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Routes to 1,3,4 - Oxadiazol-2(*3H*)-ones

Karunakar Reddy Madaram
Wright State University

ROUTES TO 1,3,4 – OXADIAZOL-2(*3H*)-ONES

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

By

Karunakar Reddy Madaram

B.S., OSMANIA UNIVERSITY, 2010

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WRIGHT STATE UNIVERSITY

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Karunakar Reddy Madaram ENTITLED Routes to 1,3,4 – oxadiazol-2(*3H*)-ones BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

_____
Kenneth Turnbull, Ph.D.
Thesis Director

_____
David Grossie, Ph.D.
Chair Department of Chemistry

Committee on Final Examination

_____
Kenneth Turnbull, Ph.D.

_____
Eric Fossum, Ph.D.

_____
William A. Feld, Ph.D.

_____
Robert E. W. Fyffe, Ph.D.
Vice President for Research and
Dean of the Graduate School

Abstract

Karunakar Reddy, Madaram M.S., Department of Chemistry, Wright State University, 2016. Routes to 1,3,4 – oxadiazol-2(*3H*)-ones.

Various 1,3,4-oxadiazol-2(*3H*)-ones were synthesized by reaction of the bromocarbonylhydrazine salt(**35**) obtained from treatment of 4-bromo-3-phenylsydnone(**34**) with HCl with the corresponding acid chlorides in DME. The structures were confirmed by their physical, analytical and spectral data (IR, GC/MS, ^{1}H and ^{13}C NMR and CHN analysis). In general these compounds were synthesized in good to excellent yields and it is planned to continue exploration of their chemical behavior as a guide to their potential antimicrobial activity.

As an initial approach to the synthesis of the desired 1,3,4-oxadiazol-2(*3H*)-ones, the starting material, 3-phenylsydnone, was prepared in 2 steps from commercially available N-phenylglycine in good overall yield. This sydnone was then converted into the versatile intermediate, 4-bromo-3-phenylsydnone. The latter was then converted by treatment with hydrochloric acid into the bromocarbonylhydrazine salt(**35**), which served as a key synthon for the preparation of a wide variety of 3,5-disubstituted oxadiazolinones. With respect to the cyclization step, the bromocarbonylhydrazine salt(**35**) was treated with an acid chloride (alkyl version) in DME and simple work-up with ice water / extraction resulted in a facile, high yield approach to the target

oxadiazolinone. However, with aryl acid chlorides the use of a subsequent base treatment was needed to remove unreacted acid chloride and provide good yields of the corresponding oxadiazolinones. With a successful avenue in hand, attempts were made to optimize the yields of the desired 1,3,4-oxadiazol-2(*3H*)-ones by changing several parameters such as the amount of acid chloride, the reaction temperature and the reaction time. The optimized approach was then used for the successful preparation of a number of oxadiazolinones, including one new compound, *viz*. 5-(3-bromophenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (**49**), which was obtained in 60% yield.

TABLE OF CONTENTS

List of Tables

Acknowledgement

I would like to express my sincere gratitude to my advisor, Dr. Kenneth Turnbull, for his kindness, patience, guidance and support throughout my whole graduation in the laboratory and in my thesis preparation. The opportunities he has provided and the way he guided me built my confidence. I am very thankful to my committee members, Dr. William Feld and Dr. Eric Fossum for their contributions and suggestions towards this thesis.

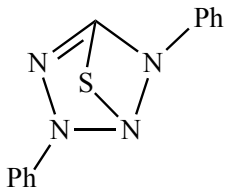
I am also very thankful to my parent's back home in India for supporting me financially throughout my educational career.

Finally, I would like to thank the faculty and staff, and all my colleagues for their support and especially the Chemistry Department for providing me with a Teaching Assistantship.

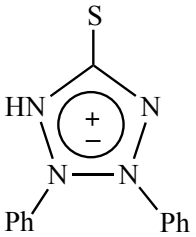
Introduction

Foreword

In 1882 Emil Fischer[1] reported the formation of dehydrodithizone (an orange, crystalline compound) from the oxidation of dithizone. He assigned the bicyclic structure **1** for the compound, however, in the late 1940's as more sophisticated analytical techniques became available, Baker, Ollis and Poole[2,3] suggested that the structure was not a bicyclic array but a monocyclic, dipolar structure **2**[4]. They coined the term mesoionic (mesomeric/ionic) for this type of molecule and developed a series of rules for any such systems that could exist.



1



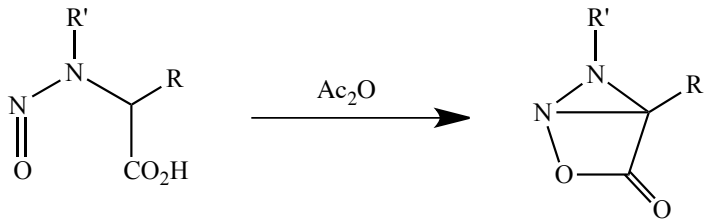
2

Although dehydrodithizone was the first mesoionic compound, sydnones are the most studied members of the class of mesoionic compounds. Sydnones are small, dipolar aromatic heterocycles which have a unique variation in electron density around the ring. They have fascinated many scientists and have been comprehensively studied due to their interesting physical, chemical and biological properties. Several reviews have been

introduce the reader to the most important features of sydnone research and also to emphasize the main discoveries in the area that have occurred in our lab during 2013-2015.

Historical

In 1935, Earl and Mackney[5], working in Sydney, Australia, discovered that treatment of N-nitroso-N-phenylglycine **3** (R=H, R'=Ph) with acetic anhydride formed a stable, crystalline, neutral anhydro derivative to which they assigned a bicyclic structure **4** (R=H, R'=Ph). Based upon this process, a variety of N-nitrosoglycines were employed and several analogous anhydro derivatives were synthesized and named "sydnones" due to their discovery in Sydney, Australia.

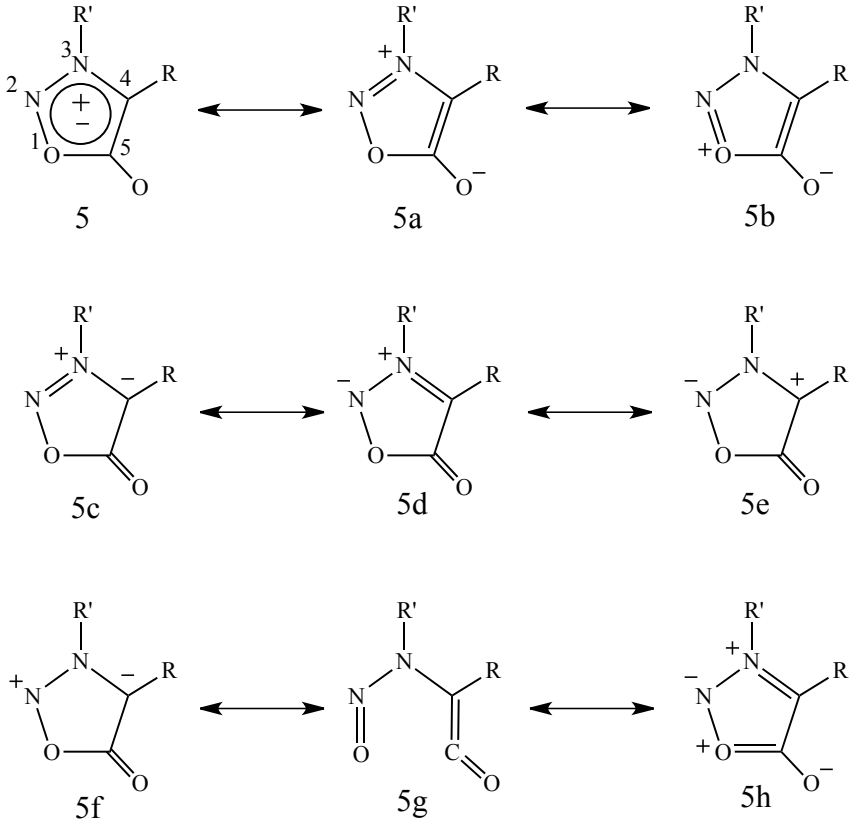


3 **4**

The bicyclic structure **4** suggested by Earl and Mackney satisfactorily rationalized the molecular formula, however, the stability and the chemical and physical properties of sydnones were at odds with a bicyclic structure. Sydnones show a greater degree of polarity, and are more stable towards heating and less reactive towards acids and bases than would be predicted for the strained, bicyclic representation **4**. Based upon this work Baker, Ollis and Poole[2,3] suggested that the assigned bicyclic structure **4** was incorrect

and they instead assigned a monocyclic, resonance stabilized, dipolar oxadiazolone structure with many resonance forms **(5a-h)**. In 1946, Baker, Ollis and Poole coined the term "mesoionic" (mesomeric/ionic) to describe the nature of such monocyclic, dipolar compounds and they suggested also that sydnones belonged to this classic group of compounds due to the uncommon characteristics of the sydnone ring system. They developed rules for a molecule to be considered mesoionic and, as such, a compound should : 1) have delocalized positive and negative charges that do not cancel out; 2) be a planar, 5-membered ring heterocycle; 3) have an exocyclic atom or group capable of bearing a substantial negative charge; 4) possess a considerable resonance energy.[4]

As mentioned earlier, sydnones can be denoted by many possible canonical representations and, in general, the resonance hybrid structure **5** is the preferred depiction.



Based upon the characteristics mentioned above, mesoionic compounds can be easily differentiated from formally related dipolar species like ylides and zwitterions where a great deal of charge localization is observed. In mesoionic systems charge distribution is delocalized resulting in more than one resonance form.

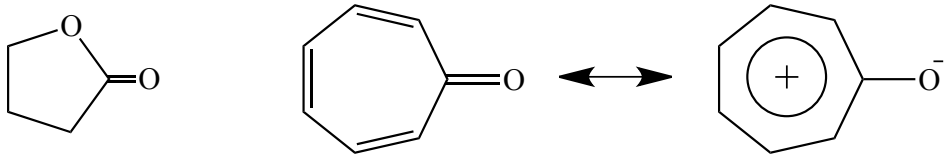
The name "sydnone" has become the most common way of describing these compounds and indeed, is used by Chemical Abstracts as a way of grouping these oxadiazole derivatives.

Physicochemical Properties and Electronic Structure

Most aryl sydnones are crystalline solids whereas alkyl sydnones are liquids or low-melting solids, which can be distilled *in vacuo* without much decomposition. In general, sydnones are soluble in common organic solvents other than petroleum ether and hexanes (non-polar), but are insoluble in water. However, their solubility in the latter tends to increase when a polar functional group is present within the molecule.

Often, characteristic features of sydnones can be determined using Infrared (IR) and NMR spectroscopies. In the IR spectrum, the most characteristic feature is the very strong carbonyl stretch at ~ 1718-1760 cm^{-1}. Usually the carbonyl stretch shows up as a single peak, however, in some cases multiple peaks can occur due to Fermi resonance splitting.[6,7] As mentioned above, the carbonyl stretch typically appears at ~ 1718-1760 cm^{-1} and, when compared to congeneric carbonyl containing species such as γ-lactones **6** (~ 1770 cm^{-1}) and tropone **7** (~1638 cm^{-1}), it is reasonable to 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] Another characteristic band that can be seen in the IR spectra of sydnones is a medium intensity peak around ~3150 cm^{-1} representing the C-H stretch at the C-4 ring position (when present).[8-11] This C-H absorption potentially differentiates sydnones from alkyls, aryls and epoxides with an identical ring strain with absorption around 2900-3050 cm^{-1}. Additionally, this absorption of the sydnone around ~3150 cm^{-1} is very helpful in determining the substitution at the C-4 position of an unresolved structure.



6 **7**

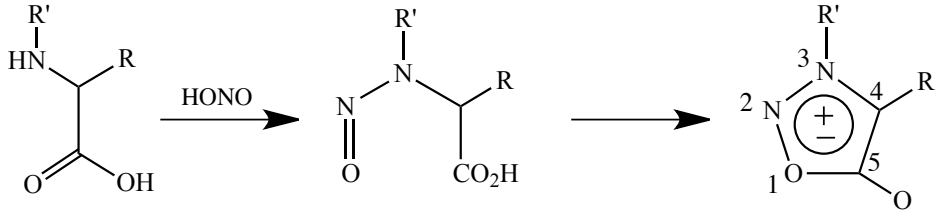
The ^{1}H-NMR spectra of sydnones show that the proton at the C-4 position of the sydnone ring (when present) is greatly shielded and usually appears between 6.5-7.5 ppm depending upon the solvent [$CDCl_3$ (more shielded) or DMSO (less shielded)]. Further, in the ^{13}C-NMR spectra of sydnones, this shielding effect is apparent in the location of the C-4 position, which appears around 95 ppm.

The carbonyl nature of the C-O exocyclic bond of various 3-substituted and 3,4-disubstituted sydnones is also well explained by assuming that the C=O bond is 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 of the sydnone carbonyl lower than those for alicyclic esters[12] thus supporting the

argument that contributions from other vibrational modes cause the sydnone carbonyl group to absorb at a higher frequency than expected. Furthermore, evidence from spectroscopic and theoretical studies shows that the protonation of the sydnone moiety occurs at the exocyclic oxygen[13-17]. This supplements earlier observations where bond orders and charge densities were correlated to the calculated and observed dipole moments and the observed UV maxima.[18,19] These studies support the earlier contention that substantial charge density resides on the exocyclic oxygen.

