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Routes to Acylated Sydnones Utilizing Microwave Chemistry

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ROUTES TO ACYLATED SYDNONES UTILIZING MICROWAVE CHEMISTRY

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

By

AMBER CALEDONIA RUMPLE
B.S., Wright State University, 2008

2010
Wright State University
I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Amber Caledonia Rumple ENTITLED Routes to Acylated Sydnones Utilizing Microwave Chemistry BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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Abstract

Rumple, Amber C., M.S., Department of Chemistry, Wright State University, 2010. Routes to Acylated Sydnones Utilizing Microwave Chemistry

In the present work, microwave chemistry was utilized to improve and optimize two methods for the acylation of sydnones. Whereas before, 4-acyl-3-arylsydnones could be synthesized by the use of Friedel-Crafts reactions utilizing either Montmorillonite K-10 or bismuth(III) triflate/lithium perchlorate as catalysts in moderate to good yields after long reaction times, with the introduction of microwave chemistry 4-acyl-3-arylsydnones can be synthesized in good to excellent yields in much shorter times. A previous method using Montmorillonite K-10 allowed for a variety of 4-acetyl-3-arylsydnones to be synthesized thermally in moderate to good yields after at least 24 hours. This method was extended in this work to include other acyl species such as 4-propionyl-, 4-butyryl-, and 4-isobutyryl-phenylsydnone. It was attempted also to extend this method to the synthesis of 4-trifluoroacetyl-3-phenylsydnone but without success. However, all of these thermal methods had reaction times of at least 24 hours and some took many days. As such it was of interest to see if microwave irradiation (MWI) could decrease the reaction times and/or improve the yields, which were at best 61%.
The yields were not much improved by the method created, optimized and presented in this work, however the reaction times were significantly decreased to as little as one hour.

Another thermal method allowed for the synthesis of these materials in greater yields but using the less “green” catalyst of bismuth triflate and lithium perchlorate. However, as with the previous thermal method, the more complex the anhydride the longer the reaction times, which ranged from at least 2 hours to overnight or longer. A MWI method was developed, and is presented here, which allowed for the synthesis of 4-acetyl-, 4-propionyl-, 4-butyryl- and 4-isobutyryl-3-phenylsydnones in better yields than achieved by Fisher (88-94%) and in much shorter reaction times (15-45 minutes). It was also attempted to utilize this MWI method in the syntheses of 4-benzoyl-3-phenylsydnone and 4-(3-carboxypropanoyl)-3-phenylsydnone, however neither method succeeded and neither was explored further due to lack of time. The overall method developed should be amenable to further development in the manner of different starting materials, such as the o-substituted 3-arylxydrones, and different anhydrides that have not been explored previously.
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Introduction

The Friedel-Crafts Reaction

I. History of the Friedel-Crafts Reaction

Before Friedel and Crafts discovered the reaction named for them, there had been many reports of alkylation and acylation of aromatic compounds using metals and metallic compounds as catalysts. The most common of the latter were with zinc compounds, such as in the formation of diphenylmethane from benzyl chloride and zinc in benzene, which was reported in 1869 by Zincke.¹ Others who reported similar reactions included Doebner and Stackman who used zinc oxide in the acylation of phenols² and Grucarevic and Merz who used zinc dust for the acylation of aromatic systems with acid halides.³ It was not until 1877 that Friedel and Crafts deduced the probable mechanics of the reaction between the metallo halide compounds and the alkylation or acylation reagents.⁴,⁵ Thus, in an attempt to assess the effect of aluminum on a variety of organic chlorides they noted that various liquid and gaseous hydrocarbons were formed, as well as a large amount of hydrogen chloride.⁶ They conjectured that aluminum chloride was formed as a result of the initial reaction between the aluminum and the organic chloride and that the aluminum chloride then reacted with more of the organic chloride to produce the alkylating reagent. They then reacted amyl chloride with benzene in the presence of aluminum chloride and formed amyl benzene, which strongly supported their conjecture (Scheme 1).⁶
Friedel and Crafts also reacted ethyl iodide and methyl bromide with benzene to obtain ethylbenzene and toluene, respectively, in order to show that the method was general and applicable equally to organic iodides and bromides as well as the organic chlorides. However, alkyl iodides were decided to be too unstable to be generally useful in these reactions. Friedel and Crafts also expanded the types of metallo-chlorides that could be used as catalysts to include ferrous, ferric, sodium, aluminum and zinc chlorides, though others such as magnesium chloride were found to be unsuitable. It was observed that only the anhydrous salts were appropriate for use in these reactions.

In another set of reactions, Friedel and Crafts reacted alkyl polyhalides with excess benzene and found that these transformations readily yielded polyphenyl compounds. Similarly, it was found that acid chlorides could be used in the reaction to form ketones. Strangely, ethyl chlorocarbonate did not behave as a normal acid halide and it broke down in the reaction with benzene to form ethylbenzene, carbon dioxide and hydrogen chloride (Scheme 2).

Buu-Hoi and Janicaud investigated this reaction and stated that ethyl chlorocarbonate broke down in the presence of AlCl₃ to form carbon dioxide and ethyl chloride, and the latter then acted as an alkylating agent. They explored other catalysts and found that FeCl₃ acted in the same manner as AlCl₃, but ZnCl₂, SnCl₄, AsCl₃, and SbCl₃ did not.
II. The Reaction

Generally, the Friedel-Crafts reaction is assumed to be the addition of an alkyl or acyl group to an aromatic group, however, the very first reaction presented by Friedel and Crafts, of amyl chloride with aluminum strips, produced long chain alkyl halides and hydrocarbons. It is interesting, then, that the class of reactions from their papers that mainly saw development through the first fifty years of discovery was only that with aromatic species. Yet more species can be reacted, and other groups besides alkyl and keto groups can be introduced; for example, nitro, carboxyl, sulfo, hydroxyl, sulfonic, nitrilo and phenyl. Other named reactions can be considered Friedel-Crafts reactions as well. For instance, the Scholl reaction couples aromatic species via AlCl₃ and a protic acid;³ the Fries, Gattermann-Koch and Hoesch-Houben reactions are acylations utilizing Lewis acids, just like the Friedel-Crafts reaction, though the Fries reaction is a rearrangement of a phenyl ester to a hydroxy aryl ketone rather than a substitution reaction.¹⁰⁻¹² Thus, the Friedel-Crafts reaction can cover a wide variety of processes; however for the sake of this thesis only the topic of Friedel-Crafts acylations shall be reviewed.
III. Acylations

Friedel-Crafts acylations involve the introduction of an acyl group to a substrate. The substrate can be aromatic, aliphatic or heterocyclic in nature. The types of acyl group added to the substrate can include keto, formyl, carboxyl and other specialized acyl species. The introduction of keto groups via reagents is one of the most studied examples of the Friedel-Crafts class of reactions thanks to the demand of industry and the relative simplicity and efficacy of many of these processes. In the case of aromatic species the classes that will undergo acylation are typically unsubstituted aromatics, alkylenes, anilines (if the amine function is protected), aromatic ethers, biphenyl, halogenobenzenes, and hydroxybenzenes. A number of heterocycles can be acylated as well, including furan, thiophene, and pyrrole and its derivatives. Aliphatic substrates including, but not limited to, alkenes, cycloalkenes and the higher orderparaffins are also susceptible to acylation.

A. Introduction of the Keto Functionality

Various reactants can be used to introduce the keto group, the most general of which are the acyl halides. Acetyl chloride, propionyl chloride, butyryl chloride and isobutyryl chloride are typical examples. They have been observed to yield the corresponding ketones with the branching of the acyl chloride intact. The latter is useful since reduction of the ketone can then give good yields of predictable hydrocarbons, which is difficult to manage through normal alkylation processes, since rearrangements and multiple alkylations often occur.
Acylations are also useful in the aspect that some heterocyclic compounds will not undergo alkylation, but will acylate readily under certain conditions. For example, furan will not alkylate, but via acyl halides and aluminum chloride will acylate readily. These acylations will occur at the 2 position unless it is blocked, at which point the 5 position is the position that is acylated. Thiophene, another heterocycle, will acylate using acyl halides and aluminum chloride, stannic chloride, titanium chloride or even phosphorus pentoxide at elevated temperatures to produce excellent yields of the 2-substituted thiophenes. Pyrroles, pyrazoles and quinolines will also acylate using acyl halides, though not many examples of pyrazole acylation have been explored and only one of the quinoline species is present in literature. Some of the few examples found in literature are the acylation of 1-phenyl-3-methyl-5-chloropyrazole with acetyl chloride (Scheme 3) and the acylation of 8-hydroxyquinoline, where the acyl group is introduced into the 5-position (Scheme 4).
One of the most valuable extensions of this work has been to the use of aromatic acyl halides, such as benzoyl chloride, which react with other aromatic species to produce diarylketones.\textsuperscript{31} The reaction can even be extended to substituted benzoyl halides.\textsuperscript{32}

Interestingly, the process has been expanded to include unsaturated acid halides. The process seems to be generally applicable in the case of higher unsaturated acid halides, such as the reaction of 2,2-dimethylacryloyl chloride with benzene, which gives the expected unsaturated ketone, 2,2-dimethylvinyl phenyl ketone in 40% yield (Scheme 5).\textsuperscript{33}

\textbf{Scheme 5:}

In some cases, however, reaction does not occur as expected and competing processes can take place, such as in the case of the reaction between acryloyl chloride and benzene, which does not give vinyl phenyl ketone but a hydridone (Scheme 6).\textsuperscript{34}
E. P. Kohler\textsuperscript{34} studied vinylphenylketone and the processes used to create it, and investigated a claim by Moureu\textsuperscript{34a} that acrylic acid (acryloyl chloride) and benzene, in the presence of aluminum chloride, would produce a small amount of vinylphenylketone. Kohler mentions another researcher, Klages, who disagreed with this conclusion, having made a similar product which he said contained no trace of unsaturated species. Also, Moureu\textsuperscript{34a} provided no evidence that his compound was unsaturated. Thus, Kohler repeated the experiment and found that an $\alpha$-hydrindone was produced instead of vinylphenylketone. He suggested that the former resulted through a vinylphenylketone intermediate, which presumably reacted with the hydrogen chloride byproduct by chlorination of the double bond. The resulting product was then susceptible to further reaction to form the two-ring system of the $\alpha$-hydrindone (\textbf{Scheme 7}).\textsuperscript{34}
An interesting set of reactions arose with the use of oxalyl chloride [(COCl)$_2$]. Oxalyl chloride can also be used in the Friedel-Crafts reaction, but the product formed depends on the initial substrate. If the substrate is more active or acylates more readily, like dimethylaniline, it can form a diketone (Figure 1, R is substrate).$^{35,36}$

Figure 1: Diketone produced from Friedel-Crafts reaction with oxalyl chloride.

