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Synthetic Routes to a Fused-Ring Sydnoquinazoline

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SYNTHETIC ROUTES TO A FUSED-RING SYDNOQUINAZOLINE

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By

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B.S., Baldwin-Wallace College, 2003

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Gregory Edmond Storer ENTITLED Synthetic Routes to a Fused-Ring Sydnoquinazoline BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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Abstract

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In this research, 5-methylsydno-[3,4-a]quinazoline was synthesized *via* multiple methodologies, the best of which yielded the target compound in 50 % overall yield for the six steps. Synthesis of this compound in reasonable yields and exploration of its chemical behavior is of particular interest as a putative NO-prodrug.

As an initial approach to the synthesis and accumulation of the compound of interest, attempts were made to optimize the existing synthetic pathway to its precursors. The starting material, 3-(2-acetylphenyl)sydnone, was prepared in 3 steps from commercially available starting material in good yields. This sydnone compound was then converted to the versatile intermediate, 3-(2-acetylphenyl)sydnone oxime. This conversion was accomplished by two distinct means, one of which was a novel microwave-assisted synthesis. Following its synthesis, 3-(2-acetylphenyl)sydnone oxime was converted to several reactive intermediates (*O*-acetate, *O*-tosylate, *O*-mesylate) in order to evaluate their utility with regards to cyclization to the aforementioned sydnoquinazoline.

With respect to cyclization, 3-(2-acetylphenyl)sydnone oxime was treated with trifluoroacetic acid, which resulted in the target sydnoquinazoline in low yields. The reactive intermediates were also treated under thermal conditions, with the *O*-tosylate and *O*-mesylate species resulting in the target fused-ring sydnone in very low yields. These more reactive sydnones were exposed also to lithiation conditions to explore the

possibility of base-induced cyclization to the desired sydnoquinazoline. Under these conditions, the *O*-tosylate and *O*-mesylate were treated with lithium diisopropyl amide. The *O*-tosylate resulted in the formation of the target quinazoline in moderate yields, while the *O*-mesylate resulted in formation of the target compound in good yields. Indeed, by adjustment in the amount of base employed, an up to 80% yield of the desired fused-ring sydnone could be realized; a considerable improvement over the methods previously employed.

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Acknowledgments

I would like to extend my sincerest gratitude to my family for their continual encouragement throughout my education. Without their unconditional love and kindness, I would not be where I am today. I especially want to thank my parents, Mary Ann and Al Storer, for helping me make it through these last few months of graduate school. They are truly a blessing to me more than they will ever know.

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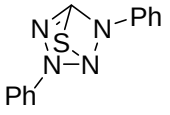
Introduction

Foreword

In 1882, Emil Fischer synthesized dehydrodithizone *via* the oxidation of dithizone. On the basis of the techniques available at the time, he proposed a bicyclic structure **1** for the compound. However, in the late 1940's, Baker, Ollis, and Poole[2, 3] were able to determine that the actual molecule has a monocylic, dipolar structure **2**[4] to which they assigned the term mesoionic (derived from mesomeric and ionic).



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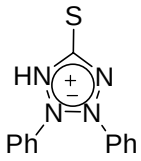


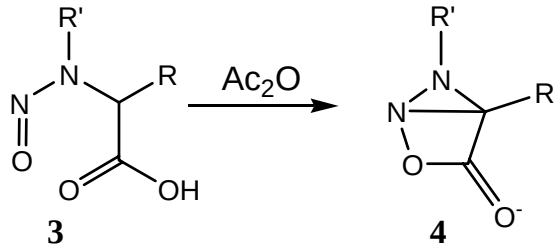
2

Amongst the various mesoionic compounds known today, the most fascinating and comprehensively studied compounds are the sydnones. First prepared in Sydney, Australia in 1935, sydnones are monocyclic, dipolar, heteroaromatic oxadiazolones. In addition to extensive studies of the chemical and physical properties of sydnones, the biological properties and applications have been explored.

Since their inception as a class of compounds in 1955, until 1989, mesoionic compounds, including sydnones, have been the subjects of a multitude of review articles in the literature[5-12]. Subsequent to that time, many M.S. theses have originated from this laboratory pertaining to the various discoveries concerning sydnones from 1989 through 2006[13-27]. The following review is intended to further illuminate the more important features of previous work on sydnones, as well as summarize the recent developments which have occurred from 2006 through 2007.

Historical

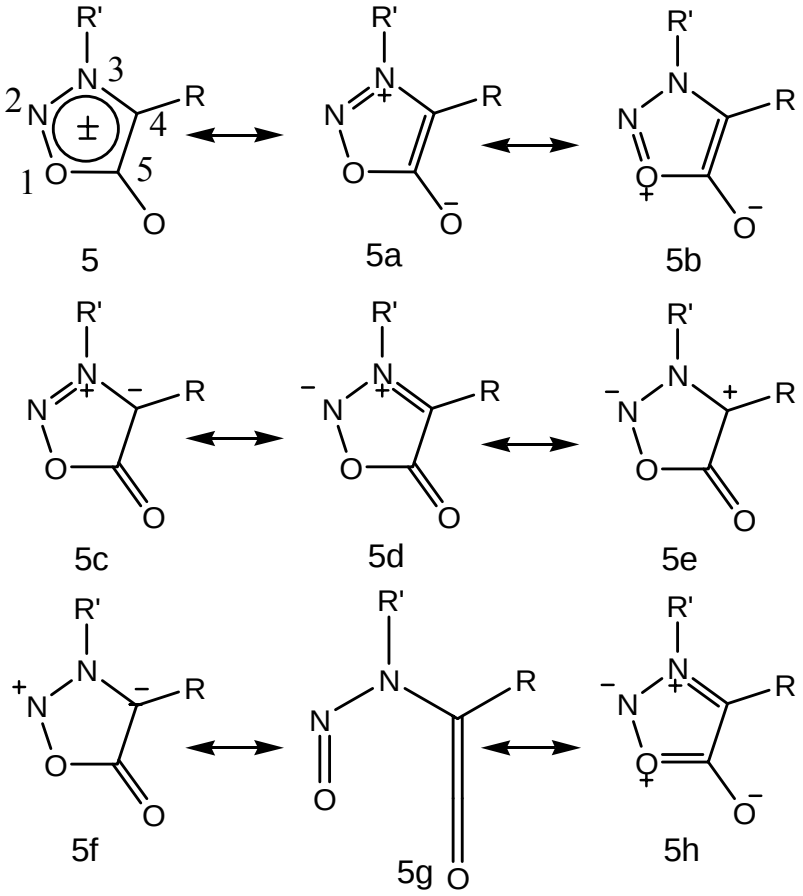
Upon treatment of N-nitroso-N-phenylglycine (**3**; R=H, R'=Ph) with acetic anhydride, Earl and Mackney obtained an anhydro derivative to which they attributed the bicyclic structure **4** (R=H, R'=Ph)[31]. This reaction was then applied to a variety of N-nitrosoglycines and afforded a variety of analogous anhydro derivatives, which have subsequently been dubbed "sydnones," alluding to their discovery in Sydney, Australia.



3 **4**

Although the structure suggested by Earl and Mackney appeared reasonable at the time, subsequent work by other investigators demonstrated that the chemical and physical properties which sydnones exhibit were inconsistent with a bicyclic structure. For instance, sydnones exhibit a greater degree of polarity, are more stable towards heating, and are less reactive towards acids and bases than would be expected for the strained, bicyclic representation **4**. Equipped with these and other data, Baker, Ollis and Poole[28, 29] showed the inaccuracy of that proposed structure and assigned a dipolar, monocyclic 1,2,3-oxadiazolone based structure to this class of compounds. The proposed, mesoionic structure consisted of many resonance forms **5a-h**, which contribute to the overall resonance hybrid, preferentially represented by structure **5**. Because of these unique characteristics the authors proposed that sydnones should be classified as mesoionic compounds. In 1953, Baker and Ollis formalized the rules such that, in order to be considered mesoionic, a molecule 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 resonance energy.[30]



While still a subclass of betaines, these three characteristics distinguish mesoionic compounds from formally related dipolar species such as ylides and zwitterions where a great deal of charge localization is observed. In the mesoionic systems, charge distribution is delocalized and no single resonance form can be drawn accurately.

Properly, sydnones are derivatives of 1,2,3-oxadiazoles; however, since 1,2,3-oxadiazoles are known to be open chain, alpha carbonyl diazo derivatives, it appears that sydnones are the only derivatives of this class that are cyclic in nature. Therefore, the name “sydnone” has become the most common way to describe these compounds.

Because of this unique distinction, the name is used by Chemical Abstracts as a way of grouping these oxadiazole derivatives.

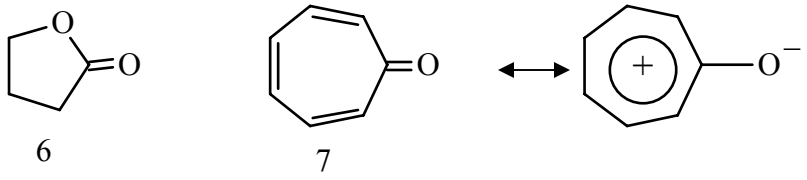
Physiochemical Properties and Electronic Structure

Almost without exclusion, sydnones are stable compounds that exhibit substantial polarity. Generally, arylsydnones are crystalline solids. Alkylsydnones are often liquids or low-melting solids that can be distilled *in vacuo* without appreciable decomposition. Sydnones are soluble in a variety of organic solvents with the main exceptions being non-polar solvents such as petroleum ether and hexanes. Additionally, 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 structure of sydnones **4**.

In their NMR spectra, the proton (when present) at the C-4 position of the sydnone ring is greatly deshielded in comparison to saturated congeners, usually shifted between 6.5-7.5 ppm (depending on solvent). This drastic shift indicates a polar nature and the presence of an aromatic ring current, further discrediting structure **4**. Additionally, the infrared spectra of sydnones include two very prominent features: a strong carbonyl stretch at ~ 1730-1760 cm^{-1} and a stretch of medium intensity at ~ 3150 cm^{-1} for the C-H absorption of the C-4 ring proton (when present)[32-35]. Moreover, the latter is different from what would be expected for either an alkyl or aryl substituent or from an epoxide with comparable ring strain, which absorb around 2900-3050 cm^{-1}, and therefore is particularly useful in determining if the C-4 position is substituted in sydnones of unresolved structure.

With regard to the carbonyl stretch, a single, strong band is usually observed. However, due to Fermi resonance splitting[36,37], in some cases multiple bands have been seen. Furthermore, as was stated above, the sydnone carbonyl typically appears at ~ 1730-1760 cm^{-1} but, in comparison with congeneric carbonyl containing species, such as a γ-lactone (**6**) [which absorbs at 1770 cm^{-1}] and tropone (**7**) [which absorbs at 1638

cm^{-1}], one might conclude that the exocyclic C=O bond at the sydnone C-5 position is closer in length to that of a double bond than a single bond.

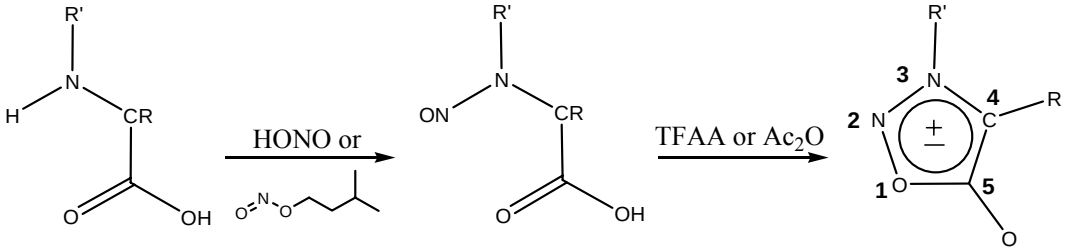


6 7

This conclusion is further supported by the results of X-ray crystallographic analysis of various 3-substituted and 3,4-disubstituted sydnones which showed that this C=O bond was closer in length to that of a double bond. 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. Additionally, molecular orbital calculations and vibrational force constants obtained from vibrational spectra indicate a π-bond order for the sydnone carbonyl lower than those for alicyclic esters, thus supporting the argument that contributions from other vibrational modes cause the sydnone carbonyl group to absorb at a higher frequency than anticipated.[38] Furthermore, it has been demonstrated, by both theoretical and spectroscopic studies, that protonation of a sydnone moiety occurs at the exocyclic oxygen.[39-43] This, then, complements earlier work in which bond orders and charge densities of various sydnones were correlated to the calculated and observed dipole moments and the observed UV maxima.[44,45] These studies thereby support the contention that substantial charge density resides on the exocyclic oxygen.

Synthesis

The conventional general route to sydnones is *via* the cyclodehydration of N-substituted N-nitroso-α-amino acids (*cf.* **3**). While the substituent R can be alkyl, aryl, or hydrogen, the R' substituent must be alkyl or aryl, since if R' is a hydrogen, prototropy occurs to afford a neutral species. Preparation of the N-nitrosoamino acid **3** involves nitrosation of an N-substituted glycine **8** with nitrous acid or, if non-acidic conditions are required, isoamyl nitrite in dimethoxymethane.[46]



8 **3** **5**

With regard to the cyclodehydration step, Earl and Mackney originally used acetic anhydride at room temperature for six days. The preferred method, however, has been cyclization with trifluoroacetic anhydride (TFAA), which occurs rapidly (< 15 minutes) at low temperature (-5ºC to 0ºC) in high yields. Other strategies include: heating in acetic anhydride or thionyl chloride, treatment with phosphorus pentoxide, acetic anhydride at room temperature facilitated by ultrasonication,[47] haloiminium salts,[48] N,N-dimethylchlorosulfitemethaninium chloride,[49] and 2-chloro-1,3,-dimethylimidazolinium chloride.[50] Although the use of TFAA is sometimes more costly than other methods, it remains the most widely used method because of its efficiency, speed and consistency.

An interesting synthetic variation was published by Azarifar in 2006.[51] Therein, 1,3-dibromo-5,5-dimethylhydantoin (DBH), in combination with $NaNO_2$ and acetic

anhydride, efficiently catalyzes the one-pot conversion of various N-arylglycines (**8**, R' = Ar) to arylsydnones (**5**, R = H, R' = Ar) in high yields (80-94%) under mild and neutral conditions. This is the first report of a one-pot conversion and should prove to be very valuable since one step has been eliminated from the usual approach and the handling of suspected carcinogens (N-nitrosated glycines) is also avoided.

Chemical and Biological Behavior

Given the interesting structural characteristics of the sydnone system, a focused effort has been made to illustrate the fact that the sydnone ring exhibits a distinct aromatic nature and dichotomy in electronic effects. A fundamental property of any aromatic system is to undergo electrophilic aromatic substitutions. It has been shown that sydnones do undergo electrophilic substitution at the C-4 position of the ring (with *e.g.* **5**, R = H).[52] Such reactions include halogenation, nitration, acylation, and sulfonation. The unexpectedly high regioselectivity of these reactions (even when an aryl group is attached to the N-3 position) is a result of two major contributing factors: (1) the considerable partial negative charge that resides at the C-4 position appears to activate this position; and (2) the considerable partial positive charge that resides at the N-3 position seems to deactivate the attached aryl ring. However, in the case where activating groups are attached to the aryl ring, the aryl ring moiety can compete successfully for the electrophile, a premise observed for both halogenation and nitration.[53,54]

Sydnones have also been evaluated for their uses as precursors to hydrazines,[55] as 1,3-dipoles in cycloaddition reactions,[56, 57] electrolytic solvents for non-aqueous batteries[58], their potential as agents in non-linear optics[59], and their ability to aid micelle production in molecular aggregation.[60] In addition, a very attractive aspect of sydnone chemistry has been their biological properties which include anti-fungal, anti-inflammatory,[61] analgesic, antibacterial, and anti-tumor activities.[62] Further, sydnones have liquid crystal properties,[63] have been incorporated into azo dyestuffs[64-67] and have been tested for use as lithium battery electrolytes.

