Bismuth Triflate Catalyzed Friedel-Crafts Acylations of Sydnones

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BISMUTH TRIFLATE CATALYZED FRIEDEL-CRAFTS ACYLATIONS OF SYDNONES

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

By

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B.S., Miami University, 2003

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Abstract


In the present work, suitably functionalized arylsydnones were used to synthesize a variety of 4-acyl-sydnones and diacyl sydnones, both as potential precursors to novel sydnoquinolines. The approach to the diacyl species is based on the discovery that activated sydnones brominate in both the 4 position of the sydnone ring and on the phenyl ring. Thus, it seemed likely that Friedel-Crafts reactions on an activated sydnone would give diacylated species for McMurray coupling to sydnoquinolines.

Friedel-Crafts acylations on the 4 position of the sydnone ring have been achieved in high yields using 4 equivalents of various alkyl anhydrides, 25 mol % of bismuth triflate and lithium perchlorate in anhydrous acetonitrile at 95 °C. Various para-substituted phenyl sydnones with different electron withdrawing and electron donating substituents were used to explore the effect of the attachment on the reaction time and yields of the acylation with acetic anhydride. Additionally, four other alkyl anhydrides were employed to test their utility with phenyl sydnone. The reaction times were consistent with the electron withdrawing or donating nature of the para substituents.
Thus, electron-donating groups appeared to speed up the process, whereas the reactions were slower in the presence of electron-withdrawing moieties. The reaction times involving phenylsydnone and other alkyl anhydrides were consistent with the steric hindrance of the anhydride; bulkier species leading to longer reaction times.

With optimized conditions available for the monoacylation process, it was of interest to explore diacylation using the activated sydnone, 3-(3, 5-dimethoxyphenyl) sydnone. Many attempts were made to prepare the diacyl sydnone, but no methods thus far have given only the desired diacyl product. For example, when the activated sydnone was reacted under the standard conditions with acetic anhydride, two different products were isolated. They were identified by $^1$H and $^{13}$C NMR as the desired 4-acetyl-3-(2-acetyl-3, 5-dimethoxyphenyl) sydnone and the mono-acyl contaminant 4-acetyl-3-(3, 5-dimethoxyphenyl) sydnone. Variations of the amount of catalysts and the anhydride have been employed in an attempt to achieve complete conversion. Further studies are focusing on optimizing this process.
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Introduction

Foreword

Over 120 years ago, Emil Fischer oxidized dithizone; yielding an orange, crystalline compound he entitled dehydrodithizone. Fischer assigned the bicyclic structure 1 to this species, however, better understanding of the nature of such species was gained as time progressed and more advanced analytical techniques became available. In 1946, Baker, Ollis, and Poole\textsuperscript{2} coined the term mesoionic (mesomeric/ionic) to describe the monocyclic, dipolar nature of compounds such as dehydrodithizone. In 1955, these three authors published a paper in \textit{Chemistry and Industry} which specifically defined the term mesoionic. Using their definition, dehydrodithizone is considered the first known mesoionic species and is assigned the dipolar, monocyclic structure 2.\textsuperscript{3}

Arguably, the most important member of the mesoionic category of compounds is the sydnone ring system. Sydnones are dipolar, pseudo-aromatic heterocycles with a unique variation in electron density around the ring. These characteristics have
encouraged extensive study of the chemical, physical, and biological properties of sydnones, as well as their potential applications.

There are numerous reviews on mesoionic heterocycles (including sydnones) that can be found through 1989. Additionally, there are several M.S. Theses that have come from this laboratory, and these fill in discoveries related to sydnones covering the years 1989-2003. The review that follows will serve to acquaint the reader with some of the more important features of previous sydnone work, as well as to summarize pertinent sydnone chemistry that has occurred from 2003 to 2005.

**Historical**

In 1935, the first sydnone was synthesized in Sydney, Australia. Earl and Mackney reported\(^5\) that treatment of N-nitroso-N-phenylglycine (3; \(R=H, R'=\text{Ph}\)) with acetic anhydride afforded a neutral, anhydro derivative to which the bicyclic structure 4 (\(R=H, R'=\text{Ph}\)) was assigned. Due to the general utility of the reaction a variety of analogous compounds were prepared and given the name “sydnone” (due to their preparation in Sydney, Australia).

\[
\begin{align*}
\text{3} & \quad \text{R'} \quad \text{N} \quad \text{N} \quad \text{CH} \quad \text{R} \quad \text{CO}_2\text{H} \\
\text{Ac}_2\text{O} & \quad \rightarrow \\
\text{4} & \quad \text{R'} \quad \text{N} \quad \text{N} \quad \text{C} \quad \text{R} \quad \text{O} \quad \text{C}=\text{O}
\end{align*}
\]
As the chemical and physical properties of the sydnones were studied in more detail it became obvious that structure 4 was in fact inaccurate. Sydnones show evidence of a greater degree of polarity, stability towards heating, and lower reactivity towards acids and bases than would be predicted for the strained, bicyclic representation 4. Thus, in the 1940’s, Baker, Ollis and Poole\(^2\) published a series of papers in which they concluded that sydnones were in fact monocyclic, dipolar derivatives of oxadiazolone. Many possible resonance hybrids allow for multiple canonical representations (5a-h), for which structure 5 is the preferred representation.

Baker, Ollis, and Poole also suggested that sydnones should be placed in a class by themselves called mesoionic (meaning mesomeric/ionic), because of the unique characteristics of the sydnone ring system. They proceeded to outline the general concepts governing their electronic structure until formal qualifications for a compound to be deemed mesoionic were set forth in 1953\(^3\). It was then proposed that to be considered mesoionic, a compound should: (1) contain a fully delocalized positive and
negative charge; (2) be planar and contain a five-membered heterocyclic ring with an exocyclic atom or group capable of bearing a considerable amount of negative charge density; and (3) possess a considerable resonance energy. These three characteristics allowed mesoionic systems to be clearly distinguished from formally related dipolar species such as ylides and zwitterions. In the latter species, there is a great deal of charge localization whereas in the mesoionic systems, charge distribution is delocalized and no single fitting resonance form can be drawn.

Formally, sydnones are derivatives of 1,2,3-oxadiazoles; however, since 1,2,3-oxadiazoles are known to be open chain, alpha carbonyl diazo derivatives, it appears that sydnones are the only derivatives of this class that are cyclic in nature. Therefore, the name “sydnone” has become the most common way to describe these compounds because of this unique distinction, and is used by Chemical Abstracts as a way of grouping these oxadiazole derivatives.
Physiochemical Properties and Electronic Structure

With few exceptions, sydnones are stable compounds that exhibit significant polarity. Aryl sydnones are generally crystalline solids while alkyl sydnones are often liquids or low-melting solids that can be distilled in vacuo without appreciable decomposition. Sydnones are soluble in many organic solvents with the main exceptions being non-polar solvents such as petroleum ether and hexanes. Furthermore, sydnones are generally not water-soluble unless a substituent is a polar functional group.

In their NMR spectra, the proton (when present) at the C-4 position of the sydnone ring is greatly deshielded in comparison to saturated congeners, usually appearing between 6.5-7.5 ppm (depending on solvent). This, then, suggests a polar nature and the presence of an aromatic ring current and, therefore, the invalidity of structure 4. Additionally, the infrared spectra of sydnones include two very prominent features: a strong carbonyl stretch at ~ 1730-1760 cm\(^{-1}\) and a stretch of medium intensity at ~ 3150 cm\(^{-1}\) for the C-H absorption of the C-4 ring proton (when present).\(^6\) Moreover, the latter is different from what would be expected for either an alkyl or aryl substituent or from an epoxide with comparable ring strain, which absorb around 2900-3050 cm\(^{-1}\), and, therefore, is particularly useful in determining if the C-4 position is substituted in sydnones of unresolved structure.

With regard to the carbonyl stretch, a single, strong band is usually observed. However, due to Fermi resonance splitting, in some cases multiple bands have been seen.\(^7\) Furthermore, as was stated above, the sydnone carbonyl typically appears at ~ 1730-1760 cm\(^{-1}\) but, in comparison with congeneric carbonyl containing species, such as a \(\gamma\)-lactone (6) [which absorbs at 1770 cm\(^{-1}\)] and tropone (7) [which absorbs at 1638 cm\(^{-1}\)].
cm$^{-1}$, one might conclude that the exocyclic C=O bond at the sydnone C-5 position is closer in length to that of a double bond than a single bond.

This argument is further supported by the results of X-ray crystallographic analysis of various 3-substituted and 3,4-disubstituted sydnones which show that this C=O bond is closer in length to that of a double bond.$^7$ However, integrated absorption measurements$^7$ suggest that a high degree of carbonyl bond polarization, rather than bond strength, is responsible for the relatively high energy of absorption. Additionally, molecular orbital calculations and vibrational force constants obtained from vibrational spectra indicate a π-bond order for the sydnone carbonyl lower than those for alicyclic esters$^8$, thus supporting the argument that contributions from other vibrational modes cause the sydnone carbonyl group to absorb at a higher frequency than anticipated. Furthermore, it has been demonstrated, by both theoretical and spectroscopic studies, that protonation of a sydnone moiety occurs at the exocyclic oxygen.$^9$ This, then, complements earlier work in which bond orders and charge densities of various sydnones were correlated to the calculated and observed dipole moments and the observed UV maxima.$^{10}$ Thus, these studies support the contention that substantial charge density resides on the exocyclic oxygen.
Synthesis

Since their original preparation in 1935, the only general route to sydnones is still via the cyclodehydration of an N-substituted N-nitroso-α-amino acid (cf. 3). While the substituent R can be alkyl, aryl, or hydrogen, the R' substituent must be alkyl or aryl, since when R' is a hydrogen, prototropy occurs to afford a neutral species. The preparation of the N-nitrosoamino acid usually involves the nitrosation of an N-substituted glycine 8 with nitrous acid. Since this nitrosation step requires the use of strongly acidic reaction conditions, sydnones containing acid-sensitive functional groups have been unattainable by this method. However, a variation upon this standard method has been developed in which nitrosation is effected under neutral conditions using isoamyl nitrite and dimethoxyethane. Thus, some otherwise unattainable sydnones are able to be successfully generated in good to excellent yield.

\[
\begin{align*}
\text{H}_2\text{O} \quad \text{(TFAA)} \\
R'\text{N} - \text{CH}_2 - \text{R} \quad \xrightarrow{\text{HONO} \text{ or } \text{ONO}_3} \quad \text{N} \text{-}\text{CH}_2 \text{R} \quad \xrightarrow{-\text{H}_2\text{O}} \quad \text{N} \text{-}\text{C}_\text{O}_2\text{H} \\
\end{align*}
\]

With regard to the cyclodehydration step, Earl and Mackney originally employed acetic anhydride at room temperature for six days. Since then, several modifications have been useful and now include: heating in acetic anhydride or thionyl chloride; treatment with phosphorus pentoxide; or the use of trifluoroacetic anhydride (TFAA). The reaction with TFAA has become the method of choice since it usually occurs rapidly
(<15 minutes), at low temperature (-5 °C to 0 °C) and in high yields (>90% for N-phenylsydnone). The only drawback to its use is the far greater cost of this reagent compared to the others.

Newer synthetic strategies for accomplishing the aforementioned cyclization have been put forth. Among these are the use of: (1) acetic anhydride at room temperature facilitated by ultrasonification\textsuperscript{12}; (2) haloiminium salts\textsuperscript{13}; (3) N,N-dimethylchloro-sulfitemethaninium chloride\textsuperscript{14}, and (4) 2-chloro-1,3-dimethylimidazolinium chloride\textsuperscript{15}. These new methods are interesting however; it is unlikely they will replace the fast, efficient, and reliable TFAA cyclization.
Chemical and Biological Behavior

From the aforementioned studies, (see Physiochemical Properties and Electronic Structure) it can be concluded that the sydnone ring possesses a distinct aromatic nature and a dichotomy in electronic effects. In fact, a large effort has been directed towards revealing how these characteristics are reflected in the chemical behavior of sydnones. The aromatic nature of the sydnone ring as well as an intrinsic property of any aromatic system is to undergo electrophilic substitution with retention of aromaticity. Thus, a great deal of work has been done to show that sydnones do undergo electrophilic aromatic substitution at the C-4 position of the ring (cf. 5, R=H). Typically, such reactions include halogenation, nitration, acylation, and sulfonation; all of which will be discussed further in the following pages. The high regioselectivity of these reactions (even when an aryl group is attached to the N-3 position) has been attributed to two factors: (1) the considerable partial negative charge that resides at the C-4 position appears to activate this position; and (2) the considerable partial positive charge that resides at the N-3 position seems to deactivate the juxtaposed aryl ring.

Even more interesting is the possibility that activating groups attached to the aryl ring might allow the aryl moiety to compete successfully for the electrophile, thus providing a route to what otherwise might be inaccessible sydnone derivatives. Indeed, as will be discussed in the following pages, this premise has been realized for both bromination, acylation, and nitration.
Other major chemical reactions of sydnones include their use as precursors to hydrazines\(^5\) and their utility as 1,3-dipoles in cycloaddition reactions\(^{16}\) sydnones have been used as electrolytic solvents for non-aqueous batteries\(^{17}\) and their ability to aid micelle production in molecular aggregation.\(^{18}\) Additionally, certain sydnones have liquid crystal properties and have been incorporated into azo dyestuffs\(^{19}\) Perhaps, the most attractive of the many potential applications of sydnones, is their biological properties, which include anti-fungal, anti-inflammatory, analgesic, antibacterial, and anti-tumor activities. However, because the majority of the work in this thesis has dealt with Friedel-Crafts reactions of sydnones, and for the sake of brevity, these latter aspects will not be addressed.
Reactions of Sydnones

I. Substitution Reactions at the Sydnone C-4 Position

Many of the recently reported reactions take advantage of the fact that sydnones undergo electrophilic aromatic substitution at the C-4 position if there is a proton at this position (cf. 5, R=H). Furthermore, since the 4-position is known to have a considerable amount of negative charge density, electrophilic substitution occurs readily using electrophiles typically employed with benzene or other aromatic compounds. Commonly, sydnones undergo halogenation, nitration, acylation, sulfonation, and metellation. These will be discussed in the following pages to give the reader an overview of such chemistry.

A. Halogenation

Sydnones (cf. 9) can be halogenated at the C-4 position by use of a variety of conditions. 4-Bromination or 4-chlorination can be affected using either bromine or chlorine (cf. 11 or 10, respectively).\(^{20}\) It is also possible to use potassium chlorate in moderately concentrated HCl\(^2^1\) or dichloroiodobenzene with triethylamine\(^2^2\) in order to obtain the 4-chloro derivative 10. Additionally, it has been shown that either N-bromosuccinimide (NBS) or N-chlorosuccinimide (NCS) in dimethylformamide will afford analogous derivatives 11 or 10, respectively, when reacted at or below room temperature.\(^2^3\)
However, more difficulty has been encountered in the synthesis of 4-iodo sydnone species, 12, as they cannot be effected using the same conditions as bromination and chlorination. Nonetheless, it has been shown that iodine monochloride in acetic acid at room temperature will iodinate sydnones at the 4-position with relative ease.\textsuperscript{24}

The apparent ease with which sydnones could be brominated led to the postulation that the 4-bromo moiety (\textit{cf.} 11) could be used as a protecting group for the sydnone ring.\textsuperscript{25} Initial methods of de-bromination were somewhat vigorous, requiring high temperatures, long reaction times, and the use of reagents that were capable of reacting with other common functional groups. However, it has been shown that the use of sodium borohydride or sodium dithionite in methanol will effectively de-brominate the sydnone C-4 position in a very regiospecific fashion.\textsuperscript{26} While both methods have their drawbacks [\textit{e.g.} sodium borohydride is capable of reacting with pendent functional groups, (\textit{e.g.} aldehydes, ketones, esters, or carboxylic acids)] and sodium dithionite is apparently more susceptible to steric factors, the complementary nature of these two methods is apparent. Additionally, Tien and coworkers have demonstrated that 4-bromo derivatives can effectively be de-brominated in high yields and in a regioselective manner using activated zinc under ultrasonification.\textsuperscript{27} However, this method is not successful when strong electron-withdrawing groups are present and the approach of choice is
undoubtedly the use of sodium sulfite,\textsuperscript{28} which suffers from none of the previously mentioned disadvantages.

**B. Nitration**

Due to the strongly acidic conditions required to effect nitration, the possibility of this substitution on a sydnone moiety has been modestly investigated. However, upon reaction with potassium nitrate in the presence of nitric acid at -5 °C, 3-phenylsydnone (13) affords the relatively unstable 4-nitro derivative 14 in modest yield.\textsuperscript{29} Additionally, bis-sydnones apparently also undergo nitration at C-4 under similar conditions.\textsuperscript{6a}

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{O} \\
\text{H} \\
\text{Ph}
\end{array}
\xrightarrow{\text{KNO}_3/\text{HNO}_3 \text{ } -5 \text{ °C}}
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{C} \\
\text{NO}_2 \\
\text{O}
\end{array}
\]

Contrary to the situation with other electrophiles, sydnone nitration appears to be very competitive, in that any group attached to the aryl ring which is even slightly activating seems to facilitate nitration of the aryl ring in preference to the sydnone C-4 position. Thus, few examples exist in which the C-4 position has been successfully nitrated. Therefore, further discussion regarding sydnone nitration will be deferred until section III (Electrophilic Substitution on the Aryl Ring of 3-Arylsydnones).