However, if the substrate does not undergo acylation readily, the oxalyl chloride will have time to decompose, facilitated by the condensing agent, and the resulting
product will acylate the substrate. Thus, the final product is a monoketone such as in the simplest case of benzene and oxalyl chloride (Scheme 8).\textsuperscript{37}

\textbf{Scheme 8}

\[
\begin{align*}
\text{\textsuperscript{1}} & \quad \text{\textsuperscript{2}} \quad \text{\textsuperscript{3}} \quad \text{\textsuperscript{4}} \\
\text{AlCl}_3 & \\
\text{HCl} & \\
\text{CO} & \\
\end{align*}
\]

Even some aliphatic substrates will undergo acylation with acyl halides. Ethylene, propylene, butylene, hexylene, heptylene and trimethylethylene are examples of open chain unsaturated hydrocarbons that will yield ketones when reacted with acyl halides.\textsuperscript{24} Some cyclic, nonaromatic species like cyclohexene and camphene also will acylate readily.\textsuperscript{38, 39} Remarkably, even saturated hydrocarbons, especially the higher numbered paraffins, will undergo acylation. Thus, pentane yields 2-acetylpentane in the presence of acetyl chloride and aluminum halide (Scheme 9).\textsuperscript{40}

\textbf{Scheme 9}

Cyclohexane, however, rearranges to afford acylated cyclopentanes and cyclopentenes under similar conditions (Scheme 10).\textsuperscript{41, 42} The yield of the cyclopentenes versus the cyclopentanes depends on the purity of the anhydrous aluminum chloride. Very pure condensing agents will produce more of the cyclopentane congeners; while less pure, moisture ridden or oxygen containing aluminum chloride, or even a different
metallo-chloride like ferric chloride, will produce mainly the cyclopentene congeners.\textsuperscript{43, 44}

\textbf{Scheme 10}

Another class of reagents commonly used to introduce a keto functionality to a substrate is the anhydrides. Simple aliphatic anhydrides react similarly to the acid halides to give the expected products without any rearrangements.\textsuperscript{45} Polyanhydrides can be used to form $\omega$-benzoyl acids and $\alpha,\omega'$-dibenzoylated hydrocarbons.\textsuperscript{46} In addition, aromatic anhydrides, like benzoic anhydride, can be used to form diarylketones.

One of the most important processes that has been developed using aromatic anhydrides is the Friedel-Crafts reaction of phthalic anhydrides with aromatic systems. This process yields a variety of $o$-aryloxybenzoic acids, which are particularly important to industry as ring closure \textit{via} sulfuric acid can afford various quinones which are useful as dye intermediates (\textbf{Scheme 11}). The process yields relatively pure materials, which are therefore superior to the anthraquinones prepared by oxidation of anthracene \textit{via} chromic
acid. The process is also a relatively inexpensive route when compared to the cost of the catalytic oxidation method of crude anthracene.\textsuperscript{47}

Scheme 11:

\[
\begin{align*}
\text{Phthalic anhydride} & \xrightarrow{\text{AlCl}_3, \text{C}_6\text{H}_6} \text{Phthalic acid} \xrightarrow{\text{H}_2\text{SO}_4} \text{Phthalide} \\
\end{align*}
\]

However, according to Rubidge, phthalic anhydride can form phthalides instead of \textit{o}-aroylbenzoic acids from the Friedel-Crafts reaction if the conditions are changed by either reducing the amount of aluminum chloride or increase the boiling time.\textsuperscript{48} Further, adding acetic anhydride can increase the yield of the phthalide to 93\%.\textsuperscript{49} This side-process actually provides an alternative route to phenolphthalein (Scheme 12).\textsuperscript{50}

Scheme 12

\[
\begin{align*}
\text{Phthalic anhydride} & \xrightarrow{\text{C}_6\text{H}_5\text{OH}} \text{Phthalic acid} \\
\text{AlCl}_3 \text{ or ZnCl}_2 & \xrightarrow{\text{C}_6\text{H}_5\text{OH}} \text{Phthalide} \\
\end{align*}
\]

Similarly to the acid chlorides, anhydrides will acylate furan at the 2 position if it is not blocked. However, if a nitro group or a bromine atom is attached at the 2 or 5 position, no reaction will occur.\textsuperscript{19,51} Strangely, methyl furoate will not acylate \textit{via} acid chlorides or acid anhydrides with aluminum chloride as the condensing agent. However, ferric or stannic chloride can be used as the condensing agent with anhydrides, acid
chlorides and acid anhydrides to produce the corresponding ketone congeners of the furans (Scheme 13).\textsuperscript{19, 28, 52}

**Scheme 13**

\[
\begin{array}{c}
\text{O} \\
\text{FeCl}_3 \\
(\text{CH}_3\text{CO})_2\text{O} \\
\text{O} \\
\end{array}
\quad \overset{\longrightarrow}{\text{O}}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

It is of interest that even anhydride fragments can acylate the substrate, increasing the yield. Groggins et al. noted that, when calculating the yield of the condensation of acetic anhydride with toluene on the basis of only one acetyl group participating in the acylation, yields of over one hundred percent of the theoretical were achieved. Further studies suggested that complexation of the acetate fragment with the aluminum chloride occurred (Scheme 14), which would break down to form another reactive species and then react further with the substrate (Scheme 15).\textsuperscript{53, 54}

**Scheme 14**

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\quad +
\begin{array}{c}
2\text{AlCl}_3 \\
\end{array}
\quad \overset{\longrightarrow}{\text{AlCl}_3}
\begin{array}{c}
\text{O} \\
\text{Cl} \\
\end{array}
\quad +
\begin{array}{c}
\text{O} \\
\text{OAICl}_2 \\
\end{array}
\]

**Scheme 15**

\[
\begin{array}{c}
\text{O} \\
\text{OAICl}_2 \\
\end{array}
\quad \overset{\longrightarrow}{\text{AlCl}_3}
\begin{array}{c}
\text{O} \\
\text{Cl} \\
\end{array}
\quad +
\begin{array}{c}
\text{AlOCl} \\
\end{array}
\]

In an interesting extension of this work it has been shown that the acid congeners of these anhydrides are able to acylate the substrates. These and other carboxylic acids
require excess anhydride, approximately three mole equivalents, and give moderate to
good yields of the expected ketones. Strong evidence has been accumulated to indicate
that the acylation does not occur directly from the acid, but through formation of the acid
halide, which could explain why a large excess of the condensing agent is required. This
applies to the aliphatic acids as well as the aromatic acids. Polycarboxylic acids will
condense as well to yield keto acids, as shown for the condensation of pyromellitic acid
with benzene (Scheme 16).

Scheme 16

Esters, ketenes and nitriles have also been used as acylating agents to introduce a
keto functionality into an aromatic species. In the case of nitriles, the reaction is
known as the Hoesch-Houben reaction. It proceeds by way of an intermediate, a
ketimine, which hydrolyzes to the ketone (Scheme 17). Typically, zinc chloride is used,
however aluminum chloride and other anhydrous metal halides can be substituted.
B. Introduction of the Carboxyl Moiety

Other extensions of the Friedel-Crafts reaction are the introduction of carboxyl, formyl and other specialized groups onto a substrate. Carbonyl chloride, carbon dioxide and urea chloride can be used in Friedel-Crafts reactions to introduce carboxyl moieties. Carbonyl chloride will react with aromatic species to form acid chlorides, which hydrolyze to the carboxylic acids. However, in order to form the acid instead of the ketone the conditions used must be adverse to the production of the ketone, such as by employing small concentrations of hydrocarbon, low temperature or shorter reaction periods.\(^4,^{60}\) Urea chloride will acylate some aromatic substrates to form amides which hydrolyze easily to the acid.\(^{61}\) Carbon dioxide will react with hydroxy- and amino-benzenes under higher pressures and at 100-150°C to form both ketones and the corresponding acids. A representative example is the carboxylation of \(p\)-cresol via carbon dioxide and aluminum chloride at 70 atm and 150°C to form \(p\)-cresotinic acid (Scheme 18).\(^{62}\) The reaction of carbon dioxide is of particular interest since carbon dioxide is a cheap, readily available and renewable resource. The combination of these factors makes the formation of carboxyl and keto species using carbon dioxide a valuable avenue for pursuit.
C. Introduction of the Formyl Group

A formyl group is in reality just a keto group where the atom once removed from the carboxyl functionality is hydrogen, so similar processes as were used for ketones can be used for introducing formyl groups. In other words, an acid or its derivative can be used to introduce the group, though in this case the acid must contain one carbon and be of the fatty acid series. This means that formic acid and its derivatives, which are the only examples, which fit the aforementioned criteria, are the acid and derivatives used to introduce formyl group functionality.

It has been shown that formic acid will directly introduce the formyl group, via the formyl chloride, which is formed in situ from the reaction of aluminum chloride and formic acid. This is more recent work, however, and the two main reactions that typically come to mind when considering the Friedel-Crafts addition of a formyl group to a substrate are the Gattermann and the Gattermann-Koch reactions. Both proceed through non-isolated intermediates, which are derivatives of formic acid; however the former involves an additional hydrolysis step to yield the aldehyde, while the latter is a direct addition of the formyl group.
The Gattermann reaction proceeds by the *in situ* formation of a hypothetical formamine chloride intermediate, which results from the combination of dry hydrogen chloride and anhydrous hydrogen cyanide. Upon reaction with the substrate, of which phenols react readily, and in the presence of aluminum chloride, the reaction produces good yields of the intermediate aldimine. Hydrolysis of the aldimine then affords the desired aldehyde (Scheme 19).64

**Scheme 19 – The Gattermann Reaction**

\[
\text{HCN} + \text{HCl} \rightarrow \left[ \begin{array}{c} \text{H} \\ \text{N} \\ \text{H} \end{array} \right] \quad \text{C}_6\text{H}_5\text{OH} \rightarrow \left[ \begin{array}{c} \text{H} \\ \text{NH} \end{array} \right] \rightarrow \left[ \begin{array}{c} \text{H} \\ \text{CO} \end{array} \right] + \text{HCl}
\]

**Scheme 20 – The Gattermann-Koch Reaction**

\[
\text{CO} + \text{HCl} \rightarrow \left[ \begin{array}{c} \text{H} \\ \text{Cl} \end{array} \right] \quad \text{AlCl}_3 \rightarrow \left[ \begin{array}{c} \text{H} \\ \text{Cl} \end{array} \right] + \text{C}_6\text{H}_5\text{OH}
\]

Furan, 2-furfural, thiophene and pyrrole will also effect acylation *via* the Gattermann or Gattermann-Koch processes to introduce the formyl functionality.65-67 However, when attempting to formylate aliphatic species the reaction does not occur as expected. Hopf combined n-pentane and 2-methylbutane with the Gatterman-Koch reagents and found that the product obtained was not a formylated aliphatic species but ethyl isopropyl ketone (Scheme 21). The actual mechanism is unknown but Hopf
suggested that the 2-methylbutane was cleaved, the carbonyl group introduced and then the fragments recombined to give the product.\textsuperscript{40}