Reactions of Sydnones

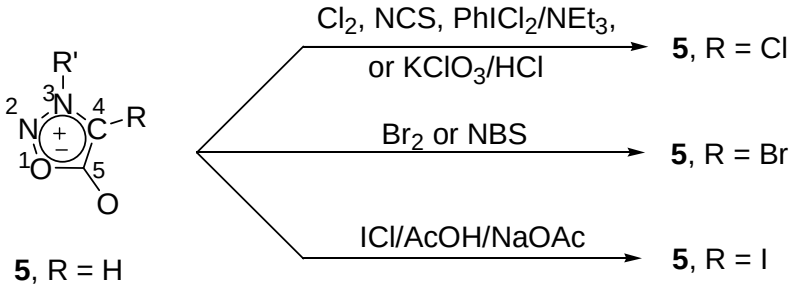
I. Electrophilic Aromatic Substitutions of Sydnones

Sydnones can undergo electrophilic aromatic substitution at the C-4 position when there is a proton at this position (*cf*. **5**, R=H). The electrophiles typically used for aromatic substitutions can also be employed with sydnones due to the considerable negative charge density at the C-4 position. Halogenation, nitration, acylation, and sulfonation of sydnones will be discussed in the following pages.

A. Halogenation and Nitration Exclusively at the C-4 position

Chlorination of sydnones (to form *e.g*. **5**, R = Cl) has been performed by treatment of **5** (R = H) with chlorine,[68-70] potassium chlorate in moderately concentrated HCl[71] , dichloroiodobenzene with triethylamine,[72] or N-chlorosuccinimide (NCS).[73] Reactions of 3-phenylsydnone, **5** (R = H), with bromine[68-70], potassium bromate in HBr or N-bromosuccinimide (NBS)[73] yield the 4-bromosydnone **5** (R = Br). It has been shown also that DBH can conveniently promote the bromination of these sydnones to their 4-bromo substituted congeners (**5**, R = Br, R' = Ar) in excellent yields in DMF at room temperature.[74]

Iodination of sydnones at the C-4 position is much less general and has been achieved only using iodine monochloride in acetic acid at room temperature.[75]



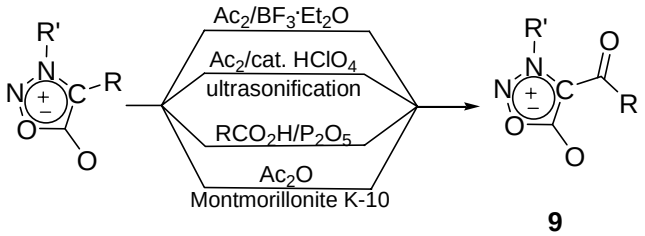
It has been shown that the use of sodium borohydride or sodium dithionite in methanol[76] or activated zinc under ultrasonification[77] can effectively debrominate a C-4 brominated sydnone in a regiospecific fashion. However, drawbacks associated with these methods include the reactivity of sodium borohydride with pendent functional groups (*e.g.* carbonyl compounds), the effects of steric factors with the use of sodium dithionite, and the inefficiency of the ultrasonification method when strong electron-withdrawing groups are present. The approach of choice is undoubtedly the use of sodium sulfite,[78] which suffers from none of these drawbacks. However, all the debromination strategies mentioned are complementary and therefore are useful tools in the chemistry of sydnones. Based upon the ease with which sydnones can be brominated and debrominated, it has been postulated that the 4-bromo moiety (*e.g.* in **5**, R = Br) can be used as a protecting group for the sydnone ring.[79]

Nitration of 3-phenylsydnone occurs when it is allowed to react with potassium nitrate in sulfuric acid at -5 ºC, affording the unstable 4-nitro derivative **5** (R = NO_2, R' = Ph).[80] However, the strongly acidic conditions required to effect nitration have made this substitution reaction on sydnones relatively unimportant.

B. Acylation, Carboxamidation, and Sulfonation at the C-4 position

It had been reported[81] that it was not possible to acylate 3-phenylsydnone, **5** (R = H, R' = Ph) with either acetic anhydride or benzoyl chloride. In the presence of a Lewis

acid catalyst, however, Yashunskii showed that it was possible to obtain the 4-acetyl derivative, **9** (R = Me, R' = Ph) *via* the use of acetic anhydride and boron trifluoride etherate; albeit in very low yield.[82] More recently, Tien and coworkers have acylated various substituted sydnones using acetic anhydride and $HClO_4$ or H_3PO_4.[83] In a different approach, Greco and coworkers[84] obtained the desired acylated sydnones by heating various 3-substituted sydnones in the presence of a carboxylic acid and P_2O_5. However, it was noted that neither aryl nor aralkyl acids reacted, thus limiting the scope of this process.

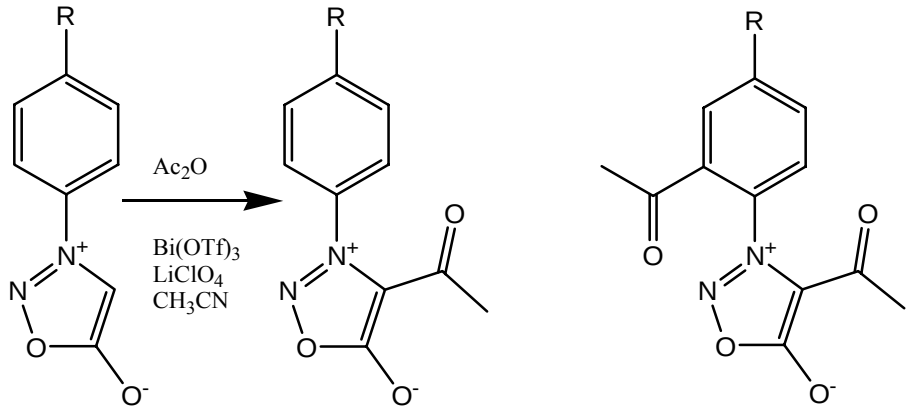


9

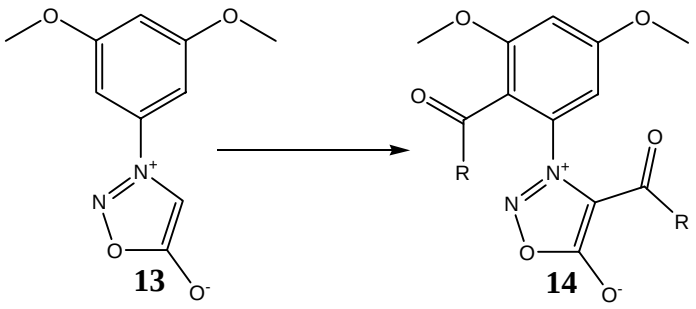
More recent methodology has shown that 4-acylsydnones can be prepared in a two-step process *from* a cuprosydnone (*cf.* Metallation of Sydnones Section) and Tien and coworkers[85] have shown that ultrasonification of 3-substituted sydnones in the presence of acetic anhydride and a catalytic amount of perchloric acid will afford the 4-acylated derivatives quickly, in moderate yield. 4-Acetyl derivatives of 3-substituted sydnones also have been obtained *via* the use of acetic anhydride and a catalytic amount of Montmorillonite K-10 at elevated temperatures.[86] This method is useful in that the catalyst can be easily removed and disposed of. However, one disadvantage is that the method is sluggish or unsuccessful with compounds containing electron-withdrawing groups *ortho* to the sydnone ring.

In recent work from our group**,** Friedel-Crafts acylations at the 4-position of the sydnone ring have been achieved in high yields using various alkyl anhydrides (mainly

acetic anhydride), bismuth triflate and lithium perchlorate in anhydrous acetonitrile at 95 ^{o}C (*cf*. **10** to **11a-d**).[87] Many attempts were made to extend this study to the preparation of the corresponding diacyl sydnone **12** (additional substitution on the *ortho*-position of the aryl ring). Several attempts at diacylation have been made using the strongly activated sydnone 3-(3,5-dimethoxyphenyl)sydnone **13** (R = 3,5-MeO), but no methods thus far have given only the desired diacyl product **14**.



10 **11a: R=Cl, 87%** **12**
11b: R=Br, 83%
11c: R=CH_3, 83%
11d: R=OCH_3, 78.5%

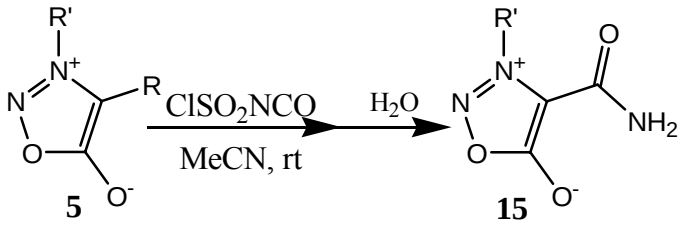


13 **14**

Additionally, it has recently been reported by Azarifar, that treatment of 3-phenylsydnone with DBH in acetic anhydride yielded the desired 4-acetyl-3-phenylsydnone in reasonable yields. Efforts to extend this study to give the diacyl sydnone **14** from 3-(3,5-dimethoxyphenyl)sydnone (**13**) have been carried out by

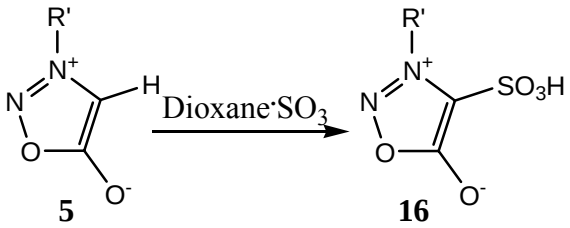
Turnbull and McGraner (unpublished work)[88], however, the results have been inconsistent.

Carboxamidation of sydnones at the C-4 position has been achieved by two means. The first of these involves the abstraction of the sydnone ring proton using a strong base, addition of carbon dioxide, followed by thionyl chloride then ammonia. More recently, Turnbull, Gross and Hall[89] found that treatment of a variety of 3-substituted sydnones **5** with chlorosulfonyl isocyanate in acetonitrile at room temperature gave the corresponding 4-carboxamido sydnones **15** in good yields. This one-step method has considerable advantages over the previous four-step approach.



R' = Ph,3-$MeOC_6H_4$, 4-ClC_6H_4, 2,3-$Me_2C_6H_3$

In 1959, it was reported by Yashunskii and coworkers that direct sulfonation of a variety of 3-substituted sydnones was possible.[90] In those reports, it was shown that treatment of sydnones **5** (R = H) with dioxane-sulfur trioxide complex (SO_3) in CH_2Cl_2 at 20 ^oC to 40 °C generated the sulfonated derivatives (**16**, R' = 4-MeO- or 4-$EtOC_6H_4$), which were characterized as either the barium or S-benzylthiuronium salts. All attempts to neutralize and, thus, prepare these compounds as the free sulfonic acids were unsuccessful and resulted in the isolation of the non-sulfonated sydnones **5** (R = H).

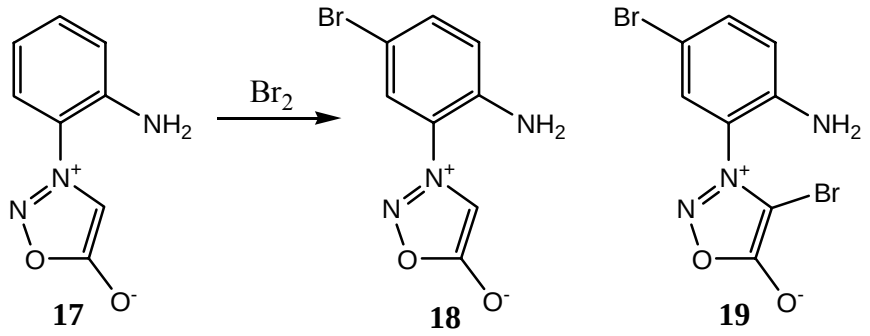


5 **16**

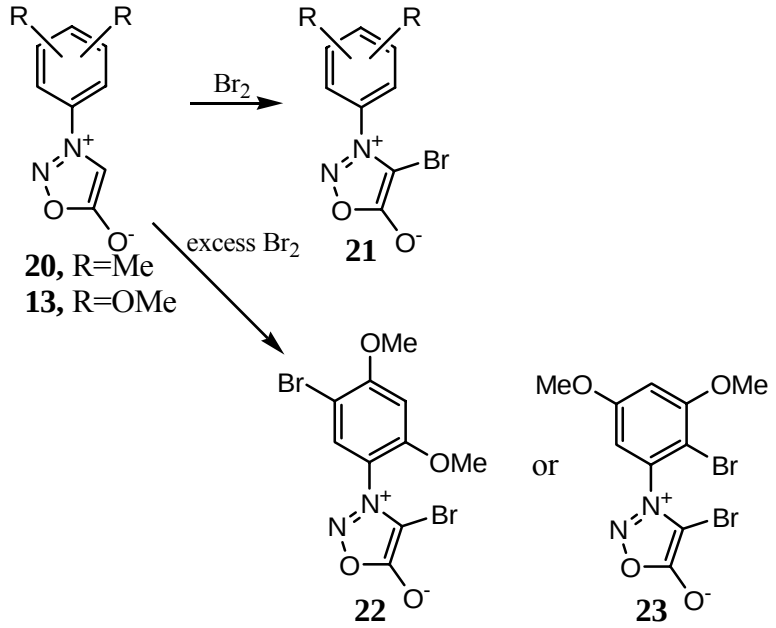
C. Substitutions at the Aryl Ring of 3-Arylsydnones

Generally, when a 3-arylsydnone is reacted with an electrophile, reaction occurs almost exclusively at the sydnone C-4 position. This is attributed to the considerable partial negative charge that is exhibited at this position. Reactivity toward substitution on the aryl moiety is significantly decreased, due to the partial positive charge that resides at the sydnone N-3 position.

