Development of a Green Method for Amide Synthesis

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I. Background Information

i. **Green Chemistry Principles**

Green chemistry is the application of ecologically friendly principles to laboratory methods to control the harmful effects of harsh chemicals and chemical wastes on both humans and the environment. Green chemistry modifications of pre-existing methodologies include the use of sustainable resources, catalysts and environmentally benign reagents and solvents. The principles applied should protect both the scientist and the laboratory conditions, and should also produce clean and efficient reactions that have a positive impact on product formation.

Warner et. al. [1] described the 12 specific aims of green chemistry applications in the use of safe methods and safe chemicals that prevent toxic waste formation and increase atom economy. Not only are environmentally-friendly methods beneficial in terms of health concerns, but they also promote better economic principles within the laboratory. Current trends show that by preventing waste, a significant portion of downstream costs associated with hazard management and damages can be eliminated from the chemical industry. As well, green chemistry methods should reduce upstream costs by using sustainable and readily-available materials in innovative processes.

Environmental agencies in the U.S. and most European countries, including the UK, have enacted numerous policies that have impacted the chemical industry. Specifically within the U.S., the Environmental Protection Agency (EPA) has strict oversight on chemical businesses, forcing quick compliance and major changes within the last thirty years. Some of the acts that affect the chemical industry’s standards include the National Environmental Protection Act (1969), the Air Quality Act (1967), Toxic

The number of US patents for green chemistry methods increased drastically from the 1980s to the turn of the century, perhaps as a result of increasing regulation in US environmental policies [3]. Patents derived from various sectors, including privatized companies, universities, and pharmaceutical companies, indicate that the standards are finding wider application. Government funding for green chemistry techniques and education has also increased significantly since the Green Chemistry Research and Development Act of 2004 (HR 3970), a bill that provides funding for the implementation of research and other green chemistry-related programs. Governments around the world have a vested interest in advancing environmentally-responsible practices to promote sustainability in accordance with adapted universal environmental legislation [4].

Currently, green chemistry principles emphasize short-term fixes within protocols; for instance, one of the popular ways of minimizing hazardous wastes is through the selection of green solvents, which are safer solvents that reduce the amount of solvent waste and decrease the environmental footprint of solvents that are used [3]. Greener solvents promote the efficiency of a reaction and are recyclable or not environmentally toxic as a waste product. Several traditional organic solvents, such as ethanol and methanol, would be included in this categorization. New solvents are being developed for green chemistry, such as cyclopentyl methyl ether [5]. Thus, traditional and developing options exist for modifying traditional chemical reactions in such a manner that the reactions are more ecologically efficient, and perhaps more efficient depending on the effects on reaction rates.
Green chemistry focuses on the need for short-term solutions, such as the incorporation of less hazardous chemicals, but also shows a need for long-term solutions. Ultimately, green chemistry must apply innovation in the use of catalytic materials and unconventional reaction conditions to help reactions proceed under milder conditions, regardless of the chemicals being used [6]. Thus, technological advancements are required to sustain environmental factors, such as the presence of harmful chemical species within the environment, and produce better efficiency of reactions, particularly in increasing atom economy and decreasing the amount of necessary chemicals. New uses of existing technology are also ideal for promoting environmentally conscious principles.

Herein, the aims of green chemistry will be applied to amide bond synthesis with the use of safe, recycled, and recyclable catalytic solid support reagents in solvent-free, efficient syntheses. These methods are practical for undergraduate laboratory settings as they should prevent unnecessary exposure to potentially harmful chemicals and fumes, as well as reduce the cost of running large-scale reaction quantities. These methods are also applicable to functional synthetic laboratories that strive to reduce expenditures and increase efficiency.

ii. Microwave Syntheses

Efficient synthesis of amide bonds requires decreasing the reaction time, especially for use in teaching laboratories. The use of microwave irradiation decreases reaction times while still providing desirable product yields [7,8]. For many purposes, microwave irradiation syntheses are more efficient and greener than many traditional reaction methods, making microwave technology an applicable adaptation to a traditional chemical reaction for environmentally conscious chemistry. Microwaves accelerate
organic reactions, and since the technology’s original use with polar solvents, it has become diversified for solvent-free reactions and transformations. The use of solid support catalysts, which are insolublized with the reactive molecules but still allow a catalytic surface for reaction, with microwave technology allows for high-yield, facile, and time-efficient reactions [9,10].