Synthesis

Sydnones can be readily prepared by cyclodehydration of *N*-substituted-N-nitrosoamino acids with reagents such as acetic anhydride. However, in general, sydnones, *cf*. **5**, are synthesized in two steps from *N*-substituted amino acids and the nitrosoamino acid **3** is prepared *via* nitrosation of an *N*-substituted glycine **8** with nitrous acid. For some sydnones with acid sensitive groups the method has been modified slightly. Thus, the use of isoamyl nitrite and dimethoxymethane ensures the desired neutral reaction conditions, making it possible to prepare some otherwise unattainable sydnones.



8 **3** **5**

The original cyclodehydration used by Earl and Mackney made use of acetic anhydride at room temperature for six days. Variations to this method have been found including heating in acetic anhydride or thionyl chloride; treatment with phosphorus

pentoxide or the use of trifluoroacetic anhydride (TFAA). The latter is the most widely used method since it is rapid (<15 minutes), is achievable at low temperatures (-5°C to 0°C) and affords high yields (>90% for *N*-phenylsydnone). The only drawback is the high cost of TFAA in comparison to other reagents.

Other synthetic strategies for the cyclization include the use of (1) acetic anhydride at room temperature facilitated by ultrasonification[20] (2) haloiminium salts[21] (3) *N*, *N*-dimethylchlorosulfitemethanium chloride[22] and (4) 2-chloro-1, 3-dimethylimidazolinium chloride.[23] However, the use of TFAA has continued to be the preferred method since it achieves fast, efficient and reliable cyclization.

Chemical and Biological behavior

Studies have shown that both the aromatic and dipolar natures of sydnones are reflected in their chemical properties. The ability of the sydnone to undergo electrophilic substitution reactions demonstrates its aromatic nature whereas the ready cleavage of the ring by acids, as well as the facile 1,3-dipolar cycloaddition reactions it undergoes, shows its dipolar nature. Electrophilic aromatic substitution[24] reactions of sydnones typically include halogenation, nitration, acylation and sulfonation. The high regioselectivity of these reactions for the C-4 position (even when an aryl group is attached to the N-3 position) has been attributed to two factors (1) the considerable partial negative charge that resides at the C-4 position appears to activate this position; and (2) the considerable partial positive charge that resides at the N-3 position seems to deactivate the juxtaposed aryl ring. In the cases when activating groups are attached to the aryl ring at the N-3 position, these may allow the aryl moiety to compete successfully for the electrophile,

thus opening avenues to a variety of sydnone derivatives. This premise has been explored in both bromination and nitration[25,26]. Sydnones are also useful precursors to hydrazines[5] (by acid hydrolysis) and this chemistry has been extended to the use of sydnones as "masked" hydrazines for heterocycle formation. In addition sydnones have liquid crystal properties[27], have been incorporated into azodyestuffs[28-31] and have been experimentally tested for use as lithium battery electrolytes.

A large number of biologically active sydnone derivatives have been synthesized and the former have been reported to possess a wide spectrum of biological and pharmacological activities such as anti-microbial, anti-inflammatory[32], analgesic, anti-pyretic and anti-tumor.[33]

Reactions of Sydnones

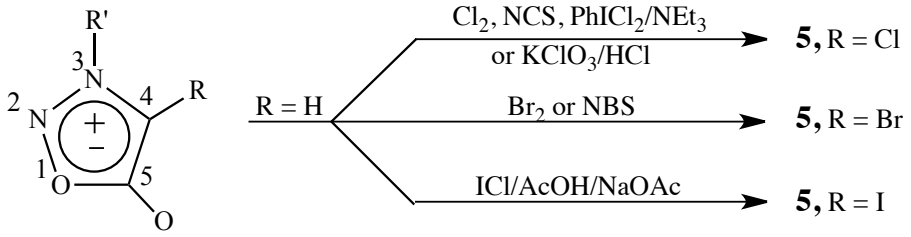
Most of the reactions performed on the sydnone ring take place at the C-4 position. The hydrogen at the C-4 position is acidic with a pKa of about 18-20 and, as mentioned above, the C-4 position is also considered to be nucleophilic. This allows two main reactions to take place at the 4-position: 1) electrophilic aromatic substitution or 2) deprotonation followed by electrophilic addition. Further, other major transformations that can take place with the sydnone ring are treatment with an acid to form a hydrazine and 1,3-dipolar cycloaddition. Since the latter two reactions are substantial areas that were not employed during the research work reported in this thesis, no further discussion will be included and the reader is directed to the referenced literature for more details.

1. Aromatic Substitution Reactions of Sydnones

As mentioned briefly, previously, sydnones with a proton attached at the C-4 position (*cf.* **5**, R=H) can undergo electrophilic aromatic substitution at this position. The same electrophiles typically employed in substitution reactions of benzene and other related arenes can be used for this approach and, in general, owing to the high negative charge density at the sydnone C-4 position, milder conditions can be employed. Sydnones thus undergo sulfonation, nitration, acylation, halogenation and metallation and these substitution reactions are discussed below.

A. Halogenation of Sydnones

A number of techniques have been developed for halogenation of the sydnone ring at the C-4 position. When sydnones such as **5** (R' = various, R = H)[34-36] are treated with chlorine, potassium chlorate in moderately concentrated HCl,[37] dichloroiodobenzene with triethylamine[38] or N-chlorosuccinimide (NCS),[39] the corresponding chlorinated sydnones (*cf.* **5**, R = Cl) are obtained. Sydnones brominated at the C-4 position, (*cf.* **5**, R = Br) can be attained by reacting the parent sydnone **5** (R = H) with bromine,[34-36] N-bromosuccinimide (NBS)[39] or potassium bromate in HBr. In general, the synthesis of 4-iodosydnones (*cf.* **5**, R = I) has proven to be much more problematic and it was not until 1997 that a general, effective process was reported using iodine monochloride in acetic acid at room temperature.[40] More recently, we have shown that NIS in acetic acid provides and even more reliable, high yield avenue to such compounds.



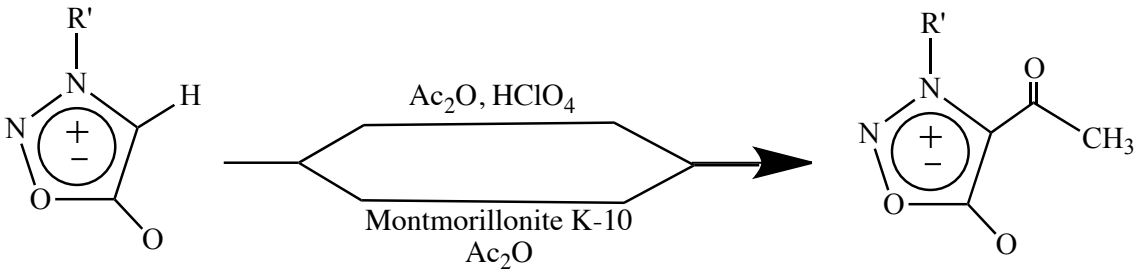
B. Nitration

Only a limited amount of research has been done on the nitration of sydnones due to the strongly acidic conditions required for this reaction and the relative instability of sydnones to the medium. However, 3-phenylsydnone (**5**, R=H, R'=Ph) reacts with potassium nitrate in the presence of sulfuric acid at -5°C to yield a relatively stable 4-nitro derivative **5** ($R=NO_2$, R'=Ph) in modest yield.[41] Of more interest is the discovery that, unlike the reactions of any other electrophiles with sydnones, even modestly activating groups attached to the 3-aryl substituent (*e.g.* Me) direct the electrophile to exclusive substitution on the aryl ring. Presumably the "hard" nature of the electrophile is the controlling factor, however, no clarifying studies have been performed.

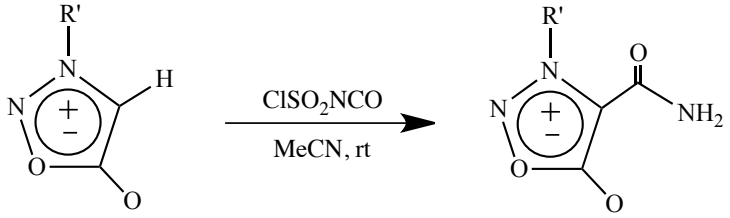
C. Acylation

Acylation of the sydnone ring at the C-4 position can be effected using the classic Friedel-Crafts reaction, however, the "normal" Friedel-Crafts conditions are apparently not ideal. Thus, treatment of sydnones with anhydrides in the presence of aluminum chloride gives poor yields, if any, of the desired product. Presumptively, the Lewis acid coordinates with the exocyclic oxygen of the ring and inhibits the reaction from taking place. Because of this aspect, alternative methods have been developed. As reported by Tien and co-workers, acylation of various substituted sydnones at the 4-position occurs

using acetic anhydride and $HClO_4$ or H_3PO_4[42] and Turnbull developed a method using Montmorillonite K-10 and acetic anhydride to yield the corresponding product **9** (R = Me, R' = Ph). More recently, Turnbull and coworkers have demonstrated the first sydnone acylations using less than stoichiometric amounts of a catalyst (bismuth triflate was the most effective) and the use of a solvent other than the anhydride reactant. Turnbull, Gross and Hall prepared 4-carboxamido sydnones **10** in good yields directly from a variety of 3-substituted sydnones by the use of chlorosulfonyl isocyanate in acetonitrile at room temperature.



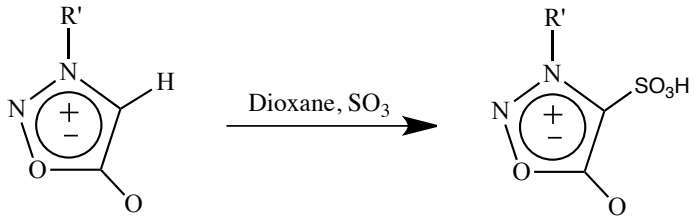
5 **9**



5 **10**

D. Sulfonation

Yashunskii and co-workers have reported the direct sulfonation of a variety of 3-substituted sydnones.[43] Therein it was shown that the treatment of sydnones **5** (R'= 4-$MeOC_6H_4$ or 4-$EtOC_6H_4$, R = H) with dioxane-sulfur trioxide complex (SO_3) in CH_2Cl_2 at 20-40°C generated the sulfone derivatives **11**, (R'= 4-$MeOC_6H_4$ or 4-$EtOC_6H_4$), which were characterized as the S-benzylthiuronium salts. However, all attempts to isolate these compounds as the free acids via neutralization were unsuccessful and resulted in the isolation of the non-sulfonated sydnones **5** (R'= 4-$MeOC_6H_4$ or 4-$EtOC_6H_4$, R = H).

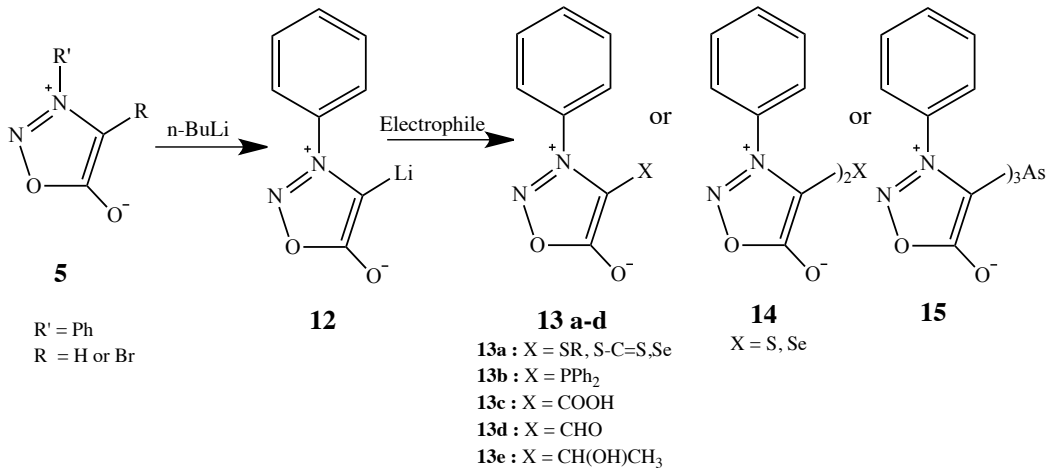


5 **11**

2. Metallation of Sydnones

The metallation of sydnones has been the second most investigated route for substitution at the sydnone C-4 position. Some of the commonly studied metal complexes include 4-lithio, 4-cupro, 4-chloromercurio and the 4-palladium(0)[44] or nickel(II).[45] The 4-lithio species (*cf.* **12**, R' = Ph) can be prepared directly from 3-phenylsydnone **5** (R=H, R'=Ph) or indirectly from metal-halogen exchange of 4-bromo-3-phenylsydnone **5** (R=Br, R'=Ph). This species appears to be the most versatile of all 4-metallo substituted sydnones in terms of its applications, however, the reactivity of the

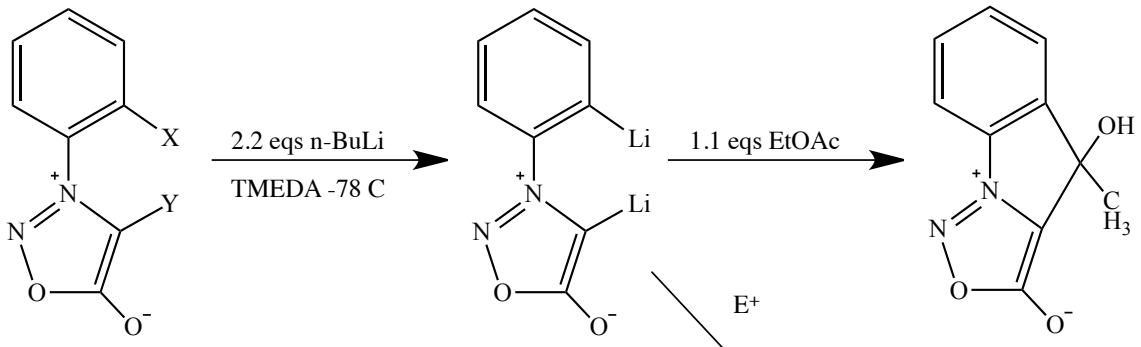
sydnone metal species can be modulated by changing the metal present at the 4-position. For this report, only the lithio sydnones will be discussed as they are by far the most studied examples.



