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SONOGASHIRA COUPLING ROUTES TO *ortho*-ALKYNYL-
AND FUSED-RING SYDNONES

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

By

ANDREW JOHN WEISNER
B.S., Wright State University, 2001

2003
Wright State University

WRIGHT STATE UNIVERSITY
SCHOOL OF GRADUATE STUDIES

April 15, 2003

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Andrew John Weisner ENTITLED Sonogashira Coupling Routes to *ortho*-Alkynyl- and Fused-Ring Sydnones BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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Abstract

Weisner, Andrew J. M.S., Department of Chemistry, Wright State University, 2003.
Sonogashira Coupling Routes to *ortho*-Alkynyl- and Fused-Ring Sydnones.

In the present work, suitably functionalized arylsydnones were used to synthesize a variety of *ortho*-alkynyl sydnones both as potential precursors to novel sydnoquinolines and to provide non-linear optical (NLO) species of interest to Wright-Patterson Air Force Base (WPAFB).

The versatile intermediate, 3-(2-(trimethylsilylethynyl)phenyl)sydnone, was prepared in good yield by the coupling of 3-(2-iodophenyl)sydnone with trimethylsilyl acetylene under Sonogashira conditions. From this intermediate, several *ortho*-alkynyl sydnones were prepared via a one-pot desilylation with tetrabutylammonium fluoride and Sonogashira coupling with *para*-substituted aryl iodides. In addition, a three-reaction-in-one-pot procedure was developed to access some of these species directly from 3-(2-iodophenyl)-sydnone. Subsequent reaction of these species with electrophiles has been examined as an avenue to novel sydnoquinolines. For example, there is evidence that the electrophile phenylselenyl chloride has induced cyclization of 3-(2-(phenylethynyl)phenyl)sydnone and 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone in moderate yield. Similarly, concentrated sulfuric acid has effected cyclization of 3-(2-(phenylethynyl)phenyl)sydnone and 3-(2-(4-bromophenylethynyl)phenyl)sydnone, also in low yield. In contrast, trifluoroacetic acid and trifluoromethanesulfonic acid

transform these species into novel cinnolines, presumably *via* sydnone ring cleavage followed by acid-induced cyclization.

Sonogashira coupling routes were used to add additional *para*-alkynylphenyl moieties to the above-mentioned *ortho*-alkynyl sydnones and generate oligomeric alkynyl sydnones. The aim of this endeavor was to fulfill an interest of the United States Air Force in these species as ligands for the preparation of platinum-centered NLO materials. 3-(2-Ethynylphenyl)sydnone was synthesized from 3-phenylsydnone in a three-step process with an overall yield of 27% to analytically pure material. Similarly, 3-(2-(4-ethynylphenyl-ethynyl)phenyl)sydnone, was synthesized in seven steps at an overall yield of 21%, and 3-(2-(4-(4-ethynyl)phenylethynyl)phenylethynyl)phenyl)sydnone was synthesized in ten steps at an overall 11% yield. A great aid to obtaining these relatively high overall yields was the ability to perform multiple steps of the syntheses in one pot (e.g. three reactions in one pot) at certain points *en route*. Finally, the above oligomeric alkynyl sydnones were converted into the corresponding 3,4-dicarbomethoxypyrazoles (potential NLO monomers) in moderate to good yield by 1,3-dipolar cycloaddition with dimethylacetylene dicarboxylate.

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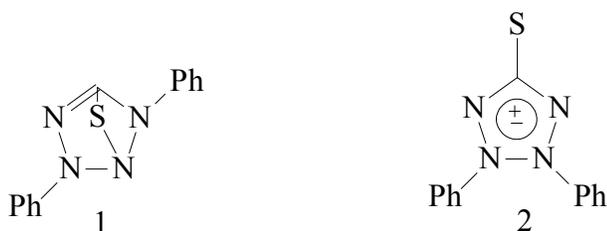
Heartfelt appreciation goes out to my parents, James and Nancy Weisner, and sister Christine Weisner, for the loving support that helped me through the tougher times of my graduate work.

I also wish to extend my gratitude to all of the students (graduate and undergraduate), staff, and faculty of the Wright State University Chemistry Department for their help in the classroom and laboratory, and for making the experience at Wright State such a pleasure.

Introduction

Foreword

Approximately 120 years ago, Emil Fischer oxidized dithizone; yielding a compound he entitled dehydrodithizone. Fischer assigned the bicyclic structure **1** to this crystalline, orange species.¹ As time progressed and more advanced tools of analysis became available, a better understanding of such species was gained. In 1946, Baker, Ollis, and Poole² minted the term mesoionic (mesomeric/ionic) to describe the monocyclic, dipolar nature of compounds such as dehydrodithizone, and in 1955, these three authors published a paper in *Chemistry and Industry* specifically defining the term mesoionic. By this definition, dehydrodithizone is considered the first known mesoionic species and is assigned the dipolar, monocyclic structure **2**.³



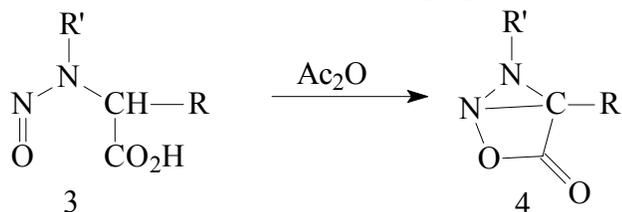
A molecule called the sydnone is another member of the mesoionic category of compounds. Sydnones are aromatic, small, and have a unique variation in electron density around the ring. These characteristics have caused the chemical, physical, and

biological properties of sydnones, as well as potential applications, to be studied extensively.

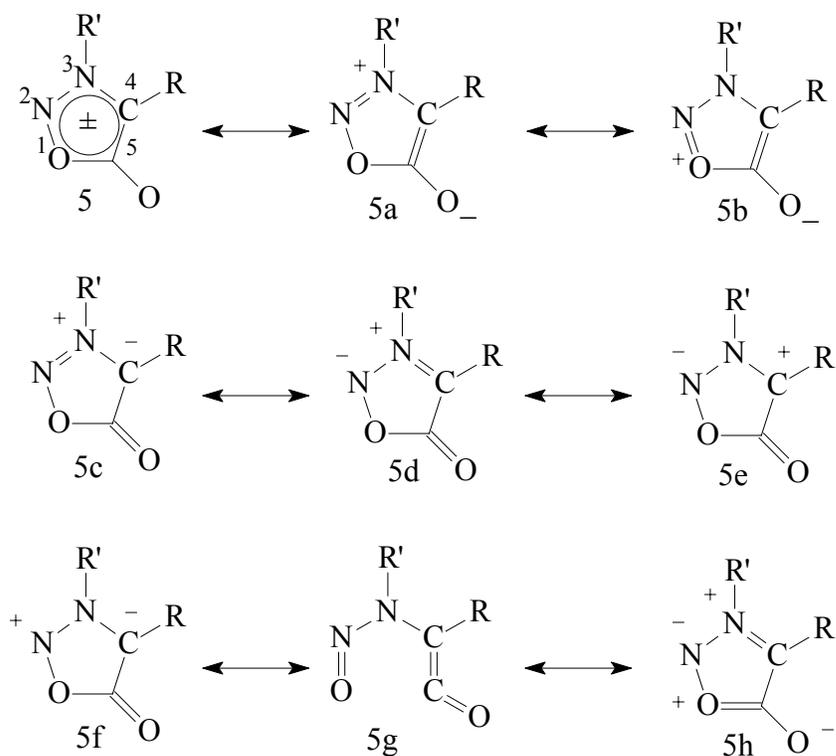
There are numerous reviews on mesoionic heterocycles (including sydnones) that can be found through 1989. Additionally, there are several M.S. Theses that have come from this laboratory, and these fill in discoveries related to sydnones covering the years 1989-1995.⁴ The review that follows will serve 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 1996 to 2001

Historical

In 1935, Earl and Mackney reported⁵ that treatment of N-nitroso-N-phenylglycine (**3**; R=H, R'=Ph) with acetic anhydride afforded a neutral, anhydro derivative to which the bicyclic structure **4** (R=H, R'=Ph) was assigned. Further examination of this reaction showed it to be of general utility and thus a variety of analogous compounds were prepared and given the name “sydnone” (due to their preparation in Sydney, Australia).



In the years following this discovery, however, further examination and subsequent compilation of data regarding both the chemical and physical properties of these compounds clearly showed that structure **4** was inaccurate. For example, sydnones exhibit a greater degree of polarity, are more stable towards heating, and are less reactive towards acids and bases than would be predicted for the strained, bicyclic representation **4**. Thus, in the 1940's, Baker, Ollis and Poole² published a series of papers wherein they concluded that sydnones were in fact monocyclic, dipolar oxadiazolone derivatives in which many possible resonance hybrids allow for multiple canonical representations (**5a-h**), for which structure **5** was the preferred representation.



Baker, Ollis, and Poole also suggested that, because of the unique characteristics of the sydnone ring system, these compounds should be placed in a class by themselves, namely mesoionic (meaning mesomeric/ionic), and thereby proceeded to outline the general concepts governing their electronic structure. However, formal qualifications for a compound to be deemed mesoionic were not set forth until 1953³; at which time it was 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. This, then, 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 fixation whereas in the mesoionic systems, charge distribution is delocalized and no satisfactory single resonance form can be drawn.

In the most formal sense, 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, because of this unique distinction, the name “sydnone” has become the most common way to describe these compounds and is used by Chemical Abstracts as a way of grouping these oxadiazole derivatives.

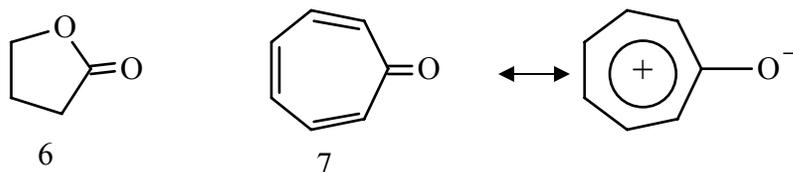
Physiochemical Properties and Electronic Structure

With few exceptions, sydnones are stable compounds that exhibit considerable polarity. Arylsydnones are generally crystalline solids. Alkylsydnones are often liquids or low-melting solids that can be distilled *in vacuo* without appreciable decomposition. Sydnones are soluble in a variety of organic solvents with the main exceptions being non-polar solvents such as petroleum ether and hexanes. Additionally, sydnones are generally not water-soluble unless a polar functional group has been incorporated. The relatively high polarity of sydnones aided in the conclusion that proposed structure **4** was incorrect.

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 $\sim 1730\text{-}1760\text{ cm}^{-1}$ and a stretch of medium intensity at $\sim 3150\text{ cm}^{-1}$ 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 $2900\text{-}3050\text{ cm}^{-1}$, 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 $\sim 1730\text{-}1760\text{ cm}^{-1}$ but, in comparison with congeneric carbonyl containing species, such

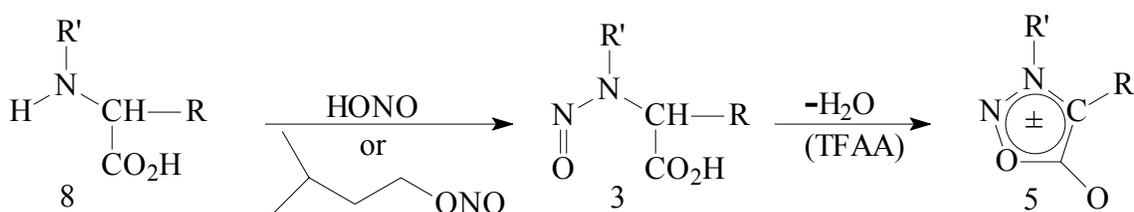
as a γ -lactone (**6**) [which absorbs at 1770 cm^{-1}] and tropone (**7**) [which absorbs at 1638 cm^{-1}], one might conclude that the exocyclic C=O bond at the sydnone C-5 position is closer in length to that of a double bond than a single bond.



This contention is further supported by the results of X-ray crystallographic analysis of various 3-substituted and 3,4-disubstituted sydnones which showed that this C=O bond was closer in length to that of a double bond.⁷ However, integrated absorption measurements⁷ 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 esters⁸, 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 These studies thereby 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 if R' is a hydrogen, prototropy occurs to afford a neutral species. The preparation of the N-nitrosoamino acid generally 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 methodology. However, a variation upon this standard method has been developed in which nitrosation is effected under neutral conditions using isoamyl nitrite and dimethoxyethane.¹¹ Thus, some otherwise unattainable sydnones can now be successfully generated in good to excellent yield.



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 forthcoming 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 foreseeable 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. Amongst these are the use of: (1) acetic anhydride at room temperature facilitated by ultrasonification¹²; (2) haloiminium salts¹³; (3) N,N-dimethylchloro-sulfitemethaninium chloride¹⁴, and (4) 2-chloro-1,3-dimethylimidazolium chloride¹⁵. Although these new methods are interesting, 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 illuminating how these characteristics are reflected in the chemical behavior of sydnones. With regard to the aromatic nature of the sydnone ring, and since an intrinsic property of any aromatic system is to undergo electrophilic substitution with retention of aromaticity, 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).^{4f} 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 and nitration.

Other major chemical reactions of sydnone include their use as precursors to hydrazines⁵, their utility as 1,3-dipoles in cycloaddition reactions¹⁶, their use as electrolytic solvents for non-aqueous batteries¹⁷ and their ability to aid micelle production in molecular aggregation.¹⁸ Additionally, of the many potential applications of sydnone, the one that has attracted the most interest is their biological properties, which include anti-fungal, anti-inflammatory, analgesic, antibacterial, and anti-tumor activities. Sydnone have been tested experimentally for use as lithium battery electrolytes. Additionally, certain sydnone have liquid crystal properties and have been incorporated into azo dyestuffs¹⁹ However, because the majority of the work in this thesis has dealt with reactions of sydnone with electrophiles, and for the sake of brevity, these latter aspects will not be addressed.

Reactions of Sydnone

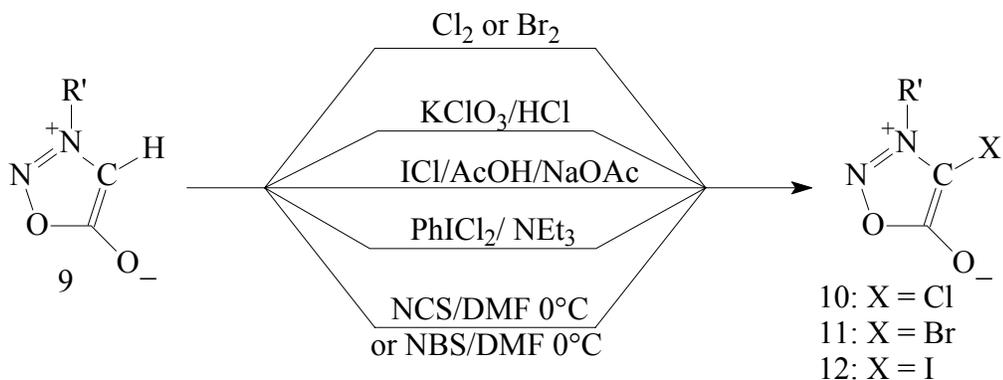
I. Substitution Reactions at the Sydnone C-4 Position

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). Moreover, 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 metallation. 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 effected using either bromine or chlorine (*cf.* **11** or **10**, respectively).²⁰ It is also possible to use potassium chlorate in moderately concentrated HCl²¹ or dichloriodobenzene with triethylamine²² in order to obtain the 4-chloro derivative **10**. Alternatively, 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.²³

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.²⁴

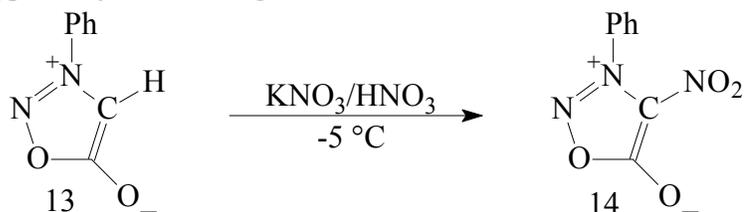


The apparent ease with which sydnones could be brominated led to the postulation that the 4-bromo moiety (*cf.* **11**) could be used as a protecting group for the sydnone ring.²⁵ Initial methods of de-bromination were somewhat vigorous, requiring high temperatures, long reaction times, and the use of 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.²⁶ While both methods have their drawbacks (*e.g.* sodium borohydride is capable of reacting with pendent functional groups, *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.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,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 little investigated. However, upon reaction with potassium nitrate in the presence of sulfuric acid at $-5\text{ }^{\circ}\text{C}$, 3-phenylsydnone (**13**) affords the relatively unstable 4-nitro derivative **14** in modest yield.²⁹ Additionally, bis-sydnone apparently also undergo nitration at C-4 under similar conditions.^{6a}



As was mentioned earlier (see Chemical Behavior), in contrast 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-Arylsydnone).

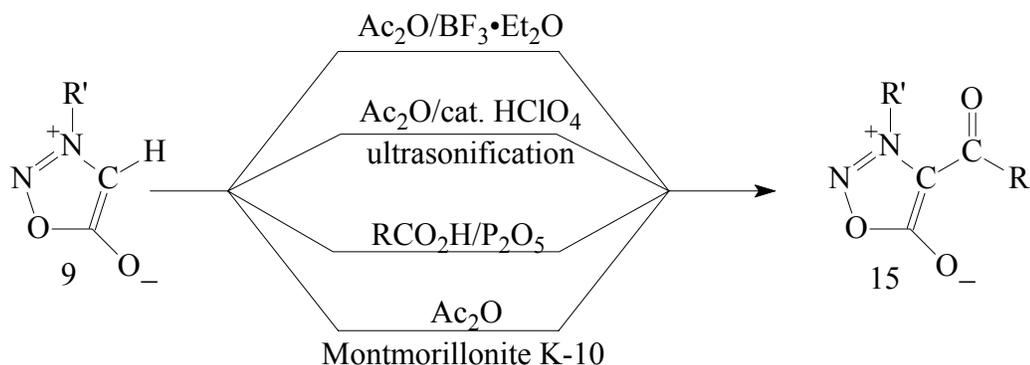
C. Acylation and Carboxamidation

It had been reported³⁰ that it was not possible to acylate 3-phenylsydnone with either acetic anhydride or benzoyl chloride in the presence of a Lewis acid catalyst, however, Yashunskii showed that it was possible to obtain the 4-acetyl derivative (**15**; R

(R = Me, R' = Ph) *via* the use of acetic anhydride and boron trifluoride etherate.³¹

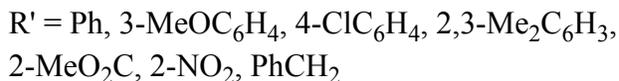
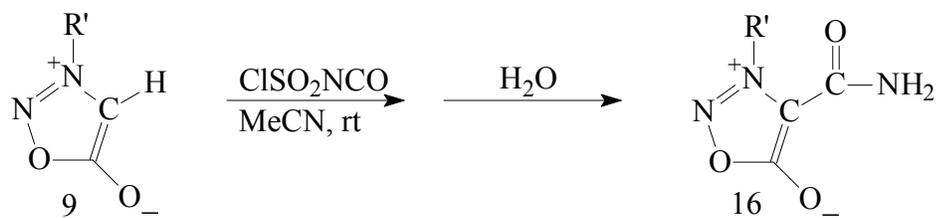
Additionally, Tien and coworkers have acylated various substituted sydnone using acetic anhydride and HClO₄ or H₃PO₄.³² This same type of transformation has been reported by Greco and coworkers,³³ wherein the desired acylated sydnone was obtained by heating various 3-substituted sydnone in the presence of a carboxylic acid and P₂O₅.

Nevertheless, 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-arylsydnone, though, recent methodology has shown that these types of compounds can be prepared in a two-step process *from* a cuprosydnone (*cf.* Metallation).



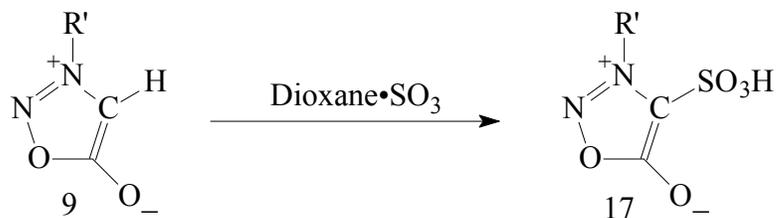
In the most recent literature regarding sydnone C-4 acylation, two novel approaches have been reported. Tien and coworkers²⁷ have shown that ultrasonification of 3-substituted sydnone in the presence of acetic anhydride and a catalytic amount of perchloric acid will afford the 4-acylated derivative quickly, in moderate yield. 4-Acetyl derivatives of 3-substituted sydnone also have been obtained *via* the use of acetic anhydride and a catalytic amount of Montmorillonite K-10 at elevated temperatures.³⁴ This 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.

In the past, 4-carboxamido sydnone species (*cf.* **16**) have been made 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. In recent years, a new method of carboxamidation at the sydnone 4-position has been developed.³⁵ By use of 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.



D. Sulfonation

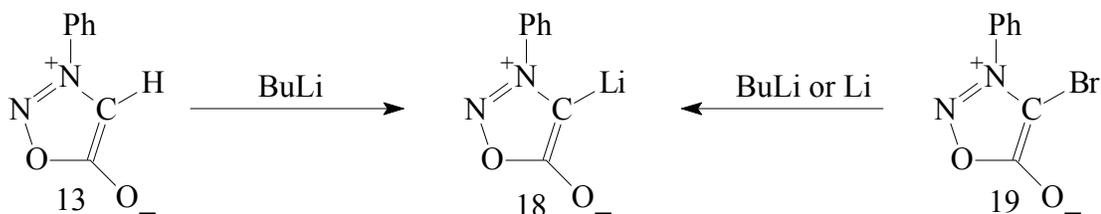
Yashunskii and coworkers have reported the direct sulfonation of a variety of 3-substituted sydnones.³⁶ Therein, it was shown that treatment of sydnones **9** with dioxane-sulfur trioxide complex (SO₃) in CH₂Cl₂ at 20 °C to 40 °C generated the sulfonated derivatives **17** (R' = 4-MeO- or 4-EtOC₆H₄), 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-chloromercurio, and the 4-palladium (0)³⁷ or nickel (II)³⁸ complexes have been prepared and investigated.

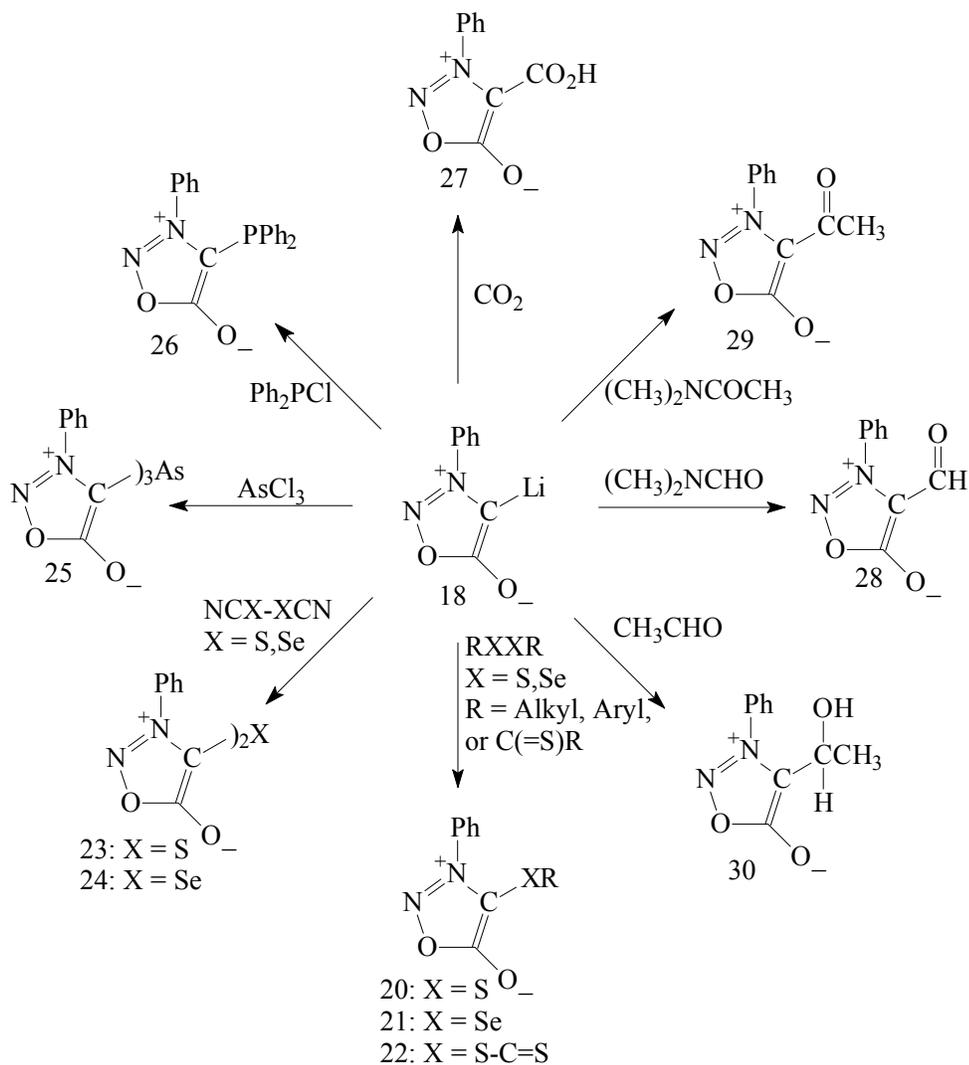
Of the above listed 4-metallo substituted sydnones it appears that the 4-lithio species (*cf.* **18**) is the most versatile in its applications. It is readily prepared either directly from 3-phenylsydnone (**13**) or indirectly from metal-halogen exchange of 4-bromo-3-phenylsydnone (**19**).³⁹



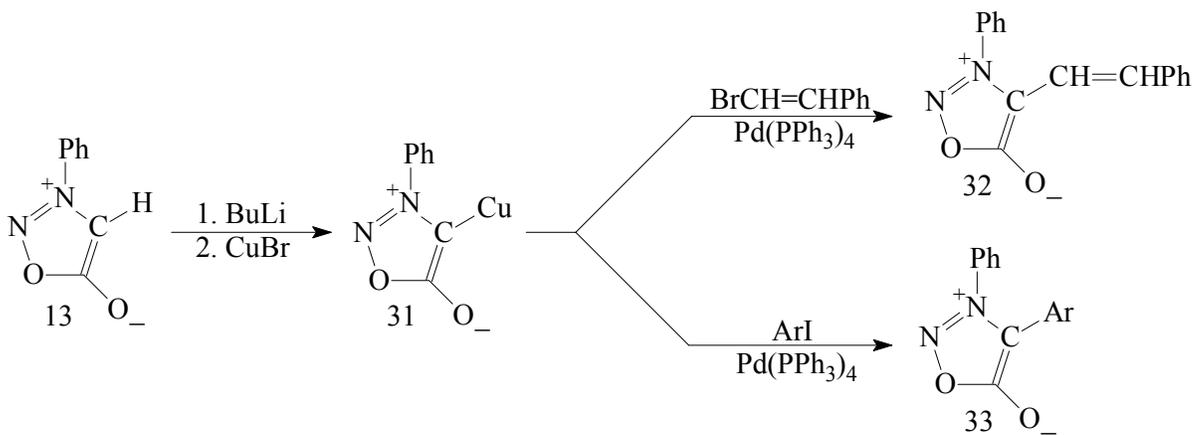
A wide variety of 4-substituted sydnones have been prepared *via* this methodology. The following examples are meant to give the reader a flavor for the applications in which it has been used and are not meant to be all-inclusive.

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

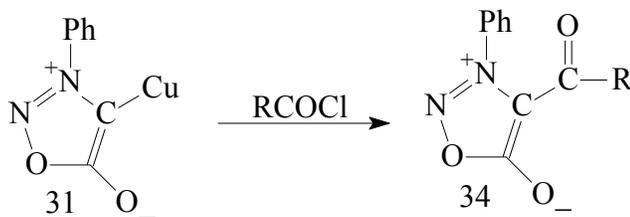
prepared in an analogous manner by treating **18** with the appropriate dicyano disulfide or diselenide.⁴¹ Extension of this methodology to arsenic trichloride and diphenylchlorophosphorane⁴² resulted in the preparation of the corresponding sydnonylarsine **25** and phosphine **26**, respectively. More recently, a variety of 4-carboxysydones **27** have been prepared by carboxylation of **18** with carbon dioxide.⁴³ Additionally, Tien and coworkers⁴⁴ have shown that various 3-substituted sydnones can be lithiated and exposed *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 modulated 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 stable at room temperature. 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** sydnes, respectively.⁴⁵



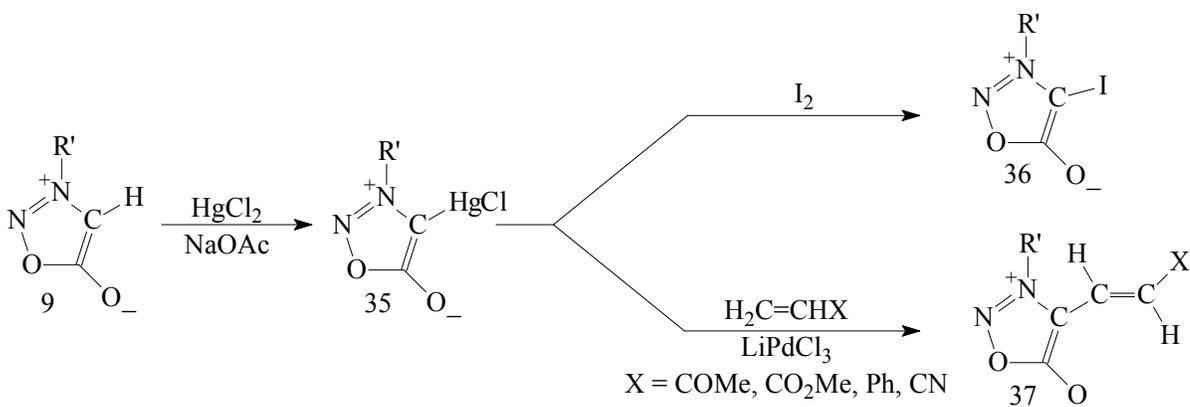
Additionally, sydnonyl cuprate **31** can be coupled with more reactive alkyl or aryl acid chlorides without the use of the palladium catalyst to afford the corresponding 4-substituted derivatives **34**.⁴⁶



Most recently, Kalinin and coworkers⁴⁷ have shown that sydnonyl cuprates **31** can undergo palladium catalyzed cross-coupling reactions with either heteroaryl iodides or

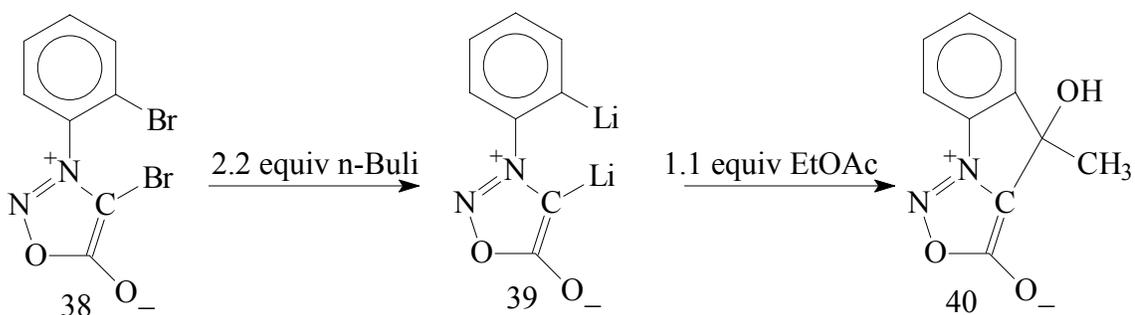
alkynyl bromides to afford the corresponding 4-substituted sydrones in good to excellent yields.

The 4-chloromercurio species **35** also can serve as an effective intermediate for substitution of the sydnone ring. Prepared by reacting 3-arylsydrones (**9**) with mercuric chloride and sodium acetate in aqueous methanol at ambient temperature⁴⁸, 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



II. Dilithiation of 3-Aryl Sydrones

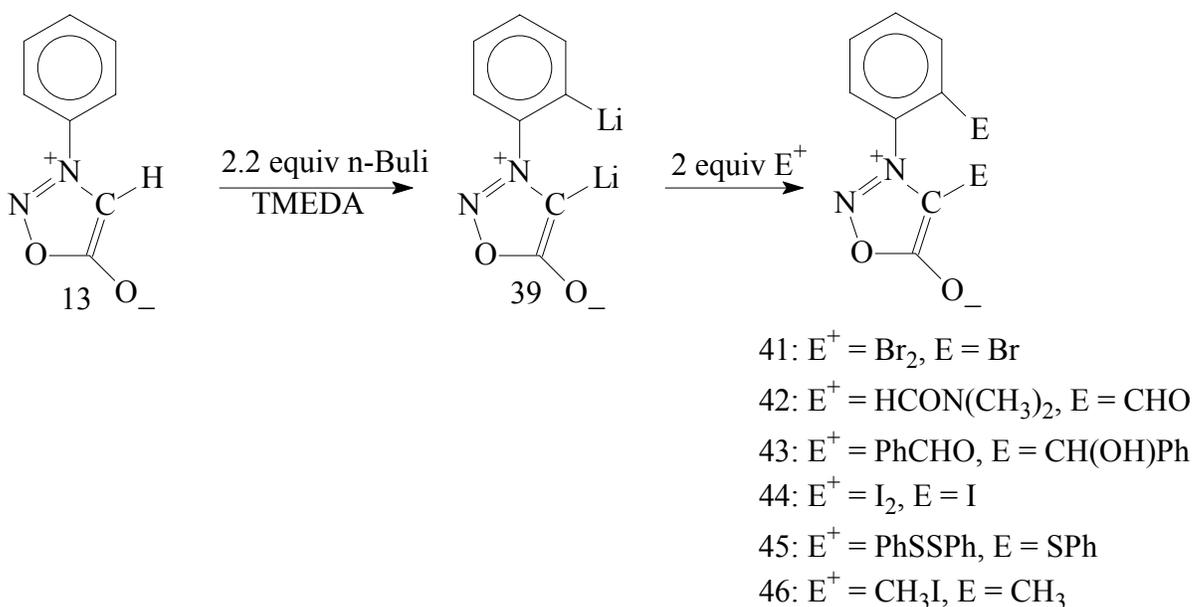
Dilithiation of 3-aryl sydrones has become a recent focus of sydnone chemistry, and has been successfully achieved by Krein and Turnbull.⁵⁰ Initially, a di-lithio sydnone species was made by the reaction of 3-(2-bromophenyl)-4-bromosydnone **38** with butyllithium at -78 °C yielding **39**. Subsequent 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. An undesirable drawback, however, was 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 (“Metallation”), 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** in the conditions shown above, and it was found the same transformations were achieved.

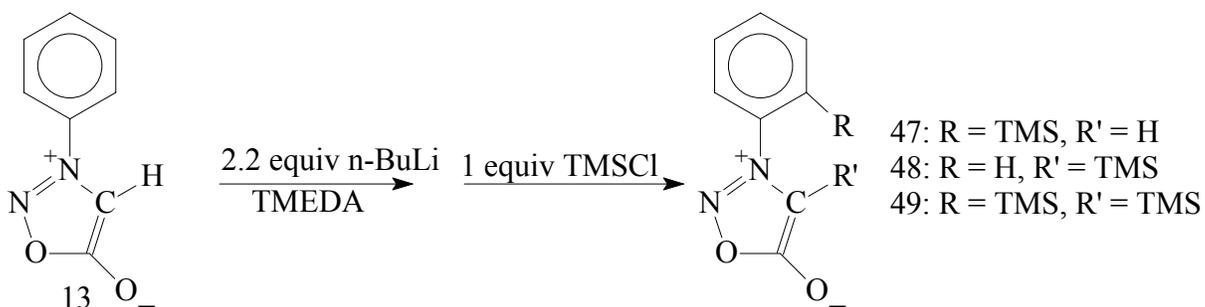
Upon further pursuance, Krein and Turnbull discovered that the di-lithio intermediate **39** could be prepared directly from 3-phenylsydnone **13** using *N,N,N',N'*-tetramethylene-diamine (TMEDA) to increase the basicity of butyllithium. This was complemented by the anticipated *ortho*-directing effect of the sydnone ring. Hence, it was possible to react at the *ortho*-aryl site without the need for metal-halogen exchange. Reaction of this di-lithio species was undertaken with a variety of electrophiles (*cf.* **13** to **41-46**).



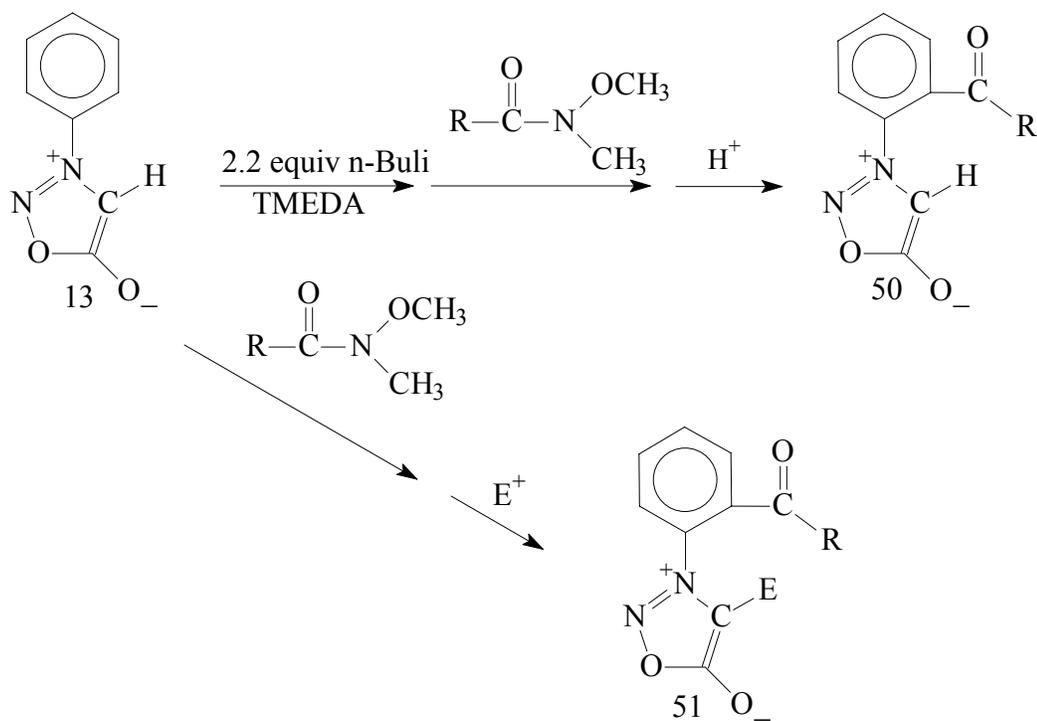
In more recent times, the same reaction has been found highly effective without the use of TMEDA by raising the reaction temperature from $-78\text{ }^\circ\text{C}$ to $-50\text{ }^\circ\text{C}$.⁵¹

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. The *ortho*-aryl proton is estimated to have a pKa of approximately 40 pKa units. Due to this difference, Krein and Turnbull decided to explore 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.



Turnbull and Krein decided to attempt reaction with a less reactive electrophile, and Weinreb's amides were chosen since they have known advantages in similar 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*-acylsydnone.⁵² Overall, this approach provided a "one-pot" synthesis of *ortho*-acyl sydnone from easily prepared 3-phenylsydnone. Since, after initial reaction at the *ortho*-aryl position, the sydnone anion remains, one equivalent of a second electrophile can be added to promote further functionalization at the C-4 position of the sydnone ring. This provides a route to many unsymmetrically functionalized sydnone species (*cf.* **51**).