Investigation of the addition of activating groups to the aryl moiety of 3-phenylsydnone was carried out in an attempt to effect aryl substitution in preference to sydnone C-4 substitution. As the first example, the bromination of 3-(2-aminophenyl)sydnone (**17**) was examined. The major products obtained from the aforementioned reaction were 3-(2-amino-5-bromophenyl)sydnone (**18**) and 3-(2-amino-5-bromophenyl)-4-bromosydnone (**19**), both of which are derived from bromination on the aryl ring. This was the first observation of competitive electrophilic substitution of the aryl moiety attached to the sydnone ring. Subsequently it was observed that when NBS was added to **17**, only **18** was formed in 70% yield.[91]

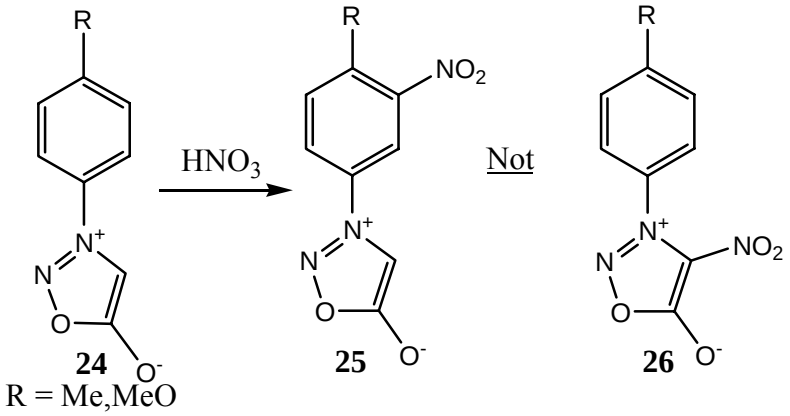


Extension of this methodology to a series of dimethylaryl- or dimethoxyarylsydnones (**13** and **20**, respectively) showed that bromination with 1 equivalent of bromine occurred only at the C-4 position of the sydnone ring (leading to **21**).[92] In fact, even with a considerable excess of bromine, only the most activated sydnones, the 3-(2,4- and 3,5-dimethoxyphenyl) derivatives, were brominated on the aryl ring but, even then, only *after* bromination had occurred at the sydnone C-4 position, giving **22** or **23**, respectively.

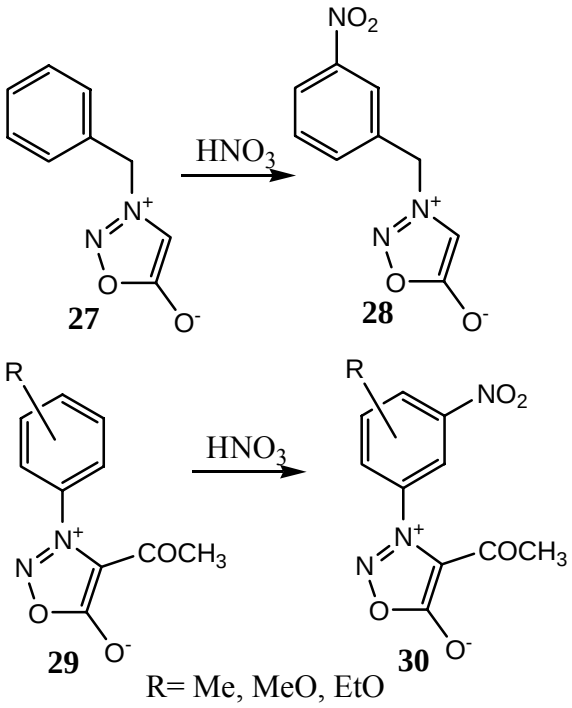


Aleem[93] and Turnbull examined further the electrophilic aromatic substitution of 3-(3,5-dimethoxyphenyl)sydnone (**13**, R = 3,5-MeO) in the hope that the strongly activated ring would allow for competitive substitution. In general, brominating agents (potassium bromate and N-bromosuccinimide), chlorinating agents (potassium chlorate and N-chlorosuccinimide), iodinating agents (potassium iodate and iodine monochloride) and a carboxamidation agent (chlorosulfonyl isocyanate) showed a preference for substitution on the sydnone ring initially. However depending on the reagent and quantities used, di- and even tri-halogenated species could be prepared *via* halogenation on the aryl ring.

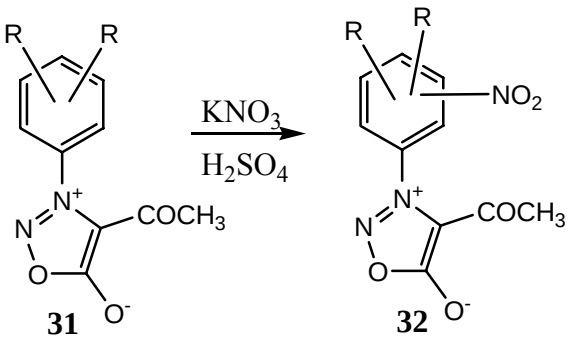
In contrast to the situation with halogenation, even mildly activated 3-arylsydnones undergo nitration preferentially at the aryl moiety and not at the sydnone C-4 position. Thus, under nitrating conditions, activated aryl sydnones (*cf.* **24**) afford the products of nitration on the aryl ring **25** instead of anticipated 4-nitro derivatives **26**.[94]



Furthermore, Tien and coworkers[95, 96] have shown that the *meta*-nitroaryl products **28** and **30** were obtained when either 3-benzylsydnone (**27**) or various 3-substituted-4-acetylsydnones **29** were subjected to nitrating conditions. In the latter case, the acetyl group in the products **30** could be removed subsequently with barium hydroxide.



Turnbull, Blackburn, and Miller examined nitration of 3-arylsydnones with multiple electron-donating groups (methyl groups) on the aryl ring **31**.[97] Consistently with similar, previous work, exclusive aryl ring nitration was observed, with a strong tendency for nitration *meta* to the sydnone ring, yielding **32**. 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.



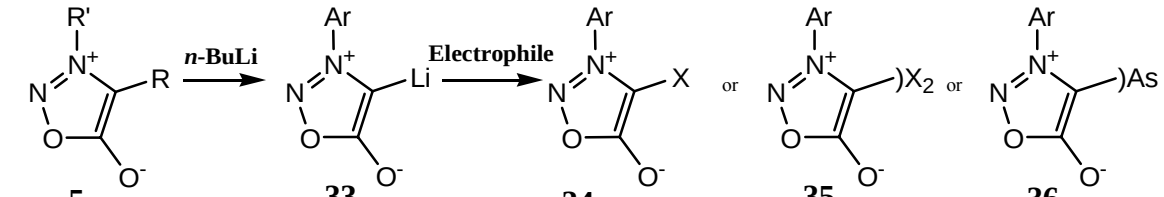
a) R = 2,4-Me; b) R = 3,4-Me; c) R = 2,5-Me;
d) R = 2,3-Me; e) R = 2,6-Me; f) R = 2,4,6-Me

II. Metalation of Sydnones

A. Metalations exclusively at the 4-position

Amongst pathways for substitution at the sydnone ring C-4 position, metalations of sydnones have been the most investigated. In fact, 4-lithio, 4-cupro, 4-chloromercurio, and the 4-palladium (0)[98] or nickel (II) [99] complexes have been prepared and investigated.

The 4-lithio sydnones **33** mentioned above have been the most versatile of the 4-metalo species. These intermediates can prepared from 3-phenylsydnone **5** (R = H, R' = Ph) or 4-bromo-3-phenylsydnone **5** (R = Br, R' = Ph). Reaction of **33** with either alkyl or aryl disulfides or diselenides gave the 4-sydnonylsulfides or 4-sydnonylselenides **34a**.[100] Additionally, the bissydnonyl sulfide and selenide **35** have been prepared in an analogous manner by treating **33** with the appropriate dicyano disulfide or diselenide.[100] Extension of this methodology to arsenic trichloride and diphenylchlorophosphorane[100] resulted in the preparation of the corresponding sydnonylarsine **36** and phosphine **34b**, respectively. More recently, 4-carboxysydnones **34c** have been prepared by carboxylation of **33** with carbon dioxide.[101] Additionally, Tien and coworkers[102] have shown that various 3-substituted sydnones can be lithiated and exposed *in situ* to either N,N-dimethylformamide, N,N-dimethylacetamide, or acetaldehyde to afford the corresponding acylated **34d**, or hydroxylated **34e** derivatives.



5
R'=Aryl
R= H or Br

33

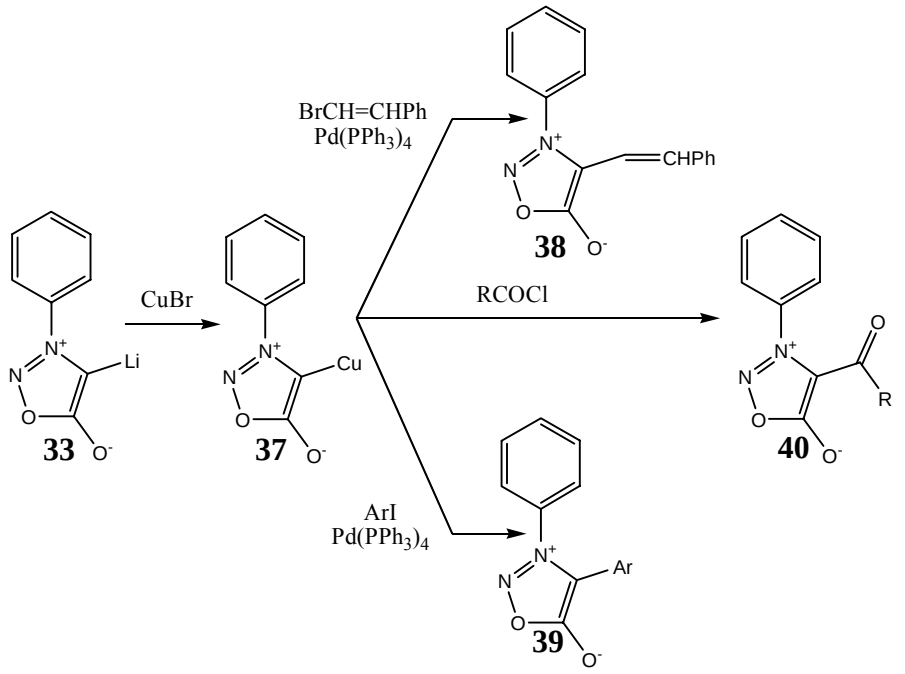
34 a-e

35
X= S, Se

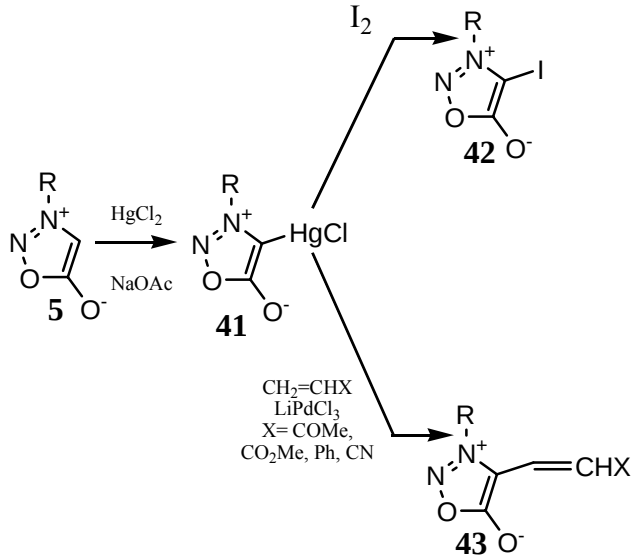
36

a: X = SR, S-C=S, Se
b: X = PPh_2
c: X = COOH
d: X = $COCH_3$, COH
e: X = $CH(OH)CH_3$

The reactivity of sydnone metal species can be modulated by changing the metal present at the 4-position. Thus, reaction of **33** with cupric bromide gives the relatively stable copper species **37** which can be coupled to vinyl or aryl halides over a palladium (0) catalyst to yield 4-alkenyl **38** or 4-arylsydnones **39**.[103] Reactions of **37** with acid chlorides yield the corresponding 4-acyl sydnones **40**.[104] More recently, Kalinin and coworkers[105] have shown that sydnonyl cuprates **37** can undergo palladium catalyzed cross-coupling reactions with either heteroaryl iodides or alkynyl bromides to afford the corresponding 4-substituted sydnones in good to excellent yields.

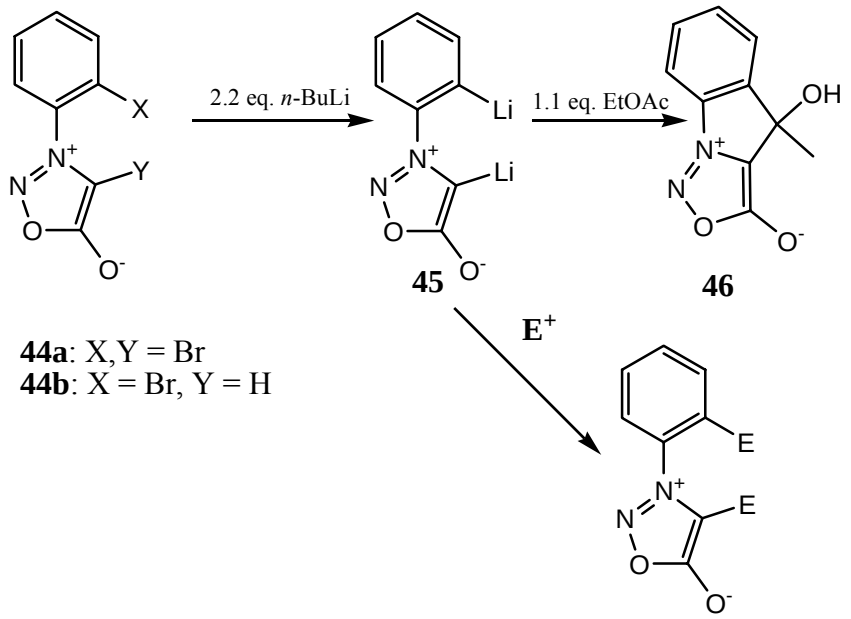


Reactions of 3-arylsydnones, **5** (R = H, R' = Ar) with mercuric chloride and sodium acetate in aqueous methanol at room temperature[106] yield the 4-chloromercurio species **41** which can be can then be treated with iodine to afford the 4-iodo derivatives **42**. More recently, Kalinin reported that reaction of the 4-chloromercurio intermediate with electron deficient olefins afforded only the *trans*-isomer of the corresponding 4-alkenyl product **43** in relatively high yields.[107]



B. Dilithiations of 3-arylsydnones

Dilithiation of 3-aryl sydnones has become a recent focus of sydnone chemistry, and has been successfully achieved by Krein and Turnbull.[96, 107-109] Initially, a dilithio sydnone species **45** was prepared by the reaction of 3-(2-bromophenyl)-4-bromosydnone **44a** with butyllithium at -78 °C. When treated with ethyl acetate, **45** afforded the known sydnoindole **46** in good yield. Krein and Turnbull successfully applied this reaction to other esters, thus, proving the versatility of the method. An undesirable drawback, however, was the loss of weight going from starting material to product caused by the sacrifice of two bromine atoms. This led to the testing of 3-(2-bromophenyl)sydnone **44b** instead of **44a** using similar conditions, and it was found the same transformations were achieved. Upon further pursuance, Krein and Turnbull discovered that the dilithio intermediate **45** could be prepared directly from 3-phenylsydnone **5** (R' = Ph, R = H) using N,N,N',N'-tetramethylenediamine (TMEDA) to increase the basicity of butyllithium. This was complemented by the anticipated, apparent *ortho*-directing effect of the sydnone ring, and, hence, it proved possible to react at the *ortho*-aryl site without the need for metal-halogen exchange. Reaction of this dilithio species was undertaken with a variety of electrophiles to yield novel disubstituted sydnones (*cf*. **45** to **47**-**52**). More recently, the same reaction has been found to be highly effective without the use of TMEDA by raising the reaction temperature from -78 °C to -50 °C.[110]

