2010

Routes to Sydno[3,4-a]Quinoxalines

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

By

Erik Dihrkop
B.S., Wright State University, 2008

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Wright State University
WRIGHT STATE UNIVERSITY
SCHOOL OF GRADUATE STUDIES

November 20, 2010

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY
SUPERVISION BY Erik Dihrkop ENTITLED Routes to Sydno[3,4-a]quinoxalines BE
ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
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Abstract

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In the present work, the reactivity of alkyl and aryl sydnoquinoxalines was studied. Using a previously developed method, triphenylphosphine-2-(3-sydnonyl)phenylimide was prepared in a two-step process via a diazotization / azidation process of 3-(2-aminophenyl)sydnone, followed by treatment with triphenylphosphine. Due to the inability to achieve previously reported yields, a new, one-step method using Mitsunobu conditions was employed to synthesize the iminophosphorane in a good yield. A similar, brominated iminophosphorane was synthesized using the same conditions in a good yield. Treatment of both the brominated and non-brominated iminophosphoranes with alkyl and aryl isocyanates or isothiocyanates in an aza-Wittig process, gave the corresponding alkyl or aryl sydnoquinoxalines. Deprotection of 4-(tert-butylamino)sydno[3,4-a]quinoxaline led to a putative amino sydnoquinoxaline. Reactions with certain anhydrides were successful, however, reactions with sulfonyl chlorides and acid chlorides were not per the expectations.

Additionally, the utility of halogenated fused-ring sydrones for Sonogashira coupling reactions has been explored. Coupling reactions of both bromo and iodo sydrones are discussed. Chemoselective reaction of an iodine over a bromine in a dihalogenated sydnoquinoxaline has been studied, and is discussed.
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Introduction

I. The Aza-Wittig Reaction

The aza-Wittig reaction is an efficient method for the production of N=C containing species such as imines. The first aza-Wittig reagent, PhN=PPh₃, was prepared by Staudinger and Meyer in 1919.¹ These aza-Wittig reagents can be termed λ⁵-phosphazenes, iminophosphoranes or phosphine imines.² The aza-Wittig reaction is a useful tool in the synthesis of nitrogen-containing cyclic and acyclic compounds. Generally, the iminophosphorane 1 will react with a carbonyl containing compound 2 to afford the resulting imine 3 along with a trisubstituted phosphine oxide byproduct 4.

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

The reactions of N-phenyltriphenylphosphazene with diphenyl ketene and carbon dioxide were the first reported aza-Wittig reactions.¹ Since then, iminophosphoranes have been shown also to react with a wide variety of carbonyl-containing compounds and compounds containing carbon-sulfur double bonds. Iminophosphoranes can undergo both inter- and intramolecular aza-Wittig reactions to construct C=N bonds. Recently, the intramolecular aza-Wittig reaction has gained interest due to its ability to synthesize nitrogen containing heterocycles.³
Mechanism of the Aza-Wittig Reaction

To understand the mechanism of the aza-Wittig reaction, the intermediates must be isolated. The instability of these intermediates, however, caused their isolation to be problematic.\textsuperscript{2} Kawashima was able to isolate the 1,3,2-$\lambda$\textsuperscript{5}-oxaazaphosphetidine intermediate 6 from the reaction of the N-apical 1,2-$\lambda$\textsuperscript{5}-azaphosphetidine and 1,1,1,3,3,3-hexafluoropropan-2-one.\textsuperscript{4} The formation of the corresponding imine 7 and phosphanoxide 8, revealed that this was indeed the aza-Wittig reaction intermediate.

Palacios and coworkers performed a theoretical-computational study of the reaction between the iminophosphorane 9 and aldehyde 10, indicating the process to be a two-step cycloaddition-cycloreversion mechanism.\textsuperscript{5}
The mechanism shows two transition states 11 and 13, along with a stable intermediate 12. Bond distances calculated in the intermediate 12 agreed with the distances found in the crystal structure of the 1,3,2-\(\lambda^5\)-oxaazaphosphetidine intermediate 6. Due to the second step having a much higher activation energy than the first step of the mechanism, the sterochemical outcome of the whole reaction depends only upon the second cycloreversion step.

**Aza-Wittig Reagents**

The aza-Wittig reagent, or iminophosphorane, is the nitrogen analog of the Wittig reagent. The iminophosphorane contains an N=P bond where the nitrogen atom is the nucleophilic site. Reactivity of the iminophosphorane is determined by the substituents attached to the nitrogen atom. The general reactivity trend is as follows:

\[
R^\prime N=PPh_3 >> ArN=PPh_3 >> R^\prime CON=PPh_3 \sim R^\prime SO_2 N=PPh_3
\]
Substituents attached to the phosphorus atom can also have an effect on the reactivity of the iminophosphorane. The general reactivity trend for substituents attached to the phosphorus atom is as follows:\(^6\)

\[ R’N=P(R’’)_3 > R’N=P(Ar)_3 > R’N=P(OR’’)_3 > R’N=P(OPh)_3 \]

The iminophosphorane can be synthesized using a variety of different conditions. Of these, the Staudinger reaction, Mitsunobu conditions, and the Kirsanov reaction will be discussed.

**The Staudinger Reaction**

Perhaps the most widely used method of synthesizing iminophosphoranes (cf. 16), the Staudinger reaction involves the reaction of an azide (cf. 14) with a trisubstituted phosphine 15, generally triphenylphosphine.\(^1\)

\[
\begin{align*}
\text{RN}_3 + R’_3P & \rightarrow RN=PR’_3 \\
14 & \quad 15 & \quad 16
\end{align*}
\]

The intermediate in this reaction is a phosphine-azide complex 17.\(^7,8\)

Staudinger reported that the iminophosphorane can subsequently be converted into an amine via ammonolysis, however it is more commonly done by hydrolysis.\(^1,8\)

**Mitsunobu Conditions**

The Mitsunobu reaction, named after its creator, forms an ester 20 from a primary alcohol 18 and a carboxylic acid 19 using triphenylphosphine and diethyl azodicarboxylate, with an inversion of stereochemistry on the alcohol.\(^9\)
Under Mitsunobu conditions, using diethyl azodicarboxylate (DEAD) and triphenylphosphine, an amine can be converted to the corresponding iminophosphorane.\textsuperscript{10,11} Wang and Hauske demonstrated this by converting an amine attached to Wang resin 21 to the resulting iminophosphorane 22.\textsuperscript{12}

The advantage to using Mitsunobu conditions rather than the Staudinger reaction comes when there is a need to convert an amine to the iminophosphorane. The Staudinger reaction involves a two-step process where the amine must be converted first to the azide and subsequently to the iminophosphorane, while under Mitsunobu conditions conversion to the iminophosphorane can be achieved in a one-step process.

**The Kirsanov Reaction**

Kirsanov and co-workers originally discovered that when amines 23 react with phosphorus pentachloride 24, two molecules of hydrogen chloride 26 are eliminated to form a monophosphazene 25.\textsuperscript{13,14}
Horner and Oediger later found that the reaction of dihalogenotriphenylphosphoranes \( 27 \) with primary amines \( 28 \) affords iminophosphoranes \( 29 \).\(^{13,15}\)

\[
\begin{align*}
\text{Ph}_3\text{PX}_2 + \text{NH}_2\text{R} & \xrightarrow{\text{NEt}_3} \text{RN=PPPh}_3 + 2\text{NHEt}_3\text{X} \\
27 & \quad 28 & \quad 29 & \quad 30
\end{align*}
\]

The mechanism suggested by Keat and co-workers for the Kirsanov reaction involves first the ionization of the phosphorane \( 31 \) to give a phosphonium ion \( 32 \), which then can act as an electrophile toward the amine \( 33 \).\(^{13}\)

\[
\begin{align*}
\text{Ph}_3\text{PX}_2 & \xleftrightarrow{\text{Ph}_3\text{PX}^+ + \text{X}^-} \\
31 & \quad 32
\end{align*}
\]

Removal of a hydrogen from the nitrogen atom bearing the positive charge on \( 34 \) by \( \text{X}^- \) gives the resulting aminophosphonium salt \( 35 \), which is thought to be the rate determining step.\(^{13,15}\) Dehydrohalogenation results in the formation of the iminophosphorane \( 36 \).

**Aza-Wittig Reactions**

The aza-Wittig reaction can be used to form numerous compounds by both intermolecular and intramolecular processes. Iminophosphoranes react with many carbonyl containing compounds and also compounds containing carbon-sulfur double bonds. In recent years, the formation of heterocycles by the aza-Wittig reaction has been of great interest.
Isocyanate and Isothiocyanate Synthesis

Reaction of the iminophosphorane 37 with carbon dioxide or carbon disulfide will form the corresponding iso(thio)cyanate 38. Due to their ability to act as substrates for the synthesis of many compounds, these iso(thio)cyanates are of great interest.

\[
\begin{array}{ccc}
R-N=PPh_3 & \xrightarrow{X=\text{C}=X} & R-N=C=X \\
37 & \text{X = O, S} & 38
\end{array}
\]

Reactions with Isocyanates and Isothiocyanates

Isocyanates and isothiocyanates can subsequently be used to react with iminophosphoranes in an aza-Wittig process. For example, reaction of the N-phosphoryl alkylphosphazene 39 with phenyl isocyanate forms the functionalized carbodiimide 40.

\[
\begin{array}{ccc}
\text{EtO} & \text{N} \equiv \text{P} & \text{R}_3 \\
\text{EtO} & \text{O} & \text{N} \equiv \text{P} \\
39 & \xrightarrow{\text{O}=\text{C}=\text{NPh}} & \text{EtO} & \text{O} & \text{N} \equiv \text{C} = \text{N} \\
\text{EtO} & \text{O} & \text{Et} & \text{Et} & \text{N} \equiv \text{C} = \text{N} & \text{Ph} \\
\end{array}
\]

The carbodiimide functionality can be used subsequently in tandem aza-Wittig / intramolecular electrocyclic ring closure for the formation of heterocycles.

Heterocyclic Synthesis

Since isocyanates and isothiocyanates are very reactive heterocumulene derivatives, they can be used in the preparation of heterocyclic compounds. Work done by Molina showed that the reaction of iminophosphorane 41 with carbon dioxide or carbon disulfide resulted in the heterocumulenes 42, which underwent subsequent electrocyclic ring closure to generate the carbolines 43.
Due to the instability of the carbodiimides formed by aza-Wittig reactions with isocyanates and isothiocyanates, tandem electrocyclic ring closure is often performed after formation of the carbodiimide intermediate.

Molina and co-workers also reported a method for the preparation of the tricyclic imidazo[1,3]benzodiazepine ring system.\textsuperscript{2,18} The synthesis of these ring systems has drawn interest due to their ability to be potent inhibitors of blood platelet low Km cAMP photodiesterase, as well as their ability to induce aggregation and also exhibit antithrombotic activity.\textsuperscript{18} Reaction of iminophosphorane \textbf{44} with different aromatic isocyanates resulted in the formation of carbodiimide intermediates \textbf{45}. Nucleophilic attack of the NH group on the center carbon of the carbodiimide led to the formation of the imidazo[1,5-c][1,3]benzodiazepines \textbf{46}.
Polymer-bound iminophosphoranes can be used for the synthesis of quinazolines. Quinazolines are of interest due to their potential as histamine H2 antagonists, thymidylate synthase inhibitors, and tumor necrosis factor α inhibitors. The use of solid-phase chemistry is important because of the ease of purification. The polymer-tethered iminophosphoranes 48 were prepared using a modified Kirsanov reaction with polystyryl triphenylphosphine in the presence of dibromotetrachloroethane and triethylamine with the N-substituted benzamide 47. Reaction of the iminophosphorane 48 with various isocyanates formed the carbodiimide intermediates 49. Intramolecular cyclization by nucleophilic attack of the NH group on the center carbon of the carbodiimides gave the desired quinazolines 50 in good yield.
**Removal of Byproduct**

The aza-Wittig reaction byproduct is a tri-substituted phosphine oxide, generally triphenylphosphine oxide. This byproduct can normally be removed by flash chromatography or precipitation by the addition of hexane. For these techniques to be used, however, the product must be stable to chromatography or soluble in hexane. Charette and co-workers prepared a triphenylphosphine-bound, non-crosslinked polystyrene soluble support 51 to separate the imines 52 which were not stable to chromatography on silica gel.

\[
\text{R}+ \text{R'}\text{N}_3^+ \rightarrow \text{R}^\text{I} \rightarrow \text{R}^\text{N}^\text{R'}
\]

\[
\text{51}
\]

\[
\text{52}
\]
The imines were produced in yields comparable to those with free triphenylphosphine, and the phosphine oxide byproduct was able to be separated by a simple precipitation / filtration or extraction procedure.\textsuperscript{20}

\textbf{II. Sydnones}

In 1882, Emil Fischer synthesized dehydrodithizone, the first mesoionic compound, by the oxidation of dithizone, and assigned it the bicyclic structure 53.\textsuperscript{21} The monocyclic structure 54 was assigned by Baker, Ollis, and Poole in 1946 after various studies concluded that the compound was dipolar in nature.\textsuperscript{22} Later, the term mesoionic (mesomeric / ionic) was assigned to the compound due to its electronic structure and unique characteristics.