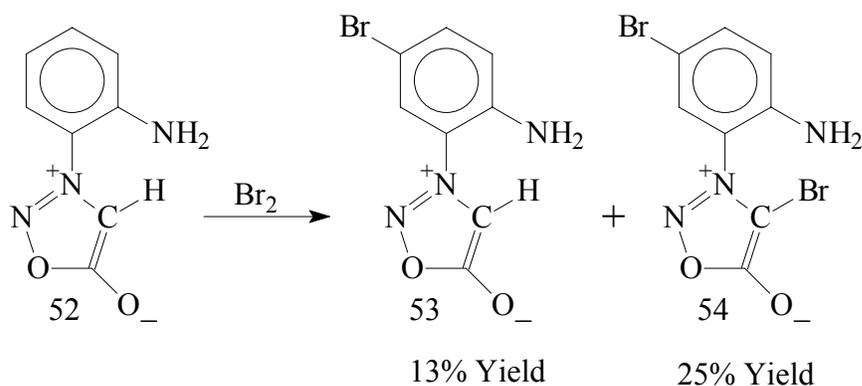


III. Electrophilic Substitution at the Aryl Ring of 3-Arylsydrones

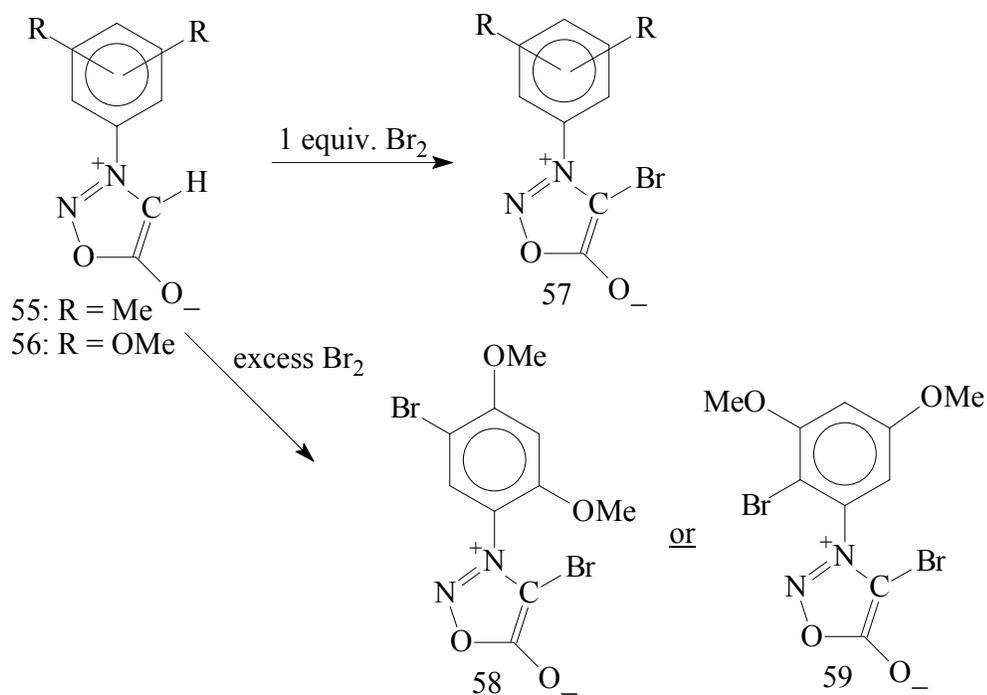
In the vast majority of 3-arylsydrones, reaction with an electrophile occurs at the sydnone C-4 position. Presumably, this is due to the considerable, partial negative charge that resides at this position and due to the considerable, partial positive charge that resides at the sydnone N-3 position, apparently 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 sydrones had afforded only the 4-bromo analogs.^{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.⁵⁶ Therein, it was reported that the major products obtained

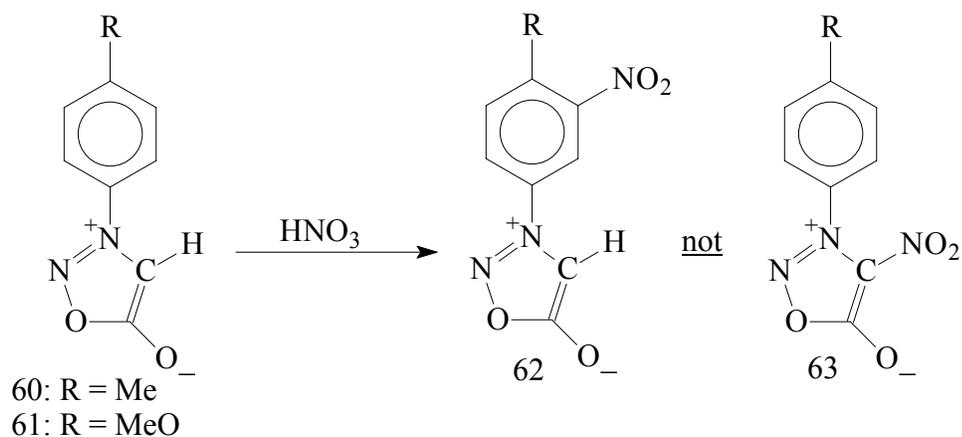
were derived from bromination on the aryl ring, *viz.* 3-(2-amino-5-bromophenyl)sydnone (**53**) and 3-(2-amino-5-bromophenyl)-4-bromosydnone (**54**). Thus, for the first time, it was demonstrated that the aryl moiety could compete with the sydnone ring for electrophilic substitution. Interestingly, with slow addition of NBS only **53** was formed in 70% yield.⁵⁷



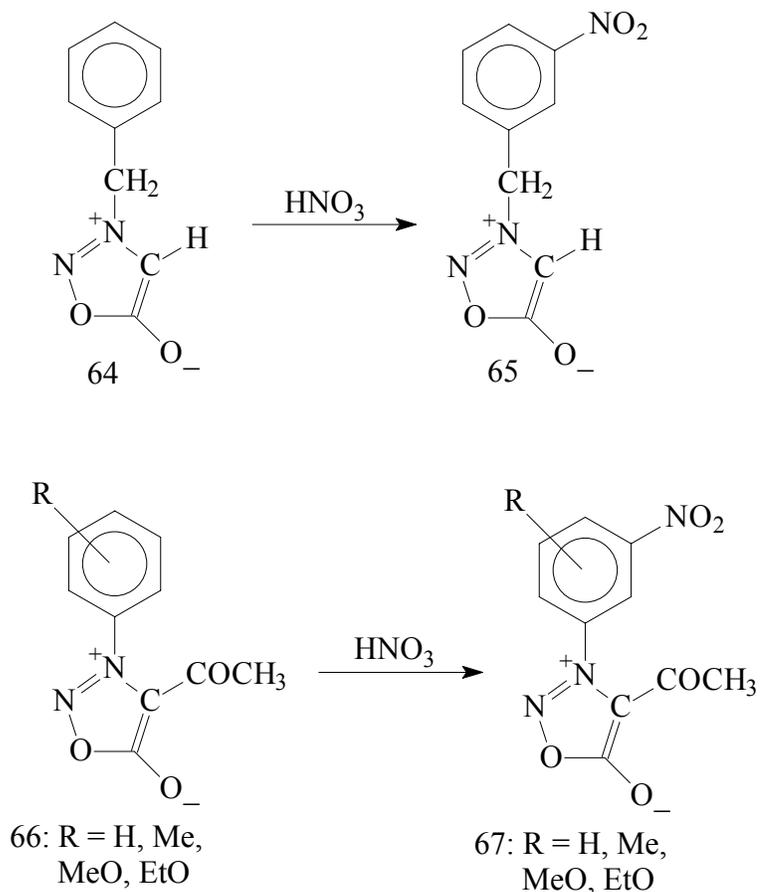
Further examination of this methodology showed that the bromination of a series of dimethylaryl- or dimethoxyarylsydnones (**55** and **56**, respectively) with 1 equivalent of bromine occurred only at the C-4 position of the sydnone ring (**57**).⁵⁸ In fact, even when treated with excess bromine, only 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**.



In contrast to bromination is the nitration of activated arylsydnones. As alluded to previously, nitration of an activated 3-arylsydnone preferentially occurs at the aryl moiety and not at 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 *viz.* **62** and not the anticipated 4-nitro derivatives **63**.⁵⁹

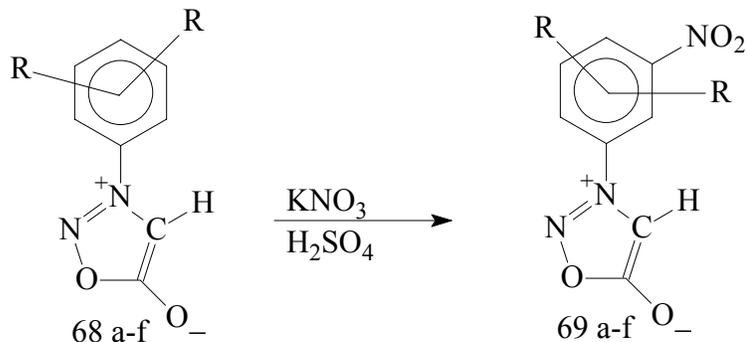


More recent investigation of nitration of 3-substituted arylsydnones has been reported by Tien and coworkers.^{60,61} Therein, it was shown that the *meta*-nitroaryl products (**65**, **67**) were obtained when either 3-benzylsydnone (**64**) or various 3-substituted-4-acetylsydnones **66** were treated under nitrating conditions. In the latter case, the acetyl group could be removed with barium hydroxide.

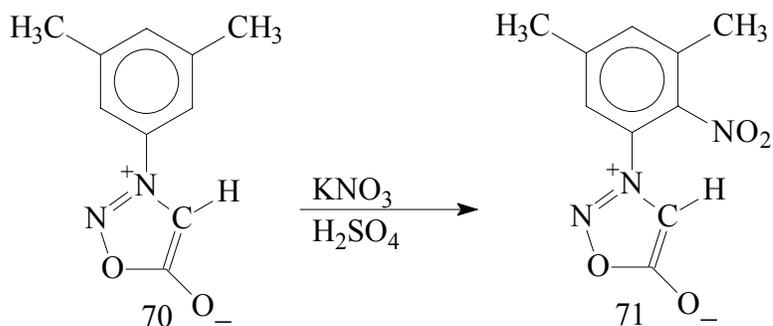


On a similar note, and most recently, Turnbull, Blackburn, and Miller have examined nitration of 3-arylsydnones with multiple electron-donating groups on the aryl ring (methyl groups).⁶² Once again, exclusive aryl ring nitration was observed, with a strong tendency for nitration *meta* to the sydnone 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**).



- a) R = 2,4-Me, b) R' = 3,4-Me, c) R' = 2,5-Me,
 d) R = 2,3-Me, e) R = 2,6-Me 5) R = 2,4,6-Me

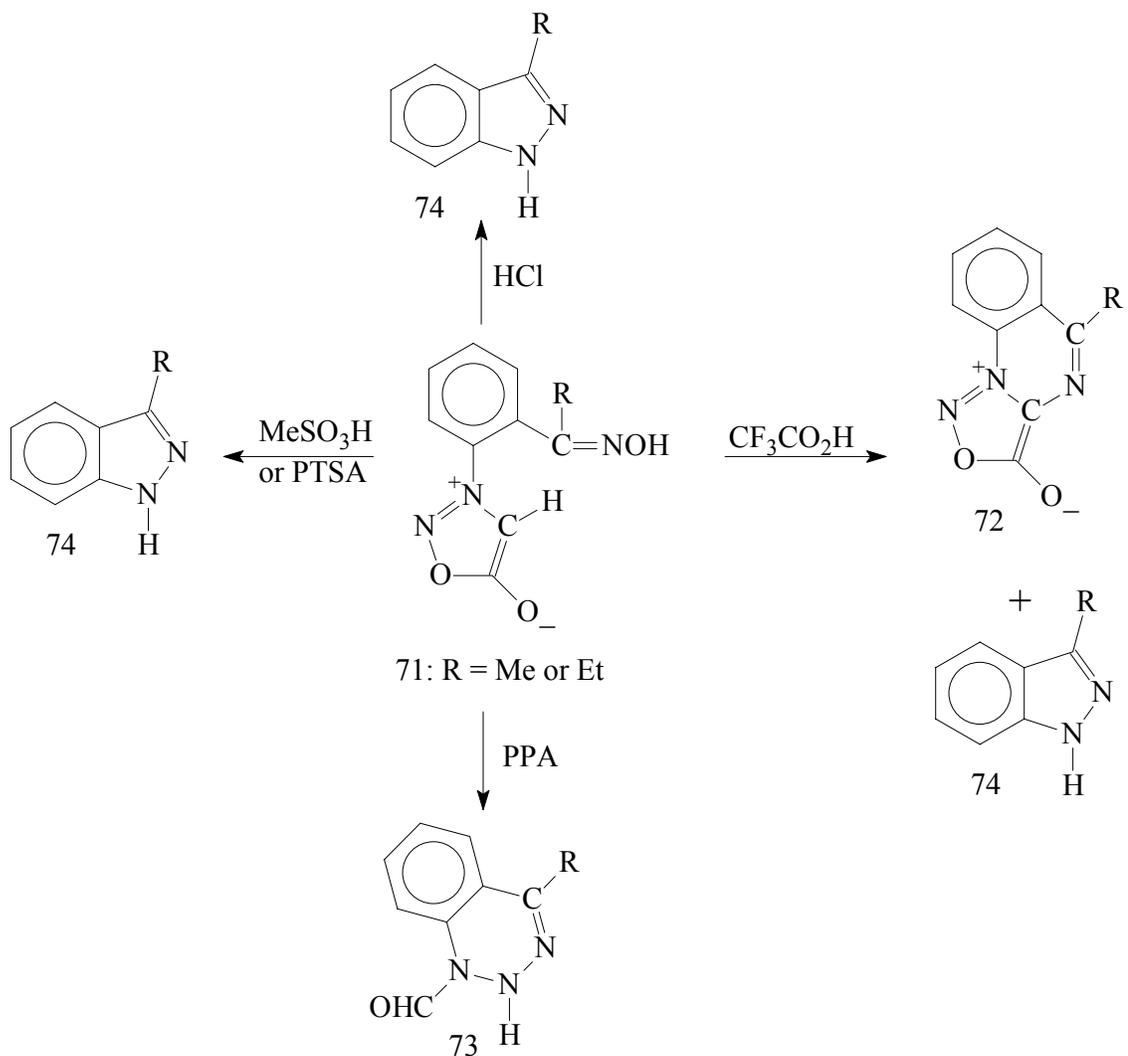


IV. Reactions of *ortho*-Substituted Aryl Sydnone

Fused ring sydnone (*cf.* **72**, **75**, **76**) 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, oximosydnone **61** have been used to prepare sydnocinazoles **72**, benzotriazines **71** and indazoles **74** while *ortho*-substituted arolysydnone have been shown to afford both the fused-ring syndoindole **76** and

substituted indazoles **78** depending on the reaction conditions. Presented here is a brief overview of this chemistry.

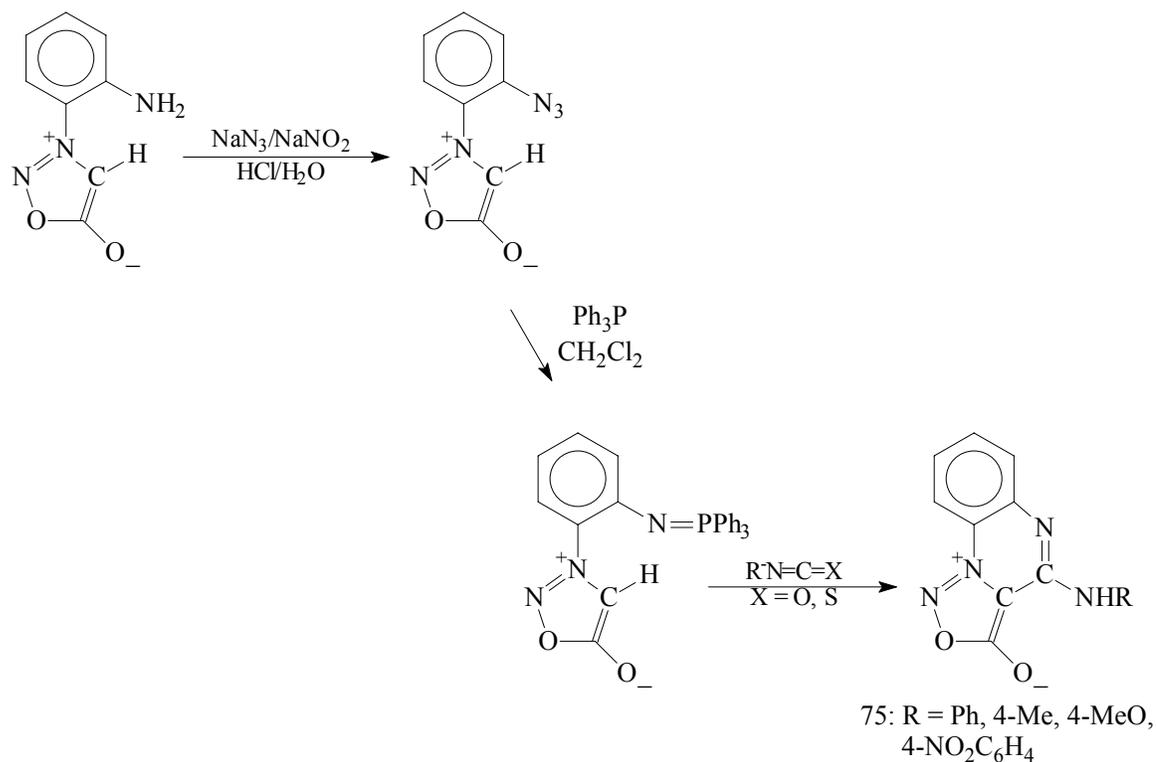
It has been reported⁶³ that by treating oximinosydrones **71**, R = Me or Et with any one of a variety of acids, it is possible to obtain the corresponding sydnoquinazoline **72**, benzotriazine **73**, or indazole **74**, depending on which acid is employed.



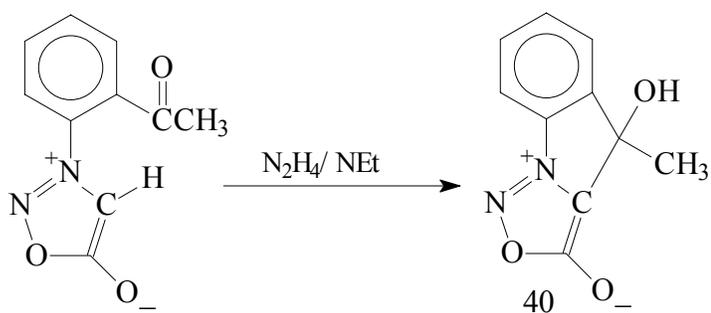
Structural isomers of the sydnoquinoline **72**, viz. 4-(arylamino)-sydno[3,4-a]quinoxalines (**75**), have been prepared in good to excellent yield (60-90%) by aza-

Wittig carbodiimide formation followed by intramolecular electrophilic cyclization
(Scheme 1).⁶⁴

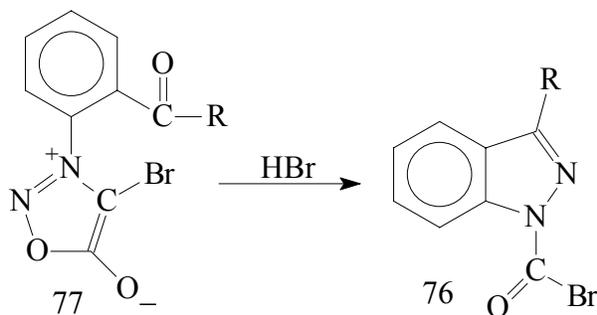
Scheme 1



Two serendipitous discoveries have resulted in the preparation of the fused-ring sydnoid **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 sydnoid **40** and not the anticipated hydrazone derivative.⁶⁵

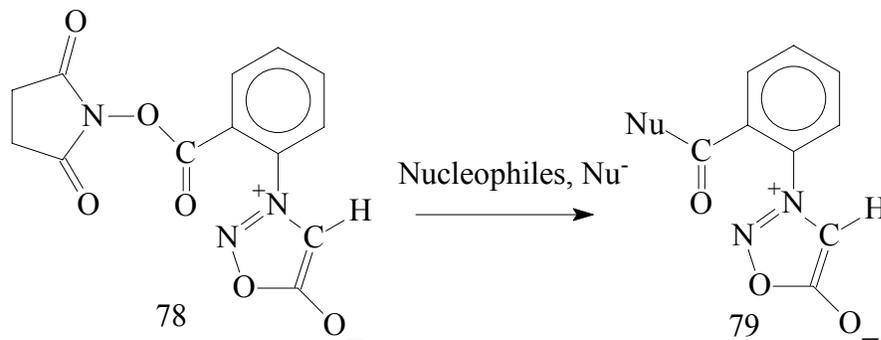


In an attempt to extend this study, it was considered of interest to place a bromo-leaving group on the acetyl methyl. Accordingly, 3-(2-acetylphenyl)-4-bromosydnone (**77**, R = Me) was treated with Br₂/hν or CuBr₂. Surprisingly, the bromocarbonylindazole **76**, R = Me was obtained rather than the expected sydnone **77**, R = CH₂Br. 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%).⁶⁶



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*-acylarylsydnones can be prepared from one or two intermediates by reacting nucleophiles with activated *ortho* carbonyl species.⁶⁷ For example, 3-[2-(N-succinimido)-oxycarbonyl]phenylsydnone **78** was reacted with twelve

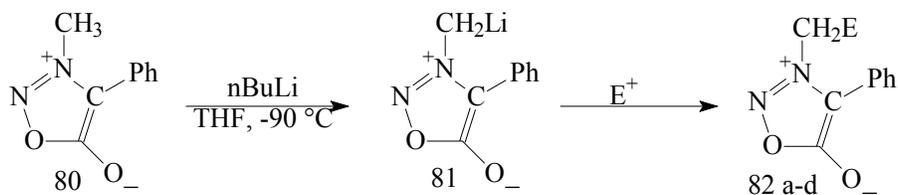
different nucleophiles to afford corresponding *ortho*-acylarylsydnone **79** in yields ranging from 23% to 63%.



V. Miscellaneous, Recent Reactions of Sydnone

In the years 1996 to 2001, 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.

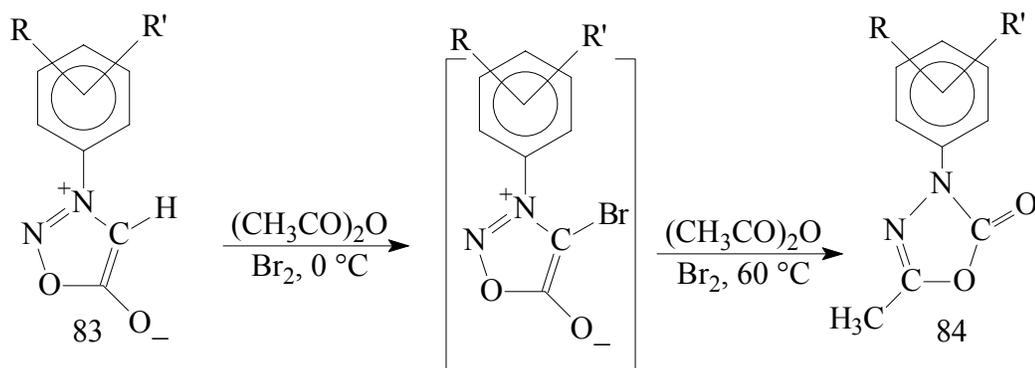
Kalinin and Cherepanov have recently explored metallation of 3-methyl-4-phenylsydnone (**80**).⁶⁸ In their study, it was found that a proton could be abstracted from the methyl group of **80** with butyllithium at $-90\text{ }^\circ\text{C}$, forming the rather unstable lithio intermediate **81**. Subsequent 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) $\text{E} = \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, 82b) $\text{E} = \text{CH}_2\text{COOCH}_3$, 82c) $\text{E} = \text{CH}_2\text{COOH}$, 82d) $\text{E} = \text{CH}_2\text{C}(\text{Ph})_2\text{O}$

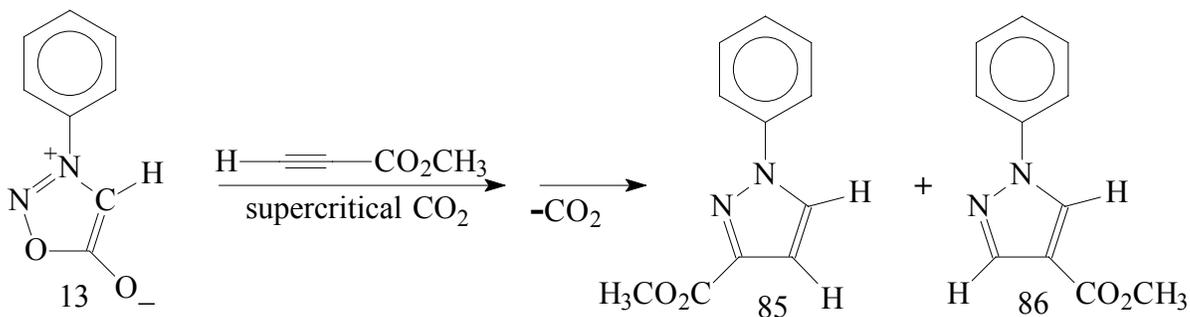
Mallur, Bharati, and Badami recently used sydrones as intermediates to 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones.⁶⁹ Their goal was to synthesize such species and test them for antimicrobial activity. The desired 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones **84** were prepared from 3-arylsydrones **83** by reaction with bromine in acetic anhydride, as is illustrated with a general example, below.



Their suggested mechanism involves initial sydrone 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 sydrone 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

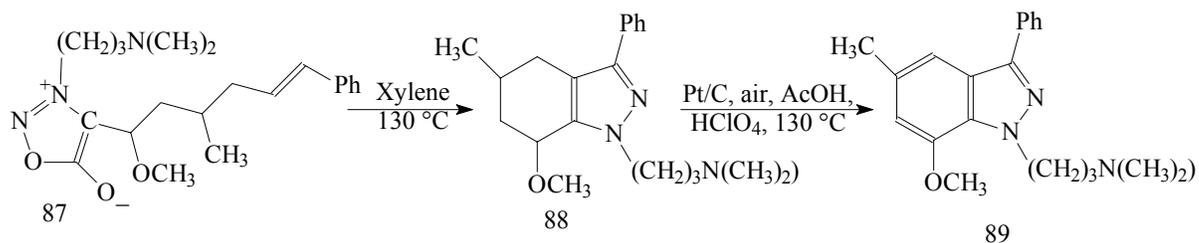
prepared in yields of 70-90%, most of which showed anti-bacterial and anti-fungal activity.

Another study taking advantage of the ability of sydnone to go through 1,3-dipolar cycloadditions involved running a known sydnone reaction under new conditions. Toteo, McGowin, and Turnbull studied the reaction of 3-phenylsydnone (**13**) with methyl propiolate in supercritical carbon dioxide.⁷⁰

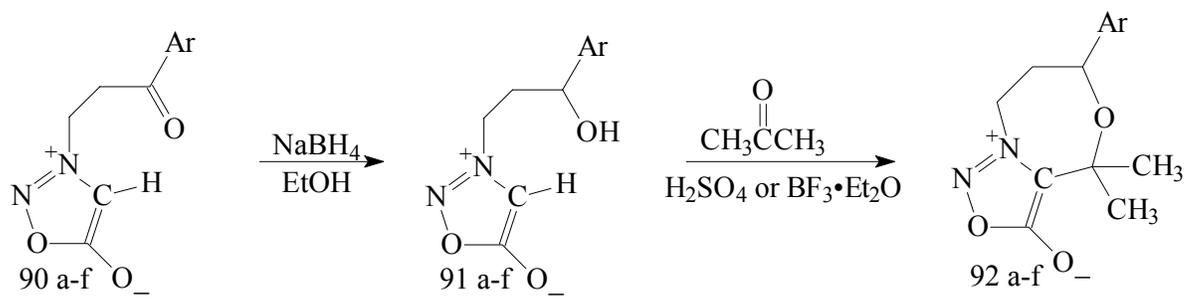


In this reaction, two regioisomers (**85** and **86**) are formed, due to methyl propiolate being unsymmetrical. The temperature in the supercritical fluid reactor was varied, as well as the pressure, to see if this had an effect on reaction selectivity (i.e. a greater amount of regioisomer **85** formation 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 their expedient synthetic route to the antidepressant 1-[3-(dimethylamino)propyl]-5-methyl-3-phenyl-1*H*-indazole (**89**).⁷¹ This synthesis involved an *intramolecular* 1,3-dipolar cycloaddition of **87** followed by aromatization to obtain the desired product.



Finally, Zhang, Wu, and Yin have made novel, fused-ring sydnones containing a seven-membered ring fusion.⁷² Their route to these species involved the reduction of 3-arylethylsydnones **90** with sodium borohydride to obtain a 3-(aryl-3-hydroxypropyl)-sydnone **91**. Subsequent treatment of these species with acetone and concentrated sulfuric acid, or boron trifluoride etherate produced the corresponding fused-ring sydnones **92** in 60% to 85% yield.

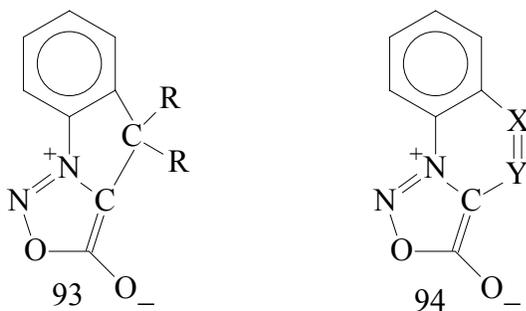


Ar = a) C₆H₅, b) 4-CH₃C₆H₄, c) 4-ClC₆H₄, d) 4-BrC₆H₄, f) 2-naphthyl

Background to the Current Research

I. Arylsydnone Ring Fusion and Routes to Other Heterocycles

In recent years, fused-ring arylsydrones have attracted attention because ring-fusion is a route to interesting new molecules that may possess useful biological activity. In the main, two types of fused-ring arylsydrones have been of interest. The first is where there is a one-carbon bridge adjacent to the sydnone ring (*cf.* **93**) and the second is where the bridge from the sydnone to aryl ring is an unsaturated, two-atom, bridge (*cf.* **94**). These species have been of special interest because it is thought the fusion may modulate *in vivo* metabolism of the sydnone ring, and therefore give rise to hitherto unobserved useful effects. On a similar note, sydrones have given rise to non-sydnone heterocycles that may also be potentially useful, including benzotriazines and indazoles.



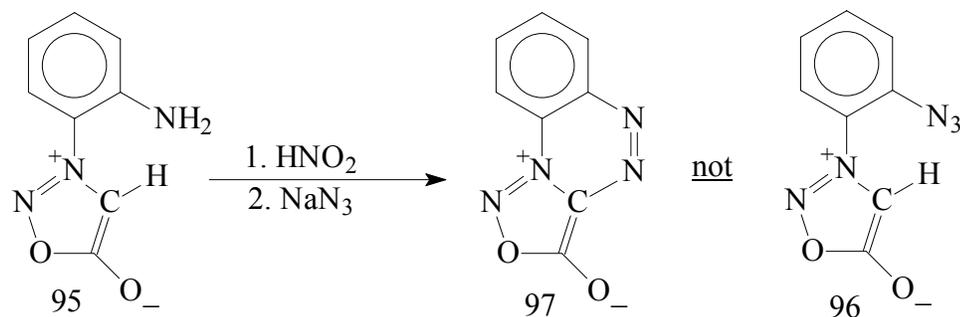
Some presentation of routes to fused-ring arylsydrones and “other” heterocycles has already been made in the introductory material (see “Dilithiation of 3-Aryl Sydrones” and “Reactions of *ortho*-Substituted Aryl Sydrones”). In this section, a few more examples of both arylsydnone ring fusion and routes to other heterocycles from

sydnones will be presented, including some more-detailed repetition of material already mentioned in the introduction. The reader will find a repeated theme, *viz.* fused-ring sydnones and “other” heterocycles have been prepared from *ortho*-substituted arylsydnones by intramolecular, electrophilic substitution. The nucleophile is either the sydnone ring or a breakdown of the sydnone ring and the electrophile is an *ortho* substituent.

It should be noted that the current research aims to follow this lead, and create a new opportunity for intramolecular, electrophilic substitution (see “Aims of the Present Work”). It is hoped that this background information will aid the reader in understanding the rationale for the current work, and how it might lead to fused-ring arylsydnones.

One of the earliest preparations of fused-ring sydnones came as a surprise of sorts. In 1977, Preston and Turnbull⁷³ treated 3-(2-aminophenyl)sydnone **95** with nitrous acid followed by sodium azide in hopes of preparing azidosydnone **96**. Unexpectedly, the product was the fused-ring sydnobenzotriazine **97** (Scheme 2).

Scheme 2

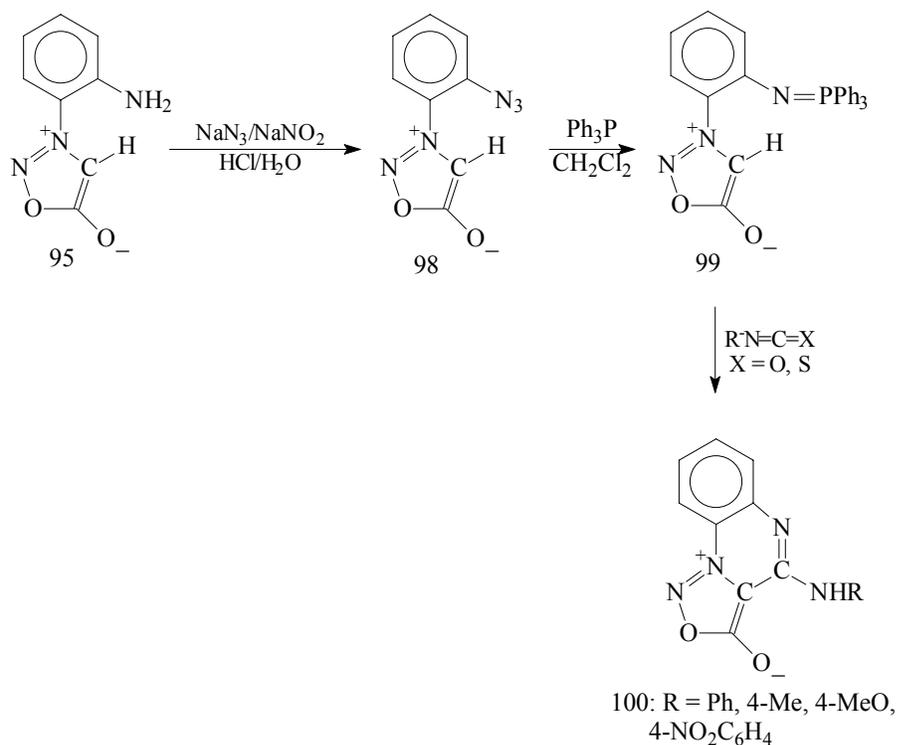


Presumably, the fused-ring sydnone formed by an intermolecular trapping of the intermediate diazonium species by the sydnone ring.

More recently (1991), a route to novel 4-(arylamino)sydno[3,4-a]quinoxalines **100** was reported by Burson, Turnbull, and coworkers from the same species **95**.⁷⁴ The

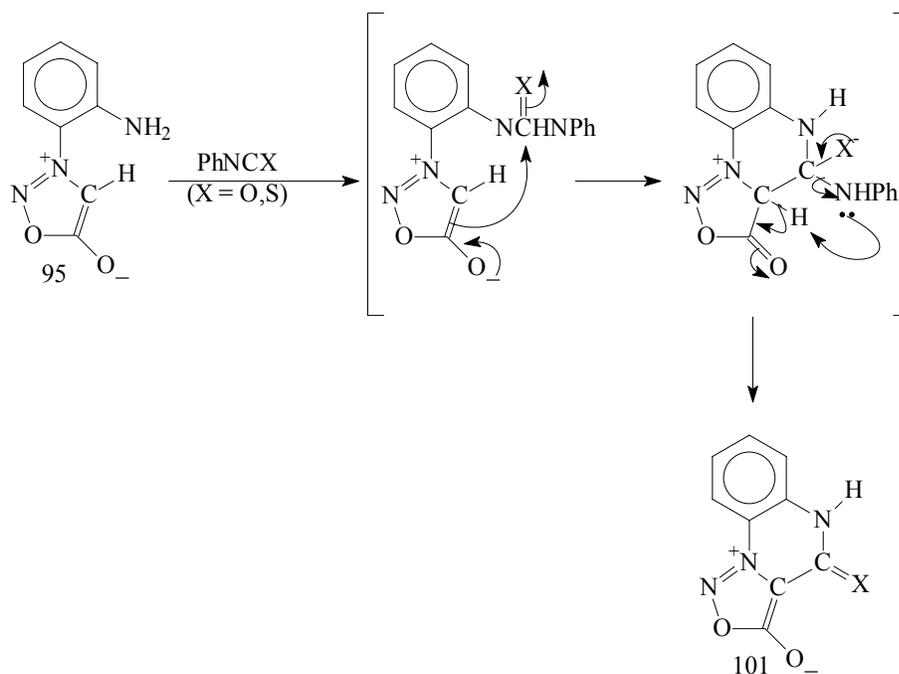
synthesis involves aza-Wittig carbodiimide formation followed by intramolecular electrophilic aromatic substitution by the sydnone ring. Yields of 60% to 90% are obtained (Scheme 3). Once again, it is clear ring fusion is effected by generating an electrophile in close proximity to the sydnone ring.

Scheme 3



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 **95**.⁷⁵ Subsequent heating effected cyclization to the sydnoquinoxaline **101**, again by intramolecular electrophilic substitution (Scheme 4).

Scheme 4

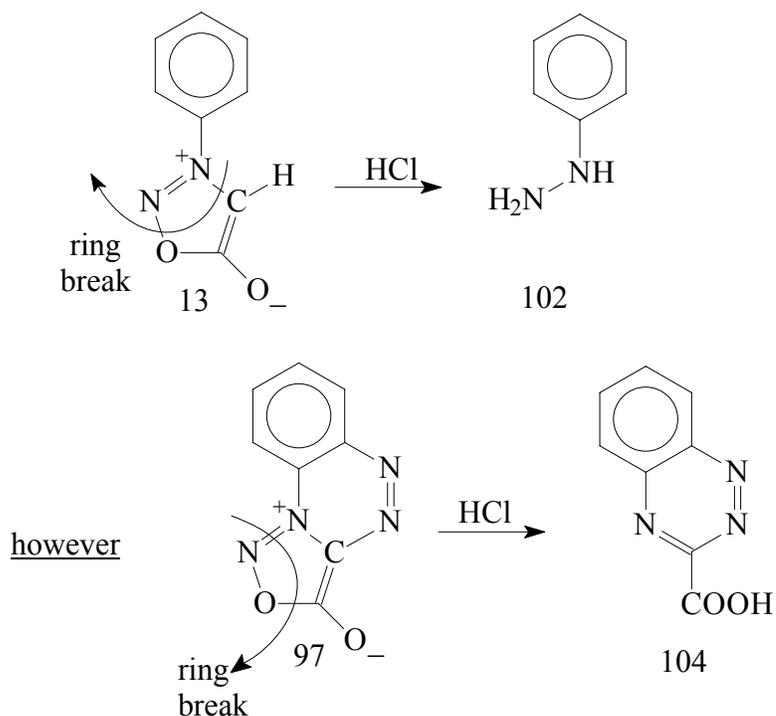


The three preceding examples illustrate the standard synthetic avenue to sydnone ring fusion, *viz* create an electrophilic center *ortho* to the sydnone ring for the sydnone to attack.

As a connection between fused ring sydnones and “other” heterocycles, there is an example of how ring fusion modulates the properties of the sydnone ring. Consider the following, where the ring fusion changes how the sydnone ring breaks, creating a heterocycle, a benzotriazine.

It is known that 3-phenylsydnone (**13**) reacts with hydrochloric acid to form phenylhydrazine (**102**).⁷⁶ However, in fused species **97**, 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 **104** (Scheme 5).