**C. Acylation and Carboxamidation**

It had been reported\textsuperscript{30} that in the presence of a Lewis acid catalyst, it was not possible to acylate 3-phenylsydnone with either acetic anhydride or benzoyl chloride. However, Yashunskii showed that it was possible to obtain the 4-acetyl derivative (15; R = Me, R' = Ph) \textit{via} the use of acetic anhydride and boron trifluoride etherate.\textsuperscript{31}
Additionally, Tien and coworkers have acylated various substituted sydnones using acetic anhydride and HClO₄ or H₃PO₄.³² This same type of transformation has been reported by Greco and coworkers;³³ by heating various 3-substituted sydnones in the presence of a carboxylic acid and P₂O₅. However, it was noted that neither aryl nor aralkyl acids reacted, thus limiting the scope of this process. In fact, there is still no direct acylative route for the preparation of 4-arylsydnones, though; recent methodology has shown that these types of compounds can be prepared in a two-step process from a cuprosydnone (see section E, Metallation).

In the most recent literature regarding sydnone C-4 acylation, two novel approaches have been reported. Tien and coworkers²⁷ have shown that ultrasonification of 3-substituted sydnones in the presence of acetic anhydride and a catalytic amount of perchloric acid will afford the 4-acylated derivative quickly, in moderate yield. 4-Acetyl derivatives of 3-substituted sydnones also have been obtained by heating acetic anhydride and a catalytic amount of Montmorillonite K-10 at elevated temperatures.³⁴ This latter method is useful in that the catalyst can be easily removed and disposed of. However, one disadvantage is that the method is sluggish with compounds containing electron-withdrawing groups ortho to the sydnone ring and, in one case, led to sydnone cleavage.

In the past, 4-carboxamido sydnone species (cf. 16) have been prepared by a multi-step process involving abstracting the sydnone ring proton with butyllithium,
treatment with carbon dioxide, and subsequent conversion to the acid chloride followed by reaction with ammonia. More recently, a new method of carboxamidation at the sydnone 4-position was developed.\textsuperscript{35} Therein, using chlorosulfonyl isocyanate in acetonitrile at room temperature, Turnbull, Gross, and Hall prepared 4-carboxamido sydnones in good yield, directly from a variety of 3-substituted sydnones.

\[ \text{ClSO}_2\text{NCO} \quad \text{MeCN, rt} \quad \text{H}_2\text{O} \]

\[ \begin{align*}
R' &= \text{Ph, 3-MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 2,3-\text{Me}_2\text{C}_6\text{H}_3, \\
&\quad 2-\text{MeO}_2\text{C}, 2-\text{NO}_2, \text{PhCH}_2
\end{align*} \]

**D. Sulfonation**

Yashunskii and coworkers have reported the direct sulfonation of a variety of 3-substituted sydnones.\textsuperscript{36} Therein, it was shown that treatment of sydnones 9 with dioxane-sulfur trioxide complex (SO\textsubscript{3}) in CH\textsubscript{2}Cl\textsubscript{2} at 20 °C to 40 °C generated the sulfonated derivatives 17 (R' = 4-MeO- or 4-EtOC\textsubscript{6}H\textsubscript{4}), which were characterized as either the barium or S-benzylthiuronium salts. However, all attempts to isolate these compounds as the free acid via neutralization were unsuccessful and resulted in the isolation of the non-sulfonated sydnone 9.
E. Metallation

In the recent past, metallation has undoubtedly been the most thoroughly investigated pathway for substitution at the sydnone C-4 position. 4-Lithio, 4-cupro, 4-chloromercuro, and 4-palladium (0)\(^{37}\) or nickel (II)\(^{38}\) complexes have been prepared and their subsequent reactions investigated.

Of the aforementioned 4-metallo substituted sydnones, it appears that the 4-lithio species (cf. 18) is the most versatile in its applications. It is readily prepared either directly from 3-phenylsydnone (13) or indirectly from metal-halogen exchange of 4-bromo-3-phenylsydnone (19).\(^{39}\)

A wide variety of 4-substituted sydnones have been prepared via this method. The following examples are meant to give the reader a flavor for the applications in which it has been used and are not meant to be all-inclusive.

It has been shown that by reacting 18 with either alkyl or aryl disulfides or diselenides it is possible to obtain the 4-sydnonylsulfides 20, 4-sydnonylselenides 21, and their derivatives 22.\(^{40}\) Additionally, the bissydnonyl sulfide 23 and selenide 24 have been prepared in a similar manner by treating 18 with the appropriate dicyano disulfide or diselenide.\(^{41}\) Extension of this methodology to arsenic trichloride and diphenylchlorophosphorane\(^{42}\) resulted in the preparation of the corresponding sydnonylarsine 25 and phosphine 26, respectively. More recently, a variety of 4-carboxysydnones 27 have been prepared by carboxylation of 18 with carbon dioxide.\(^{43}\) Furthermore, Tien and
coworkers\textsuperscript{44} have shown that various 3-substituted sydnones can be lithiated and exposed \textit{in situ} to either N,N-dimethylformamide, N,N-dimethylacetamide, or acetaldehyde to afford the corresponding formylated 28, acetylated 29, or hydroxylated 30 derivatives, respectively.

The reactivity of sydnone metal species can be modified by changing the metal present at the 4-position. The sydnonyl cuprate 31, obtained by reacting 3-phenylsydnone 13 with butyl lithium and subsequent exposure to cupric bromide, is relatively stable at room temperature (in an inert atmosphere). In the presence of a Pd(0)
catalyst, this species can be coupled with vinyl or aryl halides to yield the 4-alkenyl 32 or 4-aryl 33 sydnones, respectively.  

Additionally, sydnonyl cuprate 31 can be coupled with more reactive alkyl or aryl acid chlorides without the use of the palladium catalyst to afford the corresponding 4-substituted derivatives 34.  

Most recently, Kalinin and coworkers have shown that sydnonyl cuprates 31 can undergo palladium catalyzed cross-coupling reactions with either heteroaryl iodides or alkynyl bromides to afford the corresponding 4-substituted sydnones in good to excellent yields.  

The 4-chloromercurio species 35 also can be used as an effective intermediate for substitution of the sydnone ring. The 3-arylsydnones (9) are reacted with mercuric chloride and sodium acetate in aqueous methanol at ambient temperature, and this
intermediate can then be treated with iodine to afford the 4-iodo derivative 36 (one of the few ways that this derivative can be prepared). More recently, Kalinin reported that reaction of the 4-chloromercurio intermediate with electron deficient olefins afforded only the trans-isomer of the corresponding 4-alkenyl product 37 in relatively high yields. 49

\[
\begin{align*}
\text{O} & \text{C} \quad \text{N} \quad \text{O}_- \\
\text{R'} & \\
\text{HgCl}_2 & \text{NaOAc} \\
\to \\
\text{I}_2 \\
\text{O} & \text{C} \quad \text{N} \quad \text{O}_- \\
\text{R'} & \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \text{C} \quad \text{N} \quad \text{O}_- \\
\text{R'} & \\
\text{HgCl}_2 & \text{NaOAc} \\
\to \\
\text{H}_2\text{C} \cdots \text{CHX} & \text{LiPdCl}_3 \\
\text{X} = \text{COMe, CO}_2\text{Me, Ph, CN} \\
\end{align*}
\]

II. Dilithiation of 3-Aryl Sydnones

Dilithiation of 3-aryl sydnones has become a recent focus in sydnone chemistry, and has been successfully achieved by Krein and Turnbull. 50 Initially, a di-lithio sydnone species 39 was made by the reaction of 3-(2-bromophenyl)-4-bromosydnone 38 with butyllithium at -78 °C. Subsequent reaction with ethyl acetate afforded the known sydnoindole 40 in good yield.
Krein and Turnbull applied this reaction to other esters, and it proved to be rather versatile. However, due to an undesirable drawback, namely the loss of weight going from starting material to product caused by the sacrifice of two bromine atoms, an alternate starting material was then pursued. As was discussed previously in this section, lithium bases can easily abstract the proton from the 4-position of the sydnone ring. The pKa of this proton is estimated to be on the order of 18-20. This led to the testing of 3-(2-bromophenyl)sydnone instead of 38 using the conditions shown above, and it was found the same transformations were achieved.

Upon further investigation, Krein and Turnbull discovered that the di-lithio intermediate 39 could be prepared directly from 3-phenylsydnone 13 using N,N,N’,N’-tetramethylene-diamine (TMEDA) to increase the basicity of butyllithium. This was complemented by the anticipated ortho-directing effect of the sydnone ring. Hence, it was possible to react at the ortho-aryl site without the need for metal-halogen exchange. Thus, reaction of this di-lithio species was undertaken with a variety of electrophiles (cf. 13 to 41-46).
In more recent times, the same reaction has been found to be highly effective without the use of TMEDA by raising the reaction temperature from -78 °C to -50 °C.\textsuperscript{51}

Weisner and Turnbull found an efficient method to 3-(2-iodophenyl)sydnone (176) using a dilithiation approach rather than the low-yielding, time-consuming, five-step process to 176 starting with costly 2-iodoaniline. It was found that dilithiation of 3-phenylsydnone (13), addition of iodine and subsequent treatment of the resultant 178 with sodium sulfite in one pot removed only the 4-iodo substituent, providing a high-yield (up to 96%), 2-step route to 3-(2-iodophenyl)sydnone.

Scheme 1
Remarkably, it was found that the whole process could be accomplished at a dilution of 1 g per 100 mL tetrahydrofuran, a five-fold increase in concentration compared to previous work in our laboratory.

In regards to the second reaction setp (viz. 178 $\rightarrow$ 176), sodium borohydride was the initial reductant chosen to remove the iodine from the 4-position of the sydnone ring, however, it was found that this reagent removed both iodine atoms from 44, giving back N-phenylsydnone.

There is a substantial difference between the acidities of the protons at the ortho-aryl position and at the sydnone 4-position. As stated before, the pKa of the 4-sydnone proton is estimated to be 18-20 pKa units, and the ortho-aryl proton is estimated to have a pKa of approximately 40 pKa units. Due to this difference, Krein and Turnbull explored the idea of selective substitution at the ortho site.

The idea was initially tested by generating the di-lithio species and reacting with one equivalent of an electrophile. When the di-lithio sydnone 39 was reacted with one equivalent of chlorotrimethylsilane, it was found to produce four products: ortho-substituted, sydnone C-4-substituted, disubstituted and unsubstituted 47-49, 13, respectively. These results suggested chlorotrimethylsilane was too strong an electrophile to take advantage of the reactivity differences in the dianion 59.

Accordingly, it was decided to attempt reaction with a less reactive electrophile, and Weinreb’s amides were chosen since they have known advantages in similar

\[
\begin{align*}
\text{N-phenylsydnone} & \xrightarrow{2.2 \text{ equiv } n-\text{BuLi}} \text{di-lithio sydnone} \\
\text{di-lithio sydnone} & \xrightarrow{1 \text{ equiv TMSCl}} \text{products} \\
47: \text{R} = \text{TMS, R'} = \text{H} & \\
48: \text{R} = \text{H, R'} = \text{TMS} & \\
49: \text{R} = \text{TMS, R'} = \text{TMS}
\end{align*}
\]
transformations. Subsequently, N-methoxy-N-methylbenzamide was used to produce the ortho-benzoyl species 50 (R = Ph) in good yield, and this process was extended to the preparation of other ortho-acylsydones. This approach provided a “one-pot” synthesis of ortho-acyl sydrones from easily prepared 3-phenylsydnone. Since, after initial reaction at the ortho-aryl position, the sydnone anion remains, one equivalent of a second electrophile could be added to promote further functionalization at the C-4 position of the sydnone ring. This provided a route to various unsymmetrically functionalized sydnone species (cf. 51).

III. Electrophilic Substitution at the Aryl Ring of 3-Arylsydrones

In the vast majority of 3-arylsydones, reaction with an electrophile occurs at the sydnone C-4 position. It seems that this is due to the considerable, partial negative charge that resides at this position and due to the considerable, partial positive charge that resides at the sydnone N-3 position, apparently deactivating the juxtaposed aryl moiety.
However, as was alluded to earlier (see Chemical Behavior), in certain cases, *viz.* bromination or nitration, there is the possibility of substituting the pendent aromatic moiety.

Until recently, bromination of numerous 3-substituted sydnones had afforded only the 4-bromo analogs.\textsuperscript{53, 54, 55} In an attempt to effect aryl substitution in preference to sydnone C-4 substitution, the idea of using an activated 3-aryl sydnone, *e.g.* 3-(2-aminophenyl)sydnone (52), to generate a competitive situation for reaction with the electrophile was investigated.\textsuperscript{56} It was reported that the major products obtained were derived from bromination on the aryl ring, *viz.* 3-(2-amino-5-bromophenyl)sydnone (53) and 3-(2-amino-5-bromophenyl)-4-bromosydnone (54). Thus, for the first time, it was demonstrated that the aryl moiety could compete with the sydnone ring for electrophilic substitution. Interestingly, with slow addition of NBS only 53 was formed in 70% yield.\textsuperscript{57}

\[
\begin{align*}
\begin{array}{c}
\text{52} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{C} \\
\text{H} \\
\text{NH}_2
\end{array}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Br} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{C} \\
\text{H} \\
\text{NH}_2 \\
\text{Br}
\end{array}
\end{align*}
\]

13% Yield

\[
\begin{align*}
\begin{array}{c}
\text{53} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{C} \\
\text{H} \\
\text{NH}_2 \\
\text{Br}
\end{array}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{c}
\text{54} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{C} \\
\text{Br}
\end{array}
\end{array}
\end{align*}
\]

25% Yield

Further examination of this methodology showed that the bromination of a series of dimethylaryl- or dimethoxyarylsydnones (55 and 56, respectively) with 1 equivalent of bromine occurred only at the C-4 position of the sydnone ring (57).\textsuperscript{58} Furthermore, even when treated with excess bromine, only the most activated sydnones, *viz.* the 3-(2,4- and...
3,5-dimethoxyphenyl) derivatives, were brominated on the aryl ring after bromination had occurred at the sydnone C-4 position, giving 58 and 59.

\[
\begin{align*}
&\text{R} \quad \text{R} \\
&\text{55: } R = \text{Me} \\
&\text{56: } R = \text{OMe}
\end{align*}
\]

\[
\begin{align*}
&\text{1 equiv. } \text{Br}_2 \\
&\text{excess } \text{Br}_2 \\
&\text{57}
\end{align*}
\]

\[
\begin{align*}
&\text{OMe} \\
&\text{Br} \\
&\text{58}
\end{align*}
\]

\[
\begin{align*}
&\text{MeO} \\
&\text{Br} \\
&\text{59}
\end{align*}
\]

\[
\begin{align*}
&\text{OMe} \\
&\text{Br} \\
&\text{58}
\end{align*}
\]

\[
\begin{align*}
&\text{MeO} \\
&\text{Br} \\
&\text{59}
\end{align*}
\]

In contrast to bromination is the nitration of activated arylsydnones. Nitration of an activated 3-arylsydnone preferentially occurs on the aryl moiety and not on the sydnone C-4 position. Thus, it has been shown that when exposed to nitrating conditions; activated aryl sydnones (cf. 60 and 61) afford the products of nitration on the aryl ring \textit{viz.} 62 and not the anticipated 4-nitro derivatives 63.\textsuperscript{59}
More recent investigation of nitration of 3-substituted arylsydnones has been reported by Tien and coworkers.\textsuperscript{60, 61} It was shown that the \textit{meta}-nitroaryl products (65, 67) were obtained when either 3-benzylsydnone (64) or various 3-aryl-4-acetylsydnones 66 were treated under nitrating conditions. In the latter case, the acetyl group could be removed with barium hydroxide.
Correspondingly, and most recently, Turnbull, Blackburn, and Miller have examined nitration of 3-arylsydnones with multiple electron-donating methyl groups on the aryl ring. Once again, exclusive aryl ring nitration was observed, with a strong tendency for nitration meta to the sydnone ring (68 to 69). If nitration was forced to occur between two substituents on the aryl ring, the favored position was between the sydnone ring and a methyl group, not between the two methyl groups (cf. 70 to 71).
IV. Reactions of ortho-Substituted Aryl Sydnones

Fused ring sydnones (cf. 72, 75, 40) are of great interest because ring-fusion may in some way alter either the chemical or the biological activity of the sydnone ring. As precursors to these compounds, oximinosydnones 71 have been used to prepare sydnoquinazolines 72, benzotriazines 73 and indazoles 74 while ortho-substituted aroylsydnones have been shown to afford both the fused-ring syndoindole 40 and substituted indazoles 74 depending on the reaction conditions. Presented here is a brief overview of this chemistry.
It has been reported\textsuperscript{63} that by treating oximinosydnones 71, R = Me or Et with any one of a variety of acids, it is possible to obtain the corresponding sydnoquinazoline 72, benzotriazine 73, or indazole 74, depending on which acid is employed.