One of the most widely studied groups of mesoionic compounds are the sydnones, named after their place of discovery in Sydney, Australia. In 1935, Earl and Mackney\textsuperscript{23} synthesized the first sydnone, assigned a bicyclic structure 56, by reacting N-nitroso-N-phenylglycine 55 with acetic anhydride. However, the degree of polarity and general stability of the sydnone could not be explained by an apparently strained bicyclic structure.
Baker, Ollis, and Poole\textsuperscript{22} concluded that the sydnone ring should be represented by a dipolar, monocyclic 1,2,3-oxadiazolone based structure. The proposed structure was shown to have many resonance forms \textsuperscript{57a-1}, which contributed to the overall resonance hybrid \textsuperscript{57}. 
Baker, Ollis, and Poole concluded from these studies that in order for a molecule to be considered mesoionic, it must: 1) contain a fully delocalized positive and negative charge in the molecule; 2) be planar and contain a five-membered heterocyclic ring with an exocyclic atom or group capable of bearing a considerable amount of charge density; and 3) possess a considerable amount of resonance energy. Although mesoionic compounds are still a subclass of betaines, they differ from other similar compounds such
as ylides and zwitterions in that the charges are fully delocalized and no single resonance form can be accurately drawn.

**Physiochemical Properties and Electronic Structure**

Sydnones are stable compounds that exhibit substantial polarity. Generally, arylsydnones are crystalline solids, and 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, water solubility of sydnones is generally limited and not observed, with the exception of sydnones where a polar functional group has been incorporated. It was this relatively high polarity, which aided in the disproving of the proposed bicyclic structure of sydnones.

The physical properties of sydnones have been examined using NMR and IR spectroscopy. By representing the sydnone with a positive charge on the nitrogen at the 3 position and a negative charge on the oxygen attached at the 5 position, the aromatic nature of the sydnone can be shown. If a hydrogen is attached to the C-4 position of the sydnone ring, a distinct peak is noticed in the IR spectrum at 3150 cm\(^{-1}\). The absence of this peak in the IR spectrum indicates that a possible substitution has occurred at the C-4 position on the sydnone ring.\(^{24}\) In \(^1\)H NMR, the hydrogen at the C-4 position bears a chemical shift of approximately 6.8 \(\delta\)\(^{25}\), while a typical aromatic hydrogen attached to a carbon would have a chemical shift of 7-8 \(\delta\). The hydrogen at the C-4 position is considerably shielded, causing the chemical shift to move upfield. This effect at the C-4 position also causes the chemical shift for that carbon in \(^{13}\)C NMR to be
shifted slightly upfield at around 95 ppm, while a typical aromatic carbon would appear between 100-140 ppm.

![Chemical Structure](image)

A prominent peak is noticed between 1720 and 1749 cm\(^{-1}\) in the IR spectrum, which is due to the carbonyl moiety in sydnones at the C-5 position. Some multiple bands have been seen due to Fermi resonance splitting\(^{26,27}\). For comparison, a \(\gamma\)-lactone 59 carbonyl appears at around 1770 cm\(^{-1}\), while a tropone 60 appears at around 1638 cm\(^{-1}\). From this, it can be concluded that the carbonyl at the C-5 position in the sydnone ring is closer to that of the length of a double bond rather than a single bond.

![Chemical Structures](image)

X-ray crystallographic data for various 3-substituted and 3,4-disubstituted sydnones also showed that the carbonyl bond at the C-5 position was closer to that of a double bond rather than a single bond. However, integrated absorption measurements suggest that a high degree of carbonyl bond polarization, rather than bond strength, is responsible for the relatively high energy of absorption. Molecular orbital calculations and vibrational force constants obtained from vibrational spectra indicate a \(\pi\)-bond order for the sydnone carbonyl lower than those for alicyclic esters, thus supporting the argument that contributions from other vibrational modes cause the sydnone carbonyl group to absorb at
a higher frequency than expected.\textsuperscript{28} It has been shown by theoretical and spectroscopic studies that protonation of the sydnone ring occurs at the exocyclic oxygen atom\textsuperscript{29-33}, which complements earlier work which correlated observed dipole moments and UV maxima\textsuperscript{10}, indicating substantial charge density on the exocyclic oxygen atom.\textsuperscript{34,35} Another prominent shift for sydnones in their \textsuperscript{13}C NMR spectra is the carbon at the C-5 position bearing the exocyclic oxygen, which is observed around 165 ppm. This is a similar shift to that of a lactone carbonyl, which is observed between 169-180 ppm.

\textbf{Synthesis}

The general route for the preparation of sydnones is the cyclodehydration of N-substituted N-nitro-\(\alpha\)-amino acids (\textit{cf.} 55). While the substituent R in the sydnone 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. Nitrosation of an N-substituted glycine under acidic conditions affords the N-nitroamino acid 55. If non-acidic conditions are required due to the presence of acid sensitive functional groups, isoamyl nitrite in dimethoxyethane is a useful alternative.\textsuperscript{36}

\[
\begin{align*}
\text{H} & \quad \text{R'} \\
\text{N} & \quad \text{R} \\
\text{CO}_2\text{H} & \quad \text{61} \\
\end{align*}
\]

\[
\begin{align*}
\text{HONO} & \quad \text{or} \\
\text{ONO} & \quad \text{55} \\
\end{align*}
\]

As previously stated, Earl and Mackney originally accomplished the cyclization step using acetic anhydride at room temperature for 6 days. A much more efficient route, however, involves using trifluoroacetic anhydride at low temperatures, where cyclization occurs in <15 minutes. Other methods used in achieving cyclization include: treatment with phosphorus pentoxide, acetic anhydride at room temperature facilitated by
ultrasonication,\textsuperscript{37} haloiminium salts,\textsuperscript{38} N,N-dimethylchlorosulfitemethaninium chloride,\textsuperscript{39} and 2-chloro-1,3,-dimethylimidazolinium chloride.\textsuperscript{40} However, these methods do not compare to the efficiency of using trifluoroacetic anhydride.

**Chemical and Biological Behavior**

A large effort has been put forth to illustrate the aromatic properties of the sydnone ring. A fundamental property of any aromatic system is the ability to undergo electrophilic aromatic substitution (EAS). This has been shown in the sydnone ring to take place at the C-4 position (\textit{c.f.} 57, \textit{R}=H). The types of EAS reactions conducted at the C-4 position include halogenation, nitration, acylation, and sulfonation. Two major contributing factors account for the unexpectedly high regioselectivity of these reactions: (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 attached aryl ring. However, in the case when activating groups are attached to the aryl ring, the aryl ring moiety can compete successfully for the electrophile, a premise found for both halogenation and nitration.\textsuperscript{41,42}

Sydnones have also been evaluated for their uses as precursors to hydrazines,\textsuperscript{43} as 1,3-dipoles in cycloaddition reactions,\textsuperscript{44,45} electrolytic solvents for non-aqueous batteries\textsuperscript{46}, their potential as agents in non-linear optics\textsuperscript{47}, and their ability to aid micelle production in molecular aggregation.\textsuperscript{48}
Reactions of Sydnones

Substitution Reactions at the C-4 Position

As stated above, the considerable partial negative charge at the C-4 position of the sydnone ring (c.f. 57, R=H) allows for a variety of electrophilic aromatic substitution reactions to occur, including acylation, halogenation, nitration, and sulfonation.

a. Halogenation and Nitration

Sydnones (c.f. 62) undergo halogenation at the C-4 position by a variety of different methods. Chlorination of sydnones to form the corresponding 4-chloro species 63 has been performed by treatment of 62 with chlorine, potassium chlorate in moderately concentrated HCl, dichloroiodobenzene with triethylamine, or N-chlorosuccinimide (NCS). Bromination at the C-4 position to form the corresponding 4-bromo species 64 has been achieved by treatment of 62 with bromine, potassium bromate in HBr, or N-bromosuccinimide. Iodination of 62 to form the corresponding 4-iodo species 65 is much less common but can be achieved by using iodine monochloride in acetic acid at room temperature.

\[
\text{62} \quad \text{Cl}_2 \text{ or Br}_2 \quad \text{KClO}_3 / \text{HCl} \quad \text{ICl} / \text{AcOH} / \text{NaOAc} \quad \text{PhICl}_2 / \text{NEt}_3 \quad \text{NCS} / \text{DMF} 0^\circ\text{C} \quad \text{or NBS} / \text{DMF} 0^\circ\text{C}
\]

63: X = Cl  
64: X = Br  
65: X = I

It has been shown that debromination at the C-4 position can be achieved by the use of sodium borohydride or sodium dithionite in methanol or activated zinc under ultrasonification. However, there are several drawbacks associated with debromination.
by these methods including: (1) the reactivity of sodium borohydride with pendent functional groups (e.g. carbonyl compounds); (2) the effects of steric factors with the use of sodium dithionite; and (3) the inefficiency of the ultrasonification method when strong electron-withdrawing groups are present. The use of sodium sulfite is the preferred method for debromination at the C-4 position, as it exhibits none of the drawbacks previously listed.\textsuperscript{58} Due to the ease with which the sydnone ring can be brominated and debrominated, it has been postulated that having the bromine at the C-4 position can serve as a protecting group for the sydnone ring.\textsuperscript{59}

Although nitration at the C-4 position of 3-phenylsydnone can be realized using potassium nitrate in sulfuric acid at 0°C, the strongly acidic conditions required make this reaction relatively unimportant.\textsuperscript{60}

b. Acylation

Yashunskii\textsuperscript{61} was the first to acylate at the C-4 position of the sydnone ring to obtain the 4-acetyl derivative (\textbf{67}; R=Me, R’=Ph) by reaction of 3-phenylsydnone with acetic anhydride and boron trifluoride etherate.\textsuperscript{62} Acetic anhydride and HClO\textsubscript{4} or H\textsubscript{3}PO\textsubscript{4} were shown by Tien and coworkers to effect acylation to form various substituted sydnones.\textsuperscript{63} Using a different approach, Greco and co-workers were able to obtain the desired acylated sydnones by heating various substituted sydnones with an alkyl or aralkyl carboxylic acid in the presence of P\textsubscript{2}O\textsubscript{5}.\textsuperscript{64}
More recently, two improved routes to the 4-acyl derivatives have been developed by Tien and co-workers\textsuperscript{65} and Turnbull and coworkers.\textsuperscript{66} First, in the presence of acetic anhydride and a catalytic amount of perchloric acid, ultrasonification of a 3-substituted sydnone led to the 4-acetyl derivative. The use of ultrasonification improves safety by lowering the amount of perchloric acid needed. In the second method, 4-acetyl derivatives of 3-substituted sydnones were obtained via the use of acetic anhydride and a catalytic amount of Montmorillonite K-10 at elevated temperatures.\textsuperscript{66} This method is preferred due to the easy removal and disposal of the catalyst. However, with compounds containing electron-withdrawing groups ortho to the sydnone ring, this method proved to be sluggish or unsuccessful.