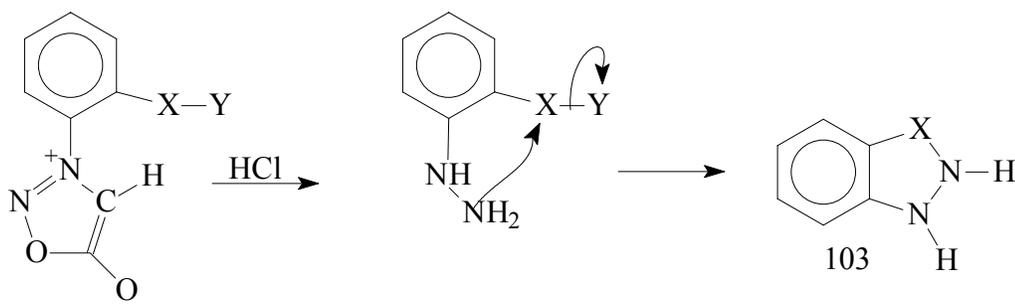
Scheme 5



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 5, under non-fused circumstances, acid cleavage of the sydnone gives rise to an arylhydrazine, a powerful, nucleophilic species that might be useful for heterocyclic synthesis use. It was postulated that an *ortho*-substituted arylhydrazine generated from an appropriate arylsydnone would lead to a unique heterocycle (*cf.* **103**) upon cleavage with HCl (Scheme 6).⁷⁷

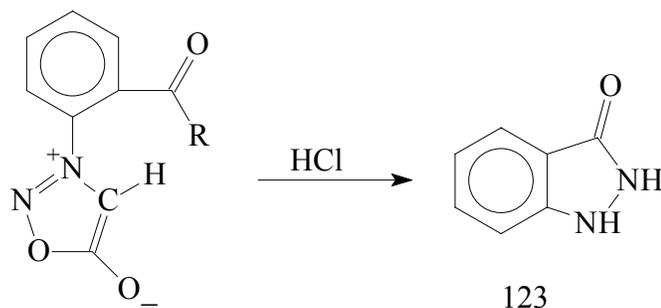
Scheme 6



Initial work in this direction aimed to prepare indazoles from *ortho*-oximino sydnones. When aldoxime **105** was treated with aqueous HCl, aminoindazole **108** was produced. It was thought the cyclization occurred *via* a nitrile intermediate **111**, supported by the observation that if 3-(2-cyanophenyl)sydnone was treated with HCl, the same aminoindazole **108** was formed. Ketoximines **106** and **107**, when treated with HCl gave corresponding 3-substituted indazoles **109** and **110**, presumably by means of hydrazine formation and subsequent cyclization with the elimination of hydroxylamine (Scheme 7).

formation followed by nucleophilic attack upon the carbonyl carbon with subsequent expulsion of the leaving group (Scheme 9).

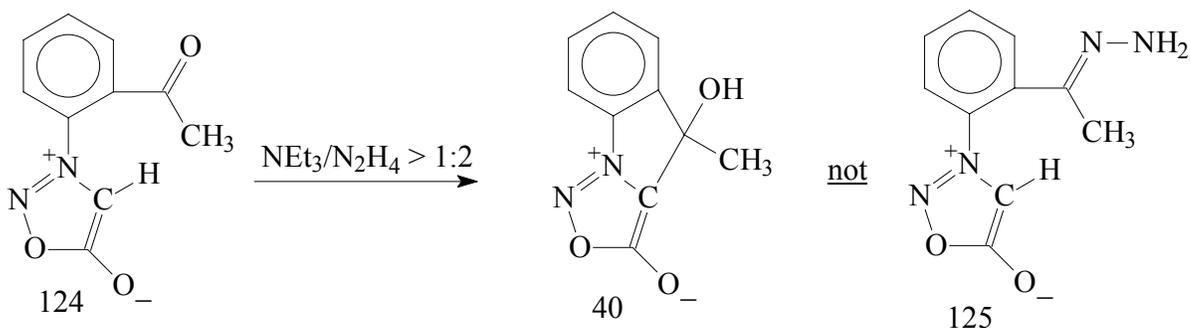
Scheme 9



- 118) R = NH₂
- 119) R = NHCH₃
- 120) R = NHNH₂
- 121) R = N₃
- 122) R = OCH₃

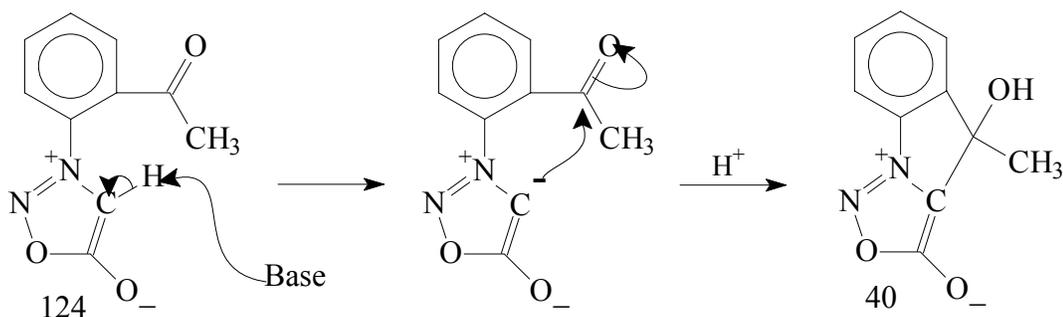
It has just been illustrated how cleavage of the sydnone ring can lead to a nucleophile (hydrazine) capable of attacking an *ortho* electrophile, mainly carbonyl and related species. It has been found that a comparable transformation can be accomplished without breaking the sydnone ring, leading to sydnoindoles, as in the reaction of 3-(2-acetylphenyl)-sydnone **124** 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 **125** (Scheme 10).

Scheme 10



The fused-ring syndnone **40** was also made 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 syndnone (Scheme 11).

Scheme 11

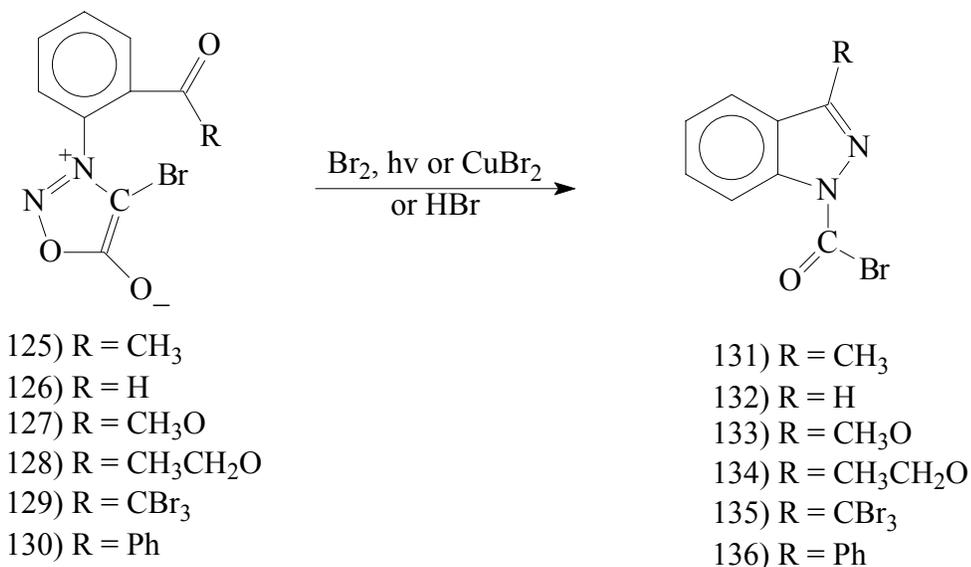


Initially, it was theorized that the ring strain generated by the one-carbon bridge of **40** would cause the species to be unstable and non-isolable, however, it has been found that under normal conditions the compound is quite stable. Due to its crystalline nature, the proposed structure was confirmed by X-ray crystallography.⁷⁸ A surprising aspect of the synthesis shown in Scheme 11 is the relatively high acidity of the proton at the 4-

position of **124**. The pKa of a “normal” sydnone hydrogen is ~18-20⁷⁹; therefore, the proton’s abstraction under such mild conditions can be directly related to the *ortho*-acetyl group’s ability to withdraw electron density away from the sydnone ring.

It was thought additional functionalization of species such as **40** might be possible if the methyl group of sydnoindole **40** was activated.⁸⁰ The method chosen was bromination, but, in order to avoid competitive bromination at the 4-position, the sydnone ring was brominated first. When side-chain bromination was then attempted on **125**, inadvertently, indazoles were once again produced. The product obtained was a 1-bromocarbonyl-3-methylindazole **130** not the expected α -bromoketone (Scheme 12).

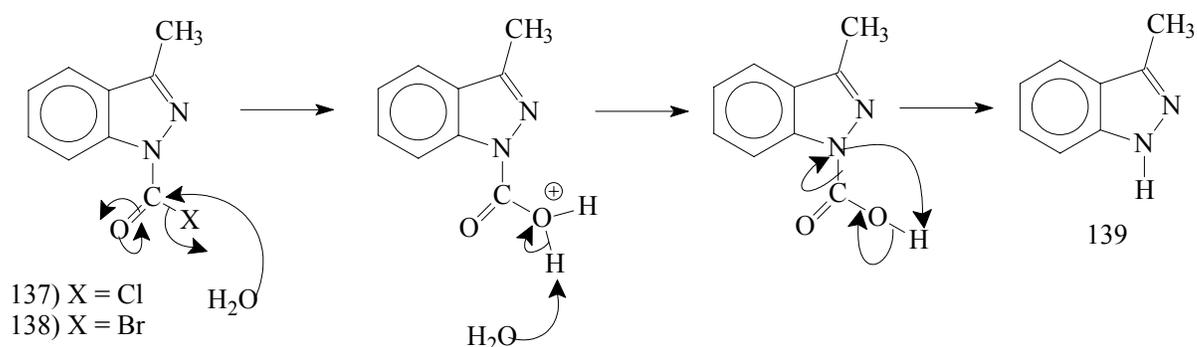
Scheme 12



It was thought that formation of HBr *in situ* was effecting this transformation, playing the same role as HCl when indazoles were intentionally sought after, producing a hydrazine intermediate. This idea was confirmed when treatment of a number of 3-(2-substituted carbonylphenyl)-4-bromosydnone **125** to **130** with HBr gas yielded the corresponding bromocarbonyl indazoles **131** to **136**.

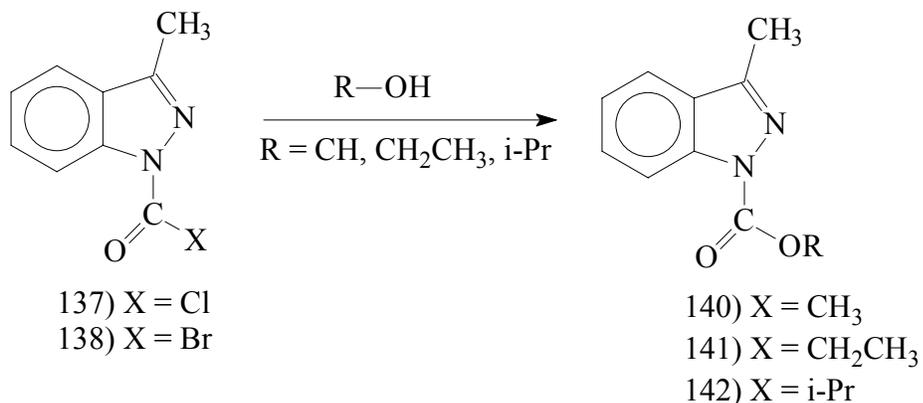
Although these 1-halocarbonyl-3-substituted indazoles were unusually stable, it was discovered that they were hydrolyzed by atmospheric water as shown in Scheme 13. This idea was tested by the deliberate addition of water to 1-chlorocarbonyl-3-methylindazole **137** and 1-bromocarbonyl-3-methylindazole **138**. In both cases 3-methylindazole **139** was formed by nucleophilic attack of water on the carbonyl followed by loss of carbon dioxide and proton transfer to the N-1 nitrogen (Scheme 13).

Scheme 13



Finally, if acid halides **137** and **138** were reacted with an alcohol, the respective esters **140** to **142** were produced as crystalline solids (Scheme 14), yielding an even greater variety of indazole species.

Scheme 14



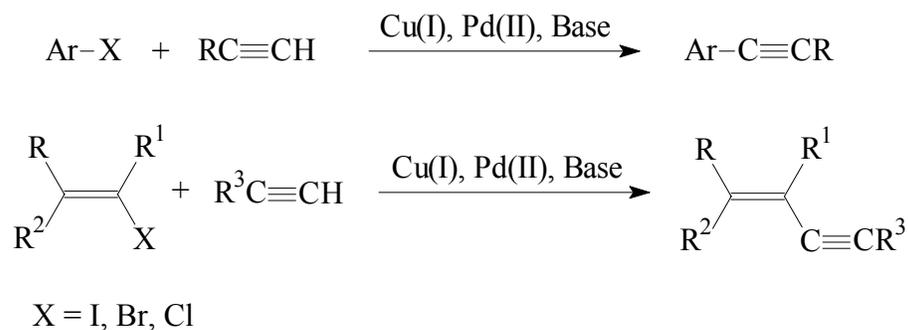
The goal of the above text was to show how arylsydnones have led to both fused-ring sydnones and other heterocycles (mainly indazoles). The potential for using intramolecular electrophilic substitution as an avenue to fused-ring sydnones was the main factor in choosing to try to synthesize *ortho*-alkynyl sydnones as presented in “Aims of the Present Work,” and an explanation lies therein. Before these aims will be addressed, however, more introductory material is required to give the background on the reaction used to create *ortho*-alkynyl sydnones, and this is found in the following section.

II. The Sonogashira Coupling Reaction

As is indicated by the title of this Thesis, a major portion of the current work involved use of the Sonogashira Coupling Reaction. Because of this, it seemed fitting to take a page or two to give some background on this reaction, with the aim of providing the reader some understanding of how it works.

In 1975, Sonogashira developed a carbon-carbon bond-forming reaction that occurred under relatively mild conditions with the aid of palladium and copper catalysts.⁸¹ Specifically, the reaction allows the coupling of an aryl or vinyl halide with a terminal acetylene as shown in Scheme 15.

Scheme 15



The copper (I) species usually used is cuprous iodide. The type of base most often employed is a tertiary amine, such as triethylamine, which may also be used as the solvent. The palladium catalyst may be a variety of species, commonly including bistriphenyl-phosphine palladium dichloride, tetrakis(triphenylphosphine) palladium(0), or bistriphenylphosphine palladium acetate.

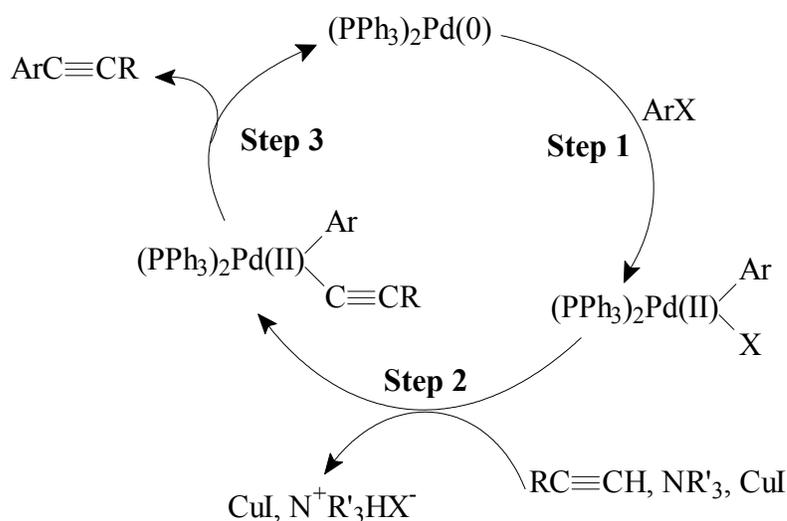
In terms of the scope of the reaction, aryl iodides are the species most frequently and most easily coupled with terminal acetylenes. Generally, these reactions occur at room temperature and can take from a few hours to overnight. Vinyl iodides react in a similar manner.⁸² Vinyl and aromatic bromides are much less reactive in the Sonogashira Coupling, often requiring refluxing conditions and extra special care in purification and deoxygenation of reagents and solvents. Reactions often take twenty-four hours or more and sometimes require the use of an autoclave when dealing with volatile reagents. The reaction of aryl chlorides under Sonogashira conditions is somewhat restricted but has been accomplished, mainly with aryl chlorides containing an appropriately positioned, strong electron-withdrawing group. Vinyl chlorides are more amenable to reaction and will do so at room temperature⁸².

Generally, the Sonogashira coupling reaction is very tolerant of other functional groups on both the vinyl/aryl halide and terminal acetylene. However, there are some specific examples of alkynes that do not react under Sonogashira conditions. Mainly these are alkynes conjugated to electron-withdrawing groups, such as methyl propiolate. When reactions are attempted with such alkynes, the resulting product is often a Michael-type addition of the organic base to the alkyne.

In terms of mechanism, the Sonogashira coupling is believed to follow the oxidative addition-reductive eliminations steps that are common to palladium catalyzed, carbon-carbon bond-forming reactions (Scheme 16). The role of the copper co-catalyst in the catalytic cycle remains uncertain. Paraphrasing from Campbell,⁸² the catalytic process may be visualized to involve a palladium(0) species generated from the

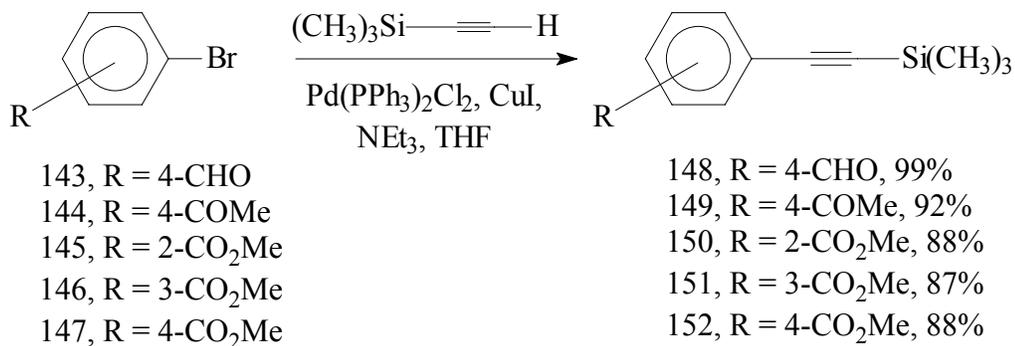
palladium(II) or palladium(0) precatalyst. This species inserts into the aryl halide bond (Step 1) to give an intermediate that, upon reaction with the alkyne (Step 2), gives an alkynylpalladium(II) derivative which collapses to the desired product and to regenerate the active palladium(0) catalyst (Step 3). It is thought the copper co-catalyst and the base form a transient copper acetylide; this may be the alkyne species that adds to the palladium catalyst in Step 2.

Scheme 16



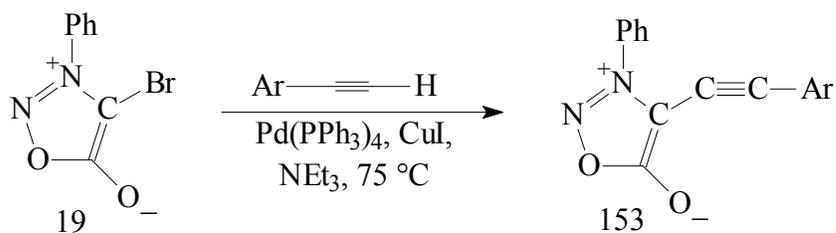
In recent times, improvements have been made to the Sonogashira process through experimentation with different reaction conditions. One improvement that became of interest in the present work was put forth by Krause and Thorand in 1998.⁸³ Although they were not the first to do so, Krause and Thorand found that the use of tetrahydrofuran as a reaction solvent, instead of triethylamine, had a considerable advantage. A variety of aryl bromides (**143** to **147**) were coupled to trimethylsilyl acetylene at room temperature in THF with 1.5 equivalents of the triethylamine base. Yields ranged from 88% to 99% and the reactions were complete in 1 to 16 hours (Scheme 17, **148** to **152**).

Scheme 17



Being that the current research deals with the Sonogashira coupling of sydnones, it should be mentioned that such reactions have been performed at the 4-position of the sydnone ring. 4-Bromo-3-phenylsydnone (**19**) has been successfully coupled with 4-substituted phenylacetylenes achieving the 4-alkynyaryl species in moderate to good yield (Scheme 18, **153**).⁸⁴

Scheme 18



Aims of the Present Work

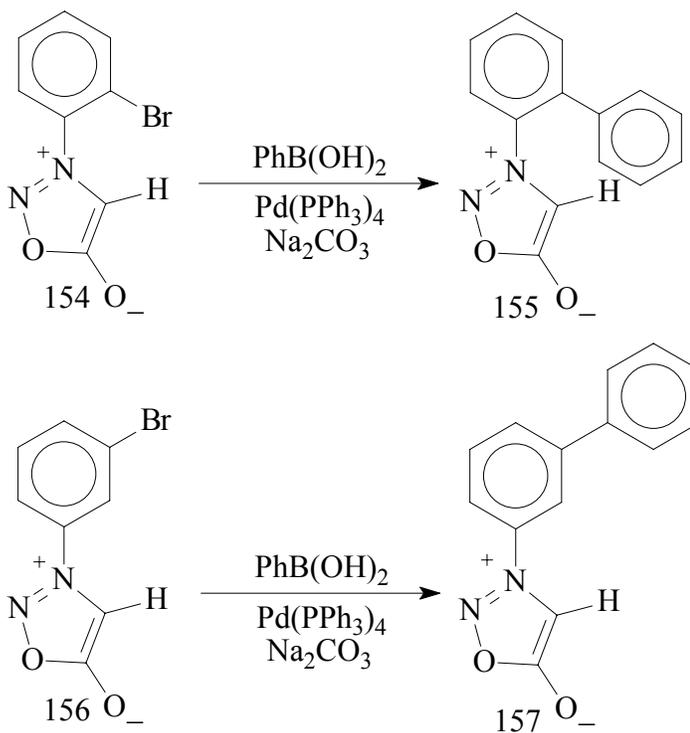
The objective of the current work fell into two separate but related goals. The first goal, as the title of this Thesis states, was to explore Sonogashira coupling routes toward the synthesis of *ortho*-alkynyl sydnone, with the further aim of transforming these species into fused-ring sydnones. The second goal went hand-in-hand with the first, and this was to synthesize specific alkyne-containing sydnones of interest to the United States Air Force as monomers for platinum-centered, non-linear optical materials.

As discussed in the background to this research, and the introduction, previous work has led to a variety of *ortho*-substituted sydnones, some of which have been transformed into fused-ring sydnones, sydnoidoles, and other species such as indazoles. There is interest in all such species as tests of methodology, but also because some of these display significant biological activity. Creation of new species will likely yield some with interesting, and potentially useful, biological properties.

In past endeavors to create functionalized sydnones, the spectrum of organic chemistry had been explored, including all those routes mentioned in the introductory material of this text, including palladium-catalyzed couplings. However, these reactions have been almost exclusively explored at the 4-position of the sydnone ring. One exception to this is the fact that Suzuki Coupling reactions, the coupling of an aryl halide and boronic acid, have been explored on the aryl ring of brominated sydnones in this laboratory (Scheme 19).⁸⁵ Specifically, 3-(2-bromophenyl)-sydnone **154** and 3-(3-bromophenyl)sydnone **156** had been successfully transformed into the corresponding arylated materials **155** and **157** in yields of 20% and 41% respectively. Although the

yields were moderate, this set a precedent that successful transformations could be achieved.

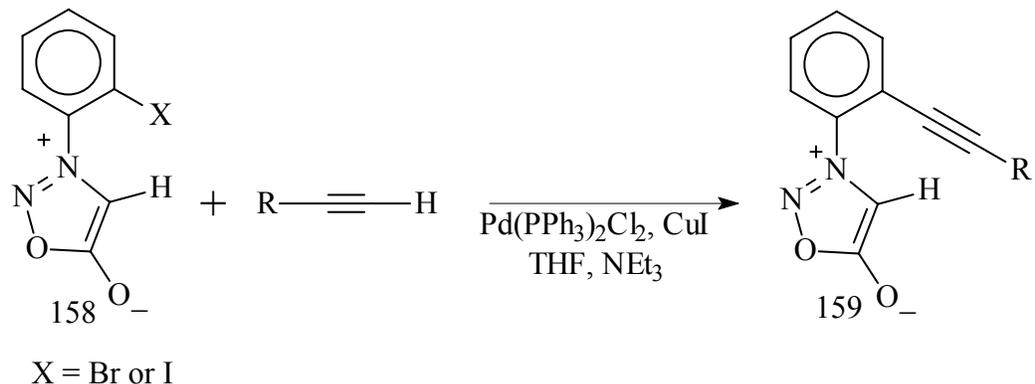
Scheme 19



Sonogashira couplings had not been explored on the aryl ring of arylsydnones, so this seemed like a next logical route to functionalization. Specifically chosen was to attempt Sonogashira coupling of 3-(2-halophenyl)sydnones **158**, since this would provide a functional group *ortho* to the sydnone ring. The reason for this will be discussed shortly.

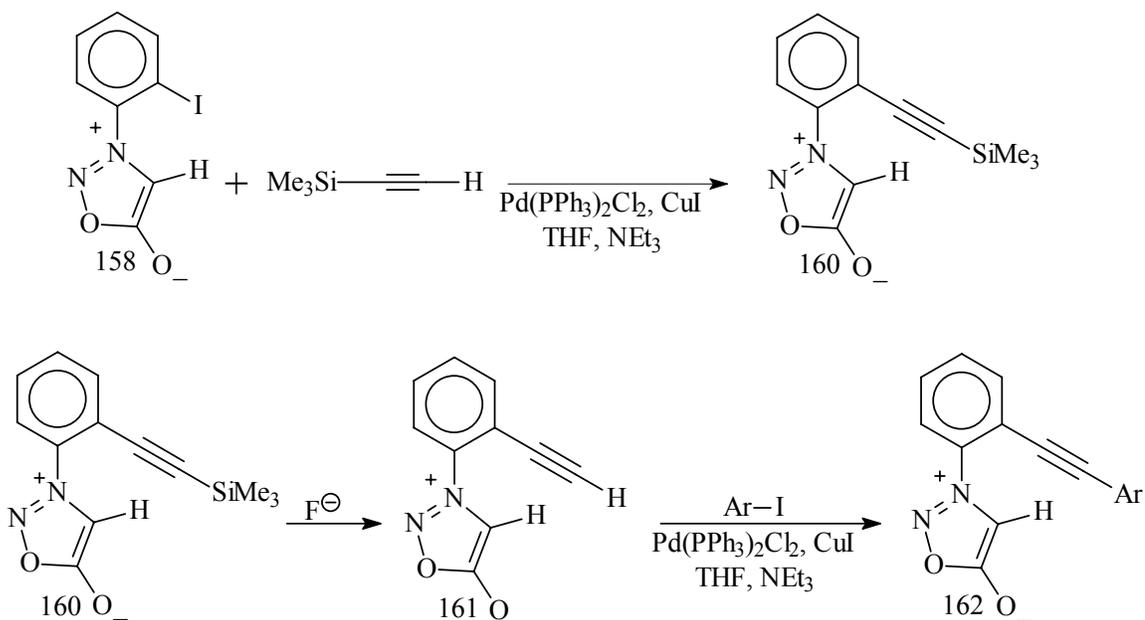
The Sonogashira coupling involves the reaction of a terminal acetylene and aryl halide. This means that various functionalized sydnones could be made by coupling 3-(2-iodophenyl)sydnone with a variety of terminal acetylenes (Scheme 20).

Scheme 20



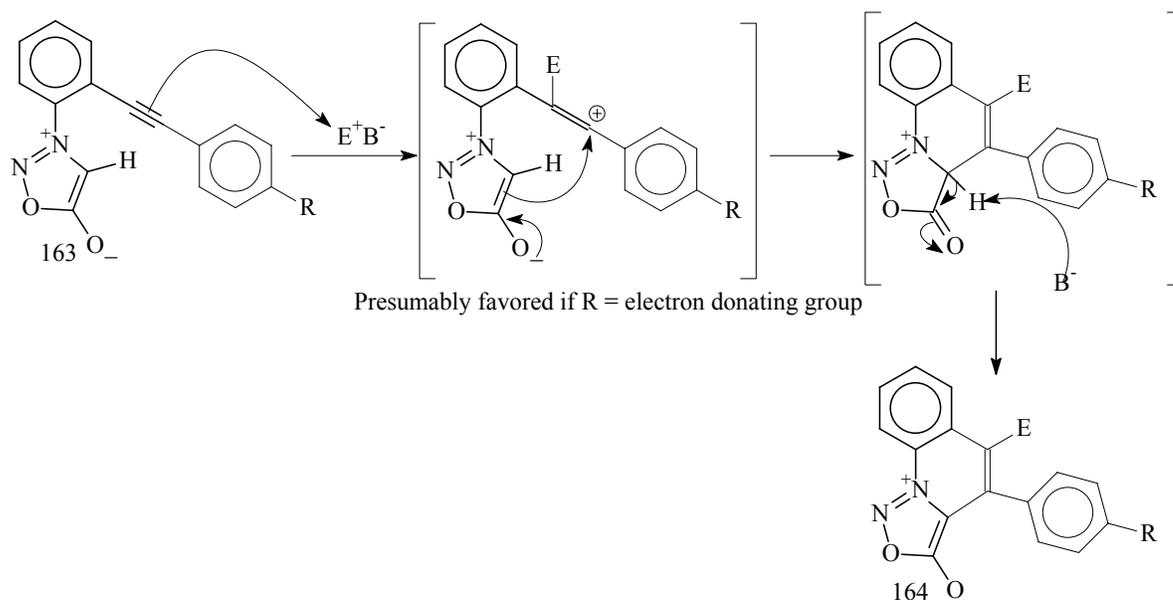
However, since the number of inexpensive, commercially available terminal acetylenes is limited, it was envisioned that even more functionalization could be achieved by putting a terminal acetylene onto the phenyl ring of the sydnone and then coupling with a readily available array of aryl iodides. The idea to accomplish this was first to couple 3-(2-iodophenyl)sydnone with trimethylsilylacetylene, then to remove the trimethylsilyl group via fluoride ion to create the versatile intermediate **161**, and finally to couple the new terminal acetylene with an aryl iodide of choice (Scheme 21).

Scheme 21



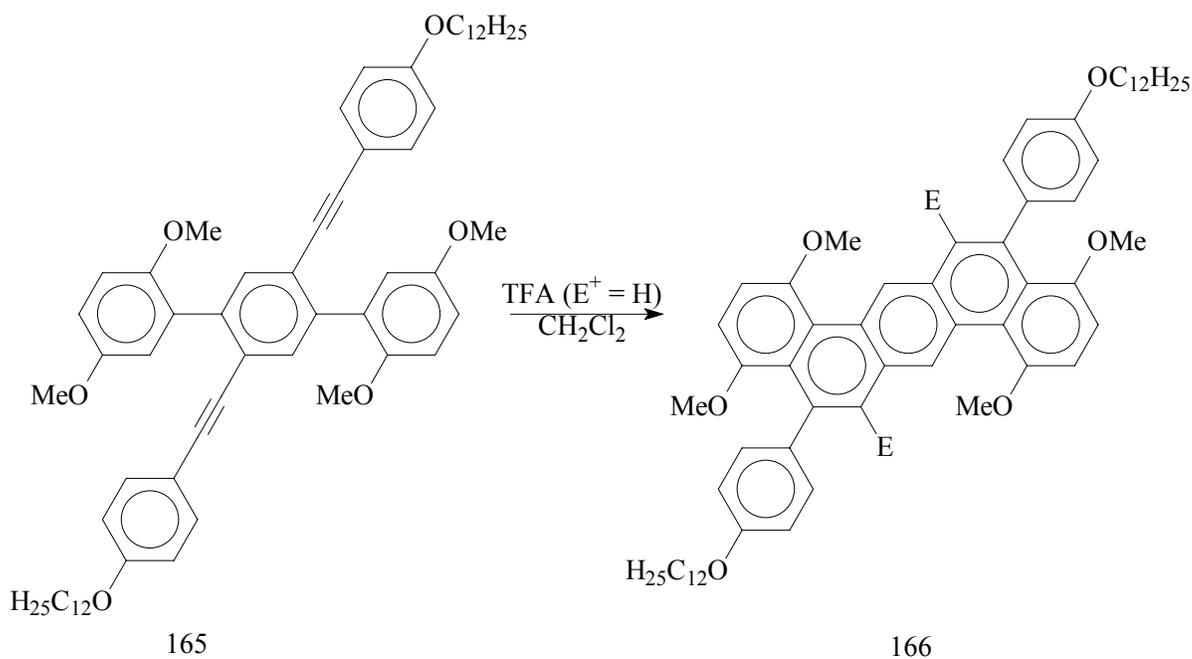
As was alluded to earlier, there was a specific reason for exploration of Sonogashira coupling reactions *ortho* to the sydnone ring. By having an alkyne in this position, a route was envisioned for the transformation of these species into novel fused-ring sydnones. The idea was this: React an electrophile with the alkyne *ortho* to the sydnone ring with the aim of generating a carbocation in close proximity to the electrophilic sydnone ring. The sydnone ring would then attack the carbocation, effecting the desired ring fusion. This process is illustrated in Scheme 22 (E^+ = an electrophile, B^- = counter ion or conjugate base).

Scheme 22



There is evidence that cyclizations such as the one presented in Scheme 22 can occur outside the sydnone realm, and many examples have been presented by Goldfinger⁸⁶. One example involves the synthesis of fused polycyclic aromatic compounds. In the example illustrated by Scheme 23, trifluoroacetic acid is used as an electrophile to induce the cyclization of a bis-alkynyl terphenyl species **165** to form an anthracene derivative **166**. Hence, in this case H^+ is the electrophile inducing cyclization.

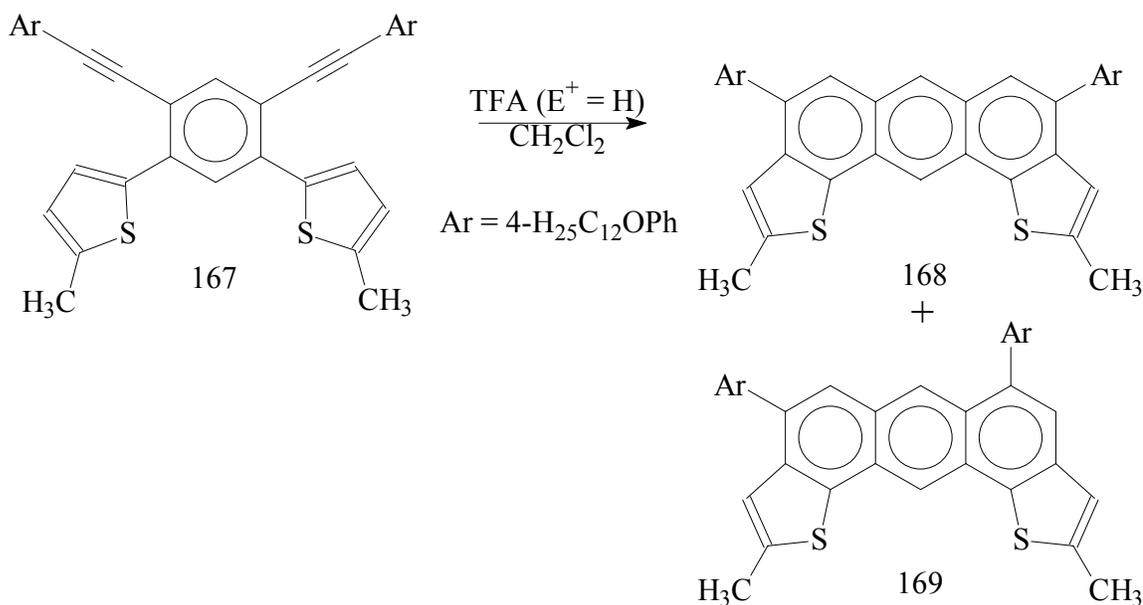
Scheme 23



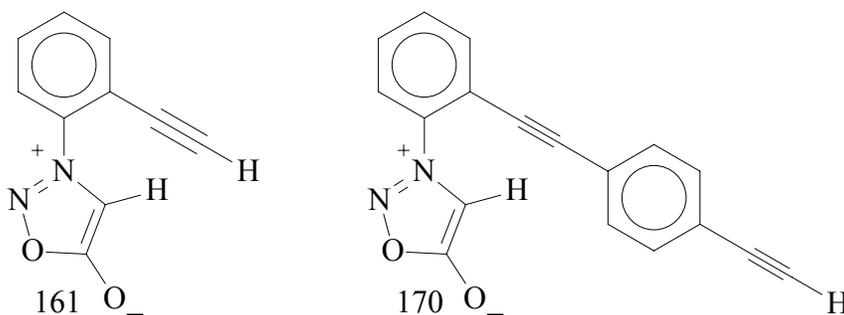
The above cyclization was achieved in 99% yield. Similar, high yielding transformations were accomplished with several other similar species, including $\text{E}^+ = \text{I}^+$ (via iodonium tetrafluoroborate). It should be noted that Goldfinger and coworkers found alkoxy groups *para* to the alkyne were necessary to facilitate successful transformations.

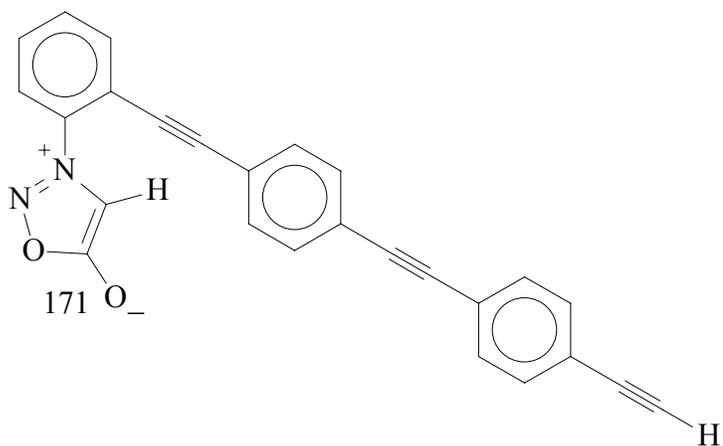
A second example of electrophile-induced cyclization involves cyclization directly onto a heterocyclic ring. The bis-thienyl compound **167** was cyclized to the desired product **168** and a phenyl-migrated isomer **169** in 69% yield (6:1 mixture of isomers) *via* treatment with trifluoroacetic acid at room temperature (Scheme 24).

Scheme 24



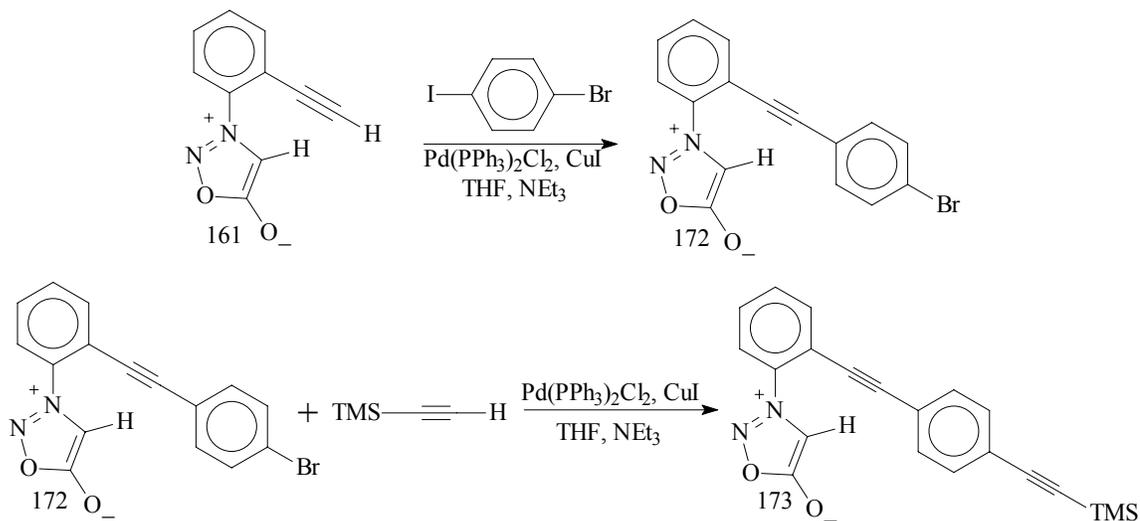
As was mentioned at the beginning of this section, there was a second, concurrent aim of the research. This aim was to use Sonogashira coupling routes to synthesize species of interest to the United States Air Force. This was a seemingly straightforward goal, as there were three species of interest, **161**, **170**, and **171**. It has already been described how **161** could be achieved, and the latter two species were thought to be accessible by building upon **161**. The interest of the Air Force in these species will not be discussed in this work, except to say that it stemmed from a desire to make platinum-centered complexes via the terminal acetylene moiety, and then test these complexes for Non-Linear Optical (NLO) activity.