The 4-lithiosydnone **12** reacts with alkyl or aryl disulfides or diselenides to afford the 4-sydnosulfides or 4-sydnoselenides and derivatives 13a.[46] Additionally, the bisydnonyl sulfide and selenide **14** can be prepared in an analogous manner by treating **12** with dicyano disulfide or diselenide.[46] Extension of this methodology to arsenic trichloride or diphenylchlorophosporane[46] resulted in the preparation of the corresponding sydnonylarsine **15** or phosphine **13b**, respectively. More recently, 4-carboxysydnones **13c** have been prepared by carboxylation of **12** with carbon dioxide.[47] Additionally, Tien and coworkers[48] have shown that various 3-substituted sydnones can be lithiated and exposed *in situ* to either *N*, *N*-dimethylformamide or acetaldehyde to yield the corresponding acylated **13d** or hydroxylated **13e** derivatives, respectively.

3. Dilithiation

Dilithiation of 3-arylsydnones has become a recent focus of sydnone chemistry, and has been successfully achieved by Krein and Turnbull.[49-51] Initially a dilithio sydnone intermediate **17** was produced by the reaction of 3-(2-bromophenyl)-4-bromosydnone **16a** with butyllithium at -78°C. Upon treatment with ethyl acetate a sydnoindole **18** was obtained in good yield.



16a : X, Y = Br
16b : X = Br, Y = H

17

18

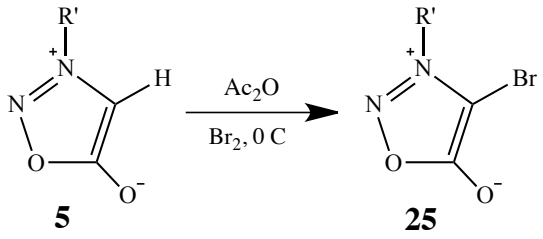
19 : $E^+ = Br_2$, E = Br
20 : $E^+ = HCON(CH_3)_2$, E = CHO
21 : E^+ = PhCHO, E = CH(OH)Ph
22 : $E^+ = I_2$, E = I
23 : E^+ = PhSSPh, E = SPh
24 : $E^+ = CH_3I$, $E = CH_3$

Krein and Turnbull have proven the versatility of this method and successfully

applied it to other esters. One undesirable drawback however, was the loss of weight going from starting material to product caused by the sacrifice of two bromine atoms. Thus, an alternative starting material had to be sought. When 3-(2-bromophenyl) sydnone **16b** was used instead of **16a** using similar conditions it was found that the same transformations were achieved. On pursuing this further, Krein and Turnbull discovered that the dilithio-intermediate **17** can be prepared directly from 3-phenylsydnone **5** (R' = Ph, R = H) using N,N,N,N-tetramethylenediamine (TMEDA) to increase the basicity of butyllithium. 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 have a pKa of approximately 40. This was complemented by the anticipated, apparent *ortho*-directing effect of the sydnone ring. Thus it was possible to react at the *ortho*-aryl site without the need for metal halogen exchange. This dilithio species was reacted with several electrophiles to yield a variety of disubstitued sydnones (*cf*. **17** to **19-24**).

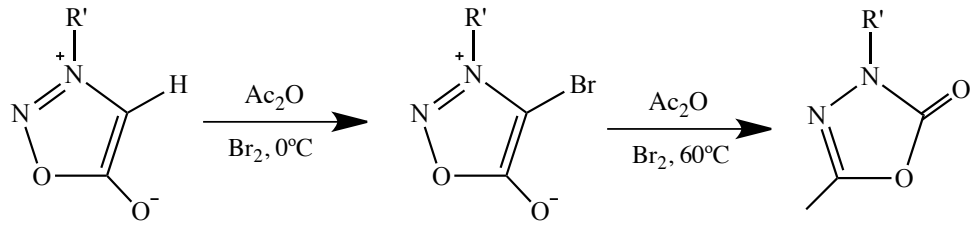
OXADIAZOLINONES

In 1949, at a time when sydnone reactions were still in their infancy, Baker, Ollis and Poole[2] re-examined the bromination of 3-phenylsydnone (5, R' = Ph) with bromine to generate 4-bromo-3-phenylsydnone **25** (R'= Ph). In the original preparation, Kenner and Mackay had reported that good yields of **25** (R' = Ph) were obtained using acetic acid as solvent and Baker, Ollis and Poole's contribution was the claim that using acetic anhydride as solvent gave the product in better yields with improved purity.



5 **25**

In 1958, Stansfield[52] reinvestigated this reaction and obtained a different result. Once again he started with 3-phenylsydnone **26** (R'= Ph) in acetic anhydride, however, while the initial temperature was 0°C he subsequently heated up to 60°C, which resulted in the formation of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one **27** (R'= Ph). He suggested the intermediacy of the 3-bromo-4-phenylsydnone **25** (R' = Ph) and speculated that the latter was undergoing hydrolysis by the liberated HBr, to give a hydrazine (a reaction already observed for 3-phenylsydnone itself) and he extended the process to the use of propionic anhydride and butyric anhydride (resulting in the formation of the ethyl and propyl analogs of **27**, R' = Ph).



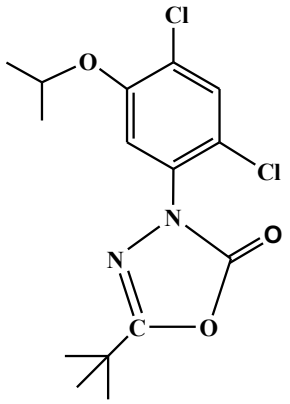
26 **27**

Surprisingly, this reaction remained dormant until 2000 when Mallur, Bharat and Badami[53] demonstrated that the process was a general one. Thus, they prepared a series of 5-methyl-3-aryl-1,3,4-oxadiazol-2(*3H*)-ones **27** (R'= Ar) from the corresponding 3-aryl sydnones **26** (R'= Ar) by reaction with bromine in acetic anhydride. Their goal was to synthesize such species and test them for antimicrobial activity.

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

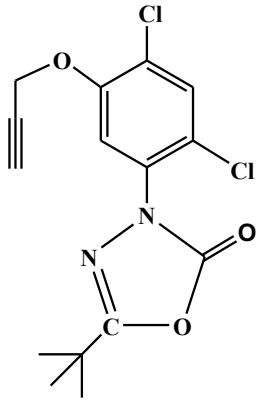
The 1,3,4-oxadiazole core is a widespread bioisostere for improving the pharmacological profile of biologically active amides, esters and ureas. Compounds containing this core have been found to exhibit a wide spectrum of biological activities such as antitumor agents, GABA Receptor agonists, herbicides, ischemic stroke therapeutics and pesticides.

Several bioactive 1,3,4-oxadiazol-2(*3H*)-ones are used as herbicides[54] and three examples are Oxadiazon (™ Ronstar) **28**, Oxadiargyl **29** and Dimefuron **30**.



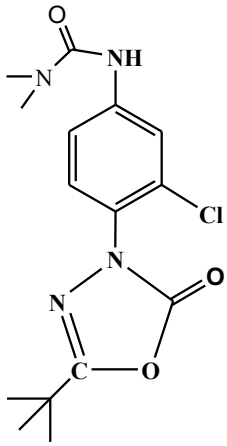
Oxadiazon(Ronstar)

28



Oxadiargyl

29



Dimefuron

30

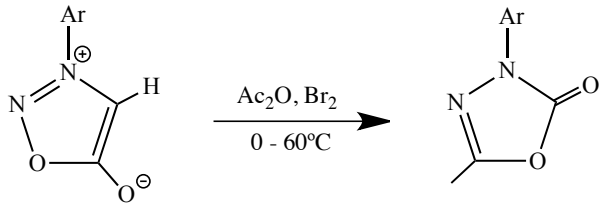
Oxadiazon **28** is the active ingredient in the herbicide ™ Ronstar, intended for pre emergence or early post emergence application, which controls the growth of certain undesirable weeds such as broadleaves, grasses, sedge, brush vines, and bramble. Its mode of action is as an inhibitor of protoporphyrinogen oxidase, an essential enzyme in plant growth, and as such has been used for weed control on established perennial turf (bluegrass, bermuda grass, St. Augustine grass, fall fescue etc.). ™ Ronstar is registered for commercial use in nurseries, on turf, for non-food crops and commercial landscapes.

Aims of the present work

The main focus of this research was to explore routes leading to the synthesis of 1,3,4-oxadiazolin-2-ones from 3-aryl sydnones **31**. Such species have been prepared previously from 3-acetyl-2-phenylcarbazic acid ethyl ester[55] and 1-phenyl-2-acetylphenyl-hydrazine,[56] however, these approaches are far from straightforward. In 2000, Badami and co-workers[57] showed that oxadiazolin-2-ones could be prepared in a

one pot synthesis from sydnones in high yields without the formation of any isomers (Scheme 1).

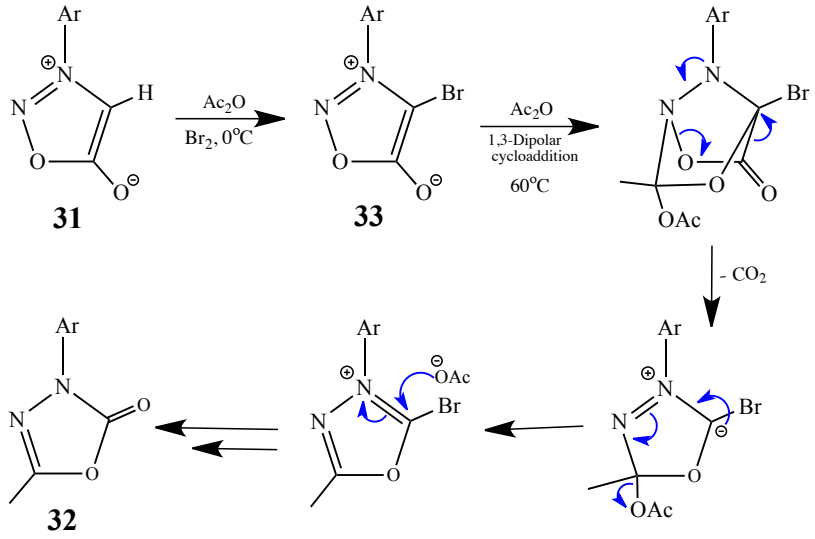
Scheme 1



31 **32**

Hence, this method proved that the sydnones could be used as versatile starting materials for the synthesis of different oxadiazolinones which would otherwise be difficult to access. The mechanism of this conversion was explained by 1,3-dipolar cycloaddition of an acid anhydride to the intermediate product 3-aryl-4-bromosydnone **33** (Scheme 2).