**Scheme 21**

\[
\begin{align*}
\text{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3} & \quad \text{CO} + \text{HCl} \\
\text{\text{AlCl}_3} & \quad \text{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3}\text{CO} \\
\end{align*}
\]

Also, interestingly, when the Gattermann-Koch reaction was attempted with alkyl halides, acid chlorides were produced. An example is the reaction with \textit{n}-propyl chloride, which produces \textit{n}-butyroyl chloride (**Scheme 22**).\textsuperscript{40}

**Scheme 22**

\[
\begin{align*}
\text{\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}} & \quad \text{CO} + \text{HCl} \\
\text{\text{AlCl}_3} & \quad \text{\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}}\text{CO} \\
\end{align*}
\]

**D. Introduction of Other Groups**

A variety of other groups can be introduced to substrates via Friedel-Crafts reactions. These groups can include sulfones, thio groups (\textit{e.g.} thioketones, thioanilides, dithiocarboxylic acids), nitro groups, nitrile groups, oxygen, sulfur, arsenic, selenium and phosphorus. The same substrates, which undergo the previously mentioned acylations will work in these processes. For example, sulfonyl chlorides will acylate benzene derivatives and reactive congeners of benzene, such as \textit{alkyl-} or \textit{halogeno-}benzenes, to produce sulfones. The sulfur analogs of compounds like phosgene will react in the same manner. Thus, thiophosgene yields the corresponding thioketones and even carbon disulfide will react, though the products are not what would generally be expected. Thus,
in the case of anisole, the product is $p$-dithiocarbomethoxyphenol. It has been suggested that this is due to cleavage of the ether linkage releasing the alkyl group and subsequent formation of methylidithiocarbonic acid chloride, which then acylates the phenol in the usual manner (Scheme 21).  

**Scheme 23**

Further, phenyl isocyanate will acylate benzene in the presence of aluminum chloride to form an anilide, as will phenyl isothiocyanate to form a thioanilide (Scheme 22).
Instead of using typical nitration methods, one can use the Friedel-Crafts version, which uses nitrogen tetroxide or ethyl nitrate with either aluminum or ferric halides, to produce the nitrated species in good yield.\textsuperscript{70, 71} This can be less vigorous than the typical method of nitration, though more expensive, since nitrogen tetroxide costs approximately $1/gram and nitric acid and sulfuric acid are approximately $0.07/gram. Another nitrogen containing group, the nitrile group, can be introduced in a similar manner, using mercury fulminate and hydrochloric acid.\textsuperscript{72}

Oxygen, when not excluded from the Friedel-Crafts reactions, has been found to produce a side reaction with benzene, forming phenolic substances.\textsuperscript{73, 74} Sulfur will behave in a similar manner to form a variety of thio- species, such as thiophenol, diphenyl sulfide and thianthrene, when reacted with benzene.\textsuperscript{75, 76} Other species that have been introduced into aromatic systems include selenium, arsenic and phosphorus, which were introduced via their chlorides and aluminum chloride.
IV. Alternative Homogenous Catalysts

Much of what has been discussed in this introduction relates to the Friedel-Crafts reaction using aluminum chloride and other metallo-chloride catalysts, however, the bulk of the recent work in the field of catalytic chemistry has focused on finding alternative catalysts that can be used in place of the metallo-chlorides. Partly, this is because metallo-chlorides typically have to be used in stoichiometric rather than catalytic amounts. Also, it is often difficult to remove the metal complexes that are formed from the reaction mixtures after reaction is complete. Some of the alternative catalysts are homogeneous catalysts, like the aluminum chlorides, which can be used in smaller amounts and/or are easier to remove from the reaction mixture. These include the metal triflates (e.g. bismuth(III) triflate, antimony(III) triflate and indium(III) triflate), trifluoroacetic acid, triflic acid, metals, and other species like iodine and perchloric acid.

The metal triflates are simple to synthesize from metal halides and triflic acid or triflic anhydride (generally at -78°C). Early studies by Olah reported the effectiveness and use of aluminum, boron and gallium triflates. Later work showed bismuth(III) triflate to be of even greater utility, since it will catalyze the acylation of both activated and deactivated aromatic compounds. It also promoted these acylations using both anhydrides and acyl chlorides, whereas previous metal triflates only catalyzed the acylations of activated aromatic compounds with acyl chlorides. Scandium triflate can be used to great effect in the acylation of methoxy- and thiomethoxyarenes with acyl chlorides or aliphatic and aromatic anhydrides. The process gives the corresponding ketones in 79-99% yields while using only 20 mol% of the catalyst.
Sometimes additives are used to increase yields of the reactions. Thus, titanium(IV) monochlorotriflate and hafnium triflate have been shown to give better yields when used in combination with triflic acid. For example, titanium monochlorotriflate with triflic acid is highly efficient in the condensation of anisole with hexanoic anhydride, giving 98% yield with 100% para selectivity (Scheme 25). 77

Scheme 25

Another additive that has been used to great affect is lithium perchlorate, which has been shown to increase the efficiency of the lanthanide triflates, especially when used as a lithium perchlorate-nitromethane solution. It can even influence the regioselectivity of a reaction. When used with antimony(III) triflate (5 mol%), 2-methoxynaphthalene and acetic anhydride, the regioselectivity of the reaction changes from the 1 position to the 6 position (Scheme 26). 77
There are many other types of metal triflates that have been used to great effect and there are numerous examples also of the use of ionic liquids and supercritical fluids as solvents to help stabilize the charged intermediates and support the recycling of the homogenous catalysts. Metal triflates are undoubtedly the largest class of such catalysts; however there are others that have been used as homogenous catalysts. Various metals have been used to catalyze Friedel-Crafts reactions, with well-known examples including indium, zinc and iron. Zinc and indium show high efficiency in the acylation of aromatic compounds with benzoyl chloride and acyl chlorides, respectively. Iron or zinc with terephthaloyl chloride will acylate two molecules of anisole to produce 1,4-bis(4-methoxybenzoyl)benzene (Scheme 27).
Iodine has been used with aliphatic and aromatic acyl chlorides or anhydrides to catalyze the acylation of electron-rich aromatic compounds. The yields are between 25 – 93% in the cases of furan and thiophene, which readily undergo acylation in the presence of iodine. This is beneficial since these particular heterocycles are sensitive to acidic treatments. The process is hypothesized to work because of iodine’s ability to act as an electron acceptor. Other homogenous catalysts can include aqueous perchloric acid, iron(III) sulfate, aluminum hydrogensulfate and bromopentacarbonylrhenium(I).77
V. Alternative Heterogeneous Catalysts

If one wishes to use a heterogeneous catalyst instead, there are many options available. These catalysts have advantages in efficiencies and in reusability. They include zeolites, clays, metal oxides, sulfated zirconia, heteropoly acids, nafion and others. Of these, the clays are of particular interest as they have a variety of uses depending upon the structure and the interchangeability of the clay, not to mention the ease of their use and their potential utilization in green chemistry. Many of the clays are reusable for many cycles with little to no change in their efficiency. Many clay catalysts are also easily removed from the reaction mixture simply by filtration followed by rinsing. They are useful in solventless reactions as well, providing inert or catalytic surfaces for the reaction, which makes them ideal for green chemistry reactions.77

Clays occur abundantly in nature and have high surface areas and a variety of sorptive and ion exchange properties which make them useful for a variety of catalytic applications. The clays can be used for bifunctional or “inert” supports, as fillers to give solid catalysts with required physical properties and as catalytically active agents, typically in the manner of solid acids.77

Clays are layered silicates with crystalline structures and very fine particle sizes from 150 to less than 1 μm. They are typically composed of tetrahedral and/or octahedral layers, the exact compositions of which have been divided into the following classes: Kaolinite clays which have alternating tetrahedral sheets (OT or 1/1); Smectite clays, which are the most common clays and have octahedral layers sandwiched between two tetrahedral layers (TOT or 2/1); and finally Chlorite clays which have 3 TOT layers alternating with brucite (which is the mineral form of magnesium hydroxide [Mg(OH)₂]).
which has the label 2/1/1. Of the most common class, the smectite clays, the most common and most often used clay type is the Montmorillonite subset.\textsuperscript{77}

Montmorillonite, named after Montmorillon in the Poitou-Charentes region in France where it is found, has a wide variety of uses besides catalytic. These uses range from making mud slurries to keep an oil rig’s drill bits cool, to utility as catalysts and drug carriers, and, for some forms, even in cosmetics.\textsuperscript{78} The interlayer cations of Montmorillonite are interchangeable and the clay has a high cation exchange capacity. It is therefore extremely useful in catalytic processes as a wide variety of catalytically active forms of clay mineral can be prepared from the initial Montmorillonite. Some of the exchanges possible are for acidic cations, metal complexes and photocatalytically active cations. Typically, Montmorillonite is used as a Bronsted acid rather than a Lewis acid, though Lewis acidity can play a role in the catalytic activity of the clay.\textsuperscript{77}

Of the variety of Montmorillonites, the K-10 variety is particularly relevant to this research. The molecular formula of K-10 is $\text{Al}_2\text{H}_2\text{O}_{12}\text{Si}_4$ and it has the structural set up as shown in Figure 2.\textsuperscript{79} This 2/1 structure is composed of two tetrahedral $\text{SiO}_2$ groups encompassing an octahedral $\text{Al}_2\text{O}_3$ layer.\textsuperscript{80} It is proposed that the catalytic activity of the Montmorillonite K-10 clay originates in the aluminum oxide molecules present in the structure.
Clay catalysts such as Montmorillonite K-10 are especially useful in a variety of green chemistries. They can be used as substrates to allow solventless reactions to proceed. This decreases the amount of organic waste, which is typically extracted at the end of the reaction and then disposed of. They are also reusable catalysts, and they can be washed to remove the reactants and then recycled. They can be reused many times with little to no lessening of their effectiveness. They have also been used in microwave chemistry to great effect. Heterocyclic quinones, for example, can be prepared using Montmorillonite K-10 and microwave irradiation (780 W for 3-5 minutes) in yields of 21-92% (Scheme 28).
Scheme 28

K10, MW
320°C, 3-5 min
92%
Microwave Chemistry

I. History

One of the most up and coming fields of chemistry is that of microwave irradiation chemistry. It is an efficient, time saving and oftentimes “green” method of performing chemical reactions. Many reactions can be shortened from the typical reaction times of hours to mere minutes, or even seconds. The process uses less energy overall than heating a reaction thermally, and often takes far less solvent than conventional methods, sometimes not requiring any solvent at all.