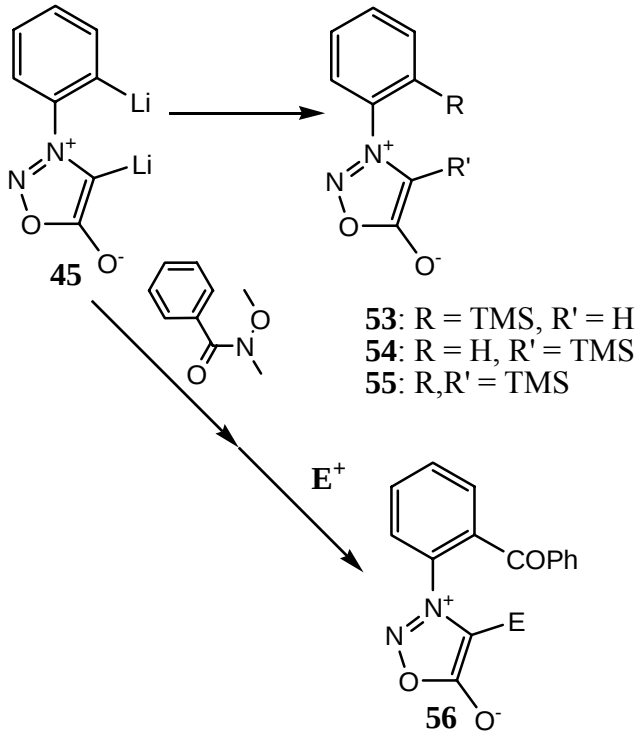


44a: X,Y = Br
44b: X = Br, Y = H

47:$E^+ = Br_2$, E = Br
48:$E^+ = HCON(CH_3)_2$, E = CHO
49:E^+ = PhCHO, E = CH(OH)Ph
50:$E^+ = I_2$, E = I
51:E^+ = PhSSPh, E = SPh
52:$E^+ = CH_3I$, E = CH_3

The pKa of the 4-sydnone proton is estimated to be 18-20 pKa units, while that of the *ortho*-aryl proton is estimated to be approximately 40. Due to this difference, Krein and Turnbull elected to explore the idea of selective substitution at the *ortho* site. When the dilithio sydnone **45** was prepared *in situ* and reacted with one equivalent of chlorotrimethylsilane, it was found to produce four products: *ortho*-substituted, sydnone C-4-substituted, disubstituted and unsubstituted **53-55**, **44b**, respectively. These results suggested that chlorotrimethylsilane was too strong an electrophile to permit *ortho* selection. Accordingly, Turnbull and Krein decided to attempt reaction with a less reactive electrophile, and Weinreb's amides were chosen since they have known advantages in similar transformations. Thus, reaction of **45** with N-methoxy-N-methylbenzamide afforded the *ortho*-benzoyl species **56** (E = H) in good yield, and this process was extended to the preparation of other *ortho*-acylsydnones.[97, 108-110] Overall, this approach provided a "one-pot" synthesis of *ortho*-acyl sydnones from easily prepared

3-phenylsydnone. Since, after initial reaction at the *ortho*-aryl position, the sydnone anion remains, one equivalent of a second electrophile can be added to promote further functionalization at the C-4 position of the sydnone ring. This provides a route to many unsymmetrically functionalized sydnone species.

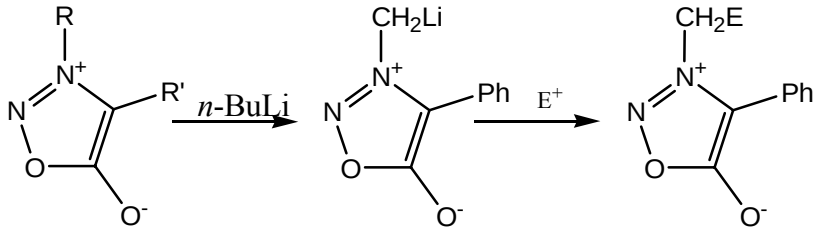


Lithiation studies[112] on mono and dimethoxy substituted arylsydnones, followed by trapping with electrophiles (e.g. iodine, trimethylsilyl chloride), led to the discovery that sodium borohydride could remove iodines attached at both the sydnone C-4 and the *ortho*-position of the aryl ring, whereas aqueous sodium sulfite selectively removed the iodo group from the sydnone ring. Also, selective desilylations of disilylsydnones were achieved using potassium carbonate or tetrabutylammonium fluoride.

C. Miscellaneous Metalations

Kalinin and Cherepanov have explored metalation of 3-methyl-4-phenylsydnone **5** (R = Ph, R' = CH_3).[113] In their work it was found that upon reaction with butyllithium,

a proton could be abstracted from the methyl group of 3-methyl-4-phenylsydnone at -90 ºC, resulting in the rather unstable lithio intermediate **57**. The latter was then reacted with a variety of electrophiles leading to the preparation of several substituted sydnones **58** (12% to 70% yields).



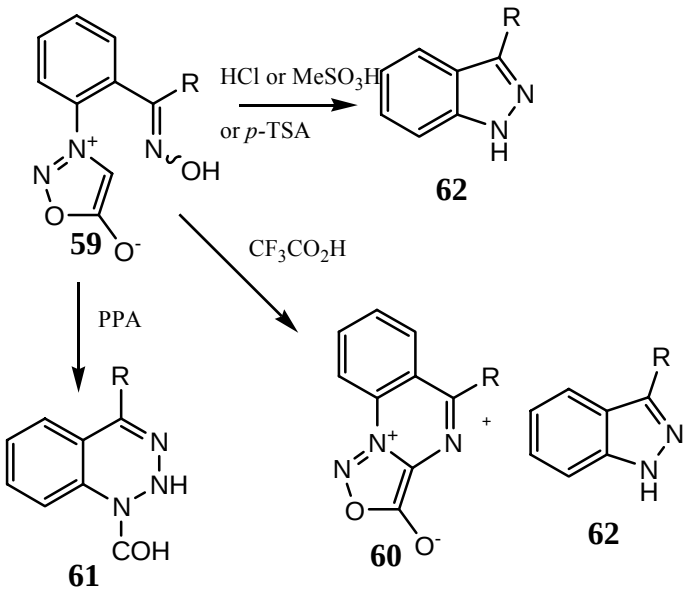
5
R = CH_3
R' = Ph

57

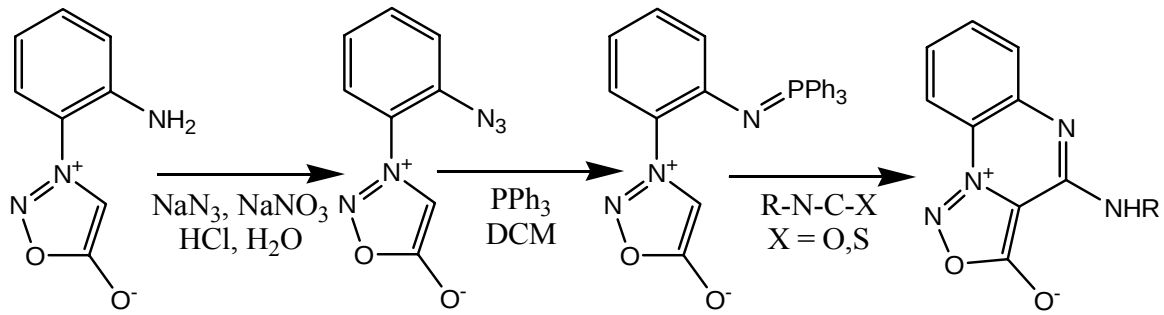
58 a: $CH_2CH{=}CH_2$
58 b: $COOCH_3$
58 c: CO_2H
58 d: $C(Ph)_2OH$

III. Reactions of *ortho*-Substituted Aryl Sydnones

Turnbull and Saljoughian reported [114] that by treating oximinosydnones **59** (R = Me or Et) with any one of a variety of acids, it was possible to obtain the corresponding sydnoquinazoline **60**, benzotriazine **61**, or indazole **62**, depending on which acid was used.



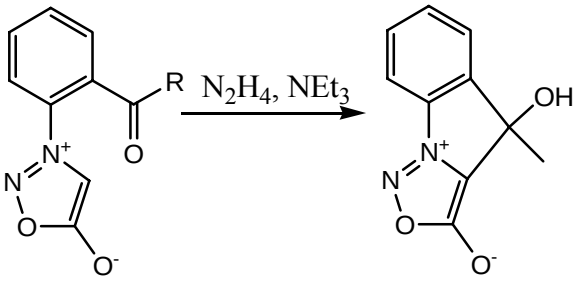
Additional fused-ring sydnone compounds, *viz*. 4-(arylamino)sydno[3,4-a]quinoxalines **63**, have been prepared in good to excellent yields (60-90%) by aza-Wittig carbodiimide formation followed by intramolecular electrophilic cyclization.[115]



17

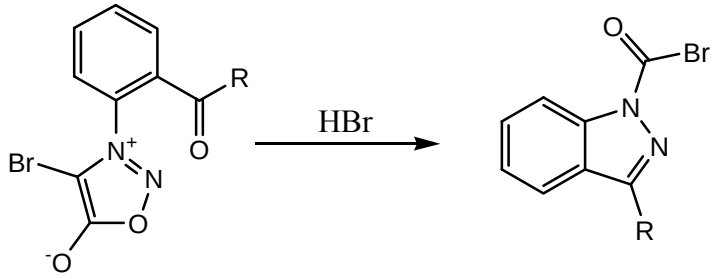
63
R = Ph, 4-MePh, 4-MeOPh, 4- NO_2PH

Two serendipitous discoveries have resulted in the preparation of the fused-ring sydnoindole **46** and various bromocarbonyl indazoles **66**. It was found that by treating 3-(2-acetylphenyl)sydnone (**64**, R = Me) with hydrazine hydrate under basic conditions, the major isolable product was the fused-ring sydnoindole **46** and not the anticipated hydrazone derivative.[116]



64 R = Me **46**

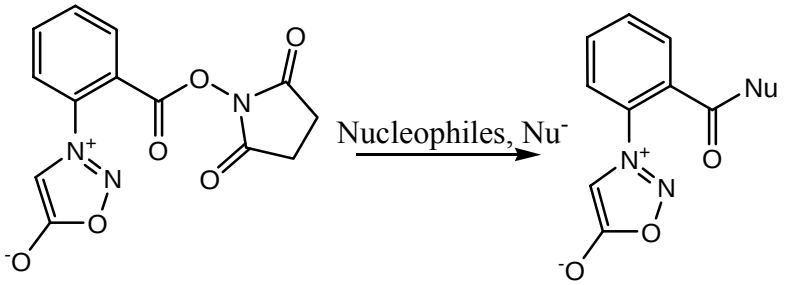
For further attempts to extend this work, it was considered of interest to place a bromo-leaving group on the methyl side-chain. Accordingly, 3-(2-acetylphenyl)-4-bromosydnone, **65** was treated with Br_2/hν or $CuBr_2$. Surprisingly, the bromocarbonylindazole **66 (**R = Me) was obtained rather than the expected sydnone **64**, R = CH_2Br. It was then speculated that the transformation was a result of the formation of HBr *in situ*, and, to test this, a variety of 4-bromo *ortho*-acyl sydnones *cf.* **65** were subjected to a stream of HBr gas; indeed the corresponding bromocarbonylindazoles **66** were formed in good yield (60-85%).[117]



65 **66**

One hindrance to the study of the reactions shown above has been that sydnones with an *ortho* carbonyl substitution are relatively hard to come by; they often must be made in several steps starting from the appropriate aniline derivative. In addition to the work done by Turnbull and Krein using the Weinreb's amides, recent work has shown that a variety of *ortho*-acylarylsydnones can be prepared from one or two intermediates

by reacting nucleophiles with activated *ortho* carbonyl species.[118] As an example, 3-[2-(N-succinimido)oxycarbonyl)phenyl]sydnone (**67**) was reacted with twelve different nucleophiles to afford the corresponding *ortho*-acylarylsydnones **68** in yields ranging from 23% to 63%.



67 **68**

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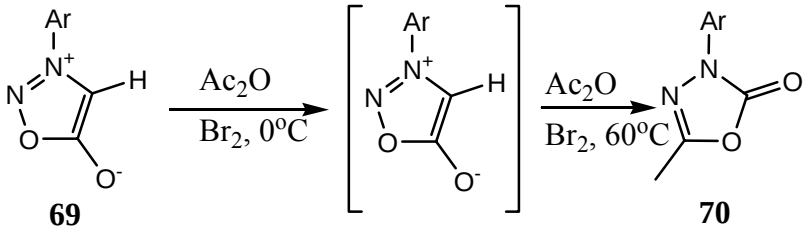
IV. Miscellaneous Reactions of Sydnones

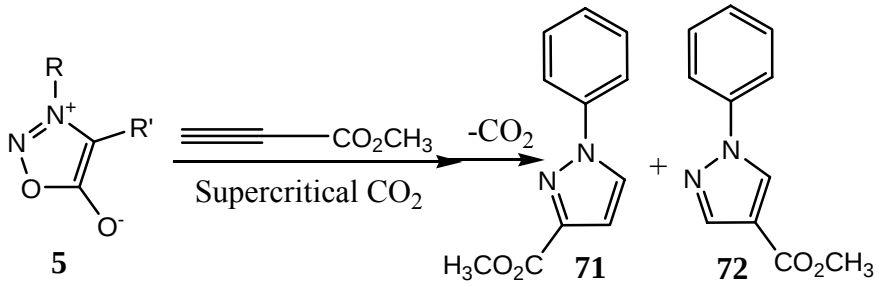
Mallur, Bharati, and Badami used sydnones as intermediates to 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones[119] with the objective of testing the latter for antimicrobial activity. The desired 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones **70** were prepared from 3-arylsydnones **69** by reaction with bromine in acetic anhydride, as is illustrated with a general example, below. The transformation is useful and, overall, twenty different oxadiazolinones were prepared in yields of 70-90%, most of which showed anti-bacterial and anti-fungal activity.



69 **70**

In their report, the suggested mechanism involves initial sydnone bromination to form a 4-bromo intermediate that is not isolated, followed, at increased temperature, by a 1,3-dipolar cycloaddition between the 4-bromosydnone and acetic anhydride. In light of the fact that no attempt was made to remove HBr formed as a by-product, and the unprecedented nature of the suggested cycloaddition, this mechanism seems suspect.

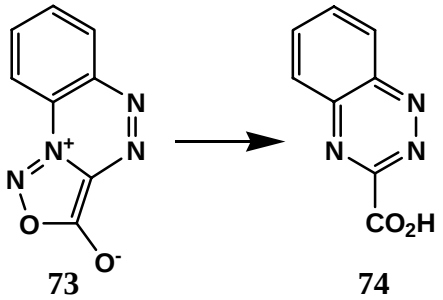
Further work concerning the ability of a sydnone to participate in 1,3 cycloadditions was carried out by Turnbull, McGowin and Totoe. This work involved a known sydnone reaction, *viz*. the reaction of 3-phenylsydnone, **5** (R = H, R' = Ph) with methyl propiolate, under slightly different conditions, namely using supercritical carbon dioxide as a solvent in place of toluene. [120]



In this reaction, two products were isolated. These two regioisomers (**71** and **72)** formed due to methyl propiolate being unsymmetrical. Variations in the temperature and pressure in the supercritical fluid reactor were tested to see if this had an effect on reaction selectivity. In summary, it was found that increasing reaction temperature decreased selectivity while increasing reaction pressure increased selectivity. This showed that reaction in supercritical carbon dioxide provided a selectivity advantage over running the reaction under the standard conditions (toluene, heat). Further, it was shown that the reaction could take place in a "green" solvent (carbon dioxide versus toluene).