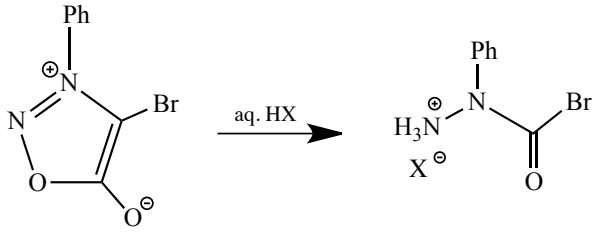
Scheme 2 :



31 **33** **32**

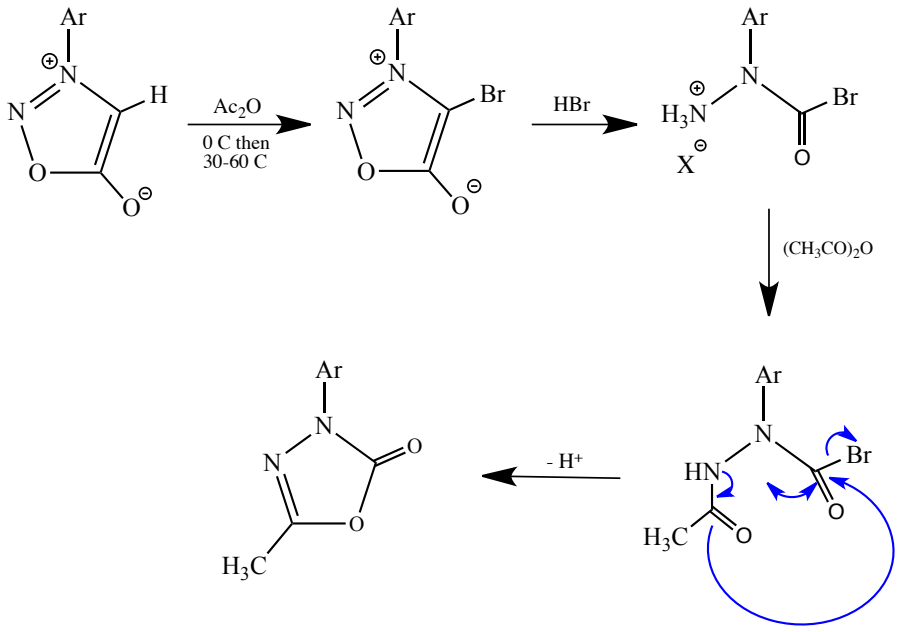
In the above scheme, Badami proposed an unprecedented mechanistic step involving the 1,3 dipolar cycloaddition of acetic anhydride to the intermediate 3-aryl-4-bromo sydnone **33** at 60°C in under 30 minutes. While cycloaddition reactions of sydnones with alkynes and alkenes are well known[58] they are invariably conducted at temperatures above 100°C and involve several hours of reaction time. In addition, Badami and coworkers failed initially to recognize that HBr is formed as a by-product in the initial sydnone bromination. In a later publication[59] they mentioned that the acid was formed but conjectured that it was catalyzing the cycloaddition. It seems likely that HBr is playing a much more fundamental role and, indeed, previous work from Yeh and coworkers[60] and the Turnbull laboratory[61] suggests what that role must be. Thus, Yeh et al. have shown that treatment of 4-bromo-3-phenylsydnone **34** with HCl or HBr results in the formation of the corresponding bromocarbonylhydrazine salts **35** (Scheme 3). It is the premise of the present research work that the bromocarbonylhydrazine salt is the real intermediate in the transformations shown in Schemes 1 and 2 and this has led to the mechanistic proposal shown in Scheme 4.

Scheme 3



34 **35**

Scheme 4



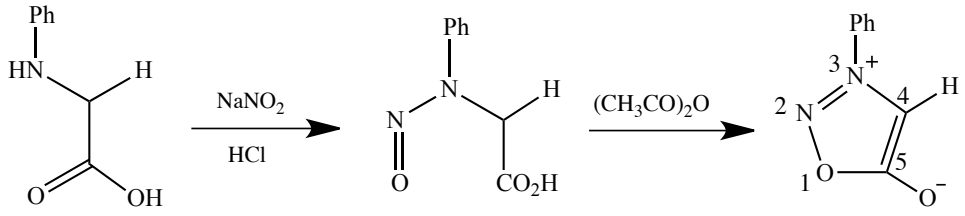
The main aims of this work, then, were to test the proposed mechanism by studying the reaction of the phenylbromocarbonylhydrazine salt **35** with acetic anhydride and to extend the study. If successful transformation to the expected 5-methyl-3-phenyloxadiazolin-2-one were to occur it was planned to examine the utility of the intermediate bromocarbonyl-hydrazines as precursors to new oxadiazolinones. Since Badami had used only acetic anhydride as reagent (and as solvent), it was hoped that a method involving a separate organic solvent would allow extension to other anhydrides and the more readily available acid chlorides. Success in these aspects would provide a much richer variety of valuable oxadiazolinone products

Discussion

As mentioned in the Aims section, the main goals of this work were to investigate the mechanism of the sydnone to oxadiazolinone transformation reported by Badami et al.[35] and to utilize the suggested intermediate bromocarbonylhydrazine derivative **35** as a "synthon" for the synthesis of different oxadiazolinones.

To do so required the preparation of the appropriate starting sydnones, *viz*. 3-phenylsydnone and 4-bromo-3-phenylsydnone. The former was synthesized using a two-step, literature[62] approach from commercially available N-phenylglycine **36** with no purification until the last step. The stepwise approach involved (1) Nitrosation of N-phenylglycine with sodium nitrite and hydrochloric acid to generate N-nitroso-N-phenylglycine **37** and (2) dehydration of the nitroso compound with acetic anhydride to generate the sydnone **38** (59% yield) (Scheme 5).

Scheme 5



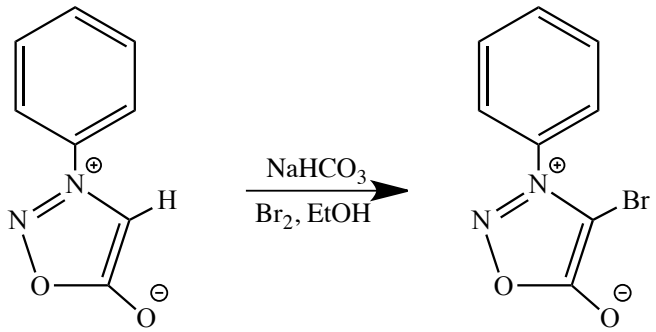
36 **37** **38**

To confirm the identity of the 3-phenylsydnone product **38**, a comparison was made (IR, TLC, m.p.) with the authentic product previously synthesized in our laboratory. Thus, as expected, the IR spectrum of the product obtained showed peaks for

the C-H stretch of the sydnone ring at 3128 cm^{-1}, aromatic C-H stretch at 3062.31 cm^{-1} as well as a strong carbonyl stretch at around 1758 cm^{-1}. The ^{1}H NMR spectrum exhibited a singlet for the proton at 4-position at 6.8 ppm, a signature of the sydnone ring, and the ^{13}C NMR spectrum also showed classic characteristics of a sydnone, with peaks at 93 ppm for the unsubstituted C-4 position and 169 ppm for the C-5 carbonyl carbon.

With the starting sydnone to hand it was necessary next to prepare the 4-bromo analog **34**. Sydnones readily undergo electrophilic aromatic substitution and bromination can be achieved with different brominating mixtures and with a large variety of 3-alkyl or aryl substituents, exclusively at the sydnone C-4 position. The most common approach for sydnone bromination is the use of bromine in the presence of sodium bicarbonate. Thus, treatment of 3-phenylsydnone with these reagents in ethanol / water gave the 4-bromo species **34** in 72% yield (Scheme 6). The identity of the product as the bromo compound **34** was confirmed by the absence of both the sydnone C-H in the infrared spectra at 3128 cm^{-1} and the signature peak at 6.8 ppm in its proton NMR spectrum.

Scheme 6



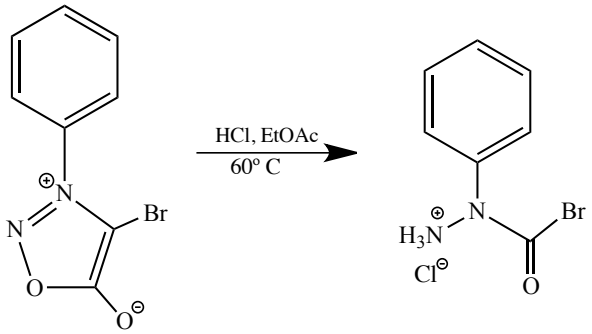
38 **34**

As mentioned previously, Badami[59] had proposed that the mechanism for the transformation of 3-phenylsydnone **38** (and related compounds) to the corresponding

oxadiazolinone (or oxadiazolinones) with bromine and acetic anhydride involved a 1,3-dipolar cycloaddition of the anhydride with the intermediate 3-aryl-4-bromosydnone. However, she had not taken into account the HBr formed in the process and, given that Yeh et al.[60] had shown that 4-bromo-3-phenylsydnone **34** cleaved under acidic conditions to produce a bromocarbonylphenylhydrazine **35**. we wished to investigate the possible intermediacy of the latter in the Badami process.

Accordingly, 4-bromo-3-phenylsydnone **34** was heated with aqueous HCl in ethyl acetate, resulting in the formation of the α-bromoformylphenylhydrazine hydrochloride **35**. This product is unstable in solution, but it can be stored as a solid in the fridge for 90 – 100 days. Accordingly, complete characterization was not possible, however, the melting point (150-1 °C) matched that reported by Yeh as did the position of the carbonyl peak (1747.37cm^{-1}) in its infrared spectrum.

Scheme 7



34 **35**

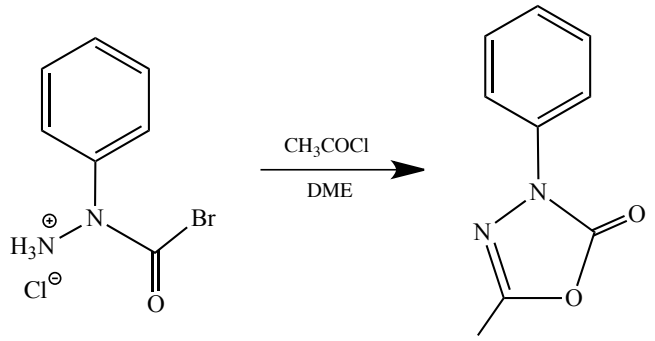
It was anticipated that treatment of Yeh's salt with acetic anhydride would provide the same oxadiazolinone **39** as reported by Badami, however, another researcher in the Turnbull lab. took over that part of the project (successfully !) and, accordingly, a

slightly different direction was pursued. Since it was now obvious that the bromocarbonylhydrazine salt **35** was the real intermediate in the overall process, and it reacted with acetic anhydride, it was elected to use acid chlorides as partners for reaction. Since acid chlorides are more readily available than anhydrides, in greater variety, and are more reactive, it was believed that they would provide real benefits. Additionally, all the previous work reported by Badami and, many years before, Stansfield[52] had utilized acetic anhydride as both solvent and reactant – an obviously inefficient process – and it was thought that the use of a solvent would allow the use of much less reagent.

While it was the aim to synthesize many different 5-substituted-1,3,4-oxadiazolin-2-ones, it seemed sensible to first examine the reaction of the hydrazine salt **35** with acetyl chloride since the latter is cheap and would provide the parent oxadiazolinone **39** (Scheme 7), which had been prepared previously in our laboratory Yeh had shown that the salt was unstable in a variety of common solvents, including ethanol and methanol (with which it reacts) and ether, so a short study of reactions in non-reactive solvents was undertaken. It was discovered that 1,2-dimethoxyethane (DME) gave the best results and, accordingly, the latter was used for the first "scaled-up" reaction of the hydrazine salt **35** with 4 equivalents of acetyl chloride. After heating at 65°C for 3.5 h, the desired 5-methyl-1,3,4-oxadiazolin-2-one **39** [identical to an authentic sample by TLC, m.p. and IR] was obtained in 75% yield. Encouraged by this result, it was decided to attempt to improve the process further by reducing the amount of the acid chloride and also by changing different parameters such as the amount of solvent, the temperature and the duration of the reaction. Not all changes improved the process, however, as shown in Table 1, it was possible to optimize the yield at 79% while reducing both the reaction

time and the number of equivalents of acetyl chloride (65°C, 2 equivalents of acetyl chloride for 1.5 h).

Scheme 8



35 **39**

Table 1

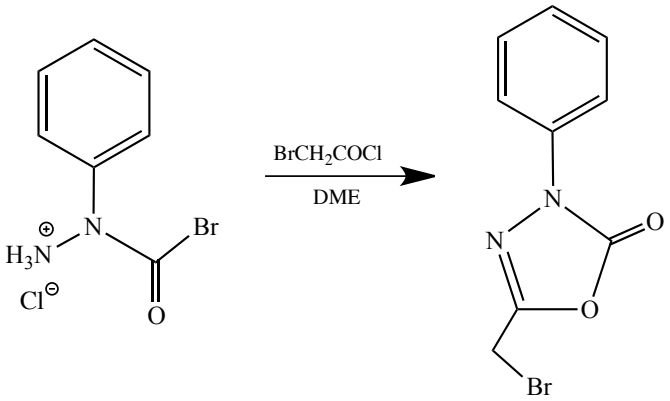
Starting Material	Trial	Equivalents of acid chloride	Temp °C	Time	% Yield of **39**	m.p. of **39**
35	a	4 eq. CH_3COCl	65°C	3.5hrs	73.5	87.5-88°C
	b	2 eq. CH_3COCl	65°C	3.5hrs	76	86-88°C
	c	1.4 eq. CH_3COCl	65°C	3.5hrs	37	85-87°C
	d	1 eq. CH_3COCl	65°C	3.5hrs	57	86-88°C
	e	2 eq. CH_3COCl	65°C	1.5hrs	79	87-88°C
	f	2 eq. CH_3COCl	45°C	1.5hrs	55	88-89°C

As mentioned above, the identity of the product **39** was confirmed from its spectral characteristics. Thus, the IR spectrum of the product obtained showed a strong

peak for carbonyl stretch at 1773.31 cm^{-1} characteristic of the oxadiazolinone ring. Its ^{1}H-NMR spectrum showed the presence of a singlet for the methyl group at 2.36ppm as well as appropriate splittings and integrations for the aromatic ring protons. The ^{13}C-NMR spectrum showed the characteristic features of the oxadiazolinone system, namely peaks at 153.79 (C-2), 151.09 (C-5) and the methyl carbon at 12.18 ppm. Further, 4 peaks were present for the phenyl ring attached at the 3-position.

