 g, 1.96 mmol) to afford the product in a 27\% yield. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.60 (br s, 1 H), 8.17 (s, 1 H), 7.92 (d, $J$ = 7.7 Hz, 2 H), 7.40 (d, $J$ = 7.7 Hz, 2 H), 4.38 (d, $J$ = 6.0 Hz, 2 H), 3.84 (s, 3 H); $^{13}$C NMR (DMSO-
$d_6$: δ 166.0, 161.2, 144.6, 142.2, 129.2, 127.4, 52.1, 40.5; IR (solid) 1720, 1655, 1630 cm$^{-1}$; HRMS (ESI): Calcd for C$_{10}$H$_{12}$NO$_3$ [M+H]$^+$ 194.0812, found 194.0809; Anal. Calcd for C$_{10}$H$_{11}$NO$_3$: C, 62.17; H, 5.74; N, 7.25; found: C, 62.39; H, 5.71; N, 6.96

$N$-(4-Formamidomethyl)benzoic acid (62).

Procedure B was used with amine 61 (0.603 g, 3.99 mol). The procedure was altered in the following way, before extraction the pH was adjusted to 1 with 3.0 M HCl, after which no further purification was necessary. The product was obtained in a 25% yield. $^1$H NMR (DMSO-$d_6$): δ 12.90 (br s, 1 H), 8.58 (br s, 1 H), 8.16 (s, 1 H), 7.89 (d, $J = 7.7$ Hz, 2 H), 7.37 (d, $J = 7.7$ Hz, 2 H), 4.37 (d, $J = 6.0$ Hz, 2 H); $^{13}$C NMR (DMSO-$d_6$): δ 167.1, 161.2, 144.1, 129.4, 129.3, 127.2, 40.5; IR (solid) 1687, 1653, 1630 cm$^{-1}$; HRMS (ESI): Calcd for C$_9$H$_{10}$NO$_3$ [M-H]$^-$ 178.0510, found 178.0514; Anal. Calcd for C$_9$H$_9$NO$_3$: C, 60.33; H, 5.06; N, 7.82; found: C, 60.28; H, 5.41; N, 7.00.

$N$-(4-(Trifluoromethyl)benzyl)formamide (64).

Procedure B was altered to use methanol (30 mL), potassium carbonate (0.829 g, 6.00 mmol) and amine 63 (0.351 g, 2.01 mmol) and afforded the product in a 23% yield. The solid was identified by comparison with literature data.$^{81}$
N-(4-Cyanobenzyl)formamide (66).

Procedure B was altered to use the HCl salt of amine 65 (0.674 g, 4.00 mmol) and potassium carbonate (2.21 g, 16.0 mmol). The product was afforded in a 17% yield. \( ^1 \text{H NMR (DMSO-}d_6\): \delta 8.62 (br s, 1 H), 8.17 (s, 1 H), 7.80 (d, \text{J} = 7.9 \text{ Hz}, 2 \text{ H}), 7.45 (d, \text{J} = 7.9 \text{ Hz}, 2 \text{ H}), 4.38 (d, \text{J} = 6.0 \text{ Hz}, 2 \text{ H})\); \( ^{13} \text{C NMR (DMSO-}d_6\): \delta 161.3, 144.9, 132.3, 128.0, 118.8, 109.6, 40.5; IR (solid) 2229, 1651 cm\(^{-1}\); HRMS (ESI): Calcd for C\(_9\)H\(_8\)N\(_2\)O [M+H]\(^+\) 161.0705, found 161.0709; Anal. Calcd for C\(_9\)H\(_8\)N\(_2\)O: C, 67.49; H, 5.03; N, 17.49; found: C, 67.50; H, 4.81; N, 17.11.

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

N-Formylpyrrolidine (82).

Procedure C was used with amine 81 (0.285 g, 4.01 mmol) and afforded the product in a 39% yield. The oil was identified by comparison with literature data.\(^{32}\)

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

N-Formylmorpholine (86).

Procedure C was used with amine 85 (0.350 g, 4.02 mmol) and afforded the product in a 66% yield. The oil was identified by comparison to literature data.\(^{82}\)
**N-Propylformamide (70).**

Procedure D was used with amine 69 (0.0543 g, 0.919 mmol) and afforded the product in a 40% yield. The oil was identified by comparison to literature data.\(^{83}\)

**N-Isopropylformamide (72).**

Procedure D was used with amine 71 (0.0564 g, 0.954 mmol) and afforded the product in a 37% yield. The oil was identified by comparison to literature data.\(^{83}\)

**N-Isobutylformamide (76).**

Procedure D was used with amine 75 (0.1470 g, 2.01 mmol) and afforded the product in a 61% yield. The oil was identified by comparison to literature data.\(^{84}\)

**N-Tertbutylformamide (78).**

Procedure D was used with amine 77 (0.0793 g, 1.08 mmol). Trace amounts of product were tentatively identified spectroscopically by comparison to literature data.\(^{48}\)
N-Cyclohexylformamide (80).

Procedure D was used with amine 79 (0.1974 g, 1.99 mmol) and afforded the product in a 71% yield. The oil was identified by comparison to literature data.
LIST OF REFERENCES


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Ciera Jane Gerack was raised in Greenville, SC. Her love of learning began at a very young age. However, her passion for chemistry came later during her junior year of high school, and she has not stopped studying the subject ever since. At the age of eighteen Ciera began attending the College of Charleston in Charleston, SC. In May of 2008, she earned her B.S. in chemistry. In August of the same year, Ciera began graduate school at the University of Florida. After five full years that were filled with learning, teaching, laughter, and tears, she earned her Ph.D., specializing in organic chemistry. She plans to continue her career in the world of academics, as teaching is her particular passion.