Aims of the Present Work

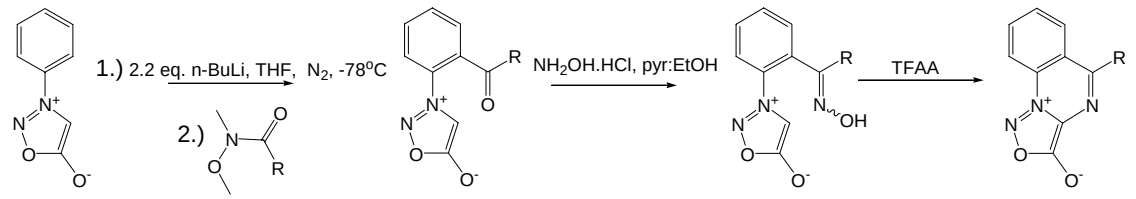
The primary objective of the current body of research was to efficiently synthesize sydnoquinazolines **60** and explore further their chemistry. Fused-ring sydnones such as **60** are of particular interest as potential nitric oxide (NO) prodrugs. The premise for this conjecture stems from work by Turnbull and Preston[121] in 1977 wherein it was observed that sydnobenzotriazine **73**, a fused-ring sydnone, cleaved hydrolytically to yield the benzotriazine carboxylic acid **74**. This unusual mode of cleavage (as compared to non-fused sydnone congeners) may arise due to the aromatic nature of the benzotriazine by-product **74** and was conjectured to involve release of NO or an NO congener.



73 **74**

Figure 1: Conversion of sydnobenzotriazine **73** to benzotriazine **74** as observed by Turnbull [121].

As shown in Scheme 1, the projected synthetic route to the target molecules **79**,**80** and their congeners **60** was to be initiated by the preparation of o-acylphenylsydnones **75** *via* our previously developed dilithiation protocol. Subsequent conversion of **75** to the corresponding oximes **77**, followed by treatment with trifluoroacetic acid (TFA) was expected to yield the corresponding sydnoquinazolines **79** on the basis of our previous findings with the acetyl oxime **78** (converted to **80**).



Scheme 1: Synthesis of sydnoquinazolines *via* lithiations using Weinreb's amides (**75,77,79** R = Phenyl; **76,78,80** R= Methyl) from 3-phenylsydnone.

With these goals in mind, it was elected to reinvestigate first the dilithiation reaction of 3-phenylsydnone and subsequent reaction of the resultant dilithio species with N-Methoxy-N-Methylbenzamide, as an avenue to 3-(2-benzoylphenyl)sydnone (**75**). The decision to begin with this approach was made based upon the commercial availability of the starting amide, the ease of synthesis of 3-phenylsydnone[122] and previous work by Krein and Turnbull[123] in this lab. It was anticipated that all of these factors would prove advantageous for the amassing of significant quantities of the desired benzoylsydnone **75** and provide a more current test of the methodology. Success therein would mandate extension to other similar systems, only a few of which had been made previously.

With the benzoylsydnone **75** in hand, the carbonyl moiety would be converted to an oxime functionality **77** on the basis of work done by Turnbull and Lowe[124] with the *o*-acetylphenylsydnone **76**. Again, it was anticipated that success in this specific step would permit extension to the preparation of several other oximinosydnones **77**.
As mentioned above, cyclization would then be attempted using trifluoroacetic acid at room temperature, which it was anticipated would result in a relatively straightforward synthesis of the 5-phenylsydno-[3,4*a*]quinazoline (**79**). This compound could then be

tested under hydrolytic conditions and assayed for biological activity. With a stockpile of fused-ring sydnone in hand, the next objectives would be to further explore the chemistry of the ring system and extend the synthesis to a variety of similar species.

Discussion

With the aims of the current research established, the initial phase of the work was the synthesis of 3-(*o*-benzoylphenyl)sydnone (**75**). Since this compound had been prepared previously *via* a lithiation approach, it was elected to utilize the same methodology, *viz*. lithiation of 3-phenylsydnone (**5**) followed by reaction with N-methoxy-N-methylbenzamide, for its preparation (see **Figure 2**). The decision to begin with the preparation of this specific compound was made based upon the commercial availability of the starting amide, the ease of synthesis of 3-phenylsydnone[122] and, as mentioned above, its previous synthesis by Krein and Turnbull[123] in this lab. 3-Phenylsydnone is synthesized in 2 steps from commercially available N-phenylglycine with relative ease, in good yields (65-75 % for the two steps) and is thus an ideal starting material compared to other sydnones. It was felt that all of these factors would prove advantageous for amassing significant quantities of sydnone materials for further study.

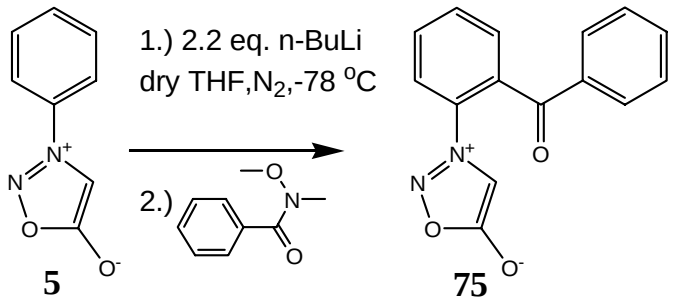


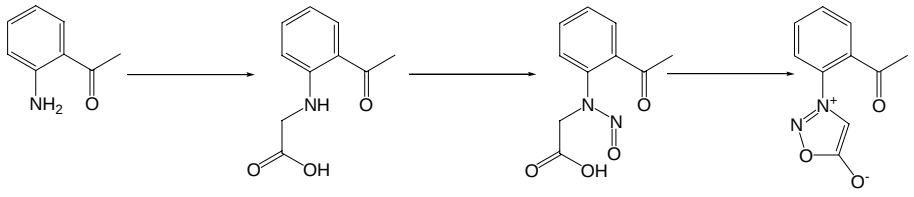
Figure 2: Lithiation scheme using N-methoxy-N-methylbenzamide as the electrophile.

While Krein and Turnbull had successfully synthesized **75**using highly dilute conditions and TMEDA (as a base-strengthening additive), it had been observed by Weisner[125] that directed lithiations could be carried out at higher concentrations and

without the assistance of TMEDA. Both of these factors would be significantly helpful in this synthesis should either, or perhaps both, apply. The benefits of increased concentration would seem obvious, in that more product could be obtained from lesser amounts of solvent in a fewer number of reactions, thus lowering material costs as well as time expenditure. The later advantageous discovery, *viz*. the removal of TMEDA from the reaction mixture, would be of benefit because the cost of material would be lower, there would be one less compound to purify and keep moisture free and, finally, one less compound to separate out of the final reaction mixture. Keeping those potential improvements in the forefront, a number of attempts were made to synthesize the benzoylsydnone **75** without the use of TMEDA at relatively higher concentrations. After several unsuccessful attempts to synthesize the benzoylsydnone *via* the modified techniques, an attempt was made to reproduce the lithiation using the method employed originally by Turnbull and Krein. Once again, however, the reaction did not result in a satisfactory or comparable yield of the benzoylsydnone **75**. Indeed, extremely complex reaction mixtures resulted and it was elected not to pursue this particular approach further. It is curious that the previous, successful result could not be reproduced but it should be pointed out that, in the decade since Krein's work was reported, no one in our lab. has attempted to reproduce this transformation. In such circumstances, it is not uncommon for "tricky" manipulations to become more difficult to reproduce since the "collective wisdom" is no longer available.

In light of the results observed from the lithiation approach to synthesis of the sydnoketones, it was decided to attempt the synthesis of such materials by more traditional means. Based upon previous work in this laboratory, the target sydnoketone

was shifted from benzoylsydnone **75** to the acetylphenylsydnone **76**. The latter compound had been synthesized in our laboratory in three steps, in moderate yields (approx 45% overall for tan colored material; pure **76** is colorless). The synthesis is conducted by reacting o-aminoacetophenone **81** with bromoacetic acid at 100 ^{o}C, resulting in N-(2'-acetyl)phenylglycine **82**, nitrosation using *iso*-amyl nitrite in DME at room temperature, forming the N-nitroso species **83**, and cyclization of the N-nitroso-N-*2*-acetylphenyl-glycine **83** with trifluoroacetic anhydride, to yield the target sydnone **76** in 45 percent overall yield (Scheme 2).



81 **82** **83** **76**

Scheme 2

Initially, this procedure was followed verbatim in order to synthesize the sydnone. However, during the synthesis of the glycine **82**, several observations were made which suggested that the conditions for the synthesis were less than optimal. For example, while the reaction was progressing at reflux, the stirring of solution was halted due to solidification of the produced glycine. In addition, there was always a distinct odor and coloration of the starting material in the resultant product, which disappeared upon washing with cold ethanol, with concomitant loss of product. The final observation suggesting that the glycine synthesis was not at optimal conditions was the low reaction yield of 67 percent. Bearing these observations in mind, combined with my industrial background and desire to reduce cost and material waste, several attempts were made to

optimize the reaction conditions for the glycine synthesis. In the traditional reported synthesis, the 2'- aminoacetophenone (**81**) is suspended in minimal amounts of water and allowed to reflux at 100 ^{o}C for 4 hours. This fact allowed for potential optimization of three factors: volume of water used, temperature of reaction and reaction time.

It seemed logical to explore first the amount of water added. Since the reaction always resulted in a sticky, non-stirrable mixture, it was felt that adding larger volumes of water should lessen that limitation. In order to optimize the volume of water necessary to allow reaction to achieve completion, several trials were conducted and these are summarized in Table 1. As shown in the Table, increasing the ratio of volume of water per gram of 2'-aminoacetophenone to 30 mL per gram gave a marked improvement over the traditional methods. As displayed from trial 4, increasing the ratio much past 30:1 did not have a dramatic effect upon the synthesis, therefore the remaining optimizations were done using the 30:1 ratio.

Two benefits were gained from the increase in the amount of water used as reaction solvent, *viz*. increased product yield and improved purity of the product *versus* traditional means. The primary reason attributed to the improvements from the water is that the 2'-aminoacetophenone is an oily material which is very hydrophobic and, when suspended in water, the hydrostatic pressure forces formation of globular spheres, which disperse with stirring providing large quantities of surface area interfaced with the reagent, sodium bromoacetate, suspended in the aqueous portion of the reaction mixture.

It was decided next to attempt the reaction at a slightly elevated temperature (*viz*. 120°C), a modification, which resulted in a modest five percent increase in product yield. The final attempt to optimize parameters for this synthesis aimed to bring the reaction to

completion by increasing reaction times. It was found that a one hour increase in reaction time brought about a 4 % increase in product yield and, thus, combined with the other improved reaction parameters gave a 94% yield of the arylglycine **82**. This 27% increase in yield would prove to increase the overall yield of the target sydnoquinazoline and reduce the overall cost of the synthetic path. Achieving yields near to 100 percent also helped alleviate the issue that this sydnoketone **76** required a 3 step synthetic process while, in principle, the *o*-benzoylphenylsydnone **75** could be synthesized in 2 steps.

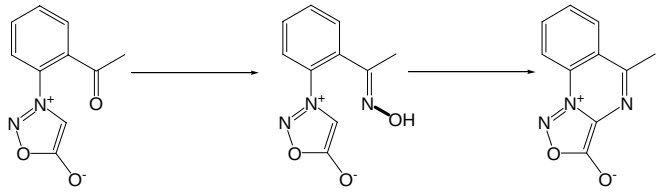
Trial #	Time, hours	Temperature, °C	Volume of water. mL	Mass starting material used, g	Volume to mass ratio	% yield
Control	4	100	50	5	10:1	67
1	4	100	75	5	15:1	73
2	4	100	300	10	30:1	85
3	4	100	400	10	40:1	84
4	4	120	300	10	30:1	90
5	5	120	450	15	30:1	94
6	5	120	150	5	30:1	93

Table 1: Optimization of N-2'-acetylphenylglycine **82** synthesis

After the glycine **82** was synthesized, the next required step toward synthesis of the sydnone ring was nitrosation to yield the N-2'-acetylphenyl-N-nitrosoglycine **83**. To facilitate this conversion, isoamyl nitrite was selected based upon previous findings in this lab. The conversion previously reported was fairly efficient and due to the expectation that the N-nitrosoglycine, and N-nitroso compounds in general, are carcinogenic, it was decided to follow the procedures as written to minimize contact and exposure to this species. The resultant N-nitrosoglycine was a red colored, amorphous solid. The product **83** was not purified or further isolated after reaction so the specific yield is not known, however the product was examined by IR and, as expected, the N-H peak at 3293 cm^{-1} had disappeared. The disappearance of that peak confirmed that reaction had indeed occurred. The nitrosated glycine was then dissolved in methylene

chloride (10 mL per gram nitrosoglycine based upon the assumption of 100% conversion of the glycine to N-nitrosoglycine) and treated with 1 mL of trifluoroacetic anhydride per gram of nitrosoglycine, again based upon the assumption of 100% nitrosoglycine formation. This reaction was performed at ~0ºC for 1 hour. After neutralization, extraction of the organic layer containing the sydnone **76** and evaporation *in vacuo*, the desired sydnone was obtain in 74% yield for both reaction steps, and 70% overall from the o-aminoacetophenone to the 3-(2-acetylphenyl)sydnone. This is a considerable improvement over the 50% yield achieved by the previous means.

Following its synthesis, the sydnoketone **76** was to be converted to the corresponding sydnooxime compound, 3-(2-acetylphenyl)sydnone oxime **78** (Scheme 3). This conversion had been performed previously in this lab[124] utilizing hydroxylamine hydrochloride refluxed for 2 hours in ethanol using pyridine as a base to liberate "free" hydroxylamine. The work-up described in this reference consisted of a reduction in volume *via* evaporation, quench with water, extraction and drying with drying agent and evaporation *in vacuo* resulting in a brown oil, which was then recrystalized to afford **78** in 36% yield.

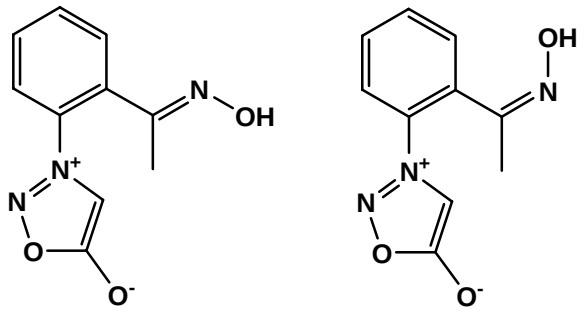


76 **78** **80**

Scheme 3

Utilizing the same reaction conditions and altering the work-up procedure by allowing for a second reduction in volume after the water quench, crystalline product was obtained in 65-75% yield with a 3:1 ratio of oxime isomers **78 a, b**. It can be safely assumed that the

predominant isomer is the *E*-isomer **78a** because of steric constraints. The isomeric ratios were determined based upon the proton NMR of the mixture. Initially, it was believed that this analysis would be best ascertained using the relative intensities of the methyl signals for the two oxime isomers **78a** and **78b**. However, while the ratio of the areas of these two peaks was approximately 3:1, the peaks were not baseline resolved and therefore not sufficiently accurate. A clearer picture of the isomeric ratio was seen when the proton of the –OH was utilized, a phenomenon that was particularly evident when DMSO-d_6 was used as the solvent. In that case, the two isomeric OH peaks are resolved by nearly 0.5 ppm (10.69 and 11.16 ppm). Using the OH peaks, the ratio of isomers is clearly 3:1. The purity of the product from this modified procedure remained comparable to that of the previous, lower-yielding method.