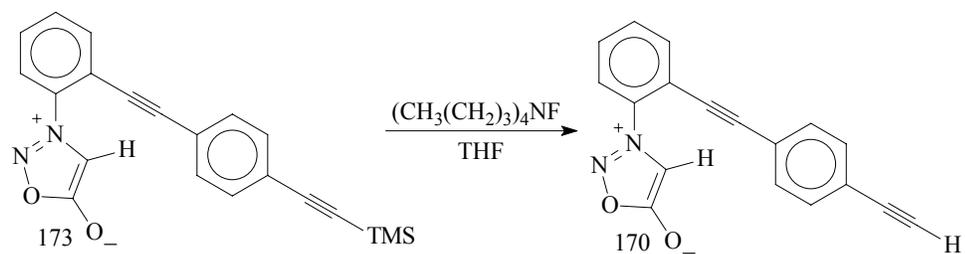




Species **170** would be synthesized as follows: First, 3-(2-ethynylphenyl)sydnone **161** would be coupled to 1-bromo-4-iodobenzene to obtain bromo species **172**. Next, **172** would be coupled with trimethylsilyl acetylene to give species **173**. Finally, the desired **170** would be achieved by removal of the trimethylsilyl group with fluoride ion (Scheme 25, TMS = SiMe₃).

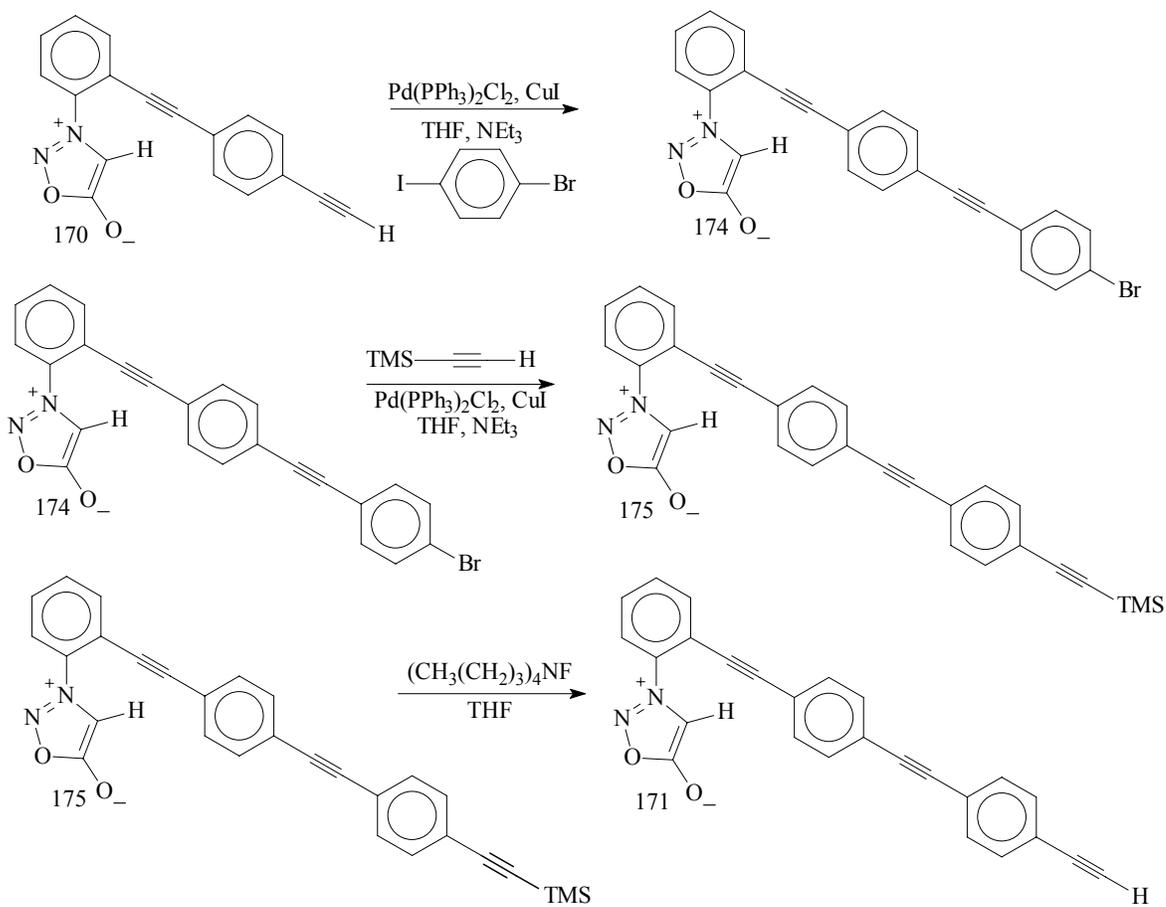
Scheme 25





In a similar fashion, species **171** would be built up from species **170**. The protocol of coupling with 1-bromo-4-iodobenzene (giving **174**), followed by coupling with trimethylsilyl acetylene (giving **175**), and subsequent removal of the trimethylsilyl group would be repeated (Scheme 26).

Scheme 26



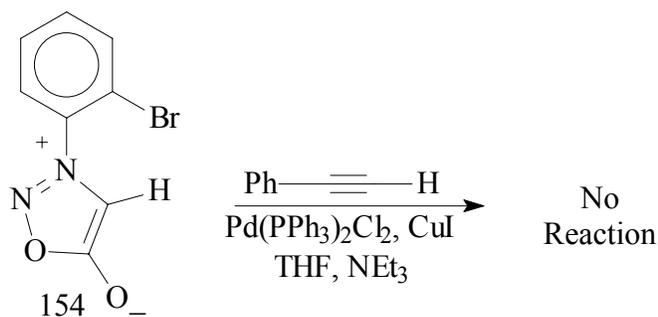
The chemistry that provides the route to species **170** and **171** on the surface appeared rather straightforward. However, it was noted that five reactions were required to reach bis-acetylene **170** from an *ortho*-halogenated arylsydnone, and eight to tris-acetylene **171**.

Discussion

I. Sonogashira Couplings and Related Reactions

With the aims of the research being based upon the idea that *ortho*-halogenated arylsydnones would undergo Sonogashira coupling, a logical place to start was with a feasibility study. 3-(2-Bromophenyl)sydnone (**154**) was available in our laboratory from the work of previous graduate students, and it provided a trial as to whether or not successful transformations were achievable. The initial attempt was with **154** and readily available, inexpensive, phenyl acetylene (Scheme 27). The conditions of Krause and Thorand⁸⁷ were followed, since they had achieved successful couplings of aryl bromides at room temperature in standard, freshly-distilled solvents. The result of the attempted coupling was recovery of starting material from a black tar of impurities.

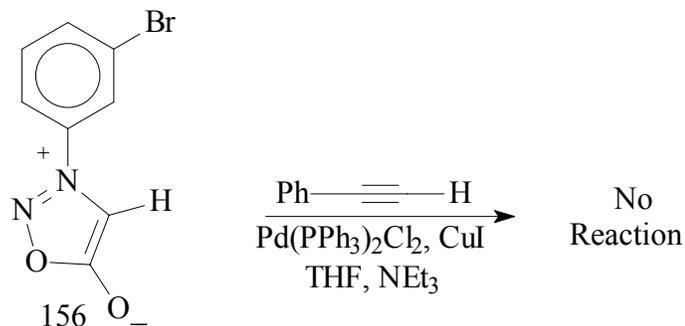
Scheme 27



Because the starting sydnone was *ortho* substituted, the thought arose that the starting substrate might be too hindered to undergo a successful coupling. With this in mind, the same coupling was attempted, on a small scale, with 3-(3-

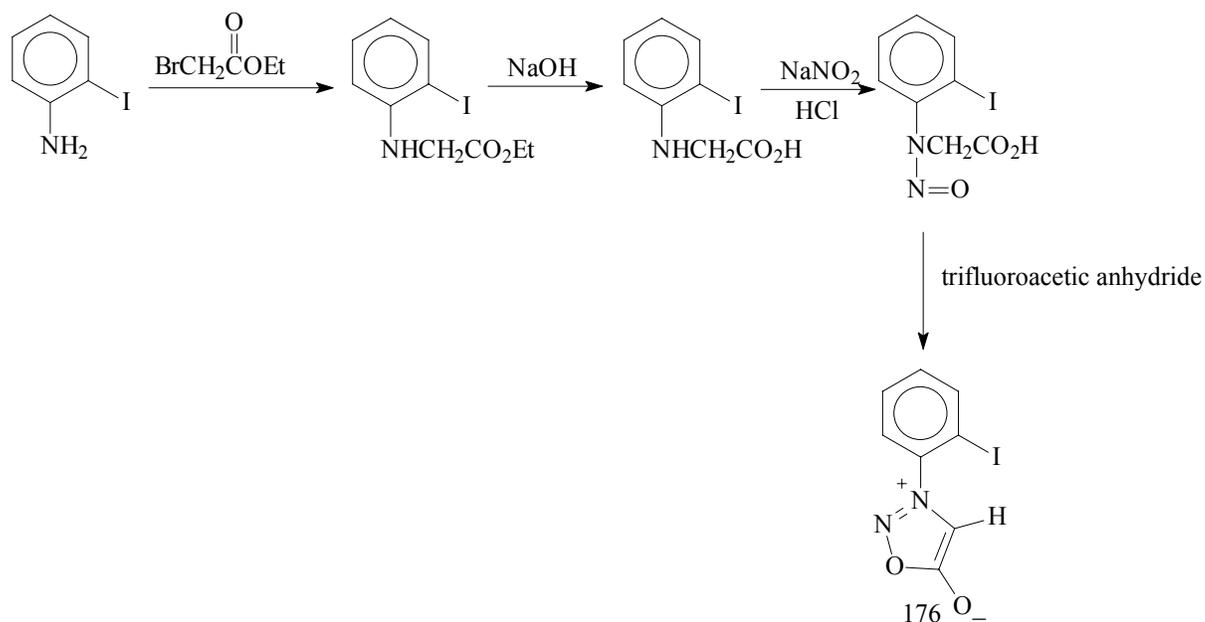
bromophenyl)sydnone (**156**) to see if a successful transformation was achieved (Scheme 28). The result was no sign of reaction by TLC under the conditions used, including heating the reaction to reflux.

Scheme 28



Although these initial results were discouraging, it was not decided to abandon the Sonogashira Coupling. It was suspected that 3-(2-bromophenyl)sydnone was not sufficiently reactive to function in the catalytic cycle, and since it is well known that aryl iodides undergo coupling with ease, the task was set to synthesize 3-(2-iodophenyl)sydnone (**176**). The standard route to **176** involves a 5-step sequence illustrated in Scheme 29. First, 2-iodo-aniline is reacted with ethyl bromoacetate followed by hydrolysis of the ester to make N-(2-iodophenyl)glycine. The glycine is then converted to the nitroso-species *via* treatment with sodium nitrite in the presence of HCl. Finally, the N-nitroso-N-(2-iodophenyl)glycine is cyclized to the corresponding sydnone with trifluoroacetic anhydride.

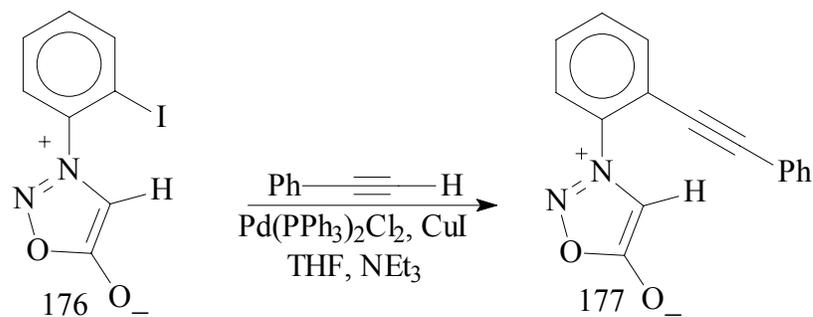
Scheme 29



The target 3-(2-iodophenyl)sydnone was successfully synthesized by the above route with an overall yield for the four steps of 6% to 10%. The identity of **176** was established by comparison with authentic material using IR, TLC, and melting point. Hence, the Sonogashira coupling could be attempted again.

Before attempting the coupling, however, it was decided to make another, additional change to the reaction conditions. It is known that molecular oxygen from the atmosphere can poison the catalyst in palladium-catalyzed reactions. Hence, in order to maximize the chances of success for coupling 3-(2-iodophenyl)sydnone) with phenyl acetylene, a deoxygenation procedure was adopted to remove oxygen from the reaction solvents *via* a freezing/purging/thawing sequence. After 24 hours at room temperature, the result was the successful coupling of 3-(2-iodophenyl)sydnone with phenyl acetylene to give the desired 3-(2-(phenylethynyl)phenyl)sydnone (**177**) in 43% yield after column chromatography and recrystallization (Scheme 30). Later work demonstrated that the reaction time could be shortened to 4-6 hours by heating to 50 °C and the yield could be increased to 80% by further optimization.

Scheme 30



The identity of **177** was established by satisfactory elemental analysis as well as by its IR and NMR spectra. The IR spectrum showed peaks similar to the spectra of other arylsydnone. Thus, the presence of the sydnone C-H was indicated by a peak at 3130 cm^{-1} , the acetylene $\text{C}\equiv\text{C}$ appeared at 2224 cm^{-1} , and the sydnone carbonyl stretch was apparent at 1750 cm^{-1} . The proton NMR spectrum was dominated by a complex multiplet in the aromatic region; however, a singlet for the sydnone C-H was observable at 6.9 ppm. The integration showed the expected ratio of nine aromatic protons to the one sydnone proton. The carbon-13 NMR also was dominated by aromatic peaks, showing ten as expected for **177**. Two of these, 135.1 ppm, and 121.3 ppm, were obviously quaternary due to their weak intensity. The former peak is likely the aryl carbon attached to the sydnone ring, since it is deshielded by the electron-withdrawing sydnone, and has a value similar to the analogous carbon in other sydnone. The latter peak could be either of the other two quaternary carbons. The sydnone carbonyl peak appeared at 169 ppm, the sydnone C-4 at 97.6 ppm and the two carbons of the alkyne at 97.2 and 82.3 ppm.

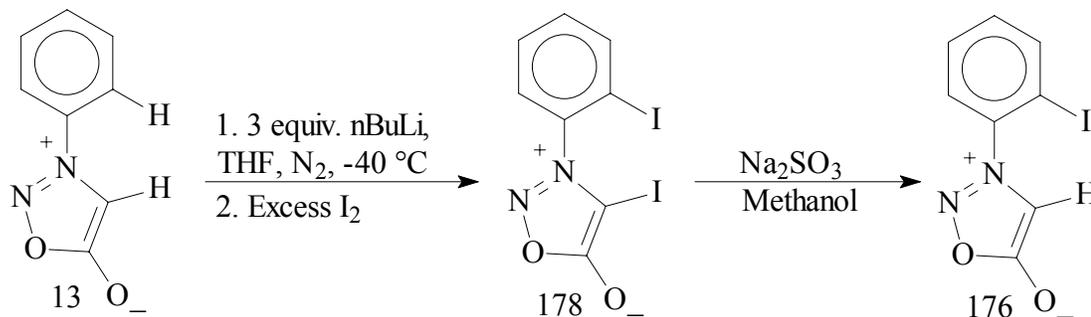
Since both the starting substrate of the attempted Sonogashira coupling had been changed (from the bromo species to the iodo species) and the deoxygenation procedure added, it was not clear which change aided the success of the reaction. To make certain that the deoxygenation procedure was not solely what made the reaction successful, the coupling of 3-(2-bromophenyl)sydnone was attempted again with the deoxygenation

protocol. The result was no sign of reaction by TLC and recovery of 90% of the starting **154**. From this point forward, the deoxygenation protocol was used in all coupling reactions.

It was gratifying that a successful coupling had been achieved starting with 3-(2-iodophenyl)sydnone, and it was decided to pursue further studies with this species. An issue with this, however, was the low-yielding, time-consuming, five-step process required to make the starting 3-(2-iodophenyl)sydnone. On top of this was the somewhat high cost of 2-iodoaniline needed at the beginning of the process. Recent, past work in our laboratory would provide a solution to this problem—the route of dilithiation developed by Turnbull and Krein.

N-phenylsydnone (**13**) is accessible from commercially available N-phenylglycine in a two-step process requiring no column chromatography or recrystallization, giving yields of 80% to 90%.⁸⁸ Further, **13** undergoes dilithiation, and subsequent reaction with iodine to form diiodo species **178** in 92% yield, as described in the introduction to this Thesis. Interestingly, subsequent treatment of **178** with sodium sulfite removes only the 4-iodo substituent, providing a 2-step route to 3-(2-iodophenyl)sydnone from N-phenylsydnone **13** (Scheme 31).

Scheme 31

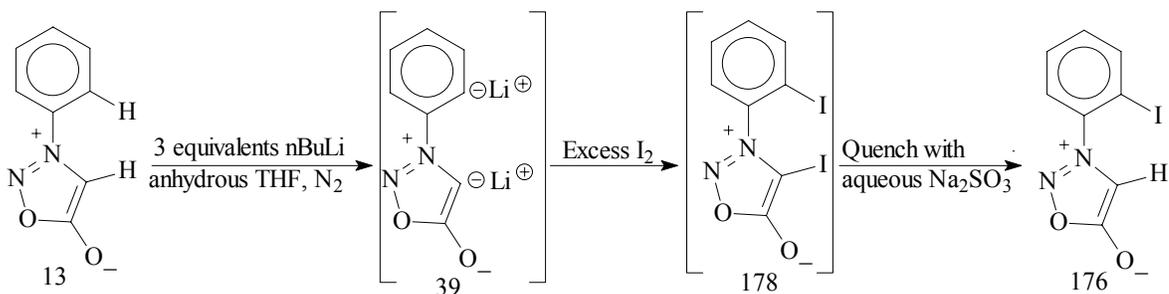


After some experimentation, this turned out to be a rather successful protocol. One initial worry in the synthesis of **178** *via* dilithiation was that such reactions had always been run on a small scale at high dilution (e.g. 0.1 g phenyl sydnone in 50 mL tetrahydrofuran). In the course of the present work, however, it was found that dilithiation with subsequent iodine treatment could be accomplished at a dilution of 1 g per 100 mL tetrahydrofuran, a five-fold increase in concentration. Yields obtained were as high as 96% (not recrystallized, but suitably pure for further reaction), the identity being established by comparison with authentic material (IR, TLC, melting point).

In regards to the second reaction, sodium borohydride was the initial reductant chosen to remove the iodine from the 4-position of the sydnone ring. However, it was found that sodium borohydride removed both iodine atoms from **178**, giving back N-phenylsydnone in 73% yield (confirmed by IR and TLC comparison to authentic N-phenylsydnone). Gratifyingly, it was discovered that sodium sulfite removed only the iodine from the 4-position in yields as high as 91%, giving material suitably pure for Sonogashira couplings.

Another gain to the synthesis of 3-(2-iodophenylsydnone) by the dilithiation route was the discovery that both reactions shown in Scheme 31 could be run essentially in one pot, with 4-iodo-3-(2-iodophenyl)sydnone (**178**) as an un-isolated intermediate (Scheme 32).

Scheme 32

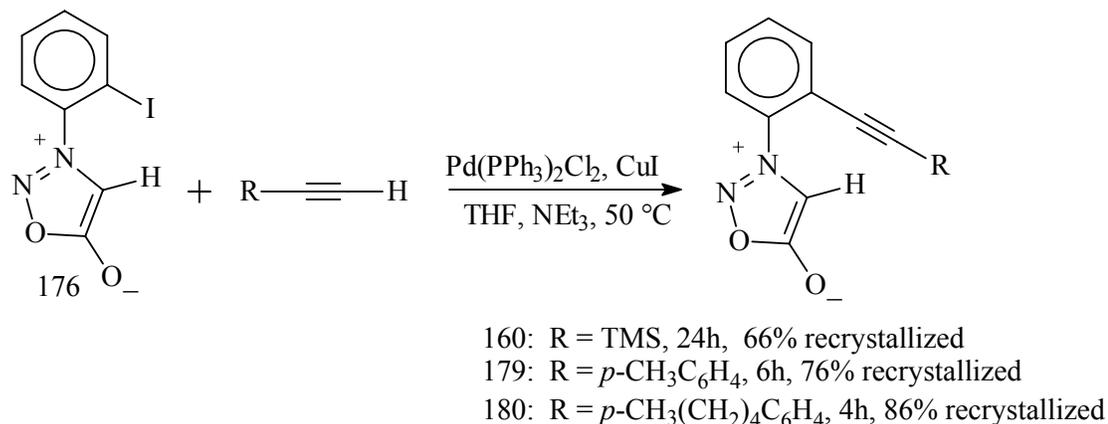


In this protocol, the dilithiation is run as normal except when it comes to the workup of the reaction. Instead of quenching the reaction with water and extracting, it is quenched with an aqueous solution of sodium sulfite and poured from the reaction flask into a large beaker. After stirring overnight in the fume hood, the desired **176** is filtered from the remaining solution in 80% yield, suitably pure for use in further reaction. Thus, the work required to isolate the 4-iodo-3-(2-iodophenyl)sydnone (**178**) is avoided as well as the setting up of a second reaction. This was a great aid in accelerating the synthesis of 3-(2-iodo-phenyl)sydnone.

One potential criticism of the above method is its lack of “atom economy,” since an iodine atom, and its rather large associated weight, is essentially “thrown away” in the protocol. If one compares the traditional five-step process, however, the advantage of the method shown in Scheme 32 is clear. First, overall efficiency of the dilithiation process is much greater in terms of final, overall product yield (80% by dilithiation versus 10% by the traditional route), meaning fewer preparations are required to obtain a desired amount of 3-(2-iodophenyl)sydnone, hence fewer resources are consumed. A second point is that the traditional process is not as “clean,” and, ideally, purification is needed between steps. This consumes chromatography solvent, silica gel, energy for solvent removal, etc., increasing overall consumption and costs. The dilithiation process allows one to produce 3-(2-iodophenyl)sydnone without column chromatography. Finally, a large amount of time is saved once again due to the increased overall efficiency. If it were not for the relative ease of the protocol presented in Scheme 32, much of the work in this Thesis would not have been accomplished.

With a convenient synthetic route to the starting material established, further focus could be put on coupling 3-(2-iodophenyl)sydnone with terminal acetylenes. The main acetylene of interest to achieve the goals of the current work was trimethylsilyl acetylene, but others available were used as well, in order to maximize the variety of *ortho*-alkynyl sydnones (Scheme 33), and to test the scope of the reaction.

Scheme 33



It was found that 3-(2-iodophenyl)sydnone **176** would couple with a variety of acetylenes rather well, with the requirement that the reaction be heated to approximately 50 °C. Yields ranged from 66% to 86% after column chromatography and recrystallization. 3-(2-(Trimethylsilylethynyl)phenyl)sydnone (**160**), 3-(2-(4-methylphenylethynyl)phenyl)sydnone (**179**), and 3-(2-(4-pentylphenylethynyl)phenyl)sydnone (**180**) were all successfully prepared and characterized by elemental analysis.

In the IR spectrum of 3-(2-(4-methylphenylethynyl)phenyl)sydnone (**179**), the sydnone C-H was observed at 3150 cm⁻¹, the alkyl C-H at 2913 cm⁻¹, the C≡C at 2215 cm⁻¹, and the sydnone carbonyl at 1732 cm⁻¹. The proton NMR spectrum showed a complex multiplet in the aromatic region representing the nine protons as expected. A singlet representing one proton, the sydnone H, was observed at 6.9 ppm, along with a singlet (three protons) representing the methyl group at 2.4 ppm. The carbon-13 NMR spectrum showed ten peaks in the aromatic region, one more than anticipated. The “rogue” is thought to be a rather strong peak at 140.3 ppm, since an aromatic peak this deshielded does not appear in the majority of the other *ortho*-alkynyl sydnones synthesized. This peak could be the aromatic carbon to which the methyl group is attached, however, this seems unlikely since the peak has an intensity atypical for a

quaternary carbon. Three, obviously quaternary, peaks appear at 135.2, 119.5, and 118.4 ppm with the first of these representing the aryl carbon attached to the sydnone ring as previously mentioned. The sydnone carbonyl carbon appeared at 169.1 ppm, the methyl carbon appeared at 21.9 ppm, and the carbons of the internal alkyne appeared at 98.3 ppm and 82.1 ppm. It is speculated that the latter of these is the alkyne carbon directly attached to the aryl ring of the sydnone since the methyl moiety may shield this carbon by its electron-donating effect. The sydnone C-4 was distinguished at 97.5 ppm from the alkyne carbons since it appears as a doublet in the undecoupled spectrum that was, fortunately, available for this species.

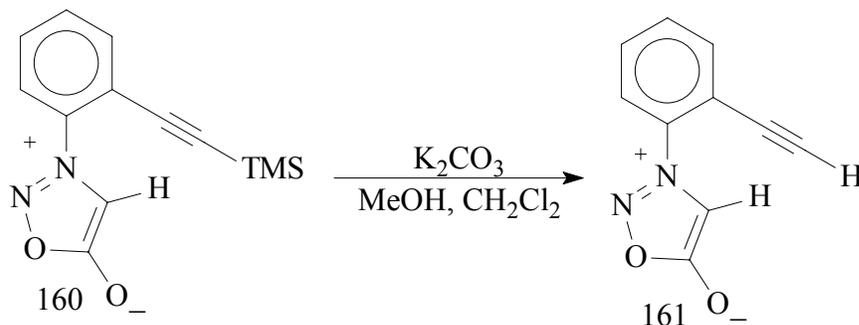
The IR spectrum of 3-(2-(4-pentylphenylethynyl)phenyl)sydnone (**180**), showed the sydnone C-H at 3150 cm^{-1} , strong alkyl peaks at 2955, 2926, and 2855 cm^{-1} , the $\text{C}\equiv\text{C}$ at 2220 cm^{-1} , and the sydnone carbonyl at 1736 cm^{-1} . As was typical with these species, the proton NMR showed a multiplet in the aromatic region and the sydnone proton at 6.91 ppm. The protons of the pentyl group were manifested as a triplet from 2.63 to 2.58 ppm (two protons) and a multiplet from 1.63-1.29 ppm (nine protons). The carbon-13 NMR spectrum had nineteen peaks as expected for this compound. The sydnone C-5 was at 169.1 ppm, the C-4 at 97.5 ppm, and the alkyne carbons were at 98.4 and 82.1 ppm. The alkyl carbons of the pentyl group were observed at 36.2, 31.6, 31.1, 22.7, and 14.3 ppm.

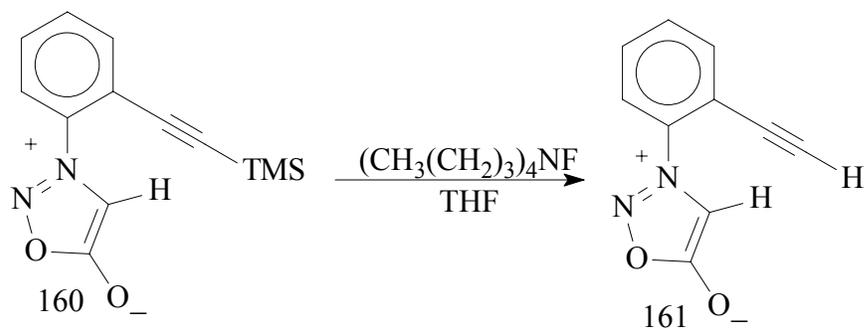
Since it was slightly different from the other *ortho*-alkynyl sydnones previously discussed, 3-(2-(trimethylsilylethynyl)phenyl)sydnone (**160**) showed some different features in its spectra. The IR spectrum showed the sydnone C-H at 3167 cm^{-1} , strong alkyl peaks were observed at 2961 and 2902 cm^{-1} , the $\text{C}\equiv\text{C}$ at 2157 cm^{-1} , and the sydnone carbonyl at 1745 cm^{-1} . Peaks specific to the trimethylsilyl group came at 851 and 759 cm^{-1} , indicating silicon-carbon stretches and bends. The aromatic region of the proton NMR spectrum showed a doublet representing one proton and a multiplet representing three protons. The sydnone proton appeared at 6.9 ppm as a singlet and the shielded

methyl protons of the trimethylsilyl group appeared as a singlet at 0.3 ppm (nine protons). The aromatic region of the carbon-13 NMR spectrum showed six peaks, the smallest being at 135.6 ppm, the aryl carbon attached to the sydnone ring. From the remaining peaks, the sydnone carbonyl carbon was readily assigned to 168.6 ppm, and the trimethylsilyl carbons to -0.6 ppm. However, it was more difficult to assign the sydnone C-4 and the two, alkyne carbons. A peak at 104.6 ppm was comparatively strong for a quaternary carbon, and hence seemed to be an unusually deshielded sydnone C-4. Notwithstanding its intensity, however, this peak could be a deshielded alkyne carbon affected by the TMS moiety. The other two unassigned peaks were 97.3 and 97.2 ppm, both of approximately the same, quaternary intensity. Either of these could be a “normal” sydnone C-4 or an alkyne carbon.

As mentioned in “Aims of the Present Work,” one goal was to use 3-(2-(trimethyl-silylethynyl)phenyl)sydnone (**160**) as a masked terminal acetylene to be de-protected and used in further couplings. In principle, removal of the trimethylsilyl group can be achieved with either potassium carbonate or fluoride ion (Scheme 34), and both methods were utilized.

Scheme 34



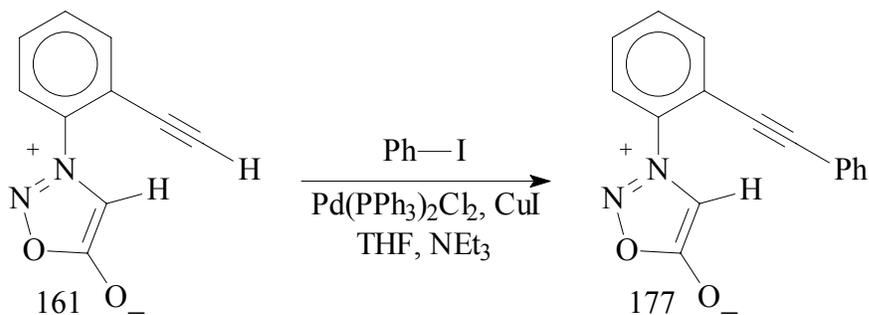


Thus, the use of potassium carbonate in methanol / dichloromethane gave a 71% yield of 3-(2-ethynylphenyl)sydnone **161** after column chromatography, suitable for further use (49% recrystallized). This material gave an acceptable elemental analysis. Peaks of interest in the IR spectrum were the terminal acetylene C-H at 3242 cm^{-1} , the sydnone C-H at 3113 cm^{-1} , a weak C≡C stretch at 2105 cm^{-1} , and the sydnone carbonyl at 1751 cm^{-1} . The proton NMR spectrum showed two multiplets in the aromatic region representing four protons. The sydnone proton was a singlet at the usual 6.9 ppm and the terminal acetylene proton a singlet at 3.4 ppm. The carbon-13 NMR showed the appropriate number of aromatic carbons, with the same general appearance as those compounds already mentioned. The sydnone C-4 appeared at 97.5 ppm, and the internal alkyne peak was easily distinguishable from the terminal peak, with the former observed at 85.8 ppm and the latter at 76.8 ppm.

The synthesis of **161** was successful also using tetrabutylammonium fluoride in tetrahydrofuran. This route gave a 63% yield, and the product matched by melting point, TLC, and IR, to the material made using potassium carbonate.

With some of the terminal alkyne in hand, and in conjunction with the goals, the next step was to test this species to see if it would couple with an aryl iodide. The compound chosen for the initial test was iodobenzene, since the product of the reaction would be the previously-made 3-(2-(phenylethynyl)phenyl)sydnone **177** (Scheme 35).

Scheme 35



The coupling occurred readily, and the identity of the product was verified by comparison with authentic **177** (TLC, IR, melting point). This reaction, run at 50 °C, was complete in two hours, and the yield of product after column chromatography was 76%. It was later found that heating was unnecessary for this transformation, and the coupling went smoothly at room temperature.

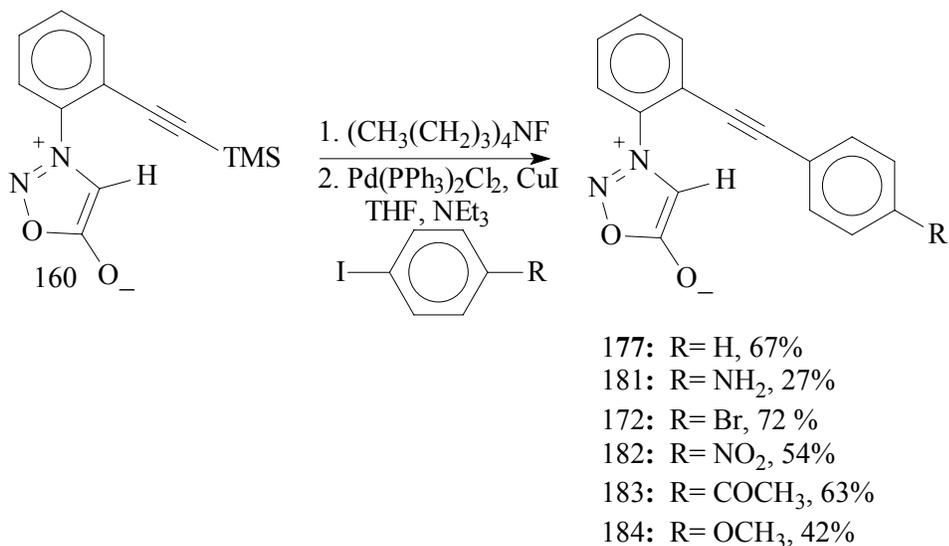
Although only with one example, at this point it was now established that a terminal alkyne *ortho* to the sydnone ring would react successfully in a further Sonogashira coupling. The next step on the journey to additional *ortho*-alkynyl sydnones was to try to expedite the process.

Obviously, one could synthesize an *ortho*-alkynyl sydnone by running the coupling with 3-(2-iodophenyl)sydnone **176** and a terminal alkyne. However, the number of inexpensive, terminal aryl alkynes is limited, which is why it was desirable to create the terminal alkyne on the arylsydnone itself (leading to **161**), allowing, presumably, for the synthesis of a greater variety of species *via* subsequent coupling with aryl iodides. This process, however, has the drawback of requiring three steps, *viz.* the coupling of 3-(2-iodophenyl)sydnone) **176** with trimethylsilyl acetylene and subsequent purification, next, the removal of the trimethylsilyl group and subsequent purification, and finally, another coupling with an aryl iodide followed by purification.

In order to expedite the synthesis, it was decided to attempt the second two steps in one pot, as shown in Scheme 36. 3-(2-Ethynylphenyl)sydnone **161** is an un-isolated

intermediate produced in situ from **160** and tetrabutylammonium fluoride followed by coupling with an aryl iodide. This protocol was successful, and hence a variety of *ortho*-alkynyl sydnones (*viz.* **172**, **177**, **181-184**) were produced using some *para*-substituted aryl iodides already available in the laboratory (Scheme 36).

Scheme 36



The synthesis of the known species **177** was the first test made of this protocol, and illustrated its success. Species **172**, and **181** to **184** were all new compounds, subjected to full characterization. All gave acceptable elemental analyses and were subjected to IR and NMR analysis.

3-(2-(4-Aminophenylethynyl)phenyl)sydnone **181** was obtained in 60% yield after column chromatography, 27% after recrystallization. Peaks of interest in the IR spectrum included the amino group N-H stretches. There appeared to be three (at 3482, 3347, and 3209 cm^{-1}) instead of the expected two, perhaps due to some hydrogen-bonding effect. The sydnone C-H appeared at a typical value of 3157 cm^{-1} , the $\text{C}\equiv\text{C}$ stretch was strong and readily apparent at 2209 cm^{-1} , and the sydnone carbonyl came at 1737 cm^{-1} . The aromatic region of the proton NMR spectrum contained a multiplet and a

doublet (7.1 to 7.4 ppm) calculated from the integration to represent six protons, not eight, as one would have expected. However, there was an additional doublet representing two, more-highly shielded protons at 6.7 to 6.5 ppm. The sydnone proton appeared as its usual singlet at 6.9 ppm. Two other peaks in the spectrum were singlets at 5.3 and 3.4 ppm. These peaks were not included in the integration. Presumably, one or both of these represent the protons of the amino group. The carbon-13 NMR spectrum showed fourteen peaks as expected. The sydnone carbonyl carbon appeared at 169.2 ppm and the sydnone C-4 carbon at 97.6 ppm. The carbons of the alkyne came at 99.4 and 81.0 ppm. Overall, it was reasonable to conclude that the compound was the desired material.

3-(2-(4-Bromophenylethynyl)phenyl)sydnone **172** was obtained in 72% yield after column chromatography and recrystallization. This was fortunate since **172** is a precursor to oligomeric alkynyl sydnones as presented in the “Aims of the Present Work.” The IR spectrum of this species showed the sydnone C-H at 2217 cm^{-1} , the alkyne $\text{C}\equiv\text{C}$ stretch at 2217 cm^{-1} , and the sydnone carbonyl at a typical 1753 cm^{-1} . In the proton NMR spectrum, two doublets, and a multiplet dominated the aromatic region and, by the integration, represented eight protons as expected. The sydnone proton came at its usual 6.9 ppm. The carbon-13 NMR showed ten peaks in the aromatic region, four of which were obviously quaternary due to their intensity. The sydnone carbonyl carbon appeared at 169.0 ppm and the C-4 carbon at 97.4 ppm. The two carbons of the alkyne appeared at 96.6 and 83.6 ppm. This compound was one of a few for which the proton-carbon-13 *un*-decoupled spectrum was available. This allowed the sydnone C-4 proton at 97.4 ppm to be distinguished from the alkyne carbon at 96.9 pm. Since it has a proton attached, the sydnone proton appears as a doublet in the *un*-decoupled spectrum whereas the alkyne carbon does not. Little else could be drawn from the *un*-decoupled spectrum due to the proximity of the peaks to each other and the complexity of long-range coupling.

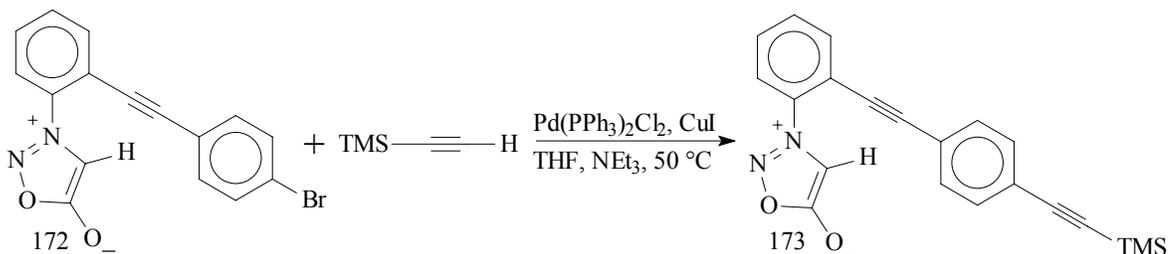
3-(2-(4-Nitrophenylethynyl)phenyl)sydnone **182** was produced in 75% yield after column chromatography and 54% after recrystallization. The IR spectrum was complex, but readily evident were the sydnone C-H stretch at 3168 cm^{-1} ppm and the sydnone carbonyl at 1787 cm^{-1} , likely shifted to these higher wavenumber values due to the electron-withdrawing effect of the nitro group. There were many small peaks (perhaps overtones of lower peaks) in the range of 1950 to 2800 cm^{-1} and the alkyne stretch was not readily distinguishable from these. There were also strong peaks at 1516 and 1340 cm^{-1} attributable to the nitro moiety. The proton NMR spectrum contained two doublets and a multiplet in the aromatic range, these representing eight protons. The sydnone proton was the usual singlet at 6.8 ppm. As expected, the carbon-13 NMR spectrum showed ten peaks in the aromatic region of the spectrum, four of which were obviously quaternary. The sydnone carbonyl carbon appeared at 168.9 ppm, the sydnone C-4 carbon at 97.4 ppm and the alkyne carbons at 94.9 and 87.0 ppm.