The theory behind the acceleration of reactions under microwave conditions deals with the rapid heating of polar solvents. Typical solvents with high dielectrics readily absorb irradiation and heat much quicker than less polar solvents. Generally, the less polar a molecule is, the less microwave energy it will absorb. In the case of neat reactions, solid supports are usually do not absorb heat and transmit the irradiation [9]. Thus, reactions that have inert solid supports, unlike liquid-phase reactions, will disperse heat to the reactive molecules more than to the non-reactive support. Neat reactions generally occur at lower temperatures overall due to this principle, but condensed heating is not impaired, increasing reactive molecule energy.

Common solid supports used in microwave syntheses that can be found in literature include clays, compounded clays, alumina, and fly ash [11-13]. These supports can be used in conventional reaction set-ups as well. These supports and their use in microwave heating is relatively novel, and the extent to which each might work for specific types of reactions is still a rapidly expanding field of research. Fly ash, in particular, has a paucity of examples in current literature, and information concerning its promotion of reactions is still yet to be fully elucidated.

Using such solid supports, which are readily available and promote atom efficiency in reactions, are consistent with green chemistry principles [1]. Thus, the
methodology of using supports to promote organic reactions is a sector of green chemistry that can and should be developed.

**iii. Traditional and Novel Amide Syntheses**

Amide bonds are both chemically and biologically significant. Within proteins, they comprise the peptide bonds that connect amino acids, and give polypeptides their high stability and proteins their shape. Pharmaceutically, amides are not as readily decomposed in the body as drugs containing esters [14]. Condensation reactions to form amide bonds are particularly useful in the synthesis of common antibiotics and analgesic drugs, such as acetaminophen, sulfacetamide, and chloramphenicol. Because of the β-lactam structure (cyclic amide structure) common to many antibiotics, the clean and efficient synthesis of these bonds is significant for large-scale productions by pharmaceutical companies.

Traditional methods for synthesizing amide bonds involve the use of N,N-dicyclohexylcarbodiimide (DCC) or similarly reacting compounds in dehydration syntheses. The mechanism for this type of reaction precedes with a DCC-bound acid intermediate in which the carboxylate terminus of a molecule is covalently bound to the central carbon of the diimide (A), creating a highly electrophilic site in the intermediate, which is then susceptible to nucleophilic attack by an amine group of another molecule (Fig. 1). This mechanism is advantageous for small, relatively reactive molecules, but normally does not produce high yields of amides with bulky or stable molecules.
Figure 1: DCC-bound carboxylic acid intermediate formation of a traditional synthesis showing the carboxylate and diimide bonding (A). "The intermediate is attacked by the amine group to form the amide bond through the loss of a water molecule."

Standard conditions for this type of reaction are liquid-phase, where solvents are polar organic, including dichloromethane (DCM), dimethylformamide (DMF), or acetonitrile as common non-green options [15-17]. Kinetic rates of reactions are usually slow and require lengthy refluxing at elevated temperatures, after which desired yields of products may still be low. Thus, improvement of the methodology of amide bond synthesis is necessary when applied in a concise, educational setting, as well as in laboratories requiring higher efficiency work with lower fume and waste production.

Research into the solid-supported synthesis of amide and peptide bonds has lead to the development of resin-bound coupling agents, which can be purchased as pre-prepared reagents. Polystyrene beads, for instance, may have a bound carbodiimide that acts as a substitute for DCC (Fig. 2) [18]. The advantage to using such resins is that it chemicals bound to them can be easily removed via normal filtration methods [9,10]. However, the disadvantage is that such reagents are costly at nearly $300.00 for a 5-gram bottle, and must be used in large molar quantities in the presence of toluene. The reagents
are also not reusable, leaving little reduction in waste, even though it is neutral with little environmental complications.

![Polystyrene-bound carbodiimide](image)

*Figure 2: A polystyrene-bound carbodiimide, a reagent bound to a polymer bead, that may be used as a solid support catalyst in amide bond formation. Biotage Chemicals.*

Solid phase synthesis is a valuable method to improving protocols for multiple dehydration reactions. Solid-phase catalysts including clays, compounded clays, and alumina have been used in various condensation reactions, and may be applicable to amide syntheses [11-13]. Fly ash, the byproduct of coal burning in power plants, is cited as a heterogeneous support that promotes organic reactions, but published reports do not indicate its applicability to amide condensations [19]. Fly ash, unlike other solid supports, may have variable characteristics (i.e. variable pH and composition), which may make certain varieties of ash applicable to organic reactions, and others not. Herein, amide condensations may be acid or base promoted, and thus fly ashes of multiple characteristics could be applicable to amide formations.