78 a **78 b**

Figure 3: **78a** *E*-3-(2-acetylphenyl)sydnone oxime **78b** *Z*-3-(2-acetylphenyl)sydnone oxime

While this method of synthesis was effective, the length of time required for the reaction, combined with the health hazards and unpleasant odor of pyridine, made designing an alternate route for the synthesis of **78** attractive. In 2005, Kamakshi and Reddy [126] reported a 1-2 minute, solvent-free, microwave synthesis of oxime derivatives of carbonyl compounds, wherein, they used K_2CO_3 as the base. Bearing these advantages

in mind, synthesis of **78** was attempted utilizing similar reaction conditions, starting from **76**. This method resulted in the oxime derivative **78** in low yields, with a relatively large amount of starting material remaining. The reason for this unexpected inefficiency seemed to stem from the solvent free conditions and, accordingly, in an effort to alleviate this limitation, ethanol was added as a solvent. While it is known that K_2CO_3 is not readily soluble in ethanol, it was hoped that the high, localized temperature and the stirring of the solution would still allow the K_2CO_3 to act as a base and facilitate the desired reaction. Unfortunately, this was not the case and no reaction was observed. Accordingly, the reaction was attempted using an organic-soluble base (*viz*. pyridine) in ethanol, giving improved results over all previous methods attempted. The yield of this method was 81% though the ratio of isomers remained 3:1 *E*:*Z*. While the initial advantage of not requiring pyridine was lost, the microwave synthesis still proved advantageous in that yields were increased and reaction time was reduced to 10 minutes from 2 hours.

In the brief, previous examinations of cyclizative routes to form 5-methylsydno-[3,4-*a*]quinazoline (**80**) two separate approaches had been attempted. The first of these methods for the synthesis involved transformation of the oxime **78** to O-sulfonate species **84,85** or an O-acetate **86** and thermolysis of these products on silica[118]. The minor product of the thermolysis with the *O*-sulfonates was the desired sydnoquinazoline **80** (Beckmann rearrangement products comprised the bulk of the product mixture). The second synthetic method was the treatment of 3-(2-acetylphenyl)sydnone oxime (**78**) with trifluoroacetic acid, as observed by Turnbull and Saljoughian[127]. Several limitations were evident from this latter methodology, primary amongst which were the lengthy reaction

time required for the synthesis and the fact that the sydnoquinazoline **80** was only a minor product synthesized in 33 % maximum yield. Given the low yields for both of these reactions, two options presented themselves for exploration. The first of these options, and most desirable given the aims of the work, was optimization of either of the existing methods to improve yields. The second option would require development of novel means of synthesis. It was decided that optimization of the existing methods made more sense and was attempted initially.

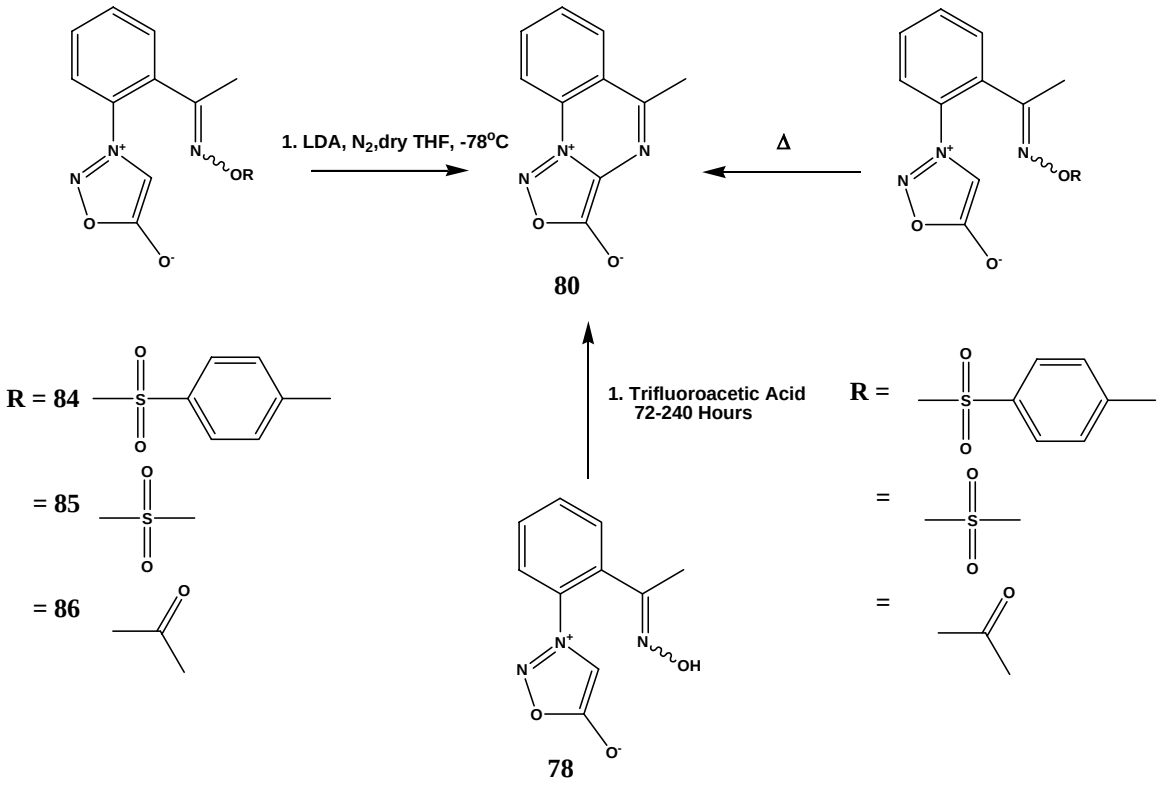


Figure 4: Routes to 5-methylsydno[3,4-*a*]quinazoline (**80**)

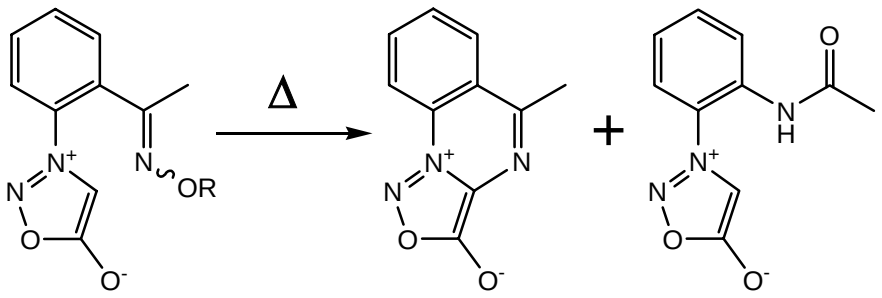
In order to carry out the thermal reactions, it was necessary to synthesize the *O*-tosylate **84**, *O*-mesylate **85** and *O*-acetate **86** species. The preparation of the tosylate was carried out following procedures developed by Turnbull in 1988, wherein the oxime derivative **78** was reacted with *p*-toluenesulfonyl chloride in methylene chloride for 2

hours. In the present case, the reaction resulted in the O-tosylate **84** in 65-70 % yields, which was identical to authentic material (IR, m.p.). Based upon the ^{1}H NMR, only one isomer for this compound was obtained. To complete characterization of this compound, a ^{13}C NMR spectrum was obtained and the latter clearly showed the 17 carbon peaks expected for the compound, again with no sign of any isomeric contamination. It is curious that only one isomer was obtained, given that the starting material was a 3:1 mixture of oxime isomers, and this may reflect either the instability and subsequent breakdown of one of the *O*-tosylate isomers or formation of the same *O*-tosylate from each oxime isomer. The acetate derivative **86** was synthesized *via* treatment of the oxime **78** with acetic anhydride. Thus, the starting oxime was dissolved in acetic anhydride, which served as both solvent and reagent, and allowed to stir for 12 hours, at which time a crystalline solid had precipitated from the solution. The colorless solid was then filtered off, which proved to be the target molecule by IR, TLC, m.p. and ^{1}H NMR. Proton NMR evidence shows the ratio of acetate isomers to be 7.9:1 (as ascertained by comparison of the peaks present for the sydnone C-H at the C-4 position, 6.581 ppm and 6.668 ppm), with the *E*-isomer being the presumed dominant species. While this compound was synthesized previously, it had not been characterized fully. In light of this, a ^{13}C NMR spectrum was obtained and analyzed for this compound. Even with the extremely high ratio of isomers, the ^{13}C NMR spectrum clearly displayed 20 carbon signals, indicative of the mixture of isomers. Given that each compound contains 12 carbons, 24 carbons would be expected for the two isomers. However, there is a possibility that several of the carbons overlap and, given that the minor isomer is in such low amount (8:1 major:minor) some of the signals may be lost in the base line noise. The pure compound

was formed in 85% yield without further purification. As reported[124], the synthesis of the mesylate **85** involved reacting methanesulfonyl chloride with 3-(2-acetylphenyl)sydnone oxime (**78**) in the presence of triethylamine as base. At first, the synthesis of the mesylate proved to be slightly more difficult than for the other two intermediates. The major issue stemmed from the reactivity of the methanesulfonyl chloride, wherein, addition of the mesyl chloride directly to the reaction mixture caused decomposition of the starting materials due to an exothermic reaction. In order to alleviate the exothermicity of the reaction mixture, the mesyl chloride was dissolved in dichloromethane and added slowly over a period of 15 minutes. Using this modification, it was not necessary to cool the reaction mixture to 0 ˚C and the product **85** was obtained in 94 % yield, with no further purification necessary. The product obtained, surprisingly, had an isomer ratio of 1.3:1 as determined by proton NMR comparison of the peaks present for the sydnone C-H. In confirmation of this conclusion, the multitude of peaks observed in the C-13 NMR also was consistent with a nearly 1:1 ratio of isomers. Nonetheless, with each of these compounds in hand, the stage was set for repetition of the thermolyses.

The thermolyses were repeated and the findings were consistent with those of the earlier work, meaning the yields of the desired product were still low. Using a vacuum drying oven set to approximately 100 ˚C, the compounds, which were spotted onto glass backed, silica gel-coated thin-layer chromatography plates, were allowed to heat for 1 hour based upon the previous research. Upon removal from the oven and cooling to room temperature, the TLC plates were eluted with 1% acetone in dichloromethane, resulting in 3 distinct spots for the mesylate **85** and tosylate **84** thermolyses. Of the three spots, the

highest running was the desired sydnoquinazoline, the middle spot matched starting material and the lower running one was identical to the Beckman-type rearrangement product **87** observed by Turnbull[124]. In an attempt to improve this distribution in favor of the desired fused-ring compound **80**, other time scales (*viz*. 15 min, 30 min, 2 h, 6 h and 24 h) were utilized to see if product yield could be increased. The shorter lengths of time were attempted to minimize potential for thermal degradation of the desired product in the event that it was also thermally unstable. The longer time periods were selected to compensate for any unreacted starting material remaining. Little variance in results was observed for the variations in time, though it was clear that the best results for the synthesis of the target compound resulted from thermolysis of the tosylate **84**. Thermolysis of the mesylate **85** also yielded small quantities of the sydnoquinazoline **80**. Interestingly, it was found that the acetate compound **86** did not thermolyze at 100 ˚C, undoubtedly due to the poorer leaving group ability of the acetate ion (relative to the tosylate and mesylate species) and, therefore, the greater relative stability of the acetate **86** *versus* either sulfonate derivative **84** or **85**.



84,85,86 **80** **87**

Scheme 4

In light of the inefficiency of the thermolyses, coupled with the extra synthetic step required to incorporate the leaving group which the thermolyses require, it was

decided to revisit the treatment of the sydnoketoxime **78** with trifluoroacetic acid (TFA). The previously reported methodology involves a 10 day reaction at room temperature in excess TFA. The maximum obtained yield from this reaction was 33%, with typical yields ranging from 20-30%. Repetition of this reaction exactly as described resulted in a 27% yield. Due to time constraints and a desire for higher yields, modifications of this reaction were attempted. Primary amongst these modifications was to shorten the length of time during which the reactants were allowed to mix and adjustment of the reaction temperature. The reasoning behind the modification of the reaction duration was that of potential breakdown of the target molecule in the strongly acid conditions upon exposure to them for such a prolonged period of time. Also, the restricted time frame spurred the decision to slightly raise the temperature in the hope of speeding up the reaction kinetics to fit those time constraints. The first attempted variation was to allow the reaction to take place for 3 days at slightly above ambient temperatures (~35-45 ˚C). These conditions resulted in a 50% yield, therefore encouraging further investigation. If reduction in reaction time from 10 days to 3 days resulted in a >50% yield improvement, it seemed logical to explore whether or not a further reduction in reaction time could be efficacious. Accordingly, the reaction was repeated and quenched after 24 hours; however, the yield of this attempt was lower than for either of the other methods, thus it was not pursued further. Having increased the yield for this cyclization step to 50%, while not ideal, this method was now considered a viable option for synthesis of the sydnoquinazoline **80** in larger quantities.

Simultaneous to the attempts at improving the acid-catalyzed cyclization to **80**, it was decided to investigate a novel means of cyclization, namely a base-induced

intramolecular cyclization from the *O*-sulfonates **84**, **85** and *O*-acetate **86** (Scheme 5). This approach was predicated on the relative acidity of the sydnone proton at C-4 (pK_a ~18-20) and the likelihood that the resultant anions **89** (after treatment of **84**, **85** or **86** with base) would "choose" a subsequent intramolecular pathway to **80**, by nucleophilic substitution, rather than an intermolecular process. To help enable this preferred avenue, it was elected to use conditions of high dilution during the reaction process. Much previous lithiation work in our laboratory has shown that the proton at the 4-position on the sydnone ring can be abstracted readily using *n*-butyllithium or LDA, however, we have shown also that dilithiation (sydnone 4-position and aryl *ortho*-position) of arylsydnones can occur, especially with *n*-butyllithium, *via* a directed lithiation process utilizing the sydnone ring. To avoid the prospect of dilithiation, or nucleophilic attack by the base at the oximino carbon atom, it was elected initially to focus on the very non-nucleophilic, somewhat weaker base (relative to *n*-butyllithium), LDA. However, recent unpublished findings[128] in this lab have shown putative evidence of LDA exhibiting some nucleophilic behavior. Bearing those findings in mind, it was decided that another hindered base should be examined for the cyclizations as well, and the highly hindered base lithium hexamethyldisilylamide (LHMDS) was chosen for this purpose. LHMDS had not previously been utilized for lithiations of sydnones prior to this study.