3-(2-(4-Acetylphenylethynyl)phenyl)sydnone **183** was produced in 72% yield after column chromatography and 63% after recrystallization. The IR spectrum had a complex appearance somewhat similar to that of species **182**. Observed were the sydnone C-H at 3118 cm^{-1} , the alkyne $\text{C}\equiv\text{C}$ stretch at 2218 cm^{-1} , and the sydnone carbonyl was split into three peaks, the central, and strongest, being at 1765 cm^{-1} . The carbonyl of the acetyl group is likely the sharp peak at 1679 cm^{-1} . The complex of peaks in the aromatic region of the proton NMR spectrum represented eight protons as expected. The sydnone C-H singlet came at 6.8 ppm and the three methyl group protons appeared as a singlet at 2.6 ppm. The carbon-13 NMR spectrum had ten aromatic carbon peaks as anticipated, four of which were comparatively weak and therefore the likely aromatic, quaternary carbons. The carbonyl carbon of the acetyl group was at 197.3 ppm, the sydnone carbonyl carbon at 169.9 ppm and the sydnone C-4 carbon at 97.5 ppm. The alkyne carbons came at 96.5 and 85.3 ppm, and, finally, the methyl carbon was observed at 26.9 ppm.

3-(2-(4-Methoxyphenylethynyl)phenyl)sydnone **184** was obtained in 60% yield after column chromatography and 42% yield after recrystallization. The IR spectrum showed the sydnone C-H at 3152 cm^{-1} , a strong alkyne $\text{C}\equiv\text{C}$ stretch at 2215 cm^{-1} , and the sydnone carbonyl stretch at 1752 cm^{-1} . The proton NMR spectrum contained a multiplet from 7.7 to 7.3 ppm (six protons), and a multiplet from 6.9 to 6.8 ppm (three protons). The sydnone proton was not readily distinguishable from the latter multiplet, though the three protons of the methyl group were apparent at 3.8 ppm. The carbon-13 NMR spectrum displayed the correct number of carbons, fifteen. As usual, the sydnone carbonyl carbon was furthest downfield at 169.1 ppm. Next was a peak at 160.9 ppm that appeared quaternary, and is likely the aromatic carbon to which the methoxy moiety is attached. The remainder of the aromatic carbons appeared in a more typical range (135 to 113 ppm). One alkyne carbon appeared at 98.3 ppm and the sydnone C-4 at 97.5 ppm. The latter was distinguished from the former due to its stronger appearance (i.e. not quaternary). The other alkyne carbon appeared at 81.6 ppm, and, finally, the carbon of the methyl moiety was observed at 55.6 ppm.

At this point, one of the major goals of the research had been achieved *viz.* to show that a variety of *ortho*-alkynyl sydnones could be synthesized, and, overall, ten such compounds were made. Consistent with the goals of the research, the next step in the route to the oligomeric alkynyl sydnones was to attempt the coupling of 3-(2-(4-bromophenylethynyl)-phenyl)sydnone **172** with trimethylsilyl acetylene (Scheme 37).

Scheme 37



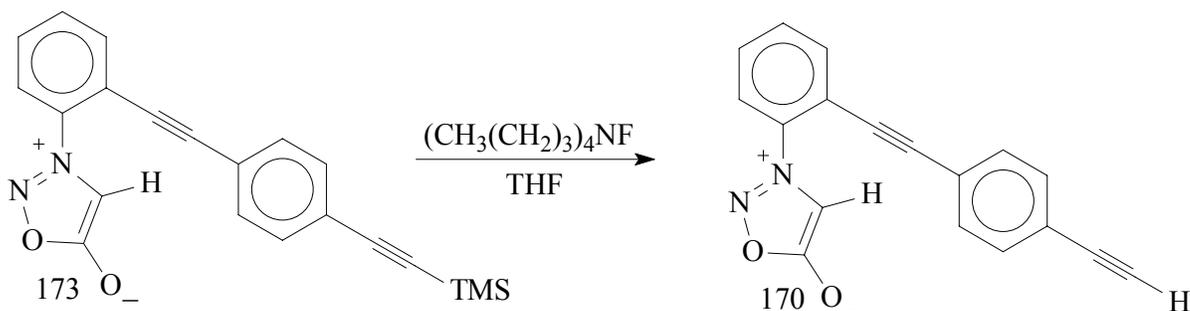
Initial attempts at these transformations were difficult, requiring several days and extra additions of reagents and catalysts during the course of the reaction. After several attempts, however, transformations were achieved with greater ease. One factor that seemed to play a role was the order and timing of catalyst addition. It was found that addition of the palladium catalyst after heating the reaction solution to 50 °C followed, in ten minutes, by the copper co-catalyst greatly aided the speed of the reaction, allowing it to be accomplished overnight.

Overall, 3-(2-(4-(trimethylsilylethynyl)phenylethynyl)phenyl)sydnone **173** was synthesized in 84% yield after chromatography, 44% yield after recrystallization, and gave a satisfactory elemental analysis. The IR spectrum showed the sydnone C-H at 3155 cm⁻¹ and a strong alkyl peak at 2959 cm⁻¹. Two alkyne C≡C stretches were observed at 2220 and 2160 cm⁻¹, indicating that the material was indeed a bis-acetylene. The sydnone carbonyl stretch appeared at 1750 cm⁻¹ and trimethylsilyl stretches and bends at 881 and 757 cm⁻¹. Proton NMR spectroscopy showed a multiplet in the aromatic region representing the eight aromatic protons. The sydnone proton singlet came at 6.9 ppm, and the nine methyl protons of the trimethylsilyl group appeared as a singlet at 0.3 ppm. The carbon-13 NMR spectrum also aided in confirming the structure, showing ten aromatic carbons, four of which were obviously quaternary due to their intensity. The sydnone carbonyl carbon was at 169.0 ppm. As desired, there were now four peaks representing the four alkyne carbons, 104.4, 97.6, 97.3, and 84.3 ppm. The sydnone C-4 carbon at 97.4 ppm was differentiated from these by its stronger intensity.

Overall, there was no reason to believe that the desired structure was not the one obtained, and the subsequent reaction would show this further.

All that was needed to obtain desired species 3-(2-(4-(ethynyl)phenylethynyl)-phenyl)sydnone **170** was removal of the trimethylsilyl group, and this was accomplished with tetrabutylammonium fluoride in tetrahydrofuran (Scheme 38).

Scheme 38

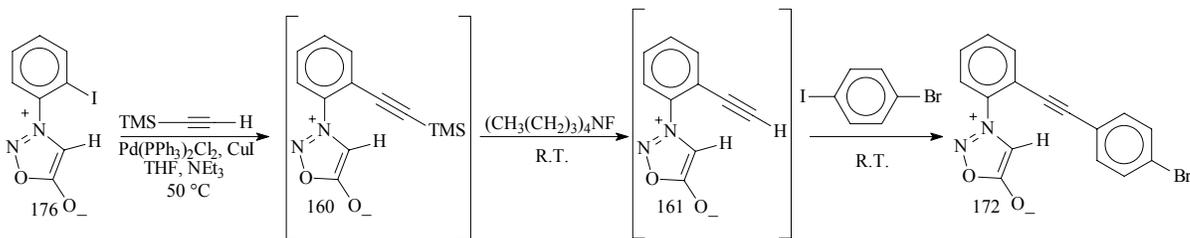


The yield after column chromatography was 47% (recrystallized yield 36%), and the transformation was accomplished with potassium carbonate in similar yield (34%). As with the other compounds, an acceptable elemental analysis was obtained. In the IR spectrum, the terminal alkyne C-H stretch appeared at 3224 cm⁻¹ next to the sydnone C-H at 3168 cm⁻¹. Only one of the alkyne C≡C stretches was evident, at 2221 cm⁻¹, and the sydnone carbonyl was observed at 1752 cm⁻¹. The proton NMR spectrum contained a multiplet from 7.8-7.2 ppm signifying the eight aromatic protons. The sydnone proton singlet came at a typical 6.9 ppm and the terminal acetylene proton was a singlet at 3.2 ppm. The expected ten aromatic carbon peaks were observed in the carbon-13 NMR spectrum, four of these being obviously quaternary. The sydnone carbonyl carbon was at 169.0 ppm and the sydnone C-4 at 97.4 ppm. The three internal, alkyne carbons were observed at 97.0, 84.3, and 83.2 ppm. The terminal alkyne carbon was easily identified as a peak at 80.1 ppm due to it being the most shielded of the alkyne carbons and its strong intensity.

Thus, species **170**, of interest to Wright Patterson Air Force Base was successfully synthesized, however, the quantity needed for their studies was greater than had been produced. Further, a suitable quantity was needed to try to make the tris-alkyne. Hence, efforts were engaged to streamline the process to **170**.

The first of these efforts was to try to make 3-(2-(4-bromophenylethynyl)phenyl)sydnone **172** in one pot from 3-(2-iodophenyl)sydnone **176**, without isolation of 3-(2-(trimethylsilylethynyl)phenyl)sydnone **160** as had been done previously (Scheme 39). This three- reaction-in-one-pot protocol worked surprisingly well, saving large amounts of time, energy, and chromatographic solvent.

Scheme 39



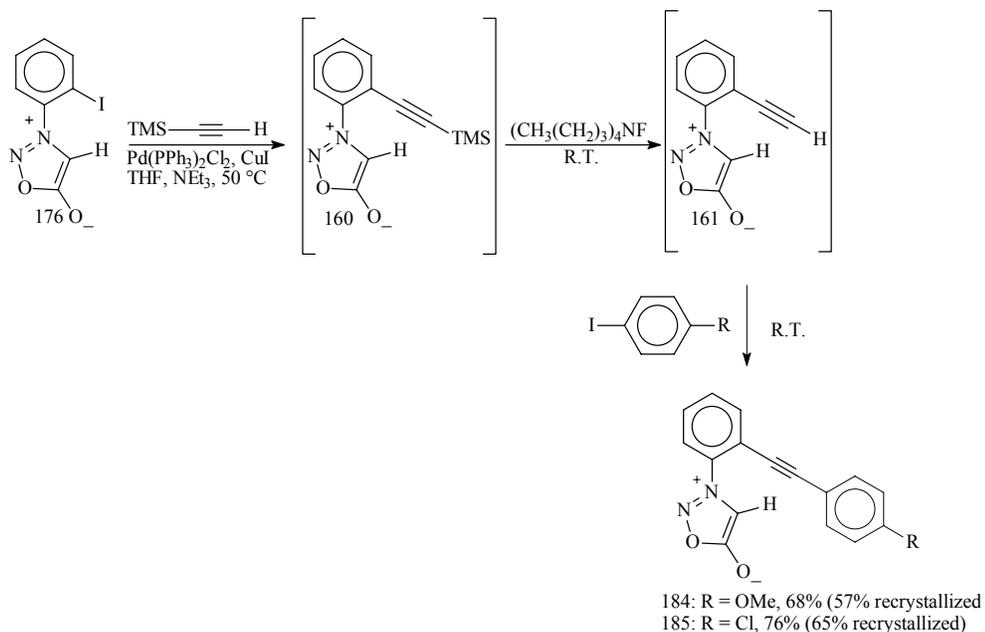
With the three-in-one protocol, 3-(2-(4-bromophenylethynyl)phenyl)sydnone **172** can be prepared from **176** in 76% yield compared to a 48% overall yield using the two-step process (identity established by TLC, IR, and melting point). As an additional bonus, the expensive catalysts serve double duty, since the second coupling occurs readily without addition of more catalyst.

As an aside, two other *ortho*-alkynyl sydnones were prepared using the three-in-one protocol, showing its utility. The previously prepared 3-(2-(4-methoxyphenylethynyl)-phenyl)sydnone **184** was synthesized by this route in 68% yield, compared to 28% if the two step process was used. Additionally, 3-(2-(4-

chlorophenylethynyl)phenyl)sydnone **185** was prepared in 76% yield for the first time using this route (Scheme 40).

3-(2-(4-Chlorophenylethynyl)phenyl)sydnone **185** was characterized by suitable elemental analysis and an IR spectrum consistent with its structure. The sydnone C-H appeared at 3124 cm^{-1} , the alkyne $\text{C}\equiv\text{C}$ stretch at 2223 cm^{-1} , and the sydnone carbonyl at 1748 cm^{-1} . The proton NMR spectrum had two multiplets in the aromatic region integrating to eight protons. The sydnone C-4 proton appeared at a typical 6.86 ppm. In regards to the carbon-13 spectrum, fourteen peaks were expected and fourteen were observed. Notable peaks were the sydnone carbonyl carbon at 169.0 ppm, the sydnone C-4 at 97.4 ppm, and the two alkyne carbons at 96.5 and 83.5 ppm. All in all, the spectral data confirmed the structure of the compound.

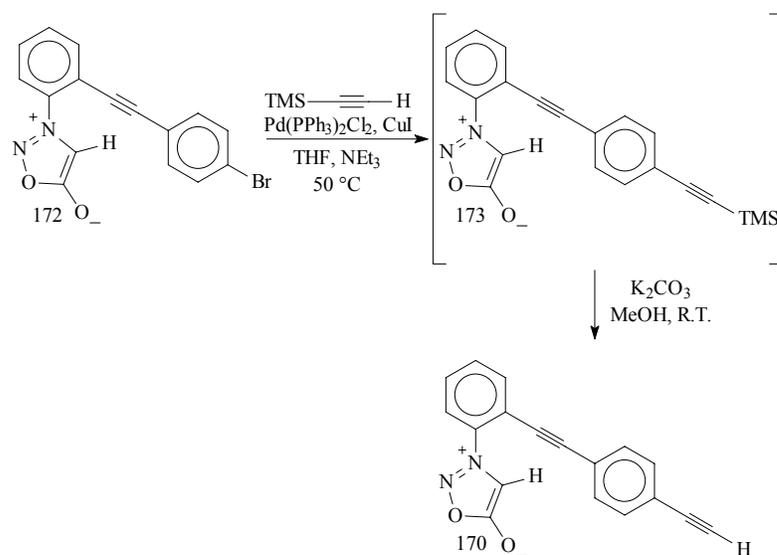
Scheme 40



Overall, the general success of the three-in-one transformation was quite gratifying, and a reasonably efficient route to 3-(2-(4-bromophenylethynyl)phenyl)sydnone **172** was established.

On the theme of multi-reactions in one pot, it was attempted to synthesize 3-(2-(4-(ethynyl)phenylethynyl)phenyl)sydnone **170** in one pot from **172**, as shown in Scheme 41.

Scheme 41



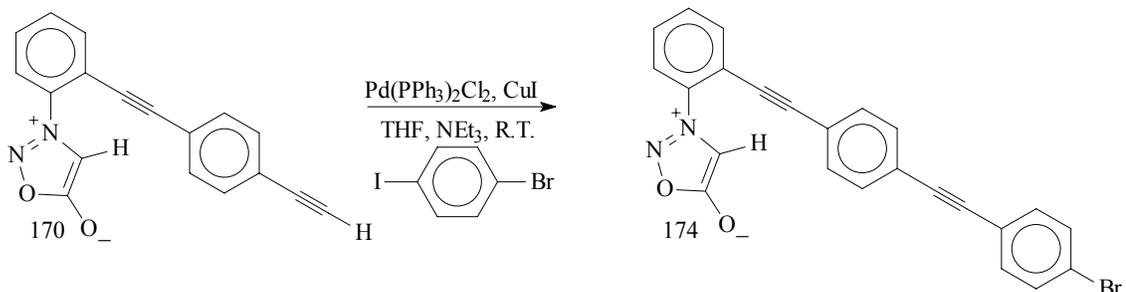
Gratifyingly, the yield of **170** was 87% (homogeneous by TLC, not recrystallized) when the reaction was performed on a three-gram scale.

With the success of these multi-reaction in one pot protocols, the idea arose to try and perform a five-reaction-in-one-pot protocol *viz.* make **170** in one pot from 3-(2-iodophenyl)sydnone **176**. Such a protocol was attempted, but the results indicated this was pushing the abilities of the reaction media too far. When all was said and done, the yield of **170** when made in one pot from **176** was 10%, homogeneous by TLC after being subjected to column chromatography twice. Therefore, the five-in-one protocol is

possible, but less efficient than following the two separate protocols shown in Schemes 39 and 41.

To reiterate, 3-(2-(4-(ethynyl)phenylethynyl)phenyl)sydnone **170** had been successfully synthesized, and, accordingly, it was elected to pursue the preparation of the tris-alkyne analogue. Hence, terminal acetylene **170** was coupled with 1-bromo-4-iodobenzene easily at room temperature to give 3-(2-(4-(4-(bromophenyl)ethynyl)phenylethynyl)phenyl)sydnone **174** in 79% yield after column chromatography, and 42% yield after recrystallization (Scheme 42).

Scheme 42

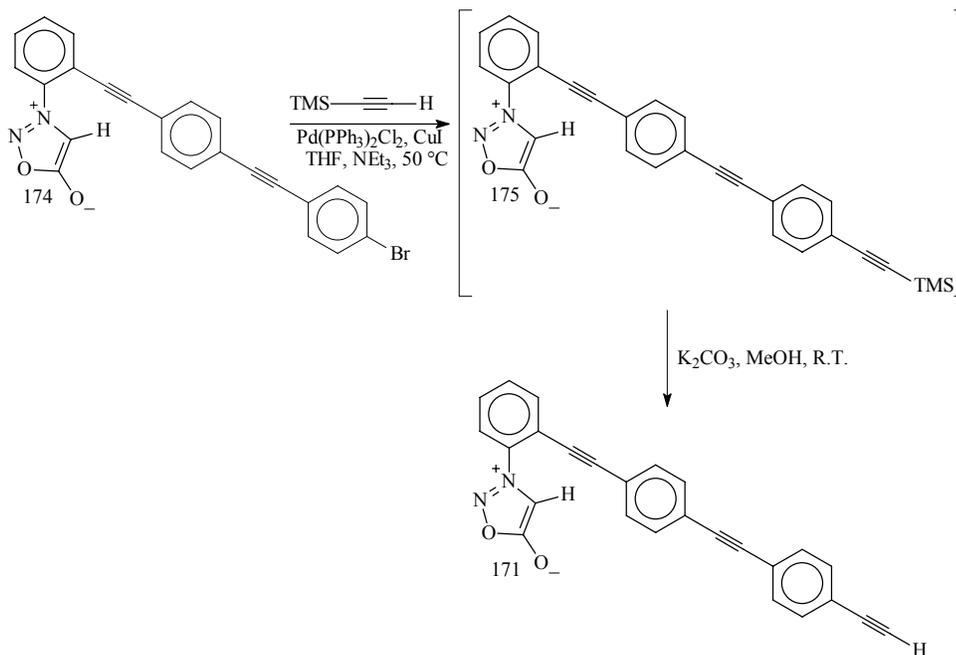


As with the other species, **174** gave a satisfactory elemental analysis. The infrared spectrum showed the sydnone C-H at 3116 cm⁻¹, and the sydnone carbonyl at 1754 cm⁻¹. Neither of the two alkyne stretches were readily observable in the spectrum. The proton NMR spectrum had a complex multiplet in the aromatic region representing twelve carbons, and the sydnone proton appeared as its usual singlet at 6.9 ppm. The carbon-13 NMR was lacking one peak, displaying a total of nineteen instead of the expected twenty. There were only thirteen peaks in the aromatic region; hence the missing peak was an aromatic carbon. Of the aromatic peaks, six were rather weak, so it seemed that all of the quaternary carbons were accounted for. Many of these peaks were close together, so perhaps the missing peak was simply not resolved from another.

Otherwise, the sydnone carbonyl carbon appeared at 169.0 ppm, the sydnone C-H at 97.4 ppm, and the four alkyne carbons were accounted for at 97.3, 91.2, 90.1, and 84.3 ppm.

With 3-(2-(4-(4-(bromophenyl)ethynyl)phenylethynyl)phenyl)sydnone **174** in hand, one could again couple with trimethylsilyl acetylene to make trimethylsilyl species **175** (Scheme 43). However, time was becoming an issue so it was decided to make **175** only *in situ*, *en route* to the needed material 3-(2-(4-(4-ethynyl)phenylethynyl)phenylethynyl)-phenyl)sydnone **171**. Hence, another two-reaction in one pot protocol was successfully pursued.

Scheme 43

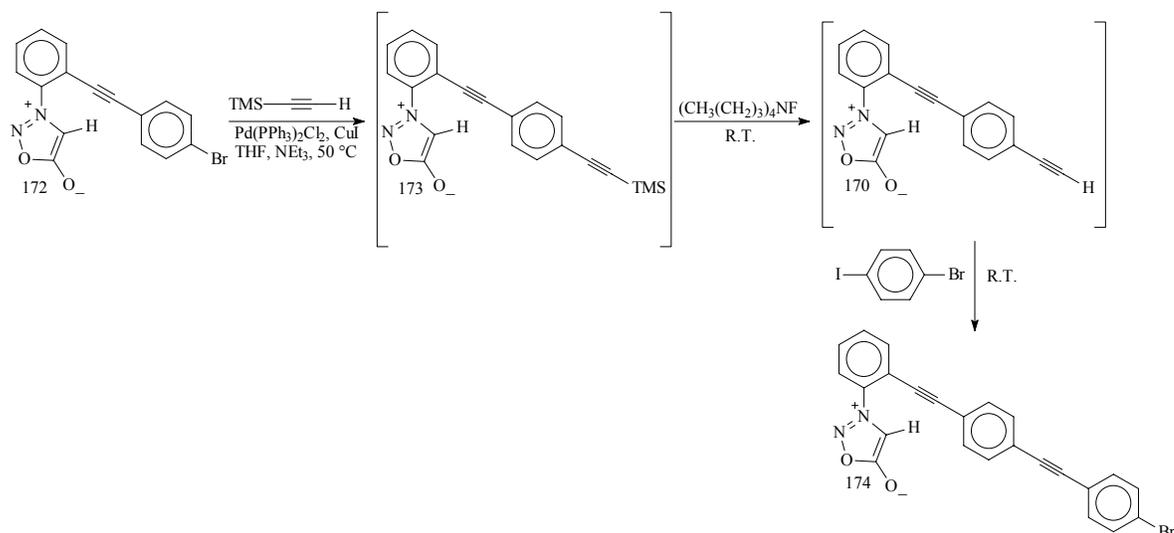


The desired **171** was obtained in 81% yield after column chromatography, 36% after recrystallization. The compound gave an acceptable elemental analysis, and in the IR spectrum, the terminal alkyne C-H stretch was observed at 3293 cm⁻¹, and the sydnone C-H at 3115 cm⁻¹. Only one weak alkyne stretch was apparent at 2218 cm⁻¹, and the sydnone carbonyl stretch was at 1756 cm⁻¹. The proton NMR spectrum displayed a

complex multiplet in the aromatic region integrating to eleven protons, not the twelve that would be expected. The sydnone proton was a singlet at 6.9 ppm, and the terminal acetylene proton was readily apparent as a singlet with a chemical shift of 3.2 ppm. Twenty-two peaks were expected in the carbon-13 NMR spectrum and twenty-two were observed. The aromatic region was complex, showing fourteen peaks; six of these appeared quaternary in nature. The sydnone carbonyl carbon was at 169.1 ppm and the sydnone C-4 at 97.5 ppm. Five peaks representing the internal alkyne carbons were observed at 97.3, 91.7, 90.9, 84.3, and 83.4 ppm. Finally, the terminal acetylene carbon was the most shielded at 79.4 ppm.

In the process of synthesizing the necessary quantities of material to ultimately make a minimum of 0.15g of **171**, one final multi-reaction-in-one-pot- protocol was developed. This was the synthesis of 3-(2-(4-(4-(bromophenyl)ethynyl)-phenylethynyl)phenyl)sydnone **174** from 3-(2-(4-bromophenylethynyl)phenyl)sydnone **172**, as shown in Scheme 44.

Scheme 44



Usage of the above protocol allowed **174** to be made from **172** in 51% yield, greatly expediting the chain of synthetic steps toward 3-(2-(4-(4-ethynyl)phenylethynyl)phenylethynyl)phenylsydnone **171**.

With the successful synthesis and characterization of terminal acetylene **171**, and production of 0.15g of analytically pure material, the three species desired by Wright Patterson Air Force had been made, and a great portion of the Aims of the research accomplished. As a gauge of the success of this work, it seems appropriate to look at the overall yields to each of the desired species, beginning from the readily made N-phenylsydnone **13**.

3-(2-Ethynylphenyl)sydnone **161** requires a total of four reactions for synthesis from N-phenylsydnone. These four transformations were accomplished in three steps and the overall yield of analytically pure material was 27%. 3-(2-(4-(Ethynyl)phenylethynyl)-phenyl)sydnone **170** requires seven total reactions from N-phenylsydnone and these seven transformations, ironically, were accomplished in three steps. The overall yield for the synthesis of this species was 21% for analytically pure material. Finally, 3-(2-(4-(4-ethynyl)phenylethynyl)phenylethynyl)phenylsydnone **171** requires a total of ten reactions from N-phenylsydnone. These reactions were streamlined into four steps for an overall yield of 11% to analytically pure material. These high, overall yields can be attributed to the power of the multi-reaction in one pot protocols. Considering the overall yields obtained, those for **170** and **171** seem in tune with what one may expect for seven and ten reaction transformations. However, it seems that the 27 % yield of mono-alkyne **161** is somewhat low when considering the number of reactions to this species. This may be explained from the fact that this material was made when the experimentalist was at the beginning of his work and the chemistry with its associated idiosyncrasies were new to him. Also, except for the steps involving the synthesis of 3-(2-iodophenyl)sydnone **176**, all reactions to make **161** were done individually, i.e. not in one pot. A third consideration is that in making **161**, a

considerable amount of molecular weight (102 g/mole) is lost in the steps going from the iodo species to the mono, terminal alkyne. Finally, the yield of final product is calculated on the idea that analytically pure product was desired; hence the material sent for study by the Air force was recrystallized, even if it was homogeneous by TLC. All the terminal acetylenes synthesized, as well as many of the other *ortho*-alkynyl sydnones, recrystallized poorly, cutting down sharply on the overall yields. If time constraints had not been such a factor, a comprehensive trial of different recrystallization solvents would have been worthwhile.

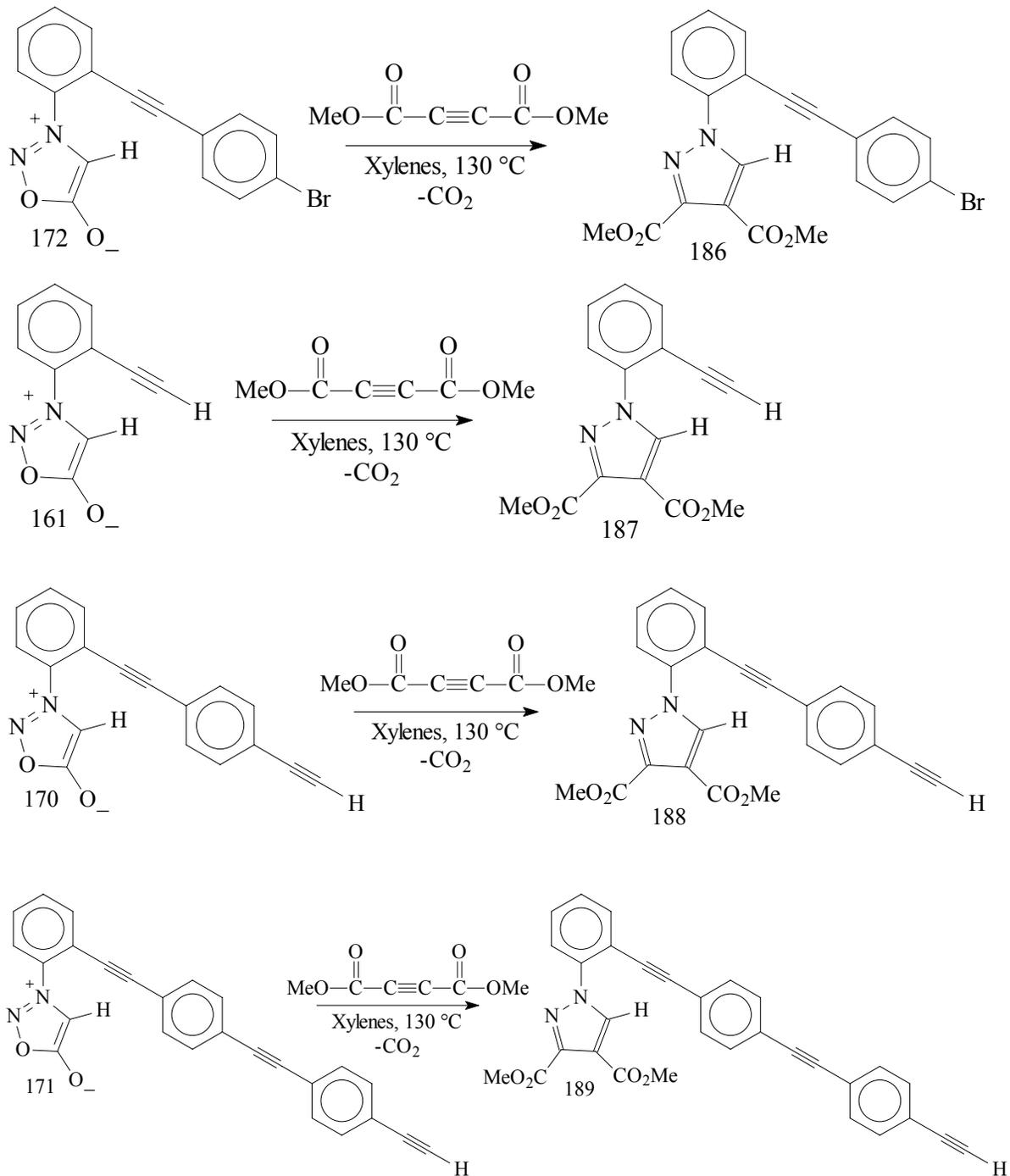
Having said this, if one calculates the overall yields on material obtained directly from column chromatography (homogenous by TLC), and using the most direct, multi-reaction in one pot protocols, the following is found. 3-(2-ethynylphenyl)sydnone **161** was made from N-phenylsydnone **13** in 37% yield, 3-(2-(4-(ethynyl)phenylethynyl)phenyl)sydnone **170** was made in 53% yield, and 3-(2-(4-(4-ethynyl)phenylethynyl)phenylethynyl)phenyl)sydnone **171** was made in 25% yield. Although the respective increases are not massive, these yields are more pleasing.

Considering everything that has been presented in the discussion so far, this portion of the research was successful. Overall, fifteen hitherto unknown *ortho-alkynyl* sydnones were made, most in moderate to good yield. Included in these were the species desired by The United States Air Force. Although it will not be discussed here, it is worth mentioning that these latter species were used in further synthesis of platinum-centered alkynyl complexes, and proved interesting when tested for non-linear optical activity.⁸⁹

Although not mentioned in “Aims of the Present Work,” the author’s synthetic role for the Air Force did not conclude with the synthesis of the aforementioned species. In order to provide further terminal alkynes for study, three more species were made. Each sydnone with a terminal alkyne moiety, as well as species **172**, was transformed

into a 3,4-dicarbo-methoxypyrazole *via* 1,3-dipolar cycloaddition with dimethylacetylene dicarboxylate, as shown in Scheme 45.

Scheme 45



3-(2-(4-Bromophenylethynyl)phenyl)sydnone **172** was chosen to test the cycloaddition because there were initial concerns that intermolecular cycloaddition between the sydnone ring and an attached acetylene moiety, especially a terminal acetylene, may be competitive. This did not seem to be the case, and 3,4-dicarbomethoxy-1-(2-bromophenyl-ethynyl)phenylpyrazole **186** was synthesized in 94% yield after column chromatography, 86% yield after recrystallization. An acceptable elemental analysis was obtained. In the IR spectrum of this compound, the pyrazole C-H was observed at 3157 cm^{-1} , aromatic C-H at 3083 cm^{-1} , alkyl C-H at 2950 cm^{-1} , two carbonyl stretches at 1748 and 1726 cm^{-1} , and C-O at 1220 cm^{-1} . The proton NMR spectrum contained a singlet, the pyrazole proton, at 8.7 ppm, a multiplet from 7.8-7.2 ppm (8 aromatic protons), and singlets at 4.0 and 3.9 ppm, the methyl protons. The carbon-13 NMR contained nineteen peaks as expected, the majority being those in the aromatic range (including the pyrazole carbons). Peaks of interest are the two carbonyl peaks at 162.3 and 162.1 ppm, the alkyne carbon peaks at 94.8 and 86.3 ppm, and the methyl-group carbon peaks at 53.0 and 52.3 ppm.

3-(2-Ethynylphenyl)sydnone **161** was converted to 3,4-dicarbomethoxy-1-(2-ethynylphenyl)pyrazole **187** in 81% yield after column chromatography and 52% yield after recrystallization. This new compound was successfully characterized by elemental analysis. The infrared spectrum showed a strong terminal alkyne C-H stretch at 3225 cm^{-1} , the pyrazole C-H stretch at 3137 cm^{-1} , the alkyne $\text{C}\equiv\text{C}$ stretch at 2104 cm^{-1} , the carbonyl stretches at 1729 and 1707 cm^{-1} , and C-O stretches at 1287 and 1239 cm^{-1} . At the time of publication of this thesis, NMR data were not available on species **187**, nonetheless, the preceding evidence causes no reason to think the assigned structure is incorrect.

3,4-Dicarbomethoxy-1-(2-(4-(ethynyl)phenylethynyl)phenyl)pyrazole **188** was obtained in 81% yield after column chromatography and 73% after recrystallization. This material gave an acceptable elemental analysis. Noteworthy peaks in the IR

spectrum were the terminal acetylene C-H, which occurred as two peaks, 3270 and 3242 cm^{-1} , the pyrazole C-H at 3140 cm^{-1} , only one carbonyl peak at 1737 cm^{-1} , and C-O stretch at 1289 and 1220 cm^{-1} . The proton NMR had a singlet at 8.8 ppm, the pyrazole proton, an eight-proton multiplet in the aromatic region, singlets at 4.0 and 3.2 ppm (six methyl protons), and the terminal acetylene proton at 3.2 ppm. The carbon-13 spectrum showed twenty-one peaks as expected. Thirteen were in the aromatic region, accounting for the aryl ring carbons as well as the pyrazole carbons. The carbons of the carbonyls were observed at 162.3 and 162.1 ppm, the three quaternary alkyne carbons at 95.3, 87.1, and 83.3 ppm, the terminal alkyne carbon at 79.7 ppm (intense compared to the other alkyne carbons), and the methyl carbons at 53.0 and 52.3 ppm.

Finally, the tris-alkyne, 3,4-dicarbomethoxy-1-2-(4-(4-(4-(ethynyl)-phenylethynyl)phenylethynyl)phenyl)pyrazole **189** was synthesized in 66% yield after column chromatography, 40% yield after recrystallization, and gave an acceptable elemental analysis. The IR spectrum showed the terminal acetylene C-H at 3240 cm^{-1} , two carbonyl peaks at 1730 and 1711 cm^{-1} , and C-O stretches at 1264 and 1239 cm^{-1} . NMR spectroscopic results were not as straightforward as with the previous pyrazoles. In the proton NMR, the pyrazole proton appeared as two, very finely-split peaks at 8.788 ppm and 8.786 ppm, however, these integrated together to represent only one proton. A complex multiplet represents the aromatic protons as one may expect, but the integration is slightly off at thirteen protons compared to the expected twelve. The peaks representing the six methyl protons are two singlets at 4.0 ppm and 3.9 ppm. Finally, the terminal acetylene proton, which should be a singlet (as with the pyrazole proton) is also split into two, very close peaks at 3.193 and 3.190 ppm. One would expect twenty-seven peaks in the carbon-13 spectrum, however, twenty-eight were observed. The rogue peak is thought to be a comparatively weak, aromatic peak at 131.9 ppm, even less intense than has been observed for a typical, quaternary, aromatic carbon. Otherwise, the carbonyl carbons appear at 162.3 and 162.1 ppm, the quaternary acetylene carbons at

95.5, 91.4, 91.0, 87.2, and 83.4 ppm, the terminal acetylene carbon at 79.4 ppm, and the methyl carbons at 53.0 and 52.3 ppm. Despite a few discrepancies, the evidence indicates that the desired species is the one that has been obtained.

During the course of synthesizing the three terminal-acetylene pyrazoles (**187**, **188**, and **189**), the author was notified by Wright Patterson Air Force Base that mono-alkyne 3,4-dicarbomethoxy-1-(2-ethynylphenyl)pyrazole **187** would not be transformed into a platinum-centered complex for NLO testing since research with similar species had not yielded interesting results. Otherwise, at the time of writing this Thesis, work to transform mono-alkyne **188** and tris-alkyne **189** into platinum-centered complexes for NLO testing had recently begun.

II. Efforts at the Synthesis of Fused-Ring Sydnones

Considering the discussion of the current work thus far, reflection upon the results is rather satisfying. The main reason for this is the fact that several major goals were achieved including: (1) Successful Sonogashira coupling of 3-(2-iodophenyl)sydnone **176** with terminal acetylenes, including trimethylsilyl acetylene. (2) Synthesis of a variety of *ortho*-alkynyl sydnones in moderate to good yield both *via* two reactions in one pot starting with 3-(2-(trimethylsilylethynyl)phenyl)sydnone **160**, and, better still, *via* a three-reaction-in-one-pot protocol directly from **176**. Finally, (3), synthesis of oligomeric, alkynyl sydnones and pyrazoles in good overall yield by the development and use of other multi-reaction-in-one-pot protocols. The author spent the majority of his time as a graduate student pursuing these objectives, and their achievement is fulfilling. Nevertheless, there remains one other objective of the research requiring examination, *viz.* reaction of *ortho*-alkynyl sydnones with electrophiles as a route to fused-ring arylsydnones.

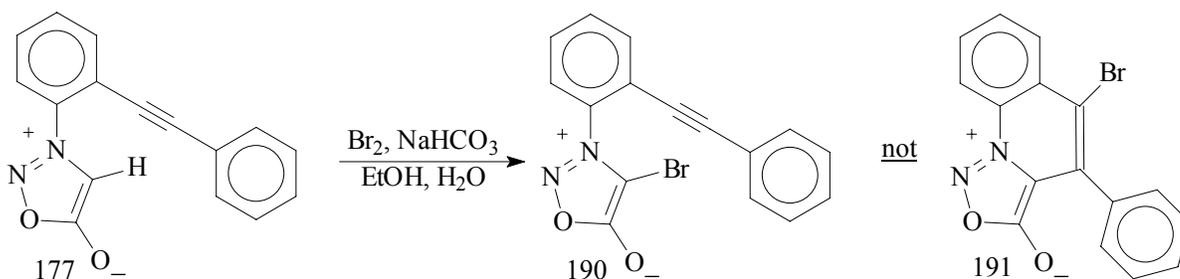
Although development of a new route to fused-ring sydnones is one of the more interesting objectives of the research, overall, its pursuance suffered. The majority of time and effort available was put into the goals mentioned above. However, at the writing of this Thesis, a few efforts to attain fused-ring sydnones had been made, and, some success achieved. In addition, there was a bonus, *viz.* the discovery of a novel route to 3-arylcinnolines as the result of efforts to make fused-ring sydnones. The details of this work are forthcoming.

One of the first *ortho*-alkynyl sydnones made was 3-(2-(phenylethynyl)phenyl)sydnone **177**. In addition, this was initially one of the more easily attained species since it could be made directly from the coupling of inexpensive phenyl acetylene and 3-(2-iodophenyl)sydnone **176**.