Structural isomers of the sydnoquinoline 72, \textit{viz.} 4-(arylamino)-sydno[3,4-a]quinoxalines (75), have been prepared in good to excellent yield (60-90\%) by aza-Wittig carbodiimide formation followed by intramolecular electrophilic cyclization (Scheme 2).\textsuperscript{64}
Two serendipitous discoveries have resulted in the preparation of the fused-ring sydnoindole 40 and various bromocarbonyl indazoles 76. It was found that by treating 3-(2-acetylphenyl)sydnone with hydrazine under basic conditions, the major isolable product was the fused-ring sydnoindole 40 and not the anticipated hydrazone derivative.\textsuperscript{65}
In an attempt to extend this study, it was considered of interest to place a bromine leaving group on the acetyl methyl. Accordingly, 3-(2-acetylphenyl)-4-bromosydnone (77, R = Me) was treated with Br$_2$/hv or CuBr$_2$. Surprisingly, the bromocarbonylindazole 76, R = Me was obtained rather than the expected sydnone 77, R = CH$_2$Br. It was suspected that the transformation resulted from the formation of HBr in situ and, indeed, when various 4-bromo ortho-acyl sydnones cf. 77 were subjected to a stream of HBr gas, the corresponding bromocarbonylindazoles 76 were formed in good yield (60-85%).

One hindrance to the study of the reactions shown above has been that sydnones with an ortho carbonyl substitution are relatively hard to come by; they often must be made in several steps starting from the appropriate aniline derivative. Recent work has shown that a variety of ortho-acylaryl sydnones can be prepared from one or two intermediates by reacting nucleophiles with activated ortho carbonyl species. For example, 3-[2-(N-succinimido)-oxycarbonyl]phenyl]sydnone 78 was reacted with twelve different nucleophiles to afford corresponding ortho-acylaryl sydnones 79 in yields ranging from 23% to 63%.
V. Miscellaneous, Recent Reactions of Sydnones

In the years 1996 to 2004, some new chemistry has been explored with sydnones, and not all of this falls neatly into the categories that have been discussed in the previous paragraphs, nor into the next section, “Background to the Current Research.” For the sake of completeness, the following reactions of, and syntheses with, sydnones are discussed to give the reader a better (not necessarily all-inclusive) taste of recent work. These papers are presented in chronological order.

Kalinin and Cherepanov have recently explored metallation of 3-methyl-4-phenylsydnone (80). In their study, it was found that a proton could be abstracted from the methyl group of 80 with butyllithium at -90 °C, forming the rather unstable lithio intermediate 81. Subsequent reaction with a variety of electrophiles led to an array of functionalized sydnones 82 (12% to 70% yields) through a common intermediate.

For example: a) $E^+ =$ allyl bromide, b) $E^+ =$ methyl chloroformate, c) $E^+ =$ carbon dioxide, d) $E^+ =$ benzophenone

82a) $E = CH_2CH_2CH=CH_2$, 82b) $CH_2CO_2CH_3$, 82c) $E = CH_2CO_2H$, 82d) $E = CH_2C(Ph)_2OH$
Mallur, Bharati, and Badami recently used sydnones as intermediates to 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones.\textsuperscript{69} Their goal was to synthesize such species and test them for antimicrobial activity. The desired 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones \textsuperscript{84} were prepared from 3-arylsydnones \textsuperscript{83} by reaction with bromine in acetic anhydride, as is illustrated with a general example, below.

\[ \text{N} \begin{array}{c} \text{C} \\ \text{O} \end{array} + \text{N} \begin{array}{c} \text{C} \\ \text{O} \end{array} \xrightarrow{\text{(CH}_3\text{CO})_2\text{O} \quad \text{Br}_2, \ 0 \ ^\circ \text{C}} \text{N} \begin{array}{c} \text{C} \\ \text{O} \end{array} + \text{N} \begin{array}{c} \text{C} \\ \text{O} \end{array} \xrightarrow{\text{(CH}_3\text{CO})_2\text{O} \quad \text{Br}_2, \ 60 \ ^\circ \text{C}} \text{N} \begin{array}{c} \text{C} \\ \text{O} \end{array} \]

Their suggested mechanism involves initial sydnone bromination to form a 4-bromo intermediate that is not isolated, followed, at increased temperature, by a 1,3-dipolar cycloaddition between the 4-bromo sydnone and acetic anhydride. In light of the fact that no attempt was made to remove HBr formed as a by-product, and the unprecedented nature of the suggested cycloaddition, this mechanism seems suspect. The transformation is useful, however, and, overall, twenty different oxadiazolinones were prepared in yields of 70-90\%, most of which showed anti-bacterial and anti-fungal activity.

Another study taking advantage of the ability of sydnones to go through 1,3-dipolar cycloadditions involved running a known sydnone reaction under new conditions. Totoe, McGowin, and Turnbull studied the reaction of 3-phenylsydnone (\textbf{13}) with methyl propiolate in supercritical carbon dioxide.\textsuperscript{70}
In this reaction, two regioisomers (85 and 86) are formed, due to methyl propiolate being unsymmetrical. The temperature in the supercritical fluid reactor was varied, as well as the pressure, to see if this had an effect on reaction selectivity (i.e. a greater amount of regioisomer 85 formation versus regioisomer 86). In short, it was found that increasing reaction temperature decreased selectivity while increasing reaction pressure increased selectivity. This showed that reaction in supercritical carbon dioxide provided a selectivity advantage over running the reaction under the standard conditions (toluene, heat). Further, it was shown that the reaction could take place in a “green” solvent (carbon dioxide versus toluene).

As another example of a sydnone being used in synthesis, Yeu et al. used 87 in a route to the antidepressant 1-[3-(dimethylamino)propyl]-5-methyl-3-phenyl-1H-indazole (89). This synthesis involved an intramolecular 1,3-dipolar cycloaddition of 87 followed by aromatization to obtain the desired product.
Zhang, Wu, and Yin have made novel, fused-ring sydnones containing a seven-membered ring fusion. Their route to these species involved the reduction of 3-aroylethylsydnones with sodium borohydride to obtain a 3-(aryl-3-hydroxypropyl)-sydnone. Subsequent treatment of these species with acetone and concentrated sulfuric acid, or boron trifluoride etherate produced the corresponding fused-ring sydnones in 60% to 85% yield.

Most recently, Weisner, Turnbull, and Cooper explored sydnone-containing platinum acetylides prepared by Sonogashira-coupling for use as potential non-linear optical materials. One-pot methods were developed to make the desired compounds.

A known protocol by Krause was modified such that heating the degassed THF solution at 50°C allowed for high yielding avenues to sydnone acetylenes and .
when Sonogashira coupling with TMS-acetylene was developed and, once each coupling reaction was complete, tetrabutyl ammonium fluoride (TBAF) was added for the desilylation of the TMS acetylenic sydnone for coupling with 1-bromo-4-iodobenzene at room temperature. Instead of isolating and purifying the product for the next step for every reaction, not only was it less time consuming to use a one-pot method, but it also increased the yields. It was found to be most efficient to make 95 with three separate one pot reactions. These materials were converted into platinum acetylides to observe non-linear optical properties.

Finally, Dunkley and Thoman\textsuperscript{74} showed that the electron withdrawing nature of the sydnone is similar to a nitro group via aromaticsition reactions. Usually a chloro leaving group is activated by nitro groups in ortho and para positions, however, in 96, when $X = \text{Cl}$, it can be replaced by a nucleophile due to resonance from the ortho-nitro group and the para-sydnonyl moiety. The resultant compounds showed antitumor activity.
Background to the Current Research

I. Arylsydnone Ring Fusion and Routes to Other Heterocycles

In recent years, fused-ring arylsydnones have attracted attention because ring-fusion is a route to interesting new molecules that may possess useful biological activity. Particularly, two types of fused-ring arylsydnones have been of interest. The first is where there is a one-carbon bridge adjacent to the sydnone ring (cf. 98) and the second is where the bridge from the sydnone to aryl ring is an unsaturated, two-atom, bridge (cf. 99). These species have been of special interest because it is possible that the fusion may modulate in vivo metabolism of the sydnone ring, and therefore give rise to previously unobserved useful effects. Furthermore, sydnones are precursors to non-sydnone heterocycles that may also be potentially useful, including benzotriazines and indazoles.

Some presentation of routes to fused-ring arylsydnones and “other” heterocycles has already been made in the introductory material (see “Dilithiation of 3-Aryl Sydnones” and “Reactions of ortho-Substituted Aryl Sydnones”).
One of the earliest preparations of fused-ring sydnones was serendipitous. In 1977, Preston and Turnbull treated 3-(2-aminophenyl) sydnone 100 with nitrous acid followed by sodium azide in hopes of preparing azidosydnone 96. Unexpectedly, the product was the fused-ring sydnobenzotriazine 101 (Scheme 1).

Scheme 1

The fused-ring sydnone was most likely formed by an intramolecular trapping of the intermediate diazonium species by the sydnone ring.

More recently (1991), a route to novel 4-(arylamino)sydno[3,4-a]quinoxalines 102 was reported by Burson, Turnbull, and coworkers from the same species 100. The synthesis involved aza-Wittig carbodiimide formation followed by intramolecular electrophilic aromatic substitution by the sydnone ring. Yields of 60% to 90% were obtained (Scheme 2). Once again, it is clear that ring fusion is effected by generating an electrophile in close proximity to the sydnone ring.

Scheme 2
Finally, in 1994, Chan and coworkers reported a route involving the addition of an isocyanate or isothiocyanate to the amino nitrogen of 3-(2-aminophenyl)sydnone 100. Subsequent heating effected cyclization to the sydnoquinoxaline 103, again by intramolecular electrophilic substitution (Scheme 3).

Scheme 3

The three previous examples illustrate the standard synthetic avenue to sydnone ring fusion, viz. create an electrophilic center ortho to the sydnone ring for the sydnone to attack.

As a connection between fused ring sydnones and “other” heterocycles, it has been shown that ring fusion modulates the properties of the sydnone ring, especially basic conditions as to how the ring breaks under aqueous acidic or basic conditions. The resulting heterocycles are of interest and are difficultly accessible by other avenues.

In this regard, it is known that 3-phenylsydnone (13) reacts with hydrochloric acid to form phenylhydrazine (104). However, in fused species 101, the sydnone ring cleaved between the 2-3 and 1-5 bonds instead of between the 1-2 and 3-4 bonds yielding a benzotriazine carboxylic acid 106 (Scheme 4).
This change in the way the sydnone ring breaks is of interest because it appears that the species nitric oxide (NO) is released, which is known to be an anti-hypertensive in vivo. This makes variants of fused-ring sydnone 97 of special interest for pharmaceutical purposes.

As shown in Scheme 4, under non-fused circumstances, acid cleavage of the sydnone gives rise to an arylhydrazine, a nucleophilic species that might be useful for heterocyclic synthesis. It was postulated, and demonstrated, that an ortho-substituted arylhydrazine generated from an appropriate arylsydnone would lead to a unique heterocycle (cf. 105) upon cleavage with HCl (Scheme 5).
As mentioned above, cleavage of the sydnone ring can lead to a nucleophile (hydrazine) capable of attacking an ortho electrophile, mainly carbonyl and related species. It has been found that a comparable transformation can be accomplished without breaking the sydnone ring, leading to sydnoindoles, as in the reaction of 3-(2-acetylphenyl)-sydnone 106 with triethylamine/hydrazine in a ratio greater than 1:2. The result was 4-hydroxy-4-methylsydno[3,4-a](4H)indole 40 instead of the anticipated hydrazone 107 (Scheme 6).

The fused-ring sydnoindole 40 also was prepared using other weakly basic mixtures including ammonia/methanol and methylamine/methanol. The formation of 40 likely follows the following mechanism: First, the C-4 proton is abstracted generating a carbanion, the carbanion undergoes intramolecular nucleophilic attack at the carbonyl
carbon of the acetyl group, and protonation upon work-up produces the fused-ring sydnone (Scheme 7).

Initially, it was theorized that the ring strain generated by the one-carbon bridge of 40 would cause the species to be unstable and non-isolable; however, it has been found that under normal conditions the compound is quite stable. Due to its crystalline nature, the proposed structure was confirmed by X-ray crystallography.80 A surprising aspect of the synthesis shown in Scheme 7 is the relatively high acidity of the proton at the 4-position of 108. The pKa of a “normal” sydnone hydrogen is ~18-2081; therefore, the ease of the proton’s abstraction under such mild conditions must be directly related to the ortho-acetyl group’s ability to withdraw electron density away from the sydnone ring.

In the “Aims of the Present Work” section, more will be discussed as to why the Friedel-Crafts reaction is of interest and how it will provide a novel precursor to a fused-ring sydnone.

II. The Friedel-Crafts Reaction
In 1877, Charles Friedel and James Mason Crafts reported that alkylation and acylation of benzene occurred using amyl chloride and acetyl chloride, respectively, in the presence of aluminum trichloride (Scheme 8).

Scheme 8

\[
\begin{align*}
\text{RX} & \quad \text{AlCl}_3 \\
\text{R} & \quad \text{Cl} \\
\text{X} & \quad \text{Cl} \\
\text{Where } R &= -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3, \ -\text{COCH}_3 \\
\end{align*}
\]

Further work by Friedel and Crafts and other investigators led to the following conclusions. In order for a reaction to be considered a Friedel-Crafts reaction it must have the following conditions: (1) reactants (arene and electrophile), (2) catalyst (Lewis or Bronsted-Lowry acid), (3) solvent (polar aprotic or excess reagent can be the solvent) and each of these aspects will be discussed in turn. Classical catalysts include AlCl\(_3\), FeCl\(_3\), ZnCl\(_2\), BF\(_3\), TiCl\(_4\), SnCl\(_4\), group XIII metals, and Cu(II) while newer catalysts include LiClO\(_4\), metal triflates (typically Ln, Bi, Re), triflic acid, graphite, solid acids, and inorganic solid supported reagents. Reagents used to acylate aryl compounds include alkyl halides, acid halides, alkyl and aryl anhydrides, and aldehydes. Solvents that are polar aprotic, chlorinated, benzene or deactivated benzenes are effective and examples include acetonitrile, nitromethane, dichloromethane, dichloroethane, chlorobenzene, and nitrobenzene. More recently, ionic liquids and supercritical CO\(_2\), environmentally friendly solvents, have been examined in the Friedel-Crafts reaction and the findings will be discussed later.
While the Friedel-Crafts reaction is a high yielding carbon-carbon bond forming reaction of aromatic compounds, it suffers from several disadvantages using classical approaches. In a typical Friedel-Crafts acylation reaction, a large excess of the Lewis acid catalyst (e.g., 6 equivalents of AlCl$_3$) is needed due to the coordination to the formed ketone. Further, the aluminum trichloride is unstable to aqueous work up and produces acidic waste. Over the years, modifications to the reaction conditions have been explored in order to find more efficient and environmentally friendly methods for Friedel-Crafts acylations. In this regard, the most compelling avenues for change are the solvent and the nature of the catalyst. Metal triflates have been of interest, particularly rare earth, lanthanide, and bismuth triflates, since they can be used in catalytic amounts, are stable to aqueous work-up, and therefore, can be reused. Many of these triflates have been used with lithium perchlorate as an additive, which in some cases increases the yields or is essential for any sign of reactivity. Most authors have not delineated the exact mechanism whereby lithium perchlorate acts as a co-catalyst.

As regards solvents, recent trends have been to examine more environmentally benign solvents such as supercritical carbon dioxide and ionic liquids. Further such protocols have often been coupled with other techniques such as the use of fluorous biphase catalysis (FBC). Fluorous solvents contain 18 or more fluorine atoms, are immiscible with other solvents, and can immobilize fluorous catalysts or other fluorous compounds. Nishikido reported$^{83}$ that the electron withdrawing nature of the fluorous ligands caused the metal to be a better Lewis acid, thus efficiently catalyzing the acylation of anisole with acetic anhydride using scandium(III) tris(perfluoroctanesulfonyl) methide and ytterbium(III) bis perfluoroctanesulfonyl) amide
fluorous as the Lewis acid catalysts in supercritical CO$_2$, as shown in scheme 9. Another experiment that utilized fluorous solvents to extract the catalysts from the reaction mixture was discussed, however; in the case of acylation the catalyst was reused by precipitating it from the reaction mixture. The catalysts were used three times without significant loss of activity, as shown in Table 1.

Scheme 9

![Scheme 9](image)

**Table 1.** Friedel-Crafts Reaction in scCO$_2$ Catalyzed by Yb and Sc Complexes

<table>
<thead>
<tr>
<th>Cycle</th>
<th>% Yield</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yb[N(SO$_2$C$<em>8$F$</em>{17}$)$_2$]$_3$</td>
<td>Sc[N(SO$_2$C$<em>8$F$</em>{17}$)$_2$]$_3$</td>
</tr>
<tr>
<td>1</td>
<td>79 (77)</td>
<td>82 (79)</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>79</td>
</tr>
</tbody>
</table>

The yields in parentheses are isolated yields while all other yields are calculated from GC analysis using $n$-decane as an internal standard. The catalysts were used without purification and were completely (>99%) recovered.