In 1946 Dr. Percy Spencer accidentally discovered that while standing near a magnetron he was testing, the candy bar in his pocket melted. Based on this and other experiments, which included placing an egg next to the magnetron and watching it explode in the face of one of his colleagues, he determined that microwave energy was heating the food much more quickly than normal thermal methods. To verify his findings, he created a high-density electromagnetic field in a metal box so it could not escape and when food was placed in the box the temperature of the food rose rapidly. Raytheon placed the first patent for Spencer’s microwave cooking process and by 1986 roughly 25% of households owned a microwave (Gallawa). In recent times, of course, they have become common-place.81

As early as the 1950’s, scientists were using microwaves for chemical applications in analytical chemistry, biochemistry, pathology and even for medical treatments. It was not until the 1980’s that scientists started using microwaves in organic chemistry, and in 1986 researchers began using microwaves to heat organic reactions. Initially they used domestic microwaves, and found that microwave heating could cause
reactions to go to completion much faster than conventional methods. However, these reactions were difficult to reproduce due to uneven heating and differing locations of high and low energy (modes) in the different microwave ovens. Even using the same microwave could lead to difficulties as one spot may have a higher energy than another spot in the same microwave. The reactions were also typically carried out in sealed glass or Teflon reaction vessels and without the help of equipment to monitor pressure and temperature they often ended explosively. Open containers had to be used to perform many of these reactions; however the solvents themselves could interfere in the extraction of the products.\textsuperscript{82}

In the 1990’s researchers began exploring solvent-free microwave chemistry using silica, aluminum, clay or graphite as essentially “microwave transparent” or strongly absorbent (graphite) inorganic supports which would allow the reaction to occur but eliminate the possibility of explosions. Sometimes, catalysts or reagents were used to dope the support and sometimes the support could actually act as a catalyst, like \textit{e.g.} Montmorillonite clays. Then microwave reactor technology began to improve and more specialized microwaves started to appear, which had the ability to monitor time, pressure and temperature, as well as being more consistent in heating and mode location. These were put to use in chemical laboratories and they effectively revitalized the microwave chemistry era, which had been dwindling due to an inability to consistently reproduce other researchers’ results.\textsuperscript{82}
II. Mechanics

Microwave irradiation is a low energy form of radiation between 300-300,000 MHz. Unlike UV rays, microwaves are low enough in energy that they will not cause the chemical bonds to break but they do cause the molecules to rotate. They consist of two fields (Figure 3), electric and magnetic, which move perpendicular to each other and travel at the speed of light. It is the electric field that primarily interacts with molecules to cause transfer of energy and generation of heat.83

Figure 3 – Electric and Magnetic Fields of a Microwave

Two types of molecules will interact with the electric field of the microwave: those with dipole moments or those that are charged. If the molecule has a dipole moment it will try to align with the electric field. However, this field is oscillating constantly at 2.45 GHz, so the molecules are unable to exactly align themselves with the field. This constant rotation of the molecules causes friction, which produces heat, and it is known as dipolar polarization. In the case of charged molecules they undergo ionic conduction, where the electric field of the microwave moves the ions back and forth through the sample. The movement of the ions causes collisions, which is what generates the heat.83
Since the interaction of the microwaves with the chemicals is direct, rather than indirect, as in traditional hotplate methods, the warm-up time is much reduced, which in itself reduces the reaction time considerably. The energy that is provided also supplies the energy to jump the energy barrier that is necessary for a reaction to go to completion, and it does so more quickly than conventional methods. As such, microwaves can decrease reaction times significantly.\(^{83}\)
III. Types of Laboratory Microwave Reactors

There are two types of laboratory microwave reactors typically employed. Which type is used is dependent on whether one needs to perform one, small reaction at a time, one large (batch) reaction or multiple smaller reactions at one time. If performing one small reaction, a monomode reactor is the preferred instrument. Monomode reactors generally perform around 300W and have a cavity for the reaction vessel that is exactly one mode of energy long, so the vessel is constantly irradiated with microwave energy. This is an improvement over domestic microwaves as the points of high and low energy (modes) vary depending on the location in the microwave.83

Multimode reactors are available for larger, batch reactions or for use with carousels that allow the researcher to irradiate multiple samples at one time. The carousel will rotate during the time of the reaction so that all vessels are irradiated mostly uniformly, despite the differing areas of high and low energy in the reactor. However, these can be trickier to use as the carousel has to be balanced correctly, or it will malfunction and malfunctions can cause explosions. Additionally, the pressure and temperature are often monitored through a fiber optic probe, which is inserted into one of the vessels, and this probe is expensive and fragile. An upside is that multimode reactors can run open vessel reactions whilst most monomode reactors only operate with sealed vessels.83
**Sydnones**

First prepared in Sydney, Australia by Earl and Mackney, sydnones are dipolar, monocyclic, heteroaromatic oxadiazolone compounds (Figure 4). Sydnones are members of a class of compounds called mesoionic. Molecules known as mesoionic must have the following properties: they must contain a fully delocalized positive and negative charge; they must be planar and contain a five-membered heterocyclic ring with an exocyclic atom or group capable of bearing a high charge density; and they must possess considerable resonance energy (Figure 5).

![Figure 4 – General Representation of a Sydnone](image-url)
Sydnones are the most studied examples of the mesoionic group of compounds and have many potential applications. They have been evaluated for their use in non-linear optics, as electrolytic solvents for non-aqueous batteries and for a variety of biological applications.\textsuperscript{85,86} They have shown activity as anti-inflammatory, anti-fungal, anti-bacterial, anti-tumor and analgesic agents.\textsuperscript{87,88}
They can undergo a variety of reactions including: electrophilic aromatic substitution at the C-4 position of the sydnone ring (if R’ (in 1) = H) by means of acylation, nitration, halogenation and sulfonation; metalation at the C-4 position; substitutions of the aryl ring in the case of 3-arylsydnones; and other examples depending on the nature of the substituents attached to the sydnone ring (Figure 6). This versatility in designing a variety of different sydnones provides for many potential applications and makes the synthesis of new sydnones a field of great interest.

Figure 6 – Representation of The Variety of Reactions that Phenylsydnone Can Undergo
Aims of the Present Work

It was noted by Turnbull and Preston in 1977 that sydnobenzotriazine, a fused-ring sydnone, cleaved hydrolytically to yield a benzotriazine carboxylic acid (Scheme 29). This unusual mode of cleavage was thought to be due to the aromatic nature of the benzotriazine product and a by-product of this reaction was conjectured to be nitric oxide (NO) or an NO congener. As such, it was proposed that fused-ring sydnones could prove to be potential NO prodrugs, which could be used for the prevention or cessation of heart attacks or strokes.\(^{93}\)

Scheme 29

Accordingly, it is of interest to synthesize a variety of fused-ring phenyl sydnones. Many routes to these fused-ring phenyl sydnones have been explored in this laboratory, including a variety of acylative methods. Among these are the acylations of 3-phenylsydnone via the reaction with anhydrides at the C-4 position. Jennifer Fisher\(^{94}\) explored the use of bismuth(III) triflate as a catalyst to effect the Friedel-Crafts acylation with a variety of anhydrides. This was a more environmentally clean method than previously reported methods because the amount of catalyst used was in the 25 mol% range. However, as the anhydride’s complexity increased the reaction times increased
significantly and the yields decreased. Jones George\textsuperscript{95} explored the use of Montmorillonite K-10 as catalyst with acetic anhydride to effect the Friedel-Crafts acylation of different sydnones, however, he did not study this reaction using different anhydrides. In both Fisher and George’s cases, the reactions could take anywhere from hours to days to go to completion, and yields were not always good. It was the aim of this work to improve these methods via microwave irradiation, develop protocols for the microwave reactor and expand them to other anhydrides or to o-aminophenylsydnone.

It was anticipated that the first steps would involve completing the thermal reactions of phenylsydnone with Montmorillonite K-10 and other anhydrides besides acetic anhydride. From there, the microwave method could be developed based upon the results of these initial studies. It was anticipated, further, that acetic anhydride and 3-phenylsydnone would be used to develop this method, since that would be the most basic model. Once the microwave reaction conditions had been optimized it was expected that expansion to propionic, butyric, isobutyric and benzoic anhydrides would be explored.
Results and Discussion

With the aims of the research established, the initial phase of the work was the completion of the Montmorillonite K-10 (K-10) series of experiments. The starting material for these reactions, 3-phenylsydnone (2), was synthesized in two steps from commercially available N-phenylglycine, in yields of 65-75% for the two steps, with relative ease. George had successfully synthesized 4-acyl-3-phenylsydnone (3) using K-10, 2 and acetic anhydride (Scheme 30) yet had not expanded this to include other anhydrides such as propionic, butyric and isobutyric anhydride.

Scheme 30

\[
\begin{align*}
\text{Mont. K-10, (RCO)_2O} & \quad \Delta \text{ or MWI} \\
2 & \quad 3: R = \text{CH}_3 \\
& \quad 4: R = \text{CH}_2\text{CH}_3 \\
& \quad 5: R = \text{CH}_2\text{CH}_2\text{CH}_3 \\
& \quad 6: R = \text{CH} (\text{CH}_3)_2 \\
& \quad 7: R = \text{Ph} \\
& \quad 8: R = \text{CF}_3
\end{align*}
\]

It was considered relevant to complete these reactions to determine the effect of the lengthening alkyl chains on the reaction and to provide a larger base for the microwave irradiation (MWI) comparisons. As such the reactions were attempted with propionic, butyric, isobutyric, benzoic and trifluoroacetic anhydrides, with the expectation that the corresponding acylated sydones 4-8 would result. It became
apparent quickly that the more complex the anhydride, the longer the reaction would take to go to completion. George\textsuperscript{95} had reported that the synthesis of 3 was achieved in 61\% yield after refluxing for 24 hours at 110°C. In the present work, the preparation of 4-propanoyl-3-phenylsydnone (4) was achieved in only 50\% yield after refluxing for 4 days at the same temperature. The identity of the product was confirmed by melting point, IR and NMR spectra. The melting point was 85-86°C, which was comparable (but obviously not identical to) to Fisher’s melting point of 78-80°C. The IR spectrum showed an absence of the 3150 cm\(^{-1}\) peak, which is seen when a hydrogen atom is present at the C-4 position of the sydnone ring, and two carbonyl peaks were observed at 1794 cm\(^{-1}\) (sydnone carbonyl) and 1663 cm\(^{-1}\) (propanoyl carbonyl). The proton NMR showed a doublet and two triplets in the aromatic region equivalent to five hydrogens, a quartet at 2.9 ppm equivalent to the methylene hydrogens of the propanoyl group, and a triplet at 1.2 ppm, which corresponds to the methyl group hydrogens. The carbon NMR showed the methylene carbon at 34 ppm and the methyl carbon at 7 ppm, the sydnone C-4 at 105 ppm and the sydnone carbonyl at 166 ppm. The carbonyl of the propanoyl group appeared at 187 ppm and four carbon peaks appeared in the aromatic region, which corresponds to an unsubstituted phenyl ring.