Initially, rudimentary, small-scale tests (i.e. in a test-tube on a few crystals of material), were done with **177** using a variety of electrophiles to search for signs of reaction by TLC. Electrophiles included were excess bromine, excess iodine, *para*-toluenesulfonic acid, perchloric acid, tetrafluoroboric acid, and trifluoroacetic acid. Of these electrophiles, bromine was the only one that showed a sign of reaction.

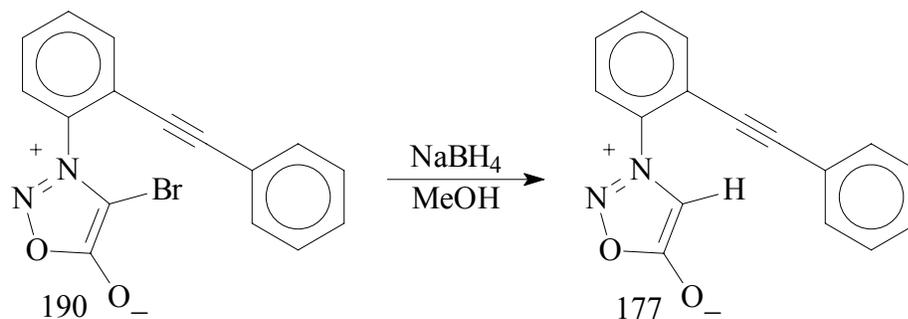
3-(2-(phenylethynyl)phenyl)sydnone **177** formed an isolable product in the presence of bromine and sodium bicarbonate. Initial hopes were that a fused-ring sydnone was formed by means of this reaction; however, this did not turn out to be the case. Under conditions of bromination, it was found 4-bromo-3-(2-(phenylethynyl)phenyl)sydnone **190** was generated, not the desired fused-ring sydnone **191** (Scheme 46). Apparently, the sydnone ring was more reactive than the alkyne, and a thought to this effect is that the electron-withdrawing sydnone ring may deactivate the alkyne.

Scheme 46



Species **190** was obtained in 59% crude yield (homogeneous by TLC) and 40% after recrystallization. An acceptable elemental analysis was obtained. From the IR spectrum, it was evident that 4-bromo-3-(2-(phenylethynyl)phenyl)sydnone **190** was the product due to the lack of a sydnone C-H stretch around 3150 cm^{-1} . A peak for the alkyne appeared at 2222 cm^{-1} (ruling out structure **191**), and the sydnone carbonyl at 1766 cm^{-1} . The proton NMR did not show a peak at 6.9 ppm, indicating the sydnone proton was not present. In the aromatic region of the proton NMR spectrum was a doublet, triplet, triplet, doublet pattern from 7.82 to 7.44 ppm integrating to four protons. These would be the aromatic protons on the aryl ring to which the sydnone is attached. A complex multiplet appears from 7.42 to 7.24 ppm integrating to five protons, those on the other aryl ring. In the carbon-13 NMR spectrum were observed fourteen carbons as expected. Peaks of interest are the sydnone C-5 at 165.5 ppm, the sydnone C-4 at 97.4 ppm, and the two carbons of the alkyne at 86.1, and 81.9 ppm. Overall, with the information at hand, there was no reason to suspect that **190** was not the correct structure, nonetheless, a simple chemical test was also done. In a test tube, a small amount of **190** was treated with excess sodium borohydride in methanol, by TLC, this generated **177**, consistent with the ability of sodium borohydride to remove bromine from the sydnone ring (Scheme 47).

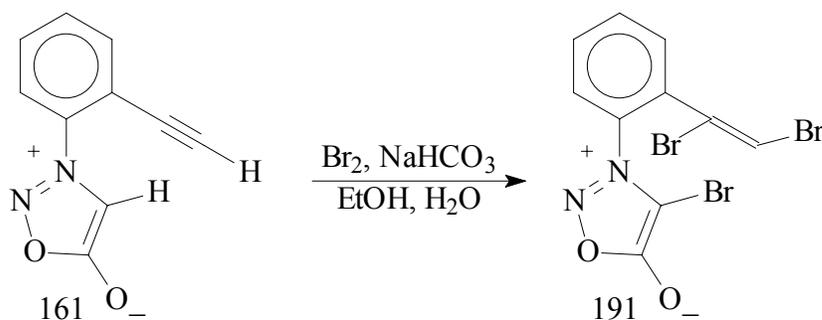
Scheme 47



As had been done with 3-(2-(phenylethynyl)phenyl)sydnone (**177**), a set of small-scale tests were done with 3-(2-ethynyl)phenylsydnone (**161**), and it was tested with excess iodine, excess bromine, *para*-toluenesulfonic acid, trifluoroacetic acid, and concentrated sulfuric acid. Of these electrophiles, bromine and sulfuric acid seemed the most promising.

As shown in Scheme 48, reaction of 3-(2-ethynylphenyl)sydnone (**161**) with excess bromine results in tri-bromo species **191**. It is apparent that a molecule of bromine adds to the alkyne, and an atom of bromine to the sydnone C-4 position.

Scheme 48

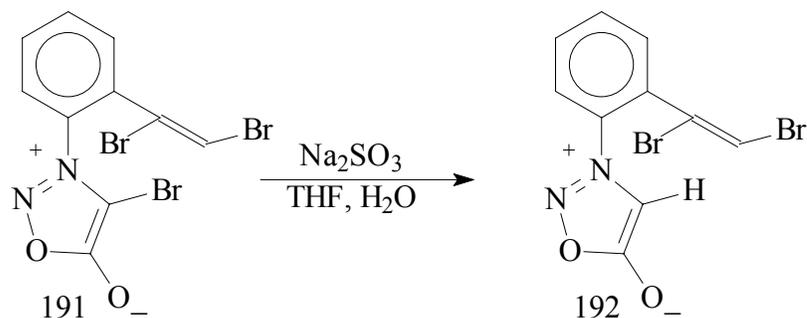


Initially, the identity of **191** was uncertain, but elemental analysis indicated the addition of three bromine atoms. All in all, 4-bromo-3-(2-(1,2-dibromovinyl)phenyl)sydnone was synthesized in 87% crude yield (81% recrystallized). It is presumed that the bromine atoms on the alkene are *trans* to one another, since

initially the alkyne would attack a molecule of bromine to form a bromonium ion, necessitating attack by bromide ion from the side opposite the bromonium ion. The infrared spectrum of **191** lacks the sydnone C-H stretch, but still shows the sydnone carbonyl stretch at 1767 cm^{-1} . The proton NMR spectrum shows a multiplet in the aromatic region (7.82-7.52 ppm) integrating to five protons. The peak representing the alkene proton appears at 6.91 ppm, very similar to a sydnone C-H. The carbon-13 spectrum contains peaks for ten carbons as expected, six of which fall in the aromatic region. The sydnone C-5 peak appears at 165.7 ppm as normal, and the non-quaternary carbon of the alkene is an obviously strong peak at 109.6 ppm (a doublet in the non-decoupled spectrum). There is more ambiguity in assigning the remaining two peaks (113.5 and 86.1 ppm), which must be the quaternary alkene carbon and the sydnone C-4. It is thought that the peak at 86.1 ppm since the former is a value more expected for an alkene.

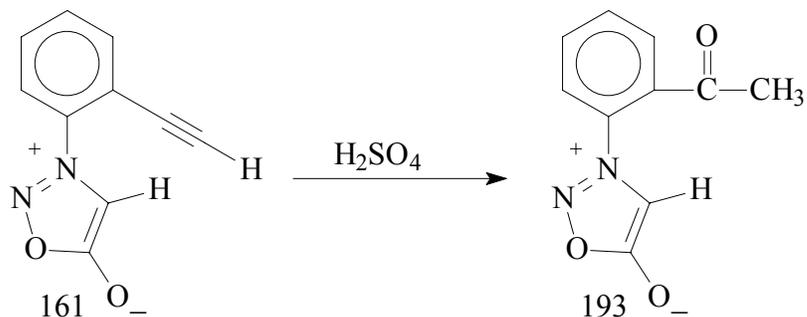
Once again, a simple chemical test was to help confirm **191** as the correct structure, or at least to illustrate that a bromine atom was indeed attached to the sydnone C-4 position. A small amount of **191** was reacted with sodium sulfite in tetrahydrofuran / water (Scheme 49) to yield a lower-running product by TLC. This product (presumably **192**) was isolated in 55% yield and an IR spectrum acquired. In contrast to the IR spectrum of **191**, there was a peak present at 3150 cm^{-1} , indicating a sydnone C-H. Further confirmation of the sydnone C-H came from the proton NMR of **192**. A peak appears at 6.63 ppm that is not in the spectrum of **191**.

Scheme 49



Reaction of 3-(2-ethynylphenyl)sydnone (**161**) with concentrated sulfuric acid led not to a fused-ring sydnone, but to known sydnone species 3-(2-acetylphenyl)sydnone **193** in 82% yield (Scheme 50).

Scheme 50

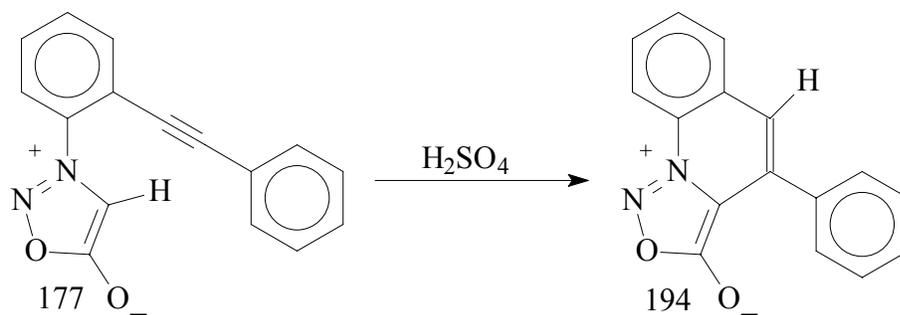


The 3-(2-acetylphenyl)sydnone **193** made by this route was identified by comparison with authentic material (TLC, IR, melting point). It is not surprising that the terminal alkyne reacts with sulfuric acid, forming a carbocation next to the aryl ring. However, it is a bit surprising that water attacks the carbocation before intramolecular cyclization with the sydnone ring could occur. Concentrated sulfuric acid was chosen for its lack of water, yet clearly, there is enough water in the acid to add to the alkyne. It is unlikely that the carbocation “waits” for the reaction to be quenched with ice before

forming the acetyl moiety. Although disappointing that a fused-ring species was not obtained, a novel route to 3-(2-acetylphenyl)sydnone was discovered.

Since the alkyne moiety of 3-(2-acetylphenyl)sydnone had reacted with sulfuric acid, it was decided to try the same reaction with 3-(2-(phenylethynyl)phenyl)sydnone **177** (Scheme 51). As is shown in the scheme, with this reaction the goal of a fused-ring sydnone was achieved.

Scheme 51

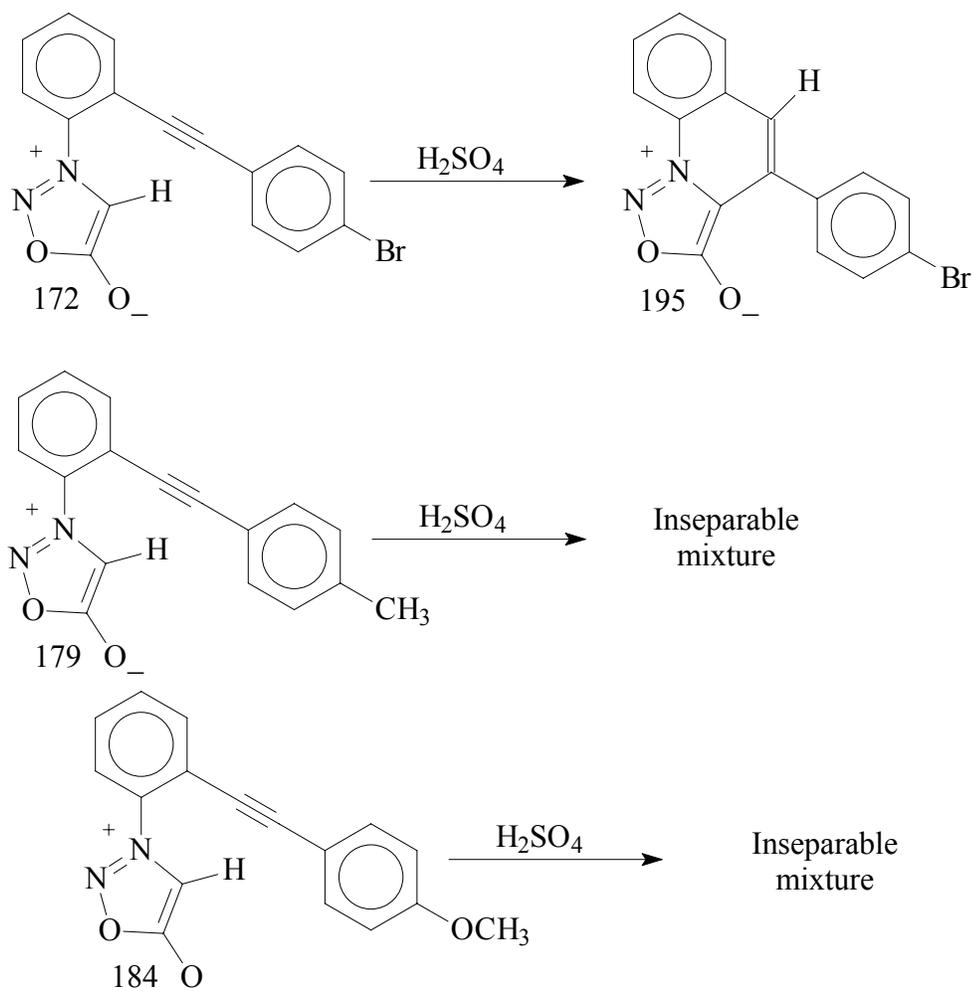


The best yield of 4-phenylsydno[3,4-a]quinoline (**194**) from this reaction was 22%. The first indication that a fused-ring sydnone was obtained came from the infrared spectrum, most notably, the lack of a sydnone C-H stretch, however, the sydnone carbonyl stretch still appeared at 1742 cm⁻¹. A second indication that a fused-ring sydnone was achieved was the 244-246 °C melting point of this species. This is about 100 °C higher than the typical melting point for an arylsydnone. The proton NMR confirmed the lack of a sydnone proton, and in the aromatic region of the spectrum was a multiplet that integrated to nine protons (eight from the aryl ring and one from the alkene). The carbon-13 NMR was slightly problematic due to the lack of one peak (thirteen were observed of fourteen expected). Acquisition of the spectrum of this species was hindered by its solubility since it was necessary to use d₆-DMSO as solvent at 100 °C, and the spectrum was acquired only over three hours instead of overnight. The sydnone carbonyl carbon was observed at 164.1 ppm; the rest of the observed carbons

were seen in the aromatic region, four of which were obviously quaternary. The missing carbon peak is likely the sydnone C-4 since no obvious peak is observed around 97 ppm.

As was mentioned before, the best yield of **194** using concentrated sulfuric acid was 22%. Repetition of this reaction gave varying yields, often these yields being lower than 5%. Overall, the reaction was not efficient or reliable. This proved to be even more the case when trying the same transformation with other *ortho*-alkynyl sydnones as shown in Scheme 52.

Scheme 52



4-(4-bromophenyl)sydno[3,4-a]quinoline **195** was achieved in 10% yield (best yield) by means of reaction with concentrated sulfuric acid. Like fused-ring sydnone **194** the melting point of this species is considerably high, *viz.* 272-274 °C. An acceptable elemental analysis of this material was obtained. The infrared spectrum of **195** was lacking a sydnone C-H stretch as expected, but did show a peak at 3071 cm⁻¹, presumably the C-H stretch of the proton attached to the alkene. A typical sydnone carbonyl stretch, split by Fermi resonance, was observed at 1748 and 1719 cm⁻¹. Overall, the available evidence affirms that sydnonquinoline **195** has been achieved. Due to the inefficiency and variability of the reaction, it was decided not to make sufficient material for NMR.

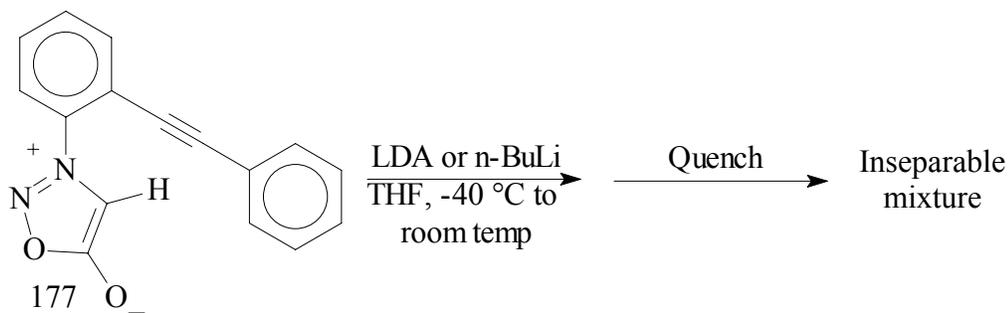
Attempts to make 4-(4-methylphenyl)sydno[3,4-a]quinoline from 3-(2-(4-methylphenylethynyl)phenyl)sydnone (**179**) and 4-(4-methoxyphenyl)sydno[3,4-a]quinoline from 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone (**184**) *via* reaction with sulfuric acid were unsuccessful, and only inseparable mixtures were obtained. This seems somewhat unexpected since it was thought the electron-donating nature of the methyl and methoxy moieties should enhance the reactivity of the alkyne, stabilizing a carbocation formed by reaction of the alkyne with the acid. Perhaps the electron-donating nature of these moieties made the alkyne too reactive, providing a greater chance for the breakdown of the starting material to by-products.

Being that sulfuric acid as an electrophile source was showing some promise in the creation of fused ring sydnones, it was decided to see if the reaction could be improved by it being performed in a solvent. Using 3-(2-(phenylethynyl)phenyl)sydnone **177** in a series of tests, several solvents were tried, including some that would react themselves with sulfuric acid. The solvents tried were anhydrous tetrahydrofuran yielding starting material, anhydrous ethylene glycol dimethyl ether yielding starting material, acetonitrile yielding starting material, methanol yielding starting material and dichloromethane yielding a complex mixture. Presumably, those solvents that could be protonated with sulfuric acid were not strong enough acids themselves to react with the

alkyne of **177**, nor to break the sydnone ring. In regards to the dichloromethane, sulfuric acid is not soluble in this solvent, so presumably the reaction that did occur was in the “clumps” of acid that were stirred in the reaction solution, more or less like a reaction in the neat acid itself.

It was apparent that sulfuric-acid induced cyclization was not working out well, so it was decided to try a different approach. At about this point in the work, a paper was discovered where an analogous cyclization was achieved using a strong base to create an intramolecular anion in close proximity to an alkyne.⁹⁰ The idea was to abstract the sydnone C-4 proton in hopes that this anion might react with the *ortho* alkyne moiety. Why would an anion attack an electron-rich alkyne? The idea is similar to that of anion additions to α,β -unsaturated species (Michael Addition). The alkyne may be polarized (*viz.* have a partial positive character) by conjugation or electron-withdrawing effects with the rest of the molecule. This type of reaction was attempted on 3-(2-(phenylethynyl)phenyl)sydnone **177** with lithium diisopropyl amide (LDA) and *n*-butyllithium as shown in Scheme 53.

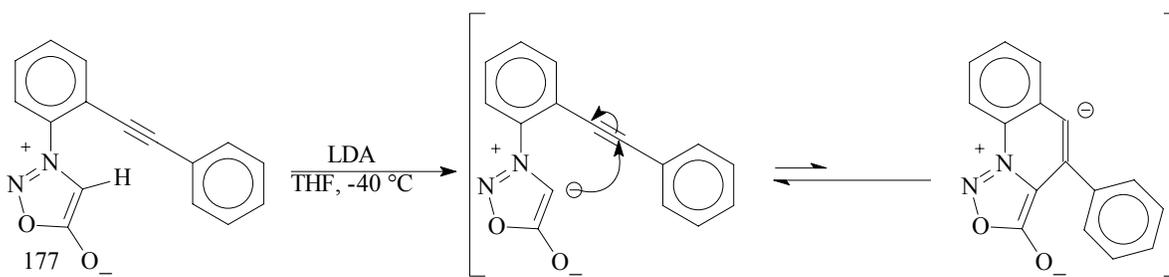
Scheme 53



Unfortunately, the starting material was destroyed, resulting in an inseparable mixture. Upon consideration in retrospect, it seems unlikely that ring-fusion could be achieved by this route. Reaction of **177** with LDA or *n*-BuLi would presumably result in formation of the C-4 anion as usual. If this anion would indeed attack the alkyne,

formation of a less-stable vinylic anion would result, and hence an equilibrium would favor the sydnone C-4 anion over the vinylic anion if it were formed at all (Scheme 54). It would be of interest to try this type of reaction again in the presence of a moderate electrophile (e.g. a Weinreb's amide) which might trap the vinylic anion if it were formed (but not react at the sydnone C-4 position).

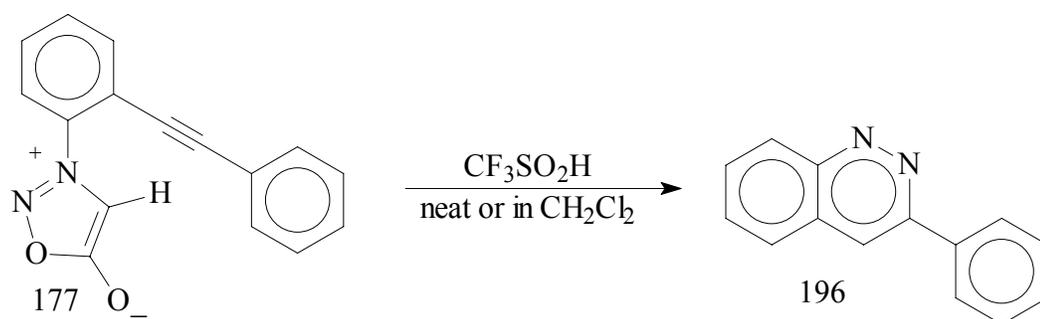
Scheme 54



Nonetheless, after this trial at base-induced cyclization, the focus on reagents to induce cyclization returned to acids, based on the small amount of success that had been achieved with sulfuric acid. From what had been observed thus far, it was apparent that a strong acid (such as sulfuric) was required to induce reaction at the alkyne. In addition, the acid needed to be free of water, which could cause complications by either acting as a nucleophile upon the protonated alkyne, or, more likely, cause sydnone ring cleavage as is known to occur under aqueous acidic conditions (and was likely causing the low yields when sulfuric acid was used, despite its lack of water). In terms of addressing the need for a strong acid, trifluoromethanesulfonic acid (triflic acid), one of the strongest organic acids known, was available in the laboratory. This acid is also soluble in organic solvents such as dichloromethane. Better still, one member of the author's Thesis Committee, Dr. Eric Fossum, was greatly experienced with the purification of trifluoromethanesulfonic acid *via* a high-vacuum, pot-to-pot distillation procedure. With his help, the author was able to procure dry, pure, trifluoromethanesulfonic acid. When this acid was used neat,

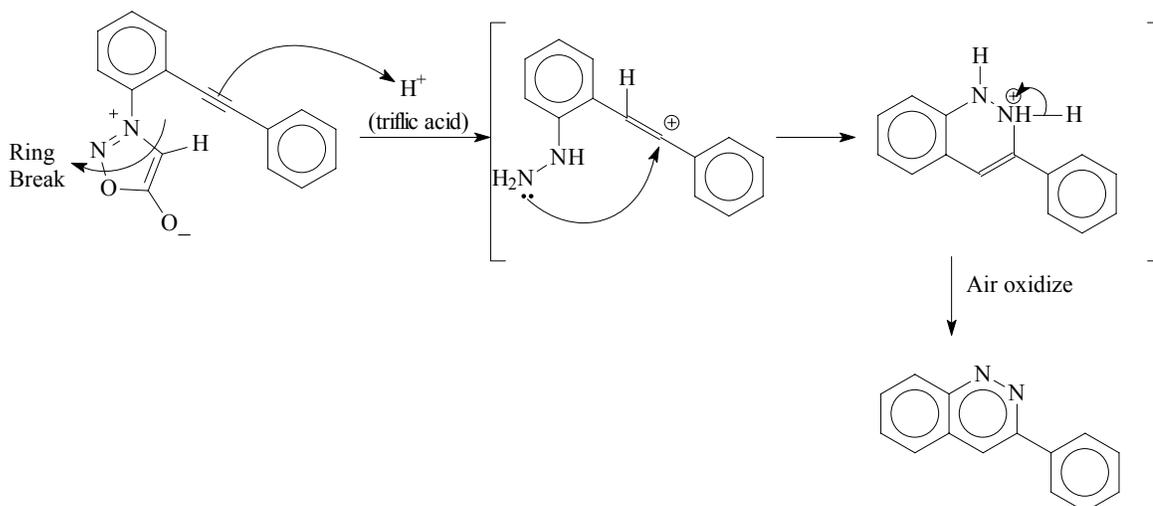
and in dichloromethane solvent, in an effort to determine if it would effect ring fusion of 3-(2-(phenylethynyl)-phenyl)sydnone **177**, a fused-ring sydnone was not obtained. However, there was a major isolable product produced. After some work it was determined this product was 3-phenylcinnoline (**196**, Scheme 55), mainly by comparison of the product melting point to that in the literature after speculation about what the product might be.⁹¹

Scheme 55



The transformation from sydnone to cinnoline is thought to occur by acid-induced sydnone ring cleavage to a hydrazine with concurrent acid-induced cyclization to the alkyne followed by spontaneous oxidation to the cinnoline. This process is illustrated in Scheme 56.

Scheme 56

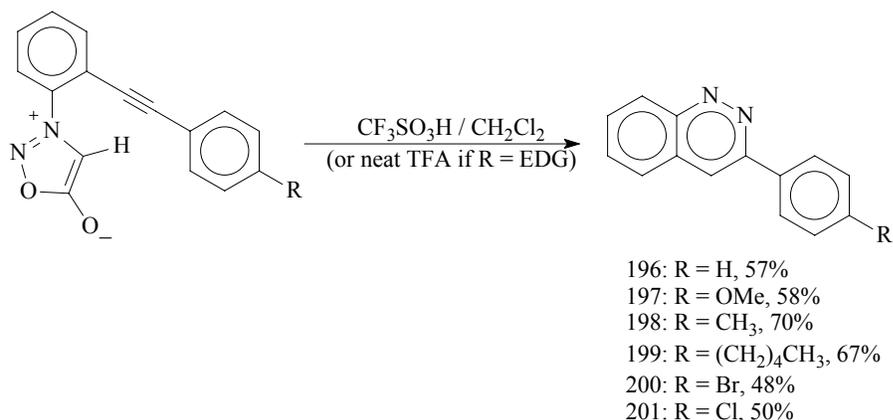


This reaction was also tested with 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone **184** and found to give a similar result.

At the same time, since it had not been tested before, 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone **184**, the *ortho*-alkynyl sydnone with the most powerful electron-donating group, was tested to see if sydnone ring fusion could be achieved with this species in the presence of trifluoroacetic acid. It was found from this reaction that a cinnoline was also the resulting product.

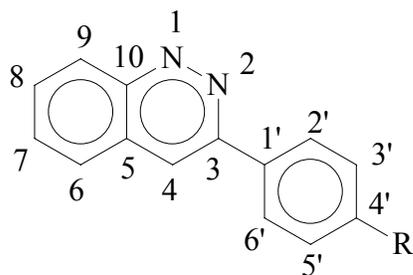
In the end, from these two discoveries it was found that *ortho*-alkynyl sydnones could be used as precursors to 3-arylquinolines, in good yield (Scheme 57).

Scheme 57



Trifluoromethanesulfonic acid in dichloromethane easily effected the transformation from sydnone to cinnoline if R was either an electron-donating or an electron-withdrawing group in Scheme 57. However, if R is an electron-donating group such as methoxy or alkyl, the transformation is effected with the milder and easier-to-handle trifluoroacetic acid (TFA), heated to reflux (the preferred route). All cinnolines made gave acceptable elemental analyses. For the sake of the following discussion, the following numbering system for the cinnolines will be employed (Scheme 58).

Scheme 58



3-phenylcinnoline (**196**) was synthesized in 82% yield after column chromatography (57% after recrystallization) using trifluoromethanesulfonic acid. The infrared spectrum shows the lack of a sydnone C-H stretch and a sydnone carbonyl

stretch, indication that the sydnone ring is no longer present. Otherwise, the spectrum is straightforward with notably strong peaks at 3033 cm^{-1} (aromatic C-H) and 747 and 698 cm^{-1} . The proton NMR is also straightforward, with only aromatic protons present. The spectrum shows a doublet, multiplet, singlet, multiplet pattern over the range 8.6 to 7.5 ppm. Presumably, the singlet at 8.14 ppm is the proton attached to the C-4 position of the cinnoline since it is not adjacent to any other protons. The carbon-13 NMR spectrum had twelve peaks as expected, all in the aromatic region of the spectrum. Four of these peaks appeared quaternary in nature, as one would expect. Two of the quaternary peaks that stood out from the rest appeared at 153.7 and 150.1 ppm. Presumably, these are the carbons at positions 10 and 3, due to the deshielding effect of the adjacent nitrogens.

3-(4-Methoxyphenyl)cinnoline (**197**) was achieved in 90% yield after column chromatography (58% after recrystallization) by means of trifluoroacetic acid. The infrared spectrum is similar to that of 3-phenylcinnoline (**196**) with the exception that alkyl C-H stretches are apparent, and the strongest peaks in the spectrum are at 1257 and 1172 cm^{-1} . The proton NMR has a doublet, multiplet, singlet, multiplet, doublet pattern similar to that of **196**, with the singlet appearing at 8.05 ppm. The methoxy protons appear at 3.87 ppm, and the integration of aromatic to methoxy protons is $3 : 1$ as expected. The carbon-13 NMR spectrum contained thirteen peaks as expected. In the aromatic region were five quaternary peaks, the most deshielded appearing at 161.1 ppm. This is likely carbon 4', deshielded by the methoxy group attached to it. Peaks at 153.4 and 149.9 represent the carbons adjacent to the nitrogen atoms in the cinnoline ring system. The carbon of the methoxy moiety appears at 55.6 ppm, confirming the structure.

As with **197**, 3-(4-methylphenyl)cinnoline **198** was achieved by use of neat trifluoroacetic acid in 86% yield after column chromatography (70% after recrystallization). The infrared spectrum was similar in appearance to the other characterized cinnolines. The same may be said for the appearance of the proton NMR

spectrum, except that there is no distinct singlet in the aromatic region. The pattern is doublet, multiplet, multiplet, doublet, with the singlet for the methyl protons appearing at 2.43 ppm. The integration of the aromatic to alkyl protons is a ratio of 3 : 1. The carbon-13 NMR spectrum appears as one would expect, except that only twelve carbons are observed instead of the expected thirteen. Even so, it seems that all of the quaternary peaks are accounted for in the aromatic region since there are five peaks that appear weak in intensity. Included in these peaks are the cinnoline C-10 and C-3 carbons at 153.6 ppm and 150.0 ppm. The carbon of the methyl group is observed at 21.6 ppm as one would expect. Overall, the evidence indicates that the assigned structure for **198** is correct.

3-(4-Pentylphenyl)cinnoline (**199**) was achieved in 77% yield after column chromatography (67% after recrystallization) by means of trifluoroacetic acid. The infrared spectrum of this species showed very strong alkyl C-H stretches in the infrared spectrum, as well as aromatic C-H at 3046 cm^{-1} . Otherwise, the fingerprint region was similar to that of the other cinnolines previously made. The proton NMR spectrum contained appropriate peaks in both the aromatic and alkyl regions of the spectrum. The doublet, multiplet, multiplet, doublet pattern was present in the range 8.55 to 7.36 ppm, integrating to nine protons. The pentyl-group protons were observed as a triplet, multiplet, multiplet, multiplet feature from 2.72 to 0.89 ppm. The integration of the alkyl protons worked out to be only ten, instead of the expected eleven. The aromatic region of the carbon-13 NMR spectrum had an appearance similar to the other cinnolines studied, with twelve aromatic carbons present as expected, the cinnoline C-10 and C-3 carbons being observed at 153.8 and 150.0 ppm respectively. The pentyl-carbons were observed at 36.0, 31.8, 31.3, 22.8, and 14.3 ppm, hence all the alkyl carbons were accounted for as anticipated.

3-(4-Bromophenyl)cinnoline (**200**) was synthesized by using trifluoromethane sulfonic acid in a yield of 60% after column chromatography and 48% after

recrystallization. The infrared spectrum of this species had an appearance similar to that of the other cinnolines, with the strongest peak in the spectrum appearing at 827 cm^{-1} . Observed in the proton NMR was a doublet, multiplet, multiplet feature from 8.5 to 7.6 ppm, slightly different from the other cinnolines already analyzed. The carbon-13 NMR spectrum contained twelve peaks as expected, all in the aromatic region, and five of them appearing quaternary in nature. The cinnoline C-10 and C-3 were observed at 152.5 and 150.2 ppm.

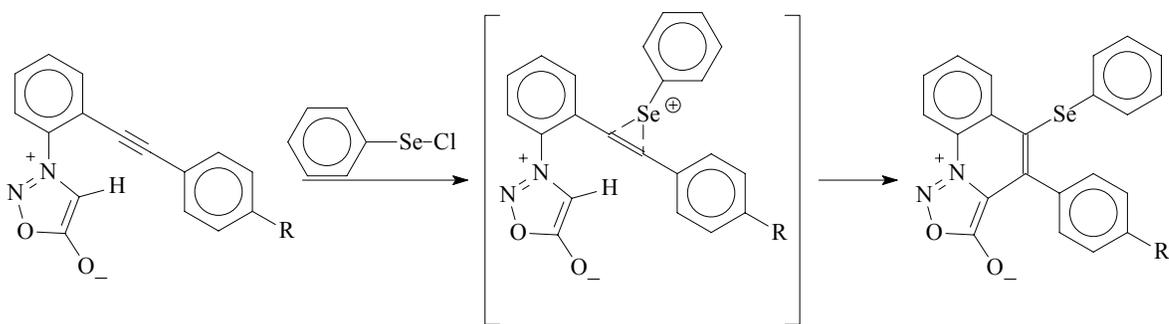
3-(4-Chlorophenyl)cinnoline (**201**) was synthesized by using trifluoromethane sulfonic acid in a yield of 69% after column chromatography and 50% after recrystallization. The infrared spectrum of this species had an appearance similar to that bromo-cinnoline **200** with indications of aryl C-H and the strongest peak appearing at 826 cm^{-1} . As with bromo-cinnoline **200**, a doublet, multiplet, multiplet, doublet pattern was found in the aromatic region of the proton NMR, with a respective integration ratio of 1 : 3 : 3 : 2, accounting for all nine protons. The carbon-13 NMR spectrum contained twelve peaks as expected, five of which appeared quaternary in nature. Of these peaks, the cinnoline C-10 appeared at 152.2 ppm and the C-3 at 150.1 ppm.

The discovery of the novel route to 3-arylcinnolines using *ortho*-alkynyl sydnone was one of the highlights of this research, and is somewhat gratifying since the efforts at fused-ring sydnone have not been as fruitful as desired. Nevertheless, the search for an electrophile that will effect sydnone ring fusion in good yield continued. The next electrophile on which some effort was placed was phenylselenenyl chloride. This is the last item that will be discussed in this Thesis, and results with this electrophile have proved to be somewhat mysterious.

Phenylselenenyl chloride is an easily handled, crystalline solid that is known to react as an electrophile with alkenes, and had been used to effect intramolecular cyclizations.⁹² It seemed logical that such a reaction could be extended to alkynes such as the *ortho*-alkynyl sydnone made. Scheme 59 shows the reaction of an *ortho*-alkynyl sydnone with

phenylselenenyl chloride that was expected (and desired). The phenylselenenyl chloride reacts with the alkyne to form an intermediate selenonium ion that is then attacked by the nucleophilic sydnone ring to effect ring fusion.

Scheme 59

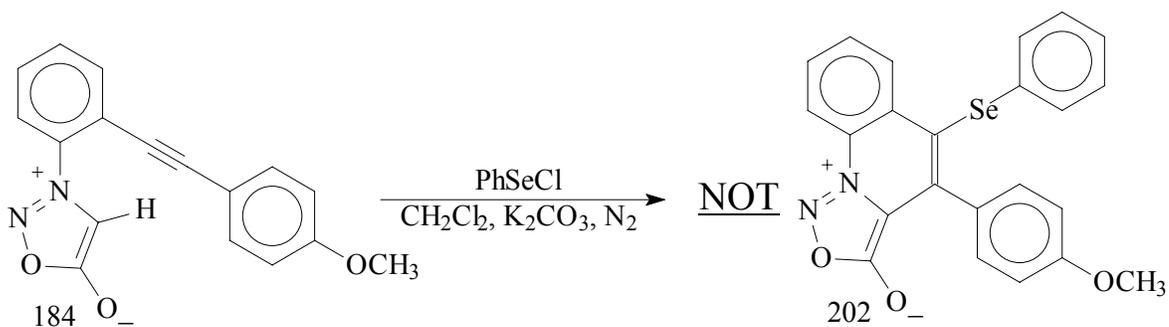


Typical reaction conditions with phenylselenenyl chloride include running the reaction at $-78\text{ }^{\circ}\text{C}$ in solvents such as dichloromethane under nitrogen. Initial trials at low temperature showed no sign of reaction. However, at room temperature reaction does occur, indicated by the presence of a new spot by TLC.

At the writing of this Thesis, the reactions of phenylselenenyl chloride with 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone **184** and 3-(2-(phenylethynyl)phenyl)sydnone **177** were the best studied.

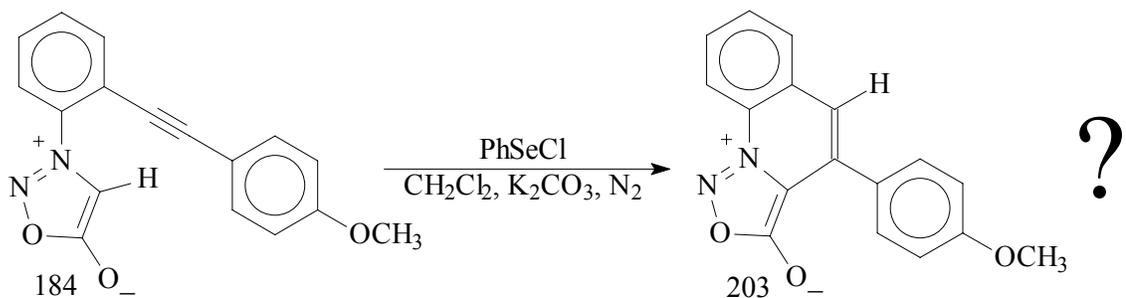
When a higher-running spot was observed by TLC from the reaction of 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone **184** with phenylselenenyl chloride, it was thought that a fused-ring sydnone **202** was achieved as shown in Scheme 60.

Scheme 60



After purification, infrared spectroscopy of putative **202** indicated the lack of a sydnone C-H stretch, helping to bolster hopes that fused species **202** had been achieved; also notable was the lack of an alkyne stretch. In addition, in the infrared spectrum was a carbonyl stretch at 1736 cm⁻¹ that would seem to indicate the presence of the sydnone carbonyl. However, in the infrared spectrum there was also a strong peak at 1651 cm⁻¹ that was hard to explain; initially, this was presumed to be an artifact of the selenium being present in the molecule. When elemental analysis results were obtained for putative **202**, it was evident that the incorrect structure was assigned. Clearly, there was no phenyl selenyl moiety in the molecule in that the elemental analysis fit a molecular formula of C₁₇H₁₂N₂O₃·½ H₂O. NMR would later illustrate this as well. Hence it was thought that the new species may be fused-ring sydnone **203** (Scheme 61), the analogue to **202** without the phenylselenyl group.