Ross and Xiao reported high yields using ionic liquids when compared to traditional solvents (cf. dichloroethane and acetonitrile) for Friedel-Crafts acylations with 10 mol% of metal triflates and a variety of activated aromatics. Copper, zinc, tin, and scandium triflates were used in this study, with copper giving the highest regioselectivity.
and conversion in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim] [BF₄].

Some of the modifications to the Friedel-Crafts reaction have been applied in the industrial realm. One example of an industrial application of Friedel-Crafts acylations is in the synthesis of a precursor of naproxen, which is an anti-inflammatory drug. Typical methods, shown in Scheme 10, involve harsh conditions that generate large amounts of acidic waste.

Scheme 10

Kobayashi reported⁸⁵ that the Friedel-Crafts reaction leading to the Naproxen precursor could be affected using metal triflates of antimony, scandium, iron, gallium, tin, ytterbium, hafnium, bismuth, and aluminum. Addition of lithium perchlorate affected the yields and regioselectivity in the reactions using triflates with acetic anhydride and 2-methoxynaphthalene as shown in Scheme 11.

Scheme 11
As shown in Table 2, the highest yields of the desired 6-acetyl isomer were obtained with antimony or gallium triflates and lithium perchlorate as an additive (entries 5 and 8).

Table 2. Effects of Lewis acids and Additives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield 1-acetyl (%)</th>
<th>Yield 6-acetyl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sb(OTf)₃</td>
<td>-</td>
<td>MeNO₂</td>
<td>rt</td>
<td>77</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Sb(OTf)₃</td>
<td>-</td>
<td>MeCN</td>
<td>50</td>
<td>83</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<td>-</td>
<td>PhNO₂</td>
<td>50</td>
<td>46</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Sb(OTf)₃</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>66</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Sb(OTf)₃</td>
<td>LiClO₄</td>
<td>MeNO₂</td>
<td>50</td>
<td>ND</td>
<td>93</td>
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<td>MeNO₂</td>
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<td>62</td>
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<tr>
<td>7</td>
<td>Fe(OTf)₃</td>
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<td>72</td>
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<tr>
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<tr>
<td>9</td>
<td>Sn(OTf)₃</td>
<td>LiClO₄</td>
<td>MeNO₂</td>
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<td>73</td>
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<tr>
<td>10</td>
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<td>LiClO₄</td>
<td>MeNO₂</td>
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<td>45</td>
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<tr>
<td>11</td>
<td>Hf(OTf)₃</td>
<td>LiClO₄</td>
<td>MeNO₂</td>
<td>50</td>
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<td>67</td>
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<tr>
<td>12</td>
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<td>MeNO₂</td>
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<td>13</td>
<td>Sb(OTf)₃</td>
<td>LiNTf₂</td>
<td>MeNO₂</td>
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<td>ND</td>
<td>76</td>
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<tr>
<td>14</td>
<td>Sb(OTf)₃</td>
<td>LiOTf</td>
<td>MeNO₂</td>
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<td>0</td>
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<tr>
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<td>Sb(OTf)₃</td>
<td>LiNO₃</td>
<td>MeNO₂</td>
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<td>1</td>
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<tr>
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<td>Sb(OTf)₃</td>
<td>LiAc</td>
<td>MeNO₂</td>
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<td>7</td>
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<tr>
<td>17</td>
<td>Sb(OTf)₃</td>
<td>NaClO₄</td>
<td>MeNO₂</td>
<td>50</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>18</td>
<td>Al(OTf)₃</td>
<td>LiClO₄</td>
<td>MeNO₂</td>
<td>50</td>
<td>ND</td>
<td>83</td>
</tr>
<tr>
<td>19</td>
<td>AlCl₃</td>
<td>LiClO₄</td>
<td>MeNO₂</td>
<td>50</td>
<td>35</td>
<td>27</td>
</tr>
</tbody>
</table>

Since bismuth triflate was an important part in the research described later in this thesis, it is worth noting that, as can be seen in Table 2, entry 12, that it was regioselective and afforded one of the best yields.
The effect lithium perchlorate had on the regioselectivity and yield can be noted from entries: 1, 5, 12-17 and it is clear that its addition favors the 6-acetyl product. Further, when lithium perchlorate was substituted for by other lithium salts or sodium perchlorate, the yields decreased significantly and, in the case of lithium acetate (entry 16) and lithium nitrate (entry 15), more of the 1-acetyl isomer was obtained. Indeed, when no lithium salts were used (entry 1), the 6-acetyl isomer was obtained in a 4% yield while the 1-acetyl isomer was obtained in a 77% yield.

Since bismuth triflate was used as the catalyst for the research project described later in this thesis it is important to discuss its activity. Bi(III) compounds, especially BiCl$_3$ and Bi(OTf)$_3$ have been effective catalysts for Friedel-Crafts acylations. Another attractive quality of bismuth triflate is its stability to aqueous work-up, thus it can be recycled. In many studies it has been shown that bismuth triflate is more active than bismuth chloride, providing shorter reaction times, a possibility of lower reaction temperatures, the use of smaller quantities of catalyst, and greater effectiveness in acylating deactivated aromatics.

Le Roux and Dubac describe bismuth triflate as a “chameleon catalyst” because of its different mechanistic activity towards acid chlorides and acid anhydrides. Acid chlorides are activated by an exchange reaction with the triflate ligand (Scheme 12).

\[
\text{Bi(OTf)}_3 + 3 \text{RCOCI} \rightarrow \text{BiCl}_3 + 3 \text{RCOOTf} \quad (107)
\]

The acylating agent in this case would be the aroyl or alkanoyl triflate (107) which would react with the arene, forming triflic acid. The resulting triflic acid could regenerate the aroyl or alkanoyl triflate; therefore, in this case, triflic acid would be the actual catalyst.
for the reaction. After work-up it has been shown that reaction between bismuth chloride and triflic acid to regenerate bismuth triflate is minimal, however, bismuth chloride and the hydrolysis product, bismuth oxychloride (BiOCl), are obtained in a ratio of 2:1. It has been reported\textsuperscript{87} by Repichet, Le Roux, Roques, and Dubac that bismuth oxychloride has been observed upon neutralization of the aqueous layer in experiments using bismuth trichloride as the catalyst. The bismuth oxychloride was chlorinated in situ by the acid chloride if efforts were made to reuse the bismuth trichloride. In the case of an expensive acid chloride, thionyl chloride was used to regenerate the bismuth trichloride.

In the case of anhydrides, the ligand exchange has not been observed.\textsuperscript{88} The use of $^{13}$C-NMR gave evidence of complexation of the bismuth to the carbonyl as evidenced by a downfield shift of the $^{13}$C=O signal. It appears that a bridged structure (108), is involved rather than the aroyl or alkanoyl triflate (107).
Aims of the Present Work

As mentioned in the introduction, acylation at the C-4 position of the sydnone has been achieved using relatively harsh conditions. Low yields were achieved using a method developed by Greco and coworkers, where the C-4 position was acylated via organic acids and phosphorus pentoxide\textsuperscript{33} (Scheme 13). However; the nature of the organic acid was limited because neither aryl nor aralkyl acids reacted.

Scheme 13

\[
\text{N} \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{R} \quad \text{O} \\
\text{H} \\
\text{RCO}_2\text{H} \\
\text{P}_2\text{O}_5 \\
\text{R} = \text{alkyl}
\]

Yashunkii reported reasonable yields of the 4-acetyl derivative (15) using boron trifluoride etherate and acetic anhydride (Scheme 14); however; the Turnbull group found that this method was not reproducible.

Scheme 14

\[
\text{N} \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{N} \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{H} \\
\text{Ac}_2\text{O} \\
\text{BF}_3\text{Et}_2\text{O} \\
\text{50}
\]
Tien reported that acetic anhydride with phosphoric and perchloric acids afforded the 4-acetyl derivative from 3-phenyl sydnone (Scheme 15). The process could be improved using ultrasonification with acetic anhydride and a catalytic amount of perchloric acid, under these conditions, the reaction was accelerated, however; a high-powered ultrasonicator had to be used. Further, these harsh conditions gave only moderate yields.

Scheme 15

Montmorillonite K-10 with acetic anhydride was able to give 4-acetyl derivatives with a variety of aryl substituted sydnones; however the reaction complete after heating at high temperatures (120 °C) overnight. The reaction (Scheme 16) was even more sluggish when the phenyl group contained a strong electron withdrawing substituent ortho to the sydnone ring. The sydnone ring actually was cleaved when an acetyl group was present ortho to the sydnone ring.

Scheme 16
Considering these all the drawbacks to Friedel-Crafts acylation at the 4-position of the sydnone ring, it was of interest to find a method with milder conditions, preferably using a catalytic amount of reagent. With Green Chemistry becoming more important, an environmentally-friendly catalyst was desirable and metal triflates (particularly Ln and Bi), were previously reported as effective catalysts in the Friedel-Crafts reaction, appeared to fit the bill. As discussed in the introduction, metal triflates are also considered “Green” reagents because they can be used in small amounts and can be reused due to their stability to aqueous work-up.

It was envisioned that using anhydrides and acid chlorides, a variety of 4-acyl compounds could be prepared. Previously, acylations with acid chlorides have not been successful on the sydnone ring, however; in the present case, it was hoped that a different catalyst would allow acylation (Scheme 17). This would be useful due to the larger variety of acid chlorides available, compared to anhydrides, thus permitting approaches to a larger variety of fused-ring sydnone.

Scheme 17

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{R'} \quad \text{COCl} \text{ or } (\text{R'}\text{CO})_2\text{O} \\
\text{M(OTf)}_3
\end{align*}
\]

The first step in this process was to determine the scope of the reaction at only the C-4 position (temperature, amount of catalyst, amount of acylating reagent, and solvent). With these conditions optimized and shown to be effective with a variety of different substituents para to the sydnone ring, the parameters for diacylation could then be investigated.
If acylation catalyzed by metal triflates could occur on the sydnone ring and the aryl ring via an activated aryl ring, then these compounds could be transformed into fused-ring sydnones (Scheme 18) via McMurry coupling. As discussed in the “Background to Current Research” section, these fused-ring sydnones have been of interest because of the perception that they may display significant biological activity.

Scheme 18

Intramolecular McMurry coupling has been found to be an efficient method to make stilbenophanes.\textsuperscript{89} A solution of zero valent titanium, TiCl\textsubscript{4}, and zinc afforded 110a-c, and 112a-c (Scheme 19). The high concentration of the TiCl\textsubscript{4} (10 equivalents relative to the dialdehyde) and zinc (20 equivalents relative to the dialdehyde) increased the yields (53-60\% for 109a-c and 25 – 35\% for 112a-c), but also decreased the formation of diols.

Scheme 19.
Aliphatic ketones have been shown to couple to an alkene using TiCl₄ or UCl₄ with a lithium amalgam to form a metallopinacol then, either a pinacol after hydrolysis or the alkene under reductive conditions (lithium amalgam) at higher temperatures (60°C).
Results and Discussion

As mentioned in the Aims section, it was anticipated that more efficient avenues (perhaps catalytic) to 4-acyl sydnones would be possible via modern variations on the Friedel-Crafts reaction, especially the use of metal triflate catalysts. With these aims in mind, it was first necessary to explore the conditions (if any) under which the metal triflates would allow 3-phenyl sydnone (13) to be converted to 4-acetyl-3-phenylsydnone (113) with acetic anhydride. In order to compare the proportions of catalysts and acetic anhydride it was convenient to use the Labmate shaker, a parallel synthesizer having four temperature-controlled rows containing eight wells, which can hold small vials. This allowed for reactions to be conducted on a 25 mg scale with small amounts of ytterbium, scandium, and bismuth triflates. Nitromethane and acetonitrile, polar aprotic solvents commonly used for this type of reaction, were employed to see which, if any, was more effective. Keeping in mind that catalytic amounts of the metal triflates and a small excess of acetic anhydride were ideal, it seemed logical to start with 5 mol% of both metal triflate and lithium perchlorate as well as 1.5 equivalents of acetic anhydride and increase the amounts as needed. Ideally, higher temperatures also were to be avoided, so room temperature, 35, and 50°C were the starting temperatures. These reactions (Table 3) were set up in small vials and were allowed to stir on the shaker with monitoring by TLC versus authentic 4-acetyl-3-phenyl sydnone (113).

Table 3. Acylation of Phenyl Sydnone Catalyzed by Metal Triflates
Entries 1 - 9 are consistent with literature reports, viz. that scandium and ytterbium triflates are less active than bismuth triflate. Entries 19 – 30 show that acetonitrile was a much more effective solvent than nitromethane. It was found that bismuth triflate and lithium perchlorate had to be used together in order for reaction to occur (entries 27 and 28).

Upon scaling up the reaction, using real-world conditions (round bottom flask equipped with a reflux condenser heated by an oil bath) and the optimum conditions
employed on the shaker (entry 25), more concerns arose. When the reaction was allowed to stir overnight at a higher temperature (70°C) to compensate for the different heat transfer on a round bottom compared to a vial, the reaction showed only about 70% conversion. There was a slight improvement in the conversion (to 80%) using 90°C and increasing the amount of catalysts and acetic anhydride to 20 mol% and 4 equivalents respectively. At this point, it was suspected that the freshness of the bismuth triflate was another unexplored parameter.

Accordingly, using freshly prepared bismuth triflate, the shaker was again employed to find the parameters that allowed complete conversion. At 70°C and 20 mol% of the catalysts, the utility of 3 equivalents of acetic anhydride versus 4 equivalents was tested (entries 29 and 30). After 3 hours, TLC showed ~50% conversion from the starting material using 3 equivalents and ~70% conversion using 4 equivalents; however, after stirring overnight both reactions had gone to completion. It is likely that the improved conversions in the capped vials, arises from the ability to heat the acetonitrile to a temperature above its boiling point of 81 – 82°C. Accordingly, it was elected to mimic this situation on a larger scale by using a sealed pressure tube and 20 mol% catalysts and 4 equivalents of acetic anhydride. However, while this improved the conversion as compared to a standard reflux, the reaction still had a trace of starting material on TLC after stirring overnight. Increasing the amount of each catalyst to 25 mol%, the reaction was complete after 6.5 hours (TLC evidence). In this latter case, after running the reaction mixture through a plug of silica gel to remove baseline material and recrystallization of the resultant product from hot ethanol, colorless crystals of 4-acetyl-3-phenyl sydnone were obtained in 53% yield. This was an exciting result in that, as
mentioned previously, all other acetylations of 13 had employed stoichiometric (or greater) amounts of catalysts and/or utilized acetic anhydride as solvent. With this protocol in hand, it was elected to repeat the reaction several times in order to find the actual time of completion. Using freshly prepared bismuth triflate, the reaction was complete in 4 hours affording, 113, in 77.5% yield. The melting point was 142°C, consistent with the literature melting point of 143 – 4 °C. The I.R spectrum showed a strong peak at 1797.34 cm\(^{-1}\) for the sydnone carbonyl and no peak was present at 3150 cm\(^{-1}\) for the sydnone C-H stretch since it was replaced by an acetyl group. Further support for the latter was indicated by a strong peak at 1666.20 cm\(^{-1}\) for the carbonyl attached to the C-4 carbon. These values for the carbonyl groups are indicative or resonance from the sydnone ring in that the sydnone carbonyl has a higher frequency compared to a “standard” sydnone (~1750 cm\(^{-1}\)) and the attached acetyl carbonyl has a lower frequency than the average aryl alkyl ketone (1700 cm\(^{-1}\)). The mechanistic rationale for this result is shown in scheme 20.

Scheme 20

![Scheme 20](image)

The proton NMR spectrum shows a singlet at 2.53 ppm for the methyl group for the acetyl at the C-4 position, and a multiplet in the aromatic region for the phenyl group. The integration showed the expected ratio of five aromatic protons to the three methyl protons. As expected, four peaks appeared in the aromatic region in the carbon spectrum.
The two carbonyl peaks appeared at 184.19 and 166.25 ppm, the latter being typical of the sydnone carbonyl. A weak signal at 106.06 ppm indicated the sydnone C-4 quaternary carbon, which is deshielded (from its “usual” position of ~ 95 ppm), due to the presence of the acetyl group. The signal for the methyl group appeared at 28.09 ppm.

The amounts of catalysts and time of reaction were varied in order to see how each affected the conversion and yield (Table 4), especially because lithium perchlorate is not a “green” reagent. It was of particular interest to find the conditions in which the minimum amount of lithium perchlorate could be used without significantly increasing time of reaction (at most four hours) or decreasing the yield even if the amount of bismuth triflate had to be increased. Using freshly prepared bismuth triflate and keeping the temperature and equivalents of acetic anhydride constant, it was shown that the original conditions (viz. 25 mol% of both bismuth triflate and lithium perchlorate) were, in fact the optimum conditions. The yields in Table 4 are calculated from the amounts of 113 after removal of baseline material (not recrystallized yields).