4-Butanoyl- (5, 28\%) and 4-isobutanoyl-3-phenylsydnone (6, 54\%) were prepared similarly after 7 and 8 days of heating, respectively. The melting points were 64-65°C for 5 (Fisher: 62-64°C) and 109-111°C for 6 (Fisher: 105-106°C). Both products showed two carbonyl peaks in their IR spectra and a lack of the 3150 cm\(^{-1}\) peak. Product 5 showed peaks at 1, 1.9 and 3 ppm in the proton NMR and at 13, 16 and 42 ppm in the carbon NMR, which correspond to the isobutanoyl group at the C-4 position of the
sydnone ring. The sydnone carbonyl appeared at 166 ppm and the isobutanoyl carbonyl at 186 ppm. The isobutanoyl product 6 displayed similar peaks for the sydnone carbonyl, the isobutanoyl carbonyl and the sydnone C-4 in the carbon NMR. It showed two peaks in the proton NMR aliphatic region: a multiplet at 3.7 ppm, integrated for one hydrogen, and a doublet at 1.2 ppm, which integrated for six hydrogens, indicative of the iso-isobutanoyl alkyl chain. Also in the proton and carbon NMR spectra were peaks in the aromatic regions that correspond to the unsubstituted phenyl ring (¹H NMR: triplet at 7.9 ppm, triplet at 7.8 ppm and doublet at 7.5 ppm; ¹³C NMR: 124, 129, 132 and 135 ppm). The carbon NMR displayed two aliphatic peaks at 17 and 39 ppm, which also accounts for the isobutanoyl group, as the two methyl groups overlap.

The increase in reaction times was believed to be due mainly to the added steric hindrance from the longer alkyl chains of the reactants. Since isobutyric anhydride does not have as much steric hindrance as n-butyric anhydride, but does have a more electron donating aspect toward the carbonyl, it took only 24 hours longer than the n-butyric to react completely with the sydnone. However, even after 18 days the reaction with benzoic anhydride did not show significant formation of the expected product 7 by TLC and the reaction with trifluoroacetic anhydride, though it would appear to be more reactive, also did not show development of product after a longer than expected period of time. Accordingly, it was decided not to pursue further either reaction.

As a baseline had now been achieved for each reaction thermally, the focus moved to the MWI reactions. The simplest reaction, that of 3-phenylsydnone (2) with acetic anhydride and K-10, was chosen initially to optimize the microwave conditions (Table 1). As the thermal reaction was carried out at 110°C for 24 hours, a conversion
chart provided with the CEM Discover 300W microwave suggested increasing the temperature to 180°C in order to reduce the reaction time to 1 hour. However, sydnones are prone to decomposition to hydrazines under acidic conditions, at high temperatures and in the presence of water. This was of particular concern since water was present in both the acetic anhydride and K-10 clay and the reaction produces acetic acid as a by-product.

Accordingly, the initial temperature decided upon for the first attempt was 130°C. Unfortunately, this produced only a 19% yield of 3 after 1 hour so the temperature was increased to 140°C, at which temperature trials were run for 1 and 2 hours. From these trials, the yields did not yet approach the yield achieved thermally, so the temperature was again raised to 150°C, at which temperature trials D-G were run. As noted in Table 1 the yields were still only moderate and, after some consideration, it was elected to increase the concentration of the solution by decreasing the amount of anhydride to 1-2 mL and try again at 150°C (H, I), which resulted in a product yield higher than those from the previous runs. With the concentration increased, the yields improved, and at 150°C for 1.5 hours a yield of 54% (I) was achieved, which was much closer to the thermal yield of 61%. The products were confirmed by melting point (137-139°C, Fisher: 134-135°C), IR [two carbonyl peaks at 1794 (sydnone) and 1664 cm⁻¹; lack of 3150 cm⁻¹], ¹H NMR [methyl at 2.6 ppm, aromatic 7.8 ppm (t), 7.76 ppm (t) and 7.5 ppm (d)] and ¹³C NMR, which showed the sydnone carbonyl (166 ppm) and C-4 position (106 ppm); the acetyl carbonyl (184 ppm) and methyl group (28 ppm); and four aromatic peaks (134, 132, 129 and 124 ppm) corresponding to the unsubstituted phenyl ring.
Table 1: Microwave Optimization of Montmorillonite K-10 Method Using Acetic Anhydride (AA)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time (hrs)</th>
<th>Temperature (°C)</th>
<th>AA (mL)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>130</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>140</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>140</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>D</td>
<td>0.5</td>
<td>150</td>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>E</td>
<td>1</td>
<td>150</td>
<td>5</td>
<td>41</td>
</tr>
<tr>
<td>F</td>
<td>1.5</td>
<td>150</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>G</td>
<td>2</td>
<td>150</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>H</td>
<td>1</td>
<td>150</td>
<td>1.2</td>
<td>47</td>
</tr>
<tr>
<td>I</td>
<td>1.5</td>
<td>150</td>
<td>1.2</td>
<td>54</td>
</tr>
</tbody>
</table>

The next trials (Table 2) involved the microwave irradiation of propionic anhydride, 3-phenylsydnone (2) and K-10. After 4 hours at 150°C, TLC examination showed complete conversion of the starting material. The reaction mixture yielded 51% of the desired product 4 after workup. Based upon this and the acetic anhydride trials, it was postulated that the optimum conversion to microwave irradiation is approximately 1 hour at 150°C for every day it took to go to completion thermally. Microwave reactions, however, are typically run for no more than a few minutes, though there have been some examples of microwave reactions occurring for longer periods, even up to 3 hours. Typically, the longer irradiation period reactions are accomplished in intervals of half an hour, or other smaller intervals of time, but occasional examples have been run in a continuous manner. However, since such reactions typically had not been run for such long periods as the longer chain anhydrides appeared to require, it was unknown what the effect on the microwave instrument would be. Having run the reactions for up to 4 hours, it was decided that a 6-hour run could be attempted carefully to prove or disprove the 1 hour/day theory. Accordingly, n-butyric anhydride, 3-phenylsydnone (2) and K-10 clay were heated in the microwave for 6 hours, after which time a TLC examination showed...
nearly full conversion and the yield of the desired product 5 after column was 31%. This result indicated that the approximately 1 hour per day conversion for the Montmorillonite K-10 reactions was probably accurate. However, further testing was not deemed safe for the microwave instrument so this could not be verified further.

Table 2: Microwave Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Anhydride</th>
<th>Time (hrs)</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Trifluoroacetic</td>
<td>1</td>
<td>150</td>
<td>---</td>
</tr>
<tr>
<td>B</td>
<td>Propionic</td>
<td>4</td>
<td>150</td>
<td>51</td>
</tr>
<tr>
<td>C</td>
<td>n-Butyric</td>
<td>6</td>
<td>150</td>
<td>31</td>
</tr>
</tbody>
</table>

The next steps in the study involved the examination of the alternate method using bismuth(III) triflate (Scheme 31). Fisher\textsuperscript{94} developed a method using acetic anhydride, 25 mol% bismuth(III) triflate and 25 mol% lithium perchlorate to acylate aryl sydnones. Similar to the Montmorillonite K-10 method, this approach used higher temperatures (95°C), for longer times (from 2 hours to overnight) though it had better yields and not nearly as long reaction times for the higher order anhydrides. Fisher synthesized the acylated sydnones 3, 4, 5 and 6 in yields of 71, 63, 73, and 59%, respectively. However, it was of interest to see if the reaction times could be shortened considerably and/or if the yields could be improved.
The initial step involved the formation of the catalyst, bismuth(III) triflate. Lithium perchlorate and acetonitrile were obtained commercially and were not purified further. The bismuth(III) triflate was synthesized from commercially available triphenylbismuthine and triflic anhydride using reported procedures\(^9\) (Scheme 32, 84%). It was then used in the microwave optimization for the synthesis of 3.

Again, the simplest synthesis, that of 4-acyl-3-phenylsydnone (3) was chosen for initial optimization of the microwave process (Table 3) for the reasons mentioned in the previous section. It was decided, based on the microwave reactions with Montmorillonite K-10, and the temperatures used in the previous thermal methodology, to try initially
three temperatures (100, 125 and 150°C) for fifteen minutes each. The hope was to have shorter reaction times than even the K-10 microwave reactions and, preferably, lower temperatures to decrease the potential for breakdown of the sydnone ring.

Table 3 – Microwave Optimization of Bismuth(III) Triflate Method Using Acetic Anhydride

<table>
<thead>
<tr>
<th>Trial</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td>B*</td>
<td>125</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>C*</td>
<td>150</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>D*</td>
<td>100</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>E</td>
<td>125</td>
<td>15</td>
<td>53</td>
</tr>
<tr>
<td>F</td>
<td>150</td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>G</td>
<td>125</td>
<td>30</td>
<td>94</td>
</tr>
</tbody>
</table>

The first trial of 100°C was run for thirty minutes, since after fifteen minutes little conversion of the sydnone could be observed by TLC, and it yielded 69% of the desired acylsydnone 3 (Fisher, 71%). While this was a satisfactory result, one issue was that the catalyst was not readily synthesized. Indeed, the first attempt at synthesizing the bismuth(III) triflate [Bi(OTf)$_3$] was not exceptionally successful (30%), though later attempts were more so when anhydrous dichloromethane was substituted for regular dichloromethane (84%). Because of the poor initial yield of the Bi(OTf)$_3$, and because it was available through Sigma-Aldrich, the choice was made to employ the commercially available material. This latter Bi(OTf)$_3$ was used for the next two trials (B and C) but it was noticed quickly that the yields were poorer. Fisher had noticed an issue with older Bi(OTf)$_3$ previously, wherein the older the Bi(OTf)$_3$ the less effective it tended to be. It was assumed that the Aldrich material might not be prone to this issue but the present data, further comparisons of the acylation process at all three temperatures (Table 3, * indicates Aldrich Bi(OTf)$_3$) and later data procured with other anhydrides (Table 4) proved this to not be the case.
Table 4 – Comparison of the Effectiveness of Aldrich and Freshly-Made Bi(OTf)₃ (150°C, 15min)

<table>
<thead>
<tr>
<th>Product</th>
<th>Aldrich Bi(OTf)₃ Yield (%)</th>
<th>Freshly-Made Bi(OTf)₃ Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>52</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>28</td>
</tr>
</tbody>
</table>

Almost uniformly, the Aldrich Bi(OTf)₃ gave poorer yields than those obtained for the identical reactions using freshly-made Bi(OTf)₃. Based on these data, the freshly-made Bi(OTf)₃ was used for the rest of the trials. After comparison of the results for the synthesis of 4 and 5 at 150°C and 125°C for 15 minutes, it was observed that the run at 125°C gave better product yields than did the run at 150°C, which was initially assumed to be the best. Accordingly, the later trials that were conducted were done so at 125°C to determine the best times, though to make absolutely sure of this, each synthesis was run also at 150°C for 30 minutes. These several comparison points allowed confirmation of this initial theory.