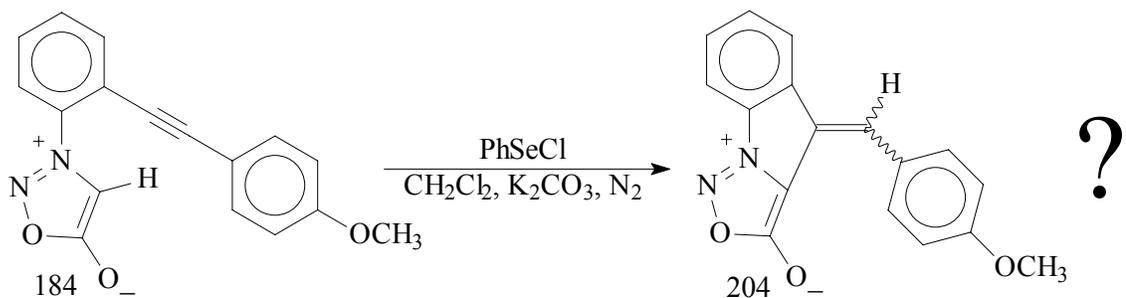
Scheme 61



Upon further examination, however, there was doubt if this was correct. First, structure **203** did not account for the strong peak in the infrared spectrum at 1651 cm^{-1} which would seem to be an extra carbonyl stretch or an alkene C=C stretch. Such a peak is not observed in fused-ring species **194** and **195** (made via sulfuric acid). Second, and more compelling, the melting point of putative **203** is only $150\text{-}152\text{ }^{\circ}\text{C}$, rather low compared to the melting points of **194** and **195**, which both melt above $240\text{ }^{\circ}\text{C}$. Finally, putative **203** is much more soluble than **194** and **195**. These facts indicate that either structure **203** is incorrect or structures **194** and **195** are incorrect. Since the properties of **194** and **195** (high melting point, low solubility) are indicative of previously made fused-ring sydnones, and since there are no anomalous peaks in their infrared spectra, it was assumed that structure **203** is incorrect.

What other structure could account for the available information? Structure **204** in Scheme 62 shows another possibility.

Scheme 62



If fused sydnone **204** were made this would be unprecedented since no fused-ring sydnone has been made where the fusion forms a five-membered ring, and where the fusing carbon is sp^2 hybridized. Nonetheless, putative structure **204** would seem to account for some of the information obtained. The elemental analysis would match, the exocyclic alkene could account for the strong infrared peak at 1651 cm^{-1} , and **204** would show physical properties (melting point, solubility) different from fused species **194** and **195**.

Unless, perchance, only one isomer of the putative alkene **204** was formed, one would expect to see evidence of *cis* and *trans* species in the NMR spectra. This is not the case, and of the two proposed structures (**203** versus **204**); the NMR spectra neither confirm nor rule out either. From this point forward, the unknown product from the reaction of 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone **184** and phenylselenenyl chloride will be referred to as **205**.

Analyzing from downfield to upfield, the proton NMR of unknown **205** shows a singlet at 9.32 ppm (1H). It seems that this could be a proton attached to an aromatic carbon but not likely to that of an alkene carbon. Next are two doublets (each 1H), 9.10-9.07 and 8.39-8.33 ppm respectively, which account for two of the protons on an *ortho* substituted aryl ring. Following these is a doublet (2H) from 8.13-8.10 ppm, accounting

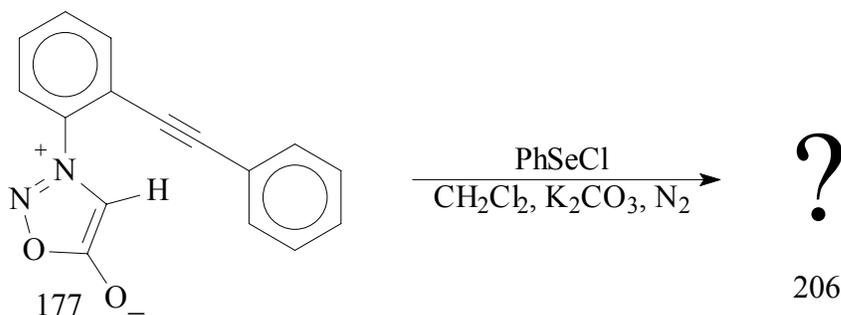
for one set of protons on the *para* substituted aryl ring to which the methoxy group is attached. Two triplets are observed (1H each) at 7.83-7.77 and 7.57-7.52 ppm, accounting for the other two protons on the ortho-substituted aryl ring. Another doublet is observed at 6.99-6.95 ppm (2H) accounting for the second set of protons on the *para* substituted aryl ring to which the methoxy group is attached. Finally is a singlet (3H) at 3.86 ppm, indicating the presence of the methoxy moiety.

After pulsing for fifteen hours, there are 15 peaks observed in the carbon-13 NMR spectrum as would be expected for a compound with the molecular formula found by elemental analysis. However, one of these peaks is very weak. Nonetheless, in concurrence with the infrared spectrum, the presence of a carbonyl carbon is evident by a quaternary peak at 171.4 ppm. Next is an intense peak at 166.2 ppm, presumably a deshielded aromatic carbon that is not quaternary. At 161.4 ppm is another peak with a quaternary intensity, likely the carbon to which the methoxy moiety is attached. Following this is a typical display of aromatic carbons (ten in number) from 148.7 to 114.0 ppm, four of these having a quaternary intensity. At 77.51 ppm is a weak peak hidden amongst the CDCl₃ solvent peaks. It is questionable if this peak is a peak attributable to the analyte since it has a quaternary intensity yet is split into a doublet in the uncoupled spectrum, indicating an attached proton. Finally, the methoxy carbon appears at 55.6 ppm.

Considering all of the data, the structure of **205** is still uncertain, and X-ray crystallography may be the only means to know the structure with confidence.

As was mentioned earlier, a similar transformation was achieved by reaction of 3-(2-(phenylethynyl)phenyl)sydnone **177** with phenylselenenyl chloride (Scheme 63) yielding unknown **206**.

Scheme 63



Full characterization data is not yet available on **206**, but from the data available (melting point and infrared spectrum) a few things can be said. First, by TLC, melting point, and infrared spectroscopy, unknown **206** is not the same as sydnocinoline **194**. In addition, it is similar to unknown **205** in terms of melting point and infrared spectroscopy. The infrared spectrum of **206** shows a carbonyl stretch at 1739 cm⁻¹ and strong, unexplainable peaks at 1641 and 1602 cm⁻¹. As of the writing of this Thesis, further data pertaining to unknown **206** were not yet available.

As a final thought in regards to the unknowns, it seems likely that the correct structure has not yet been speculated. It is good to keep the following in mind. In the phenylselenenyl chloride reaction, it is likely that HCl is produced by reaction of this electrophile with the alkyne, especially if the sydnone ring attacks a resulting selenonium ion, releasing H⁺. Despite the presence of potassium carbonate base (removal of which had little effect on the reaction), it is possible that any HCl produced is breaking the

sydnone ring, providing for formation of some species that is not a sydnone but still has some of the characteristics of sydnones.

As a general conclusion to the discussion, it can be reiterated that the aforementioned adventures in research with sydnones have been successful and fulfilling. Objectives have been achieved, including: (1) Successful Sonogashira coupling of 3-(2-iodophenyl)sydnone **176** with terminal acetylenes. (2) Synthesis of a variety of *ortho*-alkynyl sydnones *via* both two reactions and three reactions in one pot. (3) Synthesis of oligomeric, alkynyl sydnones and pyrazoles in good overall yield by the development and use of multi-reaction-in-one-pot protocols. Finally, (4), sydnoquinolines **194** and **195** were achieved, albeit in low yield. A bonus that came along with the work towards the goals was the discovery of a novel route to 3-arylcinnolines, one of the highlights of the research. Finally, some interesting “unknown” results (**205** and **206**) have been achieved through the phenylselenyl chloride reaction, providing many opportunities for future work in regards to synthesizing more of these species and other, similar species using other *ortho*-alkynyl sydnones with the aim of determining their structure.

Experimental

General notes:

All starting reagents and catalysts were purchased from commercial sources and used without further purification. Dry tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Where applicable (i.e. Sonogashira couplings, organolithium reagents), all glassware was flame-dried under an atmosphere of nitrogen prior to the use of dry reagents. 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 either a Jeol or Inova 300MHz NMR. Elemental analyses were performed by Midwest Microlab LLC, Indianapolis, Indiana.

All Sonogashira reactions were performed under an atmosphere of nitrogen. Except where indicated, Sonogashira reaction solutions were degassed in the following way prior to the addition of the palladium catalyst: The reaction solution was frozen in liquid N₂, purged with nitrogen 25 times, and allowed to thaw. This freezing, purging, and thawing was then repeated twice more.

Attempted Sonogashira couplings with bromo-sydnones

Attempted Sonogashira coupling of 3-(2-bromophenyl)sydnone (**154**) and phenyl acetylene (deoxygenation protocol not used)

This attempt was made based upon the reported procedures of Krause and Thorand⁸⁷. To a stirred solution of 3-(2-bromophenyl)sydnone (**154**) [0.102 g, 4.23×10^{-4} mol], phenyl acetylene (0.05 g, 0.06 mL, 4.9×10^{-4} mol), and triethylamine (0.73 g, 1.0 mL, 0.007 mol) in dry THF (20 mL) was added bistriphenylphosphine palladium dichloride (0.007 g, 1.0×10^{-5} mol) and the reaction allowed to stir for one hour. Subsequently, copper (I) iodide was added (0.004g, 2.1×10^{-5} mol) and the reaction allowed to stir at room temperature for twenty-four hours. After no sign of reaction by TLC, the solvents were removed *in vacuo* to give a black semi-solid. Column chromatography (silica gel, dichloromethane) gave a tan solid (0.080g, 78%) identical to the starting material by TLC and IR.

Attempted Sonogashira coupling of 3-(3-bromophenyl)sydnone (**156**) and phenyl acetylene (deoxygenation protocol not used)

To a stirred solution of 3-(3-bromophenyl)sydnone (**156**) [0.102 g, 4.23×10^{-4} mol], phenyl acetylene (0.05 g, 0.06 mL, 4.9×10^{-4} mol), and triethylamine (0.73 g, 1.0 mL, 0.007 mol) in dry THF (20 mL) was added bistriphenylphosphine palladium dichloride (0.007 g, 1.0×10^{-5} mol) and the reaction allowed to stir for one hour. Subsequently, copper (I) iodide was added (0.004g, 2.1×10^{-5} mol) and the reaction allowed to stir at room temperature for eighteen hours, whereupon no sign of reaction

was evident by TLC. The reaction was then heated at reflux for twenty-four hours, and after seeing no evidence of reaction by TLC, the reaction was not pursued further.

Attempted Sonogashira coupling of 3-(2-bromophenyl)sydnone (**154**) and phenyl acetylene including the deoxygenation protocol

A stirred solution of 3-(2-bromophenyl)sydnone (**154**) [0.100 g, 4.15×10^{-4} mol], phenyl acetylene (0.08 g, 0.1 mL, 8.3×10^{-4} mol), and triethylamine (0.73 g, 1.0 mL, 0.007 mol) in dry THF (20 mL) was deoxygenated by freezing/purging/thawing three times. Subsequently, bistriphenylphosphine palladium dichloride (0.01 g, 1.4×10^{-5} mol) was added and the reaction allowed to stir for twenty minutes. Subsequently, copper (I) iodide (0.01g, 5.3×10^{-5} mol) was added and the reaction allowed to stir at room temperature for two hours. After no sign of reaction by TLC, the solution was heated to reflux for two hours. Subsequently, the reaction was cooled, and the solvent removed *in vacuo* to afford a black oil. Column chromatography (silica gel, dichloromethane) gave a tan solid (0.090 g, 90%) identical to the starting material by TLC and IR.

Synthesis and manipulations of sydnone starting materials

Synthesis of N-phenylsydnone (**13**)

N-phenylsydnone was synthesized from commercially available N-phenylglycine according to reported procedures⁸⁸.

Synthesis of 3-(2-iodophenyl)sydnone (176)

The title compound was prepared *via* a literature method⁹³: 2-iodoaniline, sodium acetate, and ethyl bromoacetate were reacted to afford the ester. Hydrolysis by means of sodium hydroxide afforded the glycine, and sodium nitrite with hydrochloric acid was used to accomplish nitrosation. Cyclization of the resultant N-nitroso-N-(2-iodophenyl)glycine with trifluoroacetic anhydride afforded the title sydnone in 10% overall yield after column chromatography (silica gel, dichloromethane), identical to an authentic sample by TLC, IR, and melting point.

Synthesis of 4-iodo-3-(2-iodophenyl)sydnone (178)

To a stirred solution of 3-phenylsydnone (**13**) [3.00 g, 0.0185mol] in dry THF (300 mL) under an atmosphere of nitrogen at -40 to -50 °C were added three equivalents of n-butyl lithium (1.4 M cyclohexane, 39.6 mL, 0.0555 mol) and the solution was allowed to stir for 30 minutes. Excess iodine (14.550 g, 0.0574 mol) then was added and the reaction allowed to stir for one hour. Subsequently, the reaction was quenched at low temperature with water (100 mL), extracted with dichloromethane (3x100 mL) and the solvent removed *in vacuo* (the di-iodo sydnone must be in a non-polar solvent otherwise it will react with the sodium sulfite during washing). The resulting violet oil was dissolved in dichloromethane (200 mL) and washed with a saturated, aqueous solution of sodium sulfite (100 mL), using vigorous magnetic stirring, until the violet iodine color had lessened appreciably. The solution was extracted with dichloromethane (3x 100mL), dried (MgSO₄), and the solvent removed *in vacuo* to yield a yellow solid. This solid was

transferred to a vacuum funnel and washed with a 3:1 mixture of ethyl ether / hexanes (5-10 mL) affording the title compound as a tan solid (7.08 g, 92%) identical to authentic product (TLC, IR, m.p.). Optional recrystallization from hot 90 : 10 ethanol / water afforded light tan to colorless crystals (6.35 g, 83%).

Reaction of 4-iodo-3-(2-iodophenyl)sydnone (**178**) with sodium borohydride

In a small beaker, 4-iodo-3-(2-iodophenyl)sydnone (**178**) [0.150 g, 3.62×10^{-4} mol] is suspended in methanol (2 mL). Sodium borohydride (0.15 g, 0.004 mol) was added in three portions over fifteen minutes. The reaction solvents were allowed to evaporate in the fume hood followed by the addition of water (3mL). The resulting fluffy, white precipitate was filtered to give N-phenylsydnone (**13**) (0.043 g, 73%), identical to authentic material (TLC, IR, m.p.).

Reaction of 4-iodo-3-(2-iodophenyl)sydnone (**178**) with sodium sulfite

4-Iodo-3-(2-iodophenyl)sydnone (**178**) [4.002g g, 0.0097 mol] was suspended in methanol (100 mL). Aqueous sodium sulfite (10.0 g, 0.08 mol, in 40 mL water) was added and the reaction allowed to stir for two hours. Subsequently, the reaction was poured into a beaker and the solvents were allowed to evaporate in the fume hood overnight. Water was added to the beaker (100 mL) and the water-soluble materials allowed to dissolve. The resulting light-orange precipitate was filtered to give 3-(2-iodophenyl)sydnone (**176**) (2.54 g, 91%), identical to authentic material (TLC, IR, m.p.). Optional recrystallization from dichloromethane / hexanes afforded light orange crystals (1.53 g 55%).

One-pot synthesis of 3-(2-iodophenyl)sydnone (176)

To a stirred solution of 3-phenylsydnone (**13**) [3.00 g, 0.0185 mol] in dry THF (300 mL) under an atmosphere of nitrogen at -40 to -50 °C were added three equivalents of n-butyl lithium (1.4 M cyclohexane, 39.6 mL, 0.0555 mol) and the solution was allowed to stir for 30 minutes. Excess iodine (14.550 g, 0.0574 mol) then was added and the reaction allowed to stir for one hour. Subsequently, the reaction was quenched at low temperature with aqueous Na₂SO₃ [20.00 g, 0.16 mol in H₂O (600 mL)]. The solution was allowed to reduce in volume overnight with mild stirring and the title compound was isolated as an orange solid (4.27 g, 80%) by vacuum-filtration, washing with distilled water (50 mL), and drying on the funnel overnight. Optional recrystallization from dichloromethane / hexanes afforded the title compound as light-orange needles (2.6 g, 50%), m.p. 81-82 °C, identical (TLC, IR, m.p.) to an authentic sample previously made in our laboratory.

Synthesis of *ortho*-alkynyl sydnones

Synthesis of 3-(2-(phenylethynyl)phenyl)sydnone (177)

3-(2-Iodophenyl)sydnone (**176**) [3.20 g, 0.011 mol], phenyl acetylene (1.70 g, 1.8 mL, 0.017 mol) and triethylamine (5.62 g, 7.7 mL, 0.055 mol) were dissolved in dry THF (160 mL) and the solution was deoxygenated. Bistriphenylphosphinepalladium dichloride (0.40 g, 5.5×10^{-4} mol) was added and the reaction was allowed to stir for 10 minutes, followed by the addition of copper (I) iodide (0.20 g, 0.0011 mol). The solution

was heated at 50 °C for four hours, whereupon the reaction was allowed to cool, poured into a petri dish, and the solvents allowed to evaporate in the fume hood overnight. Column chromatography of the resulting black semi-solid (silica gel, 10% hexanes in dichloromethane increasing polarity to dichloromethane) gave a golden oil that solidified upon standing (3.00g, 103%). Recrystallization from dichloromethane / hexanes gave the title compound as colorless plates (2.31 g, 80%), m.p. 74-75 °C.

I.R. (KBr): 3130 (sydnone C-H), 3075, 2224 (C≡C), 1750 (C=O), 1502, 1435, 939, 761, 687 cm⁻¹.

¹H-NMR (CDCl₃): 7.8-7.3 (m, 9H), 6.9 (s, sydnone H) ppm.

¹³C-NMR (CDCl₃): 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.

Elemental analysis calculated for C₁₆H₁₀N₂O₂ (262.28): C: 73.27, H: 3.84, N: 10.68. Found C: 73.12, H: 4.00, N: 10.66.

Synthesis of 3-(2-(4-methylphenylethynyl)phenyl)sydnone (179)

3-(2-Iodophenyl)sydnone (**176**) [1.50 g, 0.0052 mol], 4-ethynyltoluene (0.91 g, 1.0 mL, 0.008 mol) and triethylamine (2.6 g, 3.6 mL, 0.026 mol) were dissolved in dry THF (75 mL) and the solution was deoxygenated. Bistriphenylphosphinepalladium dichloride (0.18 g, 2.6x10⁻⁴ mol) was added and the reaction was allowed to stir for 10 minutes, followed by the addition of copper (I) iodide (0.10 g, 5.2x10⁻⁴ mol). The solution was heated at 50 °C for five hours, whereupon the reaction was allowed to cool, poured into a petri dish, and the solvents allowed to evaporate in the fume hood overnight. Column chromatography of the resulting black semi-solid (silica gel, 10%

hexanes in dichloromethane increasing polarity to dichloromethane) gave a golden solid (1.29g, 90%). Recrystallization from dichloromethane / hexanes gave the title compound as light yellow microcrystals (1.14 g, 79%), m.p. 100-101 °C.

I.R. (KBr): 3150 (sydnone C-H), 3079, 3030, 2913, 2862, 2215 (C≡C), 1871, 1732, (C=O), 1508, 1466, 1434, 1361, 1221, 1169, 1006, 937, 813, 768, 728, 670, 535, 514 cm⁻¹.

¹H-NMR (CDCl₃): 7.8-7.1 (m, 9H), 6.9 (s, sydnone H), 2.4 (s, 3H) ppm.

¹³C-NMR (CDCl₃): 169.1 (C=O), 140.3, 135.2, 134.1, 132.2, 131.9, 129.6, 129.5, 125.0, 119.5, 118.4, 98.3, 97.5 (sydnone C-4), 82.1, 21.9 (CH₃) ppm.

Elemental analysis calculated for C₁₇H₁₂N₂O₂ (276.29): C: 73.90, H: 4.38, N: 10.14. Found C: 73.64, H: 4.37, N: 10.07.

Synthesis of 3-(2-(4-pentylphenylethynyl)phenyl)sydnone (**180**)

3-(2-Iodophenyl)sydnone (**176**) [1.01 g, 0.0035 mol], 1-ethynyl-4-pentylbenzene (0.89 g, 1.0 mL, 0.005 mol) and triethylamine (1.8 g, 2.5 mL, 0.017 mol) were dissolved in dry THF (50 mL) and the solution was deoxygenated.

Bis(triphenylphosphine)palladium dichloride (0.12 g, 1.7x10⁻⁴ mol) was added and the reaction was allowed to stir for 10 minutes, followed by the addition of copper (I) iodide (0.07 g, 53.5x10⁻⁴ mol). The solution was heated at 50 °C for four hours, whereupon the reaction was allowed to cool, poured into a petri dish, and the solvents allowed to evaporate in the fume hood overnight. Column chromatography of the resulting black semi-solid (silica gel, 10% hexanes in dichloromethane increasing polarity to dichloromethane, then 1% tetrahydrofuran in dichloromethane) gave a golden solid

(1.16g, 99%). Recrystallization from ethyl ether / hexanes gave the title compound as yellow flakes (1.01 g, 86%), m.p. 49-50 °C.

I.R. (KBr): 3150 (sydnone C-H), 2955, 2926, 2855, 2220 (C≡C), 1735, (C=O), 1508, 1465, 1435, 1350, 1219, 1167, 1006, 934, 831, 771, 728, 564, 465, 419 cm⁻¹.

¹H-NMR (CDCl₃): 7.8-7.2 (m, 8H), 6.9 (s, sydnone H), 2.63-2.58 (t, 2H), 1.63-1.29 (m, 9H) ppm.

¹³C-NMR (CDCl₃): 169.1 (C=O), 145.4, 135.2, 134.1, 132.2, 131.9, 129.5, 129.0, 125.0, 119.5, 118.6, 98.4, 97.5 (sydnone C-4), 82.1, 36.2, 31.6, 31.1, 22.7, 14.3 ppm.

Elemental analysis calculated for C₂₁H₂₀N₂O₂ (332.40): C: 75.88, H: 6.06, N: 8.43. Found C: 75.98, H: 6.36, N: 8.55.

Synthesis of 3-(2-(trimethylsilylethynyl)phenyl)sydnone (**160**)

3-(2-Iodophenyl)sydnone (**176**) [3.20 g, 0.011 mol], trimethylsilyl acetylene (1.67 g, 2.4 mL, 0.017 mol) and triethylamine (5.57 g, 7.6 mL, 0.055 mol) were dissolved in dry THF (160 mL) and the solution was deoxygenated. Bistriphenylphosphinepalladium dichloride (0.40 g, 5.5x10⁻⁴ mol) was added and the reaction was allowed to stir for 10 minutes, followed by the addition of copper (I) iodide (0.20 g, 0.0011 mol). The solution was heated at 50 °C overnight, whereupon the reaction was allowed to cool, poured into water (100 mL), extracted with dichloromethane (3x100 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo* to yield a dark brown, oily solid. Column chromatography (silica gel, 10% hexanes in dichloromethane) gave a light brown, semi-solid. Recrystallization from dichloromethane / hexanes gave the title compound as tan needles (1.89 g, 66%), m.p. 79-80 °C.

I.R. (KBr): 3167 (sydnone C-H), 3072, 2961, 2902, 2157, 1776 and 1745 (C=O), 1494, 1434, 1382, 1358, 1253, 1213, 1173, 1114, 1008, 946, 851 and 759 (trimethylsilyl stretches), 721, 645, 548 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.68-7.65 (d, 1H), 7.60-7.51 (m, 3H), 6.80 (s, sydnone H), 0.32 (s, $\text{Si}(\underline{\text{C}}\text{H}_3)_3$) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 168.6 (C=O), 135.6, 134.2, 131.8, 129.7, 124.6, 118.8, 104.6 (sydnone C-4), 97.3, 97.2, -0.6 ($\text{Si}(\underline{\text{C}}\text{H}_3)_3$) ppm.

Elemental analysis calculated for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2\text{Si}$ (258.35): C: 60.44, H: 5.46, N: 10.84. Found C: 60.40, H: 5.41, N: 10.76.

Synthesis of 3-(2-ethynylphenyl)sydnone (**161**) using potassium carbonate

3-(2-(Trimethylsilylethynyl)phenyl)sydnone (**160**) [$0.110 \text{ g}, 4.26 \times 10^{-4} \text{ mol}$] and potassium carbonate (0.160 g, 0.001 mol) were suspended in a mixture of methanol / dichloromethane (3 : 1, 15 ml). After three hours, the reaction was poured into water (15 mL), extracted with dichloromethane (2x50 mL), dried over anhydrous MgSO_4 , and the solvent removed *in vacuo* to yield a brown solid (0.079 g, 99%). Column chromatography (silica gel, dichloromethane) gave a tan solid (0.057 g, 71%). Recrystallization from dichloromethane / hexanes gave the title compound as fine, tan needles (0.039 g, 49%), m.p. 133-134 $^\circ\text{C}$.

I.R. (KBr): 3242 (terminal acetylene C-H), 3113 (sydnone C-H), 3068, 2105, 1894, 1751 (C=O), 1602, 1499, 1435, 1357, 1292, 1230, 1201, 1172, 1122, 1082, 1008, 949, 857, 769, 724, 662, 650, 526 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.79-7.76 (m, 1H), 7.69-7.63 (m, 3H), 6.86 (s, sydnone H), 3.43 (s, terminal acetylene H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 168.8 (C=O), 135.7, 134.9, 132.0, 130.3, 125.0, 117.8, 97.5 (sydnone C-4), 85.8, 76.8 ppm.

Elemental analysis calculated for $\text{C}_{10}\text{H}_6\text{N}_2\text{O}_2$ (186.16): C: 64.52, H: 3.25, N: 15.05. Found C: 64.14, H: 3.24, N: 14.76.

Synthesis of 3-(2-ethynylphenyl)sydnone (**161**) using tetrabutylammonium fluoride

3-(2-(Trimethylsilylethynyl)phenyl)sydnone (**160**) [0.109 g , $4.24 \times 10^{-4}\text{ mol}$] was dissolved in THF (10 mL) and tetrabutylammonium fluoride (0.5 ml of a 1.0 M solution in THF, $4.66 \times 10^{-4}\text{ mol}$) was added dropwise. After fifteen minutes, the reaction was poured into water (10 mL), extracted with dichloromethane ($2 \times 50\text{ mL}$), dried over anhydrous MgSO_4 , and the solvent removed *in vacuo* to yield a black semi-solid. Column chromatography (silica gel, dichloromethane) gave a tan solid (0.05 g, 63%) identical to authentic 3-(2-ethynylphenyl)sydnone (**161**) (TLC, IR, m.p.).

Coupling of 3-(2-ethynylphenyl)sydnone (**160**) with iodobenzene

3-(2-Ethynylphenyl)sydnone (**161**) [0.201 g , 0.001 mol], iodobenzene (0.55 g, 0.3 mL, 0.003 mol) and triethylamine (0.50 g, 0.7 mL, 0.005 mol) were dissolved in dry THF (15 mL) and the solution was deoxygenated. Bistriphenylphosphinepalladium dichloride (0.04 g, $5.4 \times 10^{-5}\text{ mol}$) was added and the reaction was allowed to stir for 10 minutes, followed by the addition of copper (I) iodide (0.02 g, $1.0 \times 10^{-4}\text{ mol}$). The solution was heated at $50\text{ }^\circ\text{C}$ overnight, whereupon the reaction was allowed to cool, poured into water

(20 mL), extracted with dichloromethane (3x50 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo* to yield a dark red oil. Column chromatography (silica gel, dichloromethane) gave a red-brown solid (0.215 g, 76%) recrystallized from dichloromethane/hexanes to give tan plates (0.146 g, 52%) identical to authentic 3-(2-(phenylethynyl)phenyl)sydnone (TLC, IR, m.p.)

General procedure for the one-pot desilylation of 3-(2-(trimethylsilylethynyl)-phenyl)sydnone (161) and coupling with substituted aryl iodides to give 172, 177, 181-184

Tetrabutylammonium fluoride (1.1 mL, 0.0011 mol, 1.0 M in THF) was added dropwise to a solution of 3-(2-(trimethylsilylethynyl)phenyl)sydnone (**160**) [0.258 g, 0.001 mol] dissolved in dry THF (15 mL). Ten minutes after this addition, triethylamine (0.506 g, 0.7 mL, 0.005 mol), and the aryl iodide (0.0011 mol) were added. The reaction was deoxygenated, then bistriphenylphosphinepalladium dichloride (0.040 g, 5×10^{-5} mol) was added and the reaction allowed to stir for 10 minutes, followed by the addition of copper (I) iodide (0.020 g, 1×10^{-4} mol). The solution was stirred at room temperature for a further one to four hours whereupon it was poured into water (20 mL), extracted with dichloromethane (3x50 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo*. Column chromatography followed by recrystallization gave **172, 177, 181-184**.

3-(2-(Phenylethynyl)phenyl)sydnone (177)

Column chromatography (silica gel, dichloromethane) gave a tan solid (0.206 g, 81%). Recrystallization from dichloromethane / hexanes gave the title compound as white plates (0.171 g, 67%), identical (TLC, IR, m.p.) to an authentic sample.

3-(2-(4-Aminophenylethynyl)phenyl)sydnone (181)

Column chromatography (silica gel, dichloromethane to 4% ethyl acetate in dichloromethane) gave a yellow solid (0.16 g, 60%). Recrystallization from methanol / water gave the title compound as yellow needles, (0.076 g, 27%), m.p. 126-127 °C.

I.R. (KBr): 3482, 3347, 3209, 3157 (sydnone C-H), 3062, 3034, 2209, 1737 (C=O), 1625, 1596, 1516, 1471, 1430, 1303, 1146, 943, 830, 761, 696, 524 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.4-7.8 (m, 4H), 7.1-7.3 (d, 2H), 6.9 (s, sydnone H), 6.5-6.7 (d, 2H), 5.3 (s), 3.4 (s) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 169.2 (C=O), 148.2, 134.9, 133.7, 132.1, 128.8, 124.9, 120.0, 114.9, 110.4, 97.6 (sydnone C-4), 99.4, 81.1 ppm.

Elemental analysis calculated for $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_2$ (277.28): C: 69.31, H: 4.00, N: 15.15. Found C: 69.13, H: 4.21, N: 14.95.

3-(2-(4-Bromophenylethynyl)phenyl)sydnone (172)

Column chromatography (silica gel, 10% hexanes in dichloromethane) gave a tan solid (0.259 g, 76%). Recrystallization from dichloromethane / hexanes gave the title compound as tan needles (0.244 g, 72%), m.p. 110-111 °C.

I.R. (KBr): 3117 (sydnone C-H), 3038, 2216, 1753(C=O), 1502, 1433, 1354, 1223, 1173, 1109, 1068, 1007, 943, 824, 765, 725, 702, 653, 549, 470 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.73-7.80 (d, 1H), 7.54-7.69 (m, 3H), 7.45-4.52 (d, 4H), 6.86 (s, sydnone H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 169.0 (C=O), 135.4, 134.2, 133.4, 132.3, 132.2, 130.0, 125.2, 124.4, 120.1, 119.0, 97.4 (sydnone C-4), 96.6, 83.6 ppm.

Elemental analysis calculated for $\text{C}_{16}\text{H}_9\text{BrN}_2\text{O}_2$ (341.16): C: 56.33 H: 2.66, N: 8.21. Found C: 56.17, H: 2.84, N: 8.17.

3-(2-(4-Nitrophenylethynyl)phenyl)sydnone (182)

Column chromatography (silica gel, 30% hexanes in dichloromethane to dichloromethane) gave a tan solid (0.231 g, 75%). Recrystallization from dichloromethane / hexanes gave the title compound as a colorless, amorphous solid (0.167 g, 54%), m.p. 158-159 $^\circ\text{C}$.

I.R. (KBr): 3168 (sydnone C-H), 3105, 3076, 2926, 2437, 1787 and 1753 (C=O), 1591, 1516, 1499, 1470, 1426, 1340, 1290, 1213, 1162, 1101, 1068, 1006, 936, 867, 854, 760, 749, 726, 684, 669, 510 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 8.2-8.4 (d, 2H), 7.7-7.9 (d, 1H), 7.4-7.7 (m, 5H), 6.8 (s, sydnone H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 168.9 (C=O), 148.0, 135.6, 134.4, 132.8, 132.5, 130.9, 128.2, 125.3, 124.0, 118.3, 97.4 (sydnone C-4), 94.9, 87.0 ppm.

Elemental analysis calculated for $\text{C}_{16}\text{H}_9\text{N}_3\text{O}_4$ (307.26): C: 62.54 H: 2.95, N: 13.68. Found C: 62.27, H: 3.09, N: 13.39.

3-(2-(4-Acetylphenylethynyl)phenyl)sydnone (183)

Column chromatography (silica gel, dichloromethane to 4% ethyl acetate in dichloromethane) gave a tan solid (0.218 g, 72%). Recrystallization from dichloromethane / hexanes gave the title compound as light tan plates (0.193 g, 63%), m.p. 137-139 °C.

I.R. (KBr): 3334, 3169, 3135 and 3118 (sydnone C-H), 3074, 3042, 3003, 2976, 2922, 2218, 2108, 1921, 1875, 1787 and 1765 and 1736 (sydnone C=O), 1679, 1556, 1471, 1431, 1401, 1358, 1265, 1223, 1167, 1110, 1006, 959, 942, 830, 760, 726, 663, 632, 588, 568, 501, 458 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.96-7.90 (d of t, 2H), 7.82-7.78 (d, 1H), 7.71-7.57 (m, 3H), 7.55-7.49 (d of t, 2H), 6.8 (s, sydnone H), 2.6 (s, 3H, CH_3) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 197.3, 169.9 (sydnone C=O), 137.4, 135.5, 134.3, 132.3, 132.2, 130.3, 128.7, 126.2, 125.2, 118.8, 97.5 (sydnone C-4), 96.5, 85.3, 26.9 ppm.

Elemental analysis calculated for $\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_3$ (304.30): C: 71.05 H: 3.97, N: 9.21. Found C: 70.89, H: 4.07, N: 9.11.

3-(2-(4-Methoxyphenylethynyl)phenyl)sydnone (184)

Column chromatography (silica gel, dichloromethane to 2% ethyl acetate in dichloromethane) gave a yellow-brown solid (0.176 g, 60%). Recrystallization from dichloromethane / hexanes gave the title compound as light yellow plates (0.123 g, 42%), m.p. 146-149 °C.

I.R. (KBr): 3152 (sydnone C-H), 3068, 3040, 2986, 2937, 2920, 2897, 2834, 2538, 2215, 1866, 1780 and 1752 (sydnone C=O), 1596, 1509, 1467, 1427, 1360, 1321, 1288, 1250, 1169, 1146, 1105, 1079, 1025, 938, 827, 770, 726, 673, 570, 535, 491 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.78-7.34 (m, 6H), 6.92-6.82 (m, 3H), 3.82 (s, CH_3) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 169.1 (sydnone C=O), 160.9, 135.1, 133.9, 133.6, 132.1, 129.3, 125.0, 119.7, 114.6, 113.5, 98.3, 97.5 (sydnone C-4), 81.6, 55.6 ppm.

Elemental analysis calculated for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_3$ (292.29): C: 69.86 H: 4.14, N: 9.58. Found C: 69.51, H: 4.17, N: 9.51.

Synthesis of 3-(2-(4-(trimethylsilylethynyl)phenylethynyl)phenyl)sydnone (173)

3-(2-(4-Bromophenylethynyl)phenyl)sydnone (**172**) [0.218 g , $6.38 \times 10^{-4} \text{ mol}$], triethylamine (0.097 g , 0.13 mL , $9.57 \times 10^{-4} \text{ mol}$), and trimethylsilylacetylene (0.09 g , 0.14 mL , $9.57 \times 10^{-4} \text{ mol}$) were dissolved in THF (10 mL) and the solution was deoxygenated. The reaction was heated to $50 \text{ }^\circ\text{C}$. Bistriphenylphosphinepalladium dichloride (0.020 g , $2.8 \times 10^{-5} \text{ mol}$) was added, the reaction was allowed to stir for 10 minutes, and this was followed by the addition of copper(I) iodide (0.002 g , $1.05 \times 10^{-5} \text{ mol}$). The solution was heated at $50 \text{ }^\circ\text{C}$ overnight, whereupon the solvent was removed *in vacuo* to yield a dark oil. Column chromatography (silica gel, 10% hexanes in dichloromethane to dichloromethane) gave a yellow solid (0.192 g , 84%). Recrystallization from boiling dichloromethane gave the title compound as fine white needles (0.101 g , 44%), m.p. $147\text{-}149 \text{ }^\circ\text{C}$.

I.R. (KBr): 3155 (sydnone C-H), 3081, 3040, 2959, 2899, 2220, 2160, 1765 and 1750 (sydnone C=O), 1598, 1509, 1472, 1432, 1404, 1355, 1247, 1163, 1077, 1005, 881 and 847 and 757 (trimethylsilyl stretches), 726, 702, 674, 627, 549, 463 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.78-7.35 (m, 8H), 6.87 (s, sydnone H), 0.26 (s, $\text{Si}(\text{CH}_3)_3$) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 169.0 (C=O), 135.3, 134.2, 132.3, 132.2, 131.7, 129.9, 125.1, 124.6, 121.4, 119.1, 104.4, 97.6, 97.4 (sydnone C-4), 97.3, 84.3, 0.11 ppm.

Elemental analysis calculated for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2\text{Si} \cdot 1/4 \text{H}_2\text{O}$ (362.98): C: 69.48, H: 5.14, N: 7.72. Found C: 69.53, H: 5.19, N: 7.49.

Synthesis of 3-(2-(4-(ethynyl)phenylethynyl)phenyl)sydnone (**170**) using tetrabutylammonium fluoride

Tetrabutylammonium fluoride (0.5 ml, 5.0×10^{-4} mol, 1.0 M in THF) was added dropwise to a solution of 3-(2-(4-(trimethylsilylethynyl)phenylethynyl)phenyl)sydnone (**173**) [0.150 g, 4.18×10^{-4} mol] in THF (15 mL). After ten minutes, the reaction was poured into water (15 mL), extracted with dichloromethane (3x50 mL), dried over anhydrous MgSO_4 , and the solvent removed *in vacuo* to yield a brown solid. Column chromatography (silica gel, dichloromethane) gave a light brown solid (0.56 g, 47%). Recrystallization from boiling dichloromethane gave the title compound as a tan amorphous solid (0.045 g, 38%), m.p. 176 °C (dec).

I.R. (KBr): 3224 (terminal acetylene C-H) 3168 (sydnone C-H), 3068, 3041, 2221, 1774 and 1752 (sydnone C=O), 1503, 1472, 1432, 1354, 1286, 1263, 1219, 1167, 1077, 939, 860, 840, 764, 731, 665 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.8-7.2 (m, 8H), 6.9 (s, sydnone H), 3.2 (s, terminal acetylene H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 169.0 (C=O), 135.4, 134.2, 132.5, 132.3, 131.9, 130.0, 125.1, 123.6, 121.8, 119.1, 97.4 (sydnone C-4), 97.0, 84.3, 83.2, 80.0 ppm.

Elemental analysis calculated for $\text{C}_{18}\text{H}_{10}\text{N}_2\text{O}_2 \cdot 1/4 \text{H}_2\text{O}$ (290.79): C: 74.34, H: 3.64, N: 9.64. Found C: 74.05, H: 3.55, N: 9.50.

Synthesis of 3-(2-(4-(ethynyl)phenylethynyl)phenyl)sydnone (170) using potassium carbonate

3-(2-(4-(trimethylsilylethynyl)phenylethynyl)phenyl)sydnone (**173**) [0.183 g, 5.12×10^{-4} mol] and potassium carbonate (0.200 g, 0.0015 mol) were suspended in a mixture of methanol / dichloromethane (3 : 1, 8 ml). After stirring overnight, the reaction was poured into water (10 mL), extracted with dichloromethane (3x50 mL), dried over anhydrous MgSO_4 , and the solvent removed *in vacuo* to yield a brown solid (0.109 g, 74%). Column chromatography (silica gel, dichloromethane) gave the title compound as a tan solid (0.050 g, 34%), identical to authentic material (TLC, IR, m.p.)