\textbf{c. Carboxamidation}

Previously, the only avenue to the 4-carboxamido species 68 was a 4-step process involving the abstraction of the sydnone ring proton using a strong base, addition of carbon dioxide, followed by reaction with thionyl chloride then ammonia. More recently, Turnbull, Gross, and Hall found that the treatment of a variety of 3-substituted sydnones 62 with chlorosulfonyl isocyanate in acetonitrile at room temperature provided the 4-carboxamido derivatives 68.\textsuperscript{67}
**d. Sulfonation**

In 1959, Yashunskii and co-workers showed that treatment of sydnones 62 with dioxane-sulfur trioxide complex (SO₃) in CH₂Cl₂ at 20° to 40°C, generated the sulfonated derivatives (69, R' = 4-MeO- or 4-EtOC₆H₄).⁶⁸ Since all attempts to prepare these compounds as free sulfonic acids were unsuccessful, these sulfonated derivatives were characterized as the barium or S-benzylthiuronium salts.

**Electrophilic Substitutions at the Aryl Ring of 3-Arylsydnones**

As stated previously, electrophilic substitution occurs almost exclusively at the sydnone C-4 position due to the partial negative charge that resides at this position. Additionally, the partial positive charge at the N-3 position on the sydnone ring deactivated the attached aryl moiety.
Addition of activating groups to the aryl moiety of 3-phenylsydnone was investigated in an attempt to effect aryl substitution in preference to sydnone C-4 substitution. While in the past, bromination of various 3-arylsydones afforded only 4-bromo analogs, the bromination of 3-(2-aminophenyl)sydnone (70) led to the formation of 3-(2-amino-5-bromophenyl)sydnone (71) and 3-(2-amino-5-bromophenyl)-4-bromosydnone (72). This confirmed that competitive electrophilic substitution of the 3-aryl ring could take place. Interestingly, it was reported that addition of NBS to 70 slowly over 30 minutes at 0°C, with subsequent stirring for 3 hours, afforded only the mono-bromo aryl product 71 in 78% yield.

![Chemical Structures]

Similar bromination studies were performed on activated dimethylaryl- and dimethoxyaryl-sydones (73 and 74 respectively). It was found that when 1 equivalent of bromine was added, bromination occurred only at the C-4 position, leading to 75. In fact, only the most activated sydnone, the 3-(2,4- and 3,5-dimethoxyphenyl) derivatives, were brominated on the aryl ring, but only after bromination had occurred at the sydnone C-4 position, affording 76 or 77, respectively.
In contrast to halogenation, nitration at the aryl moiety can take place without reaction at the C-4 position even with mildly activated 3-arylsydnones. Thus, under nitrating conditions, activated aryl sydnones (cf. 78) afford the products of nitration on the aryl ring 79 instead of the anticipated 4-nitro derivatives 80.71
Tien and coworkers have shown that when the aryl ring is not directly attached to the sydnone ring, it can act independently from the latter.\cite{95,96} This was shown by treating 3-benzylsydnone (81) with nitric acid to obtain the meta-nitro aryl product 82. Also, certain 3-aryl-4-acetylsydnones 83 gave the corresponding meta-nitro products 84 when subjected to nitrating conditions. In this case, the acetyl group at the C-4 position could be removed by subsequent reaction with barium hydroxide.
More recently, Turnbull, Blackburn, and Miller examined nitration of 3-arylsydrones with multiple electron-donating groups (methyl groups) on the aryl ring (cf. 85a-f). Once again, it was shown that in such cases, nitration on the aryl ring was observed with a strong tendency for nitration meta to the sydnone ring, yielding 86a-f. It was also found that when nitration was forced to occur between two substituents on the aryl ring, the preferred position of substitution was between the sydnone ring and a methyl group, not between the two methyl groups.
Reactions of ortho-Substituted Arylsydrones as Possible Precursors of Fused Ring Sydrones

Fused ring sydrones are of interest because ring-fusion may alter the chemical or biological properties of the sydnone ring. Turnbull and Saljoughian\textsuperscript{75} treated the modified ortho-substituted arylsydnone oximinosydnone \textit{87} with a variety of acids to explore avenues involving intramolecular electrophilic aromatic substitution. It was expected that the fused-ring sydnoquinazoline \textit{88} would result from these studies. It was found, however, that treatment of \textit{87} with acids led to sydnoquinazolines \textit{88}, benzotriazines \textit{89}, and/or indazoles \textit{90}, depending on which acid was employed.
Additionally, the preparation of 4-(arylamino)sydno[3,4-a] quinoxalines 91 has been achieved by aza-Wittig carbodiimide formation followed by intramolecular electrophilic cyclization in good to excellent yields (60-90%).

\[
\begin{align*}
\text{R} = \text{Ph, 4-Me, 4-MeO} \\
\text{4-NO}_2\text{Ph}
\end{align*}
\]
Two serendipitous discoveries have resulted in the preparation of the fused-ring sydnoindole 93 and various bromocarbonyl indazoles 95. It was found that treatment of 3-(2-acetylphenyl)sydnone (92) with hydrazine hydrate under basic conditions, the major isolable product was the fused-ring sydnoindole 93 and not the anticipated hydrazone derivative.\(^{77}\)

\[
\text{N}_2\text{H}_4 / \text{NEt}_3
\]

Also of interest was to place a bromine leaving group on the methyl side-chain. Accordingly, 3-(2-acetylphenyl)-4-bromosydnone 94 was treated with Br\(_2\)/hv or CuBr\(_2\). Surprisingly, the bromocarbonylindazole 95 (R = Me) was obtained rather than the expected sydnone 94 (R = CH\(_3\)Br, X = Br). It was speculated that this was the result of the formation of HBr \textit{in situ} and, when various 4-bromo ortho-acyl sydnone \textit{cf}. 94 were subjected to a stream of HBr gas, indeed the corresponding bromocarbonylindazoles 95 were formed in good yield (60-85\%).\(^{78}\)
One drawback to the reactions above is that sydnones with an \textit{ortho} carbonyl substitution are relatively hard to come by, and often must be made in numerous steps starting from the appropriate aniline derivative. More recently, Turnbull, Belakere, and McCall have shown that a variety of \textit{ortho}-acylarylsydnones can be prepared from one or two intermediates by reaction of nucleophiles with activated \textit{ortho} carbonyl species.\textsuperscript{79} As an example, 3-[(2-(N-succinimido)oxycarbonyl)phenyl]sydnone (96) was reacted with twelve different nucleophiles to afford the corresponding \textit{ortho}-acylarylsydnones 97 in yields ranging from 23\% to 63\%.
Sonogashira Coupling Reactions

The Sonogashira reaction, named after its discoverer, is a coupling reaction of terminal alkynes with aryl or alkyl halides. Recently, Weisner, Turnbull, and Cooper used the Sonogashira reaction to prepare sydnone containing platinum compounds for use as potential non-linear optical materials. A previously known protocol was modified by heating the degassed solution at 50° C, allowing high yield avenues to acetylenic sydnones 100 and 101.

First, Weisner showed that the ortho-iodinated sydnone 98 could be used to synthesize a variety of ortho-alkynyl sydnones. The intermediate 99 was prepared first by the Sonogashira coupling reaction of trimethylsilylacetylene with 98, followed by subsequent deprotection using tetrabutylammonium fluoride. Several ortho-alkynyl sydnones 100 and 101 were prepared from this intermediate via Sonogashira coupling of 99 with para-substituted aryl iodides. Additionally, a three reaction-in-one-pot procedure was developed to access some of these species directly from 3-(2-iodophenyl)sydnone (98). Subsequent reaction of 100 with electrophiles was examined as an avenue to novel fused-ring sydnones. Repetitions of the three in one coupling of 99 afforded species such as 101, which were studied as non-linear optical materials.
Aims of the Present Work

The main objective of this research was to explore routes to fused ring alkyl and aryl sydnoquinoxalines where subsequent functionalization could be achieved. In 1977, Turnbull and Preston\textsuperscript{82} treated 3-(2-aminophenyl)sydnone (70) with nitrous acid followed by sodium azide with the expectation that 3-(2-azidophenyl)sydnone (103) would result. However, it was discovered that the fused-ring sydnobenzotriazine 102 was prepared rather than 103. The rationale for the formation of the fused-ring sydnobenzotriazine 102 is intramolecular trapping of the intermediate diazonium ion by the aromatic sydnone ring.

\[
\begin{array}{c}
\text{NH}_2 \quad \text{N} \quad \text{N} \\
\text{70} \quad \text{1. HNO}_2 \quad \text{2. NaN}_3 \quad \text{not} \\
\text{N} \quad \text{N} \\
\text{102} \\
\text{N} \quad \text{N} \quad \text{N}_3 \\
\text{103} \\
\end{array}
\]

It was found also that the sydnobenzotriazine 102 cleaved under hydrolytic conditions to yield the benzotriazine carboxylic acid 104. The byproduct of this cleavage was postulated to be a congener of nitric oxide, which is contrary to the cleavage of a non-fused-ring sydnone under hydrolytic conditions.
Burson, Turnbull, and co-workers\textsuperscript{83} reported an intramolecular aza-Wittig route to arylsydnoquinoxalines 91. It was found that, in contrast to the previous findings, the diazotization of 70 could yield the azido species 105 if the diazonium species were formed in the presence of an excess of sodium azide, followed by the addition of sodium nitrite in hydrochloric acid. Addition of triphenylphosphine to 103 in dichloromethane yielded the iminophosphorane 106. An intramolecular aza-Wittig reaction of 106 with different aryl isocyanates and isothiocyanates led to the formation of the aryl sydnoquinoxalines 91 in moderate to good yields.

\[ R = \text{Ph, 4-Me, 4-MeO, 4-NO}_2\text{Ph} \]

In the present work, the synthesis of alkyl sydnoquinoxalines 107 by the intramolecular aza-Wittig reaction was of particular interest since it was anticipated that deprotection of 107 would lead to 108, where subsequent functionalization of the
resultant primary amino group would be possible. If successful, such an approach would provide avenues to a variety of fused-ring congeners from one readily available intermediate.

As an example, it was anticipated that reaction of 108 with anhydrides or acid chlorides would lead to 109.

Further, it was of interest also to attempt the synthesis of aryl sydnoquinoxalines such as 111 and 113 with potentially displaceable halogen atoms on the aryl group attached to the sydnone ring or on a pendent aryl ring. If successful, subsequent substitution could be envisaged through, e.g., Sonogashira coupling reactions, as shown for the reactions of 111 and 113 with TMS acetylene to form 112 and 114, respectively.
Assuming that halogeno species such as 111 and 113 could be made, it was anticipated that further studies on the chemoselectivity of the coupling reactions could be assessed by the preparation of a dihalogeno species such as 115.
Results and Discussion

With the goals for the current research established, the initial phase was the synthesis of the alkyl sydnoquinoxalines 107, followed by deprotection to form 108. Since avenues to aryl analogs of 107 had been developed previously it was elected to utilize a parallel process for the synthesis of the alkyl congeners 107 (R = alkyl) starting with o-fluoronitrobenzene.

Commercially available 1-fluoro-2-nitrobenzene and glycine were refluxed at 90°C for 6 hours to obtain N-(2-nitrophenyl)glycine. Nitrosation of N-(2-nitrophenyl)glycine with sodium nitrite and sulfuric acid at 0°C led to the N-nitroso-N-(2-nitrophenyl)glycine. Cyclization of the latter was achieved with trifluoroacetic anhydride at 0°C to afford 3-(2-nitrophenyl)sydnone in a 64% yield (Scheme 1). All samples were identical by melting point and IR spectra to previously prepared samples.

Scheme 1
Reduction of the 3-(2-nitrophenyl)sydnone with Fe powder in 2% AcOH at 90°C for 35 minutes, followed by Soxhlet extraction with THF, led to 3-(2-aminophenyl)-sydnone (70). The length of time for this conversion was slightly modified from the literature method,\textsuperscript{86} where a reflux for 12 minutes was used. It was found in this lab previously that 12 minutes did not lead to a full conversion to 70 and a 35 minute period was required to ensure the full conversion. The use of an overhead stirrer was also employed to ensure that the reactants were thoroughly mixed. Recrystallization from CH\textsubscript{2}Cl\textsubscript{2}/hexanes gave yellow crystals in a 72% yield, with identical melting point, TLC, and IR to an authentic sample. Conversion to 3-(2-azidophenyl)sydnone (105) was achieved by first combining the amino compound 70 with sodium azide, hydrochloric acid, and water at 0°C, followed by addition of sodium nitrite. The azido product 105 was collected in a 30% yield with a melting point of 109-110°C, identical (TLC and IR\textsuperscript{76}) to an authentic sample. The addition of 1 equivalent of triphenylphosphine to the azido species 105 in dichloromethane led to the formation of triphenylphosphine-2-(3-
sydnoneyl)phenylimide (106) in 83% yield with identical melting point, IR, and TLC characteristics to an authentic sample (Scheme 2).