Table 5 – Optimization of Microwave Synthesis of 4-Propionoyl-3-phenylsydnone (4)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>150</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td>B</td>
<td>125</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>C</td>
<td>150</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>D</td>
<td>125</td>
<td>30</td>
<td>92</td>
</tr>
</tbody>
</table>

As Table 5 shows, a 92% yield of acylsydnone 4 was achieved after 30 minutes at 125°C (Trial D). Gratifyingly, this was a better yield than reported by Fisher⁹⁴ for the thermal process (63%) and had the additional benefit of involving a shorter reaction time.
Table 6 shows the optimization of the MWI synthesis of acylsydnone 5. As shown, 125°C at 15 or 30 minutes produced the highest yield of 88%, which is higher than the 73% achieved by Fisher\textsuperscript{94} yet it was believed that it could be further improved. It was therefore surprising, initially, that the yield from Trial E was substantially lower, however, it is now believed that the bismuth triflate used for Trial E was not of good quality. This is also believed to be the case for Trial B in Table 7, which had a very poor yield as well. Time did not permit in the present work, but the trial should be repeated by a future researcher to confirm or deny these findings. As a side note, during the optimization of the synthesis of compound 5 a slight change was made to the procedure. There had been issues with emulsions during the extractions, which were found to be due to the production of a precipitate upon addition of dichloromethane to the reaction mixture. The additional step of filtering before extraction was added at this point, and this removed the problem of the emulsions. The precipitated was determined to be an inorganic compound, but could not be identified more definitively.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>150</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>B</td>
<td>125</td>
<td>15</td>
<td>88</td>
</tr>
<tr>
<td>C</td>
<td>150</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>D</td>
<td>125</td>
<td>30</td>
<td>88</td>
</tr>
<tr>
<td>E*</td>
<td>125</td>
<td>45</td>
<td>55</td>
</tr>
</tbody>
</table>
Table 7 - Optimization of Microwave Synthesis of 4-Isobutyroyl-3-phenylsydnone (6)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>150</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>B*</td>
<td>125</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>125</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>D</td>
<td>125</td>
<td>45</td>
<td>92</td>
</tr>
</tbody>
</table>

The MWI optimization of the synthesis of 6 was conducted at 125°C, except for the first trial which had been conducted at 150°C before it was confirmed that 125°C yielded better results. Trial B is suspected to be invalid by comparison with previous results, especially the yield from trial A being 28%, and this is suspected to be due to the catalyst. Fresh catalyst was made and used for Trials C and D, the results of which appear to confirm this conjecture. The yield from Trial D surpasses that achieved by Fisher (59%).

Table 8 - Determination of the Effect of Anhydrous Acetonitrile as Solvent

<table>
<thead>
<tr>
<th>Product</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>125</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>125</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>125</td>
<td>45</td>
<td>15</td>
</tr>
</tbody>
</table>

An abstract by Fisher submitted for the 229th National ACS meeting mentioned the use of anhydrous acetonitrile, which had not been brought up in either Fisher’s thesis or notebook. However, it suggested an interesting point: would using anhydrous acetonitrile affect the yields of the reaction? It was theorized that this should improve the yields and, accordingly, each of the best trials for products 3, 4, 5 and 6 were rerun using
anhydrous acetonitrile. As shown in Table 8 the effect was the opposite to what had been proposed. Each yield was lower than that found using ‘normal’ acetonitrile.

![Scheme 33](image)

At this point it was of interest to see if other acylations that had not been attempted before, or were not effective under thermal conditions, could be achieved through MWI. Attempts had been made by Fisher\textsuperscript{94} to synthesize 7 via thermal conditions which were unsuccessful. There had been some reports of MWI reactions succeeding where the corresponding thermal reactions did not. As such the acylation with benzoic anhydride was attempted via MWI at 125°C, which had the best results with the other acylations, for one hour. The initial results via TLC indicated that the reaction with benzoic anhydride resulted in 3 products, one of which appeared more prevalent than the other two, and a significant amount of unreacted starting material. Upon workup by CombiFlash column chromatography the initial and seemingly most prevalent product turned out to be less than 1mg, which was not enough to determine the composition of the product. The other product obtained was of significant enough an amount to identify.
IR, $^1$H NMR and $^{13}$C NMR spectral data identified the second product as benzoic acid, which is the breakdown product of the benzoic anhydride.

An acylation of interest, which had not been attempted before, was the acylation of 3-phenylsydnone with succinic anhydride. Initial TLC results of the reaction indicated a major product being formed which had a higher $R_f$ than the starting material, of which some was still present. However, after separation via column chromatography the major product was identified by IR, $^1$H NMR and $^{13}$C NMR as starting material. At this point the fraction and starting material were examined by TLC again and had the same $R_f$. It was deduced that the product formed was probably unstable and during the work-up process reverted to the starting material, as it did initially appear as a separate product.

Overall, the use of MWI decreased reaction times significantly, especially for those reactions involving the higher order anhydrides. Although it could not be fully tested without potential risk to the CEM microwave reactor, an approximate conversion of 1 hour MWI per day of thermal reaction was proposed and at least partially validated for the acylations utilizing Montmorillonite K-10 without significant lessening of the yields. As for the acylation method with bismuth triflate and lithium perchlorate the reaction times were significantly decreased, and the yields were significantly increased (88-94%).

The synthesis of 4-benzoyl-3-phenylsydnone was attempted to see if the MWI method could overcome the issues of the thermal reaction and produce the desired material. At 125°C for 1 hour the results did not show this to be the case. However, not all starting material had been converted so it may be of interest to future researchers to see if changing reaction times, temperatures and/or catalyst amounts could effect the desired change. It was also attempted to synthesize a novel compound, 4-(3-carboxypropanoyl)-3-phenylsydnone (9), and though it did appear that a product was formed by TLC examination this product was not stable and decomposed to the starting
material upon workup. It may be of interest to future researchers to attempt the trapping of the product formed by this reaction to try to identify what product is being formed.

Now that the foundations have been laid for the MWI synthesis using the most basic sydnone \( \mathbf{2} \) it would be ideal for future researchers to pursue the application of these processes to a variety of ortho-substituted compounds as potential routes to fused-ring sydnones. These processes can be advantageous routes to pursue because of the high yields produced after such short reaction times. However, there may need to be some testing to determine the optimum conditions for the ortho-substituted sydnone systems as they are more sterically hindered. It would also be ideal to examine other anhydrides besides the ones shown here as there is potential for the formation of novel sydnones.
Experimental

General notes:

All starting reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were acquired on a Nicolet 6700 FTIR. NMR spectra were acquired on a Bruker 300MHz NMR. Microwave reactions were run in the CEM Discover 300W Monomode commercial microwave.

Synthesis of 3-Phenylsydnone (2)

3-Phenylsydnone was synthesized from commercially available N-phenylglycine according to reported procedures.101

Synthesis of bismuth triflate

Bismuth triflate was synthesized from commercially available triphenyl-bismuthene according to reported procedures except that anhydrous dichloromethane is used instead of regular dichloromethane.99

General procedure for acylations of 3-phenylsydnone using Montmorillonite K-10 (Mont. K-10)

To a round bottom flask was added 3-phenylsydnone (~0.6 mmol), the appropriate anhydride (~5 mL) and Montmorillonite K-10 (6 weight equivalents). The mixture was stirred in an oil bath under reflux until complete conversion of the starting
material was achieved, which was assessed by TLC. The mixture was filtered, the clay washed and sonicated with several portions of dichloromethane and acetone. The combined organic layers were reduced under vacuum and then neutralized with a saturated sodium bicarbonate solution after addition of water to hydrolyze any left over anhydride. The aqueous layer was extracted with dichloromethane (3 x 50 mL) and dried (MgSO₄) then evaporated in vacuo. The crude material was then recrystallized from hot ethanol.

**Synthesis of 4-propanoyl-3-phenylsydnone (4) using Mont. K-10**

Using the general procedure, 3-phenylsydnone (0.1026 g), Montmorillonite K-10 (0.6300 g) and propionic anhydride (5 mL) were stirred under reflux for 4 days. The resulting oily solid was recrystallized from ethanol to give colorless crystals (0.0629 g, 50%), m.p. 85-86°C (Fisher 78-80°C).

I.R. (KBr): 3066.3, 2968.3, 2935.5, 2874.7, 1794.8 (sydnone C=O), 1663.2 (C=O), 1495.3, 1427.2, 1299.6, 1022.18, 961.5, 766.8, 689.0 cm⁻¹.

¹H-NMR (CDCl₃): 7.7 (m 5H), 2.9 (q, 2H), 1.1 (t, 3H) ppm.

¹³C-NMR (CDCl₃): 187.83 (C=O), 166.07 (sydnone C=O), 135.07, 132.28, 129.42, 124.89, 105.89 (sydnone C-4), 33.79, 7.13 ppm.

**Synthesis of 4-butanoyl-3-phenylsydnone (5) using Mont. K-10**

Using the general procedure, 3-phenylsydnone (0.1048 g), Montmorillonite K-10 (0.6116 g) and n-butyric anhydride (5 mL) were stirred under reflux for 7 days. The
resulting oily solid was recrystallized from ethanol to give pale yellow needle like crystals (0.0378 g, 28%), m.p. 64-65°C (Fisher 62-64°C).

I.R. (KBr): 3067.1, 2963.6, 2931.3, 2873.1, 1760.3 (sydnone C=O), 1663.9 (C=O), 1511.92, 1424.3, 1306.2, 997.8 cm⁻¹.

¹H-NMR (CDCl₃): 7.6 (m 5H), 2.9 (t, 2H), 1.7 (m, 2H) 1.0 (t, 3H) ppm.

¹³C-NMR (CDCl₃): 187.32 (C=O), 166.03 (sydnone C=O), 151.11, 132.26, 129.42, 124.89, 105.89 (sydnone C-4), 42.08, 16.83, 13.62 ppm.

**Synthesis of 4-isobutanoyl-3-phenylsydnone (6) using Mont. K-10**

Using the general procedure, 3-phenylsydnone (0.1023 g), Montmorillonite K-10 (0.6105 g) and isobutyric anhydride (5 mL) were stirred under reflux for 8 days. The resulting oily solid was recrystallized from ethanol to give pale yellow crystals (0.0733 g, 54%), m.p. 109-111°C (Fisher 105-106°C).

I.R. (KBr): 3066.1, 2970.6, 2932.3, 2873.1, 1773.3 (sydnone C=O), 1602.3 (C=O), 1566.92, 1420.3, 1158.8, 992.5 cm⁻¹.

¹H-NMR (CDCl₃): 7.6 (m 5H), 3.6 (m, 1H), 1.2 (d, 6H) ppm.

¹³C-NMR (CDCl₃): 191.60 (C=O), 165.55 (sydnone C=O), 135.22, 132.21, 129.44, 124.76, 105.47 (sydnone C-4), 39.96, 17.76 ppm.