Having demonstrated the potential of this approach it was decided to extend the process to the synthesis of substituted oxadiazolinones **32** using the same conditions but with different acid chlorides. Accordingly, hydrazine salt **35** was treated with 4 equivalents of bromoacetyl chloride in 4mL of DME at 65°C, resulting in formation of 5-(bromomethyl)-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**40**) in 82% yield. Even with the satisfactory yield obtained, it was elected to explore optimization of the process by the use of different quantities of the acid chloride and DME as well as changing physical parameters, particularly temperature and the duration of reaction. Thus, an investigation was carried out by treating hydrazine salt **35** with different quantities of bromoacetyl chloride ranging from 2 – 4 equivalents, varying amounts of DME and finally by changing the reaction time and temperature. As can be seen in Scheme 9 and Table 2, the reactions of **35** with different parameter changes gave rise to the product with different percent yields and purities.

Scheme 9



35 **40**

Table 2

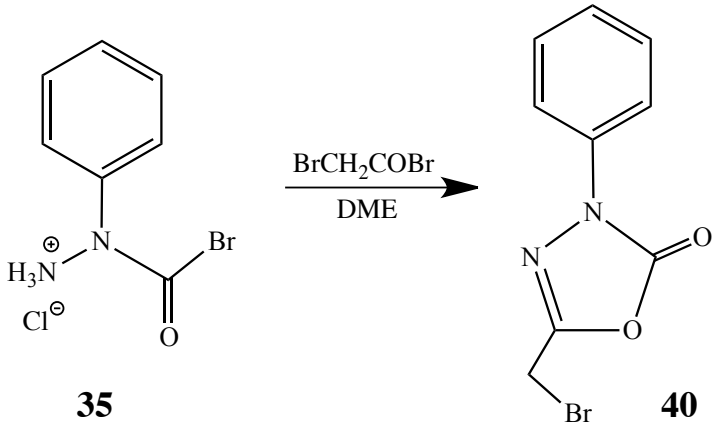
Starting Material	Trial	Equivalents of acid chloride	Temp °C	Time	% Yield of **40**	m.p. of **40**
35	a	4 eq. $BrCH_2COCl$	65°C	3.5hrs	82	78-80°C
	b	4 eq. $BrCH_2COCl$	65°C	3.5hrs	76	76-78°C
	c	2 eq $BrCH_2COCl$	65°C	2.5hrs	96	68-69.5°C
	d	2 eq. $BrCH_2COCl$	65°C	1.5hrs	83	73-73.5°C
	e	2 eq. $BrCH_2COCl$	45°C	1.5hrs	77	74-74.5°C

Confirmation for the identities of the products was made using GC/MS, IR, NMR and elemental combustion analysis (as appropriate). Thus, the I.R. spectrum of **40** shows a strong carbonyl stretch at 1777.83 cm^{-1}. The ^{1}H-NMR spectrum shows four different peaks, three for the aromatic region and a singlet around 1.8 ppm for the aliphatic methylene. The ^{13}C-NMR spectrum shows the presence of seven peaks including the

oxadiazolinone C-2 at 152 ppm, C-5 at 150.53 ppm, four peaks for the phenyl ring attached to the oxadiazolinone at the C-3 position and the methylene carbon at 17.62 ppm.

The product from trial c in Table 2 showed the highest percentage yield but the product's melting point was lower than from the other trials, indicating the presence of some impurities. Accordingly, trial a in Table 2 is considered to be the best blend of yield and purity. Interestingly, even in the latter case, the results from GC-MS showed the presence of traces of the chloromethyl analog (**40**, Br replaced by Cl) by comparision with an authentic sample. Remarkably, even recrystallized samples showed 1 or 2% of this impurity. It was not obvious as to how this latter product arose, however, it was logical to assume that it might have arisen from the use of the acid chloride reactant and, accordingly, it was decided to explore the use of bromoacetyl bromide instead.

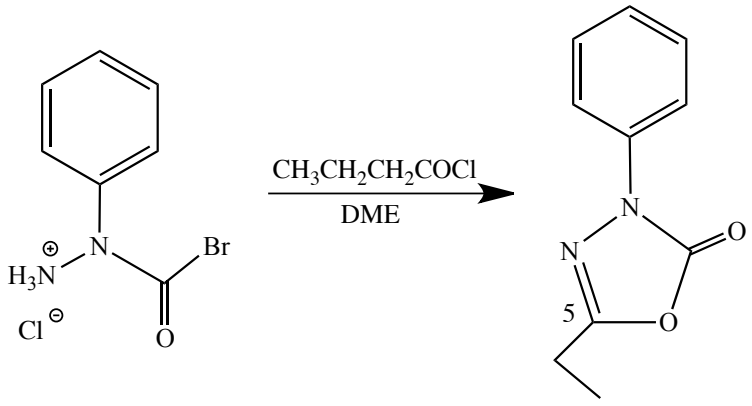
Thus, the reaction shown in Scheme 9 was repeated using bromoacetyl bromide in place of bromoacetyl chloride, resulting in the same product **40**. Thus, the hydrazine salt was treated with 2 equivalents of bromoacetyl bromide in DME resulting in the formation of 5-(bromomethyl)-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**40**), identical to an authentic sample, in 83% yield. The GC/MS showed the presence of slight impurities, but, surprisingly, the amount of the chloromethyl impurity was still 2.8% of the total. Since the hydrazine salt used was the hydrochloride salt **35** it is apparent that the chloride counterion is participating in the reaction, perhaps by nucleophilic displacement of bromide from the bromomethyl species. In general, the product purity was sufficiently pure for subsequent study and, accordingly, it was elected not to study this aspect further.



35 **40**

As a continuation of this work, a logical extension was to utilize propionoyl chloride because the 5-ethyl product **41** was a known compound, prepared previously by Stansfield[52] and in our lab. from 3-phenylsydnone. Accordingly, the hydrazine salt **35** was treated with 2 equivalents of propionoyl chloride in DME resulting in the formation of 5-ethyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**41**) with a percent yield of 83% (Scheme 10).

Scheme 10

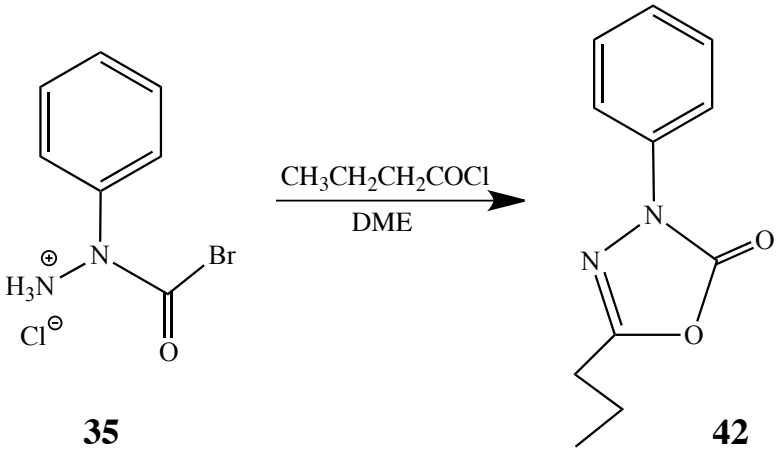


35 **41**

The identity of the product **41** was confirmed by melting point, I.R. and NMR spectroscopies. The m.p. ranged from 56 – 58°C, which compared reasonably well with the literature m.p. of 60 – 61.5°C. The I.R. spectrum showed a strong C=O stretch at 1773.45 cm^{-1} and C-H stretch around 2943.50 cm^{-1}. The ^{1}H NMR showed a triplet at 1.2 ppm for the methyl and a quartet at 2.8 ppm for the methylene group of the 5-substituent. The ^{13}C NMR spectrum showed the expected 8 peaks for **41** including the definitive peaks at 156.27 ppm for the oxadiazolinone C-2 position, at 152.52 ppm for the oxadiazolinone C-5 position and at 26.39 ppm and 12.77 ppm for the side chain CH_2 and CH_3, respectively .

Encouraged by this result, it was decided to attempt to expand the process further by using butyroyl chloride, again, because the 5-propyl product **42** was a known compound, prepared previously by Stansfield[52] and in our lab. from 3-phenylsydnone. Accordingly, the hydrazine salt was treated with 2 equivalents of butyroyl chloride in DME at 65°C, resulting in the formation of 5-propyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one **42** in 51% yield (Scheme 11). The relatively low yield of the product was almost certainly a facet of the low melting point of the product (making its handling more difficult) rather than anything to do with the reaction process itself.

Scheme 11



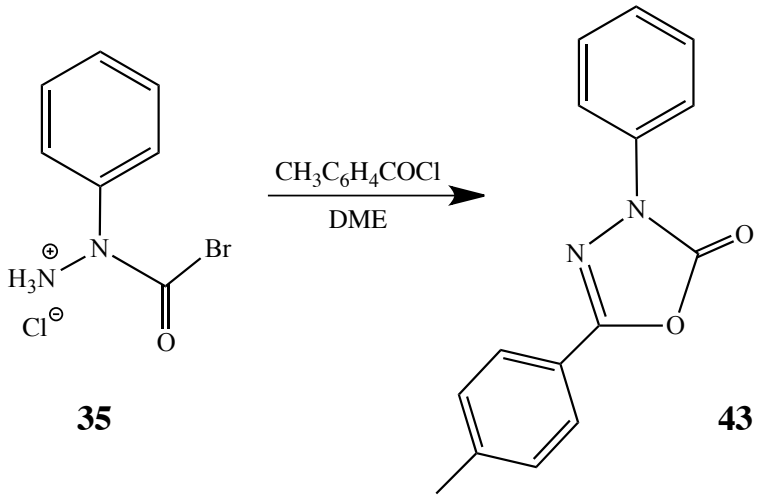
35 **42**

Confirmation of the identity of the product **42** was made through its full characterization by m.p. and I.R. and NMR spectroscopies. The m.p. ranged from 54 - 56°C (lit. m.p. 57.5 – 58.5°C) and the I.R. spectrum showed the presence of a strong carbonyl peak at 1769.89 cm^{-1} and also a peak around 2878.50 cm^{-1} for the alkyl C-H stretch. The ^{1}H NMR spectrum displayed three groups of peaks for both the aliphatic region and the aromatic region, in line with expectation. The ^{13}C NMR spectrum showed the expected 9 peaks for **42** including the characteristic peaks at 156.82 ppm and 151.17 ppm for the oxadiazolinone C-2 and C-5 positions, respectively, as well as peaks at 28.20 ppm, 18.95 ppm and 13.45 ppm for the aliphatic carbons.

To this point, all of the acid chlorides used for the reactions with **35** had been alkyl versions and, accordingly, extension to aryl acid chlorides was examined. With this change it seemed likely that removal of unreacted acid chloride after reaction completion might be more difficult since the stability to hydrolysis would be greater. Nonetheless, it was decided to use the same overall process initially with a readily available aryl acid

chloride (*p*-toluoyl chloride) to see if expectation was reality. Thus, the hydrazine salt **35** was treated with 2 equivalents of *p* - toluoyl chloride in DME at 65°C for 3.5h, resulting in the formation of 5-p-tolyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**43**) in 149% yield!) (Scheme 12). The resulting product was tested for purity by taking its m.p. and it was found that the latter was a wider range and lower overall (120 - 125°C) than the literature value (lit. m.p. 157 - 158°C). This, coupled with the >100% yield, indicated the presence of impurities, presumably including unreacted acid chloride and carboxylic by-product.

Scheme 12



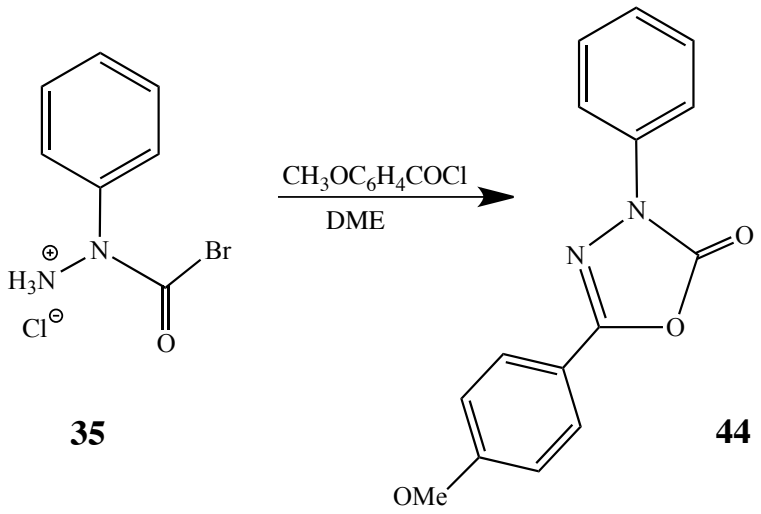
35 **43**

In an attempt to remove the impurities the resulting product was finely powdered using a mortar and pestle and added to 10 mL of base (10% aqueous NaOH solution) and heated for 60 min at 45°C. The resulting, product **43** was filtered and dried thoroughly to yield a colorless material, which melted at 142 – 146°C, much closer to the literature value of 157 – 158°C . The identity of the product was confirmed by GC/MS, where it showed a single GC peak with the molecular mass expected and the standard loss of 44

for loss of CO_2 from the oxadiazolinone ring. Due to the impure nature of the product, no spectral characteristics were obtained.