Table 4. Acylation of Phenyl Sydnone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bi(OTf)₃ (mol%)</th>
<th>LiClO₄ (mol%)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>2</td>
<td>2</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
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<td>92</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
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<td>87</td>
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<tr>
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<td>25</td>
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<td>20</td>
<td>10</td>
<td>overnight</td>
<td>47</td>
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</table>
It was shown also that longer reaction times generally had a deleterious effect on the yield. Sydnones are known to cleave to hydrazines (and derivatives) under acidic conditions and, accordingly, it was likely that this break down is taking place in the present cases as the acidity level increases with time. In order to optimize the yield, it was most effective to work-up the reaction as soon as TLC showed signs of completion. For example, using the optimized conditions, the yield decreased from 93% (entry 5) to 58% (entry 6) when the reaction was allowed to stir overnight as opposed to 2 hours. The quality of the acetic anhydride employed was also a factor in the yield, the 85 % yield in entry 7 was obtained using an older bottle of acetic anhydride. All other entries used a fresh bottle of acetic anhydride.

It was observed that the lithium perchlorate cocatalyst was essential to the success of the reaction and 113 was obtained in lower yields when the amount of lithium perchlorate was decreased relative to the amount of bismuth triflate (entries 3, 4, 8, 10, 11, 12, 13, and 14). As the amount of bismuth triflate was decreased from 25 mol %, the yield of 113 decreased. It is possible that there are certain catalytic cycles involved, which correlate to longer reaction times and smaller yields. When over 25 mol% of bismuth triflate was used the yields remained relatively high, which indicates that after a certain point the amount of catalyst present does not influence the catalytic cycle that it takes for the reaction to go to completion. When more than 25 mol% of bismuth triflate was employed and less lithium perchlorate was present (entries 3 and 4) the reaction mixture perhaps becomes acidic more readily therefore breaking down the sydnone ring.
as previously mentioned. When the there is a larger difference the effect is less noticeable (entries 1 and 2).

**Acylation of Phenyl Sydnone Using Alkyl Anhydrides**

With novel, catalytic acetylations of 3-phenyl sydnone (13) developed; it was of interest to extend the methodology anhydrides. The anhydride most commonly used in our laboratory (aside from acetic anhydride) is trifluoroacetic anhydride and, accordingly, its utility was tested. The reaction conditions were altered by decreasing the amounts of the catalysts to 20 mol%, since TFAA is more reactive than acetic anhydride. After stirring overnight, TLC showed two spots that were not phenyl sydnone and a spot that was identical to 4-acetyl-3-phenyl sydnone (113) (later identified by NMR). Only 5.1 mg of 113 were isolated after column chromatography and there was an insufficient quantity of the second product to permit characterization. Even after reducing the reaction time upon scale up, no satisfactory result was forthcoming. It is possible that the electron withdrawing nature of the fluorine atoms on the anhydride does not allow the bismuth triflate to complex to the carbonyl oxygens and thus, the anhydride is hydrolyzed to the acid, resulting in competitive cleavage of the sydnone ring. At this point, it was felt that it would be more useful to examine reaction with other available anhydrides (viz. propionic, butyric, isobutyric, and benzoic anhydrides) than attempt to improve the results using TFAA.

Scheme 21
Using the previously optimized conditions with propionic anhydride, the three and a half hour reaction time showed that reaction was not greatly sterically hindered. Obtained in a 63% yield, the melting point of 3-propionyl-3-phenyl sydnone was 92 °C and consistent with the literature melting point of 92.5 – 94 °C. As expected, the I.R spectrum showed the sydnone carbonyl stretch at 1792.9 cm$^{-1}$ and 1664.9 cm$^{-1}$ for the carbonyl on the propionyl group attached to the sydnone C-4 carbon, which would normally have a C-H stretch at 3150 cm$^{-1}$. The aromatic region in the proton NMR spectra was consistent with the three aforementioned spectra, with a multiplet in the aromatic region indicating five protons. The methylene group alpha to the carbonyl occurred as a quartet at 2.9 ppm while the methyl group occurred as a triplet at 1.2 ppm. In the carbon-13 NMR for the methylene carbon appeared at 33.78 ppm, and at the methyl carbon 7.13 ppm. The peaks for the sydnone ring occurred at 166.07 ppm for the carbonyl and at 106.90 ppm for the quaternary C-4 carbon. As expected, four signals appeared in the aromatic region and the propionyl carbonyl carbon appeared at 187.78 ppm.
Reaction with butyric anhydride using the previously optimized conditions was more sluggish, undoubtedly due to the steric hindrance of the longer alkyl side chain. Using the standard conditions, the reaction was stirred overnight and TLC showed a faint spot of starting material. After flushing through silica gel and recrystallization from ethanol, only a 36% yield was achieved. It was logical to slightly increase the amounts of catalysts to 30 mol%, and gratifyingly, with this change the yield of the 4-acyl sydnone increased to 63.8%. While it had been apparent for some time that more recently prepared bismuth triflate gave better results it became apparent in this part of the study that the results were best when the bismuth triflate was used the day it was prepared. Thus with fresh bismuth triflate (25 mol %) the yield increased to 73%. It was also necessary to wash the organic layer with aqueous potassium carbonate to eliminate the stench of butyric acid. The larger carbon chain on butyric acid causes it to partition into the organic layer, causing the product to be an oil instead of a solid. The I.R. confirmed acylation by the presence of strong carbonyl stretches at 1780.3 and 1663.9 cm\(^{-1}\) for the sydnone carbonyl and the butyryl carbonyl, respectively. The proton NMR spectrum shows a similar multiplet observed for 4-acetyl-3-phenylsydnone. The butyryl group showed a triplet, sextet, and quartet at 3.9, 1.75, and 0.9 ppm, respectively, with integrations were as expected, viz. 2:2:3. The carbon-13 NMR spectrum showed four signals in the aromatic region and three in the aliphatic region. To distinguish the aliphatic carbons on the butyryl group, a DEPT 135 spectrum showed the difference in the carbons; methyl groups and methine groups are positive peaks and methylene groups gave negative peaks. The peaks at 42.08 and 16.81 ppm were negative, thus indicating methylene groups. The carbonyl deshielded the adjacent methylene group to 42.08 ppm.
The methyl group appeared at 13.64 ppm, the new carbonyl appeared at 187.30 ppm and the sydnone carbonyl appeared at 166.04 ppm. The C-4 peak was similar deshielded to 106.00 ppm due to the butyryl group.

The effect of steric hindrance was more apparent using isobutyric anhydride, where the reaction had to stir overnight affording a 59% when recrystallized from hot ethanol. The same problem of contamination with the corresponding acid occurred with the isobutyric anhydride; therefore, the combined extracts were washed with aqueous potassium carbonate. The melting point for the product was 105-6 °C; no literature melting point was available for comparison. Acylation was apparent in the I.R. spectrum due the presence of a carbonyl stretch at 1672.95 cm\(^{-1}\), the absence of the C-H stretch at 3150 cm\(^{-1}\), and the stretch for the sydnone carbonyl at 1775 cm\(^{-1}\). Carbon-13 NMR gave more evidence of the correct structure. This, in the aromatic region, four signals were present, and two signals were apparent in the aliphatic region, the weaker one, further downfield at 36.99 ppm, being the methine carbon. The equivalent methyl groups appeared at 17.78 ppm, and the sydnone C-4 carbon at 105.50 ppm (deshielded by acylation). The sydnone carbonyl peak occurred at 166.57 and the carbonyl for the isobutyryl group was further downfield at 191.65 ppm. In the proton NMR spectra, there was a multiplet in the aromatic region for the phenyl group, with an integration accounting for the five protons, and two peaks in the aliphatic region for the isopropyl chain. The six protons for the methyl groups occurred as a doublet at 1.3 ppm and the methine group occurred as a septet at 3.5 ppm.

**Acylation of Various Aryl Sydones using Acetic Anhydride**
With successful acylation of 3-phenyl sydnone (13) with other alkyl anhydrides, it was of interest to explore the utility of acetic anhydride with sydnones having different electron withdrawing and donating substituents in the para position. Using the general procedure, their electron withdrawing and donating effects had an effect on the reaction time (Scheme 22). It was exciting to see that the yields achieved were relatively high except when a nitro group was in the para position. Further, the relative effect of the electron withdrawing substituents, chlorine and bromine, was observed when the two reactions were run simultaneously. The reaction with para-chlorophenyl sydnone was complete one half hour after para-bromophenyl sydnone was completely reacted to 4-acetyl-3-(4-bromophenyl) sydnone (119) after 4 hours.

Scheme 22

![Scheme 22](image)

The acylation of p-chlorophenyl sydnone to 118 was confirmed by the presence of a new carbonyl peak at the C-4 position at 1660.42 cm\(^{-1}\) and the absence of the C-H stretch at 3150 cm\(^{-1}\) in the I.R. spectrum. The sydnone carbonyl stretch was present at
The proton NMR spectra exhibited the appropriate coupling pattern for a para-substituted phenyl ring. Two doublets were observed at 7.45 and 7.6 ppm, each with integration for two protons. The methyl on the acetyl group appeared as a singlet at 2.5 ppm. This methyl group appeared in the carbon-13 NMR spectra at 28.11 ppm. Other key peaks in the latter were the carbonyl peaks at 166.01 ppm for the sydnone and one further downfield at 184.30 ppm for the acetyl. The quaternary C-4 peak was present at 106.01 ppm instead of its “usual” position of ~ 95 ppm and, as expected, four peaks were present in the aromatic region. The product 118, was recrystallized from hot ethanol and was achieved in 87% yield with a melting point of 127 – 8 °C, corresponding to a literature melting point of 128 – 131°C.

The melting point of 4-acetyl-3-(4-bromophenyl)sydnone (119), 168 – 70 °C was consistent with its literature melting point of 169 – 70 °C. The proton and carbon-13 NMR spectra were very similar to 118. As expected, two doublets appeared at 7.3 and 7.75 ppm for the aromatic protons, as well as a singlet for the acetyl methyl at 2.5 ppm. The methyl group appeared in the carbon-13 spectra at 28.08 ppm and the sydnone C-4 at 105.98 ppm. The aromatic carbons were represented by four signals between 133.73 and 126.41 ppm. The sydnone and acetyl carbonyl signals appeared at 166.00 and 184.28 ppm, respectively.

Acylation on para-tolylphenyl sydnone was complete after two hours and was achieved in an 83% yield. This was confirmed by the absence of the C-H stretch at 3150 cm\(^{-1}\) and the appearance of a carbonyl stretch at 1667.17 cm\(^{-1}\), while the sydnone stretch occurred at 1782.87 cm\(^{-1}\). The proton NMR spectrum four peaks should be observed. Thus, the methyl on the acetyl group and the tolyl methyl appeared at 2.53 and 2.48 ppm,
respectively. The aromatic region should have two doublets; however these doublets are apparently on top of each other and appeared as one peak at 7.37 ppm. The carbon-13 spectrum was more reassuring because it showed four peaks in the aromatic region. The two methyl groups were present at 28.14 and 21.49 ppm, the latter being the tolyl methyl. The acetyl carbonyl was at 184.22 ppm and the key peaks for a sydnone were present, viz. a carbonyl at 166.35 ppm and the C-4 at 105.97 ppm. The melting point of 113 – 4 °C was close to the literature\textsuperscript{92} melting point of 119 – 20 °C

The effect of the electron donating ability of the methoxy group even was more noticeable than the methyl group. Reaction with \textit{para}-methoxyphenyl sydnone took place in thirty minutes and 121 was achieved in 78% yield. The melting point of 96-8 °C corresponded to the literature melting point of 97 – 8 °C. The I.R. spectrum showed a peak for the sydnone carbonyl at 1776.12 cm\textsuperscript{-1} and a peak for the acetyl carbonyl stretch at 1665.24 cm\textsuperscript{-1}. The C-H stretch was not present at 3150 cm\textsuperscript{-1}. The proton NMR spectrum showed two doublets in the aromatic region for the four protons on the aromatic ring at 7.44, 7.41, 7.06, and 7.03 ppm. The methoxy protons appear as a singlet at 3.96 ppm. The acetyl methyl group appeared as a singlet at 2.57 ppm and was present at 28.16 ppm in the carbon-13 spectrum. The methoxy carbon appeared at 55.78 ppm. The methoxy group deshields the carbon to which it is attached on the aromatic ring and that carbon appears at 162.44 ppm. The other three carbon signals were present in the aromatic region. The carbonyl carbon signals appeared at 166.24 and 184.26 ppm for the sydnone carbonyl and the acetyl carbonyl, respectively. The sydnone C-4 peak appeared at 105.90 ppm.
A nitro group para to the sydnone ring, however, caused the reaction to be rather sluggish and not go to completion. In efforts to help the reaction to completion, one equivalent of acetic anhydride and 10 mol% of bismuth triflate and lithium perchlorate were added after 26 hours. The reaction was then allowed to stir for another 46 hours, but it did not go to completion. Due to solubility issues, it was difficult to completely isolate the starting material and product and only a 37% yield of the latter was obtained, which was also difficult to recrystallize. Accordingly, a satisfactory carbon-13 NMR spectrum was not obtained. The quaternary carbons did not appear, but the two aromatic C-H carbons appeared at 126.53 and 124.86 ppm and the acetyl methyl was present at 27.99 ppm. Doublets for the aromatic protons appeared at 8.5 and 7.7 ppm and the acetyl methyl group appeared as a singlet at 2.6 ppm in the proton NMR spectrum.

**Diacylations of 3,5-Dimethoxyphenyl Sydnone with Alkyl Anhydrides**

Since acylation had proven successful with a variety of sydnones and anhydrides, it was hoped that activated aromatic rings would allow acylation on the sydnone ring as well as the phenyl ring, as observed with bromination. The standard acylating conditions were used to test this phenomenon (Scheme 23). TLC showed complete conversion after one and a half hours, however two spots higher running than the starting material were observed.

Scheme 23
After column chromatography and recrystallization, the mono-acetyl product (124) was obtained in 3.2% yield and the di-acetyl product (125) was obtained in a 12% yield. It is important to mention that the close proximity of the two spots on TLC makes these products difficult to separate therefore; the yields reported are not exact, as there was still a small mixture of 124 and 125 that was not separated. As these were new compounds, there were no melting point data to compare. The melting point of 124 was 130 – 1 °C. However, even given the small amounts available, the proton and carbon-13 NMR spectra provided sufficient information to determining the structures.

As expected for 124, the proton NMR had singlets at 2.5 and 3.9 ppm for the acetyl methyl and the symmetrical methoxy groups on the phenyl ring, respectively. The aromatic region had a doublet at 6.6 and a triplet at 6.7 ppm, with integration being two to one. In the carbon-13 NMR spectrum, the C-4 peak appeared at 106.07 ppm and the the two aromatic C-H signals were located just upfield at 103.97 and 103.40 ppm. The aromatic carbon attached to the sydnone was deshielded to 136.20 ppm, and the methoxy group shifted the adjacent aromatic carbon signal downfield to 161.09 ppm. The symmetrical methoxy carbons had a signal at 55.85 ppm and the signal for the acetyl methyl was located at 28.14 ppm. The carbonyl signals were present at 167 and 183.99
ppm for the sydnone and acetyl carbonyl carbons, respectively. The I.R. spectrum had two peaks that also confirmed acylation, a peak at 1777.09 cm\(^{-1}\) for the sydnone carbonyl and a peak at 1670 cm\(^{-1}\) for the acetyl carbonyl stretch.

It had been shown previously, that bromination of 3, 5-dimethoxyphenyl sydnone (123) occurred at the 2 position but not at the 4 position of the phenyl group, although both positions were activated by the methoxy groups, which are ortho/para directors. The same phenomenon was observed with acylation, causing the phenyl group to lose symmetry, which was apparent in the proton and carbon-13 NMR spectra. The proton NMR spectrum of 125 showed two doublets in the aromatic region for the protons on the aromatic ring. The singlets for the acetyl methyl groups appeared at 2.45 and 2.5 ppm. The singlets for the methoxy groups were present at 3.9 and 4.1 ppm. As expected, 14 peaks were present in the carbon-13 spectrum. Downfield, signals for three carbonyls were present. The acetyl group attached to the phenyl ring does not experience as much resonance as the sydnone carbonyl and the acetyl group on the C-4 carbon, therefore, is most downfield at 196.86 ppm. The acetyl attached to the sydnone C-4 carbon has a signal at 184.40 ppm while the sydnone carbonyl is present at 165.85 ppm. As discussed earlier, the methoxy groups deshield their adjacent aromatic carbons, which are present at 162.55 and 160.01 ppm. The other aromatic carbons are present at 106.98, 104.41, and 101.59 ppm. The sydnone C-4 carbon is present at 106.98 ppm and the methoxy groups appear 56.31 and 56.09 ppm. The acetyl methyl signals appear at 32.00 and 27.58 ppm. In the I.R. spectrum, the sydnone carbonyl stretch is present at 1768.41 cm\(^{-1}\) and the other two carbonyl stretches appear as a double peak at 1682.59 and 1668.13 cm\(^{-1}\).
The next steps for this project were to find the conditions in which complete conversion from 124 to 125 could be achieved and to test the utility of the bulkier anhydrides. The first step was to allow more time for the reaction to stir since, previously, it was worked up once the starting material was consumed, which was about one and a half hours later. In the modified procedure, Stirring was continued overnight, but TLC indicated that 124 was still present in the reaction mixture. Table 5 shows the different amounts of catalysts and anhydride used in attempts to achieve complete conversion. None of these efforts resulted in complete conversion, however; it was evident that too much catalyst or anhydride decreased the conversion and the yield. Increasing the reaction time, apparently caused sydnone ring cleavage, thus decreasing the yield. When the amount of acetic anhydride was increased to 10 equivalents, for example, the conversion was low and small amounts of product were obtained. Although the yields decreased upon allowing the reaction to stir for a longer time, the conversion to the diacetyl product was increased, a trade-off that may be necessary to facilitate product separation.