**Attempted synthesis of 3-phenyl-4-benzoylsydnone (7) using Mont. K-10**

Using the general procedure, 3-phenylsydnone (0.1009 g), Montmorillonite K-10 (0.6033 g), benzoic anhydride (0.4721 g, 4 equivalents) and dioxane (2 mL, solvent) were stirred under reflux at 100°C. After 7 days there were faint signs of product formation via
TLC, however after 18 days the reaction did not progress. As such, the process was not pursued farther.

**Attempted synthesis of 3-phenyl-4-trifluoroacetyl sydnone (8) using Mont. K-10**

Using the general procedure, 3-phenylsydnone (0.1027 g), Mont. K-10 (0.6185 g) and trifluoroacetic anhydride (2 mL) were stirred at room temperature for two days. TLC showed no reaction so the temperature was increased to 40°C. After 5 days there was still no sign of reaction, despite addition of more anhydride, at which point it was decided not to pursue the reaction any further.

**General procedure for the acylation of 3-phenylsydnone using Mont. K-10 under Microwave Irradiation (MWI)**

To a microwave vessel was added 3-phenylsydnone (~0.6 mmol), anhydride (~5 mL), Montmorillonite K-10 clay (6 weight equivalents), and a stir bar. The reaction vessel was sealed with a crimp cap and placed in a 300 W, monomode CEM Discover. The reaction mixtures were microwaved at 150°C or the temperature otherwise indicated until complete conversion of starting material, which was assessed by TLC. The mixture was filtered and the clay was sonicated with multiple washes of dichloromethane and acetone then filtered. The combined organic layers were reduced under vacuum and then neutralized with a sodium bicarbonate solution. The water layer was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were dried (MgSO₄) and evaporated in vacuo. The crude material was then columned on the CombiFlash
instrument (12 g silica gel column, gradient of hexanes to dichloromethane to acetone) to yield the desired material.

**Attempted synthesis of 3 using Mont. K-10 and MWI for 1 hour at 130°C**

Using the general procedure, 3-phenylsydnone (0.1035 g), Mont. K-10 (0.6013 g) and acetic anhydride (5 mL) were stirred under MWI for 1 hour at 130°C. TLC analysis showed conversion, but not full conversion. Column chromatography of the crude product yielded 0.020 g (20%) of 3.

**Attempted synthesis of 3 using Mont. K-10 and MWI for 1 hour at 140°C**

Using the general procedure, 3-phenylsydnone (0.0890 g), Mont. K-10 (0.6600 g) and acetic anhydride (5 mL) were stirred under MWI for 1 hour at 140°C. TLC analysis showed conversion, but not full conversion. Column chromatography of the crude product yielded 0.028 g (27%) of 3.

**Attempted synthesis of 3 using Mont. K-10 and MWI for 2 hours at 140°C**

Using the general procedure, 3-phenylsydnone (0.1065 g), Mont. K-10 (0.6359 g) and acetic anhydride (5 mL) were stirred under MWI for 2 hour at 140°C. TLC analysis showed conversion, but not full conversion. Column chromatography of the crude product yielded 0.040 g (31%) of 3.

**Attempted synthesis of 3 using Mont. K-10 and MWI for 0.5 hour at 150°C**
Using the general procedure, 3-phenylsydnone (0.0992 g), Mont. K-10 (0.6780 g) and acetic anhydride (5 mL) were stirred under MWI for 0.5 hour at 150°C. TLC analysis showed conversion, but not full conversion. Column chromatography of the crude product yielded 0.050 g (43%) of 3.

**Attempted synthesis of 3 using Mont. K-10 and MWI for 1 hour at 150°C**

Using the general procedure, 3-phenylsydnone (0.1057 g), Mont. K-10 (0.6190 g) and acetic anhydride (5 mL) were stirred under MWI for 1 hour at 150°C. TLC analysis showed conversion, but not full conversion. Column chromatography of the crude product yielded 0.0484 g (40%) of 3.

**Attempted synthesis of 3 using Mont. K-10 and MWI for 1.5 hours at 150°C**

Using the general procedure, 3-phenylsydnone (0.1043 g), Mont. K-10 (0.6115 g) and acetic anhydride (5 mL) were stirred under MWI for 1.5 hour at 150°C. TLC analysis showed conversion, but not full conversion. Column chromatography of the crude product yielded 0.0325 g (28%) of 3.

**Attempted synthesis of 3 using Mont. K-10 and MWI for 2 hour at 150°C**

Using the general procedure, 3-phenylsydnone (0.1019 g), Mont. K-10 (0.6111 g) and acetic anhydride (5 mL) were stirred under MWI for 2 hour at 150°C. TLC analysis showed conversion, but not full conversion. Column chromatography of the crude product yielded 0.0309 g (26%) of 3.
Attempted synthesis of 3 using Mont. K-10 and MWI for 1 hour at 150°C with modifications

Using the general procedure, 3-phenylsydnone (0.1009 g), Mont. K-10 (0.5874 g), but with less acetic anhydride (1 mL) to increase the concentration of the reaction mixture, were stirred for 1 hour at 150°C. During workup, one additional change was made: while rinsing the clay, sonication was performed each time more solvent was added to the clay to facilitate removal of the crude product from the Mont. K-10. TLC showed more conversion and upon workup 0.0567 g (50%) of 3 was recovered.

Synthesis of 3 using Mont. K-10 and MWI for 1.5 hours at 150°C with modifications

Using the modified method (see previous entry) 3-phenylsydnone (0.1109 g), Mont. K-10 (0.6075 g) and acetic anhydride (1 mL) were stirred under MWI for 1.5 hour at 150°C. TLC analysis showed full conversion. Column chromatography of the crude product yielded 0.0716 g (55%) of 3.

Attempted synthesis of 4 using Mont. K-10 and MWI for 1.5 hours at 150°C

Using the modified general procedure, 3-phenylsydnone (0.1030 g), Mont. K-10 (0.6233 g) and propionic anhydride (1 mL) were stirred under MWI for 1.5 hours at 150°C. TLC analysis showed only partial conversion to 4.

Attempted synthesis of 4 using Mont. K-10 and MWI for 2 hours at 150°C
Using the modified general procedure, 3-phenylsydnone (0.1050 g), Mont. K-10 (0.6233 g) and propionic anhydride (1 mL) were stirred under MWI for 2 hours at 150°C. TLC analysis showed only partial conversion to 4.

**Attempted synthesis of 4 using Mont. K-10 and MWI for 2.5 hours at 150°C**

Using the modified general procedure, 3-phenylsydnone (0.1050 g), Mont. K-10 (0.5950 g) and propionic anhydride (1 mL) were stirred under MWI for 2.5 hours at 150°C. TLC analysis showed only partial conversion to 4.

**Attempted synthesis of 4 using Mont. K-10 and MWI for 3 hours at 150°C**

Using the modified general procedure, 3-phenylsydnone (0.1022 g), Mont. K-10 (0.5971 g) and propionic anhydride (1 mL) were stirred under MWI for 3 hours at 150°C. TLC analysis showed only partial conversion to 4.

**Synthesis of 4 using Mont. K-10 and MWI for 4 hours at 150°C**

Using the modified general procedure, 3-phenylsydnone (0.1001 g), Mont. K-10 (0.5963 g) and propionic anhydride (1 mL) were stirred under MWI for 1.5 hours at 150°C. TLC analysis showed complete conversion and recrystallization yielded 0.0637 g (51%) of 4.

**Attempted synthesis of 5 using Mont. K-10 and MWI for 6 hours at 150°C**

Using the modified general procedure, 3-phenylsydnone (0.1010 g), Mont. K-10 (0.6980 g) and n-butyric anhydride (1 mL) were stirred under MWI for 6 hours at 150°C. TLC
analysis showed nearly complete conversion and column chromatography yielded 0.041 g (31%) of 5.

**Attempted synthesis of 8 using Mont. K-10 and MWI**

Using the general procedure, 3-phenylsydnone (0.1018 g), Mont. K-10 (0.6185 g) and trifluoroacetic acid (1 mL) were stirred under MWI at 150°C. However, after a few minutes heating the pressure built to the point the safety mechanism of the CEM halted the reaction. It was not deemed safe to pursue this reaction further.

**General procedure for the synthesis of 4-acyl-3-phenylsydrones using bismuth triflate and lithium perchlorate under MWI**

To a microwave vessel was added 3-phenylsydnone (0.6 mmol), bismuth triflate (25 mole%), lithium perchlorate (25 mole%), acetonitrile (1.5 mL) and anhydride (4 molar equivalents). The reaction vessel was sealed with a crimp cap and placed in a 300 W, monomode CEM Discover. The reaction mixtures were microwaved at 125°C until complete conversion of starting material, which was assessed by TLC. The mixture was transferred to a separatory funnel by a portion of dichloromethane, neutralized (10% NaHCO₃) and then extracted (3 x 15 mL DCM). The combined organic layers were dried (MgSO₄) and evaporated in vacuo. The crude material was then columned via the CombiFlash (12 g silica gel column, gradient of hexanes to dichloromethane to acetone) to yield the desired material.
Attempted synthesis of 3 using freshly made bismuth triflate and MWI at 100°C for 30 minutes

Using the general procedure, 3-phenylsydnone (0.0521 g, 0.308 mol), freshly made Bi(OTf)$_3$ (0.0522 g), LiClO$_4$ (0.0108 g), acetonitrile (1.5 mL) and acetic anhydride (0.070 mL) were stirred under MWI at 100°C for 15 minutes. TLC showed little conversion so the reaction was run for another 15 minutes, for a total of 30 minutes. TLC analysis showed incomplete conversion of the starting material but column chromatography yielded 0.0423 g (69%) of the expected product 3.

Attempted synthesis of 3 using freshly made bismuth triflate and MWI at 125°C for 15 minutes

Using the general procedure, 3-phenylsydnone (0.1095 g), freshly made Bi(OTf)$_3$ (0.1035 g), LiClO$_4$ (0.0155 g), acetonitrile (1.5 mL) and acetic anhydride (0.070 mL) were stirred under MWI at 125°C for 15 minutes. TLC analysis showed incomplete conversion of the starting material and column chromatography yielded 0.0622 g (53%) of the expected product 3.

Attempted synthesis of 3 using freshly made bismuth triflate and MWI at 150°C for 15 minutes

Using the general procedure, 3-phenylsydnone (0.1059 g), freshly made Bi(OTf)$_3$ (0.1016 g), LiClO$_4$ (0.0204 g), acetonitrile (1.5 mL) and acetic anhydride (0.070 mL) were stirred under MWI at 150°C for 15 minutes. TLC analysis showed incomplete
conversion of the starting material but column chromatography yielded 0.0938 g (80%) of the expected product 3.

Synthesis of 3 using freshly made bismuth triflate and MWI at 125°C for 30 minutes

Using the general procedure, 3-phenylsydnone (0.1050 g), freshly made Bi(OTf)$_3$ (0.1035 g), LiClO$_4$ (0.0160 g), acetonitrile (1.5 mL) and acetic anhydride (0.070 mL) were stirred under MWI at 125°C for 30 minutes. TLC analysis showed complete conversion of the starting material and column chromatography yielded 0.1156 g (94%) of the expected product 3.