Scheme 2

After many unsuccessful attempts to raise the yield for the preparation of the azido species 105, which had been reported previously in almost 70% yield, a new avenue to the iminophosphorane 106 was explored. It was anticipated that a single step avenue from the amino compound 70 would be the most attractive, since it would remove the problematic azidation step and excise one synthetic protocol. One avenue to the iminophosphorane 106 that seemed to meet the suggested requirements was the Mitsunobu process.
Accordingly, the amino compound 70 was combined with 1.1 equivalent of triphenylphosphine in anhydrous THF at room temperature, followed by dropwise addition of diisopropyl azodicarboxylate (DIAD). After four hours of stirring, full conversion to the iminophosphorane 106 was shown by TLC. The product was isolated by column chromatography on silica gel, and recrystallized from dichloromethane / hexanes to afford colorless crystals in an 81% yield, with identical melting point, IR, and TLC characteristics to an authentic sample (Scheme 3). Due to the substantially higher yields obtained and the ability to prepare the iminophosphorane 106 directly from the amino compound 70, this method was deemed advantageous over the two-step process (Scheme 2) used previously in this lab.

**Synthesis of alkyl sydnoquinoxalines 107 and subsequent deprotection**

Once the optimization of the iminophosphorane 106 had been achieved, the preparation of the alkyl sydnoquinoxalines 107 (R = alkyl) was undertaken. The first species for which a preparation was attempted was the sydnoquinoxaline 116, where it was anticipated that the attached TMS group could be removed readily (Scheme 4).
An intramolecular aza-Wittig reaction procedure, which had been previously used in this lab to make the aryl sydnoquinoxalines 91, was used as a starting point. Thus, the iminophosphorane 106 was combined with anhydrous toluene and 1.5 equivalents of TMS isocyanate under an atmosphere of nitrogen gas and refluxed for 5 hours. After 5 hours, a reaction had not taken place (TLC evidence), so the reaction was allowed to run for an additional 12 hours. After this time, a TLC examination showed a very complex reaction mixture, from which no significant amount of material could be isolated.

After changing equivalents of the TMS isocyanate and length of time, and still resulting in the same complex reaction mixture, it was elected to utilize a different isocyanate, with the same ultimate goal to obtain the deprotected sydnoquinoxaline 108. An alkyl sydnoquinoxaline was required with a group attached to the external nitrogen atom that could easily be deprotected, so it was decided to use tert-butyl isocyanate as an avenue to 4-(t-butylamino)syndro[3,4-a]quinoxaline (117) [Scheme 5].
Due to the low boiling point of tert-butyl isocyanate (85-86°C), a sealed, high pressure reaction vessel was used without a reflux condenser such that the reaction could still be run at 90°C. After the initial 5 hours, no reaction had taken place, but, gratifyingly, after 24 hours all starting material had disappeared (TLC evidence). After separation by column chromatography on silica gel, a yellow solid was obtained in a 10% yield. After numerous attempts at optimization, it was found that the best results could be obtained by the use of 3 equivalents of tert-butyl isocyanate and a reaction time of 17 hours at 90°C in a sealed pressure tube. Under these conditions, the product had a melting point of 227-228°C, was obtained in a 60% yield, and was characterized using IR, NMR, and elemental analysis. The IR spectrum showed peaks similar to those of other sydnoquinoxalines, viz. the N-H stretch appeared at 3394 cm\(^{-1}\) as a single peak, appropriate for a secondary amine, alkyl C-H stretch appeared at 2921 cm\(^{-1}\), the sydnone carbonyl stretch was apparent at 1733 cm\(^{-1}\), and the N=C peak appeared at 1552 cm\(^{-1}\).

The \(^1\)H NMR spectrum showed a multiplet in the aromatic region (7.26-8.08 ppm), a singlet for the N-H was observable at 6.14 ppm, and a large singlet appeared for the tert-butyl group at 1.78 ppm. The integration showed four protons in the aromatic region, and 9 protons for the tert-butyl group relative to the N-H. The \(^13\)C NMR spectrum displayed
seven signals in the aromatic region, three of which were quaternary. Also in line with expectation, the sydnone carbonyl signal appeared at 163.67 ppm, and the sydnone C-4 signal appeared at 94.12 ppm. Two signals in the alkyl region were also present, one at 27.89 ppm, which accounted for the CH\textsubscript{3} groups, and one at 51.81 ppm, which accounted for the carbon on the \textit{tert}-butyl group attached to the nitrogen. The results of the elemental analysis of 117 showed 59.41 % carbon, 5.47 % hydrogen, and 21.08 % nitrogen; when the compound was associated with \(\frac{1}{4}\) of a molecule of H\textsubscript{2}O the calculated values were found to be 59.42 % carbon, 5.56 % hydrogen, and 21.32 % nitrogen.

After preparation of the alkyl sydnoquinoxaline 117, the next step was the removal of the \textit{tert}-butyl group to form 4-(amino)sydno[3,4-\textit{a}]quinoxaline (108). The removal of a \textit{tert}-butyl protective group is commonly achieved by the use of acidic conditions. Accordingly, the alkyl sydnoquinoxaline 117 was added to stirring sulfuric acid and after 30 minutes the reaction mixture was neutralized and extracted with dichloromethane to afford the presumed product 108 (96% yield, if 108) [Scheme 6].

Scheme 6

![Scheme 6](image)

Evidence by TLC examination confirmed that no starting material remained, and that a much more polar material relative to the starting material was present. However, the IR spectrum of the sample showed only a single N-H peak at 3396 cm\(^{-1}\), which contradicts the expectation of a primary NH\textsubscript{2} group in this product. Additionally, the solubility of
the product presumed to be 108 proved to be problematic in characterization since it had little to no solubility in deuteriochloroform, dimethylsulfoxide, water or ethanol.

Accordingly, the sample could not be recrystallized nor could it be dissolved for NMR identification.

Subsequent reactions with the putative 4-(amino)sydno[3,4-a]quinoxaline (108)

Despite the uncertainties associated with the identity of the isolated material (putatively 108), it was elected to explore reactions with the compound at the amino group, in the hope that a product could be isolated and characterized to confirm that 108 was actually made. The first attempt at functionalization of the amino group in 108 was with acetic anhydride to prepare 4-(acetamido)sydno[3,4-a]quinoxaline (118) [Scheme7].

Scheme 7

The sydnoquinoxaline 108 was added to acetic anhydride and refluxed at 60°C for 2 hours. Extraction with dichloromethane and water led to an impure solid (2 spots by TLC evidence). The more prominent, lower running spot was isolated by column chromatography on silica gel, and recrystallized with dichloromethane / hexanes to afford light tan crystals in a 73% yield with a melting point of 174-175°C. Elemental analysis, IR, and NMR confirmed that the target compound 118 was indeed synthesized. The IR spectrum showed a single N-H peak at 3331 cm\(^{-1}\), an alkyl C-H peak at 2923 cm\(^{-1}\), the sydnone carbonyl at 1760 cm\(^{-1}\), the acetyl carbonyl peak at 1705 cm\(^{-1}\), and the N=C peak
at 1525 cm\(^{-1}\). A typical amide carbonyl peak would appear at \(~1650\) cm\(^{-1}\) in an IR spectrum, however, it is presumed that, in this case, conjugation with the fused ring system decreases the resonance effect of the nitrogen upon the carbonyl of the amide group, causing it to have a higher wavenumber. The \(^1\)H NMR spectrum showed the N-H signal at 8.7 ppm, four aromatic protons between 7.59-8.25 ppm, and the acetyl CH\(_3\) protons at 2.64 ppm. The \(^{13}\)C NMR spectrum also showed evidence that the target compound \(\text{118}\) had been prepared. Thus, the sydnone carbonyl signal appeared at 163.2 ppm, the sydnone C-4 signal appeared at 95.3 ppm, seven aromatic carbons appeared between 115.6-144.9 ppm, the acetyl carbonyl signal appeared at 169.8 ppm, and the methyl carbon attached to the acetyl carbonyl appeared at 26.1 ppm. The elemental analysis for compound \(\text{118}\) showed 53.68% carbon, 3.43% hydrogen, and 22.53% nitrogen. The calculated values were 54.10% carbon, 3.30% hydrogen, and 22.94% nitrogen.

The successful preparation of compound \(\text{118}\) seemed to open avenues for the preparation of many other fused ring sydnones in a similar fashion. Accordingly, an attempt was made to extend these findings using trifluoroacetic anhydride (TFAA) to prepare fused ring sydnone \(\text{119}\) (Scheme 8).

Scheme 8
Since acetic anhydride reacted so readily, and, given the general expectation that TFAA is much more reactive toward nucleophiles, it appeared likely that milder conditions would be required. However, various attempts to effect the transformation under conditions ranging from milder to identical to the previously successful avenue did not provide any reaction. Assuming that some of this difficulty might be related to the volatility of the reagent (bp 40°C), the reaction was set up in a high-pressure reaction vessel, and heated to 35°C. Surprisingly, after a period of 24 hours, no reaction was observed (TLC evidence) and only starting material was recovered. Raising the temperature to 60°C, and heating for a period of 24 hours, gave the same result (TLC evidence). It is difficult to explain these findings.

One more anhydride, propionic anhydride, was attempted to determine whether other anhydrides could be reacted with the putative compound 108. Unfortunately, this reaction could be performed with only 10 mg of the putative amino compound 108 due to a lack of time to prepare more of the starting material. The putative amino compound 108 was added to propionic anhydride, and left at 75°C for 1.5 hours (Scheme 9).

Scheme 9

The reaction was stopped after this period of time after no starting material remained (TLC evidence). Unfortunately, not enough of the product could be obtained to get full characterization, and only an IR was taken. The IR spectrum revealed a single N-H
stretch at 3337 cm\(^{-1}\), alkyl C-H peaks ranging from 2958-2854 cm\(^{-1}\), the sydnone carbonyl stretch at the C-5 position at 1732 cm\(^{-1}\), a putative amide peak at 1715 cm\(^{-1}\), and the C=N peak at 1525 cm\(^{-1}\). These IR results appear to indicate that a reaction did indeed take place, and further studies should be performed to allow full characterization.

To further justify that compound 108 was indeed prepared, reactions were attempted with two sulfonyl chlorides, benzenesulfonyl chloride and methanesulfonyl chloride (Scheme 10). The starting material 108 was combined with triethylamine (TEA), dry tetrahydrofuran (THF), and 1.5 equivalents of the appropriate sulfonyl chloride at 100°C and left for a period of 48 hours. In both attempts to make compounds 120a and 120b, only starting material remained by TLC evidence.

Scheme 10

In one last effort to try and react the putative amino 108 compound, reactions were attempted with two acid chlorides, 4-fluorobenzoyl chloride and 2-chlorobenzoyl chloride (Scheme 11). The acid chlorides were added to stirring pyridine along with the putative amino compound 108. However, after adjusting temperature, time, and equivalents of acid chloride added, no reaction had taken place (TLC evidence). A reasonable explanation could not be given as to why the sydnoquinoxaline 108 only
reacted with acetic anhydride, and potentially propionic anhydride, but not trifluoroacetic anhydride, acid chlorides, or sulfonyl chlorides.