Comerford et al [20] developed the concept of using a low-cost, green-alternative catalyst in the solid-supported synthesis of amides. In the research, they propose that a modified silica gel can be used as a substitute to expensive and harsh reagents. This silica gel, activated in a high-temperature furnace at 700°C for 4 hours, behaves as a catalyst
for amide bond formation. Heating the silica activates it and alters the pH and hydrophobicity of the catalyst, which makes it ideal for amide formation. By weakening the acidity the silica, the environment prevents amine salt formation, which allows it to be more readily reactive. The catalyst also helps to remove the water that is produced in the dehydration reaction, which pushes the reaction towards completion.

This silica gel even promoted amide bond formation between poorly reactive substrates. Under standard conditions, these substrates would be hindered by their structural and chemical nature in uncatalyzed or alternatively catalyzed reactions. Reactions with acids that are hindered by steric effects and low pKa values exhibit significant yields in the presence of the activated silica.

![Figure 3: Phenylacetic acid and aniline react to form N,N-diphenylacetamide, an example of a reaction that normally exhibits low yields under traditional reaction conditions, including DCC catalysis.](image)

Even further, the silica gel could even be recycled after being removed from reactions and could be reactivated in the furnace, thus decreasing the waste of the reaction. By taking solid that was captured during filtration and reheating it, the catalyst did not appear to be inactivated by previous use. Any organics that were present in the compound were burned off and the polarity was restored. This activated silica gel catalyst is thus recyclable, which readily adheres to the principles of green chemistry and promotes even less waste production.
iv. Specific Aims

The aim of this work was to determine the scope and limitations of using microwave technology, solvent-free conditions and green chemistry-applicable solid supports for amide synthesis. We hypothesize that the method developed by Comerford et al [12] may be applicable to other solid support systems already in use (silica, fly ash, and alumina), and that combined with the use of microwave technology, green and efficient synthesis of varied amides and other dehydration reaction products may be possible. These methods should show application to undergraduate, organic chemistry laboratories as well as large-scale production laboratories.
II. Experimental Methods

i. General

Polystyrene beads (1.0-1.5 mmol/g) were obtained from Biotage Chemicals. (Sigma Aldrich, 635 Grade, 60-100 mesh) and alumina (Sigma-Aldrich) were used as solid supports. Fly ash (pH = 3.7, 23.37% silicon) was obtained as a donation from an undisclosed source [21]. Acids used included phenylacetic acid (Sigma-Aldrich, reagent grade), benzoic acid (Sigma-Aldrich, reagent grade), octanoic acid (EH Sargent & Co.), acetic acid (Sigma-Aldrich), salicylic acid (Sigma-Aldrich, reagent grade) and succinic acid (Fisher Scientific). Amines used included aniline (Sigma-Aldrich, 99% grade), butylamine (Matheson, Coleman & Bell), benzylamine (Kodak), dodecylamine (Sigma-Aldrich), diethyleamine (Sigma-Aldrich) and ethylene diamine (Sigma-Aldrich). Alcohols used included ethanol (Sigma-Aldrich, 200 proof), methanol (Sigma-Aldrich, reagent grade), and isoamyl alcohol (Baker Analyzed).

Solvents used included dichloromethane (Sigma-Aldrich, ACS reagent grade), methanol (Sigma-Aldrich), toluene (Sigma-Aldrich, 99.5%+), cyclopentyl methyl ether (Sigma-Aldrich, ReagentPlus), PEG-200 (Sigma-Aldrich), PEG-400 (Sigma-Aldrich), THF (Sigma-Aldrich), acetonitrile (Sigma-Aldrich), and hexanes (Sigma-Aldrich, bulk).

Individual microwave reactions were performed on a CEM Discover® Focused Microwave Synthesis instrument (CEM Corporation, ramp: 5 min., reaction time: 9 min., reaction temp: 140°C). Multiple microwave syntheses were performed on a CEM MARS Multimode Microwave Synthesis system (CEM Corporation, ramp: 5 min., reaction time: 9 min., reaction temp: 140°C). GC-MS analysis was carried out on a Varian 220 GC-MS TI Mass Spectrometer system (ramp: 40°C-100°C at 15°C/min, 100°C-240°C at
6°C/min). IR Spectroscopy was analyzed with EZ OMNIC technology (Thermo Electron Corporation, version 7.2a).