To further explore the process with aryl acid chlorides, the hydrazine salt **35** was treated with 2 equivalents of *p* - anisoyl chloride in DME at 65°C for 3.5h, resulting in the formation of 5-(4-methoxy-phenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**44**) in 170% yield. (Scheme 13) The resulting product was tested for purity by taking its m.p. and it was found that the latter was a wider range and lower overall (120 - 124°C) than the literature value (lit. m.p. 137 – 138°C). This, coupled with the >100% yield, indicated the presence of impurities, presumably including unreacted acid chloride and carboxylic acid by-product.

Scheme 13



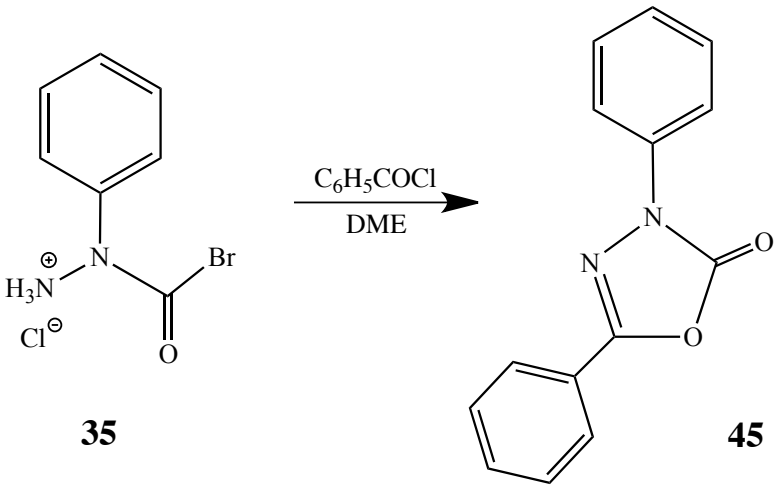
35 **44**

In an attempt to remove the impurities the resulting product was finely powdered using a mortar and pestle and added to 10mL of base (10% aqueous NaOH solution) and heated for 60min at 45°C. The resulting, product **44** was filtered and dried thoroughly to

yield 87% of the product, which melted at 138 – 142.5°C, much closer to the literature value of 137 – 138°C. The identity of the product was confirmed by GC/MS and NMR. GC/MS results showed negligible amounts of impurities and a major GC peak with the appropriate MS patterns as described previously for compound **43**. ^{1}H NMR showed six different groups of peaks including a singlet at 3.8 ppm for the methyl group, two doublets from the phenyl ring attached at the C-5 position of the oxadiazolinone ring and three groups of peaks from the phenyl ring at the C-3 position. The ^{13}C NMR spectrum showed 11 different peaks as expected for structure **44**.

As a next step using different acid chlorides, the hydrazine salt was treated with benzoyl chloride. Thus, **35** was treated with 4 equivalents of benzoyl chloride in DME at 65°C for 3.5 hrs, resulting in the formation of 3,5-diphenyl-1,3,4-oxadiazol-2(*3H*)-one (**45**) in 136% yield (Scheme 14). The resulting product was tested for purity by taking its m.p. and I.R. spectrum. It was found that the m.p. was a wider range and lower overall (80 – 94°C) than the literature value (lit. m.p. 110 – 111°C), and the I.R. spectrum showed a broad peak around 2400 – 3100 cm^{-1} indicating the presence of benzoic acid. This, coupled with the >100% yield, indicated the presence of impurities.

Scheme 14



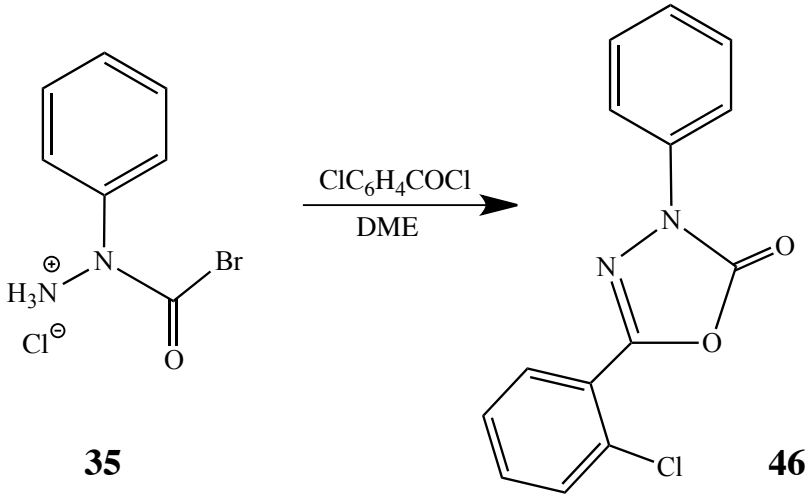
35 **45**

In an attempt to remove the impurities the resulting product was finely powdered using a mortar and pestle and added to 10mL of base (5% aqueous $NaHCO_3$ solution) and heated for 60 min at 45°C. The resulting product **45** was filtered and dried thoroughly to yield 87% of the product, which melted at 108 – 109.5°C, much closer to the literature value of 110 – 111°C. The identity of the product **45** was confirmed by I.R. and NMR. The I.R. spectrum showed a strong peak at 1738.38 cm^{-1}, indicative of the C=O stretch from the oxadiazolinone ring and no evidence of the benzoic acid OH stretch from 2400 - 3100 cm^{-1}. From these findings it was concluded that the base had reacted with the excess benzoyl chloride to form sodium benzoate, which is water soluble, resulting in the formation of pure product **45**. It was difficult to assess the identity of the product from the proton NMR spectrum since only three groups of peaks were apparent. However, there were no untoward peaks and the ^{13}C NMR spectrum showed the expected ten different peaks including the peak at 151.22 ppm indicative of the oxadiazolinone C-5 and the peak at 153.59 ppm indicative of the carbon at the oxadiazolinone C-2 position.

As expected, the other eight peaks were fell in the aromatic region, four on each aromatic ring attached at the C-5 and C-3 positions. These spectra together with the I.R. and m.p. confirmed the formation of the disubstituted product, 3,5-diphenyl-1,3,4-oxadiazol-2(*3H*)-one (**45**).

Armed with this observation, the next step was to attempt the synthesis of 5-(2-chlorophenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (**46**). Accordingly, the hydrazine salt **35** was treated with 2 equivalents of 2-chlorobenzoyl chloride in DME at 65°C for 3.5 hrs resulting in the formation of 5-(2-chlorophenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**46**) in 92.5% yield (Scheme 15). The resulting product was tested for purity by m.p., resulting in 101 – 105°C, far lower than the literature m.p. of 145 – 146.1°C.

Scheme 15



35 **46**

TLC examination also confirmed the presence of impurities and, accordingly, the crude product was finely powdered using a mortar and pestle and added to 10mL of base (10%

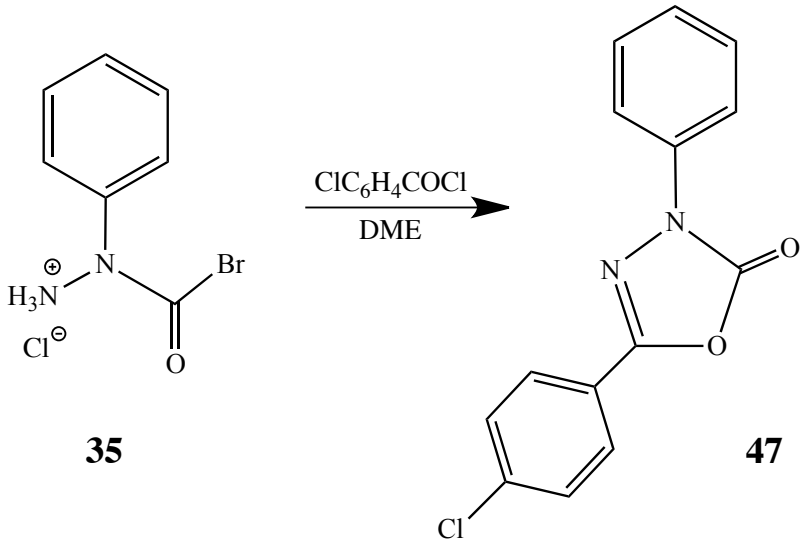
aqueous NaOH solution) and heated for 60 min at 45°C. The resulting product **46** was filtered and dried thoroughly to yield 72% of the product, which melted at 109 – 110°C, lit. m.p. 145 – 146.1°C. The identity of the product **46** was confirmed by I.R. and NMR. The I.R. spectrum showed a strong peak at 1785.18 cm^{-1}, indicative of the C=O stretch for the oxadiazolinone ring. The ^{1}H NMR indicated the presence 7 different signals including four (two multiplets and two triplets) from the aromatic ring on the C-5 position of the oxadiazolinone ring. In addition, the ^{13}C NMR spectrum showed the presence of 12 different signals, two from the oxadiazolinone ring (at 151.72 ppm and 150.29 ppm, as expected for the C-2 and C-5 positions of the oxadiazolinone ring), four from the phenyl ring attached at the C-3 position of the oxadiazolinone ring and six different signals from the phenyl ring on the C-5 position of the oxadiazolinone ring, confirming the identity as the expected product **46**. It is curious that the melting point obtained is so different from that reported in the literature, however, the spectra obtained appeared to be of a pure substance, so it is possible that the literature value is in error.

In an attempt to increase the yield of the product **46** an investigation was carried out by repeating the above scheme 15 and changing the reaction time to 1.5hrs instead of the usual 3.5hrs, resulting in the formation of the expected product **46** in 94% yield. The product was identical to the previously prepared sample, resulting in a sharp m.p. of 109 – 110.5°C. There was a distinct difference in yield depending on the length of the reaction time, showing that better yields were obtained when the reaction time was shorter.

As a continuation to the work, the reaction was extended to the preparation of the *para*-chloro analog of **46**, viz. **47** (Scheme 16). Thus, the hydrazine salt **35** was treated

with 2 equivalents of 4-chlorobenzoyl chloride in DME at 65°C for 3.5hrs, resulting in the formation of 5-(4-chlorophenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one **47** in 129% yield. The resulted was tested for purity by taking its m.p., resulting in a wide range from 110 – 125°C indicating the presence of impurities.

Scheme 16



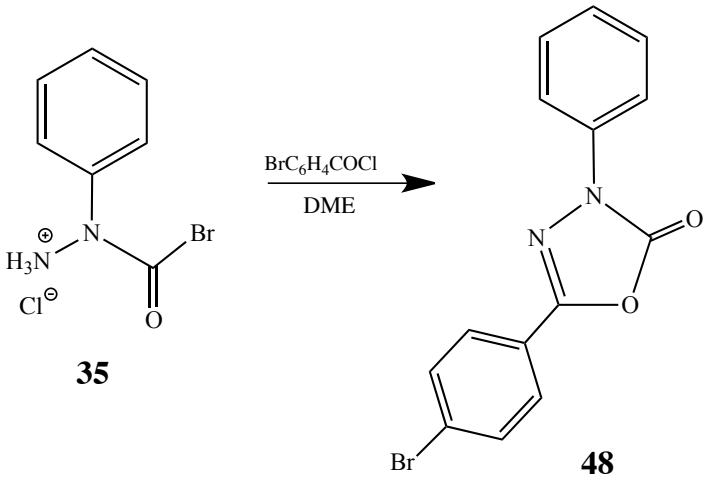
35 **47**

Accordingly, as before, the crude product was finely powdered using a mortar and pestle and added to 10mL of base (10% aqueous NaOH solution) and heated for 60 min at 45°C. The resulting product **47** was filtered and dried thoroughly to yield 74% of the product, which melted at 135 – 137°C, much higher than the literature value of 118 – 119°C. However, once again, the identity and purity of the product **47** was confirmed by both I.R. and NMR. The IR spectrum revealed a strong C=O peak at 1781.63 cm^{-1} as expected for an oxadiazolinone ring system. In line with structure **47**, the ^{1}H NMR spectrum showed five different groups of peaks and the ^{13}C NMR spectrum displayed ten

different peaks, including four from each aromatic ring and two from the C-2 and C-5 positions of the oxadiazolinone ring at 152.85 ppm and 150.45 ppm respectively.

As a further continuation of the work, the reaction was extended to the preparation of the *para*-bromo analog of **47**, viz. **48** (Scheme 17). Thus, the hydrazine salt **35** was treated with 2 equivalents of 4-bromobenzoyl chloride in DME at 65°C for 3.5hrs, resulting in the formation of 5-(4-bromophenyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**48**) in 143% yield . The crude product was tested for m.p., resulting in a wide range from 138 – 150°C, far higher than that for the literature melting point of 124 – 125°C.