Scheme 11

![Diagram]

Preparation of brominated arylsydnoquinoxalines 124, 125, and 126:

Due to the disappointing results from attempts to functionalize the sydnoquinoxaline 108, attention shifted to aryl sydnoquinoxalines. Burson, Turnbull and co workers\(^\text{83}\) had previously found an intramolecular aza-Wittig route from the iminophosphorane 106 to aryl sydnoquinoxalines 91. In an attempt to test the reactivity and nature of different aryl sydnoquinoxalines, Katta\(^\text{84}\) attempted lithiations, coupling reactions, halogenations, nitrations, and Friedel-Crafts acylations on these species. The first goal of this research was to prepare triphenylphosphine 4-bromo-2-(3-sydnonyl)-phenyl imide (123), and attempt intramolecular aza-Wittig reactions to obtain the desired aryl sydnoquinoxalines. To achieve this goal, first 3-(2-aminophenyl)sydnone (70) was combined with 2 equivalents of NBS to form 4-bromo-3-(2-amino-5-bromophenyl)sydnone (121).
It had been reported some years ago in this lab that 4-bromo-3-(2-aminophenyl)sydnone (122) could be directly prepared by using one equivalent of N-bromosuccinimide (NBS) with sydnone 70. However, it was found that one equivalent of NBS with the aminophenyl sydnone 70 gave a combination of sydnones 121 and 122 along with remaining starting material. To make sure that no starting material remained, it was decided to use 2 equivalents of NBS in methanol to afford the dibromo compound 121 and, indeed, the latter was formed in 88% yield with melting point and IR matching authentic material. The removal of the bromine at the C-4 position was performed easily with sodium sulfite in methanol at room temperature, to give the bromosydnone 122 in a 67% yield, with identical melting point and IR to authentic material. The normal route to the iminophosphorane 123 in this lab was a two-step process involving an intermediate azide species. However, since high yields were obtained using Mitsunobu conditions in the preparation of the non-brominated iminophosphorane 106, it was logical to attempt this one-step process first. The bromo aminophenyl sydnone 122 was combined with triphenylphosphine in dry THF, and DIAD was added dropwise to the solution and left for 4 hours (Scheme 12). After removal of THF, the resulting solid was flushed through a column of silica gel for purification. The resulting solid was obtained in an 85% yield, had a melting point of 164-165°C (literature 165-166°C) and was identical by IR.
spectroscopy to the published peaks which include the sydnone CH stretch at 3143 cm\(^{-1}\), aromatic CH stretch at 3052 cm\(^{-1}\), and the sydnone carbonyl stretch at 1738 cm\(^{-1}\).

Aryl sydnoquinoxalines (124, 125, 126) were prepared by an aza-Wittig reaction (Scheme 13).

Scheme 13

The bromoiminophosphorane 123 was combined with the appropriate isothiocyanate in anhydrous toluene in a high pressure reaction tube at 110°C. After 5 hours, no starting material remained (TLC evidence), and the toluene and excess isothiocyanate were removed by a flow of nitrogen. The highest running spot by TLC was presumed to be the desired product for each reaction, and each was separated by column chromatography using silica gel. Recrystallization from DCM/hexanes afforded bright yellow crystals with yields of 31% for compound 124, 36% for compound 125, and 60% for compound 126. Compounds 124 and 125 were confirmed by IR, NMR, and elemental analysis. Compound 126 was confirmed by IR and elemental analysis. The NMR for 126 was inconclusive due to the insolubility of the required amount of the product in any regular deuterated solvent.

The IR spectrum for 4-(phenylamino)-8-bromosydno[3,4-a]quinoxaline (124) showed a single N-H stretch at 3343 cm\(^{-1}\), the carbonyl stretch at the C-5 position on the
sydnone ring at 1741 cm$^{-1}$, and the N=C peak at 1555 cm$^{-1}$. The $^{13}$C NMR spectrum showed the sydnone C-4 signal at 95.31 ppm, the sydnone carbonyl signal at 164.05 ppm, and eleven aromatic carbon signals ranging from 117.87 ppm to 147.34 ppm. Five of the aromatic carbons were clearly quaternary due to the weakness in intensity. The results of elemental analysis of compound 124 showed 49.25% carbon, 2.59% hydrogen, and 14.62% nitrogen. The calculated percentages for 124 with 2/3 of a molecule of water present were 48.8% carbon, 2.82% hydrogen, and 15.18% nitrogen.

The IR spectrum for 4-(4-methoxyphenylamino)-8-bromosydno[3,4-a]-quinoxaline (125) showed a single N-H stretch at 3361 cm$^{-1}$, an alkyl C-H peak at 2913 cm$^{-1}$, the carbonyl stretch at the C-5 position on the sydnone ring at 1750 cm$^{-1}$, and the N=C peak at 1557 cm$^{-1}$. The $^1$H NMR spectrum showed a singlet for the N-H at 8.2 ppm, seven aromatic hydrogens in a complex splitting pattern between 7.9-6.9 ppm, and a singlet of 3 hydrogens for the methoxy group at 3.8 ppm. The $^{13}$C NMR spectrum showed the sydnone carbonyl at the C-5 position at 164.10 ppm, the carbon on the phenyl ring attached to the methoxy group at 156.65 ppm, ten additional aromatic carbon signals between 147.32 ppm – 114.28 ppm, the sydnone C-4 carbon at 95.20 ppm, and the methoxy group carbon at 55.52 ppm. Six of the aromatic carbons, including the carbon on the phenyl ring attached to the methoxy group, were quaternary carbons due to their weakness in intensity. Elemental analysis for compound 125 showed 49.38% carbon, 2.93% hydrogen, and 14.29% nitrogen. The calculated values were found to be 49.63% carbon, 2.86% hydrogen, and 14.47% nitrogen.

The IR spectrum for 4-(4-iodophenylamino)-8-bromosydno[3,4-a]quinoxaline (126) showed a single N-H stretch at 3349 cm$^{-1}$, the sydnone carbonyl stretch and the C-5
at 1748 cm\(^{-1}\), and the C=N peak at 1555 cm\(^{-1}\). The \(^1\)H NMR spectrum showed a singlet for the N-H at 8.06 ppm, and a multiplet for the aromatic hydrogens from 8.32-7.44 ppm. The \(^{13}\)C NMR spectrum was inconclusive due to the inability to dissolve enough of the compound in DMSO, CDCl\(_3\), or D\(_2\)O for analysis. However, a signal could be seen at 87.59 ppm in the spectrum, which accounted for the carbon attached to the iodine on the aryl ring. A melting point (255-256°C) and elemental analysis were performed on the compound to help confirm its identity. Elemental analysis showed 37.40% carbon, 1.77% hydrogen, and 11.45% nitrogen. The calculated values were found to be 37.30% carbon, 1.67% hydrogen, and 11.60% nitrogen.

**Sonogashira Coupling Reactions with Aryl Sydnoquinoxalines:**

After successfully preparing brominated aryl sydnoquinoxalines \(124, 125,\) and \(126\), subsequent substitution of the displaceable bromine was undertaken using the Sonogashira reaction. The first step was to attempt to substitute the bromine in compounds \(124\) and \(125\) to determine whether or not the coupling reaction could be successful with these fused-ring sydnones, since previous attempts in this lab had been unsuccessful.\(^8\) The previous attempts in this lab did not include the deoxygenation of the reagents using the freeze, pump, thaw method prior to starting the reaction, which proved to be crucial.
The first step was to properly flame dry and flush a Schlenk tube with \( \text{N}_2 \) prior to adding any reagents. Then the proper brominated arylsydnoquinoxaline (124, 125) was added with dry THF, PPh\(_3\), 2 eq. of TEA, and 3 eq. of TMS acetylene. The first reaction attempted used 1.5 eq. of TMS acetylene, and it was found that this did not draw the reaction to completion as there was starting material left after 13 hours (TLC evidence). This mixture was then deoxygenated using the freeze/pump/thaw method three separate times and, when complete, the Pd(II) catalyst and CuI were added. The reaction was allowed to stir for 13 hours at 55\(^\circ\)C, after which time no starting material remained (TLC evidence) (Scheme 14). The top running spot by TLC was isolated using column chromatography with silica gel, and was determined to be the target compound (127, 128) for each reaction. The target compounds 127 (44% yield) and 128 (46% yield) were fully characterized using melting point, IR, NMR, and elemental analysis.

The IR spectrum for 4-(phenylamino)-8-(2-trimethylsilyethynyl)sydno[3,4-a]quinoxaline (127) showed a single N-H stretch at 3355 cm\(^{-1}\), an alkyl C-H peak at 2957 cm\(^{-1}\), the alkyne carbon-carbon triple bond peak at 2156 cm\(^{-1}\), the sydnone carbonyl peak at the C-5 position at 1758 cm\(^{-1}\), and the C=N peak at 1541 cm\(^{-1}\). The \(^1\)H NMR spectrum showed a singlet for the N-H at 8.10 ppm, a multiplet for the aromatic hydrogens ranging
from 7.86-7.14 ppm, and a singlet for the TMS hydrogens at 0.31 ppm. The $^{13}$C NMR spectrum revealed 16 carbons as expected. The carbon at the sydnone C-4 position was observed at 164.39 ppm, eleven aromatic carbons ranging from 147.59-119.11 ppm, the carbon at the sydnone C-5 position at 102.99 ppm, the two alkyne carbons at 97.86 and 95.54 ppm, and one signal for the TMS group at 0.00 ppm. It should be noted that it is common for the carbon at the sydnone C-4 position to be observed between 100-105 ppm when substituted. Four of the aromatic carbons were clearly quaternary carbons due to their weakness in intensity. Elemental analysis showed 63.21% carbon, 4.93% hydrogen, and 14.79% nitrogen; calculated values with 1/3 molecule H$_2$O were 63.14% carbon, 4.95% hydrogen, and 14.73% nitrogen.

The IR spectrum for 4-(4-methoxyphenylamino)-8-(2-trimethylsilyl)ethyl-sydno[3,4-a]quinoxaline (128) showed a single N-H stretch at 3376 cm$^{-1}$, alkyl C-H peaks from 2956-2848 cm$^{-1}$, the alkyne carbon-carbon triple bond peak at 2160 cm$^{-1}$, the sydnone carbonyl peak at the C-5 position at 1744 cm$^{-1}$, and the C=N peak at 1551 cm$^{-1}$. The $^1$H NMR spectrum showed a singlet for the N-H at 7.98 ppm, a multiplet for the aromatic hydrogens ranging from 8.21-6.91 ppm, and a singlet for the TMS hydrogens at 0.31 ppm. The $^{13}$C NMR spectrum revealed 17 carbons as expected. The carbon at the sydnone C-4 position was observed at 164.44 ppm, eleven aromatic carbons ranging from 156.88-114.50 ppm, the carbon at the sydnone C-5 position at 103.07 ppm, the two alkyne carbons at 97.62 and 95.50 ppm, the methoxy carbon at 55.72 ppm, and one signal for the TMS group at 0.00 ppm. The carbon on the phenyl ring attached to the methoxy group was expected to be shifted downfield from a normal aromatic carbon and, indeed, was seen at 156.88 ppm. Five of the aromatic carbons were clearly quaternary carbons.
due to their weakness in intensity. Elemental analysis showed 61.84% carbon, 4.96% hydrogen, and 13.69% nitrogen; calculated values were 62.36% carbon, 4.98% hydrogen, and 13.85% nitrogen.

With a successful procedure in place for the Sonogashira coupling reaction with brominated aryl sydnoquinoxalines, it was logical to attempt the reaction using a displaceable iodine rather than a bromine. The main goal was to get selectivity with compound 126, where a coupling reaction would take place with the iodine, and not the bromine.