**ii. Activation of silica gel, fly ash, and alumina for use in condensations**

Activation of silica gel was achieved as described by Comerford et al [20]. Silica gel was heated in a micro-furnace for 4 hours at 700°C and stored under non-airtight conditions until use for up to 5 weeks. Fly ash was heated and stored by the same procedure as the activated silica gel. Alumina was also activated with the same procedure.

**iii. Amide condensation using PS-Carboxdiimide**

![Chemical Reaction](attachment:chemical реакция.png)

**Figure 4: The general reaction scheme of amide condensation using polystyrene-bound carboxdiimide as a catalyst. The reaction was performed at room temperature with overnight stirring in dichloromethane**

Following the general procedure outlined in [13], phenylacetic acid (0.75 mmol) and aniline (0.5 mmol) were added with a double-molar equivalent of PS-carboxdiimide (1.0 mmol) in dichloromethane (10 ml) and allowed to stir for 24 hours [14]. PS-carboxdiimide was removed via gravity filtration, and the product isolated upon solvent removal. The resulting crude product (1) was subjected to TLC analysis to confirm the reaction, and GC-MS analysis and IR spectroscopy to confirm formation of N,N-diphenylacetamide (98%, M+ = 211.0 g/mol, stretch: 1660.0, 3450.2, and 3688.4 cm⁻¹).

Subsequent reactions of alternative substrate combinations were performed as with reaction 1. Alternative acids included octanoic acid and benzoic acid. Alternative
amines included ethylene diamine, dodecylamine, and butylamine. Products from
different combinations of acids and amines were subjected to TLC analysis to confirm
the reaction, and the products were analyzed by GC-MS.

iv. Amide condensations using activated silica gel, fly ash, and alumina

The methodology for amide condensations followed that presented by Comerford
et al [20]. Phenylacetic acid (5 mmol) and aniline (5 mmol) were added with a 10%
molar equivalent of activated silica gel in toluene (10 ml) and allowed to reflux for 24
hours. Following reflux, silica gel was removed via suction filtration through fritted glass
and product was isolated via rotary evaporation. The resulting product was subjected to
GC-MS analysis to determine percent conversion of the amide.

To determine the optimal molar equivalent under which the reaction would
produce the highest percent conversion, the amount of silica added was increased to a
20% molar equivalent. Following confirmation of product formation, other acid and
amine substrates were tested to determine the scope and limitations of the activated silica
gel method. Activated fly ash and alumina were then tested for amide production in the
same standard.

v. Microwave synthesis

Initial microwave reactions were performed in the CEM Discover individual
reaction microwave. Temperature settings were increased to 140°C and the reaction was
allowed to proceed with stirring for 60 minutes. Pressure was not allowed to exceed 200
psi. Reactions were tested using phenylacetic acid and aniline in the presence of 10%
activated silica gel in varied solvents, as well as solvent-free. Following determination of
reactivity in the solvent-free system, the time of reaction was decreased and optimized at
9 minutes.

Multiple reactions were run in the MARS microwave system, holding 3-4 reaction
vessels per run. The system temperature probe was held constant with the reaction of
phenylacetic acid and aniline to ensure consistent heating. Reaction temperature was held
at 140°C (10 minute ramp) and the reaction time was held at 30 minutes and 9 minutes.
III. Results

Various alternative catalyzing agents were used to synthesize amide bonds, including polystyrene-bound carbodiimide beads and heterogeneous solid supports. Reactions were developed under which solvent-free, microwave-assisted dehydration could be achieved. The extent to which reactions could be applied was investigated, and the product yields of the methods were compared.

i. Amide Condensation via PS-Carbodiimide

The initial reaction of phenylacetic acid and aniline using the catalyst PS-carbodiimide resulted in a solid product formation. When analyzed under GC-MS spectroscopy, the product N,N-diphenylacetamide was produced with a 93% conversion. Under IR spectroscopy, the product formed gave key stretches at 1660.0, 3450.2, and 3688.4 cm\(^{-1}\), indicating that the amide bond was formed during the reaction. Confirmation of amide bond formation was also given in reactions of butylamine and benzoic acid (97%), octanoic acid and dodecylamine (74%), and octanoic acid and ethylenediamine (89%).

Further reactions were not investigated as the method proved costly and did not specifically follow the principles of green chemistry. The solvent, dichloromethane, was difficult to work with as it evaporated easily if the vessel leaked, and the polystyrene beads could not be reused or recycled in any fashion, and thus proved to create further waste. The reactions were also time-consuming, taking at least 24 hours to be completed. However, the method was confirmed to give products that could also be used in comparison to subsequent methods.
ii. Amide Condensation via non-activated and activated silica gel

A reaction of phenylacetic acid and aniline was refluxed for 24 hours with non-activated (non-heated) silica gel. Under these conditions, a TLC in 50:50 hexanes to ethyl acetate showed no formation of the N,N-diphenylacetamide product. This confirmed the inability of unactivated silica to catalyze the reaction.