Scheme 17



35 **48**

In an attempt to remove the impurities the crude product was finely powdered using a mortar and pestle and added to 10ml of base (10% aqueous NaOH solution) and heated for 60min at 45°C. The resulting, product **48** was filtered and dried thoroughly to yield 99% of the product, which melted at 129 – 131°C, much closer to the literature value of 124 – 125°C. The identity of the product **48** was confirmed by I.R. and NMR.

The I.R. spectrum showed the characteristic oxadiazolinone C=O peak at 1770.65 cm^{-1}. The ^{1}H NMR spectrum displayed five different groups of peaks (as expected for **48**). Further, the ^{13}C NMR spectrum contained ten different peaks (again as expected) including the characteristic oxadiazolinone C-2 and C-5 peaks around 152.85ppm and 150.45ppm.

For the reaction shown in Scheme 17, there was a distinct difference in yields by changing different parameters like the temperature and time duration of the reaction as shown in Table 3 below.

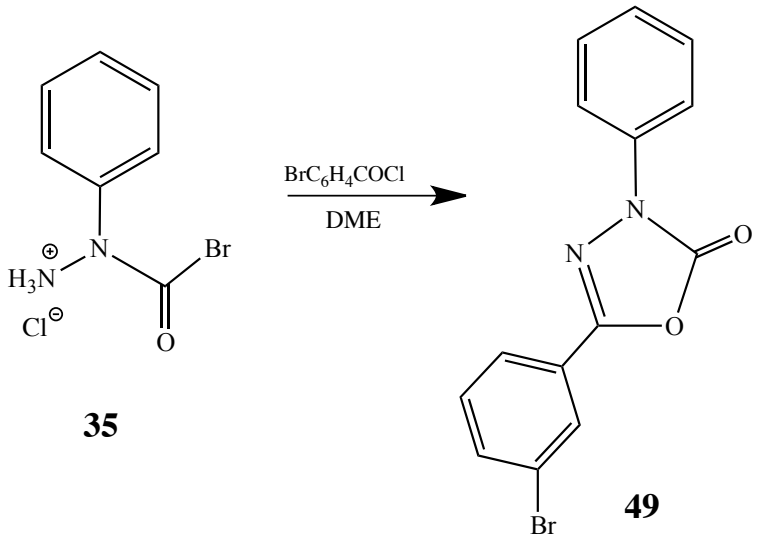
Table 3

Starting Material	Trial	Equivalents of acid chloride	Temp °C	Time	% Yield of **48**	m.p. of **48**
35	a	2 eq. BrC_6H_4COCl	65°C	3.5hrs	99	129-131°C
	b	2 eq. BrC_6H_4COCl	65°C	3.5hrs	93	131-132°C
	c	2 eq. BrC_6H_4COCl	65°C	1.5hrs	91	139-141°C
	d	2 eq. BrC_6H_4COCl	45°C	1.5hrs	59	140-150°C

As a continuation of the work the next approach was the synthesis of 5-(3-bromophenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (**49**) [Scheme 18]. The hydrazine salt **35** was treated with 2 equivalents of 3-bromobenzoyl chloride in DME at 65°C for 3.5hrs, resulting in the formation of **49** in 175% yield. The crude product was tested for purity by taking its m.p. and by TLC analysis. The latter showed more than one spot,

even though the m.p. of 96 – 98°C seemed reasonably sharp, indicating the presence of impurities.

Scheme 18



35 **49**

In an attempt to remove the impurities the crude product was finely powdered using a mortar and pestle and added to 10mL of base (10% aqueous NaOH solution) and heated for 60 min at 45°C. The resulting, product **49** was filtered and dried thoroughly to yield 72% of the product, which melted at 105 – 108°C. Since this was not a known compound, the purified product was recrystallized using a minimal amount of DCM and n-hexane (90 : 10), yielding the product in 60% yield and m.p. 115 – 116°C.

The ^{1}H NMR showed the presence of seven different groups of peaks, three from the phenyl ring at the C-3 position and four from the phenyl ring attached at the C-5 position of the oxadiazolinone ring including a singlet at 8.1ppm, a triplet around 7.3ppm and two doublets. Additionally, the ^{13}C NMR showed the presence of the 12 different peaks, including the characteristic oxadiazolinone C-2 and C-5 peaks at 152.20 ppm and

150.35 ppm, respectively, six different peaks from the phenyl ring at the oxadiazolinone C-5 position and the remaining four from the phenyl ring at the oxadiazolinone C-3 position, indicating the presence of the desired product **49**. Further, the identity was confirmed by a satisfactory elemental analysis.

In conclusion, a new, high yield approach to 3,5-disubstituted oxadiazolinones from the bromocarbonylhydrazine salt **35** has been developed. The success of this method confirms that the mechanism suggested by Badami et al. for the transformation of 3-arylsydnones, including 3-phenylsydnone (**38**), to the corresponding oxadiazolinones, is very likely to be incorrect. The present work suggests strongly that 4-bromo-3-phenylsydnone (**34**) is formed initially (from **38**) and the former is converted to the bromocarbonylhydrazine derivative **35** by HBr formed during the reaction. This intermediate, **35**, had been prepared previously by Yeh and coworkers and repetition of their work allowed isolation of **35** and subsequent exploration of its reactions with acid chlorides. Further, it is worth noting that, compared to Badami's work, where the solvent was the reagent, typically acetic anhydride, the use of a solvent allowed the use of far smaller quantities of the reagent and extension to more readily available acid chlorides, including solids. Overall, good to excellent yields of the desired oxadiazolinones were obtained, with a maximum of 90% and an average of 70%. The yields varied based on changes in the physical parameters like the amount of acid chloride, reaction temperature and reaction time.

To promote a more thorough understanding of oxadiazolinones, further research should be attempted to develop a more complete library of these compounds by

extending the process to more acid chlorides, especially those with appended functional groups, which could be further modified after formation of the corresponding oxadiazolinone. Another avenue for future research would be to start with substitution on the aryl ring of the sydnone, such as halo or nitro groups, resulting in a large variety of substituted oxadiazolinone derivatives, suitable for further functionalization.

Experimental

All starting materials were purchased from commercial sources and used without further purification. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were acquired using a Thermo Scientific (Nicolet iS5) spectrometer. GC/MS measurements were performed using an Agilent Technologies 5975 Series MSD, 7820A GC system. NMR spectra were obtained on a Bruker Avance 300 MHz NMR using $CDCl_3$ as solvent. Elemental analyses were performed by Microlab LLC, Indianapolis, Indiana.

Synthesis of 3-Phenylsydnone (38)

3-Phenylsydnone was synthesized in 2 steps from commercially available N-phenylglycine according to the reported procedure (see below).

Nitrosation of N-phenylglycine (36)

N-phenylglycine (2g, 0.0131moles) was suspended in water (24mL) and cooled to 0°C. Sodium nitrite (1g, 0.0144moles) dissolved in water (6mL) was then added slowly over a period of 40 minutes. The almost clear solution obtained was then filtered quickly

with suction, after which norit (10mg) was added and the solution stirred. The mixture was filtered again and hydrochloric acid (2mL) was added. This produced a profusion of light fluffy crystals. The suspension was stirred for 10 minutes and filtered with suction, washed twice with ice cold water and left to dry overnight.

Cyclisation of N-nitroso-N-phenylglycine (37) to 3-Phenylsydnone

N-Nitroso-N-phenylglycine (1.48g, 0.0082moles) was suspended in acetic anhydride (10mL) and the stirred mixture was heated under reflux for 1.5 hours then cooled to room temperature. The solution was poured slowly into cold water (60mL) with stirring, whereupon colorless crystals separated out, which were filtered by suction, washed twice with ice-cold water and left to dry overnight. The sydnone collected (0.98g, 59%) was identical to authentic material (TLC, IR, mp, NMR), m.p. 129-131°C.

IR (KBr) : 3128 (sydnone C-H), 3062.31 (C-H), 1758 (sydnone C=O), 1472, 1291, 1086, 948, 759 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 6.8 (s, 1H, sydnone C-4), 7.6 (t, 1H), 7.72(d, 2H), 7.74 (d, 2H) ; **^{13}C NMR ($CDCl_3$) :** 169.02 (sydnone C=O), 134.79, 132.50, 130.30, 121.30, 93.77 (sydnone C-4).

Synthesis of 4-Bromo-3-Phenylsydnone (34)

Using the known procedure, 3-phenylsydnone (1g, 0.0061moles) was suspended in ethanol (40mL) in a round bottom flask. To this mixture was added sodium bicarbonate (2.51g, 0.0298moles) in water (30mL). With stirring, a solution of bromine

(1.28mL) in ethanol (40ml) was added dropwise over 5 minutes. After 30 minutes of stirring the mixture was poured into cold water (100mL) and when complete crystallization had occurred the precipitate was filtered by suction and left to dry overnight. The well dried product weighed 1.1034g, 72% , m.p. 122-125°C and was identical to an authentic sample.

IR (KBr) : 3066.59(aryl C-H), 1777 (sydnone C=O), 1464.13, 1028.57, 764.06 cm^{-1}

Preparation of α-Bromoformylphenylhydrazine hydrochloride (35)

The title compound was prepared by a modification of a literature procedure. Thus, a solution of 4-bromo-3-phenylsydnone (1.1g, 0.00456moles) in ethyl acetate (20mL) and hydrochloric acid (1mL) was heated at 60°C for 20min and then cooled down to 25°C. The solid product was separated by filtration, washed with cold ethyl acetate and dried in vacuum. The well-dried product weighed 0.6101g, 54%, m.p. 156-160°C; lit. m.p. 177-178°C

IR (KBr) : 1747.37 (C=O), 2962-2584 cm^{-1}.

General procedure for the synthesis of 3,5-disubstituted 1,3,4-oxadiazol-2(*3H*)-ones using 4 eq of acid chloride

Bromocarbonylhydrazine salt (**35**) (0.050g, 0.00019moles) was suspended in dimethoxyethane (DME) (2mL) and to the stirred mixture was added the appropriate acid chloride (4 eq). This mixture was heated on an oil bath at 65°C for 3.5hours under reflux.

After allowing the solution to cool down to room temperature, the contents were poured into water (10mL). In all cases, this produced a creamy white precipitate but, nonetheless, the mixture was left under a stream of air to facilitate the evaporation of the DME. Subsequent vacuum filtration afforded a product which was weighed, characterized and purified, as necessary.

Synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (39)

Using the above general procedure with hydrazine salt (0.050g, 0.00019mole), DME (2mL) and then added acetyl chloride (0.057mL, 0.00072mole) gave the title compound (0.025g, 76%), m.p. 87-88°C; lit. m.p. 92.5- 93°C.

IR (KBr) : 3082.12, 2932.81, 1773.31, 1494.19, 760.85 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.83(d,2H), 7.45(m,2H), 7.25(t), 2.36(s) ppm ; **^{13}C NMR ($CDCl_3$) :** 153.79, 151.09, 136, 129.16, 125.90, 118.08, 12.18 ppm.

Synthesis of 5-(bromomethyl)-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one (40)

Using the above general procedure with hydrazine salt (0.050g, 0.00019moles), DME (2mL) and then added bromoacetyl chloride (0.060mL, 0.00072moles) gave the title compound (0.032g, 82%), m.p. 78-80°C.

IR (KBr) : 3042.37, 2981.89, 1777.83, 1491.58, 959.94 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.83(d,d,2 H), 7.46(m,2H), 7.29(t), 4.30(s) ppm ; **^{13}C NMR ($CDCl_3$) :** 152.00, 151.03 135.59, 129.28, 126.53, 118.33, 17.62 ppm.

Elemental analysis calculated for $C_9H_7BrN_2O_2$ (Mol.wt : 256.07):C, 42.38; H, 2.77; N, 10.98; Found : C, 42.87; H, 2.74 ; N, 10.96.

Synthesis of 3,5-diphenyl-1,3,4-oxadiazol-2(*3H*)-one (45)

Using the above general procedure with hydrazine salt (0.052g, 0.00020moles), DME (2mL) and then added benzoyl chloride (0.083mL, 0.00072moles) gave the title compound (0.064g,136%), m.p.80-94°C.

The product was finely powdered using a mortar and pestle, suspended into 8 -10 ml of 10% aq. NaOH solution and heated at 45°C for about 60mins. After allowing to cool down to room temperature and suction filtration, the dried product weighed 0.0375g, 82.5%, m.p. 104-107°C ; lit m.p. 110 – 111°C .

IR (KBr) : 3067.95, 1778.38, 1379.25, 1143.76, 736.15 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.96(d,2H), 7.60(t, 2H), 7.57(d,2H), 7.52(m), 7.47(t,2H), 7.30(t) ppm **; ^{13}C NMR ($CDCl_3$) :** 153.59, 151.22, 136.10, 131.96, 129.22, 129.06, 126.17, 125.99, 123.50, 118.36 ppm.