Table 5. Effect of Catalysts and Anhydride on Conversion to Diacetyl Compound

<table>
<thead>
<tr>
<th>Entry</th>
<th>mol% catalysts</th>
<th>Equivalents anhydride</th>
<th>Time (h)</th>
<th>Ratio (monoacetyl:diacetyl)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>25</td>
<td>6 acetic</td>
<td>48</td>
<td>1:3</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>6 acetic</td>
<td>overnight</td>
<td>1:4</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>6 propionic</td>
<td>overnight</td>
<td>1:1</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>6 butyric</td>
<td>overnight</td>
<td>1:2</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>8 acetic</td>
<td>overnight</td>
<td>4:9</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>4 acetic</td>
<td>overnight</td>
<td>4:9</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>4 propionic</td>
<td>overnight</td>
<td>4:9</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>4 butyric</td>
<td>overnight</td>
<td>8:10</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>6 acetic</td>
<td>2</td>
<td>1:2</td>
<td>71</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>6 acetic</td>
<td>70</td>
<td>1:6</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>8 acetic</td>
<td>overnight</td>
<td>1:5</td>
<td>83</td>
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<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>13</td>
<td>40</td>
<td>8 propionic</td>
<td>overnight</td>
<td>1:1</td>
<td>86</td>
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<tr>
<td>14</td>
<td>40</td>
<td>8 butyric</td>
<td>overnight</td>
<td>1.2</td>
<td>93</td>
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<tr>
<td>15</td>
<td>50</td>
<td>10 acetic</td>
<td>overnight</td>
<td>45:1</td>
<td>35</td>
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<tr>
<td>16</td>
<td>50</td>
<td>10 propionic</td>
<td>overnight</td>
<td>13:1</td>
<td>25</td>
</tr>
<tr>
<td>17</td>
<td>50</td>
<td>10 butyric</td>
<td>overnight</td>
<td>4:1</td>
<td>35</td>
</tr>
</tbody>
</table>

Two separate reactions (entries 10 and 11) with 40 mol% of catalysts and 6 equivalents acetic anhydride were set-up side by side. Entry 10 was quenched after 2 hours (when starting material (123) had been consumed). Entry 11 was quenched after stirring over the weekend (70 hours). Once the crude product was flushed through a plug of silica gel to remove baseline material, the proton NMR spectrum of the mixture of the two products was used to determine relative amounts of mono- and di-acetyl products. In the aromatic region, the peak for the two identical protons on 124 had the same integration as a peak containing one proton for 125, thus the ratio of 124:125 was 1:2. This was verified by the methoxy peaks. The integration of the integrations for the methoxy groups in 125 was twice the integration for the peak for the methoxy peak in 124. With the same conditions and stirring for 70 hours, however, the ratio of 124:125 was 1:6.

Reactions involving 30 mol% of catalysts with 6 equivalents of acetic anhydride (entry 2) and 40 mol% catalysts with 8 equivalents of acetic anhydride (entry 12) were stirred simultaneously overnight. The conversion of 124 to 125 increased to 1:4 (entry 2) and to 1:5 (entry 12), respectively. It seemed likely that increasing the amount of catalysts and acetic anhydride further would convert the remaining small amount of 124 to 125. Accordingly, simultaneous reactions of 100 mol% bismuth triflate, 50 mol% lithium perchlorate and 6 equivalents acetic anhydride and 100 mol% catalysts and 5
equivalents acetic anhydride, were stirred overnight. The results were surprising, in that TLC showed that the latter still had unreacted starting material while the former had formed 124 and 125 in an equal ratio. It was apparent that the presence of too much lithium perchlorate slowed the reaction. An extension of these conditions was explored with the other anhydrides.

Accordingly, 123, 6 equivalents of propionic anhydride and 30 mol% catalysts (entry 4) was stirred for 24 hours; a 1:1 ratio of 126:127 was obtained. The mixture was separated for the sake of identification. The melting point of 127 was observed to be 138-9 °C; however, a known melting point was not available for comparison. The proton NMR spectrum of 127 showed two doublets of the same intensity in the aromatic region and the methoxy groups appeared at 3.8 and 3.9 ppm. The peaks for the expected quartets overlapped around 2.8 ppm for the methylene protons and the same was observed for the triplets for the methyl protons around 1 ppm. The carbon-13 NMR spectrum was more conclusive for the formation of the diacyl species 127. The two methylene signals were present at 37.34 and 33.37 ppm, while the methyl signals were upfield at 8.18 and 7.07 ppm. The methoxy carbons were present at 56.25 and 56.04 ppm; their neighboring aromatic carbons appeared at 162.26 and 159.60 ppm. The quaternary carbon attached to the sydnone ring appeared at 135.25 ppm, while the other two were more upfield, located at 104.17 and 101.56 ppm. The two sydnone carbons appeared where expected, at 165.71 ppm for the carbonyl and 107.00 ppm for the C-4 carbon. The carbonyl attached to the C-4 carbon appeared at 187.93 ppm and the carbonyl attached to the aromatic ring was present at 200.64 ppm. The extra carbon on the anhydride had little impact on the conversion of 126 to 127; however, reactions using
30, 40, and 50 mol% catalysts with 4, 6 and 10 equivalents of propionic anhydride, never achieved complete conversion of 123 to 127 presumably for steric reasons.

In the case of butyric anhydride, the longer carbon chain on the carbonyl caused less of 128 to be converted to 129 than observed with the less hindered anhydrides. Efforts with 40, 30, 40, and 50 mol% of catalysts were used in combination with 4, 6, 8, and 10 equivalents of butyric anhydride, respectively; however the two products (mono- and di-acyl, 128 and 129, respectively) were still obtained in all four cases. Proton NMR showed 128 to have a doublet and a triplet in the aromatic region, with a ratio of 2:1. A singlet appeared at 3.9 ppm, indicating the symmetrical methoxy groups. The methylene protons on the butyryl group appeared as a triplet at 2.9 ppm and a sextet at 2.7 ppm and the methyl group appeared as a triplet around 1 ppm. In the carbon-13 NMR spectrum, the methylene adjacent to the carbonyl on the butyryl group appeared at 42.10 ppm, while the other methylene and the methyl appeared at 16.82 and 13.64 ppm, respectively. The methoxy signal was present at 55.83 ppm and the aromatic carbon attached to that methoxy group was located at 161.07 ppm. The aromatic carbon neighboring the sydnone ring was at 136.32 ppm. The other aromatic carbons were further upfield at 103.82 and 103.40 ppm while the sydnone C-4 carbon was located at 106.05 ppm and the sydnone and butyryl carbonyl were located at 165.97 and 187.05 ppm, respectively.

There was no sign of reaction when using due to the steric hindrance of the isobutyric anhydride, even when the reaction allowed to stir overnight using various conditions. Acylation on the C-4 position was not possible using 40 and 30 mol% of catalysts with 4 and 4.5 equivalents of isobutyric anhydride, respectively.
At this point, because of lack of time, no future work was done. Future plans would involve the exploration of other “green” catalysts, conditions and activated sydnones. In conclusion, a facile method for Friedel-Crafts acylation has been developed using 3-aryl sydnones with various alkyl anhydrides and bismuth triflate and lithium perchlorate as catalysts. This method was more environmentally friendly and employed milder conditions than conditions previously reported. As an extension of the project, sydnones containing activated aromatic rings were able to be acylated on the aryl ring and the sydnone ring. The diacyl compounds prepared will be used in efforts to form fused ring sydnones via McMurry coupling or reduction to form a pinacol using samarium(II) diiodide.
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 Mattson Genesis II FTIR. NMR spectra were acquired on a Bruker 300MHz NMR. Elemental analyses were performed by Midwest Microlab LLC, Indianapolis, Indiana.

Synthesis of N-phenylsydnone (13)

N-phenylsydnone was synthesized from commercially available N-phenylglycine according to reported procedures\(^{93}\).

Synthesis of bismuth triflate

Bismuth triflate was synthesize from commercially available triphenyl bismuthene according to reported procedures\(^{94}\).

Attempted preparation of 4-acetyl-3-phenyl sydnone (113) using 5 mol% metal triflate and lithium perchlorate and 1.5 equivalents of acetic anhydride in acetonitrile

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10\(^{-4}\) mol), metal triflate (7.71x10\(^{-6}\) mol), lithium perchlorate (0.0008 g, 7.71x10\(^{-6}\) mol), and acetic
anhydride (22 µL, 2.313x10^{-4} mol) were stirred on the shaker overnight at room temperature, 35 ºC, and 50 ºC.

**Bismuth triflate at room temperature**

Using bismuth triflate (0.0051 g) at room temperature, TLC versus an authentic sample showed no reaction.

**Bismuth triflate at 35 ºC**

Using bismuth triflate (0.0051 g), at 35 ºC, TLC versus an authentic sample showed no reaction.

**Bismuth triflate at 50 ºC**

Using bismuth triflate (0.0051 g), at 50 ºC, TLC versus an authentic sample showed partial conversion to 113.

**Scandium triflate at room temperature**

Using scandium triflate (0.0038 g) at room temperature, TLC versus an authentic sample showed no reaction.

**Scandium triflate at 35 ºC**

Using bismuth triflate (0.0038 g), at 35 ºC, TLC versus an authentic sample showed no reaction.
Scandium triflate at 50 ºC

Using bismuth triflate (0.0038 g), at 50 ºC, TLC versus an authentic sample showed no reaction.

Ytterbium triflate at room temperature

Using ytterbium triflate (0.0048 g) at room temperature, TLC versus an authentic sample showed no reaction.

Ytterbium triflate at 35 ºC

Using ytterbium triflate (0.0048 g), at 35 ºC, TLC versus an authentic sample showed no reaction.

Ytterbium triflate at 50 ºC

Using ytterbium triflate (0.0048 g), at 50 ºC, TLC versus an authentic sample showed no reaction.

Attempted preparation of 113 using 5 mol% metal triflate and lithium perchlorate and 1.5 equivalents of acetic anhydride in nitromethane

In a small vial nitromethane (1 mL), phenyl sydnone (0.025 g, 1.542x10^{-4} mol), metal triflate (7.71x10^{-6} mol), lithium perchlorate (0.0008 g, 7.71x10^{-6} mol), and acetic anhydride (22 µL, 2.313x10^{-4} mol) were stirred on the shaker for two days at 50 ºC.

Bismuth triflate at 50 ºC
Using bismuth triflate (0.0051 g) at 50 ºC, TLC versus an authentic sample showed no reaction after stirring overnight; however, when the reaction was allowed to stir for an additional day, slight conversion was apparent to 113.

Scandium triflate at 50 ºC

Using bismuth triflate (0.0038 g), at 50 ºC, TLC versus an authentic sample showed no reaction.

Ytterbium triflate at 50 ºC

Using ytterbium triflate (0.0048 g), at 50 ºC, TLC versus an authentic sample showed no reaction.

Attempted preparation of 113 using 10 mol% bismuth triflate and lithium perchlorate and 1.5 equivalents of acetic anhydride in acetonitrile

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^-4 mol), metal triflate (0.0102 g, 1.54x10^-5 mol), lithium perchlorate (0.0016 g, 1.54x10^-5 mol), and acetic anhydride (22 µL, 2.313x10^-4 mol) were stirred on the shaker overnight at 50 ºC. TLC versus an authentic sample showed partial conversion to 113.

Attempted preparation of 113 using 5 mol% bismuth triflate and lithium perchlorate and 2 equivalents of acetic anhydride in acetonitrile

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^-4 mol), bismuth triflate (0.0051 g, 7.71x10^-6 mol), lithium perchlorate (0.0008 g, 7.71x10^-6 mol),
and acetic anhydride (29 µL, 3.080x10^{-4} mol) were stirred on the shaker for 3 days at 50 ºC. TLC versus authentic 113 showed 50% conversion from the starting material.

**Attempted preparation of 113 using 5 mol% bismuth triflate and lithium perchlorate and 3 equivalents of acetic anhydride in acetonitrile**

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^{-4} mol), bismuth triflate (0.0051 g, 7.71x10^{-6} mol), lithium perchlorate (0.0008 g, 7.71x10^{-6} mol), and acetic anhydride (44 µL, 4.625x10^{-4} mol) were stirred on the shaker for 3 days at 50 ºC. TLC versus authentic 113 showed over 60% conversion from the starting material.

**Attempted preparation of 113 using 10 mol% bismuth triflate and lithium perchlorate and 2 equivalents of acetic anhydride in acetonitrile**

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^{-4} mol), bismuth triflate (0.0102 g, 1.542x10^{-5} mol), lithium perchlorate (0.0016 g, 1.542x10^{-5} mol), and acetic anhydride (29 µL, 3.080x10^{-4} mol) were stirred on the shaker for 2 days at 50 ºC. TLC versus authentic 113 showed over 60% conversion from the starting material.

**Attempted preparation of 113 using 15 mol% bismuth triflate and lithium perchlorate and 2 equivalents of acetic anhydride in acetonitrile**

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^{-4} mol), bismuth triflate (0.0153 g, 2.311x10^{-5} mol), lithium perchlorate (0.0024 g, 2.311x10^{-5} mol), and acetic anhydride (29 µL, 3.080x10^{-4} mol) were stirred on the shaker for 2 days
at 50 ºC. TLC versus authentic 113 showed over 60% conversion from the starting material.

**Attempted preparation of 113 using 10 mol% bismuth triflate and lithium perchlorate and 3 equivalents of acetic anhydride in acetonitrile**

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^-4 mol), bismuth triflate (0.0102 g, 1.542x10^-5 mol), lithium perchlorate (0.0016 g, 1.542x10^-5 mol), and acetic anhydride (44 µL, 4.625x10^-4 mol) were stirred on the shaker for 2 days at 50 ºC. TLC versus authentic 113 showed over 70% conversion from the starting material.

**Attempted preparation of 113 using 15 mol% bismuth triflate and lithium perchlorate and 3 equivalents of acetic anhydride in acetonitrile**

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^-4 mol), bismuth triflate (0.0153 g, 2.311x10^-5 mol), lithium perchlorate (0.0016 g, 2.311x10^-5 mol), and acetic anhydride (44 µL, 4.625x10^-4 mol) were stirred on the shaker for 2 days at 50 ºC. TLC versus authentic 113 showed it being the major spot with a trace of starting material.

**Attempted preparation of 113 using 20 mol% bismuth triflate and lithium perchlorate and 3 equivalents of acetic anhydride in acetonitrile**

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^-4 mol), bismuth triflate (0.0204 g, 3.08x10^-5 mol), lithium perchlorate (0.0032 g, 3.08x10^-5 mol),
and acetic anhydride (44 µL, 4.625x10^{-4} mol) were stirred on the shaker for 2 days at 50 ºC. TLC versus authentic 113 showed it being the major spot with a trace of starting material.

**Attempted preparation of 113 using 15 mol% bismuth triflate and lithium perchlorate and 3 equivalents of acetic anhydride in acetonitrile**

In a 50 mL round bottom flask equipped with a reflux condenser, acetonitrile (4 mL), phenyl sydnone (0.05 g, 3.048x10^{-4} mol), bismuth triflate (0.0306 g, 4.622x10^{-5} mol), lithium perchlorate (0.0048 g, 4.622x10^{-5} mol), and acetic anhydride (88 µL, 9.25x10^{-5} mol) were stirred at an oil bath temperature of 70 ºC for 19 hours and at 110 ºC for 4 hours. TLC versus authentic 113 showed about 60% conversion from the starting material.

**Attempted preparation of 113 using 20 mol% bismuth triflate and lithium perchlorate and 3 equivalents of acetic anhydride in acetonitrile**

In a 50 mL round bottom flask equipped with a reflux condenser, acetonitrile (4 mL), phenyl sydnone (0.05 g, 3.048x10^{-4} mol), bismuth triflate (0.0655 g, 6.16x10^{-5} mol), and acetic anhydride (88 µL, 9.25x10^{-4} mol) were stirred at an oil bath temperature of 70 ºC for 24 hours. TLC versus authentic 113 showed about 50% conversion from starting material.

**Attempted preparation of 113 using 20 mol% bismuth triflate and 4 equivalents of acetic anhydride in acetonitrile**
In a 50 mL round bottom flask equipped with a reflux condenser, acetonitrile (4 mL), phenyl sydnone (0.05 g, 3.048x10^{-4} mol), bismuth triflate (0.0655 g, 6.16x10^{-5} mol), and acetic anhydride (116 µL, 1.233x10^{-4} mol) were stirred at an oil bath temperature of 70 ºC for 24 hours. TLC versus authentic 113 showed about 80% conversion from starting material.