Scheme 15

The first task was to successfully prepare compound 130 to prove that coupling reactions could take place at the iodine on the aryl ring attached to the sydnone. Previous attempts in this lab were unsuccessful, however as previously stated, the freeze / pump / thaw method to deoxygenate the reagents had not been utilized. First, 4-(4-iodophenylamino)sydno[3,4-a]quinoxaline (129) had to be prepared. This was achieved using the same aza-Wittig type method as previously developed in our laboratory. Thus, the iminophosphorane 106 was reacted with \( p \)-iodophenyl isothiocyanate in anhydrous toluene at 110°C under an atmosphere of nitrogen for 5 hours (Scheme 15). After the reaction was complete (TLC evidence), the solvent was removed \textit{in vacuo}, and the desired product (top running spot by TLC) was isolated in an 87% yield by column chromatography using silica gel. The product’s melting point and IR were identical to
authentic samples prepared previously in this laboratory. The next step was to prepare 4-(4-(2-trimethylsilylethylene)phenylamino)sydno[3,4-a]quinoxaline (130) from aryl sydnoquinoxaline 129 via the Sonogashira coupling reaction. First, the 4-iodophenyl sydnoquinoxaline 129 was placed in a flame-dried Schlenk tube along with dry THF, 2 eq. of TEA, PPh₃, and 3 eq. of TMS acetylene. These reagents were deoxygenated using the freeze/pump/thaw method three times and then, the dichlorobis(triphenylphosphine)-palladium(II) catalyst and CuI were added (Scheme 14). The reaction was allowed to stir at 55°C for 13 hours, after which time there was no presence of starting material (TLC evidence). The solvent was removed in vacuo, and the desired product (top running spot by TLC) was isolated with column chromatography using silica gel. Recrystallization from DCM/hexanes afforded the target compound 130 as bright yellow crystals in a 50% yield with a melting point of 224-225°C. The product was characterized with IR, NMR, and elemental analysis. The IR spectrum showed a single N-H stretch at 3343 cm⁻¹, alkyl C-H peaks at 2948 cm⁻¹, the alkyne carbon-carbon triple bond peak at 2153 cm⁻¹, the sydnone carbonyl stretch at the C-5 position at 1738 cm⁻¹, and the C=N peak at 1557 cm⁻¹. The ¹H NMR spectrum showed a singlet for the N-H proton at 8.10 ppm, a multiplet for the aromatic hydrogens at a range of 8.16-7.41 ppm, and a singlet for the TMS group at 0.27 ppm. The ¹³C NMR spectrum showed the sydnone carbonyl at 164.21 ppm, eleven aromatic carbons ranging from 146.79-115.60 ppm, the sydnone C-4 carbon at 104.87 ppm, two alkyne carbons at 95.23 ppm and 93.94 ppm, and one signal for the TMS group at 0.00 ppm. It was clear that 5 of the aromatic carbons were quaternary due to their weakness in intensity, which fits in with the proposed structure. Elemental analysis confirmed the product assignment, showing 64.11% carbon, 4.90% hydrogen,
and 14.95% nitrogen; calculated values were 64.15% carbon, 4.84% hydrogen, and 14.96% nitrogen.

The success of the coupling reaction with 129 led to an attempt at selectively reacting the iodine in the dihalogenated species 126, without a reaction taking place with the bromine. It was felt that the previously used conditions with 3 eq. of TMS acetylene and heating the reaction mixture at 55°C would need to be modified since the iodine should be more reactive than the bromine. Accordingly, the temperature was lowered to room temperature and 1.1 eq. of TMS acetylene was used in the expectation that the bromine would remain unreacted. The dihalogenated aryl sydnoquinoxaline 126 was added to a Schlenk tube that had been flame-dried, along with dry THF, 2 eq. of TEA, and 1.1 eq. of TMS acetylene. This mixture was then deoxygenated using the freeze/pump/thaw method three times and, after this process was complete, both Pd(PPh₃)₂Cl₂ and CuI were added (Scheme 16).

Scheme 16

![Scheme 16](image)

The reaction was left for 5 hours at room temperature, after which time no reaction had taken place (TLC evidence). The reaction was then heated to 55°C, and left for 13 hours whereupon a significant amount of starting material still remained (TLC evidence). Accordingly, 2 eq. of TMS acetylene was added and the reaction mixture was left for an additional 13 hours at 55°C, after which time the reaction was complete (TLC evidence).
Three very faint spots were visible by TLC above what was thought to be the desired product, and these were separated by column chromatography using silica gel. The desired product was recrystallized from DCM/hexanes, which afforded bright yellow crystals in a 43% yield. Melting point, IR, and NMR were performed on the product. The IR spectrum for 4-(4-(2-trimethylsilylethynyl)phenylamino)-8-bromosydno[3.4-a]quionoxaline (131) contained a single N-H stretch at 3357 cm⁻¹, alkyl C-H peaks at 2922 cm⁻¹, a single peak for the alkyne carbon-carbon triple bond at 2157 cm⁻¹, the sydnone carbonyl stretch at the C-5 position at 1760 cm⁻¹, and the C=N peak at 1561 cm⁻¹. The ¹H NMR spectrum showed a singlet for the N-H at 8.12 ppm, a multiplet in the aromatic region from 8.31-7.47 ppm, and a singlet for the TMS group at 0.27 ppm. The ¹³C NMR spectrum showed a signal for the sydnone C-5 carbon at 163.98 ppm, eleven aromatic carbon signals ranging from 146.96-118.20 ppm, the sydnone C-4 carbon signal at 104.75 ppm, two signals for the alkyne carbons at 95.28 ppm and 94.19 ppm, and one signal for the TMS group at 0.00 ppm. Six of the aromatic carbons appeared to be quaternary due to the weakness in intensity of the signal, which agreed with the proposed structure of 131. It was thought that perhaps the bromine was removed during the reaction, leaving the non-brominated aryl sydnoquinoxaline 130. Had this happened, the melting point and ¹³C NMR spectrum would have been identical with an authentic sample, which was not the case. This indicated that the bromine was not removed during the reaction. Another possible outcome was that the bromine moiety could also have reacted, resulting in two alkylnyl groups in the product. Since the ¹³C NMR spectrum contained only 2 signals in the region for carbon-carbon triple bonds, this idea was discounted also. A final possible outcome for this reaction was that the reaction could
have taken place at the bromine, and not at the iodine. Had this happened, a signal for an aromatic carbon attached to the iodine around 87 ppm would have appeared, which was not the case. Accordingly, chemoselectivity was achieved in the dihalogenated species 126, where the Sonogashira coupling reaction only took place at the iodine, and not the bromine. Unfortunately, the elemental analysis results that were found did not compare to the calculated values. It was thought that the lack of a sufficient amount of sample led to an inaccurate analysis. In the future, preparation of the product 131 should be undertaken, and another elemental analysis should be performed.

**Synthesis of a brominated alkyl sydnnoquinoxaline (132)**

Once it was proven that coupling reactions could be performed on the bromine attached to the phenyl ring at the 3 position of the sydnone ring, it was decided to return to this concept using alkyl sydnnoquinoxalines. Using a similar procedure for the preparation of the non-brominated alkyl sydnnoquinoxaline 117, the bromo iminophosphorane 123 was combined with 3 eq. of tert-butyl isocyanate and anhydrous toluene in a high pressure reaction tube that was flame dried and flushed with N₂ (Scheme 17).

Scheme 17

![Scheme 17](image)

After 24 hours, no starting material remained (TLC evidence), and the solvent and excess isocyanate were removed under a flow of N₂. TLC of the reaction mixture revealed one
high running spot, which was assumed to be the product, along with a complex mixture of by-products near the baseline. The top spot was isolated using column chromatography with silica gel. The isolated solid was recrystallized with CH₂Cl₂/hexanes to afford bright yellow crystals in a 6% yield. Unfortunately, a greater yield could not be achieved for this reaction, however the target compound, 4-(4-tert-butylamino)-8-bromosydno-[3,4-a]quinoxaline (132), was characterized using melting point, IR, NMR, and elemental analysis. The IR spectrum revealed a single N-H stretch at 3379 cm⁻¹, alkyl C-H peaks at 2919 cm⁻¹, the sydnone carbonyl stretch at 1737 cm⁻¹, and the C=N peak at 1552 cm⁻¹. The ¹H NMR spectrum revealed the N-H at 6.10 ppm, 3 aromatic hydrogens ranging from 8.22-7.51 ppm, and the tert-butyl protons at 1.57 ppm. The ¹³C NMR spectrum showed the sydnone carbonyl at the C-5 position at 164.51 ppm, seven aromatic carbon signals ranging from 149.36-116.08 ppm, the sydnone C-4 carbon signal at 95.20 ppm, the center carbon on the tert-butyl group at 53.27 ppm, and the methyl carbons of the tert-butyl group as a single signal at 29.00 ppm. It appeared that four of the aromatic carbons were quaternary carbons due to the weakness in intensity of the signals, which is in agreement with the proposed structure. The elemental analysis showed 44.88% carbon, 3.79% hydrogen, and 14.46% nitrogen; the calculated values with ½ of a molecule of H₂O were 45.10% carbon, 4.08% hydrogen, and 16.18% nitrogen. It is possible that the discrepancy between the calculated nitrogen percentage and the experimentally measured percentage is due to the fact that only 715 µg of material was available for elemental analysis, which obviously could lead to an inaccurate result.
Experimental

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 (e.g. Sonogashira couplings, aza-Wittig reactions), all glassware was flame-dried under an atmosphere of nitrogen prior to the use of dry reagents. Melting points were determined on a Mel-Temperature melting point apparatus and are uncorrected. Infrared spectra were acquired on a Nicolet 6700 FT-IR. NMR spectra were acquired on a Bruker 300MHz NMR. Elemental analyses were performed by Midwest Microlab LLC, Indianapolis, Indiana.

Synthesis of 3-(2-nitrophenyl)sydnone

The title compound was prepared via a literature method. Commercially available 1-fluoro-2-nitrobenzene and glycine were refluxed at 90-100°C for 6 hours to form N-(2-nitrophenyl)glycine. Nitrosation was performed using sodium nitrite and sulfuric acid at 0°C to form N-nitroso-N-(2-nitrophenyl)glycine in 72% yield. Cyclization of the latter using trifluoroacetic anhydride (TFAA) afforded the title compound in 64% yield. The product was recrystallized from ethanol as an orange-brown solid, melting point 134-136°C, identical to an authentic sample by melting point and IR.
Synthesis of 3-(2-aminophenyl)sydnone (70)

The title compound was prepared via a literature method. This method involved a reduction of 3-(2-nitrophenyl)sydnone with Fe/2% AcOH under reflux for one hour at 90-100°C with an overhead stirrer, followed by Soxhlet extraction with THF to give the desired product. Recrystallization from CH₂Cl₂/hexanes gave the product as yellow crystals in 72% yield, melting point 135-136°C, identical to an authentic sample by TLC, melting point and IR.

Synthesis of 3-(2-azidophenyl)sydnone (105)

The title compound was prepared using a literature method. To a solution of 3-(2-aminophenyl)sydnone (70) and NaN₃ in H₂O at 0°C, was added concentrated hydrochloric acid slowly. A solution of NaNO₂ in H₂O was added dropwise, and the resultant product was filtered and recrystallized from CH₂Cl₂/hexane to yield 105, 30% yield, melting point 109-110°C, identical to a authentic sample by melting point and IR.

Synthesis of triphenylphosphine-2-(3-sydnoneyl)phenylimide (106)

Two methods were used.

Method 1:

The title compound was prepared by a modification of a literature method. To a stirred solution of 3-(2-azidophenyl)sydnone (105) (0.14g, 0.67mmol) in methylene chloride (2.25mL) was added triphenylphosphine (0.18g, 0.70mmol) at room temperature. Once
the product was formed (TLC evidence), solvent was removed \textit{in vacuo}. Recrystallization from CH$_2$Cl$_2$/hexane yielded the title compound \textbf{106} as tan needles; yield: 83\% (0.245g); mp 166-168\(^\circ\)C, identical to authentic sample by mp and IR.

Method 2:

To a stirred solution of 3-(2-aminophenyl)sydnone (\textbf{70}) (0.10g, 0.56mmol), triphenylphosphine (0.16g, 0.62mmol) in dry THF (1mL), was added diisopropyl azodicarboxylate (0.13g, 0.12mL, 0.62mmol) dropwise at room temperature. After 4 hours the product was formed (TLC evidence), and solvent was removed \textit{in vacuo}. The desired product was obtained by column chromatography using silica gel as the stationary phase and CH$_2$Cl$_2$ as the mobile phase. Recrystallization from CH$_2$Cl$_2$/hexanes yielded the title compound (\textbf{106}) as colorless crystals; yield: 81\% (0.20g); mp 166-168\(^\circ\)C, identical to authentic sample by mp and IR.

\textbf{Attempted synthesis of 4-\textit{(trimethysilylamino)sydno}[3,4-a]quinoxaline (\textbf{115})}

In a high pressure reaction tube that was flame-dried and flushed with N$_2$, triphenylphosphine-3-(2-sydnonyl)phenylimide (\textbf{106}) (0.030g, 0.067mmol) was combined with TMS isocyanate (0.014mL, 0.012g, 0.100mmol) in anhydrous toluene (1mL) and heated to 90\(^\circ\)C for 12 hours. Evidence by TLC showed a complex reaction mixture, so the reaction was discarded.