Subsequent reactions were performed with silica gel that had been activated. In 10% molar equivalence of activated silica gel, the model reaction phenylacetic acid and aniline produced an amide product like that of the PS-carbodiimide method. The product, as analyzed with GC-MS spectroscopy, showed a 99% conversion. A similar reaction between benzoic acid and butylamine, which had also been tested with the PS-carbodiimide catalyst, also showed a high percent conversion under the activated silica gel catalyst (64%).

Further work using the traditional reflux set-up was not pursued as reactions were time-consuming, taking overnight to reflux. Microwave technology was believed to be a better alternative to the traditional reflux set-up, as microwave reactions would potentially decrease the reaction time and increase the safety of the reaction.

iii. Incorporation of microwave heating in assisted reactions

The model reaction of phenylacetic acid and aniline in the production of N,N-diphenylacetamide was initially tested in the microwave to ensure that the product could be verified and the percent conversion was comparable to previous methods. The reaction was run on a small scale to determine the exact microwave parameters necessary to allow the reaction to go to completion. The first reactions were run with 10% activated silica in toluene, as toluene allowed for product formation in conventional reactions. Upon an
hour of heating, the reaction did produce a 99% conversion to N,N-diphenylacetamide, as was verified by GC-MS.

Toluene is not a green solvent and is also difficult to fully extract from the product. Other organic solvents with similar boiling points were tested to determine their applicability in producing the reaction. Acetonitrile, hexanes, tetrahydrofuran (THF), cyclopentyl methyl ether (CPME) and polyethylene glycol-200 and -400 were used in similar test reactions in the same amount as toluene, and allowed to heat for the same amount of time. However, none of the reaction conditions produced an isolatable solid. As well, PEG-200 and PEG-400, though ideal green solvents, were also difficult to remove from the product due to the solubility of PEG in the solvents used for amide extraction. Thus, these reactions could have produced amides that were not isolatable from the PEG solvent.

iv. **Solvent-free microwave-assisted reactions**

As no green-applicable solvents other than toluene appeared to enhance the reaction of the acid and amine, the reaction was performed solvent-free. The reaction time was reduced from 30 minutes to a 9 minute run at 140° to prevent overheating of the reaction. Desorbing the product from the solid support with methanol followed green chemistry protocol, while making product isolation clean and efficient. The reaction at 9 minutes produced an N,N-diphenylacetamide product conversion of 50%. The product also appeared slightly burnt compared to the previously isolated products.

To increase the yield of the product under solvent-free conditions, two procedural alterations were made. First, the reaction vessel contents were stirred thoroughly until homogeneity was achieved in order to prevent “hot spots” from developing and to fully
allow the product to interact with the catalyst. In addition, the catalytic amount of activated silica was increased to 20%. This also increased the volume present in the microwave vessel, which allowed for more consistent heating. The product conversion was markedly increased (90%) from the initial reaction, showing that increasing the amount of solid support and preventing overheating are critical to proper amide formation.

Once the parameters were optimized for neat reactions in the individual-run microwave, multiple solvent free amide reactions were run concurrently using the MARS-5 system. Along with the reaction of phenylacetic acid and aniline, which was used in the temperature probe to ensure proper heating, multiple acids and multiple amines were combined to form various amides. The conversions were all analyzed by GC-MS, and the general conversion rates for the majority of reactions were high (Table 1).

*Table 1: Percent conversions of varied amides under solvent-free microwave conditions in the presence of 20% activated silica. Reaction parameters included a 9 min. heating time at 140°C.*

<table>
<thead>
<tr>
<th>Acid Used</th>
<th>Amine Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylacetic Acid (1.36 g)</td>
<td>Aniline (0.91 ml) 25%</td>
</tr>
<tr>
<td>Benzoic Acid (1.22 g)</td>
<td>22%</td>
</tr>
<tr>
<td>Octanoic Acid (1.57 ml)</td>
<td>21%</td>
</tr>
</tbody>
</table>
For amide formations where either the amine or the acid was a liquid or low-melting solid (herein, reactions with butylamine, benzylamine, octanoic acid, or acetic acid), the conversions were generally high (80-90%), whereas for reactions with high-melting solids the results were not as optimal (0-40%). The presence of a liquid or low-melting reactant may contribute to the success of the reaction without needing a solvent; however, when using high-melting solids, the addition of a minimal amount of water (10 drops) might be used to increase the yield of product in the absence of a liquid-state reagent and without having to add solvent. The water should not affect the overall reaction, other than allowing the initial temperature heating in the vessel. This protocol has been preliminarily tested, but the results as the product conversion has not been confirmed.