Attempted preparation of 113 using 20 mol% bismuth triflate lithium perchlorate and 3 equivalents of acetic anhydride in acetonitrile

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^{-4} mol), fresh bismuth triflate (0.0204 g, 3.08x10^{-5} mol), lithium perchlorate (0.0204 g, 3.08x10^{-5} mol), and acetic anhydride (44 µL, 4.625x10^{-4} mmol) were stirred on the shaker overnight at 70 ºC. TLC versus authentic 113 showed about 50% conversion of the starting material after three hours and complete conversion after stirring overnight.

Attempted preparation of 113 using 20 mol% bismuth triflate lithium perchlorate and 4 equivalents of acetic anhydride in acetonitrile

In a small vial acetonitrile (1 mL), phenyl sydnone (0.025 g, 1.542x10^{-4} mol), fresh bismuth triflate (0.0204 g, 3.08x10^{-5} mol), lithium perchlorate (0.0204 g, 3.08x10^{-5} mol), and acetic anhydride (58 µL, 6.168x10^{-4} mol) were stirred on the shaker overnight at 70 ºC. TLC versus authentic 113 showed about 70% conversion of the starting material after three hours and complete conversion after stirring overnight.
Attempted preparation of 113 using 20 mol% bismuth triflate lithium perchlorate and 4 equivalents of acetic anhydride in acetonitrile

In a pressure tube acetonitrile (5 mL), phenyl sydnone (0.1000 g, 6.167x10^{-4} mol), bismuth triflate (0.1013 g, 1.542x10^{-4} mol, 25 mol%), lithium perchlorate (0.0164 g, 1.542x10^{-4} mol, 25 mol%), and acetic anhydride (232 µL, 2.467x10^{-3} mol) were stirred at an oil bath temperature of 95 °C. After 6 hours, 5 mL of water was added; the stirring was continued for 5 minutes then allowed to cool to room temperature. The reaction mixture was extracted with methylene chloride (3 x 10 mL), and the combined extracts were removed in vacuo. Baseline material was removed by running through a plug of silica gel (methylene chloride) and afforded tan crystals (0.0763 g, 60%), which were recrystallized from hot ethanol to afford colorless crystals (0.0670 g, 53%). TLC and melting point (143 °C) corresponded with 113.

General procedure for Friedel-Crafts acylations of sydnones

In a pressure tube acetonitrile (5 mL), phenyl sydnone (6.167x10^{-4} mol), bismuth triflate (1.542x10^{-4} mol, 25 mol%), lithium perchlorate (1.542x10^{-4} mol, 25 mol%), and alkyl anhydride (2.467x10^{-4} mol) were stirred at an oil bath temperature of 95 °C. After six and a half hours the reaction was complete, 5 mL of water was added; the stirring was continued for 5 minutes then allowed to cool to room temperature. The reaction mixture was extracted with methylene chloride (3 x 10 mL), and the combined extracts were removed in vacuo. The resulting solid was recrystallized from hot ethanol.

Synthesis of 4-acetyl-3-phenyl sydnone (113)
Using the standard procedure, phenyl sydnone (0.1000 g), bismuth triflate (0.1012 g), lithium perchlorate (0.0164 g), and acetic anhydride (232 µL) were stirred for 2h. The resulting solid was recrystallized from ethanol producing colorless crystals (0.08946 g, 71%), m.p. 142.

I.R. (KBr): 3060.49, 1997.34 (C=O), 1666.20 (C=O), 1427.07, 1052.94, 769.46 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\)): 7.8-7.3 (m, 9H), 6.9 (s, sydnone H) ppm.

\(^1\)C-NMR (CDCl\(_3\)): 169.0 (C=O), 135.1, 134.0, 132.0, 131.8, 129.7, 129.5, 128.7, 124.9, 121.3, 119.1, 97.6 (sydnone C-4), 97.2, 82.3 ppm.

**Synthesis of 4-acetyl-3-(4-tolyl) sydnone (120)**

Using the standard procedure, 4-tolyl sydnone (0.1089 g), bismuth triflate (0.1012 g), lithium perchlorate (0.0164 g), and acetic anhydride (232 µL) were stirred for 2h. The resulting solid was recrystallized from hot ethanol and afforded colorless crystals (0.1116 g, 83%), m.p. 113 – 4 °C.

I.R. (KBr): 2924.53, 1782.87 (sydnone C=O), 1667.17 (acetyl C=O), 1506.63, 1430.93, 1051.02, 824.42 cm\(^{-1}\)

\(^1\)H-NMR (CDCl\(_3\)): 7.37 (s, 4H), 2.53 (s, 3H), 2.48 (s, 3H) ppm.

\(^1\)C-NMR (CDCl\(_3\)): 184.33, 166.35 (C=O), 143.12, 132.45, 129.96, 124.58, 105.97 (sydnone C-4), 28.14, 21.49 ppm.

**Synthesis of 4-acetyl-3-(4-bromophenyl) sydnone (119)**
Using the standard procedure, 4-bromophenyl sydnone (0.1438 g), bismuth triflate (0.1012 g), lithium perchlorate (0.0164 g), and acetic anhydride (232 µL) were stirred for 4h. The resulting solid was recrystallized from hot ethanol (0.1442 g, 83%), m.p. 168 – 70 °C.

I.R. (KBr): 3095.58, 1788.66 (sydnone C=O), 1662.34 (acetyl C=O), 1432.85, 832.13 cm⁻¹.

¹H-NMR (CDCl₃): 7.75 (d, 2 H), 7.3 (d, 2 H), 2.5 (s, 3H) ppm.

¹³C-NMR (CDCl₃): 184.28, 166.00 (C=O), 133.73, 132.74, 127.03, 126.41, 105.98 (sydnone C-4), 28.08 ppm.

Synthesis of 4-acetyl-3-(4-chlorophenyl) sydnone (118)

Using the standard procedure, 4-chlorophenyl sydnone (0.1219 g), bismuth triflate (0.1012g), lithium perchlorate (0.0164 g), and acetic anhydride (232 µL) were stirred for 4.5h. The resulting solid was recrystallized with hot ethanol (0.1287 g, 87.4%) m.p. 127 - 8 °C.

I.R. (KBr): 3099.06, 1784.80 (sydnone C=O), 1660.42 (acetyl C=O), 1493.60, 1434.78, 1405.86, 1321.97, 1089.59, 837.92 cm⁻¹.

¹H-NMR (CDCl₃): 7.75 (d, 2 H), 7.3 (d, 2 H), 2.5 (s, 3H) ppm.

¹³C-NMR (CDCl₃): 184.30, 166.01 (C=O), 138.85, 133.21, 129.75, 126.26, 106.01 (sydnone C-4), 28.11 ppm.

Synthesis of 4-acetyl-3-(4-methoxyphenyl) sydnone (121)
In a pressure tube 5 mL acetonitrile, 4-methoxyphenyl sydnone (0.1185 g), bismuth triflate (0.1012 g), lithium perchlorate (0.0164 g), and acetic anhydride (232 µL,) were for ½ h. The resulting solid was recrystallized from ethanol to afford colorless crystals (0.1134 g, 79 %), m.p. 96 – 98 °C.

I.R. (KBr): 3079.78, 1788.66, 1776.12 (sydnone C=O), 1665.24 (acetyl C=O), 1606.42, 1511.92, 1438.64, 1408.75, 1259.29, 1175.40, 1051.02, 1024.02, 833.10, 593.00 cm⁻¹.

1H-NMR (CDCl₃): 7.65 (d, 2 H), 7.1 (d, 2 H), 3.9 (s, 3H), 2.6 (s, 3H) ppm.

13C-NMR (CDCl₃): 184.260, 166.42 (C=O), 162.44, 127.45, 126.31 114.44, 105.90 (sydnone C-4), 55.78, 28.16 ppm.

Synthesis of 4-acetyl-3-(4-nitrophenyl) sydnone (122)

In a pressure tube 5 mL acetonitrile, 4-nitrophenyl sydnone (0.0927 g, 4.475x10⁻⁴ mol), bismuth triflate (0.1118 g, 7.34x10⁻⁵ mol, 25 mol%), lithium perchlorate (0.0138 g, 1.301x10⁻⁵ mol, 25 mol%), and acetic anhydride (169 µL, 1.79x10⁻³ mol) were for 26h. TLC showed incomplete conversion of starting material so bismuth triflate (0.0294 g, 4.475x10⁻⁵ mol), lithium perchlorate (0.0047 g, 4.475x10⁻⁵ mol), and acetic anhydride (42 µL, 4.475x10⁻⁴ mol) were added and after stirring was continued for 24 hours. No improvement was made on the conversion so standard-work-up was employed. After column chromatography (methylene chloride) a dark brown solid was obtained (0.041 g, 1.645x10⁻⁴ mol, 37%), which was recrystallized from hot ethanol and afforded a dark brown solid (0.0050 g, 2.007x10⁻⁵ mol, 5%)
I.R. (KBr): 3099.06, 1784.80 (sydnone C=O), 1660.42 (acetyl C=O), 1493.60, 1434.78, 1405.86, 1321.97, 1089.59, 837.92 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$): 8.5 (d, 2 H), 7.7 (d, 2 H), 26 (s, 3H) ppm.

$^{13}$C-NMR (CDCl$_3$): 126.53, 124.86, 27.99 ppm.

Synthesis of 4-propionyl-3-phenyl sydnone (114)

Using the standard procedure, phenyl sydnone (0.1000 g), bismuth triflate (0.1012 g), lithium perchlorate (0.0164 g), and propionic anhydride (318 µL) were stirred at an oil bath temperature of 95 °C for 4h. The resulting solid was recrystallized from hot ethanol and afforded (0.0848 g, 63%), m.p. 92 °C.

I.R. (KBr): 3069.5, 2962.4, 2968.4, 2835.0, 1793.9 (sydnone C=O), 1663.5 (C=O), 1491.3, 1426.2, 1299.9, 1022.4, 961.5, 766.5, 689.1 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$): 7.7 (m 5H), 2.9 (q, 2H), 1.1 (t, 3H) ppm.

$^{13}$C-NMR (CDCl$_3$): 187.78 (C=O), 166.07 (sydnone C=O), 135.05, 132.28, 129.42, 124.89, 105.90 (sydnone C-4), 33.78, 7.13 ppm.

Synthesis of 4-butyryl-3-phenyl sydnone (115)

Using the standard procedure, phenyl sydnone (0.1000 g), bismuth triflate (0.1012 g), lithium perchlorate (0.0164 g), and butyric anhydride (404 µL) were stirred overnight. The combined organic layers were washed with aqueous potassium carbonate and removed in vacuo. The resulting solid was recrystallized with hot ethanol, (0.1045 g, 73%), m.p. 62 – 4 °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\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\)): 7.7 (m 5H), 2.9 (t, 2H), 1.7 (s, 2H), 0.9 (t, 3H) ppm.

\(^13\)C-NMR (CDCl\(_3\)): 197.30 (C=O), 166.04 (sydnone C=O), 135.09, 132.28, 129.43, 124.87, 106.00 (sydnone C-4), 42.08, 16.81, 13.64 ppm.

Synthesis of 4-isobutyryl-3-phenyl sydnone (116)

Using the standard procedure, phenyl sydnone (0.1000 g), bismuth triflate (0.1012 g), lithium perchlorate (0.0164 g), and acetic anhydride (403 µL) were stirred at an oil bath temperature of 95 °C overnight. The resulting solid was recrystallized from hot ethanol affording colorless crystals (0.0845 g, 59%), m.p. 105 - 6 °C.

I.R. (KBr): 3023.85, 2972.75, 2933.85, 2876.32, 1775.16 (sydnone C=O), 1672.95 (C=O), 1422.25, 1297.86, 1168.86, 955.09, 764.64, 688.46 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\)): 7.7 (m 5H), 3.6 (s, 1H), 1.1 (d, 6H) ppm.

\(^13\)C-NMR (CDCl\(_3\)): 191.65 (C=O), 165.57 (sydnone C=O), 135.21, 132.28, 129.6 124.77, 105.50 (sydnone C-4), 36.99, 17.78 ppm.

General Procedure for synthesis of 4-acetyl-3-phenyl sydnone (113) exploring catalyst effects

In a pressure tube acetonitrile (5 mL), phenyl sydnone (0.1000 g, 6.167x10\(^{-4}\) mol), acetic anhydride from a new bottle (232 µL, 2.467x10\(^{-3}\) mol) with varied amounts bismuth triflate and lithium perchlorate were stirred at an oil bath temperature of 95 °C. When the reaction was complete, 5 mL of water was added, the stirring was continued for
5 minutes then allowed to cool to room temperature. The reaction mixture was extracted with methylene chloride (3 x 10 mL), and the combined extracts were removed in vacuo. The crude product was flushed through a plug of silica gel with methylene chloride to remove baseline material.

**Synthesis using bismuth triflate (45 mol%) and lithium perchlorate (2 mol%)**

Using the general procedure, bismuth triflate (0.1821 g, 2.775x10^{-4} mol) and 0.1 M LiClO$_4$/acetonitrile solution (1.23x10^{-5} mol, 123 µL) were stirred for two hours. The resulting product was colorless crystals (0.1035 g, 82%).

**Synthesis using bismuth triflate (40 mol%) and lithium perchlorate (5 mol%)**

Using the general procedure, bismuth triflate (0.1619 g, 2.467x10^{-4} mol) and 0.1 M LiClO$_4$/acetonitrile solution (3.81x10^{-5} mol, 381 µL) were stirred for two hours. The resulting product was colorless crystals (0.1160 g, 92%).

**Synthesis using bismuth triflate (30 mol%) and lithium perchlorate (30 mol%)**

Using the general procedure, bismuth triflate (0.1214 g, 1.850x10^{-4} mol), 0.1 M LiClO$_4$/acetonitrile solution (1.850x10^{-4} mol, 1.850 mL) were stirred for two hours. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.1091 g, 87%).

**Synthesis using bismuth triflate (30 mol%) and lithium perchlorate (10 mol%)**
Using the general procedure, bismuth triflate (0.1214 g, 1.850x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (6.17x10^{-5} mol, 617 µL) were stirred for two hours. The resulting product was colorless crystals (0.0926 g, 73.5%).

**Synthesis using bismuth triflate (25 mol%) and lithium perchlorate (25 mol%)**

Using the general procedure, bismuth triflate (0.1012 g, 1.542x10^{-4} mol) and lithium perchlorate (0.0164 g, 1.542x10^{-4} mol) were stirred overnight. The resulting product was colorless crystals (0.0731 g, 58%).

**Synthesis using bismuth triflate (25 mol%) and lithium perchlorate (25 mol%)**

Using the general procedure, bismuth triflate (0.1012 g, 1.542x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (1.542x10^{-4} mol, 1.54 mL) were stirred for two hours. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.1172 g, 93%).

**Synthesis using bismuth triflate (25 mol%) and lithium perchlorate (25 mol%)**

Using the general procedure, bismuth triflate (0.1012 g, 1.542x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (1.542x10^{-4} mol, 1.54 mL) were stirred for two hours. An older bottle of acetic anhydride was used in this experiment and the next reaction was run at the same time with a fresh bottle. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.1071 g, 85%).

**Synthesis using bismuth triflate (25 mol%) and lithium perchlorate (20 mol%)**

Using the general procedure, bismuth triflate (0.1012 g, 1.542x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (1.542x10^{-4} mol, 1.54 mL) were stirred for two hours. An older bottle of acetic anhydride was used in this experiment and the next reaction was run at the same time with a fresh bottle. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.1071 g, 85%).
Using the general procedure, bismuth triflate (0.1012 g, 1.542x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (1.234x10^{-4} mol, 1.23 mL,) were stirred overnight. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.0877 g, 70%).

**Synthesis using bismuth triflate (25 mol%) and lithium perchlorate (20 mol%)**

Using the general procedure, bismuth triflate (0.1012g, 1.542x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (1.234x10^{-4} mol, 1.23 mL) were stirred for four hours. The resulting product was colorless crystals (0.0964 g, 76%).

**Synthesis using bismuth triflate (25 mol%) and lithium perchlorate (15 mol%)**

Using the general procedure, bismuth triflate (0.1012 g, 1.542x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (9.25x10^{-5} mol, 925 µL) were stirred overnight. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.0611 g, 48%).

**Synthesis using bismuth triflate (20 mol%) and lithium perchlorate (20 mol%)**

Using the general procedure, bismuth triflate (0.0814 g, 1.234x10^{-4} mol) and 0.1 M LiClO₄/acetonitrile solution (1.234x10^{-4} mol, 123 µL) were stirred overnight. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.0717 g, 57%).

**Synthesis using bismuth triflate (20 mol%) and lithium perchlorate (20 mol%)**
Using the general procedure, bismuth triflate (0.0814 g, 1.234\times10^{-4} \text{ mol}) and 0.1 M LiClO$_4$/acetonitrile solution (1.234\times10^{-4} \text{ mol, 123 } \mu\text{L}) were stirred for four hours. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.0862 g, 68%).

**Synthesis using bismuth triflate (20 mol%) and lithium perchlorate (15 mol%)**

Using the general procedure, bismuth triflate (0.0814 g, 1.234\times10^{-4} \text{ mol}) and 0.1 M LiClO$_4$/acetonitrile solution (9.25\times10^{-5} \text{ mol, 93 } \mu\text{L}) were stirred overnight. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.0848 g, 67%).