\textbf{Synthesis of 4-(\textit{t}-butylamino)sydno[3,4-a]quinoxaline (\textbf{116})}
In a high pressure reaction tube that was flame-dried and flushed with N₂, triphenylphosphine-3-(2-sydnonyl)phenylimide (106) (0.63g, 1.45mmol) was combined with tert-butyl isocyanate (0.37mL, 0.43g, 4.35mmol) in anhydrous toluene (25mL) and heated at 90°C for 18 hours. The solvent and excess tert-butyl isocyanate were removed by a flow of nitrogen over the reaction mixture. The desired product was obtained through column chromatography using silica gel and CH₂Cl₂ as the eluent. Recrystallization from CH₂Cl₂/hexanes yielded the title compound (116) as yellow crystals; yield: 68% (0.216g); mp 227-228°C.

I.R. (KBr): 3394, 2923, 1736 (sydnone C=O), 1554, 1400, 1248, 1212, 758 cm⁻¹; ¹H-NMR (CDCl₃): aromatic H’s (8.08-7.26 δ), NH (6.14 δ), tert-butyl group (1.78 δ); ¹³C-NMR (CDCl₃): 163.67, 148.13, 142.09, 131.81, 126.90, 122.61, 118.36, 114.44, 94.12, 51.81, 27.89 ppm. Elemental analysis: C₁₁H₈N₄O₃ * ¼ H₂O (MW: 258.28): Calculated: C: 59.42; H: 5.56; N: 21.32; Found: C: 59.41; H: 5.47; N: 21.08

Synthesis of 4-(amino)sydno[3,4-a]quinoxaline (108)

4-(t-Butylamino)sydno[3,4-a]quinoxaline (116) (0.0216g, 0.088mmol) was added to stirring sulfuric acid (1mL) at room temperature. After 30 minutes no sign of starting material remained (TLC evidence), so water (3mL) was added, followed by the addition of 10% NaOH until the reaction mixture was slightly basic by pH paper. Extraction with dichloromethane, and removal of solvent in vacuo afforded the title compound as a yellow solid; yield: 96% (0.017g); IR (KBr): 3396, 2923, 1751 (sydnone C=O), 1654, 1548, 1212, 1072, 753 cm⁻¹.
Synthesis of 4-(acetamido)sydno[3,4-a]quinoxaline (118)

4-(Amino)sydno[3,4-a]quinoxaline (108) (0.0125g, 0.062mmol) was added to stirring acetic anhydride (1.5mL). The mixture was allowed to reflux at 60°C for 2 hours. Water (10mL) was then added, and the reaction mixture was extracted with 10% aqueous sodium bicarbonate and dichloromethane. The dichloromethane was removed *in vacuo*. The desired product was obtained through column chromatography using silica gel and CH$_2$Cl$_2$ as the eluent. Recrystallization from CH$_2$Cl$_2$/hexanes afforded the title compound 118 as tan crystals; yield: 72% (0.011g); mp 174-175°C. I.R. (KBr): 3331, 2923, 1760 (sydnone C=O), 1705, 1525, 1368, 1272, 1016, 763, 778 cm$^{-1}$; $^1$H-NMR (CDCl$_3$): 8.69 (s, 1H (N-H)), 8.26 (d, 1H), 7.95 (m, 2H), 7.63 (m, 1H), 2.66 (s, 3H) ppm; $^{13}$C-NMR (CDCl$_3$): 169.84, 163.26 (sydnone C=O), 144.97, 141.01, 133.65, 129.35, 127.68, 120.80, 115.63, 95.31 (sydnone C-4), 26.12 ppm; Elemental analysis: C$_{11}$H$_8$N$_4$O$_3$ (MW: 244.21): Calculated: C: 54.10; H: 3.30; N: 22.94; Found: C: 53.68; H: 3.43; N: 22.53

Reaction of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) with propionic anhydride

In a small round bottom flask with stirring propionic anhydride (1mL), was added 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) (0.010g, 0.049mmol). The reaction was allowed to reflux at 75°C for 1.5 hours. After this time, no starting material remained by TLC evidence. Water (15mL) was added to the reaction mixture and allowed to stir for 45 minutes. Then, extraction with CH$_2$Cl$_2$ and 10% aqueous sodium bicarbonate was
done. The solvent was removed *in vacuo*, leaving a tan smear on the flask. An accurate weight could not be measured, therefore no percent yield was calculated. I.R. (KBr): 3337, 2958, 2924, 2854, 1732 (sydnone C=O), 1715, 1583, 1566, 1525, 1460, 1370, 1262, 1121, 1074 cm⁻¹.

**Attempted reaction of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) with trifluoracetic anhydride**

In a flame-dried high pressure reaction tube, 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) (0.0109g, 0.054mmol) was added to stirring trifluoroacetic anhydride (2.0mL). The reaction was allowed to stir at 60°C. After 4 hours, no reaction had taken place by TLC evidence, and the reaction was left overnight. After 18 hours, no reaction had taken place by TLC evidence.

**Attempted reaction of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) with 4-fluorobenzoyl chloride**

To a stirred mixture of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) (0.0151g, 0.075mmol) in pyridine (1mL) was added 4-fluorobenzoyl chloride (0.0177mL, 0.15mmol). The reaction was allowed to reflux at 60°C for 5 hours. No reaction had taken place by TLC evidence, as all starting material remained. Increased time (18 hours) yielded the same result.
Attempted reaction of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) with 2-chlorobenzoyl chloride

To a stirred mixture of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) (0.0102g, 0.050mmol) in pyridine (1mL) was added 2-chlorobenzoyl chloride (0.013mL, 0.109mmol). The reaction was allowed to reflux at 60°C for 16 hours. No reaction had taken place by TLC evidence as all starting material remained. Increased temperature (90°C), time (24 hours), and equivalents of 2-chlorobenzoyl chloride (3 eq.) yielded the same results.

Attempted reaction of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) with methanesulfonyl chloride

In a high pressure reaction tube that had been flushed with N₂ and flame-dried was added dry THF (2mL) and 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) (0.022g, 0.109mmol). Then, triethylamine (0.07mL, 0.50mmol) was added at 100°C. Next, the methanesulfonyl chloride (0.013mL, 0.16mmol) was added dropwise to the solution. The reaction was allowed to reflux at 100°C for 48 hours. No reaction had taken place by TLC evidence as all starting material remained. Increased equivalents of methanesulfonyl chloride (3 eq.) yielded the same results.

Attempted reaction of 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) with benzenesulfonyl chloride
In a high pressure reaction tube that had been flushed with N\textsubscript{2} and flame-dried was added dry THF (2 mL) and 4-(4-aminophenyl)sydno[3,4-a]quinoxaline (108) (0.023g, 0.150mmol). Then, triethylamine (0.072mL, 0.52mmol) was added at 100°C. Next, the benzenesulfonyl chloride (0.022mL, 0.17mmol) was added dropwise to the solution. The reaction was allowed to reflux at 100°C for 48 hours. No reaction had taken place by TLC evidence as all starting material remained. Increased equivalents of benzenesulfonyl chloride (3 eq.) yielded the same results.

Synthesis of 4-bromo-3-(2-amino-5-bromophenyl)sydnone (121)

The title compound was prepared via a literature method.\textsuperscript{85} To a stirred solution of 3-(2-aminophenyl)sydnone (70) (0.200g, 0.001mol) and methanol (12mL) was added N-bromosuccinimide (0.4045g, 0.0023mol) over a 30 minute period at room temperature. The mixture was then left for an additional 45 minutes, after which no starting material remained by TLC evidence. Then, water (20mL) was added to the reaction mixture, and extraction was done with CH\textsubscript{2}Cl\textsubscript{2} (3 times 20mL). Solvent was removed in vacuo, and a brown solid formed as the title compound 121; yield 88\% (0.3309g); melting point 151-152°C. Melting point, IR, and TLC were identical to an authentic sample.

Synthesis of 3-(2-amino-5-bromophenyl)sydnone (122)

To a stirring solution of 4-bromo-3-(2-amino-5-bromophenyl)sydnone (121) (0.1111g, 0.33mmol) in methanol (2mL) was added sodium sulfite (0.165g, 1.32mmol) in H\textsubscript{2}O (2mL). After 20 minutes the reaction showed no signs of starting material by TLC evidence, and the mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 times 15mL). The solvent was
removed \textit{in vacuo}, and a tan solid formed as the title compound \textbf{122}; yield: 67\% (0.056g); melting point 168-169\degree C. Melting point, IR, and TLC were identical to an authentic sample.

\textbf{Synthesis of triphenylphosphine 2-(4-bromo-3-sydnonyl)phenyl imide (123)}

To a stirred solution of 3-(2-amino-5-bromophenyl)sydnone (\textbf{122}) (0.0523g, 0.204mmol) in dry THF (1mL), was added triphenylphosphine (0.059g, 0.224mmol). Diisopropyl azodicarboxylate (0.044mL, 0.224mmol) was added dropwise and the reaction mixture was allowed to stir. After 4 hours, no starting material remained by TLC evidence. The solvent was removed \textit{in vacuo}, and the product was isolated with column chromatography using silica gel and CH$_2$Cl$_2$ as the eluent. Recrystallization from CH$_2$Cl$_2$/hexanes afforded the title compound \textbf{123} as light tan crystals; yield: 85\% (0.09g); melting point 162-163\degree C. Melting point and IR were identical to an authentic sample.

\textbf{Synthesis of 4-(phenylamino)-8-bromosydno[3,4-a]quinoxaline (124)}

To a stirred solution of triphenylphosphine 2-(4-bromo-3-sydnonyl)phenyl imide (\textbf{123}) (0.100g, 0.195mmol) and anhydrous toluene (2mL) in a high pressure reaction tube that was flushed with N$_2$ and flame-dried, was added phenyl isothiocyanate (0.029g, 0.026mL, 0.215mmol) dropwise at 110\degree C. After 5 hours, no starting material remained by TLC evidence. The solvent was removed \textit{in vacuo}, and the desired product was isolated using column chromatography with silica gel and CH$_2$Cl$_2$ as the eluent. Recrystallization from CH$_2$Cl$_2$/hexanes afforded the title compound \textbf{124} as bright yellow
crystals. yield: 31% (0.021g); mp 227-228°C. I.R. (KBr): 3343, 1741 (sydnone C=O), 1620, 1555, 1495, 1258, 1045, 748, cm⁻¹; ¹H-NMR (CDCl₃): 8.29 (s, 1H), 8.05 (s, 1H (N-H)), 7.55 (m, 6H) ppm; ¹³C-NMR (CDCl₃): 164.05 (sydnone C=O), 147.34, 141.70, 137.78, 136.56, 129.78, 129.22, 124.47, 120.79, 120.40, 118.42, 117.87, 95.31 (sydnone C-4) ppm; Elemental analysis: C₁₅H₉BrN₄O₂ * 2/3 H₂O (MW: 357.16): Calculated: C: 48.80; H: 2.82; N: 15.18; Found: C: 49.25; H: 2.59; N: 14.62

Synthesis of 4-(4-methoxyphenylamino)-8-bromosydno[3,4-a]quinoxaline (125)

To a stirred solution of triphenylphosphine 2-(4-bromo-3-sydnonyl)phenyl imide (123) (0.049g, 0.094mmol) and anhydrous toluene (2mL) in a high pressure reaction tube that was flushed with N₂ and flame-dried, was added 4-methoxyphenyl isothiocyanate (0.017g, 0.014mL, 0.104mmol) dropwise at 110°C. After 4 hours, no starting material remained by TLC evidence. The solvent was removed in vacuo, and the desired product was isolated using column chromatography with silica gel and CH₂Cl₂ as the eluent. Recrystallization from CH₂Cl₂/hexanes afforded the title compound 124 as bright yellow crystals, yield: 38% (0.014g); mp 206-207°C. I.R. (KBr): 3361, 1750 (sydnone C=O), 1616, 1557, 1496, 1245, 1044, 831, cm⁻¹; ¹H-NMR (CDCl₃): 8.25 (d, 1H), 7.93 (s, 1H (N-H)), 7.63 (m, 4H) 7.25 (m, 2H), 3.83 (s, 3H) ppm; ¹³C-NMR (CDCl₃): 164.10 (sydnone C=O), 156.65, 147.32, 141.65, 136.46, 130.58, 129.47, 122.23, 120.52, 118.36, 117.32, 114.28, 95.20 (sydnone C-4), 55.52, 29.69 ppm; Elemental analysis: C₁₆H₁₁BrN₄O₃ (MW: 387.19): Calculated: C: 49.63; H: 2.86; N: 14.47; Found: C: 49.38; H: 2.93; N: 14.29
Synthesis of 4-(4-iodophenylamino)-8-bromosydno[3,4-a]quinoxaline (124)