General procedure for the synthesis of 3,5-disubstituted 1,3,4-oxadiazol-2(*3H*)-ones using 2equivalents of acid chloride

α-Bromocarbonylhydrazine salt (**35**) (0.050g, 0.00019moles) was suspended in dimethoxyethane (DME) (2mL) and to the stirred mixture was added the appropriate acid chloride (2 eq). This mixture was heated on an oil bath at 65°C for 3.5hours under reflux. After allowing the solution to cool down to room temperature, the contents were poured into water (10mL). In all cases, this produced a creamy white precipitate but, nonetheless, the mixture was left under a stream of air to facilitate the evaporation of the DME.

Subsequent vacuum filtration afforded a product, which was weighed, characterized and purified, as necessary.

Synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (39)

Using the above general procedure with hydrazine salt (0.150g, 0.00056moles), DME (2mL) and then added acetyl chloride (0.080mL, 0.00112moles) gave the title compound (0.0754g, 75.75%), m.p.86-89°C, identical to an authentic sample. **IR (KBr) :** 3063.71, 2901.11, 1750.93, 1441.23, 782.36 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.83(d,2H), 7.45(m,2H), 7.25(t), 2.36(s) ppm ; **^{13}C NMR ($CDCl_3$) :** 152.09, 151.23, 136.78, 128.11, 125.70, 117.67, 12.18 ppm.

Synthesis of 5-(bromomethyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (40)

Using the above general procedure with hydrazine salt (0.053g, 0.00019moles), DME (1mL) and then added bromoacetyl chloride (0.032mL, 0.00038moles) gave the title compound (0.0387g, 76%), m.p.76-78°C, identical to an authentic sample. **IR (KBr) :** 3068.56, 2901.36, 1778.61, 1448.39, 757.20 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.91(d,2H), 7.51(m,2H), 7.13(t), 4.19(s) ppm ; **^{13}C NMR ($CDCl_3$) :** 152, 150.53, 135.59, 129.28, 126.53, 118.33, 17.62 ppm.

Synthesis of 5-ethyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (41)

Using the above general procedure with hydrazine salt (0.150g, 0.00056moles), DME (3mL) and then added propionoyl chloride (0.097mL, 0.00112moles) gave the title

compound (0.0889g, 83%), m.p.56-58°C; lit. m.p. 60 – 61.5°C, identical to an authentic sample.

IR (KBr) : 2983.50, 2943.50, 1773.45, 1597.87, 975.10, 692.59 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.88(d,2H), 7.85(m, 2H), 7.45(t), 2.70(q), 1.37(t) ; **^{13}C NMR ($CDCl_3$) :** 156.27, 152.52, 137.7, 128.9, 124.6, 119.53, 26.39, 12.77.

Synthesis of 5-propyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (42)

Using the above general procedure with hydrazine salt (0.150g, 0.00056moles), DME (3mL) and then added butyroyl chloride (0.115mL, 0.00112moles) gave the title compound (0.0586g, 50.82%), m.p. 54-56°C; lit. m. p. 57.5 – 58.5°C, identical to an authentic sample.

IR (KBr) : 2966.35, 2878.50, 1769.89, 1495.17, 960.56, 693.99 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.88 (d,2H), 7.85 (m,2H), 7.45(t), 2.65(t), 1.84(m), 1.08(t) ; **^{13}C NMR ($CDCl_3$) :** 156.82, 151.17, 136.07, 129.14, 125.86, 118.12, 28.20, 18.95, 13.45.

Synthesis of 5-(bromomethyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (40) using 2eqs of acid bromide (with change in time parameter)

α-Bromoformylphenylhydrazine hydrochloride (**35**) (0.051g, 0.00020moles) was suspended in dimethoxyethane (DME) (2mL) and to the stirred mixture was added the bromoacetyl bromide (0.035mL, 0.00040moles). This mixture was heated on an oil bath at 65°C for 1.5 hours under reflux. After allowing the solution to cool down to room temperature, the contents were poured into water (10mL), this produced a creamy white precipitate but, nonetheless, the mixture was left under a stream of air to facilitate the

evaporation of the DME. This gave the title compound (0.0428g, 83%), m.p. 73-73.5°C, identical to an authentic sample.

General procedure for synthesis of 3,5-disubstituted 1,3,4-oxadiazol-2(*3H*)-ones using 2eqs of aryl acid chlorides)

Bromocarbonylhydrazine salt (**35**) (0.050g, 0.00019moles) was suspended in dimethoxyethane (DME) (2mL) and to the stirred mixture was added the appropriate acid chloride (2 eq). This mixture was heated on an oil bath at 65°C for 3.5hours under reflux. After allowing the solution to cool down to room temperature, the contents were poured into water (10mL). In all cases, this produced a creamy white precipitate but, nonetheless, the mixture was left under a stream of air to facilitate the evaporation of the DME. Subsequent vacuum filtration afforded a product, which was weighed, characterized and purified by the following process.

The product was finely powdered using a mortar and pestle, suspended into 8 -10 mL of 10% aq. NaOH solution and heated at 45°C for about 60mins. After allowing to cool down to room temperature and suction filtration, the final product was dried and weighed.

Synthesis of 3,5-diphenyl-1,3,4-oxadiazol-2(*3H*)-one (45)

Using the above general procedure with hydrazine salt (0.050g, 0.00019moles), DME (2mL) and then added benzoyl chloride (0.083mL, 0.00072moles) gave the title compound (0.0372g, 77%), m.p.88-94°C

The product was finely powdered and base washed using the above general procedure and the dried product weighed (0.0364g, 76%), m.p.107.5-109°C; lit. m.p. 110 - 111°C, identical to an authentic sample.

IR (KBr) : 3054.73, 1778.18, 1448.47, 1068.15, 914.07, 681.68 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.96(d,2H), 7.60(t,2H), 7.57(d,2H), 7.52(m), 7.47(t,2H), 7.30(t) ppm ; **^{13}C NMR ($CDCl_3$) :** 153.59, 151.22, 136.10, 131.96, 129.22, 129.06, 126.17, 125.99, 123.50, 118.36.

Synthesis of 5-p-tolyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (43)

Using the above general procedure with hydrazine salt (0.0507g, 0.00020moles), DME (2mL) and then added *para* toluoyl chloride (0.050mL, 0.00040moles) gave the title compound (0.0748g, 149%), m.p.120-124°C.

The product was finely powdered and base washed using the above general procedure and the dried product weighed (0.0515g, 102%), m.p.142-146°C, lit. m.p. 157-158°C.

The above product was recrystallized using dichloromethane (DCM) as solvent. The fine crystals were filtered using suction and the product weighed (0.0322gms, 63.32%), m.p. 143-145°C, lit. m.p. 157-158°C.

IR (KBr) : 3060.27, 1725, 1658, 1421, 742 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.8(dd,2H), 7.65(d,2H), 7.61(m,2H),7.32(dd,2H), 7.20(m), 2.1(s,3H) ; **^{13}C NMR ($CDCl_3$) :** 153.79, 151.09, 136, 132.21, 129.56, 129.11, 127.87, 126.01, 119.27, 18.76(CH_3).

Synthesis of 5-(4-methoxyphenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (44)

Using the above general procedure with hydrazine salt (0.052g, 0.00020moles), DME (2mL) and then added p-anisoyl chloride (0.056mL, 0.00041moles) gave the title compound (0.0955g, 170%), m.p.120-124°C.

The product was finely powdered and base washed using the above general procedure and the dried product weighed (0.0482g, 87%), m.p.138 – 142.5°C; lit. m.p. 137 – 138°C.

IR (KBr) : 3100, 1767.69, 1428.83, 1263.91, 741.41 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.96(dd,2H), 7.91(d,2H), 7.48(t,2H), 7.29(t), 7.03(d,2H), 3.90(s,3H) ppm ; **^{13}C NMR ($CDCl_3$) :** 162.53, 153.62, 150.81, 138.18, 129.16, 127.79, 125.96, 118.27, 115.87, 114.52, 55.49

Synthesis of 5-(4-chlorophenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (47)

Using the above general procedure with hydrazine salt (0.050g, 0.00019moles), DME (2mL) and then added 4-chlorobenzoyl chloride (0.049mL, 0.0665moles) gave the title compound (0.0453g, 84%), m.p.120-132°C.

The product was finely powdered and base washed using the above general procedure and the dried product weighed (0.040g, 74%), m.p.135-137°C ; lit m.p. 118-119°C.

IR (KBr) : 3064.04 (C-H), 1781.63 (C=O) cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.95(d,2H), 7.90(d,2H), 7.61(m,2H), 7.5(t,2H) 7.31(t) ppm ; **^{13}C NMR ($CDCl_3$) :** 152.85, 150.45, 138.29, 136.21, 129.50, 129.25, 127.24, 126.31, 121.96, 118.35.

Synthesis of 5-(2-chlorophenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (46)

Using the above general procedure with hydrazine salt (0.050g, 0.00019moles), DME (2mL) and then added 2-chlorobenzoyl chloride (0.051mL, 0.00040moles) gave the title compound (0.0583g, 107%), m.p.98-104°C.

The product was finely powdered and base washed using the above general procedure and the dried product weighed (0.051g, 94%), m.p.109-110.5°C; lit. mp 145 – 146°C.

IR (KBr) : 3090.21, 1785.18, 1480.10, 1029.40, 973.11, 749.12, 687.13 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 8.0(d), 7.91(d,2H), 7.58(m,2H), 7.54(t), 7.46(t) 7.42(d), 7.31(t) ; **^{13}C NMR ($CDCl_3$) :** 151.72, 150.29, 136, 132.95, 132.42, 131.58, 130.07, 129.48, 127.08, 126.29, 122.29, 118.36.

Synthesis of 5-(4-bromophenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (48)

Using the above general procedure with hydrazine salt (0.051g, 0.00020moles), DME (2mL) and then added 4-bromobenzoyl chloride (0.0877gms, 0.00040moles) gave the title compound (0.0923g, 143%), m.p.138-150°C.

The product was finely powdered and base washed using the above general procedure and the dried product weighed (0.0625g, 99%), m.p.129-131°C ; lit m.p. 124-125°C.

IR (KBr) : 3063.22, 1770.65, 1487.30, 1070.83, 689.69 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 7.95(dd, 2H), 7.82(d, 2H), 7.67(m, 2H), 7.49(d,2H), 7.31(t) ; **^{13}C NMR ($CDCl_3$) :** 152.85, 150.45, 135.95, 132.44, 129.25, 127.34, 126.69, 126.31, 122.39, 118.33.

Synthesis of 5-(3-bromophenyl)-3-phenyl-1, 3, 4-oxadiazol-2(*3H*)-one (49)

Using the above general procedure with hydrazine salt (0.050gms 0.00020moles) dimethoxyethane (DME) (2mL) and then added 3-bromobenzoyl chloride (0.053mL, 0.00040moles) gave the title compound (0.1105gms, 175%), m.p. 97-102°C.

The product was finely powdered and base washed using the above general procedure and the dried product weighed (0.0459gms, 72%), m.p 105-108°C.

The above product was recrystallized using dichloromethane (DCM): n-hexane (95:5) as solvent. The fine crystals were filtered using suction and the product weighed (0.0325gms, 52%), m.p. 115-116°C.

IR (KBr): 3066.38, 1878.22, 1775.41, 1405.79, 1143.34, 940.01, 685.66 cm^{-1} ; **^{1}H NMR ($CDCl_3$) :** 8.11(s), 7.95(d), 7.88(d), 7.68(m), 7.49(t), 7.40(t), 7.30(t) ppm ; **^{13}C NMR ($CDCl_3$) :** 152.20, 150.35, 135.90, 134.91, 130.62, 129.27, 128.83, 126.36, 125.33, 124.47, 123.17, 118.32.

Elemental analysis calculated for $C_{14}H_9BrN_2O_2$ (Mol.wt :317.14): C, 53.02; H, 2.86; N, 8.83; Found : C, 53.03; H, 2.89 ; N,8.96.

General procedure for synthesis of 3,5-disubstituted 1,3,4-oxadiazol-2(*3H*)-ones (with change in time parameter, 1.5hr)

α-Bromoformylphenylhydrazine hydrochloride (**35**) (0.050g, 0.00019moles) was suspended in dimethoxyethane (DME) (2mL) and to the stirred mixture was added the appropriate acid chloride (2 eq). This mixture was heated on an oil bath at 65°C for 1.5hours under reflux. After allowing the solution to cool down to room temperature, the

contents were poured into water (10mL). In all cases, this produced a creamy white precipitate but, nonetheless, the mixture was left under a stream of air to facilitate the evaporation of the DME. Subsequent vacuum filtration afforded a product, which was weighed, characterized and purified, as necessary.

Synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (39)

Using the above general procedure with hydrazine salt (0.050g, 0.00019moles), DME (2mL) and then added acetyl chloride (0.057mL, 0.00072moles) gave the title compound (0.025g, 76%), m.p. 87-88°C

IR (KBr) : 3082.12, 2932.81, 1773.31, 1494.19, 760.85 cm^{-1}, identical to an authentic sample.

Synthesis of 5-(bromomethyl)-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one (40)

Using the above general procedure with hydrazine salt (0.050g, 0.00019moles), DME (2mL) and then added bromoacetyl chloride (0.060mL, 0.00072moles) gave the title compound (0.032g, 82%), m.p. 78-80°C, identical to an authentic sample.

IR (KBr) : 3068.56, 2901.36, 1778.61, 1448.39, 757.20 cm^{-1}.

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