As the results would indicate, functional group does not appear to be a major factor in determining the applicability of the method to the desired reaction. Thus, the reaction conditions appear to be ideal for amide formation using molecules that would otherwise be sterically-hindered, or generally unreactive because of their high pKa values.

Solvent-free amide condensations using activated fly ash

The fly ash obtained was initially tested in the same manner as the silica method, beginning with using unheated fly ash in a reflux reaction using phenylacetic acid and aniline. This reaction yielded no isolatable product, thus showing a similar result to unheated silica gel. Activated fly ash was used in the same reaction with a 24-hour reflux, and the yield improved significantly, but was increased further upon solvent-free
microwave heating at 140° for the same amount of time utilized for silica gel (9 minutes).
The result of the initial neat microwave reaction showed a 49% conversion to amide product. The maximal conversion of the specified reaction in the individual run-microwave system was 88%.

Following the initial reaction and confirmation of amide product, multiple reactions were run solvent-free with fly ash in the MARS microwave. The parameters appeared to hold for fly ash as they did for silica gel, and no further modifications were made. Again, reactions were necessarily mixed thoroughly before being heated to ensure that no hot-spot heating occurred, and the temperature probe was kept consistent through each microwave run.

Table 2: Percent conversions of varied amides under solvent-free microwave conditions in the presence of 20% activated fly ash. Reaction parameters included a 9 min. heating time at 140°C.

<table>
<thead>
<tr>
<th>Acid Used</th>
<th>Amine Used</th>
<th>Amine Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylacetic Acid</td>
<td>Aniline (0.91 ml)</td>
<td>Dodecylamine (1.85 g)</td>
</tr>
<tr>
<td>(1.36 g)</td>
<td>49%</td>
<td>-0%</td>
</tr>
<tr>
<td>Benzoic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1.22 g)</td>
<td>22%</td>
<td>-0%</td>
</tr>
<tr>
<td>Octanoic Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1.57 ml)</td>
<td>0%</td>
<td>-0%</td>
</tr>
</tbody>
</table>

As shown in Table 2, the percent conversions to amides were slightly lower than for the same method with silica, but the results still showed promise for activated fly ash as being a universal solid support. Unlike the silica gel, the fly ash was never tested to see if the minimal addition of water to reactions with two solid substrates increased the
product. Likely, this would increase the product, especially with reactions of dodecylamine. Further optimization using the MARS system, including the infrared temperature probe, should provide even higher yields, as indicated by the maximal conversion seen in individual runs.

vi. **Solvent-free amide condensations using activated alumina**

Normally, amide dehydrations are base-catalyzed. Activated alumina was used in amide condensations to test if the reaction between the amine and the acid could proceed under more basic solvent-free conditions in the microwave. Initial reactions used only phenylacetic acid and acetic acid reacted with aniline, butylamine, benzylamine, and diethylamine with the same gram amount (1.02 g) of activated alumina as in silica and fly ash reactions. The results (as shown in Table 3) appeared similar to reactions with activated silica, indicating a similar amount of catalytic activity between the two solids. The work with alumina was not as extensive due to time limitations of the study.

*Table 3: Percent conversions of varied amides under solvent-free microwave conditions in the presence of 20% activated alumina. Reaction parameters included a 9 min. heating time at 140 °C.*

<table>
<thead>
<tr>
<th>Acid Used</th>
<th>Amine Used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aniline (0.91 ml)</td>
</tr>
<tr>
<td>Phenylacetic Acid</td>
<td>44%</td>
</tr>
<tr>
<td>Phenylacetic Acid</td>
<td>Diethylamine (1.04 ml)</td>
</tr>
<tr>
<td>Phenylacetic Acid</td>
<td>66%</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>40%</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>Butylamine (0.99 ml)</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>98%</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>Benzylamine (1.09 ml)</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>92%</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>70%</td>
</tr>
</tbody>
</table>

vii. **Applicability to other dehydration reactions**
Based on the results seen with amide dehydrations, the applicability of activated solid supports were tested in other dehydration reactions, particularly in ester formation. A model ester reaction was performed using a 1 mol: 1 mol ratio of salicylic acid and methanol with the same catalytic amount of activated silica (20% mol wt) under the same reaction conditions as used in the amide reactions for the Discover microwave. The product was desorbed using diethyl ether with a 5% NaHCO₃ base wash, and a 17% conversion to methyl salicylate was calculated.