To a stirred solution of triphenylphosphine 2-(4-bromo-3-sydnonyl)phenyl imide (123) (0.103g, 0.198mmol) and anhydrous toluene (2mL) in a high pressure reaction tube that was flushed with N₂ and flame-dried, was added 4-iodophenyl isothiocyanate (0.057g, 0.026mL, 0.218mmol) at 110°C. After 5 hours, no starting material remained by TLC evidence. The solvent was removed in vacuo, and the desired product was isolated using column chromatography with silica gel and CH₂Cl₂ as the eluent. Recrystallization from CH₂Cl₂/hexanes afforded the title compound 124 as bright yellow crystals. yield: 60% (0.058g); mp 255-256°C. I.R. (KBr): 3349, 3076, 1748 (sydnone C=O), 1613, 1555, 1482, 1433, 1302, 1285, 1228, 1103, 999, 714, cm⁻¹; Elemental analysis: C₁₅H₈BrIN₄O₂ * (MW: 483.06): Calculated: C: 37.30; H: 1.67; N: 11.60; Found: C: 37.40; H: 1.77; N: 11.45

Synthesis of 4-(phenylamino)-8-(2-trimethylsilylvinyl)sydno[3,4-a]quinoxaline (127)

To 4-(phenylamino)-8-bromosydno[3,4-a]quinoxaline (124) (0.040g, 0.112mmol) in dry THF (7mL) in a Schlenk tube under an atmosphere of N₂, was added PPh₃ (0.0008g, 3.05x10⁻³ mmol), TEA (0.027mL, 0.195mmol), and TMS acetylene (0.063mL, 0.443mmol). This solution was freeze/pump/thawed three times. Then, Pd(PPh₃)₂Cl₂ (0.0047 g, 6.7x10⁻³ mmol) was added. After 20 minutes, CuI (0.0004g) was added. The reaction was allowed to stir at 55°C for 13 hours, at which point no starting material remained by TLC evidence. The solvent was removed in vacuo, and the desired product (top running spot) was isolated using column chromatography with silica gel and CH₂Cl₂ as the eluent. Recrystallization from CH₂Cl₂/hexanes afforded the title compound 127 as
bright yellow crystals, yield: 46% (0.019g); mp 179-180°C. I.R. (KBr): 3355, 2957, 2156, 1758 (sydnone C=O), 1616, 1541, 1429, 1290, 1242, 1047, 860 cm⁻¹; ¹H-NMR (CDCl₃): 8.23 (d, 1H), 8.10 (s, 1H (N-H)), 7.85 (m, 4H) 7.43 (m, 2H), 7.26 (m, 2H), 0.30 (s, 9H) ppm; ¹³C-NMR (CDCl₃): 164.39 (sydnone C=O), 147.59, 142.43, 137.92, 136.65, 129.31, 128.30, 124.65, 120.64, 120.28, 120.04, 119.11, 102.99 (sydnone C-4), 97.86, 95.54, 0.00 ppm; Elemental analysis: C₂₀H₁₈N₄O₂Si (MW: 374.47) * 1/3 H₂O:
Calculated: C: 63.14; H: 4.95; N: 14.73; Found: C: 63.21; H: 4.93; N: 14.79

Synthesis of 4-(4-methoxyphenylamino)-8-(2-trimethylsilyl ethynyl)sydnö[3,4-a]quinoxaline (128)

To 4-(4-methoxyphenylamino)-8-bromosydnö[3,4-a]quinoxaline (125) (0.054g, 0.139mmol) in dry THF (7mL) in a Schlenk tube under an atmosphere of N₂, was added PPh₃ (0.0008g, 3.05*10⁻³mmol), TEA (0.029mL, 0.209mmol), and TMS acetylene (0.08mL, 0.556mmol). This solution was freeze/pump/thawed three times. Then, Pd(PPh₃)₂Cl₂ (0.006g, 8.6*10⁻³mmol) was added. After 20 minutes, CuI (0.0005g, 2.6*10⁻³mmol) was added. The reaction was allowed to stir at 55°C for 13 hours, at which no starting material remained by TLC evidence. The solvent was removed in vacuo, and the desired product (top running spot) was isolated using column chromatography with silica gel and CH₂Cl₂ as the eluent. Recrystallization from CH₂Cl₂/hexanes afforded the title compound 128 as bright yellow crystals. yield: 44% (0.025g); mp 222-223°C. I.R. (KBr): 3376, 2956, 2916, 2848, 2160, 1744 (sydnone C=O), 1617, 1551, 1507, 1462, 1264, 1126, 1048, 844 cm⁻¹; ¹H-NMR (CDCl₃): 8.21 (d, 1H), 7.98 (s, 1H (N-H)), 7.73 (m, 4H) 6.95 (d, 2H), 3.83 (s, 3H), 0.30 (s, 9H) ppm; ¹³C-
NMR (CDCl₃): 164.44 (sydnone C=O), 156.88, 147.65, 142.65, 136.58, 130.83, 128.13, 122.56, 119.95, 119.85, 119.10, 114.50, 103.07 (sydnone C-4), 97.62, 95.50, 0.00 ppm;  
Elemental analysis: C₂₁H₂₀N₄O₃Si (MW: 404.49): Calculated: C: 62.36; H: 4.98; N: 13.85; Found: C: 61.84; H: 4.96; N: 13.69

**Synthesis of 4-(4-iodophenylamino)sydno[3,4-a]quinoxaline (129)**

The title compound was prepared via a literature method.⁸⁴ To triphenylphosphine-2-(3-sydnone)phenylimide (106) (0.300g, 0.069mmol) in anhydrous toluene (6mL), was added 4-iodophenyl isothiocyanate (0.269g, 0.100mmol) at 100°C in a high pressure reaction tube that was flame-dried and flushed with N₂. After 5 hours, no starting material remained by TLC evidence, and the solvent was removed in vacuo. The product (top running spot by TLC) was isolated using column chromatography with silica gel and CH₂Cl₂ as the eluent. Recrystallization with CH₂Cl₂/hexanes afforded the title compound 129 in an 87% yield (0.241g). Melting point and IR were identical to an authentic sample.

**Synthesis of 4-(4-(2-trimethylsilylethynyl)phenylamino)sydno[3,4-a]quinoxaline (130)**

To 4-(4-iodophenylamino)sydno[3,4-a]quinoxaline (129) (0.100g, 0.248mmol) in dry THF (8 mL) in a Schlenk tube under an atmosphere of N₂, was added PPh₃ (0.0017g), TEA (0.070mL, 0.496mmol), and TMS acetylene (0.135mL, 0.955 mmol). This solution was freeze/pump/thawed three times. Then, Pd(PPh₃)₂Cl₂ (0.010g, 1.5*10⁻²mmol) was added. After 20 minutes, Cul (0.0009g) was added. The reaction was allowed to stir at 55°C for 13 hours, at which no starting material remained by TLC evidence. The solvent
was removed in vacuo, and the desired product (top running spot) was isolated using column chromatography with silica gel and CH$_2$Cl$_2$ as the eluent. Recrystallization from CH$_2$Cl$_2$/hexanes afforded the title compound 130 as bright yellow crystals. yield: 48% (0.046g); mp 224-225°C. I.R. (KBr): 3343, 2948, 2153, 1738 (sydnone C=O), 1605, 1557, 1531, 1504, 1397, 1290, 1248, 1115, 1044, 1019, 837 cm$^{-1}$; $^1$H-NMR (CDCl$_3$): 8.17 (m, 1H), 8.10 (s, 1H (N-H)), 7.85 (m, 3H) 7.76 (m, 1H), 7.51 (m, 3H), 0.27 (s, 9H) ppm; $^{13}$C-NMR (CDCl$_3$): 164.21 (sydnone C=O), 146.79, 142.20, 138.19, 133.35, 132.84, 128.42, 125.46, 120.15, 119.55, 118.53, 115.60, 104.87 (sydnone C-4), 95.23, 93.94, 0.00 ppm; Elemental analysis: C$_{20}$H$_{18}$N$_4$O$\text{Si}$ (MW: 374.47): Calculated: C: 64.15; H: 4.84; N: 14.96; Found: C: 64.11; H: 4.90; N: 14.95

Synthesis of 4-(4-(2-trimethylsilylethynyl)phenylamino)-8-bromosydno[3,4-a]quionoxaline (131)

To 4-(4-iodophenylamino)-8-bromosydno[3,4-a]quionoxaline (124) (0.023g, 0.048mmol) in dry THF (3mL) in a Schlenk tube under an atmosphere of N$_2$, was added PPh$_3$ (0.0003g), TEA (0.012mL, 0.086mmol), and TMS acetylene (0.021mL, 0.440mmol). This solution was freeze/pump/thawed three times. Then, Pd(PPh$_3$)$_2$Cl$_2$ (0.002g, 2.9*10$^{-3}$mmol) was added. After 20 minutes, CuI (0.0002g) was added. The reaction was allowed to stir at 55°C for 13 hours, at which no starting material remained by TLC evidence. The solvent was removed in vacuo, and the desired product (top running spot) was isolated using column chromatography with silica gel and CH$_2$Cl$_2$ as the eluent. Recrystallization from CH$_2$Cl$_2$/hexanes afforded the title compound 131 as bright yellow crystals. yield: 45% (0.010g); mp 256-257°C. I.R. (KBr): 3357, 2922, 2851, 2157, 1760
(sydnone C=O), 1620, 1561, 1434, 1103, 843, 755 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)): 8.31 (d, 1H), 8.12 (s, 1H (N-H)), 7.82 (m, 3H) 7.70 (d, 2H), 7.50 (d, 1H), 0.27 (s, 9H) ppm; \(^{13}\)C-NMR (CDCl\(_3\)): 163.98 (sydnone C=O), 146.96, 141.25, 137.89, 136.68, 132.88, 129.74, 120.69, 119.74, 118.91, 118.47, 118.20, 104.75 (sydnone C-4), 95.28, 94.19, 0.00 ppm.

**Synthesis of 4-(4-tert-butyllamino)-8-bromosydno-[3,4-a]quinoxaline (132)**

To a stirred solution of triphenylphosphine 2-(4-bromo-3-sydnonyl)phenyl imide (123) (0.049g, 0.095mmol) and anhydrous toluene (3mL) in a high pressure reaction tube that was flushed with \(\text{N}_2\) and flame-dried, was added \(t\)-butyl isocyanate (0.029g, 0.033mL, 0.290mmol) dropwise at 90\(^\circ\)C. After 18 hours, no starting material remained by TLC evidence. The solvent was removed by a flow of \(\text{N}_2\), and the desired product (top running spot by TLC) was isolated using column chromatography with silica gel and CH\(_2\)Cl\(_2\) as the eluent. Recrystallization from CH\(_2\)Cl\(_2\)/hexanes afforded the title compound 132 as bright yellow crystals. yield: 6% (0.0017g); mp 241-242\(^\circ\)C. I.R. (KBr): 3379, 2919, 1737 (sydnone C=O), 1581, 1552, 1283, 995, 827, 755 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)): 8.22 (d, 1H), 7.72 (m, 1H), 7.54 (s, 1H) 6.10 (s, 1H (N-H)), 1.57 (s, 9H) ppm; \(^{13}\)C-NMR (CDCl\(_3\)): 164.51 (sydnone C=O), 149.36, 142.14, 136.17, 129.36, 119.87, 118.32, 116.08, 95.20 (sydnone C-4), 53.27, 29.00 ppm; Elemental analysis: C\(_{13}\)H\(_{13}\)BrN\(_4\)O\(_2\) (MW: 326.01) * \(\frac{1}{2}\) H\(_2\)O: Calculated: C: 45.10; H: 4.08; N: 16.18; Found: C: 44.88; H: 3.79; N: 14.46
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