Synthesis of 3-(2-(4-(4-(bromophenyl)ethynyl)phenylethynyl)phenyl)sydnone (174)

3-(2-(4-(Ethynyl)phenylethynyl)phenyl)sydnone (**170**) [0.287 g, 0.001 mol], 1-bromo-4-iodobenzene (0.30 g, 0.00105 mol), and triethylamine (0.506 g, 0.7 mL, 0.005 mol) were dissolved in THF (15 mL). The reaction solution was deoxygenated, bistriphenylphosphine-palladium dichloride (0.040 g, 5×10^{-5} mol) was added and the reaction allowed to stir for 10 minutes, followed by the addition of copper(I) iodide

(0.020 g, 1×10^{-4} mol). The reaction was allowed to stir at room temperature for four hours whereupon it was poured into water (20 mL), extracted with dichloromethane (3x50 mL), dried over anhydrous MgSO_4 , and the solvent removed *in vacuo* to give a dark brown semi-solid. Column chromatography (silica gel, 30% hexanes in dichloromethane) gave a yellow-orange solid (0.347 g, 79%). Recrystallization from boiling dichloromethane gave the title compound as yellow plates (0.187 g, 42%), m.p. 202-204 °C.

I.R. (KBr): 3116 (sydnone C-H), 2216, 2108, 1754 (sydnone C=O), 1510, 1433, 1357, 1225, 1172, 1069, 1008, 824, 829, 765, 726, 520 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.82-7.36 (m, 12H), 6.89 (s, sydnone H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 169.0 (C=O), 135.4, 134.2, 133.3, 132.3, 132.0, 131.9, 130.0, 125.1, 124.5, 123.2, 122.0, 121.4, 119.1, 97.4 (sydnone C-4), 97.3, 91.2, 90.1, 84.3 ppm.

Elemental analysis calculated for $\text{C}_{24}\text{H}_{13}\text{BrN}_2\text{O}_2$ (441.28) C: 65.32, H: 2.97, N: 6.35. Found C: 65.11, H: 3.05, N: 6.25.

Two reaction, one pot synthesis of 3-(2-(4-(4-ethynyl)phenylethynyl)phenylethynyl)phenyl)-sydnone (171)

3-(2-(4-(4-(Bromophenyl)ethynyl)phenylethynyl)phenyl)sydnone (**174**) [1.03 g, 0.002 mol], trimethylsilyl acetylene (0.59 g, 0.9 mL, 0.006 mol), and triethylamine (1.01 g, 1.4 mL, 0.01 mol) were dissolved in THF (60 mL) and the reaction solution was deoxygenated. The reaction was heated to 50 °C. Bistriphenylphosphinepalladium dichloride (0.080 g, 1.0×10^{-4} mol) was added, the reaction was allowed to stir for 10 minutes, and this was followed by the addition of copper(I) iodide (0.040 g, 2.0×10^{-4}

mol). The solution was maintained at 50 °C overnight whereupon it was allowed to cool to room temperature. Potassium carbonate was added (1.27 g, 0.009 mol) and methanol (30 mL). The reaction was allowed to stir overnight whereupon it was poured into water (100 mL), extracted with dichloromethane (3x100 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo* to yield a dark brown solid. Column chromatography (silica gel, 30% hexanes in dichloromethane to dichloromethane) gave a yellow solid (0.630 g, 81%). Recrystallization from boiling dichloromethane gave the title compound as a yellow, powdery solid (0.280 g, 36%), m.p. 220 °C (chars; does not melt up to 400 °C).

I.R. (KBr): 3293 (terminal acetylene C-H) 3115 (sydnone C-H), 3038, 2218, 2106, 1876, 1756 (sydnone C=O), 1600, 1515, 1433, 1357, 1224, 1171, 1104, 1006, 941, 838, 763, 544 cm⁻¹.

¹H-NMR (CDCl₃): 7.9-7.3 (m, 11H), 6.9 (s, sydnone H), 3.2 (s, terminal acetylene H) ppm.

¹³C-NMR (CDCl₃): 169.1 (C=O), 135.4, 134.2, 132.4, 132.3, 132.0, 132.0, 131.8, 129.9, 125.1, 124.5, 123.5, 122.5, 121.4, 119.1, 97.5 (sydnone C-4), 97.3, 91.7, 90.9, 84.3, 83.4, 79.4 (terminal acetylene carbon) ppm.

Elemental analysis calculated for C₂₆H₁₄N₂O₂ • 1/4 H₂O (390.91): C: 79.88, H: 3.74, N: 7.16. Found C: 79.86, H: 3.80, N: 6.93.

Three reaction, one pot synthesis of 3-(2-(4-bromophenylethynyl)phenyl)sydnone (172) from 3-(2-iodophenyl)sydnone (176)

3-(2-Iodophenyl)sydnone (**176**) [3.20 g, 0.011 mol], trimethylsilyl acetylene (1.67 g, 2.4 mL, 0.017 mol) and triethylamine (5.57 g, 7.6 mL, 0.055 mol) were dissolved in dry THF (160 mL) and the solution was deoxygenated. Bistriphenylphosphinepalladium dichloride (0.40 g, 5.5×10^{-4} mol) was added and the reaction allowed to stir for 10 minutes, followed by the addition of copper(I) iodide (0.20 g, 0.0011 mol). The solution was heated at 50 °C overnight, whereupon the reaction was allowed to cool. Tetrabutylammonium fluoride (1.7 mL, 0.0017 mol, 1.0 M in THF) was added dropwise and the reaction was allowed to stir for 10 minutes. 1-Bromo-4-iodobenzene (3.31 g, 0.012 mol) was added, and the reaction allowed to stir at room temperature for four hours, whereupon it was poured into water (100 mL), extracted with dichloromethane (3x100 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo* to yield a black, semi-solid. Column chromatography (silica gel, 30% hexanes in dichloromethane to dichloromethane) gave the title compound as a golden-brown solid (2.86 g, 76%), identical (TLC, IR) to an authentic sample.

Three reaction, one pot synthesis of 3-(2-(4-(4-(bromophenyl)ethynyl)-phenylethynyl)phenyl)-sydnone (174) from 3-(2-(4-bromophenylethynyl)phenyl)sydnone (172)

3-(2-(4-Bromophenylethynyl)phenyl)sydnone (**172**) [2.62 g, 0.008 mol], trimethylsilyl acetylene (2.26 g, 3.3 mL, 0.023 mol) and triethylamine (3.88 g, 5.3 mL, 0.038 mol), were dissolved in THF (120 mL), and the solution was deoxygenated.

Bistriphenylphosphine-palladium dichloride (0.270 g, 3.8×10^{-4} mol) was added, the reaction was allowed to stir for 10 minutes, and this was followed by the addition of copper(I) iodide (0.150 g, 7.7×10^{-4} mol). The solution was heated at 50 °C overnight whereupon it was allowed to cool to room temperature. Tetrabutylammonium fluoride (25 mL, 0.025 mol, 1.0M in THF) was added dropwise, and after one hour, 1-bromo-4-iodobenzene (2.28 g, 0.008 mol) was added. The reaction was allowed to stir at room temperature overnight whereupon it was poured into water (100 mL), extracted with dichloromethane (3x100 mL), dried over anhydrous MgSO_4 , and the solvent removed *in vacuo* to yield a black tar. Column chromatography (silica gel, 30% hexanes in dichloromethane) gave the title compound as a tan-yellow solid (1.81 g, 51%), identical (TLC, IR) to an authentic sample.

Three reaction, one pot synthesis of 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone (184) from 3-(2-iodophenyl)sydnone (176)

3-(2-Iodophenyl)sydnone (**176**) [3.20 g, 0.011 mol], trimethylsilyl acetylene (1.67 g, 2.4 mL, 0.017 mol) and triethylamine (5.57 g, 7.6 mL, 0.055 mol) were dissolved in dry THF (160 mL) and the solution was deoxygenated. Bistriphenylphosphinepalladium dichloride (0.40 g, 5.5×10^{-4} mol) was added and the reaction allowed to stir for 10 minutes, followed by the addition of copper(I) iodide (0.20 g, 0.0011 mol). The solution was heated at 50 °C overnight, whereupon the reaction was allowed to cool. Tetrabutylammonium fluoride (1.7 mL, 0.0017 mol, 1.0 M in THF) was added dropwise and the reaction was allowed to stir for 10 minutes. 4-Iodoanisole (2.70 g, 0.012 mol) was added, and the reaction allowed to stir at room temperature for five hours,

whereupon it was poured into water (100 mL), extracted with dichloromethane (4x100 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo* to yield a black, semi-solid. Column chromatography (silica gel, 10% hexanes in dichloromethane to 1% THF in dichloromethane) gave the title compound as a tan solid (2.22 g, 68%). Recrystallization from dichloromethane/hexanes afforded yellow crystals (1.82 g, 57%) identical (TLC, IR, m.p.) to an authentic sample.

Three reaction, one pot synthesis of 3-(2-(4-chlorophenylethynyl)phenyl)sydnone (185) from 3-(2-iodophenyl)sydnone (176)

3-(2-Iodophenyl)sydnone (**176**) [1.50 g, 0.005 mol], trimethylsilyl acetylene (0.77 g, 1.1 mL, 0.008 mol) and triethylamine (2.63 g, 3.6 mL, 0.026 mol) were dissolved in dry THF (75 mL) and the solution was deoxygenated. Bistriphenylphosphinepalladium dichloride (0.18 g, 2.6×10^{-4} mol) was added and the reaction allowed to stir for 10 minutes, followed by the addition of copper(I) iodide (0.10 g, 5.2×10^{-4} mol). The solution was heated at 50 °C overnight, whereupon the reaction was allowed to cool. Tetrabutylammonium fluoride (8.0 mL, 0.008 mol, 1.0 M in THF) was added dropwise and the reaction was allowed to stir for 10 minutes. 1-Chloro-4-iodobenzene (1.31 g, 0.0055 mol) was added, and the reaction allowed to stir at room temperature for five hours, whereupon it was poured into water (50 mL), extracted with dichloromethane (3x100 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo* to yield a black, semi-solid. Column chromatography (silica gel, 10% hexanes in dichloromethane to 1% THF in dichloromethane) gave the title compound as a tan solid (1.12 g, 76%).

Recrystallization from dichloromethane/hexanes afforded colorless microcrystals (0.96 g, 65%), m.p. 110-112 °C.

I.R. (KBr): 3124 (sydnone C-H), 3073, 2223 (C≡C), 1748 (sydnone C=O), 1502, 1485, 1434, 1397, 1352, 1222, 1166, 1088, 1013, 936, 836, 766, 727, 658, 569, 512, 467 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.78-7.58 (m, 4H), 7.39-7.30 (m, 4H) 6.86 (s, sydnone H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 169.0 (C=O), 136.1, 135.4, 134.2, 133.2, 132.3, 130.0, 129.3, 125.1, 120.0, 119.1, 97.4 (sydnone C-4), 96.5, 83.5 ppm.

Elemental analysis calculated for $\text{C}_{16}\text{H}_9\text{ClN}_2\text{O}_2$ (296.71): C: 64.77, H: 3.06, N: 9.44. Found C: 64.87, H: 3.08, N: 9.23.

Synthesis of Pyrazoles

Synthesis of 3,4-dicarbomethoxy-1-(2-bromophenyl-ethynyl)phenylpyrazole (186)

3-(2-(4-Bromophenylethynyl)phenyl)sydnone (**172**) [0.200 g, 5.87×10^{-4} mol] and dimethylacetylene dicarboxylate (0.43 g, 0.4 mL, 0.003 mol) were suspended in xylenes (10 mL) and heated to 130 °C. After one hour, the reaction was cooled, diluted with dichloromethane (10 mL), poured into a petri dish, and allowed to evaporate to dryness in the fume hood overnight. Column chromatography (silica gel, dichloromethane) of the resulting brown residue afforded the title compound as a light-yellow solid (0.243 g, 94%), that was recrystallized from ethyl ether / hexanes to yield light-yellow needles (0.223 g, 86%), m.p. 118-120 °C.

I.R. (KBr): 3157 (pyrazole C-H), 3083, 2999, 2950, 2919, 1748 and 1726 (carbonyl stretches), 1533, 1469, 1458, 1428, 1379, 1292, 1220, 1161, 1083, 1069, 1009, 822, 759 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 8.7 (s, pyrazole H), 7.8-7.2 (m, 8H), 4.0 (s, CH_3), 3.9 (s, CH_3) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 162.3 (C=O), 162.1 (C=O), 144.6, 139.8, 135.8, 133.6, 133.2, 132.0, 130.0, 129.0, 125.4, 123.7, 121.3, 117.2, 115.6, 94.8, 86.3, 53.0, 52.3 ppm.

Elemental analysis calculated for $\text{C}_{21}\text{H}_{15}\text{BrN}_2\text{O}_4$ (439.26) C: 57.42, H: 3.44, N: 6.38. Found C: 57.19, H: 3.38, N: 6.29.

Synthesis of 3,4-dicarbomethoxy-1-(2-ethynylphenyl)pyrazole (**187**)

3-(2-ethynylphenyl)sydnone (**161**) [$0.101 \text{ g}, 5.46 \times 10^{-4} \text{ mol}$] and dimethylacetylene dicarboxylate (0.38 g, 0.3 mL, 0.003 mol) were suspended in xylenes (10 mL) and heated to 130 °C. After one hour, the reaction was cooled, diluted with dichloromethane (10 mL), poured into a petri dish, and allowed to evaporate to dryness in the fume hood overnight. Column chromatography (silica gel, dichloromethane) of the resulting oily, brown residue afforded a red oil that solidified upon standing (0.142 g, 91%). Recrystallization from dichloromethane / hexanes gave the title compound as orange needles (0.082g, 52%), m.p. 82-83 °C.

I.R. (KBr): 3225 (terminal acetylene H), 3137 (pyrazole C-H), 3005, 2954, 2924, 2104 ($\text{C}\equiv\text{C}$), 1729 and 1707 (carbonyl stretches), 1540, 1462, 1438, 1386, 1287, 1239, 1189, 1160, 1078, 964, 754, 689 cm^{-1} .

Elemental analysis calculated for C₁₅H₁₂N₂O₄ (284.27) C: 63.38, H: 4.25, N: 9.85.
Found C: 63.48, H: 4.19, N: 9.92.

Synthesis of 3,4-dicarbomethoxy-1-(2-(4-(ethynyl)phenylethynyl)phenyl)pyrazole (188)

3-(2-(4-(Ethynyl)phenylethynyl)phenyl)sydnone (**170**) [0.305 g, 0.001 mol] and dimethylacetylene dicarboxylate (0.75 g, 0.7 mL, 0.005 mol) were suspended in xylenes (12 mL) and heated to 130 °C. After one hour, the reaction was cooled, diluted with dichloromethane (10 mL), poured into a petri dish, and allowed to evaporate to dryness in the fume hood overnight. Column chromatography (silica gel, dichloromethane) of the resulting brown residue afforded the title compound as a light-yellow solid (0.313 g, 81%), that was recrystallized from dichloromethane / hexanes to yield light-yellow microcrystals (0.285 g, 73%), m.p. 126-127 °C.

I.R. (KBr): 3270 and 3242 (terminal acetylene H), 3140 (pyrazole C-H), 3080, 3050, 2959, 2924, 1737 (C=O), 1532, 1477, 1460, 1427, 1405, 1381, 1289, 1238, 1220, 1159, 1086, 1055, 960, 832, 760, 682, 547 cm⁻¹.

¹H-NMR (CDCl₃): 8.8 (s, pyrazole H), 7.8-7.4 (m, 8H), 4.0 (s, CH₃), 3.9 (s, CH₃), 3.2 (s, terminal acetylene H) ppm.

¹³C-NMR (CDCl₃): 162.3 (C=O), 162.1 (C=O), 144.6, 139.9, 135.9, 133.7, 132.4, 131.7, 130.0, 129.0, 125.3, 123.0, 122.7, 117.2, 115.6, 95.3, 87.1, 83.3, 79.7 (terminal acetylene carbon), 53.0, 52.3 ppm.

Elemental analysis calculated for C₂₃H₁₆N₂O₄ · ¼ H₂O (388.89) C: 71.03, H: 4.28, N: 7.21. Found C: 70.95, H: 4.15, N: 7.24.

Synthesis of 3,4-dicarbomethoxy-1-2-(4-(4-(4-(ethynyl)phenylethynyl)-phenylethynyl)-phenyl)pyrazole (189)

3-(2-(4-(4-Ethynyl)phenylethynyl)phenylethynyl)phenylsydnone (**171**) [0.170 g, 4.41×10^{-4} mol] and dimethylacetylene dicarboxylate (0.37 g, 0.3 mL, 0.003 mol) were suspended in xylenes (15 mL) and heated to 130 °C. After one hour, the reaction was cooled, diluted with dichloromethane (20 mL), poured into a petri dish, and allowed to evaporate to dryness in the fume hood overnight. Column chromatography (silica gel, dichloromethane) of the resulting brown residue afforded the title compound as a yellow solid (0.140 g, 66%), that was recrystallized from dichloromethane / hexanes to yield orange plates (0.085 g, 40%), m.p. 165-167 °C.

I.R. (KBr): 3240 (terminal acetylene H), 3164 (pyrazole C-H), 2951, 2921, 2848, 1720 and 1711 (carbonyl stretches), 1541, 1513, 1472, 1454, 1433, 1386, 1264, 1239, 1157, 1082, 1038, 955, 876, 834, 795, 763, 688, 579, 520, 448 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 8.788 and 8.786 (singlets, pyrazole H), 7.9-7.3 (m, 13H), 4.0 (s, CH_3), 3.9 (s, CH_3), 3.193 and 3.190 (s, terminal acetylene H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 162.3 (C=O), 162.1 (C=O), 144.7, 139.8, 135.9, 133.6, 132.4, 131.94, 131.89, 131.83, 131.75, 129.1, 129.0, 125.3, 123.9, 123.6, 122.5, 122.3, 117.2, 115.7, 95.5, 91.4, 91.1, 87.2, 83.4, 79.4 (terminal acetylene carbon), 53.0, 52.3 ppm.

Elemental analysis calculated for $\text{C}_{31}\text{H}_{20}\text{N}_2\text{O}_4 \cdot \frac{3}{4} \text{H}_2\text{O}$ (498.02) C: 74.76, H: 4.36, N: 5.63. Found C: 74.98, H: 4.26, N: 5.53.

Efforts at the Synthesis of Fused-Ring Sydnone

Synthesis of 4-bromo-3-(2-(phenylethynyl)phenyl)sydnone (190)

3-(2-(phenylethynyl)phenyl)-sydnone (**177**) [0.170 g, 6.66×10^{-4} mol] was suspended in ethanol (10 mL) and an aqueous solution of sodium bicarbonate added (0.20 g, 0.002 mol in 5 mL water). A solution of bromine (0.43 g, 0.14 mL, 0.002 mol in 5 mL ethanol) was added dropwise over two minutes. After ninety minutes the yellow precipitate was filtered from the reaction, the filtrate poured into water (25 mL), and filtered again. The material from the two filtrations was combined to yield 0.13 g of the title compound (59%). Recrystallization from dichloromethane / hexanes yielded colorless crystals (0.09g, 40%), m.p. 142-143 °C (dec.).

I.R. (KBr): 3082, 3063, 3021, 2222 (acetylene stretch), 1766 and 1741 (C=O), 1497, 1460, 1423, 1331, 1293, 1204, 1158, 1022, 973, 912, 876, 764, 752, 704, 685, 668, 523 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.82-7.68 (d, 1H), 7.67-7.63 (t, 1H), 7.62-7.48 (t, 1H), 7.47-7.44 (d, 1H), 7.42-7.24 (m, 5H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 165.5 (C=O), 134.3, 133.3, 132.5, 131.8, 129.6, 129.3, 128.6, 126.2, 121.4, 121.2, 97.4 (sydnone C-4), 86.1, 81.9 ppm.

Elemental analysis calculated for $\text{C}_{16}\text{H}_9\text{BrN}_2\text{O}_2$ (341.16) C: 56.33, H: 2.66, N: 8.21. Found C: 56.12, H: 2.68, N: 8.05.

Synthesis of 4-bromo-3-(2-(1,2-dibromovinyl)phenyl)sydnone (191)

3-(2-ethynylphenyl)sydnone (**161**) [0.132 g, 7.07×10^{-4} mol] was suspended in ethanol (10 mL) and an aqueous solution of sodium bicarbonate added (0.25 g, 0.003 mol in 5 mL water). A solution of bromine (3.4 g, 1.10 mL, 0.02 mol in 5 mL ethanol) was added dropwise over two minutes. The reaction was allowed to stir overnight and was subsequently poured over a 25 mL volume of crushed ice. The ice was allowed to melt and the volume of the solution to reduce in the fume hood. The resulting white precipitate was filtered to yield 0.2626g of the title compound (87%). Recrystallization from dichloromethane / hexanes yielded tan prisms (0.2434g, 81%) m.p. 159-143 °C (dec.).

I.R. (KBr): 3077, 3057, 1767 (C=O), 1488, 1425, 1336, 1207, 1022, 974, 863, 794, 771, 707, 683, 650, 568, 447 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 7.82-7.52 (m, 4H), 6.91 (s, 1H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 165.7 (C=O), 134.2, 133.1, 132.2, 131.6, 131.2, 127.3, 113.5, 109.6, 86.1 (sydnone C-4) ppm.

Elemental analysis calculated for $\text{C}_{16}\text{H}_5\text{Br}_3\text{N}_2\text{O}_2$ (424.87) C: 28.27, H: 1.19, N: 6.59. Found C: 28.12, H: 1.29, N: 6.43.

Synthesis of 3-(2-(1,2-dibromovinyl)phenyl)sydnone (192)

4-bromo-3-(2-(1,2-dibromovinyl)phenyl)sydnone (**191**) [0.044 g, 1.00×10^{-4} mol] was dissolved in tetrahydrofuran (2.5 mL) and an aqueous solution of sodium sulfite added (0.10 g, 7.9×10^{-4} mol in 2.5 mL water). After stirring for two hours, the reaction was poured into 10 mL of water, extracted with dichloromethane (3x30 mL), dried

(MgSO₄), and the solvent removed *in vacuo* to yield a tan solid (0.019 g, 55%).

Recrystallization from dichloromethane / hexanes afforded colorless needles (0.012 g, 33%), m.p. 124-125 °C.

I.R. (KBr): 3150 (sydnone C-H), 3090, 3058, 1749 (C=O), 1462, 1427, 1355, 1219, 1164, 1073, 936, 832, 773, 724, 678, 650, 435 cm⁻¹.

¹H-NMR (CDCl₃): 7.75-7.55 (m, 4H), 6.94 (s, 1H), 6.63 (s, 1H) ppm.

Synthesis of 3-(2-acetylphenyl)sydnone (193)

To a small beaker containing 3-(2-ethynylphenyl)sydnone (**161**) [0.145 g, 7.81x10⁻⁴ mol] was added concentrated sulfuric acid, dropwise, until all the starting material was dissolved. The solution was then poured over a copious amount of ice, yielding approximately 30 mL total of liquid after the ice melted. The organics were extracted with dichloromethane (3x50 mL), dried (MgSO₄), and the solvent removed *in vacuo* to afford the title compound as a light tan solid (0.130 g, 82%), identical to authentic 3-(2-acetylphenyl)sydnone (TLC, IR, melting point).

Synthesis of 4-phenylsydno[3,4-a]quinoline (194)

Under an atmosphere of nitrogen, 3-(2-(phenylethynyl)phenyl)sydnone (**177**) [0.10 g, 3.81x10⁻⁴ mol], was added to a flask containing concentrated sulfuric acid (2 ml, previously dried over molecular sieves) frozen at -40 °C. The flask was allowed to warm slowly to room temperature whereupon the reaction was poured into a 15 mL volume of crushed ice, extracted with dichloromethane (3x30 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo*. Purification of the resulting brown solid (silica gel,

dichloromethane) gave a light yellow solid, (0.022 g, 22%). Subsequent recrystallization (dichloromethane / hexanes) afforded a sheet of cross-linked needles (0.12 g, 12%), m.p. 250-251 °C.

I.R. (KBr): 3058, 1742 (C=O), 1722, 1560, 1497, 1449, 1312, 1204, 1058, 947, 888, 768, 748, 693, 550 cm^{-1} .

$^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$, 100 °C): 8.7-8.4 (m, 9H) ppm.

$^{13}\text{C-NMR}$ ($\text{d}_6\text{-DMSO}$, 100 °C): 164.1 (C=O), 134.0, 133.5, 132.0, 130.6, 129.9, 129.8, 129.5, 129.1, 128.7, 127.5, 121.9, 116.4 ppm.

Elemental analysis calculated for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2$ (262.26) C: 73.27, H: 3.84, N: 10.68. Found C: 72.99, H: 3.83, N: 10.57.

4-(4-bromophenyl)sydno[3,4-a]quinoline (195)

Under an atmosphere of nitrogen, 3-(2-(4-bromophenylethynyl)phenyl)sydnone (**172**) [0.15 g, 4.40×10^{-4} mol], was added to a flask containing concentrated sulfuric acid (2 ml, previously dried over molecular sieves) cooled to 0 °C. After five minutes, the reaction was poured into a 15 mL volume of crushed ice, extracted with dichloromethane (3x30 mL), dried over anhydrous MgSO_4 , and the solvent removed *in vacuo*. Column chromatography resulting brown solid (silica gel, dichloromethane) afforded a light yellow solid, (0.0256 g, 17%). Recrystallization from dichloromethane / hexanes afforded a sheet of cross-linked needles (0.0164 g, 11%), m.p. 272-274 °C.

I.R. (KBr): 3071, 1748 and 1719 (C=O), 1655, 1589, 1491, 1441, 1396, 1314, 1057, 1013, 939, 888, 827, 811, 749, 658, 555, 496 cm^{-1} .

Elemental analysis calculated for C₁₆H₉BrN₂O₂ (341.16) C: 56.33, H: 2.66, N: 8.21. Found C: 56.05, H: 2.88, N: 7.94.

General procedure for the attempted reaction of 3-(2-(4-methylphenylethynyl)phenyl)-sydnone (179) and 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone (184) with concentrated sulfuric acid

Under an atmosphere of nitrogen, the starting *ortho*-alkynyl sydnone [0.10 g,], was added to a flask containing concentrated sulfuric acid (2 ml, previously dried over molecular sieves) cooled to 0 °C. After five minutes, the reaction was poured into a 15 mL volume of crushed ice, extracted with dichloromethane (3x30 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo*. The resulting semi-solids were subjected to column chromatography (silica gel, dichloromethane) in an attempt to obtain potential products from the complex mixture but to no avail. Accordingly, the reaction was not pursued further.

General procedure for the attempted reaction of 3-(2-(phenylethynyl)phenyl)-sydnone (177) with sulfuric acid in the presence of a solvent

Under an atmosphere of nitrogen, 3-(2-(phenylethynyl)phenyl)sydnone (177) [0.05 g, 1.91x10⁻⁴ mol] was dissolved in a solvent (2 mL) (tetrahydrofuran, ethylene glycol dimethyl ether, acetonitrile, methanol, or dichloromethane). Subsequently, concentrated sulfuric acid (0.25 to 0.5 mL) was added dropwise and the reaction allowed to stir for 15 minutes to 3 hours with monitoring by TLC, and with a further sulfuric acid (0.5 mL) addition in attempt to induce reaction (in all cases but dichloromethane).

Subsequently, the reaction was poured into a 15 mL volume of crushed ice, basified with sodium bicarbonate, extracted with dichloromethane (3x30 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo* to afford impure starting material (verified by TLC) in all cases except dichloromethane which afforded an inseparable mixture which was not pursued further.

General procedure for the attempted reaction of 3-(2-(phenylethynyl)phenyl)sydnone (177) with a strong base to induce cyclization

Under an atmosphere of nitrogen, 3-(2-(phenylethynyl)phenyl)sydnone (**177**) [0.10 g, 3.84x10⁻⁴ mol] was dissolved in anhydrous tetrahydrofuran (20 mL) and cooled to -40 °C. Subsequently, lithium diisopropyl amide or n-butyllithium (5x10⁻⁴ mol, from a solution in THF or hexanes) was added dropwise. The reaction was allowed to warm to room temperature over 2-3 hours, quenched with brine (30 mL), extracted with dichloromethane (3x30 mL), dried (MgSO₄), and the solvent removed *in vacuo* to afford a brown solid that was a complex mixture by TLC and not pursued further.

General procedure for the synthesis of 3-Arylcinnolines (**196**, **200**, and **201**) from the corresponding *ortho*-alkynyl sydnones using trifluoromethanesulfonic acid

Freshly distilled trifluoromethanesulfonic acid (0.5 mL, 0.85 g, 0.006 mol) was added dropwise to a solution of the *ortho*-alkynyl sydnone(**160**) [0.10 g] dissolved in dichloromethane (20 mL). After 15 minutes, the reaction was poured into a 15 mL volume of crushed ice, basified with sodium bicarbonate, extracted with dichloromethane

(3x20 mL), dried over anhydrous MgSO₄, and the solvent removed *in vacuo*. Column chromatography followed by recrystallization afforded **196**, **200**, and **201**.

3-Phenylcinnoline (196)

Column chromatography (silica gel, dichloromethane) gave a yellow solid (0.065 g, 82%). Recrystallization from dichloromethane / hexanes gave the title compound as yellow needles (0.045 g, 57%), m.p. 118-120 °C.

I.R. (KBr): 3062, 3033, 1584, 1497, 1438, 1396, 1328, 1097, 1076, 1018, 959, 909, 870, 799, 767, 747, 698, 547, 467 cm⁻¹.

¹H-NMR (CDCl₃): 8.62-8.52(d), 8.25-8.23 (m), 8.14 (s), 7.86-7.44 (m) ppm (integration not available).

¹³C-NMR (CDCl₃): 153.7, 150.1, 137.2, 131.5, 130.5, 130.1, 129.37, 129.3, 127.35, 127.2, 126.7, 119.0 ppm.

Elemental analysis calculated for C₁₄H₁₀N₂ (206.24) C: 81.53, H: 4.89, N: 13.58. Found C: 81.59, H: 4.97, N: 13.43.

3-(4-Bromophenyl)cinnoline (200)

Column chromatography (silica gel, dichloromethane to 0.5% THF in dichloromethane) gave a yellow solid (0.052 g, 60%). Recrystallization from boiling ethyl ether afforded the title compound as yellow needles (0.042 g, 48%), m.p. 141-142 °C.

I.R. (KBr): 3036, 1621, 1593, 1493, 1439, 1329, 1182, 1108, 1074, 1011, 969, 931, 872, 827, 750, 713, 675, 545 cm⁻¹.

$^1\text{H-NMR}$ (CDCl_3): 8.55-8.52 (d), 8.13-8.10 (m), 7.86-7.65 (m) ppm (integration not available).

$^{13}\text{C-NMR}$ (CDCl_3): 152.5, 150.2, 136.0, 132.5, 131.7, 130.8, 130.1, 129.0, 127.2, 126.6, 124.3, 118.8 ppm.

Elemental analysis calculated for $\text{C}_{14}\text{H}_9\text{BrN}_2$ (285.14) C: 58.97, H: 3.18, N: 9.82.
Found C: 58.68, H: 3.29, N: 9.69.

3-(4-Chlorophenyl)cinnoline (201)

Column chromatography (silica gel, dichloromethane) gave a yellow solid (0.057 g, 69%). Recrystallization from boiling ethyl ether afforded the title compound as yellow needles (0.041 g, 50%), m.p. 142-143 °C.

I.R. (KBr): 3030, 1596, 1492, 1437, 1352, 1327, 1179, 1089, 1011, 967, 930, 826, 753, 713, 541, 461 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 8.54-8.50 (d, 1H), 8.18-8.09 (m, 3H), 7.85-7.75 (m, 2H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 152.5, 150.1, 135.9, 135.6, 131.7, 130.7, 130.1, 129.5, 128.7, 127.2, 126.6, 118.8 ppm.

Elemental analysis calculated for $\text{C}_{14}\text{H}_9\text{ClN}_2$ (240.69) C: 69.86, H: 3.77, N: 11.64.
Found C: 69.91, H: 3.75, N: 11.58.

General procedure for the synthesis of 3-Arylcinnolines (197, 198, and 199) from the corresponding *ortho*-alkynyl sydnones using trifluoroacetic acid

The *ortho*-alkynyl sydnone (**160**) [0.10 g] was dissolved in trifluoroacetic acid (5 mL) and gently heated at reflux for 3-6 hours. Subsequently, the reaction was cooled,

diluted with dichloromethane (10 mL), and poured into a Petri dish to evaporate to dryness in the fume hood. The residue was taken up in dichloromethane (30 mL), washed with saturated sodium bicarbonate solution (3x10 mL), dried (MgSO₄), and the solvent removed *in vacuo*. Column chromatography followed by recrystallization afforded **197**, **198**, and **199**.

3-(4-Methoxyphenyl)cinnoline (**197**)

Column chromatography (silica gel, dichloromethane to 1% THF in dichloromethane) gave a yellow solid (0.073 g, 90%). Recrystallization from dichloromethane / hexanes afforded the title compound as yellow microcrystals (0.041 g, 58%), m.p. 104-105 °C.

I.R. (KBr): 2930, 2855, 1786, 1741, 1604, 1511, 1438, 1327, 1290, 1257, 1172, 1018, 833, 746, 725, 677, 553 cm⁻¹.

¹H-NMR (CDCl₃): 8.52-8.49 (d), 8.22-8.18 (m), 8.05 (s), 7.82-7.62 (m), 7.09-7.20 (d) (all the peaks listed thus far integrate to 9H), 3.88(s, OCH₃) ppm.

¹³C-NMR (CDCl₃): 161.1, 153.4, 149.9, 131.4, 130.1, 130.0, 129.7, 128.8, 127.1, 126.8, 117.9, 114.7, 55.6 (OCH₃) ppm.

Elemental analysis calculated for C₁₅H₁₂N₂O (236.27) C: 76.25, H: 5.12, N: 11.86. Found C: 75.85, H: 5.12, N: 11.72.

3-(4-Methylphenyl)cinnoline (**198**)

Column chromatography (silica gel, dichloromethane to 0.5% THF in dichloromethane) gave a yellow solid (0.079 g, 90%). Recrystallization from

dichloromethane / hexanes afforded the title compound as yellow needles (0.065 g, 70%), m.p. 121-122 °C.

I.R. (KBr): 3050, 3026, 2919, 1916, 1607, 1584, 1512, 1436, 1350, 1323, 1183, 1070, 1011, 963, 917, 822, 740, 676, 551, 459 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 8.54-8.51 (d), 8.16-8.10 (m), 7.84-7.67 (m), 7.36-7.34 (d) (all the peaks listed thus far integrate to 9H), 2.43 (s, CH_3) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 153.7, 150.0, 139.8, 134.3, 131.4, 130.3, 130.0, 127.3, 127.2, 126.38, 118.5, 21.6 (CH_3) ppm.

Elemental analysis calculated for $\text{C}_{15}\text{H}_{12}\text{N}_2$ (220.27) C: 81.79, H: 5.49, N: 12.72. Found C: 81.52, H: 5.60, N: 12.70.

3-(4-Pentylphenyl)cinnoline (199)

Column chromatography (silica gel, dichloromethane to 1% THF in dichloromethane) gave a yellow solid (0.087 g, 77%). Recrystallization from ethanol / water afforded the title compound as orange stars or needles (0.060 g, 67%), m.p. 71-72 °C.

I.R. (KBr): 3046, 2949, 2920, 2849, 1608, 1582, 1557, 1505, 1457, 1434, 1414, 1349, 1321, 1234, 1177, 1117, 1090, 836, 746, 674, 607, 566, 542, 432 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): 8.55-8.52 (d, 1H), 8.19-8.12 (m, 3H), 7.85-7.68 (m, 3H), 7.39-7.36 (d, 2H), 2.72-2.67 (t, 2H), 1.71-1.66 (m, 2H), 1.38-1.34 (m, 2H), 0.94-0.89 (m, 4H) ppm.

$^{13}\text{C-NMR}$ (CDCl_3): 153.8, 150.0, 144.8, 134.6, 131.4, 130.2, 130.1, 129.4, 127.4, 127.2, 126.7, 118.5, 36.0, 31.8, 31.3, 22.8, 14.3 ppm.

Elemental analysis calculated for C₁₅H₂₀N₂ (276.38) C: 82.57, H: 7.29, N: 10.14.

Found C: 82.22, H: 7.21, N: 10.12.

Synthesis of unknown **205** from 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone **184** using phenylselenyl chloride.

Under an atmosphere of nitrogen, 3-(2-(4-methoxyphenylethynyl)phenyl)sydnone (**184**) [0.094 g, 3.21x10⁻⁴ mol] was dissolved in dichloromethane (5 mL). (Optionally, potassium carbonate (0.1 g, 7.6x10⁻⁴ mol) may be added.) Subsequently, phenylselenyl chloride was added (0.09 g, 4.8x10⁻⁴ mol). After four hours of stirring additional phenylselenyl chloride was added (0.04 g, 2.1x10⁻⁴ mol). After allowing the reaction to stir overnight, the reaction was filtered to remove potassium carbonate if included, and the solvents removed *in vacuo*. Column chromatography of the residue (silica gel, 10% hexanes in dichloromethane to 1% THF in dichloromethane) afforded the title compound as a yellow solid (0.032 g, 34% assuming a molecular weight the same as the starting material). Further elution of the column afforded starting material (0.026g). Recrystallization of the title compound from dichloromethane / hexanes afforded yellow needles (0.023 g, 24% assuming a molecular weight the same as the starting material, or 33% converted yield), m.p. 150-152 °C.

I.R. (KBr): 3088, 2966, 1736 (C=O), 1651, 1603, 1514, 1470, 1374, 1287, 1255, 1169, 1153, 1085, 1063, 1032, 874, 836, 791, 755, 739, 565, 533, 438 cm⁻¹.

¹H-NMR (CDCl₃): 9.33 (s, 1H), 9.10-9.07 (d, 1H), 8.66-8.33 (d, 1H), 8.13-8.10 (d, 2H), 7.83-7.77 (t, 1H), 7.57-7.52 (t, 1H), 6.99-6.95 (d, 2H), 3.86 (s, OCH₃) ppm.

^{13}C -NMR (CDCl_3): 171.4, 166.2, 161.4, 148.4, 138.7, 135.25, 130.8, 127.3, 126.5, 125.1, 123.6, 117.9, 113.9, 77.5, 55.6 (OCH_3) ppm.

Elemental analysis calculated for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2 \cdot \frac{1}{2}\text{H}_2\text{O}$ (301.30) C: 67.76, H: 4.36, N: 9.30. Found C: 67.53, H: 4.40, N: 9.80.

Synthesis of unknown **206** from 3-(2-(phenylethynyl)phenyl)sydnone **177** using phenylselenyl chloride.

Under an atmosphere of nitrogen, 3-(2-(phenylethynyl)phenyl)sydnone (**177**) [0.104 g, 3.98×10^{-4} mol] was dissolved in dichloromethane (5 mL). (Optionally, potassium carbonate (0.1 g, 7.6×10^{-4} mol) may be added.) Subsequently, phenylselenyl chloride was added (0.1 g, 6.0×10^{-4} mol). After four hours of stirring additional phenylselenyl chloride was added (0.1 g, 6.0×10^{-4} mol). After allowing the reaction to stir overnight, the reaction was filtered to remove potassium carbonate if included, and the solvents removed *in vacuo*. Column chromatography of the residue (silica gel, 10% hexanes in dichloromethane to 1% THF in dichloromethane) afforded the title compound as a yellow solid (0.047 g, 45% assuming a molecular weight the same as the starting material). Further elution of the column afforded a second unknown product (yellow oil, 0.048 g) followed by starting material (0.025g). Recrystallization of the title compound from dichloromethane / hexanes afforded tan beads (0.018 g, 17% assuming a molecular weight the same as the starting material, or 23% converted yield), m.p. 126-128 °C.

I.R. (KBr): 3128, 3049, 3034, 1966, 1740 (C=O), 1641, 1602, 1468, 1386, 1220, 1063, 1021, 269, 850, 806, 766, 741, 694, 600, 537 cm^{-1} .

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