**Synthesis using bismuth triflate (20 mol%) and lithium perchlorate (10 mol%)**

Using the general procedure, bismuth triflate (0.0814 g, 0.1234\times10^{-4} \text{ mol}) and 0.1 M LiClO$_4$/acetonitrile solution (6.167\times10^{-5} \text{ mol, 62 } \mu\text{L}) were stirred for four hours. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.0599 g, 47%).

**Synthesis using bismuth triflate (10 mol%) and lithium perchlorate (10 mol%)**

Using the general procedure, bismuth triflate (0.0407 g, 6.167\times10^{-5} \text{ mol}) and 0.1 M LiClO$_4$/acetonitrile solution (6.167\times10^{-5} \text{ mol, 62 } \mu\text{L}) were stirred overnight. 4 mL of acetonitrile was used instead of 5 mL. The resulting product was colorless crystals (0.0608 g, 48%).

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General Procedure for synthesis of 4-acyl-3-(2, acyl-3,5-dimethoxyphenyl)sydnones and 4-acyl-3-(3,5-dimethoxyphenyl)sydnones

In a pressure tube acetonitrile (5 mL), 3-(3,5-dimethoxyphenyl)sydnone (0.1000 g, 4.5x10^{-4} mol), with varied amounts acetic anhydride, bismuth triflate and lithium perchlorate were stirred at an oil bath temperature of 95 °C. When the reaction was complete, 5 mL of water was added, the stirring was continued for 5 minutes then allowed to cool to room temperature. The reaction mixture was extracted with methylene chloride (3 x 10 mL), and the combined extracts were removed in vacuo. The crude product was flushed through a plug of silica gel with methylene chloride to remove baseline material.

Synthesis of 124 and 125 using 25 mol% catalysts and 4 equivalents acetic anhydride

In a pressure tube acetonitrile (5 mL), 3-(3,5-dimethoxyphenyl)sydnone (0.1370 g, 6.167x10^{-4} mol), acetic anhydride, (bismuth triflate (0.1012 g, 1.542x10^{-4} mol), and lithium perchlorate (0.0164 g, 1.542x10^{-4} mol) were stirred at an oil bath temperature of 95 °C. When the reaction was complete, water (5 mL) was added, the stirring was continued for 5 minutes then allowed to cool to room temperature. The reaction mixture was extracted with methylene chloride (3 x 10 mL), and the combined extracts were removed in vacuo. The crude product was separated by column chromatography (silica gel, methylene chloride) followed by recrystallization from hot ethanol gave 124 and 125.

4-acetyl-3-(3,5-dimethoxyphenyl) sydnone (124)
Column chromatography (silica gel, methylene chloride) followed by recrystallization from hot ethanol afforded yellow crystals (0.0052 g, 3.2%) m.p. 130-1 °C.

I.R. (KBr): 2920.68, 1777.09 (sydnone C=O), 1670.06 (C=O), 1617.99, 1490.71, 1411.64, 1217.83, 1161.90, 1067.41, 1041.37, 841.78, 620.97 cm⁻¹.

¹H-NMR (CDCl₃): 6.6 (t 1H), 6.4 (d, 2H), 3.7 (s, 6H), 2.4 (s, 3H) ppm.

¹³C-NMR (CDCl₃): 183.95 (C=O), 166.17 (sydnone C=O), 161.08, 136.20, 106.07 (sydnone C-4), 103.97, 103.40, 55.85, 28.14 ppm.

4-acetyl-3-(2-acetyl-3,5-dimethoxyphenyl) sydnone (125)

Column chromatography (silica gel, dichloromethane) followed by recrystallization from hot ethanol afforded tan crystals (0.0225 g, 12 %) m.p. 150-1 °C.

I.R. (KBr): 3114.49, 3010.35, 2946.71, 2844.50, 1768.41 (sydnone C=O), 1682.59 (C=O), 1618.95, 1575.56, 1437.68, 1316.18, 1164.80 cm⁻¹.

¹H-NMR (CDCl₃): 6.75 (d, 1H), 6.45 (d, 1H), 3.9 (s, 3H), 3.7 (s, 3H), 3.7 (s, 3H), 2.6 (s, 3H), 2.5 (s, 3H) ppm.

¹³C-NMR (CDCl₃): 196.86, 184.40 (C=O), 164.85 (sydnone C=O), 162.55, 106.01, 135.32, 118.67, 106.98 (sydnone C-4), 103.97, 104.41, 101.59, 56.31, 56.09, 32.00, 27.58 ppm.

Synthesis of 124 and 125 using 30 mol% catalysts and 6 equivalents acetic anhydride

Using the general procedure, acetic anhydride (254 µL, 2.70x10⁻³ mol), bismuth triflate (0.1033 g, 1.35x10⁻⁴ mol), and lithium perchlorate (0.0143 g, and 1.35x10⁻⁴ mol)
were stirred overnight. The resulting combination of products were yellow crystals (0.0686 g, 51%), NMR showed that the products were obtained in a ratio of 1:4, **124:125**.

**Synthesis of 124 and 125 using 35 mol% catalysts and 8 equivalents acetic anhydride**

Using the general procedure, acetic anhydride (340 µL, 3.60x10⁻³ mol), bismuth triflate (0.1033 g, 1.575x10⁻⁴ mol), and lithium perchlorate (0.0167 g, and 1.575x10⁻⁴ mol) were stirred overnight. The resulting combination of products were yellow crystals (0.0765 g, 58%), NMR showed that the products were obtained in a ratio of 4:9, **124:125**.

**Synthesis of 124 and 125 using 40 mol% catalysts and 4 equivalents acetic anhydride**

Using the general procedure, acetic anhydride (169 µL, 1.800x10⁻³ mol), bismuth triflate (0.1110 g, 1.800x10⁻⁴ mol), and lithium perchlorate (0.0191 g, 1.800x10⁻⁴ mol) were stirred overnight. The resulting combination of products were yellow crystals (0.0817 g, 62%), NMR showed that the products were obtained in a ratio of 4:9, **124:125**.

**Synthesis of 124 and 125 using 40 mol% catalysts and 6 equivalents acetic anhydride**

Using the general procedure, acetic anhydride (255 µL, 2.7x10⁻³ mol), bismuth triflate (0.1181 g, 1.800x10⁻⁴ mol), and lithium perchlorate (0.0192 g, 1.800x10⁻⁴ mol) were stirred for 2 hours. The resulting combination of products were yellow crystals (0.0930 g, 71%), NMR showed that the products were obtained in a ratio of 1:2, **124:125**.

**Synthesis of 124 and 125 using 40 mol% catalysts and 6 equivalents acetic anhydride**
Using the general procedure, acetic anhydride (255 µL, 2.70x10^{-3} mol), bismuth triflate (0.1181 g, 1.800x10^{-4} mol), and lithium perchlorate (0.0192 g, 1.800x10^{-4} mol) were stirred for 70 hours. The resulting combination of products were yellow crystals (0.0821 g, 61%), NMR showed that the products were obtained in a ratio, 1:6, 124:125.

Synthesis of 124 and 125 using 40 mol% catalysts and 8 equivalents acetic anhydride

Using the general procedure, acetic anhydride (340 µL, 3.60x10^{-3} mol), bismuth triflate (0.1181 g, 1.800x10^{-4} mol), and lithium perchlorate (0.0192 g, 1.800x10^{-4} mol) were stirred for 70 hours. The resulting combination of products were yellow crystals (0.1222 g, 91%), NMR showed that the products were obtained in a ratio, 1:5, 124:125.

Synthesis of 124 and 125 using 50 mol% catalysts and 10 equivalents acetic anhydride

Using the general procedure, acetic anhydride (425 µL, 4.5x10^{-3} mol), bismuth triflate (0.1471 g, 2.25x10^{-4} mol), and lithium perchlorate (0.0479 g, and 4.500x10^{-4} mol) were stirred overnight. The resulting combination of products were yellow crystals (0.0418 g, 35%), NMR showed that the products were obtained in a ratio of 45:1, 124:125.

Synthesis of 4-propionyl-3-(2-propionyl-3,5-dimethoxyphenyl)sydnone 127 and 4-propionyl-3-(3,5-dimethoxyphenyl)sydnone 126 using 30 mol% catalysts and 6 equivalents propionic anhydride

Using the general procedure, propionic anhydride (347 µL, 2.70x10^{-3} mol), bismuth triflate (0.1033 g, 1.35x10^{-4} mol), and lithium perchlorate (0.0143 g, and
1.35x10^{-4} \text{ mol}) were stirred overnight. The resulting combination of products were yellow crystals (0.0430 g, 31%), NMR showed that the products were obtained in a ratio of 1:1, 126:127.

4-propionyl-3-(3,5-dimethoxyphenyl) sydnone (126)

Column chromatography (silica gel, dichloromethane) followed by recrystallization from hot ethanol afforded tan crystals m.p. 110-1°C.

\text{I.R. (KBr): 2920.68, 1777.09 (sydnone C=O), 1670.06 (C=O), 1617.99, 1490.71, 1411.64, 1217.83, 1161.90, 1067.41, 1041.37, 841.78, 620.97 \text{ cm}^{-1}.}

\text{^1H-NMR (CDCl}_3): 6.65 (t 1H), 6.5 (d, 2H), 3.75 (s, 6H), 2.8 (q, 2H), 1.1 (t, 3H) ppm.

\text{^13C-NMR (CDCl}_3): 186.53 (C=O), 164.98 (sydnone C=O), 160.07, 135.29, 104.93 (sydnone C-4), 102.80, 102.44, 54.82, 32.80, 6.13 ppm.

4-propionyl-3-(2-propionyl-3,5-dimethoxyphenyl) sydnone (127)

Column chromatography (silica gel, dichloromethane) followed by recrystallization from hot ethanol afforded tan crystals m.p. 138-9 °C.

\text{I.R. (KBr): 2921.64, 2851.25, 1778.05 (sydnone C=O), 1674.88 (C=O), 1673.92 (C=O), 1610.28, 1571.71, 1438.64, 1296.90, 1234.22, 1158.05 \text{ cm}^{-1}.}

\text{^1H-NMR (CDCl}_3): 6.75 (d 1H), 6.5 (d, 1H), 4. (s, 3H), 3.9 (s, 3H), 2.8 (m, 4H), 1.2 (m, 6H) ppm.
$^{13}$C-NMR (CDCl$_3$): 200.64 (C=O), 187.96 (C=O), 165.72 (sydnone C=O), 162.26, 162.26, 159.60, 135.26, 119.00, 106.96 (sydnone C-4), 104.14, 101.57, 56.25, 56.04, 37.35, 33.38, 8.19, 7.07 ppm.

Synthesis of 126 and 127 using 40 mol% catalysts and 4 equivalents propionic anhydride

Using the general procedure, acetic anhydride (232 µL, 1.800x$10^{-3}$ mol), bismuth triflate (0.1110 g, 1.800x$10^{-4}$ mol), and lithium perchlorate (0.0191 g, 1.800x$10^{-4}$ mol) were stirred overnight. The resulting combination of products were yellow crystals (0.1256 g, 88%), NMR showed that the products were obtained in a ratio of 4:9, 126:127.

Synthesis of 126 and 127 using 40 mol% catalysts and 8 equivalents propionic anhydride

Using the general procedure, acetic anhydride (463 µL, 3.60x$10^{-3}$ mol), bismuth triflate (0.1181 g, 1.800x$10^{-4}$ mol), and lithium perchlorate (0.0192 g, 1.800x$10^{-4}$ mol) were stirred for 70 hours. The resulting combination of products were yellow crystals (0.1180 g, 31%), NMR showed that the products were obtained in a ratio, 1:1, 126:127.

Synthesis of 126 and 127 using 50 mol% catalysts and 10 equivalents propionic anhydride

Using the general procedure, propionic anhydride (580 µL, 4.5x$10^{-3}$ mol), bismuth triflate (0.1471 g, 2.25x$10^{-4}$ mol), and lithium perchlorate (0.0239 g, 2.25x$10^{-4}$ mol) were stirred overnight. The resulting combination of products were yellow crystals (0.0318 g, 25%), NMR showed that the products were obtained in a ratio of 13:1, 126:127.
Synthesis of 4-butyryl-3-(2-butyryl-3,5-dimethoxyphenyl)sydnone 129 and 4-butyrl-3-(3,5-dimethoxyphenyl)sydnone 128 using 30 mol% catalysts and 6 equivalents butyric anhydride

Using the general procedure, propionic anhydride (441 µL, 2.70x10^{-3} mol), bismuth triflate (0.1033 g, 1.35x10^{-4} mol), and lithium perchlorate (0.0143 g, and 1.35x10^{-4} mol) were stirred overnight. The resulting combination of products were yellow crystals (0.0777 g, 56%), NMR showed that the products were obtained in a ratio of 1:2, 128:129.

4-butyryl-3-(3,5-dimethoxyphenyl) sydnone (128)

Column chromatography (silica gel, dichloromethane) followed by recrystallization from hot ethanol afforded tan crystals m.p. 117-8 °C.

^1H-NMR (CDCl$_3$): 6.75 (t 1H), 6.55 (d, 2H), 3.8 (s, 6H), 2.8 (t, 2H), 1.7 (s, 2H), 1.0 (t, 3H) ppm.

^13C-NMR (CDCl$_3$): 187.07 (C=O), 165.97 (sydnone C=O), 161.09, 136.34, 106.05 (sydnone C-4), 103.84, 103.42, 55.84, 42.11, 16.85, 13.65 ppm.

4-butyryl-3-(2-butyryl-3,5-dimethoxyphenyl) sydnone (129)

Column chromatography (silica gel, dichloromethane) followed by recrystallization from hot ethanol afforded tan crystals m.p. 57-8 °C.

^1H-NMR (CDCl$_3$): 6.75 (d 1H), 6.5 (d, 1H), 4. (s, 3H), 3.9 (s, 3H), 2.8 (m, 4H), 1.2 (m, 6H) ppm.
$^{13}$C-NMR (CDCl$_3$): 199.97 (C=O), 187.34 (C=O), 165.67 (sydnone C=O), 162.24, 159.58, 135.25, 119.10, 107.25 (sydnone C-4), 104.15, 101.52, 56.22, 56.04, 45.98, 41.68, 17.41, 16.71, 13, 70, 13.60 ppm

Synthesis of 128 and 129 using 40 mol% catalysts and 4 equivalents butyric anhydride

Using the general procedure, butyric anhydride (294 µL, 1.800x10^{-3} mol), bismuth triflate (0.1110 g, 1.800x10^{-4} mol), and lithium perchlorate (0.0191 g, 1.800x10^{-4} mol) were stirred overnight. The resulting combination of products were yellow crystals (0.1394 g, 93%), NMR showed that the products were obtained in a ratio of 8:10, 128:129.

Synthesis of 128 and 129 using 40 mol% catalysts and 8 equivalents butyric anhydride

Using the general procedure, butyric anhydride (463 µL, 3.60x10^{-3} mol), bismuth triflate (0.1181 g, 1.800x10^{-4} mol), and lithium perchlorate (0.0192 g, 1.800x10^{-4} mol) were stirred for 70 hours. The resulting combination of products were yellow crystals (0.1422 g, 93%), NMR showed that the products were obtained in a ratio, 1:2, 128:129.

Synthesis of 128 and 129 using 50 mol% catalysts and 10 equivalents butyric anhydride

Using the general procedure, butyric anhydride (736 µL, 4.5x10^{-3} mol), bismuth triflate (0.1471 g, 2.25x10^{-4} mol), and lithium perchlorate (0.0239 g, 2.25x10^{-4} mol) were stirred overnight. After 10 minutes of stirring with activated carbon (2 mg), the resulting combination of products were yellow crystals (0.0480 g, 35%), NMR showed that the products were obtained in a ratio of 4:1, 128:129.
Attempted synthesis of 4-isobutyryl-3-(3, 5-dimethoxyphenyl) sydnone and 4-isobutyryl-3-(2-isobutyryl-3, 5-dimethoxyphenyl) sydnone using 30 mol% catalysts and 4 equivalents isobutyric anhydride

Using the general procedure, isobutyric anhydride (294 μL, 1.800x10^{-3} mol), bismuth triflate (0.1110 g, 1.35x10^{-4} mol), and lithium perchlorate (0.0143 g, 1.35x10^{-4} mol) were stirred overnight. TLC showed no sign of reaction.

Attempted synthesis of 4-isobutyryl-3-(3, 5-dimethoxyphenyl) sydnone and 4-isobutyryl-3-(2-isobutyryl-3, 5-dimethoxyphenyl) sydnone using 40 mol% catalysts and 4 equivalents isobutyric anhydride

Using the general procedure, isobutyric anhydride (331 μL, 3.200x10^{-3} mol), bismuth triflate (0.1180 g, 1.8x10^{-4} mol), and lithium perchlorate (0.0191 g, 1.8x10^{-4} mol) were stirred overnight. TLC showed no sign of reaction.
References


57 S. J. Hodson and K. Turnbull, unpublished results.