Table 4: Percent conversions of varied esters under solvent-free microwave conditions in the presence of 20% activated fly ash. Reaction parameters were set at 9 min. of heating at 140 °C.

<table>
<thead>
<tr>
<th>Alcohol Used</th>
<th>Methanol</th>
<th>Ethanol</th>
<th>Isoamyl Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic Acid</td>
<td>12%</td>
<td>6.70%</td>
<td>29%</td>
</tr>
<tr>
<td>Octanoic Acid</td>
<td>13%</td>
<td>90%</td>
<td>94%</td>
</tr>
<tr>
<td>Undecanoic Acid</td>
<td>11%</td>
<td>10.50%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Activated fly ash was subsequently used to perform the ester dehydrations in the MARS system, with the results of various combinations of acids and alcohols shown in Table 4. While the majority of conversions were not large, the method shows promise for ester condensations. One of the potential challenges of the reaction and work-up may have been that the base wash might have been too strong for the weak ester formation and might have deteriorated some of the product.

Another condensation that was seen as a by-product of succinic acid with secondary amines was an imide formation. Succinic acid was used in trial reactions to
determine if a di-substituted amide would form using primary amines. A 1 mol equivalent of succinic acid and a 2 mol equivalent of aniline, butylamine, or benzylamine with 20% catalytic silica gel was reacted in the microwave, and the GCMS results showed a high presence of imide formation over the di-substituted products, particularly in formation of the N-phenylsuccinimide product (M+ = 175.0 g/mol). When run in a 1:1 molar reaction, substituted succinimide products of aniline and butylamine reactions showed 75% and 79% conversions, respectively. The full scope and limitations of using activated silica or fly ash to catalyze imide formation was not determined.
IV. Discussion

The method developed herein for using an activated form of several solid supports in solvent-free, microwave-assisted reactions proved advantageous for amide condensations while also showing potential applicability in other dehydrations. Solid catalyst "activation" via heating proves to be an absolutely necessary step for providing the requisite conditions for product formation.

A solid support catalyst has a tri-fold role in solvent-free reactions. Firstly, it acts as a catalyst, providing an advantageous environment for the reactants. Here, silica gel provided an acidic and hydrophobic environment that supports the acid and amine substrates to formation of the amide bond. The heating process likely changed the acidity of the solid, as well as removed the vast majority of water previously absorbed from the environment. Thus, the "activated" silica provides an even more formidable environment for the dehydration, but also remaining weak enough to not protonate the amine and prevent the reaction. Comerford et al proposed that heating the silica gel above 700°C irreversibly alters the tetrahedral lattice by relaxing strain and preventing natural rehydration [20].

Secondly, the solid absorbs the water as a side product of the dehydration reaction. By absorbing the water produced, the dehydration is further driven forward, aiding the kinetics of the reaction. The reactivity of acids and amines to form the amide bond is generally low, especially for large and bulky reagents, such as phenyl-alkane-substituted groups (represented by phenylacetic acid and dodecylamine in the preceding reactions). However, the solvent-free method appeared to aid the reactivity of unlikely substrates, perhaps because of the removal of water molecules.
Thirdly, the solid catalyst must heat the acid and the amine without absorbing the microwave energy. Here, both silica and fly ash appear to be suitable for acting as inert solids and dispersing heat to the reactive molecules. Two challenges were presented with working under solvent-free conditions: uneven heating creating “hot spots” and lack of heating due to the MARS temperature probe not accurately measuring the reaction temperature. The problem of “hot spot” heating was overcome by thoroughly mixing the solid support and the reagents, ensuring a homogeneous mixture within the reaction vessels. The second problem was a result of the MARS microwave temperature probe, and likely not due to the methodology. It could also be corrected by a small addition of water, not enough to solvate the system but enough to allow the infrared detection system to operate correctly with two solid reagents.

Recycling of activated silica gel, as studied by Comerford et al, was previously determined to be effective upon reheating to 700°C. The silica gel used in the preceding work was kept after being filtered from reactions, but it was never “reactivated” for recycling purposes. However, speculating with the given results, it could likely be recycled. The recycling process may be applicable to fly ash and alumina as well, given their similarities as heterogeneous catalysts. The reheating process removes any water held in the matrix, as well as burns off any organic molecules that may still be present. The only difficulty that may present with reheating fly ash is the potential loss of trace metals over time; however, most content outside of silicon and aluminum is usually in small amounts.