Attempted synthesis of 3 using Aldrich bismuth triflate and MWI at 100°C for 30 minutes

Using the general procedure, 3-phenylsydnone (0.1021 g), Aldrich Bi(OTf)$_3$ (0.1090 g), LiClO$_4$ (0.0173 g), acetonitrile (1.5 mL) and acetic anhydride (0.070 mL) were stirred under MWI at 100°C for 30 minutes. TLC analysis showed incomplete conversion of the starting material and column chromatography yielded 0.0241 g (20%) of the expected product 3.

Attempted synthesis of 3 using Aldrich bismuth triflate and MWI at 125°C for 15 minutes

Using the general procedure, 3-phenylsydnone (0.0996 g), Aldrich Bi(OTf)$_3$ (0.1011 g), LiClO$_4$ (0.0159 g), acetonitrile (1.5 mL) and acetic anhydride (0.070 mL) were stirred under MWI at 125°C for 15 minutes. TLC analysis showed incomplete
conversion of the starting material and column chromatography yielded 0.0748 g (60%) of the expected product 3.

**Attempted synthesis of 3 using Aldrich bismuth triflate and MWI at 150°C for 15 minutes**

Using the general procedure, 3-phenylsydnone (0.1044 g), Aldrich Bi(OTf)₃ (0.1081 g), LiClO₄ (0.0181 g), acetonitrile (1.5 mL) and acetic anhydride (0.070 mL) were stirred under MWI at 150°C for 15 minutes. TLC analysis showed incomplete conversion of the starting material and column chromatography yielded 0.0603 g (52%) of the expected product 3.

**Attempted synthesis of 4 using Aldrich bismuth triflate and MWI at 150°C for 15 minutes**

Using the general procedure, 3-phenylsydnone (0.1015 g), Aldrich Bi(OTf)₃ (0.1016 g), LiClO₄ (0.0203 g), acetonitrile (1.5 mL) and propionic anhydride (0.310 mL) were stirred under MWI at 150°C for 15 minutes. TLC analysis showed incomplete conversion of the starting material and column chromatography yielded 0.0453 g (37%) of the expected product 4.

**Attempted synthesis of 5 using Aldrich bismuth triflate and MWI at 150°C for 15 minutes**

Using the general procedure, 3-phenylsydnone (0.0999 g), Aldrich Bi(OTf)₃ (0.1014 g), LiClO₄ (0.0195 g), acetonitrile (1.5 mL) and n-butyric anhydride (0.3900 mL)
were stirred under MWI at 150°C for 15 minutes. TLC analysis showed incomplete conversion of the starting material and column chromatography yielded 0.0326 g (24%) of the expected product 5.

**Attempted synthesis of 6 using Aldrich bismuth triflate and MWI at 150°C for 15 minutes**

Using the general procedure, 3-phenylsydnone (0.1030 g), Aldrich Bi(OTf)$_3$ (0.1015 g), LiClO$_4$ (0.0179 g), acetonitrile (1.5 mL) and isobutyric anhydride (0.3900 mL) were stirred under MWI at 150°C for 15 minutes. TLC analysis showed incomplete conversion of the starting material and column chromatography yielded 0.0484 g (36%) of the expected product 6.

**Attempted synthesis of 4 using freshly made bismuth triflate and MWI at 150°C for 15 minutes**

Using the general procedure, 3-phenylsydnone (0.1016 g), freshly made Bi(OTf)$_3$ (0.1032 g), LiClO$_4$ (0.0156 g), acetonitrile (1.5 mL) and propionic anhydride (0.310 mL) were stirred under MWI at 150°C for 15 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0526 g (42%) of the expected product 4.

**Attempted synthesis of 4 using freshly made bismuth triflate and MWI at 125°C for 15 minutes**
Using the general procedure, 3-phenylsydnone (0.1050), freshly made Bi(OTf)$_3$ (0.1047 g), LiClO$_4$ (0.0165 g), acetonitrile (1.5 mL) and propionic anhydride (0.310 mL) were stirred under MWI at 125°C for 15 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0685 g (55%) of the expected product 4.

**Attempted synthesis of 4 using freshly made bismuth triflate and MWI at 150°C for 30 minutes**

Using the general procedure, 3-phenylsydnone (0.1059), freshly made Bi(OTf)$_3$ (0.1061 g), LiClO$_4$ (0.0269 g), acetonitrile (1.5 mL) and propionic anhydride (0.310 mL) were stirred under MWI at 150°C for 30 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0675 g (55%) of the expected product 4.

**Attempted synthesis of 4 using freshly made bismuth triflate and MWI at 125°C for 30 minutes**

Using the general procedure, 3-phenylsydnone (0.1049), freshly made Bi(OTf)$_3$ (0.1039 g), LiClO$_4$ (0.0166 g), acetonitrile (1.5 mL) and propionic anhydride (0.310 mL) were stirred under MWI at 125°C for 30 minutes. TLC analysis showed almost complete conversion of the starting material and column chromatography yielded 0.1218 g (92%) of the expected product 4.
Attempted synthesis of 5 using freshly made bismuth triflate and MWI at 150°C for 15 minutes

Using the general procedure, 3-phenylsydnone (0.1028), freshly made Bi(OTf)$_3$ (0.1065 g), LiClO$_4$ (0.0195 g), acetonitrile (1.5 mL) and n-butyric anhydride (0.390 mL) were stirred under MWI at 150°C for 15 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0561 g (43%) of the expected product 5.

Attempted synthesis of 5 using freshly made bismuth triflate and MWI at 125°C for 15 minutes

Using the general procedure, 3-phenylsydnone (0.1040), freshly made Bi(OTf)$_3$ (0.1059 g), LiClO$_4$ (0.0167 g), acetonitrile (1.5 mL) and n-butyric anhydride (0.390 mL) were stirred under MWI at 125°C for 15 minutes. TLC analysis showed almost complete conversion of the starting material and column chromatography yielded 0.1196 g (88%) of the expected product 5.

Attempted synthesis of 5 using freshly made bismuth triflate and MWI at 150°C for 30 minutes

Using the general procedure, 3-phenylsydnone (0.1062), freshly made Bi(OTf)$_3$ (0.1094 g), LiClO$_4$ (0.0194 g), acetonitrile (1.5 mL) and n-butyric anhydride (0.390 mL) were stirred under MWI at 150°C for 30 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0492 (36%) of the expected product 5.
Synthesis of 5 using freshly made bismuth triflate and MWI at 125°C for 30 minutes

Using the general procedure, 3-phenylsydnone (0.1054), freshly made Bi(OTf)$_3$ (0.1067 g), LiClO$_4$ (0.0201 g), acetonitrile (1.5 mL) and n-butyric anhydride (0.390 mL) were stirred under MWI at 125°C for 30 minutes. TLC analysis showed near complete conversion of the starting material and column chromatography yielded 0.1170 g (88%) of the expected product 5.

Attempted synthesis of 5 using freshly made bismuth triflate and MWI at 125°C for 45 minutes

Using the general procedure, 3-phenylsydnone (0.1063), freshly made Bi(OTf)$_3$ (0.1059 g), LiClO$_4$ (0.0170 g), acetonitrile (1.5 mL) and n-butyric anhydride (0.390 mL) were stirred under MWI at 125°C for 45 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0737 (55%) of the expected product 5.

Attempted synthesis of 6 using freshly made bismuth triflate and MWI at 150°C for 15 minutes

Using the general procedure, 3-phenylsydnone (0.1052), freshly made Bi(OTf)$_3$ (0.1068 g), LiClO$_4$ (0.0207 g), acetonitrile (1.5 mL) and isobutyric anhydride (0.390 mL) were stirred under MWI at 150°C for 15 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0373 g (28%) of the expected product 6.
Attempted synthesis of 6 using freshly made bismuth triflate and MWI at 125°C for 15 minutes

Using the general procedure, 3-phenylsydnone (0.1013), freshly made Bi(OTf)$_3$ (0.1043 g), LiClO$_4$ (0.0180 g), acetonitrile (1.5 mL) and isobutyric anhydride (0.390 mL) were stirred under MWI at 125°C for 15 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0172 g (2%) of the expected product 6.

Attempted synthesis of 6 using freshly made bismuth triflate and MWI at 125°C for 30 minutes

Using the general procedure, 3-phenylsydnone (0.1049), freshly made Bi(OTf)$_3$ (0.1048 g), LiClO$_4$ (0.0177 g), acetonitrile (1.5 mL) and isobutyric anhydride (0.390 mL) were stirred under MWI at 125°C for 30 minutes. TLC analysis showed some conversion of the starting material and column chromatography yielded 0.0390 g (30%) of the expected product 6.

Synthesis of 6 using freshly made bismuth triflate and MWI at 125°C for 45 minutes

Using the general procedure, 3-phenylsydnone (0.1045), freshly made Bi(OTf)$_3$ (0.1032 g), LiClO$_4$ (0.0194 g), acetonitrile (1.5 mL) and isobutyric anhydride (0.390 mL) were stirred under MWI at 125°C for 45 minutes. TLC analysis showed almost complete conversion of the starting material and column chromatography yielded 0.1297 g (92%) of the expected product 6.
Attempted synthesis of 7 using freshly made bismuth triflate and MWI at 125°C for 1 hour

Using the general procedure, 3-phenylsydnone (0.1048), freshly made Bi(OTf)$_3$ (0.1059 g), LiClO$_4$ (0.0207 g), acetonitrile (1.5 mL) and benzoic anhydride (0.4721 g) were stirred under MWI at 125°C for 1 hour. TLC analysis showed the formation of products and the presence of unconverted starting material. The first product seemed most prevalent by TLC, however column chromatography yielded less than 1 mg of material. The second combined fraction from the column was identified as benzoic acid. A majority of the starting material (0.1015 g) was recovered.

Attempted synthesis of 9 using freshly made bismuth triflate and MWI at 125°C for 1 hour

Using the general procedure, 3-phenylsydnone (0.1050), freshly made Bi(OTf)$_3$ (0.1068 g), LiClO$_4$ (0.0195 g), acetonitrile (1.5 mL) and succinic anhydride (0.242 g) were stirred under MWI at 125°C for 1 hour. TLC analysis showed formation of one product (about 40% conversion, seemingly, and of a higher R$_f$ than the starting material) and unreacted starting material. The reaction mixture was worked up and columned on the CombiFlash. The UV-VIS detector on the CombiFlash detected and separated two unique fractions, the later of which was the unreacted starting material. However, upon workup IR, $^1$H and $^{13}$C NMR spectral data all identified the first combined fraction as the starting material. The fraction and the starting material were again analyzed by TLC and this time showed as the same spot. It was decided that whatever product was formed must
not have been stable and was reduced to the starting material when exposed to the air after column chromatography, while still in solution.
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