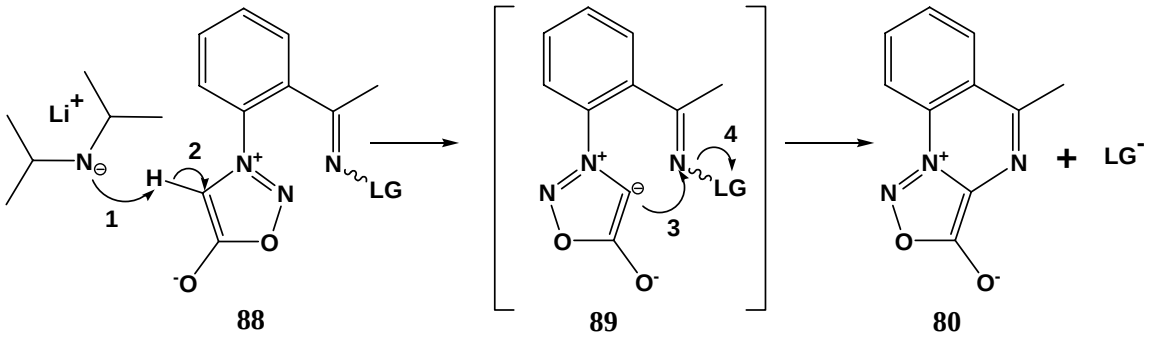
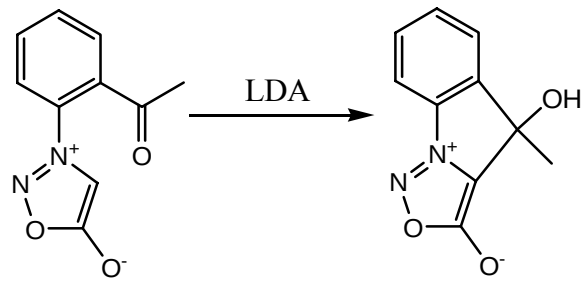


Figure 5: Proposed Mechanism for the base-induced cyclization to 5-methylsydno-[3.4-*a*]-quinazoline **80**, using LDA as a model base. LG is a generic leaving group. (LG = OAc,OMs,OTs)

Prior to attempting this base-induced cyclization, in an effort to validate the ability to perform intramolecular lithiation reactions and ascertain the reaction conditions (*viz*. dilution factors, time), model reactions were performed upon 3-(2-acetylphenyl)sydnone **76** using LDA. This reaction was selected because the expected result was novel and the proposed product, the methyl sydnoindole **46**, had been synthesized previously in our lab and was therefore available for comparison purposes. Performing the reaction in relatively dilute conditions (100 mg **76**: 250 mL THF) for 1 hour, resulted in 67% conversion to the target molecule. These results confirmed the expectation that intramolecular lithiations were not only possible, but efficient as well. In addition to confirming these conjectures, this reaction also provides a more efficient means to **46**.



76 **46**

Armed with this lithiation expertise, and based on the considerable amounts of tosylate **84** and acetate **86** remaining from their synthesis for the thermolyses, it was logical to begin the studies of the base-induced methods with these two compounds. As with the thermolysis, no significant reaction occurred when the acetate compound **86** was reacted with either base. Due to these results, the utility of the acetate was not examined further. Treatment of the tosylate compound **84** with 1.2 equivalents of LHMDS gave encouraging results, providing the target molecule **80** in 40 % yield with the remainder of the reaction mixture being unreacted starting material. Reaction of the tosylate **84** with the same number of equivalents of LDA proved promising as well, giving comparable yields to those from the LHMDS. Guided by the residual starting material, it was then decided to increase the quantity of base equivalents to a ratio of 1.5 mol: 1 mol in an effort to increase the extent of reaction. Using the higher molar equivalent with the tosylate improved the results obtained slightly, increasing the desired product yield to 46%.

Having synthesized a more significant quantity of the mesylate **85** at this point, it was sensible to attempt to apply these base-induced techniques to that molecule. It was felt that many benefits would be evident if the mesylate were to be a viable option. First, the reaction to synthesize the mesylate is more efficient than that for the tosylate (94% vs. 85%) and that increased yield could be carried through the remaining steps, improving overall yields. Also, from a strictly atom economy stand-point, the mesylate is preferable because it has a significantly lower molecular weight than the tosylate. With an already bulky sulfur-based leaving group, simply losing a methyl is much more desirable than losing both a methyl and a phenyl, as would be the case with the tosylate. Additionally,

typically, a mesylate is a better leaving group than a tosylate, which if that were to hold true should realize a higher reaction yield of the desired product **80** than with the tosylate. Based upon the reaction of the tosylate with 1.5 equivalents of base, and the comparable yields with either base, the mesylate was reacted with 1.5 equivalents of LDA. Due to the previously observed similarity in reactivity between the bases, it was elected to remain with LDA as the base of choice, as it is cheaper to purchase than the LHMDS. In the event, as expected, reaction of the mesylate **85** with 1.5 equivalents of LDA yielded higher quantities of the sydnoquinazoline **80**, *viz*. a 67% yield. Gratifyingly, further repetition of the reaction of the mesylate **85** with 2.2 equivalents of LDA yielded an even higher quantity of the sydnoquinazoline **80**, *viz*. an 80% yield. While, due to a lack of time, further study was not conducted, within reason, higher equivalents of base may be expected to continue to improve overall yields.

Overall, the yield of the desired sydnoquinazoline **80** from the starting aminoacetophenone **81** was 50% maximum and 43% on average. These improvements were significant, in comparison with the 6-26% overall yields attained previously in this lab. The best yields resulted from the use of lithiation reactions to facilitate cyclizations, even though that scheme required the addition of a sixth step in the synthetic pathway. The five step synthesis involving the acid catalyzed cyclization gave the target **80** in 35% maximum yield and 28% average yield, but this is of little advantage as the *O*-mesylate synthesis is actually more efficient and requires less time to complete. It is also worth noting that LDA proved to be an effective base to facilitate these conversions.

To develop a more thorough understanding of sydnoquinazolines, further research should be attempted to develop a more complete library of these compounds. One

possible way to achieve this would be the synthesis of a variety of sydnoketones and application of the methods developed in this research to these systems. The sydnoketones could be synthesized either from the corresponding aminoacylphenones and o-aminobenzaldehyde or from the lithiation of 3-phenylsydnone with various Weinreb's amides, should that reaction prove successful again in the future. Some chemical transformations might also be possible at the exocyclic methyl in 5-methylsydno-[3.4-*a*]-sydnoquinazoline (**80**), as well as any exocyclic moieties in other sydnoquinazolines.

Another avenue for future research involves substitution on the phenyl ring on the arylsydnones, particularly halogenations. Addition of a halogen provides a handle for further functionalization, such as Suzuki and Sonagishira couplings as well as metal halogen exchange followed by subsequent reaction with various electrophiles, resulting in a large variety of substituted derivatives.

Additionally with all of these fused-ring compounds, it is desirable to study the response to hydrolytic conditions to observe how these compounds break down under such circumstances. If the break-down products are analogous to that observed by Turnbull using the sydnobenzotriazine **73** (*viz*. apparent loss of NO or a congener), then biological assays of the sydnoquinazolines will be in order.

Experimental

General Notes

All starting reagents and catalysts were purchased from commercial sources and used without further purification. Dry tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Where applicable (e.g. organolithium reagents), all glassware was flame-dried under an atmosphere of nitrogen prior to the use of dry reagents. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were acquired on a Mattson Genesis II FTIR. NMR spectra were acquired on a Bruker 300 MHz NMR. Samples were dissolved in deuterated dimethyl sulfoxide, deuterated chloroform or a mixture thereof. All microwave syntheses were performed on a Biotage Creator 300 Watt monomode microwave.

All lithiations were done in dry THF under an atmposhere of nitrogen. Unless specified all lithiations were preformed at -78 ˚C, utilizing a Dry Ice/Acetone slush bath. All bases utilized were assumed to be at the molarities listed on the reagent bottle.

General Procedure for the synthesis of 3-(2-acetylphenyl)sydnone (**76**)

The desired glycine **82** was produced from the reaction of o-aminoacetophenone (**81**) with 1.1 equivalents of sodium bromoacetate in water at a ratio of 10 mL per gram of amino compound. This reaction was carried out at 100-105 ºC for 4 hours. Treatment with isoamyl nitrite in 1,2-dimethoxyethane yielded the N-nitrosoglycine **83**. Cyclization of the resulting nitrosated glycine with trifluoroacetic anhydride afforded the desired

sydnone **76** in 67% yield. After crystallization, the identity of the sydnone obtained was determined by comparison to authentic samples by TLC, IR, NMR and melting point.

Optimized Route to the glycine **82** from *o*-aminoacetophenone (**81**)

To a stirred solution of *o*-aminoacetophenone (**81**) [15.00g, 0.111 mol] in water (450 mL) was added 1.1 equivalents of sodium bromoacetate, from neutralization of bromoacetic acid (17.030 g, 0.1226 mol) with sodium hydroxide (4.90g, 0.1225 mol). The solution was heated at 120 ˚C for 5 hours. After the allotted time, the yellow needle-like product was filtered off and dried *in vacuo* at 90˚C for 24 hours. After drying, 20.179 g (0.1043 mol, 94%) of **82** was formed. The product was characterized by IR, TLC and melting point (212-213 ˚C) and matched known values.

IR (KBr): 3293(N-H), 2903, 2655, 1974, 1872, 1720, 1637, 1602, 1561, 1518, 1454, 1429, 1362, 1324, 1253, 2257, 1113, 1066, 1037, 997, 952, 928, 887, 755, 672, 619, 581, 522 cm^{-1}.

Nitrosation of **82** to form N-(2-acetylphenyl)-N-nitrosoglycine (**83**)

To N-(2-acetylphenyl)glycine (**82**) [3.32g, 0.01716 mol] in dimethoxyethane (30 mL) was added isoamyl nitrite (4.40 mL, 0.03260 mol). The solution was allowed to stir (covered with a watch glass) at room temperature for 5 hours, after which time the solvent and excess isoamyl nitrite were evaporated off in a fume hood overnight. A dark red, brown solid resulted. The said solid was identified by IR, but no further analysis was performed due to the potential health risks associated with the target N-(2-acetylphenyl)-N-nitrosoglycine (**83**).

IR (NaCl): 3179, 3108, 3076, 3003, 2959, 2602, 2531, 1739, 1687, 1598, 1490, 1444, 1359, 1296, 1253, 1156, 954, 866, 819, 679, 593, 508 cm^{-1}.

Synthesis of sydnone **76** *via* cyclization of **83**

Due to the potential health risks of **83** the masses used are based on the assumption of its complete formation from **82**. To a solution of **83** (1.00g, 0.45 mmol) in dichloromethane (10 mL) at approximately 0˚C, trifluoroacetic anhydride (1 mL, 7.19 mmol) was added. The mixture was allowed to stir for 1 hour, after which time complete conversion of starting material had occurred by TLC. The solution was neutralized with aqueous sodium bicarbonate solution (5% w:v) and extracted with dichloromethane (3 x 25 mL). The combined organic layers were evaporated *in vacuo* resulting in a red solid material. Upon recrystalization from dichloromethane: hexane, a tan solid remained, suitable for analysis. The compound was identical to known **76** by IR, TLC, ^{1}H NMR, ^{13}C NMR and melting point (114-115˚C, lit. mp[124] 113-115°C)

IR (KBr): 3460, 3163, 3079, 1751, 1683, 1601, 1492, 1466, 1434, 1365, 1302, 1261, 1221, 1168, 1096, 1075, 941, 842, 766, 725, 704, 653, 604, 558, 520, 479, 436 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.87 (m, 4 H), 6.64 (s, 1H), 2.54 (s, 3 H) ppm

^{13} NMR ($CDCl_3$): 196.84, 168.67, 134.97, 132.85, 132.73, 132.02, 129.97, 126.17, 97.59, 28.75 ppm

General synthesis of 3-(2-acetylphenyl)sydnone oxime (**78**) from **76**

A solution of 3-(2-acetylphenyl)sydnone **76** (2.00 g, 0.0098 mol) and hydroxylamine hydrochloride (2.10 g, 0.0302 mol) in pyridine (10 mL) and ethanol (40 mL) was refluxed for 2 hours. The volume was reduced to 10 mL, at which time water (40mL) was added to quench the reaction. The solution was extracted with methylene chloride (3 x 50 mL) and the organic layers were combined. The combined organic layers were then washed with hydrochloric acid (5% v/v, 2 x 25 mL) and sodium bicarbonate (5% v/v, 3 x 25 mL). The solution was then dried and evaporated *in vacuo*. A brown solid material (0.773g, 36%) resulted which matched literature values for IR, ^{1}H NMR, and melting point (123-126˚C, lit. mp[124] 124-126°C) for **76**. ^{13}C NMR was also performed since it had not been reported previously for this compound.

IR (KBr):3293, 3118, 2927, 2846, 2125, 2044, 1984, 1955, 1903, 1733, 1716, 1506, 1438, 1367, 1311, 1000, 948, 767, 742, 674, 638 cm^{-1}.

^{1}H NMR ($CDCl_3$): 9.36 , 9.07 (s, 1 H, 3:1 ratio) 7.66 (m, 4 H) 6.68, 6.61(s, 1 H, 1:3 ratio) 2.14, 2.12 (s, 3 H, approx. 1 : 2.9 ratio, but not baseline resolved) ppm

^{13}C NMR ($CDCl_3$): 168.76, 168.70, 150.91, 149.43, 133.95, 132.21, 131.71, 130.18, 129.67, 129.44, 128.75, 125.53, 124.31, 97.80, 96.39, 96.32, 21.26, 14.12 ppm

Modified "work-up" of 3-(2-acetylphenyl)sydnone oxime (**76**) synthesis

A solution of 3-(2-acetylphenyl)sydnone **76** (4.00 g, 0.0196 mol) and hydroxylamine hydrochloride (4.20 g, 0.0604 mol) in pyridine (20 mL) and ethanol (80 mL) was refluxed for 2 hours. The volume was reduced to 20 mL, at which time water (80 mL) was added to quench the reaction. The quenched reaction mixture was placed in a fume hood and allowed to evaporate overnight resulting in the formation of pale, yellow plates

(2.793g, 0.0127 mol, 65% yield) which matched literature values for IR, ^{1}H NMR, ^{13}C NMR and melting point (123-126˚C, lit. mp[124] 124-126°C) for **76**.

Solvent-free microwave synthesis of oxime **76** from ketone **74**

A mixture of **74** (0.197 g, 0.965 mmol), hydroxylamine hydrochloride (0.214 g, 3.07 mmol) and potassium carbonate (1.00 g) was irradiated with microwaves at 130˚C for 10 minutes at 3.5 bar. The resultant mixture was washed with water (2 x 5 mL) and extracted with methylene chloride (3 x 25 mL). After extraction the combined organic layers were evaporated *in vacuo* and a TLC was run (5% acetone in DCM). Two distinct spots were observed, the major being starting material **74** and the minor being **76**. These compounds were separated by silica-gel column chromatography. Compound **74** was recovered at 83% (0.163 g), while compound **76** was synthesized at 17% yield (0.035 g, 1.6405 x 10^{-4} mol). The synthesized **76** matched known material by TLC, IR, ^{1}H NMR and melting point.

Microwave synthesis of oxime **76** using ethanol as a solvent

A solution of **74** (0.200 g, mol), hydroxylamine hydrochloride (0.210 g, mol) and potassium carbonate (1.000 g, mol) in ethanol (3 mL) was irradiated with microwaves at 130˚C for 10 minutes at 3.5 bar. The resultant mixture was washed with water (2 x 5 mL) to remove excess sodium bicarbonate and hydroxylamine, extracted with dichloromethane (3 x 20 mL), and the combined extracts reduced *in vacuo*. The resultant solid was matched starting sydnone **74** by TLC, IR and melting point. Accordingly, this approach was not pursued further.