Silica, alumina, and fly ash show promise as green-alternative solid supports for solvent-free dehydrations, particularly in amide and ester formations. Fly ash specifically
is readily available as a large-scale waste product from many power plants across the world that burn billions of tons of coal per year. Fly ash has been used as a low-cost, effective substitute for silica gel in countries where silica gel is overly expensive for chemical reactions [19]. Yet, in the United States fly ash has seen very limited use for chemical research. If used for mass chemical syntheses, recycling of the ash would cut back on how much is buried in the landfills, as well as provide another safe support to be used in the laboratory. Further work with fly ash is needed to elucidate its application in synthetic, green chemistry; however, the results shown indicate that fly ash is a promising solid support.

The chemical composition of the fly ash is variable dependent upon the source; however, whether fly ash is acidic or basic, the differential composition could be another point of interest in future research, as different dehydration reactions could proceed in either environment. Present amounts of elements in fly ash depend on coal composition and combustion processes. Most fly ashes are composed primarily of silicon and aluminum, with varying amounts of calcium, iron, magnesium, and sodium [22]. The fly ash used in the preceding reactions was acidic, largely because of the limestone content of the coal found in Indiana. However, the rock of the Appalachian region contains high concentrations of calcium, making it a likely high pH buffer. Fly ash such as this would likely act similarly to alumina, whereas acidic fly ash acts more like silica. Whether or not acidic or basic fly ash act differentially to produce amide dehydrations should be further investigated. Likely, if both silica and alumina act equally well as solid supports, fly should also catalyze dehydration reactions at varied pH levels.
Other heterogeneous acidic catalysts have also been shown to promote reactions of amines. Recently, sulfamic acid, a similarly weak inorganic acid solid, was used in the production of pyrroles [23]. The work showed that a weak acid environment helps to catalyze the reactivity of the amines, particularly in the lack of a solvent system. Yields were in fact increased with the use of this catalyst under solvent-free conditions compared with solvents such as DCM and methanol. These results are similar to the findings herein, confirming a similar mechanistic effect of heterogeneous, weak acid catalysts on amine reactions.

Thus, this method may also be applicable to a wide range of dehydrations. The full scope and limitations of using activated heterogeneous catalysts, including but not limited to silica, fly ash, and alumina, to promote the condensation of amides, esters, imides, and many more organic compounds will require systematic, extensive work. The method must also be validated in other microwave reaction systems that may require different time or temperature limits. This work, however, provides a basis for using activated silica, fly ash, and alumina to catalyze varied and normally unreactive amides in both undergraduate and large-scale laboratory settings while maintaining green principles.

The method of amide condensation under solvent-free, microwave-assisted conditions using heterogeneous “activated” catalysts proves to be facile and readily applicable to multiple laboratory settings. The alternative synthesis conditions prove to be comparable in product yields to traditional reactions, including those that utilize severe catalyzing agents and liquid-phase syntheses. The results herein show that reactions using heterogeneous catalysts are similarly efficient to using polystyrene-bound coupling
agents, which are costly and not recyclable. Solvent-free microwave synthesis using heterogeneous catalysts are also time-effective and ideal for rapid dehydrations.

The novel use of heterogeneous catalysts with microwave technology improves upon the efficiency and safety of traditional dehydration reaction conditions. Overall, the alternative method of using activated solid supports with microwave-assisted synthesis is readily applicable for amide syntheses and other dehydrations on small and large scales and promotes the aims of green chemistry methods.
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References


15. MSDS Acetonitrile, Sigma-Aldrich. 28 April 2010.


17. MSDS Dichloromethane, Sigma-Aldrich. 12 March 2010.


Appendix

Graph A: GC-MS analysis of a reaction between phenylacetic acid and aniline with activated silica gel under solvent-free microwave conditions, showing N,N-diphenylacetamide product with 25% conversion.
Graph B: GC-MS analysis of a reaction between phenylacetic acid and aniline with activated alumina under solvent-free microwave conditions, showing N,N-diphenylacetamide product with 44% conversion.
Graph C: GC-MS analysis of a reaction between acetic acid and benzylamine with activated silica gel under solvent-free microwave conditions, showing product with 93% conversion.
Graph D: GC-MS analysis of a reaction between acetic acid and benzylamine with activated alumina under solvent-free microwave conditions, showing product with 70% conversion.