Microwave synthesis of oxime **76** using ethanol as a solvent and pyridine as a base

A solution of **74** (0.5 g, 0.00245 mol) and hydroxylamine hydrochloride (0.5 g, 0.00719 mol) in pyridine (2.5 mL) and ethanol (2 mL) was irradiated with microwaves at 120˚C for 10 minutes at 3.5 bar. The resultant mixture was allowed to reduce in volume to 2 mL. Following this reduction, water (10 mL) was added and allowed to evaporate to 5 mL, resulting in crystal formation. The resultant pale, yellow-colored solid matched the target sydnooxime **76** (0.4392g, 0.0020 mol, 82% yield) by TLC, IR ^{1}H NMR and melting point.

Synthesis of 5-methylsydno[3,4-*a*]quinazoline (**80**) *via* treatment of **76** with trifluoroacetic acid

A solution of 3-(2-acetylphenyl)sydnone oxime (**76**) [0.500 g, 0.0023 mol] was dissolved in trifluoroacetic acid (10 mL) at 35-40˚C for 3 days. Following this reaction, the solvent was blown off using a stream of nitrogen gas and the resultant dark, oily mixture was washed with water (10 mL), neutralized with sodium bicarbonate (aqueous, 5%), extracted with dichloromethane (3 x 20 mL) and the combined extracts were evaporated *in vacuo* to yield a dark oil. The oil was then purified by column chromatography (silica gel, 1% acetone in dichloromethane as eluant), resulting in a bright yellow, orange solid (0.2212 g, 0.0011 mol, 50%) which matched 5-methylsydno-[3,4-a]quinazoline (**80**) by IR, ^{1}H NMR and melting point (242-243˚C, lit. mp[124] 242-243°C). Carbon-13 NMR was also obtained for the compound since it had not been reported previously.

IR (KBr): 3450, 3075, 3002, 2921, 2852, 1889, 1839, 1741 (sydnone C=O), 1612, 1533, 1504, 1434, 1375, 1322, 1257, 1070, 971, 889, 782, 725, 696, 638, 601, 460 cm^{-1}.

^{1}H NMR ($CDCl_3$:DMSO-d_6): 8.41 (dd, 1 H), 8.16 (dd, 1 H), 8.02 (td, 1 H), 7.96 (td, 1 H), 2.96 (s, 3 H) ppm

^{13}C NMR: 155.32, 147.25, 134.29, 132.02, 127.51, 122.03, 115.61, 78.66, 77.05, 21.56 ppm.

Synthesis of 3-(2-acetylphenyl)sydnone oxime *O*-acetate (**85**)

A solution of 3-(2-acetylphenyl)sydnone oxime (**76**) (0.502 g, 2.29 x 10^{-3} mol) in acetic anhydride (5 mL) was allowed to stir at room temperature for 12 hours at the conclusion of which a colorless needle-like, crystalline solid precipitated. The solid was then filtered off by vacuum filtration, weighed and characterized by TLC, IR, ^{1}H NMR, ^{13}C NMR and melting point (145-146˚C, lit. mp.[124] 146-147°C). 3-(2-acetylphenyl)sydnone oxime *O*-acetate (**85**) was synthesized in 85% yield (0.5085 g, 1.94 x 10^{-3} mol) without need for further purification.

IR (KBr): 3220, 3133, 2921, 1736, 1437, 1336, 1228, 1167, 1078, 1007, 930, 769, 727, 637 cm^{-1}

^{1}H NMR ($CDCl_3$): 7.67 (m, 4 H), 6.69 (s, 1 H), 2.22 (s, 6 H) ppm

^{13}C NMR: 168.54, 167.73, 167.59, 160.49, 159.10, 132.61, 131.96, 131.16, 131.04, 130.67, 129.95, 128.36, 125.48, 124.56, 97.94, 95.74, 22.01, 19.44, 19.25, 16.94 ppm

Synthesis of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**)

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime (**76**) (0.102 g, 4.74 x 10^{-4} mol) in dichloromethane (2 mL) was added *p*-toluenesulfonyl chloride (0.100 g, 5.25 x 10^{-4} mol) in dichloromethane (2 mL) over a period of 10 minutes. The resultant mixture was stirred for 4 hours whereupon the mixture was poured into water (10 mL), washed with hydrochloric acid (5%, 2 x 5 mL), sodium carbonate solution (saturated, 2 x 5 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with magnesium sulfate, filtered and evaporated *in vacuo*. The resultant tan powder (0.1184 g, 3.17 x 10^{4} mol, 67% yield) was analyzed by TLC, IR, ^{1}H NMR, ^{13} NMR and melting point (133-135˚C, lit.m.p.[124] 133-134 °C), matching the literature values for 3-(2-acetylphenyl)-sydnone oxime *O*-tosylate (**83**).

IR (KBr): 3480, 3174, 2977, 2944, 2883, 2738, 2495, 1751, 1596, 1477, 1442, 1398, 1365, 1317, 1226, 1180, 1122, 1035, 937, 819, 754, 674, 619, 566, 545, 464 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.75 (m, 8 H), 6.33 (s, 1 H), 2.45 (s, 3 H) 2.25 (s, 3 H) ppm

^{13}C NMR: 161.55, 145.96, 132.60, 132.35, 131.72, 131.44, 130.76, 130.50, 129.88, 128.48, 125.59, 97.02, 53.03, 45.84, 21.77, 17.23, 8.63 ppm

Synthesis of 3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**)

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime (**76**) (1.004g, 4.58 x 10^{-3} mol) in dichloromethane (20 mL) was added methanesulfonyl chloride (7.5mL, 11.1g, 0.0969 mol) in dichloromethane (20 mL) over a period of 10 minutes. The resultant mixture was stirred for a period of 20 minutes whereupon it was poured into water (40 mL), washed with hydrochloric acid (5%, 2 x 20 mL), sodium carbonate solution (saturated, 2 x 20 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic layers

were dried with magnesium sulfate, filtered and evaporated *in vacuo*. The resultant light tan powder (1.239 g, 4.16 mmol, 91% yield) was analyzed by TLC, IR, ^{1}H NMR, ^{13}C NMR and melting point (133-135˚C, lit. m.p.[124] 134-137°C), matching the literature values for 3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**).

IR (KBr): 3480, 3162, 3147, 3089, 3027, 2937, 2680, 2096, 1997, 1957, 1735, 1506, 1442, 1352, 1183, 1093, 964, 819, 767, 688, 524 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.89 (m, 4 H), 7.26 (s,1 H), 3.22 (s, 3 H), 2.49 (s, 3 H) ppm

^{13}C NMR: 173.24, 173.20, 167.08, 166.23, 137.59, 137.53, 137.18, 136.58, 136.43, 136.22, 135.14, 133.35, 132.81, 131.05, 129.72, 103.14, 101.34, 41.38, 41.34, 26.76, 21.80 ppm

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* thermolysis of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**)

3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) (0.100g, 2.678 x 10^{-4} mol) was dissolved in a minimum amount of dichloromethane. The resultant solution was spotted onto a glass-backed preparative thin-layer chromatography plate. The TLC plate was then baked at 100˚C for 20 minutes. Upon cooling, the plate was eluted (1% acetone in DCM). The high running yellow spot was then isolated, dissolved off of the silica gel (dichloromethane), rotary evaporated and characterized. The compound was confirmed to be 5-methylsydno-[3,4-a]quinazoline (**80**) (0.0092 g, 4.55 x 10^{-5} mol, 17% yield) by IR, TLC and melting point (242-243˚C, lit. mp[124] 242-243°C).

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* thermolysis of 3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**)

3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**) (0.100g, 3.36 x 10^{-4} mol) was dissolved in a minimum amount of dichloromethane. The resultant solution was spotted onto a glass-backed preparative thin-layer chromatography plate. The TLC plate was then baked at 100˚C for 20 minutes. Upon cooling, the plate was eluted (1% acetone in DCM). The high running yellow spot was then isolated, dissolved off of the silica gel (dichloromethane), rotary evaporated and characterized. The compound was confirmed to be 5-methylsydno[3,4-a]quinazoline (**80**) (0.0092 g, 4.55 x 10^{-5} mol, 17% yield) by IR, TLC and melting point (242-243˚C, lit. mp[124] 242-243°C).

Thermolysis of 3-(2-acetylphenyl)sydnone oxime *O*-acetate (**85**)

3-(2-acetylphenyl)sydnone oxime *O*-acetate (**85**) (0.100g, 3.83 x 10^{-4} mol) was dissolved in a minimum amount of dichloromethane. The resultant solution was spotted onto a glass-backed preparative thin-layer chromatography plate. The TLC plate was then baked at 100˚C for 20 minutes. Upon cooling, the plate was eluted (1% acetone in DCM). The only spot was confirmed to be starting material by IR, TLC and melting point.

Intramolecular lithiation of 3-(2-acetylphenyl)sydnone (**76**) to sydnoindole **46**

To a solution of 3-(2-acetylphenyl)sydnone (**76**) [0.107 g, 5.240 x 10^{-4} mol] in THF (100 mL) at -78˚C was added 1.2 eq. LDA (0.50 mL, 0.75 mmol). After 2 hours, the reaction was quenched with water (100 mL). The combined mixture was allowed to evaporate to 100 mL, extracted with dichloromethane (3 x 100 mL), and the combined extracts were

dried with magnesium sulfate, filtered and evaporated *in vacuo* resulting in a tan solid material. Upon characterization of the compound by IR, ^{1}H NMR and melting point (180-181˚C, lit. m.p.[116]184-187˚C), it was found to be the fused-ring sydnoindole **46** (0.067g, 3.510 x 10^{-4} mol, 66%).

IR (KBr): 3336, 2923, 1727, 1623, 1483, 1423, 1400, 1305, 1137, 1103, 769, 734, 684, 630, 445, 422 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.82 (m, 4 H), 6.31 (s, 1H) 1.86 (s, 3 H) ppm

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* intramolecular lithiation of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) with 1.2 eq. LHMDS

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) (0.248g, 6.61 x 10^{-4} mol) in tetrahydrofuran (100 mL) at -78˚C was added 1.2 eq. LHMDS (0.79 mL, 7.93 x 10^{-4} mol). The mixture was stirred for 4 hours and then quenched with water (100 mL). The combined mixture was allowed to evaporate to 100 mL, extracted with dichloromethane (3 x 100 mL), dried with magnesium sulfate, filtered and evaporated *in vacuo* resulting in a orange, brown solid material resulted. The material was purified by column (1% acetone in DCM), giving 5-methylsydno-[3,4-*a*]quinazoline (**80**) (0.0532 g, 2.645 x 10^{-4} mol, 40% yield) matching previously synthesized material by IR, ^{1}H NMR and melting point (242-244˚C, lit. mp[124] 242-243°C).

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* intramolecular lithiation of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) with 1.5 eq. LHMDS

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) (0.250g, 6.69 x 10^{-4} mol) in tetrahydrofuran (100 mL) at -78˚C was added 1.5 eq. LHMDS (1.0 mL, 0.0010 mol). The mixture was stirred for 4 hours and then quenched with water (100 mL). The combined mixture was allowed to evaporate to 100 mL, extracted with dichloromethane (3 x 100 mL), dried with magnesium sulfate, filtered and evaporated *in vacuo* resulting in a orange, brown solid material resulted. The material was purified by column (1% acetone in DCM), giving 5-methylsydno-[3,4-*a*]quinazoline (**80**) (0.0619 g, 3.077 x 10^{-4} mol, 46% yield) matching previously synthesized material by IR, ^{1}H NMR and melting point (242-243˚C, lit. mp[124] 242-243°C).

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* intramolecular lithiation of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) with 1.2 eq. LDA

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) (0.247g, 6.614 x 10^{-4} mol) in tetrahydrofuran (100 mL) at -78˚C was added 1.2 eq. LDA (0.55 mL, 7.937 x 10^{-4} mol). The mixture was stirred for 4 hours and then quenched with water (100 mL). The combined mixture was allowed to evaporate to 100 mL, extracted with dichloromethane (3 x 100 mL), dried with magnesium sulfate, filtered and evaporated *in vacuo* resulting in a orange, brown solid material resulted. The material was purified by column (1% acetone in DCM), giving 5-methylsydno-[3,4-*a*]quinazoline (**80**) (0.0545 g, 2.711 x 10^{-4} mol, 41% yield) matching previously synthesized material by IR, ^{1}H NMR and melting point (242-244˚C, lit. mp[124] 242-243°C).

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* intramolecular lithiation of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) with 1.5 eq. LDA

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime *O*-tosylate (**83**) (0.253g, 6.691 x 10^{-4} mol) in tetrahydrofuran (100 mL) at -78˚C was added 1.5 eq. LDA (0.7 mL, 0.0010 mol). The mixture was stirred for 4 hours and then quenched with water (100 mL). The combined mixture was allowed to evaporate to 100 mL, extracted with dichloromethane (3 x 100 mL), dried with magnesium sulfate, filtered and evaporated *in vacuo* resulting in a orange, brown solid material resulted. The material was purified by column (1% acetone in DCM), giving 5-methylsydno-[3,4-*a*]quinazoline (**80**) (0.0605 g, 3.011 x 10^{-4} mol, 45% yield) matching previously synthesized material by IR, ^{1}H NMR and melting point (242-243˚C, lit. mp[124] 242-243°C).

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* intramolecular lithiation of 3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**) with 1.5 eq LDA

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**) (0.503g, 1.691 x 10^{-3} mol) in tetrahydrofuran (150 mL) at -78˚C was added 1.5 eq. LDA (1.7 mL, 0.0025 mol). The mixture was stirred for 4 hours and then quenched with water (100 mL). The combined mixture was allowed to evaporate to 100 mL, extracted with dichloromethane (3 x 100 mL), dried with magnesium sulfate, filtered and evaporated *in vacuo* resulting in a orange, brown solid material resulted. The material was purified by column (1% acetone in DCM), giving 5-methylsydno-[3,4-*a*]quinazoline (**80**) (0.2279 g, 1.132 x 10^{-3}

mol, 67% yield) matching previously synthesized material by IR, ^{1}H NMR and melting point (242-243˚C, lit. mp[124] 242-243°C).

Synthesis of 5-methylsydno-[3,4-*a*]quinazoline (**80**) *via* intramolecular lithiation of 3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**) with 2.2 eq. LDA

To a stirred solution of 3-(2-acetylphenyl)sydnone oxime *O*-mesylate (**84**) (0.513g, 1.724 x 10^{-3} mol) in tetrahydrofuran (150 mL) at -78˚C was added 2.2 eq. LDA (2.5 mL, 0.0038 mol). The mixture was stirred for 4 hours and then quenched with water (100 mL). The combined mixture was allowed to evaporate to 100 mL, extracted with dichloromethane (3 x 100 mL), dried with magnesium sulfate, filtered and evaporated *in vacuo* resulting in a orange, brown solid material resulted. The material was purified by column (1% acetone in DCM), giving 5-methylsydno-[3,4-*a*]quinazoline (**80**) (0.2796 g, 1.389 x 10^{-3} mol, 80% yield) matching previously synthesized material by IR, ^{1}H NMR and melting point (242-243˚C, lit. mp[124] 242-243°C).

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